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Cycloadditions of Nitrile Oxides to α,β-Unsaturated Aldehydes. Frontier Orbital Interactions and Secondary Orbital Interactions at Work in Determining Regiochemistry

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Dedicated to Professor Rolf Huisgen on the occasion of his 80th birthday

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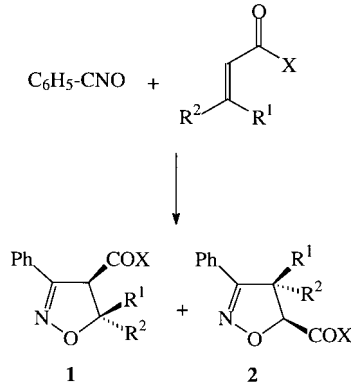
Abstract—The regiochemistry of the cycloadditions of nitrile oxides to crotonaldehyde and cinnamaldehyde has been determined and is dictated by frontier orbital interactions and secondary orbital interactions as well. In cycloadditions to α,β-unsaturated compounds the directive effect of the frontier orbital interactions can be diverted by steric drifts and secondary orbital interactions.

Introduction

The regiochemistry of the 1,3-dipolar cycloadditions[1] has remained for a long time an unsolved problem (the 'biggest unsolved')[2] until the frontier orbital (FO) theory[3] provided in 1973 a satisfactory rationalization of the main regiochemical trends involved in this area. In the same year, Huisgen reported a thorough study on the cycloadditions of nitrile oxides to α,β-unsaturated esters,[4] which is the obligatory reference and canon for any other regiochemical result in nitrile oxide cycloadditions to α,β-unsaturated compounds, and a FO analysis of the regiochemistry as well. As a typical case benzonitrile oxide (BNO) adds to crotonate and cinnamate esters yielding mixtures of 4- and 5-acyl-isoxazolines **1** and **2** (Scheme 1), where the 4-acyl isomers are the major products (Table 1) in keeping with the preferred binding of the nitrile oxide oxygen, which has the highest *HOMO* coefficient,[3] to the β-carbon of the α,β-unsaturated esters.

Over the years a few other regiochemical data on the cycloadditions to α,β-unsaturated compounds became available.[5–7] Somewhat surprisingly the regioselectivity of the cycloadditions to acyclic α,β-unsaturated ketones was found to be slightly reduced (entry 4)[8] relatively to the esters, while the related cyclic dipolarophiles,



1 **2**

Scheme 1.

Table 1. Ratio of regioisomers **1/2** in the cycloadditions of BNO to crotonoyl derivatives. The ratios related to the cinnamoyl derivatives are given in parentheses

Entry	X	R^1	R^2	**1/2**	Ref.
1	OCH_3	H	CH_3	66:34 (70:30)	4
2	NH_2	H	CH_3	56:44 (72:28)	12
3	$NHCH_3$	H	CH_3	55:45 (66:34)	12
4	CH_3	H	CH_3	50:50 (59:41)	8
5	$N(CH_3)_2$	H	CH_3	15:85 (24:76)	12
6	$-OCH_3-$		H	>9:1	9
7	$-CH_2CH_2-$		H	91:9	10
8	$-NHCH_2-$		H	91:9	12

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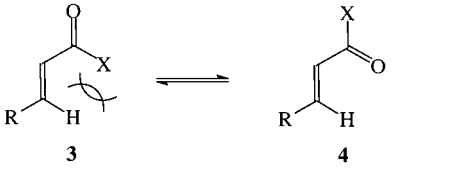
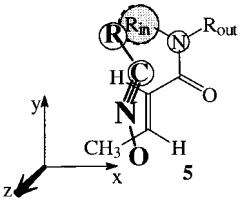
α,β-unsaturated lactones (entry 6)[9] or cyclic alkenones (entry 7)[10] afford mainly the 4-acyl cycloadducts **1** with high regioselection.

A possible origin of the marked difference between the cyclic and acyclic α,β-unsaturated carbonyl compounds as well as the differences between the latter ones could reside in the conformational equilibrium of the acyclic compounds, which is determined by the steric interaction between the acyl substituent X and the β-vinylic hydrogen.[11] While the aldehydes adopt mainly the transoid conformation **3**, the esters and even more the ketones prefer the cisoid conformation **4**, which becomes almost exclusive in the case of amides.



3 **4**

X = H X = OR < CH_3 << NRR'



5

The tempting hypothesis is then that the changes in regioselectivity reflect the changes in the conformational equilibria. While the transoid arrangement of the cyclic dipolarophiles gives rise to highly regioselective cycloadditions, in keeping well with FO expectations, the cisoid arrangement apparently is associated with a lower regioselection. In the latter case some unidentified factors must tip the balance away from cycloadduct **1** and/or toward cycloadduct **2**.

Following this hypothesis, we have recently investigated the cycloadditions to some crotonamides and cinnamamides, which firmly adopt the cisoid conformation, and, for comparison, to a few unsaturated lactams, which are constrained in a transoid conformation.[12] As usual for the cyclic derivatives the unsaturated lactams display high regioselection (entry 8) while the primary amides and their *N*-methyl derivatives show ratios (entries 2,3) comparable to the esters and the ketones and are intermediate between them. The *N*,*N*-dimethyl derivatives display instead a neat reversal of regioselection (entry 5) and the reversal becomes larger with increasing bulk of the *N*,*N*-dialkyl substituents.

Taking into account the larger steric sensitivity of the C end of the 1,3-dipole,[5,13] we attributed the changes in regioselection to the steric hindrance of the acyl substituents in the approach **5**, leading to the 4-acyl regioisomer **1**. In the case of the amides the *N*-substituents R_{in}, which are close to the plane of attack of the nitrile oxide and are shown in the shaded circle, have the largest steric effect. The steric model works successfully in accounting for the changes in regioselection observed with the derivatives reported in Table 1 because of the minor changes in the FOs of these cross-conjugated systems[14] and the drift of regioselection could be satisfactorily related to the *A* values of substituents X, a convenient and widely accessible steric parameter.[15]

The following is a study of the regioselection in the cycloaddition of BNO and the stable mesitonitrile oxide (MNO) to crotonaldehyde and cinnamaldehyde as well as to acrolein. Since the α,β-unsaturated aldehydes definitely adopt a transoid conformation in the ground state, regioselection should be high and approach that of the cyclic derivatives, in the absence of other diverting effects.

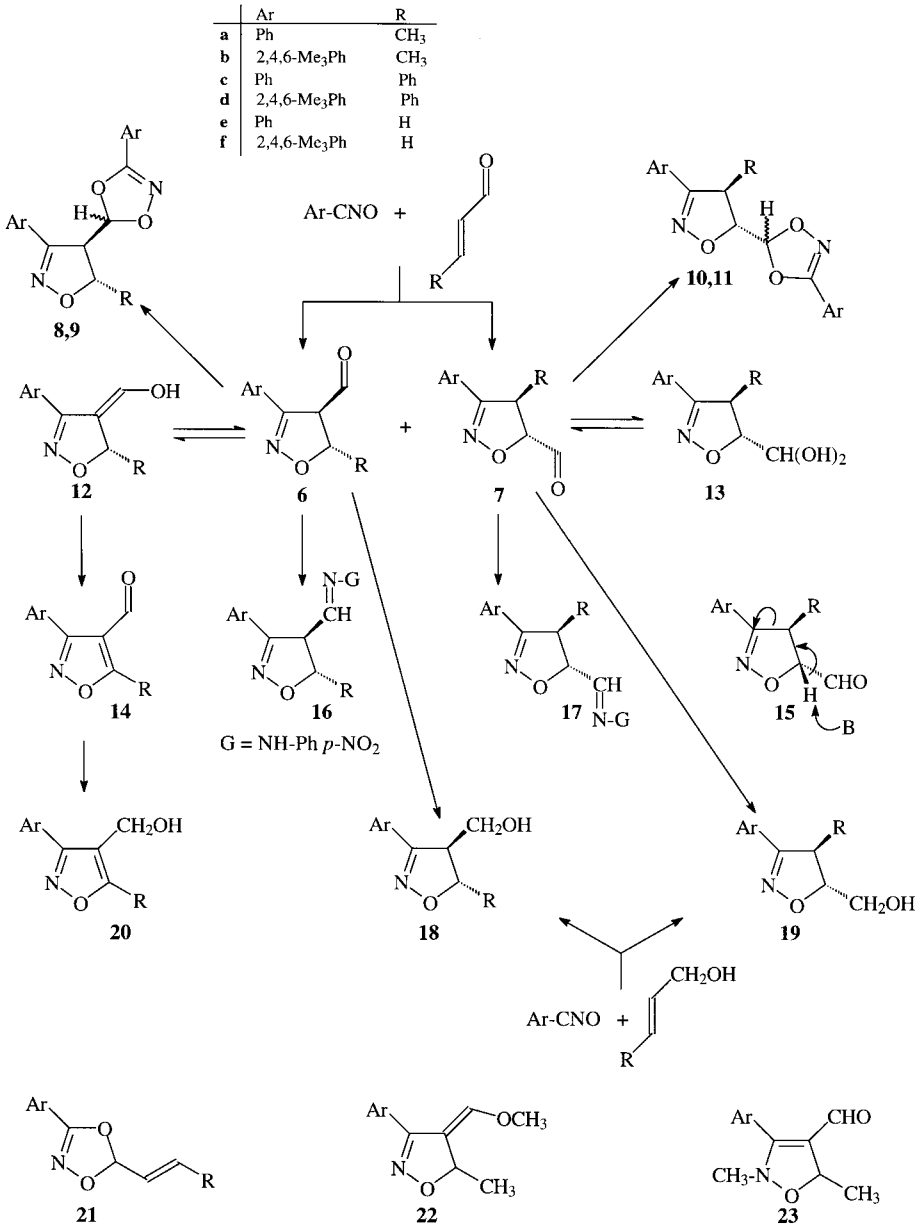
Only a few papers dealt with the cycloadditions of nitrile oxide to α,β-unsaturated aldehydes. By performing the reaction with preformed BNO Stagno d'Alcontres[16] isolated the 3-phenyl-4,5-dihydro-isoxazole-5-carbaldehyde in the cycloaddition to acrolein while De Sarlo[17] obtained the 3,5-diphenyl-4,5-dihydro-isoxazole-4-carboxaldehyde and bisadducts deriving from it in the case of cinnamaldehyde. The in situ technique cannot be used here, since the presence of a base causes fragmentation of the adducts.[18,19] The in situ technique applies well in cycloadditions to acetals, which have been more frequently reported.[16,17,19,20]

Results

Crotonaldehyde

Cycloadditions of BNO to crotonaldehyde were performed by adding the aldehyde to a neutral solution of preformed BNO in diethyl ether at 0–5°C. When using an excess of crotonaldehyde (10 equiv.), evaporation of the solvent and excess dipolarophile left a mixture containing mainly the adduct **6a** along with minor amounts of aromatic aldehyde **14a**, the regioisomeric adduct **7a** and the hydrated aldehyde **13a** as well (Scheme 2). In the presence of a slight excess of the aldehyde (1.5 equiv.) cycloadditions to the aldehyde moieties of the adducts **6a** and **7a** compete and about a half of them are converted in the diastereomeric couples of bisadducts **8a**, **9a** and **10a**, **11a** respectively. These further cycloadditions take place rather unselectively affording comparable amounts of the diastereomeric bisadducts **8a** and **9a** and resp. **10a** and **11a**.

The adducts were separated by column chromatography. From the reaction performed with excess crotonaldehyde, the isoxazolinic aldehydes **6a** (53%) and **7a** (12%) were obtained as thick and rather unstable oils. The aldehyde **6a** undergoes oxidation to **14a** upon standing in solvents and the oxidation is faster in the presence of triethylamine. The NMR spectrum of the oily **6a** in $CDCl_3$ shows the presence of small peaks (3–5%) attributable to the enol tautomer **12a**, which disappears in a few hours with a corresponding increase of the formyl and 5-methyl signals of the aromatic aldehyde **14a**. The relatively easy enolization of **6a** follows from its β-dicarbonyl structure, where the 4-isoxazolinic proton is α to the formyl and the C=N bond. The enol **12a** is well suited for autoxidation since the detachment of the 5-isoxazolinic proton occurs with aromatization. On the other hand the regioisomeric aldehyde **7a** hydrates easily because of the presence of the



Scheme 2.

Table 2. Ratios of the 4-acyl/ 5-acyl regioisomers **1/2** (reaction yields) in the cycloadditions of BNO and MNO to α,β-unsaturated aldehydes as determined by quantitative GC determinations of the corresponding alcohols after $NaBH_4$ reduction of the reaction mixtures. The ratios **1/2** reported for the related α,β-unsaturated esters are included for comparison

X	R	BNO	MNO
H	CH_3	81:19 (78%)	89:11 (70%)
OCH_3	CH_3	66:34[a]	73:27[a]
H	C_6H_5	85:15 (73%)	57:43 (65%)
OCH_3	C_6H_5	70:30[a]	52:48[b]
H	H	6:94 (83%)	11:89 (74%)
OCH_3	H	3.6:96.4[a]	6.6:93.4[a]

[a] Ref. 4.
[b] Ref. 12.

α-electronegative substituent[21] and was obtained from the chromatographic separation essentially in the hydrated form **13a**. The NMR spectra of the crude sample were rather complex but showed however an almost complete equilibration towards the free aldehyde **7a** after standing a few hours in $CDCl_3$. In the presence of bases **7a** undergoes fragmentation to benzonitrile as shown in **15**.[18]

Stable derivatives of the aldehydes could be obtained with *p*-nitrophenylhydrazine, which afforded the crystalline *p*-nitrophenylhydrazones **16a** and **17a**, while $NaBH_4$ reduction in methanol afforded the alcohols **18a** and **19a**, identical with samples obtained by cycloaddition to crotyl alcohol.

In view of the difficulties encountered in dealing with the fragile aldehydes, for quantitative determinations we chose

to reduce the reaction mixtures with $NaBH_4$ and analyze the mixture of the alcohols **18a** and **19a** by GC. Minor amounts of the alcohol **20a**, deriving from the reduction of the isoxazole aldehyde **14a**, were also observed and taken into account in deriving the regiochemical ratio. The latter is reported as the ratio of the 4-acyl/5-acyl regioisomers **1/2** in Table 2 along with the ratios of the esters for comparison.

Cycloaddition of MNO to crotonaldehyde takes place similarly with a few noteworthy differences. MNO cycloadditions display a higher propensity towards the formation of bisadducts and the MNO cycloadduct **6b** undergoes an easier and almost complete tautomerization to the enol **12b**. The formation of the bisadducts can be reduced by using a larger excess of the dipolarophile (20 equiv.) and their enhanced formation can be ascribed to the more nucleophilic character of MNO. No sizeable amounts of the monocycloadduct **21b** to the aldehyde moiety of crotonaldehyde could however be isolated or clearly detected in the NMR spectra of the reaction mixtures.

While the NMR spectra of the reaction mixtures show prominent signals attributable to the main cycloadduct **6b**, crystallization afforded instead the rather insoluble crystalline enol **12b** in fair yields (46%). In $CDCl_3$ solution **12b** shows a minute tendency to equilibrate with **6b**, while the oxidation of **12b** to the aromatic aldehyde **14b** goes smoothly to completion in a few days. The almost complete tautomerization of **6b** to **12b** is presumably due to the relief of the strain present in **6b** owing to the hindrance between the mesityl group at C-3, orthogonal to the plane of the isoxazolinic ring, and the proximal formyl group present on the sp^3 C-4 carbon atom. Methylation of **12b** with NaH/CH_3I in THF afforded the *O*- and *N*-methyl derivative **22b** and **23b** in a 3:1 ratio. The NMR spectrum of the *O*-methyl derivative **22b** shows an allylic coupling between the vinylic proton (6.01 δ, d, J=3.0 Hz) and the 5-isoxazolinic proton (5.49 δ, dq) and closely resembles the spectrum of **12b**. The *N*-methyl derivative shows instead the formyl proton as a singlet at 8.74 δ and the 5-isoxazolinic proton as a quartet at 5.71 δ.

Chromatographic separation afforded the enol **12b** and the hydrated aldehyde **13b**, which were converted to the stable and crystalline *p*-nitrophenylhydrazones **16b** and **17b** and by $NaBH_4$ reduction to the alcohols **18b** and **19b**. Reduction of the reaction mixtures with $NaBH_4$ yielded the alcohols **18b** (+**20b**) and **19b**, which were quantitatively determined by GC.

Cinnamaldehyde and acrolein

In cycloadditions of BNO to cinnamaldehyde, the excess cinnamaldehyde was distilled under vacuum up to $120°C/_{0.1\ mmHg}$, and the NMR spectrum of the residue showed the regioisomeric cycloadducts **6c**[17] and **7c** and the aromatic aldehyde **14c** in a 7:1:1 ratio. On the other hand in cycloadditions to acrolein the solvent and excess acrolein were evaporated under vacuum without heating, and the NMR spectrum of the residue showed a mixture of **7e** and its hydrated form **13e** along with minor signals of the regioisomeric adduct **6e** and its oxidation product **14e**. In the latter case colourless crystals mp 83–84°C[16] separated out from the moist ether and spectroscopic data support the structure **13e**. Upon standing a few hours in $CDCl_3$ **13e** undergoes an almost complete equilibration towards the free aldehyde **7e**.

The spectra of the MNO cycloaddition mixtures are rather complex, showing the presence of the aldehydes **6d**,**f** and **7d**,**f** as well as the enol **12d**,**f**, the aromatic aldehyde **14d**,**f** and the hydrated form **13d**,**f** in varying compositions depending upon the runs and the story of the samples.

For quantitative purposes the BNO and MNO cycloaddition mixtures were again reduced with $NaBH_4$ to yield the alcohols **18c**–**f** (+**20c**–**f**) and **19c**–**f**, which were quantitatively determined by GLC. Samples of the alcohols **18c**–**f** and **19c**–**f** were independently obtained by cycloaddition to cinnamyl and allyl alcohols.

Discussion

Cycloadditions of nitrile oxide to α,β-unsaturated aldehydes afford fragile cycloadducts. The 4-formyl isoxazolines **6** undergo enolization and subsequent oxidation while the 5-formyl isoxazolines **7** are easily hydrated and fragment in the presence of a base. In spite of these complications the ratios of Table 2 clearly show that nitrile oxide cycloaddition to the α,β-unsaturated aldehydes are more inclined to yield the 4-acyl cycloadducts **1** than the cycloadditions to the corresponding esters. On going from BNO to the more nucleophilic MNO this preference increases in the case of crotonaldehyde and acrolein, owing to their highly polarized LUMOs, while it decreases in the case of cinnamaldehyde, which has an almost unpolarized LUMO.[12]

The regioselection in cycloadditions to crotonaldehyde remains however well below the high standards observed with the cyclic dipolarophiles of fixed transoid conformation. Why does crotonaldehyde resist the combined directive effect of the two FO interactions?

We have performed a few model calculations on the cycloaddition of HCNO to acrolein and crotonaldehyde. The transition structures (TSs) have been located at the HF 6-31G* level, which gives satisfactory geometries for pericyclic reactions,[22] and single-point energies have been evaluated at the B3LYP/6-31G* level, to take into account electron correlation.[23] The acrolein TSs were also optimized at the B3LYP/6-31G* level but showed only minor energy

Table 3. Electronic activation energies calculated for the cycloadditions of fulminic acid to crotonaldehyde and acrolein relative to reactants (in kcal/mol)

	Cisoid aldehyde	T4	T5	C4	C5
Crotonaldehyde					
HF/6-31G*	1.4	31.5	38.3	34.0	36.7
B3LYP/6-31G*//HF/6-31G*	1.3	13.1	15.3	15.0	13.6
Acrolein					
HF/6-31G*	1.7	30.9	33.8	33.4	32.8
B3LYP/6-31G*//HF/6-31G*	1.6	11.7	11.3	13.7	10.0
B3LYP/6-31G*	1.7	11.6	10.9	13.4	10.1

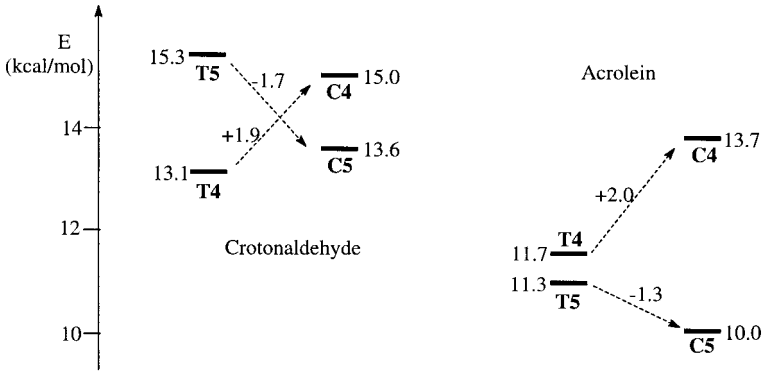


Figure 1. Transition structures for cycloadditions of fulminic acid to crotonaldehyde and acrolein at the B3LYP/HF(6-31G*) level. The arrows point out the energy changes which accompany the conformational switch of the α,β-unsaturated aldehyde.

and geometric changes. Inclusion of electron correlation is essential to afford reliable TS energies of pericyclic reactions[22] and reproduce regioisomeric phenomena in HCNO cycloadditions.[24]

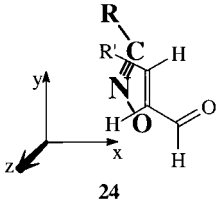
The four possible TSs were labeled **T4**, **T5**, **C4** and **C5** where **T** and **C** refer to the transoid or cisoid conformation of the α,β-unsaturated aldehydes and the numbers specify the positions of the formyl group in the forming heterocyclic ring. At all levels of calculation the more stable conformation of the α,β-unsaturated aldehydes in the ground state is the transoid conformation. The energies of the cisoid conformations and the energies of the TSs relative to the reactants are given in Table 3. The four barriers for the cycloadditions to crotonaldehyde are displayed in Fig. 1 by using the more reliable B3LYP energies along with the four barriers of acrolein evaluated at the same level.

Fig. 1 clearly shows that the two TSs **T4** and **T5** for the HCNO cycloaddition to the transoid crotonaldehyde are well separated and maintain the ~2 kcal/mol difference implied in the regiochemistry of cycloadditions to the transoid cyclic derivatives. On going to the cisoid TS, **C4** increases in energies by 1.9 kcal/mol with respect to **T4**, in keeping with the similar albeit lower preference (1.3 kcal/mol) of crotonaldehyde for the transoid conformation in the ground state, while **C5** drops instead by 1.7 kcal/mol relatively to **T5**.

Therefore the two more favorable passes to the cycloadducts **1** and **2** are **T4** and **C5** and involve respectively the transoid and the cisoid conformation of the α,β-unsaturated aldehyde. The observed leak of regioselection can then be attributed to the special factors which stabilize the TS **C5**, allowing for avoidance of the high lying TS **T5** in the formation of the 5-acyl cycloadduct **2**. On going to the case of acrolein all the four barriers decrease because of the reduced steric hindrance between the reactants and the decrease is larger for the less hindered TSs **T5** and **C5**. The latter eventually becomes the more easily viable pass for the cycloadditions to acrolein and regioselection reverses.

Alternatively viewed, the introduction of a β-*trans* methyl in acrolein reduces the rate of formation of the 4-acyl cycloadduct **1** (raises **T4** by 1.4 kcal/mol) but reduces even more the formation of the 5-acyl cycloadduct **2** (raises **C5** and **T5** by 3.6 and 3.0 kcal/mol, respectively). The observed changes nicely agree with the abundant experimental evidence and discussions on the role and positional dependence of steric effects in nitrile oxide cycloadditions, which was provided by Huisgen in a thorough dissection of rate and orientation data of α,β-unsaturated esters and other dipolarophiles.[25]

We attribute the remarkable stabilization of the TS **C5** of crotonaldehyde and acrolein to the very favorable secondary orbital interactions between the nitrile oxide oxygen and the aldehyde carbonyl. Indeed, as sketched in **24**, the nucleophilic nitrile oxide oxygen is located in a position which reminds the best Bürgi-Dunitz trajectory for the attack of a nucleophile to a carbonyl carbon,[26] with the oxygen p_x lone pair pointing towards the p_z orbital of the carbonyl carbon. A more familiar way to illustrate the interaction is sketched in **25** and **26**, where the partial negative charge on the nitrile oxide oxygen is spread towards the aldehyde oxygen.



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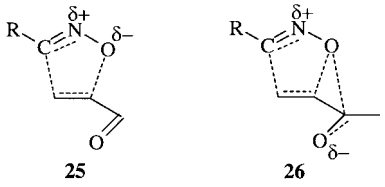

25 **26**

The geometries of the reactants and the TSs are shown in Fig. 2. The geometries of the TSs of acrolein and crotonaldehyde are only slightly different. In the TSs **T4** and **T5** the aldehyde moiety is rotated with the aldehyde oxygen moving downward relatively to the C1, C2, C3 plane of the α,β-unsaturated aldehyde, to align the π,π^* orbitals with the adjacent forming bond. In TS **C4** rotation occurs upward for the same reason, while in TS **C5** the rotation is minute (2–3°) and downwards. In the latter case the upward rotation should occur with loss of overlap between the nitrile oxide oxygen p_x lone pair and the p_z orbital of the

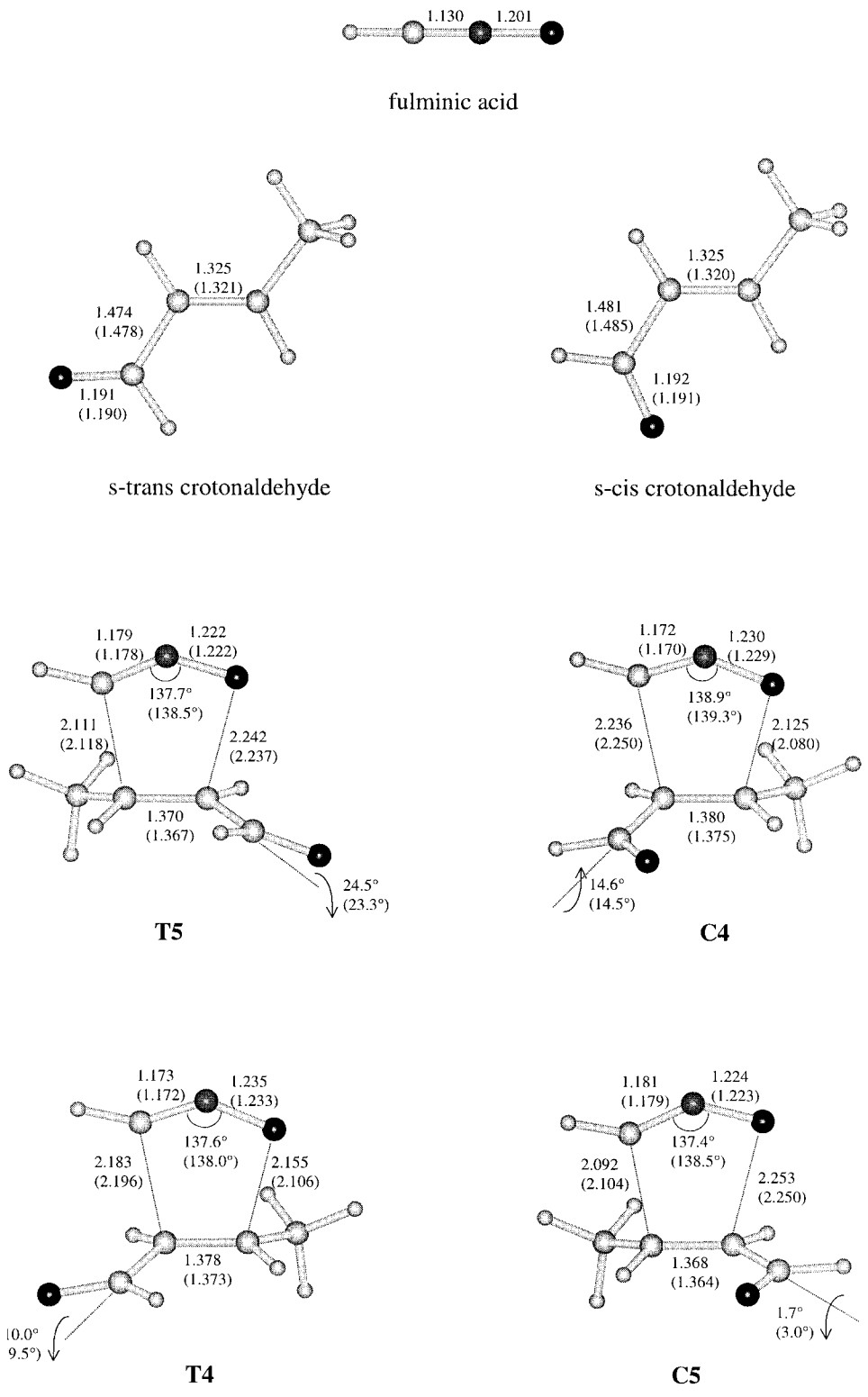

Figure 2. Geometric features of the reactants and TSs in the cycloaddition of HCNO to crotonaldehyde. The related data of acrolein are shown in parentheses. The curved arrows specify the rotation of the aldehyde oxygen out of the plane of the C1, C2, C3 aldehyde carbons in the directions shown.

carbonyl carbon as shown in **24** and is then avoided. In TS **C5** the distance between the nitrile oxide oxygen and the aldehyde carbon is 2.58 Å, only slightly longer than the adjacent forming O···C bond (2.25 Å).

The involvement of the less stable cisoid conformation of acrolein in Diels–Alder cycloadditions has been often reported[22,25,27] in connection with studies on the Lewis acid catalyzed Diels–Alder cycloadditions. Secondary orbital interactions offer the most viable interpretation and, the several possible secondary orbital interactions involved in Diels–Alder stereoselectivities curiously seem

to merge into the original Alder rule of 'maximum accumulation of unsaturations'.[28] Other cases of conformational switches in cycloadditions to enol ethers have been recently reported by Rastelli[24] and Houk.[29]

Conclusions

The nitrile oxide cycloadditions to crotonaldehyde take place with moderate regioselection in spite of the combined directive effects of both the FO interactions. Model calculations show that the leak of regioselection occurs because of a competitive transition state involving the cisoid conformer of the α,β-unsaturated aldehyde. A remarkably efficient secondary orbital interaction between the nitrile oxide oxygen and the aldehyde carbonyl more than compensate the cost of the conformational change.

Secondary orbital interactions are presumably at work in cycloadditions with α,β-unsaturated ketones, esters and amides, thereby modifying the FO prescriptions. The effect should be however attenuated in the series because of the expected raising of the π^* carbonyl.

Experimental

All mps are uncorrected. Elemental analyses were done on a C. Erba 1106 elemental analyzer. ^{1}H NMR spectra were recorded on a Bruker AC 300 spectrometer in $CDCl_3$ solutions, unless otherwise stated. Chemical shifts are expressed in ppm from internal tetramethylsilane (δ) and coupling constants are in Hertz (Hz): b, broad; s, singlet; bs, broad singlet; d, doublet; t, triplet; q, quartet; m, multiplet. IR spectra (nujol mulls) were recordered on an FT-IR Perkin–Elmer Paragon 1000 spectrophotometer and absorptions (ν) are in cm^{-1}. Column chromatography and tlc: silica gel H60 and GF_{254} (Merck) respectively, eluent cyclohexane/ethyl acetate 9:1 to ethyl acetate. GC analyses have been carried out by means of an HP 5890 equipped with a FID with an HP 5 column (30 m, 0.3 id) using nitrogen as carrier, using the internal standard method for quantitative determinations. The identification of samples from different experiments was secured by mixed mps and superimposable IR spectra.

Starting and reference materials

Benzhydroximoyl chloride was obtained by treatment of benzaldoxime with sodium hypochlorite[30] and mesitonitrile oxide by oxidation of 2,4,6-trimethylbenzaldoxime with bromine.[31] Solutions of BNO in diethyl ether were prepared with the procedure of Quilico and Speroni.[32]

The regioisomeric alcohols **18a**, mp 79–80°C (lit.[33] oil) from diisopropyl ether and **19a**, mp 48–50°C (lit.[33] oil) from petroleum ether, the regioisomeric alcohols **18c**, mp 122–122.5°C,[33] and **19c**, mp 93.5–95.5°C,[33] and alcohol **19e**, mp 79–79.5°C[34] are known compounds and were obtained by cycloaddition of BNO to crotyl,[33] cinnamyl[33] and allyl[34] alcohols. In the BNO cycloaddition to allyl alcohol (10 equiv.) in diethyl ether the main adduct **19e** and the regioisomeric adduct **18e** are formed in a 99:1 ratio. Crystallization from benzene afforded **19e** (73%). The mother liquors were evaporated and separated by column chromatography giving **18e** (0.8%) and further **19e** (11%). Adduct **18e**: mp 67–68°C from ethanol/water; (found C, 67.6; H, 6.3; N, 8.0. $C_{10}H_{11}NO_2$ requires C, 67.78; H, 6.26; N, 7.91); ν_{OH} 3350 cm^{-1}; δ_H: 2.02 (bs, 1H, *OH*); 3.6–4.0 (m, 3H, CH_2 and *H-4*); 4.4–4.7 (m, 2H, *H-5*); 7.4–7.5 (m, 3H, *arom.*); 7.7–7.8 (m, 2H, *arom.*). Cycloadditions of MNO to the allylic alcohols (5 equiv.) in benzene have been similarly performed. After keeping the solutions 1 month at r.t., the solvent and excess allylic alcohol was evaporated under vacuum and column chromatography of the residues afforded the couples of the regioisomeric alcohols:

18b (35%) oil, bp 190°C (bath/0.1 mmHg); (found C, 72.1; H, 8.2; N, 6.0. $C_{14}H_{19}NO_2$ requires C, 72.07; H, 8.21; N, 6.00); ν_{OH} 3400 cm^{-1}; δ_H: 1.50 (d, 3H, CH_3, J=6.2 Hz); 2.26 (s, 6H, *o,o′-*CH_3); 2.30 (s, 3H, *p-*CH_3); 3.33 (m, 1H, *H-4*); 3.67 (m, 2H, CH_2); 1.80 (bs, 1H, *OH*); 4.72 (m, 1H, *H-5*); 6.90 (s, 2H, *Mes-H*).

19b (40%), mp 56–58°C from ligroin; (found C, 72.0; H, 8.0; N, 5.9. $C_{14}H_{19}NO_2$ requires C, 72.07; H, 8.21; N, 6.00); ν_{OH} 3500 cm^{-1}; δ_H: 1.16 (d, 3H, CH_3, J=7.2 Hz); 2.03 (bs, 1H, *OH*); 2.27 (s, 6H, *o,o′-*CH_3); 2.31 (s, 3H, *p-*CH_3); 3.57 (m, 1H, *H-4*); 3.75 and 3.96 (m, 2H, CH_2); 4.40 (m, 1H, *H-5*); 6.91 (s, 2H, *Mes-H).*

18d (22%), mp 89–90°C from petroleum ether; (found C, 77.3; H, 7.1; N, 4.7. $C_{19}H_{21}NO_2$ requires C, 77.26; H, 7.17; N, 4.74); ν_{OH} 3380 cm^{-1}; δ_H: 1.55 (bs, 1H, *OH*); 2.21 (s, 6H, *o,o′-*CH_3); 2.30 (s, 3H, *p-*CH_3); 3.65–3.85 (m, 3H, *H-4* and CH_2); 5.68 (d, 1H, *H-5*, J=7.0 Hz); 6.90 (s, 2H, *Mes-H*); 7.3–7.5 (m, 5H, *arom.*).

19d (47%), mp 140–141°C from benzene; (found C, 77.3; H, 7.2; N, 4.8. $C_{19}H_{21}NO_2$ requires C, 77.26; H, 7.17; N, 4.74); ν_{OH} 3330 cm^{-1}; δ_H: 2.11 (s, 6H, *o,o′-*CH_3); 2.23 (s, 3H, *p-*CH_3); 2.55 (bs, 1H, *OH*); 3.8–4.0 (m, 2H, CH_2); 4.60 (d, 1H, *H-4*, J=6.2 Hz); 5.02 (m, 1H, *H-5*); 6.78 (s, 2H, *Mes-H*); 7.15–7.3 (m, 5H, *arom.*).

18f (1%) oil, bp 190°C (bath/0.1 mmHg); (found C, 71.2; H, 7.8; N, 6.4. $C_{13}H_{17}NO_2$ requires C, 71.20; H, 7.82; N, 6.39); ν_{OH} 3370 cm^{-1}; δ_H: 1.92 (bs, 1H, *OH*); 2.27 (s, 6H, *o,o′-*CH_3); 2.30 (s, 3H, *p-*CH_3); 3.6–4.0 (m, 3H, *H*-4 and CH_2); 4.50 (m, 1H, *H-5*); 6.93 (s, 2H, *Mes-H*).

19f (71%), mp 82–83°C from ligroin; (found C, 71.1; H, 7.8; N, 6.4. $C_{13}H_{17}NO_2$ requires C, 71.20; H, 7.82; N, 6.39); ν_{OH} 3420 cm^{-1}; δ_H: 2.25 (s, 6H, *o,o′-*CH_3); 2.29 (s, 3H, *p-*CH_3); 2.67 (bs, 1H, *OH*); 3.15 (m, 2H, *H-4*); 3.6–3.8 (m, 2H, CH_2O); 4.85 (m, 1H, *H-5*); 6.90 (s, 2H, *Mes-H*).

The isoxazole aldehydes **14a**, mp 55–56°C[35] and **14c**, mp 113–114°C[17] were obtained according to the literature and the aldehydes **14e**, mp 44°C and **14f**, mp 68–69°C were available from previous work.[36] The aldehydes were quantitatively reduced to the alcohols with $NaBH_4$ in methanol. After keeping 2 h at r.t. the mixtures were evaporated, taken up in chloroform and washed with water. Drying over Na_2SO_4 and evaporation afforded almost

quantitatively the alcohols **20a**,[37] mp 80–2°C from benzene, **20c**, mp 138–139°C (lit.[38] mp 137–139°C), 20e, oil; (found C, 68.4; H, 5.3; N, 8.1. $C_{10}H_9NO_2$ requires C, 68.56; H, 5.18; N, 8.00); ν_{OH} 3390 cm^{-1}; δ_H: 1.80 (bs, 1H, *OH*); 4.73 (s, 2H, CH_2); 7.5–7.8 (m, 5H, *arom.*); 8.50 (s, 1H, *H-5*), **20f**, mp 90–91°C from petroleum ether; (found C, 71.9; H, 7.1; N, 6.3. $C_{13}H_{15}NO_2$ requires C, 71.86; H, 6.96; N, 6.45); ν_{OH} 3380 cm^{-1}; δ_H: 1.55 (bs, 1H, *OH*); 2.09 (s, 6H, *o,o'-*CH_3); 2.35 (s, 3H, *p-*CH_3); 4.38 (s, 1H, CH_2); 6.96 (s, 2H, *Mes-H*); 8.36 (s, 1H, *H-5*).

General procedure for the cycloadditions of BNO to the α,β-unsaturated aldehydes

To a stirred solution of preformed BNO (10 mmol) in diethyl ether at 0°C the α,β-unsaturated aldehyde (10 equiv.) was added. After keeping the reaction mixture 2 days at 0–5°C the solvent and excess aldehyde was evaporated under vacuum and in the case of cinnamaldehyde up to 120°C (bath)/0.1 mmHg. The residue was separated by column chromatography or dissolved in methanol and reduced by adding excess $NaBH_4$ (2 equiv.) to the stirred and ice-cooled solution. After keeping 2 h at r.t. the mixtures were evaporated, taken up in chloroform and washed with water. The organic layer, dried over Na_2SO_4 and evaporated, left a residue which was separated by column chromatography and/or analyzed by GC. In a few cases the cycloadditions and the subsequent reductions have been performed under nitrogen. GC analyses showed the same **18**+**20/19** ratio and the expected change in the **18/20** ratio. In the reactions performed under nitrogen the isoxazole alcohols **20** are almost absent.

MNO cycloadditions have been similarly performed by adding the aldehyde (10 equiv.) to a solution of MNO (10 mmol) in anhydrous benzene (100 mL) ar r.t.. The reactions went to completion in 3 days at r.t. (1 day for acrolein).

Cycloadditions of BNO to crotonaldehyde

(A) Column chromatography afforded the aromatic aldehyde **14a** (7%), mp 55–56°C from petroleum ether and identical with the reference compound, and the isoxazolinic aldehydes **6a** (53%) and **7a** (12%) as thick oils.

6a: thick oil; $\nu_{C=O}$ 1721 cm^{-1}; δ_H: 1.48 (d, 3H, CH_3, *J*=6.5 Hz); 4.12 (dd, 1H, *H-4*, *J*=3.5, 5.8 Hz); 5.19 (m, 1H, *H-5*); 7.4–7.8 (m, 5H, *arom.*); 9.68 (d, 1H, *CHO*, *J*=3.5 Hz). The spectrum showed also a minor peak attributable to the enol tautomer **12a** [δ_H: 1.55 (d, 3H, CH_3, *J*=6.3 Hz); 5.59 (dq, 1H, *H-5*, *J*=2.8, 6.3 Hz); 7.05 (d, 1H, *CH*=, *J*=2.8 Hz)] which disappeared after a few hours with a corresponding increase of the signals of **14a** at δ_H: 2.80 (s, 3H, CH_3) and 9.98 (s, 1H, *CHO*). *p*-Nitrophenylhydrazone **16a**: yellow crystals, mp 163–165°C from ethanol/water; (found C, 62.8; H, 5.0; N, 17.1. $C_{17}H_{16}N_4O_3$ requires C, 62.95; H, 4.97; N, 17.28); δ_H (Acetone): 1.44 (d, 3H, CH_3, *J*=6.5 Hz); 4.40 (t, 1H, *H-4*, *J*=7 Hz); 4.95 (m, 1H, *H-5*); 7.1–8.1 (m, 10H, *arom.* and *CH*=*N*); 10.05 (bs, 1H, *NH*).

7a: thick oil. The spectroscopic data indicated a mixture of **7a** and the hydrated form **13a**: ν_{OH} 3480, $\nu_{C=O}$ 1725 cm^{-1}. The NMR spectrum showed complex signals between 3–5.5 δ, which simplified upon standing. After a few hours the aldehyde **7a** was the major constituent: δ_H: 1.42 (d, 3H, CH_3, *J*=7.0 Hz); 3.94 (dq, 1H, *H-4*, *J*=3.8, 7.0 Hz); 4.64 (dd, 1H, *H-5*, *J*=3.8, 1.0 Hz); 7.3–7.7 (m, 5H, *arom.*); 9.79 (d, 1H, *CHO*, *J*=1.0 Hz). *p*-Nitrophenylhydrazone **17a**: yellow crystals, mp 185–186°C from ethanol; (found C, 62.8; H, 4.8; N, 17.1. $C_{17}H_{16}N_4O_3$ requires C, 62.95; H, 4.97; N, 17.28); δ_H (Acetone): 1.40 (d, 3H, CH_3, *J*=7 Hz); 4.14 (m, 1H, *H-4*); 5.01 (t, 1H, *H-5*, *J*=6 Hz); 7.0–8.2 (m, 10H, *arom.* and *CH*=*N*); 10.13 (bs, 1H, *NH*).

Reduction of the aldehydes **6a** and **7a** with $NaBH_4$ in methanol afforded the alcohols **18a** (78%), mp 79–80°C from diisopropyl ether and respectively **19a** (65%), mp 48–50°C from petroleum ether, identical with the reference compounds.

(B) When performing the cycloaddition with 2 equiv. of crotonaldehyde, column chromatography afforded an inseparable mixture of the four bisadducts **8a**, **9a**, **10a** and **11a** (26%) along with **14a** (5%), **6a** (24%) and **7a** (8%). The four bisadducts can be readily distinguished by NMR, which shows well separated signals for the dioxazolinic protons at δ_H 6.32 (d, *J*=3.5 Hz), 6.21 (d, *J*=5.8 Hz), 6.18 (d, *J*=3.0 Hz) and 6.04 (d, *J*=5.8 Hz) in a 4:4:1:1 ratio. The major bisadducts **8a** and **9a** were independently obtained by exposure of aldehyde **6a** to excess preformed BNO (2 equiv.) and column chromatography, eluant benzene, afforded the two bisadducts **8a** and **9a** in fair yields (72%) and with a partial separation. The faster running oily diastereoisomer displayed signals at δ_H 1.46 (d, 3H, CH_3, *J*=6.5 Hz); 3.87 (dd, 1H, *H-4*, *J*=3.5, 5.8 Hz); 5.07 (dq, 1H, *H-5*, *J*=5.8, 6.5 Hz); 6.32 (d, 1H, *dioxazolinic-H*, *J*=3.5 Hz); 7.3–7.9 (m, 10H, *arom.*) while the slower running oily diastereoisomer has signals at δ_H 1.43 (d, 3H, CH_3, *J*=6.5 Hz); 3.83 (dd, 1H, *H-4*, *J*=4.0, 5.8 Hz); 5.03 (dq, 1H, *H-5*, *J*=4.0, 6.5 Hz); 6.21 (d, 1H, *dioxazolinic-H*, *J*=5.8 Hz); 7.4–7.8 (m, 10H, *arom.*).

The minor bisadducts **10a** and **11a** were similarly obtained from **7a** and partially separated by column chromatography, eluant benzene. The faster running oily diastereoisomer displayed signals at δ_H 1.42 (d, 3H, CH_3, *J*=7.2 Hz); 3.86 (dq, 1H, *H-4*, *J*=4.0, 7.2 Hz); 4.55 (dq, 1H, *H-5*, *J*=4.0, 5.8 Hz); 6.04 (d, 1H, *dioxazolinic-H*, *J*=5.8 Hz); 7.4–7.9 (m, 10H, *arom.*) while the slower running diastereoisomer could be purified by crystallization: mp 168–169°C from ethanol, (found C, 70.5; H, 5.3; N, 9.2; $C_{18}H_{16}N_2O_3$ requires C, 70.11; H, 5.23; N, 9.09); δ_H 1.42 (d, 3H, CH_3, *J*=7.2 Hz); 3.85 (dq, 1H, *H-4*, *J*=4.0, 7.2 Hz); 4.62 (dd, 1H, *H-5*, *J*=3.0, 4.0 Hz); 6.18 (d, 1H, *dioxazolinic-H*, *J*=3.0 Hz); 7.4–7.8 (m, 10H, *arom.*).

Cycloaddition of MNO to crotonaldehyde

Column chromatography afforded the aromatic aldehyde **14b** (6%), the couple of diastereoisomeric bisadducts **8b** (8%) and **9b** (9%), a mixture (2%) of the diastereomeric bisadducts **10b** and **11b**, the enol **12b** (47%) and the hydrated aldehyde **13b** (9%). In a duplicate experiment the residue was taken up with diisopropyl ether and the colorless crystals of **12b** (43%) were filtered off.

14b: mp 40–41°C from petroleum ether; (found C, 73.2; H, 6.5; N 6.1. $C_{14}H_{15}NO_2$ requires C, 73.34; H, 6.59; N, 6.11); $\nu_{C=O}$ 1682 cm^{-1}; δ_H: 2.11 (s, 3H, *p-CH*$_3$); 2.36 (s, 6H, *o,o′-CH*$_3$); 2.82 (s, 3H, *CH*$_3$); 6.98 (s, 2H, *Mes-H*); 9.49 (s, 1H, *CHO*).

8b: mp 150–151°C from ethanol; (found C, 73.7; H, 7.2; N 7.2. $C_{24}H_{28}N_2O_3$ requires C, 73.44; H, 7.19; N, 7.14); δ_H: 1.53 (d, 3H, *CH*$_3$, *J*=6.5 Hz); 2.2–2.32 (m, 18H, *CH*$_3$); 3.78 (d, 1H, *H-4*, J=6.5, 3.0 Hz); 5.05 (m, 1H, *H-5*); 5.95 (d, 1H, *H-dioxazolinic*, *J*=3 Hz); 6.88 (s, 2H, *Mes-H*); 6.91 (s, 2H, *Mes-H*).

9b: mp 146°C from ligroin; (found C, 73.3; H, 7.2; N 7.2. $C_{24}H_{28}N_2O_3$ requires C, 73.44; H, 7.19; N, 7.14); δ_H: 1.55 (d, 3H, *CH*$_3$, *J*=6.5 Hz); 2.1–2.3 (m, 18H, *CH*$_3$); 3.75 (dd, 1H, *H-4*, J=7.0, 4.6 Hz); 5.15 (m, 1H, *H-5*); 6.01 (d, 1H, *dioxazolinic-H*, *J*=4.6 Hz); 6.92 (s, 2H, *Mes-H*); 6.93 (s, 2H, *Mes-H*).

10+11b: the oily mixture shows well separated doublets of the dioxazolinic proton at δ_H 6.20 (d, *J*=5.0 Hz) and 6.22 (d, *J*=3.2 Hz). Upon standing it solidified and crystallization from ligroin afford a pure diastereoisomer, mp 130–133°C (found C, 73.3; H, 7.2; N 7.2. $C_{24}H_{28}N_2O_3$ requires C, 73.44; H, 7.19; N, 7.14); δ_H: 1.23 (d, 3H, *CH*$_3$, *J*=6.5 Hz); 2.2–2.3 (m, 18H, *CH*$_3$); 3.70 (m, 1H, *H-4*); 4.57 (dd, 1H, *H-5*, J=6.5, 5.0 Hz); 6.20 (d, 1H, *dioxazolinic-H*, *J*=5.0 Hz); 6.92 (s, 4H, *Mes-H*).

12b: mp 163°C from diisopropyl ether; (found C, 72.5; H, 7.5; N 6.3. $C_{14}H_{17}NO_2$ requires C, 72.70; H, 7.41; N, 6.06); δ_H: 1.52 (d, 3H, *CH*$_3$, *J*=6.5 Hz); 2.11, 2.13, 2.32 (s, 3H, *CH*$_3$); 5.51 (dq, 1H, *H-5*, *J*=3.0, 6.5 Hz); 6.35 (d, 1H, *CH*═, *J*=3.0 Hz); 6.86 (s, 2H, *Mes-H*); 6.93 (bs, 1H, *OH*). After standing a few hours the NMR displayed the signals of the aromatic aldehyde **14b** and minute signals attributable to aldehyde **6b**: 1.53 (d, 3H, *CH*$_3$, *J*=6.5 Hz); 2.25 (s, 6H, *o,o′-CH*$_3$); 2.32 (s, 3H, *p- CH*$_3$); 4.02 (dd, 1H, *H-4*, *J*=1.6, 8.0 Hz); 5.26 (dq, 1H, *H-5*, *J*=8.0, 6.5 Hz); 6.94 (s, 2H, *Mes-H*); 9.52 (d, 1H, *CHO*, *J*=1.6 Hz). *p*-Nitrophenylhydrazone **16b**: yellow crystals, mp 176–177°C from ethanol; (found C, 65.2; H, 15.2; N, 6.0. $C_{20}H_{22}N_4O_3$ requires C, 65.55; H, 6.05; N, 15.29); δ_H (Acetone): 1.49 (d, 3H, *CH*$_3$, *J*=6.5 Hz); 2.20 (s, 9H, *CH*$_3$); 4.20 (dd, 1H, *H-4*, *J*=7.0, 5.0 Hz); 4.98 (m, 1H, *H-5*); 6.95 (s, 2H, *Mes-H*); 7.02 (d, 2H, *arom*, *J*=8.0 Hz.); 7.25 (d, 1H, *CH═N*, *J*=7.0 Hz); 8.10 (d, 2H, *arom.*, *J*=8.0 Hz); 10.5 (bs, 1H, *NH*).

13b, thick oil. It was converted into the *p*-nitrophenylhydrazone **17b**: yellow crystals, mp 223–224°C from ethanol; (found C, 65.3; H, 15.4; N, 5.9. $C_{20}H_{22}N_4O_3$ requires C, 65.55; H, 6.05; N, 15.29); δ_H (Acetone): 1.15 (d, 3H, *CH*$_3$, *J*=7.0 Hz); 2.15 (s, 6H, *CH*$_3$); 3.95 (m, 1H, *H-4*); 4.95 (dd, 1H, *H-5*, *J*=5.1, 7.2 Hz); 6.85 (s, 2H, *Mes-H*); 7.15 (d, 2H, *arom*, *J*=7.0 Hz); 7.50 (d, 1H, *CH═N*, *J*=5.1 Hz); 10.2 (bs, 1H, *NH*).

$NaBH_4$ reduction of **12b**, **13b** and **14b** afforded the stable alcohols **18b**, **19b**, **20b**. The alcohols **18b**, thick oil, and **19b**, mp 56–58°C, are identical to the reference samples obtained by MNO cycloaddition to crotyl alcohol. The alcohol **20b** was obtained as colorless crystals, mp 121–122°C from ligroin (found C, 72.5; H, 7.3; N, 6.2. $C_{14}H_{17}NO_2$ requires C, 72.70; H, 7.41; N, 6.06); ν_{OH} 3360 cm^{-1}; δ_H: 2.10 (s, 6H, *o,o′-CH*$_3$); 2.17 (s, 3H, *p-CH*$_3$); 2.49 (d, 3H, *CH*$_3$); 4.20 (bs, 1H, *OH*); 6.95 (s, 2H, *Mes-H*).

Methylation of **12b** was performed by adding NaH (1.5 equiv.) to a stirred solution of **13b** (0.3 mmol) and MeI (5 equiv.) in anhydrous THF (30 mL) at r.t. After standing 2 h, 1 mL of methanol was added. After pouring in ice, extraction with chloroform, drying over Na_2SO_4 and evaporation of the solvent, column chromatography afforded the *O*- and *N*-derivatives **22b** and **23b** in a 3:1 ratio. **22b** (53%), mp 110–111°C from diisopropyl ether, (found C, 73.3; H, 7.8; N, 5.7. $C_{15}H_{19}NO_2$ requires C, 73.44; H, 7.81; N, 5.71); δ_H: 1.53 (d, 3H, *CH*$_3$, *J*=6.2 Hz); 2.22 (s, 6H, *o,o′-CH*$_3$); 2.32 (s, 3H, *p-CH*$_3$); 3.65 (s, 3H, *OCH*$_3$); 5.49 (dq, 1H, *H-5*, *J*=3.0, 6.2 Hz); 6.01 (d, 1H, *CH═*, *J*=3.0 Hz); 6.92 (s, 2H, *Mes-H*). The *Z* configuration of **22b** is based on a NOESY experiment which showed NOE correlation between the vinylic proton and the *o,o′*-CH_3. **23b**, (20%), thick oil; (found C, 73.4; H, 7.8; N, 5.6. $C_{15}H_{19}NO_2$ requires C, 73.44; H, 7.81; N, 5.71); $\nu_{C=O}$ 1630 cm^{-1}; δ_H: 1.60 (d, 3H, *CH*$_3$, *J*=6.0 Hz); 2.24, 2.27, 2.34 (s, 3H, *CH*$_3$); 2.98 (s, 3H, *NCH*$_3$); 5.71 (q, 1H, *H-5*, *J*=6.0 Hz); 6.97 (s, 2H, *Mes-H*); 8.75 (s, 1H, *CHO*).

Cycloaddition of BNO to cinnamaldehyde

The NMR spectrum of the mixture showed the signals of the aldehydes **6c**, **7c** and **14c** in a 7:1:1 ratio. Column chromatography afforded **14c** (8%), mp 113–114°C, and **6c** (53%), oil,[17] along with the hydrated aldehyde **13c** (11%) as a thick oil. The NMR spectrum of **13c** showed broad signals at 4.4–5.5 δ and, upon standing a few hours in $CDCl_3$, **13c** underwent an almost complete equilibration to **7c**: δ_H: 4.85 (dd, 1H, H-4, *J*=3.5, 0.7 Hz); 4.98 (d, 1H, H-5, *J*=3.5 Hz); 7.2–7.7 (m, 10H, arom.); 9.86 (d, 1H, CHO, *J*=0.7 Hz). $NaBH_4$ reduction of **13c** afforded the alcohol **19c** (83%), mp 93.5–95.5°C, identical to the reference sample.

$NaBH_4$ reduction of the cycloaddition mixture afforded the alcohols **18c** (+**20c**) and **19c** in a 85:15 ratio.

Cycloaddition of MNO to cinnamaldehyde

Column chromatography afforded a sample of the isoxazole aldehyde **14d** (11%), mp 88°C from ethanol/water; (found C, 78.0; H, 5.9; N, 4.8. $C_{19}H_{17}NO_2$ requires C, 78.33; H, 5.88; N, 4.81); $\nu_{C=O}$ 1692 cm^{-1}; δ_H: 2.17 (s, 6H, *o,o′-CH*$_3$); 2.38 (s, 3H, *p-CH*$_3$); 7.11 (s, 2H, *Mes-H*); 7.6 (m, 3H, *arom.*); 8.27 (m, 2H, *arom.*); 9.68 (s, 1H, *CHO*), which was reduced to the alcohol **20d**, mp 139°C from ethanol/water; (found C, 77.8; H, 6.4; N, 4.8. $C_{19}H_{19}NO_2$ requires C, 77.79; H, 6.53; N, 4.77); ν_{OH} 3320 cm^{-1}; δ_H: 1.70 (bs, 1H, *OH*); 2.15 (s, 6H, *o,o′-CH*$_3$); 2.36 (s, 3H, *p-CH*$_3$); 4.46 (s, 2H, *CH*$_2$); 6.99 (s, 2H, *Mes-H*); 7.5 (m, 3H, *arom.*); 7.97 (m, 2H, *arom.*). The cycloaddition mixture, when reduced with $NaBH_4$, afforded a comparable amounts of the alcohols **18d** and **19d**, identical with the reference compounds, along with minor amounts of the isoxazole alcohol **20d**. GC analyses gave a 57:43 ratio of **18d**+**20d**/**19d**.

Cycloaddition of BNO to acrolein

From the ethereal solution kept at 0–5°C for 2 days, the hydrated aldehyde **13e** (16%) separated out: mp 83–84°C from water (lit.[16] mp 84–85°C); ν_{OH} 3300 cm^{-1}; δ_H (DMSO): 3.3–3.4 (m, 2H, H-4); 4.48 (m, 1H, H-5); 4.80 (m, 1H, OCHO); 6.08 (m, 2H, OH); 7.4–7.7 (m, 5H, arom.). δ_H ($CDCl_3$): 2.95 (bs, 2H, OH); 3.3–3.5 (m, 2H, H-4); 4.80 (m, 1H, H-5); 5.10 (m, 1H, OCHO); 7.4–7.7 (m, 5H, arom.). Upon standing a few hours in $CDCl_3$ the sample underwent a smooth conversion to the free aldehyde 7e, δ_H: 3.5–3.7 (m, 2H, H-4); 5.07 (ddd, 1H, H-5, J=11.2, 6.0, 0.9 Hz); 7.4–7.7 (m, 5H, arom.); 9.83 (d, 1H, CHO, J=0.9 Hz). *p*-Nitrophenylhydrazone **17e**: yellow crystals, mp 221–222°C from ethanol; (lit.[16] mp 199–200°C). δ_H (Acetone): 3.72 (d, 2H, H-4, J=9.2 Hz); 5.42 (dt, 1H, H-5, J=5.8, 9.2 Hz); 7.18 (d, 2H, arom., J=9.0 Hz); 7.4–7.5 (m, 4H, arom. and CH=N); 7.77 (m, 2H, arom.); 8.15 (d, 2H, arom., J=9.0 Hz); 10.24 (bs, 1H, NH). $NaBH_4$ reduction of a sample of **13e** afforded quantitatively the alcohol **19e**, mp 79–80°C, identical with the reference compound.

The ethereal mother liquors were evaporated and the residue was separated by column chromatography affording the aldehyde **14e** (3%), mp 44°C, identical with the reference compound and further **13e** (54%).

On performing the cycloaddition under nitrogen, the $NaBH_4$ reduction of the mixture afforded the alcohol **19e** (70%), along with **20e** (1%), mp 50°C and **18e** (5%), mp 67–68°C, identical with the reference samples.

Cycloaddition of MNO to acrolein

Column chromatography afforded the isoxazole aldehyde **14f** (5%), mp 68–69°C from petroleum ether, identical with a reference sample, and the hydrated aldehyde **13f** (63%).

13f: thick oil. The NMR showed broad signals at 3.2–3.3, 4.7–4.9 and 5.2 δ attributable to **13e**, which decreased upon standing a few hours in $CDCl_3$ because of the almost complete conversion to the free aldehyde **7f**: δ_H: 2.20 (s, 6H, *o,o′-CH*$_3$); 2.32 (s, 3H, *p-CH*$_3$); 3.5–3.5 (m, 2H, *H-4*); 5.06 (ddd, 1H, *H-5*, J=10.8, 5.8, 0.9 Hz); 6.91 (s, 2H, *Mes-H*); 9.89 (d, 1H, *CHO*, J=0.9 Hz). *p*-Nitrophenylhydrazone **17f:** yellow crystals, mp 232–234°C from ethanol; (found C, 64.8; H, 5.9; N, 15.8. $C_{19}H_{20}N_4O_3$ requires C, 64.76; H, 5.72; N, 15.90); δ_H (Acetone): 2.25 (s, 6H, *o,o′-CH*$_3$); 2.29 (s, 3H, *p-CH*$_3$); 3.5–3.6 (m, 2H, *H-4*); 5.44 (m, 1H, *H-5*); 6.95 (s, 2H, *Mes-H*); 7.21 (d, 2H, *arom.*, J=9.0 Hz); 7.51 (d, 1H, *CH*=, J=6.0 Hz); 8.16 (d, 2H, *arom.*, J=9.0 Hz); 10.21 (bs, 1H, *NH*). $NaBH_4$ reduction of **13f** afforded the alcohol **19f**, mp 82–83°C, identical to the reference sample.

$NaBH_4$ reduction of the cycloaddition mixture gave the alcohols **18f**, **19f** and **20f**. GC analysis gave a 11:89 ratio of **18f**+**20f/19f**.

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