Pergamon

Tetrahedron, Vol. 53, No. 27, pp. 9279-9292, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)00539-5

Facial Selectivity in the Reactions of 1,3-Dipoles with cis- and trans-3,4-Dimethyl-1-methoxycarbonyl Cyclobutenes.

Enrico Cinquini,[a] Mauro Freccero,[a] Remo Gandolfi,[a]* Mirko Sarzi Amade',[a] Augusto Rastelli[b]

[a]Dipartimento di Chimica Organica, Universita' di Pavia, V.le Taramelli 10, 27100 Pavia, Italy
[b]Dipartimento di Chimica, Universita' di Modena, Via Campi 183, 41100 Modena, Italy

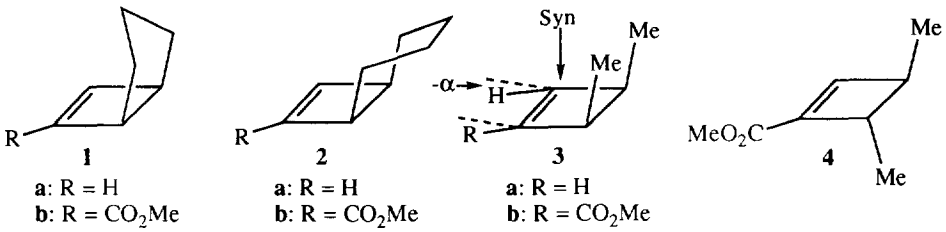
Abstract. Face selectivity of the regiospecific reactions of 1,3-dipoles [diazomethane (**5**), 3,4-dihydroisoquinoline-N-oxide (**6**) and nitrile oxides (**7**)] with trans-3,4-dimethyl-1-methoxycarbonyl cyclobutene (**4**) is controlled by steric factors with dominant formation of the anti diastereoisomer (anti/syn: 82:18 for **5**, 54:46 for **6** and ≈ 74:26 for **7**) through the sterically less crowded transition state. On passing to cis-3,4-dimethyl-1-methoxycarbonyl cyclobutene (**3b**) the expected increase in diastereoselectivity is observed only in the case of the reaction of **3b** with 3,4-dihydroisoquinoline-N-oxide (anti/syn = 94:6) while face selectivity decreases in the reaction of **3b** with diazomethane (anti/syn = 72:28) and there is a reversal of face selectivity in the reactions of **3b** with nitrile oxides (anti/syn ≈ 42:58). In the latter reaction the dominant syn diastereoisomer is formed via the sterically more congested TS. A syn orienting electronic effect (not yet clearly identified) is evidently present in the reactions of **3b** with 1,3-dipoles and in the reaction of **3b** with nitrile oxides it is strong enough to overcome relevant anti orienting steric effects.

INTRODUCTION

Facial selectivity of 1,3-dipolar cycloadditions (in particular of diazoalkanes, nitrile oxides and nitrones) of cis-3,4-disubstituted cyclobutenes has been thoroughly investigated by us and others from both theoretical and experimental points of view.[1-4] A peculiar and very interesting feature of these reactions is that the presence of electron-attracting substituents on the cyclobutene (such as Cl and OR groups) gives rise to clear-cut dominance of syn[5] attack by 1,3-dipoles whereas small carbocyclic substituents as in bicyclo[2.1.0]pent-2-ene or bicyclo[2.2.0]hex-2-ene[6] lead to ≥ 93% anti attack. We were able to show by systematic ab initio calculations that the double bond of all these cyclobutenes exhibits a significant non-planarity.[2] There is a resultant syn[5] pyramidalization of the carbon atoms of the double bond (i.e., the olefinic hydrogens are anti[5] bent by ≈ -3° for Cl and OR substituents)[2,3] and a related more facile anti than syn deformability of the olefinic hydrogens in the former derivatives. The opposite is true (i.e, the olefinic hydrogens are syn bent by +7° in bicyclo[2.1.0]pent-2-ene and by +4° in bicyclo[2.2.0]hex-2-ene and their syn deformations are easier than anti deformations)[2,3] for the latter derivatives. Then, on the basis of extensive computational work, we could conclude that syn (anti) pyramidalization of the double bond and the related more facile anti (syn) deformability of the olefinic hydrogens (both were traced back by us to the tendency of these systems to maximize hyperconjugative vicinal delocalizations between the σ allylic bonds and the π bond) are intrinsic factors of the dipolarophile that adequately parallel the observed facial selectivity.[1-4] This delocalization is at work in the isolated dipolarophile and it is progressively replaced, on the pathway to the transition state of 1,3-dipolar cycloadditions, by the vicinal delocalizations between the forming bonds and the allylic σ bonds. Actually, it is this latter electronic interaction, fully operative at the transition state, which tends to control the face selectivity of the reaction and

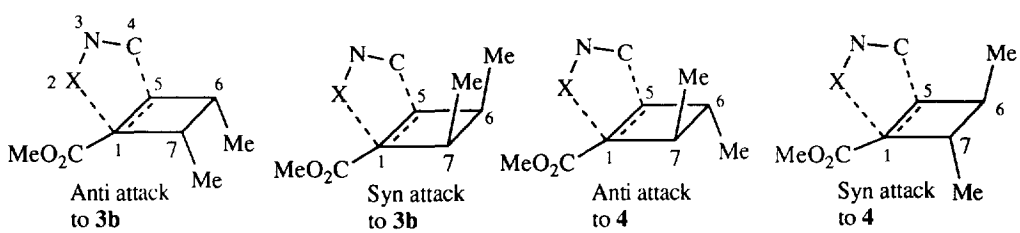
whose effect is either reinforced or counteracted by through space steric and electrostatic interactions between the attacking dipole and the substituents on the dipolarophile.[1-4]

In this context the lack of data about face selectivity of the reactions of cis-3,4-disubstituted cyclobutenes bearing acyclic alkyl groups and in particular methyl groups is disturbing. In fact, the only known result is that of the reaction of diazomethane with cis-3,4-dimethylcyclobutene (**3a**)[7] (Scheme 1) which affords a mixture of anti and syn adduct with the former predominant (anti:syn = 70:30). This result clearly parallels steric factors but it is not possible to evaluate if these factors are to some extent counteracted by electronic effects. The importance of the cis-3,4-dimethyl derivative called for further experimental data in order to more precisely assess the role of different effects in determining facial selectivity of cis 3,4-disubstituted cyclobutenes.



Scheme 1

Cis-3,4-dimethyl-1-methoxycarbonylcyclobutene (**3b**) is easily available *via* a two step Lewis acid catalyzed [2+2] cycloaddition from cis-2-butene and methyl propiolate.[8] Thus, we decided to start to produce systematic data about the facial orienting ability of allylic methyl groups, in the reactions of plane-non-symmetric double bonds of cyclobutenes, by investigating the 1,3-dipolar cycloadditions of **5-7** to **3b**. In particular, our first aim was to assess whether or not these factors consist only of repulsive steric (non bonded) interactions. To this end we deemed it useful also to study the reactions of 1,3-dipoles with trans-3,4-dimethyl-1-methoxycarbonylcyclobutene (**4**). In the case of the cis dipolarophile **3b** the two methyl groups cooperate in dictating facial selectivity, in particular through steric effects by interacting at the same time (although to a different extent) with the two ends of the 1,3-dipole in the syn attack (Scheme 2), but it is not easy to evaluate their relative role. If we assume that the attack by the 1,3-dipole on the diastereotopic faces of trans **4** is regiospecific and that the regiochemistry is the same for both faces (e.g., Scheme 2), the two ends of the 1,3-dipole compete with each other, through their interaction with one of the Me groups of the dipolarohile (i.e., the "C" end with Me-6 for the syn attack and, respectively, the "X" end with Me-7 for the anti attack, Scheme 2), in governing syn-anti selectivity. Thus, one can get an idea about the relative importance of these two interactions



Scheme 2

from selectivity data of the reactions of **4**.

Notice that the steric interaction between the COOMe group and the methyl groups [in particular that between COOMe and Me-7 in the anti attack to **3b** and the syn attack to **4** (Scheme 2)] should be almost negligible in the early TSs of 1,3-dipolar cycloadditions in which the out-of-plane bending of the methoxycarbonyl group should be of the order of 20°.

Our study was extended to the reactions of 1,3-dipoles with bicyclo[3.2.0]hept-6-ene (**1a**) as well as bicyclo[4.2.0]oct-7-ene (**2a**) and their methoxycarbonyl derivatives (**1b**) and (**2b**), respectively.

RESULTS

The reactions of cyclobutenes **1-4** were carried out at room temperature (≈ 21-23 °C) in the presence of excess dipolarophile in the case of **2a** and of excess 1,3-dipole in the case of **1a**, **1b-3b** and **4** in order to guarantee, in the latter case, a quantitative conversion of the dipolarophile. The reactions of diazomethane (**5**) were conducted in ethyl ether while those of 3,4-dihydroisoquinoline-N-oxide (**6**) and nitrile oxides (**7**) were carried out in benzene. The nitrile oxides were generated in situ from the corresponding benzohydroximic acid chlorides with excess solid sodium bicarbonate. Ratios of the adducts were evaluated by ^{1}H NMR and by column chromatography. Claimed 100:0 ratios simply mean that careful TLC and ^{1}H NMR (300 MHz) analysis of the crude reaction mixture and of the separated products did not reveal the presence of the missing adduct.

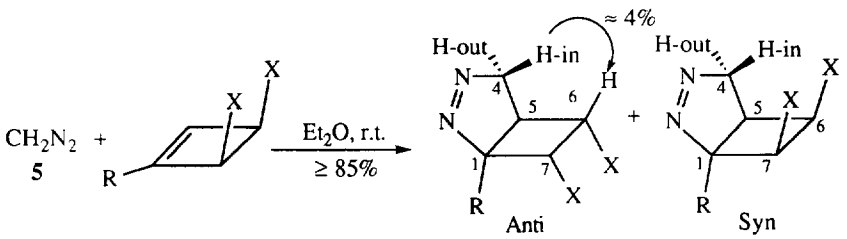
We will now describe our results by illustrating first the reactions of the cis-3,4-disubstituted derivatives **1-3** with diazomethane, nitrones and nitrile oxides, respectively.

Diazomethane (**5**) has already been reported to react with **1a** to give only the anti adduct **8a**[9] and with **2a**[3] and **3a**[7] to afford anti/syn mixtures (**10a+11a** and **12a+13a**, respectively) (Scheme 3). As expected the reactions of diazomethane with the methoxycarbonyl derivatives **1b-3b** were fast and regiospecific. The nucleophilic methylene moiety of the 1,3-dipole attacked the β position of the conjugated double bond to give only the regioisomers **8b-13b** in ≥ 85% yields.

Less obvious was the finding that face selectivity is not significantly perturbed by the introduction of the methoxycarbonyl group. Actually, the results with the substituted derivatives **1b-3b** almost exactly duplicated those with the unsubstituted ones **1a-3a** (Scheme 3).

Structures **8b-13b** are firmly based on ^{1}H NMR data. In particular, regiochemistry is definitely established by the observation that the methylene protons of the former diazomethane (i.e., H-4-in and H-4-out) are involved in vicinal coupling to a cyclobutyl proton (i.e., H-5) (Table 1 and Table 2, Experimental).

Proton chemical shifts show a regular trend in the syn vs anti adducts. Thus, the chemical shift difference

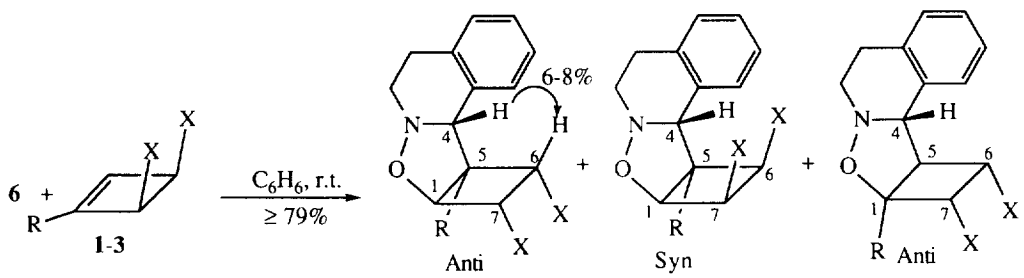


	1a	X-X = $(CH_2)_3$	**8a** (100%)[9]	**9a** (-)
a: R = H	**2a**	X-X = $(CH_2)_4$	**10a** (96%)[3]	**11a** (4%)
	3a	X = Me	**12a** (70%)[7]	**13a** (30%)
	1b	X-X = $(CH_2)_3$	**8b** (100%)	**9b** (-)
b: R = CO_2Me	**2b**	X-X = $(CH_2)_4$	**10b** (95%)	**11b** (5%)
	3b	X = Me	**12b** (72%)	**13b** (28%)

Scheme 3

between H-4-in and H-4-out is consistently higher in syn adducts than in their anti counterparts while H-5, H-6 and H-7 resonate at lower fields in syn than in anti adducts (Table 1). A more reliable diagnostic feature for assigning syn/anti stereochemistry is provided by $J_{5,6}$: it is larger than 8.0 Hz in syn adducts and smaller than 5.5 Hz in anti adducts.[10] Structure attributions were eventually confirmed by NOE experiments. Irradiation of H-4-in in **8b**, **10b** and **12b** brought about an increase in intensity of H-6 signal (by, respectively, 4.1%, 4% and 3.5% while the methyl signals in **12b** were left unperturbed) whereas upon irradiation of the same proton in **13b** the only measurable signal enhancement observed (1%) was that of the methyl group at position 6.

The reactions of 3,4-dihydroisoquinoline-N-oxide (**6**) with **1a** and **2a** afforded only anti adducts and 100% anti diastereoselectivity was also observed for the reactions of the same 1,3-dipole with the substituted derivatives **1b** and **2b** (Scheme 4). In the case of the latter two derivatives a mixture of regioisomers was obtained in which the adduct (i.e., **14b** and **15b**, respectively) bearing the methoxycarbonyl group at position 5 (position 4 of the isoxazolidine ring) was strongly dominant over that one (i.e., **16b** and **17b**, respectively) with the methoxycarbonyl group at position 1 (position 5 of the isoxazolidine ring). It should be emphasized that regioselectivity of attack by **6** on the conjugated double bond of **1b**, **2b** and, in particular, **3b** is definitely higher than that of the reaction of the same 1,3-dipole with methyl acrylate [4-COOMe-isoxazolidine/5-COOMe-isoxazolidine ≈ 80:20].[11] That is, on going from methyl acrylate to **1b**-**3b** the introduction of two equivalent cyclic cis alkyl substituents at α and β positions of the conjugated double bond appreciably changes, by enhancing it, the ability of the COOMe group in controlling regiochemistry. In fact, the reaction of **6** with **3b** was regiospecific while face selectivity remained very high and only minor amounts of the syn adduct **19b**



a: R = H	**1a**	X-X = $(CH_2)_3$	**14a** (100%)	–	
	2a	X-X = $(CH_2)_4$	**15a** (100%)	–	
b: R = CO_2Me	**1b**	X-X = $(CH_2)_3$	**14b** (96%)	–	**16b** (4%)
	2b	X-X = $(CH_2)_4$	**15b** (95%)	–	**17b** (5%)
	3b	X = Me	**18b** (94%)	**19b** (6%)	–

Scheme 4

were present in the reaction mixture. Similar results were obtained in the reaction of these dipolarophiles with the acyclic N-t-butyl nitrone.[12] The tendency of nitrones to attack the syn face of **2a**,**2b** and **3a**,**3b** is very low and significantly lower than that of diazomethane and of nitrile oxides.

The regiochemistry of compounds **14b**, **15b**, **18b** and **19b** was established on the basis of the following observations which hold for all these compounds: (i) the ^{1}H NMR spectra exhibited a singlet for H-4 (ii) the signal of the methoxy group was shifted to higher fields (≥ 0.3 ppm with respect to the signal of the same group in **16b** and **17b**) as a result of the deshielding effect of the aromatic moiety of the former dihydroisoquinoline-N-oxide and (iii) the presence of a signal at low fields (i.e., δ ≥ 4.60 ppm) attributable to a proton (i.e., H-1) attached to a carbon also bearing a strong electron-attracting atom (Tables 3 and 4, Experimental).

Assignment of anti stereochemistry to all the adducts except **19b** rests on the small value of the vicinal coupling constants $J_{1,7}$ (≤ 4.3 Hz vs $J_{1,7}$ = 6.3 Hz in **19b**) and $J_{5,6}$ (≤ 5.5 Hz)[10] and on NOE experiments.

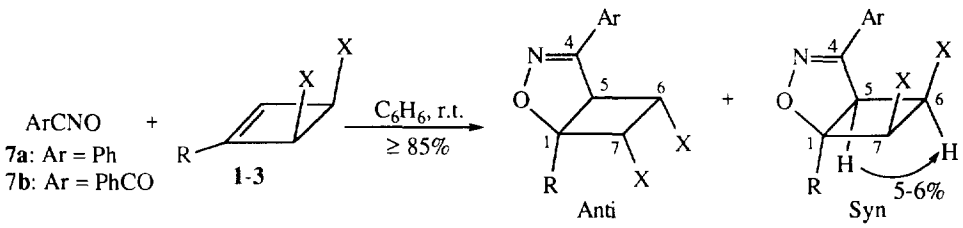
Irradiation of H-4 in **14a** and **14b** led to increase in intensity of the signal of H-6 (6% and 7%, respectively). Likewise, irradiation of H-4 in **15b** and **18b** gave rise to relevant NOE effects for the signal of H-6 (8% and 7.7%, respectively) and H-7 (5.2% and 3.2%, respectively). Finally, the only significant signal enhancement (2%) observed upon irradiation of H-4 in **19b** was that of the methyl group at position 6.

The above NOE data, [as well as the small coupling constants $J_{4,5}$ = 2.9 Hz, 2.5 Hz and 3.5 Hz in **15a**, **16b** and **17b**, respectively], also clearly demonstrate that H-4 points "inside" in all the adducts, that is, all the adducts are formed through exo [of the nitrone system with respect to the cyclobutene ring, e.g. TSs **38** and **39** in Scheme 7] transition states. Endo orientations experience insurmountable steric repulsions.

The reactions of nitrile oxides **7a** and **7b** with **1b-3b** were found to be regiospecific with formation, as expected, of the adducts bearing the methoxycarbonyl group at position 1 (position 5 of the isoxazoline ring) (Scheme 5).

As for face selectivity, cyclobutenes **1a** and **1b** gave only anti adducts while an anti/syn mixture was obtained in the reactions of **2a** and **2b** however with anti adducts still clearly prevalent over their syn counterparts. Notice how, once again, face selectivity of the methoxycarbonyl derivatives **1b** and **2b** closely resembles that of the unsubstituted derivatives **1a** and **2a**.

The reaction of **3b** with nitrile oxides came as a surprise because for the first time syn adducts (**24b** and **29b**) deriving from sterically disfavored syn transition states were slightly in excess of their anti diastereoisomers (**23b** and **28b**, respectively).



			Ar = Ph		Ar = PhCO	
			Anti	Syn	Anti	Syn
a: R = H	**1a**	X-X = $(CH_2)_3$	**20a** (100%)	–	**25a** (100%)[9]	–
	2a	X-X = $(CH_2)_4$	**21a** (88%)	**22a** (12%)	**26a** (87%)	**27a** (13%)
b: R = CO_2Me	**1b**	X-X = $(CH_2)_3$	**20b** (100%)	–	**25b** (100%)	–
	2b	X-X = $(CH_2)_4$	**21b** (89%)	**22b** (11%)	**26b** (86%)	**27b** (14%)
	3b	X = Me	**23b** (45%)	**24b** (55%)	**28b** (39%)	**29b** (61%)

Scheme 5

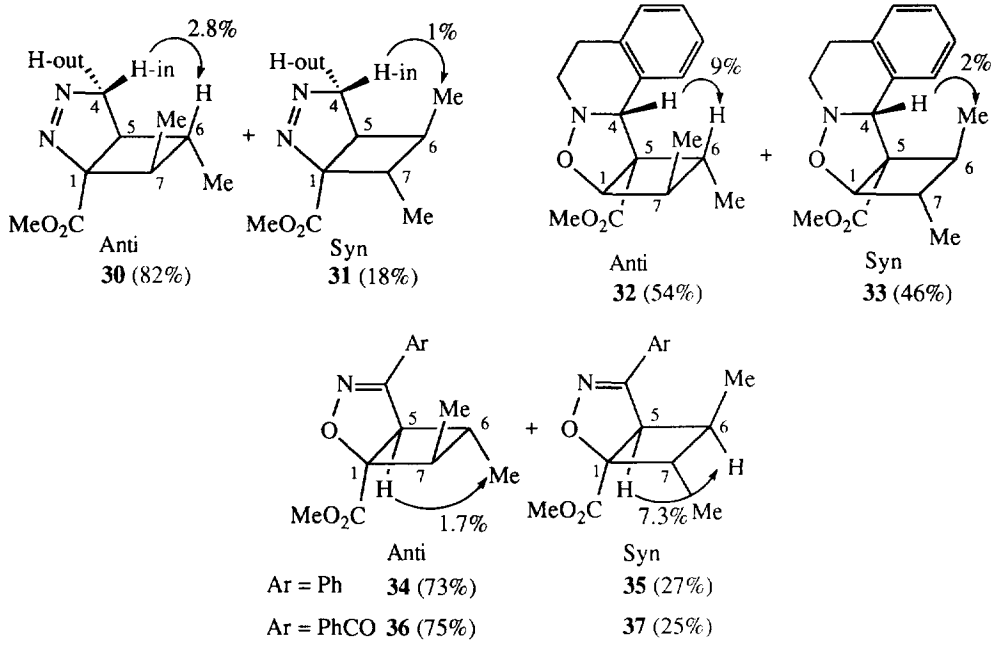
The regiochemistry of adducts of nitrile oxides with **1b-3b** is safely based on ^{13}C NMR spectra. In fact, the lowest field signal of the saturated carbons [i.e., C-1; e.g., $\delta(CDCl_3)$ 90.6 and 88.0 for **21b** and **22b**, respectively] was a singlet in the off-resonance spectrum while the other isoxazoline carbon [i.e., C-5; e.g., $\delta(CDCl_3)$ 54.8 and 55.2 for **21b** and **22b**, respectively] resonated as a doublet in that type of spectrum.

Syn/anti stereochemistry of adducts **20-29** was assigned on the basis of the following evidence: (i) $J_{5,6} \geq$ 8.0 Hz in syn adducts and $\leq$ 4.2 Hz in anti adducts (Tables 5 and 6, Experimental) (ii) in the case of adducts with **3b** the methyl group at position 6 experienced an upfield shift in syn adducts (**24b** and **29b**) as compared to anti adducts (**23b** and **28b**) while the methyl group at position 7 in anti adducts resonated downfield with respect to the same group in syn adducts (Table 6); these two observations are the result of shielding and, respectively, deshielding by the Ar and COOMe groups on their vicinal methyl groups and (iii) irradiation of H-5 in **23b** and **28b** gave rise to increase in intensity (by 1%) of the Me-6 signal while irradiation of the same proton

in **24b** and **29b** gave rise to a relevant intensity enhancement (5.2% and 6.2%, respectively) of the H-6 signal. These NMR data do not left any doubt about face selectivity of these reactions and, in particular, about dominance of syn attack in the reaction of **3b** with both nitrile oxides.

The reactions of trans-3,4-dimethyl-1-methoxycarbonyl cyclobutene (**4**) with 1,3-dipoles **5-7** took place readily to give high yields (≥ 92%) of mixtures of facial isomers (Scheme 6). All the reactions were found to be regiospecific. The reaction of 3,4-dihydroisoquinoline-N-oxide was practically facially unselective while the anti isomer, deriving from the sterically less congested TS, was clearly prevalent in the reactions with nitrile oxides and even more in the reaction with diazomethane.

The regiochemistry of adducts **30-37** was attributed on the basis of the very same diagnostic ^{1}H and ^{13}C NMR features illustrated above for the adducts with **1b-3b**. Likewise chemical shifts, coupling constants and NOE experiments allowed assignment of syn/anti stereochemistry to **30-37**. Here we will cite only NOE data: (i) upon irradiation of H-4-in **30** and **31** we observed NOE effects for the signal of H-6 (2.8%) and of Me-6

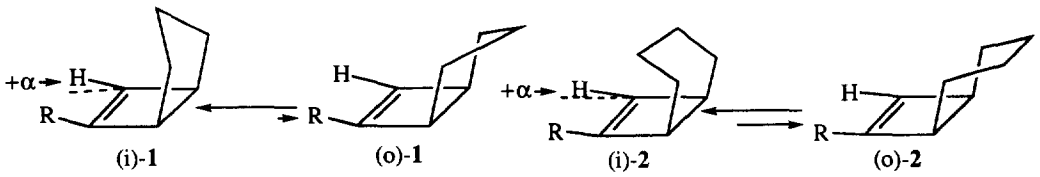


Scheme 6

(1.0%), respectively (ii) signal intensity of H-6 in **32** was increased by 9.0% and that of Me-6 and H-7 in **33** by 2.0% and 2.7%, respectively, upon irradiation of H-4 and (iii) NOE enhancements of the signal of Me-6 (1.7%) and of H-7 (2.7%), respectively, in **36** and of H-6 (7.3%) in **37** were induced by irradiation of H-5.

DISCUSSION

MM2 calculations show that the conformational behavior of **1b** and **2b**, respectively, is very similar to that of **1a** and **2a**. The inward envelope conformation of the cyclopentane ring [(i)-**1**, Scheme 7] is more stable than the outward envelope conformation [(o)-**1**, Scheme 7] by ≈ 2.4 kcal mol^{-1} for both **1a** and **1b** while the difference in stability between the inward boat conformation [(i)-**2**, more stable] and its outward boat counterpart [(o)-**2**] reduces to 0.5 kcal mol^{-1} in **2a** and ≈ 0.7 kcal mol^{-1} in **2b**. In the case of compounds **2** there is a further local minimum, i.e. a chair conformation (not shown), less stable than (i)-**2** (by 0.13 kcal mol^{-1} for compound **2a** and ≈ 0.4 kcal mol^{-1} for compound **2b**). These data strongly suggest that (i)-**1a** and (i)-**1b** are the only (almost) populated conformations of compounds **1a** and **1b**, respectively, while aside from (i)-**2** also (o)-**2**



a: R = H; **b**: R = CO_2Me **a**: R = H; **b**: R = CO_2Me

Scheme 7

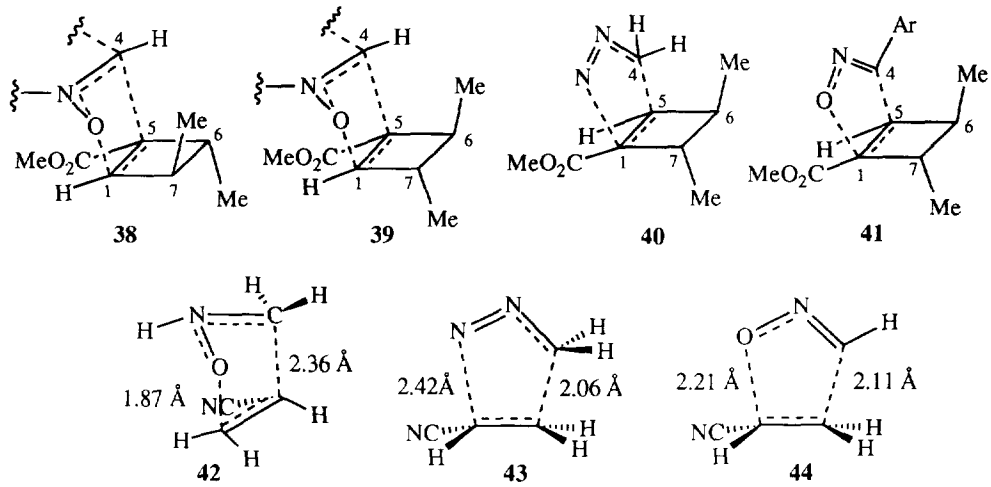
and chair conformations are appreciably populated in the case of compounds **2**. It is evident that syn attack on (i)-**1** and (i)-**2** conformations is energetically very expensive owing to the very efficient steric shielding of their syn face.[9] Thus, the most straightforward explanation of the complete anti selectivity of the reactions of compounds **1** is provided by steric effects[9] while the presence of chair and (o) conformations in the case of compounds **2** leaves room for some syn attack.[3] Moreover, out-of-plane syn bending of the olefinic hydrogens is sizable both in (i)-**1a** (α = +4.0°) and (i)-**1b** (α = +2.6°) thus cooperating in promoting anti selectivity while on passing to compounds **2** the double bond flattens somewhat [$\alpha \approx 1°$ for (i)-**2a** and (o)-**2a**; $\alpha = 2°$ for (i)-**2b** and 1° for (o)-**2b**] with a lessening of this effect.

Passing to dimethyl derivatives we consider first the reactions of trans-3,4-dimethyl-1-methoxycarbonyl cyclobutene (**4**). In the case of (**4**) we are dealing with a dipolarophile whose facial selectivity is controlled, as stressed in the introduction, by competition between repulsive interactions involving the "C" end of the 1,3-dipole and the methyl group at position 6 [for attacks leading to syn adducts] and the "X" (N or O) end of the 1,3-dipole and the methyl group at position 7 [for attacks leading to anti adducts] (Scheme 2).

The "C" end of 1,3-dipoles **5-7** is certainly sterically more demanding than the "X" end so that dominance of anti attack is expected for the reactions of **4**. This expectation is borne out by the face selectivity observed in all reactions of **4** (Scheme 6) even if to a different extent: anti adducts clearly overcome their syn diastereoisomers in the reaction of diazomethane (anti:syn = 82:18) and, to a lower extent, in those of nitrile oxides (anti:syn ≈ 74:26) but syn attack competes on almost the same foot with anti attack in the reactions of dihydroisoquinoline-N-oxide (anti:syn = 54:46).

This different behavior can be traced back to the different geometry of nitrone cycloaddition TSs vs TSs of diazomethane and nitrile oxide reactions. The heavy atoms of the nitrone system lie in a plane which is roughly parallel to that of the cyclobutene plane (e.g., the schematic exo transition states **38** and **39** in Scheme 8) whereas in the case of diazomethane (e.g., the syn TS **40**) and of nitrile oxides (e.g., the syn TS **41**) the two planes are almost perpendicular to each other. But, probably more important is the different timing in bond formation. Qualitative reasoning based on FO theory leads one to predict a strong asynchronicity in bond formation in the "nucleophilic" addition of dihydroisoquinoline-N-oxide and diazomethane to the electron-poor **4**. However, in the reaction of the former 1,3-dipole the shorter incipient bond should be the C_1---O bond (as schematically described in **38** and **39**) while in the reaction of the latter one the shorter forming bond should be the C_4---C_5 bond (see **40**). Less bias is expected in bond formation between **4** and the "electrophilic" nitrile oxides. This qualitative arguing about forming bond lengths, in the reactions of 1,3-dipoles with electron-poor conjugated double bonds, has fully been confirmed by good level HF ab initio calculations on simpler systems as shown by the HF/6-31G* geometries of the transition structures of the reactions of diazomethane (i.e., **43**), formonitrile oxide (i.e., **44**) and the parent nitrone (i.e., the endo-TS **42**) with acrylonitrile (Scheme 8).[13]

As a consequence of the different geometry of TS structures, the non bonded interaction between H-4 (pointing inside) and Me-6 is stronger in **40** than in **39** while at the same time the interaction between the X end of the 1,3-dipole and Me-7 is stronger in **38** than in the anti counterpart of **40**. All this is in keeping with the higher face selectivity observed in the reaction of **4** with diazomethane (**5**) as compared to that of the reaction of **4** with dihydroisoquinoline-N-oxide (**6**).[14] Our experimental results also suggest that steric repulsion is slightly higher in **40** than in **41** (diastereoselectivity is larger in the reaction of diazomethane than in those of nitrile oxides). This finding can be explained by stressing that H-4-in points inside toward Me-6 in **40** while the bulkier aryl



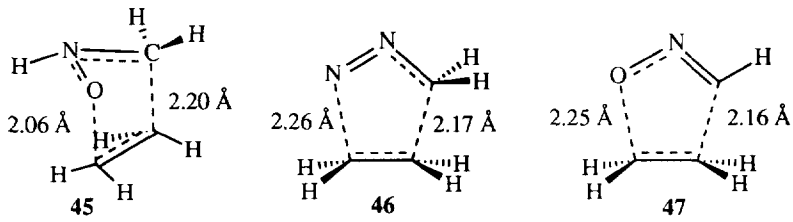
Scheme 8

group at position 4 in **41** points away from Me-6.

Steric effects involving the two ends of the attacking 1,3-dipole counteract each other in dictating face selectivity in the reactions of **4** but they must cooperate in the reactions of **3b** in disfavoring syn approach (Scheme 2). Thus, assuming that face selectivity keeps on being under steric control, one must anticipate a higher face selectivity for the reactions of the latter cyclobutene than for those of the former. This was actually observed only for nitrone **6** which exhibited very low diastereoselectivity (anti/syn = 54:46) in its reaction with **4** and very high diastereoselectivity (anti/syn = 94:6) in its reaction with **3b**. In contrast to the above prediction, face selectivity of the reaction of diazomethane with **3b** fell down to 72:28 (even if the pyrazoline deriving from the less congested TS was still dominant) from 82:18 of the reaction of diazomethane with **4**. More striking was the finding that in the reactions of nitrile oxides there was a reversal of diastereoselectivity from anti/syn ≈ 74:26 in favor of the isomer formed through the less crowded TS in the reaction with **4** to anti/syn ≈ 42:58 in favor of the isomer formed via the more crowded TS in the reaction with **3b**. Thus, there seems to be a small (but not negligible) inherent "electronic" effect which certainly favors the syn attack in the reactions of diazomethane and nitrile oxides with **3b**. It emerges clearly in the reactions of nitrile oxides while in the reaction of diazomethane it is overshadowed by steric effects. In fact, as in the case of trans-**4**, also in the case of cis-**3b** (and for the very same reason) steric factors should be more important in the reaction with diazomethane than in the reactions with nitrile oxides.

It should also be stressed that the tendency of cyclobutenes **2a**, **2b** and **3b** to accept syn attack by nitrile oxides is higher than that of the same cyclobutenes to accept syn attack by diazomethane (see above). This finding stands in contrast to what has been reported for cis-3,4-disubstituted cyclobutenes bearing substituents such as Cl and OR: syn selectivity of their reactions with diazomethane is always higher than that of their reactions with nitrile oxides.[3,9] On going from alkyl substituents to OR and Cl groups there is a decrease in steric interactions and an increase in repulsive electrostatic interactions during syn attack. The latter are definitely stronger for nitrile oxides than for diazomethane owing to the high electron density on the oxygen atom of nitrile oxides (the dipole moment of benzonitrile oxide is 4.0 D and that of diazomethane 1.5 D).[15]

The intrinsic syn orienting electronic effect in **3b** is far from being dramatic but we feel that the theoretical explanation of its origin will certainly help to further assess the factors that control facial selectivity in the reactions of cyclobutenes. For now it is important to realize that syn orienting effects are not confined only to electron attracting substituents (in particular those with heteroatoms directly attached to the cyclobutene ring) but that they extend (even if to a reduced extent) also to alkyl substituents. MM2, AM1 and PM3 calculations suggest that in **3b** there is a small out-of-plane bending of H and COOMe groups in the right direction, i.e. anti



Scheme 9

($\alpha \approx -1°$) with respect to the methyl groups, which should favor syn attack.

To conclude a comment is in order on the (surprising) observation that the introduction of the COOMe group on the double bond, i.e., on passing from **1a-3a** to **1b-3b** did not give rise to appreciable changes in face selectivity of 1,3-dipolar cycloadditions to these dipolarophiles. The replacement of a hydrogen atom by a COOMe group not only should significantly increase the amount of electron transfer from the 1,3-dipole to the dipolarophile but also there should be some change in the geometry of the transition states in particular in the asynchronicity of bond formation. This latter statement is clearly supported by a comparison of transition structures of the reactions of nitrone and diazomethane with acrylonitrile (i.e., **42** and **43**, Scheme 8) with the HF/6-31G* transition structures of the same 1,3-dipoles with ethylene (i.e., **45**[16] and **46**,[13] Scheme 9): the difference in forming bond lengths is less than 0.14 Å in **45** and **46** while it is larger than 0.36 Å in **42** and **43**. As for nitrile oxides, asynchronicity does not change on passing from **44** to **47** however there is some lengthening in forming bonds.[13]

It is easy to accept that a variation in net charges on the 1,3-dipole does not have any appreciable effect on face selectivity of a reaction in which electrostatic effects are not important[17] while it is less understandable why geometry changes of transition state structure apparently do not influence diastereoselectivity in reactions in which steric effects certainly play an important role (as in the reactions of diazomethane with **2a,b** and **3a,b**).

This observation needs further confirmation by a systematic experimental study of face selectivity of 1,3-dipolar cycloadditions to the parent cis-3,4-dimethyl cyclobutene **3a.** Transition structures of the latter reactions should be amenable to good level MO ab initio calculations. Both these studies are under way in our laboratories.

EXPERIMENTAL

Melting points are uncorrected and were determined on a Büchi 335 melting point apparatus. Elemental analyses were made on a Carlo Erba CHN analyzer, model 1106. Infrared spectra were recorded as either Nujol suspensions or films on a Perkin-Elmer 881 spectrophotometer.

^1H and ^{13}C NMR spectra were recorded on a Bruker AE 300 (operating at 300.13 and 75.47 MHz, respectively) spectrometer with tetramethylsilane as internal standard for $CDCl_3$ solutions unless otherwise stated. The chemical shifts of aromatic protons as well as those of the CH_2-CH_2 group of the tetrahydroisoquinoline moiety of the adducts from the reaction of **6** will not be reported. Protons were correlated by decoupling and COSY experiments while protons were correlated to carbons by ^1H-^{13}C heterocorrelated spectra. ^1H NMR spectra were evaluated as first order spectra.

GC analyses were carried out with a DANI 6500, PTV injector, CP-Sil-19CB (25 m) capillary column and carrier H_2. Thin-layer chromatograms were done on plates precoated with silicagel 60 GF_{254} (Merck) Spots were visualized either by spraying with 3% chromic oxide in sulfuric acid (50%) followed by heating at 120 °C or under UV light. Column chromatography was performed with Silicagel 60 (70-230 mesh) Merck eluting with cyclohexane/ethyl acetate mixtures (from 98:2 to 70:30).Cyclobutenes **1a**,[18a] **2a**,[18b] **1b-3b**[8] and **4**[8] as well as diazomethane (**5**), 3,4-dihydroisoquinoline-N-oxide (**6**)[18c] and the precursors[18d,18e] of nitrile oxides **7a** and **7b** were prepared according to literature procedures.

The reactions of diazomethane with **1a**[9] and **2a**,[3] respectively, and that of **7b** with **1a**[9] have already been reported.

Reactions of diazomethane (5) with cyclobutenes 1b-3b and 4, respectively.

The cycloaddition reactions of diazomethane (**5**) with **1b-3b** and **4** (100-200 mg), respectively, were carried out in ethyl ether at room temperature (≈20-23 °C) by using a large (≈ 4 molequiv) excess of a concentrated solution of the 1,3-dipole. After a few hours (≤ 3 h) the dipolarophile had totally been consumed (as judged by TLC). The reactions were clean and only the spots of the adducts were present on TLC. The reaction product was purified by short column chromatography and the adduct(s) obtained in a pure state in the following total yields : **8b** (95%), **10b+11b** (85%), **12b+13b** (96%) and **30+31** (97%). Syn/anti ratios (**10b/11b**, **12b/13b** and **30/31**, respectively) were evaluated by ^{1}H NMR. The diastereoisomers **10b/11b** could not be separated from each other by column chromatography while elution with cyclohexane/ethyl acetate 98:2 allowed separation of **12b/13b** mixture as well as of **30/31** mixture (R_f order: **13b>12b** and **30>31**). All the adducts exhibited in the IR spectrum the very weak absorption of the N=N group at ≈ 1540 cm^{-1} and the strong absorption of the methoxycarbonyl group at ≈ 1740 cm^{-1}. The adducts were stable under reaction and work-up conditions and, in particular, no evidence of isomerization from the 1-pyrazoline structure to the 2-pyrazoline one was found.

Adduct **8b** : colorless platelets from petrol ether, mp 48-49 °C; Anal. Calcd for $C_{10}H_{14}N_2O_2$: C, 61.8; H, 7.3; N, 14.4. Found: C, 61.7; H, 7.3; N, 14.3. Adducts **10b+11b**: colorless solid, mp 48-50 °C; Anal. Calcd for $C_{11}H_{16}N_2O_2$: C, 63.4; H, 7.7; N, 13.5. Found: C, 63.4; H, 7.9; N, 13.5. Adduct **10b** was obtained in a pure state (colorless platelets, mp 51-52 °C) by repeated crystallizations from petrol ether of the mixture **10b+11b**. Adduct **12b**: slightly yellow oil; Anal. Calcd for $C_9H_{14}N_2O_2$: C, 59.3; H, 7.7; N, 15.4. Found: C, 59.4; H, 7.8; N, 15.4. Adduct **13b**: slightly yellow oil; Anal. Found: C, 59.5; H, 7.9; N, 15.6. Adduct **30**: slightly yellow oil; Anal. Found: C, 59.3; H, 8.0 ; N, 15.5. Adduct **31**: slightly yellow oil; Anal. Found: C, 59.1; H, 7.5; N, 15.3.

Table 1. Chemical shifts (ppm, $CDCl_3$) of protons in adducts of diazomethane (**5**) to **1b**, **2b**, **3b** and **4**.

Comp.	H-4-in	H-4-out	H-5	H-6	H-7	Me-6	Me-7	OMe
8b	4.75	4.60	2.36	2.02	2.95	-	-	3.80
10b	4.65	4.52	2.75	1.62	2.65	-	-	3.82
11b	4.83	4.40	2.98	2.38	3.31	-	-	3.76
12b	4.66	4.58	2.51	1.83	2.68	1.05	1.15	3.82
13b	4.81	4.41	2.93	2.59	3.43	0.69	0.96	3.77
30	4.69	4.42	2.33	1.15	2.83	1.10	1.10	3.76
31	4.70	4.54	2.93	2.21	1.84	0.85	1.21	3.87

Table 2. Coupling constants (Hz) between protons in adducts of diazomethane to **1b**, **2b**, **3b** and **4**.

Comp.	$J_{4\text{-in},4\text{-out}}$	$J_{4\text{-in},5}$	$J_{4\text{-out},5}$	$J_{5,6}$	$J_{5,7}$	$J_{6,7}$
8b	18.2	1.8	7.6	4.0	1.2	6.8
10b	18.0	2.0	7.0	5.5	1.2	8.3
11b	18.5	1.8	8.0	8.0	1.0	8.5
12b[a]	18.4	2.8	7.2	5.3	1.2	9.2
13b[a]	18.5	1.8	8.4	9.2	1.0	10.5
30[b]	18.0	1.3	7.4	5.6	1.0	7.3
31[b]	18.8	3.5	9.0	9.0	1.2	7.3

[a] $J_{6,Me\text{-}6} \approx J_{7,Me\text{-}7} = 7.5$ Hz [b] $J_{6,Me\text{-}6} \approx J_{7,Me\text{-}7} = 7.0$ Hz

Reactions of 3,4-dihydroisoquinoline-N-oxide (6) with cyclobutenes 1a, 2a, 1b-3b and 4, respectively.

A solution of 3,4-dihydroisoquinoline-N-oxide (**6**) (350 mg, 2.3 mmol) and excess **2a** (1.1 g, 10 mmol) in benzene (10 ml) was heated under reflux for 8 hours. Evaporation of the solvent and of excess dipolarophile afforded almost quantitative yields (98%) of a pure single adduct, i.e., **15a**. This reaction was also carried out at room temperature (4 days) and once again **15a** was the only detected and isolated (85 %) adduct.

A solution of excess **6** (2 molequiv.) and **1a**, **1b-3b** and **4** (100-200 mg), respectively, in benzene (5 ml) was kept at room temperature (≈20-23 °C) for five days. After that time the starting dipolarophile had completely disappeared (TLC and GC) and after evaporation of the solvent the adducts were separated by column chromatography eluting with cyclohexane/ethyl acetate 95:5 (R_f order: **14b>16b**, **15b>17b**, **19b>18b** and **32>33**). Isomer ratios were also evaluated by ^{1}H NMR analysis of the crude reaction mixture. Total yields were the following: **14a** (79%), **14b+16b** (97%), **15b+17b** (97%), **18b+19b** (98%) and **32+33** (92%). All the adducts to **1b-3b** exhibited in the IR spectrum the strong absorption of the methoxycarbonyl group at ≈ 1740 cm^{-1}. The isoxazolidine derivatives were stable under reaction and work-up conditions and, in particular, no evidence for equilibration processes between the two diastereoisomers (via a cycloreversion reaction) was found.

Table 3. Chemical shifts (ppm, $CDCl_3$) of protons in adducts of nitrone **6** to **1a**, **2a**, **1b**, **2b**, **3b** and **4**.

Comp.	**14a**[a]	**15a**[a]	**14b**	**16b**	**15b**	**17b**	**18b**	**19b**	**32**	**33**
H-1	3.86	4.21	4.60	-	4.90	-	4.69	5.02	4.96	4.51
H-4	4.26	4.28	4.79	4.50	4.82	4.51	4.78	4.88	4.61	4.91
H-5	2.88	2.88	-	3.14	-	3.32	-	-	-	-
H-6	2.53	2.33	3.01	2.78	2.70	2.39	2.84	3.10	2.47	2.23
H-7	2.53	2.65	2.72	2.92	2.53	2.82	2.53	2.60	1.98	2.01
Me-6	-	-	-	-	-	-	1.08	1.29	1.20	1.40
Me-7	-	-	-	-	-	-	1.02	1.02	1.14	1.12
OMe	-	-	3.20	3.65	3.22	3.68	3.24	3.21	3.38	3.21

[a]In C_6D_6

Table 4. Coupling constants (Hz) between protons in adducts of nitrone **6** to **1a**, **2a**, **1b**, **2b**, **3b** and **4**.

Comp.	**14a**[a]	**15a**[a]	**14b**	**16b**	**15b**	**17b**	**18b**[b]	**19b**[b]	**32**[c]	**33**[c]
$J_{1,5}$	6.2	6.5	-	-	-	-	-	-	-	-
$J_{1,6}$	d	<0.5	<0.5	-	<0.5	-	<0.5	1.4	<0.5	<0.5
$J_{1,7}$	1.5	3.0	2.4	-	4.3	-	3.7	6.3	6.5	3.8
$J_{4,5}$	≤1.0	2.9	-	2.5	-	3.7	-	-	-	-
$J_{5,6}$	5.5	4.0	-	3.9	-	3.6	-	-	-	-
$J_{5,7}$	d	1.5	-	1.0	-	1.1	-	-	-	-
$J_{6,7}$	d	d	7.0	7.0	8.8	9.2	9.4	10.5	7.9	7.5

[a]In C_6D_6 [b]$J_{6,Me\text{-}6} \approx J_{7,Me\text{-}7} = 7.5$ Hz [b]$J_{6,Me\text{-}6} \approx J_{7,Me\text{-}7} = 7.0$ Hz [d]Not evaluated due to the complexity of the signals

Adduct **14a**: colorless prisms from MeOH/H_2O, mp 62-64 °C; Anal. Calcd for $C_{16}H_{19}NO$: C, 79.6; H, 7.9; N, 5.8. Found: C, 79.7 ; H, 7.9 ; N, 5.7. Adduct **15a**: colorless needles from petrol ether, mp 70-71 °C; Anal. Calcd for $C_{17}H_{21}NO$: C, 80.0; H, 8.3; N, 5.5. Found: C, 79.8 ; H, 8.6 ; N, 5.4.

Adduct **14b**: colorless prisms from petrol ether, mp 87-88 °C; Anal. Calcd for $C_{18}H_{21}NO_3$: C, 72.2; H, 7.1; N, 4.7. Found: C, 72.3 ; H, 7.3 ; N, 4.6. Adduct **16b**: colorless oil; Anal. Found: C, 72.4 ; H, 7.0 ; N, 4.8.

Adduct **15b**: colorless prisms from petrol ether, mp 88-89 °C; Anal. Calcd for $C_{19}H_{23}NO_3$: C, 72.8; H, 7.4; N, 4.5. Found: C, 72.6 ; H, 7.4 ; N, 4.6. Adduct **17b**: colorless oil; Anal. Found: C, 72.5 ; H, 7.2 ; N, 4.7.

Adduct **18b**: colorless needles from petrol ether, mp 70-71 °C; Anal. Calcd for $C_{17}H_{21}NO_3$: C, 71.1; H, 7.4; N, 4.9. Found: C, 71.4 ; H, 7.2 ; N, 5.0. Adduct **19b**: colorless oil; Anal. Found: C, 71.3; H, 7.3 ; N, 4.8.

Adduct **32**: colorless needles from petrol ether, mp 63-64 °C; Anal. Found: C, 71.0 ; H, 7.3 ; N, 5.1. Adduct **33**: colorless oil; Anal. Found: C, 71.4; H, 7.4 ; N, 4.6.

Reactions of nitrile oxides 7a and 7b with cyclobutenes 1a, 2a, 1b-3b and 4, respectively.

The nitrile oxides **7a** and **7b** were generated in situ from the related hydroximic acid chloride.

A solution of the hydroximic acid chloride (2.00 mmol) and of excess **2a** (8.0 mmol) in anhydrous benzene (15 mL) was stirred at room temperature (≈ 21-23 °C) for 36 hours in the presence of excess solid sodium bicarbonate (6.0 mmol). The inorganic salts were filtered off, the solvent evaporated and the reaction product (only one spot on TLC for the reaction of both **7a** and **7b**) purified by column chromatography (cyclohexane/ethyl acetate = 90:10 as eluant) to give the **21a+22a** (91%) and **26a+27a** (98%) mixtures, respectively. The diastereoisomer ratios (i.e., **21a/22a** and **26a/27a**) were evaluated by ^{1}H NMR and the single diastereoisomers could not be obtained in a pure state by column chromatography.

In the case of dipolarophiles **1a**, **1b-3b** and **4** a similar protocol to that described above was used but with an excess of the nitrile oxide. Thus, a solution of the hydroximic acid chloride (1.2 mmol) and of **1a**, **1b-3b** and **4** (1.0 mmol), respectively, in anhydrous benzene (10 mL) was stirred at room temperature for 36 hours in the presence of excess solid sodium bicarbonate. The adducts were separated from the nitrile oxide dimer by column chromatography [cyclohexane/ethyl acetate 95:5 as eluant; total yields: **20a** (71%), **20b** (90%), **21b+22b** (93%), **23b+24b** (92%), **26a+27a** (98%), **25b** (93%), **26b+27b** (95%), **28b+29b** (92%), **34+35** (94%) and **36+37** (96%)] and diastereoisomer ratios evaluated by ^{1}H NMR. In the case of the **21b+22b**, **23b+24b** and **28b+29b** mixtures (R_f order: **21b>22b**, **23b>24b** and **28b>29b**) the single diastereoisomers could be separated by column chromatography. All the adducts with **1b-3b** exhibited in the IR spectrum the strong band of the methoxycarbonyl group (≈ 1740 cm^{-1}) while the adducts from **7b** also displayed the strong absorption of the conjugated carbonyl group (≈ 1660 cm^{-1}).

Adduct **20a**: colorless prisms from cyclohexane, mp 96-97 °C; Anal. Calcd for $C_{14}H_{15}NO$: C, 78.8; H, 7.1; N, 6.6. Found: C, 78.7 ; H, 7.0 ; N, 6.8.

Adducts **21a+22a**: colorless waxy solid, Anal. Calcd for $C_{15}H_{17}NO$: C, 79.3; H, 7.5; N, 6.2. Found: C, 79.5 ; H, 7.6 ; N, 6.4. Compound **21a** was obtained in a pure state (colorless platelets, mp 66-67 °C) by crystallization of the mixture **21a+22a** from petrol ether or methanol.

Adducts **26a+27a**: colorless oil, Anal. Calcd for $C_{16}H_{17}NO_2$: C, 75.3; H, 6.7; N, 5.5. Found: C, 75.1; H, 6.6 ; N, 5.4. ^{13}C NMR δ(C_6D_6), **26a**: 22.1, 22.4, 24.6 and 29.4 (four t, CH_2), 36.2 (d, C-6), 41.5 (d, C-7), 55.3 (d, C-5), 86.0 (d, C-1), 162.0 (s, C-4), 186.7 (s, CO); **27a**: 20.7, 21.5, 21.8 and 23.3 (four t, CH_2), 34.9 (d, C-6), 40.0 (d, C-7), 53.4 (d, C-5), 83.2 (d, C-1), 162.2 (s, C-4), 190.0 (s, CO).

Adduct **20b**: colorless needles from methanol, mp 136-137 °C; Anal. Calcd for $C_{16}H_{17}NO_3$: C, 70.8; H, 6.3; N, 5.2. Found: C, 70.7; H, 6.3; N, 5.1; ^{13}C NMR δ($CDCl_3$), 24.8, 28.5 and 31.7 (three t, CH_2), 42.3 (d, C-6), 49.0 (d, C-7), 52.0 (q, OMe), 52.3 (d, C-5), 88.4 (s, C-1), 159.3 (s, C-4), 167.7 (s, CO).

Adduct **21b**: colorless prism from methanol or petrol ether, mp 58-59 °C; Anal. Calcd for $C_{17}H_{19}NO_3$: C, 71.6; H, 6.7; N, 4.9. Anal. Found: C, 71.7 ; H, 6.6 ; N, 5.0; ^{13}C NMR δ($CDCl_3$), 20.1, 20.8, 21.4, 25.6 (four t, CH_2), 34.8 (d, C-6), 42.5 (d, C-7), 52.2 (q, OMe), 54.8 (d, C-5), 90.6 (s, C-1), 159.8 (s, C-4), 168.3 (s, CO). Adduct **22b**: colorless oil; Anal. Found: 71.4; H, 6.8; N, 4.9; ^{13}C NMR δ($CDCl_3$), 19.2, 19.8, 20.0, 21.6 (four t, CH_2), 32.0 (d, C-6), 40.3 (d, C-7), 52.6 (q, OMe), 55.2 (d, C-5), 88.0 (s, C-1), 158.7 (s, C-4), 170.8 (s, CO).

Adduct **23b**: colorless oil; Anal. Calcd for $C_{15}H_{17}NO_3$: C, 69.5; H, 6.6; N, 5.4. Found: C, 69.4; H, 6.7 ; N, 5.2; ^{13}C NMR δ($CDCl_3$), 10.0 (q, Me-7), 14.0 (q, Me-6), 34.5 (d, C-6), 42.4 (d, C-7), 52.2 (q, OMe), 54.9 (d, C-5), 90.2 (s, C-1), 159.9 (s, C-4), 168.7 (s, CO). Adduct **24b**: colorless oil; Anal. Found: C, 69.3; H, 6.5 ; N, 5.5; ^{13}C NMR δ($CDCl_3$), 8.6 (q, Me-7), 10.9 (q, Me-6), 31.3 (d, C-6), 40.0 (d, C-7), 52.5 (q, OMe), 54.2 (d, C-5), 87.5 (s, C-1), 157.9 (s, C-4), 170.7 (s, CO).

Adduct **25b**: colorless needles from methanol, mp 104-105 °C; Anal. Calcd for $C_{17}H_{17}NO_4$: C, 68.2; H, 5.7; N, 4.7. Found: C, 68.0; H, 5.6; N, 5.1. Adduct **26b+27b**: viscous oil; Anal. Calcd for $C_{18}H_{19}NO_4$: C, 69.0; H, 6.1; N, 4.5. Found: C, 69.3; H, 6.0; N, 4.5. Crystallization from methanol led to isolation of pure **26b** as colorless prisms (mp 65-66 °C).

Adduct **28b**: colorless oil; Anal. Calcd for $C_{16}H_{17}NO_4$: C, 66.9; H, 6.0; N, 4.9. Found: C, 67.0; H, 5.8 ; N, 5.1; ^{13}C NMR δ($CDCl_3$), 10.0 (q, Me-7), 13.9 (q, Me-6), 35.6 (d, C-6), 43.3 (d, C-7), 52.2 (q, OMe),

54.6 (d, C-5), 91.6 (s, C-1), 160.8 (s, C-4), 167.6 (s, COOMe), 185.3 (CO). Adduct **29b**: colorless oil; Anal. Found: C, 67.1; H, 5.9 ; N, 5.1; ^{13}C NMR δ($CDCl_3$), 8.8 (q, Me-7), 10.5 (q, Me-6), 32.0 (d, C-6), 40.4 (d, C-7), 52.5 (q, OMe), 54.8 (d, C-5), 88.9 (s, C-1), 159.1 (s, C-4), 169.4 (s, COOMe), 185.8 (s, CO).

Adducts **34+35**: colorless oil; Anal. Found: C, 69.5; H, 6.8 ; N, 5.3. ^{13}C NMR δ($CDCl_3$), **34**: 13.8 (q, Me-7), 19.6 (q, Me-6), 40.2 (d, C-6), 45.1 (d, C-7), 52.6 (q, OMe), 55.9 (d, C-5), 85.7 (s, C-1), 158.7 (s, C-4), 170.6 (s, CO); **35**: 14.4 (q, Me-7), 16.1 (q, Me-6), 37.4 (d, C-6), 49.1 (d, C-7), 52.0 (d, C-5), 53.0 (q, OMe), 89.2 (s, C-1), 158.3 (s, C-4), 168.4 (s, CO).

Adducts **36+37**: colorless oil; Anal. Found: C, 67.0; H, 5.9 ; N, 4.8. ^{13}C NMR δ($CDCl_3$), **36**: 13.8 (q, Me-7), 19.6 (q, Me-6), 41.4 (d, C-6), 46.1 (d, C-7), 52.6 (q, OMe), 55.6 (d, C-5), 87.2 (s, C-1), 160.7 (s, C-4), 169.5 (s, COOMe), 185.1 (s, CO); **37**: 14.4 (q, Me-7), 15.7 (q, Me-6), 38.3 (d, C-6), 50.0 (d, C-7), 52.2 (q, OMe), 52.8 (d, C-5), 90.4 (s, C-1), 159.6 (s, C-4), 167.4 (s, COOMe), 186.2 (CO).

Table 5. ^{1}H NMR data [δ ($CDCl_3$) in ppm and J in Hz] for adducts of nitrile oxides **7a** and **7b** with **1a** and **2a**.

Comp.	H-1	H-5	H-6	H-7	$J_{1,5}$	$J_{1,6}$	$J_{1,7}$	$J_{5,6}$	$J_{5,7}$	$J_{6,7}$
20a	4.61	3.62	2.93	2.93	7.3	<0.5	1.6	1.7	<0.5	-
21a	5.10	3.83	2.58	2.79	7.1	<0.5	5.0	2.3	1.4	8.5
22a	5.25	4.27	a	a	7.8	1.4	6.2	8.0	2.6	a
26a[b]	4.69	3.55	2.29	2.51	7.2	<0.5	4.8	2.5	1.5	8.5
27a[b]	4.75	3.95	a	a	7.8	1.0	6.3	8.2	2.6	a

[a]Buried under the signals of the dominant diastereoisomer [b]In C_6D_6

Table 6. ^{1}H NMR data [δ($CDCl_3$) in ppm and J in Hz] for adducts of nitrile oxides **7a** and **7b** with **1b-3b** and **4**.

Comp.	H-5	H-6	H-7	Me-6	Me-7	OMe	$J_{5,6}$	$J_{5,7}$	$J_{6,7}$
20b	3.92	2.91	3.23	-	-	3.80	4.2	1.3	6.8
25b	3.96	2.90	3.25	-	-	3.82	4.2	1.4	6.9
21b	4.12	2.60	3.02	-	-	3.81	3.5	1.4	9.2
22b	4.46	2.93	3.18	-	-	3.81	8.5	2.2	9.5
26b[a]	4.19	2.29	2.80	-	-	3.32	3.6	1.4	9.2
27b[a]	4.24	2.59	2.97	-	-	3.33	8.7	2.5	9.5
23b[b]	4.01	2.73	3.15	1.31	1.04	3.85	4.0	1.5	9.5
24b[b]	4.48	3.06	3.32	0.88	1.09	3.81	8.6	2.0	10.1
28b[b]	4.00	2.75	3.13	1.28	1.04	3.87	4.0	1.5	9.5
29b[b]	4.50	3.08	3.34	0.92	1.10	3.82	8.8	2.3	10.0
34[c]	3.88	2.11	2.78	1.38	1.20	3.80	5.0	1.8	7.0
35[d]	4.45	2.50	2.50	0.90	1.11	3.83	7.5	-	-
36[c]	3.91	2.10	2.83	1.34	1.19	3.82	5.5	1.8	7.1
37[d]	4.48	2.50	2.50	1.01	1.13	3.86	7.3	-	-

[a]In C_6D_6 [b]$J_{6,Me-6} \approx J_{7,Me-7} \approx 7.5$ Hz [c]$J_{6,Me-6} \approx J_{7,Me-7} \approx 7.0$ Hz [d]$J_{6,Me-6} \approx J_{7,Me-7} \approx 6.5$ Hz

Acknowledgments. This work was financially supported by CNR, MURST and Progetto Strategico Tecnologie Chimiche Innovative.

REFERENCES AND NOTES

1. Burdisso, M.; Gandolfi, R.; Lucchi, M.; Rastelli, A. *J. Org. Chem.* **1990**, *55*, 2123-2125.
2. Rastelli, A.; Burdisso, M.; Gandolfi, R. *J. Phys. Org. Chem.* **1990**, 3, 159-173.
3. Burdisso, M.; Gamba, A.; Gandolfi, R.; Toma, L.; Rastelli, A.; Schiatti, E. *J. Org. Chem.* **1990**, *55*, 3311-3321 and references cited therein.

4. Rastelli, M.; Bagatti, M.; Gandolfi, R. *J.C.S. Faraday Trans.* **1993**, *83*, 3913-3920 and references cited therein.
5. Throughout we will use the syn (anti) descriptor for attack on the double bond of **1-3** on the same (opposite) side of the allylic substituents. The same descriptors are used for out-of-plane bending , i.e., in syn (anti) bent cyclobutenes the olefinic hydrogen(s) and the COOMe group bend toward (away from) the substituents and the bending angle α is given plus (minus) sign. Anti bending of the olefinic hydrogens means also syn pyramidalization of the carbon atoms of the double bond.
In the case of the trans derivative **4**, in syn (anti) attacks the "C" end, i.e. the sterically more demanding end, of the 1,3-dipole is on the same (opposite) side of its vicinal methyl group, i.e. Me-6.
6. Adam, W.; Beinhauer, A.; De Lucchi, O.; Rosenthal, R. J. *Tetrahedron Lett.* **1983**, *24*, 5727-5730; Christl, M.; Mattauch, B. *Chem. Ber.* **1985**, *118*, 4203-4223.
7. Keppel, R. A.; Bergman, R. G. *J. Am. Chem. Soc.* **1972**, *94*, 1350-1351.
8. Snider, B. B.; Rondini, D. J.; Robin, S. E.; Sealfon, S. *J. Am. Chem. Soc.* **1979**, *101*, 5283-5293.
9. Burdisso, M.; Gandolfi, R.; Pevarello, P.; Rastelli, A. *J. C. S. Perkin II* **1988**, 753-758.
10. For previous data and discussion on coupling constants involving protons of a cyclobutane ring fused to five membered heterocyclic rings see Mondelli, R.; Gamba, A. *Tetrahedron Lett.* **1971**, 2133-2136 and *Org. Magn. Res.* **1973**, *5*, 101-111.
11. For the kinetically controlled reaction in benzene/cyclohexane (1:1) at room temperature. This ratio refers to the 4-COOMe-isoxazolidine and 5-COOMe-isoxazolidine with the same stereochemistry (i.e., with the COOMe group and the bicyclic residue of the former **6** cis to each other) as that of **14b** (**15b**) and **16b** (**17b**), respectively. Actually, all the possible four isomers were present in the reaction of **6** with methyl acrylate [4-COOMe (with H-3 and H-4 cis to each other)/4-COOMe (with H-3 and H-4 trans to each other)/5-COOMe (with H-3 and H-5 cis to each other)/5-COOMe (with H-3 and H-5 trans to each other) = 51.5:12:12.5:24]. Huisgen et al. have reported formation of a 5-COOR-isoxazolidine as the only product in the reaction of **6** with ethyl acrylate and methyl acrylate (Huisgen, R.; Hauck, H.; Grashey, R.; Seidl, H. *Chem. Ber.* **1968**, *101*, 2568-2584). However, we did not manage to reproduce this result and a mixture of four isomers were obtained under all the conditions [in benzene, in benzene/cyclohexane, in acetonitrile, in methyl acrylate as solvent at r.t.; yields ≥ 86%] investigated by us. Under thermodynamic control [3 days at 100 °C in benzene/methyl acrylate (1:1)] a mixture of three adducts (the 4-COOMe-isoxazolidine with H-3 and H-4 cis to each other, dominant under kinetic control, was missing) was obtained (Gandolfi, R. unpublished results).
12. Only anti adducts were obtained in the reaction of N-t-butyl nitrone with **1b**, **2b** and **3b**, respectively, as mixtures of regioisomers (79:21, 70:30 and 73:27, respectively) in which the regioisomer with the methoxycarbonyl group at position 5 of the isoxazolidine ring (position 1 of the fused system) was dominant. In the reaction of this nitrone with methyl acrylate only the 5-substituted isoxazolidine was detected: Houk, K. N.; Bimanand, A.; Mukherjee, D.; Joyner, S.; Chang, Y. M.; Kaufman, D. C.; Domelsmith, L. N. *Heterocycles*, **1977**, *7*, 293-299. We have confirmed this observation.
13. Rastelli, A.; Gandolfi, R. submitted for publication.
14. In other words, TS geometry lessens and, respectively, increases the difference in size, between the C end and the X end of the 1,3-dipole, felt by the methyl groups in the reaction of **6** and, respectively, of **5**.
15. Gandolfi, R.; Tonoletti, G.; Rastelli, A.; Bagatti, M *J. Org. Chem.* **1993**, *58*, 6038-6048 and references cited therein.
16. Sustmann, R.; Sicking, W.; Huisgen, R. *J. Am. Chem. Soc.*, **1995**, *117*, 9675-9685.
17. When electrostatic interactions are important the replacement of a hydrogen atom with a COOMe group on a double bond gives rise to a significant change in face selectivity of its reactions with 1,3-dipoles: Gandolfi, R.; Sarzi Amade', M.; Rastelli, A.; Bagatti, M.; Montanari, D. *Tetrahedron Lett.* **1996**, *37*, 517-520.
18. a) Chapman, O. L.; Pasto, D. J.; Broden, G. W.; Griswold, A. A. J. J. *Am. Chem. Soc.* **1962**, *84*, 1220-1224. b) Liu, R. S. *J. Am. Chem. Soc.* **1967**, *89*, 112-114. c) Schmitz, E. *Chem. Ber.* **1958**, *91*, 1488-1494. d) Corsico Coda, A.; Tacconi, G. *Gazz. Chim. Ital.* **1984**, *114*, 131-132. e) Levin, N.; Hartung, W. H. *Org. Syntheses Coll. Vol. 3* , 191-193.

(*Received in UK* 21 *April* 1997; *revised* 14 *May* 1997; *accepted* 15 *May* 1997)