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Enhancement in Facial Selectivity of a Plane Nonsymmetric Double Bond Induced by a Conjugating Methoxycarbonyl Group

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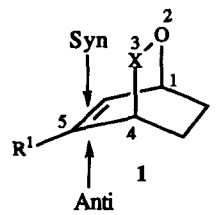
Abstract. *Introduction of a methoxycarbonyl group on the plane nonsymmetric double bond of 2,3-dioxa and 2,3-oxaza bicyclo[2.2.2]oct-5-enes brought about a clear-cut increase in syn selectivity of their reactions with 1,3-dipoles.*

Pursuit of higher facial selectivity in the reactions of plane nonsymmetric unsaturated systems is certainly a central target of synthetic organic chemistry while understanding of the factors that control stereochemical outcomes continue to be a challenging subject for theoretical studies.[1] Thus, there is a heightened expectation for every finding which can help to achieve the synthetic goal and can throw light on the theoretical aspects of this problem. Much discussion has been focused on the role of substituents, in particular heteroatoms, at an allylic stereogenic center in determining selectivity of attack to plane nonsymmetric double bonds and dienes *via* steric, electrostatic and stereoelectronic effects.[1] In this context, substituents directly attached to the double bond, but without stereogenic centers, can only play a complementary role, if any, and have received much less attention.

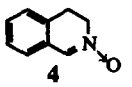
For example, it is known that in acyclic olefins introduction of a substituent in cis position with respect to an allylic stereogenic center can highly influence the stereochemical outcome of their reactions mostly by making the inside position (Felkin-Anh-Houk model) more sterically congested than the outside one.[2] Very few data have so far been reported for cyclic olefins.[3] Farina et al. made the interesting, but difficult to rationalize, observation that syn selectivity of attack of diazomethane to 5-methoxyfuran-2(5H)-one was increased when a vinyl hydrogen was replaced by either chlorine or bromine atoms.[3a] Continuing our studies about diastereoselectivity of the reactions of cyclic olefins,[4] we here report the interesting finding that a significant increase in syn selectivity of 1,3-dipolar cycloadditions to 2,3-dioxa and 2,3-oxazabicyclo[2.2.2]oct-5-enes could be achieved by introducing a methoxycarbonyl group on the double bond, i.e., on going from **1a-c** to **1d-f**.[5,6]

The Table gathers the facial selectivity data for the reactions of diazomethane (**2**), 2-diazopropane (**3**) and a cyclic nitrone, i.e., 3,4-dihydroisoquinoline-N-oxide (**4**), with the dipolarophiles **1** (Scheme).[7,8] On passing from the reaction of diazomethane with **1a** (X = O, syn:anti = 91:9) to those of the same 1,3-dipole with **1b** (X = NCOPh, syn/anti = 82:28) and **1c** (X = NPh, syn/anti = 48.5:51.5) there was a progressive decrease in syn attack with respect to the dihetero bridge which parallels not only a decrease in electronegativity of the X substituent but also an increase in steric crowding of the syn face. However, all the more remarkable, a clear-cut increase in syn diastereoselectivity was observed when a vinyl hydrogen in **1a-c** was replaced by a methoxycarbonyl group, i.e., in the case of **1d-f**. In fact, not only, as expected, the reactions of diazomethane with **1d-f** were found to be fast and regiospecific but also the reaction of **1d** was 100% diastereoselective and in the case of **1e** and **1f** syn selectivity was at least as high as 90%. Selectivity data for the reactions of 2-diazopropane with compounds **1** fully confirmed the effect of the methoxycarbonyl group, that is, the presence of this group adds a favor of ≥ 0.7 kcal mol^{-1} for the syn attack in the reactions of diazoalkanes with compounds **1**.

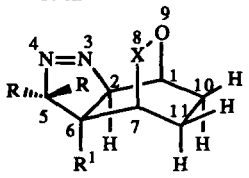


a: R^1 = H, X = O; **d**: R^1 = CO_2Me, X = O;
b: R^1 = H, X = NCOPh; **e**: R^1 = CO_2Me, X = NCOPh;
c: R^1 = H, X = NPh; **f**: R^1 = CO_2Me, X = NPh;

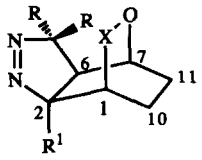
CR_2N_2
2: R = H; **3**: R = Me



ArCNO
5



R = H **6**
R = Me **10**



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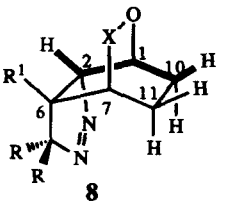

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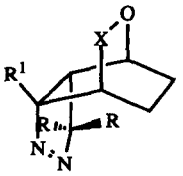

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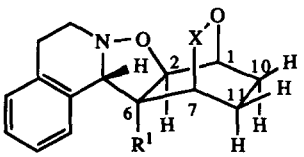

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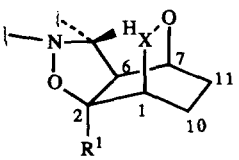

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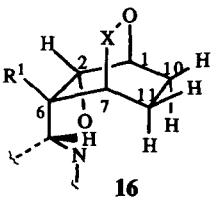

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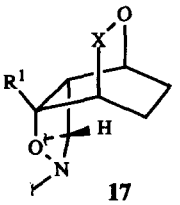

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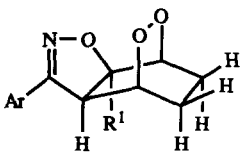

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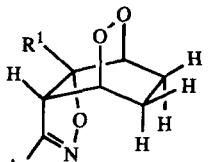
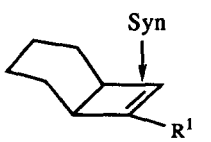


19

	R^1 = H **18:19**	R^1 = CO_2Me **18:19**
Ar = Mes	82:18[a]	≥95:5
Ar = PhCO	64:36[a]	77:23

[a]Ref. 4b



20a: R^1 = H; **20b**: R^1 = CO_2Me

	R^1 = H Anti:Syn	R^1 = CO_2Me Anti:Syn
CH_2N_2	96:4[b]	95:5
PhCOCNO	87:13	86:14
PhCNO	88:12	89:11

[b]Ref. 4a

The effect of the methoxycarbonyl group was found even stronger, i.e., higher than 1.2 kcal mol^{-1}, in the reactions of the highly polar dihydroisoquinoline-N-oxide (**4**). For example, on going from **1c** to **1f** there was an increase in reaction rate and regioselectivity accompanied by a complete reversal of diastereoselectivity: from clearly prevalent anti attack in the case of **1c** (syn/anti = 32:68) to excellent syn selectivity for **1f** (syn/anti = 94.5:5.5). Also t-Bu nitrone exhibited a similar behavior to that of **4**.

Less interesting were the results of the reactions of nitrile oxides **5** with **1a** and **1d** to afford **18** and **19** (Scheme): the observed selectivity enhancement , in particular in the reactions of electron-poor derivatives (e.g., PhCOCNO), was not so dramatic as in the case of diazoalkanes and nitrones.

In contrast to above results, syn/anti ratios in 1,3-dipolar cycloadditions to bicyclo[4.2.0]oct-7-enes **20** were found independent of the presence of a methoxycarbonyl group on the double bond as clearly documented by the facial selectivity data reported in the Scheme and by the fact that only anti adducts were detected and

Table. Syn/anti ratios of the reactions of diazoalkanes and nitrones with dipolarophiles **1** at room temperature.[7]

	Reactions with diazomethane (**2**, R = H)				Total	$\Delta G^{\#}_{anti}-\Delta G^{\#}_{syn}$
Dipolarophile	**6**-(syn)	**7**-(syn)	**8**-(anti)	**9**-(anti)	yield (%)	(kcal mol^{-1})
1a[a]	91		9		82	1.37
1b	55	27	13	5	78	0.85[b], 1.00[c]
1c	28.5	20	35	16.5	95	-0.12[b], 0.11[c]
1d	-	100[d]	-	-	90	>2.5[c]
1e	-	95	-	5	95	1.74[c]
1f	-	90	-	10	95	1.30[c]
	Reactions with 2-diazopropane (**3**, R = Me)					
Dipolarophile	**10**-(syn)	**11**-(syn)	**12**-(anti)	**13**-(anti)		
1a[a]	97.5		2.5		72	2.16
1c	32	34.5	18.5	15	90[e]	0.32[b], 0.49[c]
1d	-	100[d]	-	-	78	>2.5[c]
1f	-	97	-	3	86	2.05[c]
	Reactions with 3,4-dihydroisoquinoline-N-oxide (**4**)					
Dipolarophile	**14**-(syn)	**15**-(syn)	**16**-(anti)	**17**-(anti)		
1a[a]	70		30		29	0.50
1c	21	11	34	34	83	-0.28[b],-0.67[c]
1d	95	f	5	f	90	1.74[b]
1f	92	2.5	5.5	f	83	1.66[b]

[a]Reference 4b [b]For the **6/8**, **10/12** and **14/16** syn/anti pairs. [c]For the **7/9**, **11/13** and **15/17** syn/anti pairs. [d]In the limits of detection of ^{1}H NMR (300 MHz) and TLC analysis. [e]On the reacted **1c**. [f]Not detected.

isolated from the reaction of dihydroisoquinoline-N-oxide and t-Bu nitrone, respectively, with both **20a** and **20b**. Compounds **20** do not contain heteroatoms. This observation strongly suggests that the increase in syn selectivity on going from **1a-c** to **1d-f** is mostly the result of reduction in repulsive electrostatic interactions between the attacking 1,3-dipole and the heteroatoms of **1** which disfavor the syn attack.[1b,c] In fact, the presence of the methoxycarbonyl group should substantially increase the electron accepting character of the double bond with a strengthening of the $HOMO_{1,3\text{-dipole}}$-$LUMO_{dipolarophile}$ interaction. As a result, at the transition state there should be an enhanced electron transfer from the 1,3-dipole to the double bond moiety of the dipolarophile accompanied by a dispersal of this charge on the conjugating and electron attracting group. The resultant reduction in electron density on the 1,3-dipole should leads to a lessening of repulsive coulombic interactions with the high electron density located on the heteroatoms of the dipolarophile. However, the fact that the largest syn selectivity enhancement occurs on going from **1c** to **1f**, i.e., for compounds containing the least electronegative X substituent, clearly demonstrates that other factors should be at work.[9] Thus, we are now computationally testing the above hypothesis as well as the influence of the COOMe group both on the planarity of the double bond[10] in the ground state and on the hyperconjugative interactions, at the TS, between the incipient bonds and the allylic σ bonds.[11] The presence of the methoxycarbonyl group could also alter the trajectory of approach of the 1,3-dipole to the dipolarophile thus changing the relative effect of the steric factors in the two approaches.[4b] To clarify this problem it will also be mandatory to investigate what is the effect of other groups (e.g., Me and OMe).

But, for the time being, we feel that it is very interesting to realize that the presence of electron attracting groups on a double bond of a rigid cyclic olefin can impressively change the stereodirecting power of allylic heteroatoms. Moreover, our results and those by others[2,3] demonstrate that substituents (without stereogenic centers) on a plane nonsymmetric double bond, of both cyclic and acyclic olefins, must be taken into account explicitly (not only for their steric but also for their electronic effects) in the discussion of face selectivity.[12]

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5. Compounds **1** were prepared by reacting 1,3-cyclohexadiene or 2-methoxycarbonyl-1,3-cyclohexadiene with singlet oxygen or nitroso derivatives (PhNO and PhCONO). Unknown **1d** [20% yield, colorless oil; ν_{max} 1710 cm^{-1}; ^1H NMR δ ($CDCl_3$) 1.49 (m, 2 H), 2.34 (m, 2H), 3.82 (s, OMe), 4.82 (m, H-1), 5.23 (m, H-4), 7.51 (dd, H-6, $J_{1,6}$ = 6.3 Hz and $J_{4,6}$ = 1.7 Hz)] and **1f**[6] [85% yield, slightly yellow prisms, mp 49-51 °C; ν_{max} 1715 cm^{-1}; ^1H NMR δ ($CDCl_3$) 1.48 (m, 1 H), 1.60 (m, 1H), 2.32 (m, 2 H), 3.62 (s, OMe), 4.86 (m, H-1), 5.02 (m, H-4), 6.89, 6.98 and 7.18 (1 H, 2 H and 2 H, p, o and m aromatic protons), 7.38 (dd, H-6, $J_{1,6}$ = 6.1 Hz and $J_{4,6}$ = 2.2 Hz); irradiation of ortho protons of the phenyl group gave rise to a significant (6%) NOE enhancement in intensity of H-4); ^{13}C NMR δ ($CDCl_3$) 20.9 (t), 23.3 (t), 51.7 (q), 54.9 (d, C-4), 68.8 (d, C-1), 116.6 (d), 122.2 (d), 128.2 (d), 132.7 (s), 138.4 (d, C-6), 151.1 (s), 163.5 (s)] were fully characterized. In principle, two invertomers are possible for **1b**,**1c**,**1e** and **1f**. However, only one isomer was detected (from -50 to +50 °C, ^1H and ^{13}C NMR) in the case of **1c** and **1f** and two isomers (60:40 in $CDCl_3$ at -50 °C) in the case of **1b** and **1e**. These observations are consistent with the presence of one invertomer and, in the case **1b** and **1e**, of two rotamers about the amidic CON bond.
6. Compound **1f** was the only detected product in the reaction of 2-methoxycarbonyl-1,3-cyclohexadiene with PhNO in contrast to the fact that **1e** was formed as the minor product (rel.yield: 25%) in the reaction of the same diene with PhCONO : Boger, D. L.; Patel, P.; Takusagawa, F. *J. Org. Chem.*, **1985**, *50*, 1911-1916.
7. Diazoalkanes (in ethyl ether, r.t.) and dihydroisoquinoline-N-oxide (in benzene, r.t.) reacted sluggishly with **1a-c** (reactivity order: **1a>1b>1c**) and **20a** but high yields of adducts could be obtained by using excess 1,3-dipole and long reaction times (e.g., 14 days for CH_2N_2 + **1c** and 7 weeks for **4** + **1c**). The reaction of these 1,3-dipoles with **1d-f** and **20b** took place much more rapidly (e.g., less than 2 hours for CH_2N_2 + **1f** and 8 days for **4** + **1f**). As for nitrile oxides, mesitonitrile oxide was reacted as such while PhCOCNO and PhCNO were liberated in situ (benzene, r.t.) with sodium bicarbonate from the corresponding hydroximic acid chloride. All adducts to compounds **1** were, either individually or as a mixture of regioisomers, isolated by column chromatography and a combination of this technique with ^1H and ^{13}C NMR measurements allowed a precise evaluation of isomer ratios. The higher dipole moment of syn adducts led them to exhibit a lower Rf on TLC (eluants: cyclohexane/ethyl acetate mixtures) than their anti counterparts thus providing an apparently rough but very reliable diagnostic tool to assign syn/anti stereochemistry. These assignments were firmly secured mostly on the basis of the following data: i) anti adducts displayed long range W couplings (1.0-2.0 Hz) between H-2 (H-6) and H-10-syn (H-11-syn), which were missing in syn adducts ii) $J_{1,2}$ and $J_{6,7}$ of anti adducts are higher by 1.0-2.0 Hz than related Js in syn adducts iii) irradiation of H-2 in **14d** and **14f** brought about an intensity increase of 5% of H-10-anti and, likewise, irradiation of H-6 in **7d** and **11d** induced a 5-6% NOE effect on H-11-anti iv) a single crystal X-ray analysis of **14d** (B. Bovio, Universita' di Pavia, private communication). Stereochemistry of adducts to compounds **20** was established, as in previous papers, on the basis of higher cis than trans vicinal coupling constants of the cyclobutane protons.[4a]
8. Regiochemistry of adducts also rests firmly on ^1H and ^{13}C NMR and heterocorrelated spectra. Only exo adducts were isolated from the reactions of **4** because endo TSs experience insurmountable steric strains.
9. We thank the referee for stressing this point.
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12. This is not usually done, see Kahn, S. D.; Pau, C. F.; Chamberlin, A. R.; Hehre, W. J. *J. Am. Chem. Soc.*, **1987**, 109, 650-666 and Boger, D. L.; Patel, P. *Tetrahedron Lett.*, **1986**, *27*, 683-686.

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