Stereoselective Nitrile Oxide Cycloadditions to Chiral Allyl Ethers and Alcohols. The "Inside Alkoxy" Effect

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We have studied the stereoselectivities of nitrile oxide cycloadditions to a variety of alkenes substituted by chiral allylic ether and alcohol units.[2-8] The experimental results, combined with theoretical studies, lead us to propose that allylic ethers adopt the *inside* position and alkyl substituents prefer the sterically less crowded anti conformation in transition states for these electrophilic cycloadditions. This "*inside* alkoxy" effect is useful for predicting stereoselectivities of a host of electrophilic reactions with chiral allylic ethers.

The experimental results are given in Table I.[9] Allylic ethers give the erythro product selectively,[3-5] regardless of the nature of the substituent on the allylic oxygen. Selectivity increases as the size of the alkyl group, R, attached to the chiral center, is increased. By contrast, the alcohols give the threo products preferentially but with low selectivity.

We showed earlier that allylic substituents are staggered with respect to forming bonds in cycloaddition transition states.[10-12] Thus, there are three erythro and three threo staggered transition structures for nitrile oxide cycloaddition to chiral allyl ethers. These are drawn in Figure 1. Kozikowski and Ghosh proposed that the allylic alkoxy group should be aligned antiperiplanar to the forming CO bond in the transition state, as shown in B.[3] However, the influence of substituent variations on diastereomer ratios and various computational tests that we have performed indicate that erythro-A is the lowest energy transition state, while threo-A′ is the preferred transition state leading to the minor isomer.

Two types of computational tests were performed. First, ab initio computations were performed on transition-state models for attack of HCNO on 1-butene, allyl alcohol, and an allyl ether

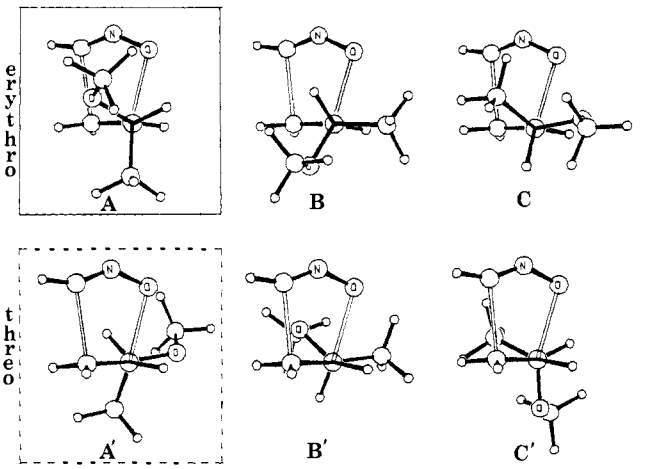
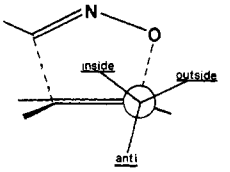


Figure 1. Staggered transition structures for the reaction of a nitrile oxide with 3-methoxy-1-butene. The calculated relative energies of the six transition structures, A, B, C, A′, B′, and C′ are 0, 1.2, 2.8, 0.5, 1.3, and 2.1, respectively, from the MM2 model. STO-3G single-point calculations with standard geometries give relative energies of 0.0, 1.1, 5.4, 0.8, 1.6, and 4.2, respectively. The drawings shown are obtained from the MM2 model. The full rectangle surrounds the preferred transition state for allyl ether reactions, while the dashed rectangle encloses the preferred transition structure for the formation of the minor diastereomer.

model.[13] The ether group was modeled by constraining the CCOH angle of allyl alcohol to 180° in order to mimic the conformation expected for an allyl ether. The relative energies of different transition-state conformers, given below in kcal/mol,



	Me	OH	OR
anti	0.0	4.9	0.7
inside	1.1	0.8	0.0
outside	0.6	0.0	2.9

indicate that a methyl group favors the sterically least crowded *anti* position, OH prefers the *outside* position to maximize hydrogen bonding with the nitrile oxide oxygen, and an ether prefers the *inside* conformation.

MM2 calculations were also used to evaluate the relative energies of the six staggered transition states shown in Figure 1. The HCNO–ethylene fragment was frozen in the ab initio HCNO–ethylene transition-state model geometry,[10,11] and the substituents were fully optimized by MM2. Figure 1 shows the six transition-state models obtained by MM2 calculations for the reaction of HCNO with 3-methoxy-1-butene. These calculations predict an erythro/threo ratio of 68:32, to be compared to the experimental ratio of 64:36 (reaction 3). Computations on transition

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(2) Over 30 nitrile oxide cycloadditions to chiral alkenes have been reported previously. In a few cases, useful diastereoselectivities have been observed.[3-7]

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(9) The adduct ratios from the *p*-nitrobenzonitrile oxide reactions, studied in Pittsburgh, and the benzonitrile oxide reactions, studied in Würzburg, were determined by HPLC and NMR. Reaction 13 was reported previously.[4] Products from reactions 14, 22, 24, and 27 were established by X-ray crystallography at LSU. Chemical interconversions established relationships between adducts from the corresponding alcohol and ether reactions.

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(13) (a) The calculations were performed with the GAUSSIAN 80 programs and the 3-21G basis set. GAUSSIAN 80: Binkley, J. S.; Whiteside, R. A.; Krishnan, R.; Seeger, R.; DeFrees, D. J.; Schleel, H. B.; Topiol, S.; Kahn, L. R.; Pople, J. A. GAUSSIAN 80, QCPE 406, Indiana University, Bloomington, IN. 3-21G: Binkley, J. S.; Pople, J. A.; Hehre, W. J. *J. Am. Chem. Soc.* **1980**, *102*, 939. (b) The fulminic acid–ethylene transition state model described earlier[10,11] was used. One hydrogen at the carbon attacked by the O of fulminic acid was replaced by the substituent, CH_2X, and CH_2X was fully optimized for each staggered conformation.

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(15) A ~1:1 ratio of adducts was also observed in the benzonitrile oxide/3-chlorobutene reaction: Burrowes, T. G.; Jackson, W. R.; Faulks, S.; Sharp, I. *Aust. J. Chem.* **1977**, *30*, 1855.

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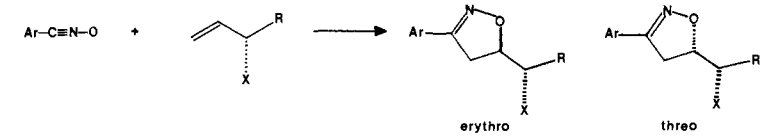
Table I. Experimental Ratios of Diastereomers for Nitrile Oxide Cycloadditions to Chiral Allyl Ethers and Alcohols



reaction	Ar	R	X	erythro[a]/threo	$\Delta\Delta G^{\ddagger}$ [b]
1	Ph	Me	OH	40:60	−0.24
2	*p*-NO_2Ph	Me	OH	45:55	−0.12
3	*p*-NO_2Ph	Me	OMe	64:36	0.34
4	Ph	Me	OCH_2Ph	64:36	0.34
5	Ph	Me	OTHP	63:37	0.31
6	Ph	Me	$OSiMe_3$	71:29	0.53
7	Ph	Me	$OSiMe_2tBu$	72:28	0.56
8	*p*-NO_2Ph	Me	$OSiMe_2Ph$	65:35	0.37
9	Ph	CH_2O		69:31	0.47
10	Ph	CH_2OCMe_2O		85:15	0.94
11	Ph	$CH_2OC(CH_2)_5O$		81:19	0.79
12	Ph	CH_2OCOO		82:18	0.88
13[3]	EtO_2C	CH_2OCMe_2O		80:20	0.82
14	*p*-NO_2Ph	Ph	OH	44:56	−0.14
15	*p*-NO_2Ph	Ph	OMe	67:33	0.42
16	*p*-NO_2Ph	Ph	$OSiMe_3$	69:31	0.47
17	*p*-NO_2Ph	Et	OH	36:64	−0.34
18	*p*-NO_2Ph	Et	$OSiMe_2Ph$	80:20	0.82
19	*p*-NO_2Ph	*i*-Pr	OH	*c*	
20	*p*-NO_2Ph	*i*-Pr	$OSiMe_2Ph$	91:9	1.37
21	*p*-NO_2Ph	*t*-Bu	OH	35:65	0.37
22	*p*-NO_2Ph	*t*-Bu	OMe	>95:5	>1.74
23	*p*-NO_2Ph	*t*-Bu	$OSiMe_3$	>95:5	>1.74
24	*p*-NO_2Ph	Me (+α-Me)	OH	50:50	0
25	*p*-NO_2Ph	Me (+α-Me)	$OSiMe_2Ph$	60:40	0.24
26	*p*-NO_2Ph	Me	Cl	50:50	0
27	*p*-NO_2Ph	Me	Ph	55:45	0.12

[a] *p*-NO_2PhCNO cycloadditions were carried out in CH_2Cl_2 at 25 °C, while PhCNO cycloadditions were performed in ether at 20 °C. All ratios ±4%. [b] $\Delta G^{\ddagger}$(threo) − $\Delta G^{\ddagger}$(erythro) in kcal/mol; *T* is 25 °C for *p*-NO_2PhCNO reactions and 20 °C for PhCNO reactions. [c] Mixture of isomers; ratios not determined.

states for other allylic ether reactions give similarly gratifying results. STO-3G single-point calculations were also carried out on six transition-state models. Here, two allylic hydrogens on the HCNO–propene transition state[10,11] were replaced by standard substituents. As summarized in Figure 1, the energies of A–C′ are in the same order according to both MM2 and STO-3G models.

Thus, theory predicts that the diastereomeric preferences observed in cycloadditions to chiral allyl ethers result from the alkoxy group preference for the *inside* conformation and the alkyl group preference for *anti*. The second best transition state is A′, which leads to the threo product. This conformation permits both R and R′O to rotate slightly to a more relaxed conformation (Figure 1A′), whereas B′ cannot rotate without increases in repulsion of either R or R′O with the nitrile oxide oxygen.

The preference for transition state A is also consistent with the diastereoselectivity as R increases in size: Me, Ph < Et < *i*-Pr < *t*-Bu (cf. reactions 3, 15, 22; 6, 16, 23; 8, 18, 20). As R increases in size beyond CH_3, the preference for A increases over A′; when R is large, the C=CCR dihedral is large and A′ has OR in an unfavorable conformation near the nitrile oxide oxygen and away from the alkene plane. B′ also increases in energy, due to the greater repulsion between R and the nitrile oxide oxygen.

Why does the allylic ether prefer the *inside* conformation in these transition states? In electrophilic attack upon an allylic ether, the π bond becomes electron deficient. Electron-donor substituents on the alkene stabilize the transition state, while electron-withdrawing substituents destabilize the transition state. When the allylic ether is *anti*, the CHROR′ group is electron withdrawing, since the σ^*_{CO} orbital overlaps with, and withdraws electron density from, the alkene π orbital. When CO is *inside*, it is near the plane, and overlap of σ^*_{CO} with π is minimized. Now, overlap of electron-donating σ_{CH} and σ_{CR} orbitals with the π orbital is maximized, and the transition state is stabilized.

This explanation is closely related to conformational preferences observed for allylic ethers. Allyl methyl ether has the allylic CO bond eclipsed with the CC double bond. The eclipsed conformation (∠OCC=C = 0°) is only 0.1 kcal/mol more stable than the gauche (∠OCC=C = 120°).[16] Donor-substituted alkenes (e.g., 2-methoxymethylenecyclohexane) prefer a gauche OCC=C conformation, while electron-withdrawing substituents on the alkene increase the preference for the eclipsed OCC=C conformation.[17]

The preference for allylic ethers to adopt the *inside* conformation should hold generally for electrophilic additions and cycloadditions, unless bulky electrophiles or *cis*-alkene substituents disfavor this conformation. The inside CO preference can also be used to rationalize osmium tetroxide hydroxylations.[18] Iodolactonizations of allylic ethers and alcohols[20a] and iodinations and brominations of allylic alcohols[20] require an attractive interaction of the allylic oxygen and the partially positive halogen on the developing halonium ion.

For cyclic allyl alcohols, hydrogen-bonding stabilization between the incoming nitrile oxide oxygen and the allylic alcohol has been proposed.[6] The relatively low stereoselectivity found in the reactions with acyclic allylic alcohols (see Table I) indicates that hydrogen-bonded conformations related to A′ and A (but with OH hydrogen bonded to the nitrile oxide oxygen) may compete as preferred transition states. While our MM2 model does not

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incorporate hydrogen bonding, we find by ab initio calculations that the *outside* OH position is preferred over the *inside*. The product ratios obtained for reaction 1 are solvent dependent, ranging from a 40:60 ratio in Et_2O to 60:40 in the good hydrogen-bonding acceptor DMF.[4] Hydrogen bonding between the allyl alcohol and the solvent eliminates hydrogen bonding of the reactants in the TS, resulting in ratios nearly identical with those found for the corresponding allyl ether. Threo preferences similar to those found here are observed in peracid epoxidations of allylic alcohols, for which transition structures analogous to A′ (with OH instead of OMe) have been proposed.[21]

Details of these results and computational modeling of related reactions will be reported at a later date.

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Registry No. PhCNO, 873-67-6; *p*-NO_2PhCNO, 2574-03-0; CH_2=CHCH(CH_3)OH, 627-27-0; CH_2=CHCH(CH_3)OMe, 17351-24-5; CH_2=CHCH(CH_3)OCH_2Ph, 53329-00-3; CH_2=CHCH(CH_3)OTHP, 72908-63-5; CH_2=CHCH(CH_3)$OSiMe_3$, 18269-41-5; CH_2=CHCH(CH_3)$OSiMe_2$Bu-*t*, 90270-45-4; CH_2=CHCH(CH_3)$OSiMe_2$Ph, 90270-46-5; CH_2=CHCH(Ph)OH, 4393-06-0; CH_2=CHCH(Ph)OMe, 22665-13-0; CH_2=CHCH(Ph)$OSiMe_3$, 19917-00-1; CH_2=CHCH(CH_2CH_3)OH, 616-25-1; CH_2=CHCH(CH_2CH_3)$OSiMe_2$Ph, 90270-47-6; CH_2=CHCH(*i*-C_3H_7)OH, 4798-45-2; CH_2=CHCH(*i*-C_3H_7)-$OSiMe_2$Ph, 90270-48-7; CH_2=CHCH(*t*-C_4H_9)OH, 24580-44-7; CH_2=CHCH(*t*-C_4H_9)OMe, 36024-28-9; CH_2=CHCH(*t*-C_4H_9)$OSiMe_3$, 90270-49-8; CH_2=C(CH_3)CH(CH_3)OH, 10473-14-0; CH_2=C(CH_3)-CH(CH_3)$OSiMe_2$Ph, 90270-50-1; CH_2=CHCH(CH_3)Cl, 563-52-0; CH_2=CHCH(CH_3)Ph, 934-10-1; vinyloxirane, 930-22-3; 2,2-dimethyl-4-vinyl-1,3-dioxolane, 83968-02-9; 2,2-pentamethylene-4-vinyl-1,3-dioxolane, 62999-51-3; 4-vinyl-1,3-dioxolane-2-one, 4427-96-7; *erythro*-α-methyl-3-phenyl-2-isoxazoline-5-methanol, 90270-51-2; *threo*-α-methyl-3-phenyl-2-isoxazoline-5-methanol, 90270-52-3; *erythro*-α-methyl-3-(*p*-nitrophenyl)-2-isoxazoline-5-methanol, 90270-53-4; *threo*-α-methyl-3-(*p*-nitrophenyl)-2-isoxazoline-5-methanol, 90270-54-5; *erythro*-3-(*p*-nitrophenyl)-5-(1-methoxyethyl)-2-isoxazoline, 90270-55-6; *threo*-3-(*p*-nitrophenyl)-5-(1-methoxyethyl)-2-isoxazoline, 90270-56-7; *erythro*-3-phenyl-5-(1-benzyloxyethyl)-2-isoxazoline, 90270-57-8; *threo*-3-phenyl-5-(1-benzyloxyethyl)-2-isoxazoline, 90270-58-9; *erythro*-3-phenyl-5-[1-(tetrahydropyranyloxy)ethyl]-2-isoxazoline, 90270-59-0; *threo*-3-phenyl-5-[1-(tetrahydropyranyloxy)ethyl]-2-isoxazoline, 90364-62-8; *erythro*-3-phenyl-5-[1-(trimethylsilyloxy)ethyl]-2-isoxazoline, 90270-60-3; *threo*-3-phenyl-5-[1-(trimethylsilyloxy)ethyl]-2-isoxazoline, 90270-61-4; *erythro*-3-phenyl-5-[1-(*tert*-butyldimethylsilyloxy)ethyl]-2-isoxazoline, 90270-62-5; *threo*-3-phenyl-5-[1-(*tert*-butyldimethylsilyloxy)ethyl]-2-isoxazoline, 90270-63-6; *erythro*-3-(*p*-nitrophenyl)-[1-(phenyldimethylsilyloxy)ethyl]-2-isoxazoline, 90270-64-7; *threo*-3-(*p*-nitrophenyl)-[1-(phenyldimethylsilyloxy)ethyl]-2-isoxazoline, 90270-65-8; *erythro*-3-phenyl-5-oxiranyl-2-isoxazoline, 89543-95-3; *threo*-3-phenyl-5-oxiranyl-2-oxazoline, 89543-96-4; *erythro*-3-phenyl-5-(2,2-dimethyl-1,3-dioxolan-4-yl)-2-isoxazoline, 89543-99-7; *threo*-3-phenyl-5-(2,2-dimethyl-1,3-dioxolan-4-yl)-2-isoxazoline, 89544-00-3; *erythro*-3-phenyl-5-(2,2-pentamethylene-1,3-dioxolen-4-yl)-2-isoxazoline, 89544-01-4; *threo*-3-phenyl-5-(2,2-pentamethylene-1,3-dioxolan-4-yl)-2-isoxazoline, 89544-02-5; *erythro*-3-phenyl-5-(2-oxo-1,3-dioxolan-4-yl)-2-isoxazoline, 89544-03-6; *threo*-3-phenyl-5-(2-oxo-1,3-dioxolan-4-yl)-2-isoxazoline, 89544-04-7; ethyl *erythro*-5-(2,2-dimethyl-1,3-dioxolan-4-yl)-2-isoxazoline-3-carboxylate, 90364-63-9; ethyl *threo*-5-(2,2-dimethyl-1,3-dioxolan-4-yl)-2-isoxazoline-3-carboxylate, 90364-64-0; *erythro*-3-(*p*-nitrophenyl)-α-phenyl-2-isoxazoline-5-methanol, 90270-66-9; *threo*-3-(*p*-nitrophenyl)-α-phenyl-2-isoxazoline-5-methanol, 90270-67-0; *erythro*-3-(*p*-nitrophenyl)-5-(methoxyphenylmethyl)-2-isoxazoline, 90270-68-1; *threo*-3-(*p*-nitrophenyl)-5-(methoxyphenylmethyl)-2-isoxazoline, 90270-69-2; *erythro*-3-(*p*-nitrophenyl)-5-[(phenyl)(trimethylsilyloxy)-methyl]-2-isoxazoline, 90270-70-5; *threo*-3-(*p*-nitrophenyl)-5-[(phenyl)(trimethylsilyloxy)methyl]-2-isoxazoline, 90270-71-6; *erythro*-α-ethyl-3-(*p*-nitrophenyl)-2-isoxazoline-5-methanol, 90270-72-7; *threo*-α-ethyl-3-(*p*-nitrophenyl)-2-isoxazoline-5-methanol, 90270-73-8; *erythro*-3-(*p*-nitrophenyl)-5-[1-(phenyldimethylsilyloxy)propyl]-2-isoxazoline, 90270-74-9; *threo*-3-(*p*-nitrophenyl)-5-[1-(phenyldimethylsilyloxy)-propyl]-2-isoxazoline, 90270-75-0; *erythro*-α-isopropyl-3-(*p*-nitrophenyl)-2-isoxazoline-5-methanol, 90270-76-1; *threo*-α-isopropyl-3-(*p*-nitrophenyl)-2-isoxazoline-5-methanol, 90270-77-2; *erythro*-3-(*p*-nitrophenyl)-5-[1-(phenyldimethylsilyloxy)-2-methylpropyl]-2-isoxazoline, 90270-78-3; *threo*-3-(*p*-nitrophenyl)-5-[1-(phenyldimethylsilyloxy)-2-methylpropyl]-2-isoxazoline, 90270-79-4; *erythro*-α-*tert*-butyl-3-(*p*-nitrophenyl)-2-isoxazoline-5-methanol, 90270-80-7; *threo*-α-*tert*-butyl-3-(*p*-nitrophenyl)-2-isoxazoline-5-methanol, 90270-81-8; *erythro*-3-(*p*-nitrophenyl)-5-(1-methoxy-2,2-dimethylpropyl)-2-isoxazoline, 90295-41-3; *threo*-3-(*p*-nitrophenyl)-5-(1-methoxy-2,2-dimethylpropyl)-2-isoxazoline, 90270-82-9; *erythro*-3-(*p*-nitrophenyl)-5-[1-(trimethylsilyloxy)-2,2-dimethylpropyl]-2-isoxazoline, 90270-83-0; *threo*-3-(*p*-nitrophenyl)-5-[1-(trimethylsilyloxy)-2,2-dimethylpropyl]-2-isoxazoline, 90270-84-1; *erythro*-α,5-dimethyl-3-(*p*-nitrophenyl)-2-isoxazoline-5-methanol, 90270-85-2; *threo*-α,5-dimethyl-3-(*p*-nitrophenyl)-2-isoxazoline-5-methanol, 90270-86-3; *erythro*-5-methyl-3-(*p*-nitrophenyl)-5-[1-(phenyldimethylsilyloxy)ethyl]-2-isoxazoline, 90270-87-4; *threo*-5-methyl-3-(*p*-nitrophenyl)-5-[1-(phenyldimethylsilyloxy)ethyl]-2-isoxazoline, 90270-88-5; *erythro*-3-(*p*-nitrophenyl)-5-(1-chloroethyl)-2-isoxazoline, 90270-89-6; *threo*-3-(*p*-nitrophenyl)-5-(1-chloroethyl)-2-isoxazoline, 90270-90-9; *erythro*-3-(*p*-nitrophenyl)-5-(1-phenylethyl)-2-isoxazoline, 90270-91-0; *threo*-3-(*p*-nitrophenyl)-5-(1-phenylethyl)-2-isoxazoline, 90270-92-1.

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"Even" Regioselectivity in [6 + 4] Cycloadditions of Unsymmetrical Tropones with Dienes

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The regioselectivity of [4 + 2] cycloadditions can be rationalized by frontier molecular orbital (FMO) theory. The major adduct is that which arises from maximum overlap of the FMOs of the two addends.[2-4] Alston et al. suggested that secondary FMO interactions, rather than primary FMO interactions, control regioselectivity in some cases.[5] This conclusion remains controversial.[6,7] We have now found that the [6 + 4] cycloadditions of unsymmetrically substituted tropones with unsymmetrical dienes proceed with high regioselectivity; the exo stereoselectivities of these reactions preclude secondary orbital interactions between π centers that do not become bonded in the product. These results

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