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Regio- and Facial-Selective Effects of Allylic Heteroatoms in 1,3-Dipolar Cycloaddition of a Nitrile Oxide

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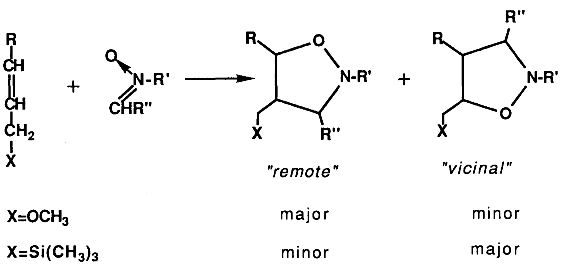
The 1,3-dipolar cycloaddition of nitrile oxides to 2-X-bicyclo[2.2.2]oct-5-enes (X=O, NMe, S, SO_2) were investigated together with acyclic and alicyclic analogues. The regioselectivity in an *exo*-attack was controlled by the heteroatom present at an allylic position — a remote attack was predominant in the cases of O and SO_2 but a vicinal attack in those of NMe and S— and the results were rationalized from the electronic nature of the heteroatom, X. In an *endo*-attack, a remote attack was observed in every case and the dipole-dipole repulsion between X and the oxygen of the nitrile oxide was considered to be a predominant factor. The steric environment around the heteroatom controled the facial-selectivity.

Allylic heteroatoms have been of continuous interested due to their characteristic effects on the regio- and/or facial-selectivity in intermolecular cycloaddition reactions from both synthetic and mechanistic viewpoints.[1)] In the course of our synthetic studies concerning natural products, we found previously that the regioselectivity in the 1,3-dipolar cycloaddition of nitrones is affected by the nature of allylic heteroatoms present in a dipolarophile. The regiochemistry of the products favored the direction as the oxygen atom of the dipole apt to repel with the allylic oxygen atom (remote attack) while to proximate with the allylic silicon atom (vicinal attack)(Scheme 1).[2)] We also found that the regioselectivity was independent of the geometry of the double bonds of dipolarophiles.[3)]

There has been mainly three explanations concerning the origin of the effect of allylic heteroatoms. The first is based on the polarization of the Frontier π-orbital, due to the electronic effect of the heteroatoms.[1a)] The second is based on the steric environment of substituents at the allylic position.[1b)] The final one is based on the electrostatic repulsion or attraction between the heteroatom and the oxygen of the 1,3-dipole.[1g)] In the case of acyclic olefins, the conformation at the allylic position is so flexible that the results are not necessarily estimated directly regarding the regio- and/or facial-selectivity. Thus, it is important to fix the geometry of the dipolarophiles in order to clarify the nature of the effect. We noticed the angle (θ) between the C–X bond and the π-orbital, as shown in Fig. 1, because, if any electronic effect is present, the effect may be maximum when θ is 0 degrees (parallel), but minimum when 90 (or −90) degrees (rectangular). We chose bicyclo[2.2.2]oct-2-ene (**1**) and its heterocyclic analogues (**2**—**6**) as a parallel model. A heteroatom (O, N, or S) is placed at the 2-position where θ become nearly 30 degrees. In the case of oxygen, both 2-oxabicyclo[2.2.2]oct-5-ene (**2**) and 1,4-dimethyl-2-oxabicyclo[2.2.2]oct-5-ene (**3**) were used because **2** is so volatile that the compound could



Scheme 1.

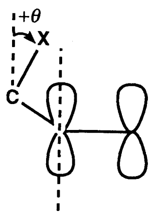
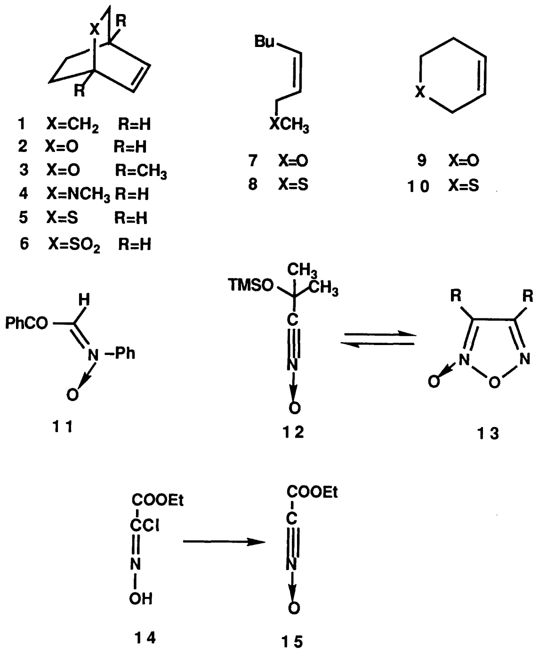


Fig. 1. The definition of θ.

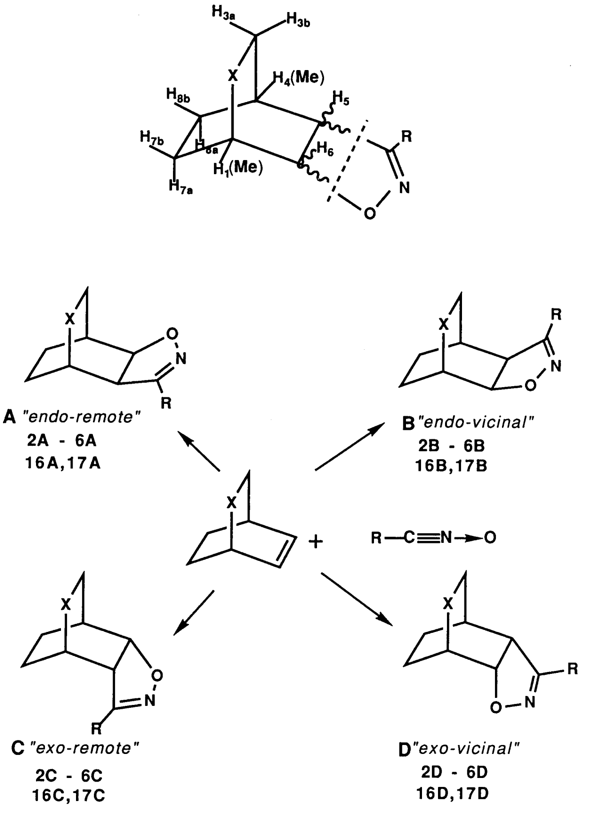


Scheme 2.

not be isolated in a pure state.[4] Also (*Z*)-1-methoxy-2-heptene (**7**) and (*Z*)-1-methylthio-2-heptene (**8**) were used as a flexible model and 5,6-dihydro-2*H*-pyran (**9**) and 5,6-dihydro-2*H*-thiopyran (**10**) were used as a rectangular model (θ=90).

Results and Discussion

1,3-Dipolar Cycloaddition and Assignment of Stereochemistry. The regioselectivity of (*Z*)-1-methoxy-2-heptene (**7**) toward a reactive nitrone, *N*-phenylbenzoylmethanimine *N*-oxide (**11**), at room temperature was previously found as 96:4.[3] In the present work, however, we selected as a dipole, 2-(trimethylsilyloxy)-2-methylpropanenitrile oxide (**12**),[6] generated in situ under equilibration with 3,4-bis[1-methyl-1-(trimethylsilyloxy)ethyl]furazan 2-oxide (TOP-furoxan, **13**), for two reasons. The low reactivity of the cyclohexene ring toward nitrones[5] requires that the reactions should be carried out at higher temperature, though the yield using nitrone **11** was generally low under this conditions. The second reason was to avoid complexity due to the formation of stereoisomeric adducts at the C$_3$ position of the isoxazolidine ring when nitrone is used. Besides, among the ordinary methods to generate in situ a nitrile oxide, those that from nitroalkane[7] or chloro oxime[8] in the presence of a base were found to be unsuitable for **4**; the amine function in **4** behaved as a base to compete with the addition (see Experimental).



Scheme 3.

A mixture of a given dipolarophile and a slight excess of TOP-furoxan (**13**) in C$_6$D$_6$ was sealed in a NMR-tube and heated at 165 °C. The reaction was continued until the signals of the dipolarophile in ^{1}H NMR spectrum disappeared. Products were separated by chromatography and characterized by 500 MHz NMR spectra.

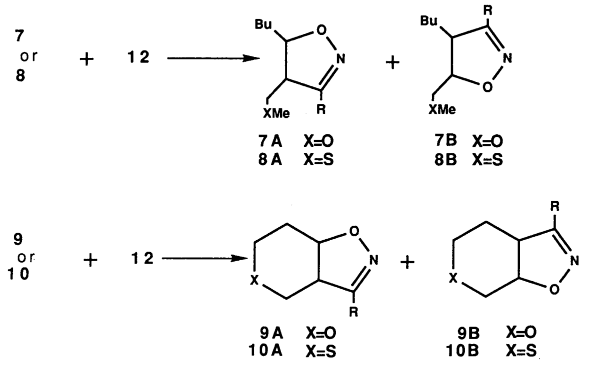
The reaction of **3**, **4**, or **5** with another nitrile oxide, ethyl cyanoformate *N*-oxide (**15**),[8] generated in situ at room temperature by the slow-addition of base on ethyl chloro(hydroxyimino)acetate (**14**), was also examined for a comparison with the above-mentioned reactions.

As shown in Scheme 3, there are four possible approaches of the nitrile oxide to the bicyclic dipolarophiles (**2**—**6**) to give adducts **A** (*endo*-remote addition), **B** (*endo*-vicinal), **C** (*exo*-remote), and **D** (*exo*-vicinal), respectively. The terms *"endo"* or *"exo"* shown in parentheses are with respect to the heteroatom of the dipolarophiles. The stereochemical assignments of products were based on the long-range W-coupling in the ^{1}H NMR spectra: in *endo*-type adducts (**A** and **B**) two W-couplings (H3a–H5 and H3b–H8a) were observed in every case; in *exo*-type adducts (**C** and **D**), however, three W-couplings (H3b–H8a, H5–H8b, and H6–H7b) were observed. The chemical shifts and coupling patterns on those products are summarized in Table 1.

On the other hand, in acyclic or alicyclic dipolarophiles (**7**—**10**), only two products (derived formally from remote and vicinal attacks) are possible and, regiochemistry, could be easily assigned by a decoupling technique in the ^{1}H NMR spectra (Scheme 4).

The ratio of the products were analyzed by the ^{1}H NMR spectra of the mixture. The results are summarized in Table 2.

The progress of the reaction was monitored by ^{1}H NMR; neither serious decomposition nor cycloreversion was obseved in all bicyclic dipolarophiles. In the cases of oxygen (Runs 2 and 4), the yields were so low relative to the other bicyclic dipolarophiles that the product ratio between **3** and **12** was analyzed after



Scheme 4.

Table 1. 500 MHz ^{1}H NMR Spectra[a] of Adducts from Bicyclic Dipolarophiles (**2**—**6**) in $CDCl_3$

Adduct[b]		H_1	H_{3a}	H_{3b}	H_4	H_5	H_6
X=O	**2A′**	4.24 (ddd) 3.9, 2.1, 1.8	3.73 (ddd) 9.0, 1.9, 1.8	4.04 (ddd) 9.0, 2.5, 2.4	1.94 (m)	4.76 (ddd) 11.9, 3.9, 1.9	3.44 (dd) 11.9, 2.1
	2B′	3.88 (ddd) 4.7, 2.3, 2.0	3.78 (ddd) 9.2, 1.9, 1.9	3.85 (ddd) 9.2, 2.6, 2.4	2.20 (m)	3.50 (ddd) 11.8, 3.1, 1.9	4.59 (dd) 11.8, 3.4
	2C′	4.11 (ddd) 4.3, 4.2, 1.9	3.95 (dd) 9.3, 2.2	3.72 (ddd) 9.3, 2.7, 2.1	2.07 (m)	4.88 (ddd) 11.4, 4.3, 1.4	3.75 (ddd) 11.4, 4.3, 2.0
	2D′					3.59 (ddd)	4.81 (ddd)
X=O (Me)	**3A**	1.39 (s, Me)	3.41 (dd) 8.7, 2.1	3.81 (dd) 8.7, 3.1	0.90 (s, Me)	4.40 (dd) 11.8, 2.1	3.29 (d) 11.8
	3B	1.20 (s, Me)	3.45 (dd) 8.9, 2.3	3.76 (dd) 8.9, 2.7	1.11 (s, Me)	3.28 (dd) 12.0, 2.3	4.38 (d) 12.0
	3C	1.41 (s, Me)	3.65 (d) 9.0	3.42 (dd) 9.0, 3.0	0.89 (s, Me)	4.48 (dd) 11.8, 2.2	3.49 (dd) 11.8, 2.4
	3D	1.19 (s, Me)	3.55 (d) 8.9	3.46 (dd) 8.9, 3.3	1.07 (s, Me)	3.30 (dd) 11.9, 2.3	4.43 (dd) 11.9, 2.0
X=NMe	**4A′**	3.15	2.24 (ddd) 11.5, sm, sm	3.31 (ddd) 11.5, sm, sm	1.86	4.67 (ddd) 11.6, 3.3, 1.7	3.58 (dd) 11.6, 3.9
	4C′	2.95	2.91 (dd) 10.7, 2.0	2.44 (ddd) 10.7, 2.3, 2.3	2.01 (m)	4.72 (ddd) 11.4, 4.6, 1.5	3.68 (ddd) 11.4, 3.6, 1.9
	4D′	2.81 (ddd) 5.0, 2.8, 2.8	2.46 (dd) 10.2, 2.0	2.93 (dddd)[c] 10.0, 3.3, 1.6, 1.6	2.09 (m)	3.46 (br. dd) 11.2, 3.2, sm	4.80 (br. dd) 11.2, 5.1, 1.0
X=S	**5A**	3.00 (m)	2.56 (ddd) 10.7, 3.1, 0.9	3.10 (ddd) 10.7, 2.9, 2.9	2.30 (m)	4.63 (ddd) 12.1, 4.9, 0.9	3.64 (dd) 12.1, 3.6
	5B	2.77	2.55 (ddd) 10.5, 3.4, 1.6	2.83 (ddd) 10.5, 2.0, 2.0	2.45 (m)	3.38 (ddd) 12.1, 4.5, 1.6	4.77 (dd) 12.1, 4.2
	5C	3.05	2.91 (dd) 11.1, 4.2	2.70 (ddd) 11.1, 2.5, 2.5	2.36 (m)	4.72 (ddd) 11.5, 4.2, 1.7	3.84(ddd) 11.5, 2.7, 2.2
	5D	2.73	2.83 (dd) 10.6, 3.0	2.64 (ddd) 10.6, 3.1, 2.8	2.53 (m)	3.45 (ddd) 11.5, 2.4, 2.0	4.99 (ddd) 11.5, 4.3, 1.4
X=SO_2	**6A**	3.50	3.05 (br. dd) 13.5, 4.0, sm	3.64 (ddd) 13.5, 2.9, 2.7	2.79 (m)	4.61 (br. dd) 12.1, 4.8, sm	3.77 (dd) 12.1, 3.7
	6C	3.34	3.25 (dd) 13.6, 4.0	3.14 (ddd) 13.6, 3.5, 2.0	2.65 (m)	4.82 (ddd) 11.5, 3.6, 1.7	4.24 (ddd) 11.5, 2.7, 2.5
	6D	3.28	3.14—3.22 (AB)		2.91 (m)	3.66 (ddd) 11.0, 2.2, 2.0	5.16 (ddd) 11.0, 4.3, 1.6
X=O (Me)	**16A**	1.13 (s, Me)	3.48 (dd) 9.0, 1.9	3.83 (dd) 9.0, 3.3	0.94 (s, Me)	4.62 (dd) 11.9, 1.9	3.47 (d) 11.9
	16B	1.23 (s, Me)	3.48 (dd) 9.1, 2.5	3.55 (dd) 9.1, 2.5	0.88 (s, Me)	3.49 (dd) 12.3, 2.5	4.60 (d) 12.3
	16C	1.21 (s, Me)	3.66 (d) 9.4,	3.49 (dd) 9.4, 3.2	0.94 (s, Me)	4.71 (dd) 11.8, 2.1	3.67 (dd) 11.8, 2.4
	16D	1.21 (s, Me)	3.60 (d) 9.0	3.51 (dd) 9.0, 3.1	0.89 (s, Me)	3.53 (dd) 11.8, 2.0	4.63 (dd) 11.8, 1.9
X=S	**17A**	3.17 (m)	2.58 (ddd) 11.0, 3.6, 1.2	3.01 (ddd) 11.0, 2.6, 2.6	2.33 (m)	4.93 (ddd) 12.3, 4.8, 1.2	3.84 (dd) 12.3, 4.3
	17C	3.11 (m)	2.93 (dd) 11.1, 3.8	2.73	2.37 (m)	4.97 (ddd) 12.0, 3.8, 1.7	4.00 (ddd) 12.0, 3.5, 2.0
	17D	2.76 (m)	2.83 (dd) 10.8, 3.2	2.70 (ddd) 10.8, 2.9, 2.9	2.62 (m)	3.59 (ddd) 11.7, 3.0, 2.0	5.21 (ddd) 11.7, 4.2, 1.7

a) First column shows chemical shifts with splitting pattern in parentheses and second one shows coupling constants. sm is small coupling constant. b) Those with (′) shows the data being of a corresponding de-TMS derivative. c) Changed to dd (J=10.0 and 3.3) when δ=1.78 (AB, H7a, and H7b) was irradiated.

6 hours. However, the results (**3A**:**3B**:**3C**:**3D**=28:7:36:29, Run 3 in Table 2) were the same as those values after 38 hours. Thus, we safely concluded for the bicyclic dipolarophiles that the values in Table 2 reflect the kinetic product ratio.

On the Origin of Regio- and Facial-Selectivity of the Allylic Heteroatoms. From Table 2, the following several features can be pointed out in the case of nitrile oxide, **12**. 1) Although no details concerning kinetic measurements had been found, the approximate reaction rate decreased in order bicyclic > acyclic > alicyclic based on the structural type of dipolarophile; it was N-Me > CH_2 > O > S (or SO_2) based on the species of the allylic heteroatom. 2) Regarding the facial selectivity observed among bicyclic dipolarophiles, the adducts (**C** and **D**, see Scheme 3) derived

Table 2. Reaction Conditions and the Ratio of Cycloadducts

Run	Nitrile oxide	Olefin	Reaction conditions		Yield[b]	Cycloadducts			
			Concn/mmol[a]	Time/h	%	Ratio in %			
1	**12**	**1**	1.19	24	84	**1A**			
2		**2**	0.87	32	45	**2A** (47)	**2B** (8)	**2C** (26)	**2D** (19)
3		**3**	0.77	6	ca. 20	**3A** (28)	**3B** (7)	**3C** (36)	**3D** (29)
4		**3**	0.77	38	51	**3A** (28)	**3B** (8)	**3C** (36)	**3D** (28)
5		**4**	1.4	10	93	**4A** (24)	—	**4C** (34)	**4D** (42)
6		**5**	0.91	47	95	**5A** (6)	**5B** (2)	**5C** (30)	**5D** (62)
7		**6**	0.70	65	100	**6A** (4)	—	**6C** (51)	**6D** (45)
8		**7**	0.98	70	66	**7A** (79)	**7B** (21)		
9		**8**	0.90	154	44 (63)	**8A** (61)	**8B** (39)		
10		**9**	1.40	60	48	**9A** (54)	**9B** (46)		
11		**10**	1.24	146	1>				
12	**15**	**3**			34	**16A** (37)	**16B** (11)	**16C** (28)	**16D** (24)
13		**4**			0[c]				
14		**5**			74	**17A** (5)	—	**17C** (18)	**17D** (77)

a) The amount of an olefin in 0.3 ml of C_6H_6 in the case of **12**. b) Isolated yield. Those in parentheses were based on the olefin consumed. c) No adducts formed but only starting **4** recovered.

from the *exo* (rear side) attack were major in all cases, except for **2**. The *exo* attack increased in the order O < N-Me < S < SO_2. 3) The regioselectivity in the *endo* attack favored in all cases the direction to produce **A**, in which the heteroatom of the dipolarophiles repels the dipole oxygen to a remote position. 4) The regioselectivity in an *exo* attack favored a vicinal attack to give **D** in the case of N-Me or S, but favored **C** in the case of O or SO_2. 4) When the alicyclic dipolarophile (**9**), was used, the regioselectivity was almost diminished, though very little predominance in remote-attack was observed (Run 10). In **10**, the values could not be obtained due to an instability of the dipolarophile under prolonged heating. 5) The apparent regioselectivity to produce a remote-attack product was recognized in the case of acyclic dipolarophiles (**7** and **8**). The selectivity was slightly lower, compared to the case of the nitrone **11**.[13]

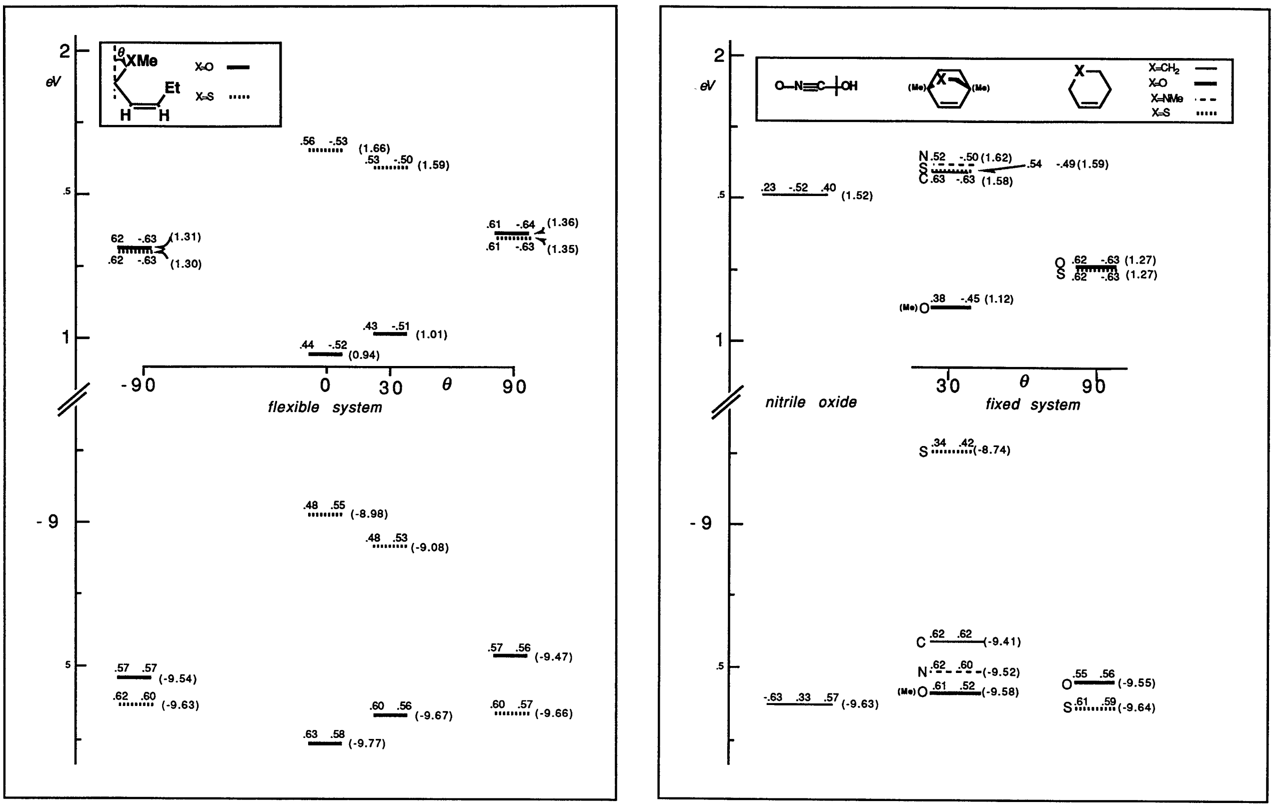
The facial- and regioselective features with another nitrile oxide **15** under different conditions (Runs 12—14) were similar to those with **12**; the present results can be considered as showing general features in 1,3-dipolar cycloaddition of nitrile oxide to dipolarophiles having an allylic heteroatom.

As shown in the oxygen series (Runs 8, 10, and 2 or 4), the regioselectivity differed from one another regarding the structure of the dipolarophiles. This shows that the effect of the heteroatom changes as the angle between the π-orbital and the C–X bond.

The selectivity observed in the present bicyclic dipolarophiles was finally considered. Regarding the facial-selectivity, an *exo*-attack becomes predominant in the order O, NMe, S, SO_2; the order might be only explained by the steric environment around the heteroatom.

On the other hand, the regioselectivity differed regarding the *exo*- or *endo*-attack. It is reasonable to assume that only the electronic effect of the heteroatom could operate in an *exo*-attack, but that both steric and electronic effects should be considered in an *endo*-attack.[1a]

In order to examine the usually accepted HOMO–LUMO correlation, MINDO/3 calculations[9] concerning both dipolarophiles and the dipole were performed. To simplify the calculations, (*Z*)-1-methoxy-2-pentene (**7′**), (*Z*)-1-methylthio-2-pentene (**8′**), and 2-hydroxypropanenitrile oxide (**12′**) were used instead of **7**, **8**, and **12**, respectively. In the case of acyclic models, the several conformations derived from changing the angle (θ) were also calculated. The frontier π-orbitals obtained are illustrated with their energy and coefficients in Fig. 2. The energy and the coefficients of the frontier π-orbital change as the angle (θ) between the π-bond and C–X bond varies[Fig 2 (a)]. The characteristic features derived by calculations involving acyclic models are as follows: 1) in the case of oxygen, both HOMO and LUMO states are stabilized according to an increase in the overlap of the C–X bond, but destabilize in the case of sulfur. 2) The coefficients of the frontier π-orbital also change according to θ; the situtation is again opposite for oxygen and sulfur. This tendency is also observed in the bicyclic dipolarophiles **3** and **5**; the coefficient in HOMO is larger at the vicinal carbon (C_6) in oxygen, but at the remote carbon (C_5) in sulfur[Fig. 2 (b)]. Thus, the present results were consistent with the predictions of regiochemistry from a simple HOMO–LUMO interaction, which predicts, at least, in an *exo*-attack the regiochemistry is opposite either the oxygen or the sulfur. This reverse phenomena can be considered qualitatively, as shown in Fig. 3; the electronegative oxygen atom pulls the bonding electrons to give a so-called "allylcation" [Fig. 3 (a)], the polarization of which is larger at the adjacent carbon to the C–O group(b). When the sulfur atom is present at the



(a) (b)

Fig. 2. HOMO and LUMO energies and coefficients of the π-bond calculated by MINDO/3. (a) Flexible system: the calculations were performed with θ=−90, 0, 30, and 90. (b) Fixed system.

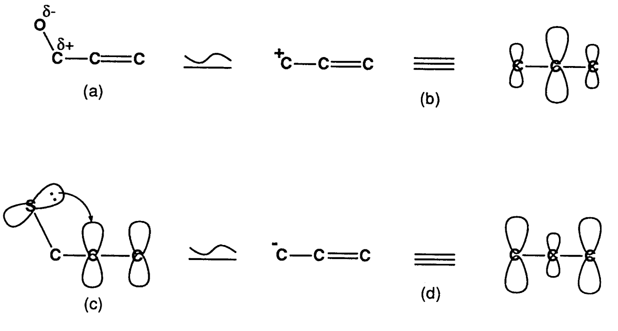


Fig 3. Schematic representations of orbital polarization of π-bond caused by the allylic heteroatom.

allylic position, the interaction of the lone pair on the sulfur atom to the π-orbital through space results in an "allyl anion"(c), the polarization of which is larger at the remote carbon(d). When the lone pairs on the sulfur atom are replaced by the oxygen atom, this through-space interaction diminishes and, thus, the electronegative property of the sulfonyl group reverses the regiochemistry (Run 7). The direction of polarization is roughly comparable to the difference in chemical shifts of the double bond in the ^{13}C NMR spectra, as shown in Table 3.

In the nitrogen analogue, the polarization became

Table 3. ^{13}C- and ^{1}H NMR Data of the Double Bond in Bicyclic Dipolarophiles

	^{13}C NMR (125 MHz)		^{1}H NMR (500 MHz)		
	C_5	C_6	H_5		H_6
1 (CH_2)[a]	134.2	134.2		6.25 (dd) 4.5, 3.0	
2 (O)	133.6	133.3		6.44 (m)	
3 (O, Me)	138.3	135.9	6.12_5 (d) 8.2		6.15_6 (d) 8.2
4 (NMe)	133.2	131.5	6.34_8 (ddd) 8.2, 6.6, 1.5		6.23_4 (ddd) 8.2, 5.4, 1.4
5 (S)	131.9	134.8	6.19_5 (dd) 7.7, 7.7		6.53_2 (dd) 7.7, 7.6
6 (SO_2)	135.0	128.2	6.44_9 (ddd) 8.5, 6.0, 1.8		6.42_5 (ddd) 8.5, 6.4, 1.9

a) 90 MHz and 22.5 MHz for ^{1}H and ^{13}C, respectively.

smaller, as compared to those of the oxygen or sulfur, that the regioselectivity lowered slightly.

Contrary to an *exo*-attack, the regiochemistry is not coincident with the polarization of the π-orbital in an *endo*-attack. We estimate at the present time that a dipole–dipole repulsion between the heteroatom of dipolarophiles and the oxygen of the nitrile oxide is the predominant factor to decide the regiochemistry. The use of a more electropositive heteroatom (e.g., Si) or 2,5-dioxabicyclo[2.2.2]oct-7-ene is attractive for the decision of the control factor.

Experimental

Melting points are uncorrected. ^{1}H NMR spectra were measured in $CDCl_3$, except otherwise stated, either on a JEOL FX90Q (90 MHz) or on a Brucker AM500 (500 MHz) spectrometer; the chemical shifts were recorded relative to the TMS as an internal standard. Flash chromatographies were performed using a Wakogel C-300 with the stated solvent. Recycle-HPLC was performed on a JAI LC-908 chromatograph with columns JAIGEL-1H and -2H. Micro analyses were performed at the Analytical Center, University of Tsukuba. High-resolution mass spectra were taken at Nippon Roche Research Center, Kamakura.

Materials. Bicyclo[2.2.2]oct-2-ene(**1**) was purchased from Aldrich Co., Ltd. 2-Oxabicyclo[2.2.2]oct-5-ene(**2**),[4] 1,4-dimethyl-2-oxabicyclo[2.2.2]oct-5-ene(**3**),[4] 2-methyl-2-azabicyclo[2.2.2]oct-5-ene(**4**),[10] 2-thiabicyclo[2.2.2]oct-5-ene(**5**),[11] 2-thiabicyclo[2.2.2]oct-5-ene 2,2-dioxide(**6**),[11] (*Z*)-1-methoxy-2-heptene(**7**),[12] (*Z*)-1-methylthio-2-heptene(**8**),[13] 5,6-dihydro-2*H*-pyran(**9**),[14] 5,6-dihydro-2*H*-thiopyran(**10**),[15] 3,4-bis[1-methyl-1-(trimethylsilyloxy)ethyl]furazan 2-oxide(TOP-furoxan, **13**),[16] and ethyl chloro(hydroxyimino)acetate(**14**)[8] were prepared to methods described in the literature.

General Procedure of 1,3-Dipolar Cycloaddition Reactions with 2-(Trimethylsilyloxy)-2-methylpropanenitrile Oxide (12). A mixture of 0.5—1 mmol of a given dipolarophile (**1**—**10**) and a slight excess of TOP-furoxan **13** in 0.3 ml of C_6D_6 was heated in a sealed tube at 165 °C. The reaction was monitored by ^{1}H NMR. After the solvent had been evaporated, the residue was purified by chromatography. The following give the amount of materials, reaction time, yield of the product(s), and separation conditions.

Run 1: **1** (128 mg) and **13** (280 mg); 24 h; 84%; flash chromatography (hexane–EtOAc=10:1) gave a pure adduct **1A** as an oil.

1A; ^{1}H NMR (90 MHz) δ=0.14 (s, 9H), 1.51 (s, 3H), 1.56 (s, 3H), 1.35—2.02 (m, 10H), 3.25 (br. dd, 1H, *J*=12 and 3 Hz), and 4.56 (br. dd, 1H, *J*=12 and 4 Hz). Found: C, 63.69; H, 9.69; N, 4.97%. Calcd for $C_{15}H_{27}NO_2Si$: C, 64.01; H, 9.67; N, 4.98%.

Run 2: **2** containing 25% 6-oxabicyclo[3.2.1]oct-3-ene (96 mg) and **13** (199 mg); 32 h; 45%; recycle-HPLC ($CHCl_3$) gave 56 mg of a mixture of **2A** and I, and 75 mg of a mixture of **2B**, **2C**, **2D**, **II**, **III**, and **IV**. **I**—**IV** were adducts derived from 6-oxabicyclo[3.2.1]oct-3-ene. **2A** was isolated in pure form by flash chromatography (hexane–EtOAc=1:6). PTLC (CH_2Cl_2, 4 times) gave three fractions, (**2D**), (**2C**, **II**, and **III**), and (**2B** and **2C**).

2A: Oil. Found: C, 59.06; H, 8.36; N, 4.99%. Calcd for $C_{14}H_{25}NO_3Si$: C, 59.33; H, 8.89; N, 4.94%.

Run 3: **3** (106 mg) and **13** (177 mg); 6 h; ca. 20%; chromatography (ether:CH_2Cl_2=1:1) gave a mixture of adducts (**3A**:**3B**:**3C**:**3D**=28:7:36:29).

Run 4: **3** (106 mg) and **13** (177 mg); 38 h; 51%; chromatography (ether:CH_2Cl_2=1:1) gave a mixture of adducts (**3A**:**3B**:**3C**:**3D**=28:8:36:28); recycle-HPLC ($CHCl_3$) gave 29 mg of **3A** and 73 mg of a mixture of **3B**, **3C**, and **3D**; **3B** was separated by flash chromatography (hexane–EtOAc=6:1);

3A: Oil. Found: C, 61.79; H, 9.54; N, 4.54%. Calcd for $C_{16}H_{29}NO_3Si$: C, 61.79; H, 9.38%; N, 4.50%.

Run 5: **4** (158 mg) and **13** (291 mg); 10 h; 93%; flash chromatography (EtOAc) gave 303 mg of a mixture of **4C**, **4D**, and **4A′** (de-TMS derivative)(**4C**:**4D**:**4A′**=39:49:12) and 34 mg of **4A′**. After **4C** and **4D** had been converted into de-TMS derivatives, **4C′** and **4D′**, respectively, pure **4C′** and **4D′** were separated by flash chromatography (hexane–EtOAc=3:7).

4A′: Oil. Found: *m/z* 224.152. Calcd for $C_{12}H_{20}N_2O_2$: M^+ 224.152.

4C′: Crystal. Found: *m/z* 224.152. Calcd for $C_{12}H_{20}N_2O_2$: M^+ 224.152.

4D′: Oil. Found: *m/z* 224.152. Calcd for $C_{12}H_{20}N_2O_2$: M^+ 224.152.

Run 6: **5** (115 mg) and **13** (196 mg); 47 h; 95%; ^{1}H NMR of the residue revealed the ratio of **5A**:**5B**:**5C**:**5D**=6:2:30:62. Column-chromatography on silica gel (hexane–CH_2Cl_2–EtOAc=10:1:1) afforded 241 mg of a mixture of **5C** and **5D**, 12 mg of **5A**, and 4 mg of **5B**. After **5C** and **5D** had been converted into de-TMS derivatives **5C′** and **5D′**, a pure **5D′** was obtained by recrystallization from benzene-pentane.

5D′: Mp 104.5—105 °C. Found: C, 58.20; H, 7.67; N, 6.12%. Calcd for $C_{11}H_{17}NO_2S$: C, 58.12; H, 7.54; N, 6.16%.

Run 7: **6** (111 mg) and **13** (154 mg); 65 h; ca. 100%; ^{1}H NMR of the residue revealed the ratio of **6A**:**6C**:**6D** as being 4:51:45. Column-chromatography on silica gel (hexane–EtOAc=1:1) gave 158 mg of **6C** and **6D**, and 6 mg of **6A**. **6C** and **6D** were separated by column-chromatography on silica gel (hexane–EtOAc=2:1).

6C: Mp 90—90.5 °C. Found: C, 50.69; H, 7.62; N, 4.23%. Calcd for $C_{14}H_{25}NO_4SSi$: C, 50.72; H, 7.60; N, 4.23%.

6D: Mp 103.5—104.5 °C. Found: C, 50.46; H, 7.54; N, 4.27%. Calcd for $C_{14}H_{25}NO_4SSi$: C, 50.72; H, 7.60; N, 4.23%.

Run 8: **7** (125 mg) and **13** (213 mg); 70 h; 66%. Flash chromatography (hexane–EtOAc=5:1) gave 155 mg of **7A** and 43 mg of **7B**. **7A** and **7B** were converted into de-TMS derivatives **7A′** and **7B′**, respectively, by the action of Bu_4NF.

7A′: Oil; ^{1}H NMR δ=0.91 (t, 3H, *J*=7.2 Hz), 1.3—1.7 (m, 6H), 1.45 (s, 3H), 1.50 (s, 3H), 3.39 (s, 3H), 3.41 (ddd, 1H, *J*=9.0, 9.0, and 4.7 Hz), 3.53 (dd, 1H, *J*=9.0 and 9.0 Hz), 3.60 (dd, 1H, *J*=9.0 and 4.7 Hz), and 4.39(ddd, 1H, *J*=9.0, 9.0, and 4.8 Hz). Found: C, 62.33; H, 10.19; N, 6.04%. Calcd for $C_{12}H_{23}NO_3$: C, 62.85; H, 10.11; N, 6.11%.

7B′: Oil; ^{1}H NMR δ=0.90 (t, 3H, *J*=7.2 Hz), 1.3—1.8 (m, 6H), 1.49 (s, 3H), 1.52 (s, 3H), 3.39 (s, 3H), 3.30 (ddd, 1H, *J*=9.1, 9.1, and 2.8 Hz), 3.61 (dd, 1H, *J*=10.5 and 5.9 Hz), 3.65 (dd, 1H, *J*=10.5 and 4.9 Hz), and 4.57 (ddd, 1H, *J*=9.1, 5.9, and 4.9 Hz). Found: C, 63.03; H, 10.02; N, 6.37%. Calcd for $C_{12}H_{23}NO_3$: C, 62.85; H. 10.11; N, 6.11%.

Run 9: **8** (131 mg) and **13** (202 mg); 154 h; 44%. Flash chromatography (hexane–EtOAc=20:1) gave 77 mg of **8A** and 49 mg of **8B**.

8A: Oil; ^{1}H NMR δ=0.15 (s, 9H), 0.91 (t, 3H, J=5.6 Hz), 1.3—1.8 (m, 6H), 1.50 (s, 3H), 1.56 (s, 3H), 2.13 (s, 3H), 2.68 (dd, 1H, J=13.0 and 10.4 Hz), 2.95 (dd, 1H, J=13.0 and 2.5 Hz), 3.43 (ddd, 1H, J=10.4, 8.5, and 2.5 Hz), and 4.38 (ddd, 1H, J=8.5, 8.5, and 4.0 Hz). Found: C, 57.19; H, 9.83; N, 4.94%. Calcd for $C_{15}H_{31}NO_2SSi$: C, 56.73; H, 9.84; N, 4.41%.

8A′ (de-TMS derivative): Oil. Found: C, 58.72; H, 9.59; N, 5.70%. Calcd for $C_{12}H_{23}NO_2S$: C, 58.74; H, 9.45; N, 5.71%.

8B: Oil; ^{1}H NMR δ=0.14 (s, 9H), 0.90 (t, 3H, J=5.6 Hz), 1.3—1.8 (m, 6H), 1.50 (s, 3H), 1.55 (s, 3H), 2.21 (s, 3H), 2.76 (dd, 1H, J=13.8 and 6.3 Hz), 2.78 (dd, 1H, J=13.8 and 7.2 Hz), 3.25 (ddd, 1H, J=8.5, 8.5, and 2.8 Hz), 4.53 (ddd, 1H, J=8.5, 6.5, and 6.5 Hz). Found: C, 57.14; H, 9.91; N, 4.73%. Calcd for $C_{15}H_{31}NO_2SSi$: C, 56.73; H, 9.84; N, 4.41%.

Run 10: **9** (118mg) and **13** (243 mg); 60 h; 48%. Flash chromatography (hexane–EtOAc=6:1) gave 95 mg of **9A** and 79 mg of **9B**. Both were converted into de-TMS derivatives, **9A′** and **9B′**, respectively.

9A′: Oil; ^{1}H NMR δ=1.46 (s, 3H), 1.51 (s, 3H), 2.0—2.1 (m, 2H), 3.22 (ddd, 1H, J=9.4, 6.8, and 6.8 Hz), 3.44 (dd, 1H, J=11.8 and 9.4 Hz), 3.63 (ddd, 1H, J=11.6, 10.0, and 4.3 Hz), 3.78(ddd, 1H, J=11.6, 5.3, and 3.2 Hz), 4.02 (dd, 1H, J=11.8 and 6.8 Hz), and 4.52 (ddd, 1H, J=6.8, 3.8, and 3.8 Hz). Found: C, 57.94; H, 8.19; N, 7.47%. Calcd for $C_9H_{15}NO_3$: C, 58.36; H, 8.16; N, 7.56.

9B′: Mp 76—78 °C (benzene–hexane); ^{1}H NMR δ=1.50 (s, 3H), 1.53 (s, 3H), 1.65—1.95 (m, 2H), 3.19 (ddd, 1H, J=10.3, 7.3, and 7.3 Hz), 3.31 (ddd, 1H, J=11.5, 11.5, and 2.5 Hz), 3.75 (dd, 1H, J=13.5 and 3.0 Hz), 3.90 (ddd, 1H, J=11.5, 4.1, and 3.9 Hz), 4.18 (ddd, 1H, J=7.3, 3.0, and 1.9 Hz), and 4.23 (dd, 1H, J=13.5 and 1.9 Hz). Found: C, 58.42; H, 8.19; N, 7.56%. Calcd for $C_9H_{15}NO_3$: C, 58.36; H, 8.16; N, 7.56.

Run 11: **10** (124 mg) and **13** (262 mg); 146 h; serious decomposition with less than 1% adducts.

General Procedure of 1,3-Dipolar Cycloaddition Reactions with Ethyl Cyanoformate *N*-Oxide (15). To a solution of ethyl chloro(hydroxyimino)acetate (**14**)[8] and a given dipolarophiles (**3**—**5**) in ether, was added an aqueous sodium carbonate solution by a microfeeder during 3 h per 1 ml. The whole was stirred for 2 h and extracted with ether. The ether layer was washed with saline and dried over anhyd Na_2SO_4. After removal of the solvent, the residue was purified by chromatography.

Run 12: **3** (117 mg) and **14** (114 mg); Na_2CO_3 (116 mg)/1.5 ml H_2O (4.5 h); 34%; chromatography (CH_2Cl_2) gave 74 mg of a mixture of **16A**, **16B**, **16C**, and **16D** (=37:11:28:24). **16B** was separated by PTLC (CH_2Cl_2–EtOAc=49:1, 4 times). **16A**, **16C**, and **16D** were separated by recycle-HPLC ($CHCl_3$).

16A: Oil. Found: C, 61.10; H, 7.59; N, 5.48%. Calcd for $C_{13}H_{19}NO_4$: C, 61.64; H, 7.56; N, 5.53%.

Run 13: **4** (176 mg) and **14** (262 mg); Na_2CO_3 (255 mg)/4 ml H_2O (12 h); 0%. The residue was found as a mixture of 3,4-bis(ethoxycarbonyl)furazan 2-oxide and the starting **4**.

Run 14: **5** (103 mg) and **14** (374 mg); Na_2CO_3 (262 mg)/3.5 ml H_2O (11 h); 74%; chromatography (CH_2Cl_2) gave 145 mg of a mixture of **17A**, **17C**, and **17D** (=5:18:77). By PTLC (hexane–EtOAc=9:1, 5 times), **17A** was separated from other two isomers.

17C and **17D**: Oil. Found: C, 54.57; H, 6.27; N, 5.72%. Calcd for $C_{11}H_{15}NO_3S$: C, 54.75; H, 6.27; N, 5.80%.

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References

1) a) E. J. McAlduff, P. Caramella, and K. N. Houk, *J. Am. Chem. Soc.*, **100**, 105 (1978). b) R. W. Frank, T. V. John, and K. Olejniczak, *ibid.*, **104**, 1106 (1982). c) Y. Kishi, *Tetrahedron Lett.*, **1983**, 3943. d) K. N. Houk, S. R. Moser, Y.-D. Wu, N. A. Rondan, V. Jager, R. Schone, and F. R. Fronczek, *J. Am. Chem. Soc.*, **106**, 3880 (1984). e) A. P. Kozikowski and A. K. Ghash, *J. Org. Chem.*, **49**, 2762 (1984). f) D. L. Boger and M. Patel, *Tetrahedron Lett.*, **27**, 683 (1986). g) S. D. Kahn, C. F. Pau, and W. J. Hehre, *J. Am. Chem. Soc.*, **108**, 7396 (1986).

2) S. Niwayama, S. Dan, Y. Inouye, and H. Kakisawa, *Chem. Lett.*, **1985**, 957.

3) Y. Inouye, S. Niwayama, T. Okada, and H. Kakisawa, *Heterocycles*, **25**, 109 (1987).

4) Y. Inouye, K. Tokuhisa, M. Mitsuya, and H. Kakisawa, *Bull. Chem. Soc. Jpn.*, **63**, 2444 (1990).

5) a) K. Bast, M. Christl, R. Huisgen, and W.Mack, *Chem. Ber.*, **106**, 3312 (1973). b) F. Freeman, *Chem. Rev.*, **75**, 439 (1975).

6) D. P. Curraan and C. J. Fenk, *J. Am. Chem. Soc.*, **107**, 6023 (1985).

7) T. Mukaiyama and T. Hosino, *J. Am. Chem. Soc.*, **82**, 5339 (1960).

8) A. P. Kozikowski and M. Adamaczyk, *J. Org. Chem.*, **48**, 366 (1983).

9) Program MOSEMI coded by Professor Osamu Kikuchi, University of Tsukuba, was used.

10) P. A. Grieco and S. D. Larsen, *J. Org. Chem.*, **51**, 3553 (1986).

11) H. J. Reich and J. E. Trend, *J. Org. Chem.*, **38**, 2637 (1973).

12) J. F. Normant, A. Commercon, Y. Gendreau, M. Bourgain, and J. Villeras, *Bull. Soc. Chim. Fr.*, **1979**, II-309.

13) C. Germon, A. Alexakio, and J. F. Normant, *Synthesis*, **1984**, 43.

14) I. Colonge and P. Basde, *Bull. Soc. Chim. Fr.*, **1956**, 824.

15) C. H. Chen, G. A. Reynolds, N. Zumbulyadis, and J. A. VanAllen, *J. Heterocycl. Chem.*, **15**, 289 (1978).

16) a) A. Lambert and A. Lowe, *J. Chem. Soc.*, **1947**, 1517. b) D. P. Curran, S. A. Scanga, and C. J. Fenk, *J. Org. Chem.*, **49**, 3474 (1984).