

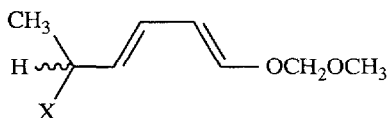
**DIELS-ALDER REACTIONS OF ACYCLIC CHIRAL ALKOXY DIENES:
 OXYGEN VERSUS SULFUR AS AN ALLYLIC DIRECTING GROUP**

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Summary: Facial selectivity in the Diels-Alder reaction of homochiral dienes **1** and **2** was probed using three dienophiles: *N*-phenylmaleimide (**5a**), benzoquinone (**5b**) and 4-phenyl-1,2,4-triazoline-3,5-dione (**5c**).

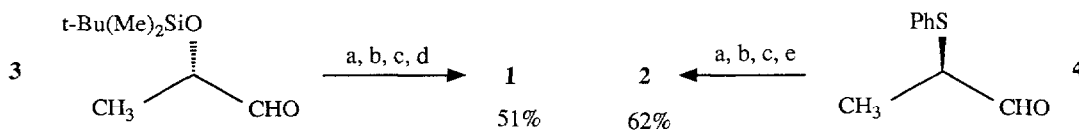
The ability of heteroatoms to control the addition of reagents to the π -face of olefins and carbonyls has been well utilized in the context of asymmetric synthesis.¹ One variation on this general theme, namely the Diels-Alder reaction of dienes containing heteroatoms at a chiral allylic carbon has attracted considerable attention in recent years.² In an effort to uncover the factors which influence facial selectivity in these reactions we have begun to probe the facial selectivity of some simple acyclic alkoxy dienes which contain chiral allylic carbons. The dienes **1** and **2** reported in this communication were designed with two purposes in mind. First, we wished to establish the effect of changing the 'directing' heteroatom from oxygen, as in diene **1**, to sulfur as in diene **2**. Fallis has reported



- 1** X = OSi(Me)₂t-Bu
 (*S*-enantiomer)
2 X = SPh
 (*R*-enantiomer)

that such a switch in 5-substituted-cyclopentadienes completely reversed the sense of the facial selectivity.^{2c} Our results indicate a similar but less dramatic switch is observed between the acyclic dienes **1** and **2**. Second, we wanted to establish whether the nature of the substituent at the 1-position had an effect on the facial selectivity. Although quite remote from the stereogenic center one could envision that the 1-substituent, via its effect on the relative size of molecular orbitals, might cant the transition state in such a way as to influence facial selectivity. As will be seen the nature of the substituent at C-1 does influence facial selectivity.

The requisite dienes **1** and **2** were prepared from the corresponding homochiral aldehydes **3**^{3a} and **4**.^{3b} Our recently reported four-step procedure for the elaboration of aldehydes to *E,E*-4-substituted-1-alkoxy-1,3-butadienes was utilized.⁴ The key base-catalyzed 1,4-elimination proceeded to give the *E,E*-diene in 95% isomeric purity. In



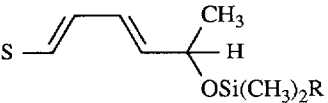
Reagents: (a) LiC≡CCH₂OMOM, THF, -78°; (B) NaH, CH₃I, THF, 25°; (c) H₂, Pd/C, pyridine, hexane; (d) LDA, THF, -50°, 6h; (e) LiTMP, THF, -50°, 6h.

the sulfur series (**4-2**, step c) lithium tetramethylpiperide (LiTMP) was required for the elimination step. The optical purity of diene **1** ($[\alpha]_D = +21.1$ ($c=1.0$, CCl_4)) was checked by reduction of the olefins (H_2 , Pd/C), desilylation of the secondary alcohol and conversion into a Mosher's ester derivative. Comparison of the ^1H NMR spectra with a Mosher derivative derived from racemic material showed it to be >95% optically pure. The optical purity of diene **2** ($[\alpha]_D = +3.2$ ($c=1.0$, CCl_4)) has not been checked.

The Diels-Alder reaction of dienes such as **1** and **2** can lead to two face isomers designated as *lk* and *ul* (see Table 1).⁵ It should be noted that regardless of the absolute configuration of our starting homochiral dienes, products with the same stereochemical descriptor (i.e. *lk* or *ul*) arise from reactions with the same relative reaction topology. In this study the facial selectivity was probed with three dienophiles: N-phenylmaleimide (**5a**: Y = C, Z = N-Ph), benzoquinone (**5b**: Y = C, Z = -CH=CH-) and 4-phenyl-1,2,4-triazoline-3,5-dione (**5c**: Y = N, Z = N-Ph). The results of these reactions along with the exact reaction conditions are shown in Table 1.⁶ In general the isolated yields of cycloadducts are good except in cases of prolonged heating where decomposition of **1** and **2** to sorbaldehyde decreases the yield.

TABLE 1: Face Selectivity of Dienes 1 and 2 with Dienophiles 5a-c . ⁶			
<p>For 1, X = OSi(Me)₂t-Bu (<i>S</i>) $\xrightarrow{\hspace{2cm}}$ <i>lk</i> For 2, X = SPh (<i>R</i>) $\xrightarrow{\hspace{2cm}}$ <i>ul</i></p>			
Diene	N-phenylmaleimide (5a) <i>lk:ul</i> (yield)	benzoquinone (5b) <i>lk:ul</i> (yield)	4-phenyl-1,2,4-triazoline-1,3-dione (5c) <i>lk:ul</i> (yield)
1	> 95:5 (67%) toluene, 25°, 48 h	75:25 (58%) toluene, 80°, 24 h	45:55 (82%) THF, 25°, 2 h
2	60:40 (87%) ^a toluene, 25°, 8 days	45:55 (24%) toluene, 80°, 70 h	20:80 (82%) THF, 25°, 0.5 h
^a Stereochemical assignment uncertain, see ft 6.			

The data in Table 1 in conjunction with other published data allow a number of useful trends to be recognized. First, as noted by others,^{2,7} facial selectivity is highly dependent on the nature of the dienophile with maleimides and maleic anhydride being more *lk* selective than azo or acetylenic^{2d} dienophiles. Second, placing electron-donating substituents at the 1-position increases the *lk* selectivity. This statement is supported by the data presented in Table 2 and is valid for both N-phenylmaleimide and the triazodione **5c**. While it might be argued that an electron-donating substituent at C-1 cants the transition state toward the stereogenic center,⁸ it is not obvious why this should lead to increased *lk*-selectivity. In the past we,^{2f} as well as others,^{9,2a,b,d} have discussed facial selectivity in terms of the reactive conformers **a** and **b** shown in Figure 1. The observed trend in facial selectivity could reflect an increase in the stabilization of conformer **b** as the dienyl substituent (*S*) becomes more electron-donating. Specifically when *S* equals oxygen the X substituent can be thought to be bisvinylogously anomeric with the oxygen. Such a relationship

TABLE 2: Effect of Diene Substituents on Facial Selectivity		
DIENE	DIENOPHILE	
	N-Phenylmaleimide (5a) (solvent = benzene) <i>lk</i> : <i>ul</i>	4-phenyl-1,2,4-triazoline-1,3-dione (5c) (solvent = THF) <i>lk</i> : <i>ul</i>
S = H (6) ^a	3.5 : 1 ^c	
S = CH ₃ (7) ^a	7.3 : 1 ^c	1 : 5.5 ^c
S = OCH ₂ OCH ₃ (1) ^b	> 20 : 1 ^d	1 : 1.2 ^d
^a R = CH ₃ ; ^b R = <i>t</i> -Bu; ^c ref 2b; ^d this work - see Table 1.		

has been shown to influence conformational preferences in related systems¹⁰ and the term vinylogous anomeric effect^{10c} has been used in this context.¹¹ Finally it can be seen that changing the allylic heteroatom from oxygen to sulfur results in an increase in the *ul* product for all three dienophiles. This change, while not as dramatic, is identical to that observed in the cyclopentadienyl system.^{2c} We would suggest that a possible explanation of this phenomena is that when the heteroatom X is a good σ donor it occupies the perpendicular position in order to donate its electron-density to the LUMO of the transition state.^{9c} Consequently when X is a sulfur atom conformer **c** in Figure 1 becomes a viable transition state structure leading to *ul* product.

We have briefly explored the effect of Lewis acid catalysts and pressure on the facial selectivity of diene **1** reacting with benzoquinone (**5b**). The diene undergoes facile decomposition to sorbaldehyde in the presence of most Lewis acids so that only ZrCl₄ (toluene, -78°) gave useful yields of Diels-Alder product. In this instance the facial selectivity fell to 1.2:1 in favor of the *lk*-isomer. Preabsorbing the benzoquinone onto silica gel gave the expected¹² increase in the rate of the reaction (-78°, 11 h) but with no change in the 3:1 facial selectivity seen in Table 1. Similarly the use of high pressure (5.2 kbar) had no effect on facial selectivity.

It would seem from our results and those already in the literature that there are numerous factors, most notably the nature of the dienophile, which influence the facial selectivity of dienes containing chiral allylic carbons. Consequently the use of these systems in future synthetic endeavors will necessitate the careful matching of diene and dienophile to achieve the desired sense and degree of diastereoselectivity.

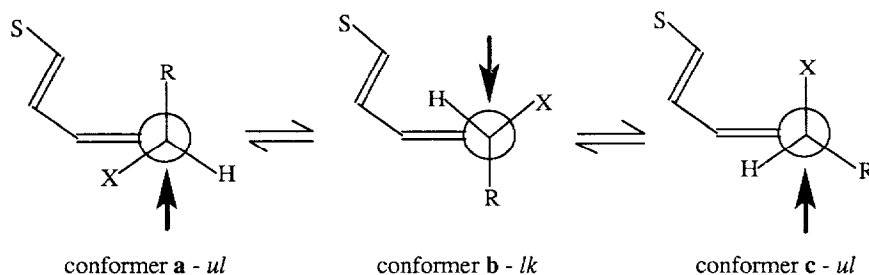


FIGURE 1

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References and Notes

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- The ratio of stereoisomers has been determined from the integration of the NMR spectra (300 MHz). The assignment of stereochemistry for the various Diels-Alder adducts is as follows: **1+5a**-analogy to previous results (see ref 2a and 3); **1+5b**- ^1H NMR spectroscopy shows a significant shielding (~ 0.2 ppm) of the X group in one stereoisomer and the methyl group in the other stereoisomer due to their proximity to the carbonyl group. Since the sidechain prefers a conformation in which the hydrogen on the sidechain is *antiperiplanar* to the hydrogen on the cyclohexane ring ($J = 10.5$ Hz) the relative stereochemistry can be assigned; **1+5c**-X-ray structure of the *ul* stereoisomer; **2+5a**-not certain but so close to 50:50 that it does not effect our conclusions; **2+5b**-same type of ^1H NMR difference as described for **1+5b**; **2+5c**-based on the similarities between the ^1H NMR spectra for this pair of diastereomers and that from **1+5c** where an X-ray structure distinguished *lk* from *ul*.
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- In MO terms one can rationalize this effect by inspecting the stabilizing two-electron interaction of the C-X σ^* orbital and the dienyl π orbital. As the energy of the dienyl HOMO is raised, i.e. it becomes more electron-rich, its stabilizing interaction with the C-X σ^* is enhanced thereby favoring conformations which maximize overlap between the two orbitals.
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