Asymmetric 1,3-Dipolar Cycloaddition Reactions

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Contents

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1. Introduction

The addition of a 1,3-dipole to an alkene for the synthesis of five-membered rings is a classic reaction in organic chemistry. The 1,3-dipolar cycloaddition (1,3-DC) reactions are used for the preparation of molecules of fundamental importance for both academia and industry.

The history of 1,3-dipoles goes back to Curtius, who in 1883 discovered diazoacetic ester.[1] Five years later his younger colleague Buchner studied the reaction of diazoacetic ester with α,β-unsaturated esters and described the first 1,3-DC reaction.[2] In 1893 he suggested that the product of the reaction of methyl diazoacetate and methyl acrylate was a 1-pyrazoline and that the isolated 2-pyrazole was formed after rearrangement of the 1-pyrazole.[3] Five years later nitrones and nitrile oxides were discovered by Beckmann, and Werner and Buss, respectively.[4,5] The Diels−Alder reaction was found in 1928,[6] and the synthetic value of this reaction soon became obvious. The chemistry of the 1,3-DC reaction has thus evolved for more than 100 years, and a

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variety of different 1,3-dipoles have been discovered.[7] However, only a few dipoles have found general application in synthesis during the first 70 years after the discovery of the diazoacetic ester. Two well-known exceptions are ozone and diazo compounds.[8,9] The general application of 1,3-dipoles in organic chemistry was first established by the systematic studies by Huisgen in the 1960s.[10] At the same time, the new concept of conservation of orbital symmetry, developed by Woodward and Hoffmann, appeared.[11,12] Their work was a milestone for the understanding of the mechanism of concerted cycloaddition reactions. On the basis of the concept by Woodward and Hoffmann, Houk et al. have further contributed to our present understanding and ability to predict relative reactivity and regioselectivity, of 1,3-DC reactions.[13−15]

The development of 1,3-DC reactions has in recent years entered a new stage as control of the stereochemistry in the addition step is now the major challenge. The selectivity challenge is to control the regio-, diastereo-, and enantioselectivity of the 1,3-DC reaction. The stereochemistry of the 1,3-DC reaction can be controlled by either choosing the appropriate substrates or controlling the reaction by a metal complex acting as a catalyst.

Compared to the development of the asymmetric metal-catalyzed carbo- and hetero-Diels−Alder reactions, the development of the analogous approach to asymmetric 1,3-DC reactions is several years behind. Probably the most important aspect of the 1,3-DC reaction is to control diastereo- and enantioselectivity and the present review is devoted to this topic. The enantioselectivity can be controlled by either choosing a chiral 1,3-dipole—if possible—ozone and nitrous oxide are exceptions, a chiral alkene, or a chiral catalyst of which the latter probably has the greatest potential. The present review will mainly try to cover the development of the asymmetric 1,3-DC reactions with alkenes, but the application in natural product synthesis will also be described in some cases.

This review will deal with the asymmetric 1,3-DC reactions of a series of dipoles with alkenes. For each of the major 1,3-DC reactions the following topics will be presented: reactions of chiral 1,3-dipoles, chiral alkenes, intramolecular 1,3-DC reactions, and metal-catalyzed 1,3-DC reactions. The review will also be restricted to primarily cover reactions in which the 1,3-DC product is optically active. When the reaction described is racemic, this will be indicated.

2. Basic Aspects

A 1,3-dipole is defined as an *a*−*b*−*c* structure that undergoes 1,3-DC reactions and is portrayed by a dipolar structure as outlined in Figure 1.[7,16,17] Basically, 1,3-dipoles can be divided into two different types: the allyl anion type and the propargyl/allenyl anion type. The allyl anion type is characterized by four electrons in three parallel p_z orbitals—perpendicular to the plane of the dipole and that the 1,3-dipole is bent. Two resonance structures in which the three centers have an electron octet, and two structures in which *a* or *c* has an electron sextet, can be drawn. The central atom *b* can be nitrogen, oxygen, or sulfur (Figure 1A). The propargyl/allenyl anion type has an extra π orbital located in the plane orthogonal to the allenyl anion type molecular orbital (MO), and the former orbital is therefore not directly involved in the resonance structures and reactions of the dipole. The propargyl/allenyl anion type is linear and the central atom *b* is limited to nitrogen (Figure 1B). The three sextet resonance structures that also can be drawn are omitted in Figure 1. The 1,3-dipoles are occasionally presented as hypervalent structures (Figure 1C).

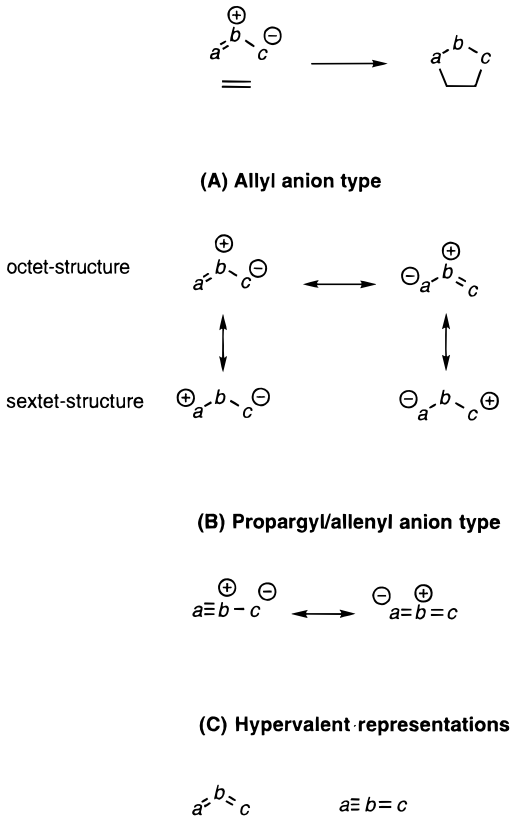


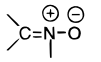
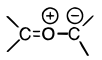
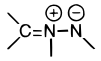
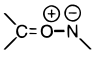
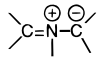
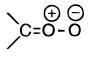
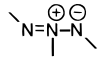
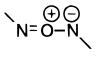
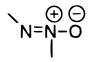
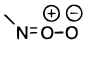
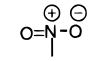
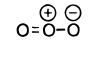
Figure 1. The basic resonance structure of 1,3-dipoles.

The 1,3-dipoles consist mainly of elements from main group IV, V, and VI. Since the parent 1,3-dipoles consist of elements from the second row, and considering the above limitations on the central atom of the dipole, a limited number of structures can be formed by permutations of nitrogen, carbon, and oxygen. Higher row elements such as sulfur and phosphorus can also be incorporated in 1,3-dipoles, but according to our knowledge, only few asymmetric reactions involving these types of dipoles have been published. Hence, 12 dipoles of the allyl anion type and 6 dipoles of the propargyl/allenyl anion type are obtained. The classification and presentation of the parent 1,3-dipoles is depicted in Table 1.[7]

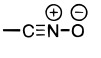
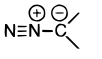
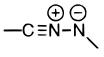
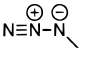
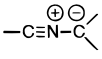
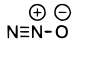
The 1,3-DC reaction of the parent 1,3-dipoles, with alkenes, and alkynes involves 4 π electrons from the dipole and 2 π electrons from the alkene. If the 1,3-DC reaction proceeds via a concerted mechanism it is thermally allowed with the description $[{}_{\pi}4_s + {}_{\pi}2_s]$ according to the Woodward−Hoffmann rules.[11] This means that the three p_z orbitals of the 1,3-dipole and the two p_z orbitals of the alkene both combine suprafacially. However, in the 1960s the reaction

Table 1. Classification of the Parent 1,3-Dipoles

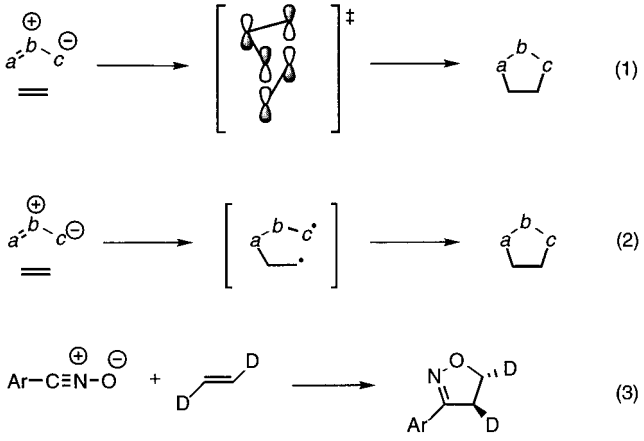
Allyl anion type

Nitrogen in the middle		Oxygen in the middle	
	Nitrones		Carbonyl Ylides
	Azomethine Imines		Carbonyl Imines
	Azomethine Ylides		Carbonyl Oxides
	Azimines		Nitrosimines
	Azoxy Componds		Nitrosoxides
	Nitro Compounds		Ozone

Propargyl/allenyl anion type

Nitrillium Betaines		Diazonium Betaines	
	Nitrile Oxides		Diazoalkanes
	Nitrile Imines		Azides
	Nitrile Yildes		Nitrous Oxide

Scheme 1



mechanism was subject to a great deal of debate.[5] This dispute will be described only briefly. On the basis of an extraordinary series of investigations which led to a monumental collection of data Huisgen et al. developed a detailed rationale for a concerted mechanism for the 1,3-DC reaction (Scheme 1, eq 1). Firestone considered the 1,3-DC reaction to proceed via a singlet diradical intermediate (Scheme 1, eq 2). Both sides in the debate based their arguments on a series of experimental facts.[5] On the basis of the stereospecificity of the 1,3-DC reaction, the dispute was settled in favor of the concerted mechanism: The 1,3-DC reaction of benzonitrile oxide with trans-dideuterated ethylene gave exclusively the *trans*-isoxazoline (Scheme 1, eq 3). A diradical intermediate would allow for a 180° rotation of the terminal bond and would thus be expected to yield a mixture of the cis and trans isomers. Huisgen et al. have later shown that the 1,3-DC reaction can take place by a stepwise reaction involving an intermediate and in these cases the stereospecificity of the reaction may be destroyed.

The transition state of the concerted 1,3-DC reaction is thus controlled by the frontier molecular orbitals (FMO) of the substrates. The $LUMO_{dipole}$ can interact with the $HOMO_{alkene}$ and the $HOMO_{dipole}$ with the $LUMO_{alkene}$. Sustman has classified 1,3-DC reactions into three types, on the basis of the relative FMO energies between the dipole and the alkene (Figure 2).[14,15,18,19]

In type I 1,3-DC reactions the dominant FMO interaction is that of the $HOMO_{dipole}$ with the $LUMO_{alkene}$ as outlined Figure 2. For type II 1,3-DC reactions the similarity of the dipole and alkene FMO energies implies that both HOMO−LUMO interactions are important. 1,3-DC reactions of type III are dominated by the interaction between the $LUMO_{dipole}$ and the $HOMO_{alkene}$.

1,3-DC reactions of type I are typical for substrates such as azomethine ylides and azomethine imines, while reactions of nitrones are normally classified as type II. 1,3-DC reactions of nitrile oxides are also classified as type II, but they are better classified as borderline to type III, since nitrile oxides have relatively low lying HOMO energies. Examples of type III interactions are 1,3-DC reactions of ozone and nitrous oxide. However, the introduction of electron-donating or electron-withdrawing substituents on the dipole or the alkene can alter the relative FMO energies, and therefore the reaction type dramatically. The 1,3-DC reaction of *N*-methyl-*C*-phenylnitrone with methyl acrylate is controlled by the $HOMO_{dipole}$−$LUMO_{alkene}$ interaction, whereas the 1,3-DC reaction of the same nitrone with methyl vinyl ether is controlled by the $LUMO_{dipole}$−$HOMO_{alkene}$ interaction. It should be noted that there is some confusion about the Sustmann classification. Some authors classify the 1,3-dipoles into type I, II, and III, respectively, and this interpretation of the Sustmann classification, no attention is taken to the FMO energies of the alkene.

The presence of metals, such as a Lewis acid, in 1,3-DC reactions, can alter both the orbital coefficients of the reacting atoms and the energy of the frontier orbitals of both the 1,3-dipole or the alkene depending on the electronic properties of these reagents or the Lewis acid. The coordination of a Lewis acid to the 1,3-dipole, or the alkene, is of fundamental importance for asymmetric 1,3-DC reactions since the metal can catalyze the reaction. Furthermore, the Lewis acid may also have influence on the selectivity of the 1,3-DC reaction, since both regio-, diastereo-, and enantioselectivity can be controlled by the presence of a metal−ligand complex.

The catalytic effect of a Lewis acid on the 1,3-DC reaction can be accounted for by the FMOs of either the 1,3-dipole, or the alkene, when coordinated to the metal. The influence of the coordination of a 1,3-dipole or an alkene to a Lewis acid is presented in Figure 3 for type I and III interactions.

The reactivity of the 1,3-dipole with an alkene can be accounted for by using a simple frontier orbital

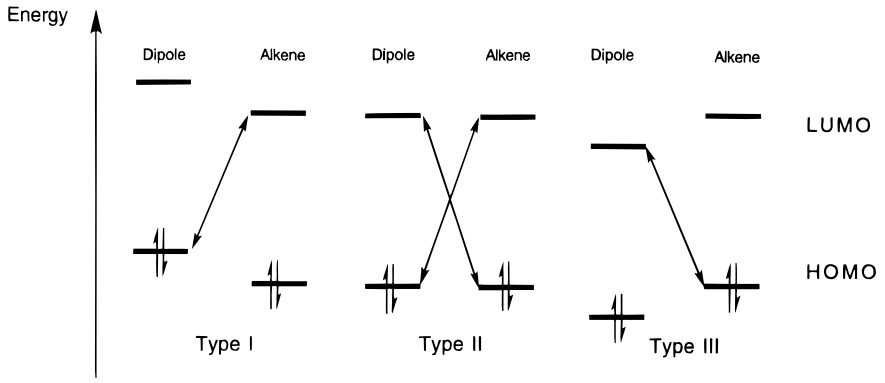


Figure 2. The classification of 1,3-DC reactions on the basis of the FMOs: type I, a $HOMO_{dipole}-LUMO_{alkene}$ interaction; type II, interaction of both $HOMO_{dipole}-LUMO_{alkene}$ and $LUMO_{dipole}-HOMO_{alkene}$; type III, a $LUMO_{dipole}-HOMO_{alkene}$ interaction.

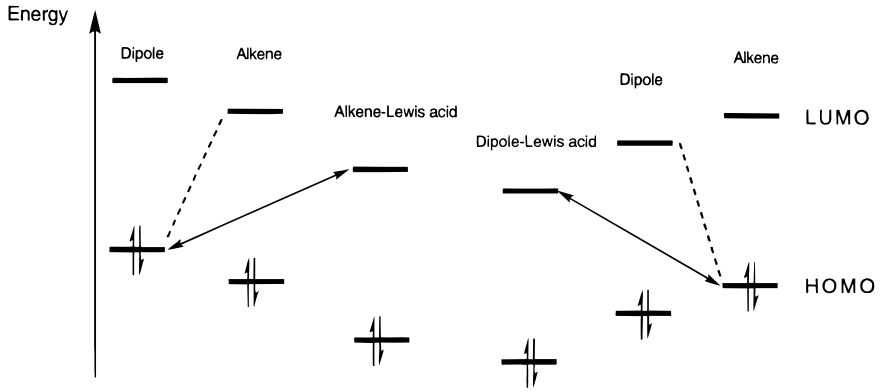


Figure 3. The change in frontier orbitals by coordination of a Lewis acid to the alkene (left) and to the dipole (right).

line of reasoning, i.e., the energy term from second-order perturbation theory

$$\Delta E \propto \frac{c_{\mathrm{HOMO}} c_{\mathrm{LUMO}}}{E_{\mathrm{HOMO}} - E_{\mathrm{LUMO}}} \qquad (4)$$

where c_{HOMO} and c_{LUMO} are the orbital coefficients at the reacting atoms in the HOMO and LUMO, respectively. The $E_{\mathrm{HOMO}} - E_{\mathrm{LUMO}}$ in the denominator is the energy difference between the HOMO and LUMO. In eq 4, which is a very simplified expression of the second-order perturbation theory, it is assumed that it is only the HOMO−LUMO interaction which mainly determines the reactivity.

The coordination of a Lewis acid to the alkene, e.g., via a conjugated carbonyl group (Figure 3, left) will lower the energy of the FMOs of the alkene, relative to uncoordinated alkene. The lowering in energy of the $LUMO_{alkene}$ will lead to a decrease in the energy difference between E_{HOMO} of the dipole and E_{LUMO} of the alkene coordinated to the Lewis acid, compared to the interaction in the absence of the Lewis acid. The decrease in E_{LUMO} of the alkene coordinated to the Lewis acid leads to an increase in ΔE in eq 4 and thus a faster reaction should be expected. In a similar manner will coordination of a Lewis acid to the dipole lower the energy of the FMOs of the dipole, relative to uncoordinated dipole (Figure 3, right) and a similar argument as above will also lead to an increased reactivity in this case, compared to the 1,3-DC reaction in the absence of a catalyst. In this simplified version the increase in reactivity of the 1,3-dipole and the alkene in the presence of metal catalysts is due to a change of the FMO energy of the substrate interacting with the catalyst. However, it should also be mentioned that other factors as the coordination ability of the substrate to the Lewis acid can alter the reactivity significantly.

Concerted cycloaddition reactions are among the most powerful tools for stereospecific creation of new chiral centers in organic molecules. When 1,2-disubstituted alkenes are involved in concerted [$_{\pi}4_{s}$ + $_{\pi}2_{s}$] cycloaddition reactions with 1,3-dipoles, two new chiral centers can be formed in a stereospecific manner due to the syn attack of the dipole on the double bond. In the 1,3-DC reactions considered in this review, substrates such as nitrones, may also lead to formation of a new chiral center at the carbon atom of the nitrone. If the alkene, or the 1,3-dipole, contain a chiral center(s), the approach toward one of the faces of the alkene or the 1,3-dipole can be discriminated, leading to a diastereoselective reaction. This type of selectivity will be referred to as diastereofacial selectivity and will be given as diastereomeric excess (de). The term enantioselectivity will only be applied when optically active products are obtained from achiral or racemic starting materials. The endo/exo selectivity is also defined as diastereoselectivity, but for clarity, the term endo/exo selectivity, or occasionally cis/trans selectivity, will be used and this type of selectivity will be given as a ratio—endo:exo. For the reaction of a 1,3-dipole, such as a nitrone, with an alkene, a pair of diaster-

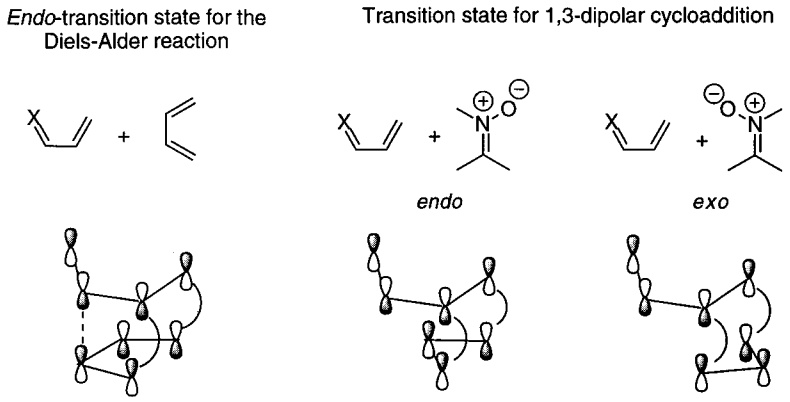
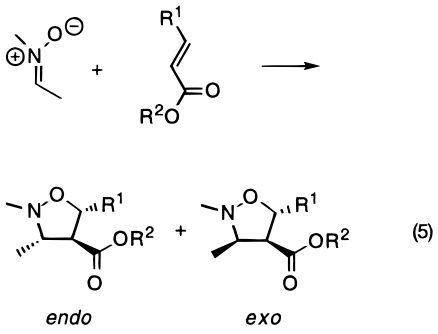


Figure 4. Endo selectivity of the Diels−Alder reaction compared the with endo and exo selectivity in the 1,3-DC reaction.

eomers, the endo and exo isomers can be formed (eq 5).

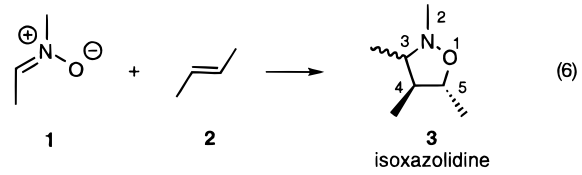


(5)

The nomenclature endo and exo is well-known from the Diels−Alder reaction.[11] The endo isomer arises from the reaction in which the transition state is stabilized by secondary π orbital interactions as outlined in Figure 4. The same nomenclature is also applied to the 1,3-DC reaction of alkenes with nitrones and other dipoles, but the actual interaction of the *N*-nitrone p_z orbital with a vicinal p_z orbital on the alkene, and thus the stabilization, is small.[20] The endo/exo selectivity in the 1,3-DC reaction is therefore primarily controlled by the structure of the substrates or by a catalyst.

3. Nitrones

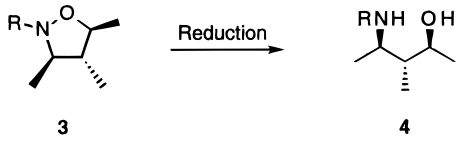
The 1,3-DC reactions of nitrones **1** with alkenes **2** leading to isoxazolidines **3** is a fundamental reaction in organic chemistry and the available literature on this topic of organic chemistry is vast (eq 6). In this



(6)

reaction until three contiguous asymmetric centers can be formed as outlined for the reaction between nitrone **1** and an 1,2-disubstituted alkene **2** in eq 6. The relative stereochemistry at C-4 and C-5 is always controlled by the geometric relationship of the substituents on the alkene.

1,3-DC reactions of nitrones with alkenes have found general application in organic synthesis. The major reason for the synthetic utility of this reaction is the variety of attractive compounds which are available from isoxazolidines **3**. Important β-amino alcohols **4** can be obtained from isoxazolidine ring upon reduction, with retention of the configuration at the chiral centers (eq 7).



(7)

The most common reductive ring-opening reactions are catalytic hydrogenation with palladium or Raney nickel or treatment of the isoxazolidine with zinc and acid, but a variety of other methods are also accessible.[21,22] The primary amine is often desired, and to obtain this the *N*-substituent in the isoxazolidine ring is occasionally removed during the reduction step. β-Amino alcohols obtained in this manner are important building blocks in total synthesis, and there are numerous of examples on the synthesis of optically active natural products.

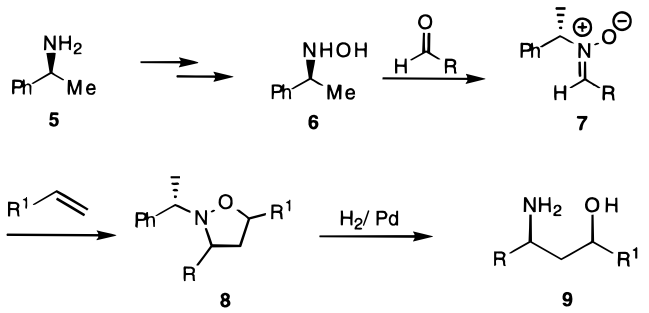
Recently, the reactions between nitrones and alkenes leading to optically active isoxazolidines have been reviewed by Frederickson[23] and in this review a number of examples were given on the application of asymmetric nitrone−alkene 1,3-DC reactions in the synthesis of target molecules. Hence, we have tried to accentuate some other parts of this area, especially reactions in which metal complexes have been applied.

3.1. Chiral Nitrones

The presentation of intermolecular 1,3-DC reactions involving chiral nitrones is divided into three parts. First, reactions in which the chiral substituent on the nitrone is located at the nitrogen atom will be described, then reactions in which the chiral center is located at the carbon atom, and finally reactions of chiral cyclic nitrones.

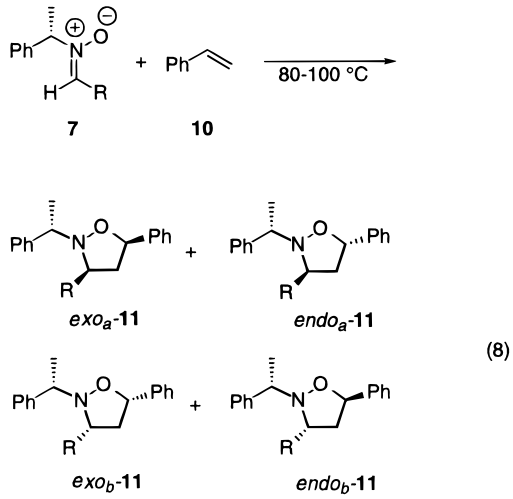
The most commonly used chiral substituent at the nitrogen atom is the 1-phenylethyl group.[24−30] The derived nitrones **7** are available from 1-phenethylamine **5** (Scheme 2) and the substituent has the advantage that it can be removed from the resulting isoxazolidine product **8**, by hydrogenolysis. In the

Scheme 2



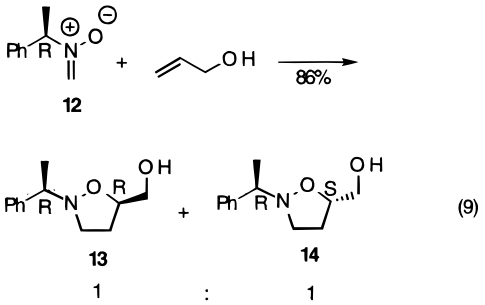
reduction step the isoxazolidine ring **8** is also opened to give the primary 3-amino alcohol **9** as outlined in Scheme 2.

Nitrones **7**, bearing the 1-phenylethyl substituent at the nitrogen atom and with different substituents at the carbon atom, have been subjected to 1,3-DC reactions, e.g., with styrene **10**.[26,28] The reactions proceed to give a mixture of the exo and endo isomers in ratios between 68:32 to 87:13 (eq 8). The diastereofacial selectivity of the reaction is fair to excellent. The product exo_a-**11** and $endo_a$-**11** are formed by addition of styrene to the *si* face of the nitrone. exo_b-**11** and $endo_b$-**11** to the *re* face. The minor endo isomers are occasionally obtained with a de close to 100%.



(8)

Tice and Ganem have applied nitrone **12** in a 1,3-DC reaction with allyl alcohol (eq 9).[29] In this reaction, only the two diastereomers **13** and **14** can be formed, since the nitrone carbon atom is not prochiral. Disappointingly, the reaction gave **13** and **14** in a 1:1 ratio. However, the two diastereomers can be separated to give the enantiomerically pure products. By further reactions of isoxazolidine **13**, the natural product (+)-hypusine was obtained.



(9)

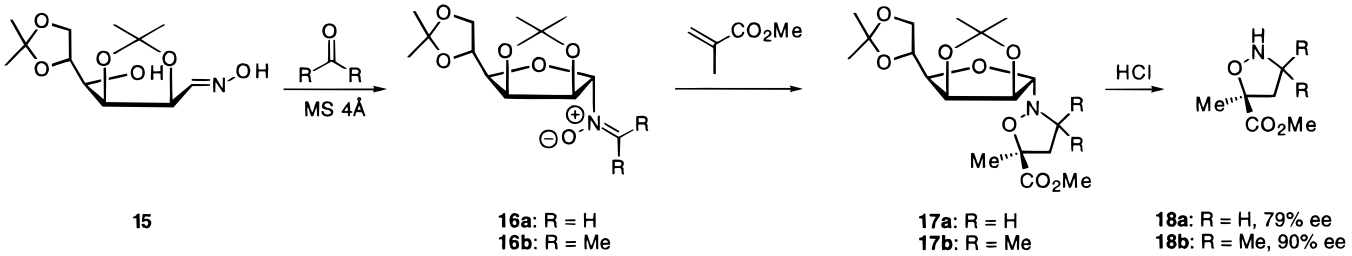
Kametani et al. applied 1,3-DC reactions of *N*-α-methylbenzyl nitrones with benzyl crotonates in the synthesis of (+)- and (−)-thienamycin and penem and carbapenem precursors.[27,30] In a similar manner, Overton et al. have applied this type of nitrones in the 1,3-DC reaction with vinyl acetates for the synthesis of naturally occurring β-amino acids.[25] The α-methylbenzyl group offers relatively poor discrimination, since mixtures of diastereomers are generally obtained in reactions of this type of nitrones.

Another type of nitrones bearing the chiral substituent at the nitrogen atom was developed by Vasella et al.[31−36] The optically active nitrones are obtained in an elegant manner from inexpensive glycosides. When partially protected D-mannose oxime **15** reacts with formaldehyde or acetone, nitrones **16a**,**b**, respectively, are formed (Scheme 3).[31,36] In the presence of methyl methacrylate, **16a**,**b** react in a 1,3-DC reaction to give the isoxazolidines **17a**,**b** as a mixture of two diastereomers. One of the advantages of this method developed by Vasella et al. is that the chiral auxiliary is easily recovered upon acidic hydrolysis. The N-unsubstituted isoxazolidine **18a**,**b** are formed with optical purities of 79% and 90% ee, respectively.

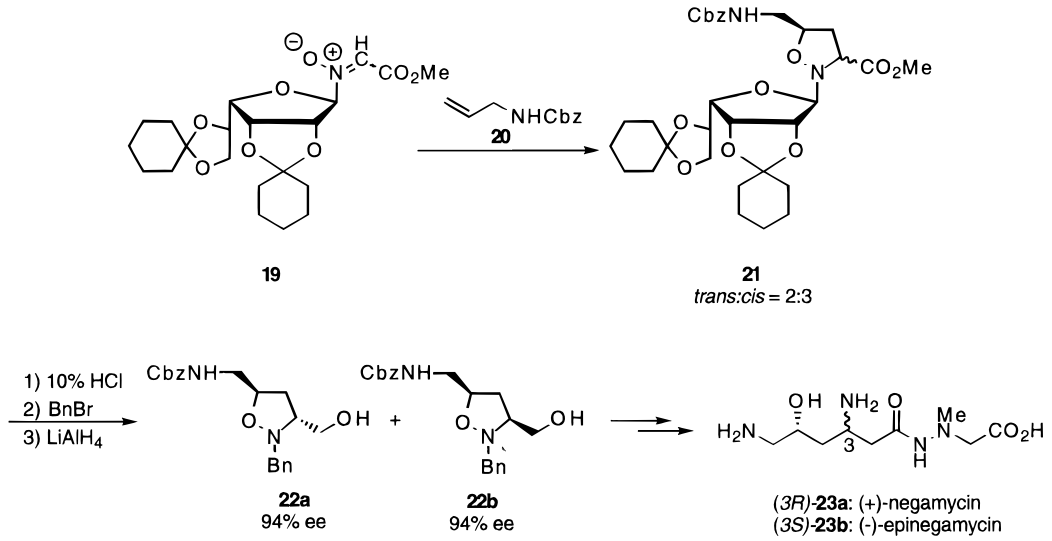
Recently, analogous nitrones have been applied by others in the synthesis of (2*S*)-4-oxopipecolic acid.[37] Vasella et al. have also applied partly protected D-ribofuranose oximes for the formation of optically active nitrones.[31,32] However, the selectivities obtained from the reactions of this type of nitrones are often lower than those formed from the reactions of **16a**,**b** and analogous. As a part of these extensive studies several different alkenes have been applied in 1,3-DC reactions leading to optically active proline analogous,[33] isoxazolidine nucleosides,[32] and α-aminophosphonic acids.[34]

More recently Kibayashi et al. have extended these studies to the application of partially protected *N*-gulonofuranosyl nitrones in the synthesis of (+)-

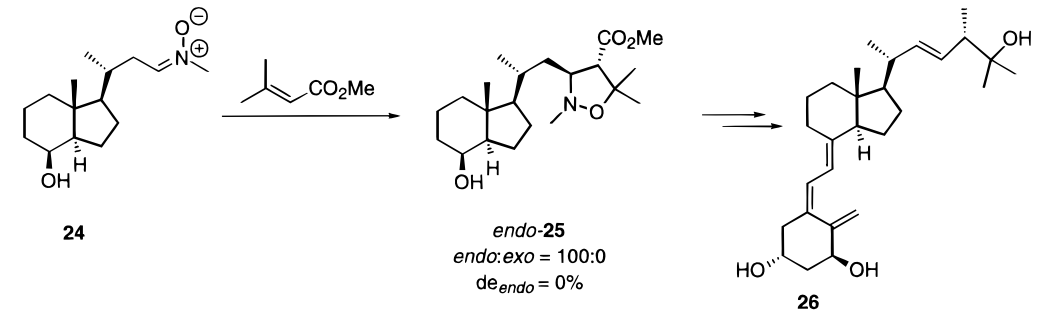
Scheme 3



Scheme 4



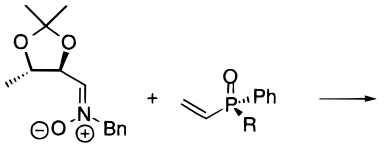
Scheme 5



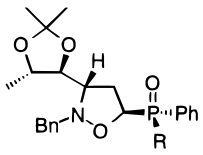
negamycin and (−)-epinegamycin.[38,39] They applied a protected gulonofuranosyl group a chiral auxiliary (Scheme 4). The nitrone **19**, formed from the corresponding glucose oxime and methyl glyoxylate, exists as a mixture of the *Z* and *E* isomer and hence, the 1,3-DC reaction with allylamine **20** gives **21** in a 2:3 ratio of the trans and cis isomers. Similar observations have been reported by Vasella et al.[31,33] Contrary to the poor cis/trans selectivity, the diastereofacial selectivity of the 1,3-DC reaction between **19** and **20** is high. This selectivity is determined after hydrolysis, benzylation, and reduction of the ester to give **22a**,**b** in high optical purities. By further reactions of **22a** and **22b**, respectively, (+)-negamycin **23a** and (−)-epinegamycin **23b** are obtained.

The chiral moiety of the nitrone can also be located at the carbon atom. Baggiolini et al. have used this approach in the total synthesis of 1α,25-dihydroxyergocalciferol (**26**), a molecule arising from the degradation of vitamin D_3 in human liver and kidney.[40] The nitrone **24** is obtained from the corresponding aldehyde, and the 1,3-DC reaction with methyl 3,3-dimethylacrylate affords isoxazolidine *endo*-**25** (Scheme 5). The reaction proceeds with a high degree of endo selectivity, but shows no diastereofacial selectivity. However, the two endo isomers are separated by chromatography and after several synthetic steps **26** is achieved. A similar synthetic sequence has been carried out to reach a related target molecule.[41]

Brandi et al. have studied the 1,3-DC reactions of chiral α,β-dialkoxynitrones with vinylphosphine oxides (eq 10).[42] The reaction of optically active **27** with vinylphosphine oxide **28a** gives a 65:14 mixture of the endo:exo isomers, along with 21% of the other regioisomer. The endo isomer is formed with a high diastereofacial selectivity of 94% de. By the application of the optically active vinylphosphine oxide **28b**, the 1,3-DC reaction with **27** proceeds to form **29b** with a high degree of endo selectivity and without



27 **28a**: R = Ph
28b: R = Me



(10)

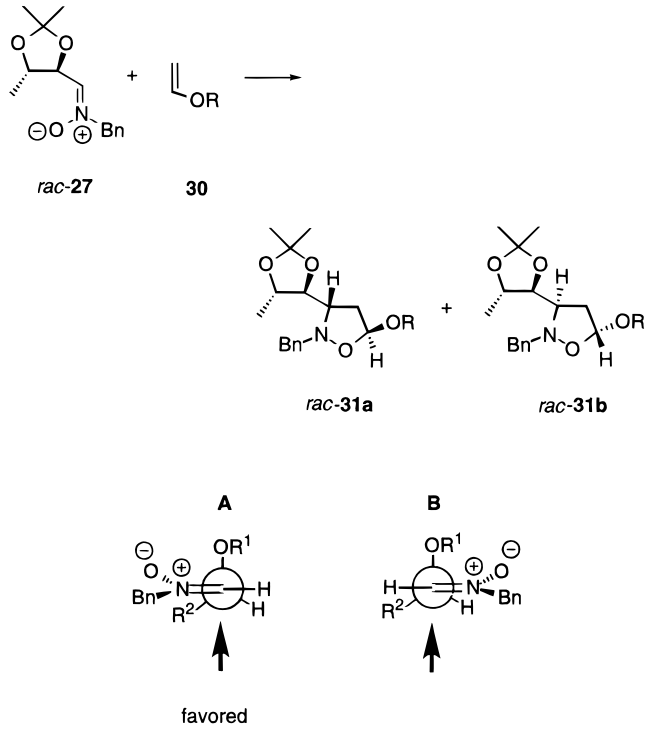
29a: R = Ph
endo:exo:regioisomers = 65:14:21
de *endo* = 94%

29b: R = Me
endo:exo = 95:5
de *endo* = 96%

the appearance of the other regioisomer. The reaction also displays an excellent diastereofacial selectivity, since the product is obtained with 96% de.

A racemate of nitrone **27** has been used in a 1,3-DC reaction with vinyl ethers or esters **30** by DeShong et al.[43] The reaction proceeds with high endo selectivity and diastereofacial selectivity to give *rac*-**31a** in up to 100% de (Scheme 6). The product of

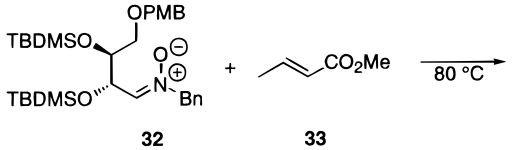
Scheme 6

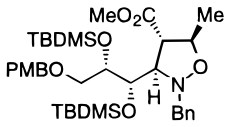


the reaction has been utilized in the synthesis of the amino sugar (±)-daunosamine. The preferred formation of *rac*-**31a** in the 1,3-DC of *rac*-**27** with **30**, has been explained by assuming that conformation **A** (Scheme 6) is the reactive conformation of the reaction. According to Felkin−Anh **A** is expected to be the more reactive conformer because as the alkene approaches the sp^2-hybridized carbon atom it avoids interaction with the bulky R^2 substituent.[43]

Nitrones similar to **27** have also been applied to give >90% of one isoxazolidine isomer in the 1,3-DC reaction with methyl crotonate.[44]

Saito et al. have developed a tartaric acid derived chiral nitrone **32**.[45a] In a reaction of **32** with methyl

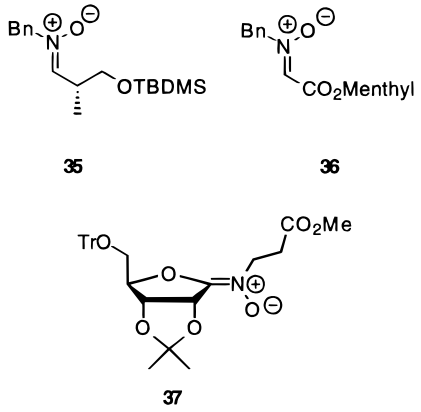




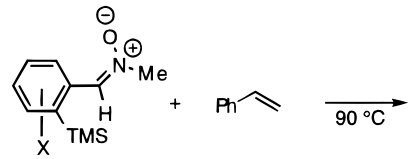
endo-**34**
endo:exo = 10:1
de_{endo} >95% (11)

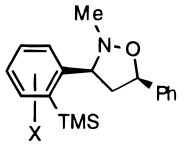
crotonate **33**, the 1,3-DC product **34** is obtained in an endo:exo ratio of 10:1 and with a high diastereofacial induction of the endo isomer (eq 11).

Other nitrones **35**−**37** in which the chiral moiety is located at the carbon atom have been applied in reactions with acryloyl or crotonoyl esters.[46−48] Nitrones **35** and **36** offer poor discrimination in the 1,3-DC reactions with benzyl crotonate as all four diastereomers are obtained in both reactions.[47,48] The ribose-derived nitrone **37** is obtained in situ from the corresponding oxime by Michael addition to methyl acrylate.[46] This nitrone reacts with another equivalent of methyl acrylate in a 1,3-DC reaction to give, in the best case, a 44:21:0:0 ratio of the four possible diastereomers.



Mukai et al. have applied a chiral tricarbonyl(η^6-arene)chromium(0)-derived nitrone **39** in the 1,3-DC reaction with various alkenes, such as styrene **10** (eq 12).[49,50] The analogous nonmetallic nitrone **38** is used





exo-**40**: X absent
endo:exo = 82:18

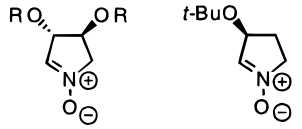
exo-**41**: X = $Cr(CO)_3$
endo:exo = <2:>98
de_{exo} = 96-98% (12)

in a reference reaction with **10**, giving isoxazolidine **40**, with an endo:exo ratio of 82:18. By the application of nitrone **39** in the 1,3-DC reaction with **10** the endo:exo selectivity changed significantly to give *exo*-**41** as the only observable product. The tricarbonylchromium moiety effectively shields one face of the nitrone, leading to high diastereofacial selectivity of

the reaction. The product *exo*-**41** is obtained with 96−98% de.

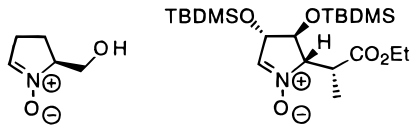
The chiral moiety in a nitrone can be attached to both the carbon and nitrogen atoms at the same time in cyclic nitrones. The cyclic structure offers a more rigid conformation than acyclic compounds, leading to a more efficient shielding of one of the nitrone faces, when the chirality is located in the ring. Furthermore, in this approach the possible *E*/*Z* interconversion of the nitrone is avoided.

The first application of an optically active cyclic nitrone in 1,3-DC reactions was reported by Vasella et al. in 1985[51] and during the last 5 years a number of successful reactions of optically active cyclic nitrones have been published.[52−66] Brandi et al. have studied the application of the L-tartaric acid derived nitrones **42a**−**d**.[55−57,63,65,66] Nitrone **42e** shows a high degree of chiral discrimination in the 1,3-DC reaction with methylenecyclopropane at rt, leading to one regioisomer in a yield of 75% with a de of 82%.[56] This approach has successfully been applied in the synthesis of optically active hydroxylated indolizidines.[55,56,61,63] Nitrone **42a** which was developed by Petrini and co-workers[65] has also been applied by others in a highly diastereoselective 1,3-DC reaction with a silyl-protected allylic alcohol.[61] Two similar nitrones **43** and **44**, synthesized from L-malic acid and L-prolinol, respectively, have been subjected to 1,3-DC reactions with various alkenes, such as methylenecyclopropane, showing moderate to excellent diastereofacial selectivities.[62,64,66] Saito et al. applied nitrone **45** in reactions with fumaric and maleic acid derivatives at 70 °C in benzene and all reactions proceeded with complete regio- and diastereoselectivity.[52]



42a: R = CH_2OMe
42b: R = Me
42c: R = *t*-Bu
42d: R = CH_2Ph
42e: R = $SiPh_2$*t*-Bu

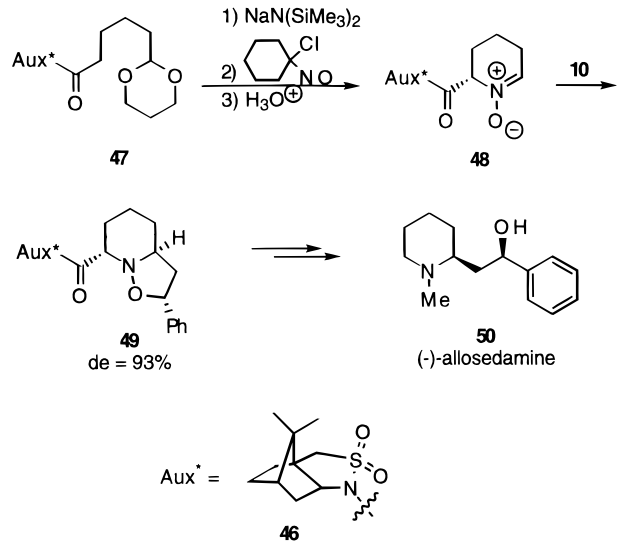
43



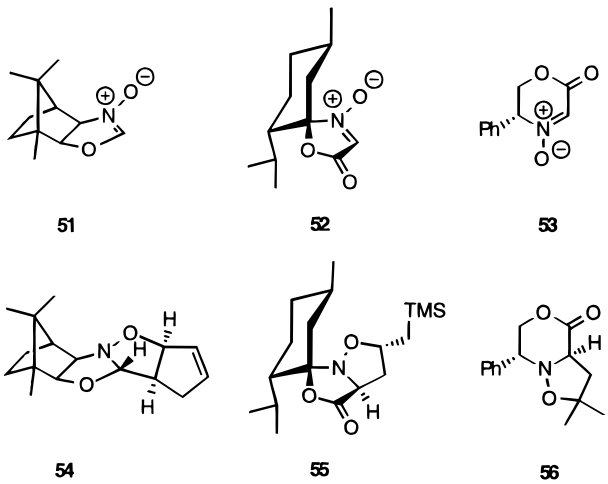
44 **45**

In 1994, Oppolzer et al. applied a chiral cyclic nitrone in the synthesis of (−)-allosedamine Scheme 7.[60] They used the well-known chiral sultam **46** as the chiral auxiliary.[67,68] The enantiomerically pure nitrone **48** is synthesized in an ingenious manner from **47**. The enolate of **47**, generated upon base treatment, attacks 1-chloro-1-nitrosocyclohexane at the nitrogen atom and subsequent elimination of chloride yields a nitrone. Addition of aqueous HCl hydrolyzes the acetal as well as the intermediate acyclic nitrone to give the cyclic nitrone **48** by condensation between the aldehyde and the hydroxylamine moiety generated this way. The nitrone takes part in a 1,3-DC reaction with styrene **10** and the reaction proceeds with absolute exo specificity. The product **49** is obtained with a de of 93%. Two further reaction steps yield the piperidine alkaloid (−)-allosedamine **50** in an overall yield of 21%.

Scheme 7



Finally, three other types of chiral cyclic nitrones **51**−**53** have been described. They are all characterized by having an oxygen atom in the ring and by providing excellent selectivities in 1,3-DC reactions with alkenes. Langlois et al. applied nitrone **51** in the synthesis of (−)-carbovir, a potential agent in treating AIDS.[58,59,69] The 1,3-DC reaction between cyclopentadiene and **51** proceeds at 40 °C with high regio- and diastereoselectivity and **54** is the only product isolated. In the proceeding synthetic steps toward (−)-carbovir the camphor skeleton is recovered. From L-menthone and an in situ generated nitrosoketene, nitrone **52**, was obtained by Katagiri et al.[54,70] In a reaction with allyltrimethylsilane at 40 °C and at a pressure of 800 MPa, isoxazolidine **55** was obtained as the sole product isomer in 90% yield. After hydrolysis and hydrogenolysis, enantiomerically pure α-amino acids were synthesized and L-menthone was recovered. Tamura et al. prepared nitrone **53** which was subjected to react with various



51 **52** **53**

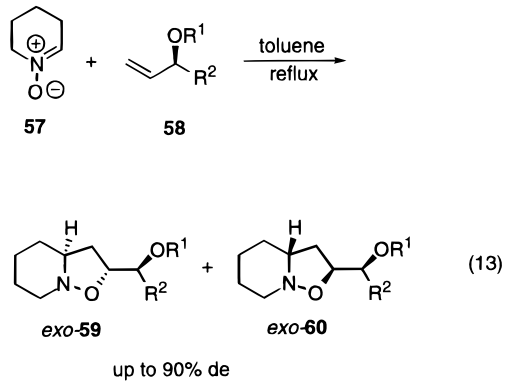
54 **55** **56**

alkenes.[53] In the reaction between **53** and 2-methylpropene, isoxazolidine **56** is formed in 87% yield as a single isomer.

3.2. Chiral Alkenes

For 1,3-DC reactions, as well as for other reactions, it is important that the chiral center intended to control the stereoselectivity of the reaction is localized as close as possible to the functional group of the molecule at which the reaction takes place. Hence, alkenes bearing the chiral center vicinal to the double bond are most frequently applied in asymmetric 1,3-DC reactions with nitrones. The alkenes employed can be divided into three main groups: (i) chiral allylic alcohols, (ii) chiral allylic amines, mostly β,γ-unsaturated amino acid derivatives, and (iii) chiral vinyl sulfoxides or vinylphosphine oxides. Examples of the application of chiral auxiliaries with the chiral center localized two or more bonds apart from the alkene, will also be mentioned.

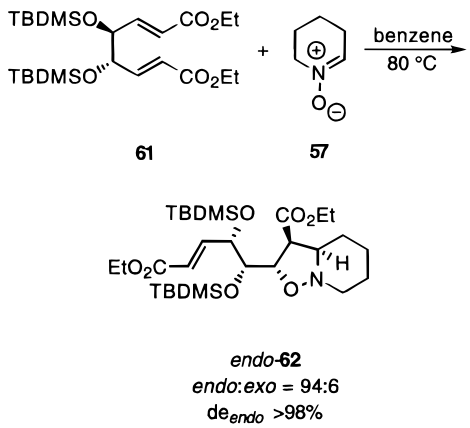
Kibayashi et al. have used enantiomerically pure allylic ethers/alcohols obtained from natural sources in 1,3-DC reactions with nitrones.[71−75] They have applied this approach in the synthesis of optically active alkaloids containing a piperidine ring such as (+)-monomorine I,[71,74] (+)-coniine,[72] and (−)-oncinotine.[75] Nitrone **57** reacts with allyl ether **58** to give selectively the exo products **59** and **60**, and only minor amounts of the endo isomers (eq 13).[72] The



(13)

best diastereofacial selectivities are obtained when the substituents R^1 is either benzyl or $SiPh_2t$-Bu, and when R^2 is *i*-Pr or *t*-Bu. The mechanism for the addition of the nitrone to the chiral alkene was briefly discussed.[71,72,74] From these substrates, the products *exo*-**59** and *exo*-**60** are obtained with a preference for *exo*-**59** in up to 90% de. Related investigations have been performed by others.[76,77]

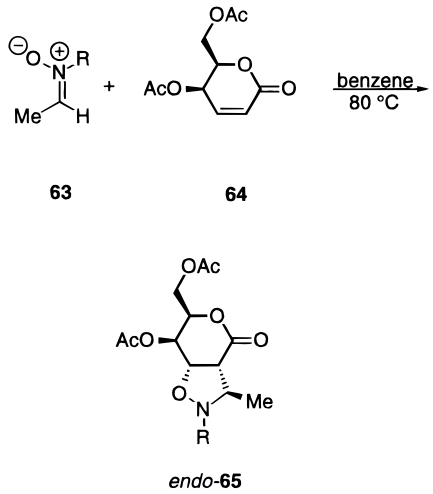
Saito et al. have developed a variety of tartaric acid derivatives, including C_2-symmetrical chiral alkenes such as **61**.[45] The 1,3-DC reaction between **61** and **57** gives primarily *endo*-**62** (eq 14). The diastereofacial selectivity of the reaction is excellent, as *endo*-**62** is obtained with a de >98%. Other cyclic and acyclic nitrones have been employed in reactions with **61**, and in all cases, moderate to excellent endo:exo selectivities and excellent diastereofacial selectivities are obtained.[45] Three other research groups have been applying various γ-hydroxylated α,β-unsaturated carbonyl compounds in related reactions with



(14)

nitrones;[78−80] however, the selectivities were somewhat lower than those obtained by Saito et al.[45]

Chiral allylic alcohols may also be cyclic, such as the sugar lactones used by Chmielewski et al.[81−83] *C*-Methylnitrones **63** approach **64** in an endo-selective manner to the face of the alkene anti to the substituents of the lactone ring. In this reaction *endo*-**65** is obtained as the sole product (eq 15).



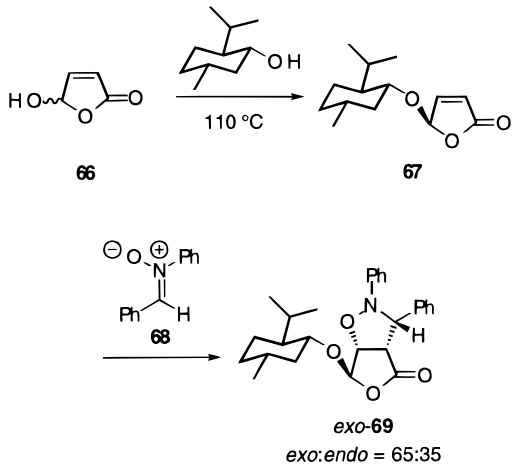
(15)

Feringa et al. have used a similar principle by employing chiral furanones (butenolides). In this case, however, the asymmetry is obtained from a chiral auxiliary. The chiral 4-substituted butenolide **67** is prepared from **66** and menthol (Scheme 8).[84,85] The single diastereomer **67** is obtained by crystallization and epimerization of the other diastereomer, as the amount of **67** in solution decreases. In the 1,3-DC reaction of **67** with *C,N*-diphenylnitrone **68**, one face of the alkene is selectively shielded by the menthol moiety, leading exclusively to the anti adduct **69** as a 65:35 mixture of the exo and endo isomers, respectively. The alkene **67** has been used in several highly diastereoselective 1,3-DC reactions with other types of 1,3-dipoles (vide infra).

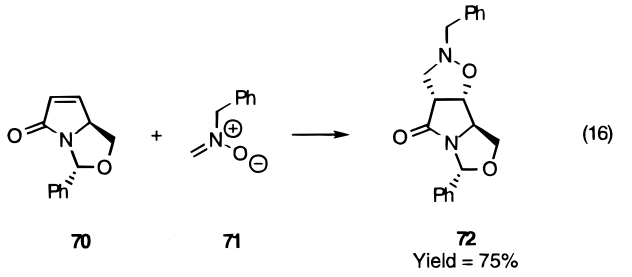
Reed and Hegedus have applied optically pure 4,4-disubsituted butenolides in a 1,3-DC reaction with 1-pyrroline 1-oxide in a highly selective reaction giving the exo isomer with >97% de.[86]

Similarly, other derivatives of chiral cyclic α,β-unsaturated carbonyl compounds have been subjected to 1,3-DC reactions with nitrones.[30,87−90] Langlois et al. have applied α,β-unsaturated γ-lactams

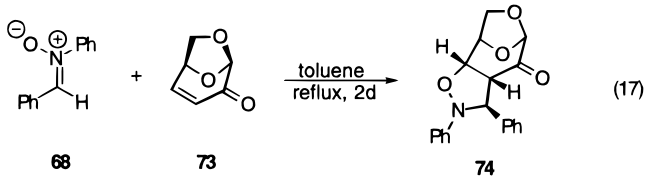
Scheme 8



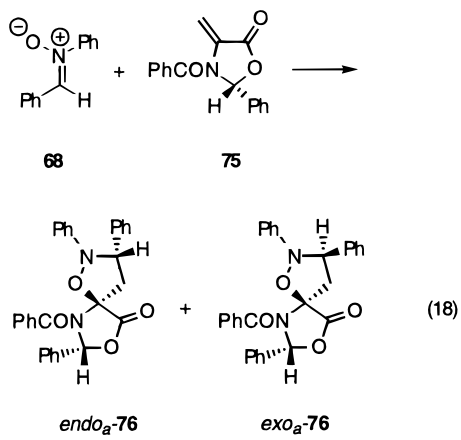
derived from (*S*)-pyroglutaminol, such as **70**, in the 1,3-DC with *N*-benzylnitrone **71** (eq 16).[87] One of the 1,3-DC product isomers, compound **72** was isolated in 75% yield, whereas only 5% and 3% of two other isomers were obtained.



Paton et al. have applied the bicyclic lactone levoglucosenone **73** in the reaction with various different 1,3-dipoles.[88,89] In the reaction with *C,N*-diphenylnitrone **68** the reaction proceeds to give **74** as the only observable product (eq 17).

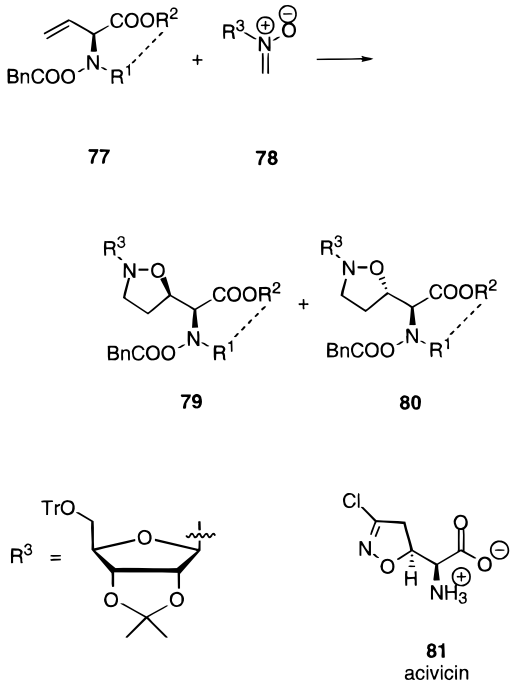


In two recent papers the use of exo-cyclic alkenes have been applied in reactions with *C,N*-diphenylnitrone **68**.[91,92] The 1,3-DC of **68** with the chiral oxazolidinone **75**, proceeded to give *endo*$_a$-**76** and *exo*$_a$-**76** in a ratio of 70:30 (eq 18). Both product isomers arise from attack of the nitrone **68** to the face of the alkene **75** anti to the phenyl substituent.



Four research groups have applied 1,3-DC reactions between nitrones and amino acid derived allylic amines **77** for natural product synthesis. The formaldehyde-derived nitrones **78** are used in 1,3-DC reactions to give the isoxazolidines **79** and **80** (Scheme 9).[93−97] However, only by the contemporary use of a chiral nitrone were satisfying selectivities obtained. Whitney et al. applied a ribose derivative as the chiral substituent and in the reaction with **77** the products **79** and **80** could be obtained in a ratio of 1:19.[94−96] The major product **80** obtained in this reaction has been applied in the total synthesis of acivicin **81**, a naturally occurring antitumor antibiotic.[95,96] Naito et al. have applied a similar amino acid derived alkene in the synthesis of tetrahydropseudodistomin.[98]

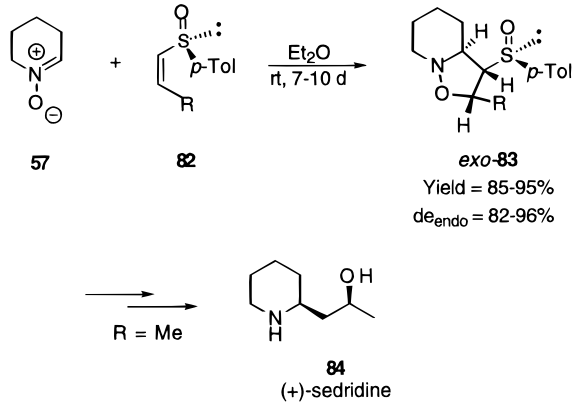
Scheme 9



Another type of chiral alkenes applied in 1,3-DC reactions with nitrones are vinyl groups attached to chiral heteroatoms such as phosphine oxides and sulfine oxides. Brandi et al. have used chiral vinylphosphine oxide derivatives as alkenes in 1,3-DC reactions with chiral nitrones.[99,100] This group also studied reactions of achiral nitrones with chiral vinylphosphine oxide derivatives. By using this type of substrates high endo/exo selectivities were obtained and in reactions involving optically pure vinylphosphine oxides diastereofacial selectivities of up to 42% de were obtained.[99,100] Chiral vinyl sulfoxides have also been applied in 1,3-DC reactions.[101−105] These substrates were first used successfully in the 1,3-DC reaction by Koizumi et al. in 1982.[103,104] In the 1,3-DC reaction of an (*R*)-*p*-tolyl

vinyl sulfoxide and *C,N*-diphenylnitrone high selectivities were obtained. Louis and Hootelé have studied the 1,3-DC reactions of vinyl sulfoxides **82** in the 1,3-DC reaction with the cyclic nitrone **57** (Scheme 10).[101,105] The reactions proceed with abso-

Scheme 10



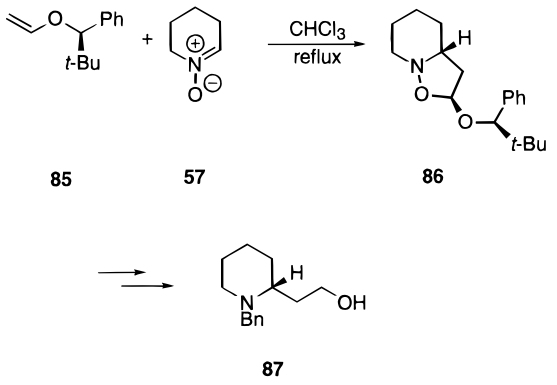
57 **82** ***exo*-83** Yield = 85-95% de_{endo} = 82-96%

84 (+)-sedridine

lute exo selectivity, and, especially when the substituent at the (*Z*)-alkene is phenyl a high de of 96% is obtained. In the case where R = Me (de = 82%) the product **83** has been applied in the synthesis of the natural product (+)-sedridine **84**.

Finally, some examples of 1,3-DC reactions of nitrones with chiral alkenes, in which a chiral auxiliary directs the stereochemical outcome of the reaction, will be presented.[106] The first example implies chiral vinyl ethers. The selectivities obtained for most derivatives are low. However, using alkene **85** and the cyclic nitrone **57**, the reaction proceeds with high selectivity (Scheme 11). The endo:exo

Scheme 11

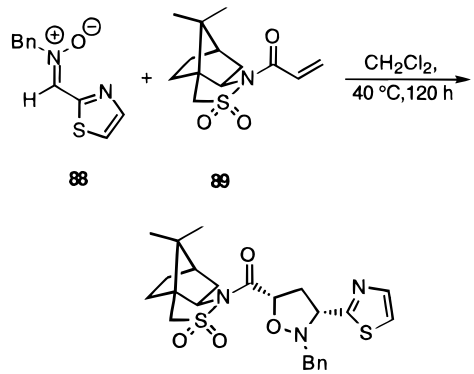


85 **57** **86**

87

selectivity is not given in this communication by Carruthers et al.,[107] but this is of minor importance for the final outcome of this work, since one of the chiral centers was destroyed in the conversion of **86** into the final product **87**. The chiral auxiliary can by recovered in this reaction sequence and **87** was obtained with an optical purity of >95% ee.

Several attempts to control the regio- and stereoselectivity of reactions of nitrones with acrylates and other α,β-unsaturated carbonyl compounds have been made by using chiral auxiliaries.[67,108−113] Acrylates of Oppolzer's chiral sultam **89**[68] have successfully been applied in asymmetric Diels−Alder reactions and to a smaller extent these derivatives have also been used in 1,3-DC reactions of nitrones.[108,110,113] Recently, Tejero et al. studied reactions of *C*-(2-thiazolyl)nitrone **88** with various chiral acrylates.[113] In contrast to reactions of simple acryl esters, the reaction of **88** with **89** proceeded with complete regioselectivity to give the 3,5-disubstituted isoxazolidine **90** (eq 19) The product was obtained with complete endo selectivity and with a diastereofacial selectivity of 56% de. In a related reaction using a sterically crowded nitrone high selectivity has been obtained.[108]

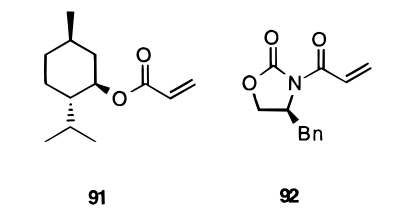


88 **89**

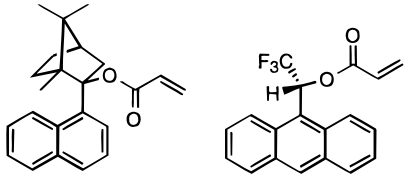
90 (19)

endo:exo = 100:0
de = 56%

Tejero et al. also studied the use of other auxiliaries such as **91** and **92** in the 1,3-DC reaction. However, application of **91** led to a very low selectivity. In the reaction between **88** and **92** no conversion was obtained even in refluxing toluene.[113] On the other hand, Murahashi et al. were able to obtain conversion in the reaction of **92** with 1-pyrroline 1-oxide.[110] Relatively poor selectivities were observed for this reaction, but by the addition of ZnI_2 selectivities were dramatically improved (vide infra). Using the same type of cyclic nitrones Olsson et al. observed a low endo/exo selectivity, but excellent diastereofacial discrimination in the reaction with the camphor-derived chiral acrylate **93**.[111] Finally, it should be mentioned that application of the optically active 9-anthrylcarbinol derivative **94** in a reaction with 1-pyrroline 1-oxide gave rise to a complex mixture of regioisomers and diastereomers.[109]



91 **92**

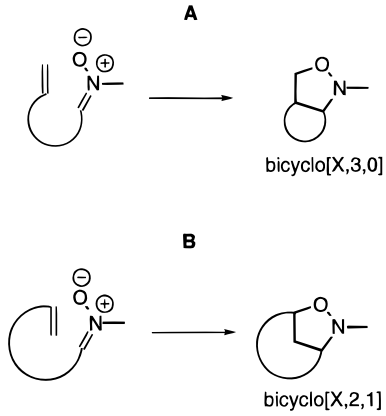


93 **94**

3.3. Intramolecular Reactions

Since the pioneering work by LeBel[114,115] intramolecular 1,3-DC reactions of alkenylnitrones have found broad application in organic synthesis.[22,116] Intramolecular 1,3-DC reactions have several advantages over the corresponding intermolecular reactions. Due to entropy factors the activation barrier for the reaction is lower, allowing for lower reaction temperatures and for the use of dipoles and dipolarophiles of lower reactivity. The degree of spatial freedom in the transition state of an intramolecular reaction is, of course, limited compared with the intermolecular reactions. Hence, a higher degree of regioselectivity, endo/exo selectivity, and diastereofacial selectivity is normally observed in intramolecular 1,3-DC reactions. The intramolecular reactions of nitrones bound to alkenes can be divided into two types. The alkene part may be linked to the carbon atom or to the nitrogen atom of the nitrone. The majority of the reported intramolecular 1,3-DC reactions are those in which the alkene part is linked to the carbon atom of the nitrone. This type of reaction gives rise to two regioisomers, in which the isoxazolidine product formed is either a bicyclo[*x*,3,0] or a bicyclo[*x*,2,1] compound **A** and **B** (Scheme 12). The most frequently observed product is the bicyclo-[*x*,3,0] compound. As for intermolecular 1,3-DC reactions, the endo and exo isomers of each of the regioisomers can be formed in intramolecular reactions. In most cases the exo isomer is favored for sterical reasons.

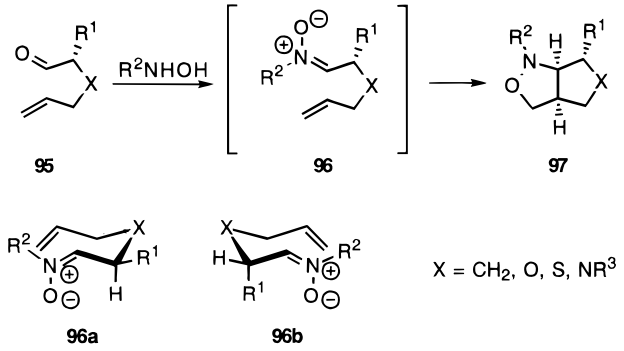
Scheme 12



This chapter is organized on the basis of the structure of the nitrones and the nature of the reactions. Reactions in which the alkene is connected to the nitrone carbon atom will be presented. These reactions are further divided in reactions (i) in which the chirality is located in the resulting bicyclic isoxazolidine, (ii) similar reactions of oximes, (iii) reactions involving sugar derivatives as starting material, (iv) reactions in which the chirality is located outside the resulting bicyclic isoxazolidine, (v) reactions of cyclic alkenes leading to tricyclic products, and (vi) reactions in which the chiral group is located at the nitrone nitrogen atom. Finally, (vii) reactions in which the alkene is connected to the nitrone nitrogen atom will be described.

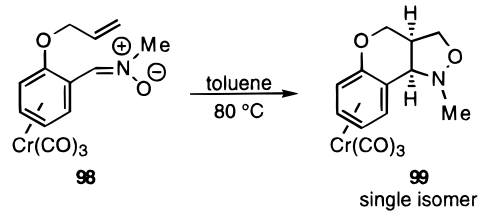
Several groups have reported intramolecular reactions of 5-alkenylnitrones in which the chiral center

Scheme 13



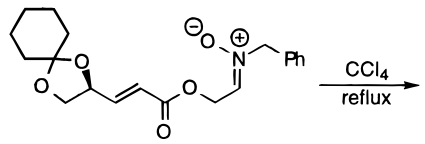
is located on a carbon atom in the alkene−nitrone link, leading to 3-oxa-2-azabicyclo[3.3.0]octanes and heteroanalogues.[115,117−125] Aurich et al. have made extensive studies on reactions involving alkenylnitrones **96**, formed in situ from 5-alkenylaldehydes **95**.[117,119,121,122,124] The substituent located vicinal to the nitrone carbon atom, directing the facial selectivity of the reaction is most frequently alkyl, benzyl, or phenyl, but occasionally other oxygen or nitrogen substituents have been applied.[118,123] The reaction of **95** proceeds in CH_2Cl_2 or Et_2O at 0 °C to rt to give, most frequently, only one (**97**) out of four possible diastereomers (Scheme 13). As previously mentioned the exo diastereomer is generally favored in intramolecular reactions of this type, and the excellent diastereofacial selectivity is proposed to be due to the sterically favored equatorial position of the R^1 substituent in intermediate **96a** compared to **96b**.[119,121,124]

In a similar manner optically active 6-alkenylnitrones and heteroanalogues have been applied in the synthesis of bicyclo[4.3.0] derivatives.[90,114,126,127] Fukumoto et al. used this type of reaction in the synthesis of a 1β-methylcarbapenem antibiotic.[90,127] Baldoli et al. utilized the optical active tricarbonylchromium(0)-derived 6-alkenylnitrone **98** (eq 20).[128] The $Cr(CO)_3$ moiety offers an effective asymmetrical induction and the [4,3,0] bicyclic isoxazolidine **99** is formed as the single stereoisomer. The formation of optically pure [3.2.0]-bicycles from 4-alkenylnitrone has also been reported.[126]

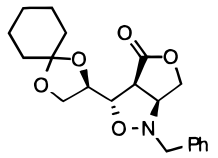


(20)

The chiral center which controls the diastereofacial selectivity of the reaction may also be located outside the resulting bicyclic isoxazolidine (eq 21).[129,130] The double bond of **100** is generated in situ and undergoes a 1,3-DC reaction with the nitrone moiety of the molecule in refluxing CCl_4 to form **101** (eq 21). In the present reaction the exo-cyclic chiral center directs the selectivity completely, since only one product isomer arises. However, application of other derivatives of starting materials in some cases led to poor diastereofacial selectivities.



100

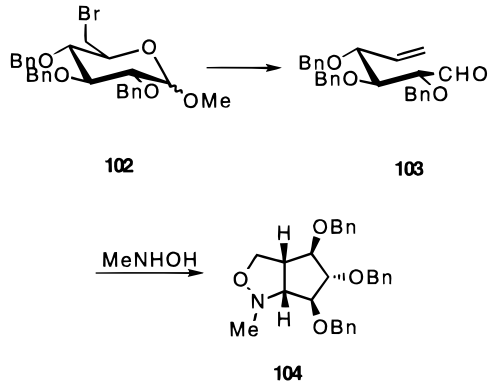


101
55%
single isomer

(21)

In addition to the above-described reactions a number of alkenylnitrones derived from sugar derivatives have been applied in intramolecular 1,3-DC reactions.[131−146] The reactions leading to bicyclo-[3.3.0] compounds will be described first. Bernet and Vasella were the first to perform extensive studies in this field.[138−140] Glucose derivative **102** was converted into the 5-alkenyl aldehyde **103** and upon treatment with methylhydroxylamine, the resulting nitrone underwent intramolecular 1,3-DC reaction to give **104** as the only diastereomer in good yields (Scheme 14).[140] Mannose and galactose were sub-

Scheme 14



102 103

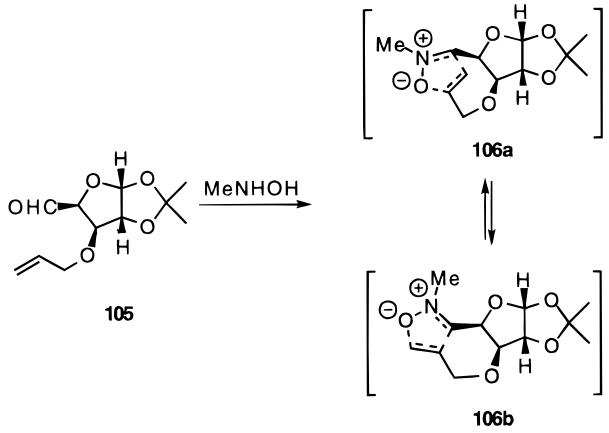
104

jected to the same procedure, giving rise to the formation of compounds similar to **104** with a high degree of selectivity.[138,139] This approach has been applied in the synthesis of a prostaglandin precursor,[144] an α-mannosidase inhibitor[147] and other optically active hydroxylated cyclopentanes.[141,143] Furthermore, a modified method has been applied for the synthesis of isoxazolidine nucleosides.[148,149]

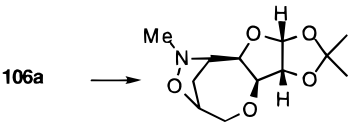
In a similar way sugar-derived 6-alkenylnitrones have been applied in intramolecular 1,3-DC reactions to form [4,3,0]-bicyclic products. Wightman et al. utilized this approach in the synthesis of (−)-shikimic acid,[145] and Farr et al. applied a less selective reaction for the preparation of amino inositol derivatives.[146]

Carbohydrate-derived alkenylnitrones have been used in an alternative manner for the synthesis of oxepanes.[133−135,137,142,150] Shing et al. found that upon treatment of the glucose-derived aldehyde **105** with

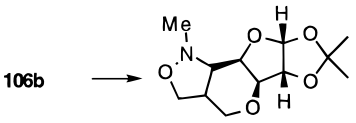
Scheme 15



105 106a 106b



107a
64%



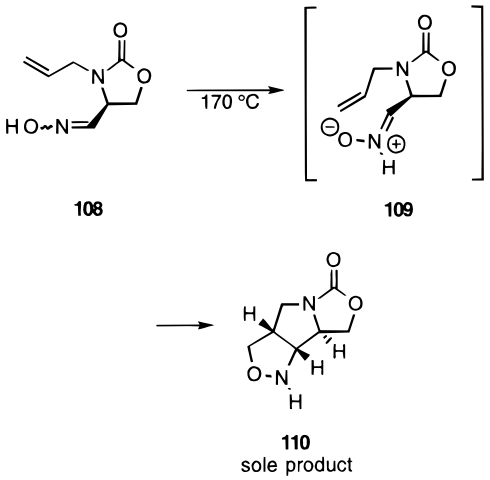
107b
6%

methylhydroxylamine, the resulting nitrone reacted to give a mixture of the oxepane **107a** and tetrahydropyrane **107b**, as pure diastereomers (Scheme 15).[132,142] In this case the transition state **106a**, in which the alkene termini is attached to the nitrone carbon atom is preferred over transition state **106b** and the desired oxepane **107a** is obtained as the major product. However, the regioselectivity is strongly controlled by the configuration of the C-3 of the furanose ring. Earlier studies by Bhattacharjya et al. have also shown that the introduction of a methyl substituent at the C-3 position of the furanose ring dramatically alters the regioselectivity.[133,134,137]

An alternative and elegant approach to [3.3.0]-bicyclic isoxazolidines from alkenyloximes was developed by Grigg et al.[151] and applied in asymmetric reactions by Hassner et al.[152−155] and recently also by others.[156] The optically active L-serine derived oxime **108** is proposed to be in a thermal tautomeric equilibrium with the nitrone tautomer **109**, which undergoes an intramolecular 1,3-DC reaction to form the product **110** in 80% yield as the sole stereoisomer (Scheme 16).[155]

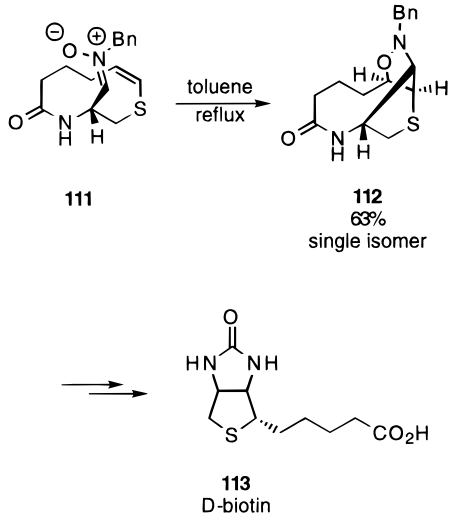
If the alkene moiety of the alkenylnitrone is incorporated into a cyclic compound, complex tricyclic compounds are formed in the intramolecular 1,3-DC reaction. Baggiolini et al. applied this approach in an ingenious synthesis of D-biotin **113**.[157] The cysteine-derived alkenylnitrone **111**, which as an exception is stable at rt, was able to form the isoxazolidine **112** in a satisfying yield as the single diastereomer

Scheme 16



(Scheme 17). Further synthetic steps led to the desired optically pure target molecule **113**. Other research groups have applied cyclic alkenes in intramolecular nitrone 1,3-DC reactions, especially in the formation of 2-oxa-3-azatricyclo[5.3.1.$0^{4,11}$] compounds.[158−163]

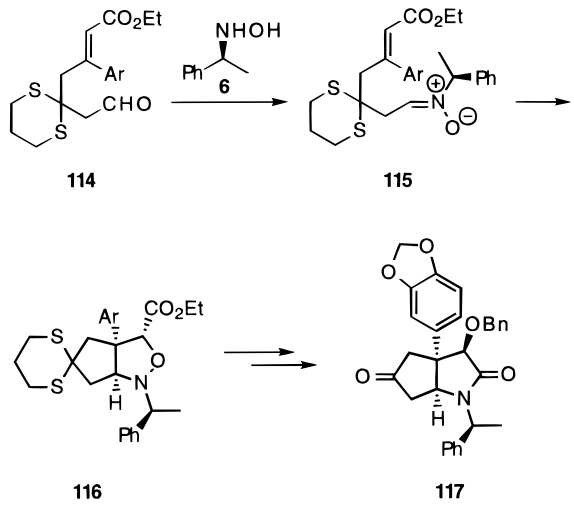
Scheme 17



The chiral center controlling the diastereofacial selectivity of the reaction may also be located at the nitrogen atom of the nitrone.[136,164−166] Baldwin et al. employed the previously described 1-phenylethylhydroxylamine **6** as the chiral group. Alkenylnitrone **115**, generated in situ from the achiral aldehyde **114**, undergoes an intramolecular 1,3-DC reaction to give **116** with a de of 94% (Scheme 18).[164] Further reactions were performed to give **117**, which was used as a model compound for a planned asymmetric synthesis of the alkaloid pretazettine. L-Acosamine and L-daunosamine have also been synthesized using **6** as the chiral fragment.[165,166]

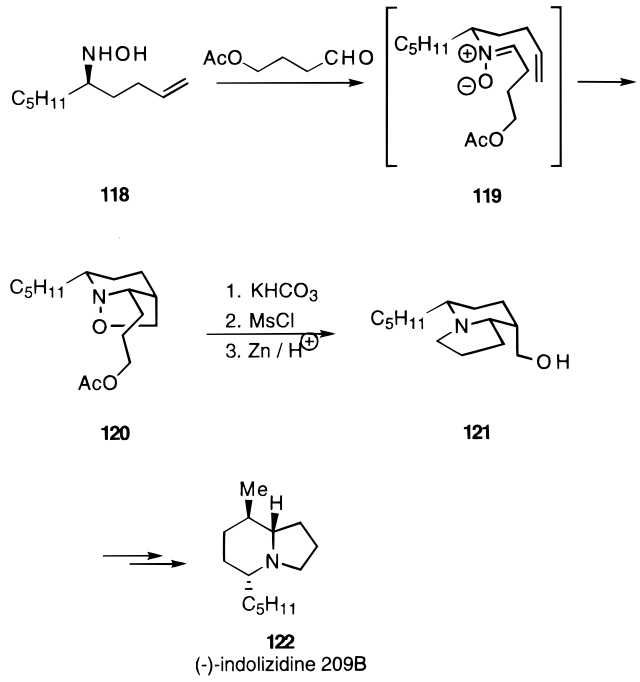
In all the above-described intramolecular 1,3-DC reactions the alkene moieties have been linked to the nitrone via the nitrone carbon atom. However, in a limited number of contributions the utilization of optically active alkenylnitrones, in which the alkene is connected to the nitrone nitrogen atom, is reported.[167−172] Holmes et al. have used this ap-

Scheme 18



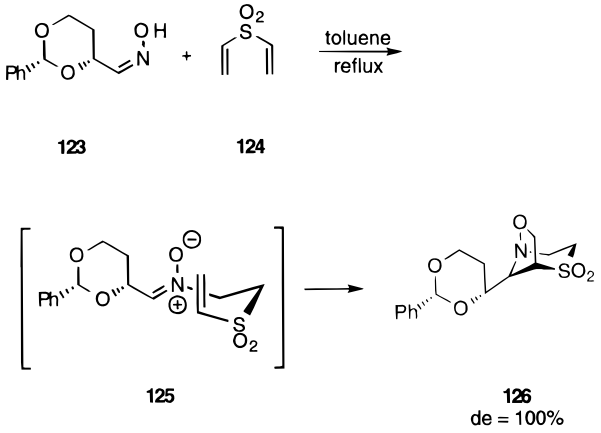
proach in the synthesis of the alkaloid (−)-indolizidine 209B **122**.[156,167] The alkenylnitrone **119**, is obtained from the chiral hydroxylamine **118**, and an aldehyde. In the intramolecular 1,3-DC reaction **120** is formed as the only product isomer (Scheme 19). The diastereofacial selectivity is controlled by the favored conformation of the cyclohexane-like transition state in which the pentyl group is in a pseudoequatorial position, as indicated in **119**. Further transformation of **121** leads to the desired product **122**.

Scheme 19



A new approach to optically active *N*-linked alkenylnitrones was developed by Frederickson et al.[171,172] The intermediate nitrone **125** was formed by attack of the nitrogen atom of oxime **123** to divinyl sulfone **124** (Scheme 20). The 1,3-DC reaction is proposed to proceed via **125** to yield the bicyclic isoxazolidine **126** as the sole diastereomer. Oximes derived from D-galactose and D-ribose have been applied in analo-

Scheme 20

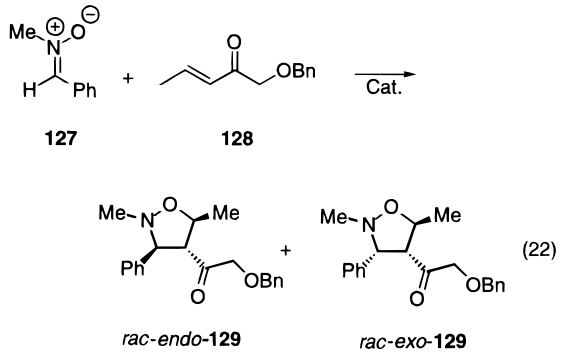


gous reactions also proceeding with high diastereoselectivity.

3.4. Metal-Catalyzed Reactions

Contrary to the broad application of catalysts in asymmetric carbo- and hetero-Diels−Alder reactions,[173] the use of metal catalysts in asymmetric 1,3-DC reaction between alkenes and nitrones remained an unexplored area until recently.

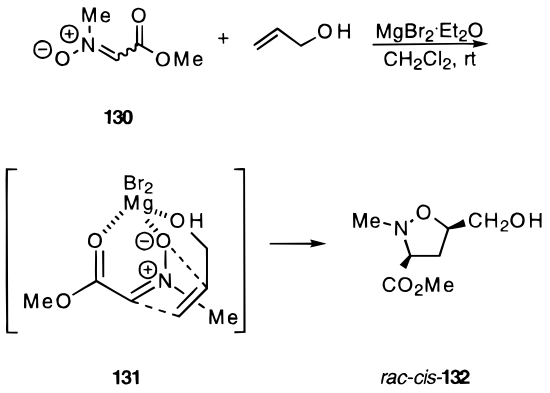
Kanemasa et al. did important pioneering work in this field, although the reactions performed were racemic. The first contribution was published in 1992 and describes the impact of ZnI_2, $TiCl(Oi\text{-}Pr)_3$ and $TiCl_2(Oi\text{-}Pr)_2$ upon the 1,3-DC reaction between nitrone **127** and enone **128**[174] (eq 22). The reaction



proceeds at 80 °C in the absence of a metal complex to give **129** in an endo:exo ratio of 40:60. Upon addition of $ZnCl_2$, the reaction proceeds at rt, but a reaction time of 52 h is required to give a yield comparable to that of the uncatalyzed reaction. The addition of $ZnCl_2$ has a rather dramatic impact on the endo:exo ratio as the endo isomer is now formed predominantly. In the presence of 1 equiv of $Ti(Oi\text{-}Pr)_2Cl_2$ the reaction proceeds at 0 °C to give a yield of 50% after 32 h and in this reaction the *rac-endo*-**129** is formed as the only isomer. These early results indicate that a certain degree of rate acceleration can be obtained, at least by the addition of stoichiometric amounts of Lewis acids and that the additives have a high impact on the endo/exo selectivity of the reaction.

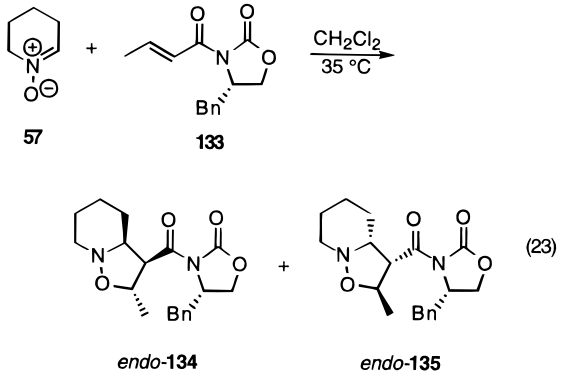
In extension of this work Kanemasa et al. studied reactions of allylic alcohols with nitrones in the

Scheme 21



presence of Mg(II) salts, $ZnBr_2$, $TiCl_2(Oi\text{-}Pr)_2$, or $BF_3{\cdot}Et_2O$.[175,176] The reaction of nitrone **130** with allyl alcohol at rt yields a cis:trans mixture of 44:56 of the product isoxazolidine **132**. The lack of selectivity is presumed to be caused by the *Z*/*E* isomerization of **130**. In the presence of 100 mol % $MgBr_2{\cdot}Et_2O$, the reaction of **130** with allyl alcohol proceeds at approximately the same rate, but with a high selectivity as *rac-cis*-**132** is obtained as the only product (Scheme 21). The selectivity of the reaction is explained by a favored chelation of the (*Z*)-nitrone and concomitant coordination of allyl alcohol to $MgBr_2$, as outlined in **131**.[176]

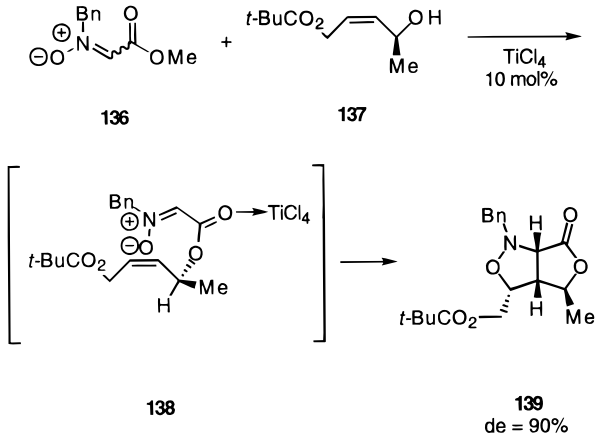
A related, but asymmetric work appeared in 1993 from Murahashi et al.[110] They used cyclic nitrones such as **57** and the chiral phenylalanine derived alkene **133** (eq 23). The 1,3-DC reaction proceeds at



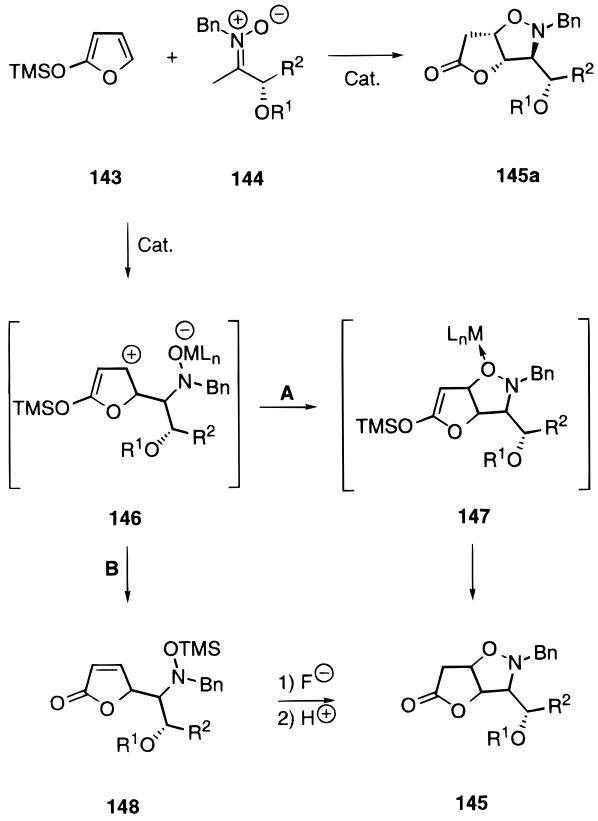
35 °C in the absence of a metal complex. The endo:exo ratio of the reaction is 82:18, and the diastereofacial selectivity of *endo*-**134** is 18% de. By the addition of 150 mol % of ZnI_2, the endo:exo ratio is improved to 89:11, and most remarkably the diastereofacial selectivity is improved to 92% de giving *endo*-**135** as the major isomer. However, the addition of ZnI_2 decreases the reaction rate as a reaction time of 48 h is needed to obtain a yield of 82%.

Tamura et al. have reported a metal-catalyzed tandem transesterification−intramolecular 1,3-DC reaction,[177,178] which only proceeds in the presence of $Ti(i\text{-}PrO)_4$ or $TiCl_4$. The reaction of the methyl glyoxylate derived nitrone **136** and an optically active (*Z*)-alkene, such as **137**, takes place at rt in the presence of 10% $TiCl_4$, presumably via intermediate **138**, to afford the product **139** quantitatively with a high de (Scheme 22). In the absence of titanium salts

Scheme 22



Scheme 24



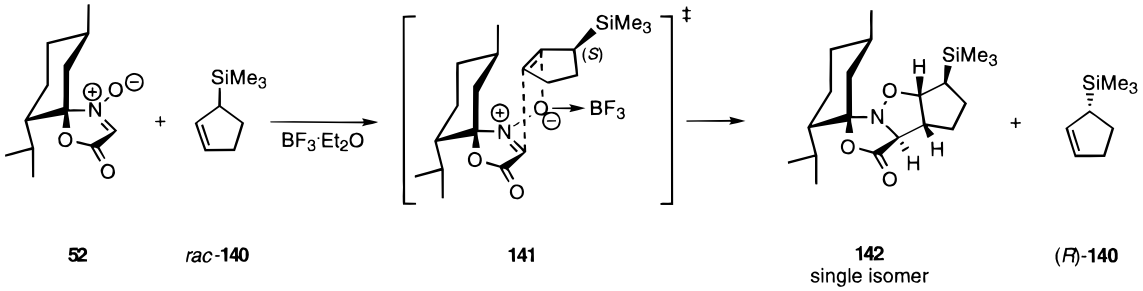
and at elevated temperatures, an intermolecular 1,3-DC reaction occurs, and it is therefore obvious that $TiCl_4$ catalyzes the transesterfication; however, the role of $TiCl_4$ in the cycloaddition step is less obvious.

In a recent work by Katagiri et al. the application of $BF_3{\cdot}Et_2O$ as catalyst for the reaction of nitrone **52** with allylsilane *rac*-**140** was described (Scheme 23).[54,70] The reaction between **52** and 2 equiv of the racemic alkene **140** proceeds only in the presence of 1 equiv og $BF_3{\cdot}Et_2O$ at rt; hence, there is no doubt about the catalytical effect of the Lewis acid. The product of the reaction, **142**, is formed in 69% yield as the sole stereoisomer and what is especially noteworthy is that only the *S* isomer of **140** reacts with **52**. The kinetic resolution of *rac*-**140** is proposed to be due to a transition state **141**, in which the sterical arrangement of $SiMe_3$ and BF_3 only allows for the *S* isomer of **140** to undergo 1,3-DC reaction with **52**.[70]

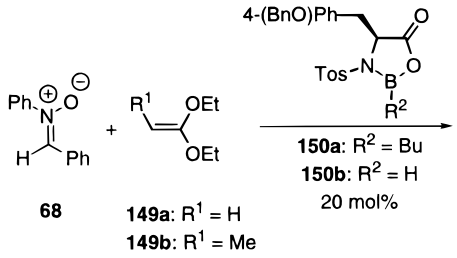
Trombini et al. have described the formal 1,3-DC reaction of 2-[(trimethylsilyl)oxy]furan **143** with chiral nitrones **144** catalyzed by various metal complexes (Scheme 24).[179−181] The reaction proceeds in the presence of stoichiometric amounts of an activator, such as (+)- or (−)-$(Ipc)_2BOTf$. In both cases **145a** is obtained as the major stereoisomer with a high endo selectivity and a diastereofacial selectivity of up to 96% de.[179] Since, the same diastereomer is obtained in similar selectivities from both (+)- and (−)-$(Ipc)_2BOTf$, the face selection is controlled by the chiral substrate **144**. The reaction is, however, assumed to proceed via a stepwise mechanism (Scheme 24). By the use of stoichiometric amounts of boron, aluminum, zinc, or titanium catalysts the reaction of **143** with **144**, gives the allyl cation **146**. This intermediate cyclizes (route **A**) to give **147** and after hydrolysis **145** is obtained. When the above catalysts are used in catalytic amounts or when TMSOTf is used as the catalyst, the reaction proceeds from **146** via route **B** to give the butenolide **148** as the product. The 1,3-DC product **145** was obtained after treatment with flouride. A catalytic cycle was proposed for this approach.[179] Especially, TMSOTf is an effective catalyst for the reaction when used in a catalytic amount; however, by this method a mixture of all for diatereromers of **145** was obtained.

In the above-described reactions the asymmetry was induced by chiral substituent in the starting material; however, in 1994 the first two, and quiet different, approaches to asymmetric 1,3-DC reactions of achiral alkenes with achiral nitrones catalyzed by chiral metal complexes appeared.[182,183] Scheeren et al. reported the first enantioselective metal-catalyzed 1,3-DC reaction of a nitrone with alkenes.[183] Their approach involves *C,N*-diphenylnitrone **68** and ketene acetals **149**. This reaction of an electron-rich alkene is controlled by the $LUMO_{nitrone}-HOMO_{alkene}$ interaction. They found that coordination of the nitrone to

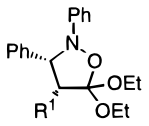
Scheme 23



a Lewis acid strongly accelerated the 1,3-DC reaction with ketene acetals. To obtain asymmetric induction the amino acid derived chiral oxazaborolidines which have successfully been applied in asymmetric Diels–Alder reactions[184,185] were tested as catalysts for the 1,3-DC reaction. The reactions of **68** with **149a**,**b**, catalyzed by 20 mol % of oxazaborolidinone such as **150a**,**b**, are outlined in eq 24. The reaction is carried out at −78 °C and gives the C-3, C-4 cis isomer **151b** as the only diastereomer of the product when R^1 = Me (**149b**). In some reactions good enantioselectivities are induced by the catalysts, thus, **151a** is obtained with an optical purity of 74% ee, and isoxazolidine **151b** with an ee of 62%.



68 **149a**: R^1 = H; **149b**: R^1 = Me



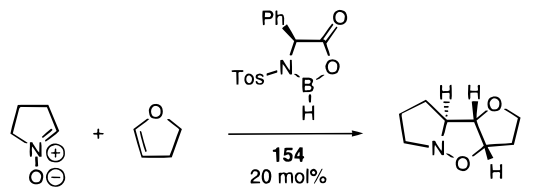
(24)

151a: R^1 = H, cat. = **150a**
Yield = 10%, ee = 74%

151b: R^1 = Me, cat. = **150b**
cis:trans = 100:0, ee = 62%

In an extension of this work Scheeren et al. studied various derivatives of *N*-tosyloxazaborolidinones as catalysts for the 1,3-DC reaction of **68** with **149b**.[186] The addition of a cosolvent appeared to be of major importance. Catalyst **150b** is synthesized from the corresponding amino acid and BH_3·THF; hence, THF is present as a cosolvent. In this reaction (−)-**151b** is obtained with 62% ee. If the catalyst is synthesized from the amino acid and BH_3·SMe_2, and diphenyl ether is added, a remarkable reversal of the enantioselectivity of the reaction occurs, since (+)-**151b** is now obtained as the major isomer. Furthermore the ee in this approach is improved to be 79%.

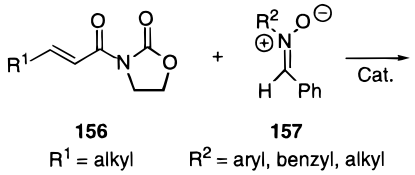
In a very recent work Scheeren et al. have applied cyclic and acyclic vinyl ethers in the oxazaborolidinone catalyzed 1,3-DC reaction with nitrones.[187] The reaction between nitrone **152** and 2,3-dihydrofuran **153** was catalyzed by 20 mol % **154** to give the product **155** in 56% yield as the sole diastereomer; however, the ee was 38% (eq 25).



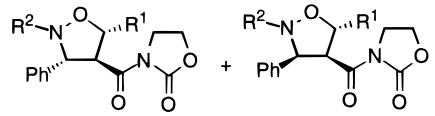
152 **153** **155**
endo:exo = 0:100
ee = 38%

(25)

Later in 1994 a different approach to a 1,3-DC reaction between alkenes and nitrones catalyzed by a chiral metal catalyst appeared.[182,188] The reaction between 3-*N*-alk-2-enoyloxazolidinones **156** and nitrone **157** need elevated temperatures to proceed in the absence of a catalyst (eq 26). However, in the



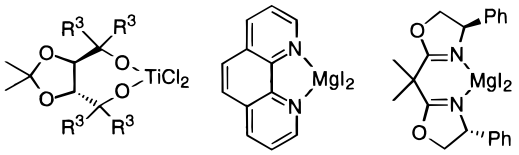
156 R^1 = alkyl **157** R^2 = aryl, benzyl, alkyl



endo-**158** *exo*-**158**

(26)

presence of 10 mol % of the TADDOLate−$TiCl_2$ catalyst **159a** the reaction proceeds at 0 °C to rt in toluene/petroleum ether. This type of catalysts has successfully been applied in a number of asymmetric reactions, especially the Diels–Alder reaction.[189−191] It is proposed that the rate acceleration is achieved via a bidentate coordination of **156** to the titanium catalyst. By this coordination the energy of the $LUMO_{alkene}$ is significantly decreased compared to the free alkene and this change of the $LUMO_{alkene}$ energy increases the rate of the reaction with the relatively electron-rich nitrone **157**. Hence, compared to the work described above by Scheeren et al. in which a nitrone is activated by a metal catalyst for reaction with an electron-rich alkene, the approach in the present work employ catalyst-induced activation of the alkene part and is controlled by the opposite electron demand. In the presence of catalyst **159a** the reaction proceeded to give the product **158** in high yield with an endo:exo ratio of up to 10:90 (R^1 = Me, R^2 = Ph). Enantioselectivities of 60% and 62% ee of the endo and exo isomers, respectively, were obtained. The optical purity of the major exo isomer was improved to 95% ee by recrystallization. Catalyst **159b** induced a lower enantioselectivity, but, the endo:exo ratio was improved to 5:95%.

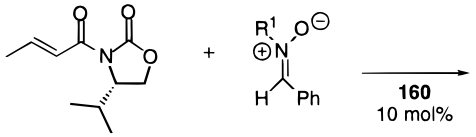


159a: R^3 = Ph
159b: R^3 = Et

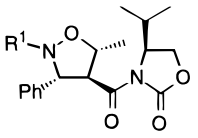
160 **161**

In an extension of this work the impact of various achiral and chiral Cu(II) and Mg(II) complexes on the reaction was introduced. Application of 10 mol % the achiral MgI_2–phenanthroline catalyst **160** and an additional amount of I_2, strongly accelerated the reaction and also led to a high degree of endo selectivity (eq 26).[20] The reaction of the valin-derived alkene **162** and nitrone **157a**,**b** was also catalyzed

in the presence 10 mol % of **160** as the catalyst and the reaction proceeded to give *endo*-**163a** as the sole product out of four possible in 99% yield (eq 27). To



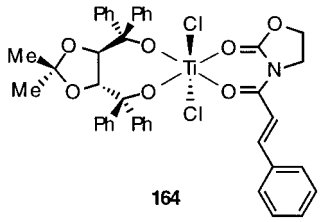
162 **157a**: R^1 = Ph
157b: R^1 = Bn



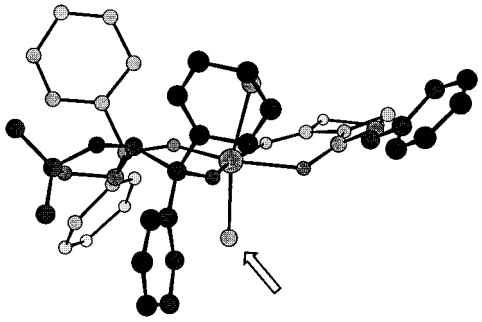
endo-**163a**,**b** (27)

obtain catalyst induced asymmetry in the Mg(II)-catalyzed 1,3-DC reaction of achiral starting material, the chiral MgI_2−bisoxazoline catalyst **161**, was applied. In some entries the catalyst induced high endo selectivities and up to 82% ee (eq 26). On the basis of an X-ray structure of *endo*-**163b**, which contains a chiral center with a known configuration, the absolute structure of this product was determined.[20] By deriving *endo*-**163b** and the corresponding derivative of *endo*-**158** into the isopropyl esters the absolute configuration of the 1,3-DC products was determined.[20,192]

In connection with the work on the titanium-catalyzed reactions an intermediate **164** consisting of the catalyst **159a** and *N*-cinnamoyloxazolidinone was isolated as crystals and characterized by X-ray crystallography.[193] The complex **164** was proposed to be an intermediate, not only in the 1,3-DC reaction of nitrones with alkenes, but probably also in the asymmetric TADDOLate−$TiCl_2$-catalyzed Diels−Alder reaction.[193,194] Whether or not this complex actually represents the key intermediate in the reactions has been a subject of debate.[194−197] DiMare et al. and Seebach et al. assumed that in intermediates similar to **164**, neither of the alkene faces are shielded sufficiently to account for the high enantioselectivities frequently obtained in the $TiCl_2$−TADDOLate-catalyzed Diels−Alder reaction.[195,196] They proposed another intermediate in which the two chloride ligands are arranged cis to each other to be more reactive and to offer a more effective shielding of one of the faces of the alkene. In this cis intermediate one of the alkenoyloxazolidinone carbonyls is arranged trans to one of the chloride ligands and this is supposed to lead to a higher reactivity of this intermediate compared to **164** where both carbonyls are arranged trans to the TADDOLate oxygen atoms. However, for the 1,3-DC reaction experimental results have indicated that an intermediate in which the chloride (or tosylate) ligand(s) is located trans to the plane consisting of titanium and the two alkenoyloxazolidinone carbonyls is the most reactive one.[192,197] In a recent work Seebach et al. suggested the Ti−TADDOLate-catalyzed Diels−Alder reaction



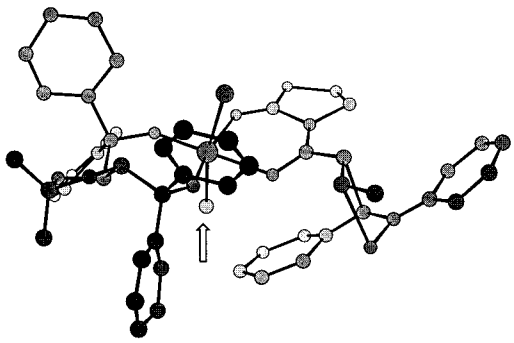
164



164

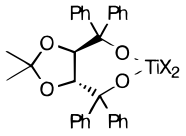
to proceed via a cationic intermediate in which one of the chloride ligands is dissociated from the catalyst.[198]

If one assumes that **164** represents a key intermediate in the 1,3-DC reaction between an *N*-alkenoyloxazolidinone and nitrone, the axial ligand (indicated by an arrow in **164**) would be of major importance for the endo/exo selectivity of the reaction. Due to steric repulsion between the axial ligand and the *C*-phenyl substituent of nitrone **157b**, the exo transition state **165** (please observe that the cinnamoyl fragment in **164** has been exchanged with a crotonyl fragment) is less favored as the bulkiness of the axial ligand (indicated by an arrow in **165**) is increased.[192]



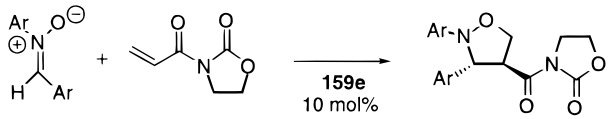
165

Experiments have shown that exchange of the chloride ligand in catalyst **159a** with bulkier ligands such as bromide (**159c**) or triflate (**159d**) changes the endo:exo ratio of the reaction in (eq 26) from 10:90 to 64:36 and 82:18, respectively. Introduction of the bulky tosylato ligands in catalyst **159e** to some extent decreases the activity of the catalyst since 50 mol % is necessary to obtain a fair conversion. However, the catalyst provided excellent endo selectivities of >90% de in eight reactions of various substrates and more notable enantioselectivities of 91−93% ee were obtained for several reactions of different substrates (eq 26).[192]



159a: X = Cl
159c: X = Br
159d: X = OTf
159e: X = OTs

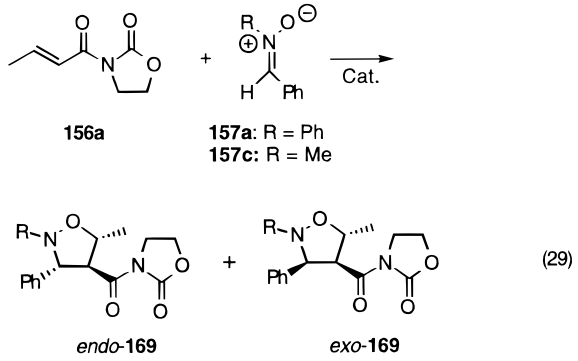
The Ti−TADDOLate-catalyzed 1,3-DC reactions have also been extended to include an acrylate derivative.[199] In the absence of a catalyst, the reaction between nitrone **166** and acryloyloxazolidinone **167** proceeds to give a mixture of all regio- and diastereomers (eq 28). However, application of 10 mol % of $Ti(OTs)_2$−TADDOLate **159e** as catalyst for the reaction of various nitrones such as **166** with alkene **167** leads to complete regioselectivity and high endo selectivity in the reaction and the endo product **168** is obtained with 48−70% ee (eq 28).[199]



166 **167** **159e** 10 mol% *endo*-**168** de = 92-100% ee = 48-70%

(28)

Seebach et al. have developed a number of polymer- and dendrimer-bound $TiCl_2$−TADDOLate catalysts derived from the TADDOLs **170**, **171**, and others.[198] Application of 10 mol % of this type of catalysts in the reaction between alkene **156a** and nitrone **157a** led to endo:exo ratios between 18:82 and 8:92 and enantioselectivities of until 56% ee (eq 29). The

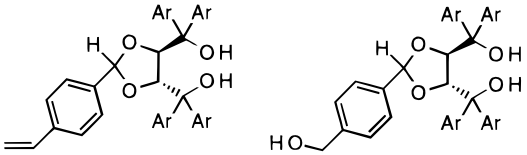


156a **157a**: R = Ph **157c:** R = Me Cat. *endo*-**169** *exo*-**169**

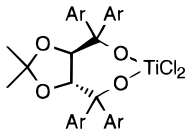
(29)

selectivities are thus slightly decreased compared to the similar reactions of the homogeneous catalysts.[182,198] They also made a study of the relationship between the enantiomerically purity of the ligand of the homogeneous catalyst **172**, and the products obtained in both the 1,3-DC reaction of **156a** and **157a** and in the Diels−Alder reaction of **156a** with cyclopentadiene. Surprisingly, the 1,3-DC shows a linear relationship, whereas the Diels−Alder reaction shows a positive nonlinear relationship.[198,200]

Further development was made by Furukawa et al. by investigations of chiral complexes of palladium as catalysts for the reaction (eq 29).[106] The cationic palladium catalysts were obtained from $PdCl_2$, Ag-

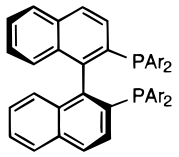


170 **171**



172: Ar = 2-naphthyl

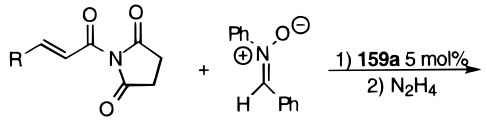
BF_3, and chiral (*S*)-BINAP derivatives **173a** or **173b**.



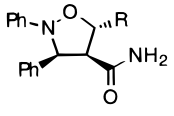
173a: Ar = Ph
173b: Ar = *p*-Tol

In the presence of 10 mol % of the catalyst the reaction of **156a** and **157c** proceeds in refluxing $CHCl_3$ to give the products as a mixture of the endo and exo isomers (eq 29). Yields are satisfying and most remarkable enantioselectivity of up to 91% of the endo isomer is achieved.

In a recent work the exo selectivity of the $TiCl_2$−TADDOLate-catalyzed 1,3-DC reaction was improved by the use of succinimide instead of oxazolidinone as auxiliary for the α,β-unsaturated carbonyl moiety.[201] The succinimide derivatives **174a**,**b** are more reactive toward the 1,3-DC reaction with **157a**, and the reaction proceeds at rt in the absence of a catalyst, and after conversion of the unstable succinimide adduct into the amide derivative, the endo isomer of **175** is obtained as the major isomer. In the presence of $TiCl_2$−TADDOLate catalyst **159a** (5 mol %) the reaction of **174a** with **157a** proceeds at −20 to −10 °C to give **175** in an endo:exo ratio of <5:>95 (eq 30). Additionally, the enantioselectivity of the reaction of 72% is also an improvement compared to the analogous reaction of the oxazolidinone derivative **156a**. Similar improvements were obtained in reactions of other related nitrones with **174a**,**b**.



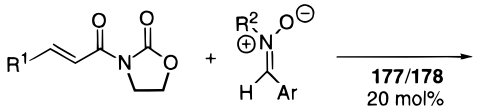
174a: R = Me **174b**: R = Pr **157a** 1) **159a** 5 mol% 2) N_2H_4



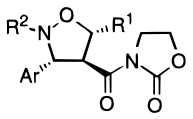
exo-**175**

(30)

Two independent research groups have developed an ytterbium-catalyzed 1,3-DC reaction. Kobayashi et al. utilized 20 mol % of complex **177** consisting of $Yb(OTf)_3$−BINOL and trimethylpiperidine in the presence of MS 4 Å as the catalyst for the 1,3-DC reaction between alkene **156** (R^1 = Me) and nitrone **166** (R^2 = Bn, Ar = Ph) (eq 31).[202] In this reaction,

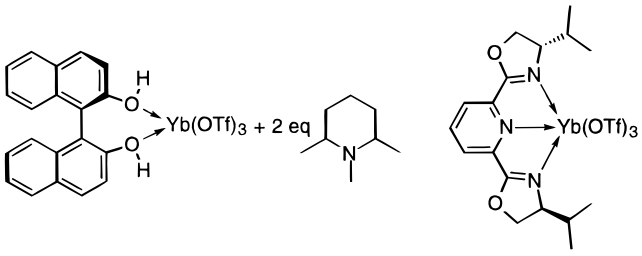


156 **166**



endo-**176** (31)

the nitrone is generated in situ from benzaldehyde and benzylhydroxylamine. The reaction proceeds to give the product **176** in 72% yield with a high endo:exo ratio of >99:<1 and with a ee of 78%. Others have been using 20 mol % $Yb(OTf)_3$−PyBOX **178** in the presence of MS 4 Å as the catalyst for the reaction between various alkenes **156** and nitrones **166** and for R^2 = Ph the reaction proceeds well to give the products in high yields with endo:exo ratios of 92:8 to 97:3 and with 67−73% ee of *endo*-**176**.[203]



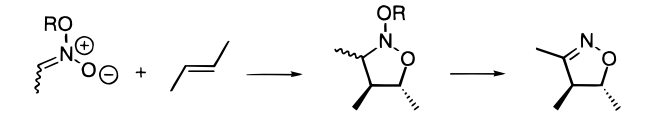
177 **178**

A highly enantioselective Zn(II)−(*R*,*R*)-diisopropyl tartrate-catalyzed 1,3-DC reaction between allyl alcohol and nitrile oxides has been developed by Ukaji et al. as described later in this paper.[204,205] Recently, this method was extended to include also the 1,3-DC reaction of allyl alcohol **179** with nitrones **180a**,**b** (Scheme 25).[206] The Zn(II) catalyst complex which is used in a stoichiometric amount is generated from allyl alcohol **179**, Et_2Zn, (*R*,*R*)-diisopropyl tartrate (DIPT), and EtZnCl. Addition of the nitrones **180a**,**b** led to the proposed intermediate **181a**,**b**. The product **182a** is obtained in moderate yields of 14−42%, however, with high ee's of up to 95% of *trans*-**182a**. Application of **180b** as the nitrone in the reaction leads to higher yields of **182b** (47−68%), high trans selectivities and up to 93% ee.

4. Nitronates

Alkyl and silyl nitronates are in principle *N*-alkoxy- and *N*-silyloxynitrones, but the asymmetric 1,3-DC reactions of this type of 1,3-dipoles are described in a separate part. Nitronates **183** can react with alkenes **184** in a 1,3-DC reaction to form *N*-alkoxy- or *N*-silyloxyisoxazolidines **185** (Scheme 26).[21] The

Scheme 26



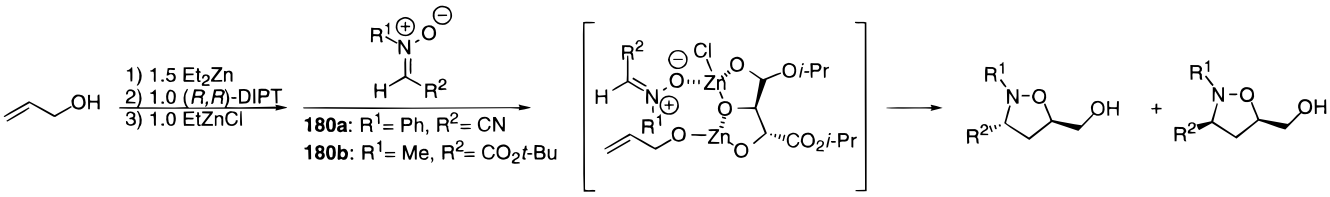
183 R = silyl, alkyl **184** **185** isoxazolidine **186** 2-isoxazoline

1,3-DC adducts **185**, obtained from acyclic nitronates, having a proton at the 3 position of the isoxazolidine ring, can easily eliminate the alkoxy or silyloxy group upon heating or by acid treatment, to form 2-isoxazolines **186**. It should be noticed that isoxazolines are also obtained in the reaction of nitrile oxides with alkenes (vide infra), thus, nitronates can be considered as synthetic equivalents of nitrile oxides.[21]

Since 1990 a few papers concerning asymmetric 1,3-DC reactions of silyl nitronates have appeared and these will be described first. To our knowledge the only asymmetric 1,3-DC reactions of alkyl nitronates is in connection with tandem [4 + 2]/[3 + 2] cycloaddition reactions, which will be described next.

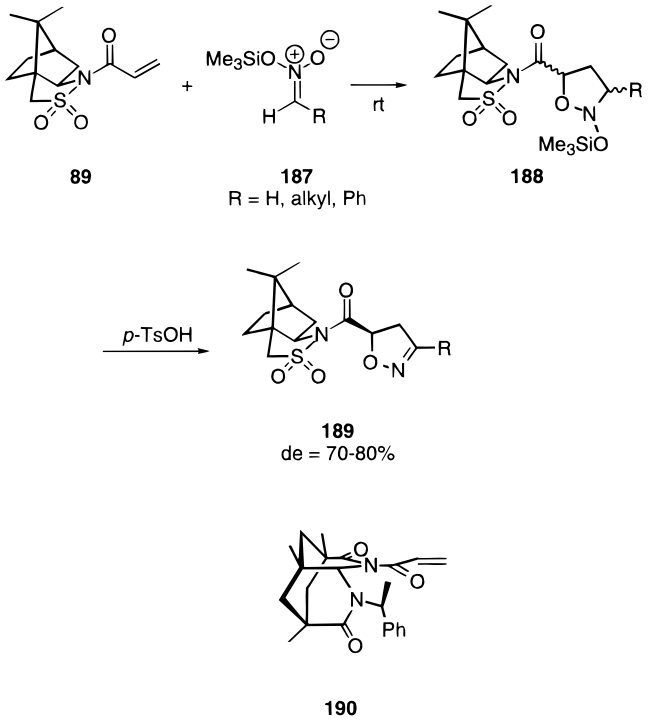
Since the pioneering work by Torssell et al.[21,207] on the development of silyl nitronates this type of compounds has become a versatile tool in 1,3-DC reactions.[21] Kim et al. applied the acrylate of Oppolzer's chiral sultam **89** in the first asymmetric intermolecular 1,3-DC reaction with silyl nitronates **187** (Scheme 27).[208,209] The 1,3-DC adducts **188** were converted into the corresponding isoxazolines **189**. Generation of the silyl nitronates **187** by silylation of the primary nitro compound, the 1,3-DC reaction, and the conversion of **188** into **189**, were performed as an one-pot reaction. The isoxazolines **189** were obtained in high yields with 70−80% de.

Scheme 25



179 **181a,b** *trans*-**182a,b** up to 95% ee *cis*-**182a,b**

Scheme 27



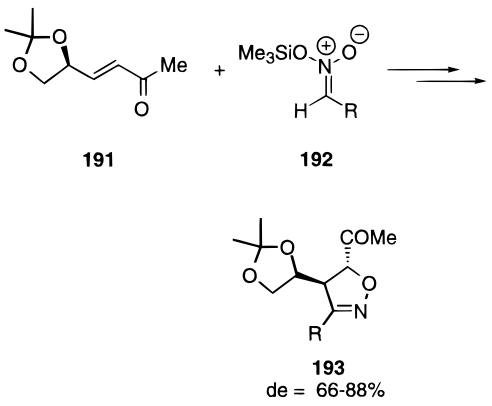
89 187 188

189
de = 70-80%

190

In a related approach Curran et al. applied the acrylate of the chiral bis-lactam **190**, as the chiral auxiliary.[210] Application of *tert*-butyldimethylsilyl ethylnitronate in the 1,3-DC reaction with **190**, led, after acid treatment of the intermediate isoxazolidine, to the isoxazoline with 86% de.

A chiral β-substituted enone **191** has also been applied in the 1,3-DC reaction with silyl nitronates **192** (eq 32).[211] The present reaction is slow at rt; however, after 3 days moderate to good yields were obtained of the isoxazolidines, which were converted into the isoxazolines **193** by acid treatment. The products **193** are obtained with complete regioselectivity and with 66−88% de.



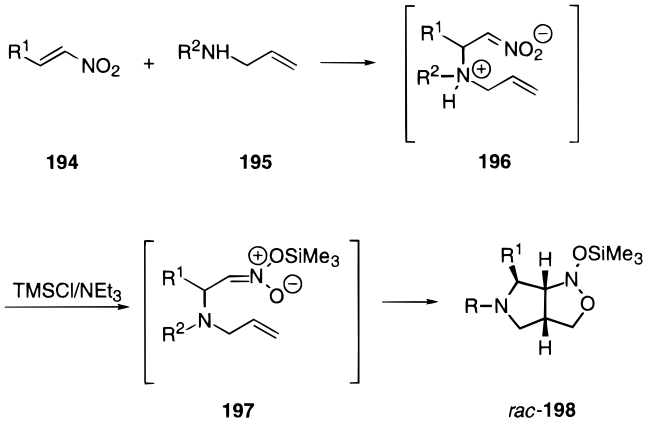
191 192

193
de = 66-88%

(32)

Hassner et al. have described a racemic intramolecular silyl nitronate 1,3-DC reaction.[212,213] In this approach the nitronate **196**, obtained from a Michael addition of nitroalkene **194** to allylamine **195**, is trapped by TMSCl to give the silyl nitronate **197** (Scheme 28). Compound **197** reacts in an intramolecular 1,3-DC reaction to give the racemic isoxazolidine **198** as the sole diastereomer.[213]

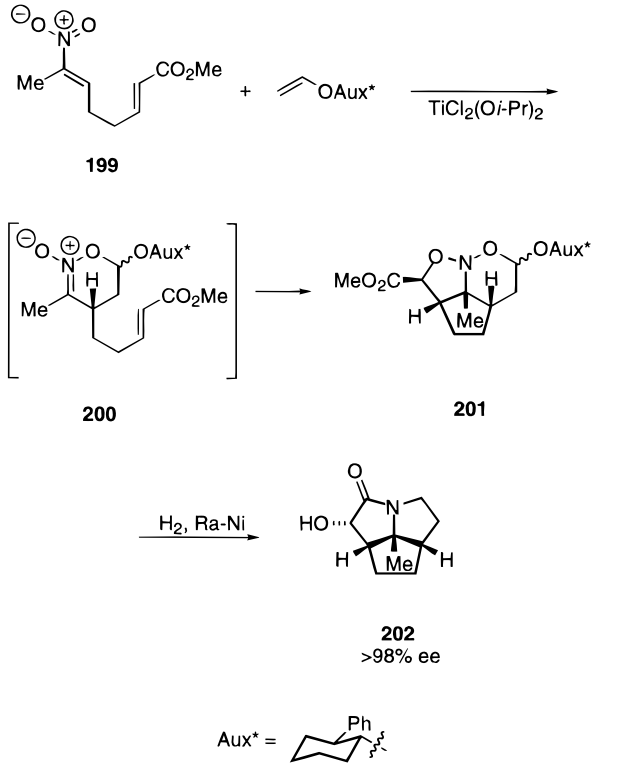
Scheme 28



194 195 196

197 *rac*-198

Scheme 29



199

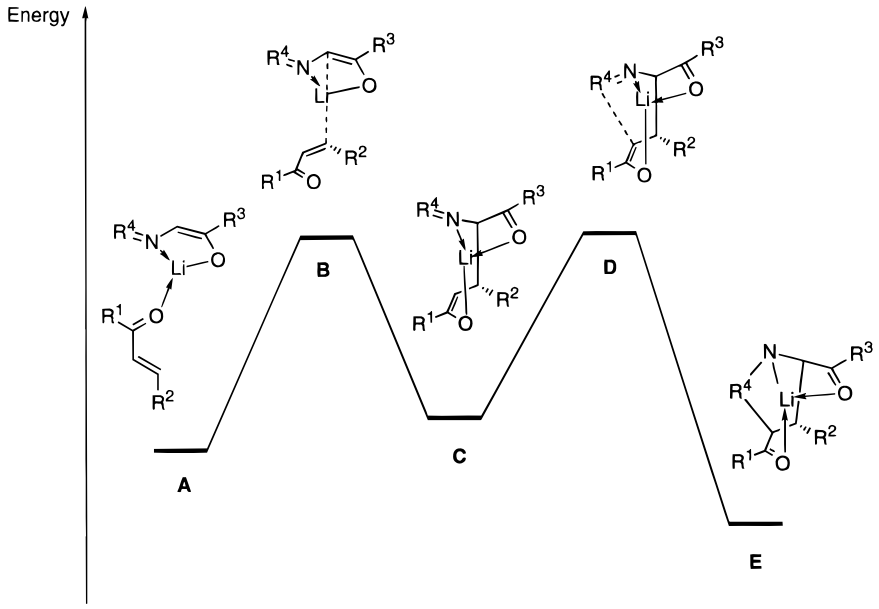
200 201

202
>98% ee

Cyclic alkyl nitronates are involved in tandem [4 + 2]/[3 + 2] cycloaddition reactions of nitroalkanes and this reaction has been extensively studied by Denmark et al.,[214,215] and recently this type of reactions was reviewed in this journal.[215] A typical example of such a reaction is outlined in Scheme 29. The nitroalkene **199** reacts with an alkene having an chiral auxiliary, in a Lewis acid catalyzed hetero-Diels−Alder reaction to form the intermediate chiral cycloalkyl nitronate **200**. The tandem reaction proceeds from **200** with an intramolecular 1,3-DC reaction to form **201**. Finally, **202** is obtained by reduction of **201**. The two cycloaddition reactions involved in the tandem reaction proceed with a high degree of selectivity since the final product is obtained with >98% ee.

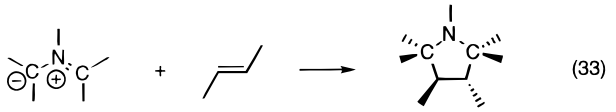
This type of tandem reaction has also been applied by Chattopadhyaya et al., who used 2′,3′-dideoxy-3′-nitro-2′,3′-didehydrothymidine as the starting material.[216]

Scheme 30



5. Azomethine Ylides

The 1,3-DC reaction of azomethine ylides **203** with alkenes **204** leads to the formation of the pyrrolidines **205** (eq 33). Azomethine ylides are unstable species



203 **204** **205** pyrrolidine (33)

which have to be prepared in situ. A number of methods has been developed for the generation of azomethine ylides, such as proton abstraction from imine derivatives of α-amino acids, thermolysis or photolysis of aziridines, and dehydrohalogenation of imonium salts.[217]

The reaction of azomethine ylides with alkenes has been investigated from a theoretical point of view in order to understand the reaction course, selectivity, and influence of Lewis acids on the reaction.[80,84,218] Kanemasa et al. have studied the reaction of lithium (*Z*)-enolates derived from *N*-alkylideneglycinates with α,*β*-unsaturated esters by theoretical calculations using the MNDO and PM3 procedures.[218] The reaction was proposed to proceed by a stepwise mechanism via an intermediate formation of a Michael adduct as outlined by the reaction path shown in Scheme 30.

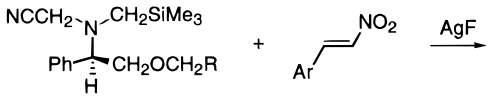
The initial step in the reaction outlined in Scheme 30 is an anti-selective carbon−carbon bond formation by a Michael addition process leading to **C** via transition state **B**. The second step takes place via transition state **D** which is a Mannich-type reaction, leading to the 1,3-DC product **E**.[218] The energy differences between the transition states **B** and **D** were calculated to depend on the steric hindrance caused by the alkylidene moiety R^4 as the bulky alkylidene substituents prefer the formation of Michael adducts, while small ones prefer the 1,3-DC products. The energy barrier for the step leading to the 1,3-DC product **E** from the Michael adduct is calculated to be in the range 9.2−28.5 kcal mol^{-1}, depending on the substituents and the calculation method.[218]

The reaction of 5-(*R*)-menthyloxy-2(5H)-furanone with an *N*-benzyl-α-ethoxycarbonyl-substituted ylide was investigated by a FMO analysis using AM1 calculations.[84] On the basis of the FMOs it was supposed that the α-ester carbon atom of the ethoxycarbonyl azomethine ylide reacts with the *β*-enone carbon atom of the alkene, and that the reaction is $HOMO_{dipole}$−$LUMO_{alkene}$-controlled.[84] Annunziata et al. have used a series of PM3 and ab initio calculations to locate the transition state for the reaction of the simplest azomethine ylide (CH_2NHCH_2) with ethylene.[80] The transition state was calculated by the ab initio calculations at a RHF/3-21G* level and on the basis of the calculated bond length (2.479 Å) of the carbon−carbon bond in the transition state, it was claimed that the reaction proceeds via an early transition state. Furthermore, the favored endo approach for the unsymmetrical substituted alkene to the azomethine ylide was found to be due to steric reasons as the distance between the ethyl hydrogen atoms and the azomethine hydrogen atoms was calculated to be relatively short (2.45 Å).

5.1. Chiral Azomethine Ylides

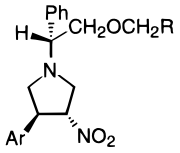
In 1985 Padwa et al. published the first diastereofacial selective 1,3-DC reaction of chiral azomethine ylides with alkenes leading to optically active products (eq 34).[219]

In the 1,3-DC reaction of the azomethine ylide precursor **206a** with 1-nitro-2-[3,4-(methylenedioxy)-phenyl]ethene **207**, the product **208a** was obtained with 20% de, while **206b** gave a de of 60%.[219] To account for the diastereoselectivity, two different



206a: R = H
206b: R = OCH_3

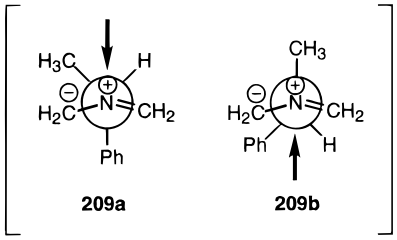
207



(34)

208a: R = H
208b: R = OCH_3

conformations of the azomethine ylide were considered **209a**,**b**. The approach of the alkene toward

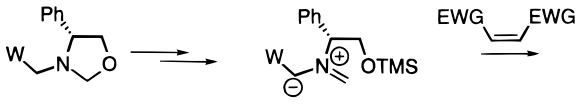


209a **209b**

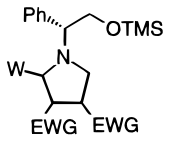
209a is to the face of the azomethine ylide anti to the phenyl group, while anti attack in **209b** results in an approach of the alkene to the opposite face of the dipole. It was argued that since the groups bound to the nitrogen atom in the azomethine ylide are similar both in size and electronic makeup, the excess of diastereoselectivity was small.[219]

In a series of papers Husson et al. have investigated the 1,3-DC reaction of electron-deficient alkenes with optically active azomethine ylides derived from mainly (−)-*N*-(cyanomethyl)-4-phenyl-1,3-oxazolidine **210**, prepared in one step from (*R*)-(−)-phenylglycinol (Scheme 31).[220−222] In the reaction of

Scheme 31



210 **211**

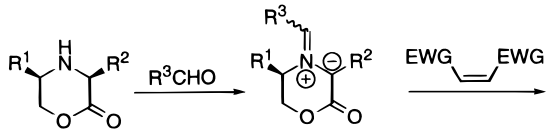


212
up to >95% de

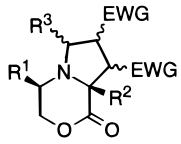
211 (W = CN) with *N*-phenylmaleimide four adducts were isolated with 41% yield of the major diastereomer, while in the reaction of **211** (W = CO_2Et) two isomers were formed in nearly equal amounts. It is interesting to note that moving the phenyl substituent in **210** from position 4 to 5 leads to a significant improvement of the diastereoselectivity in the 1,3-DC reaction, as both the exo and endo products now are formed with excellent de's (>95%).[220] The reaction has been further improved by introducing a menthyl ester as the W substituent in **210**.[221] Using this chiral azomethyl ylide, only the exo product was obtained with a de >95%.

The chiral template for the azomethine ylide outlined in Scheme 31 has been further developed to a chiral cyclic one by Harwood et al (Scheme 32).[223−232] The chiral azomethine precursor **213**

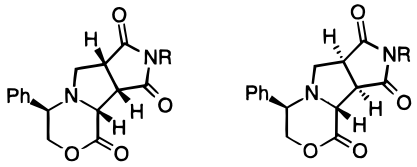
Scheme 32



213 **214**



215

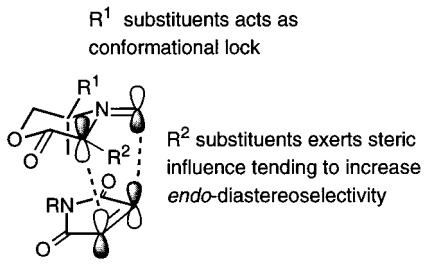


216 *endo* **217** *exo*

reacts with an aldehyde, mainly formaldehyde (R^3 = H), under formation of the azomethine ylide **214** which then reacts with an alkene, having electron-withdrawing substituents to give the 1,3-DC product **215**. Removal of the chiral template in **215** leads to the formation of substituted proline derivatives.

Reaction of **214** (R^1 = Ph, R^2 = R^3 = H) with maleimides leads to the formation of both the endo- and exo-cycloaddition products **216** and **217**, respectively, with the former product in excess (Scheme 32).[230] Changing to maleic anhydride as the alkene leads to the formation of the endo isomer as the sole product. The reaction of **214** (R^3 = Ph) with *N*-methylmaleimide leads to four products, the two endo- and two exo isomers, with a slight excess of the former. The preferred endo isomer is obtained from both the syn and anti orientations, respectively, of the phenyl substituent R^3 relative to the chiral center in **214**. In the reaction of **214** (R^1 = Ph, R^2 = *i*-Pr) with *N*-phenyl- or *N*-methylmaleimides the endo:exo ratio of the 1,3-DC product was improved.[231] The presence of a Lewis acids, such as $MgBr_2 \cdot Et_2O$, leads to an improvement of the yield of the 1,3-DC reaction; however, the diastereo- and regioselectivities are inversed compared to the corresponding uncatalyzed reactions.[226] The presence of the Lewis acid was proposed to change the interaction between the azomethine ylide and the alkene from a dominant $HOMO_{dipole}$−

$LUMO_{alkene}$ interaction to a $LUMO_{dipole}-HOMO_{alkene}$ interaction, but no thorough investigations were performed.[226] The suggested FMO interaction between the azomethine ylide and maleimide leading to the endo diastereomer is presented in **218**.[223]

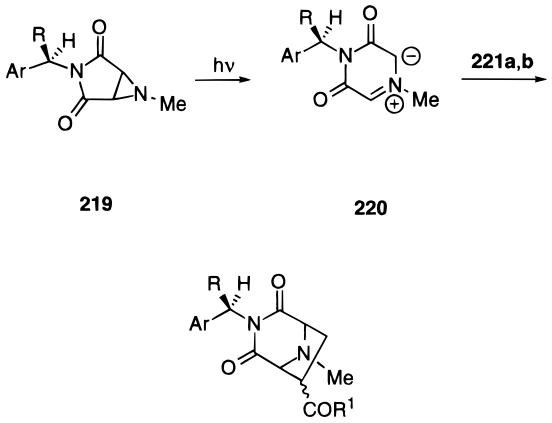


218

Moloney et al. have extended this reaction further by reaction of **214** (R^3 = H) with a variety of unactivated alkenes and alkenes having an EWG substituent and found that the 1,3-DC products can be successfully deprotected to give chiral, functionalized proline derivatives.[233]

Chiral aziridines have also been used as precursors for azomethine ylides.[234−239] Photolysis of the aziridine **219** produces the azomethine ylide **220**, which was found to add smoothly to methyl acrylate **221a** (Scheme 33).[235,237−239] The 1,3-DC reaction proceeds with little or no de, but this was not really surprising as the chiral center in **220** is somewhat remote from the reacting centers of the azomethine ylide. The de can be improved significantly by substitution of the acrylate with chiral ligands; especially, the concomitant use of the acrylate of Oppolzer's chiral sultam **221b** leads to the formation of the exo adduct in reasonable yields and with >90% de. These results are in sharp contrast to the results obtained by the use of chiral acryl esters as dipolarphiles, which react with **220**, giving no appreciable facial selectivity.

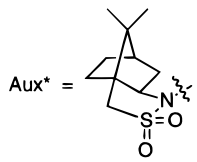
Scheme 33

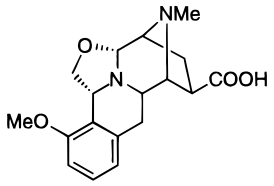


219 **220**

222a: R^1 = Me, *endo:exo* = 1:5, low de
222b: R^1 = Aux*, *endo:exo* = 0:100, de >90%

$H_2C=CHCOR^1$
221a: R^1 = OMe
221b: R^1 = Aux*

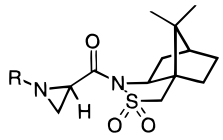




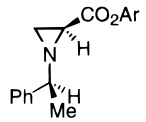
223
(-)-quinocarcin

A 1,3-DC reaction related to the one outlined in Scheme 33 has been used for the asymmetric synthesis and complete structure elucidation of (−)-quinocarcin **223**.[235]

Garner et al. later demonstrated that using aziridines substituted with Oppolzer's sultam leads to an azomethine ylide precursor **224** which adds to various electron-deficient alkenes, such as dimethyl maleate, *N*-phenylmaleimide and methyl acrylate, giving the 1,3-DC product in good yield and up to 82% de for *N*-phenylmaleimide.[234] Aziridines, such as **225**, have also been used as precursors for the chiral azomethine ylide, but in reactions with vinylene carbonates relative low de were obtained.[236]



224



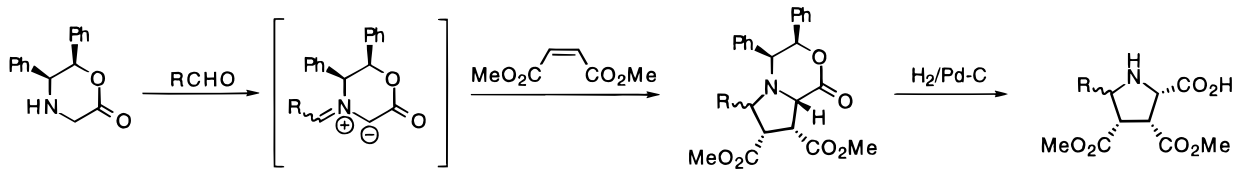
225

Azomethine ylides **227** derived from (5*S*,6*R*)-2,3,5,6-tetrahydro-5,6-diphenyl-1,4-oxazin-2-one (**226**) and various aldehydes have been prepared and used in the 1,3-DC with dimethyl maleate (Scheme 34).[240] In the case of higher aliphatic and aromatic aldehydes the endo selectivity in the 1,3-DC reaction was excellent, but the stereoselectivity of the C-7 position of **228**—the carbon atom to which the aldehyde substituent is bound—was generally low, due to the syn−anti interconvertion of the R substituent in **227**. However, as an exception the use of isobutyraldehyde gave selectively a single diastereomer in the reaction. The 1,3-DC products **228** are converted into the corresponding pyrrolidines **229**, which proved to have high ee's.[240]

Other chiral azomethine ylides, derived from 2-(*tert*-butyl)-3-imidazolidin-4-one, have also been tested as chiral controller in 1,3-DC reactions.[241] 2-(*tert*-Butyl)-3-imidazolidin-4-one reacted with various aldehydes to produce azomethine ylides, which then were reacted with a series of different electron-deficient alkenes to give the 1,3-DC products in moderate diastereoselectivity—up to 60% de.

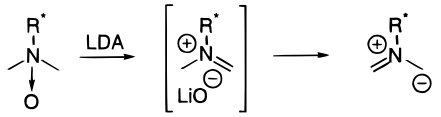
Azomethine ylides **232** can be generated from tertiary amine *N*-oxides **230** by reaction with LDA (Scheme 35).[242] Several different chiral R*-substituted azomethine ylides **232** prepared in this manner were used in the 1,3-DC reaction with alkenes, but the de's obtained of the products **233** were low.

Scheme 34

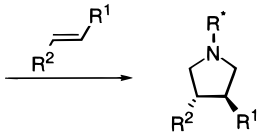


226 **227** *endo*-**228** **229** (Only one isomer from **226** for R = *i*-Pr)

Scheme 35



230 **231** **232**

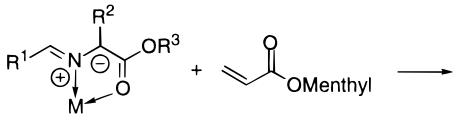


233

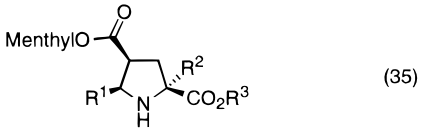
Other 1,3-DC reactions of chiral azomethine ylides with C_{60}[243] and reactions of chiral azomethine ylides derived from 1-benzyl-4-phenyl-2-imidazoline with different electron-deficient alkenes have been performed.[244]

5.2. Chiral Alkenes

In a series of papers Grigg et al. have studied the 1,3-DC reaction of various azomethine ylides with chiral alkenes.[245−253] The principle for the reaction is outlined in eq 35. The metallaazomethine ylide **234** reacts with an electron-deficient alkene, such as menthyl acrylate **91**, when M = Ag(I), Li(I), Tl(I), or Ti(IV) to give the 1,3-DC product **235** in good yield and with high endo and diastereofacial selectivity induction with de's up to >95% (eq 35). The azomethine ylide substrates for the 1,3-DC reaction can be both aromatic, heteroaromatic and aliphatic aldimines. It is observed that the use of **234** and Ti(O*i*-Pr)$_3$Cl as the metallaazomethine ylide gives a reversal of the regioselectivity in the 1,3-DC reaction with **91** while retaining the stereospecificity.[249]



234 **91**

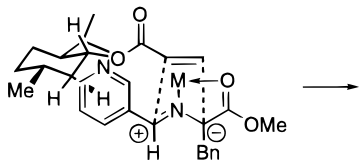


235
up to >95% de

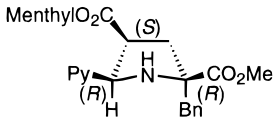
(35)

The 1,3-DC reaction of azomethine ylides with menthyl acrylate is significantly slower compared with the analogous reaction of methyl acrylate as the dienophile, which often leads to lower yield due to a slow metal ion induced hydrolysis of the imine by traces of water. However, this can be overcome by the addition of a base and the stronger the base the faster the reaction.[246,247] The mechanism of the 1,3-DC reaction of these metallaazomethine ylides generated from imines by the action of amine bases in combination with especially LiBr and AgOAc has been studied extensively.[247] It has e.g. been found by the application of X-ray analysis of a series of representative cycloadducts that the established absolute configuration of the pyrrolidine stereocenters is independent of the metal salt and the size of the pyrrolidine C-2-substituent for a series of aromatic and aliphatic imines.

On the basis of the observed regioselectivities, endo selectivities, and diastereofacial selectivities of the 1,3-DC reaction and with the absolute configuration of the products, a transition state model **236** for the facial shielding effect of the menthyl isopropyl moiety was proposed (eq 36).[245,247]



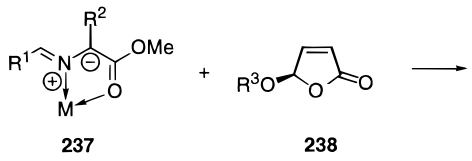
236



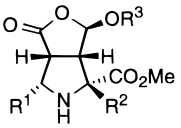
(36)

The azomethine ylides **237**, generated from both aromatic and aliphatic imines of α-amino acids, react with chiral cyclic alkenes **238**, such as 5-menthyl-2(5*H*)-furanone (R^3 = menthyl) (eq 37) in the presence silver acetate and various bases.[246,254] The 1,3-DC products **239** are formed with complete regioselectivity and endo selectivity with >95% de via the syn dipoles. The proper choice of base showed the to be 2-*tert*-butyl-1,1,3,3-tetramethylguanidine > DBU > NEt$_3$. By the use of a chiral 5(*R*)-lactam in the reaction with **237** leads to optical pure cycloadducts.[246]

Feringa et al. used 5-methoxy-2(5H)-furanone **238** (R^3 = Me) in the reaction with an ester-substituted



237 238



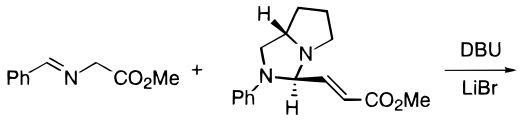
239
R^3 = menthyl:
endo:exo = 100:0
de >95%

(37)

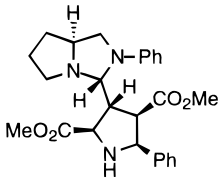
azomethine ylide prepared in situ from *N*-benzylglycine and formaldehyde.[254] In this reaction four 1,3-DC products were formed, but although the regioselectivity was poor, a complete *anti*-π diastereofacial selectivity was observed. Related cyclic alkenes have also been used by Wee,[255] giving high diastereofacial selectivity, whereas for the acyclic alkenes the π-facial selectivity and mode of 1,3-DC reaction is dependent on the structure of the alkene. Hegedus et al. have prepared optically active 4,4-disubstituted butenolides by photolysis of chromium alkoxycarbene complexes with optically active enecarbamates, followed by Baeyer−Villiger oxidation.[86] These butenolides react with both achiral and chiral azomethine ylides, but low diastereoselectiveties were found.

In a series of papers Kanemasa et al. have used the concept of lithium bromide/Et_3N-mediated 1,3-DC reactions of *N*-alkylidene-2-amino esters and amides with chiral electron-deficient alkenes.[256−260] These reactions proceed with high regio- and stereoselectivities. The first diastereoselective 1,3-DC reaction of chiral alkenes with azomethine ylides from Kanemasa et al. was by the use of α,β-unsaturated carbonyl compounds bearing a 2-pyrrolidinyl chiral controller, or analogues.[258,259] The reaction of methyl (benzylideneamino)acetate (**240**) with methyl (3*R*,7a*S*)-2-phenylperhydropyrrole[1,2-*c*]imidazole-3(*E*)-propenoate (**241**) is outlined in eq 38. The reaction proceeds well in the presence of LiBr and DBU with complete regioselectivities, endo selectivities, and diastereofacial selectivities by attack of the *syn*-azomethine ylide to the α-*si* face of the alkene. If the metal is changed from lithium to magnesium a slower reaction is observed.[259] The 1,3-DC product **242** can easily be converted to polyfunctionalized 2,4-pyrrolidinedicarboxylates.

The two epimers of methyl (*E*)-3-[(4*S*)-3-benzyl-4-isopropyloxazolidin-2-yl]propenoate **243a**,**b** (which could not be separated by chromatography) were also reacted with methyl(benzylideneamino)acetate **240** under the same reaction conditions as above. Two diastereomers, corresponding to the epimers of the chiral alkene, of the 1,3-DC product were formed, indicating a reaction with an absolute diastereofacial selectivity. The absolute stereochemistry of the minor cycloadduct was assigned by X-ray analysis.[258] The work has been extended to include α,β-unsaturated esters bearing a C_2-symmetric imidazolidine



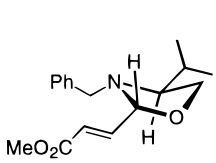
240 241



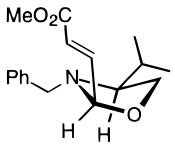
242
sole stereoisomer

(38)

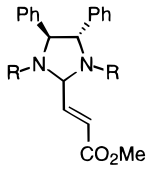
chiral controller at the β position, such as **244**.[257] The 1,3-DC reaction of the azomethine ylide **240** with **244** leads to the formation of the cycloaddition product in high yield and with a satisfactory de of 92%. The reaction was found to be very dependent on the substituents in both **240** and **244**. Reactions in which the R substituent in **240** is *tert*-butyl and the R substituent in **244** methyl, high stereocontrol is achieved. If the methyl substituent in **244** is exchanged with phenyl a lower selectivity is observed. The reaction proceeds under $HOMO_{dipole}$−$LUMO_{alkene}$ control with the dipole approaching the *si* face of the alkene as the *re* face is hindered by the R substituent as outlined **245**.



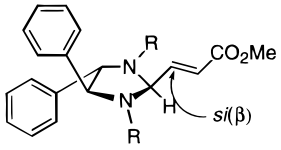
243a



243b



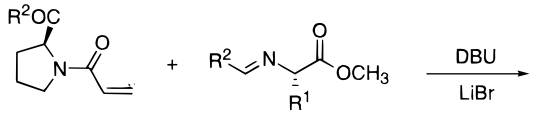
244



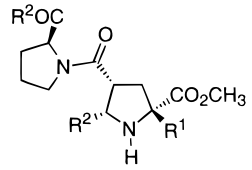
245

A related approach has been applied by Waldmann et al. who used *N*-acryloyl-(*S*)-proline esters **246** as the chiral alkenes.[261,262] The 1,3-DC reaction of **246** with metallaazomethine ylides (especially Li(I)) derived from imines **247** with aliphatic and aromatic amino acids gave the desired cycloadduct **248** with almost complete endo selectivity (>99:<1) and with de's of 82% to >98% (eq 39). To account for the high selectivity in this 1,3-DC reaction, it was proposed that the lithium cation is coordinated to both the azomethine ylide and to **246** in the transition state and that it coordinates through the amide and ester carbonyl groups in **246** in such a way that the acryl amide must possess a cis−anti conformation.[261,262]

The azomethine ylide derived from **249** has also been used in the reaction with chiral (*E*)-γ-alkoxy-



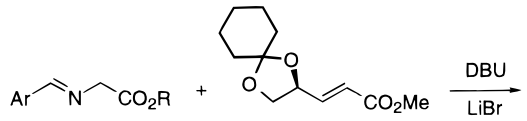
246 247



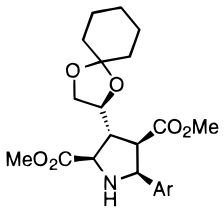
248
endo:exo >99:<1
up to >98% de

(39)

α,β-unsaturated esters **250** (eq 40). The corresponding tetrasubstituted pyrrolidines are obtained with complete regiocontrol in fair to excellent de.[263]



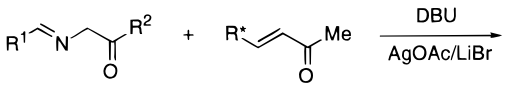
249 250



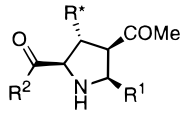
251
major stereoisomer
up to 92% de

(40)

The 1,3-DC reaction of chiral α,β-unsaturated ketones **253**, substituted by alkoxy or amino groups in the γ position, with the azomethine ylide derived from **252** have also been investigated (eq 41).[264,265] The reaction proceeds in the presence of LiBr to give a diastereomeric mixture of **254**, whereas using AgOAc leads to a highly regio- and diastereoselective reaction, with de's >90%. The use of AgOAc gave a higher yield of **254** compared with the use of LiBr. The reactivity is also dependent on the substituents in the azomethine ylide, as the use of carboxamides ($R^2 = NH_2$) leads to a slower reaction compared with the use of glycine esters (R^2 = OEt). Furthermore, the use of the AgOAc/DBU system also allowed the use of aliphatic amines (R^2 = cyclohexyl). The 1,3-DC reaction of **252** and **253a**−**e** is very dependent on the chiral substituent R* and the highest stereoselectivity was achieved using the bulky dibenzylamino substituent in the γ position (**253d**,**e**). On the basis of an X-ray analysis of the major isomer **254a** an anti orientation of the substituents at C-3 and the stereocenter C-1′ of the R*-substituent was found. This anti orientation was accounted for by the inside



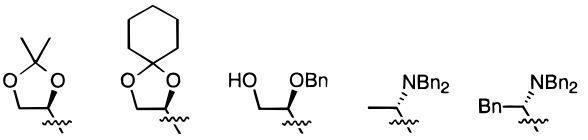
252 253a-e



254a-e
for **254d**,**e**
de >95%

(41)

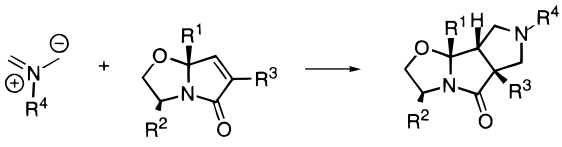
R*:



a b c d e

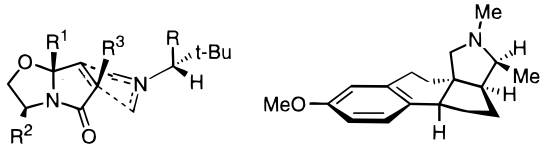
alkoxy effect described by Houk et al.,[266,267] by which the major stereoisomer is formed by an attack of the azomethine ylide with the alkene oriented away from the most bulky alkyl moiety. The alkoxy substituent thus occupies the stereoelectronically favored inside position and the small hydrogen atom the crowded outside region (vide infra).[264]

Meyers et al. have studied the addition of azomethine ylides **255** to chiral unsaturated bicyclic lactams **256** (eq 42).[268−271] The diastereoselectivities are dependent on the various substituents R[1]−R.[4] For R^1 = Me, Ph, the major storeoisomer obtained is **257** (eq 42), whereas for R^1 = H the other diastereomer is formed.[269] Furthermore, it was found that for R^3 = H, the π-facial selectivity is insensitive to the chiral substituents of the dipole (R^4 = chiral group), whereas for $R^3 = CO_2Me$ or CO_2t-Bu lower selectivities were observed.[268] On the basis of the experimentally observed results the approach of the chiral azomethine ylide to the alkene as outlined in **258** was suggested. The 1,3-DC reaction of these azomethine ylides with chiral unsaturated bicyclic lactams was used for the synthesis of the (+)-conessine precursor (+)-benzohydrindan **259**.[270]



255 256 257

(42)



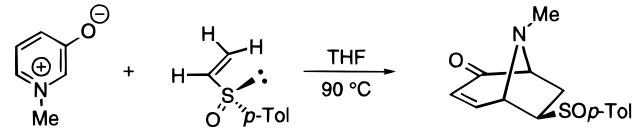
258

259
(+)-benzohydrindan

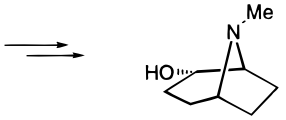
Cross-conjugated polyenones bearing a planar chirality introduced by an organometallic moiety have also been reacted with an azomethine ylide in a 1,3-DC reaction, but low diastereoselectivity was observed.[272]

The 1,3-DC reaction of $(R)_s$-*p*-tolyl vinyl sulfoxide **261** with 1-methyl-3-oxidopyridinum **260** gave three of the four possible diastereomers, and one of these isomers **262** was used for the enantioselective synthesis of (*1S*)-(−)-2α-tropanol **263** (Scheme 36).[273]

Scheme 36

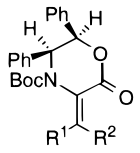


260 **261** **262**



263
(1*S*)-(-)-2α-tropanol

(5*R*,6*S*)-2,3,5,6-Tetrahydro-5,6-diphenyl-1,4-oxazin-2-one has been used as precursor for the formation of chiral alkenes **264** which was reacted with *N*-benzyl-*N*-(methoxymethyl)trimethylsilylmethylamines in a key reaction for the asymmetric synthesis of (*S*)-(−)-cucurbitine.[274]

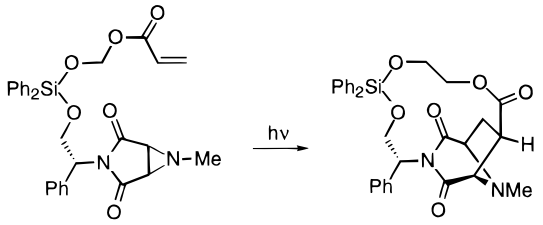


264

5.3. Intramolecular Reactions

Asymmetric intramolecular 1,3-DC reactions of azomethine ylides with alkenes has mainly been utilized in relation to total synthesis and with aziridines as the precursors for the azomethine ylide. Takano et al. used this approach for the synthesis of natural products, such as acromelic acid A (**268**),[275] (−)-kainic acid,[276] and (−)-mesembrine[277] where thermolysis of the aziridine was used to generate the azomethine ylide required for the intramolecular reaction as presented in Scheme 37. The synthesis of acromelic acid A **268** uses aziridine **265** as precursor and the reaction, which proceeds with very high diastereofacial selectivity to give **267**, is proposed to go via intermediate **266**.[275] A related approach was used by Weinreb et al. for the racemic construction of the tricyclic core of the marine alkaloid sarine A.[278] Nearly the same approach was used by Heathcock et al. for a racemic intramolecular 1,3-DC reaction of stabilized azomethine ylides to unactivated alkenes.[279] Ogasaware et al. used also this approach for the synthesis of the necine base dihydroxyheliotridane.[280]

Garner et al. have used an intramolecular 1,3-DC reaction of azomethine ylides with alkenes related to the intermolecular reaction outlined in Scheme 33 (vide supra).[281] The syntheses of naphthyridinomycin and quinocarcin were based on the introduction of an electron-deficient alkene as the R substituent in **219** (Scheme 33) to which the azomethine ylide moiety of **220** adds diastereoselectively in a 1,3-dipolar fashion. The work has been extended to a silicon-based tethered reaction and an example of the reaction of **269** is shown (eq 43).[282] It was found that



(43)

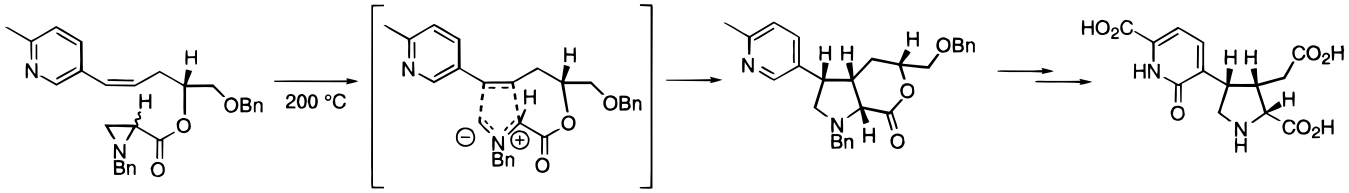
269 **270**

reactions with products with a ring size greater than nine atoms lead to preference for the 1,3-DC products such as **270** arising from a *si*-face attack, whereas reactions with products with a ring size equal to nine atoms lead to the opposite face selection. Both methyl and phenyl substituents, in the tether gave a similar results.[282]

The intermolecular approach developed by Harwood et al. shown in Scheme 32 (vide supra) has been extended to also include intramolecular reactions.[227,228] The reaction of the chiral template **271** with the alkenyl aldehyde **272** leads to the formation of the azomethine ylide **273**, which undergoes an intramolecular 1,3-DC reaction to furnish **274** (Scheme 38). The reaction is found to proceed with high diastereoselectivity as only one diastereomer of **274** is formed. By a reduction of **274**, the proline derivative **275** was obtained.

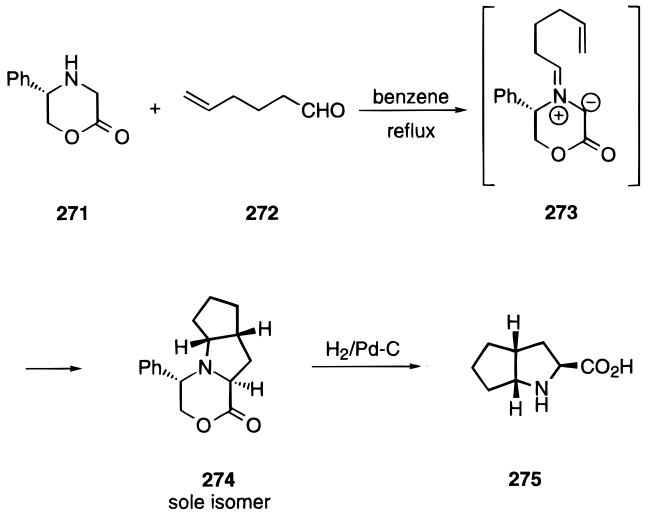
It should also be noted that the intermolecular reaction between alkenes and nonstablized azome-

Scheme 37



265 **266** **267** **268**
acromelic acid A

Scheme 38



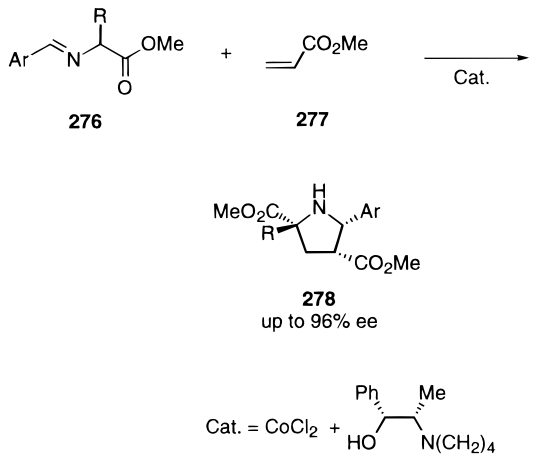
271 272 273

274 sole isomer 275

thine ylides generated from tertiary amine *N*-oxides presented in Scheme 35 (vide supra) has been extended to an intramolecular reaction.[283]

5.4. Metal-Catalyzed Reactions

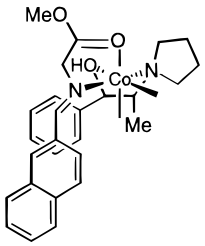
Grigg et al. have found that chiral Co(II) and Mn(II) complexes are excellent catalysts for the 1,3-DC reaction of azomethine ylides derived from arylidene imines of glycine.[284] Reaction of the azomethine ylides **276** with methyl acrylate **277** in the presence of a stoichiometric amount of Co(II) and the chiral ephedrine ligand gave the best yield and ee of the 1,3-DC product **278** (eq 44).



276 277

278 up to 96% ee (44)

The yields of **278** were in the range of 45−84% and the ee's up to 96%, with the highest ee obtained when Ar = 2-naphthyl, 4-BrC_6H_4, or 4-MeOC_6H_4, and when methyl acrylate was used as the solvent. Both the reaction time and ee are dependent on the counteranion, as the use of CoF_2 as the catalyst leads to a very slow 1,3-DC reaction with low chiral induction compared with the use of $CoCl_2$.[284] A proposed working model for the asymmetric induction is shown in **279**. The cis arrangement of the methyl and phenyl group of the ligand result in a pseudoequatorial conformation of the phenyl group and provides an effective blockade of one face of the dipole.[284]



279

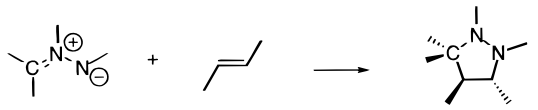
It has also been found that Ag(I) salts in combination with chiral ligands can catalyze similar 1,3-DC reaction with ee's of about 70%.[245]

6. Other Allyl Anion Type Dipoles

Contrary to the numerous reports on asymmetric 1,3-DC reactions of nitronates, azomethine ylides and especially nitrones, only a few asymmetric 1,3-DC reactions of other allyl type dipoles have been reported and they will be presented in the following.

6.1. Azomethine Imines

The 1,3-DC reaction of azomethine imines **280** with alkenes **281** leads to the formation of pyrazolines **282** (eq 45).

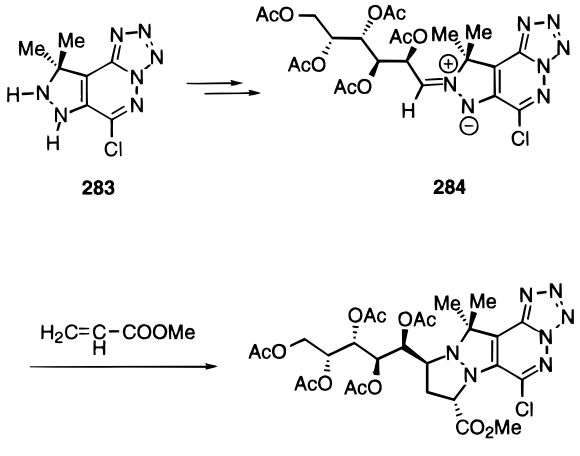


280 281 282 pyrazoline (45)

The use of azomethine imines in asymmetric 1,3-DC reactions with alkenes is limited, and the attention has been focused on the use of chiral azomethine imines for the stereoselective synthesis of *C*-nucleosides.

The dihydropyrazole derivative **283** has been transformed into chiral azomethine imines, such as **284** by reaction with carbohydrate-derived aldehydes.[285] The 1,3-DC reaction of **284**, as well as other chiral azomethine imines, with methyl acrylate affords the nucleoside **285** (Scheme 39). The 1,3-DC reactions

Scheme 39



283 284

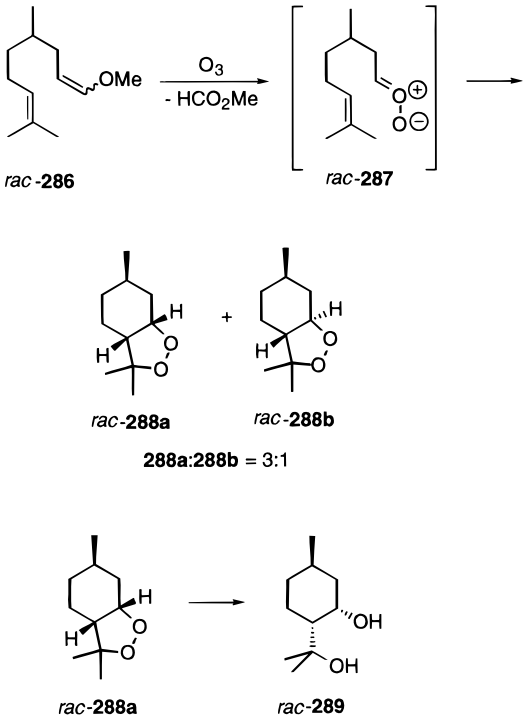
285 de >95%

were found to be highly stereoselective with >95% de in nearly all the reactions studied.[285−287]

6.2. Carbonyl Oxides

Carbonyl oxides are very reactive intermediates in the ozonolysis of alkenes and they are known to react immediately in a 1,3-DC reaction with the aldehyde or ketone formed by decomposition of the primary ozonide.[288] However, by the ozonolysis of enol ethers the primary ozonide undergoes cleavage to give carbonyl oxides and esters and the esters are unreactive toward carbonyl ylides. Thus, the carbonyl ylide can be trapped.[289] Only a few reactions of this type have been reported and to our knowledge only in work by Casey and Culshaw has the diastereofacial electivity of this reaction been studied.[290] By the ozonolysis of the racemic enol ether **286**, *rac*-**288a**, and *rac*-**288b** were obtained in a 3:1 ratio (Scheme 40). The products are formed in a 1,3-DC reaction

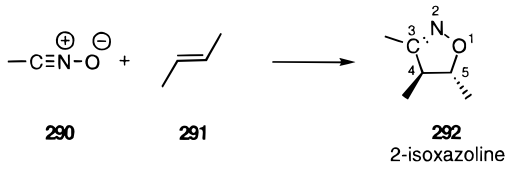
Scheme 40



from the reactive intermediate **287**. By hydrogenolysis of *rac*-**288a** the naturally occurring 1,3-diol *rac*-**289** was obtained in an overall yield of 41%.[290]

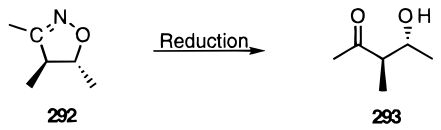
7. Nitrile Oxides

The 1,3-DC reaction of nitrile oxides with alkenes provides a straightforward access to 2-isoxazolines and the reports on synthetic application of this reaction are numerous (eq 46).[21,291−293] The nitrile oxide can be formed either in the Mukaiyama reaction from a primary nitro compound and phenyl isocyanate,[294] or from an aldoxime by treatment with a chlorinating agent and a weak base.[21,291,295] Nitrile oxides **290** are almost always generated in situ in order to avoid dimerization. The 1,3-DC reaction of a nitrile oxide **290** with an alkene **291** can give rise to two regioisomers of the 2-isoxazoline **292**, each as a pair of enantiomers in which the relative configuration between the 4- and 5-substituents is determined from the geometry of the alkene. Generally, nitrile oxides react with terminal alkenes to give the 5-isomer of the isoxazoline, i.e. the nitrile oxide carbon atom attacks the terminal carbon atom of the alkene.



(46)

The 2-isoxazolines **292** formed in the reaction between nitrile oxides and alkenes are useful building blocks, since they are readily converted into 3-hydroxycarbonyl compounds **293** upon a mild reduction with retention of the configuration of the chiral centers (eq 47).[291] Other useful functional groups, such as 3-amino alcohols, may also be obtained from isoxazolines.[21,291]

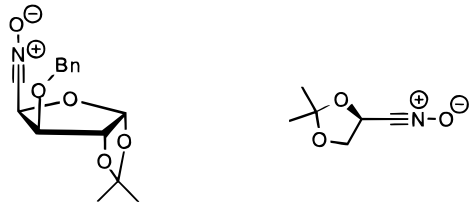


(47)

Due to the versatility of this reaction for the construction of chiral compounds, the demand for asymmetric versions of this reaction has increased over the last 20 years. Thus, several publications on asymmetric 1,3-DC reactions of nitrile oxides with alkenes have appeared. The majority of the reactions described involve optically active alkenes or are intramolecular reactions. However, during the last 5 years the application of metal catalysts in this reaction for control of the stereoselectivity has been described.

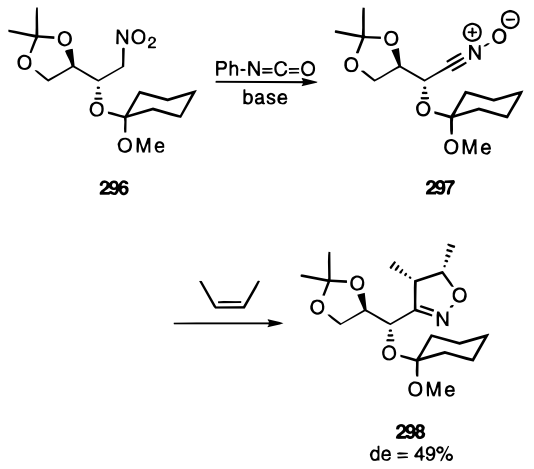
7.1. Chiral Nitrile Oxides

Only a few reports have described the application of optically active nitrile oxides in 1,3-DC reactions.[267,295−297] A few reactions involving racemic nitrile oxides have also been published.[298,299] In the first report Tronchet et al. report the application of a glucoside-derived nitrile oxide **294** in the reaction with styrene; however, no selectivity was observed, since the product was obtained as a 1:1 mixture of two diastereomers.[297] In later work by others the glyceraldehyde-derived nitrile oxide **295** was subjected to 1,3-DC reactions with alkenes, but, very low or absence of diastereoselectivity was found.[295,299]



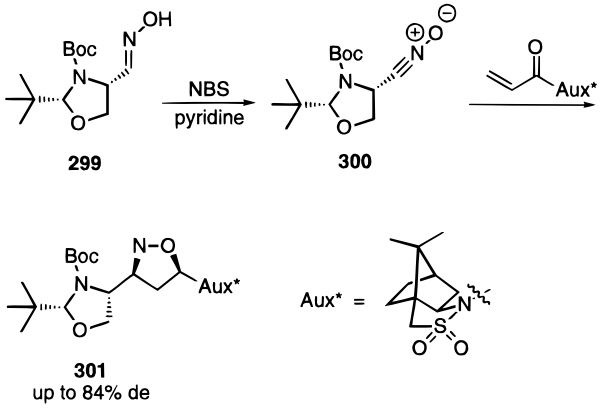
Kozikowski et al. describe the application of glyceraldehyde-derived nitro compound **296**, which upon treatment with phenyl isocyanate and base is converted into nitrile oxide **297** (Scheme 41).[296] In the reaction between in situ generated **297** and (*Z*)-2-butene the isoxazoline **298** is formed in 49% de.

Scheme 41



In more recent work Kim et al. demonstrated that by the concomitant application of the chiral nitrile oxide **300**, in this case obtained from the oxime **299**, and a chiral alkene, selectivities of up to 84% de were obtained of product **301** in the 1,3-DC reaction (Scheme 42).[300] However, as shall be shown later in this chapter, even better selectivities have been obtained in reactions of achiral nitrile oxides with the acrylate of Oppolzer's chiral sultam.

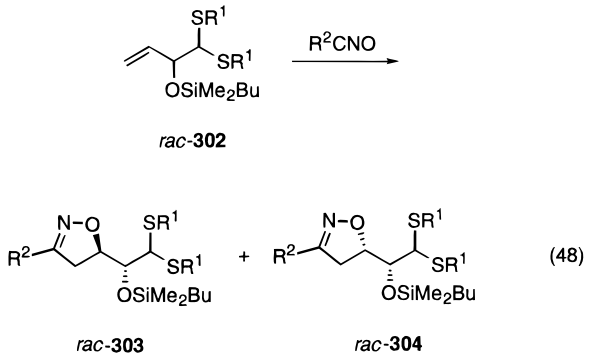
Scheme 42



7.2. Chiral Alkenes

Contrary to the small number of publication dealing with 1,3-DC reactions of chiral nitrile oxides with alkenes several research groups have applied optically active alkenes in these reactions. The description of reactions of the various different types of chiral alkenes is divided in two major parts: (i) alkenes in which the chiral center is located vicinal to the double bond, which includes allylic alcohols, allylic amines, and chiral vinyl sulfoxides, and (ii) derivatives in which the chiral center is located two or more bonds from the alkene moiety. The latter part includes vinyl ethers, metalla complexes, chiral auxiliaries attached to acrylates, and chiral auxiliaries attached to acryl amides.

Annunziata et al. performed a study on the reaction of the protected allylic alcohol *rac*-**302** with nitrile oxides (eq 48).[301] The alkenes applied were racemic; however, for most derivatives the product isoxazolines *rac*-**303** and *rac*-**304** were obtained with high diastereoselectivities with a preference of *rac*-**303** of 87−96% de.



Studies toward the understanding of the stereochemical outcome of the addition of nitrile oxides to chiral allyl ethers have been performed.[266,267,302] According to Houk et al. the major product arises from transition state **A** in which the largest group (L) occupies the anti position, the medium group (M) the inside position, and the smallest group (S) occupy the outside position (Figure 5).[266,267] Out of the other five possible conformations the minor product is proposed to arise from transition state **B**. It is assumed that the inside position is less sterically demanding than the outside position due to the oxygen atom of the incoming nitrile oxide. This proposal is in good agreement with the experimentally obtained selectivities;[266,267,301−303] however, if the medium group is a hydroxy group, transition state **C** (similar to **B**) is favored, due to hydrogen bonding of the nitrile oxide oxygen atom to the hydroxy group.[302]

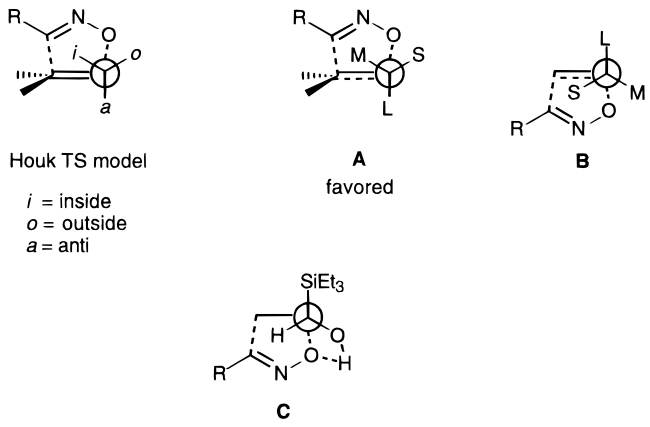
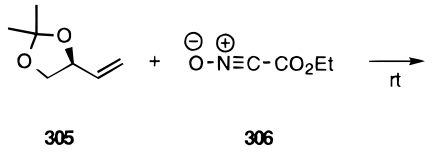


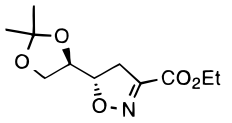
Figure 5. A model for the transition state of the 1,3-DC reaction of nitrile oxides to alkenes.[266,267]

As a crucial step in the synthesis of 2-deoxy-D-ribose Kozikowski and Ghosh reported the 1,3-DC reaction between the glyceraldehyde-derived alkene **305** and nitrile oxide **306** (eq 49).[304,305] The reaction proceeds with fair selectivity, and the isoxazolidine **307** is obtained as the major isomer with 60% de. By

the application of other nitrile oxides selectivities of up to 86% de were observed in the reaction with **305**.[306] Reactions of nitrile oxides with alkenes similar to **305** have also been investigated by others.[303,307]



305 **306**

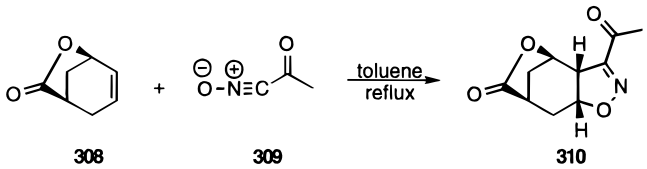


(49)

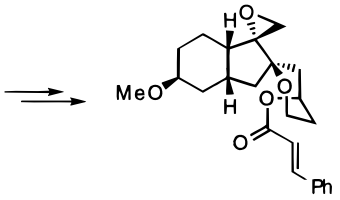
307
de = 60%

Martin et al. utilized the chiral bicyclic lactone **308** in the enantioselective total synthesis (+)-phyllanthocin (**311**).[308] The 1,3-DC reaction between **308** and **309** proceeds in refluxing toluene to give **310** in a yield of 45% along with 15% and 19% of other diastereo- and regioisomers, respectively (Scheme 43). After several further synthetic steps compound **311** was obtained from **310**.

Scheme 43



308 **309** **310**



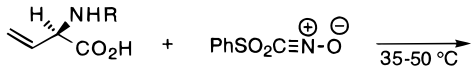
311
(+)-phyllanthocin

Feringa et al. synthesized an optically active L-(menthyloxy)furanone **67** as described in section 3.2 (Scheme 8). This chiral alkene was also subjected to 1,3-DC reactions with benzonitrile oxide and the reactions proceeded with a high degree of selectivity to furnish the products in regioisomeric ratios of >90:10, each as a single diastereomers.[84,85]

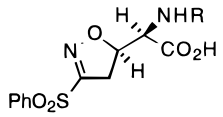
Chiral allylamines **312** have been applied in reactions with benzenesulfonylcarbonitrile oxide **313** by Wade et al. (eq 50).[309] The reaction proceeds at 35−50 °C to give product **314** in reasonable yields, but the diastereofacial selectivities were modest.

Racemic allylsilanes have also been applied in the 1,3-DC reaction with nitrile oxides but moderate diastereoselectivities were obtained.[310,311]

The chiral allylic center may also be a sulfur or phosphorus atom. Fluoro-substituted chiral vinyl



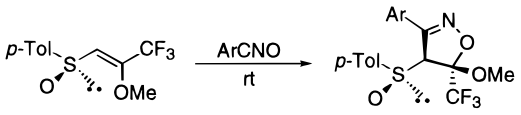
312 **313**



(50)

314
de = 32-40%

sulfoxides such as **315** have been applied in 1,3-DC reactions with various benzonitrile oxides (eq 51).[312]



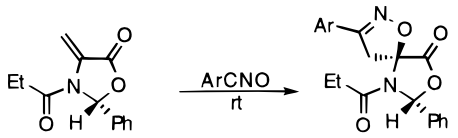
(51)

315 **316**
de = 100%

The reaction proceeds slowly at rt; however after 5−10 days the isoxazoline **316** is obtained with an excellent de in good yield. In some cases the product tends to eliminate the 5-methoxy substituent of the isoxazoline, thus, under loss of two chiral centers, an isoxazole is obtained.[312,313] Other chiral sulfinyl derivatives have also been applied in 1,3-DC reactions with nitrile oxides[314,315] and in one case a racemic vinylphosphine oxide was applied in the reaction with various nitrile oxides, but with moderate selectivities.[100]

In all the above-described reactions, the chiral center of the alkene was located in the allylic position; however, as shall be demonstrated in the following part, more distant chiral centers may also lead to highly selective 1,3-DC reactions with nitrile oxides.

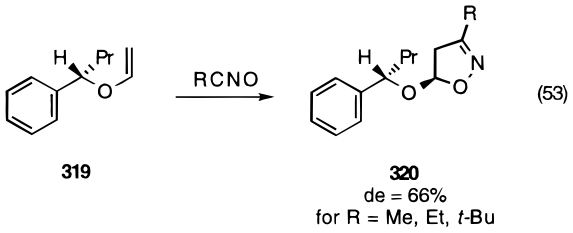
The optically active alkene **317** obtained from (*S*)-methyl cysteine, reacts with 3,5-dichlorobenzonitrile oxide at rt to furnish the spiroisoxazoline **318** as the sole regio- and diastereomer in 72% yield (eq 52).[316]



(52)

317 **318**
de =100%

Nitrile oxides are relatively electron-deficient compounds and react smoothly with electron-rich vinyl ethers. Jenkins et al. investigated the reactions of L-menthyl, 8-phenylmenthyl, and (1*S*)-*endo*-bornylvinyl ethers with nitrile oxides, but generally the de's were <33%.[317] However, application of the chiral vinyl ether **319** in the reaction with a number of alkyl and benzonitrile oxides provided product **320** with de's of up to 66% (eq 53). It is proposed that the syn-staggered conformation is preferred for the vinyl ether **319** as indicated in eq 53 and that the nitrile oxide attacks the double bond from the least hindered *re* face leading to diastereomer **320** as the major product.

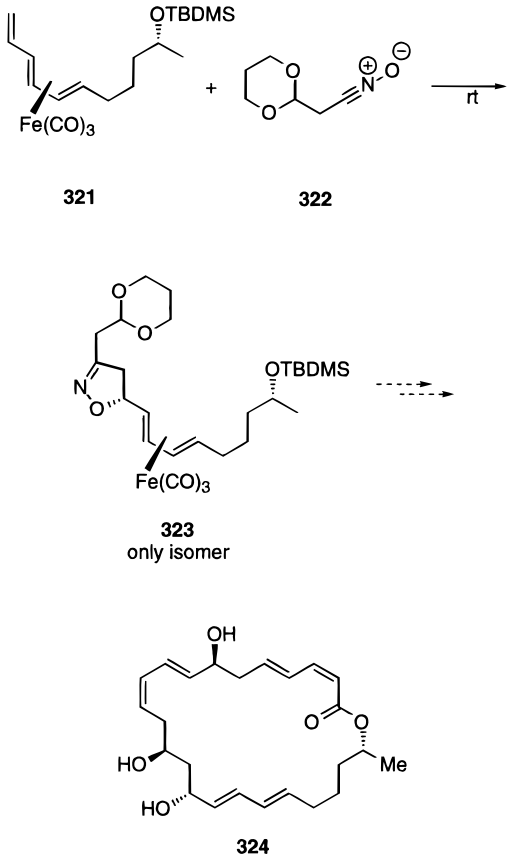


319

320
de = 66%
for R = Me, Et, *t*-Bu

In a study toward the total synthesis of macrolactin A (**324**), Prahlad and Donaldson introduced an additional stereocenter to the $Fe(CO)_3$-complexed segment **321** (optical purity = 55% ee), by a 1,3-DC reaction with nitrile oxide **322** (Scheme 44).[318,319] The reaction proceeded to give **323** as the only diastereomer in 60% yield.

Scheme 44



321 322

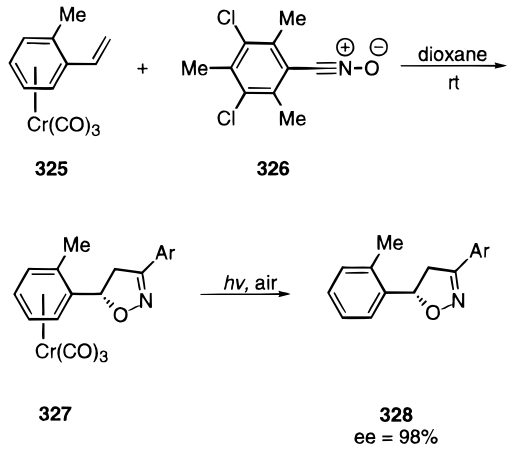
323
only isomer

324

Tricarbonylchromium(0) complexes of ortho-substituted styrenes were proven to offer an effective shielding of one of the faces of the alkene. The optically pure complex **325** was subjected to a 1,3-DC reaction with the sterically crowded nitrile oxide **326** (Scheme 45).[320] The reaction proceeds at rt to give 70% yield of **327** and after removal of the tricarbonylchromium moiety by a light-induced oxidation with air, compound **328** was obtained in an optical purity of 98% ee.

A series of chiral auxiliaries have been developed for α,β-unsaturated carbonyl compounds, linked to the alkene via an ester or amide. The majority of 1,3-DC reaction of nitrile oxides to this type of alkenes involve acryl derivatives, probably due to the lack of regioselectivity in reactions of β-substituted

Scheme 45

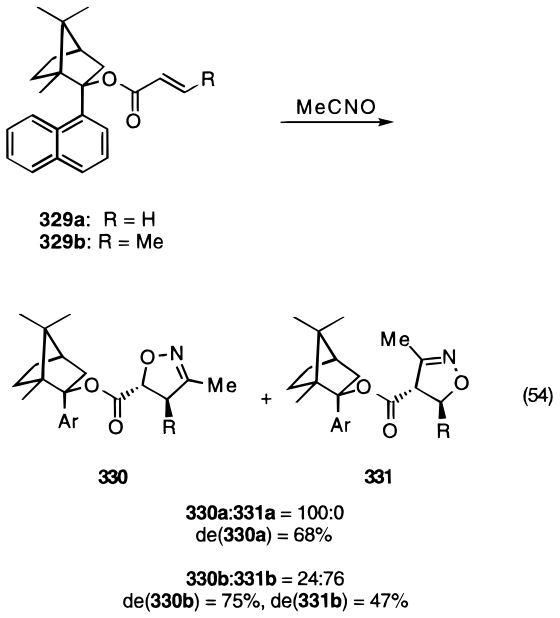


325 326

327

328
ee = 98%

derivatives such as crotonates or cinnamates. As demonstrated by Olsson et al., the acrylate of the chiral auxiliary **329a** reacts with acetonitrile oxide to afford **330a** as the single regioisomer with 68% de, whereas the crotonoyl derivative **329b** reacts to give a mixture of regioisomers (eq 54).[111,321] The camphor-derived auxiliary provides a good face selectivity since up to 75% de is achieved in the reaction.



329a: R = H
329b: R = Me

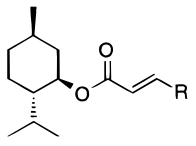
330 331

330a:**331a** = 100:0
de(**330a**) = 68%

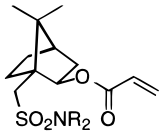
330b:**331b** = 24:76
de(**330b**) = 75%, de(**331b**) = 47%

Similarly, the acrylate and crotonate esters of L-menthol **332** have been applied in reactions with nitrile oxides. The acrylate reacted to give one regioisomer while a mixture was obtained for the crotonoyl derivative. In both cases poor diastereoselectivities were obtained.[322,323] The camphor-derived acrylate **333** underwent a 1,3-DC reaction with benzonitrile oxide with up to 56% de.[322] The auxiliary in acrylate **334** is derived from the naturally occurring L-quebrachitol and provided an effective shielding of the *re* face of the alkene in the reaction with benzonitrile oxide as 90% de was obtained.[324]

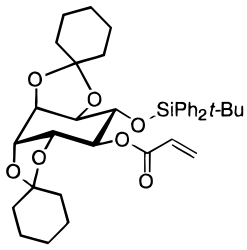
Extensive studies were performed by Curran et al.[210,325−329] as well as others[330−334] on the application of chiral auxiliaries attached to the nitrogen atom of



332

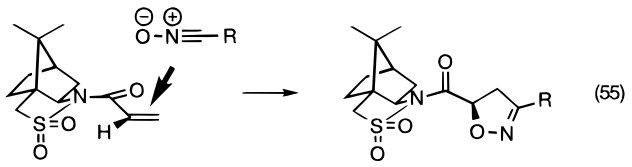


333: R_2 = cyclohexyl



334

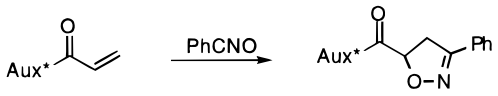
α,β-unsaturated amides in 1,3-DC reactions, and this approach has been developed to be one of the most effective methods for the synthesis of isoxazolines with high optical purities. The acryl amide of Oppolzer's chiral sultam proved to be an effective auxiliary for the acryloyl moiety in the reaction with nitrile oxides (eq 55). The reaction of various nitrile oxides



89 → **335** de = 62-90% (55)

proceed to give the product **335** with 62−90% de.[327] It is proposed that the preferred conformation of the acryl moiety in **89** is s-cis in which the carbonyl group points away from the sultam oxygen atom.[327,335] The face selection of the nitrile oxide 1,3-DC reaction with **89** cannot be explained in terms of the conventional face shielding by sterically bulky groups. On the basis of theoretical semiempirical and ab initio calculations, Kim et al. suggested that the *si* face is shielded by electrostatic repulsion between the sultam oxygen atoms and the oxygen atom of the incoming nitrile oxide.[335] In calculations where the sultam oxygens were removed and the geometry of the acryl moiety locked, no face selection was found by the calculations. Curran et al. have applied Oppolzer's chiral sultam as the auxiliary for the preparation of (+)-hepialone and (−)-pestalotin.[325,329]

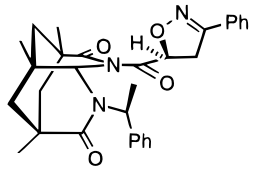
As an extension of the work by Curran et al. a variety of new chiral auxiliaries for the 1,3-DC reaction of acrylates with nitrile oxides has been developed. In most cases the different acrylates **336** have been applied in the 1,3-DC reaction with benzonitrile oxide, and the relative effectivity of the chiral auxiliaries in the reaction with the same nitrile oxide can thus be compared. The chiral auxiliary in **337** has been synthesized from the commercially available Kemp's triacid and provides an excellent face selectivity in the reaction with benzontrile oxide (eq 56).[326] They also developed a number of related



336 → **335,337-341** (56)

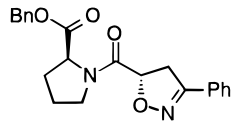
auxiliaries, and in reactions with other nitrile oxides excellent de's were obtained.[210,328] The easily available benzyl ester of proline was used as the chiral auxiliary by Waldmann in eq 56, and product **338** was obtained with moderate selectivity.[334] In extension of this work Kim et al. applied a number of (*S*)-proline derivatives as auxiliaries in reactions with nitrile oxides and in these studies **339** was obtained with a high de.[330] Oppolzer et al. synthesized both enantiomers of a new chiral sultam and applied it as described in eq 56 and the *R* enantiomer reacted to give **340** with 94% de.[333] The easily available auxiliary in **341**, was developed by Kanemasa et al. and was applied as descrbed in eq 56 to give the product **341** with 86% de.[331,336,337] A number of both optically active and racemic derivatives of the auxiliary in **341** was applied in this work and one of the racemic auxiliaries induced >98% de in the reaction with benzonitrile oxide.

Curran *et al.* 1989



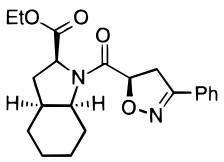
337
de >98%

Waldmann 1990



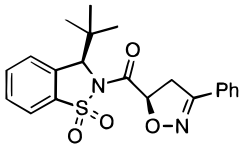
338
de = 50%

Kim *et al.* 1993



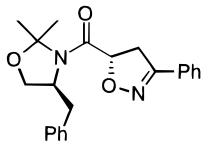
339
de = 90%

Oppolzer *et al.* 1991



340
de >94%

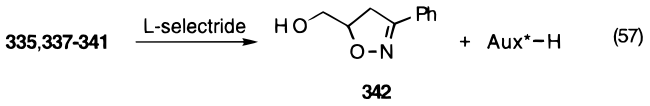
Kanemasa *et al.* 1991



341
de = 86%

For all the adducts **335**, **337**−**341** the chiral auxiliary was recovered by reaction with L-selectride under formation of the optically active isoxazolinylmethanols **342** (eq 57).

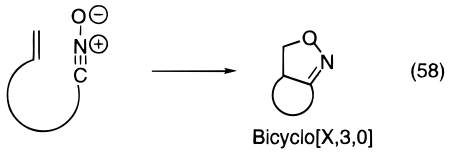
Curran's chiral auxiliary in **337** has also been applied in reactions of β-substituted acryloyl deriva-



tives with nitrile oxides.[328] The reactions offer similar high selectivities, but mixtures of regioisomers are obtained. A fumaric acid derivative in which one of the carbonyl groups were reduced and linked via an cyclic aminal to a chiral 1,2-diamine auxiliary (see eq 38) was subjected to a 1,3-DC reaction with nitrile oxides.[332] Despite moderate yields and mixtures of regioisomers, the products were occasionally obtained with a high degree of diastereoselectivity.

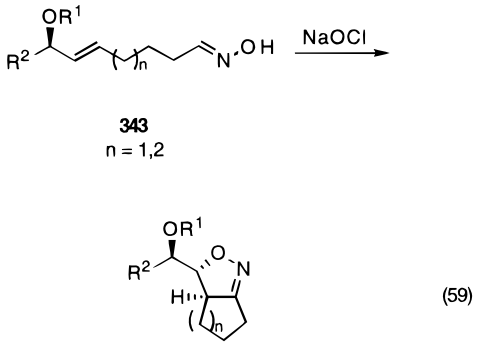
7.3. Intramolecular Reactions

The intramolecular 1,3-DC of nitrile oxides, often abbreviated INOC, with alkenes is an effective tool for the construction of bi- and polycyclic isoxazolines.[17,21,116,146,292,338] Due to the rigid linear structure of the nitrile oxide the reaction of alkenylnitrile oxides almost always proceeds to give bicyclo[*x*,3,0] derivatives for $x = 3-5$ (eq 58).



Like other intramolecular reactions it is easier to control the stereoselectivity than in the intermolecular counterpart. The chiral center(s) controlling the diastereoselectivity of the reaction can be located outside the bicyclic isoxazoline formed and this type of reactions will be described first. Most frequently the diastereoselectivity is controlled by a chiral center in the rings formed which will be presented next. The alkenyl nitrile oxides derived from sugar derivatives will finally be reviewed. According to our knowledge no reports have appeared on metal-catalyzed/assisted INOC reactions.

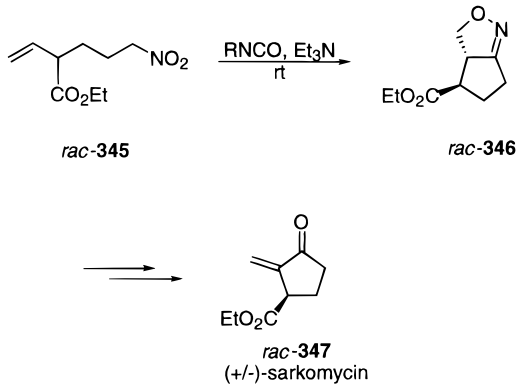
In 1987 three papers on the application of 5- and 6-alkenylnitrile oxides were published by Annunziata et al. in which the chiral center was an allylic ether located outside the ring formed.[339,340] The nitrile oxide was formed by chlorination of the oxime **343**, and the reaction proceed at 0 °C to give the product **344** with a de of up to 72% (eq 59). The reactions of



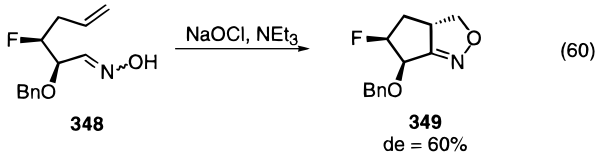
both (*E*)- and (*Z*)-alkenes were tested and similar selectivities were obtained. They also applied 5-alkenylnitrile oxides in which one of the methylene groups in the ring was substituted by a sulfur atom.[339] In one case a diastereoselectivity of 90% de was obtained by using the sulfur derivative. In earlier studies Kozikowski and Chen utilized a related reaction in the total synthesis of (+)-paliclavine.[341,342]

The reaction of racemic 5-alkenylnitrile oxides in which the chiral center is located in the resulting ring was applied by Kozikowski and Stein in the synthesis of (±)-sarkomycin (**347**, Scheme 46).[343] The nitrile oxide is generated from nitroalkene **345** and reacts to give *rac*-**346** as the single diastereomer in 55% yield. In two additional steps (±)-sarkomycin (**347**) was obtained. Similar reactions of racemic 5-alkenyl nitrile oxides were investigated by Kurth et al. and depending on the substituent of the generated ring low to excellent selectivities were obtained.[344]

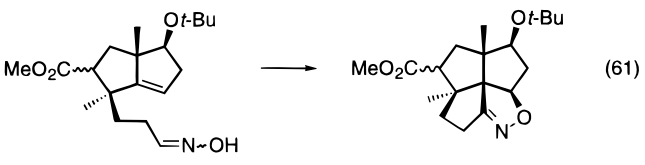
Scheme 46



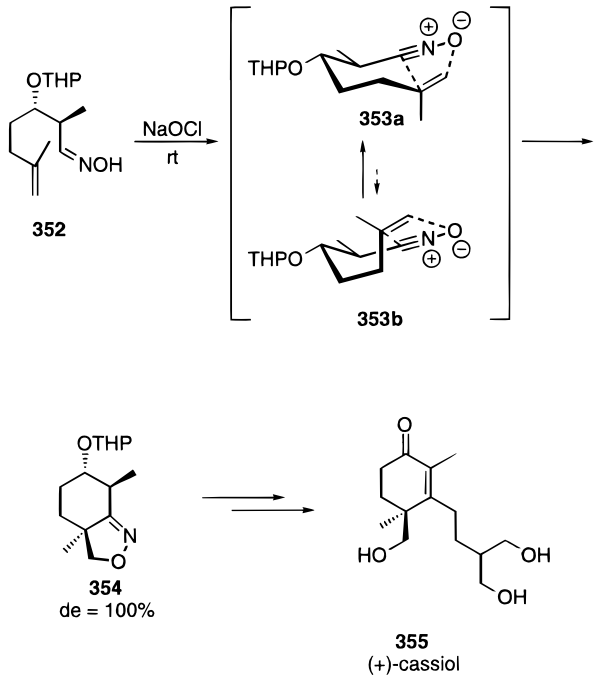
An optically active 3-flouro-5-alkenyloxime **348** was applied in the INOC reaction by Resnati et al. (eq 60).[125] The nitrile oxide generated in situ from **348**, attacks preferently the face of the alkene moiety trans to the benzyloxy substituent, to give the bicyclic product **349** with 60% de.



Fukumoto et al. applied the optically active bicyclic alkenylnitrile oxide **350** precurser in the synthesis of triquinanes (eq 61).[345] The starting material for the reaction of **350** consisted of a 1:2 mixture of epimers at the chiral center connected to the methoxycarbonyl moiety; however, the reaction proceeded with complete face selectivity to give the two pure epimers of **351**.

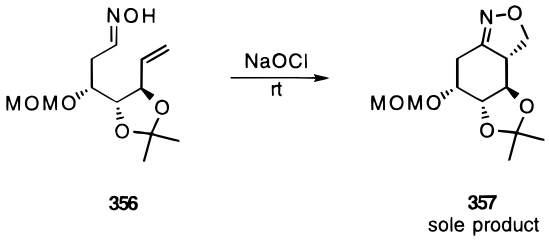


Scheme 47



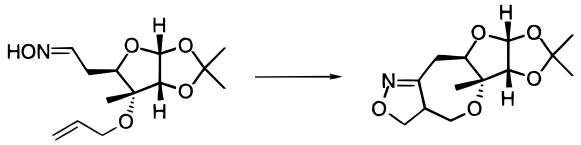
The same authors applied a 6-alkenylnitrile oxide in the synthesis of testosterone.[346] Reactions of 6-alkenylnitrile oxide were extensively studied by Shishido et al. who applied this approach in the syntheses of (+)-albicanol,[347] (−)-mintlactone,[348] (+)-isomintlactone,[348] (+)-menthofuran,[349] and (+)-cassiol **355**.[350] The INOC reaction performed in the synthesis of the latter compound is outlined in Scheme 47. The oxime **352** was treated with aqueous sodium hypochlorite and base to generate the nitrile oxide, which reacted to give **354** as the sole product in 88% yield. It is proposed the reaction proceeds via transition state **353a**. By the use a Monte Carlo search for optimized structures of transition states of compounds very similar to **353a** and **353b**, it was found that transition state **353a** is favored by 3.7 kcal/mol over **353b**.[350]

As described for nitrones (vide supra) the carbohydrate skeleton provides an effective basis for the induction of stereoselectivity in intramolecular 1,3-DC reactions. In a contribution from Takahashi et al. the mannitol-derived oxime **356** underwent INOC upon chlorination in the presence of a base to give **357** as the sole product (eq 62).[351] The stereochemical outcome of the reaction was predicted using the same line of reasoning as described above. The product **357** was an adduct in the synthesis of a trihydroxyvitamin D_3 synthon.[351] Theoretical calculations provided a rationale for the 1,3-DC product as a chairlike transition state was calculated to be 3.6 kcal/mol lower in energy than the boatlike transition state.[351]



(62)

Reactions of 7-alkenylnitrile oxides have also been described. The glucose-derived oxime **358** was transformed into the corresponding nitrile oxide which reacted to give **359**, and the reaction is an effective method for the construction of seven-membered rings such as **359**, which was obtained in 65% yield as the sole isomer as in eq 63 but a de of only 13% was reported.[132,352]



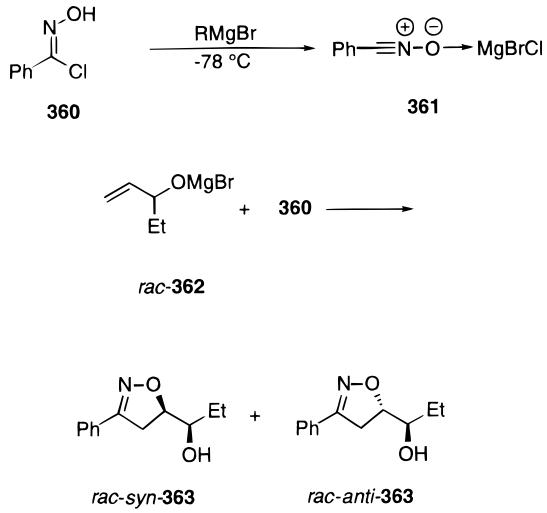
(63)

7.4. Metal-Catalyzed Reactions

Compared to the related reactions of nitrones there have only appeared a few publications on metal-assisted or metal-catalyzed 1,3-DC reactions of nitrile oxides. Some of the obstacles for controlling the stereoselectivity with metal complexes are (i) most nitrile oxides are very reactive short-lived species that must be generated in situ, (ii) in the two general procedures for the generation of nitrile oxides, bases such as triethylamine are used, which may destroy the catalyst, and (iii) the nitrile oxide have low-lying FMOs and therefore attempts to use the traditional activation of α,β-unsaturated carbonyl compounds with Lewis acids would probably fail.

At least one of these obstacles was overcome by Kanemasa et al.[353−357] Instead of using amines as bases for the generation of the nitrile oxide they applied alkylmagnesium bromide or alkoxymagnesium bromide (Scheme 48). The nitrile oxide is

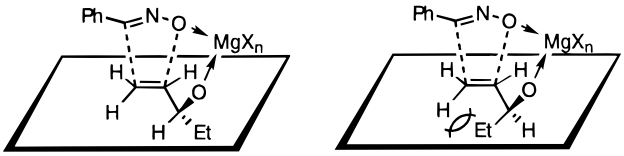
Scheme 48



smoothly generated at low temperature under these conditions probably coordinated to the magnesium salt. In the reaction of chiral allylic alcohols with nitrile oxides generated by the conventional method, low diastereoselectivity is mostly obtained; however, when the magnesium alkoxide is mixed with hydroximoyl chloride **360**, the resulting nitrile oxide

reacts with the alkene to give **363** with a syn selectivity of up to 98% de.

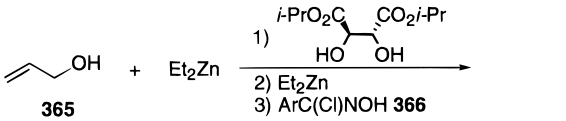
It is proposed that the syn selectivity and also rate accelerations observed are due to chelation via the metal salt. Of the two transition states *syn*-**364** and *anti*-**364**, the former is favored since steric repulsion between the substituent at the chiral center and the allylic proton is to be expected.[353,354,356] In reactions of 1,2-disubstituted alkenes of allylic alcohols this approach also offers an excellent control of the regioselectivity.[353,355]



syn-**364** favored

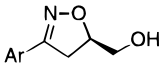
anti-**364**

Ukaji et al. applied a related approach to the first and so far only asymmetric metal-catalyzed 1,3-DC reaction of nitrile oxides with alkenes.[204,205] Upon treatment of allyl alcohol **365** with diethylzinc and (*R*,*R*)-diisopropyl tartrate, followed by the addition of diethylzinc and substituted benzoximoyl chlorides **366**, the isoxazolidines **367** are formed with impressive enantioselectivities of up to 96% ee (eq 64).[204]



365

1) *i*-PrO$_2$C, CO$_2$*i*-Pr, HO, OH
2) Et$_2$Zn
3) ArC(Cl)NOH **366**



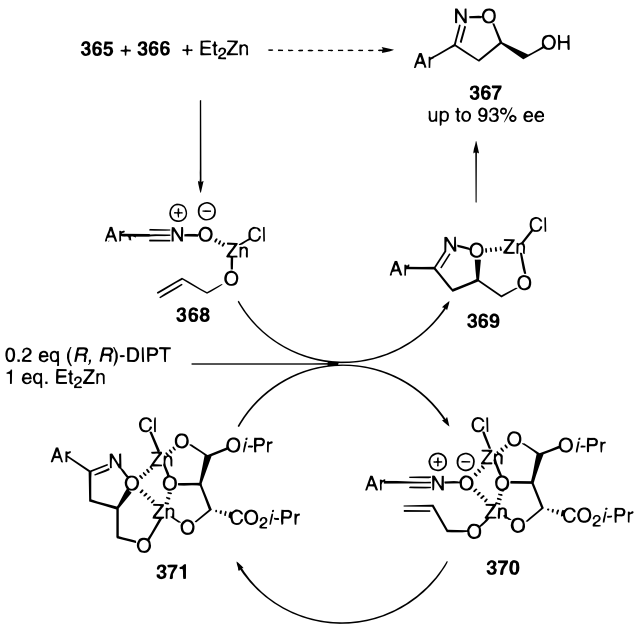
367
Ar = *p*-anisol, ee = 96%

(64)

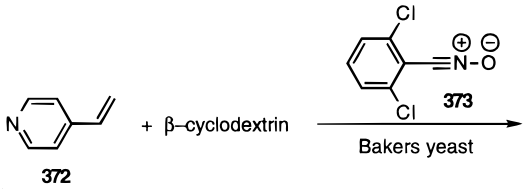
In an extension of this work they developed a catalytic version of the reaction in which the chiral ligand (*R*,*R*)-diisopropyl tartrate (DIPT) was applied at a concentration of 20 mol %.[205] Despite the reduction of the amount of the chiral ligand similar high enantioselectivities of up to 93% ee are obtained in this work. The addition of a small amount of 1,4-dioxane prove to be crucial for the enantioselectivity of the reaction. A proposal for the reaction mechanism was given, and it is outlined in Scheme 49.[205] Allyl alcohol **365**, hydroximoyl chloride **366**, and diethylzinc react to form **368**, which is mixed with the ligand and an additional amount of diethylzinc to form **370**. The achiral complex **368** is apparently much less activated for a 1,3-DC reaction compared **370**, which controls the enantioselectivity of the reaction. The increased reactivity of **370** compared to **368** may be due to a ligand accelerating effect of DIPT when coordinated to the metal. After formation of the isoxazoline **371**, the Zn-DIPT moiety of **371** proceeds in the catalytic cycle to form complex **370** with **368**. When the reaction is complete **369** is hydrolyzed to give **367**.[205]

In a rather peculiar work by Rao et al. which does not involve metal catalysis, the induction of enantio-

Scheme 49



selectivity in 1,3-DCs of nitrile oxides with alkenes by the application of bakers' yeast is described.[358] The enantioselectivities obtained were low (<25%); however, by the concomitant presence of cyclodextrines up to 64% ee was obtained. The alkene **372** forms an inclusion compound with an equimolar amount of β-cyclodextrin in water and is added to a mixture of the stable nitrile oxide **373** and bakers' yeast in a buffer solution (eq 65). After incubation at 37 °C for 20 h the product **374** is obtained in 85% yield, with an optical purity of 64% ee.

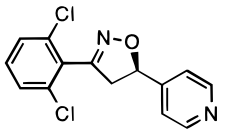


372

+ β–cyclodextrin

373

Bakers yeast

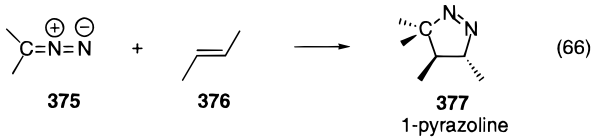


374
ee = 64%

(65)

8. Diazoalkanes

The 1,3-DC reaction of diazoalkane **375** with an alkene **376** leads to the formation of 1-pyrazoline **3** in a stereospecific manner (eq 66).



375 **376** **377**
1-pyrazoline

(66)

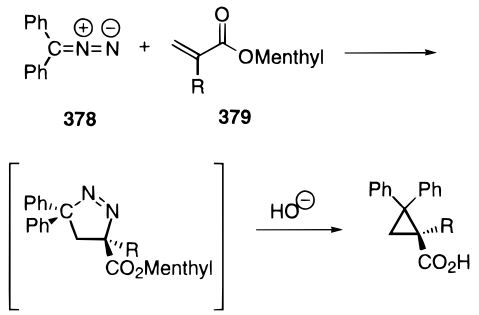
Much attention has been devoted to the asymmetric reactions of alkenes with diazoalkanes, but the majority of the work is in relation to cyclopropanation chemistry—which will *not* be covered in the present review and readers interested in this topic should consult the enormous amount of literature

related to this field. With a few exceptions, only reactions in which the pyrazoline **377** is obtained as a stable product from the 1,3-DC reaction will be considered in the following.

8.1. Chiral Alkenes

Walborsky et al. were probably the first to focus on the pyrazoline intermediate in the 1,3-DC reaction of diazoalkanes with chiral alkenes.[359] They studied the reaction of diphenyl diazomethane **378** with menthyl acrylates **379** in order to investigate the stereoselectivity of the cyclopropane formation (Scheme 50). In an attempt to account for the

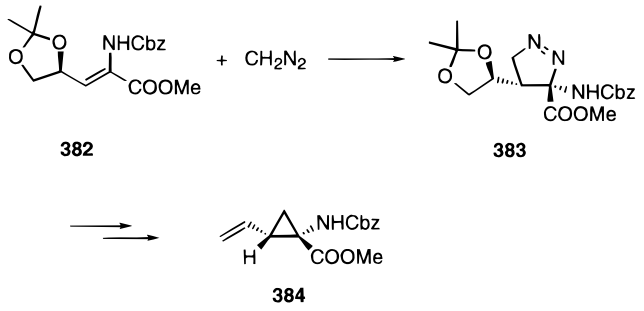
Scheme 50



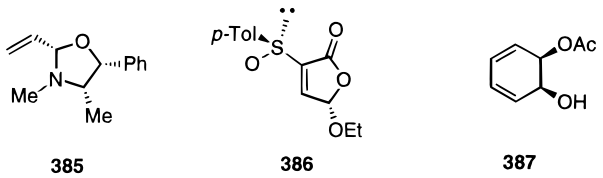
asymmetric induction of about 10% de, the pyrazoline **380** was proposed as an intermediate in the formation of the cyclopropane derivative **381**.

The pyrazoline intermediate has been discussed in several other papers dealing with the 1,3-DC reaction of diazoalkanes with chiral alkenes. The reactions of a chiral dehydroamino acid derivative **382**[360,361] with diazomethane proceeds to give **383** as the sole isomer in quantitative yield (Scheme 51). After

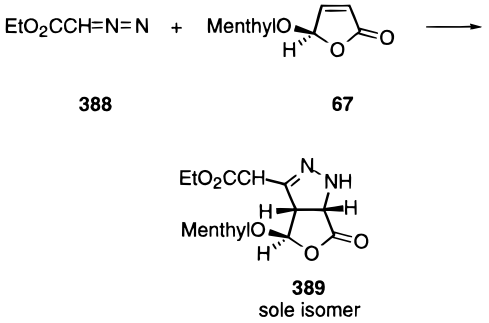
Scheme 51



further synthetic steps the coronamic acid derivative **384** was obtained in 65% overall yield. In related studies the reactions of 2-alkenyloxazolidines **385**,[362] chiral vinyl sulfoxides **386**,[363] and (1*R*)-acetoxy-(2*S*)-hydroxycyclohexa-3,5-diene **387**[364] with diazomethane have been performed, and in all cases high diastereoselectivities are obtained. In the reaction of **387** with diazomethane a 3:1 mixture of two isomeric pyrazolines is obtained, arising from the two different double bonds in **387**.[364] Other related reactions in which the intermediate pyrazolines were not isolated have also been performed.[365,366]



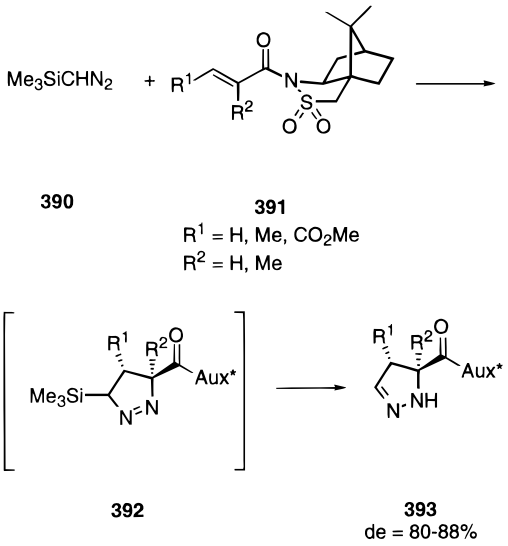
The 1,3-DC reaction of other diazoalkanes with chiral butenolides has been briefly studied (eq 67).[85,254,367] One example is the 1,3-DC reaction of ethyl diazoacetate **388** with 5-methoxy-2(5*H*)-furanone **67**, which resulted in formation of the 2-pyrazoline **389** as the sole product. The major diastereomer is formed by an anti-facial approach, and it should be noted that an isomerization to the 2-pyrazoline takes place.[254]



(67)

In a recent work Carriera et al. described the 1,3-DC reaction of (trimethylsilyl)diazomethane **390** with the camphor sultam derived alkenes **391** (Scheme 52).[368] The intermediate 1-pyrazoline **392** obtained

Scheme 52

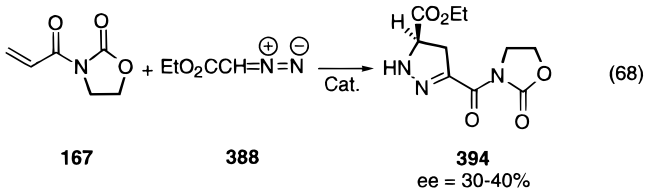


from this reaction rearranges following acidic work up to furnish the 2-pyrazoline **393** with 80−88% de. By further conversion of **393**, optically active azaprolines can be synthesized.

8.2. Asymmetric Catalysis

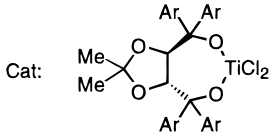
The 1,3-DC reaction of alkenes with diazoalkanes in the presence of chiral catalysts has been attempted.[369] Reaction of acryloyl oxazolidinone **167** with ethyl diazoacetate **388** in the presence of a Ti−

TADDOLate catalyst **159a** afforded the 1,3-DC product **394** in good yield an with an ee of about 30−40% (eq 68).



(68)

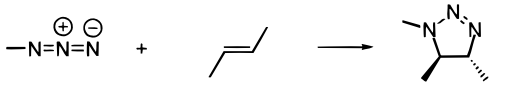
167 **388** **394**
ee = 30-40%



159a

9. Azides

The 1,3-DC reaction of an azide **395** with an alkene **396** leads to the formation of triazolines **397** (eq 69). For alkenes containing an electron-withdrawing substituent high regioselectivity is obtained.



(69)

395 **396** **397**
triazoline

The intermolacular 1,3-DC reactions of azides with alkenes are most frequently slow at rt and need very long reaction times.[370] This may be the reason that only asymmetric intramolecular 1,3-DC reactions of azides with alkenes has been described according to our knowledge.

9.1. Intramolecular Reactions

On the basis of the use of an intramolecular azide 1,3-DC reaction, Cha et al. have synthesized a series of natural products.[371−373] The stereoselective synthesis of (−)-swainsonine was achieved by this reaction. By using the same approach, followed by a cyclopropylimine rearrangement, (+)-crotanecine[373a] was prepared, and the same approach was also used for the synthesis of (−)-slaframine[372] and 6,7-di-*epi*-castanospermine **400**.[371] In these reactions the 1,3-DC adduct, the triazole, is not observed, and most often the chiral center(s) formed in the 1,3-DC reaction is destroyed in the following rearrangement. One exception of the latter is the reaction outlined in Scheme 53.[371] The intramolecular 1,3-DC reaction of the azide **398**, proceeds at 50 °C in pyridine to give the aziridine **399** as the sole product isomer in 52% yield.[371] By further synthetic steps 6,7-di-*epi*-castanospermine **400** was obtained.

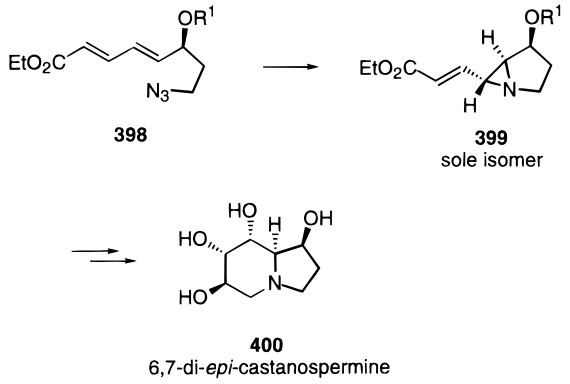
The intramolecular 1,3-DC reaction of azides with alkenes has been applied for the synthesis of the chiral hydroxypyrrolidines.[374] 2,3-*O*-Isopropylidene-D-erythrose (**401**) was converted to the azide **402** in two steps (Scheme 54). The azide **402** reacts immediately to give dihydrotriazole **403**, which was isolated. Formation of pyrrolidine **404** followed after base treatment. By the use of a compound similar to **402**, but with *Z* configuration of the alkene, diastereomeric pure **405** could be obtained. In this approach, the triazole isomeric with **403**, was not a stable compound and the corresponding pyrrolidine was obtained directly from the cycloaddition step.[374]

A tandem Wittig intramolecular 1,3-DC reaction has been used for the synthesis of piperidines, such as the homo-1-deoxyaza sugar **410**.[375] The intermediate compound **407** and the triazoline **408** could not be isolated, but it was observed that **408** isomerizes quantitatively to the diazoamine **409**, which was formed as a single diastereomer (Scheme 55).

Several other research groups have also used intramolecular 1,3-DC of azidoalkenes to produce different products such as Vasella et al. that used this approach for the synthesis of analogues of sialic acid.[376]

The asymmetric intramolecular 1,3-DC reaction of an azide with one of the alkenes in a conjugated diene has been developed by Hudlicky et al. and Pearson et al. for the preparation of pyrrolizidine alkaloids.[377−382] The general principle of this reaction is outlined in Scheme 56.

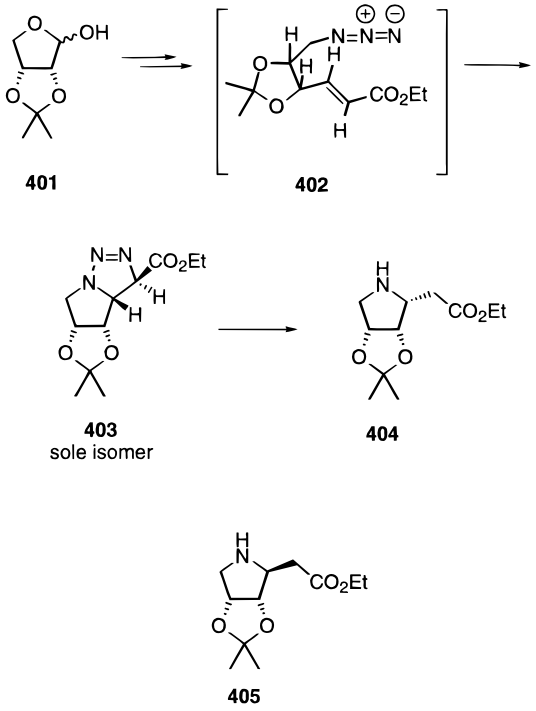
Scheme 53



398 **399** sole isomer

400
6,7-di-*epi*-castanospermine

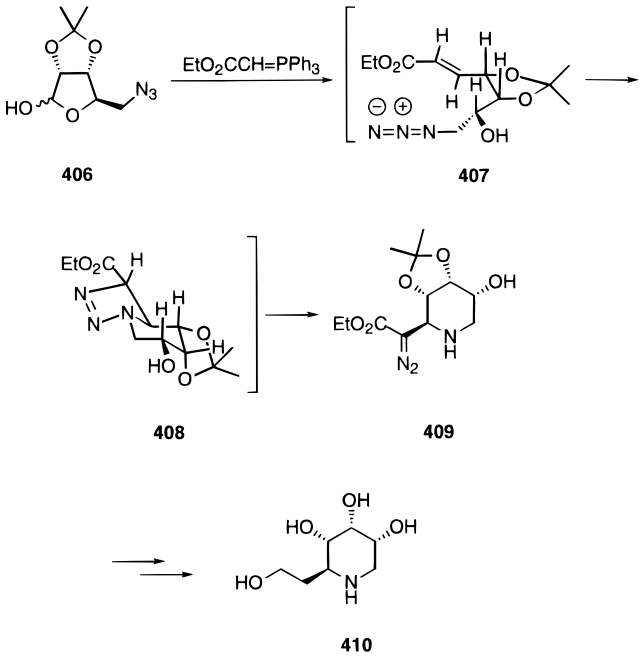
Scheme 54



401 **402** **403** sole isomer **404**

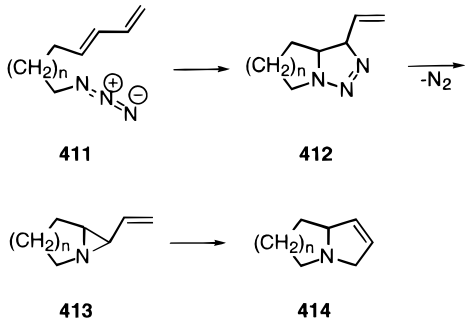
405

Scheme 55



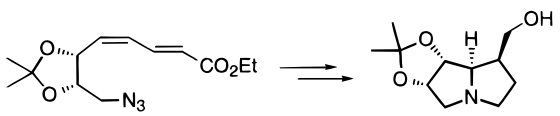
406 **407** **408** **409** **410**

Scheme 56



411 **412** **413** **414**

The azidodiene **411** undergoes an intramolecular 1,3-DC reaction, giving the triazoline **412**. Elimination of N_2 from **412** gives the vinylaziridine **413** which rearranges to the bicyclic 3-pyrroline **414**.[378−380] Hudlicky et al. have used this approach for the synthesis of pyrrozidine alkaloids such as **416**, which was formed as a single isomer, using the chiral substrate **415** (eq 70).[381]



415 **416** sole isomer (70)

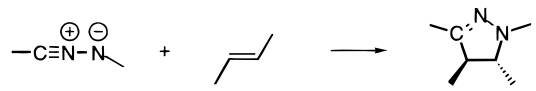
Pearson et al. studied the influence of the alkoxy group in the allylic position of the diene and found that the cyclization was very smooth, providing only one detectable isomer.[382]

10. Other Allenyl/Propargyl Anion Type Dipoles

In addition to the allenyl/propargyl anion type dipoles that have been described above are nitrile ylides, nitrile imines, and nitrous oxide. The 1,3-DC chemistry of nitrile ylides is well-known and has been described in several papers.[383] Surprisingly, no investigations of the asymmetric 1,3-DC reaction of nitrile ylides with alkenes have been published according to our knowledge. A few studies of asymmetric 1,3-DC reactions of nitrile imines have been performed, whereas the number of reports on the 1,3-DC chemistry of nitrous oxide is very limited and no asymmetric reactions have been described.[370]

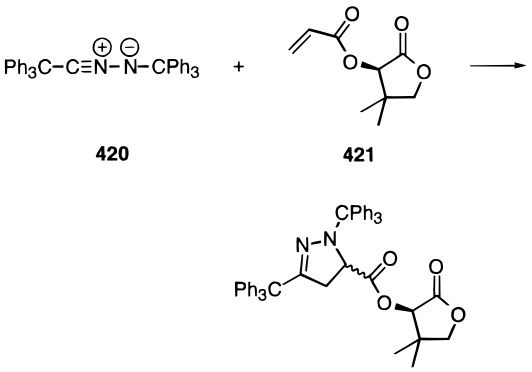
10.1. Nitrile Imines

The 1,3-DC reaction of nitrile imine **417** with an alkene **418** leads to the formation of a 2-pyrazoline **419** (eq 71).



417 **418** **419** 2-pyrazoline (71)

Only very few studies have been performed in the field of asymmetric 1,3-DC reactions involving nitrile imines. The bis(trityl)nitrile imine **420** is found to undergo a diastereoselective 1,3-DC reaction with (*R*)-α-(acyloxy)-*β*,*β*-dimethyl-*γ*-butyrolactone **421** to give 2-pyrazoline **422** which is formed in 60% yield and with a diastereomeric excess of 50% according to ^{1}H NMR spectroscopy (eq 72).[384]



420 **421** **422** 50% de (72)

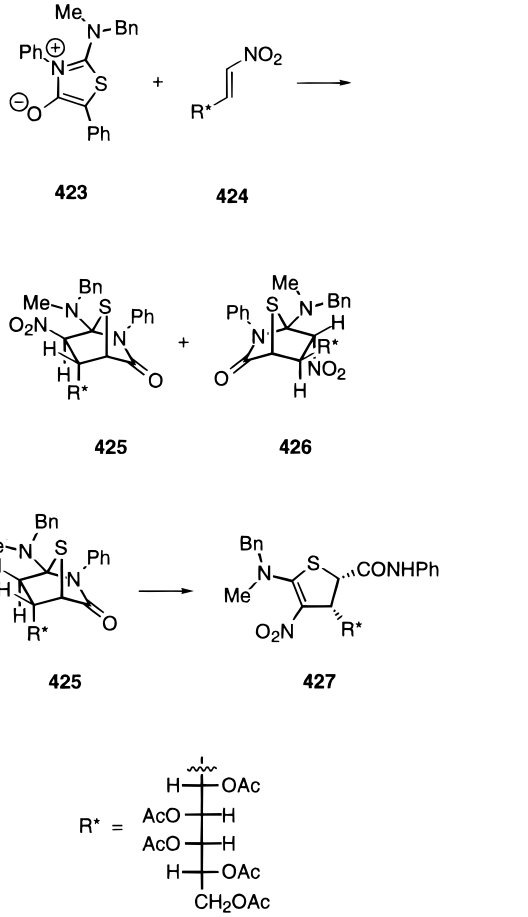
11. Other Types of 1,3-Dipoles

The 1,3-dipoles listed in Table 1 are made up of carbon, oxygen, and/or nitrogen, and they are of either the allyl anion type or the propargyl/allenyl anion type, but other types of 1,3-dipoles also exist. Higher row elements may also be incorporated in 1,3-dipoles. The 1,3-dipole may also be masked as, *i.e.*, in mesoionic compounds. However, only a few reports on asymmetric reactions of these types have been reported.

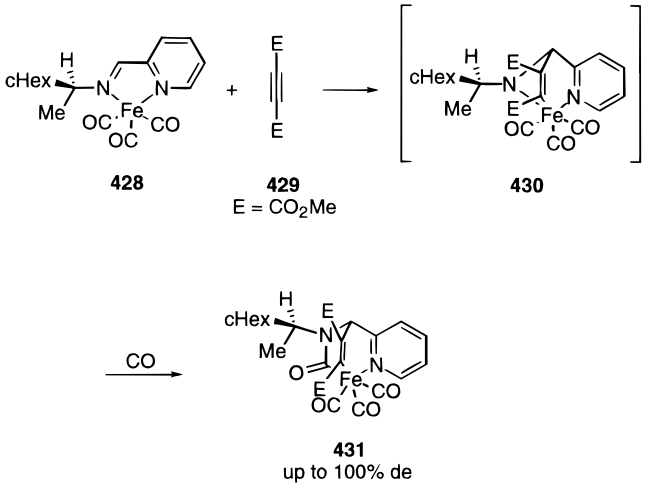
Avalos et al. have studied the 1,3-DC reaction of mesoionic compounds such as thioisomünchnone **423** with a chiral nitroalkene **424** (Scheme 57).[385−387] The reaction proceeds in CH_2Cl_2 at rt to give only two products **425** and **426**, out of four possible. The 1,3-DC products **425** and **426** are relatively unstable and tends to rearrange, as shown for **425**, into the final product **427**.[385]

In a few papers the asymmetric reactions of metalla dipoles have been described. Frühauf et al.

Scheme 57



Scheme 58



have described the reaction of the chiral iron compound **428**, in which the Fe−N=C fragment constitutes the 1,3-dipole, with dimethyl acetylenedicarboxylate **429** (Scheme 58).[388,389] After formation of the cycloadduct **430**, a CO insertion occurs and **431** is obtained with a high de. In some cases compounds related to **431** were converted into pyrrolinones.[388]

A number of related [3 + 2] cycloaddition reactions of alkenes with C−C−C or C−C−O fragments leading to cyclopentanes or hydrofurans, respectively, have also been described.[390−393] However, since such structures are not defined as 1,3-dipoles these reactions are excluded in this review.

12. Final Remarks

The 1,3-DC reaction is one of the most important methods for the construction of five-membered rings. By the application of chiral starting material it has often been possible to control both the regioselectivity, endo/exo selectivity, and diastereofacial selectivity in 1,3-DC reaction where one to four new chiral centers are formed. High stereocontrol has in many cases also been obtained using chiral auxiliaries, where the chiral moiety could be recovered. Several examples on the successful application of 1,3-DC reactions as the key step in the synthesis of optically active target molecules have been shown. The application of the 1,3-DC products is especially pronounced for products formed from dipoles such as nitrones, nitrile oxides, and azomethine ylides.

The application of metal catalysts in 1,3-dipolar cycloaddition reactions is a relative new field. Since 1994 several papers appeared on the asymmetric metal-catalyzed 1,3-DC reactions of nitrones and in three cases >90% ee have been obtained in these reactions. However, for the 1,3-DC reactions of other types of dipoles the number of contributions on asymmetric metal catalysis is very limited. In one case high enantioselectivities were obtained in a 1,3-DC reactions of nitrile oxides and in another case high ee's were obtained in a reaction of azomethine ylides.

With the increased demand for optically active compounds in the future and with the development in asymmetric metal catalysis, the development of new approaches to asymmetric metal-catalyzed 1,3-DC reactions is to be expected. The development of these reactions might be a difficult task to overcome—but not impossible!

13. Abbreviations

1,3-DC	1,3-dipolar cycloaddition
Aux*	auxiliary (chiral)
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
BINOL	1,1′-bi-2-naphthol
Bn	benzyl
BNP	1,1′-bi-2-naphthol phosphate
Cbz	benzyloxycarbonyl
cHex	cyclohexyl
DBU	1,8-diazabicyclo[5.4.0]undecyl-7-ene
DIPT	diisopropyl tartrate
EWG	electron-withdrawing group
FMO	frontier molecular orbitals
HOMO	higest occupied molecular orbital
INOC	intramolecular nitrile oxide cycloaddition
Ipc	isopinocampheyl
LDA	lithium diisopropyl amide
LUMO	lowest unoccupied molecular orbital
MO	molecular orbital
MOM	methoxymethyl
NBS	*N*-bromosuccinimide
p-Tol	*p*-tolyl
PMB	*p*-methoxybenzyl
rac	racemic
rt	room temperature
TADDOL	α,α,α′,α′-tetraaryl-1,3-dioxolane-4,5-dimethanol
TBDMS	*tert*-butyldimethylsilyl
Tf	triflouromethanesulfonyl
THP	tetrahydropyranyl

TMS	trimethylsilyl
Tos = Ts	*p*-toluenesulfonyl
Tr	trityl
W	electron-withdrawing group

14. Acknowledgments

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