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; 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*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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Table I. Products of Cycloadditions of Unsymmetrical Tropones to Dienes

tropone substituent	diene	reaction conditions	products[a]	[6 + 4] regioselectivity
3-CO_2Et	isoprene	110 °C/PhH/15 h	38% **3**	even
	piperylene	120 °C/PhH/16 h	21% **1** + 3% **9a**	even
	1-acetoxybutadiene	110 °C/PhMe/16 h	20% **1** + 10% **9**[b]	even
	2-methoxyfuran	80 °C/PhH/8 h	74% **9b**[d]	
4-CO_2Et	isoprene	110 °C/PhH/40 h	25% **7**	even
	piperylene	110 °C/PhH/62 h	28% **5** + **9**[b]	even
	1-acetoxybutadiene	80 °C/PhH/48 h	22% **5** + 5% **9**[b]	even
	2-methoxyfuran	110 °C/PhMe/24 h	32% **9c**[d] + 16% **9d**[d]	
3-MeO	isoprene	160 °C/PhH/140 h	15% **3** + 15% **4**	50:50 even:odd
	piperylene	200 °C/PhH/92 h	25% **9e** + 25% **9f**	
4-MeO[c]	isoprene	175 °C/PhH/120 h	5% **7** + 15% **8** + 45% **9**[b]	25:75 even:odd
	2-methoxyfuran	200 °C/PhH/115 h	10% **9g**[d]	

[a] Isolated yields. [b] Complex mixture of adducts. [c] Piperylene and 1-acetoxybutadiene react slowly with 4-methoxytropone to give inseparable mixtures of adducts in low yield. [d] Adducts isolated after hydrolysis.

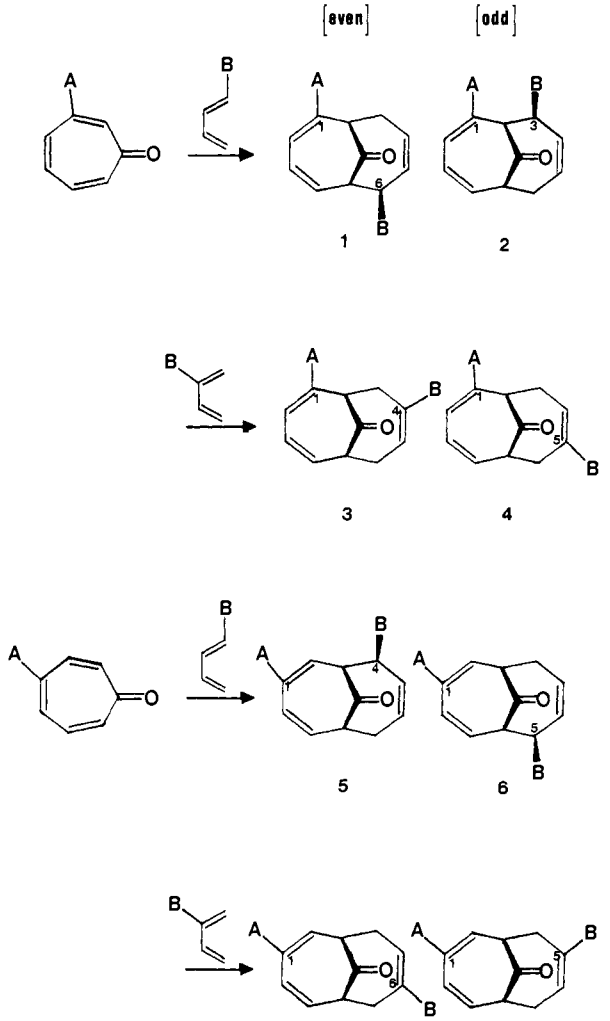


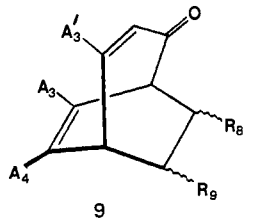
Figure 1. Possible regioisomers in [6 + 4] cycloadditions of 3- and 4-substituted tropones with 1- and 2-substituted butadienes. "Even" and "odd" regioselectivity are defined in the text.

show that secondary orbital interactions are not a prerequisite for high cycloaddition regioselectivity.

Tropones undergo [6 + 4] cycloadditions with a variety of dienes.[8] Exo stereoselectivity is preferred, presumably because secondary FMO interactions are repulsive.[9,10] For 3- or 4-substituted tropones, the regiochemical possibilities with unsymmetrical dienes are shown in Figure 1. We propose the terms "odd" and "even" to define cycloaddition regioselectivity in general. That is, Diels–Alder cycloadditions generally occur with "ortho" (1,2-) or "para" (1,4-) regioselectivity. We define these as "even" regioselectivity. The rare cases of "meta" (1,3-) regioselectivity are defined as "odd". By analogy with [4 + 2] cycloadditions and on the basis of FMO considerations, we expected [6 + 4] cycloadditions to exhibit "even" regioselectivity.[11]

The reactions of the 3-ethoxycarbonyl, 4-ethoxycarbonyl, 3-methoxy, and 4-methoxy derivatives of tropone[12] with unsymmetrical dienes were examined. The reactions were run in sealed NMR tubes in benzene-d_6 and were monitored by NMR or were effected in refluxing aromatic solvents and were monitored by GC and TLC. Yields were determined after column chromatography on silica gel, which caused some decomposition of most of the adducts. Structure proofs are based on 220- or 360-MHz NMR analysis.[13] The results are summarized in Table I.

Only [6 + 4] adducts, **1–8**, or Diels–Alder adducts, **9**, were



9

	A_3	A_3'	A_4	R_8	R_9
a:	CO_2Et	H	H	H	exo-CH=CH-CH$_2$-Me
b:	CO_2Et	H	H	exo-$OCOCH_2$-	
c:	H	H	CO_2Et	exo-CH_2CO_2-	
d:	H	H	CO_2Et	endo-CH_2CO_2-	
e:	H	MeO	H	H	exo-CH=CH-CH$_2$-Me
f:	H	MeO	H	H	endo-CH=CH-CH$_2$-Me
g:	H	H	MeO	exo-$OCOCH_2$-	

obtained in each reaction. Only one [6 + 4] isomer, with *even* regiochemistry, was obtained from each of the reactions of 3- and 4-ethoxycarbonyltropones with electron-rich 1- and 2-substituted

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(13) NMR analyses followed those described previously.[8,10] Experimental details and complete NMR analyses are contained in: Roberts, V. A. Ph.D. Dissertation, University of California at San Diego, La Jolla, CA, 1983.

dienes. The 1-substituted dienes gave only exo isomers. By analogy, we assume that the 2-substituted dienes also react via exo transition states. Reactions were followed by NMR, but no resonances attributable to nonisolated [6 + 4] adducts were observed. Yields are modest in the ethoxycarbonyltropones, since these substances underwent substantial decomposition during the reactions. The products in Table I were stable to the reaction conditions.

The regioselectivity observed is similar to that found in the analogous Diels–Alder reactions of these dienes with alkyl acrylates, except that the *even* regioselectivity is higher for the [6 + 4] cycloadditions.[14]

The reactions of 3- and 4-methoxytropone with dienes showed lower regioselectivity than those of the tropones substituted by electron-withdrawing groups. Higher temperatures and longer reaction times were also required. Often the reactions were not carried to completion, and a substantial amount of the starting tropone was recovered. Both methoxytropones react with 2,5-dimethyl-3,4-diphenylcyclopentadienone to give exo-[6 + 4] adducts, while 4-methoxytropone reacts with cyclopentadiene to give a 4:1 ratio of Diels–Alder adducts analogous to **9e** and **9f**.

There are relatively few cases of Diels–Alder reactions with unsymmetrical electron donor substitution on both diene and dienophile.[15,16] The low regioselectivity observed with isoprene is similar to that observed in Diels–Alder reactions of isoprene with methoxybenzoquinones.[16]

We conclude that the same factors influence Diels–Alder and [6 + 4] regioselectivity, and since secondary orbital interactions cannot influence the latter, they are unlikely to be significant for Diels–Alder reactions either.

In order to confirm further the effect of acceptors and donors on the terminal FMO coefficients of tropone, the structures of tropone, 3- and 4-cyanotropone and 3- and 4-hydroxytropone were optimized using Hehre's ab initio gradient program[17] and the STO-3G basis set.[18] The cyano group serves as a smaller, but electronically similar, model for the ethoxycarbonyl group, and the hydroxy group is a model for methoxy. Aside from a planarity constraint, all bond lengths and angles were fully optimized.[19]

The cycloadditions of tropone with electron-rich dienes occur so as to maximize the stabilizing interaction of the tropone LUMO with the diene HOMO and to minimize the destabilizing interactions involving the HOMO's of these two species. The acceptor, CN, polarizes the LUMO and lowers all orbital energies. The most nucleophilic terminus is C-2 for 3-CN and C-7 for 4-CN, as expected in analogy to the FMOs of alkenes and dienes[2] and by chemical intuition about which triene terminus becomes more electrophilic as a result of acceptor substitution. *Even* regioselectivity is expected with electron-rich dienes, since C-1 of isoprene and C-4 of piperylene are the more nucleophilic diene termini.[2]

Donor substituents raise the LUMO of tropone, accounting for the slower rate of reaction with electron-rich dienes (see conditions in Table I). Donors polarize the HOMO most and the LUMO to a small extent in the opposite direction. FMO theory for a synchronous reaction model predicts low *odd* regioselectivity for the reactions of donor-substituted tropones with electron-rich dienes, consistent with the observations. With electron-deficient unsymmetrical dienes, *even* regioselectivity is predicted.

We conclude that primary orbital interactions can control regioselectivity in cycloadditions, unaided by secondary orbital interactions.

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Book Reviews

Methods in Enzymology. Volumes 75 and 92. Edited by S. P. Colowick and N. O. Kaplan. Academic Press, New York, N.Y. Volume 75: Edited by S. P. Colowick and N. O. Kaplan. 1982. xxix + 824 pp. $85.00. Volume 92: Edited by John J. Langone and Helen Van Vunakis. 1983. xxiv + 647 pp. $65.00.

Volume 92 in this series, entitled "Immunological Techniques, Part E, Monoclonal Antibodies and General Immunoassay Methods", is edited by John J. Langone and Helen Van Vunakis.

This 1983 addition to the series is yet another excellent contribution, maintaining the highest standards in presentation of detailed procedures in this rapidly developing and active field. Chapters in each section are clearly and concisely written. This volume will find very wide usage in the research community. State-of-the-art chapters are offered in various aspects of hybridoma technology and in immunoassay of antigens and antibodies. Subsections on the former subject deal with production of monoclonal antibodies, including some applications, as well as detection and assessment of monoclonal antibodies, whereas subsections for the latter topic include methods for labeling antigens and antibodies, separation methods in immunoassay, immunoassay methods, and lastly, means of data analysis. Ten chapters cover various aspects dealing with production of monoclonal antibody-producing hybridomas, in addition to purification and immunoassay of monoclonal antibodies. An additional ten chapters relate to detecting and assessing monoclonal antibodies by utilizing such methods as enzyme labeled second antibody, two-dimensional gel electrophoresis, immunofixation on cellulose acetate, and solid-phase immunofluorescence. The second part covers principles and procedures for linking haptens and proteins to erythrocyte surfaces, radioiodination of proteins with ICI, as well as iodination by $^{125}I^-$ with lactoperoxidase or Chloramine T and separation of iodinated proteins and peptides by HPLC and PAGE. Additional chapters present means of separation of bound from unbound fractions of antigens by application of activated Thiol-Sepharose, affinity exclusion, various chromatography tubes, as well as a unique solid–liquid separation system which does not require centrifugation. A number of different immunoassay procedures are described in detail for different antigens. Lastly, a section is included dealing with the use of computer analysis in the evaluation of data. This volume should be an invaluable tool as a reference for the active researcher in the field. Volume 75 is the Cumulative Subject Index for Volumes XXXI, XXXII, and XXXIV–LX, and it appears to be complete and accurate, based upon a random check of referenced topics therein.

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