Stereoselection in Reactions of Chiral Allyl Ethers: The Case of 1,3-Dipolar Cycloaddition

Laura Raimondi*[a] and Maurizio Benaglia[a]

Dedicated to Professor Mauro Cinquini on the occasion of his 60th birthday

Keywords: Asymmetric synthesis / Cycloadditions / Chirality / Transition states

The stereochemical outcome of 1,3-dipolar cycloaddition reactions to chiral allyl ethers is described, and a proposed interpretation is discussed.

Introduction

The achievement of good levels of stereoselection in reactions of nonrigid acyclic substrates represents a difficult task in organic synthesis. Several studies over the last two decades have dealt with this issue, and solutions ranging from substrate control to the use of chiral reagents or − better − chiral catalysts have been proposed.[1] We will discuss here a particular case of substrate-controlled stereoselectivity: the cycloaddition of 1,3-dipoles to acyclic chiral allyl ethers. This topic has received considerable attention over the past few years, due to the synthetic versatility of the cycloadducts, and represents an example of excellent interplay between experimental work and theoretical investigation.[2]

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1,3-Allylic Strain

The stereoselectivity observed in reactions of chiral allylic systems is generally explained on the basis of the 1,3-allylic strain effect, believed to determine the preferred conformations of an allylic stereocenter in the ground state, and thus the different shielding of the two diastereotopic faces of the alkene.[3] According to this theory, the preferred conformation presents the less hindering allylic substituent in an eclipsed conformation with the double bond. Ab initio calculations have confirmed this effect, and demonstrated the purely steric origin of the strain, allowing quantitative evaluation of the energies involved (Figure 1).[4,5]

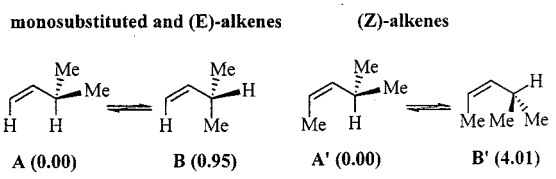

Figure 1. Ab initio (RHF/6−31G*//3−21G) relative energies (kcal/mol) of different conformations of 3-methyl-1-butene and (*Z*)-4-methyl-2-pentene in the ground state

Laura Raimondi was born in Milano in 1960. She received her laurea in Chemistry at the University of Milano in 1984, and her PhD in Chemical Sciences in 1989, working with Prof. Cinquini on 1,3-dipolar cycloadditions and osmylation reactions of chiral alkenes. After an 18-month post-doctoral fellowship at the University of California at Los Angeles, working with Professor Houk on theoretical studies of cycloaddition reactions, in 1990 she became Research Associate at the University of Milano, where she is now Associate Professor. Her more recent research topics are the stereochemical outcome of 1,3-dipolar cycloadditions, the stereoselective synthesis of 1,2-diols and amines, and conformational studies of organic and bioactive molecules.

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MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

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For terminally unsubstituted alkenes and (*E*)-olefins, two conformations − **A** and **B** − are favored (Figure 1). Conformation **A**, featuring the allylic hydrogen atom eclipsed with the double bond, is preferred over **B** (in which the same position is occupied by a methyl group) by about 1 kcal/mol at the RHF/6−31G*//3−21G level. On the other hand, (*Z*)-alkenes are almost completely locked in conformation **A′**, due to the steric requirements of the double bond, which force the smallest residue (the hydrogen atom) into the plane of the alkene. The structure with one methyl group eclipsed with the alkene presents severe steric repulsions between the two methyl groups, and is a maximum on the potential energy surface. Therefore, on the basis of purely steric considerations, reactions of (*Z*)-alkenes should be more stereoselective than those of their (*E*) counterparts, since the difference in shielding of the two diastereofaces of the olefin should, due to the different substituents at the allylic stereocenter, be amplified by conformational lock.

Such a picture, however, is a static one, and small deviations from the conformations shown in Figure 1 are not so costly.[4a] This is actually what happens when a substrate changes its geometry from that of the ground state to that of the transition state. Barriers to internal rotations are in general lower than the energy barrier of a reaction:[5] However, this theory assumes that the factors influencing the conformational preferences of the substrate in its ground state will also influence those of the corresponding transition states − and eventually, according to the Curtin−Hammet principle, the stereochemical outcome of the reaction.

When the allylic stereocenter features heteroatomic substituents capable of stereoelectronic effects, as in the case of allylic ethers, the general picture can be quite different. The presence of an allylic oxygen atom significantly alters the conformational preferences of the allylic stereocenter: Stereoelectronic effects superimpose on the steric effects caused by the 1,3-allylic strain. Since this stereoelectronic tuning involves energies of 1−2 kcal/mol at most,[6] chiral (*Z*)-allyl ethers will not be significantly affected by the stereoelectronic effect of the ethereal oxygen atom, the allylic strain conformational preferences being worth about 4 kcal/mol (see Figure 1). On the other hand, stereoelectronic effects can enhance the stereochemical preferences in (*E*)-alkenes by cooperating with steric factors.

Figure 2 gives the ab initio (RHF/6−31G*) located conformational minima for 3-buten-2-ol.[6] Conformation **E**, with a methyl group eclipsing the double bond, is considerably higher in energy than its deoxygenated counterpart (conformation **B** of Figure 1), the relative energy raising from 0.95 to 1.53 kcal/mol. This effect is attributable to the preference of the C−O bond to stay in the plane of the π-system, due to stereoelectronic factors and orbital interactions.[6] As a consequence, the two conformations **C** and **D** of Figure 2, featuring the hydrogen atom and the hydroxy group eclipsed with the alkene, respectively, are calculated to have almost the same energy at the RHF/6−31G* level.

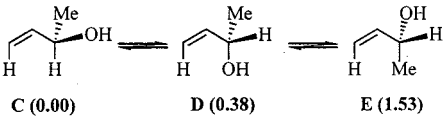


Figure 2. Ab initio (RHF/6−31G*) relative energies (kcal/mol) for different conformations of 3-buten-2-ol in the ground state

The Inside and Outside Alkoxy Effects

As previously stated, provided that only small conformational changes are required, the conformational preferences of the substrate in the ground state will be reflected in the transition state. This means that these preferences superimpose on, and have be reconciled with, the transition state's geometrical and electronic requirements.[7] Thus, in the case of 1,3-dipolar cycloaddition, the conformational preferences of the allylic stereocenter have to fit with the requirements of the reacting double bond and with the steric and electrostatic demands of the 1,3-dipole in a 5-membered, cyclic transition structure.[8−10] The 1,3-dipoles can be divided roughly into two classes: the linear, "propargylic" ones (such as nitrile oxides and diazo derivatives), and the bent, "allylic" ones (i.e. nitrones, azomethine ylides, and such).[2] The transition structure for the reaction of a linear 1,3-dipole with an alkene is planar, while allylic 1,3-dipoles approach the alkene in a nonparallel plane, Diels−Alder-like fashion. Two approaches, *endo* and *exo*, are thus possible for substituents on the reacting moieties (see Figure 3).[8−11]

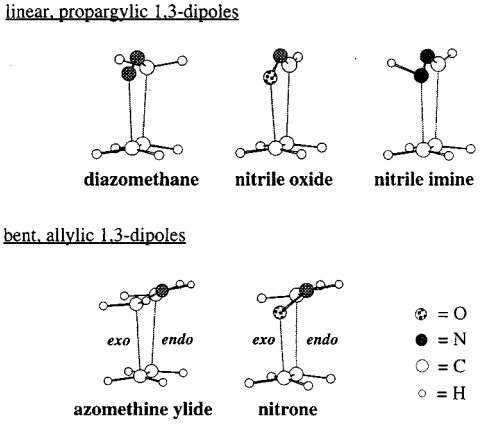


Figure 3. Ab initio (RHF/3−21G) transition structures for the cycloaddition reaction of different 1,3-dipoles to ethylene

The constraints imposed by the concerted nature of the reaction have two major consequences: (i) the five-membered ring causes crowding of the so-called *inside* position with respect to the *outside* and *anti* ones, the last being the least hindered (Figure 4), and (ii) partial atomic charges on the 1,3-dipole moiety exert an electrostatic influence (Figure 5).[7,10a] In general, when the regioselectivity of the reaction brings the allylic substituents close to the negatively charged terminus of the 1,3-dipole, a destabilization of the *outside* region is observed for an electronegative residue (e.g., an oxygen atom) in the allylic position.[8,10,12] In this case, direct determination of the relative energies for different substituents at the allylic stereocenter in the *inside*, *outside*, and *anti* conformations was performed using ab initio

(RHF/3−21G and 6−31G*) methods for nitrile oxide cycloadditions to substituted alkenes, resulting in the proposal of the "inside alkoxy" theory. Relative energies are given in Figure 4.[12]

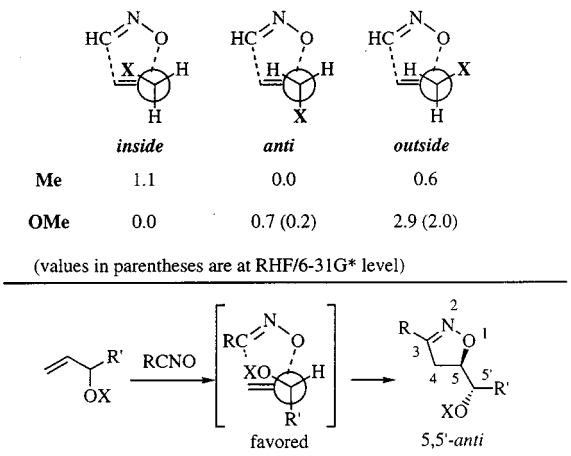


Figure 4. Ab initio (RHF/3−21G) relative energies (kcal/mol) for different conformations of the transition structures of fulminic acid with 3-methyl-1-butene and 3-methoxy-1-butene

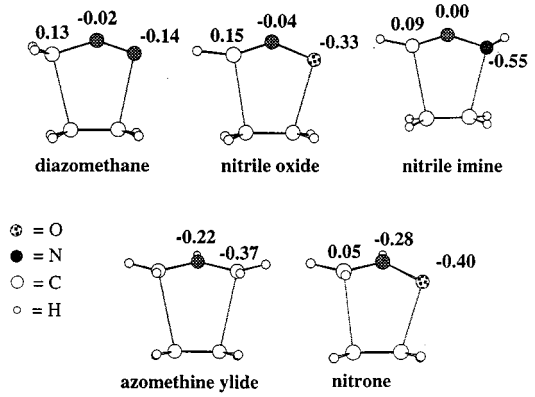


Figure 5. CHELPG charges in the transition structures for the cycloaddition reaction of different 1,3-dipoles to ethylene

On the basis of purely steric considerations (Figure 4, X = Me), the *anti* position is preferred, while the *inside* one is the most severely crowded, the steric destabilization amounting to about 1 kcal/mol. Alkoxy substituents, however, tend to avoid the *anti* conformation, because the overlap between $\pi^{b}_{C=C}$ and σ^{*}_{C-O} orbitals withdraws electrons from the reacting alkene, and destabilizes the corresponding TS. This effect is minimized when the oxygen-containing group occupies either the *inside* or the *outside* position, but the latter is electrostatically destabilized by repulsive interaction between the two partial negative charges on the approaching oxygen atoms. This electrostatic effect represents at least 2 kcal/mol, and causes a reversal of the conformational preferences for an oxygenated allylic substituent, the most crowded *inside* position being its favorite one. Thus, with reactions of chiral allyl ethers, the conformation of the TS featuring the alkoxy residue in the *inside* position and the alkyl group in the *anti* one is favored for both steric (the *anti* position is the less crowded) and stereoelectronic (the alkoxy residue prefers the *inside* position) reasons. As a consequence, a relatively high degree of stereoselectivity results, favoring the 5,5′-*anti* cycloadducts (Figure 4).[7,12] This effect is obviously stronger when the dipolarophile features electron-rich ethereal oxygen atoms; electron-poor oxygenated residues, such as esters, allow only small levels of stereoselectivity.[2,12b,12c]

In this model, the partial atomic charges on the 1,3-dipole in the transition structure of the reaction are of great importance. Figure 5 shows CHELPG charges at the RHF/3−21G level.[10a] On the basis of purely electrostatic considerations, nitrile oxides and nitrones are expected to produce comparable levels of *anti* selectivity, since in both instances, similarly negatively charged oxygen atoms (Figure 5) interact with the allylic substituents. Experimentally, nitrones show comparable − or better − *anti* selectivities than nitrile oxides;[2] it must be noted that geometrical considerations also play a role in the stereochemical outcome of the reaction, nitrones being bent dipoles while nitrile oxides are of the propargylic type (Figure 3). Nitrile imines behave similarly to nitrile oxides, as expected on the basis of their geometries and charge distributions.[2,13]

On the other hand, when the reaction occurs with the opposite regioselection, and the negatively charged dipole terminus hence attacks the alkene carbon atom β to the allylic stereocenter, a reversal of stereoselectivity from *anti* to *syn* is possible, as may be anticipated if the atomic charges depicted in Figure 5 are considered. In this case, an "outside alkoxy effect" can be regarded as responsible for the stereochemical course of the reaction, and indeed a preference for *syn* adducts has been observed in some reactions of diazomethane and nitrones with alkenes.[2b,14,15] Figure 6 shows the relative energies for diazomethane/alkene cycloaddition for the formation of both regioisomers, evaluated at a semiempirical (PM3) level.[2b,14,16] Depending on the regioisomeric outcome of the reaction, an "inside" or an "outside" effect is operative for the alkoxy residue. Both "inside alkoxy" and "outside alkoxy" effects, however, have common roots: the unfavorable orbital overlap that destabilizes the conformation in which the OR group is in the *anti* position, and electrostatic interactions with charged termini of the 1,3-dipole in the cycloaddition transition structure.

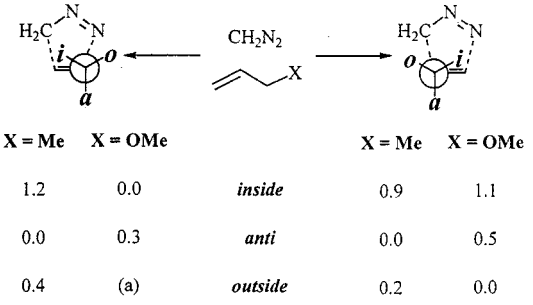
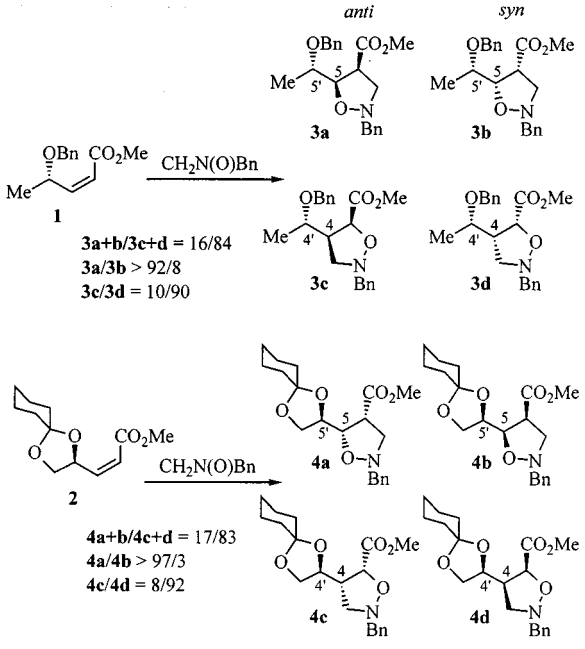


Figure 6. PM3 relative energies (kcal/mol) for different conformations of the transition structures of diazomethane with 1-butene and 3-methoxy-1-propene (both regioisomers are considered); (a) not a true minimum on the potential energy surface

In this review, we will focus on both inter- and intramolecular 1,3-dipolar cycloadditions of various dipoles to acyclic chiral allyl ethers.

1,3-Dipolar Cycloadditions of (*Z*)-Alkenes

Reaction with (*Z*)-alkenes can, in principle, be extremely stereoselective. The major problem resides in the often low level of reactivity of the alkene itself toward 1,3-dipoles, due to the severe steric requirements of the substrate.[2] Another serious problem derives from regioselection in the reaction: Intermolecular cycloadditions to 1,2-disubstituted alkenes are often regiorandom, and the lack of regioselectivity severely diminishes the synthetic utility of the methodology. For instance, the reaction between formaldehyde *N*-benzylnitrone and methyl (4*S*)-(*Z*)-4-benzyloxy-2-pentenoate results in the formation of both regioisomers, each as a mixture of two diastereoisomers (Scheme 1).[15] Inspection of the data, however, is extremely interesting: The reaction is slightly regioselective, favoring the cycloadducts bearing the stereocenter at the 4-position of the isoxazolidine. For both regioisomers, however, the stereoselectivity is high, and an explanation for this is to be found in the transition state conformations shown in Figure 7. As stated previously, the requirements of a (*Z*)-alkene both in the ground state and in the transition state strongly favor the conformation in which the small allylic substituent is in the sterically crowded *inside* region. Favored TS **F** also features the benzyloxy residue in the *anti* conformation, avoiding the electrostatically unfavorable *outside* one; the result is a 5,5′-*anti* stereoselectivity (**3a/3b** > 92:8; **4a/4b** > 97:3).[17] The regioisomeric transition structure **G**, on the other side, still maintains the hydrogen atom *inside*, but features the alkoxy group in the *outside* (not destabilized) region, and allows for the preferential formation of the 4,4′-*syn* cycloadducts (**3c/3d** = 10:90; **4c/4d** = 8:92).



Scheme 1. Intermolecular 1,3-dipolar cycloaddition of nitrones to chiral (*Z*)-alkenes

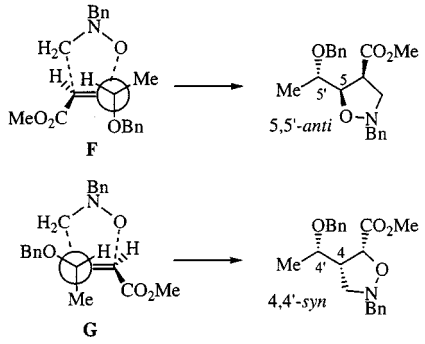
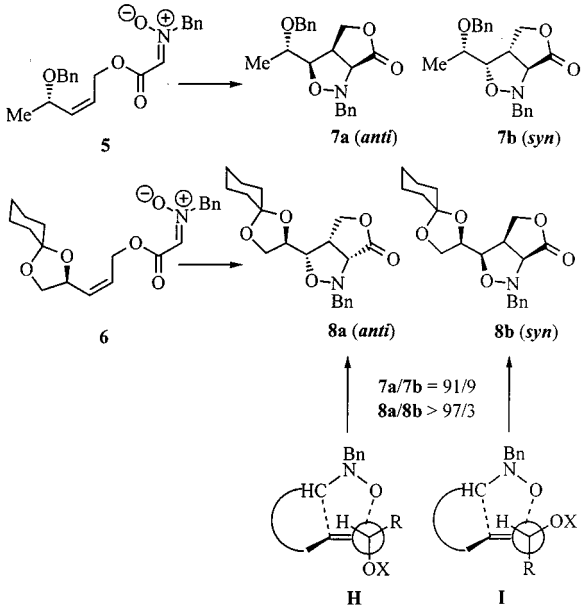


Figure 7. Favored transition structures for the preferential formation of 5,5′-*anti* or 4,4′-*syn* regio- and diastereoisomeric adducts (cf. Scheme 1)

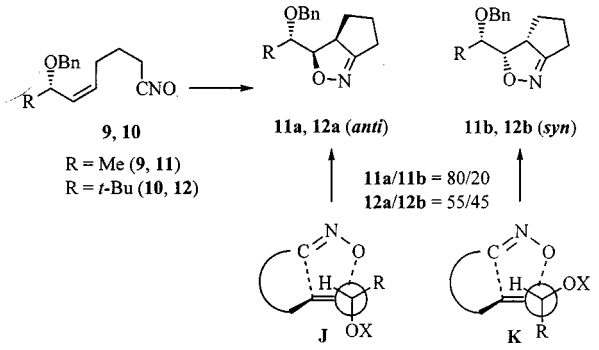
A simple way to avoid undesired formation of regioisomeric mixtures can, however, be found in intramolecular reactions.[2,18,19] A three- or four-atom chain connecting dipole and dipolarophile will ensure complete regioselectivity and avoid too much strain on the bicyclic transition structure. In this fashion, completely regioselective cycloadditions of nitrones and nitrile oxides to chiral allyl ethers have been accomplished, affording only isoxazolidines and isoxazolines bearing the stereocenter at the 5-position of the heterocyclic ring: One example is depicted in Scheme 2. The stereoselectivity of intramolecular nitrone cycloaddition to a (*Z*)-alkene is extremely high, because of the conformational lock imposed by the alkene (*Z*) geometry. Obviously, only the two diastereoisomeric transition structures featuring the hydrogen atom in the *inside* position are relevant, and the alkoxy group preference for the *anti* position over the *outside* one determines the reaction stereoselectivity, in favor of the 5,5′-*anti* adduct.



Scheme 2. Intramolecular 1,3-dipolar cycloaddition of nitrones to chiral (*Z*)-alkenes

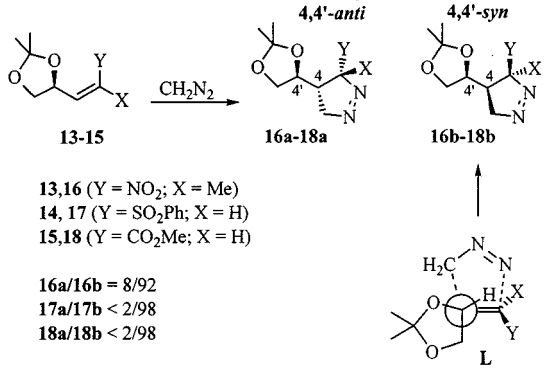
A related study carried out on a structurally similar nitrile oxide also led to interesting conclusions (Scheme 3).[19a] In this case, an increase in the steric require-

ments of the alkyl residue at the allylic stereocenter (from methyl to *tert*-butyl) resulted in an impressive decrease in the 5,5′-*anti* stereoselectivity. In fact, in the reaction of the methyl derivative **9**, transition structure **J** predominates, and a 80:20 diastereoisomeric ratio results. A more hindered *tert*-butyl group, however, strongly prefers the less crowded *anti* position: This tendency overrides that of the alkoxy group to avoid the *outside* region. Both TS **J** and **K** are operative, and a stereorandom reaction results.



Scheme 3. Intramolecular 1,3-dipolar cycloaddition of nitrile oxides to chiral (*Z*)-alkenes

Intermolecular diazomethane cycloadditions with chiral, electron-poor allyl ethers are completely regioselective; the isomers possessing the allylic stereocenter at the 4-position of the pyrazoline are formed exclusively.[2b,14,20−22] Several chiral alkoxy-substituted (*Z*)-alkenes (nitro olefins, vinyl sulfones and enoates) were studied with the purpose of establishing the origin of the high π-facial selectivity: in all cases, the chemical yields were almost quantitative, and the 4,4′-*syn* stereoselectivities were − as expected − extremely high (Scheme 4). The preferred transition structure **L**, shown in Scheme 4, should be favored on the basis of the "outside alkoxy" effect. Conversion of pyrazolines **16**−**18** to the corresponding cyclopropane derivatives was achieved in good yields and with complete stereocontrol.[20a]



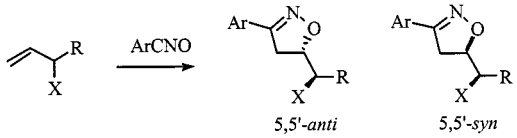
Scheme 4. Intermolecular 1,3-dipolar cycloaddition of diazomethane to chiral (*Z*)-alkenes

1,3-Dipolar Cycloadditions on Monosubstituted and (*E*)-Alkenes

The stereochemical outcome of 1,3-dipolar cycloaddition to monosubstituted and (*E*) chiral allyl ethers was not easily rationalized until the formulation of the "inside alkoxy" theory.[2,7,12] Since, as with (*Z*)-alkenes, intermolecular reactions involving (*E*)-olefins are often nonregioselective, the bulk of experimental data has been collected for terminal alkenes. The steric requirements imposed by the terminal or the (*E*) double bond on the conformation of the allylic stereocenter are indeed the same, since the substituent in the *inside* position of the transition structure is close to a hydrogen atom in both cases.

Ab initio determination of the conformational preferences in reactions between fulminic acid (the simplest nitrile oxide) and substituted alkenes (as depicted in Figure 3) resulted in the postulation of the so-called "inside alkoxy" effect, and stimulated an increasing number of studies to assess the reliability and limitations of this theory. For nitrile oxide reactions, a few points are well established: (i) the favored 5,5′-*anti* selectivity derives from a balance between the tendency of the allylic alkoxy residue to avoid both the *outside* and the *anti* positions (because of electrostatic repulsion with the incoming oxygen atom of the 1,3-dipole and the unfavorable orbital overlap, respectively), and the tendency of the alkyl group to stay in the less hindered *anti* region (Figure 3); (ii) this effect is stronger for electron-rich allylic oxygen atoms and bulky alkyl groups; (iii) other allylic heteroatoms have the same effect (allylic amines, for instance, behave similarly to allylic ethers); (iv) if the allylic heteroatom bears a hydrogen atom, the conformational preferences in the transition state can be significantly altered because of H-bond formation with the dipole oxygen atom. Selected results are collected in Table 1.[2,12,23,24]

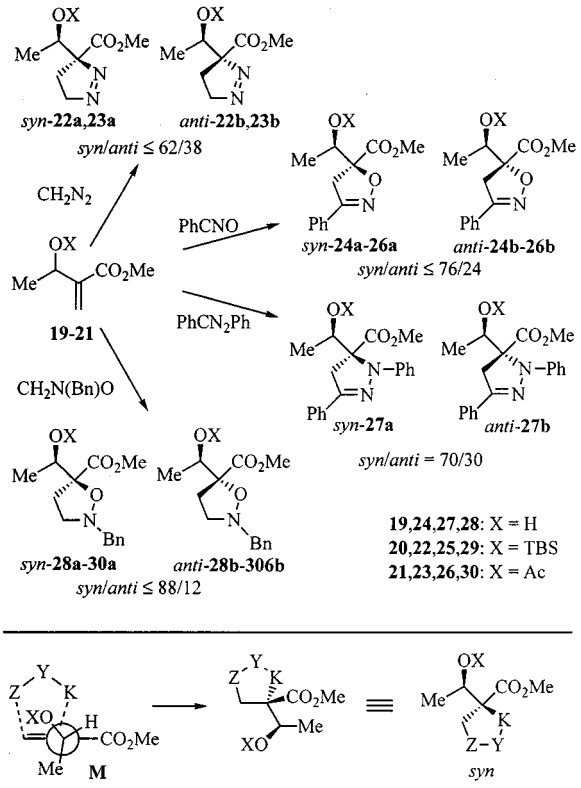
Table 1. Stereochemical outcome of the 1,3-dipolar cycloaddition of aryl nitrile oxides to chiral alkenes[2,22]



entry	R	X	5,5′-*anti*/*syn*	ref.
1	Et	Me	50/50	[2b]
2	*t*-Bu	Me	77/23	[2b]
3	Me	OBn	64/36	[2b]
4	*t*-Bu	OMe	97/3	[2b]
5	$(MeS)_3C$	OTBS	>98/2	[2b]
6	Me	OAc	55/45	[2b]
7	Me	Cl	50/50	[2b]
8	CH_2O-$C(Me_2)$-O		84/16	[2b]
9	CH_2O-C(Ph)=N		76/24	[23]

The conclusions derived for intermolecular nitrile oxide cycloadditions also maintain their validity for the corresponding inter- and intramolecular reactions of (*E*)-alkenes.[2,19] More interestingly, the "inside alkoxy" theory also works for other 1,3-dipolar cycloadditions, resulting in regioisomers bearing the stereocenter close to the former negatively charged atom of the 1,3-dipole. Inspection of

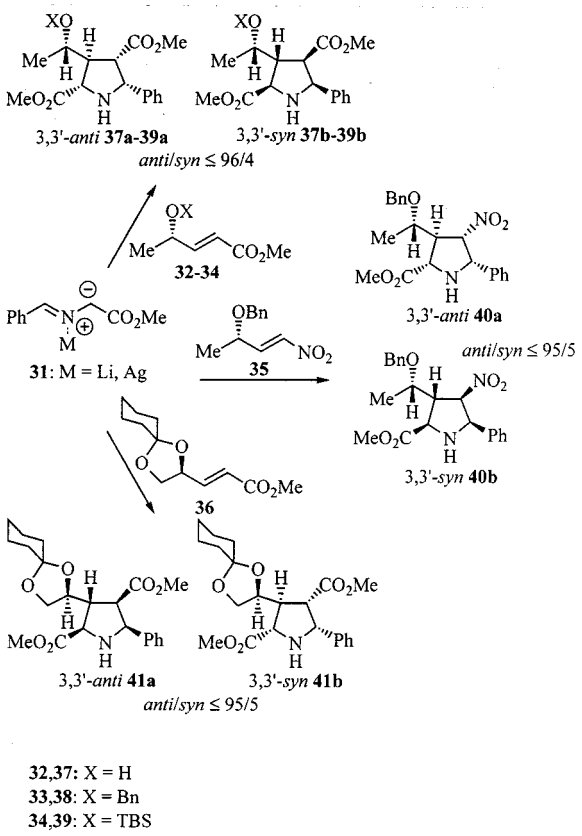
atomic charges in the TS clearly suggests that, for the reactions of 1,3-dipoles shown in Figure 5, the formation of the "inside alkoxy" product should be favored, diazomethane cycloadditions being less selective because of the low negative charge on the terminal nitrogen atom.[10a] A direct comparison between different 1,3-dipoles can be made for cycloadditions to the same chiral alkene. This was achieved by investigation of reactions of chiral α′-alkoxy-α,β-unsaturated esters (the so-called Baylis−Hillman adducts), which react with nitrile oxides, nitrones, nitrile imines, and diazomethane with complete and identical regioselectivities (some examples are shown in Scheme 5). Unfortunately, azomethine ylides do not react under these conditions.[2,13,15,16]



Scheme 5. Intermolecular 1,3-dipolar cycloadditions of various 1,3-dipoles to Baylis−Hillmann adducts

The *syn* diastereoisomers (deriving from the "inside alkoxy"-type transition structure **M**) are favored in all cases. Clearly, the different geometrical requirements of the transition state geometries do play a role in tuning the stereoselectivity of the reactions; however, it does appear that diazomethane cycloadditions are generally less selective than those of nitrile oxides and nitrones[15,16] (only a few data are available for nitrile imine reactions).[13] This effect can be ascribed to the low degree of electrostatic destabilization of the *outside* region in the reaction TS, because of the low negative charge on the nitrogen atom, and finds an excellent explanation in the "inside alkoxy" theory.

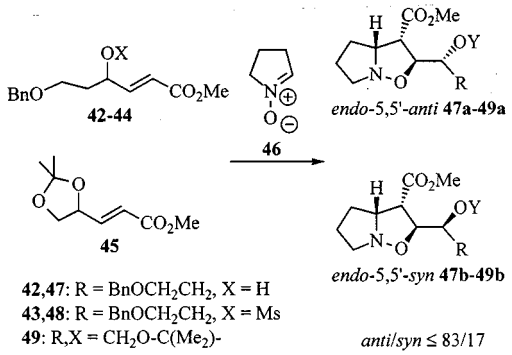
Other substrates widely tested in 1,3-dipolar cycloadditions are chiral γ-alkoxy-substituted, electron-poor (*E*)-alkenes (Scheme 6). For example, azomethine ylides react with esters in a completely regioselective fashion, affording



Scheme 6. Intermolecular 1,3-dipolar cycloadditions of azomethine ylides to electron-poor chiral (*E*)-alkenes

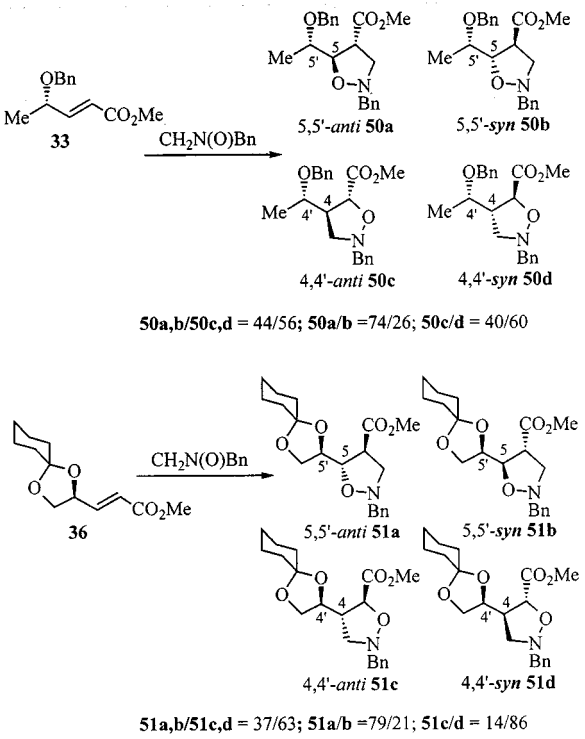
"inside alkoxy" 3,3′-*anti* products with good to excellent stereoselectivity.[2,25−27]

Cyclic nitrones are also completely regioselective in their reaction with (*E*)-γ-alkoxy-α,β-unsaturated esters. For example, five-membered cyclic nitrone **46** reacts with alkenes **42**−**45** with complete regioselectivity and excellent *endo* selectivity (Scheme 7). The diastereoisomeric ratios, that range from 73:27 (**47a/b**) to 83:17 (**49a/b**), may be explained by "inside alkoxy" transition structures. Analogous results were obtained for cycloadditions with the corresponding carboxylic acids. The reactions of six-membered cyclic nitrones are less *endo*-selective.[28]



Scheme 7. Intermolecular 1,3-dipolar cycloaddition of cyclic nitrones to chiral (*E*)-alkenes

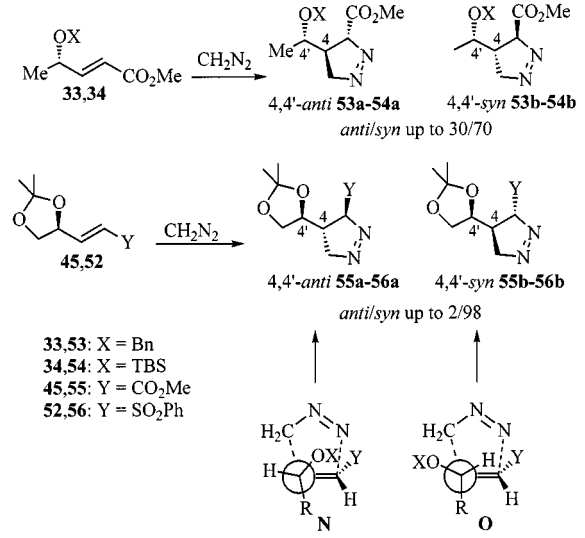
On the other hand, the nonstereogenic formaldehyde *N*-benzyl nitrone reacts with (*E*)-γ-alkoxy-α,β-unsaturated es-



Scheme 8. Intermolecular 1,3-dipolar cycloaddition of nitrones to chiral (*E*)-alkenes

ters with poor regioselectivity, as was the case for their (*Z*) counterparts (Scheme 8; cf. Scheme 1).[15] In the formation of 4-methoxycarbonyl-5-alkyl-substituted isoxazolidines (**50a**, **50b**, **51a**, and **51b**), the 5,5′-*anti* "inside alkoxy" product prevails. When the corresponding regioisomers **c** and **d** are formed, however, a reversal of stereoselectivity to 4,4′-*syn* adducts is observed, in accordance with the "outside alkoxy" effect. Obviously, intramolecular reactions are completely regioselective.[18]

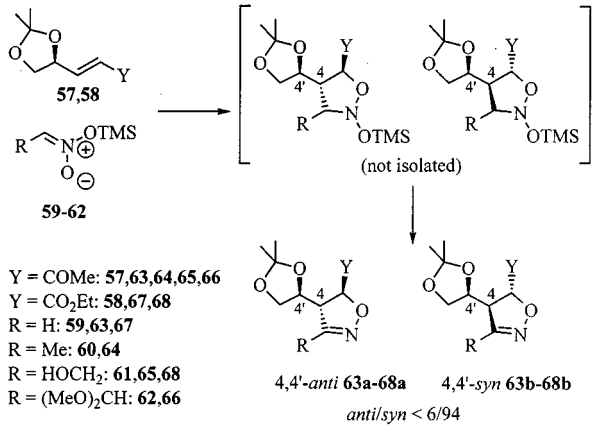
Cycloadditions of diazomethane to (*E*)-γ-alkoxy-α,β-unsaturated esters are completely regioselective, affording only 3-methoxycarbonyl-4-alkylpyrazolines with high 4,4′-*syn* selectivity. Scheme 9 shows some examples. TSs **N** and **O**



Scheme 9. Intermolecular 1,3-dipolar cycloaddition of diazomethane to chiral (*E*)-alkenes

provide an explanation of the experimentally observed stereoselectivities: The allylic alkoxy residue avoids the *anti* position (preferred by the alkyl residue) and occupies the *inside* position in TS **N** and the *outside* position in TS **O**. 1,3-Allylic strain slightly destabilizes the *inside* position and TS **N**, thus leading to a preference for 4,4′-*syn* pyrazolines that increases with increasing bulkiness of the alkoxy residue.[2,14,20–22,29]

Intermolecular cycloadditions of silyl nitronates to (*E*)-γ-alkoxy-α,β-unsaturated esters and enones are also completely regioselective, and the "outside alkoxy" products are favored (Scheme 10). The cycloadducts were easily converted in the corresponding isoxazolines in good yields and with excellent stereoselectivity.[30] This procedure is particularly interesting since cycloaddition of nitrile oxides with the same substrates is only poorly regio- and stereoselective.[2b,31]



Scheme 10. Intermolecular 1,3-dipolar cycloaddition of silyl nitronates to chiral (*E*)-alkenes

Metal Coordination Control in 1,3-Dipolar Cycloaddition Reactions

While the stereoselectivity achieved in 1,3-dipolar cycloaddition reactions to chiral allyl ethers is predictable on the basis of the 1,3-allylic strain [for (*Z*)-alkenes] and of "inside" and "outside" alkoxy effects [in the case of non-hindered terminal and (*E*)-alkenes], chiral allylic alcohols display an erratic behavior, resulting in either *anti* or *syn* selectivity. This effect is due to the possibility of hydrogen bond formation between the incoming negatively charged terminus of the 1,3-dipole and the hydroxy group in the *outside* position (Figure 8).

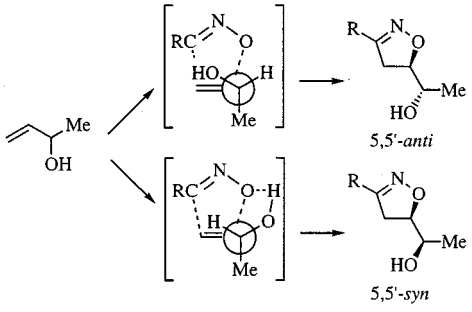
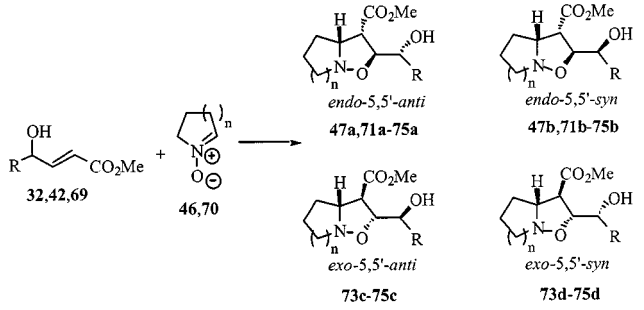


Figure 8. Proposed conformations for the transition structure of fulminic acid with 3-buten-2-ol

The stereochemical outcome of the reaction depends strongly on the solvent, the reagent dilution, and other geometrical characteristics of the TS. The results are often unpredictable, and in general no significant stereoselectivity is observed.[2] A typical example is shown in Table 2. Reaction of five-membered cyclic nitrone **46** with various allylic alcohols is always completely *endo*-selective; the 5,5′ selectivity is generally low, and can be either *anti* or *syn*. On the other hand, the corresponding six-membered cyclic nitrone **70** affords both *endo* and *exo* adducts, again with a low 5,5′-*anti*/*syn* ratio.[28]

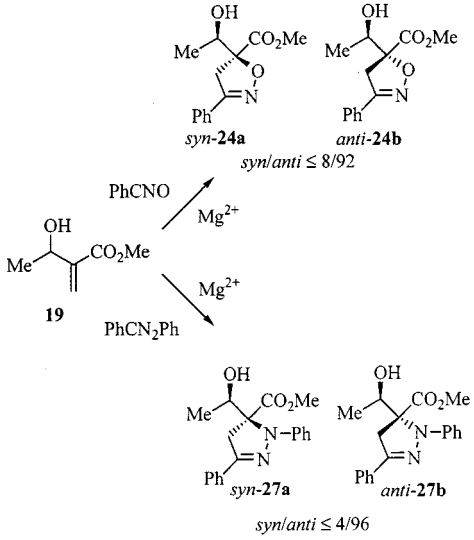
Table 2. Stereochemical outcome of the 1,3-dipolar cycloaddition of cyclic nitrones to chiral allylic alcohols



entry	alkene	nitrone	R	n	products	a/b/c/d
1	**42**	**46**	$BnO(CH_2)_2$	1	**47a,b**	73/27
2	**69**	**46**	$HOCH_2$	1	**71a,b**	41/59
3	**32**	**46**	Me	1	**72a,b**	33/67
4	**42**	**70**	$BnO(CH_2)_2$	2	**73a-d**	57/24/4/15
5	**69**	**70**	$HOCH_2$	2	**74a-d**	37/45/4/14
6	**32**	**70**	Me	2	**75a-d**	35/40/5/20

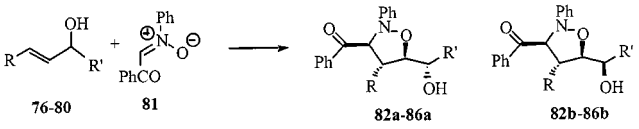
A major breakthrough in this field was achieved by performing the cycloaddition reaction in the presence of chelating Lewis acids. Best results were obtained with magnesium salts in noncoordinating solvents such as dichloromethane. Under these conditions, nitrile oxides reacted with chiral allylic alcohols to afford 5,5′-*syn* cycloadducts in excellent chemical yields and with high degrees of stereoselectivity. Nitrile imine and nitrone cycloadditions to allylic alcohols are also highly stereoselective under Mg^{2+} complexation conditions: some data are reported in Scheme 11 and in Table 3.[13,32]

Several Lewis acids were tested for their ability to promote the 1,3-dipolar cycloaddition; attention is currently focussed on the use of chiral, enantiomerically pure ligands at the metal center. The possibility of employing efficient chiral catalysts should greatly enhance the synthetic versatility of 1,3-dipolar cycloadditions: Chiral catalysts, in fact, allow in principle for complete stereocontrol over the reaction, independent of the absolute configuration of the reactants. Different complexes featuring various metals (such as B, Al, Ti, Pd, Yb) and chiral ligands are currently under investigation, and should find widespread applications in organic synthesis.[2a,33]



Scheme 11. Intermolecular 1,3-dipolar cycloadditions of nitrile oxides and nitrile imines to chiral alcohols in the presence of Mg^{2+} salts (cf. Scheme 5)

Table 3. Stereochemical outcome of the 1,3-dipolar cycloaddition of nitrones to chiral allylic alcohols in the presence of $MgBr_2$



entry	alkene	R	R'	Lewis Acid	products	a/b
1	**76**	H	Me	-	**82a,b**	47/53
2	**76**	H	Me	$MgBr_2$	**82a,b**	16/86
3	**77**	H	*n*-Pr	-	**83a,b**	45/55
4	**77**	H	*n*-Pr	$MgBr_2$	**83a,b**	15/85
5	**78**	H	Ph	$MgBr_2$	**84a,b**	12/88
6	**79**	Me	Me	$MgBr_2$	**85a,b**	4/96
7	**80**	Me	*i*-Pr	$MgBr_2$	**86b**	0/100

Theoretical Models of the Transition Structures in 1,3-Dipolar Cycloadditions

Previously we discussed several examples of theoretical methods applied to the case of 1,3-dipolar cycloaddition. Transition structures have been efficiently identified by the use of either ab initio (MO, DFT) or of semiempirical methods, and inspection of these is extremely useful in predicting reaction selectivity.[2,7−9] However, despite the enormous progress achieved in the last few years, direct appraisal of "real" substrates by these methods is often a prohibitive task. Synthetically useful molecular systems in general have too many heavy atoms (i.e. atoms other than hydrogen), and can populate too many significant conformations to be treatable efficiently at high levels of theory in a reasonable amount of time. At present, the use of more reliable high-level theoretical methods is confined to model systems, with all the limits of this approach. On the other hand, computational methods widely in use nowadays, such

as force field methods,[34] allow quick conformational analysis on molecules of great complexity, but cannot be applied as such to the study of transition structures. Forming and breaking of bonds, in fact, requires an electronic treatment which must be performed with quantum mechanical methods. This statement holds even truer with cycloaddition reactions, in which two bonds are formed in a concerted way.

In order to circumvent these problems, two solutions have been proposed. In the first one, the so-called QM/MM method, a quantum mechanical (QM) treatment of the molecular component involved in the transition state of the reaction is alternated with a molecular mechanical (MM) optimization of the remaining portions of the molecule. These two steps are performed in sequence until the convergence criteria of the method are met. Partitioning of the molecular system into two portions, however, is not so simple, and several problems have been encountered; application of the method is thus not yet widespread. In the case of 1,3-dipolar cycloadditions of nitrile oxides, however, results have been encouraging.[35]

A more simple approach – "transition state modeling" – was proposed by Houk and has found several applications in the past years.[7] The idea is extremely simple: From the ab initio, high-level transition structures identified for simple model systems, it is possible to derive geometrical parameters and introduce them into the parameter set of standard force fields. In this way, transition structures (saddle points on the potential energy surface) can be treated artificially as minima; standard molecular mechanics methods can thus be applied. The level of agreement between experimental and computed stereoselectivities achieved by this approach, in a wide variety of different reactions, is amazing.

Nitrile oxide reactions, in both their inter- and intramolecular varieties, were the first to be treated by modified MM methods. Geometrical parameters (bond lengths, bond angles, torsional preferences) derived for the reaction between fulminic acid and ethylene were used in the MM2 force field, and the parameter set was further augmented to allow for the "inside alkoxy effect".[7,12] The MM2 force field thus implemented was used in several cases to predict cycloaddition stereoselectivity.[36] Some examples are reported in Figure 9.

Simple inspection of transition structures for cycloadditions of other 1,3-dipoles to alkenes allowed the extension of the parameter set for nitrile oxide reactions to other 1,3-dipoles. Only the atomic charges on the atoms involved in the formation of the five-membered ring and the parameters for the dipole moiety were modified in the parameter set. With this simple tuning of the modified MM2 force field, modeling of nitrones (Figure 10) proved possible.[15,37]

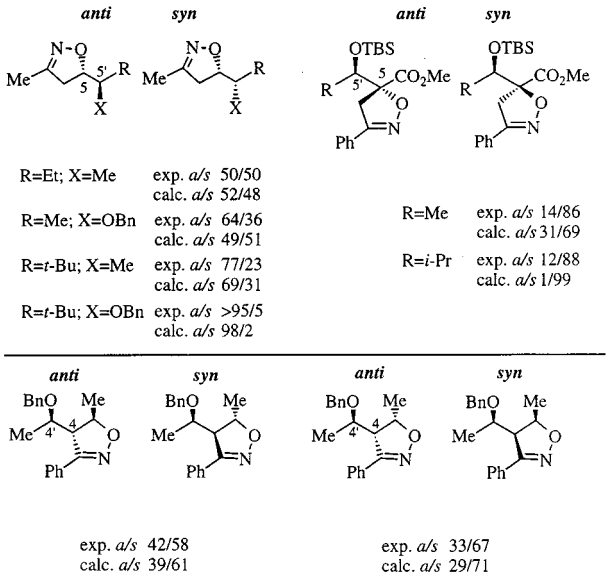


Figure 9. Calculated vs. experimental *anti*/*syn* ratios for nitrile oxide cycloadditions with alkenes

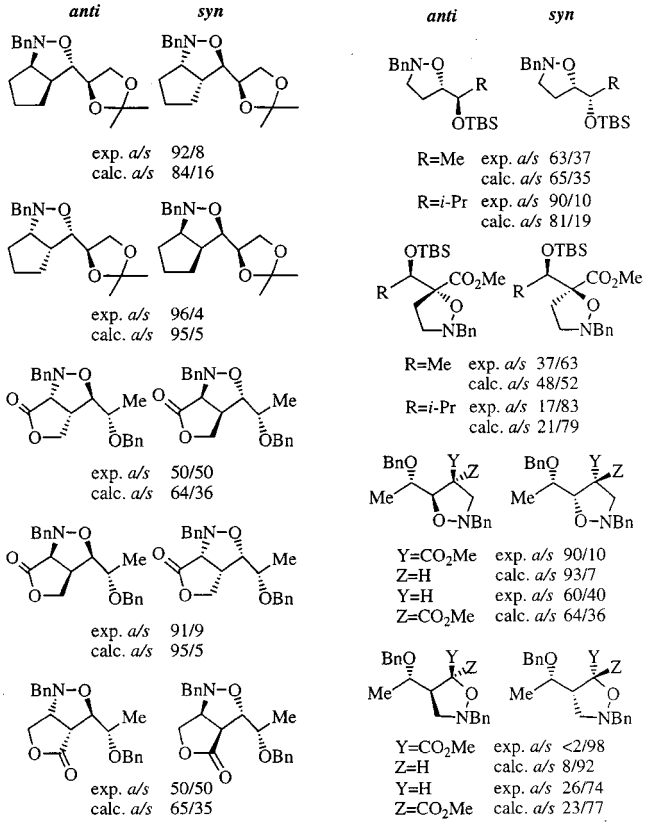


Figure 10. Calculated vs. experimental *anti*/*syn* ratios for inter- and intramolecular nitrone cycloadditions with alkenes

Conclusions

In organic synthesis, we frequently encounter efficient procedures, but often with deficient explanations of their mechanisms and/or stereochemical outcomes. The case reviewed here shows, to an extent, an opposite trend. Several theories have been advanced to explain the stereochemical outcome of 1,3-dipolar cycloadditions to different chiral al-

kenes, and planning of successful synthetic strategies is nowadays possible. We can only wish that such a fruitful interplay between theoretical investigation and experimental work will in the near future spread to all fields of organic chemistry.

Acknowledgments

We thank professors Mauro Cinquini and Franco Cozzi for our many lively and stimulating discussions. CNR and MURST funding is gratefully acknowledged.

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Received July 18, 2000
[O00368]