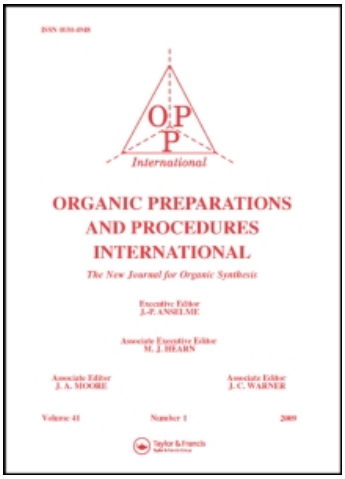

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ASYMMETRIC 1,3-DIPOLAR CYCLOADDITIONS FOR THE CONSTRUCTION OF ENANTIOMERICALLY PURE HETEROCYCLES. A REVIEW

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INTRODUCTION

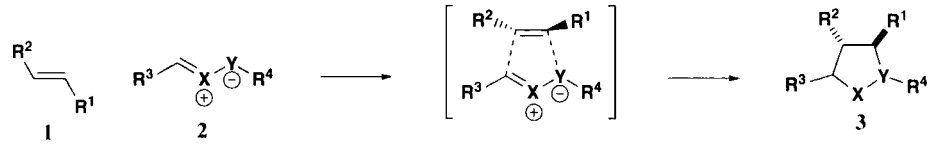
Asymmetric 1,3-dipolar [2+3] cycloadditions (***1,3-DCA***) are reactions involving a 1,3-dipole and a dipolarophile. The dipole is a 4π-system (*an ylide*) and the dipolarophile is a 2π-system, usually a CC or CX double bond or triple bond. Such ***1,3-DCA*** reactions have become one of the most powerful tools for the construction of enantiomerically pure five-membered heterocycles. Up to four stereocenters can be introduced in a stereoselective manner in one single step! Moreover, a range of different substituents can be included in the dipole and the dipolarophile resulting in a broad range of possible cycloadducts, which can serve as useful synthetic building blocks. Stereogenic centers can be introduced by means of chiral dipoles and/or chiral dipolarophiles, *e.g.* using chiral auxiliaries. For a recent example, see a review by Kim and Curran, where they describe the use of the popular auxiliary camphorsultam in ***1,3-DCA*** as well as other types of reactions.[1] Compared with auxiliary induced selectivity, asymmetric catalysis by *e.g.* chiral Lewis acids has a wider scope in synthesis. The latter approach is more efficient because it allows the chirality to be introduced in the presence of a *catalytic* amount of a chiral Lewis acid, leading to low cost processes. In addition, recovery of a chiral catalyst is often much more convenient than for a chiral auxiliary. Therefore it comes as no surprise that much attention has now been focused on the chiral Lewis acid catalyzed asymmetric ***1,3-DCA***.

This review is an effort to present the recent developments in asymmetric ***1,3-DCA*** reactions involving a variety of different heteroylides (or ylide equivalents) and dipolarophiles and covers the literature from 1997. It serves as a complement to earlier review articles and in particular to those written recently by Jörgensen *et al.*[2] and Dell.[3] Other reviews on ***1,3-DCA*** reactions are available.[4,5,6] An additional review describe asymmetric nitrone cycloadditions to alkenes as a tool for preparing enantiomerically pure natural products.[7] For reasons of simplicity, most ***1,3-DCA*** resulting in racemic products will be excluded. In addition, it will describe mainly reactions resulting from a concerted mechanism, where the geometry of the starting alkene is conserved in the cycloadduct. Two-step processes, where the intermediate cycloadducts have the possibility to isomerize to more stable conformers are, with a few exceptions, not included. Because this review aims to illustrate the

majority of recent achievements in the field, the emphasis is on the ***1,3-DCA*** step, leaving other details to the reader to find in the literature cited.

I. GENERAL ASPECTS

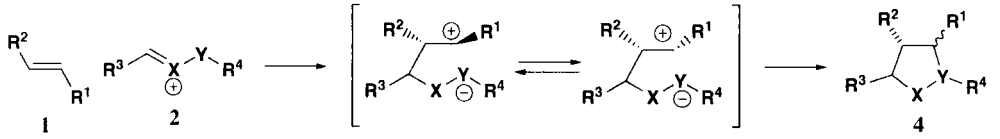
The reactants in a [2+3]-***1,3-DCA*** consist of a 2π alkene part exemplified by dipolarophile **1** (*Scheme 1*) and a 4π dipole component exemplified by **2**. It must be noted that other 1,3-dipole types exist, such as for example diazoalkanes, azides, nitrile imines and nitrile oxides. The result of the concerted cycloaddition reaction is a five-membered ring heterocycle **3**. The stereochemistry of the alkene partner is conserved in the product from the cycloaddition process.



General concerted 1,3-DCA between a dipolarophile **1** and a dipole **2**

Scheme 1

The dipole might be stabilized by the adjacent central heteroatom X through resonance. X in dipole **2** can be either nitrogen, oxygen, sulfur or phosphorous, although the latter has rarely been used. For Y the most common atom used is carbon, nitrogen or oxygen. A non-concerted reaction pathway might also exist (two-step process). In some cases, the product of such a process can be the *cis*-isomer of **4** (*Scheme 2*). Thus an isomerization of the substituents on the alkene part has occurred. The original stereochemistry of the *trans*-alkene **1** is not necessarily conserved during the two-step cycloaddition process (*Scheme 2*).

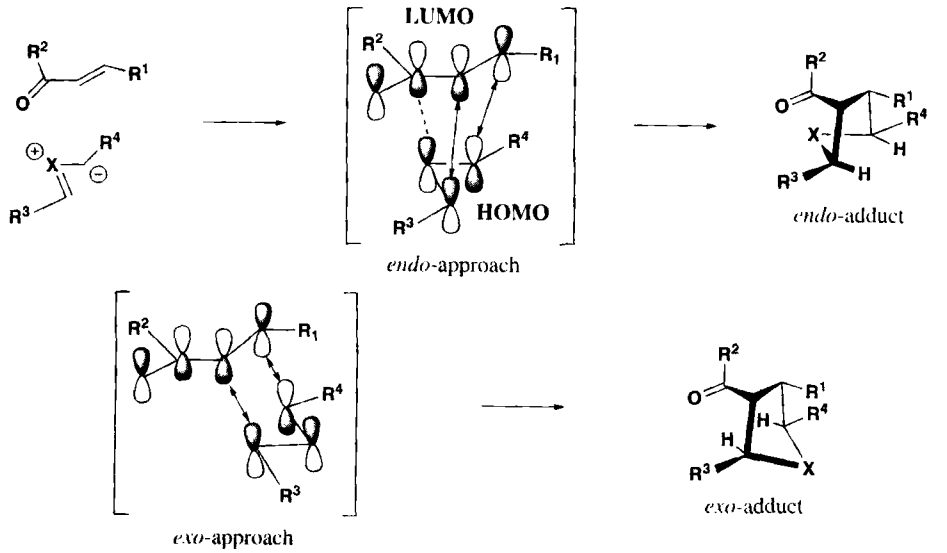


General non-concerted two step cycloaddition sequence resulting in isomerisation around C-R^1

Scheme 2

The reaction of dipoles with dipolarophiles involves either a LUMO-dipole/HOMO-dipolarophile interaction or a HOMO-dipole/LUMO-dipolarophile interaction depending on the nature of the dipole and the dipolarophile. However, if the frontier molecular orbital energies of the dipole and the dipolarophile are very similar, a combination of both modes of interactions can also exist. For example, ***1,3-DCA*** of nitrones and nitrile oxides with electron-rich dipolarophiles such as vinyl ether involve in most cases a LUMO-nitrone/HOMO-dipolarophile interaction or a combination of both

modes; in contrast, for example ***1,3-DCA*** between azomethine ylides and electron-deficient dipolarophiles such as α,β-unsaturated acyl derivatives involves a HOMO-dipole/LUMO-dipolarophile interaction. A schematic overview over a LUMO-dipolarophile/HOMO-dipole interaction is given in Fig. 1. These interactions can also be referred to as either *exo-* or *endo-*, where the *endo*-transition state is stabilized by small secondary π-orbital interactions or *via* an *exo*-transition state lacking such a stabilization (*Fig. 1*). However, steric effects can also be an important factor for the *endo*/*exo* selectivity and override the secondary orbital interactions.[8]



Exo- and endo-approaches of a 1,3-dipole to a dipolarophile. Primary orbital interactions are indicated with double headedarrows and secondary orbital interactions with dotted lines

Fig. 1

Depending on the substitution pattern in the reacting partners, the stereochemical outcome of those processes give rise, in relevant cases, to either the *endo-* or *exo*-cycloadducts. These are often referred to as *cis-* or *trans*-adducts.

II. ACYCLIC DIPOLES AND DIPOLAROPHILES

In contrast to cyclic ones, acyclic dipoles can undergo Z/E isomerization around a double bond. In some cases, this fact makes it difficult to make a direct correlation between the product distribution and the Z/E isomer equilibrium distribution of the starting dipole, since one of the Z/E isomer can react faster under kinetic control. Jörgensen *et al.* have carried out some analyses on C,N-diphenylnitrone **5** and found that the Z-isomer is the most stable one by 11 kcal (*Fig. 2*).[9] Because the transition state for interconversion between *Z-* and *E*-**5** was calculated to be 33 kcal/mole, the inter-

conversion should be very slow at ambient temperature. In addition, dipolarophiles can in some cases undergo Z/E isomerization although it is not as commonly noted as for the dipoles.

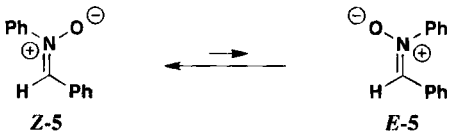


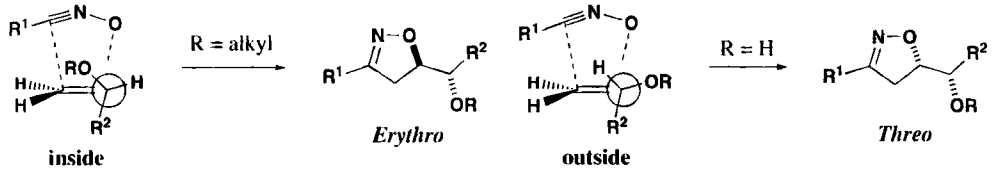
Fig. 2

III. CYCLIC DIPOLES AND DIPOLAROPHILES

1,3-DCA reactions of chiral non-racemic cyclic dipoles or dipolarophiles in general give higher stereoselectivity than their acyclic counterpart due to a more rigid skeleton where one face of the molecule is often effectively shielded from attack by the chiral substituent. Moreover, in contrast to the acyclic ones, small ring cyclic dipoles and dipolarophiles do not suffer from E/Z isomerism, since one of the isomers is much more thermodynamically stable than the other one. These facts make them very useful in terms of direct correlation of the product distribution (*exo/endo*) with the observed selectivity of the reaction.

IV. HOUK'S "INSIDE ALKOXY" MODEL

Among a range of different "rules" to predict the stereochemical outcome (*erythro/threo*) of a ***1,3-DCA***, Houk's "inside alkoxy" model has been used with great frequency in the nitrile oxide ***1,3-DCA*** to chiral allyl ethers and alcohols for example.[10-12] The "inside alkoxy" model has also successfully been applied in predicting the stereochemical outcome of ***1,3-DCA*** reactions involving other dipoles such as for example diazoalkanes and nitrones and is based on the preferential location of the alkoxy moiety of an allyl ether in the inside position in the transition state as shown in *Fig. 3*, because of stabilization of the electron-deficient π-bond which results when the dipole approaches the allyl ether shown.



Favoured Transition state model, -OR (R = alkyl) in inside position, H in outside position and R^2 in anti position leading to the erythro isomer (Left). If R = H the hydroxyl group can occupy the outside position due to favourable hydrogen bonding to the incoming oxygen of the nitrile oxide (Right). This conformation will lead to the threo isomer.

Fig. 3

Because of the electron-withdrawing effect of the alkoxy moiety, this stabilization effect transforms into a destabilizing one if the alkoxy group is in the *anti* position. The outside position on the other hand results in destabilizing electrostatic interactions between the two oxygen atoms of the nitrile oxide and the alkoxy moiety. The most sterically demanding alkyl group R^2 adopts the *anti* position and the proton the outside position. This transition state will lead to the *erythro*-isomer as shown in *Fig. 3*. However, if an allylic alcohol is used (R = H), the outside position for a hydroxyl group is stabilized through hydrogen bonding between the –OH of the allyl alcohol and the oxygen of the incoming nitrile oxide. The alkyl residue will now adopt the least sterically demanding *anti* position and the proton the inside position. The resulting transition state will lead to the *threo*-isomer. Since Houk's model was reported, a range of more extensive studies have been reported, and the model has been applied also for other types of ylides. For example, in two recent publications Raimondi *et al.* have studied the "inside alkoxy" model more extensively with differently substituted alkenes and have evaluated a model including a force field factor.[13,14] Thus, they investigated different 1,3-dipoles (*i.e.* nitrones, nitrile oxides and diazomethane) in their reactions with β'-alkoxy-α,β-unsaturated esters and found that the stereochemical outcome was in accordance with the "inside alkoxy" model. In addition, they found a good relationship between the extent of stereoselection and the amount of negative charge on the dipole terminus using electronically different 1,3-dipoles. Thus, the higher the negative charge on the dipole terminus, the higher the repulsion was between the allylic oxygen and the terminus of the dipole in the outside position. This means that a higher preference for the "inside alkoxy" position exists. Similarly, they varied the substituent on the allylic oxygen to achieve either a more or a less electron-rich oxygen which might give the same effect. Indeed, they showed that more electron-rich allylic oxygen gave a higher stereoselection. This is also in accordance with the results obtained by varying the electronic nature of the dipole terminus. However, when the terminus of the dipole interacting with the allylic oxygen is positively charged, a stabilizing effect in the outside position was observed due to favorable electrostatic interaction, resulting in an "outside alkoxy" effect.

V. INTRAMOLECULAR REACTIONS

Asymmetric intramolecular ***1,3-DCA*** is an effective approach for the synthesis of enantiopure polycyclic compounds in a single step. Moreover, in most cases the asymmetric intramolecular ***1,3-DCA*** is known to proceed with higher diastereoselectivity than that of the intermolecular variant, because the flexibility of the reactant is much more restricted. Therefore, it might be advantageous to temporarily introduce a tether between the two reaction partners to allow an intramolecular reaction to take place followed by a simple removal of the tether. Also, due to a favored entropy term compared to the intermolecular variant, the reactivity of the intramolecular reactions is higher in general. Therefore, when using dipoles with low reactivity, one often has to use an intramolecular reaction for example when using azides. Moreover, the cycloadducts in such a process can lead to interesting enantiopure polycyclic compounds, either suitable as chiral ligands, or products suitable as building blocks for natural product synthesis.

VI. METAL-CATALYZED REACTIONS

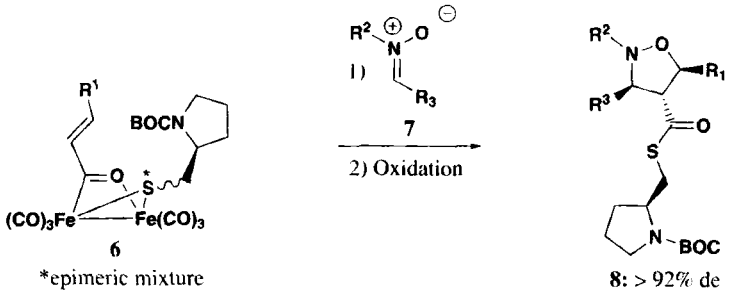
Metal-catalyzed asymmetric ***1,3-DCA*** have become an important research field. The aim has been to find metal-based chiral compounds that are able to efficiently catalyze the addition of dipoles to a range of dipolarophiles in an asymmetric manner.[15] The efficiency of such catalysts relies not only on the capability of the enantiopure catalyst to help discriminate between the two π-faces of the dipolarophile but also on its ability to control both the *exo*/*endo* selectivity and the regiochemistry as well as the yield. There is also a demand for catalysts that can be used in small amounts and with a range of different substrates. Up to date and especially for the nitrone and the nitrile oxide ***1,3-DCA***, many different metal complexes that are able to catalyze the ***1,3-DCA*** have been reported. When coordinating to the dipole or the dipolarophile, the Lewis acid catalysts lower the energy difference between the LUMO-HOMO of the reacting species. The net result is that the LUMO energy of one of the reacting species is lowered. This decreases the energy gap between the HOMO and the LUMO of the dipole and the dipolarophile leading to an increased reactivity. In addition, when a Lewis acid coordinates one of the reaction partners, a change of the orbital coefficients of the reacting atoms involved is expected, which can affect the regioselectivity. Because steric hindrance is also a decisive factor for regioselectivity, there is a competition between this and the former effect. Hence, these factors can either be "matched" or "mismatched". The enantioselectivity (or more correctly diastereoselectivity) of the Lewis acid catalyzed reactions can either be achieved through a combination of chiral non-racemic substrates in combination with either an achiral Lewis acid or a chiral non-racemic one (double asymmetric induction). Alternatively and of greater importance, the enantioselectivity can be introduced by employing a chiral non-racemic Lewis acid with racemic or achiral substrates. As will be shown, a range of chiral Lewis acids able to catalyze Diels-Alder reactions have been employed with success in ***1,3-DCA*** reactions.

VII. NITRONES

Nitrones, which contain both a nitrogen and an oxygen atom, belong to a class of dipoles, which have been subjected to numerous studies as substrates in ***1,3-DCA*** reactions. This is due to their stability and ease of generation from simple dipole precursors such as an aldehyde and a hydroxylamine. For the description of other methods for nitrone generation see for example a very recent publication by Murahashi *et al.*[16] In addition, reductive cleavage of the five-membered ring ***1,3-DCA*** product (*i.e.* an isoxazolidine derivative) furnishes amino alcohols whose functional groups can be found in many natural products. Amino alcohols have also been used as chiral ligands in asymmetric catalytic reactions (see section **VII. 5**). The most common reagents for the cleavage of the five-membered rings include Zn/acetic acid, Raney-Ni, H_2 Pd/C and $LiAlH_4$, but other methods exist as well.[4,5] When nitrones react with allyl alcohols and allyl ethers the stereochemistry of the products often follow Houk's "inside alkoxy" model (see *Fig. 3*).

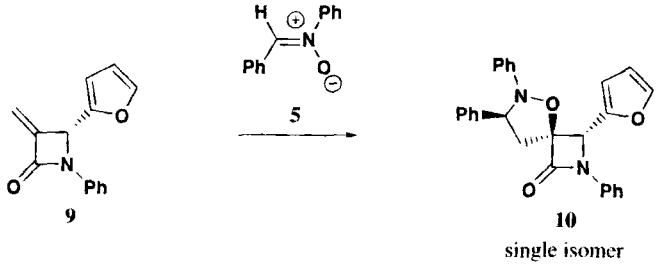
1. Acyclic Nitrones

Gilbertson *et al.* have studied diiron complexes as dipolarophiles. They react with cyclic and acyclic nitrones (see also *Scheme 22*).[17] When a chiral non-racemic diastereomeric mixture of diiron complex **6** (epimeric at sulfur) reacts with a range of different acyclic nitrones **7**, thioester ***1,3-DCA*** products of type **8** are formed in high diastereoselectivity (up to > 92% de), after oxidative removal of the metal.



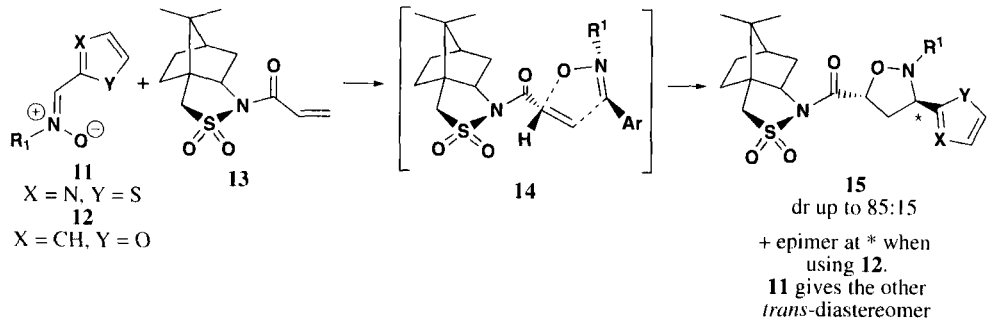
Scheme 3

Basak *et al.* have reported some diastereoselective nitrone ***1,3-DCA*** to chiral racemic and non-racemic β-lactams.[18] They found that a nitrone such as **5** added to the chiral non-racemic β-lactam **9** both regio- and diastereoselectivily (*Scheme 4*). The face opposite to the bulky substituent of the dipolarophile was attacked giving the spiro-cycloadduct **10** as the only isolable diastereomer.



Scheme 4

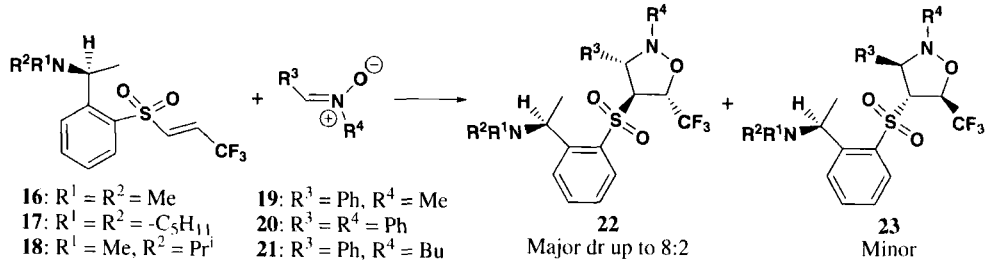
Tejero and Dondoni *et al.* investigated the additions of nitrones **11** and **12** to various kinds of acrylates attached to chiral auxiliaries (*Scheme 5*). Using the camphorsultam derived acrylate **13** in reactions with both nitrones **11** and **12** gave complete control of the regioselectivity furnishing *trans*-cycloadducts **15** (85:15 dr at best).[19,20] The furfuryl derived dipolarophile **12** gave cycloadducts containing a masked carboxylic acid, which opened a new route to the construction of enantiomerically pure 4-hydroxypyroglutamic acids.[20]



Scheme 5

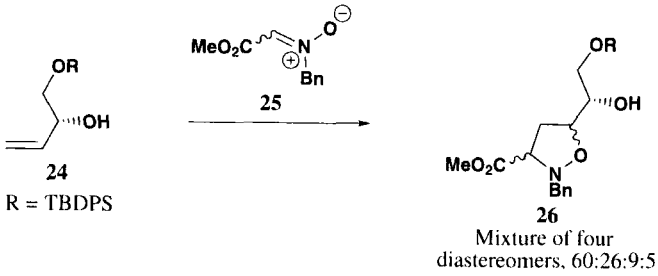
A rationale for the observed selectivity was proposed where the Z-isomer of the nitrone attacks on the "top face" of the thermodynamically most stable *anti, s-cis* rotamer of the acrylate **13** (*Scheme 5*, intermediate **14**).

Recently Eguchi *et al.* found that trifluoromethylated α,β-unsaturated aryl sulfones **16-18** reacted with acyclic nitrones **19-21** (*Scheme 6*) to give two diastereomeric cycloadducts **22** and **23** (dr: 7/3 up to 8/2).[21]



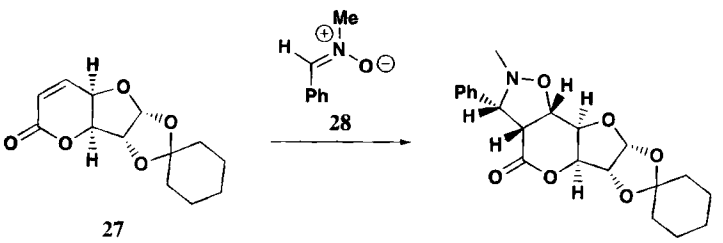
Scheme 6

An asymmetric *1,3-DCA* between nitrone **25** and the chiral non-racemic allyl alcohol **24** was utilized by Ohta *et al.* as a key step in the synthesis of (-)-bulgecinine (*Scheme 7*).[22] The crude mixture of cycloadducts **26**, consisted of a 60:26:9:5 mixture of four diastereomers.



Scheme 7

Trivedi *et al.* have been investigating chiral non-racemic sugar derived esters and lactones as dipolarophiles in nitrone *1,3-DCA*. They demonstrated the utility of such dipolarophiles in reactions with acyclic (as well as cyclic) nitrones.[23] Thus, among a range of different acyclic and cyclic dipolarophiles investigated, reaction between nitrone **28** and dipolarophile **27** was found to give one single *exo*-cycloadduct **29**. Other acyclic types (for example menthol derived dipolarophiles) also gave good results.

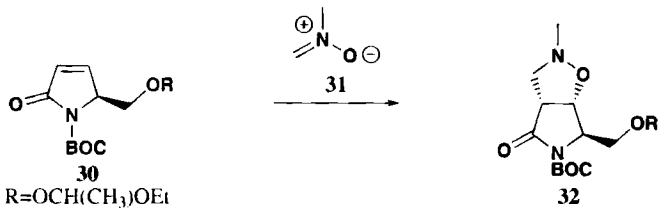


27

29
Single isomer

Scheme 8

Langlois utilized an asymmetric *1,3-DCA* for the construction of an unusual amino acid.[24] Nitrone **31** reacted with the chiral dipolarophile **30** *anti* to the bulky alkoxy group to give the cycloadduct **32**.

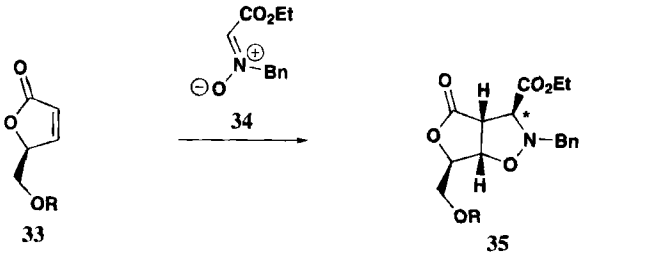


30
R=OCH(CH$_3$)OEt

32

Scheme 9

Ondrus and Fisera *et al.* have studied the reactions between nitrone **34** (as well as other substituted nitrones) and cyclic dipolarophiles of the type **33** where R was varied between a range of substituents with different steric demands.[25-27] Thus, *1,3-DCA* using the hydroxymethyl substituted derivative **33** (R = H) gave the cycloadduct **35** (dr 1.4:1) together with small amount of another regioisomer (not shown). However *1,3-DCA* with substituted lactones **33** (R ≠ H) gave higher stereoselectivity with increased steric bulk of the R-substituent on the lactone. Up to 5.5:1 diastereoselectivity was obtained with the lactone **33** (R = TBDPS). All of the cycloadducts formed resulted from an *anti* addition of the nitrone relative to the R-substituent of the lactone **33**. Microwave irradiation accelerated the *1,3-DCA* with only small changes in stereoselectivity.



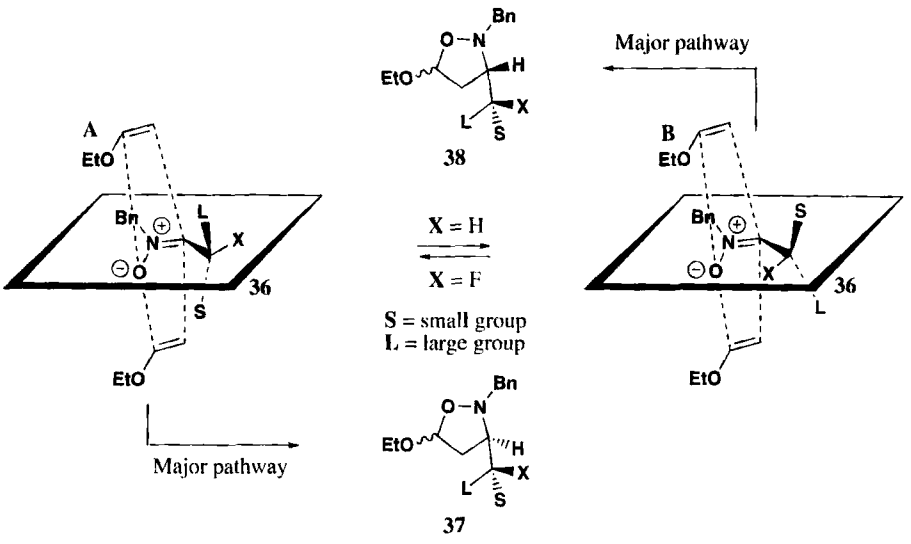
33

35
dr up to 5.5:1.
Minor diastereomer is
epimer to **35** at starred carbon

Scheme 10

2. Chiral Acyclic Nitrones

The influence of a 2-fluoro substituent in an acyclic nitrone in its ***1,3-DCA*** with vinyl ethers was investigated by Ihara *et al.*[28] A number of substituted chiral non-racemic and racemic nitrones of type **36**, either carrying a fluorine at the C-2 position (X = F) or of the type **36** (X = H), were allowed to react with ethyl vinyl ether (*Scheme 11*). The reactions were found to be completely regioselective but afforded mixtures of the two stereoisomers **37** and **38**, each isolated as a mixture of acetal anomers. The fluorinated nitrones showed preference for the **37** anomeric mixture whereas the **38** anomers dominated from the non-fluorinated nitrones (X = H).

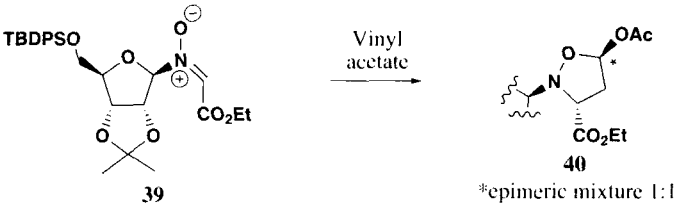


Scheme 11

Scheme 11 shows the explanation for the reversal in selectivity. The most favored conformation for the non-fluorinated nitrones **36** (X = H) is **B**, which should suffer the least from 1,3-allylic strain. Attack from the least hindered side of the nitrone will give **38** (major pathway). However,

conformation **A** should be the most favored one for the fluorinated nitrones because the electronic repulsion between the fluorine and the oxygen of the nitrone is relieved. Attack at the least hindered side of the nitrone will now give **37**. Diastereoselectivity of up to 4.6:1, **38**:**37** (X = H) was reported.

Chiacchio *et al.* utilized the natural products (-)-menthol, (-)-methyl lactate and a sugar derivative as chiral precursors for the preparation of chiral non-racemic nitrones.[29,30] For example, the sugar derived dipole **39** was allowed to react with vinyl acetate to give cycloadduct **40** in low diastereoselectivity (*exo*/*endo* 1:1) but with high diastereofacial selectivity (*Scheme 12*). Serine-derived nitrones have also very recently been found to react with vinyl acetate in low to moderate diastereoselectivity.[31]

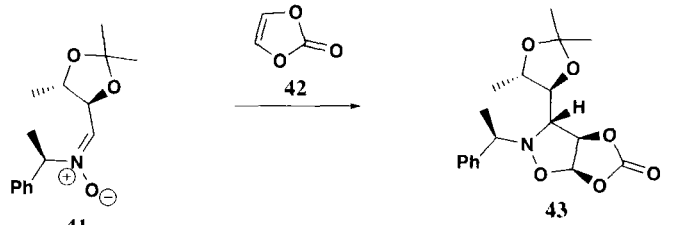


39 **40**

*epimeric mixture 1:1

Scheme 12

An efficient approach to the synthesis of a carbohydrate moiety of an antifungal agent, has been demonstrated by Hoveyda *et al.*[32] Thus, the chiral non-racemic nitrone **41** was found to undergo a highly diastereoselective ***1,3-DCA*** with vinylene carbonate **42**. Cycloadduct **43** was obtained in facial diastereoselectivity 20:1 and *endo*/*exo* selectivity > 25:1. It was found that the chiral N-α-methylbenzyl substituent of the dipole **41** was crucial for obtaining a reasonable level of diastereoselectivity since a benzyl substituent led to a much lower diastereoselectivity. See a recent work by Fisera *et al.* where C-α-alkoxy-substituted chiral nitrones of type **41** containing an achiral N-benzyl substituent, were investigated in cycloaddition reactions with styrene; low to moderate diastereoselectivity was reported.[33] Merino *et al.* used the same nitrone of type **41** for reactions with vinyl acetate and vinyl thymine for the purpose of synthesizing isoxazolidinyl nucleosides, low to moderate diastereoselectivity was obtained in these ***1,3-DCA*** reactions.[34]

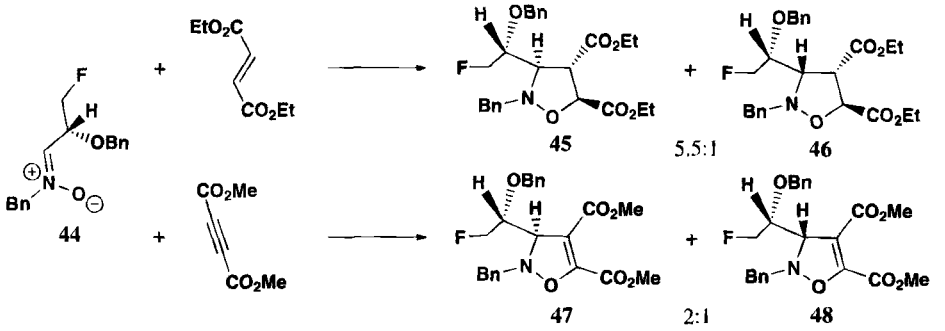


41 **43**

Facial selectivity 20:1
endo/exo > 25:1

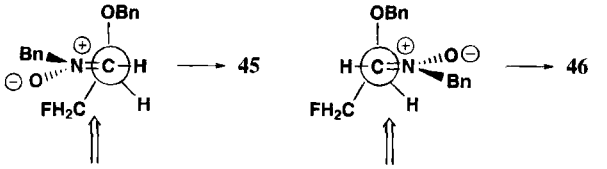
Scheme 13

Bruché *et al.* prepared the enantiomerically pure β-fluoromethyl nitrone **44** (*Scheme 14*) and reacted it with vinylic and acetylenic dipolarophiles.[35]



Scheme 14

1,3-DCA with diethyl fumarate gave two cycloadducts, **45** and **46**, in a 5.5:1 ratio resulting from a 100% *endo* attack. The complete *endo* selectivity was explained by steric interaction in the transition state between one of the ethoxy groups of the dipolarophile and the bulky C-substituent of the nitrone. The facial selectivity was explained by comparing the two preferred conformations postulated for the nitrone in the transition state (*Fig. 4*).



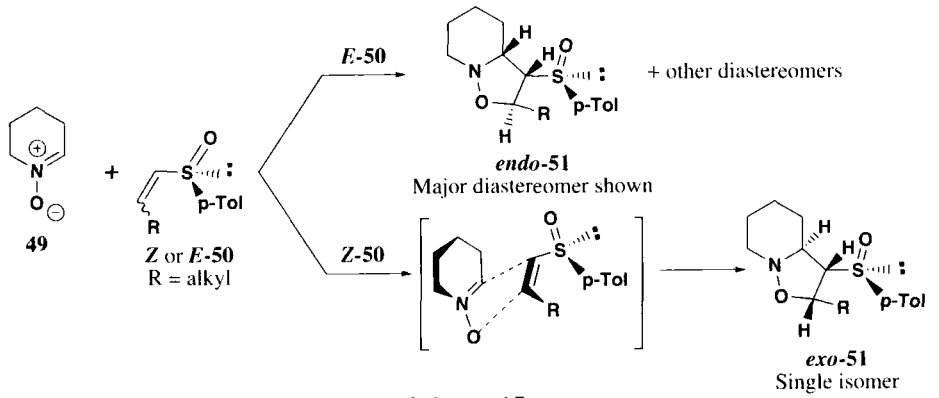
Conformations of **44** in the transition state and the approach of diethyl fumarate (arrows) leading to major cycloadduct **45** and minor cycloadduct **46.**

Fig. 4

The dipolarophile preferentially attacks the most reactive conformer of the nitrone (left), which is the one with smallest interaction with the bulky C-substituent of the nitrone (leading to **45**) compared with the minor pathway (right, leading to **46**). The acetylenic dipolarophile (dimethyl acetylenedicarboxylate) reacted with nitrone **44** in a less selective manner to give **47** and **48** in a ratio of 2:1 (*Scheme 14*).

3. Cyclic Nitrones

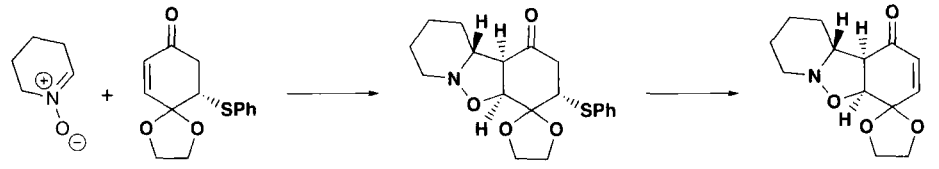
Reactions between the diasteromeric enantiopure sulfoxides *E*- and *Z*-**50** and the cyclic nitrone **49** and an analogue of this (*Scheme 15*) have recently been used by Hootelé *et al.* as a starting point for the synthesis of the alkaloids (+)-sedridine and (-)-hygroline.[36]



Scheme 15

Nitrone **49** and *E*-sulfoxide **50** were found to react predominantly in the *endo* fashion (*endo/exo*, 80/20) to give ***endo*-51** as the major product in moderate diastereoselectivity (de 40%) along with three minor diastereomeric cycloadducts. In contrast, *Z*-sulfoxide **Z-50** and nitrone **49** furnished exclusively the *exo*-adduct ***exo*-51** as a single diastereomer. A transition state was proposed in which the *Z*-sulfoxide **Z-50** adopts its less crowded face towards attack of the nitrone **49** (*Scheme 15*). Similar ***1,3-DCA*** reactions with acetylenic sulfoxides proceeded with very low stereoselectivity.[36]

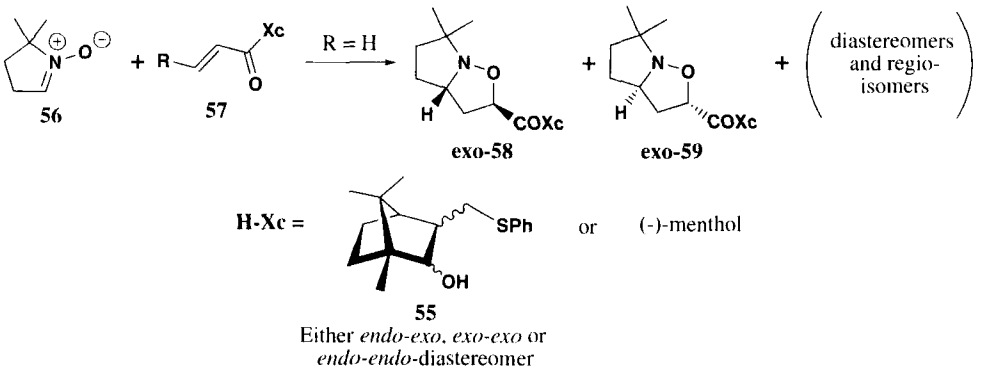
A range of chiral non-racemic α,β-unsaturated lactones and esters have been investigated in reactions both with acyclic nitrones and a cyclic nitrone by Trivedi *et al.*[23] The best results were described in an earlier paper by the authors.



Scheme 16

The enantiomerically pure masked *p*-benzoquinone (+)-**52** has been used in ***1,3-DCA*** reactions by March and Figueredo *et al.*[37] This compound was obtained from *p*-benzoquinone monoketal followed by thiophenol addition and resolution of the resulting enantiomers. The dipolarophile (+)-**52**, reacted with the cyclic nitrone **49** to give (+)-**53** as a practically single diastereomer. Elimination furnished the enantiopure fused tricycle (+)-**54**.

Baskaran *et al.* used the camphor derived alcohol of the type **55** and (-)-menthol as chiral auxiliaries in asymmetric ***1,3-DCA*** with the cyclic nitrone **56** (*Scheme 17*).[38]

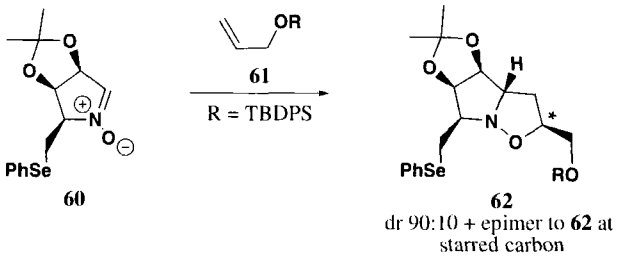


Scheme 17

Dipolarophiles **57** were allowed to react with **56** in different solvents. With the acrylates (R = H), cycloadducts *exo*-**58** and *exo*-**59** were obtained with low selectivity (1.1:1→ 2.1:1) with all chiral auxiliaries used, together with *endo*-isomers and in some cases regioisomers. When crotonates were used as dipolarophiles (R = Me), the *endo*-cycloadducts were the major isomers and the reversed regioselectivity was observed. However, the diastereoselectivity was low in all cases and was explained from the low conformational energy difference between S-*cis*/S-*trans* enoate conformers of the crotonates.

4. Chiral Cyclic Nitrones

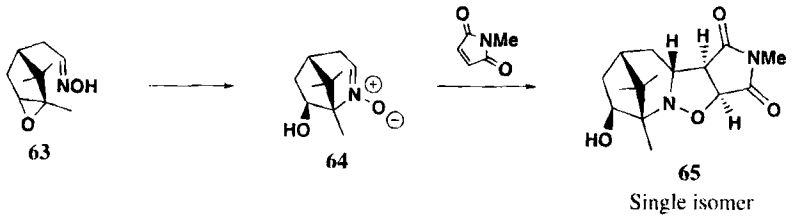
For a recent review concerning asymmetric ***1,3-DCA*** with chiral cyclic pyrroline *N*-oxides see Goti and Brandi *et al.*[39] Recently Wightman *et al.* reported a method for the construction of polyhydroxylated pyrrolizidines related to the natural products alexine and australine, using a ***1,3-DCA*** as a key reaction.[40] L-Arabinose derived nitrone **60** reacted with silyl ether **61** which furnished *exo*-cycloadduct **62** (*Scheme 18*), together with the epimer *endo*-adduct (dr 90:10).



Scheme 18

Grigg *et al.* have demonstrated that epoxides can serve as electrophiles in the nitrone generation step. In a recent paper they used chiral non-racemic epoxides as the source of chirality.[41] Chiral

epoxy oximes such as compound **63** (*Scheme 19*) were transformed to the corresponding nitrone **64**, and added to alkenes such as N-methylmaleimide to give the single cycloadduct **65**.

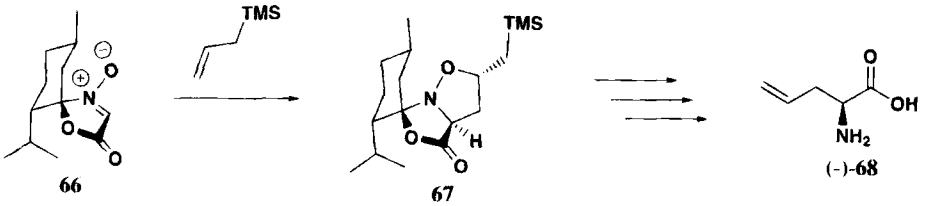


63 **64** **65**

Single isomer

Scheme 19

Cyclic spironitrones can be obtained from nitrosoketene and enantiomerically pure ketones such as (-)-menthone, (+)-nopinone and (+)-camphenilone.[42] Some of these nitrones have been found to react in a highly diastereoselective manner. For example, menthone derived nitrone **66** reacted with allyltrimethylsilane in the presence of BF_3-OEt_2, to give cycloadduct **67** as the only isolable stereoisomer (*Scheme 20*).[42] Moreover, this cycloadduct can easily be transformed to the (-)-amino



66 **67** **(-)-68**

Single isomer

Scheme 20

acid **68**. In the reaction with *rac*-3-trimethylsilylcyclopent-1-ene the nitrone **66** was also found to discriminate between the enantiomers resulting in a kinetic resolution of the former. An explanation for this is found in *Fig. 5* where the Lewis acid (BF_3-OEt_2) is coordinating to the oxygen of the nitrone in the transition state and where only one enantiomer of the racemate is recognized.

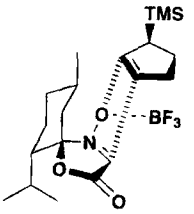
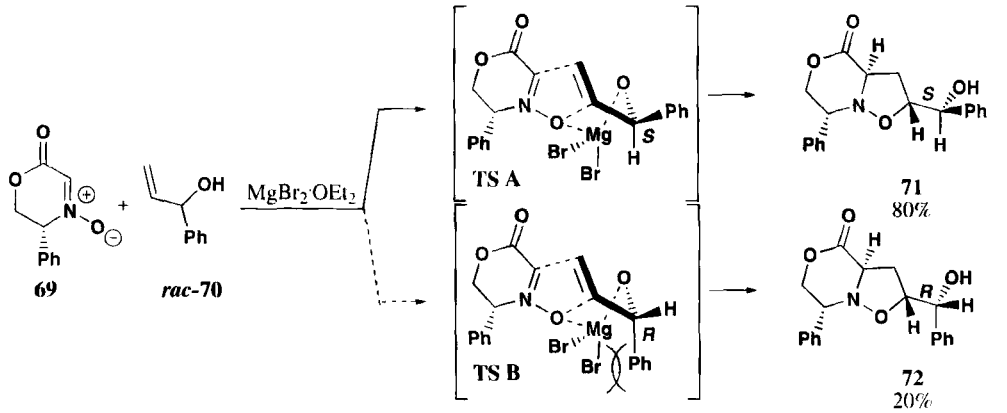


Figure 5.

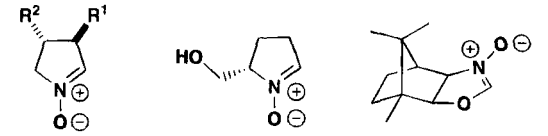
Tamura and Sakamoto *et al.* have been investigating ***1,3-DCA*** reactions of the chiral non-racemic cyclic nitrone **69** (*Scheme 21*) with alkenes, and recently reported the behavior of **69** in reactions with allyl alcohols in the presence of Lewis acids such as $MgBr_2$, BF_3-OEt_2, $Ti(O^iPr)_4$,



Scheme 21

$Eu(fod)_3$.[43] Highly diastereoselective reactions were obtained with achiral allyl alcohols. Furthermore, in the presence of one of the Lewis acids mentioned above, chiral racemic allyl alcohols, such as **70** underwent kinetic resolutions. Thus, when the nitrone **69** was reacted with rac-**70** only two cycloadducts were formed (**71** and **72**) in up to 80:20 diastereoselectivity resulting from a preference for the (*S*)-enantiomer of **70**. A rationale for this discrimination is depicted in Scheme 21, where a chelated transition state accounts for the high diastereoselectivity. In transition state B (**TS B**), severe steric interaction exists between the bromine atom and the phenyl group of the (*R*)-allyl alcohol, whereas in the preferred (*S*)-enantiomer of the allyl alcohol this interaction is absent (**TS A**).

Five-membered functionalized substituted cyclic nitrones, *e.g.* of the type **73** and **74** (*Fig. 6*) have frequently been used in reactions with alkenes.



73
Relative configuration

74

75

Fig. 6

For example Cicchi *et al.* have reacted a range of alkenes such as styrene, diphenylethylene and methylenefluorene with the L-malic acid methyl ester derived nitrone **73** (R^1 = O'Bu, R^2 = H) which gave cycloadducts in low to moderate diastereoselectivity.[44] However, reaction with norbornene was found to give one single cycloadduct **76** (*Fig. 7*) formed through an *exo* approach of the dipole *anti* to the bulky tert-butoxy group.

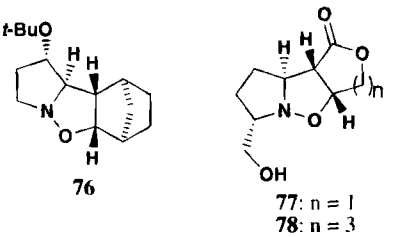
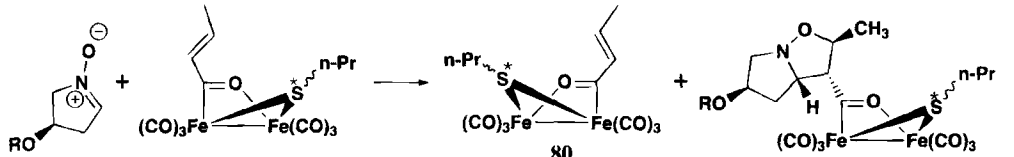


Fig. 7

Goti *et al.* have used nitrone **73** (R^1 = $PhCO_2$, R^2 = H) in a moderately diastereoselective reaction with dimethyl maleate as the key step in the synthesis of (-)-hastanecine.[45] In a subsequent paper Goti and Brandi *et al.* further investigated the reactions of chiral cyclic nitrones of type **73** with various dipolarophiles such as 3-butenol and maleic acid isopropylester in order to explore new routes for the construction of highly functionalized indolizidines and pyrrolizidine skeletons.[46] In another paper a highly diastereoselective reaction of a chiral cyclic nitrone of type **73** to bicyclopropylidene is described.[47] Other examples of successful additions of cyclic chiral/achiral pyrroline N-oxide derivatives to chiral glycals in excellent diastereoselectivity[48,49] and under high pressure enhancement[50] have been reported. Kinetic resolution of a chiral racemic α,β-unsaturated δ-lactone[51] in up to 77% ee and of a chiral racemic cyclic organophosphorous compound[52] in excellent ee have also been achieved in reactions with the cyclic nitrone **73** (R^1 = R^2 = ^{t}BuO, *Fig. 6*) by Brandi *et al.* The L-(+)-prolinol derived nitrone **74**, has been investigated in reactions with a range of dipolarophiles by Figueredo *et al.*[53] Thus for example, reactions with cyclic five and seven membered lactones proceeded with complete diastereofacial differentiation, to give the cycloadducts **77** and **78** exclusively (*Fig. 7*).

Langlois *et. al.* have demonstrated that camphor derivatives function as useful precursors for the preparation of chiral cyclic nitrones[54] and that they undergo highly regio- and diastereoselective ***1,3-DCA*** reactions with electron-poor dipolarophiles.[55] For example, the camphor derived cyclic nitrone **75** (*Fig. 6*) has recently been used in efficient asymmetric ***1,3-DCA*** reactions as key steps in the synthesis of a β-methylcarbapenem derivative[56] and an oxetanone derivative.[57] It has also been used in a double diastereoselective reaction with a chiral non-racemic as well as a racemic α,β-unsaturated δ-lactone.[58] The latter was recovered in up to 70% ee as the result of the kinetic resolution.

Gilbertson *et al.* found that when the cyclic chiral nitrone **79** was allowed to react with the chiral racemic diiron acyl complex **80** epimeric at sulfur (*Scheme 22*) an elegant kinetic resolution took place.[59]

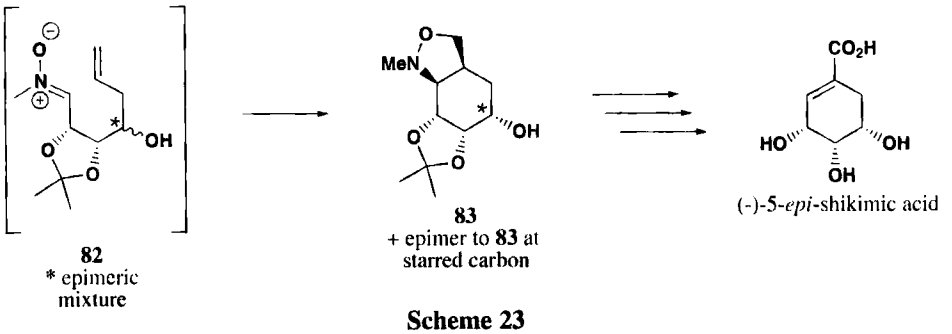


Scheme 22

The reactive face of the nitrone **79** was that opposite to the *tert*-butyldimethylsilyl group, and attack of the nitrone on the iron complex **80** occurred on the face not shielded by the sulfur moiety. Thus, one enantiomer of **80** could be recovered in enantiomerically enriched form as a mixture of epimers at sulfur together with the stereoisomerically highly pure cycloadduct **81** which was, however, a mixture of epimers at sulfur. Compound **81** was further utilized in the synthesis of a carbapenem.

5. Intramolecular Reactions

(-)-5-*epi*-Shikimic acid and (-)-shikimic acid were recently synthesized by Jiang *et al. via* an intramolecular nitrone ***1,3-DCA*** as one key step.[60] The synthesis of (-)-5-*epi*-shikimic acid started from D-ribose, and through a short sequence the intermediate alkenyl nitrone **82**, a mixture of epimers at starred carbon was obtained. In a highly efficient intramolecular reaction, **82** gave the cycloadduct **83** and the epimer to **83** (starred carbon), *via* attack of the nitrone on the only accessible π-face of the alkene part (*Scheme 23*). The synthesis of (-)-shikimic acid followed a similar protocol.



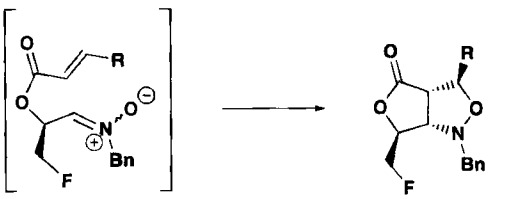
82
* epimeric mixture

83
+ epimer to **83** at starred carbon

(-)-5-*epi*-shikimic acid

Scheme 23

An elegant synthesis of a bicyclic compound was presented by Resnati *et al.*[61] The intermediate alkenyl nitrone **84** was prepared and underwent intramolecular cyclization to **85**, obtained as a single stereoisomer (*Scheme 24*). When the fluoromethyl chain is *trans* to the *cis*-fused isoxazolidine ring, low steric hindrance should result which explains the stereoselectivity.



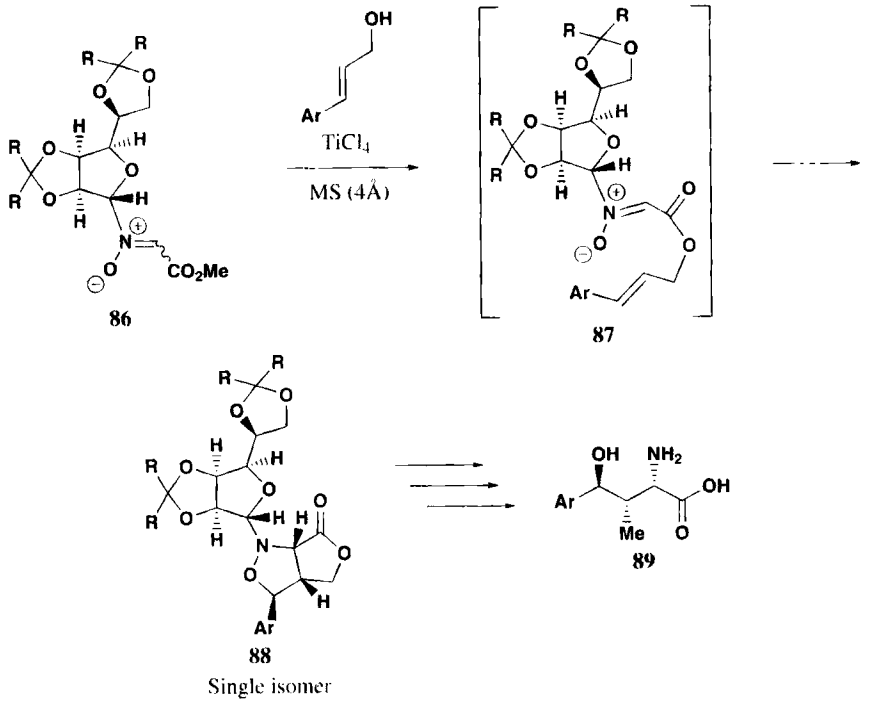
84

85
Single isomer

Scheme 24

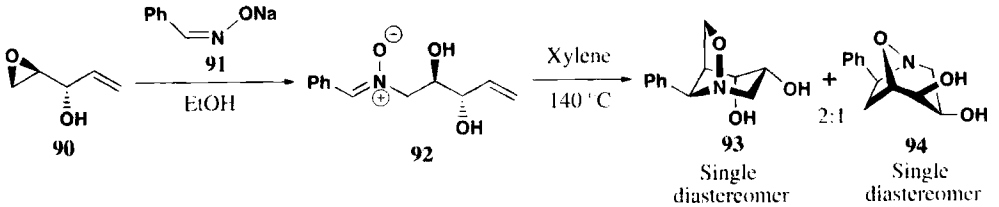
Tamura and Sakamoto *et al.* recently reported a short synthesis of the N-terminal amino acid component of nikkomycin Bz through a highly diastereoselective intramolecular nitrone ***1,3-DCA***.[62]

Starting from commercially available L-gulonic-γ-lactone, they prepared the chiral non-racemic nitrone **86**, which in the presence of an allyl alcohol such as (E)-p-methoxycinnamyl alcohol and $TiCl_4$ underwent a transesterification reaction of the methyl ester moiety (intermediate **87**); this was followed by an intramolecular ***1,3-DCA*** to give the cycloadduct **88** as a single isomer (*Scheme 25*). Cleavage of the chiral auxiliary and a few more manipulations afforded the desired amino acid **89**.



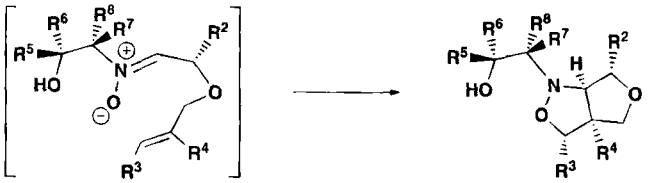
Scheme 25

Grigg *et al.*, who described the use of epoxides as electrophiles in the nitrone generation step (see section **VII**, **4**), have also studied an intramolecular nitrone ***1,3-DCA*** variant using this approach.[41] Thus, chiral non-racemic epoxide **90** was treated with the sodium salt of (Z)-benzaldoxime **91** to give nitrone **92**, which was heated so that an intramolecular ***1,3-DCA*** took place (*Scheme 26*). Hence, the two regioisomers **93** and **94** were obtained, each as a diastereomerically pure compound in a 2:1 ratio.



Scheme 26

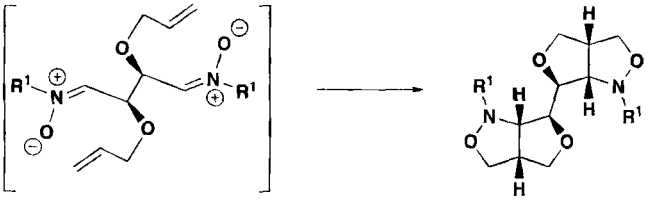
Chiral non-racemic ligands for use as catalysts in the enantioselective addition of diethylzinc to aldehydes can be prepared efficiently using asymmetric intramolecular nitrone ***1,3-DCA*** as a key step. Aurich *et al.* have made a major contribution in this area. For example, in a recent publication his group prepared bicyclic and tricyclic compounds suitable as chiral ligands[63] (see also a recent related work[64]). Thus the alkenyl nitrones **95** were prepared *in situ*, from aldehydes and hydroxylamines, or alternatively through oxidation of the corresponding secondary amines with hydrogen peroxide in the presence of sodium tungstate.[65] Compounds **95** spontaneously cyclized to bicycles **96**, which were obtained as pure stereoisomers in most cases (*Scheme 27*).



95 **96**

Scheme 27

Dinitrones **97**, prepared from diethyl (*R,R*)-tartrate, spontaneously cyclized to form tetracycles **98** as pure diastereomers (*Scheme 28*).[66]

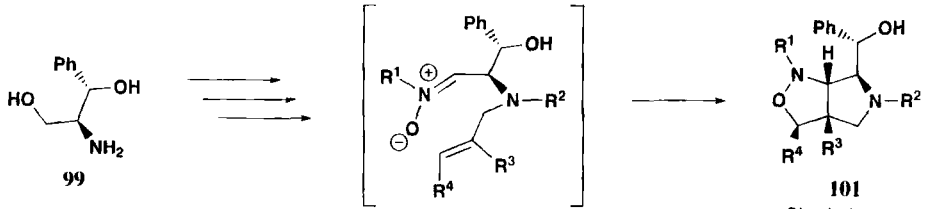


97 **98**

Single isomers

Scheme 28

Starting from commercially available (*1S,2S*)-2-amino-1-phenylpropane-1,3-diol **99**, Aurich *et al.* synthesized a range of different alkenylnitrone intermediates **100**, which spontaneously underwent intramolecular ***1,3-DCA*** to give enantiopure bicycles **101** (*Scheme 29*).[67] No traces of other diastereomers were detected by NMR analysis.

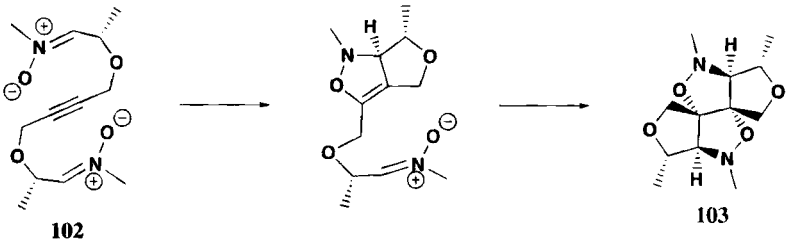


99 **100** **101**

Single isomer

Scheme 29

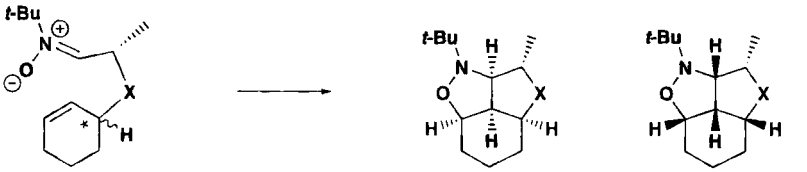
A double intramolecular ***1,3-DCA*** has recently been presented by Aurich *et al.*[68] Thus the alkenyldinitrone **102** prepared *in situ*, spontaneously underwent two highly efficient consecutive cyclization steps to give the optically active tetracycle **103** (*Scheme 30*). Subsequently, they synthesized



102 **103**

Scheme 30

tricyclic adducts from compounds **104** and **105** (*Scheme 31*) which were prepared from (S)-ethyl lactate, (S)-*N*-benzyl alananol and racemic 3-bromo cyclohexene.[69] These underwent asymmetric intramolecular ***1,3-DCA*** and afforded diastereomeric mixtures of tricycles **106**, **107** and **108**, **109**, respectively. Diastereomerically pure compounds could be obtained after separation. Fluorinated cyclohexenyl derived nitrones with chirality residing on nitrogen have been found by Bruché *et al.* to undergo diastereoselective intramolecular reactions.[70] Finally, Aurich *et al.* in a very recent extensive study, describes intramolecular ***1,3-DCA*** reactions of nitrones and have prepared chiral non-racemic eight membered heterocycles for example.[71]



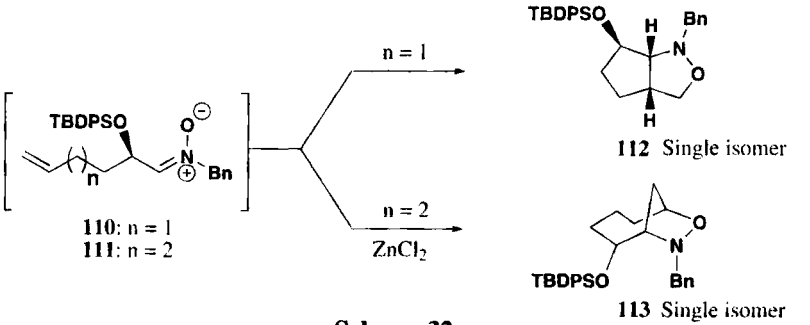
104: X = O
105: X = N-Bzl
* epimeric

106: X = O
108: X = N-Bzl

107: X = O
109: X = N-Bzl

Scheme 31

Brussee *et al.* prepared bicycle **112** from enantiopure alkenylnitrone **110** which was prepared *in situ* from the corresponding aldehyde (*Scheme 32*).[72] The intramolecular ***1,3-DCA*** took



110: n = 1
111: n = 2

n = 1

n = 2

$ZnCl_2$

112 Single isomer

113 Single isomer

Scheme 32

place to give **112** as a single isomer. A similar reaction with the homologue **111** required the presence of $ZnCl_2$ to afford a reasonable yield of the cycloadduct **113**. In the latter case the cycloaddition could in principle proceed along two reaction pathways, either *via* formation of a fused C6 transition state or a bridged C7 one. The authors suggested the following explanation for the exclusive formation of **113** in the presence of $ZnCl_2$ (*Fig. 8*). The Lewis acid was proposed to bind to and neutralize the negatively charged oxygen of the nitrone. This would lead to the development of a more advanced C-C bond formation in comparison with the C-O bond in the transition state. This should consequently have a certain cationic character in the alkene derived part. Because a secondary carbocation is more stable than a primary one, there should be a preference for the bridge C-7 transition state leading to **113** (*Fig. 8*). Bagley *et. al.* have recently reported an auxiliary controlled (camphorsultam) intramolecular nitrone ***1,3-DCA*** reaction where this type of regioselectivity was a serious problem.[73]

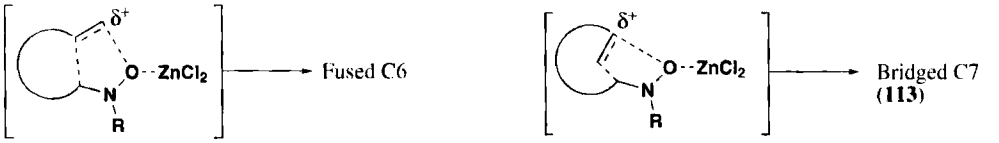
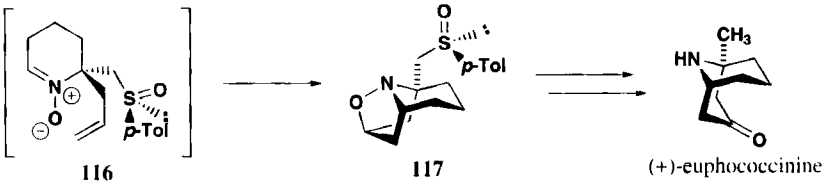


Figure 8

Bruché *et al.* synthesized some bicyclic compounds **115** through highly efficient intramolecular ***1,3-DCA*** reactions of the precursors **114** which were prepared from chiral non-racemic β-ketosulfoxides (*Scheme 33*).[74] As reported by the authors, the reactions proceeded with complete stereocontrol.

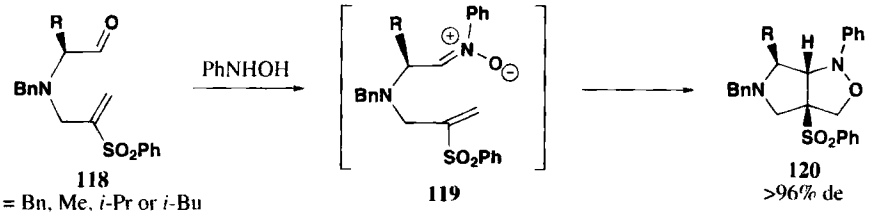
Scheme 33

Very recently, Murahashi *et al.* developed an efficient method for the synthesis of chiral non-racemic β-sulfinyl nitrones from secondary amines.[75] Thus, **116** was prepared from the corresponding hydroxylamine through treatment with Ni_2O_3. Intermediate **116** underwent an intramolecular reaction (*Scheme 34*) yielding compound **117**. Raney nickel reduction followed by PCC oxidation finally furnished (+)-euphococcinine.



Scheme 34

Yamamoto *et al.* studied intramolecular ***1,3-DCA*** reactions of nitrones (as well as nitrile oxides), where the alkene part consisted of α,β-unsaturated sulfones.[76] Chiral non-racemic compounds such as **118** (*Scheme 35*) were utilized as precursors for the generation of either nitrones or nitrile oxides.



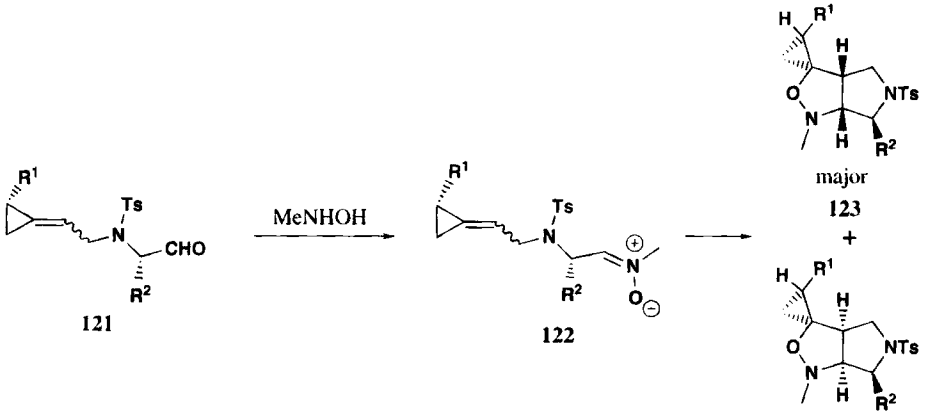
118
R = Bn, Me, *i*-Pr or *i*-Bu

119

Scheme 35

For example, when aldehydes **118** were treated with *N*-phenylhydroxylamine, the corresponding nitrones **119** were generated and immediately cyclized to nearly stereoisomerically pure bicycles **120.**

Salaün and Brandi *et al.* have been studying asymmetric intramolecular ***1,3-DCA*** reactions of alkylidenecyclopropane nitrones (**122**, *Scheme 36*).[77-79] When **121** was treated with MeNHOH, the corresponding nitrones **122** were formed which immediately cyclized to bicycles **123** (major) and **124** (minor). Excellent diastereoselectivity (> 99:1 dr) was obtained with R^1 = H, R^2 = Ph or if R^1 = Me, R^2 = H for example. The cycloadducts could be further ring expanded into optically active diazaheterocycles of biological importance. For example, in a recent paper these authors used the cycloadducts as precursors for the synthesis of β-lactams.[80] For a review which describes the preparation of methylene- and alkylidenecyclopropane derivatives, see Brandi and Goti.[81]



121

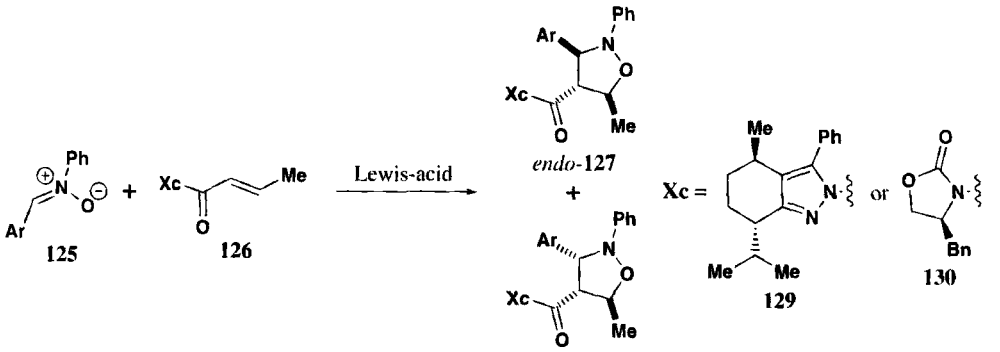
122

Scheme 36

Tandem Michael additions of chiral oximes, derived from precursors such as (-)-menthone and (+)-camphor, to divinyl sulfone followed by intramolecular ***1,3-DCA*** with excellent diastereoselectivity have very recently been described by Yamamoto *et al.*[82]

6. Metal-catalyzed Reactions

For two very recent reviews, see Gothelf *et al.*[83,84] Auxiliary-controlled metal-catalyzed nitrone and nitrile oxide ***1,3-DCA*** reactions have been studied by Kashima *et al.*[85] and Desimoni and Faita *et al.*[86] (*Scheme 37*). For example when nitrone **125** was treated with the dipolarophile **126** attached to the new chiral auxiliary **129** in the presence of a Lewis acid such as $MgBr_2$ or $ZnBr_2$, the cycloadducts *endo*-**127** (major) and *exo*-**128** were obtained in a 91:9 ratio. Each diastereomer was isolated in > 95 and 48% de respectively.[85] Improved diastereoselectivity was obtained if the oxazolidinone auxiliary **130** was used in the presence of $Sc(OTf)_3$ and molecular sieves; only the cycloadducts *endo*-**127** (major) and *exo*-**128** were obtained in a 95:5 ratio.[86] Among a range of different catalysts investigated, those containing Mg^{2+}, Sc^{3+}, Eu^{3+} and Yb^{3+} were the most efficient ones. Additives such as molecular sieves and H_2O had a great influence on the product distribution. In some cases, even the *exo*/*endo* preference could be reversed.



Scheme 37

The reactions most probably proceed *via* attack of the nitrone at the least hindered *Si*-face of the chelated dipolarophile (*Fig. 9*).

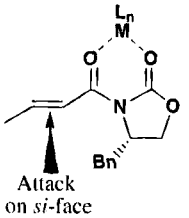
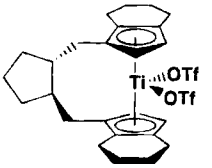
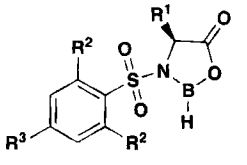


Fig. 9

Reactions between nitrones and dipolarophiles can be catalyzed by chiral Ti-catalyst **131**[87] and chiral oxazaborolidines **132**[88,89] (*Fig. 10*). However, even though the *endo*/*exo* selectivity of the reactions were high in some cases, the enantioselectivity was low (up to 38% ee). Other chiral Ti-catalysts derived from C-2 symmetrical diols and amines have been applied in the reaction between *tert*-butyl vinyl ether and nitrones with high *endo*/*exo* selectivity but unfortunately in low ee:s.[90]



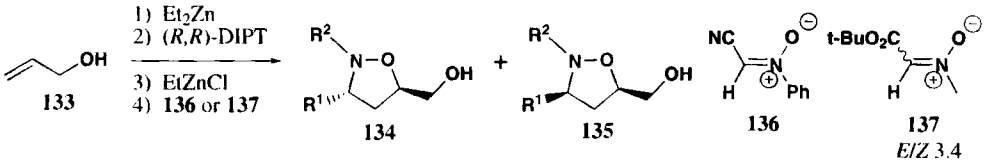
131



132

Fig. 10

Recently Ukaji and Inomata *et al.* found that diisopropyl (*R,R*)-tartrate (*R,R*-DIPT) could serve as an efficient chiral catalyst together with EtZnCl in the reaction between electron-deficient nitrones and allyl alcohols.[91] Thus, they allowed nitrones **136** and **137** to react with allyl alcohol **133** in the presence of 1 molar equivalent of *R,R*-DIPT and Et_2Zn and EtZnCl (*Scheme 38*) to give a mixture of *trans*-/*cis*-isoxazolidines **134** and **135**.



133 134 135 136 137

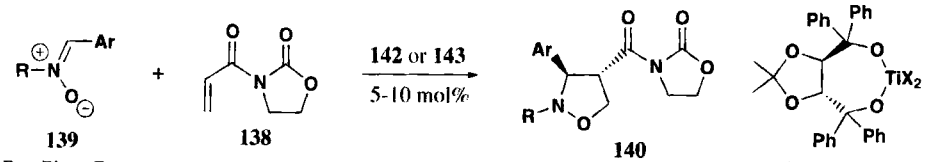
E/*Z* 3.4

Scheme 38

Reaction of **133** with nitrone **136** gave for example cycloadduct **134** in 42% yield and 94% ee with only a trace of the *cis*-isomer **135**; similarly, nitrone **137** gave **134** in 68% yield as the sole diastereomer in 92% ee.

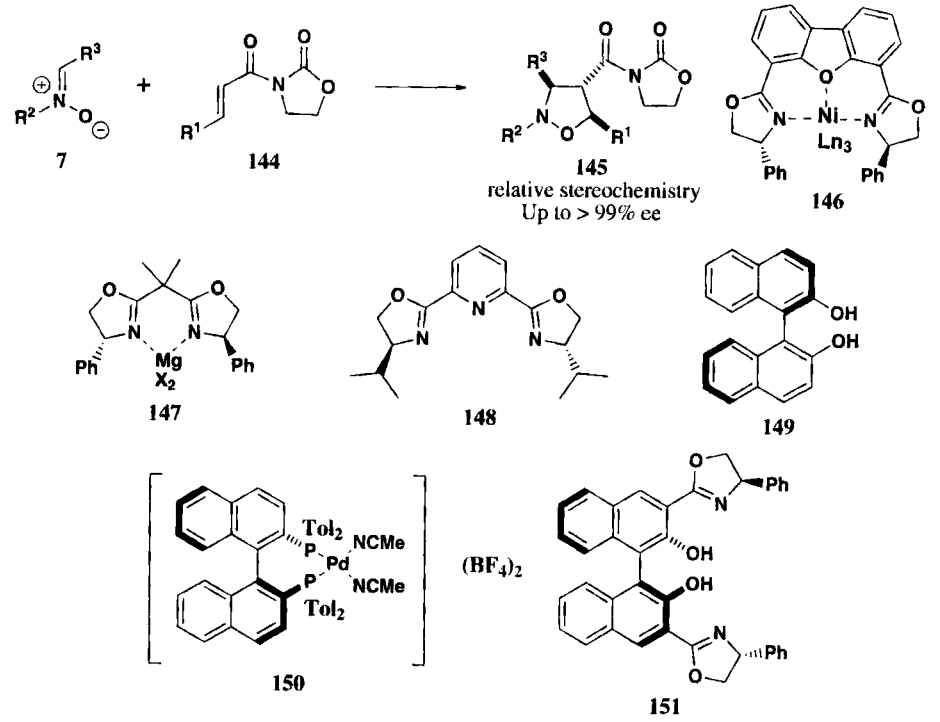
Jörgensen *et al.* applied the chiral catalysts [TiX_2(TADDOLato)] **141-143**, (*Scheme 39*) in the reaction between 3-acryloyloxazolidin-2-one **138** and a range of acyclic nitrones **139**.[92] Without catalyst, the reaction between **138** and **139** (R = Ar = Ph) gave a mixture of *endo*/*exo* and regioisomers with poor selectivity. However, in the presence of catalyst **142** or **143** (5-10 mol%) the reaction proceeded with complete regioselectivity and nearly complete *endo*/*exo* selectivity. In all cases the ee:s were between 48-70% for the *endo*-adduct **140** in the presence of catalyst **142**. On the contrary, catalyst **141** was less selective and gave reversed *endo*/*exo* selectivity. The selectivity of the TiX_2-TADDOLate catalyzed ***1,3-DCA*** was dependent on the ligands on Ti which can assume a range of different conformations in the complexation of a dipolarophile such as **138**. A rationale for the observed selectivity was proposed in another paper by Jörgensen *et al.*[93] The steric repulsion between the chlorine ligands of the catalyst **141** and the C-phenyl substituent of nitrone **139** (R = Ar = Ph) was the main factor determining the selectivity according to the authors. In another paper Jörgensen *et al.*

demonstrated that the use of succinimide instead of oxazolidinone as auxiliary resulted in an improvement in the *endo*/*exo* and enantioselectivity.[94]



Scheme 39

Jörgensen *et al.* also found that metals such as scandium and ytterbium were able to catalyze the reaction between oxazolidinone derived dipolarophiles and nitrones.[95] Thus, ***1,3-DCA*** between **144** and **7** in the presence of $Yb(OTf)_3(H_2O)$ and the chiral ligand 2,6-bis[4-(*S*)-isopropyl-2-oxazolidin-2-yl]pyridine (pyBOX)-**148** (20 mol %) gave *endo*-**145** in up to 73% ee and in 97:3 *endo*/*exo* selectivity (*Scheme 40*).



Scheme 40

However, when $Sc(OTf)_3$ was used instead of $Yb(OTf)_3$ under the same conditions, no enantioselectivity was achieved. Jörgensen *et al.* also studied the influence of additives such as molecular sieves in the magnesium-catalyzed reaction between dipolarophiles **144** and nitrones **7** (*Scheme 40*).[96] Thus, they found for example that the reaction between **144** and **7** in the presence of the chiral magne-

sium catalysts **147** (X = I^-) and molecular sieves (MS, 4Å) gave the ***1,3-DCA*** products **145** in 79% ee almost exclusively. However, in the absence of MS, the reversed enantioselectivity (46% ee) was obtained. The authors explained the reversal of enantioselectivity as a result of an interaction between two oxygens at the surface of the MS and the metal center of the magnesium-bisoxazoline complex **147**. Desimoni and Faita *et al.* also found that changing the counterion of Mg^{2+} in catalyst **147** can have a dramatic effect on the selectivity.[97] Thus, reversed enantioselectivity was obtained in the reaction between **144** and **7** if the counterion (X = I^-) was exchanged for $CF_3SO_3^-$ in the absence of MS (48 and 86% ee, respectively) or by switching from I^- to ClO_4^- in the presence of MS (82 and 70% ee, respectively). In another paper they exchanged the magnesium metal in **147** for Zn^{2+} and obtained an *exo* preference for the cycloadducts in high enantioselectivity, in contrast with the corresponding Mg^{2+} catalyzed reactions, where an *endo* preference was observed.[98]

Kobayashi *et al.* used $Yb(OTf)_3$ in combination with the binaphtol ligand **149** and an amine base such as 1,2,6-trimethylpiperidine. They found that in the reaction between acyclic nitrones **7** and dipolarophiles **144**, *endo/exo* ratios >99/1 of **145** (*Scheme 40*) were obtained with good enantioselectivity (up to 78% ee).[99] When the ytterbium metal was exchanged for scandium in the binaphtol catalyst, good enantioselectivity was obtained and, more interestingly, a reversal of enantioselectivity (69% ee) was observed.[100] Moreover, Kobayashi *et al.* also showed that exchanging the trimethylpiperidine base for a chiral amine influenced the enantioselectivity further affording cycloadducts **145** in *endo/exo* ratios of up to 99/1 in excellent ee:s (96%).[101] The influence of the chiral base on the enantioselectivity was rationalized by the authors as arising from an interaction between the phenolic protons of the binaphtol and the chiral amine through hydrogen bonding. Recently, Kobayashi *et al.* also reported a reversal of the enantioselectivity, depending on whether the reaction was performed in the absence or presence of molecular sieves (4Å) with the above catalyst.[102]

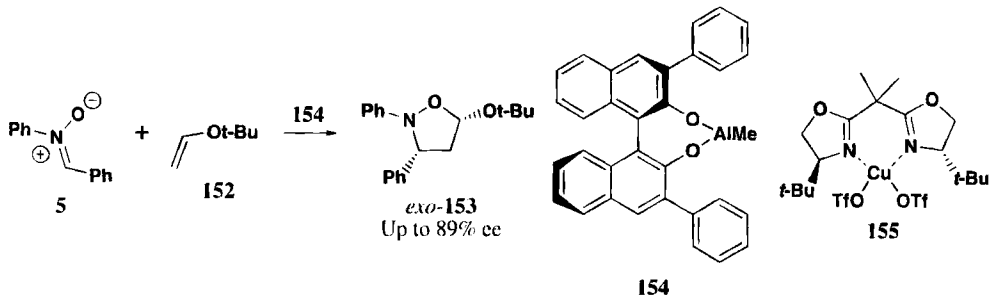
Kanemasa *et al.* found that the Ni-derived catalyst **146** (*Scheme 40*) efficiently catalyzed the reaction between dipolarophiles **144** and nitrones **7**, because *endo/exo* ratios of up to 99:1 of the cycloadducts **145** in >99% ee were obtained with 10 mol% loading of the catalyst **146** (Ln = none).[103] The authors also reported that when Ln in the catalyst **146** was H_2O it was important to add molecular sieves (4Å), in order to obtain high enantio- and diastereoselectivity. The role of MS was evidently to act as a dehydrating agent supressing a less selective octahedral transition state complex in favor of a more reactive and selective trigonal bipyramid one.

Modified BINOL-Box ligands have recently been synthesized and applied in the reaction between dipolarophiles **144** and nitrones **7** (*Scheme 40*) in the presence of different metals.[104] Excellent diastereoselectivity (97:3, *endo/exo*) and high enantioselectivity (87% ee) were obtained for the cycloadducts **145** if the appropriate ligand and salt were selected and used under optimal conditions, [(ligand **151**, 6 mol%), $Sc(OTf)_3$ (5 mol%) and molecular sieves].

Very recently a chiral palladium(II)-catalyzed nitrone ***1,3-DCA*** was reported by Furukawa *et al.*[105] A range of chiral phospine-palladium(II)-complexes were screened as catalysts in the reaction between dipolarophiles **144** and nitrones **7** (*Scheme 40*). They found the chiral palladium catalyst **150**

to be the most efficient one for this type of reaction. The reaction between **144** and **7** proceeded in the presence of catalyst **150** to give isoxazolidines **145** in moderate to high *endo/exo* selectivity in up to 89% ee. The reactive species was proposed to include a complex where the dipolarophiles **144** coordinate to the palladium center in a bidentate fashion. This intermediate might be more activated for attack of the nitrones **7** than the uncomplexed dipolarophiles. When the same chiral Pd-catalyst **150** was applied in the reaction between enol ethers and nitrones, the cycloadducts were found to be racemic.[106]

High enantioselectivity has, however, been obtained in the reaction between enol ethers and nitrones if catalysts **154** and **155** are used (*Scheme 41*). Jörgensen *et al.* developed a general reaction protocol for the enantioselective reaction between nitrones and electron-rich alkenes catalyzed by various chiral BINOL-AlMe complexes giving isoxazolidines in high diastereo- and enantioselectivity.[107]



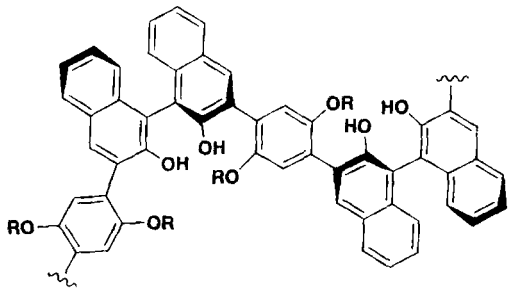
Scheme 41

Thus, a range of differently substituted BINOL-AlMe catalysts (20 mol%) were screened in the reaction between nitrone **5** and vinyl ether **152**. The authors found catalyst **154** to be the superior catalyst giving the ***1,3-DCA*** product *exo*-**153** as the major isomer in better than 95:5 diastereoselectivity and in an ee of 89% (*Scheme 41*). The reactive catalyst was proposed to consist of a monomeric (R)-BINOL-AlMe **154** species. This proposal was supported by the linear relationship between the ee of the catalyst and ee of the cycloadduct. The complex **155** has also been found to be an excellent catalyst in the reaction between electron-rich alkenes and nitrones furnishing cycloadducts in up to 94% ee.[108]

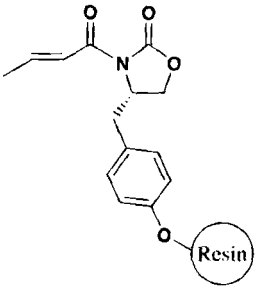
7. Polymeric and Solid-supported Catalysts and Dipolarophiles

Jörgensen and Pu *et al.* reported a series of highly enantio- and diastereoselective nitrone cycloadditions catalyzed by chiral polybinaphtyl Lewis acids.[109] Such catalysts have also been reported to work efficiently in other types of reactions.[110] The reaction between a range of different acyclic nitrones and vinyl ethers in the presence of polymeric ligand **156** (20 mol%, *Fig. 11*) and $AlMe_3$, gave cycloadducts in excellent ee (up to 99% ee) and diastereoselectivity >98:<2 *exo/endo* in

all cases. The catalyst could easily be recovered and re-used with a slight decrease in yield and selectivity. Lower catalyst loading had the same effect.



156: R = C_6H_{13}



157

Fig. 11

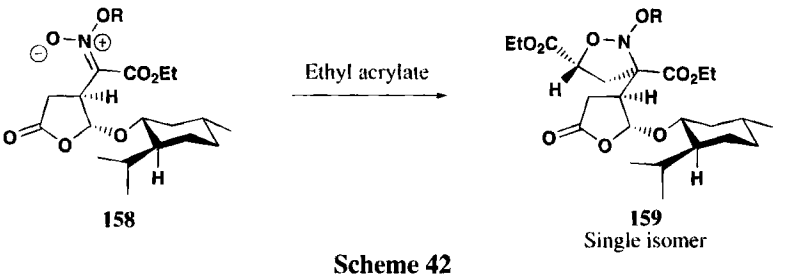
Faita and Quadrelli *et al* reported a resin-bound chiral dipolarophile for use in nitrile oxide and nitrone ***1,3-DCA***.[111] Thus, a chiral oxazolidinone derived dipolarophile was attached to a Wang (W) and a chlorobenzyl Merrifield (M) resin to form the solid supported chiral dipolarophile **157** (*Fig. 11*). When **157** reacted with a C,N-diphenylnitrone, the *exo/endo* selectivity was found to be virtually independent of the resin used (W or M). Cycloadducts in up to 70/30 *endo/exo* selectivity were obtained under certain conditions (Lewis acids etc.). The individual diastereomeric cycloadducts after cleavage of the chiral auxiliary, were found to have ee:s of up to 89% (*exo*) and 29% (*endo*). Finally, Seebach *et al.* have very recently performed an enantioselective nitrone ***1,3-DCA*** using a Ti-TADDOLate catalyst immobilized on silica gel.[112] The cycloadducts were found to have ee:s of up to 85%.

VIII. NITRONATES

Nitronates are synthetic equivalents to nitrile oxides since the cycloadducts (isoxazolidines) in some cases can be transformed to the corresponding isoxazolines (the cycloadducts of nitrile oxide ***1,3-DCA***) through elimination of the substituent on nitrogen. On the other hand, stereoselectivity can differ significantly since nitrile oxides are linear molecules whereas nitronates are not. For example Hoveyda *et al.* have studied diastereoselective intramolecular silyl nitronate ***1,3-DCA*** reactions and found that they were far more diastereoselective than the corresponding intramolecular nitrile oxide ones.[113] Nitronate ylides can, for example, be generated through functionalization of one of the oxygens of a nitro compound followed by treatment with an aryl isocyanate.[5]

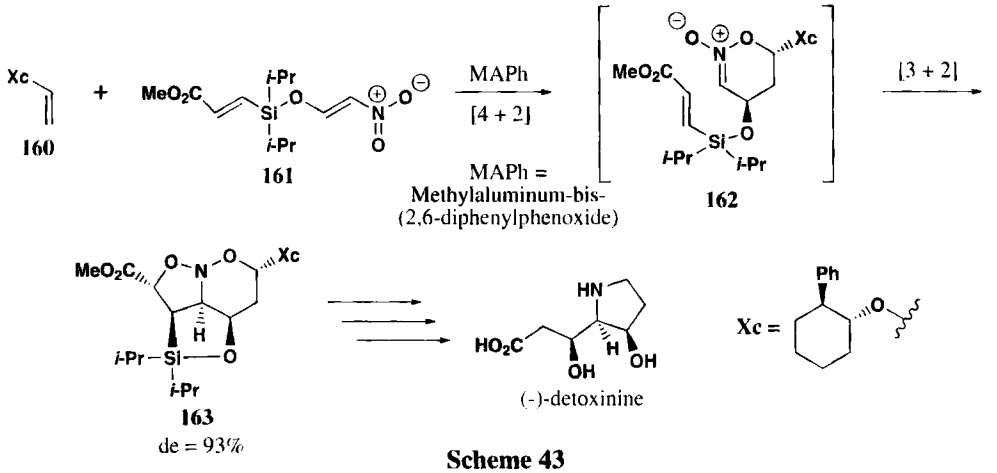
1. Reactions with Nitronates

Kang *et al.* have prepared the chiral nitronic ester **158** and allowed it to react with ethyl acrylate (*Scheme 42*).[114,115] This afforded a single product **159** that was assumed to have the configuration shown which would have arisen from an addition of ethyl acrylate in an *endo* mode from the opposite side of that occupied by the menthyloxy group.



Scheme 42

An efficient intramolecular nitronate ***1,3-DCA*** was used as a key step in the synthesis of a highly functionalized amino acid by Denmark *et al.*[116] By utilizing a removable silica tether separating the two reaction partners, a highly efficient intramolecular nitronate ***1,3-DCA*** could take place. Thus, the tethered nitro compound **161** was coupled with the chiral vinyl ether **160** through an intermolecular [4 + 2] cycloaddition of the alkenoic ester moiety to the dienic nitroene moiety, followed by a highly diastereoselective nitronate intramolecular ***1,3-DCA*** of the intermediate **162** to give compound **163** (*Scheme 43*) in 93% de (the other diastereomer was not identified). After a few more steps, in which the chiral auxiliary (Xc) was recovered, the target molecule [(-)-detoxinine] was obtained in 13.4% overall yield (10 steps).



Scheme 43

A similar tandem [4 + 2]/[3 + 2] cycloaddition approach was utilized in the synthesis of (+)-crotanecine and (-)-platynecine by Denmark *et al.*[117,118] See also a review on tandem [4+2]/[3+2] cycloadditions of nitroalkenes.[119]

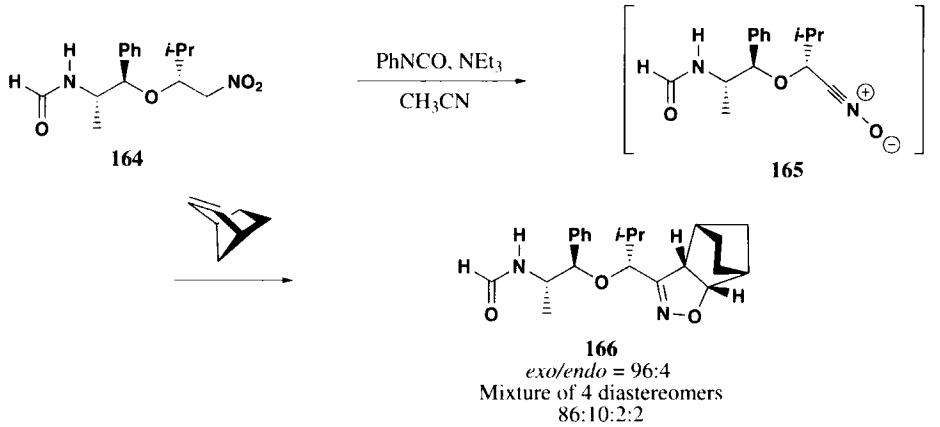
IX. NITRILE OXIDES

Nitrile oxides are reactive, linear molecules which may be generated from nitro compounds by treatment with aromatic isocyanates[120] or from aldoximes by chlorination followed by *in situ* elimination using a base such as Et_3N.[121-123] Moreover, by choosing an organometallic base (for example

MeMgBr) for the ylide generation step, the metal can function as a Lewis acid which results in chelation, leading in some cases to higher stereoselectivity. The resulting isoxazoline cycloadducts can for example, either be cleaved to the corresponding acyclic hydroxy carbonyl compound or be reduced to an amino alcohol derivative.[124]

1. Chiral Nitrile Oxides

Enders *et al.* prepared the enantiopure nitrile oxide precursor **164** from (1R,2S)-(-)-N-formylnorephedrine from which nitrile oxide **165** was generated and reacted with a range of cyclic and acyclic dipolarophiles to give ***1,3-DCA***-products with varying selectivity (*Scheme 44*).[125] The best result was obtained with the dipolarophile norbornene where cycloadduct **166** was obtained with an *exo/endo* selectivity of 96:4 in 75% de (*Scheme 44*).

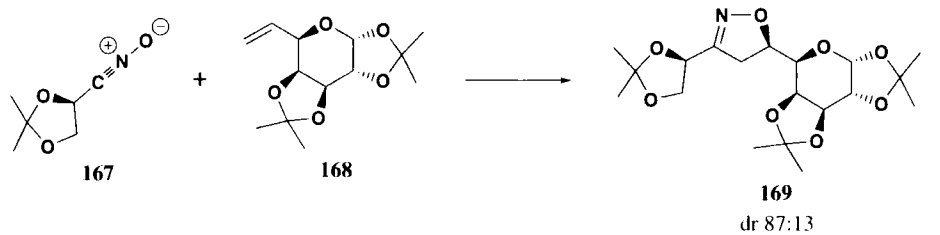


164 **165**

166
exo/endo = 96:4
Mixture of 4 diastereomers
86:10:2:2

Scheme 44

Paton *et al.* investigated a chiral as well as an achiral nitrile oxide in reactions with a dipolarophile derived from D-galactose. Thus, the nitrile oxide **167** reacted with the dipolarophile **168** to give the cycloadduct **169** assumed to have the configuration shown of the newly created stereocenter, in 87:13 diastereoselectivity (*Scheme 45*).[126] The selectivity (*cis/trans*) is in accordance with Houk's "inside alkoxy" model (see *Fig. 3*).

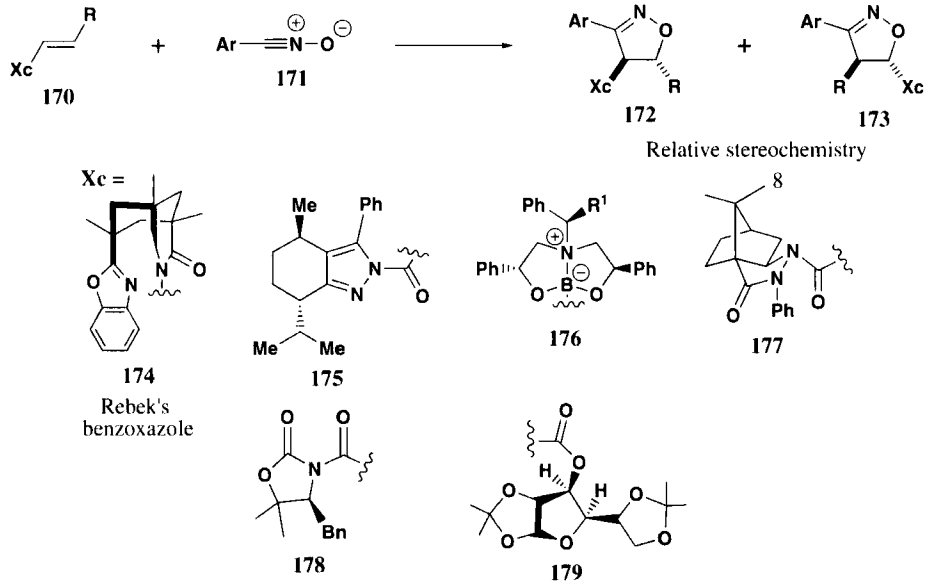


167 **168** **169**
dr 87:13

Scheme 45

2. Chiral Dipolarophiles

A range of different chiral auxiliaries attached to dipolarophiles have been investigated in reactions with nitrile oxides. An excellent chiral auxiliary (Rebek's benzoxazole **174**, *Scheme 46*), which effective shields one π-face of the alkene due to the U-shaped geometry of the auxiliary, has for example been used successfully in nitrile oxide ***1,3-DCA***.[127] Kashima *et al.* obtained isoxazolines **172** and **173** in low to excellent regioselectivity, each regioisomer as a mixture of diastereomers. The latter was obtained in very low to moderate diastereoselectivity with auxiliary **175**.[85] Chiral vinyl dioxazaborocines (Xc **176**, R^1 = H, *Scheme 46*) were attached to alkenes **170**, which reacted with nitrile oxides **171** to give, after deboronation (Xc = H), the cycloadduct **172** in up to 36% ee.[128] If **176** contains a chiral N-substituent (*i.e.* R^1 = Me), 70% ee was obtained.[129] Moreover, high diastereoselectivity was also obtained in the corresponding nitrone ***1,3-DCA***.

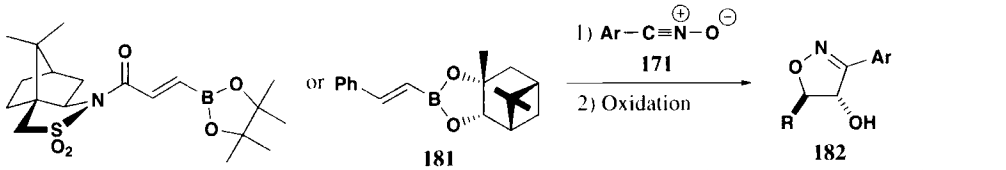


Scheme 46

Chen *et al.* developed the novel camphor-based auxiliary **177** which was used in the reaction above to give the cycloadduct **173** in excellent diastereoselectivity (up to 99:1 dr, *Scheme 46*)[130] The C-8 methyl group in **177** was proposed to effectively shield one of the π-faces of **170**. Yamamoto *et al.* investigated metal ion-mediated nitrile oxide ***1,3-DCA*** reactions with chiral dipolarophiles derived from chiral non-racemic oxazolidinone derivatives (*i.e.* Xc = **178**, *Scheme 46*).[131] It was found that $MgBr_2$, among a range of other salts investigated as additives, efficiently increased the diastereoselectivity in the reaction between **170** and **171** furnishing cycloadduct **173** in up to 96:4 dr. When no salts were added, or when the salt loading was decreased from 1 molar equivalent to 0.5, much lower and reversed diastereoselectivity was observed. The reaction probably proceeded *via* a dipolarophile-$MgBr_2$ complex and not *via* a tethered nitrile oxide-$MgBr_2$-dipolarophile one. When the dipo-

larophiles **170** (Xc = **179**, *Scheme 46*) reacted with aromatic nitrile oxides **171**, cycloadducts **173** were obtained in up to 5:1 diastereoselectivity (R = H).[132]

Wallace *et al.* have shown that boronic esters are excellent dipolarophiles in nitrile oxide ***1,3-DCA*** in terms of regioselectivity, and in a recent paper they also demonstrated highly efficient diastereoselective nitrile oxide ***1,3-DCA*** by employing Oppolzer's camphorsultam as the chiral auxiliary, for the preparation of optically active 4-hydroxy-Δ^2-isoxazolines.[133] Thus, the boronic ester **180** (*Scheme 47*) reacted with benzonitrile oxide **171** (as well as other nitrile oxides) to give the cycloadduct **182** after oxidation of the boronic functionality, as a single diastereomer and regioisomer. A procedure was also developed, where the ***1,3-DCA***, boronic moiety oxidation and cleavage of the chiral auxiliary were achieved in a one pot sequence.[134] According to Biao *et al.* cycloaddition with boronic ester **181** (*Scheme 47*) with aromatic nitrile oxides **171** gave the cycloadducts **182**, after oxidation of the boronic ester functionality, in low diastereoselectivity (up to 60:40 dr).[135]

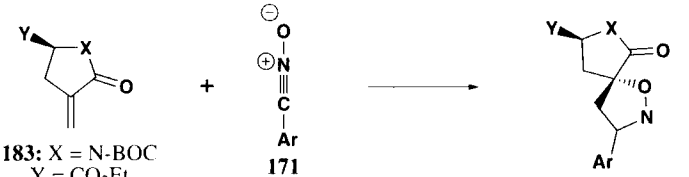


180 **181** **182**

R = COXc (Xc = camphorsultam) or Ph, relative stereochemistry. Single diastereomer from **180**

Scheme 47

Fisera *et al.* have studied the reaction of chiral and achiral nitrile oxides with chiral and achiral dipolarophiles.[136] The reaction between aromatic nitrile oxide **171** and chiral cyclic dipolarophile **183** (*Scheme 48*) gave spiro cycloadducts **185** in up to 2:1 diastereoselectivity, resulting from a major attack of the dipole at the least hindered face of the dipolarophile **183**. Higher diastereoselectivity was obtained with the dipolarophile **184** since **185** was obtained in 90:10 dr.

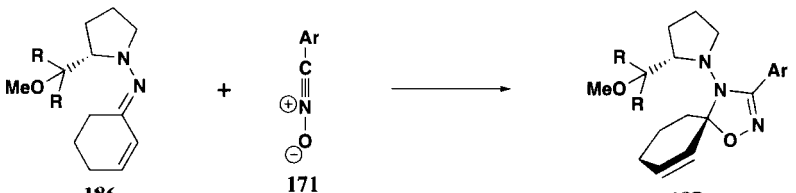


183: X = N-BOC
Y = CO_2Et
184: X = O,
Y = Ph

185
dr up to 90:10

Scheme 48

Enders *et al.* found that proline derived hydrazones serve as good dipolarophiles in reactions with nitrile oxides.[137] Aromatic nitrile oxides **171** (*Scheme 49*) reacted exclusively onto the C=N double bond of hydrazones **186** to give spiro cycloadducts **187** in low to excellent diastereoselectivity (up to > 99:1 dr). Reaction with the *E* isomers of **186** resulted in reversed diastereoselectivity. Also acyclic proline derived hydrazones reacted with nitrile oxides in low to excellent diastereoselectivity.[137]



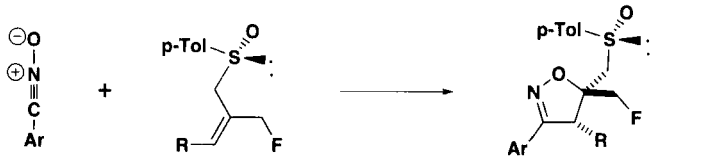
186
R = H, alkyl or Ph

171

187
dr up to > 99:1

Scheme 49

Chiral induction mediated by a sulfoxide moiety has been investigated by Bruché *et al.*[138] Reaction between aromatic nitrile oxides **171** and chiral non-racemic compounds **188** and **189** gave **190** in up to 2:1 diastereoselectivity (*Scheme 50*).



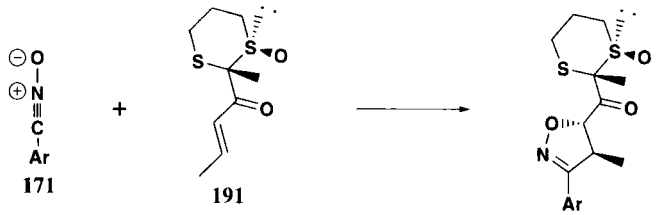
171

188: R = H
189: R = CO_2Me

190
Relative stereochemistry
dr 2:1

Scheme 50

Page *et al.* have been studying nitrile oxide ***1,3-DCA*** reactions with a range of racemic and non-racemic 2-crotyl-1,3-dithiane-1-oxides.[139] For example, dipolarophile **191** was prepared in 92% ee and was allowed to react with nitrile oxide **171** to give **192** in 3:1 diastereoselectivity (*Scheme 51*). They found that the stereochemistry at the 2-position of the dithiane unit had the greatest influence on the stereochemical course of the reaction. In another paper they also studied the influence of adding Lewis acids to the reaction depicted below (although on racemic substrates). They found that when such acids were added, a reversed diastereoselectivity was observed in some cases.[140]



171

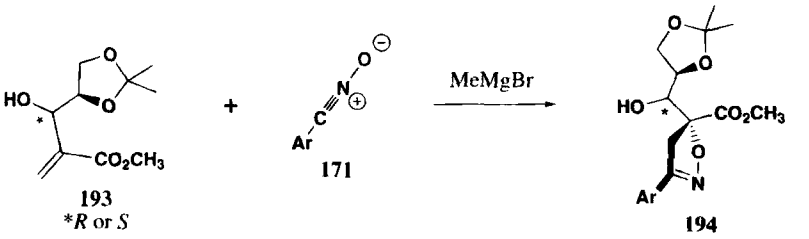
191

192
Ar = Ph, dr 3:1

Scheme 51

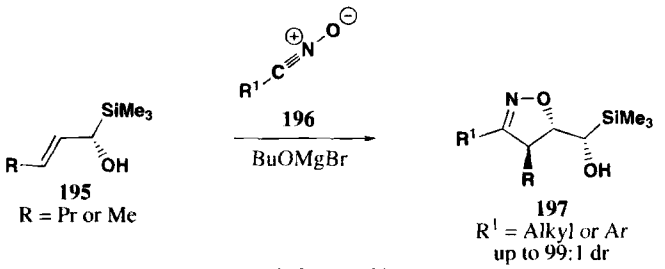
Fisera *et al.* investigated the influence of Mg^{2+} in the reaction between nitrile oxides and chiral dipolarophiles.[141,142] When **193**, with *S*-configuration at the hydroxylated carbon, was allowed to react with an aromatic nitrile oxide **171** in the presence of MeMgBr, cycloadduct **194** was obtained in higher than 95/5 diastereoselectivity (*Scheme 52*). Slightly lower diastereoselectivity was achieved

if the configuration was *R* (85/15), however still with the same preference for the cycloadduct **194**. On the other hand, in the absence of MeMgBr, lower and reversed diastereoselectivity was obtained. The reversal in diastereoselectivity was explained by either a tethered (Mg^{2+}) or a non-tethered transition state, which would result in opposite selectivity.



Scheme 52

Kamimura *et al.* have also investigated some allyl alcohols as dipolarophiles in cycloadditions with some nitrile oxides controlled by Mg^{2+} tethering.[143] Thus, the allyl alcohols **195** (*Scheme 53*) were reacted with aliphatic and aromatic nitrile oxides **196** to give the major cycloadducts **197**,



Scheme 53

together with small amounts of other diastereomers, in high diastereoselectivity (from 94:6 up to 99:1 diastereoselectivity). The high stereoselectivity was explained from a tethered transition state, where the allylic alkoxide and the nitrile oxide coordinate to the same magnesium ion (*Fig. 12*).

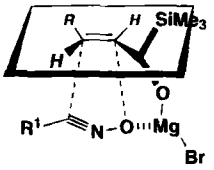
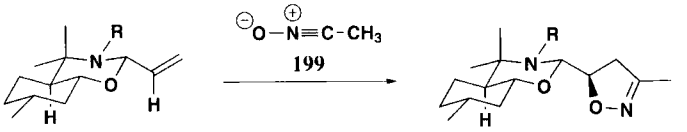


Figure 12

Breau *et al.* employed (±)-norephedrine and (-)-8-benzylaminomenthol as chiral auxiliaries in the cycloaddition between α,β-unsaturated carbonyl dipolarophiles and nitrile oxides.[144,145] The (-)-benzylaminomenthol derived dipolarophiles **198** (*Scheme 54*) reacted with acetonitrile oxide **199** to give the isoxazoline cycloadducts **200** in up to 20:1 diastereoselectivity. With **198** in the conformation depicted, major attack of the nitrile oxide occurred on the face opposite to the N- substituent (R = Bn or $PhSO_2$).



198
R = Bn or $PhSO_2$

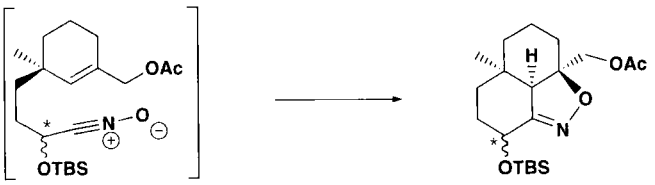
200
Up to 20:1 dr

Scheme 54

Finally, a solid supported chiral dipolarophile **157** (*Fig. 11*, see page 133) was very recently investigated in the reaction with mesitonitrile oxide by Faita and Quadrelli *et al.*[111] One of the regioisomers formed was found to have 60% ee. Lewis acids added had no significant influence on the yield or regio- or enantioselectivity.

3. Intramolecular Reactions

Shishido *et al.* have reported a highly efficient procedure for the synthesis of a functionalized *cis*-decalin, with an intramolecular nitrile oxide ***1,3-DCA*** as the key step.[146] Starting from geraniol, chiral non-racemic nitrile oxide **201** (*Scheme 55*) was generated from the corresponding nitro compound. An intramolecular reaction spontaneously occurred to give **202** as a mixture of two separable diastereomers (epimeric around C-OTBS).

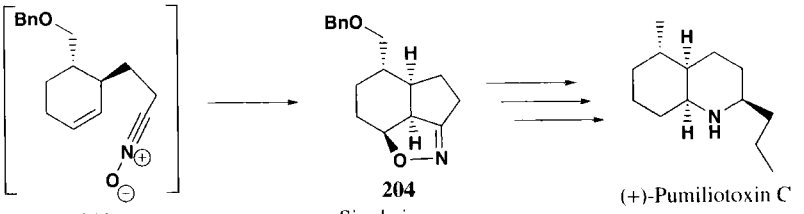


201

202
* epimeric mixture

Scheme 55

The synthesis of (+)-pumiliotoxin C was recently reported by Toyota *et al.*[147] They synthesized the chiral non-racemic nitrileoxide **203** (*Scheme 56*) through a short sequence, and a highly diastereoselective intramolecular **1,3-DCA** took place to furnish the cycloadduct **204** as a single diastereomer. From this compound (+)-pumiliotoxin C was synthesized *via* a few synthetic steps.



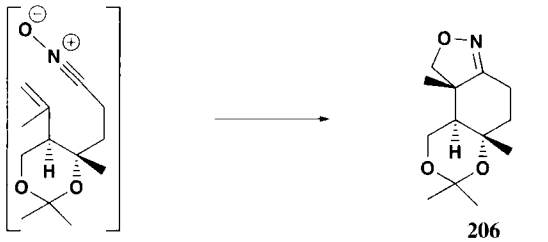
203

204
Single isomer

(+)-Pumiliotoxin C

Scheme 56

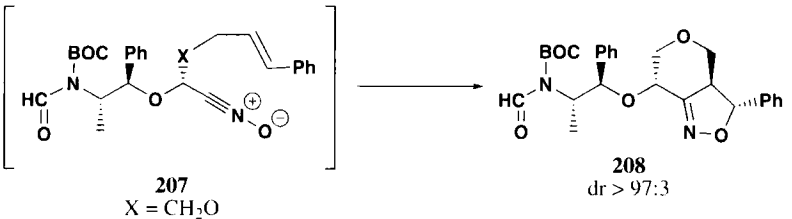
Takahashi *et al.* prepared a key intermediate for taxol synthesis using a highly efficient intramolecular nitrile oxide ***1,3-DCA*** as the key step.[148] Thus, chiral non-racemic nitrile oxide **205**, generated from the corresponding hydroxylamine, was prepared starting from geraniol (*Scheme 57*). An intramolecular reaction gave compound **206** as the sole diastereomer. This is a key intermediate for the construction of both the A and C ring of taxol.



205 **206** Single isomer

Scheme 57

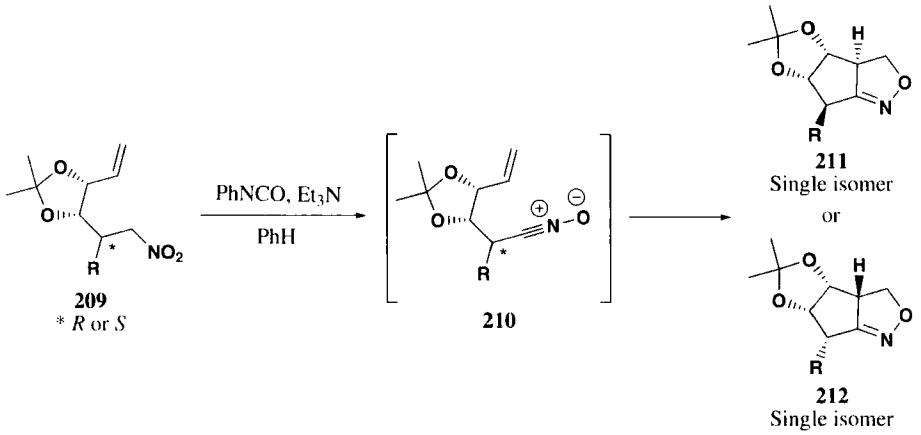
From (1*R*,2*S*)-(-)-formylnorephedrine, Enders *et al.* prepared the chiral nitrile oxide **207** (X = CH_2O) containing an alkene functionality (*Scheme 58*), which allowed an intramolecular ***1,3-DCA*** to take place.[125] Thus, cycloadduct **208** was obtained in > 97/3 dr. However, reactions with nitrile oxides **207** with shorter tether lengths (*i.e.* X = CH_2) were less stereoselective and this was explained as follows. In the transition state for the formation of the five-membered ring, the energy difference between the two envelope conformations, leading to different isomers, is much smaller than the energy difference between the chair and the twist conformation of the six-membered ring transition states obtained from **207** (X = CH_2O).



207 X = CH_2O **208** dr > 97:3

Scheme 58

Recently Gallos *et al.* studied some intramolecular nitrile oxide ***1,3-DCA*** reactions with sugar-derived substrates.[149] They investigated the effect of having a 2-substituent (starred) in 3,4-isopropylidenedioxyhex-5-enenitrile oxides **210** (*Scheme 59*) and the effect of the nature of the 2-substituent and the configuration at position 2. D-Ribose was selected as the starting material for the preparation of various nitrile oxide precursors of type **209**.



Scheme 59

Starting from each of the diastereomers of **209**, nitrile oxide generation followed by intramolecular ***1,3-DCA*** afforded either the single diastereomer **211** or **212** (*Scheme 59*). The high diastereoselectivity observed for the *erythro*-derivatives was explained from unfavorable interaction between the 2-substituent (-R) and one of the methyl groups in the acetonide group in one conformation in the transition state. This interaction is not present in the reacting conformer (*Fig. 13*).

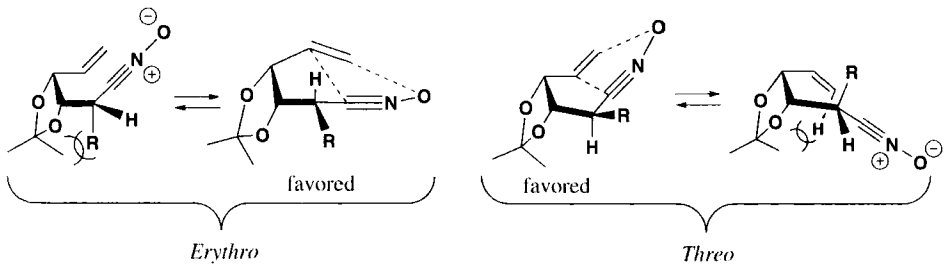


Figure 13

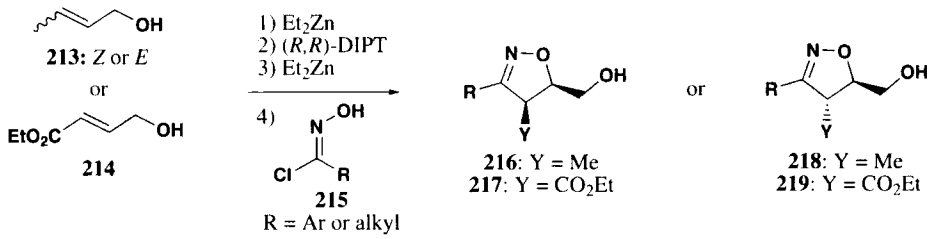
The authors claim that the *threo*-isomers have one preferred conformation in the transition state. In this case, steric interaction between the vinylic proton and the methyl group of the acetonide moiety is absent.

Finally Yamamoto *et al.* investigated the intramolecular nitrile oxide ***1,3-DCA*** starting from precursor **118**.[76] Thus highly efficient reactions were reported affording bicyclic isoxazolines in up to >96% de.

4. Metal- and Antibody-catalyzed Reactions

Ukaji and Inomata *et al.* described nitrile oxide ***1,3-DCA*** with γ-substituted allyl alcohols and these were found to be catalyzed by diisopropyl (*R,R*)-tartrate (DIPT).[150] Thus, in the presence of 1 molar equivalent of DIPT, the allyl alcohol **213** (*Z* isomer) was reacted with Et_2Zn and nitrile oxide

precursors **215** to give *cis*-cycloadducts **216** which were obtained in 94-98% ee depending on the R-group in the nitrile oxide precursor (*Scheme 60*).



Scheme 60

Similarly, *E*-**213** gave the *trans*-isoxazoline **218** in similar high enantioselectivity. Also, the dipolarophile **214** containing an ethoxycarbonyl group reacted with nitrile oxide precursors **215** in the presence of the catalyst to afford almost exclusively *trans*-isoxazolines **219** in high ee (91-96%). In a later paper they also demonstrated the preparative utility of such an enantioselective nitrile oxide ***1,3-DCA*** catalyzed by DIPT, namely in the total synthesis of a chiral non-racemic alkaloid, *lasubine II*.[151]

Jiang *et al.* set up a solid phase enantioselective ***1,3-DCA***, by employing DIPT as a chiral ligand and Mg^{2+} (EtMgBr for nitrile oxide generation) as a Lewis acid in the reaction between a range of differently substituted aromatic nitrile oxides attached to a solid support and an allyl alcohol as dipolarophile.[152] Excellent results were achieved since ee:s of up to 95% of the cycloadducts (isoxazolines) were reported for some substrates.

A remarkable antibody catalyzed nitrile oxide ***1,3-DCA*** was recently reported by Houk and Janda *et al.*[153] They prepared a range of antibodies specific for a certain hapten, and found two of them to be catalytically active in the reaction between *N,N*-dimethylacrylamide and an aromatic nitrile oxide. Because ee of the cycloadduct of up to 98% was reported and because this is the first report in this area, it opens the door for the exploitation of biocatalyzed ***1,3-DCA***.

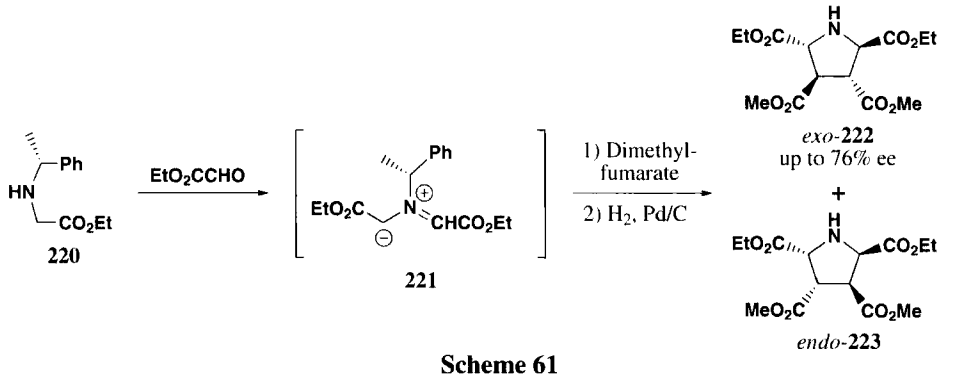
X. AZOMETHINE YLIDES

The result of an azomethine ylide ***1,3-DCA*** to a dipolarophile is a pyrrolidine derivative. The azomethine ylides can be divided into two classes of 1,3-dipoles, namely stabilized and non-stabilized ylides: the former has a stabilizing group such as a carbonyl adjacent to the dipole, whereas the latter has not. In some cases N-metalated stabilized ylides react *via* a two-step sequence instead of a concerted one. The consequence is that the original stereochemistry of the alkene moiety of the dipolarophile is not necessarily conserved in the cycloadduct.[154] Depending on the reaction conditions and the nature of the dipolarophile, both processes can occur. Although metal-catalyzed reactions have, to our knowledge, been reported only for the stabilized ylide types and are few,[2] there have been non metal-catalyzed reactions reported, where added metals function as a chelating agent increasing the rigidity of the reacting partners in the transition state. Most of the ylides are prepared *in situ*, since they are often very reactive and unstable dipoles, and are generated from either a stable dipole

precursor through acid catalysis, or *via in situ* condensation of an amine with an aldehyde. Other methods exists as well.[4]

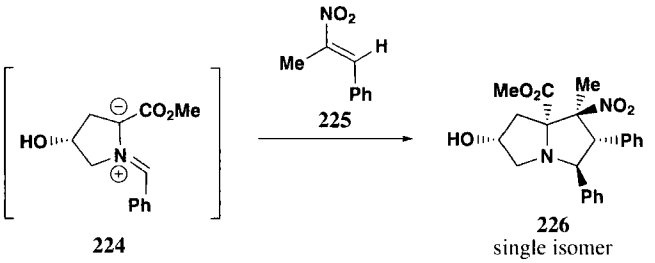
1. Chiral Azomethine Ylides

Risch *et al.* studied an *in situ* generated chiral azomethine ylide in ***1,3-DCA*** reactions with some dipolarophiles.[155] Chiral non-racemic 1-phenylethylamine, which is a common chiral amine used for the preparation of enantiopure ylides, served as the template for the construction of the precursor **220** (*Scheme 61*) which was allowed to react *in situ* with ethyl glyoxalate to form the corresponding ylide **221**, which immediately added to a dipolarophile such as dimethyl fumarate to give, after debenzylation, two diastereomeric *exo*- and *endo*-adducts **222** and **223** (*exo*/*endo* = 59:41), the *exo*-adduct **222** in up to 76% ee (ee of the *endo*-adduct was not determined). In a later publication they also utilized phenyl vinyl sulfone as dipolarophile in the reaction with the same dipole with similar results.[156]



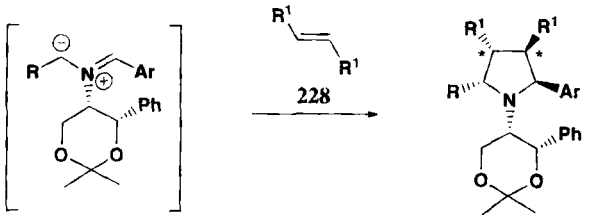
Scheme 61

Valentin *et al.* studied some chiral azomethine ylides derived from chiral non-racemic proline derivatives, and investigated their cycloaddition reactions with nitroalkenes as dipolarophiles.[157] Ylide **224**, generated *in situ* from benzaldehyde and the corresponding amine, reacted with a nitroolefin such as **225** exclusively *anti* to the hydroxyl substituent of the ylide, and gave the cycloadduct **226** as a single stereoisomer (*Scheme 62*). In a few cases the authors observed a stepwise mechanism instead of a concerted one.



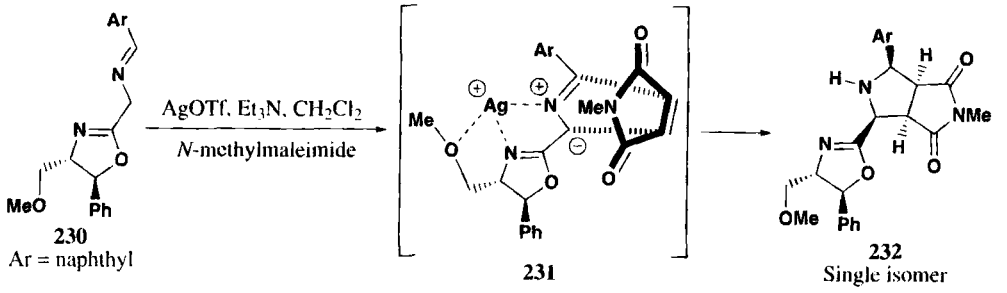
Scheme 62

Enders *et al.* generated chiral azomethine ylides **227** (*Scheme 63*) and allowed these to react with alkenes **228** to give cycloadducts *endo*-**229** together with *exo*-diastereomers (epimers to *endo*-**229** at starred carbons) in selectivity 65-30:70-35, (*endo*-isomer predominating except when R = C_6H_5 and R^1 = CO_2CH_3).[158] Also, cycloadditions with *N*-phenylmaleimide were performed with similar results as for the acyclic dipolarophiles.



Scheme 63

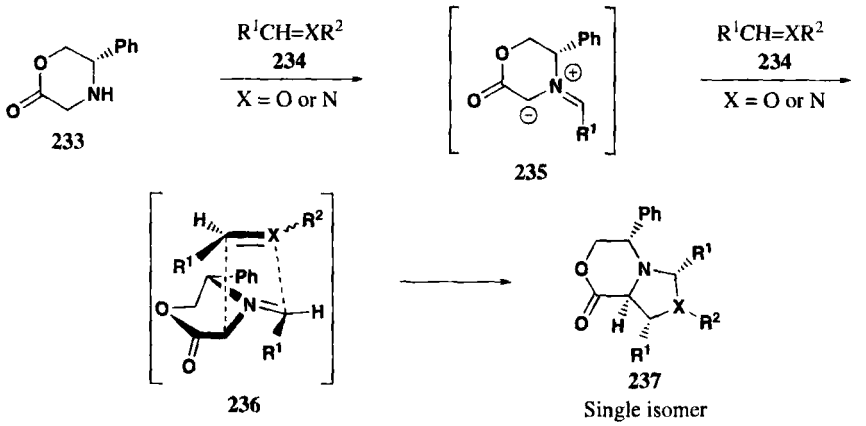
Husinec *et al.* investigated the potential of utilizing oxazoline derived chiral dipoles in reactions with achiral dipolarophiles.[159] Thus, they prepared for example chiral azomethine ylide precursor **230** that was treated with AgOTf /Et_3N and a dipolarophile such as *N*-methylmaleimide (*Scheme 64*) to give one single diastereomer **232**, obtained *via* approach of the dipolarophile from the less shielded face of the dipole (intermediate **231**). Monosubstituted dipolarophiles such as methyl acrylate gave low stereoselectivity due to lack of interaction of the dipolarophile with the oxazoline auxiliary.



Scheme 64

Cyclic chiral azomethine ylides, derived from (5*S*)-5-phenylmorpholin-2-one **233** and aldehydes (*Scheme 65*), have been investigated by Harwood *et al.*[160] and in a recent paper they also described the preparation and reaction of ylides derived from **233** and aromatic imines.[161] These ylides

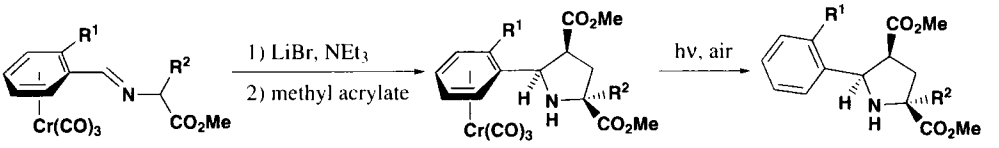
reacted over the double bond of the aldehydes and the imines respectively and furnished cycloadducts suitable for the final synthesis of enantiopure β-hydroxy-α-amino acids and 2,3-diamino acids respectively. When **233** was treated with aldehydes or imines **234**, azomethine ylides **235** were formed which reacted with the C=X bond of an additional mole equivalent of the aldehydes or the imines **234** to give the only detectable cycloadducts **237** (*Scheme 65*).



Scheme 65

A rationale for the observed stereoselectivity was given and is depicted in Scheme 65. Thus in **236**, the dipolarophile **234** approaches the most accessible face of the ylide with the alkyl or aryl group (R^1) in the sterically least demanding environment. A double asymmetric induction (matched case) in the above reaction has also been demonstrated by applying a chiral non-racemic aldehyde in the ylide generation step and in the trapping of the ylide.[162] Harwood *et al.* have also evaluated a method for the preparation of stable azomethine ylide precursors of ylide **235**.[163] 5,6-Diphenylmorpholin-2-one, a chiral non-racemic morpholine derivative structurally related to **233**, has very recently been used as an azomethine ylide precursor in a synthetic sequence, where (+)- and (-)-spirotryprostatin B were ultimately obtained.[164]

Kundig *et al.* studied chiral arene tricarbonyl chromium complexes as dipoles in reactions with simple dipolarophiles.[165] They prepared the chiral non-racemic chromium complexes **238** (*Scheme 66*), which after treatment with LiBr and Et_3N, revealed the azomethine ylides, which reacted with methyl acrylate to give the cycloadducts **239** as the only detectable diastereomers. Decomplexation by irradiation and air oxidation gave **240**. The high diastereoselectivity observed was explained by chelation between the lithium, the imine nitrogen and the carbonyl oxygen of the dipole, which effectively made one of the π-faces more accessible for the dipolarophile, namely that opposite to the chromium complex. When the reaction was performed in the presence of $TiCl(OiPr)_3$ a switch in regioselectivity occurred.



238
R^1 = OMe, Cl or Me
R^2 = H, Me or Ph

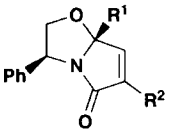
239
Single isomer

240

Scheme 66

2. Chiral Dipolarophiles

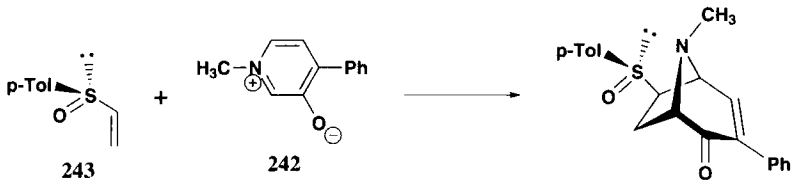
Meyers *et al.* have studied chiral non-racemic, unsaturated bicyclic lactams **241** (*Fig. 14*) as chiral dipolarophiles in asymmetric azomethine ylide ***1,3-DCA*** and in a recent paper they described the modifications of the cycloadducts, required for obtaining a range of substituted pyrrolidines.[166]



241

Figure 14

Potential cocaine antagonists were prepared by Kozikowski *et al.* using the reaction of a masked azomethine ylide (an oxido-pyridinium-betaine ylide) with a chiral non-racemic vinyl sulfoxide as the key step.[167] Thus, ylide **242** was allowed to react with dipolarophile **243** to give a mixture of two *exo*- (44 and 11% yield respectively) and one *endo*-cycloadduct (22%). The *exo*-cycloadduct **244** predominated (*Scheme 67*). The individual diastereomers were further transformed to non-racemic alkyltropanes. Structurally related fluorotropanes have also very recently been synthesized using a similar approach as that described above.[168]



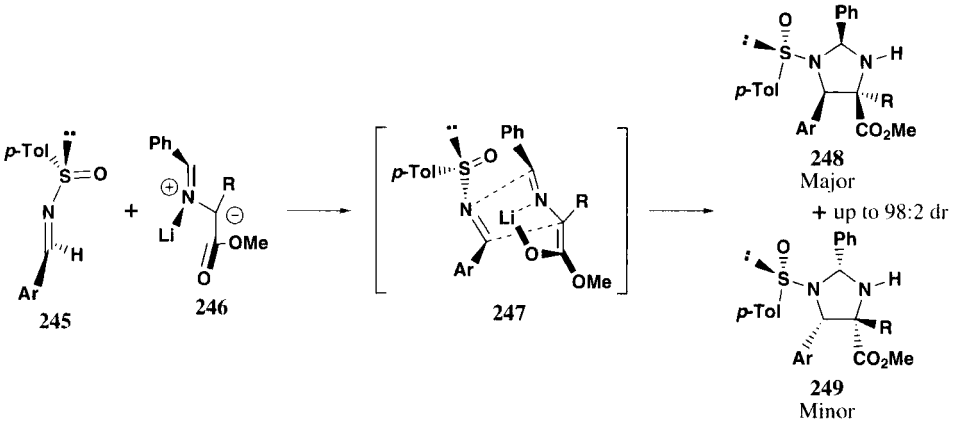
243 + **242**

244
+ diastereomers
44:22:11

Scheme 67

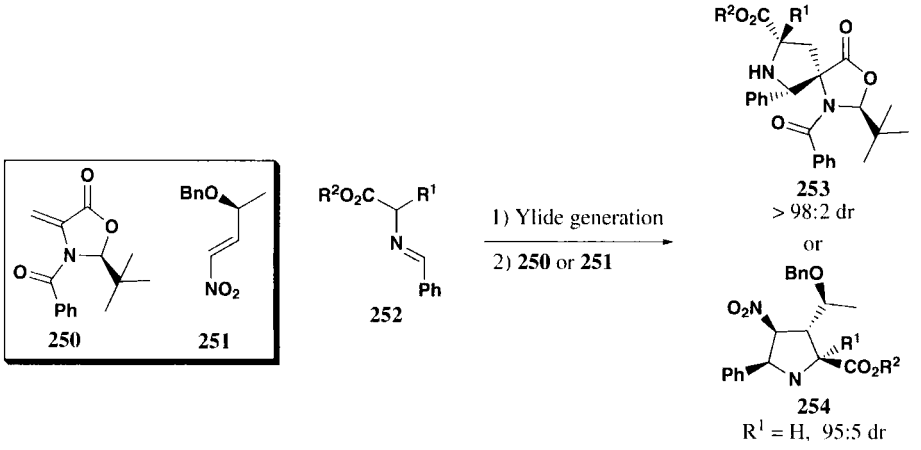
Viso, Pradilla *et al.* reacted the chiral sulfinimines **245** (*Scheme 68*) with stabilized azomethine ylides **246** and obtained cycloadducts **248** and **249** in excellent diastereoselectivity (up to 98/2

dr), *via* an *endo*-chelated approach of the ylide (intermediate **247**).[169] The reaction was also found to be catalyzed by a Lewis acid such as $BF_3{\cdot}OEt_2$ but in this case the reaction proceeded through a two-step mechanism instead of a concerted one.[170]



Scheme 68

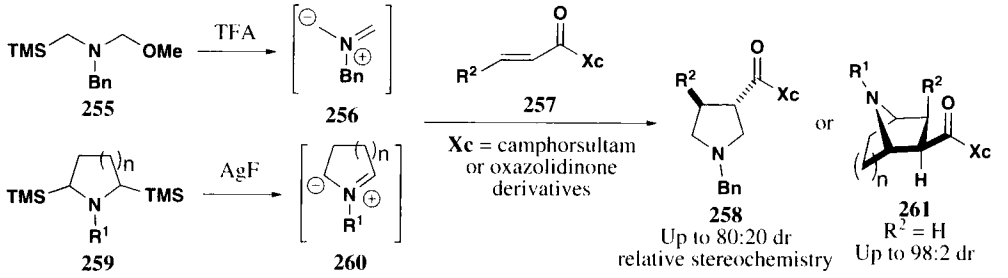
The reactions of chiral non-racemic cyclic dipolarophiles with azomethine ylides derived from imines have been investigated by Pyne *et al.*[171] When the ylide precursors **252** (*Scheme 69*) were treated with LiBr/DBU/THF, the corresponding ylides were formed, which reacted with chiral dipolarophiles such as **250** yielding the cycloadducts **253** in excellent diastereoselectivity (>98:<2 dr). Reactions with acyclic nitroalkenes such as **251** furnished the cycloadducts **254** in 95:5 diastereoselectivity, although *via* a non-concerted process.[172]



Scheme 69

We[173] and others[174] have been studying the addition of non-stabilized azomethine ylide **256** (*Scheme 70*) to dipolarophiles attached to chiral auxiliaries such as substituted oxazolidinone derivatives and camphorsultam. Trifluoroacetic acid (TFA) catalyzed azomethine ylide generation from the precursor **255** followed by addition to the dipolarophiles **257** furnished the cycloadducts **258** together

with the other *trans*-diastereomers in up to 80:20 diastereoselectivity, and the two diastereomers were separable in most cases. Addition of Lewis acids to the reaction only results in decomposition of the dipole. However, chiral ligands in combination with Lewis acids, added in a substantial amount could induce a certain but small enantioselectivity.[173]



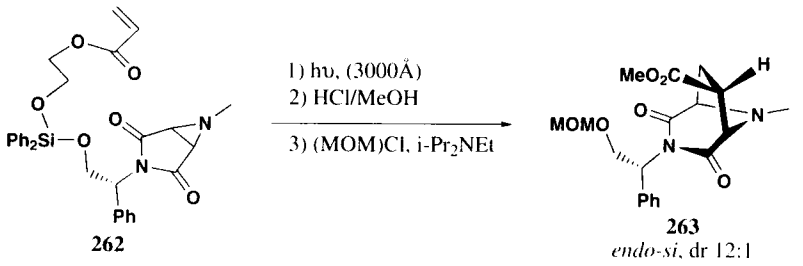
Scheme 70

The diastereoselectivity could also be increased slightly by introducing chirality into the ylide precursor **255** (double asymmetric induction),[175] *i.e.* ylide precursor was derived from enantiomerically pure phenyl ethyl amine.

Improved diastereoselectivity can be obtained if a cyclic azomethine ylide is used. Pandey *et al.* reacted azomethine ylides **260** (*Scheme 70*), derived from the precursors **259**, with a chiral acryloyl camphor sultam **257** (R^2 = H, Xc = 1(*R*)-(+)-camphorsultam) which produced the major *exo*-cycloadduct **261** in up to 98:2 diastereoselectivity (n = 1, R^1 = Bn) together with a minor *endo*-diastereomer.[176] The cycloadducts can for example be used for further synthesis of natural products such as the tropane alkaloids.

3. Intramolecular Reactions

Intramolecular azomethine ylide ***1,3-DCA*** reactions were recently reported by Garner *et al.*[177] They prepared a range of azomethine ylide precursors containing a silica tether connecting the dipole and the dipolarophile. Compound **262** (*Scheme 71*), when irradiated generated an ylide, which

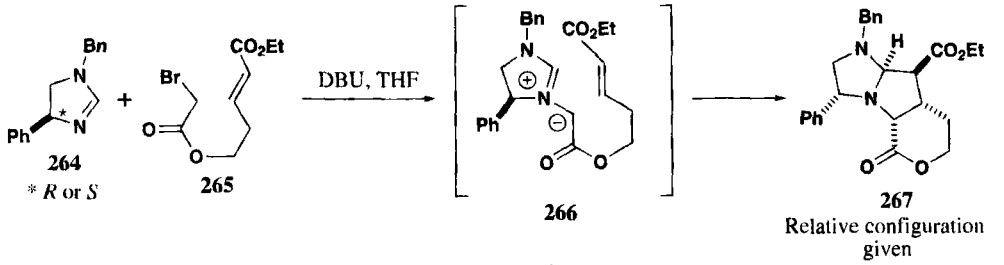


Scheme 71

cyclized to give a cycloadduct, which after cleavage of the silica tether and protection of the alcohol furnished compound **263**, which is the *endo-si* diastereomer, in high diastereoselectivity (12:1 dr).

Compounds containing shorter tethers cyclized with opposite π-facial selectivity to give an *endo-re* diastereomer, in high selectivity, dr = 16:1. Thus, the authors demonstrated that the length of the tether directed the diastereofacial selectivity of the intramolecular ***1,3-DCA***.

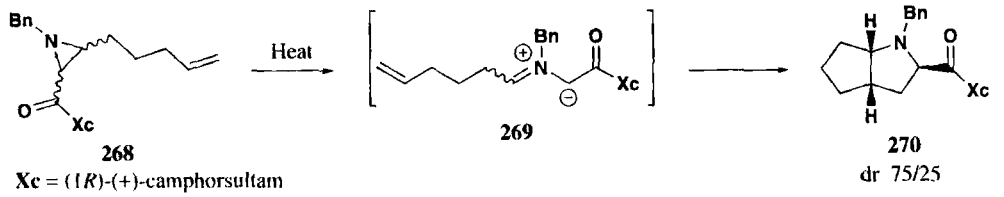
Compound **264** (*Scheme 72*) served as an excellent precursor for a chiral non-racemic cyclic azomethine ylide as shown by Jones *et al.* in inter- as well as intramolecular ***1,3-DCA***.[178] Thus, one of



Scheme 72

the enantiomers of **264** was allowed to react with the dipolarophile **265** to give one azomethine ylide enantiomer **266** containing also the alkene. An efficient intramolecular cycloaddition took place to give tricycle **267**.

Dogan *et al.* have investigated some camphorsultam derived aziridines as precursors for ylides and their intramolecular ***1,3-DCA*** reactions.[179] Thus, upon heating, the aziridine **268** (*Scheme 73*) decomposed to the corresponding azomethine ylide **269** which readily underwent intramolecular ***1,3-DCA*** furnishing the fused bicycle **270** (de 50%).



Scheme 73

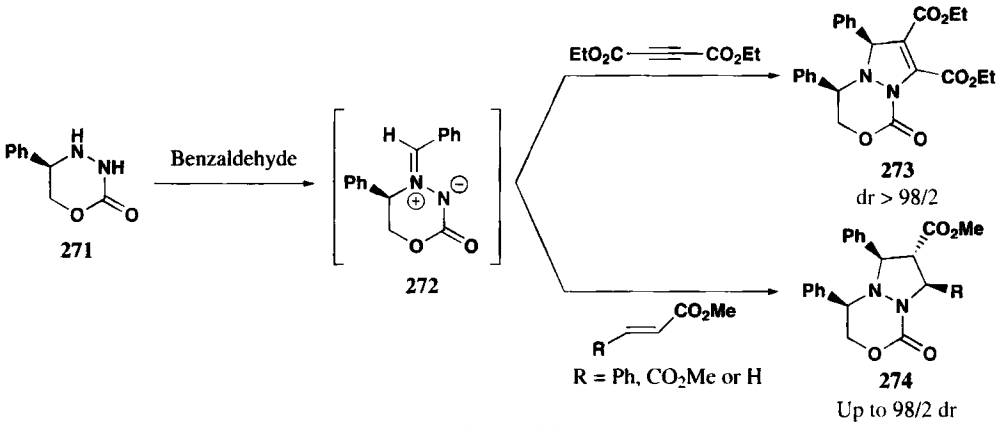
Finally, computational studies have been performed on intramolecular reactions of azomethine ylides derived from (*S*)-5-phenyl-morpholin-2-one **233** and these were found to be in good agreement with experimental results.[180]

XI. AZOMETHINE IMINES

There are very few reports concerning the asymmetric ***1,3-DCA*** of azomethine imine resulting in chiral non-racemic pyrazolines. The pyrazoline cycloadducts can be transformed to interesting functionalized optically active diamines. The ylides are most easily prepared *via* reaction of a hydrazine derivative with an aldehyde.

1. Reactions with Azomethine Imines

Husson *et al.* utilized (R)-(-)-phenylglycinol as a precursor for the preparation of chiral azomethine imines, and studied their ***1,3-DCA*** reactions with a range of dipolarophiles.[181] Thus, compound **271** was prepared and reacted with either benzaldehyde or its dimethyl acetal to form azomethine imine **272** (*Scheme 74*). This species reacts with a dipolarophile such as diethyl acetylenedicarboxylate, or other simple α,β-unsaturated dipolarophiles such as for example dimethyl fumarate or methyl acrylate, to give cycloadducts **273** and **274**, formed *via* approach from the less hindered face of the 1,3-dipole, in up to 97% de. When styrene was used as the dipolarophile, opposite regioselectivity and *endo/exo* selectivity were observed. Cycloadditions with simple aliphatic alkenes and reactions where benzaldehyde is exchanged for a range of heteroaromatic and aliphatic aldehydes have also been demonstrated.[182]



Scheme 74

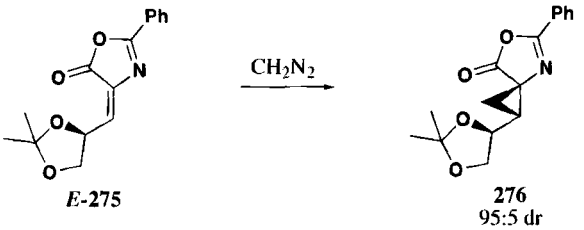
XII. DIAZOALKANES

The reaction between diazoalkanes and dipolarophiles result in 1-pyrazoline derivatives that under certain conditions (spontaneously or *via* photolysis) stereospecifically decompose to the corresponding cyclopropane derivative. Since this review concerns the construction of five-membered heterocycles, most of the ***1,3-DCA*** reactions which are followed by spontaneous cyclopropane formation will be excluded. Moreover, the initially formed pyrazoline derivative can in some cases rearrange to a more stable 2-pyrazoline derivative, for example compound **278**, where the double bond is conjugated to a carbonyl functionality.

1. Reactions with Diazoalkanes

Barluenga *et al.* have been studying chiral non-racemic Fischer carbene complexes as dipolarophiles in reactions with different types of 1,3-dipoles (see also section **XIV**).[183,184] They have for example shown that diazomethane adds to a complex such as dipolarophile **300** (*Scheme 86*) in a highly diastereoselective manner.

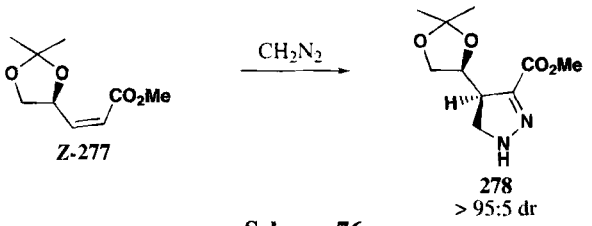
Villegas *et al.* made theoretical calculations for the diazomethane addition to chiral dipolarophiles such as **275** (*Scheme 75*) and compared them to the experimental results obtained and found that good predictions in terms of diastereoselectivity could be made.[185] However, in the experiments no five-membered ***1,3-DCA*** products were detected because the intermediate Δ^1-pyrazolines immediately decomposed to the corresponding cyclopropane derivative **276** which was obtained in excellent diastereoselectivity (95:5 dr).



E-275 **276** 95:5 dr

Scheme 75

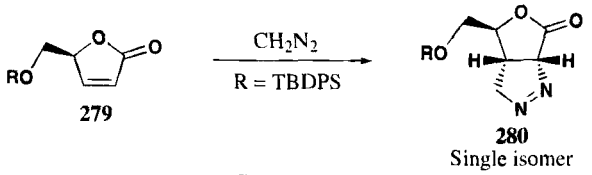
However, Ortuno *et al.* reacted the D-glyceraldehyde derived dipolarophile **277** (*Scheme 76*) with diazomethane to give five-membered cycloadduct **278** in >95:5 dr.[186] The observed *syn* selectivity was opposite to that predicted by Houk's model, and could instead be explained by the "outside



Z-277 **278** > 95:5 dr

Scheme 76

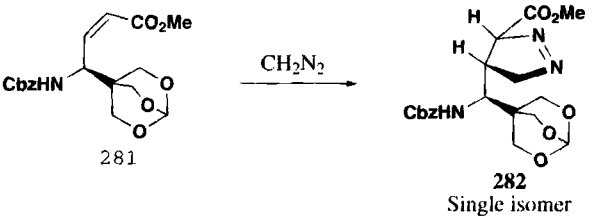
alkoxy" model,[14] and was more extensively studied in another paper.[187] When **279** (*Scheme 77*) was treated with diazomethane, pyrazoline **280** was obtained as the sole isomer derived from attack of



279 **280** Single isomer

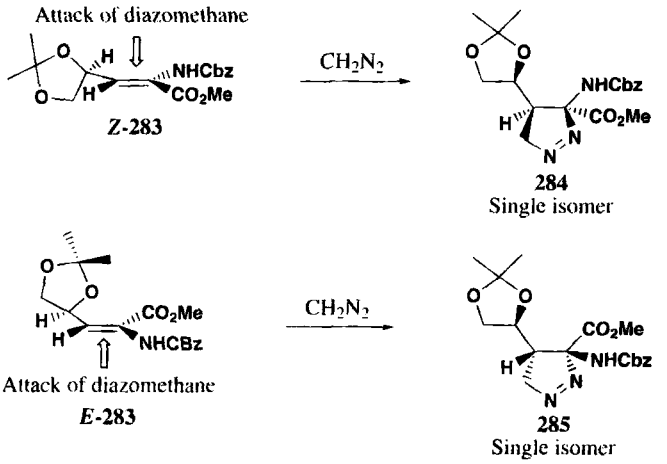
Scheme 77

diazomethane *anti* to the substituent of dipolarophile **279**.[186] Diazomethane reacted with **281** to give **282**, which was used for further manipulation into an interesting amino acid, as a single diastereomer (*Scheme 78*).[188] Liebscher *et al.* have demonstrated highly diastereoselective diazoalkane cycloadditions with chiral non-racemic substituted 1,3-dioxan-4-ones and substituted β-lactones.[189]



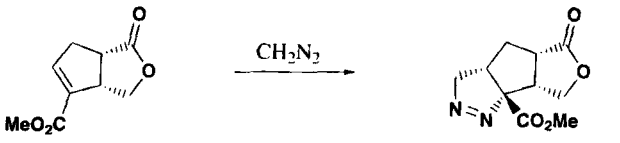
Scheme 78

In another recent work by Bourdelande and Ortuno *et al.* some diazomethane ***1,3-DCA*** reactions with chiral non-racemic amino pentenoates were studied.[190] ***Z*-283** reacts with diazomethane to give only one single pyrazoline cycloadduct **284** (*Scheme 79*). However when the starting dipolarophile had a *E*-geometry (***E*-283**) the opposite facial diastereoselection was obtained, resulting in the cycloadduct **285** still with the same high diastereoselectivity. The stereochemical outcome came from a *syn* attack of diazomethane on conformer ***Z*-283**. The *E*-olefin, however, reacted preferentially in conformer ***E*-283** *via anti* attack of diazomethane.



Scheme 79

Gais, Binger and Lindner *et al.* found that diazomethane added to **286** (*Scheme 80*) exclusively to the most sterically hindered concave side to give one single cycloadduct **287**.[191] One rationale for



Scheme 80

the observed selectivity, is an electrostatic interaction of the methylene carbon of diazomethane and the carbonyl carbon of the lactone moiety (*Fig. 15*), which directed the dipole to the concave side of the dipolarophile and resulted in the unexpected selectivity.

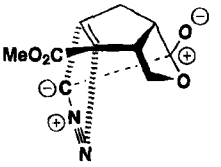
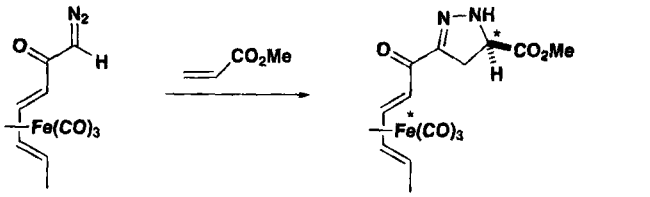


Fig. 15

Neumann *et al.* have been studying diazo compounds complexed to $Fe(CO)_3$ and their reactions with simple acetylenic and olefinic dipolarophiles.[192] Non-racemic dipolarophiles (-)-**288** and (+)-**288** (*Scheme 81*) were allowed to react with methyl acrylate to give cycloadduct **289** with no diastereoselectivity. However, the diastereomers formed were easily separable on SiO_2 to give stereoisomerically pure compounds.

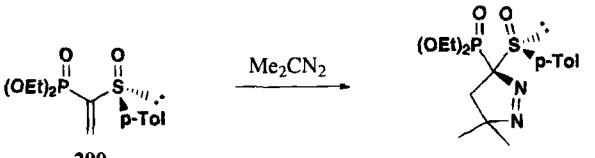


288: (-) or (+)

289
dr 1/1
* absolute configuration not given

Scheme 81

Midura and Mikolajczyk *et al.* studied diazoalkane additions to chiral vinyl sulfoxides.[193] When compound **290** (*Scheme 82*) reacted with diazopropane a single diastereomer **291**



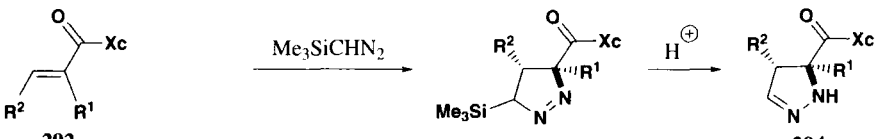
290

291
single isomer

Scheme 82

was formed as its stable pyrazoline derivative. However, although proceeding in excellent diastereoselectivity, reaction with diphenyldiazomethane resulted in decomposition of the initially formed pyrazoline derivative.

Oppolzer's camphorsultam auxiliary has been used frequently in a range of different ***1,3-DCA*** reactions and was also recently used as an efficient chiral auxiliary in asymmetric diazoalkane ***1,3-DCA*** reactions studied by Carreira *et al.*[194] They employed a commercially available silylated diazomethane derivative (Me_3SiCHN_2) in the reaction with various substituted α,β-unsaturated camphorsultam amides **292** (*Scheme 83*) and found that highly diastereoselective reactions were achieved, because the products **294**, formed from the cycloadducts **293** after treatment with acid (desilylation), were obtained in up to 94:6 dr (R^1 = Me, R^2 = H). The cycloadducts could be transformed to interesting azaproline derivatives. This approach has also been used as a key step in the synthesis of *ent*-stellettamide A.[195]



292
Xc = (1R)-(+)-camphorsultam
R^1 = Me or H, R^2 = CO_2Me, Me or H

293
Δ^1-pyrazoline

294
Δ^2-pyrazoline
up to 94:6 dr

Scheme 83

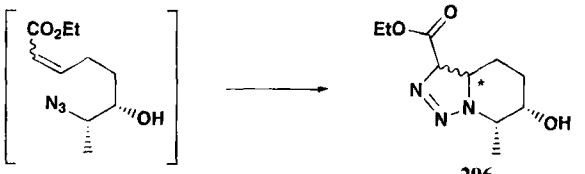
Finally, very recently the first highly enantioselective Lewis acid catalyzed diazomethane ***1,3-DCA*** was reported by Kanemasa *et al.*[196] They applied the nickel derived catalyst **146** (*Scheme 40*) as well as the corresponding magnesium and zinc derived catalysts, in the reaction with Me_3SiCHN_2 and achiral oxazolidinone derived dipolarophiles of type **144**. The pyrazoline cycloadducts obtained were in some cases isolated as almost single enantiomers (up to 99% ee).

XIII. AZIDES

Azides react with dipolarophiles to form triazolines that may be stable or decompose, to aziridines for example. The intermolecular variant of azide ***1,3-DCA*** is not very common because the reaction is very slow. Thus, the intramolecular variant is more frequently employed.

1. Reactions with Azides

Herdeis *et al.* used an asymmetric intramolecular azide ***1,3-DCA*** as a key step in the synthesis of substituted piperidines.[197] The chiral non-racemic azido-functionalized compound **295**, (*Scheme 84*) prepared *via* a Wittig reaction, underwent intramolecular cycloaddition and gave



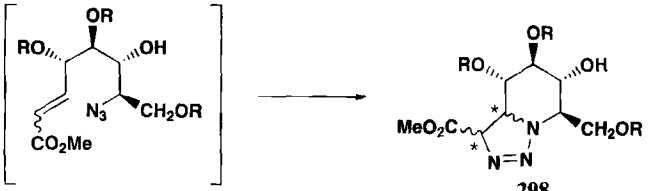
295

296
* dr 2:1

Scheme 84

cycloadduct **296** in low diastereoselectivity together with a decomposition product. However, this mixture could further be transformed to some stereoisomerically pure alkaloids. A diastereoselective route to obtain *cis*-2-alkyl-5-hydroxypiperidines has been reported earlier by Herdeis *et al* using a similar approach.[198]

Fleet *et al.* reported some highly efficient intramolecular azide ***1,3-DCA*** by employing sugar derivatives as templates.[199] For example, azide **297** (*Scheme 85*), containing alkene functionality, was prepared *in situ* which spontaneously underwent an intramolecular ***1,3-DCA*** to give triazoline **298** as a single isomer. However, the absolute configuration of the newly created stereogenic centers was not reported, but was in this case of no importance since those centers were lost in the next step.



297
R=TBDMS

298
Single isomer
* Configuration not determined

Scheme 85

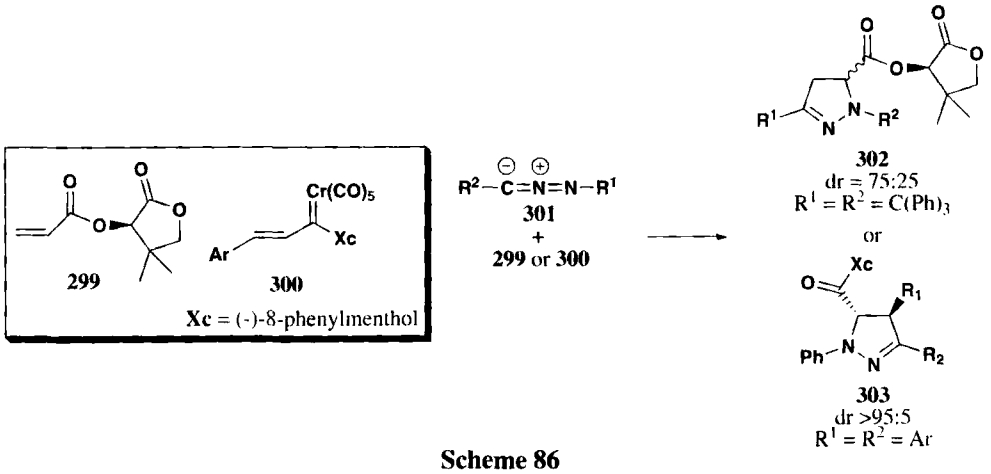
XIV. NITRILE IMINES

The cycloadduct from the reaction of a dipolarophile and a nitrile imine, which is most conveniently generated from dehydrohalogenation of hydrazidic halides,[200] is a 2-pyrazoline derivative. The asymmetric variant of ***1,3-DCA*** between nitrile imines and dipolarophiles has not been a subject of research until very recently and only a few reports have been published.

1. Reactions with Nitrile Imines

Wong, Wentrup and Bertrand *et al.* have been studying nitrile imines and performed the first diastereoselective [3+2]-cycloaddition between a nitrile imine and a chiral dipolarophile.[201] Reaction between nitrile imine **301** ($R^1 = R^2 = C(Ph)_3$) and chiral non-racemic dipolarophile **299** (*Scheme 86*)

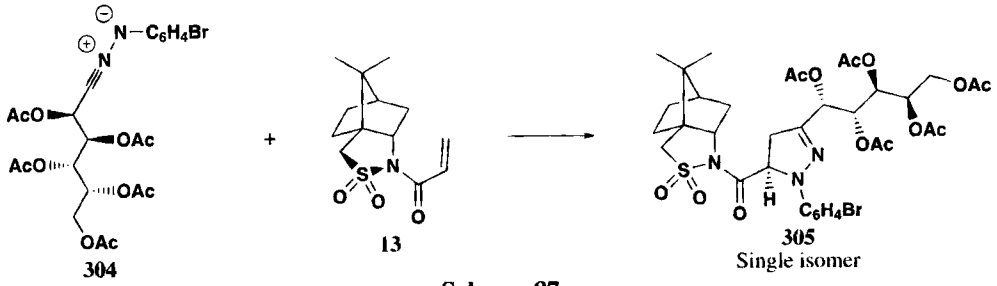
afforded a diastereomeric mixture of cycloadduct **302** in 75:25 diastereoselectivity. The absolute configuration of the major diastereomer was not given.



Scheme 86

Later, Barluenga *et al.* prepared some chiral non-racemic alkenyl Fischer carbene complexes **300** and reacted them with nitrile imines (*Scheme 86*).[202,203] Thus, in reactions with aromatic nitrile imines **301** ($R^1 = R^2 = Ar$) the cycloadducts **303**, were obtained in >95:5 dr in most cases, after removal of the metal, together with small amount of regioisomers not shown. The metal pentacarbonyl moiety was found to be crucial for obtaining both high regio- and diastereoselectivity because cycloadditions with the corresponding cinnamate derivatives afforded complex mixtures of regio- and diastereomers almost without any selectivity.

Herczegh *et al.* have reported double diastereoselective reactions between chiral nitrile imines and chiral dipolarophiles.[204] For example the sugar derived chiral nitrile imine **304** (*Scheme 87*) was reacted with the chiral dipolarophile, N-acryloyl-(-)-camphor sultam **13**, with matched diastereoselectivity. Thus, pyrazoline **305** was obtained as a single isomer.



Scheme 87

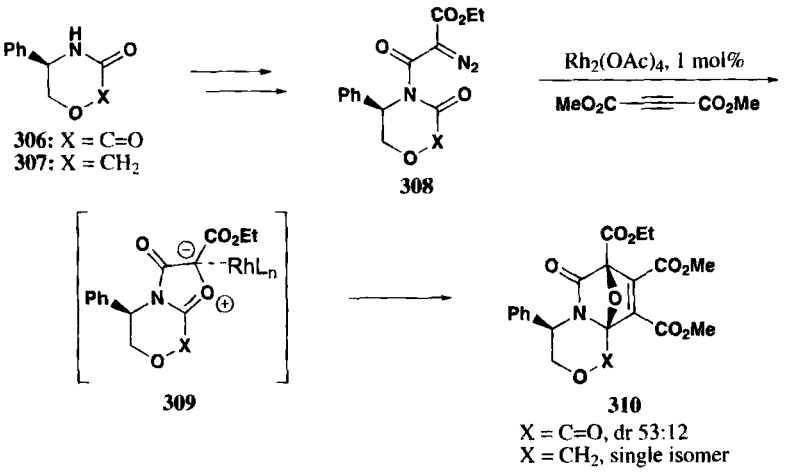
XV. ISOMÜNCHNONE DIPOLES (CARBONYL YLIDES)

The isomünchnone dipoles are simply masked carbonyl ylides and are very reactive intermediates, and in the presence of either an external dipolarophile, or, alternatively, an alkene function-

ality in the substrate, inter- or intramolecular cycloaddition occurs readily. The ylides are most efficiently generated through Rh(II) catalyzed decomposition of diazoimides. Very few reports have dealt with the asymmetric variant of this process. However, since rhodium was found to catalyze the diazo decomposition, chiral rhodium catalysts have been reported to effectively *catalyze* the ***1,3-DCA*** through tandem carbonyl ylide formation-***1,3-DCA*** in an enantioselective manner.

1. Chiral Isomünchnone Dipoles

Chiral non-racemic phenyloxazin-2,3-dione **306** and phenyloxazin-3-one **307** (*Scheme 88*) were utilized as templates for the synthesis of chiral non-racemic isomünchnone dipole precursors in two sequential publications by Harwood *et al.*[205,206]

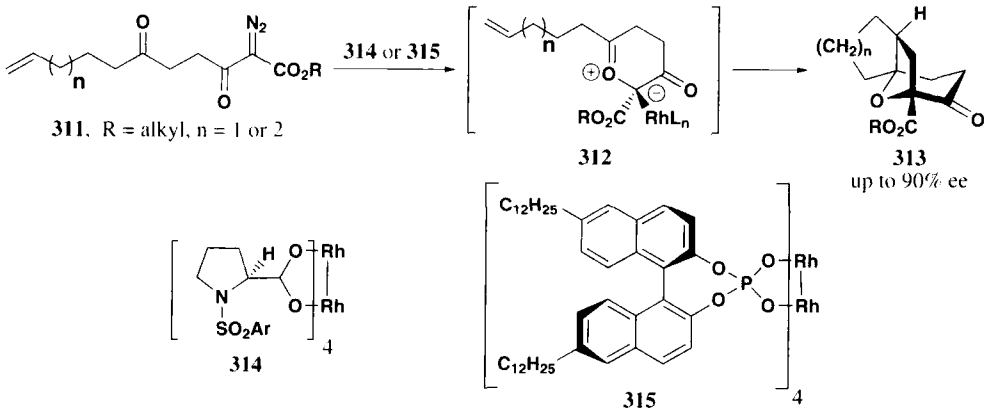


Scheme 88

Thus, isomünchnone dipole precursor **308** (X = CO or CH_2) for example, was prepared from chiral non-racemic **306** or **307** respectively (*Scheme 88*). When **308** was treated with $Rh_2(OAc)_4$ the corresponding ylide **309** was formed, which in the presence of a dipolarophile such as DMAD, reacted to give cycloadduct **310** in a yield of 53% together with the other diastereomer in 12% yield (X = CO). However, the less flattened oxazinone ring (X = CH_2) gave only one single cycloadduct **310**. Other dipolarophiles gave moderate to excellent diastereoselectivity. The major cycloadduct is obtained *via* approach of the dipolarophile from the less sterically demanding side of the ylide.

2. Metal-catalyzed Enantioselective Intramolecular Reactions

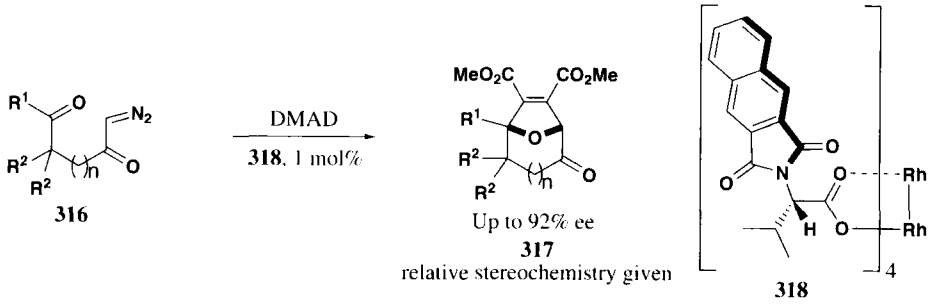
Hodgson *et al.* reported some intramolecular enantioselective ***1,3-DCA*** of carbonyl ylides catalyzed by a Rh-catalyst (*Scheme 89*).[207] Thus, in the presence of the chiral catalyst **314** carbonyl ylides **312** were formed which immediately cyclized to give the cycloadducts **313** which were formed in 53% ee under optimized conditions. Better enantioselectivity (up to 90% ee) has more recently been reported, when chiral Rh-catalyst **315** was used (0.5 mol%).[208]



Scheme 89

3. Metal-catalyzed Enantioselective Intermolecular Reactions

Following the suggestion of Padwa *et al.* that the Rh-catalyst, necessary for the decomposition of the diazo derivative to the corresponding isomünchnone dipole, might be bound to the original site of attachment during the whole cycloaddition sequence,[209] Hashimoto *et al.* set up an enantioselective type of isomünchnone dipole ***1,3-DCA*** to an acetylenic dipolarophile mediated by a chiral Rh-catalyst.[210] Thus, isomünchnone dipole precursors **316** (*Scheme 90*) reacted with dimethyl acetylenedicarboxylate (DMAD) in the presence of a range of different chiral Rh(II)-complexes derived from different amino acids as catalysts (1 mol%).



Scheme 90

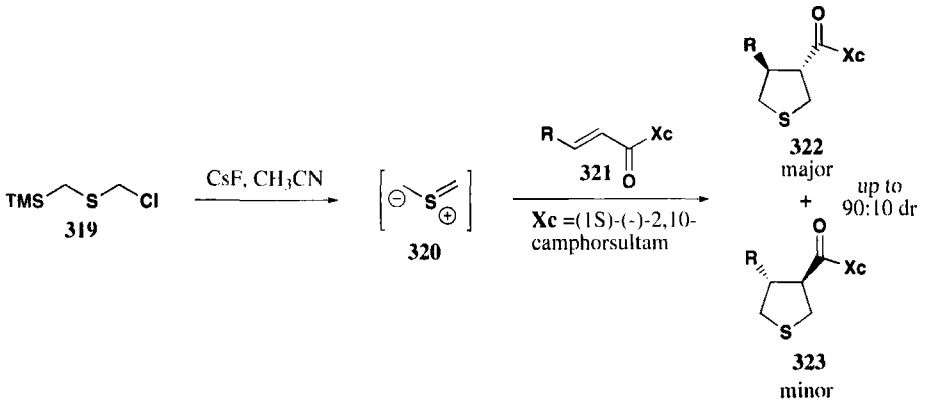
Cycloadducts of the type **317** were obtained in low to high ee:s (20-92%) depending on the catalyst used. The highest ee:s were obtained with catalyst **318**, derived from $Rh_2(OAc)_4$ and a *N*-benzoannulated phthaloyl-(*S*)-valine. Ester derived dipole precursors of type **316** have also been found to undergo highly enantioselective cycloaddition with a range of different dipolarophiles if the appropriate amino acid derived Rh-catalyst of type **318** was applied.[211] Finally, Doyle *et al.* applied a chiral Rh-catalyst in an intermolecular cycloaddition between an acetylenic dipolarophile and a diazoacetate derived carbonyl ylide, although in low enantioselectivity (< 10% ee).[212]

XVI. THIOCARBONYL YLIDES

There are many reports concerning stabilized and non-stabilized sulfur ylides.[213] However, the asymmetric ***1,3-DCA*** variant, where the cycloadduct is chiral and non-racemic, still remains a nearly unexplored area. The ylides can for example be generated from a stable precursor *in situ* in the presence of a dipolarophile to give substituted tetrahydrothiophenes.

1. Reactions with Thiocarbonyl Ylides

With the exception of a few ***1,3-DCA*** of thioisomünchnones to chiral nitroalkenes resulting in dihydrothiophenes after rearrangement (reviewed by Jörgenson *et al.*[2]), there are to our knowledge, no other papers dealing with ***1,3-DCA*** of thiocarbonyl ylides resulting in tetrahydrothiophenes than those two recently published by us.[214,215] Thus, the asymmetric ***1,3-DCA*** between the thiocarbonyl ylide precursor **319** and α,β-unsaturated-camphorsultam amides **321** (*Scheme 91*) was examined. In the presence of CsF, dipole precursor **319** formed the ylide **320** which added to a variety of chiral dipolarophiles **321** to give exclusively *trans*-cycloadducts **322** as the major diastereomers and *trans*-**323** as the minor diastereomers in all cases with high diastereoselectivity (dr approximately 90:10 for all dipolarophiles investigated, R = Ph, Bu and BnO).



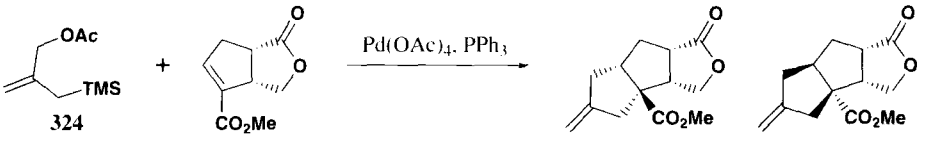
Scheme 91

When the dipolarophile was **321** (R = BnO), the cycloadduct **322** contained a masked alcohol group. This product was used by us as a chiral building block in the synthesis of the active stereoisomer of the pheromone of the pine sawfly *Macrodiprion nemoralis*.[215]

XVII. 1,3-DIPOLE EQUIVALENTS

Although C-C-C "dipoles" are actually not defined as ylides, they might behave as 1,3-dipoles. Thus, when such C-C-C "dipoles" are reacted with suitable dipolarophiles, five-membered cyclopentane derivatives can be obtained. Because one example of such a dipole equivalent was recently reported by Gais *et al.* in an asymmetric variant, we choose to review their results.[191] They

investigated palladium-trimethylenemethane cycloadditions to chiral non-racemic bicyclic dipolarophiles. Thus, allylic acetate **324** in the presence of a Pd-catalyst and a dipolarophile such as **286** (*Scheme 92*) underwent cycloaddition to give the corresponding tricycles **325** and **326** in a ratio of up



Scheme 92

to 5.3:1. This reaction was a result of addition of the trimethylenemethane equivalent to the more sterically hindered side of the dipolarophile much like their results obtained with other dipoles such as diazomethane (see *Scheme 80*). However, when a more sterically demanding trimethylene dipole equivalent precursor was used, preferential attack on the convex side of dipolarophile **286** was observed.

Finally, Pyne *et al.* have recently investigated a substituted C-C-C dipole equivalent derived from allenes in its cycloaddition with oxazolidinone-derived dipolarophiles in moderate to excellent diastereoselectivity.[216]

XVIII. NOTE ADDED IN PROOF

The following relevant articles have appeared during the period between manuscript acceptance and proofreading.[217]

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