Secondary Orbital Interactions Determining Regioselectivity in the Diels-Alder Reaction. 5. Thio-Substituted 1,3-Butadienes

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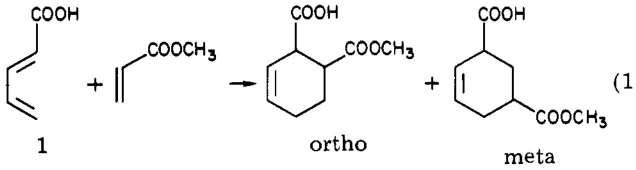
The Diels-Alder regioselectivities of thio-substituted 1,3-butadienes under thermal and catalyzed conditions have been explained by using primary and secondary interactions of the frontier molecular orbitals. The effect of the electron-donating character of the substituents on regioselectivity was accounted for. The LUMO(diene)-HOMO(dienophile) interaction was found to influence the regioselectivity of several of these normal-electron-demand reactions. For 1-(phenylthio)-2-methoxy-1,3-butadiene, the correct regioisomer is favored by the theory only when the secondary interactions are considered.

Frontier molecular orbital (FMO) theory has been highly successful in explaining the regioselectivity of the Diels-Alder reaction. Most investigators[2-5] have used an FMO approach in which the regioselectivity is predicted from the primary interactions of the frontier molecular orbitals. However, there are numerous cases which involve 1,2-disubstituted dienes for which this approach fails. We have shown that these discrepancies are eliminated when the secondary interactions of the FMOs are included.[6]

A comparison of the regioisomer ratios in the endo and exo modes of cycloaddition has provided experimental evidence which supports the contribution of these secondary interactions to the regioselectivity of the Diels-Alder reaction. Fleming et al.[7] found that the primary and secondary interactions contributed equally to the regioselectivity of *trans*-penta-2,4-dienoic acid (1) and methyl acrylate in the endo addition (eq 1). In this case the ortho regioisomer was preferred in both stereochemical modes of addition; however, the ortho/meta ratio was substantially greater in the endo addition (6.7:1) than in the exo addition (2.8:1). Similarly, we found greater regioselectivity in the endo addition (11:1) than in the exo (3.4:1) for the reaction of 1-(phenylthio)-2-methoxy-1,3-butadiene (**2**) with acrylonitrile (eq 2).[6c]



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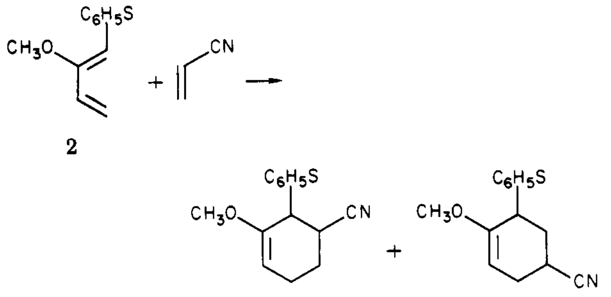

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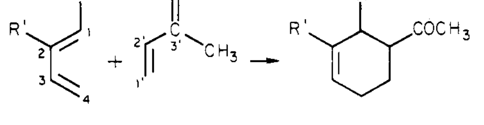
In this paper we have used FMO theory including secondary orbital interactions, to explain the Diels-Alder regioselectivity of various thio-substituted 1,3-butadienes under thermal and Lewis acid catalyzed conditions. A previous investigation[8] was unable to rationalize the regioselectivity in many of these cases from MINDO/3 FMOs. Another critical test of primary vs. secondary orbital control is presented in the Lewis acid catalyzed addition of **2** to methyl vinyl ketone.

Theory



(3)

The FMO approach is derived from the second-order perturbation equation for the energy change which accompanies the orbital interactions of two molecules involved in a cycloaddition reaction[9,10] (eq 3). The perturbation equation simplifies into eq 4 for the FMO ap-

$$\Delta E = \frac{2[C_1C_{2'}\gamma_{cc} + C_4C_{1'}\gamma_{cc} + C_2C_{3'}\gamma'_{cc}]^2}{E_{HOMO} - E'_{LUMO}} - \frac{2[C_1C_{2'}\gamma_{cc} + C_4C_{1'}\gamma_{cc} + C_2C_{3'}\gamma'_{cc}]^2}{E_{LUMO} - E'_{HOMO}} \quad (4)$$

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[1] (a) Du Pont, Textile Fibers Department. (b) Du Pont, Chemical and Pigments Department. (c) Virginia Commonwealth University. (d) University of Pittsburgh.

[2] I. Fleming, "Frontier Orbitals and Organic Chemical Reactions", Wiley, New York, 1976.

[3] N. D. Epiotis, *J. Am. Chem. Soc.*, **95**, 5624 (1973).

[4] K. N. Houk, *Acc. Chem. Res.*, **8**, 361 (1975), and references cited therein.

[5] O. Eisentein, J. M. Lefour, N. T. Anh, and R. F. Hudson, *Tetrahedron*, **33**, 523 (1977), and references cited therein.

[6] (a) P. V. Alston and R. M. Ottenbrite, *J. Org. Chem.*, **40**, 1111 (1975); (b) P. V. Alston, R. M. Ottenbrite, and T. Cohen, *ibid.*, **43**, 1864 (1978), and references cited therein; (c) T. Cohen, R. J. Ruffner, D. W. Shull, W. M. Daniewski, R. M. Ottenbrite, and P. V. Alston, *ibid.*, **43**, 4052 (1978).

[7] I. Fleming, J. P. Michael, L. E. Overman, and G. F. Taylor, *Tetrahedron Lett.*, 1313 (1978). In this investigation the stereoisomer favored by the secondary orbital interactions was not preferred in the reaction of 1-methoxycyclohexa-1,3-diene and fumaroyl chloride. Kushima [*Can. J. Chem.*, **57**, 2564 (1979)] has shown that closed-shell repulsion apparently overcomes the secondary orbital interactions in this case. When 1-methoxy-1,3-butadiene is reacted, the stereoisomer favored by the secondary orbital interactions is preferred because the difference between the secondary orbital coefficients is large and overcomes the closed-shell repulsion.

[8] B. M. Trost, W. C. Vladuchick, and A. J. Bridges, *J. Am. Chem. Soc.*, **102**, 3554 (1980).

[9] R. Sustmann, *Pure Appl. Chem.*, **40**, 569 (1974).

[10] W. C. Herndon, *Chem. Rev.*, **72**, 157 (1972).

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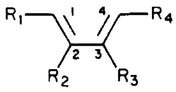
Table I. Highest Occupied Molecular Orbitals



compd	substituents				MO method	HOMO coefficients				HOMO, eV
	R_1	R_2	R_3	R_4		C-1	C-2	C-3	C-4	
2	C_6H_5S	CH_3O	H	H	CNDO/2	−0.296	−0.300	0.094	0.231	−9.94
					PPP	−0.485	−0.399	0.098	0.326	−8.09
5	H	CH_3O	C_6H_5S	H	CNDO/2	−0.079	−0.039	0.140	0.329	−10.50
					PPP	−0.487	−0.237	0.238	0.515	−8.69
8	H	CH_3COO	p-HOC_6H_4S	H	PPP	−0.196	−0.086	0.182	0.424	−8.57
11	CH_3COO	H	H	C_6H_5S	PPP	−0.412	−0.316	0.376	0.385	−8.61
14	H	CH_3O	p-HOC_6H_4S	H	PPP	−0.278	−0.118	0.187	0.444	−8.55
15	H	CH_3O	p-$CHOC_6H_4S$	H	PPP	−0.542	−0.274	0.235	0.505	−8.85
16	H	CH_3O	$C_4H_3N_2S$	H	PPP	−0.589	−0.301	0.245	0.499	−8.71

proach. In this expression, the E' values are the FMO energies of the dienophile, the E values are the FMO energies of the diene, the C values are the frontier orbital coefficients of the diene and the dienophile, and the γ_{cc} values are the transition-state resonance integrals for carbon p orbitals.

The Diels–Alder reaction has been classified into three general types depending on the HOMO–LUMO arrangement of the diene and dienophile.[9] The normal-electron-demand reaction is controlled by the HOMO (diene)–LUMO (dienophile) interaction, while the inverse-electron-demand reaction is controlled by the HOMO (dienophile)–LUMO (diene) interaction. Both FMO interactions significantly affect regioselectivity in the neutral-electron-demand case. In this study, all of the Diels–Alder reactions have normal electron demand; thus, their regioselectivity should originate from the HOMO (diene)–LUMO (dienophile) interaction. However, the theoretical calculations indicate that the HOMO(dienophile)–LUMO(diene) interaction has a major effect on the thermal regioselectivities of some of the thio-substituted butadienes. In these cases, the selectivity of the diene HOMO is small (similar coefficients), and the selectivity of the diene LUMO is large (substantially different coefficients).

The effect of Lewis acid catalysis on the FMO's of the dienophile has been established:[11,12] (1) substantial lowering of the FMO energies, (2) larger secondary LUMO coefficient ($C_{3'}$), and (3) larger difference between the primary LUMO coefficients. With these changes, a transition state completely dominated by the HOMO(diene)–LUMO(dienophile) interaction and having enhanced secondary orbital interactions is predicted for the catalyzed Diels–Alder reaction. Previously, we have explained[6a] the different regioselectivities of thermal and catalyzed reactions without considering the LUMO of diene; however, the theoretical calculations indicate that this MO has a major effect on the thermal regioselectivities of some of the thio-substituted butadienes. In these cases, the elimination of the diene LUMO's contribution to regioselectivity with catalysis must also be considered.

The frontier molecular orbitals were determined by the CNDO/2[13] and PPP methods.[14-17] The molecular geometries used in the MO calculations were calculated from standard bond angles and bond lengths[13] except for the sulfur–carbon bond which was assigned a value[18] of 1.75 Å. Reasonable changes in these bond angles and bond lengths did not affect the interpretations.

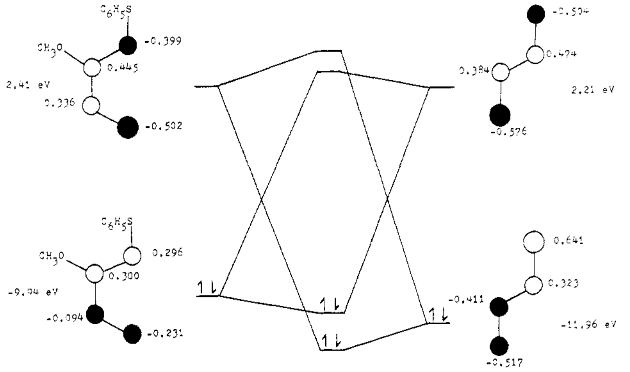
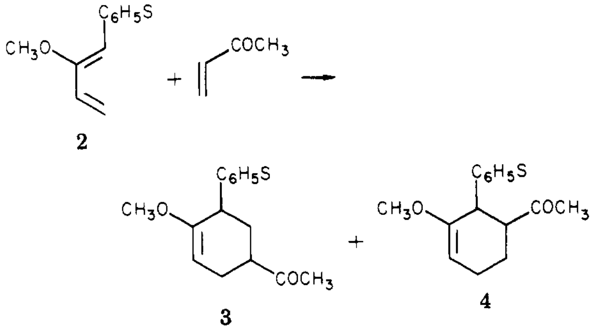


Figure 1. CNDO/2 frontier molecular orbital interaction diagram for the Diels–Alder reaction between 1-(phenylthio)-2-methoxy-1,3-butadiene and methyl vinyl ketone.

Discussion

The primary HOMO coefficients of 1-(phenylthio)-2-methoxy-1,3-butadiene (**2**) favor regioisomer **3** (eq 5) while the secondary HOMO coefficients favor regioisomer **4** (Table I). However, the difference between the secondary HOMO coefficients is much larger than the difference between the primary HOMO coefficients; thus, the secondary coefficients are predicted to control the regioselectivity. Since Lewis acid catalysis strengthens the secondary interactions, an increase in selectivity with catalysis is predicted vs. the thermal reaction. In agreement with



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[11] N. T. Anh and J. Seyden-Penne, *Tetrahedron*, **29**, 3259 (1973).

[12] K. N. Houk and R. W. Strozier, *J. Am. Chem. Soc.*, **95**, 4094 (1973).

[13] CNDO/2 method: J. A. Pople and D. L. Beveridge, "Approximate Molecular Orbital Theory", McGraw-Hill, New York, 1970.

[14] Standard PPP π-electron parameters were used[15a,16,17] Calculational details have been published.[15]

[15] (a) M. D. Gordon and J. F. Neumer, *J. Phys. Chem.*, **78**, 1868 (1974). (b) M. D. Gordon, *Tetrahedron*, **36**, 2113 (1980).

[16] A. I. Kiss, M. Kertesz, P. Carsky, and H. Wedel, *Tetrahedron*, **35**, 515 (1979).

[17] M. Witanowski, L. Stefaniak, H. Januszewski, and G. A. Webb, *Tetrahedron*, **27**, 3129 (1971).

[18] W. R. Blackmore and S. C. Abrahams, *Acta Crystallogr.*, **8**, 323 (1955).

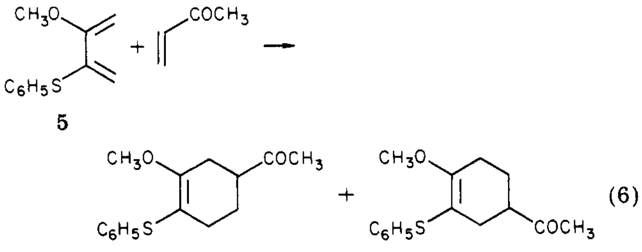
Table II. Lowest Unoccupied Molecular Orbitals[a]

compd	substituents				MO method	LUMO coefficients				LUMO, eV
	R_1	R_2	R_3	R_4		C-1	C-2	C-3	C-4	
2	C_6H_5S	CH_3O	H	H	CNDO/2	−0.399	0.445	0.336	−0.502	2.41
					PPP	−0.472	0.309	0.437	−0.575	−1.14
5	H	CH_3O	C_6H_5S	H	CNDO/2	−0.431	0.323	0.415	−0.615	2.18
					PPP	−0.471	0.325	0.428	−0.569	−1.13
8	H	CH_3COO	p-HOC_6H_4S	H	PPP	−0.564	0.367	0.377	−0.533	−1.27
11	CH_3COO	H	H	C_6H_5S	PPP	−0.503	0.339	0.349	−0.509	−1.58
14	H	CH_3O	p-HOC_6H_4S	H	PPP	−0.498	0.351	0.440	−0.584	−1.01
15	H	CH_3O	p-$CHOC_6H_4S$	H	PPP	−0.507	0.356	0.447	−0.581	−1.18
16	H	CH_3O	$C_4H_3N_2S$	H	PPP	−0.418	0.283	0.391	−0.533	−1.34

[a] See the structure in Table I for the numbering scheme.

the theory, only regioisomer **4** was observed in both the thermal and catalyzed reactions.[19] If both the HOMO and LUMO interactions are considered, the incorrect regioisomer is still favored by the primary interactions in this case. The primary LUMO coefficients favor the preferred regioisomer; however, the difference between the coefficients is not large enough to control the regioselectivity (Figure 1). As further support for secondary orbital control, this reaction and several other acid-catalyzed additions of alkyl-substituted analogues of **2** with methyl vinyl ketone and 2-cyclohexen-1-one, which also occur with complete regiospecificity in the same sense, proceed with complete endo stereospecificity.[19]

Diene **5**, which has the phenylthio and methoxy groups in the chemically equivalent 2,3-positions, also yielded regioselectivity controlled by the phenylthio substituent; however, the selectivity was less under catalyzed than thermal conditions.[8,20] This experimental difference in the regioselectivity between 1,2 and 2,3 substitution is predicted by the FMO treatment. The primary HOMO coefficients of 2-methoxy-3-(phenylthio)-1,3-butadiene (**5**) favor the preferred regioisomer **6** (eq 6), and their difference is larger than the difference between the secondary HOMO coefficients (Table I). However, the directing strength of HOMO is small;[21] thus, the effect of the diene LUMO on regioselectivity must also be considered. The LUMO of the diene strongly reinforces the selectivity of HOMO and is the major factor because of the large difference between its primary coefficients (Table II). Since the LUMO(diene)–HOMO(dienophile) interaction is unimportant with catalysis, a decrease in regioselectivity is predicted for the catalyzed reaction. Experimentally, the regioisomer ratio decreased from 4:1 under thermal conditions to 1.5:1 under catalyzed conditions.[20]



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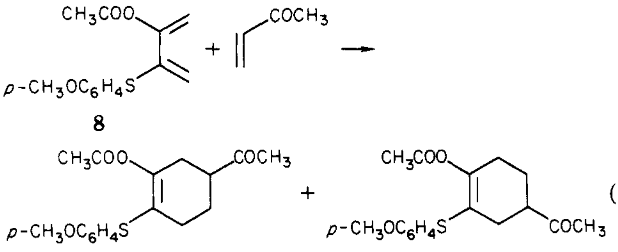
(6)

6 **7**

The difference between the primary HOMO coefficients was increased in the 2,3-substitution case when the methoxy group was replaced with the weaker electron-donating acetoxy group and the phenylthio group strengthened by p-methoxy substitution (diene **8**). In this case the theory predicts that the primary HOMO coefficients will control the regioselectivity because of their large difference (0.23). Thus, regioisomer **9** is predicted to be preferred, and an increase in regioselectivity with catalysis is expected. Consistent with this interpretation, regioisomer **9** (eq 7) is preferred in the thermal reaction by 13:1 and in the catalyzed reaction by 50:1.[8,20]



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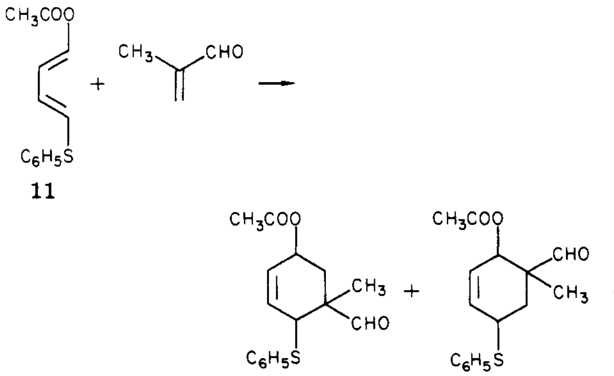
(7)

9 **10**

Diene **11**, which has the phenylthio and acetoxy groups at the chemically equivalent 1,4-positions, exhibited regioselectivity controlled by the phenylthio group. In this case the differences between the primary coefficients and also between the secondary coefficients were small; however, both interactions favored regioisomer **12** (eq 8). Thus, the theory favors regioisomer **12** and predicts an increase in regioselectivity with catalysis because of the additive effects of the primary and secondary interactions. The LUMO of the diene is nonselective with respect to the two regioisomers in this case. Experimentally, regioisomer **12** was preferred 15:1 in the thermal reaction, and this



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(8)

12 **13**

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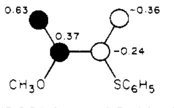
(19) T. Cohen and Z. Kosarych, *J. Org. Chem.*, **47**, 4005 (1982).

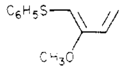
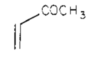
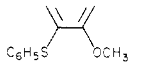
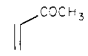
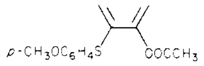
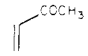
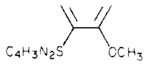
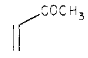
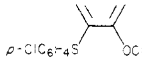
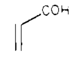
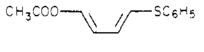
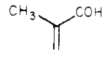
(20) B. M. Trost and A. J. Bridges, *J. Am. Chem. Soc.*, **98**, 5017 (1976).

(21) The PPP method predicts that the difference between the primary HOMO coefficients is only 0.028 while the CNDO/2 predicts a difference of 0.25. The CNDO/2 MO calculation has a π MO just below the HOMO which favors methoxy control of the regioselectivity. The CNDO/2 calculations also predict a small selectivity when this occupied MO is considered with the HOMO.



NHOMO = −12.41 eV

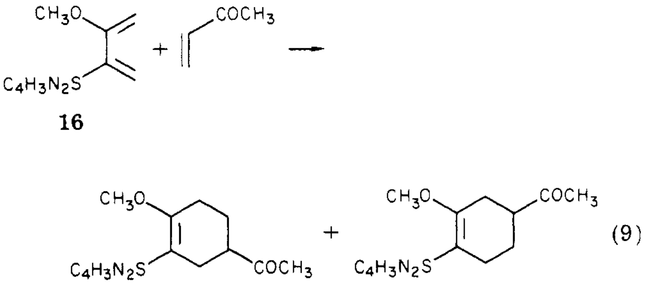
Table III. FMO Predictions of Regioselectivity

		exptl regioisomer ratios, meta:para to methoxy/acetoxy			FMO predictions[d]	
diene	dienophile	thermal	catalyzed	ref	thermal	catalyzed
		100:0	100:0	*a*	meta preferred	meta preferred/increased selectivity
		4:1	1.5:1	*b*	meta preferred	meta preferred/lower selectivity
		13:1	50:1	*b*	meta preferred	meta preferred/increased selectivity
		1:1.3	1:8	*b*	para preferred	para preferred/increased selectivity
		1.5:1	1:1.5	*b*	meta preferred	para preferred
		15:1[e]	20:1[e]	*c*	meta preferred	meta preferred/increased selectivity

[a] Reference 19. [b] Reference 8. [c] Reference 22. [d] Both FMO interactions are considered. [e] Meta/ortho.

preference increased to 20:1 with catalysis.[22]

The effect of the electron-donating character of the phenylthio group on the FMO coefficients was determined for the 2-methoxy-3-(phenylthio)-1,3-butadiene case (Tables I and II). An increase in electron donation by para substitution of a hydroxyl group on the ring (**14**) increased the difference between the primary HOMO coefficients without an appreciable change in the primary LUMO coefficients. A reduction in electron donation through para substitution of a CHO group on the ring (**15**) or replacement of the phenyl moiety with a pyrimidyl group (**16**) reversed the primary HOMO coefficients and only slightly changed the difference between the primary LUMO coefficients. Thus, enhanced phenylthio control is predicted in the former case and reduced phenylthio control in the latter case. In agreement with the theory, the regioselectivity of 2-methoxy-3-(2-pyrimidylthio)-1,3-butadiene (**16**) was controlled by the methoxy group for both the thermal and catalyzed reactions. However, the preference for regioisomer **17** (eq 9) was small (1.3:1)[8] because



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17

18

(9)

the LUMO of the diene which favors regioisomer **18** makes a significant contribution to the regioselectivity. Since the diene LUMO is unimportant in catalyzed reactions, a substantial increase in the preference for regioisomer **17** is predicted for the catalyzed case. In agreement with the theory, the regioisomer ratio increased to 8:1 under catalyzed conditions.[8]

An intermediate case, 2-methoxy-3-[(*p*-chlorophenyl)thio]-1,3-butadiene, exhibited regiochemistry controlled by the phenylthio group under thermal conditions and by the methoxy group under catalyzed conditions.[8] These results are consistent with the FMO treatment. The theory predicts that the diene LUMO is the origin of the phenylthio control in the thermal reaction because the difference between the primary LUMO coefficients is much larger than the difference between the primary HOMO coefficients.[23] Reversal of the thermal regioselectivity is predicted by the theory for the catalyzed reaction since the diene HOMO controls the regiochemistry.

Conclusion

The Diels–Alder regioselectivity of various thio-substituted 1,3-butadienes under thermal and catalyzed conditions can be rationalized from the FMOs of the reactants when both primary and secondary orbital interactions are considered. The predictions of the theory are summarized in Table III. If only the primary orbital interactions are considered, the incorrect regioisomer is favored by the theory for 1-(phenylthio)-2-methoxy-1,3-butadiene. The differing effects of Lewis acid catalysis on the regioselectivities of 1-(phenylthio)-2-methoxy-1,3-butadiene and 2-methoxy-3-(phenylthio)-1,3-butadiene is attributed to secondary orbital control of the regioselectivity for the former.

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Registry No. (*Z*)-**2**, 60466-66-2; **5**, 60603-16-9; **8**, 65174-13-2; (*E,E*)-**11**, 67700-05-4; **14**, 87517-42-8; **15**, 87517-43-9; **16**, 74851-98-2; $H_2C{=}C(SC_6H_4\text{-}p\text{-}Cl)CH(OCH){=}CH_2$, 74851-97-1; $H_2C{=}CHCOCH_3$, 78-94-4; $H_2C{=}CHCOH$, 107-02-8; $H_2C{=}C(CH_3)COH$, 78-85-3.

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[22] B. M. Trost, J. Ippen, W. C. Vladuchick, *J. Am. Chem. Soc.*, **99**, 8116 (1977).

[23] PPP parameters are not available for the chloro substituent. The CHO group has similar electron character; thus, its FMO's were used to make the prediction.