The Inside Alkoxy Effect Revisited

The Importance of Electrostatic Interactions in the Stereoselective 1,3-Dipolar Cycloadditions of Nitrones to Chiral Allyl Ethers: An Experimental and Force Field Approach

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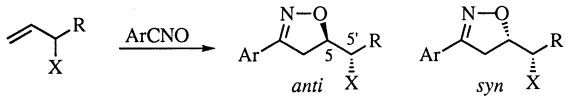
The 1,3-dipolar cycloaddition of formaldehyde *N*-benzylnitrone with β′-alkoxy- and γ-alkoxy-α,β-unsaturated esters was investigated. The stereochemical outcome of these reactions was nicely rationalized on the basis of an interpretation of the *inside alkoxy* theory emphasizing the electrostatic interactions in the reaction TS. The force field approach previously developed for evaluating the stereoselection in nitrile oxide cycloadditions to chiral alkenes was successfully extended to nitrones′ reactions.

Introduction

1,3-Dipolar cycloadditions to alkenes are reactions of broad synthetic versatility, and have been extensively studied from both the experimental and the theoretical point of view.[1] Houk′s *inside alkoxy* theory[2] offers a powerful tool for predicting the stereochemical outcome of the reaction: the theory, originally proposed for nitrile oxide reactions with terminal alkenes to give 5-substituted 4,5-dihydroisoxazoles, predicts the predominant formation of the 5,5′-*anti* stereoisomer (Figure 1).

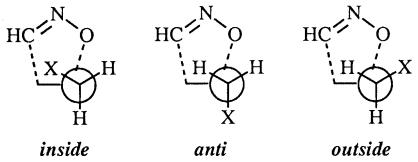
Figure 1. *Anti* and *syn* cycloadducts formed in the reaction of a nitrile oxide with a terminal alkene bearing a stereocenter in the allylic position



A rationale was found in the conformational preference for the alkoxy residue at the stereocenter to occupy the *inside* position in the transition structure of the reaction (Figure 2). This preference was believed to originate from stereoelectronic factors.[2a][2b] A force field approach was successfully developed from ab initio calculations to allow a prediction of the reaction stereoselectivity for inter- and intramolecular nitrile oxide *plus* chiral alkenes reactions.[2c][3]

After Houk′s and Jäger′s studies on nitrile oxide cycloadditions, the reactions of chiral allyl ethers with others dipoles were investigated by others′ and our group.[1b] To tentatively explain the different levels of stereoselectivity experimentally observed for these reactions we proposed a rationale that, within the framework of the *inside alkoxy* theory, correlates the stereoselection of the cycloaddition with the different atomic charges featured by the dipole terminus attacking the alkene carbon close to the stereocenter in the transition state (Figure 3).[1c][4][5]

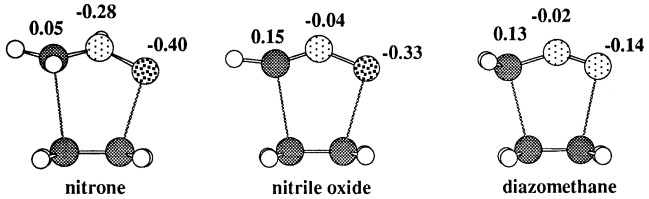
Figure 2. The *inside alkoxy* theory: ab initio results. ΔE in kcal/mol (ref.[2a])[a]



	inside	*anti*	*outside*
Me	1.1	0.0	0.6
OMe	0.0	0.7 (0.2)	2.9 (2.0)
OH	0.8	4.9	0.0

[a] Values in parentheses are from ref.[2c].

Figure 3. Atomic charges on the 1,3-dipolar unit in the RHF/3-21G TS (ref.[4])



Indeed, oxygen-containing 1,3-dipoles such as nitrile oxides and nitrones exhibit the strongest partial negative charge on the terminal oxygen atom and lead to the higher stereoselectivity. On the other hand, when the dipole terminus is a nitrogen, both the negative charge and the stereoselectivity decrease, and the diastereoisomeric ratios mainly depend on steric effects. Therefore, the origin of the stereo-

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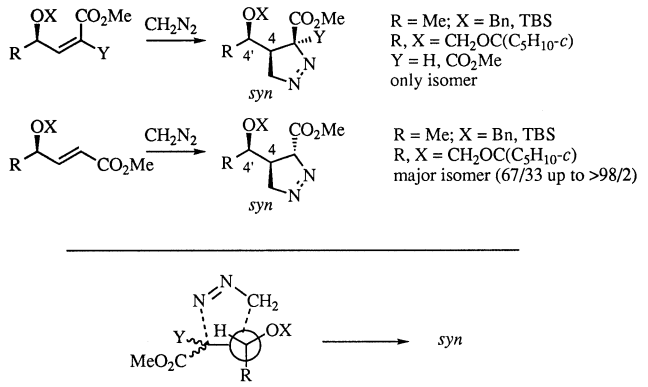
selectivity was mainly ascribed to electrostatic rather than to orbital interactions, and was believed to be due to the destabilizing repulsion generated between the negatively charged terminus of the 1,3-dipole and the electron rich allylic oxygen in the *outside* position (Figure 2).

Experimental support to this interpretation was collected comparing the reactions of benzonitrile oxide and diazomethane with a series of β′-alkoxy-α,β-unsaturated esters (see below).[5] Gratifyingly, this rationalization turned out to be helpful also to explain the surprising stereochemical outcome of the diazomethane cycloaddition to γ-alkoxy-α,β-unsaturated esters and diesters that mainly produces the *syn* adducts (Figure 4).[6] This result can nicely be explained by taking into account the stabilizing attractive interaction between the electron rich allylic oxygen in the *outside* position and the positively charged carbon atom of diazomethane (Figure 3). Thus, this new interpretation of the *inside alkoxy* theory seemed general enough to maintain its validity and predictive power also for reactions affording a non-conventional stereochemical result and even not following the *inside alkoxy* model.

Figure 4. Diazomethane cycloaddition to γ-alkoxy-α,β-unsaturated esters (ref.[6])



To conclude our investigations on the origin of stereocontrol in the 1,3-dipolar cycloadditions to chiral allyl ethers, we decided to extend our study to nitrone cycloadditions. A nitrone is electronically very similar to a nitrile oxide (both dipoles contain the same C−N−O dipolar unit and have similar negative charges on the oxygen atom), but is sterically quite different , being a bent and not a linear 1,3-dipole. In some previous studies we already observed some analogies between the sense of the stereoselectivity of inter-[7] and intramolecular[8] nitrone and nitrile oxide[1b] cycloadditions to chiral allyl ethers. Our goal in the present study was to compare the stereoselectivity of the cycloadditions of nitrones with β′-alkoxy- and γ-alkoxy-α,β-unsaturated esters to those observed for nitrile oxides and diazomethane reactions on similar substrates.[1b][5][6] In addition, we wanted to extend the force field treatment of nitrile oxide *plus* chiral alkene cycloadditions[2c][3] to other 1,3-dipoles with the hope that, if indeed the different stereoselectivities are due to the different atomic charges on the dipole in the TS, simply changing the parameters for the dipole in the force field should allow for a reliable predictivity in all different cases.

Cycloadditions to β′-Alkoxy-α,β-Unsaturated Esters

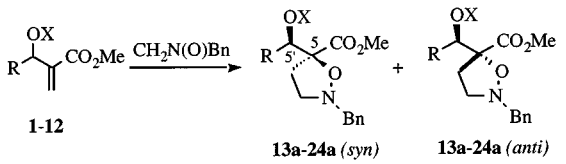
As mentioned above, β′-alkoxy-α,β-unsaturated esters (the so-called Baylis-Hillman adducts), differently protected at the allylic oxygen, were selected as substrates to compare the stereochemical outcome of the reactions of electronically different but sterically analogous (both are linear dipoles) benzonitrile oxide and diazomethane.[1][4][5] The experimental results showed that these cycloadditions predominantly afforded the *syn* isomer as predicted by the *inside alkoxy* rationale.[9] However, the benzonitrile oxide reactions were more stereoselective and more sensitive to the nature of the allylic oxygen than the diazomethane ones. Thus, the preferential formation of the *syn* adducts and the differences in the diastereoisomeric ratios were in full agreement with the rationale that relates the sense and the extent of the stereoselectivity to the different amount of negative charge on the dipole terminus in the transition structure: the higher the negative charge, the higher the *inside alkoxy* stereoselection.[5]

To complete this study and to further validate the electrostatic interpretation of the *inside alkoxy* theory, in the present study a series of nitrone cycloadditions on the same Baylis-Hillman adducts were performed. In order to avoid the formation of a new stereocenter at C-3 of the generated isoxazolidine, the reactions were carried out with a non-stereogenic nitrone. This was prepared by reaction of formaldehyde and benzyl hydroxylamine in the presence of 4 Å molecular sieves (r.t., overnight) and was not isolated but directly reacted with alkenes **1**−**12** (1−18 hours, 80°C). Chromatographic purification of the crude products allowed isolation of isoxazolidines **13a**,**b**−**24a**,**b**; all results are collected in Table 1.

The *syn*/*anti* ratios were determined by ^{1}H- and ^{13}C-NMR spectroscopy, and the relative configurations were assigned to the cycloadducts on the basis of NMR analysis and chemical correlation. All major isomers obtained from the *n*-propyl derivatives were chemically interconverted: thus, from **15a** (purified by flash chromatography) both pure **19a** and **23a** were obtained (Scheme 1). The observation of chemical shift trends for diagnostic protons (for instance, *H*C-5 always resonates at lower fields in the major isomers of **13**−**24**; for a collection of relevant NMR data see Table 4 in the Experimental Section), allowed us to assign the same relative configuration to all major adducts **a**. The unambiguous establishment of the *syn* relative stereochemistry was obtained by converting pure **14a** into acetonide **26a** via the diol **25a** (Scheme 1).

NMR analysis of this rigid, bicyclic compound revealed strong NOEs between the two axial protons *H*C-5′ and *H*C-5′′, and between these and the same (*pro-S*) H at C-4 of the isoxazoline ring. Molecular Mechanics (MM2*) calculations performed on the diastereoisomeric acetonides **26a** and **26b** confirmed our stereochemical assignment, since only a *cis* relationship between these three hydrogens

Table 1. Nitrone cycloadditions to Baylis-Hillman adducts

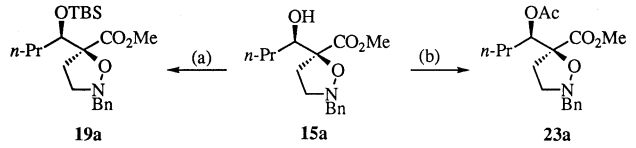


1-12 **13a-24a** *(syn)* **13a-24a** *(anti)*

Entry	Alkene	R	X	Product	Yield%	*syn*/*anti*
1	**1**	Me	H	**13a,b**	74	88:12
2	**2**	Ph	H	**14a,b**	73	81:19
3	**3**	*n*-Pr	H	**15a,b**	82	90:10[a]
4	**4**	*i*-Pr	H	**16a,b**	68	80:20
5	**5**	Me	TBS	**17a,b**	52	63:37
6	**6**	Ph	TBS	**18a,b**	95	68:32
7	**7**	*n*-Pr	TBS	**19a,b**	53	74:26
8	**8**	*i*-Pr	TBS	**20a,b**	72	83:17
9	**9**	Me	Ac	**21a,b**	88	60:40
10	**10**	Ph	Ac	**22a,b**	80	52:48
11	**11**	*n*-Pr	Ac	**23a,b**	84	67:33
12	**12**	*i*-Pr	Ac	**24a,b**	77	65:35
13[b]	**5**	Me	TBS	**17a,b**	68	83:17[c]
14[b]	**11**	*n*-Pr	Ac	**23a,b**	52	70:30[d]

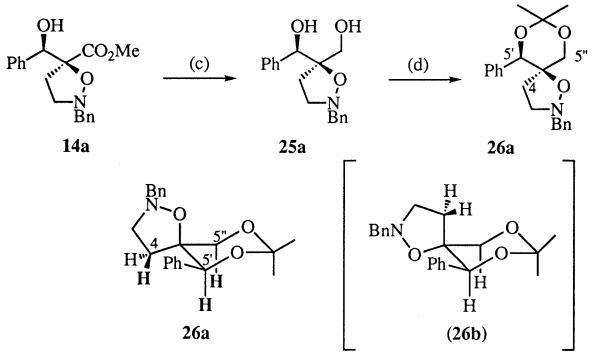
[a] Diastereoisomeric ratio determined via ^{13}C-NMR spectroscopy. – [b] reaction performed for 48 hours at 20°C. – [c] in the reaction of **5** with benzonitrile oxide a *syn*/*anti* ratio of 86:14 was obtained.[b] – [d] in the reaction of **11** with benzonitrile oxide a 77:23 *syn*/*anti* ratio was obtained.[b]

Scheme 1. Chemical correlation between compounds **15a**, **19a**, and **23a**, and synthesis of compound **26a**



19a **15a** **23a**

a) TBSCl, imidazole, DMF; b) AcCl, TEA, CH_2Cl_2



14a **25a** **26a**

26a **(26b)**

c) $LiAlH_4$, Et_2O; d) $Me_2C(OMe)_2$, PTSA

(as in **26a**), calling for a *syn* relative configuration of **14a**, can account for the experimentally observed NOEs.

In commenting these results we can say that the sense of stereoselectivity of these nitrone cycloadditions to Baylis-Hillman adducts agrees with that of nitrile oxide and diazomethane reactions, predominantly producing the *syn* cycloadduct.[5] However, the *syn*/*anti* ratios observed in the nitrone reactions were lower than those observed for the benzonitrile oxide ones. Likely the different reaction temperature can account for this result, and indeed, when cycloadded to alkenes at the same temperature (20°C), the two dipoles exhibited similar stereoselections (Table 1, # 13, 14). The characteristic effect exerted on the stereoselection by the different protective groups of the allylic oxygen in the nitrile oxide reactions[5] was maintained also in nitrone cycloadditions; thus the *syn*/*anti* ratios observed for the silyl ethers **5–8**, featuring an electron rich, silicon protected allylic oxygen, were higher than those observed for the corresponding acetates **9–12**, featuring an electron poor allylic oxygen (Table 1, # 5–8 vs 9–12). When the reaction temperature was decreased from 80° down to 20°C, the allylic oxygen effect on the stereoselectivity became more evident, the *syn* stereoselectivity increasing more for the silyl than for the acetyl derivatives (Table 1, # 13 vs 5 and 14 vs 11). This dependence of the stereoselection on the nature of the allylic oxygen nicely fits in our rationale based on electrostatic interaction: the more electron rich the allylic oxygen, the stronger the electrostatic repulsion with the negatively charged dipole oxygen when the allylic oxygen is in the *outside* position, the higher the *inside alkoxy* stereoselectivity.

In concluding the discussion on these cycloadditions, the remarkably high level of *syn* stereoselectivity observed in the reactions carried out on the unprotected alcohols **1–4** must be commented. Generally,[1b] unprotected chiral allylic alcohols undergo poorly stereoselective 1,3-dipolar cycloadditions, the stereochemical outcome being the result of the contrasting tendency of the OH group to occupy the *inside* position for stereoelectronic reasons, or the *outside* one to form a H bond with the negatively charged terminus of the incoming dipole. In the case of substrates **1–4**, the formation of a H bond between the OH group and the nitrone oxygen would lead to the production of the *anti* diastereoisomer, and thus can be ruled out on the basis of the observed stereoselections. On the other hand, the cycloaddition can occur on a substrate conformation in which the OH group is H-bonded to the carbonyl oxygen, but, this being the case, the formation of the *syn* isomer would arise from a sterically very unfavorable attack of the nitrone oxygen antiperiplanar to the C-H bond at the stereocenter. It is likely therefore that the reaction occurs on the inside hydroxy conformation of alcohols **1-4**, particularly stabilized by the reduced steric requirements of the OH group, that, being smaller than the OTBS or the OCOMe group of **5–12**, more easily occupy the inside position.[10] A similar behaviour was observed also for benzonitrile oxide and diazomethane cycloadditions to alcohols **1–4**.[5]

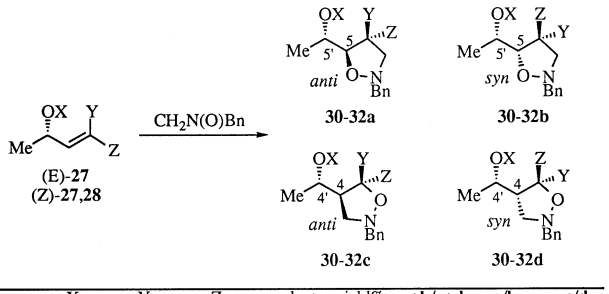
Nitrone Cycloadditions to γ-Alkoxy-α,β-Unsaturated Esters and Diesters

As mentioned in the introduction, diazomethane has been found to react with γ-alkoxy-α,β-unsaturated esters and diesters with complete regiocontrol and good to excellent degrees of *syn* stereoselectivity (Figure 4).[6] In previous studies on the cycloadditions of a nitrile oxide to these substrates,[1c][11] the reaction was shown to be poorly regioselective. The available data, however, indicate a moderate *anti* stereoselection for the regioisomer in which the dipole

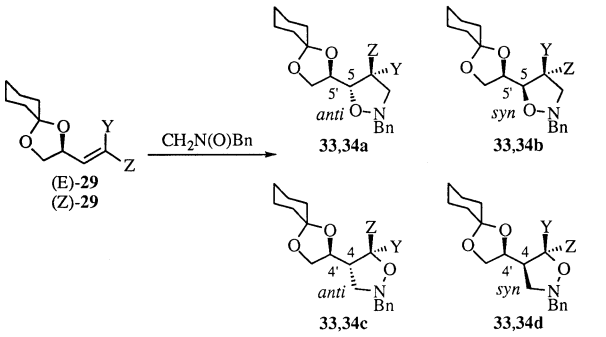
oxygen attacks the β-carbon of the unsaturated ester. On the basis of the electronic similarity between nitrile oxides and nitrones, we anticipated a poor regiocontrol also for the nitrone cycloadditions. Nevertheless, we thought that evaluation of *syn*/*anti* stereoselectivity in both regioisomers arising from the attack of differently charged dipole termini to the alkene carbon close to the stereocenter could be a probing test for assessing the real importance of electrostatic effects in the stereochemical outcome of these reactions.

Thus, esters (*E*)- and (*Z*)-**27**, (*Z*)-**28**, and (*E*)- and (*Z*)-**29** were prepared and reacted with formaldehyde *N*−benzylnitrone (1−4 h, 80°C) to afford isoxazolidines **30**−**34** as mixtures of regio- and diastereoisomers (Scheme 2). Chromatographic purification followed by ^{1}H- and ^{13}C-NMR analysis (see Tables 5 and 6 in the Experimental Section) allowed regioisomer identification and evaluation of diastereoisomeric ratios.

Scheme 2. Nitrone cycloaddition to (*E*)- and (*Z*)-**27**−**32**



alkene	X	Y	Z	product	yield%	a+b/c+d	a/b	c/d
(E)-**27**	Bn	H	COOMe	**30**	82	44/56	74/26	40/60
(Z)-**27**	Bn	COOMe	H	**31**	82	16/84	>92/8	10/90
(Z)-**28**	TBS	COOMe	H	**32**	46	32/68	62/38	<2/98

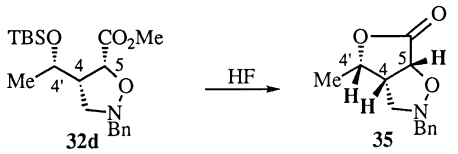


alkene	Y	Z	product	yield %	a+b/c+d	a/b	c/d
(E)-**29**	H	COOMe	**33**	98	37/63	79/21	14/86
(Z)-**29**	COOMe	H	**34**	76	17/83	>97/3	8/92

As far as the regioselection is concerned, the 4-methoxycarbonyl substituted derivatives **30a**,**b**−**34a**,**b** were always obtained in minor amount. For these compounds the stereoselectivity ranged from fair to excellent in favor of the **a** isomers, to which, on the basis of NMR chemical shift trends and of comparison of NMR data with those already available for similar cycloadducts,[7][8] the 5,5′-*anti* configuration was assigned. The attribution of the stereochemistry at C-4 and C-5 was trivial, the relative configuration at these stereocenters being pre-determined by the alkene structure.[1]

Also in the case of the 5-methoxycarbonyl substituted compounds **30c,d**−**34c,d**, the preferential formation of one of the two isomers, namely **d**, was observed. Chemical shift trends strongly suggested that all the major isomers featured the same relative configuration at the C-4/C-4′ stereocenters. Unambiguous configurational assignment required the transformation of one of the cycloadducts into a rigid derivative amenable to NMR analysis. Thus, isoxazolidine **32d** was converted (40% aqueous HF, THF, r.t., Scheme 3) into the bicyclic lactone **35**. The observation of NOEs between *H*C-5, *H*C-4, and *H*C-4′ indicated that all these protons are located on the same side of the convex structure, and allowed the attribution of the 4,5-*cis*-4,4′-*syn* configuration to **32d**.

Scheme 3. Synthesis of bicyclic lactone **35**

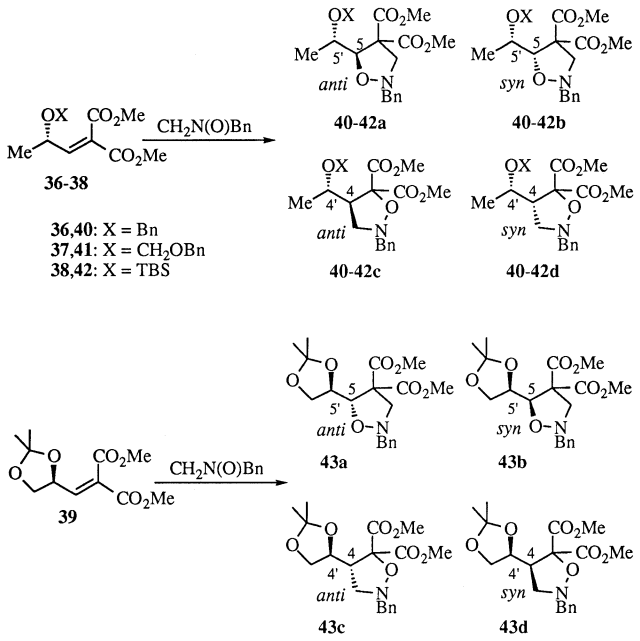


In commenting these data the following observations can be made. In the case of the cycloadditions leading to **a**, **b** adducts, the observed *anti* stereoselectivity is in agreement with the sense of stereoselection observed in nitrile oxide cycloadditions to similar substrates,[1c][11] and confirms the tendency of nitrones to behave similarly to nitrile oxides and to react with chiral allyl ethers as predicted by the *inside alkoxy* theory (*anti* stereoselection).[12] Since no quantitative data were available for nitrile oxide cycloadditions, comparison of the levels of stereocontrol for these reactions was not possible.

The results of the nitrone cycloadditions leading to **c**, **d** isoxazolidines are much more interesting, since their stereoselectivity can be compared qualitatively and quantitatively with that of the diazomethane reactions with the same substrates. First of all, it must be noted that both reactions are always *syn* stereoselective.[6][13] As mentioned before, this result can be rationalized on the basis of a favorable electrostatic interaction between the partially positively charged C terminus of both dipoles and the allylic oxygen located in the *outside* position. Secondly, when the reactions are individually compared, the nitrone cycloadditions are constantly slightly less stereoselective than the diazomethane ones. Even if this comparison must be cautiously considered (the two dipoles clearly have different steric requirements and react at different temperatures), it is remarkable that the dipole featuring the more positively charged C atom (i.e. diazomethane) reacts more stereoselectively, in full agreement with our rationalization of the *inside alkoxy* theory that relates the extent of stereoselection to the dipole/substrate electrostatic interaction in the transition state.

As those to esters **27**−**29**, also the nitrone cycloadditions to diesters **36**−**39** were poorly regioselective, generally affording a slight excess of the 5,5-dimethoxycarbonyl substituted compounds, that, as expected, were obtained only as the *syn* isomers **40d**−**43d** (Scheme 4).

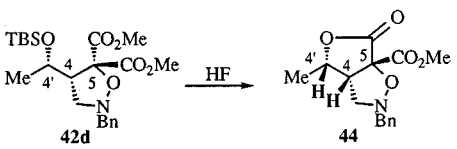
Scheme 4. Nitrone cycloadditions to **36–39**



alkene	product	yield %	a+b/c+d	a/b	c/d
36	**40**	96	36/64	48/52	<2/98
37	**41**	82	42/58	>63/37	<2/98
38	**42**	85	50/50	>63/37	<2/98
39	**43**	60	38/62	55/45	<2/98

For one of these compounds, namely **42d**, the configuration was unambiguously established by NMR analysis of the bicyclic lactone **44** obtained as described above for **35** (Scheme 5). In this case the strong NOE interaction between H-4 and H-4′ showed the *syn* disposition of these protons. The cycloadditions affording the 4,4-dimethoxycarbonyl substituted regioisomers occurred with a much lower degree of stereocontrol, generally producing a low excess of the expected *anti* **a** isomers over the *syn* **b** ones. At present we are not able to explain this poor stereocontrol; it must be noted, however, that the *anti*/*syn* ratios closely resemble those observed for Michael-type reactions of the same substrates;[14] this competitive reaction mechanism can influence the stereoselection.

Scheme 5. Synthesis of bicyclic lactone **44**



Molecular Mechanics Studies of 1,3-Dipolar Cycloadditions

When the *inside alkoxy* theory was proposed for the nitrile oxide *plus* alkene reaction, a force field was parameterized on the basis of ab initio data[2c][3] within the frame of the "Transition State Modeling".[15] Within this approach, a simple model of the reaction TS is studied with ab initio (or semiempirical) methods, thus obtaining suitable parameters to be included in commonly used force fields. In this way, energy differences can be evaluated for diastereoisomeric transition structures, as is usually done for diastereoisomeric ground states. Because of its good performances in the treatment of small organic molecules, MM2 force field[16] was selected to be parameterized. The "Transition State Modeling" has been applied successfully to various organic reactions,[15] and in particular to nitrile oxide cycloadditions to chiral alkenes.[2c][3] This set of parameters was subsequenty included as a substructure in the MacroModel/Batchmin[17] MM2* force field, thus allowing application of the usual conformational analysis techniques (e.g. Monte Carlo procedures) to the nitrile oxide *plus* chiral alkene transition structures.

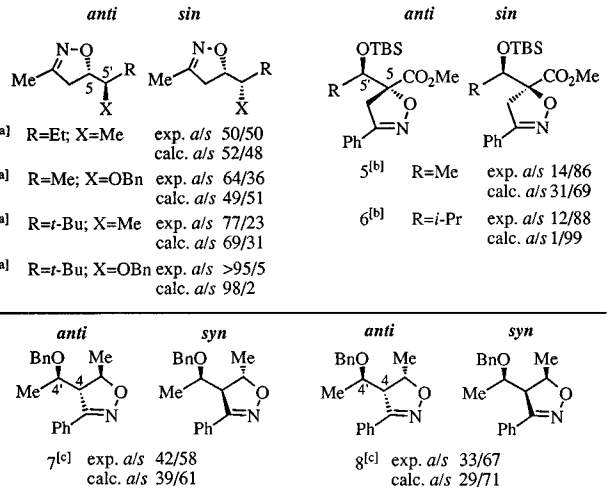
It is well known in the literature that it′s the nature of the chiral alkene that determines the sense of stereoselectivity in the 1,3-dipolar cycloaddition reactions. However, the role of the 1,3-dipole was deeply investigated, and its effect on the reaction stereoselectivity was correlated to its structure[1] as well as to the charge distribution on the dipolar moiety in the reaction TS.[4][5][6] Thus, the stronger the negative charge on the dipole terminus interacting with the allylic substituent, the more destabilized the *outside* position for an allylic oxygenated residue, the more reinforced the *inside alkoxy* effect. On the other hand, when the dipole terminus interacting with the allylic substituent is positively charged, an opposite effect was observed: the *outside* conformation is electrostatically stabilized, resulting in an *outside alkoxy* effect.

We reasoned that the force field treatment of the nitrile oxide *plus* alkenes could be extended to other 1,3-dipolar cycloadditions. The parameters describing the alkene moiety can be left unchanged, and different parameters can be included to describe the different 1,3-dipoles; of course, also atomic charges must be changed on changing the nature of the 1,3-dipole. The original formulation of the parameter set for the nitrile oxide *plus* alkene TS,[2c][3] however, treated the electrostatic interactions by inclusion of bond dipoles, while only atomic charges are easily obtained from ab initio calculations. A preliminary step was thus necessary to allow a charge-based electrostatic parameterization of the force field. Thus the nitrile oxide *plus* alkenes substructure included in MM2* force field (MacroModel/Batchmin 5.5 package)[17] was slightly modified to allow direct inclusion of atomic charges instead of dipoles. The dipole and the alkene non-hydrogen atoms were given charges evaluated from fitting of the electrostatic potential at the 3-21G level,[4] with hydrogen contributions summed in the heavy atoms to which they are bonded. The *inside alkoxy* parameters had to be slightly modified to account for the differences included by switching from empirically evaluated dipoles to ab initio calculated atomic charges.

The performance of the force field was tested against previous calculations to verify that it was left unchanged from the original parameterization.[2c][3] Systematic pseudo-Monte Carlo techniques,[18] together with subsequent energy minimization (MC/EM), were applied to the conformational analysis of the transition structures for all isomers

(see the Experimental Section for details). Selected results are collected in Table 2.

Table 2. Calculated *vs* experimental *anti*/*syn* ratios for nitrile oxide cycloadditions to alkenes



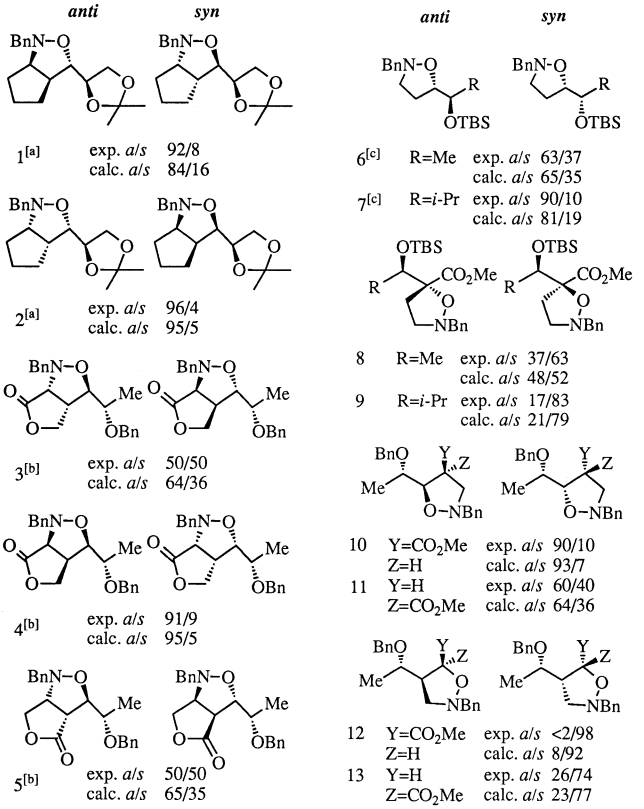
In all calculations, Bn was replaced with Me, and TBS with TMS. – [a] For previously calculated and experimental *anti*/*syn* ratios, see ref.[2c]. – [b] For experimental *anti*/*syn* ratios, see ref.[5]. – [c] For experimental *anti*/*syn* ratios, see refs.[1c] and[11].

Gratifyingly, the behaviour of the force field was left unchanged from the original parameterization in all test calculations (Table 2, # 1–4).[2c][3] We thus proceeded to evaluate the diastereoisomeric ratios for benzonitrile oxide cycloadditions to Baylis-Hillman adducts, and were pleased to observe also in this case a good agreement with the experimental data (# 5, 6). Moreover, the performance of the force field remains reliable also when the regioisomeric cycloadducts are considered: when the carbon atom of the nitrile oxide is the terminus interacting with the allylic oxygen in the reaction TS, the cycloaddition is slightly *syn*-selective (# 7, 8).[1c][11] Also in this case, the agreement within the experimental and the calculated data is completely satisfying.

The subsequent parameterization of MM2* force field for nitrone *plus* alkene cycloadditions was almost trivial. To make the matter simpler, a new substructure was included for this TS in MM2* force field, with geometric parameters derived from Bernardi's RHF/4-31G transition structure[19] and atomic charges derived from 3-21G fitting of the electrostatic potential.[4] All the parameters involving the alkene portion were exactly the same included in the nitrile oxide *plus* alkene substructure. Conformational analysis of the transition structures (MC/EM procedure) were performed considering both *endo* and *exo* approaches between the reactants. Some results (calculated *vs* experimental diastereoisomeric ratios) are collected in Table 3.

The calculated diastereoisomeric ratios are always in agreement with the experimentally observed ones; this is true for intramolecular reactions on electron rich as well as electron poor alkenes (Table 3, # 1–5), for intermolecular cycloadditions on terminal alkenes – including Baylis-Hillman adducts (# 6–9), and for intermolecular reactions of γ–alkoxy-α,β-unsaturated esters (# 10–13). In this last case, the different stereoselectivity obtained within the different regioisomers is well reproduced by the calculation: within the 4-methoxycarbonyl substituted regioisomers the 5,5′-*anti* cycloadduct is favored, deriving from an *inside alkoxy* conformation of the TS. The TS leading to the 5-methoxycarbonyl substituted regioisomers, on the other hand, prefers an *outside alkoxy* conformation. The difference in the two regioisomeric TSs is mainly due to electrostatic interactions within the oxygenated allylic substituent and the 1,3-dipolar moiety.

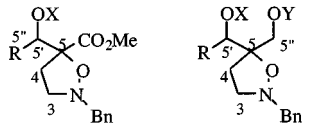
Table 3. Calculated vs experimental *anti*/*syn* ratios for nitrone cycloadditions to alkenes



In all calculations, Bn was replaced with Me, and TBS with TMS. – [a] For experimental *anti*/*syn* ratios, see ref.[8a]. – [b] For experimental *anti*/*syn* ratios, see ref.[8b]. – [c] For experimental *anti*/*syn* ratios, see ref.[7].

A final observation can be derived from the calculated TSs. In the cycloaddition to non-conjugated alkenes, the alkyl residue on the alkene bearing the allylic stereocenter tends to occupy the *exo* region in the transition structure. For intramolecular reactions on (*E*)-alkenes, this effect is counteracted by the same configurational preference of the connecting chain. When the reaction on α,β-unsaturated esters is examined, on the other hand, the *endo* region is always occupied by the activating ester group, both in inter- and in intramolecular reactions. This fact seems to suggest that the secondary orbital overlap, responsible for this effect, can be simulated within a force field treatment via electrostatic interactions.

Table 4. Significant ^{1}H- and ^{13}C-NMR chemical shifts for isoxazolidines **13**−**26a**, **b**



13-24a,b **25a,b**; **26a**

	H-3	H-4	H-5′	H-5″	C-3	C-4	C-5	C-5′
13a	2.93	2.80; 2.35	4.04	1.12	54.8	31.7	88.7	69.5
13b	2.93	2.80; 2.55	4.02	1.16	54.5	35.4	88.5	70.7
14a	2.90	2.58	5.10	-	54.7	32.2	89.0	75.9
14b	2.90	2.58	4.98	-	54.4	35.6	87.6	76.5
15a	2.98; 2.91	2.68; 2.52	3.85	-	54.7	33.8	88.6	73.0
15b	2.98; 2.91	2.68; 2.52	3.85	-	54.4	35.9	88.0	74.4
16a	2.97; 2.90	2.72; 2.59	3.70	-	54.9	32.6	88.4	77.8
16b	2.91	2.71; 2.57	3.68	-	54.0	37.8	87.5	78.5
17a	3.02; 2.77	2.77; 2.38	4.09	1.10	54.6	32.5	89.4	69.8
17b	3.02; 2.77	2.77; 2.38	4.24	1.19	54.6	31.8	88.5	70.4
18a	2.93; 2.07	2.60	5.05	-	54.2	32.2	89.8	76.8
18b	2.83; 2.07	2.40; 2.80	5.01	-	54.2	31.8	89.0	75.7
19a	3.08; 2.76	2.82; 2.41	3.97	-	54.9	30.8	89.5	72.6
19b	2.97; 2.83	2.71; 2.31	3.99	-	54.5	34.2	88.7	75.4
20a	3.12; 2.69	2.85; 2.52	3.93	-	55.2	30.9	90.0	76.0
20b	2.97; 2.79	2.70; 2.37	3.87	-	54.3	35.2	88.7	75.5
21a	3.01; 2.78	2.70; 2.33	5.26	1.22	54.0	34.1	86.9	71.4
21b	3.01; 2.78	2.70; 2.33	5.31	1.24	54.1	34.4	86.4	71.3
22a	2.96; 2.40	2.65; 2.40	6.22	-	54.1	34.0	87.2	75.4
22b	2.87; 2.40	2.79; 2.40	6.19	-	53.6	34.7	86.9	76.8
23a	3.00; 2.73	2.73; 2.32	5.30	-	54.1	33.8	87.0	73.8
23b	3.00; 2.73	2.67; 2.32	5.24	-	54.2	34.8	86.4	74.2
24a	3.01; 2.77	2.80; 2.42	5.19	-	54.2	33.7	87.4	77.3
24b	3.01; 2.77	2.57; 2.33	5.24	-	53.7	36.6	86.7	78.1
25a	2.86	2.60; 1.83	4.99	3.53; 3.46	56.1	30.2	87.5	77.2
25b	2.86	2.50; 2.30	4.73	4.03; 3.90	n.d.	n.d.	n.d.	n.d.
26a	2.90; 2.73	2.60; 1.73	5.06	3.47; 3.20	55.4	48.6	94.0	85.8

In all calculations, Bn was replaced with Me, and TBS with TMS. − [a] For previously calculated and experimental *anti*/*syn* ratios, see ref.[2c]. − [b] For experimental *anti*/*syn* ratios, see ref.[5]. − [c] For experimental *anti*/*syn* ratios, see refs.[1c] and[11].

Conclusions

Atomic charges on the transition structure allow for a rationale of the stereoselectivity observed in different 1,3-dipolar cycloadditions. It is well known that the sense of the stereoselectivity is determined by the nature of the alkene, while different stereoisomeric ratios are obtained by varying the 1,3-dipole. This effect was shown to be dependent on the differences in the charge distribution in the reaction TS, while the TS geometry plays a minor role. Inclusion of force field parameters for the different 1,3-dipolar moieties of the TS, while leaving unchanged the alkene′s parameterization, allows for a reliable evaluation of the reaction stereoselectivity.

Special thanks are due to *Valentina Molteni*, *Valeria Affaticati*, *Alberto Palaveri* and *Domenico Zanferrari* for their helpful collaboration.

Experimental Section

CHN Analyses: Perkin-Elmer 240 instrument. − ^{1}H and ^{13}C-NMR: Bruker AM300 at 300.133 and 75.47 MHz, respectively; $CDCl_3$ as solvent; chemical shifts are reported in δ relative to TMS. − All NMR spectra were recorded at 50°C.

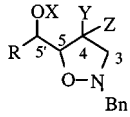
Silica gel (230−400 mesh) was used for flash chromatography. Organic extracts were dried with Na_2SO_4 and filtered before removal of the solvent. Dry solvents were prepared as follows: benzene[20] was distilled from Na, Et_2O from Na and subsequently from $LiAlH_4$, CH_2Cl_2 from CaH_2; these solvents were stored on 4-Å molecular sieves. Commercial DMF was used without additional purification and stored on 4-Å molecular sieves; pyridine was stored on KOH. All reactions employing dry solvents were performed in a nitrogen atmosphere.

Alkenes **1**−**12**,[5] **27**−**29**,[6] are known compounds; **36**−**39** were prepared from the appropriated aldehyde following the known procedure.[14a] All spectroscopic data were in agreement with the chemical structure.

General Procedure for the 1,3-Dipolar Cycloaddition of Formaldehyde N-Benzylnitrone to Alkenes **1**−**12**, **27**−**29**, **36**−**39**: To a 0.1 M solution of benzyl hydroxylamine (1.5 eq) in dry benzene, paraformaldehyde (8 eq) and 4 Å molecular sieves were added, and the mixture stirred overnight under nitrogen. A 0.1 M solution of the appropriate alkene (1 eq) in dry benzene was then added, and the reaction temperature was raised to 80°C. The reaction was monitored via TLC; after 1.5−8 hours, the reaction mixture was cooled to 20°C and filtered. After removal of the solvent, the crude was purified by flash chromatography (hexanes/Et_2O as eluant). All cycloadducts were obtained as oils. Chemical yields are reported in Table 1 and Schemes 2 and 4; significant ^{1}H- and ^{13}C-NMR chemical shifts are collected in Tables 4−6.

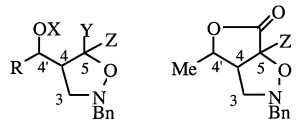
13a, **b**: hexanes/Et_2O, 2:8. $C_{14}H_{19}NO_4$: calcd. C 63.38, H 7.22, N 5.28; found C 63.42, H 7.15, N 5.33. − **14a**, **b**: hexanes/Et_2O, 3:7. $C_{19}H_{21}NO_4$: calcd. C 69.71, H 6.47, N 4.28; found C 69.71, H

Table 5. Significant ^{1}H- and ^{13}C-NMR chemical shifts for cycloadducts **30**−**43a**, **b**.



	H-3	H-4	H-5	H-5′	C-3	C-4	C-5	C-5′
30a	3.27	3.48	4.38	3.74	58.0	49.0	83.9	75.2
30b	3.20	3.32	4.43	3.74	57.9	48.7	83.2	74.2
31a	3.27; 3.13	3.55	4.18	3.90	58.2	48.2	82.1	73.6
32a	3.33; 3.13	3.43	4.07	4.11	58.3	48.0	83.6	67.4
32b	3.27; 3.13	n.d.	4.63	4.21	-	-	-	-
33a	3.20	3.45	4.36	4.17	57.9	50.1	80.9	76.2
33b	3.27	3.37	4.42	4.32	57.6	49.0	79.9	75.5
34a	3.23	3.60	4.23	4.23	57.8	48.7	80.0	73.7
40a	4.00; 3.92	-	4.76	3.91	63.0	65.7	84.6	73.6
40b	4.10; 3.95	-	4.78	3.95	62.1	65.8	84.7	73.0
41a	3.30; 3.20	-	4.70	4.08	62.5	65.8	84.6	72.7
41b	3.23	-	4.76	4.07	62.9	61.5	84.7	72.6
42a	4.03; 3.92	-	4.54	4.13	63.4	66.0	85.7	67.9
42b	4.03; 3.90	-	4.67	4.24	63.7	64.3	86.2	67.6
43a	3.33; 3.07	-	4.80	4.23	62.3	n.d.	81.8	74.0
43b	3.57	-	4.74	4.37	62.1	65.8	81.0	74.2

Table 6. Significant ^{1}H- and ^{13}C-NMR chemical shifts for isoxazolidines **30**−**44c**, **d**.



30-34c,d; 40-43d **35, 44**

	H-3	H-4	H-5	H-4′	C-3	C-4	C-5	C-4′
30c	3.20; 2.67	3.13	4.47	3.64	57.0	52.1	77.5	74.9
30d	3.17; 2.90	3.02	4.33	3.74	56.9	52.1	77.3	74.4
31c	3.13; 2.90	3.13	4.70	3.76	56.7	53.2	77.9	74.1
31d	3.33; 3.07	3.07	4.42	3.73	55.3	53.0	76.9	72.0
32d	3.33; 3.00	3.00	4.53	3.80	57.6	55.2	77.1	67.5
33c	n.d.	n.d.	4.50	n.d.	56.8	50.0	77.2	75.5
33d	3.20; 2.93	3.00	4.27	4.27	57.6	51.0	77.4	76.2
34d	3.30; 3.03	3.03	4.55	4.07	56.6	50.3	76.4	73.4
35	3.28; 2.58	3.33	4.70	4.79	55.2	55.2	77.8	75.2
40d	3.33; 3.20	3.62	-	3.97	55.2	54.9	88.0	71.4
41d	3.33; 3.20	3.59	-	n.d.	55.4	54.0	85.4	72.3
42d	3.37; 3.00	3.53	-	3.96	58.6	56.8	85.4	67.8
43d	3.33; 3.07	3.60	-	4.16	57.0	52.1	87.0	74.1
44	3.20; 2.80	3.45	-	4.85	61.8	55.2	86.1	74.8

6.49, N 4.25. − **15a**, **b**: hexanes/Et_2O, 3:7. $C_{16}H_{23}NO_4$: calcd. C 65.51, H 7.90, N 4.77; found C 65.46, H 7.86, N 4.80. − **16a**, **b**: hexanes/Et_2O 3:7. $C_{16}H_{23}NO_4$: calcd. C 65.51, H 7.90, N 4.77; found C 65.55, H 7.87, N 4.81. − **17a**, **b**: hexanes/Et_2O, 8:2. $C_{20}H_{33}NO_4Si$: calcd. C 63.29, H 8.76, N 3.69; found C 63.24, H 8.80, N 3.72. − **18a**, **b**: hexanes/Et_2O, 1:1. $C_{25}H_{35}NO_4Si$: calcd. C 67.99, H 7.99, N 3.17; found C 67.89, H 8.03, N 3.15. − **19a**, **b**: hexanes/Et_2O, 1:1. $C_{22}H_{37}NO_4Si$: calcd. C 64.82, H 9.15, N 3.44; found C 64.88, H 9.20, N 3.40. − **20a**, **b**: hexanes/Et_2O, 7:3. $C_{22}H_{37}NO_4Si$: calcd. C 64.82, H 9.15, N 3.44; found C 64.77, H 9.11, N 3.47. − **21a**, **b**: hexanes/Et_2O, 9:1. $C_{16}H_{21}NO_5$: calcd. C 62.53, H 6.89, N 4.56; found C 62.59, H 6.92, N 4.58. − **22a**, **b**: hexanes/Et_2O, 8:2. $C_{21}H_{23}NO_5$: calcd. C 68.28, H 6.28, N 3.79; found C 68.20, H 6.32, N 3.82. − **23a**, **b**: hexanes/Et_2O, 9:1. $C_{18}H_{25}NO_5$: calcd. C 64.46, H 7.51, N 4.18; found C 64.36, H 7.53, N 4.20. − **24a**, **b**: hexanes/Et_2O, 9:1. $C_{18}H_{25}NO_5$: calcd. C 64.46, H 7.51, N 4.18; found C 64.54, H 7.55, N 4.14. − **30a**−**d**: hexanes/Et_2O, 7:3. $C_{21}H_{25}NO_4$: calcd. C 70.96, H 7.09, N 3.94; found C 70.90, H 7.12, N 3.91. − **31a**−**d**: hexanes/Et_2O, 7:3. $C_{21}H_{25}NO_4$: calcd. C 70.96, H:7.09, N 3.94; found C 70.89, H 7.10, N 3.99. **32a**−**d**: hexanes/Et_2O, 7:3. $C_{20}H_{33}NO_4Si$: calcd. C 62.57, H 8.67, N 3.65; found C 62.50, H 8.72, N 3.70. − **33a**−**d**: hexanes/Et_2O, 6:4. $C_{20}H_{27}NO_5$: calcd. C 66.46, H 7.53, N 3.87; found C 66.54, H 7.50, N 3.90. − **34a**−**d**: hexanes/Et_2O, 6:4. $C_{20}H_{27}NO_5$: calcd. C 66.46, H 7.53, N 3.87; found C 66.41, H 7.51, N 3.82. − **40a**−**d**: hexanes/Et_2O, 7:3. $C_{23}H_{27}NO_6$: calcd. C 66.81, H 6.58, N 3.39; found C 66.75, H 6.53, N 3.42. − **41a**−**d**: hexanes/Et_2O, 6:4. $C_{24}H_{29}NO_7$: calcd. C 63.64, H 6.59, N 3.16; found C 63.57, H 6.62, N 3.18. − **42a**−**d**: hexanes/Et_2O, 75:25. $C_{22}H_{35}NO_6Si$: calcd. C 60.38, H 8.06, N 3.20; found C 60.31, H 8.04, N:3.16. − **43a**−**d**:

hexanes/Et_2O, 6:4. $C_{19}H_{25}NO_7$: calcd. C 60.15, H 6.64, N 3.69; found C 60.09, H 6.60, N 3.74.

Chemical Correlation Between **15a** *and* **19a**: To compound **15a** (1 mmol), dissolved in dry DMF (0.3 ml), 2 mmols of TBSCl and 2.5 mmols of imidazole were added, and the mixture allowed to stir overnight. Water was added, and the product was extracted with ethyl ether and purified by flash chromatography. **19a** was obtained in 95% yield.

Chemical Correlation Between **15a** *and* **23a**: to compound **15a** (1 mmol), dissolved in dry CH_2Cl_2 (2.5 ml), 1.1 mmols of pyridine and 1.1 mmols of AcCl were added at 0°C. After 1 h, the mixture was treated with 3.7% HCl and extracted with CH_2Cl_2. The crude was purified by flash chromatography. **23a** was obtained in 84% yield.

Synthesis of **26a** *from* **14a**: to a suspension of $LiAlH_4$ (1 mmol) in dry Et_2O (10 ml) a solution of **14a** (1 mmol) in dry Et_2O (5 ml) was slowly added at 0°C. After 1 h, the reaction was quenched at 0°C by a slow addition of H_2O (0.184 ml), 10% NaOH (0.184 ml) and H_2O (0.368 ml), and then filtered. Flash chromatography (Et_2O) afforded pure **25a** in 58% yield as an oil. ^1H and ^{13}C-NMR significant data are collected in Table 4. $C_{18}H_{21}NO_3$: calcd. C 72.22, H 7.07, N 4.68; found C 72.29, H 7.10, N 4.64.

25a (0.2 mmols) was dissolved in 2,2-dimethoxypropane (2 ml) and a crystal of PTSA was added. After stirring overnight, solid $NaHCO_3$ was added, the mixture was filtered and the crude purified by flash chromatography on Florisil (200−300 mesh; hexanes/Et_2O, 6:4), to avoid decomposition of the product. **26a** was recovered as an oil in 60% yield. − ^1H and ^{13}C-NMR significant data are collected in Table 4. − $C_{21}H_{25}NO_3$: calcd. C 74.31, H 7.42, N 4.13; found C 74.40, H 7.45, N 4.10.

Synthesis of **35** *from* **32d**: To a solution of **32d** (0.14 mmols) in THF (4 ml), 40% HF (100 μl) was added, and the mixture was stirred at RT for 2 hours. After addition of solid $NaHCO_3$, additional stirring (15′) and filtration, the crude was purified by flash chromatography (hexanes/Et_2O 6:4; 38%). − **35** was a pale oil; $C_{13}H_{15}NO_3$: calcd. C 66.94, H 6.48, N 6.00; found C 67.00, H 6.42, N 5.95. − Significant ^1H- and ^{13}C-NMR data are collected in Table 6.

Synthesis of **44** *from* **42d**: The same procedure described for the synthesis of **35** was applied. − **44** was obtained as an oil in 41% yield (hexanes/Et_2O, 1:1). − $C_{15}H_{17}NO_5$: calcd. C 61.85, H 5.88, N 4.81; found C 61.84, H 5.93, N 4.78. − Significant ^1H- and ^{13}C-NMR data are collected in Table 6.

2D NOESY Spectra: for all 2D NOESY NMR experiments the samples were prepared by dissolving 5-6 mg of the required compound in 0.75 ml of $CDCl_3$. The temperature employed for running the 2D experiment was 50°C and the solution was degassed. Pure absorption 2D spectra were recorded using NOESY pulse sequence[21] $90° - t_1 - 90° - \tau_m - 90° - t_2$ and the method of phase-cycling described by Wüthrich[22] with time-proportional phase incrementation (TPPI).[22] The following parameter and procedures are commonly employed: spectral width of 2800 Hz, a 1024 × 1024 data matrix, 256 time increments of 80 transients each; Fourier transformation were carried out with zero-filling only in f_1 using shifted sine-bell apodization function in both dimensions. A mixing time of 1.5 s and a relaxation delay of 10.0 s were used for the acetonide **26a** . The mixing time and the relaxation delay values employed were 3.0 and 15.0 s for the bicyclic lactones **35** and **44** .

Computational Procedures: All calculations were performed using the MacroModel/Batchmin 5.5 package[17] and the MM2* [16] force field, augmented with a substructure for the nitrone *plus* alkene TS.[23] This substructure was obtained starting from the one for nitrile oxide *plus* alkene, previously modified by inclusion of atomic charges instead of dipoles.[23] The new parameters for the nitrone moiety were obtained from the RHF/4-31G transition structure located by Bernardi et al.;[19] for the electrostatic calculations, the RHF/3-21G CHELPG charges were used.[4]

The conformational searches were performed for each diastereoisomer (when the case, in both the *endo* and *exo* approach) in vacuo, using the systematic pseudo-Monte Carlo/energy minimization (MC/EM) procedure.[18] The extraannular bonds of the isoxazolines and isoxazolidines which can undergo free rotation were used as variables (in the case of intramolecular cycloadditions, the conformational mobility of the fused ring was considered by including ring bonds as variables in the Monte Carlo search). 250 Monte Carlo steps per torsion were shown to ensure convergence of the conformational search (on test jobs, a higher number of step *per* torsional variable did not locate any new minimum within 20 kJ/mol with respect to the first 250 steps). Standard convergence criteria (0.05 kJ $Å^{-1}$ mol^{-1}) and the truncated Newton conjugate gradient procedure[23] were used for energy minimization. All uniques conformations within 20 kJ mol^{-1} were stored, and the diastereoisomeric ratios were evaluated in each case considering a Boltzmann distribution at the suitable temperature (the temperature at which the corresponding experimental ratio was obtained).

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