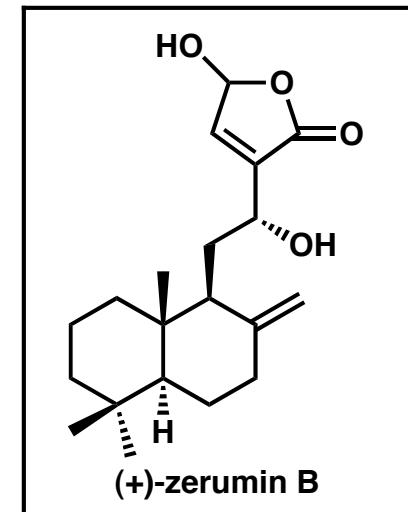
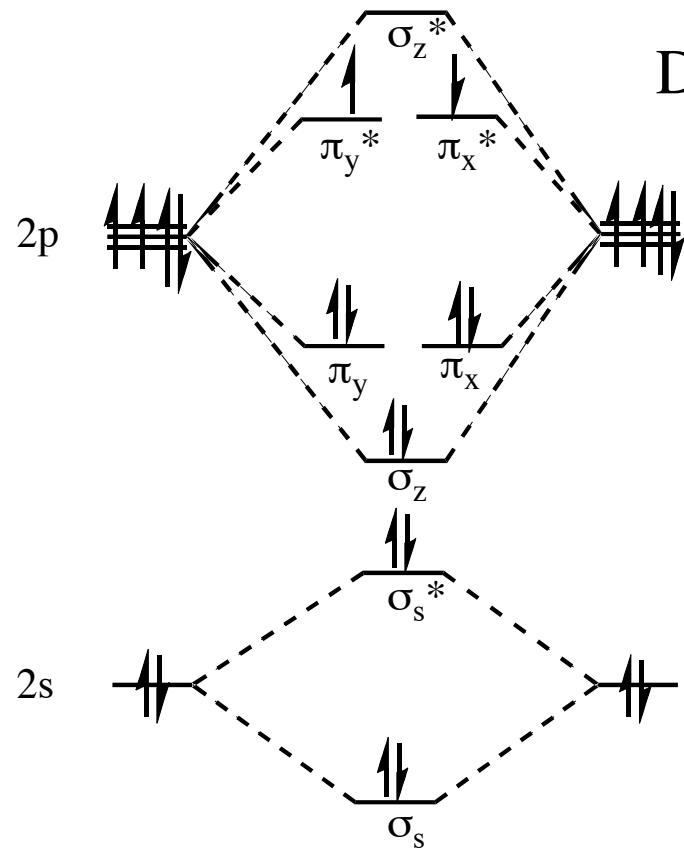


# *Mechanisms of Singlet Oxygen Reactions*

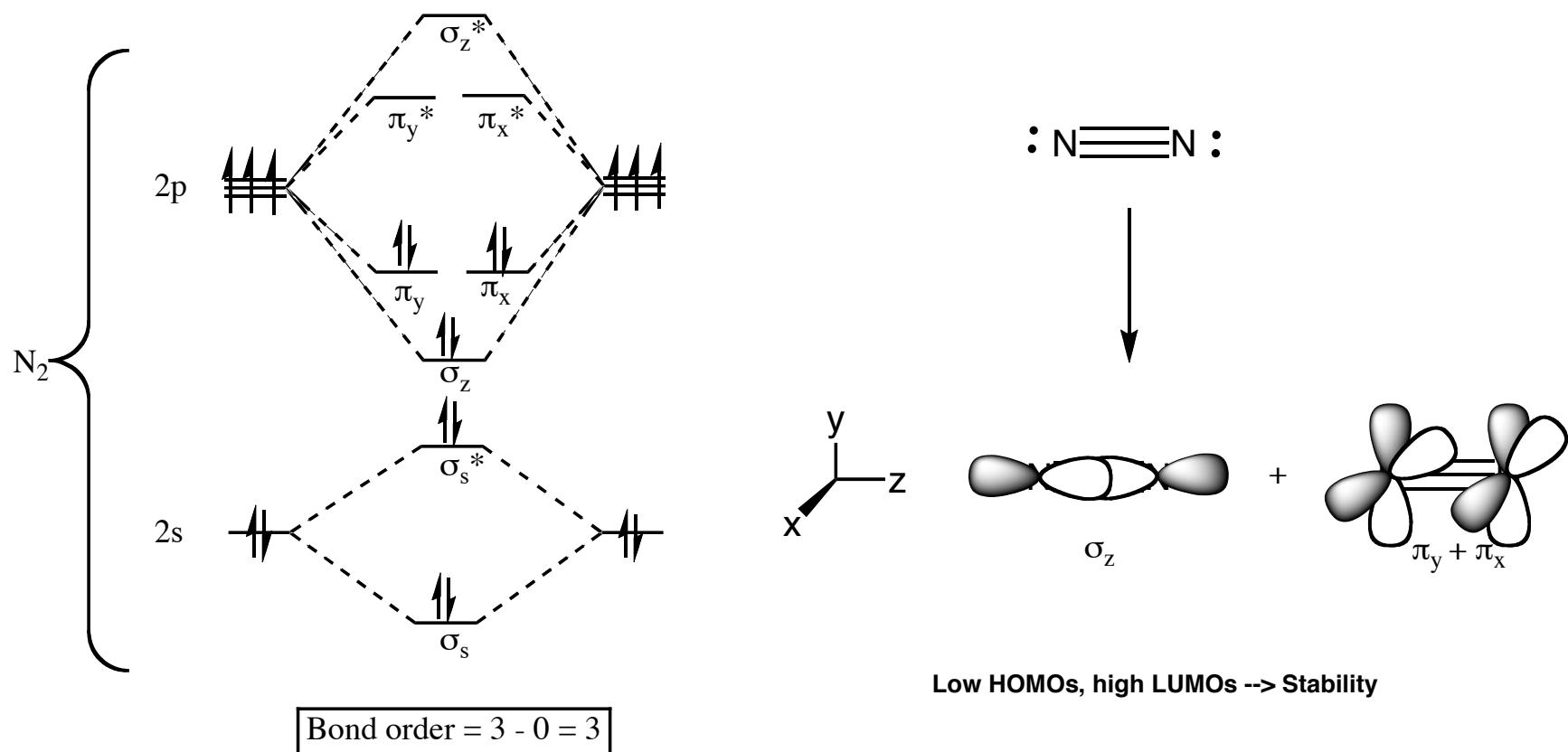
Matt Winston

Stoltz Research Group

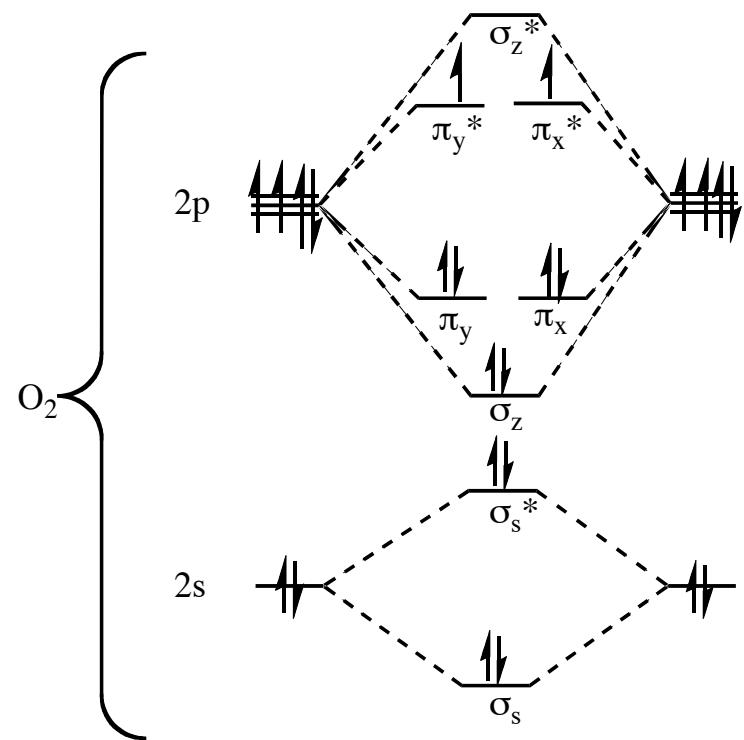
December 1, 2008



## *Molecular Orbital Theory Treatment of Dinitrogen*



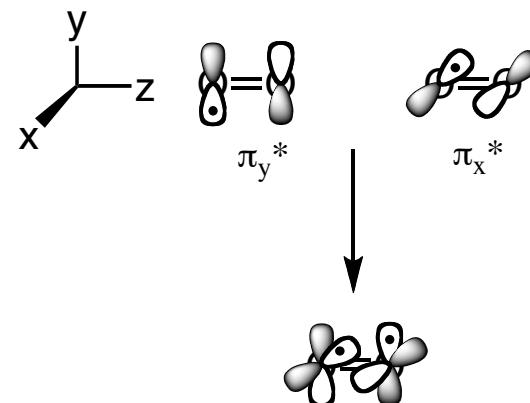
# *Molecular Orbital Theory Treatment of Dioxxygen*



-Spin  $S = (1/2) + (1/2) = 1 \rightarrow$  Paramagnetic

-Two electrons in two orthogonal, antibonding orbitals.

-Significant radical character on both oxygens contributes to reactivity of triplet oxygen.



$$\boxed{\text{Bond order} = 3 - 1 = 2}$$

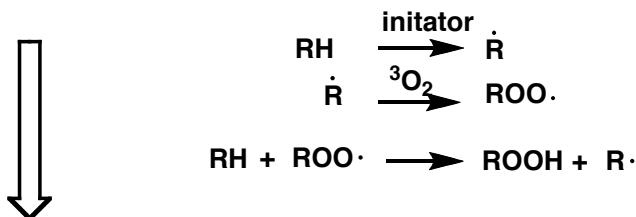


# A Brief Overview of $^3O_2$ Chemistry

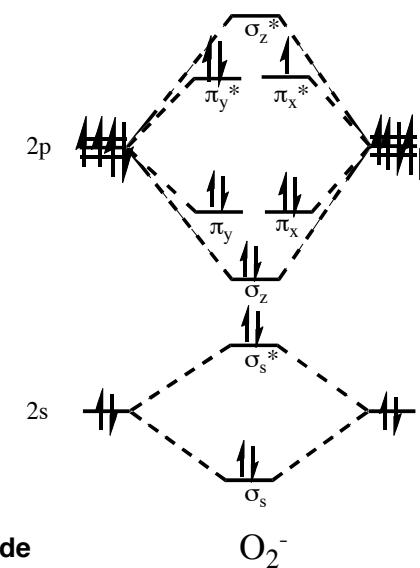
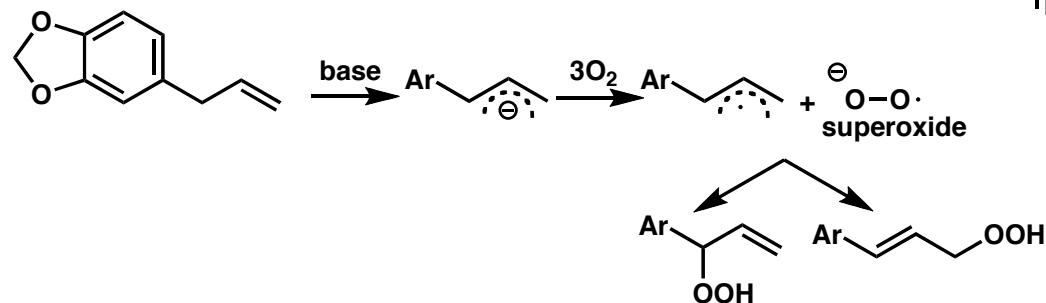
-Radical reactions a result of triplet ground state ( $S = 1$ ).

-Reactions with metals:  $M_n + O_2 \rightarrow M_{n+1} + O^{2-}$

-Autoxidation of organics:

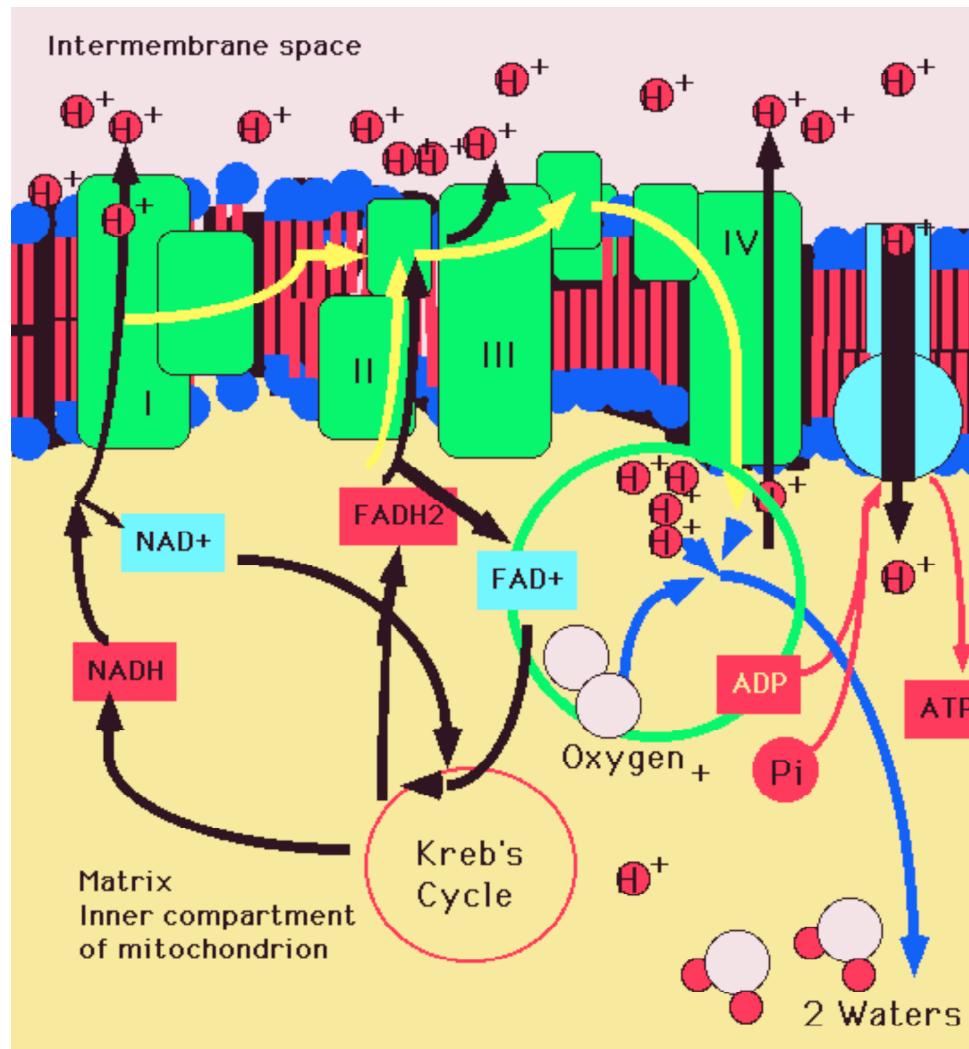


-Stabilized carbanions may be radicalized:



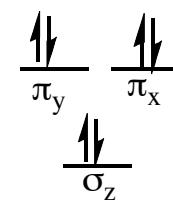
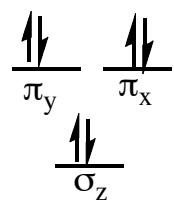
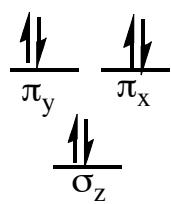
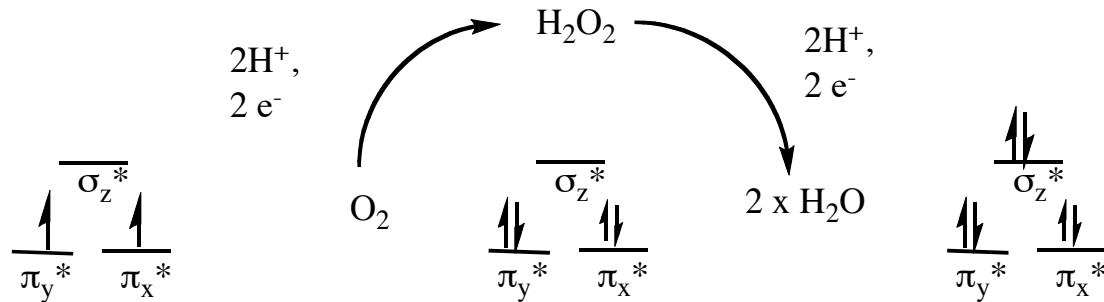
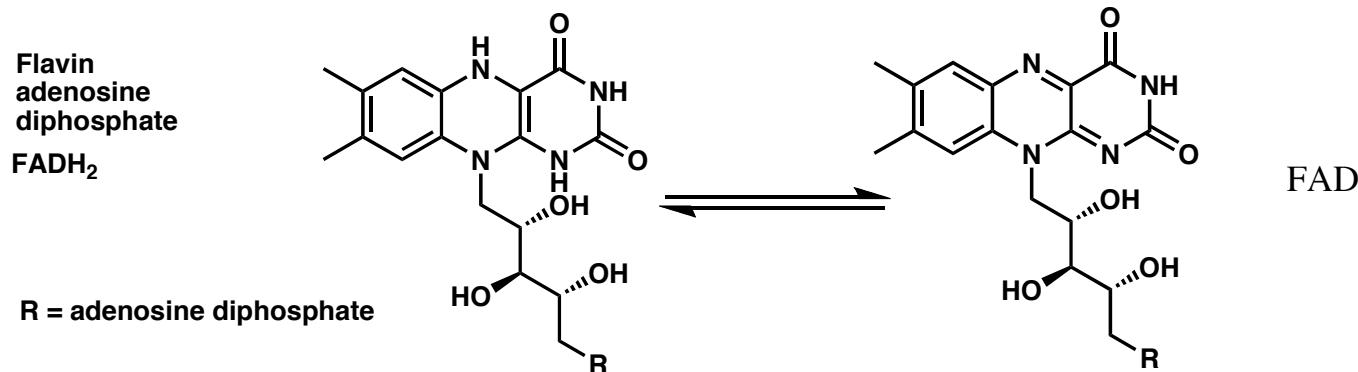
Sosnovsky, G.; Zaret, E.H., Dwern, D. *Organic Peroxides*, Vol. 1, Wiley, NY 1970, pp. 517-560.

### $^3O_2$ in Biological Systems



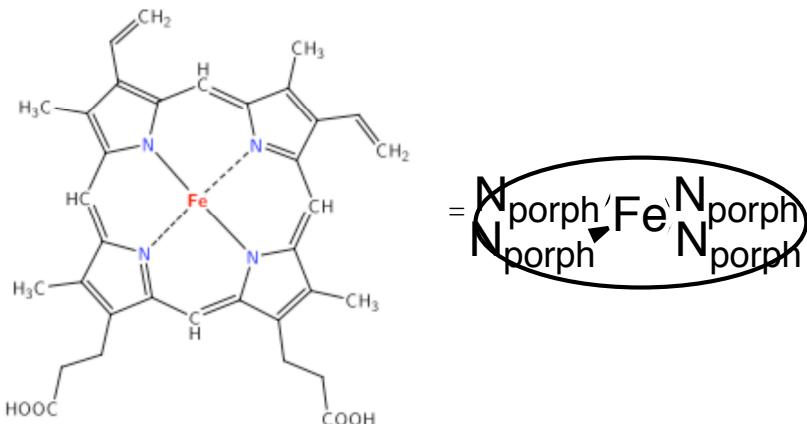
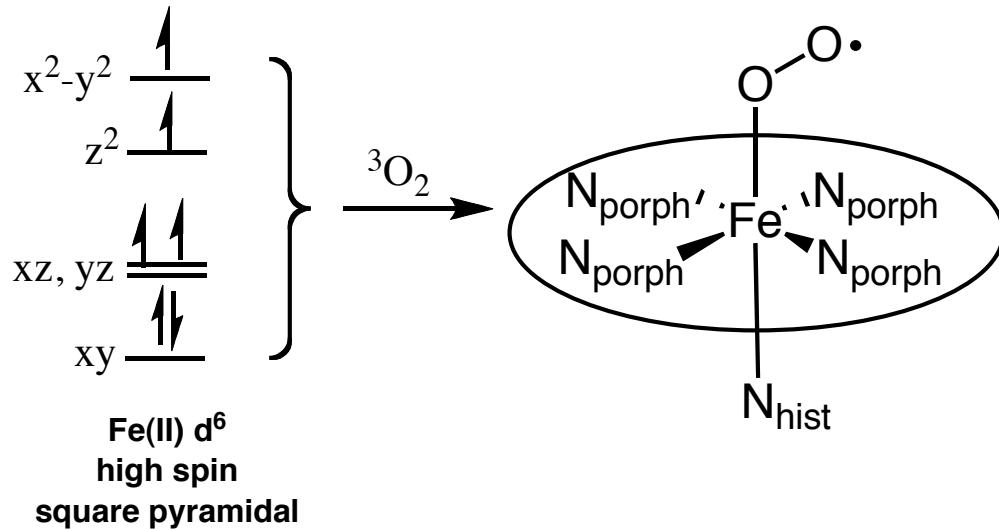
Aerobic oxidation:  $O_2$  as an electron sink.

## $^3\text{O}_2$ in Biological Systems

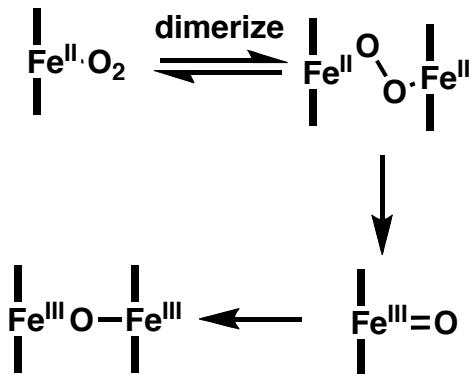


Essential in establishing the chemiosmotic gradient that drives ATP production from ADP phosphorylation.

# $^3O_2$ in Biological Systems (Hemoglobin)



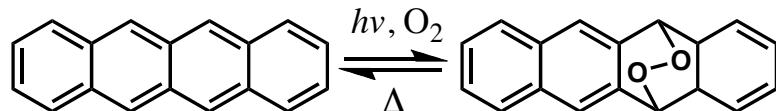
Irreversible iron oxidation and formation of a m-oxo dimer in non-biological systems.



Prevented by steric bulk and along distal edges of heme porphyrin and rigidity of hemoglobin protein backbone.

## Early Discoveries and Mechanistic Proposals of $^1O_2$ -Mediated Reactions

1867:



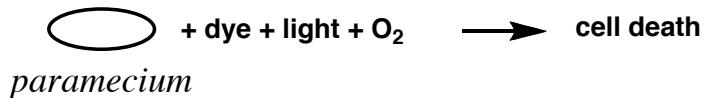
Fritzsche, M. *Compt. Rend.*, 64, 1035 (1867).

1900:



Raab, O. *Z. Biol.*, 39, 524 (1900).

1905:



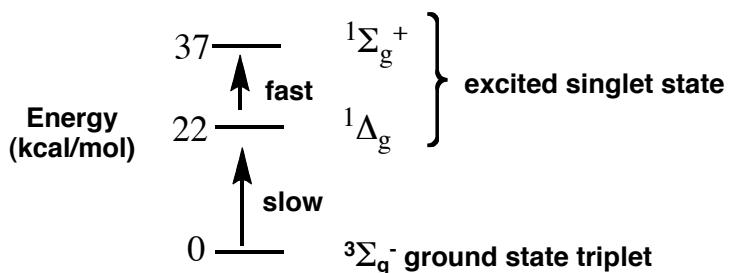
Jodlbauer, A.; von Tappeiner, H. *Deut. Arch. Klin Med.*, 82, 520 (1905).

1924:

Ground-state  $O_2$  is a triplet diradical species.

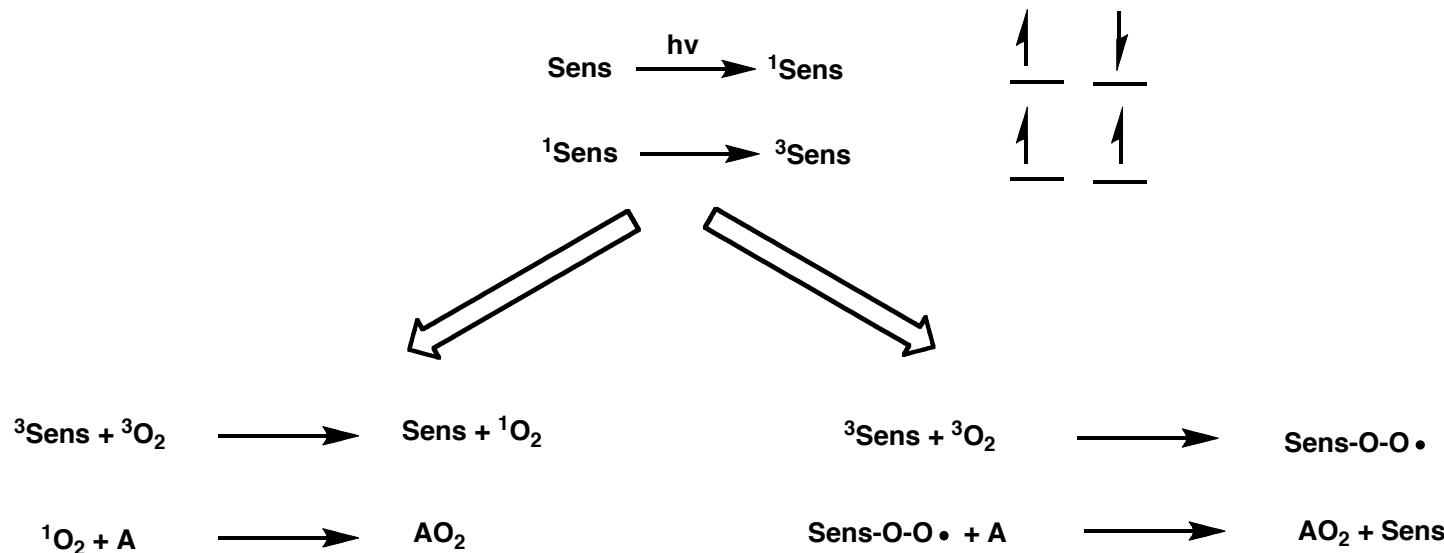
Lewis, G.N. *Chem. Rev.*, 1924, 231 (1924).

1928:



Mulliken, R.S. *Nature*, 122, 505 (1928).

# *Early Discoveries and Mechanistic Proposals of $^1\text{O}_2$ -Mediated Reactions*

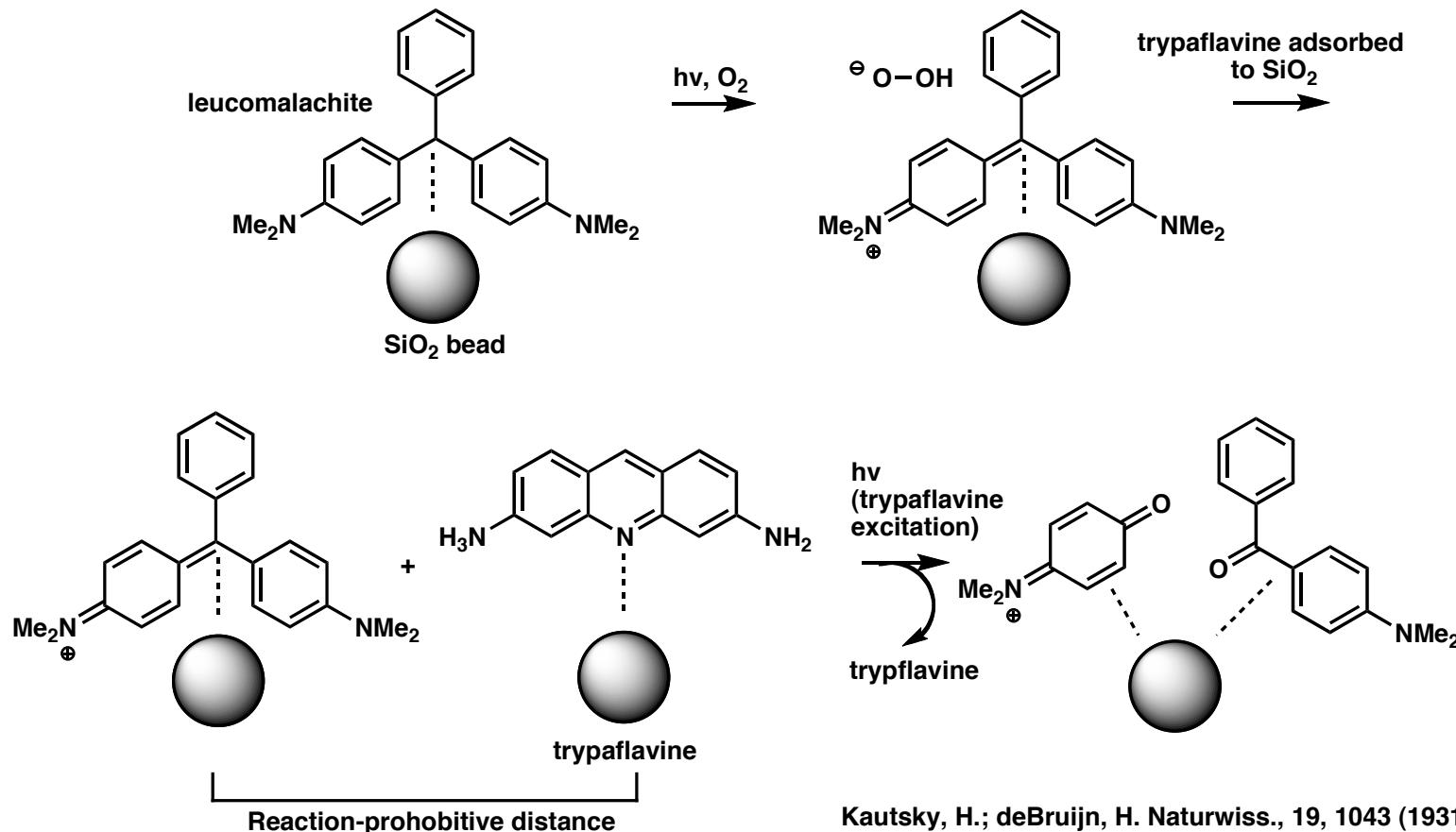


Kautsky, H.; de Bruijn, H. *Naturwiss.*, 19, 1043 (1931).

Gaffron, H. *J. Am. Chem. Soc.* 287, 130 (1936).

## Early Discoveries and Mechanistic Proposals of $^1O_2$ -Mediated Reactions

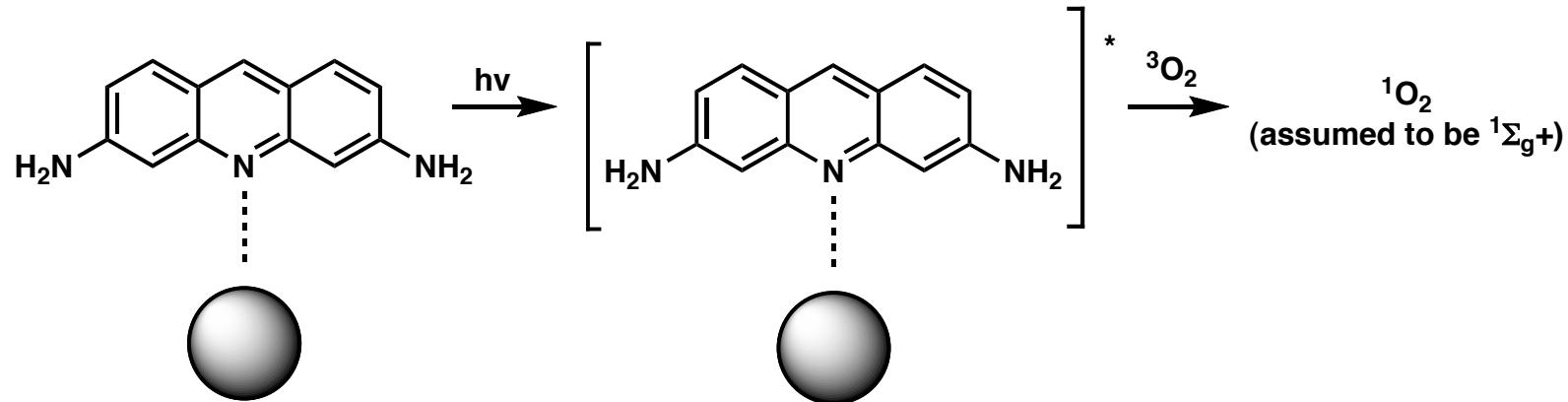
- 1931:** Leucomalachite and trypaflavine adsorbed to  $\text{SiO}_2$  beads, mixed, and irradiated at trypaflavine excitation wavelength in dry conditions under  $\text{O}_2$  to yield oxygenated products.
1. Immobilized starting materials cannot physically interact with one another.
  2. Dry conditions suggests that oxygenation cannot originate from water.
  3. Trypaflavine luminescence dependent upon oxygen pressure.



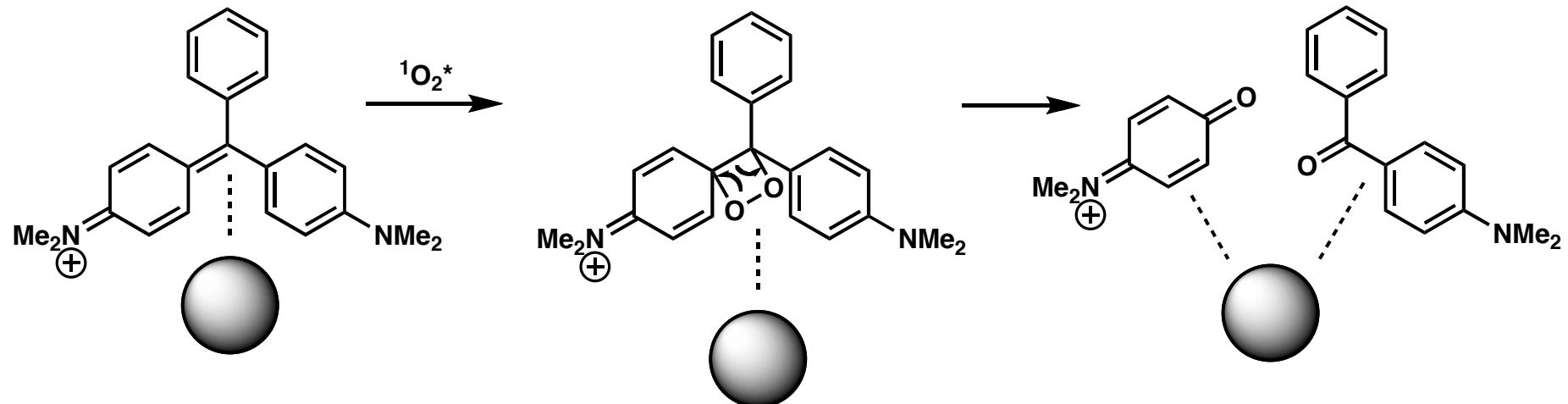
Kautsky, H.; deBruijn, H. Naturwiss., 19, 1043 (1931).

# *Early Discoveries and Mechanistic Proposals of $^1\text{O}_2$ -Mediated Reactions*

## 1. Excitation of mobile, ground-state triplet oxygen to mobile, excited-state singlet oxygen.

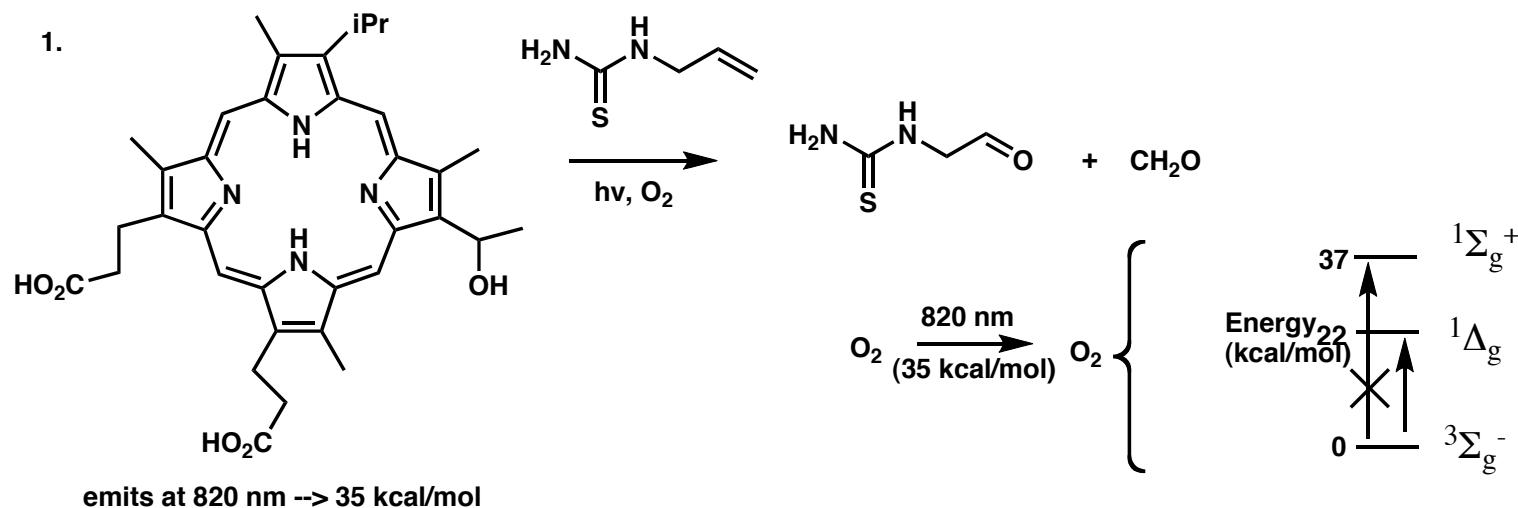


## 2. Reaction of mobile, excited-state singlet oxygen with oxidized leucomalachite.



Suggestive of a diffusable reactive intermediate such as  $^1\text{O}_2$ .

## Early Discoveries and Mechanistic Proposals of $^1O_2$ -Mediated Reactions

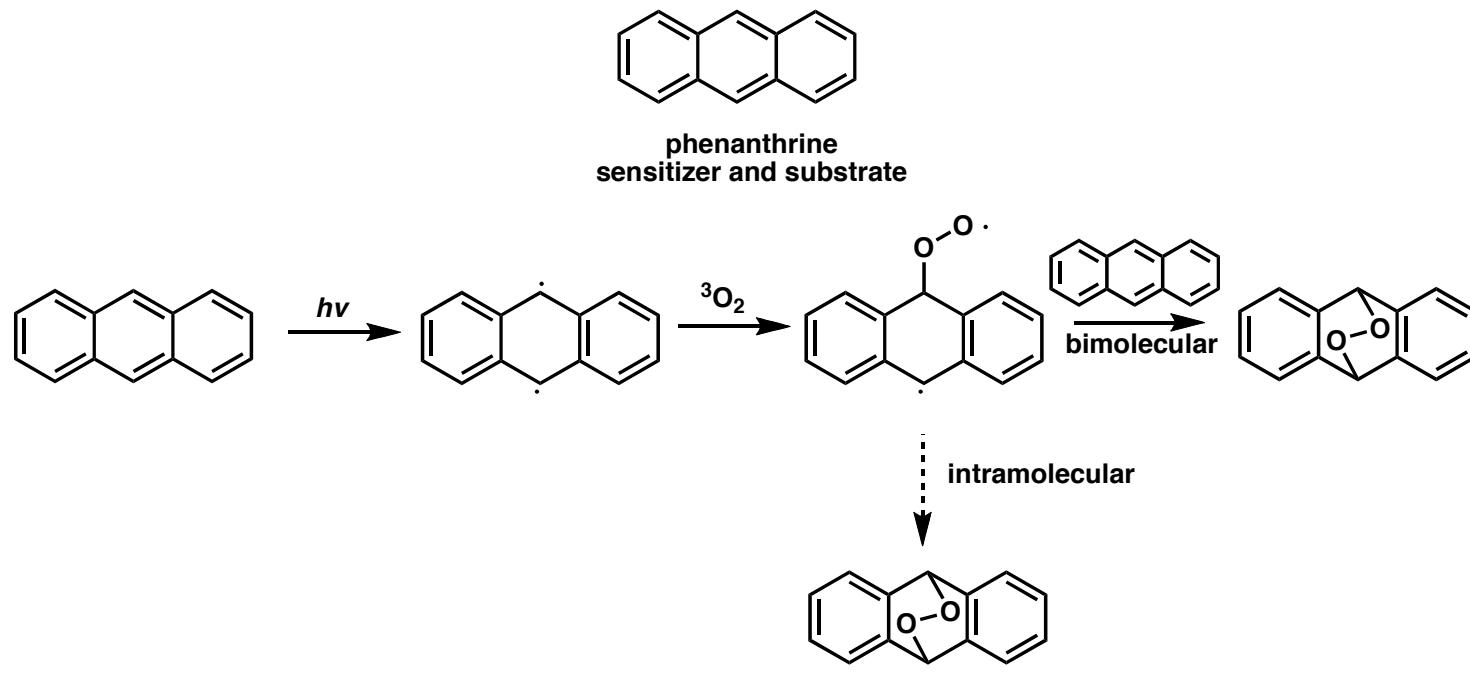


$^1\Delta_g$  energy not fully characterized, so existence of singlet oxygen in this mechanism disputed.

2. Different kinetic behavior of active intermediate when formed with anthracene and diphenylanthracene as sensitizer.

Livingston, R.; Subba Rao, V. *J. Phys. Chem.*, 63, 794 (1959).

# *Early Discoveries and Mechanistic Proposals of $^1O_2$ -Mediated Reactions*



Kinetics suggest intramolecular reaction.

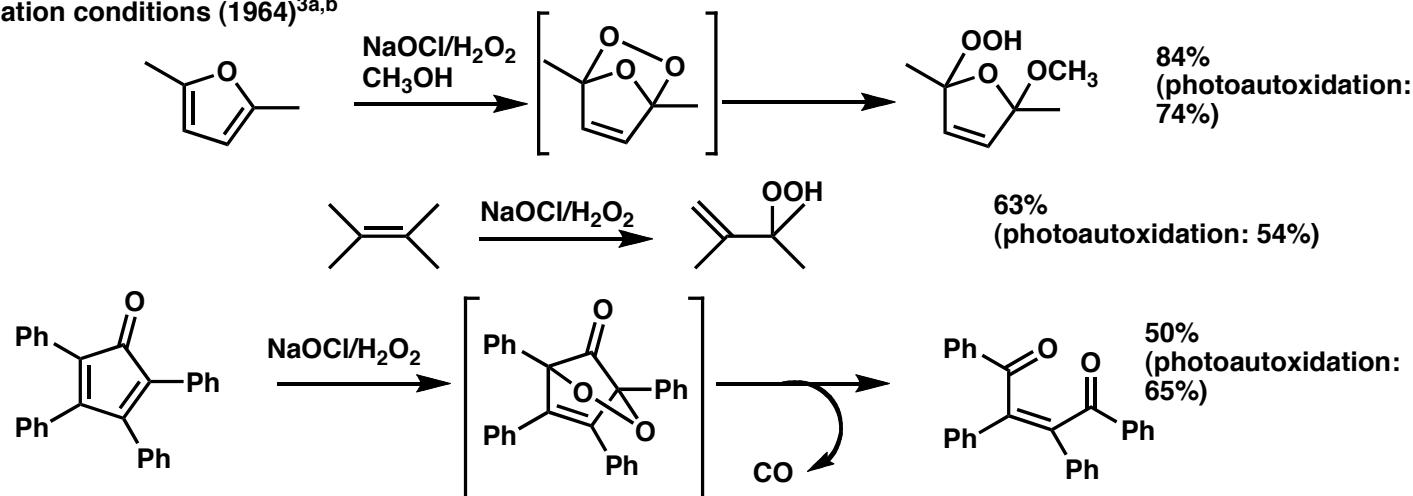
Schenk, G.O. Naturwiss, 41, 452 (1954).

# *Support for $^1\text{O}_2$ -Mediated Photosensitized Autoxidations*



2. Chemiluminescence of  $^1\text{O}_2$  detected in  $\text{NaOCl}-\text{H}_2\text{O}_2$  solutions (1964)<sup>2</sup>

3. Same products and similar yields observed for substrate oxidations under  $\text{NaOCl}-\text{H}_2\text{O}_2$  and photosensitized autoxidation conditions (1964)<sup>3a,b</sup>



4. Rates of photooxidation independent of sensitizer (1965)<sup>4</sup>

5. No steric influence by sensitizers (1965)<sup>5</sup>

6. No effect by radical scavengers (1965)<sup>5</sup>

1. Seliger, H. *Anal. Biochem.* 1, 60 (1960).

2. Khan, A.U.; Kasha, M. *Nature* 204, 241 (1964).

3a. Foote, C.S.; Wexler, S. *J. Am. Chem. Soc.*, 86, 3879 (1964).

3b. Corey, E.J.; Taylor, W.C. *J. Am. Chem. Soc.*, 86, 3881 (1964).

4. Kopecky, K.R.; Reich, H.J. *Can. J. Chem.* 43, 2265 (1965).

5. Foote, C.S.; Wexler, S.; Ando, W. *Tetrahedron Lett.* 46, 4111 (1965).

# *Direct Spectroscopic Evidence of $^1O_2$ in Photosensitized Autoxidations*

1. EPR absorption of  $^1\Delta_g$  state detected.

- a. Kearns, D.R.; Khan, A.U.; Duncan, C.K.; Maki, A.H. *J. Am. Chem. Soc.* 91, 1039 (1969).
- b. Wasserman, E.; Kuck, V.J.; Delavan, W.M.; Yager, W.A. *J. Am. Chem. Soc.* 91, 1040-1041 (1969).

2. 1268-nm emission of the  $^1\Delta_g \rightarrow ^3\Sigma_g^-$  transition of molecular oxygen in liquid solution at room temperature is reported in multiple cases.

- a. Snelling, D.R. *Chem. Phys. Lett.* 2, 346 (1968).
- b. Krasnovsky, A.A. *Biophys. USSR* 2, 748 (1976).
- c. Krasnovsky, A.A. *Photochem. Photobiol.* 29, 29 (1979).
- d. Khan, A.U.; Kasha, M. *Proc. Natl. Acad. Sci. USA* 76, 6047 (1979).

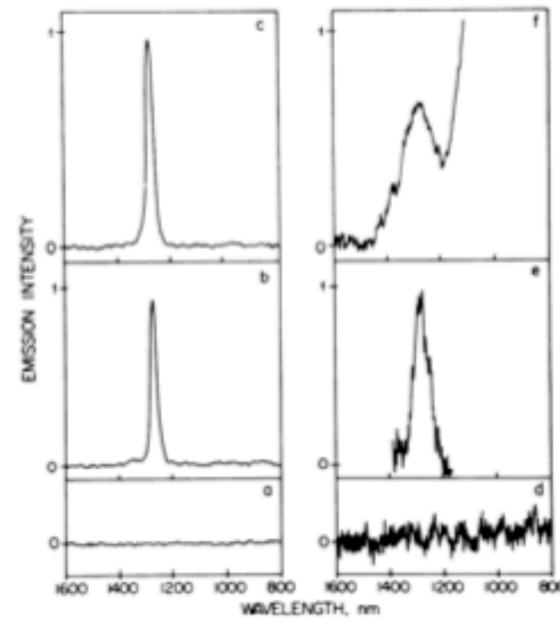
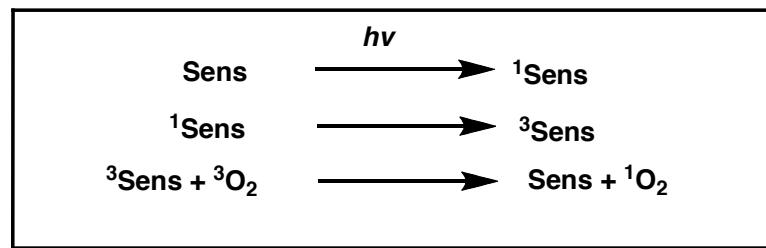
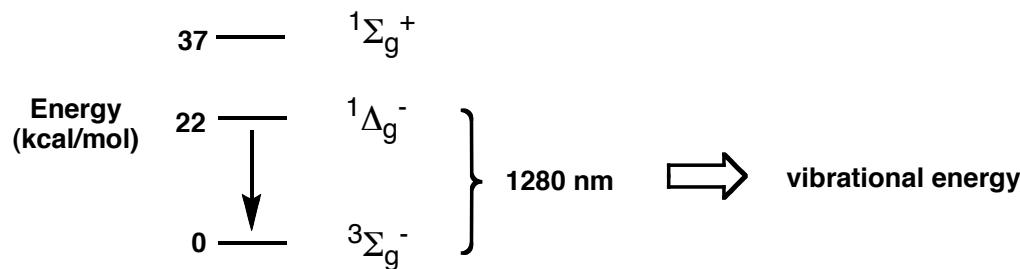


FIG. 2. Dye photosensitized  $^1\Delta_g \rightarrow ^3\Sigma_g^-$  emission at 1268 nm in liquid solutions at 20°C. (a) Background; (b) decalfluorobenzophenone in perfluorohexane; (c) 3,4-benzpyrene in carbon tetrachloride; (d) high-gain background; (e) hematoporphyrin in carbon tetrachloride; and (f) methylene blue in water.

# $^1O_2$ Relaxation to $^3O_2$

-Intersystem crossing from singlet to triplet state:



-Relaxation time is highly solvent dependent (solvent vibrational frequencies.)

Solvent	Lifetime (ms)	
$H_2O$	3.8	
$D_2O$	62.0	
$CH_3OH$	10.0	
$CHCl_3$	264.0	
$CDCl_3$	740.0	
$(CH_3)_2C=O$	50	
$(CD_3)_2C=O$	723	
$C_6H_6$	30	
$C_6D_6$	630	
Freon-113	15,800	

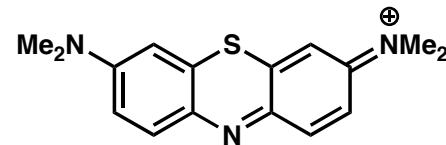
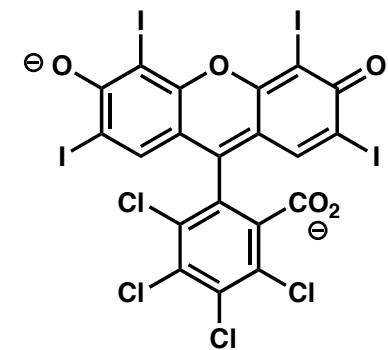
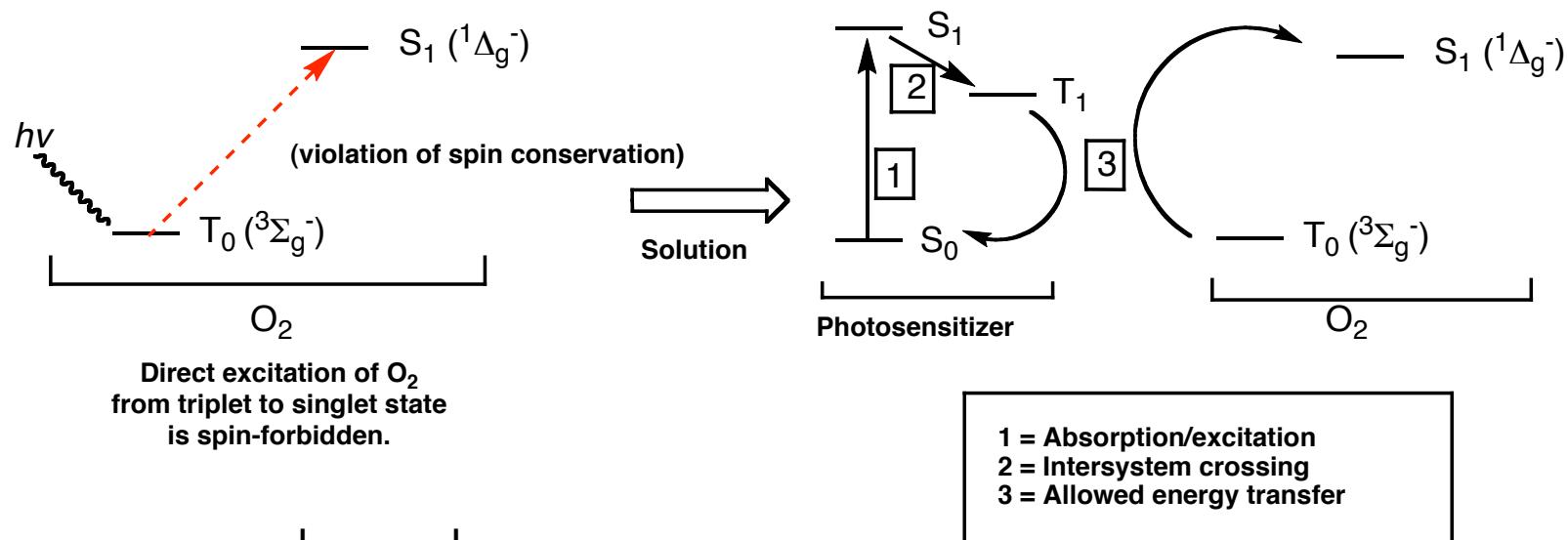
Solvents with larger vibrational frequencies are easier to excite, and are more efficient quenchers of  $^1O_2$ .

- $H_2O$  vibrational frequency =  $3600\text{ cm}^{-1}$

-Organics  $\sim 3000\text{ cm}^{-1}$

-Freon-113 (no O-H/C-H bonds)

# *Preparation of $^1O_2$ via Sensitized Irradiation*

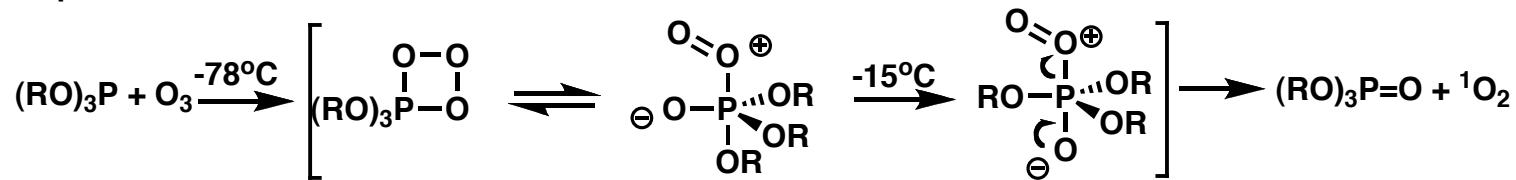


# *Preparation of $^1O_2$ via Chemical Processes*

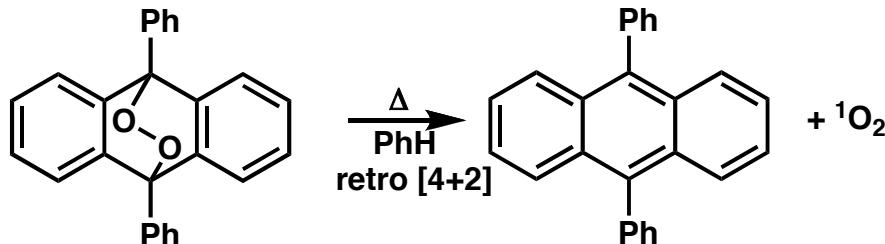
Peroxide/bleach



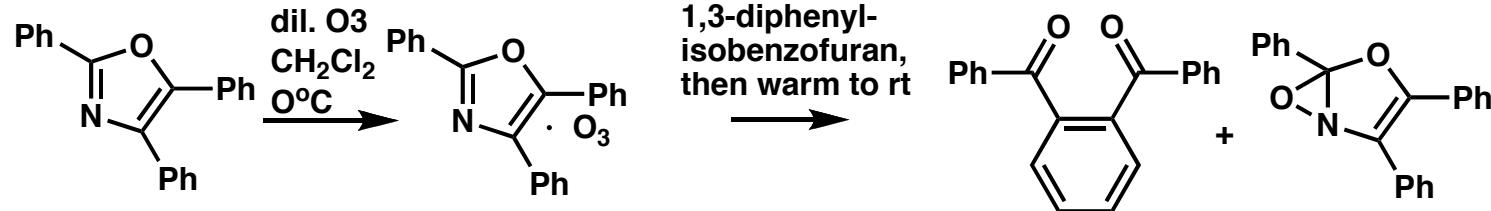
Phosphite ozonide



Aromatic endoperoxides



Heterocycle/ozone adducts

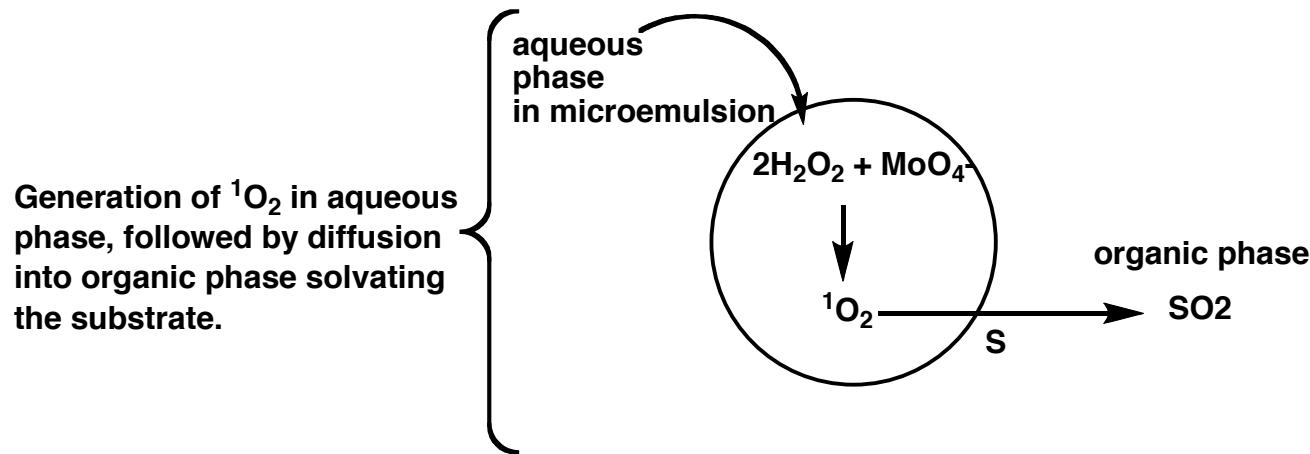


Clennan, E.L.; Pace, A. *Tetrahedron* 61, 6665 (2001).

# *Preparation of $^1\text{O}_2$ via Chemical Processes*



Proceeds in very polar environments (water, aqueous methanol/ethanol)<sup>1</sup>

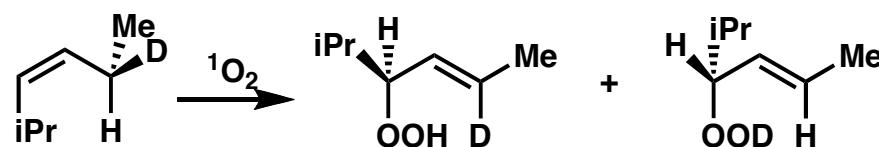
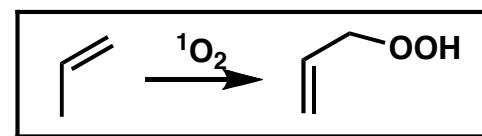


*"Microemulsion was prepared at room temperature by adding dropwise [aq. NaMoO<sub>4</sub>] to a stirred slurry of sodium dodecylsulfate (SDS - surfactant), n-butanol, and methylene chloride." Add 9,10-diphenylanthracene and 1.0 mmol of 50% H<sub>2</sub>O<sub>2</sub>. Stir at room temperature for 13 minutes.<sup>2</sup>*

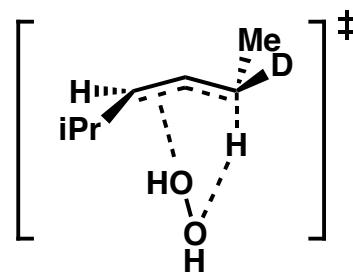
1. Aubry, J.M.; J. Am. Chem. Soc. 107, 5844 (1985).

2. Aubry, J.M.; Bouttemy, S. J. Am. Chem. Soc. 119, 5286 (1997).

## $^1O_2$ Ene Reactions



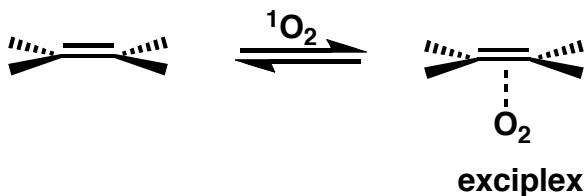
- Olefin shifts to allylic position.
- Syn formation of C-O bond and breakage of C-H/D bond.



## *Exciplex Formation in the Ene Reaction*

Olefin	$\Delta H^\ddagger$ (kcal/mol)	$\Delta S^\ddagger$ (eu)	$k_r$ ( $M^{-1} s^{-1}$ )
	1.6	-35	$4.8 \times 10^4$
	0.3	-45	$7.2 \times 10^3$
	2.0	-34	$3.9 \times 10^4$
	0.4	-42	$7.7 \times 10^3$

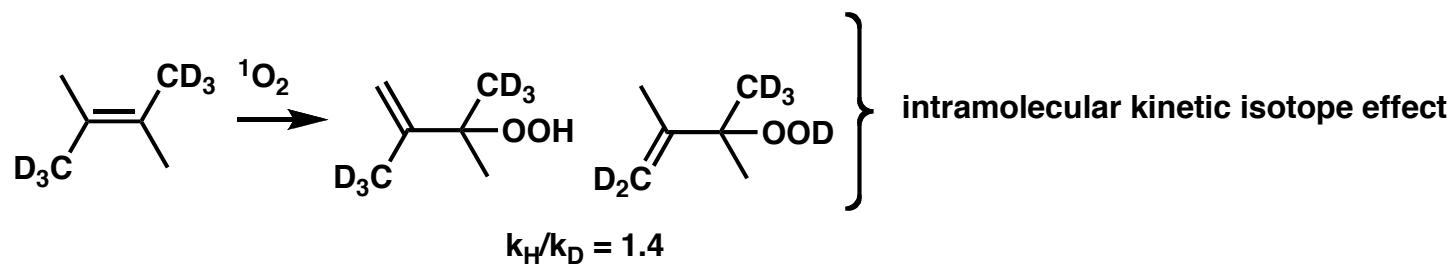
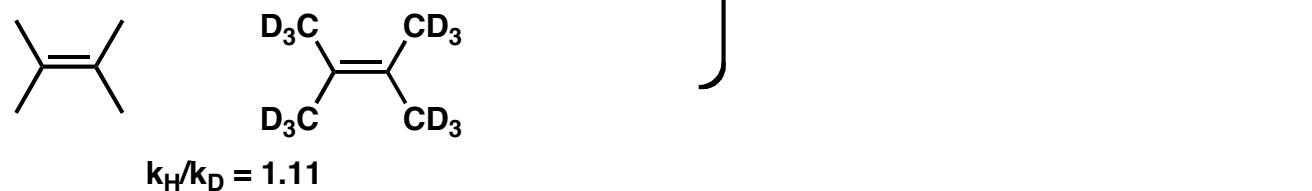
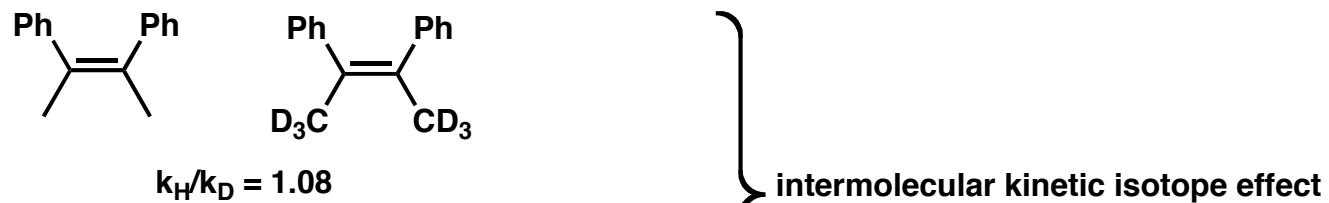
- Small or slightly negative activation enthalpies and highly negative activation entropies.
- Electron rich olefins react with  ${}^1O_2$  at rates 10<sup>3</sup> less than diffusion control.



Electrophilic dioxygen stabilized by association with alkene, but entropic penalty of association.

Hurst, J.R.; Wilson, S.L.; Schuster, G.B. *Tetrahedron*, 41, 2191 (1985).  
 Gorman, A.A.; Hamblett, I.; Lambert, C.; Spencer, B.; Standen, MC. *J. Am. Chem. Soc.* 110, 8053 (1988).

## *Identifying Intermediates in the Ene Reaction*



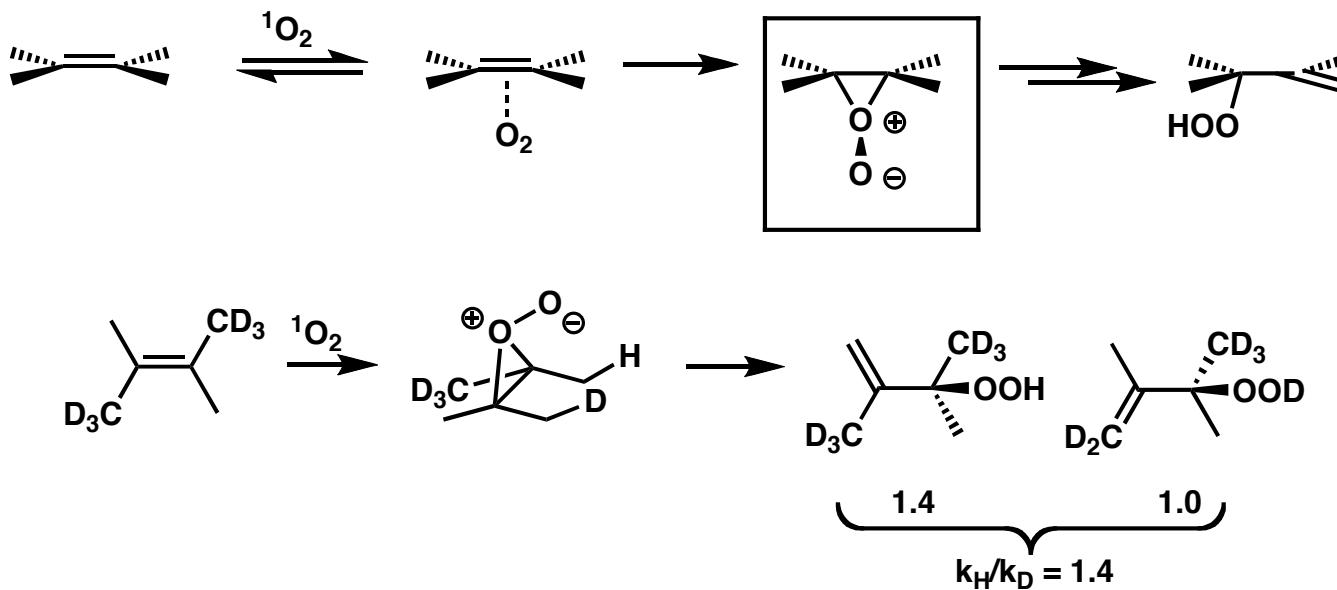
Stephenson, L.M.; Grdina, M.J.; Orfanopoulos, M. Acc. Chem. Res. 13, 419 (1980).

# *Identifying Intermediates in the Ene Reaction*

intermolecular KIE  $\neq$  intramolecular KIE

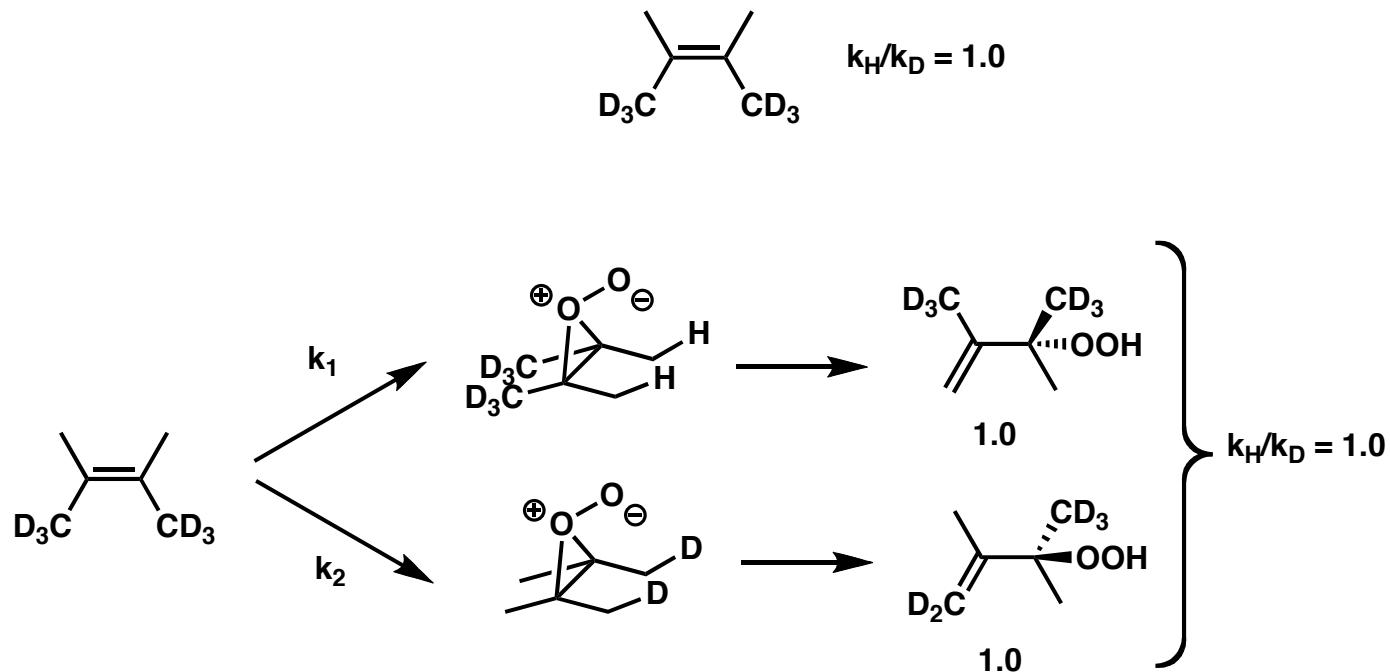


Rate-determining and product-determining steps  
must be distinct.



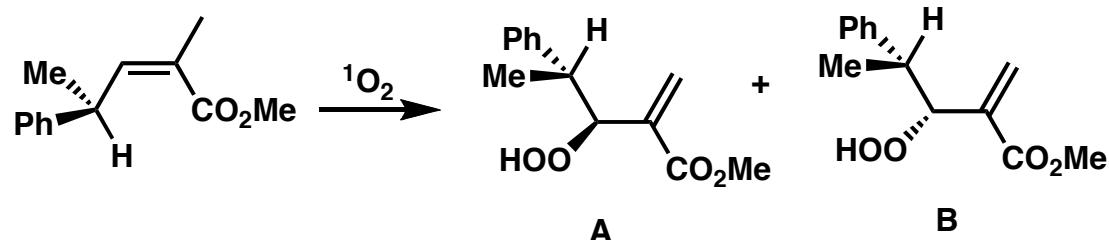
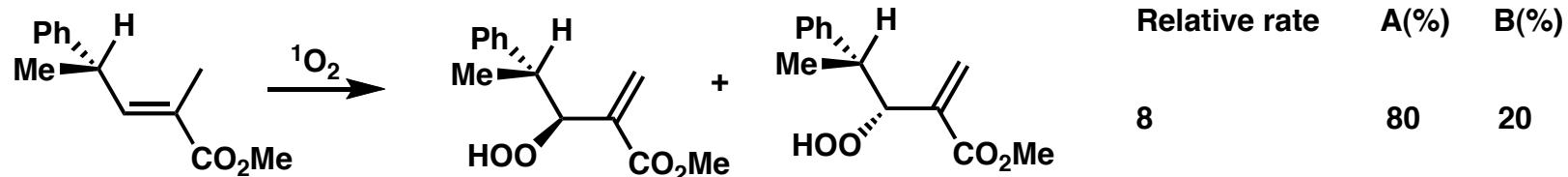
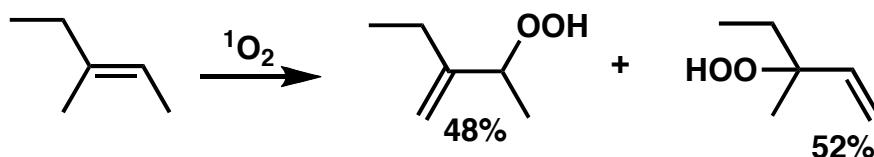
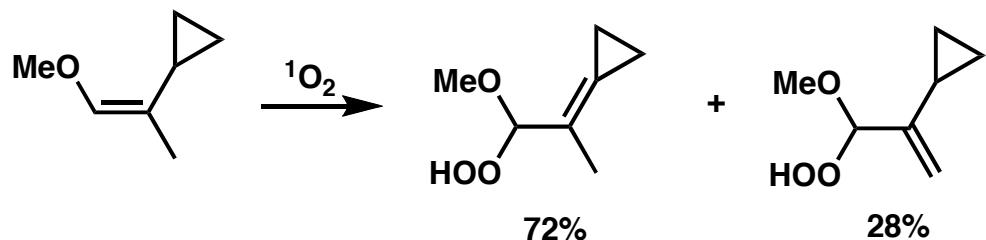
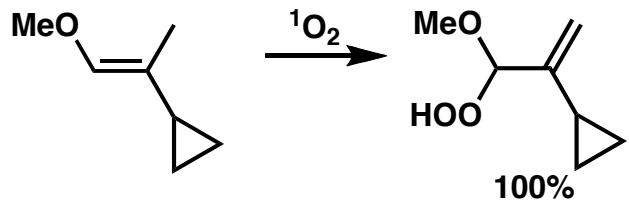
Stephenson, L.M.; Grdina, M.J.; Orfanopoulos, M. Acc. Chem. Res. 13, 419 (1980).

## *Identifying Intermediates in the Ene Reaction*



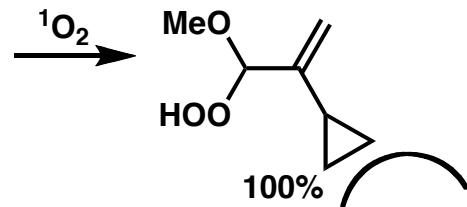
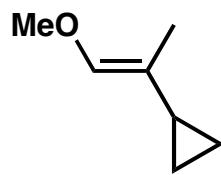
-Perepoxide formation does not involve breaking C-isotope bond, so  $k_1/k_2 = 1$ .  
-Perepoxide formation is irreversible.

## Regiochemical Issues

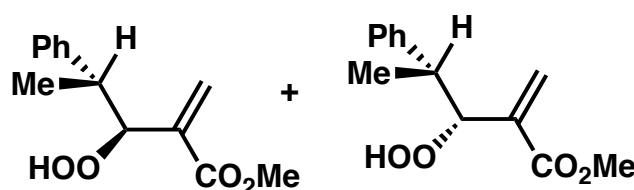
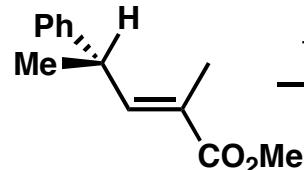
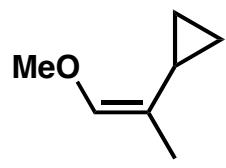


Rousseau, G.; LePerche, P.; Conia, J.M. *Tetrahedron Lett.* 2517 (1977).  
 Lerdal, D.; Foote, C.S. *Tetrahedron Lett.* 3227 (1978).

## Regiochemical Issues

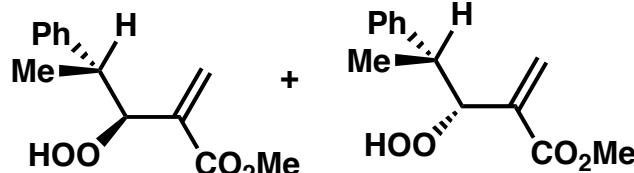
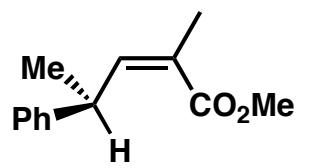


Preference for "cis abstraction" overrides  
unfavorability of an olefin exocyclic to the  
cyclopropane ring.



Relative rate      A(%)      B(%)

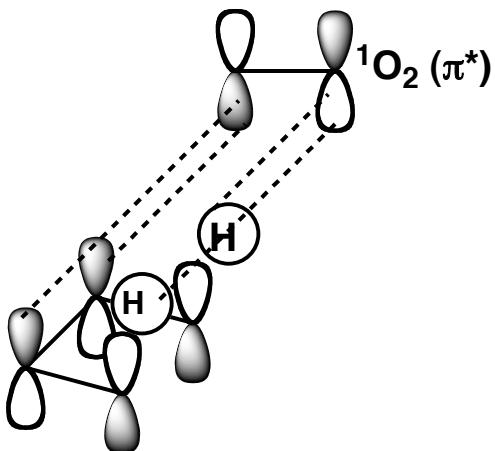
8                    80            20



A                    B

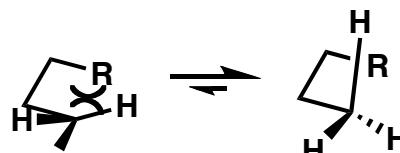
Rousseau, G.; LePerche, P.; Conia, J.M. *Tetrahedron Lett.* 2517 (1977).  
Lerdal, D.; Foote, C.S. *Tetrahedron Lett.* 3227 (1978).

## Secondary Orbital Overlap



Olefin	$\Delta H^\ddagger$ (kcal/mol)	$\Delta S^\ddagger$ (eu)	$k_r$ ( $M^{-1} s^{-1}$ )
	1.6	-35	$4.8 \times 10^4$
	0.3	-45	$7.2 \times 10^3$
	2.0	-34	$3.9 \times 10^4$
	0.4	-42	$7.7 \times 10^3$

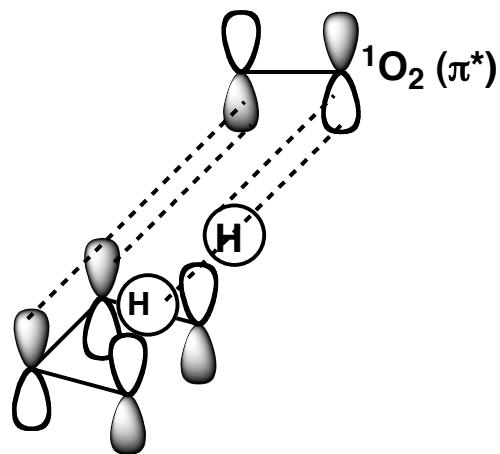
Less structural reorganization required upon forming perepoxide, since rotational barriers of cis vinyl substituents already exist.



Stephenson, L.M. *Tetrahedron Lett.* 21, 1005 (1980).

Houk, K.N.; Williams Jr., J.C.; Mitchell, P.A.; Yamaguchi, K. *J. Am. Chem. Soc.* 103, 949 (1981).

## *Secondary Orbital Overlap*

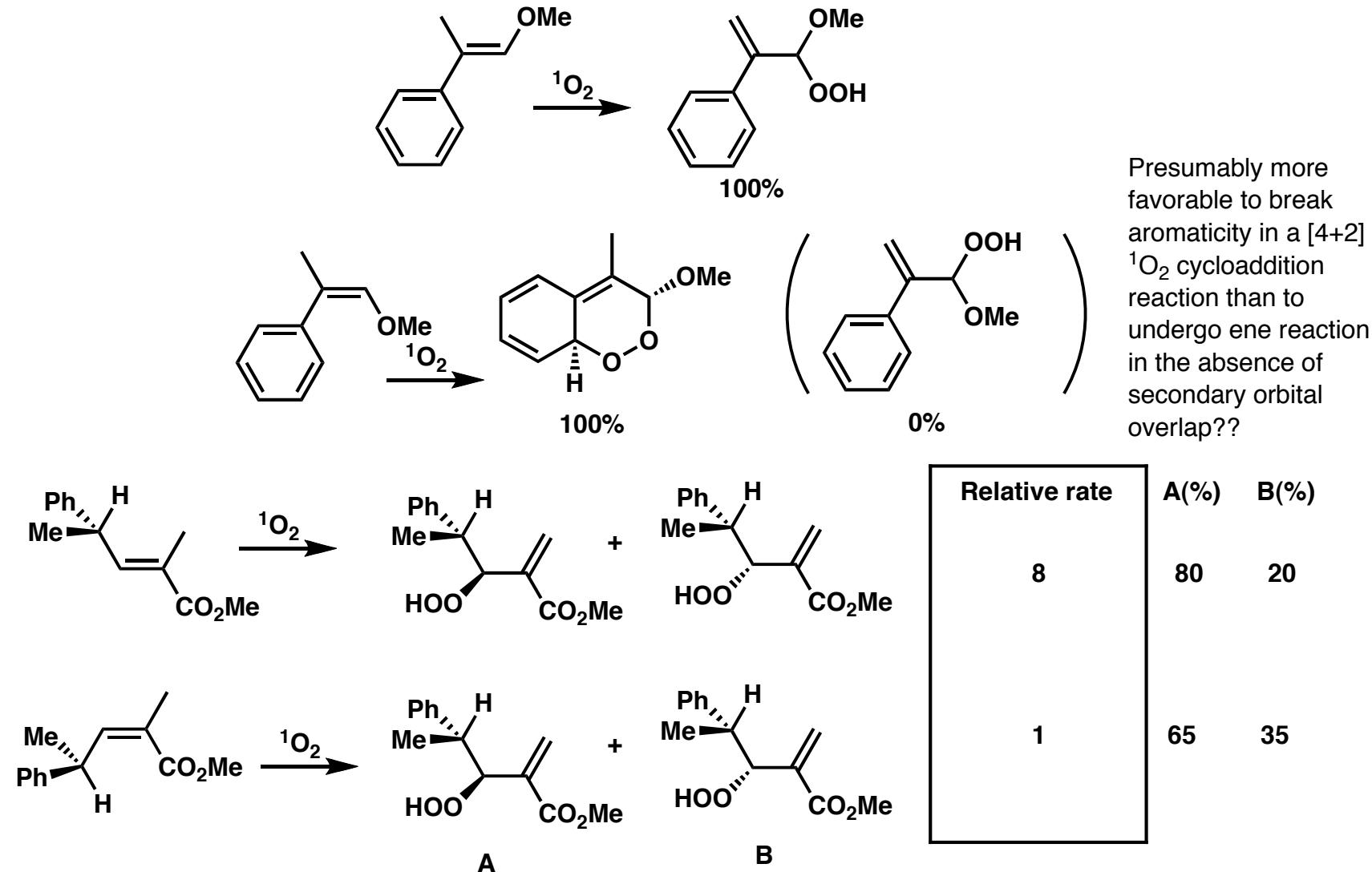


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Houk, K.N.; Williams Jr., J.C.; Mitchell, P.A.; Yamaguchi, K. *J. Am. Chem. Soc.* 103, 949 (1981).

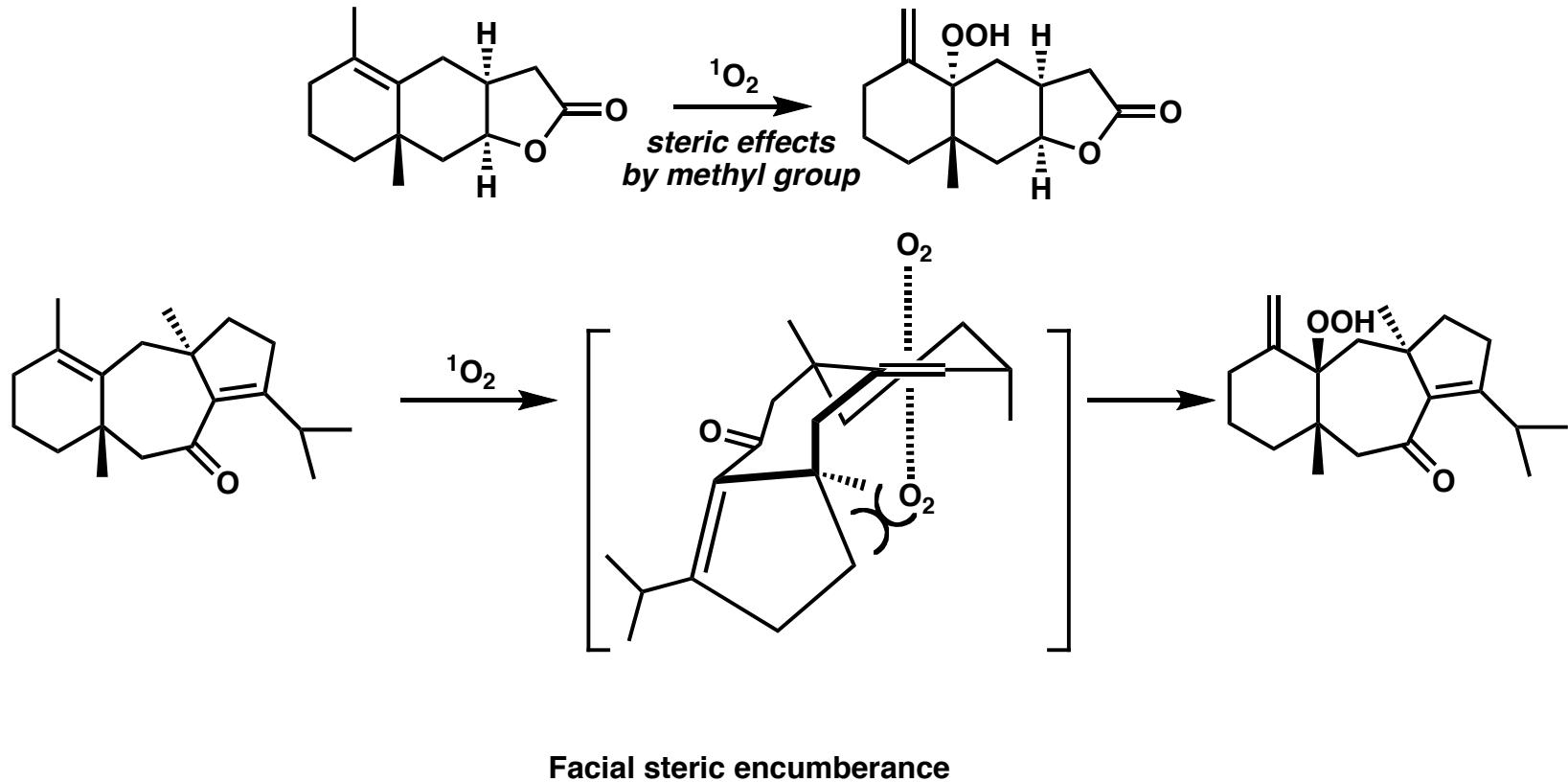
## *Effects of Secondary Orbital Overlap*



Lerdal, D.; Foote, C.S. *Tetrahedron Lett.* 3227 (1978).

# *Substituent Effects in the $^1\text{O}_2$ Ene Reaction*

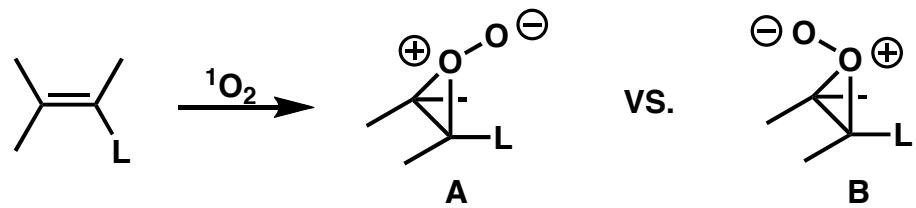
These range from the obvious....



Lin, H.-S.; Paquette, L.A. *Synth. Commun.* 16, 1275 (1986).

# *Substituent Effects in the ${}^1O_2$ Ene Reaction*

... to subtle...

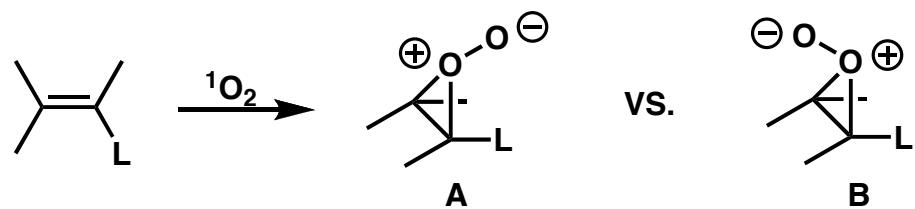


-Steric interactions between pendant O and L to favor structure B.

-Interactions between the perepoxide and L can lengthen the (L)C-O+ bond and encourage hydrogen abstraction from the geminal alkyl group.

# *Substituent Effects in the $^1O_2$ Ene Reaction*

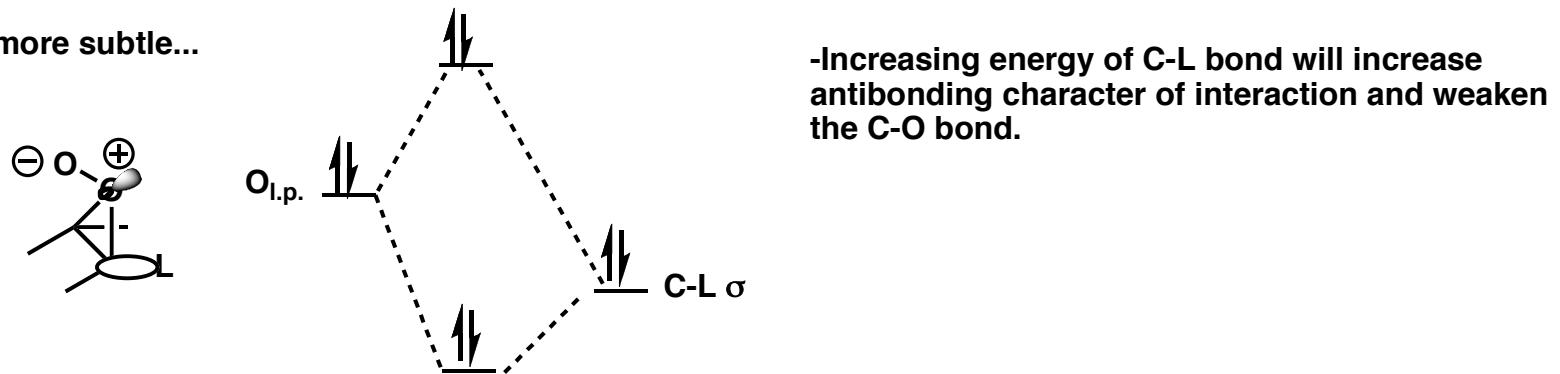
... to subtle...



-Steric interactions between pendant O and L to favor structure B.

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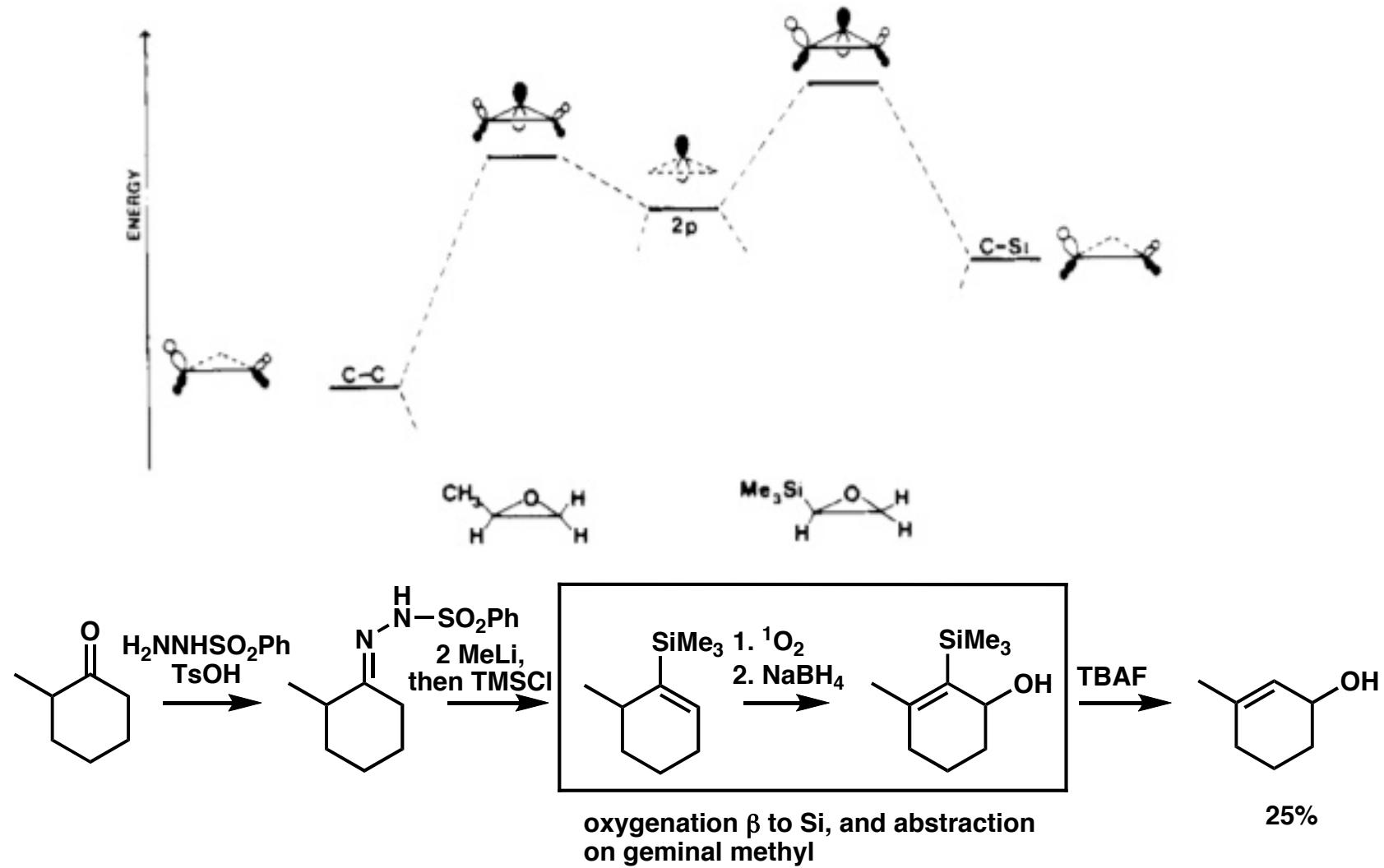
...to the more subtle...



-Increasing energy of C-L bond will increase antibonding character of interaction and weaken the C-O bond.

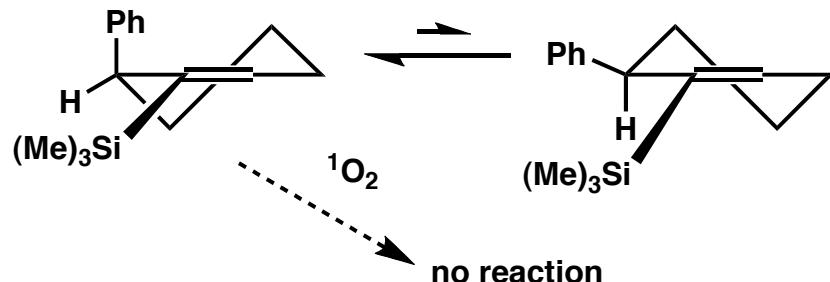
Fristad, W.E.; Bailey, T.R.; Paquette, L.A.; Gleiter, R.; Bohm, M.C. *J. Am. Chem. Soc.* 101, 4420 (1979).

# Stereoelectronic Effects Governing Regiochemistry

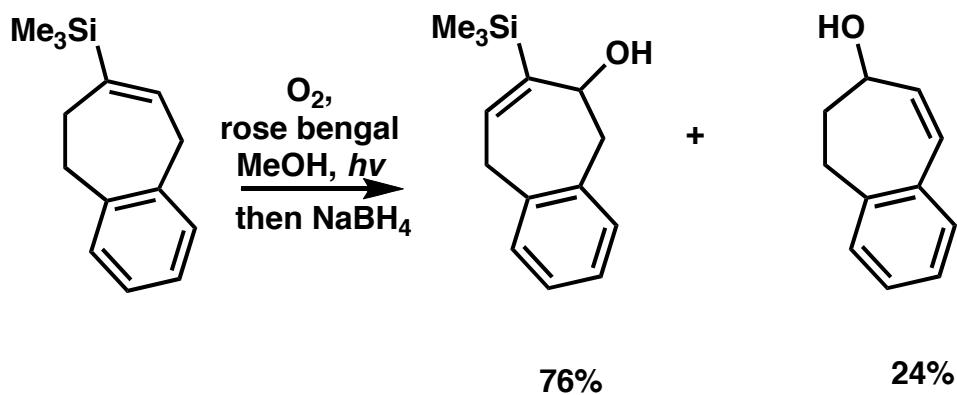


Fristad, W.E.; Bailey, T.R.; Paquette, L.A. *J. Am. Chem. Soc.* 101, 4420 (1979).

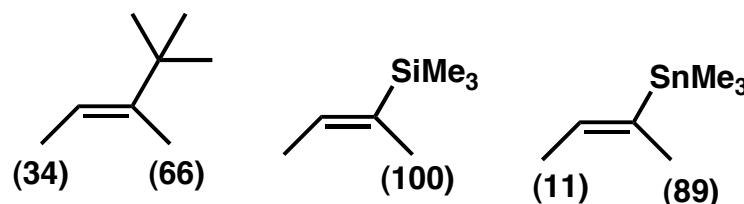
## *Interesting Regiochemical Effects*



Minimizing A[1,2] strain, the proton remains pseudoequatorial and cannot be abstracted by the perepoxide complex.



Despite the reactivity of the benzylic hydrogen, abstraction still occurs at the geminal methyl, presumably due to the stereoelectronic effect mentioned earlier.

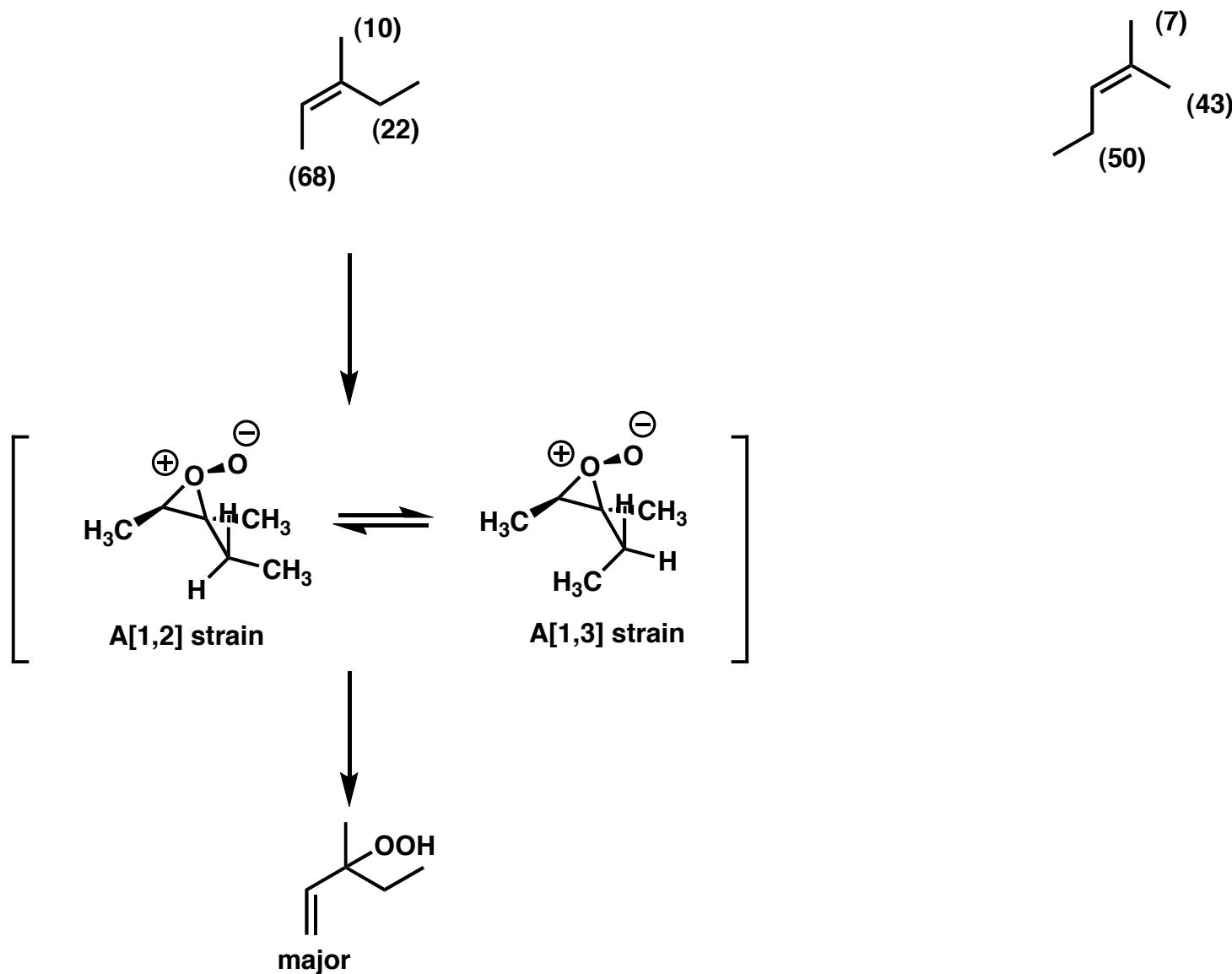


Steric and stereoelectronic effects work hand-in-hand. C-Sn, C-Si bonds are longest, and should mitigate steric effects, but electron rich C-Sn/Si bond strengthens stereoelectronic effect.

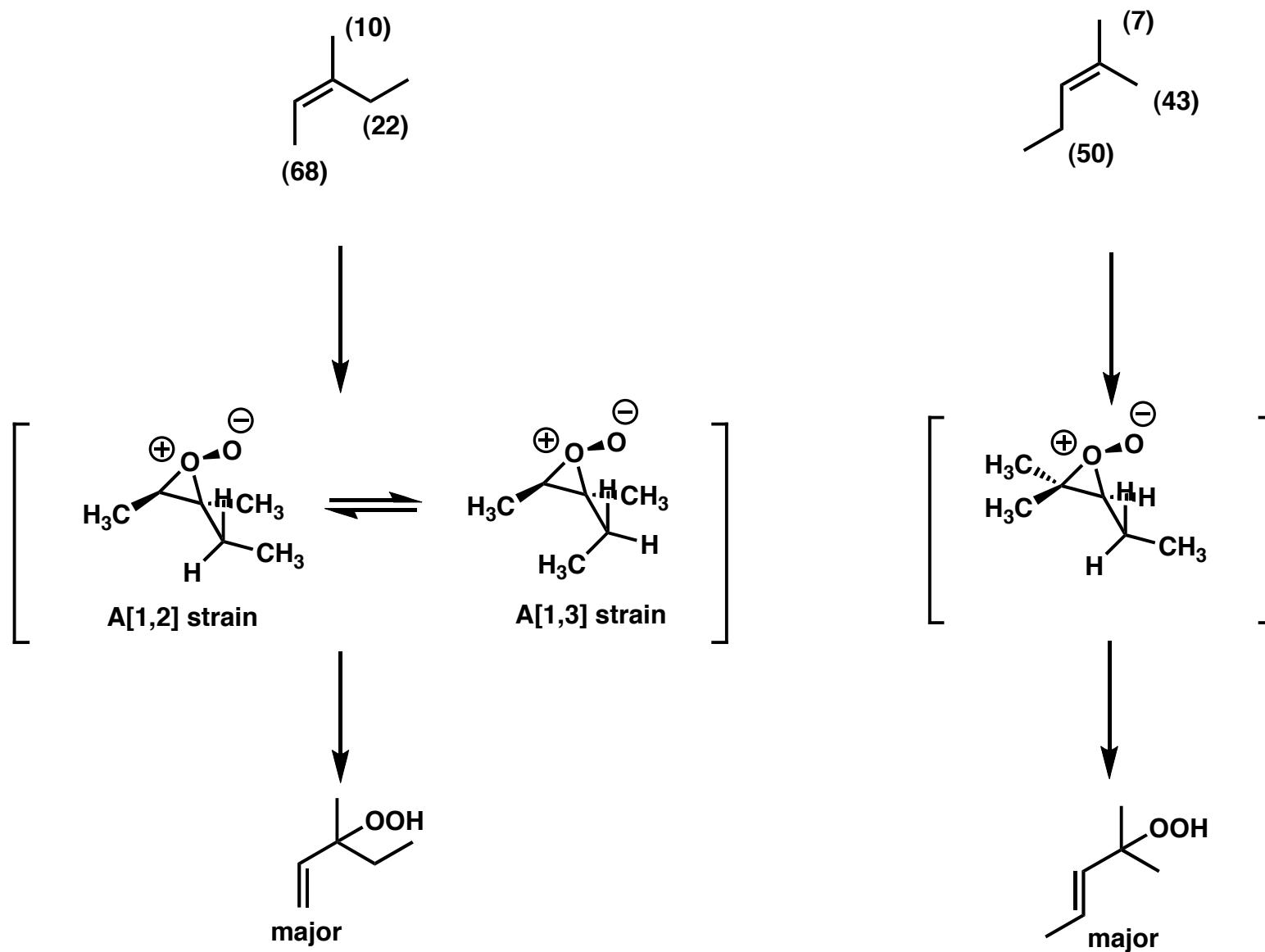
(x) = percent abstraction

Fristad, W.E.; Bailey, T.R.; Paquette, L.A. *J. Am. Chem. Soc.* 101, 4420 (1979).

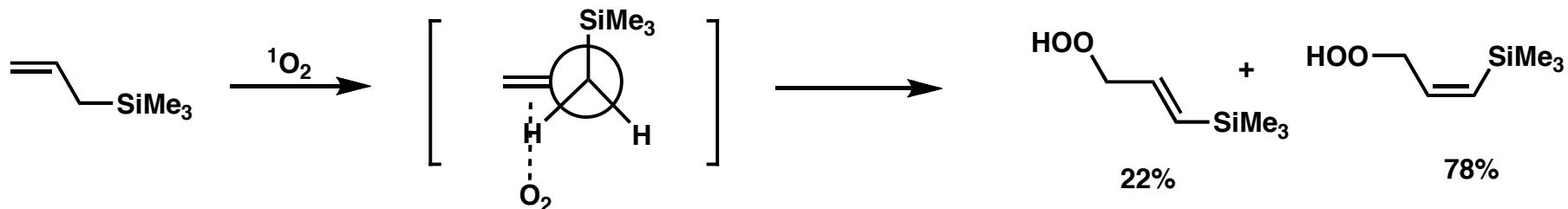
## *Allylic Strain As a Determining Factor*



## *Allylic Strain As a Determining Factor*

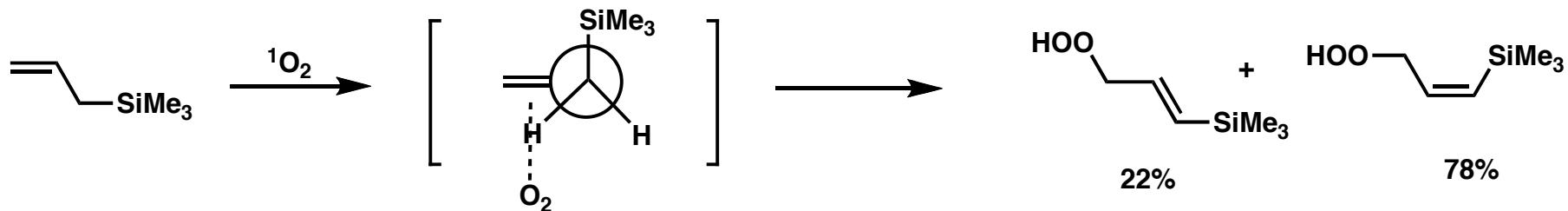


## *Electronic Effects*



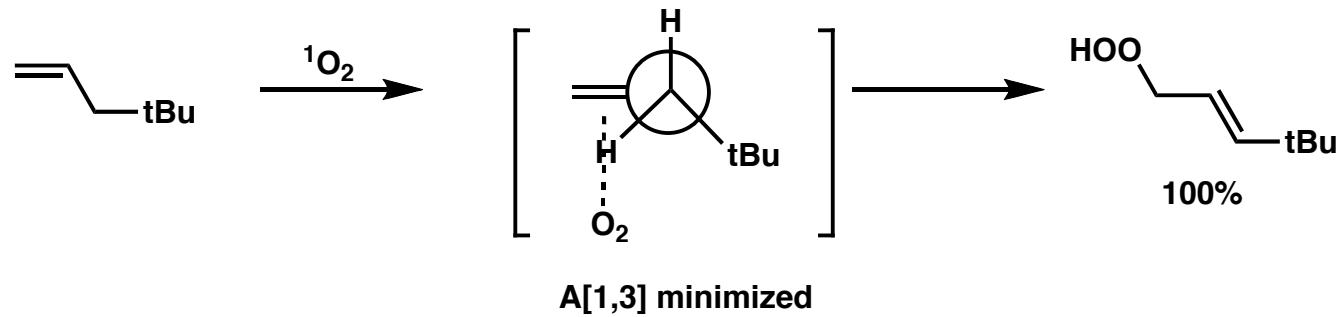
1. Hyperconjugation of C-Si bond into  $\pi$  bond forces C-Si bond perpendicular to the plane containing the olefin.
2.  $\text{O}_2$  approaches olefin face *anti* to the silyl group.

## *Electronic Effects*

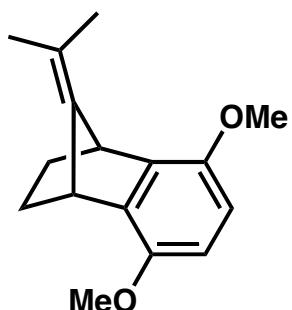
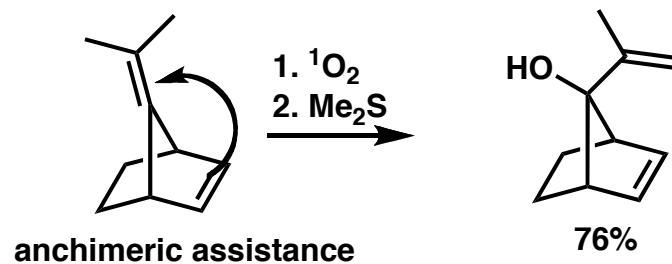


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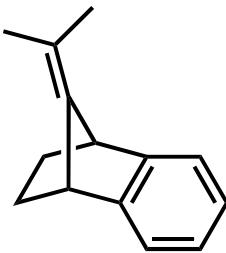
2.  $\text{O}_2$  approaches olefin face *anti* to the silyl group.



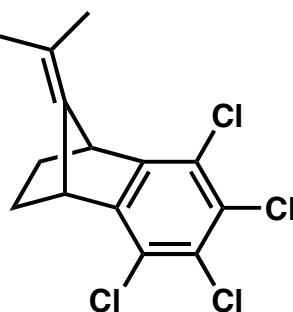
## *Electronic Effects*



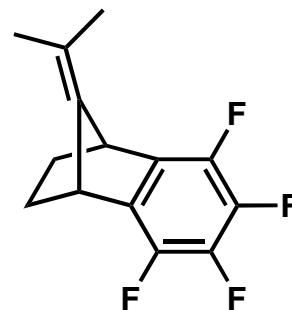
anti=79  
syn=21  
 $k(M^{-1}s^{-1}) = 4.28 \times 10^6$



anti=80  
syn=20  
 $k(M^{-1}s^{-1}) = 1.36 \times 10^5$



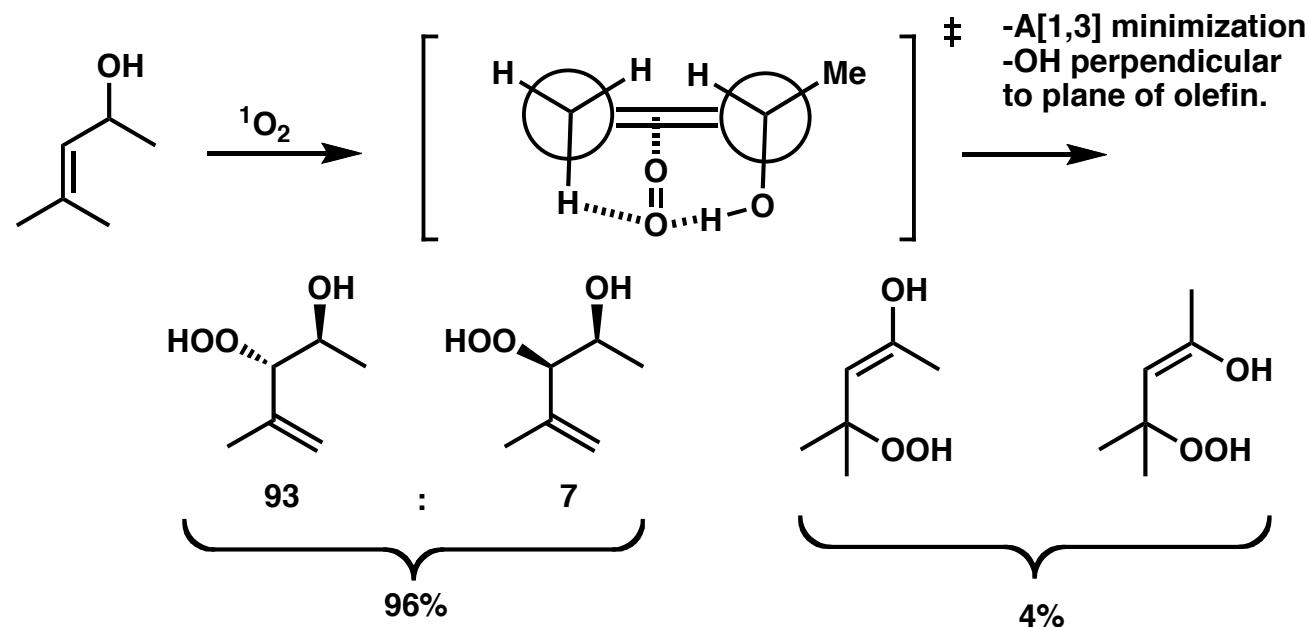
anti=48  
syn=52  
 $k(M^{-1}s^{-1}) = 9.63 \times 10^4$



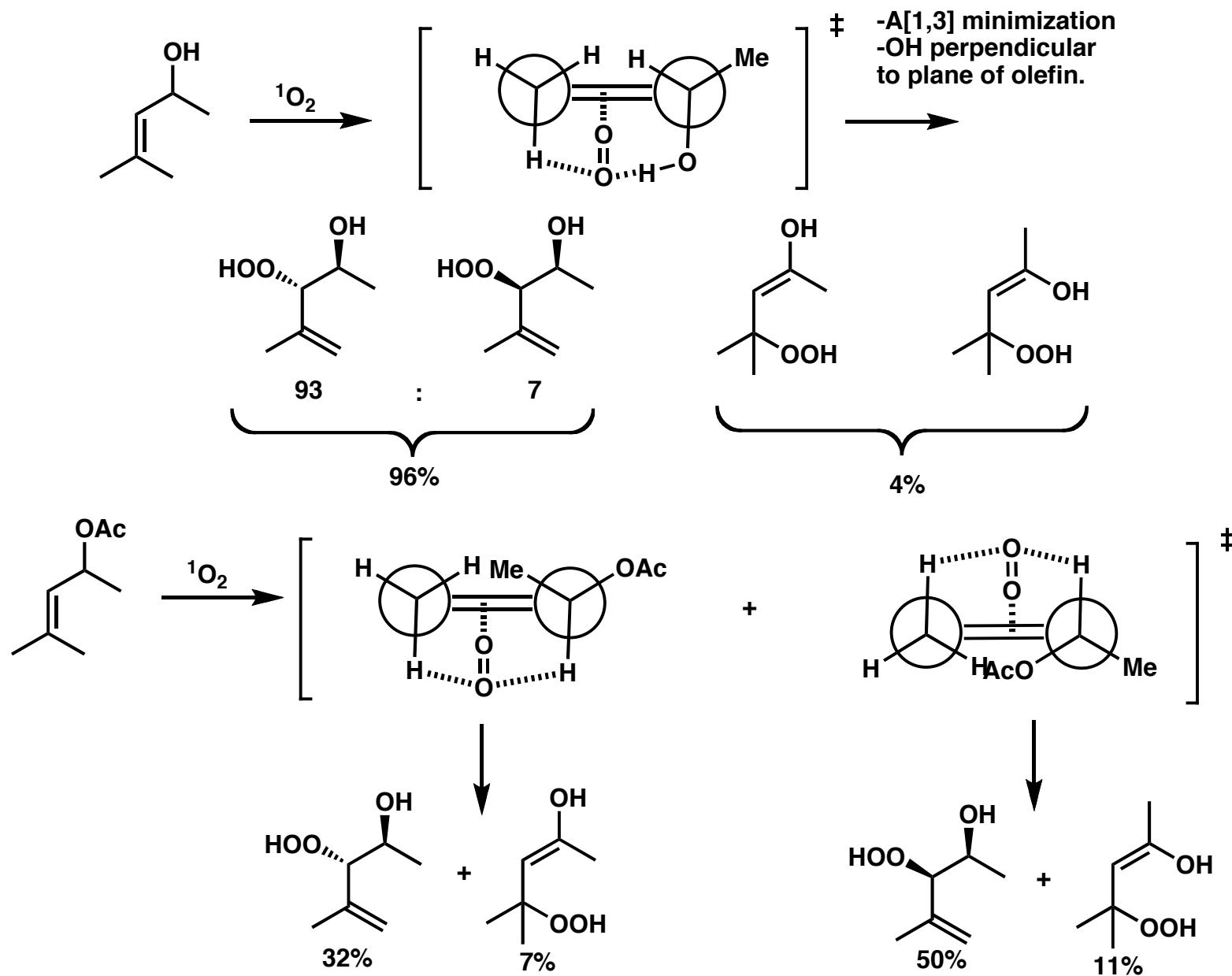
anti=46  
syn=54  
 $k(M^{-1}s^{-1}) = 5.24 \times 10^4$

Okada, K.; Mukai, T. *J. Am. Chem. Soc.* 100, 6509 (1978).  
Hertel, L.W.; Paquette, L.A. *J. Am. Chem. Soc.* 101, 7620 (1979).

## *Hydrogen Bonding Effects*

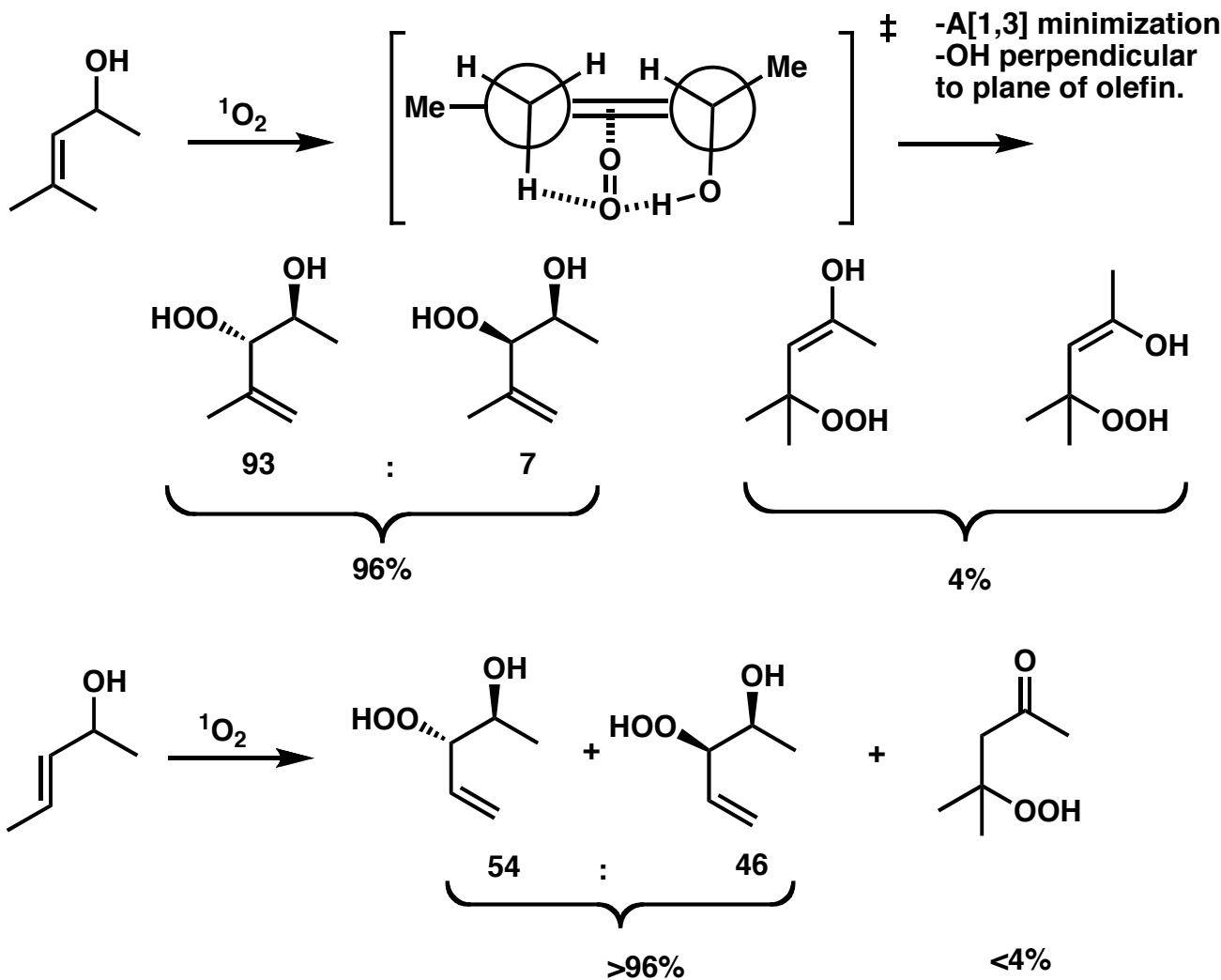


## Hydrogen Bonding Effects



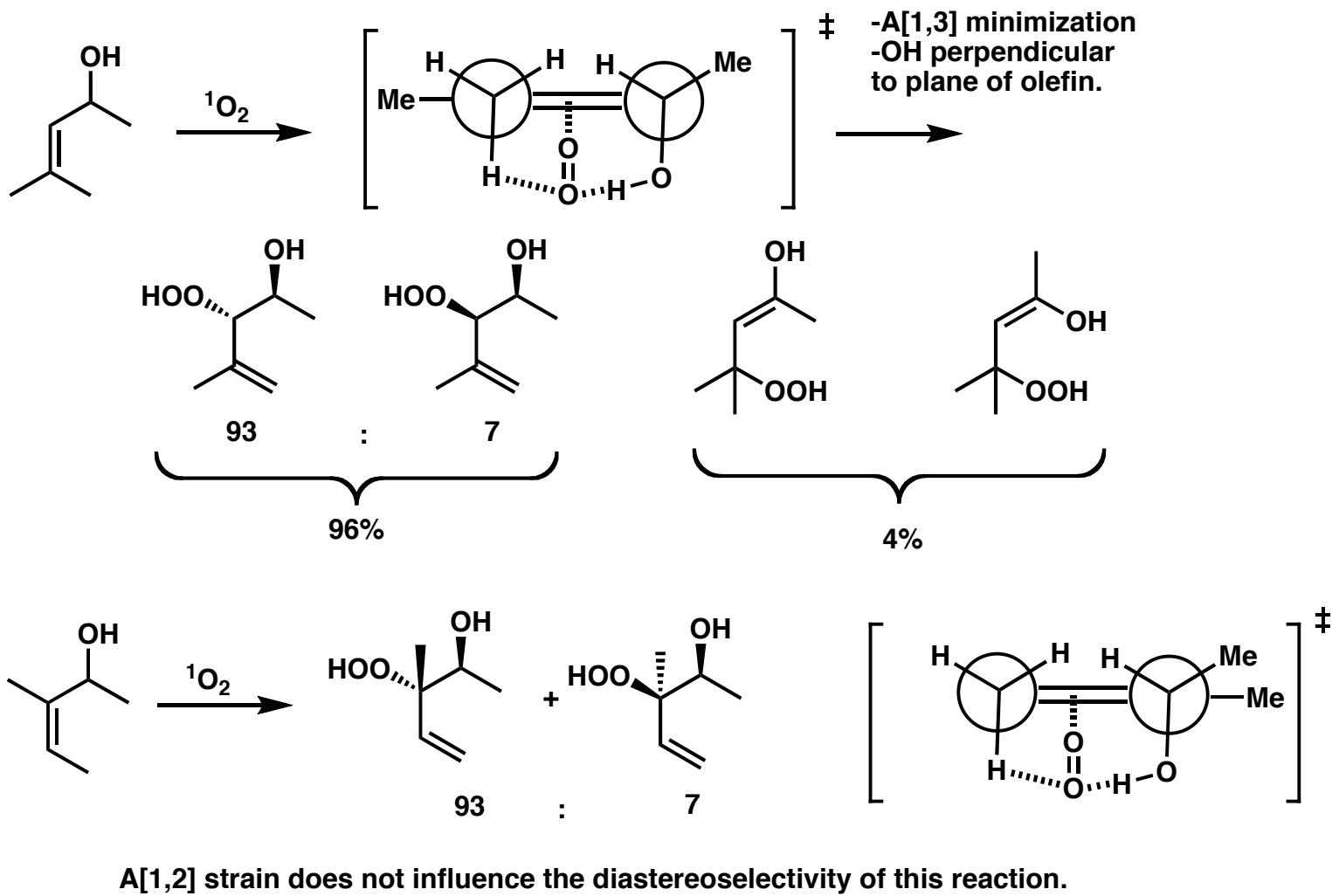
Adam, W.; Nestler, B. *J. Am. Chem. Soc.* 115, 5041 (1993).

## Hydrogen Bonding Effects



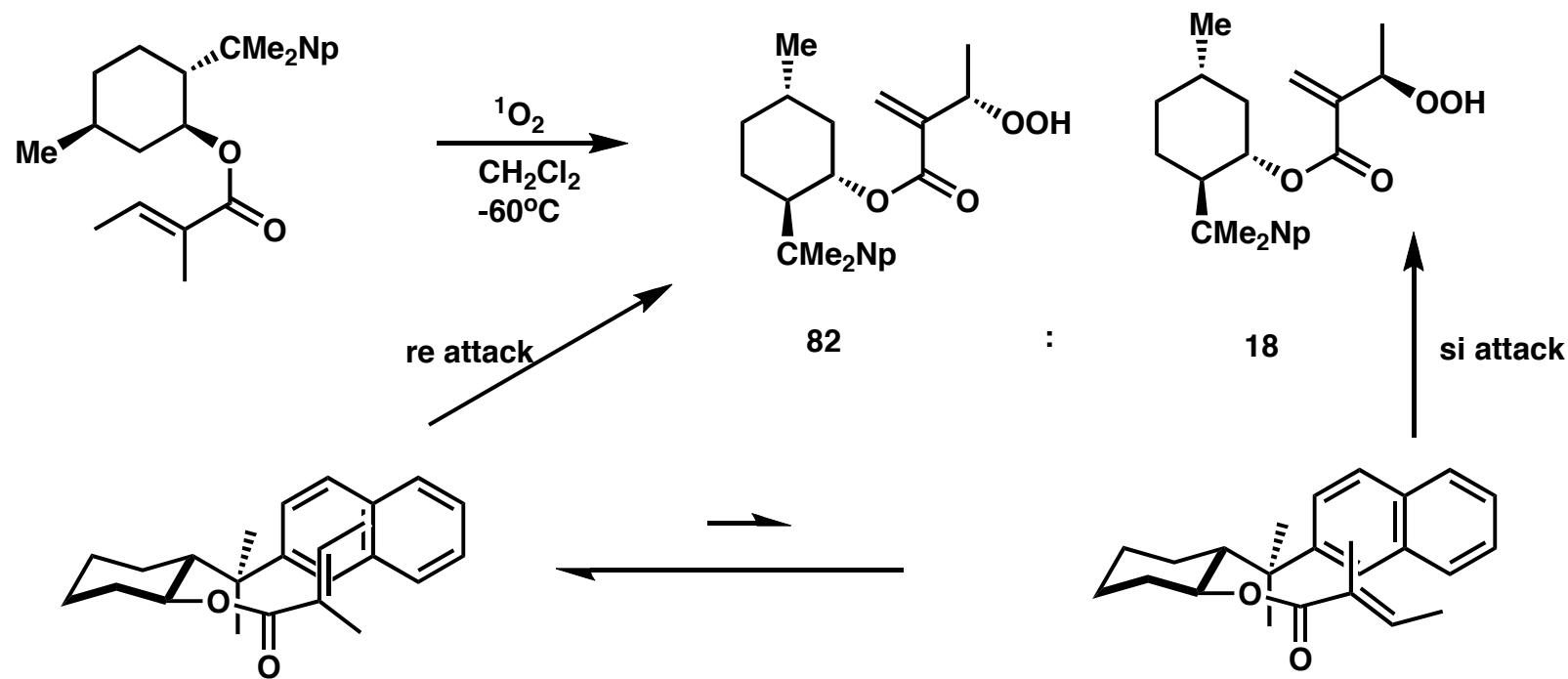
No A[1,3] strain to direct preference of one conformation over the other.  
 Perepoxide can hydrogen bond to -OH or participate in *cis* effect with *anti* methyl.

## Hydrogen Bonding Effects



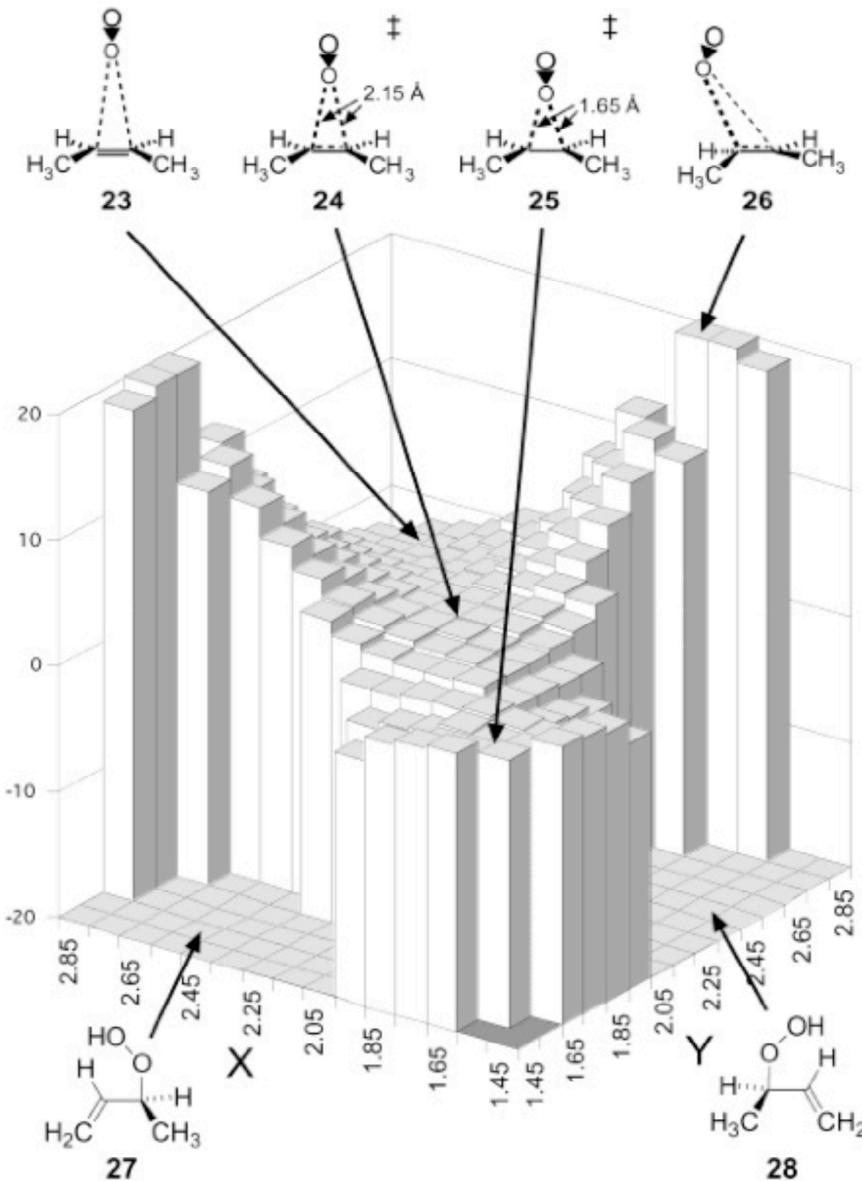
Adam, W.; Nestler, B. *J. Am. Chem. Soc.* 115, 5041 (1993).

## *Chiral Auxiliaries in the $^1O_2$ Ene Reaction*

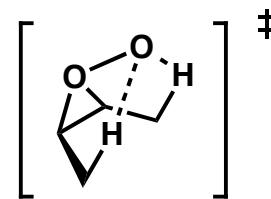


Dussault, P.H.; Woller, K.R., Hillier, M.C. *Tetrahedron* 50, 8929 (1994).

# *A Two-Step, No-Intermediate Ene Reaction?*



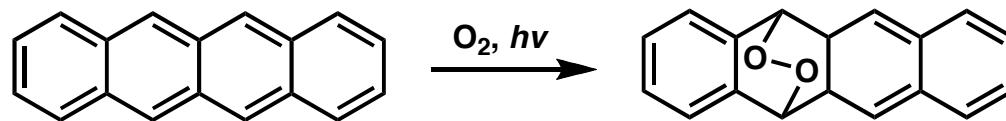
- At 24, we see the reaction heading towards a perepoxide intermediate.
- Structure 25 is not an intermediate, but a transition state!
- At 25, the reaction path can bifurcate toward one of two products.



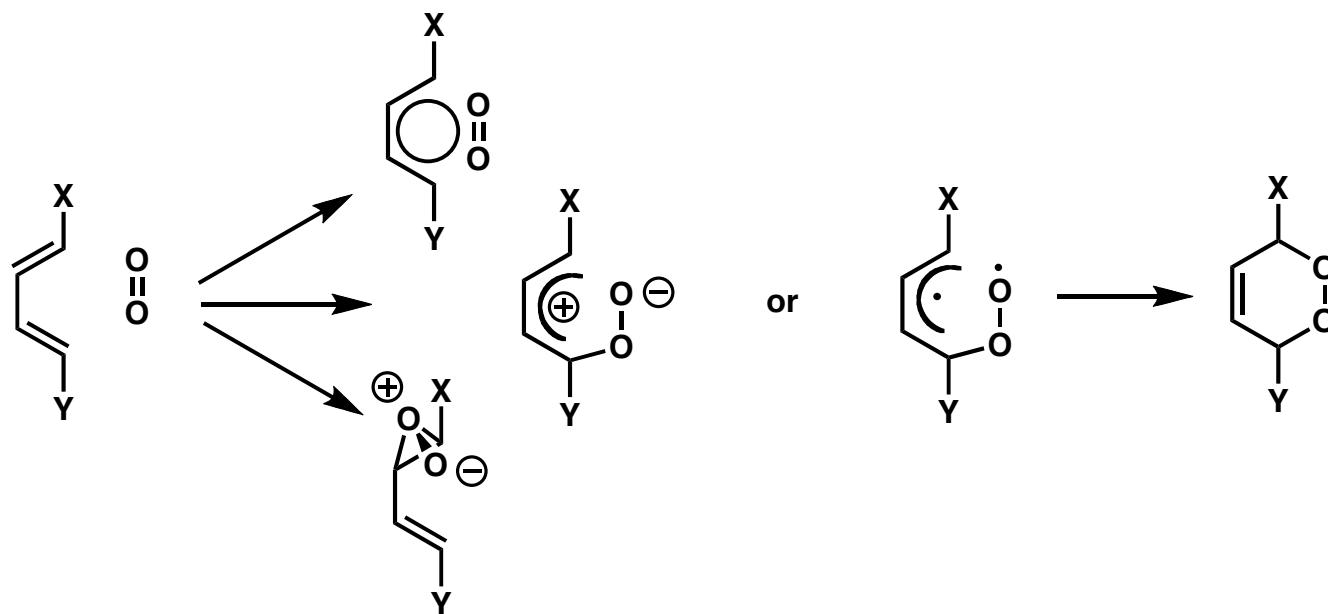
- Not a concerted reaction, because there are two kinetically distinguishable steps that can be influenced through isotopic substitution.
- "Two-step, no-intermediate mechanism."

Houk et al. *J. Am. Chem. Soc.* 125, 1319 (2003).

## $^1O_2$ [4+2] Cycloadditions

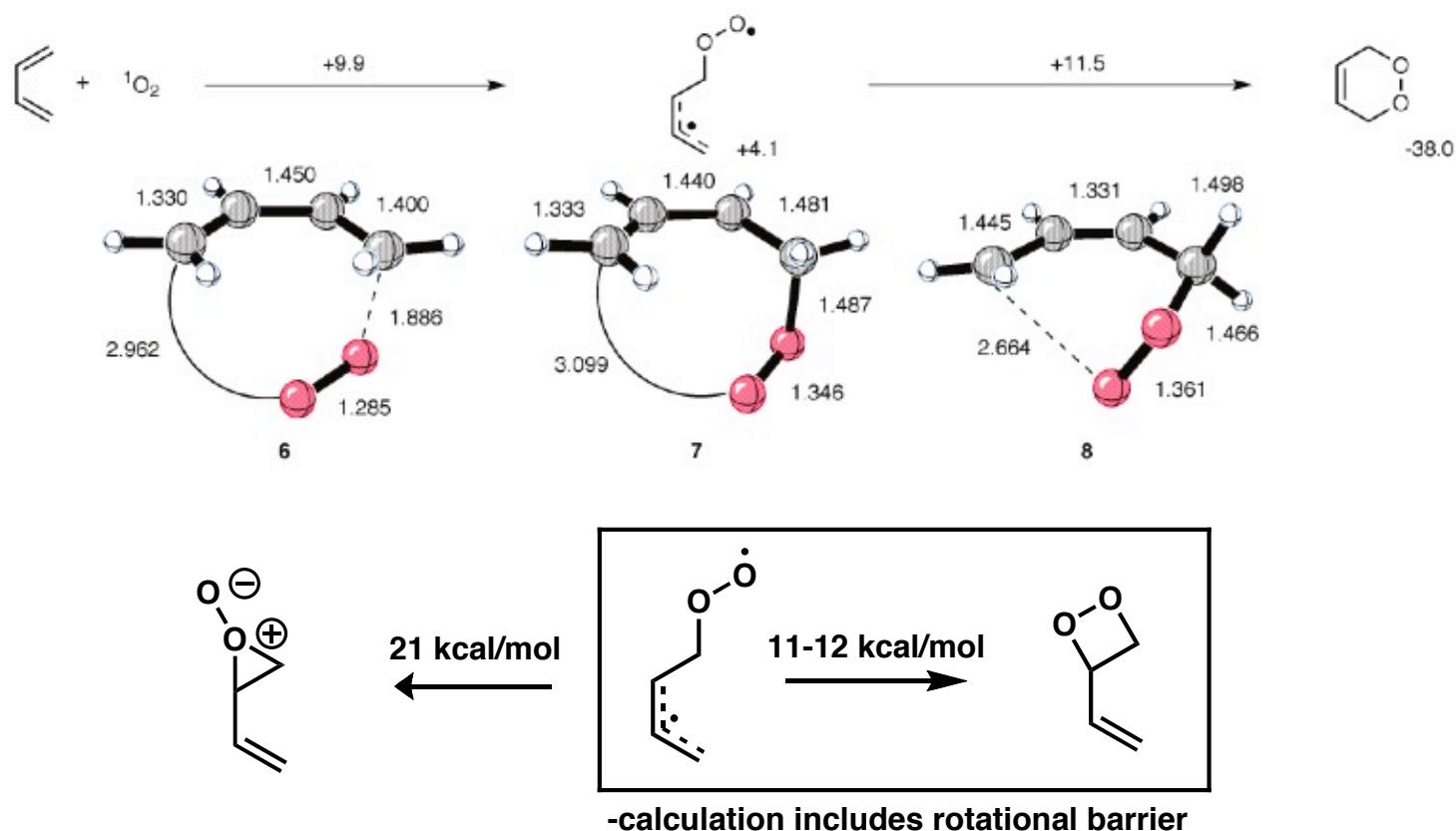


-At least a formal [4+2] reaction, but is it concerted or stepwise?  
 $^1O_2$  is a superdienophile by virtue of its dipole.



# *Quantum Chemical Treatment of the [4+2] Cycloaddition of $^1O_2$*

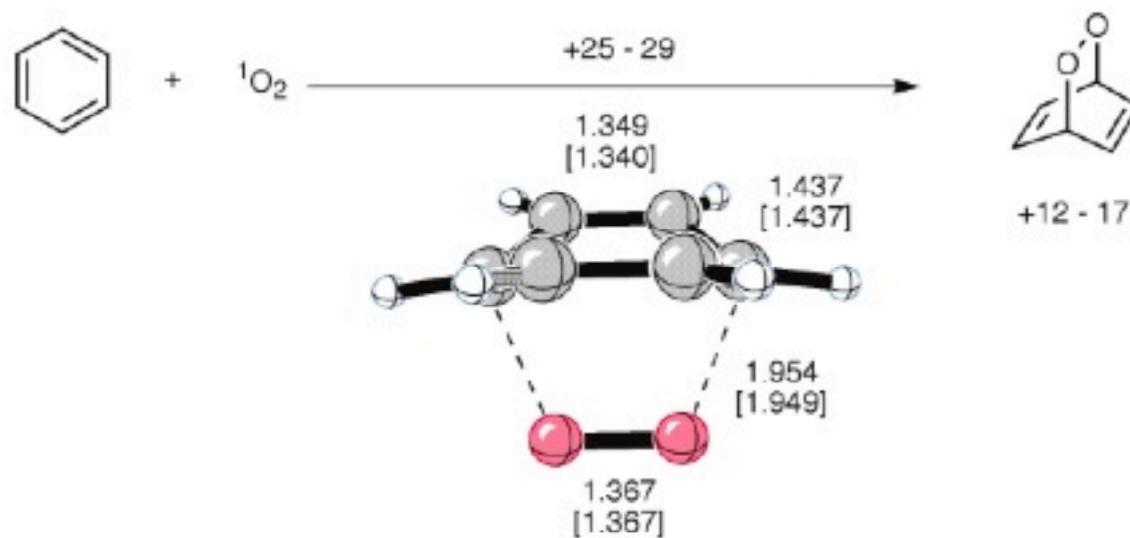
-Path of least energy to the endoperoxide involves a singlet diradical intermediate, followed by ring closure.



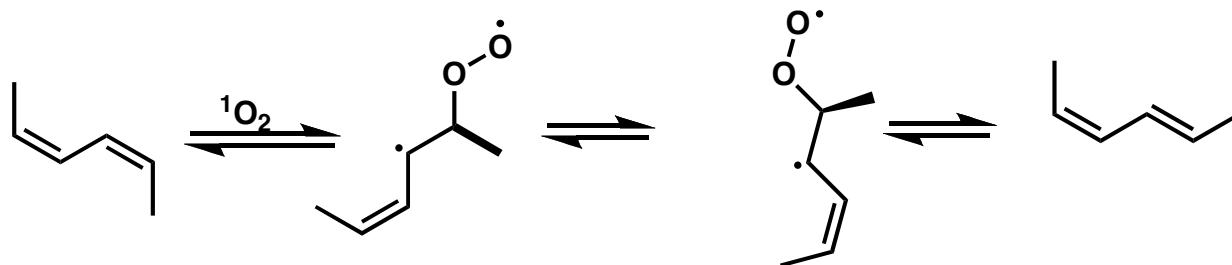
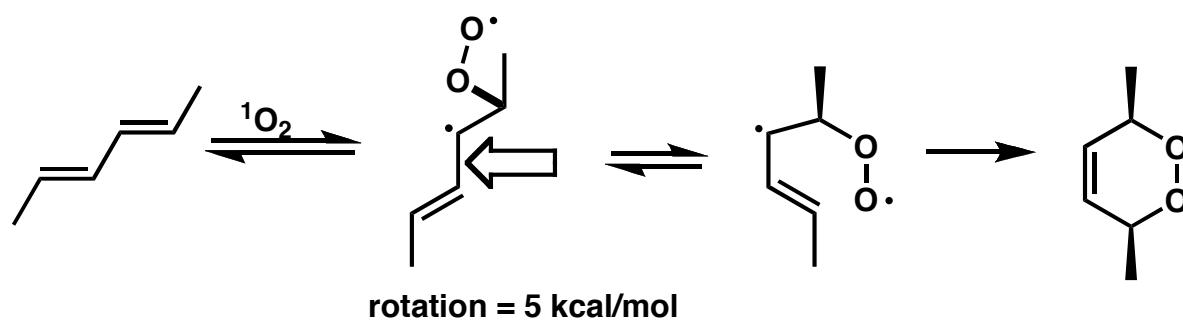
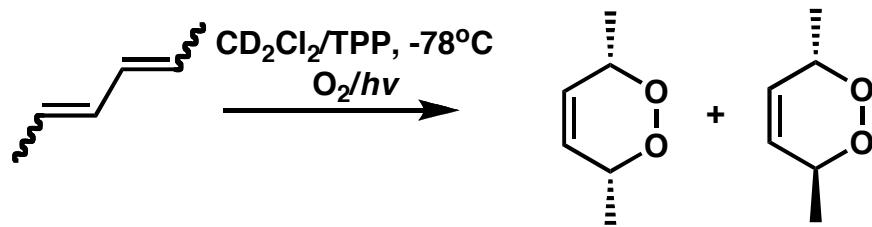
Bobrowski, M.; Liwo, A.; Odziej, S.; Jeziorek, D.; Ossowki, T. *J. Am. Chem. Soc.* 122, 8112 (2000).

# *Quantum Chemical Treatment of the [4+2] Cycloaddition of $^1\text{O}_2$*

- A concerted mechanism prevails with aromatics.
- A diradical intermediate at 26.7 kcal/mol could not be linked to the reactants via a transition state.



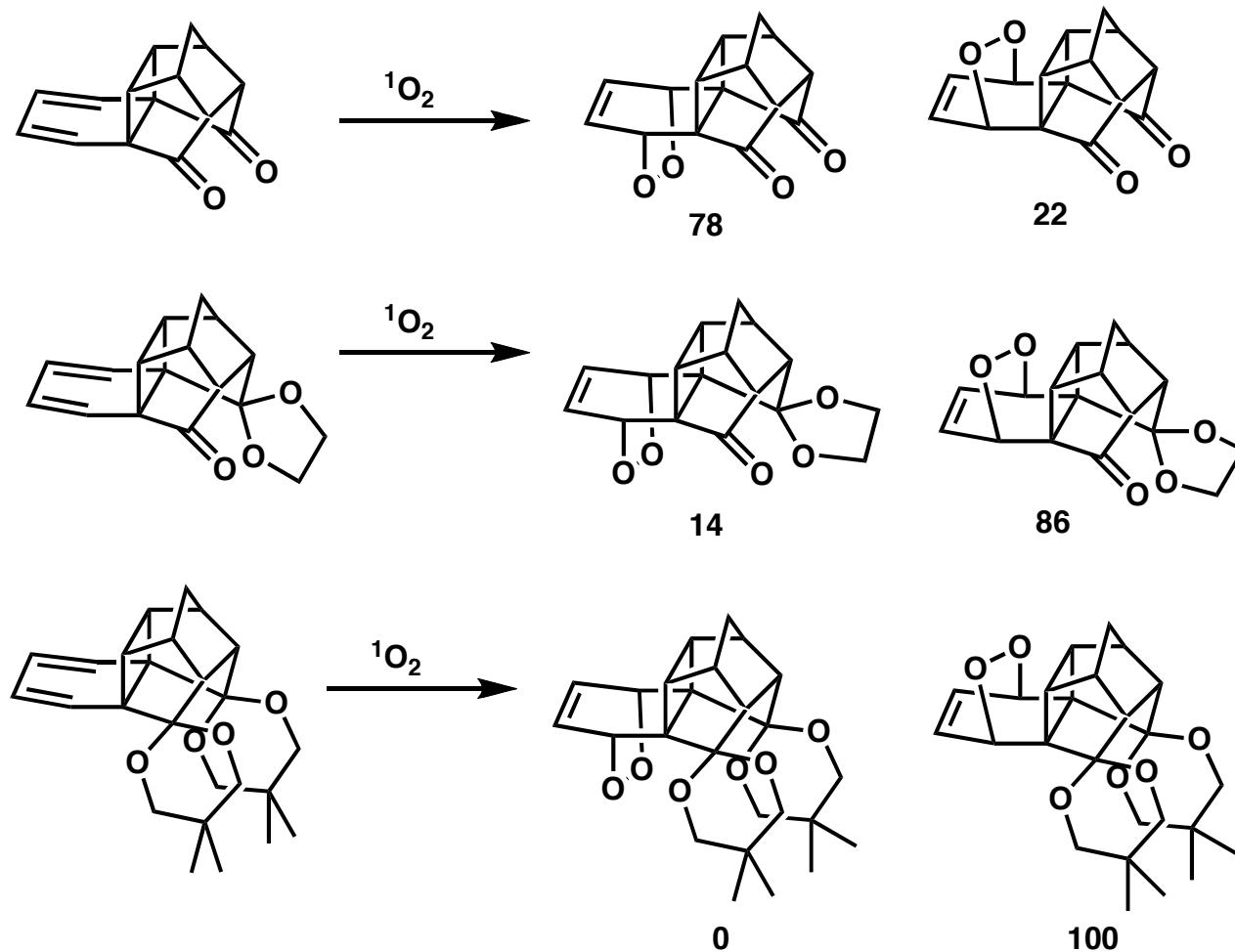
## *Experimental Evidence for Stepwise Mechanism*



-Isomerization leads to most stable diene, which can undergo oxygenation.

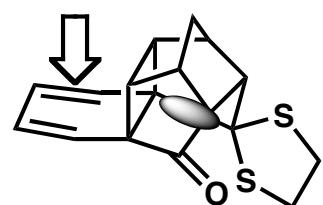
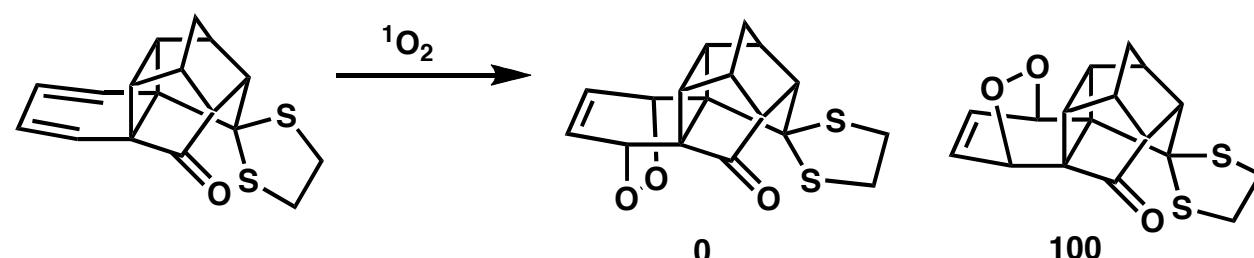
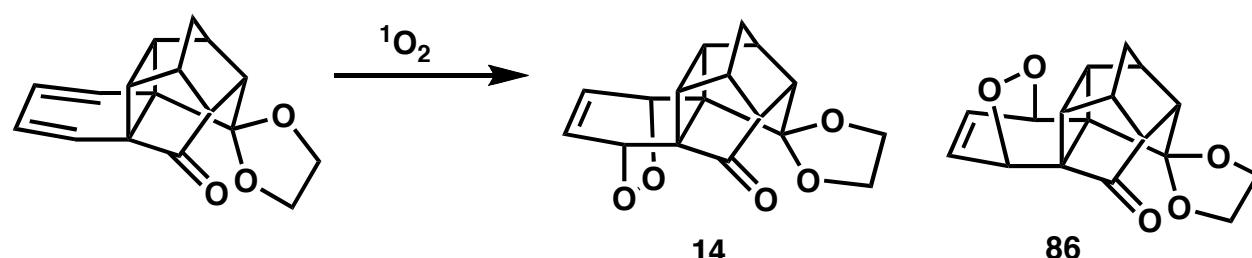
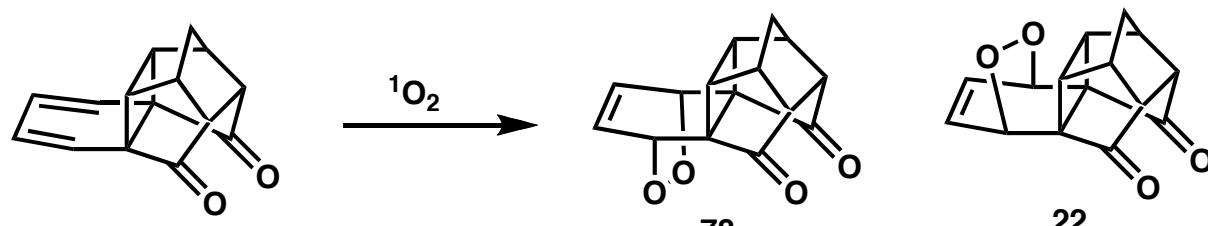
O'Shea, K.E.; Foote, C.S. *J. Am. Chem. Soc.* 110, 7167 (1988).

*Guiding Effects in the [4+2] Cycloaddition of  $^1O_2$*



Mehta, G.; Uma, R. *J. Org. Chem.* 65, 1685 (2000).

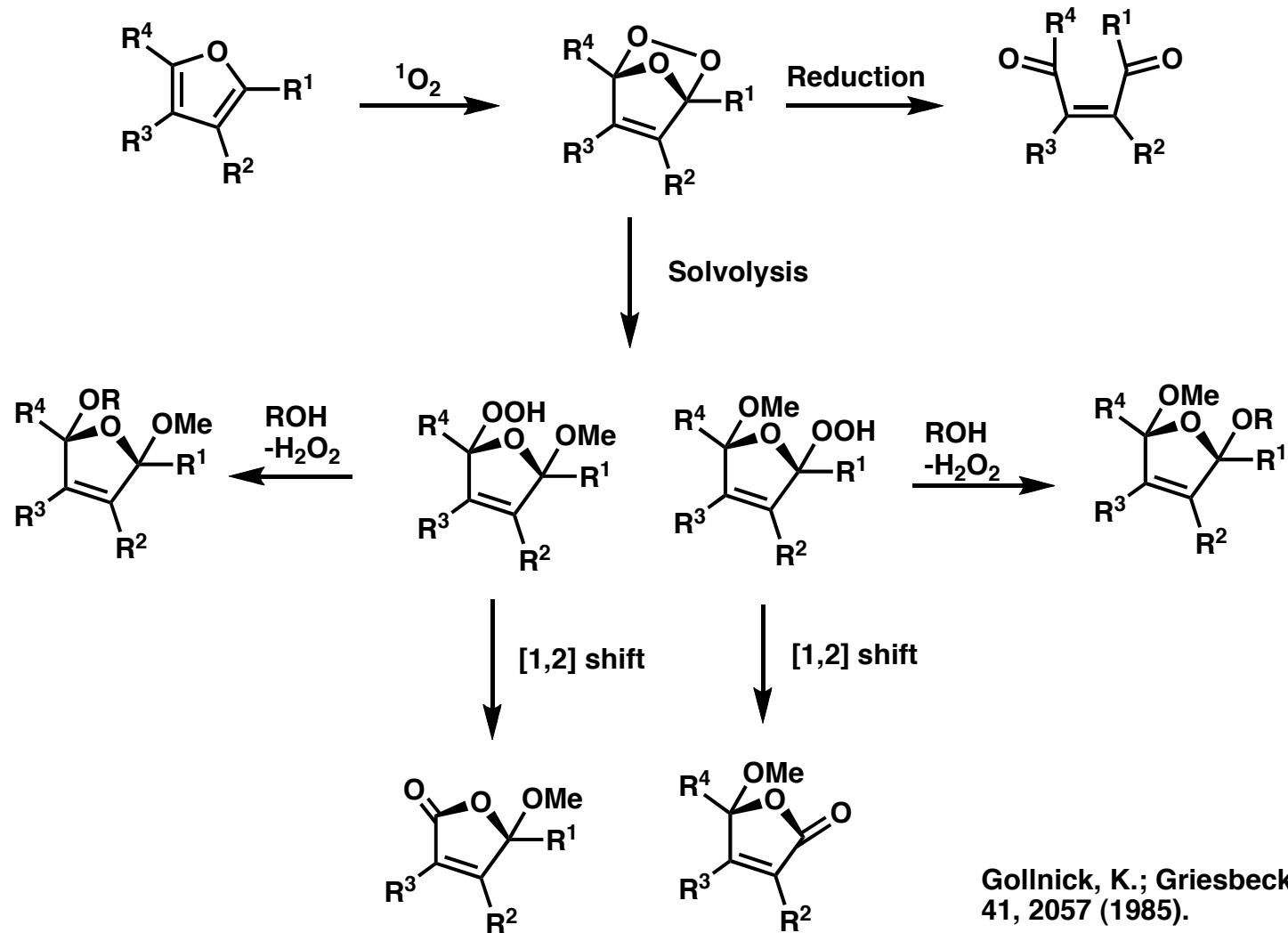
## *Guiding Effects in the [4+2] Cycloaddition of $^1O_2$*



C-thioacetal bond is more electron rich than cyclobutane bonds.  
Cieplak model predicts  $^1O_2$  addition from opposite face to minimize dipole.

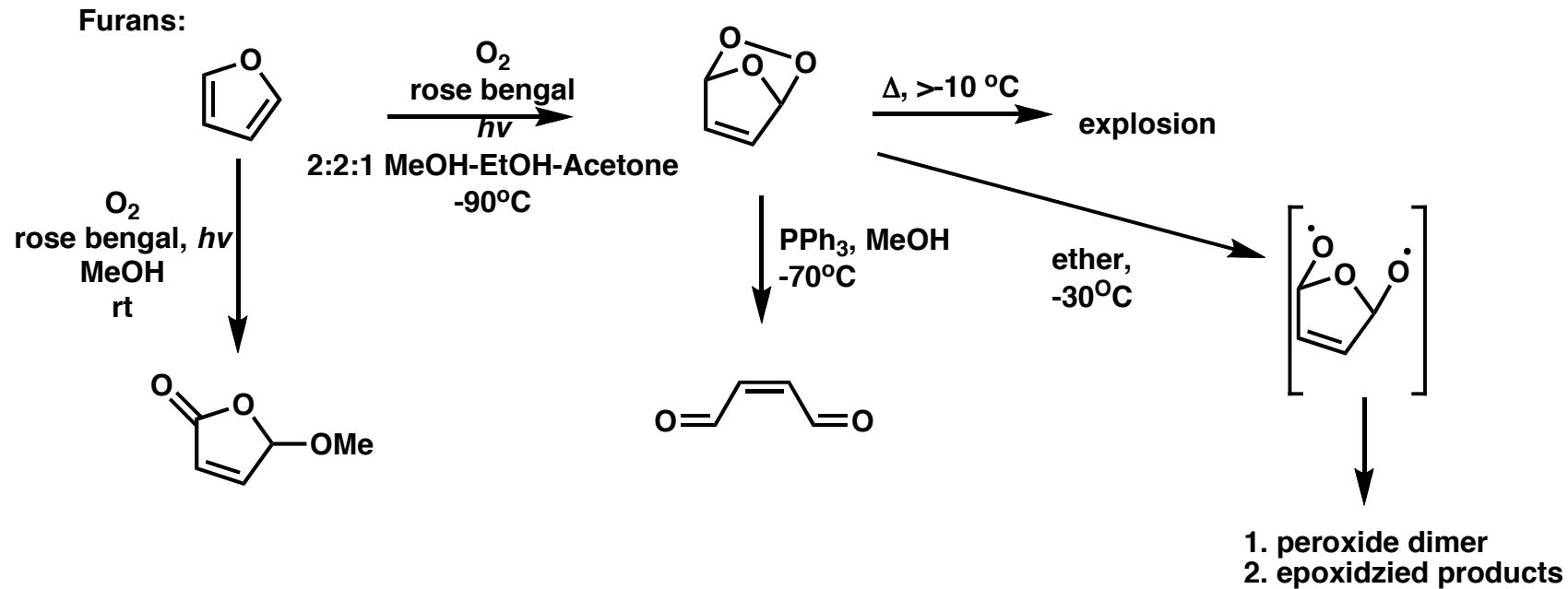
# *Heterocycles as Cycloaddition Substrates*

Furans:



Gollnick, K.; Griesbeck, A. *Tetrahedron*, 41, 2057 (1985).

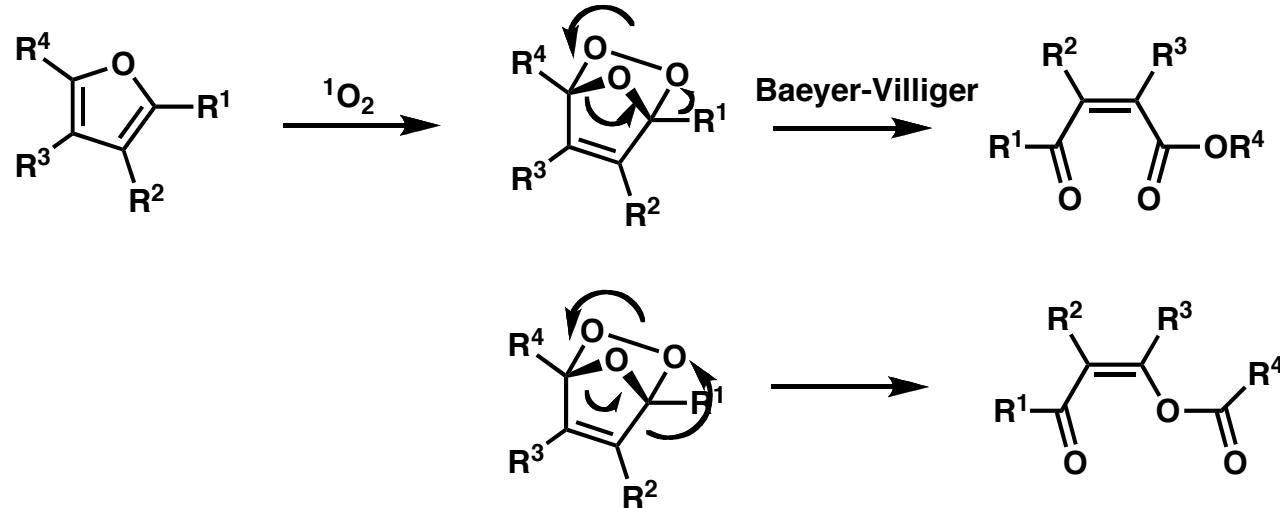
# Heterocycles as Cycloaddition Substrates



Gollnick, K.; Griesbeck, A. *Tetrahedron*, 41, 2057 (1985).  
Koch, E.; Schenck, G.O. *Chem. Ber.* 99, 1984 (1966).

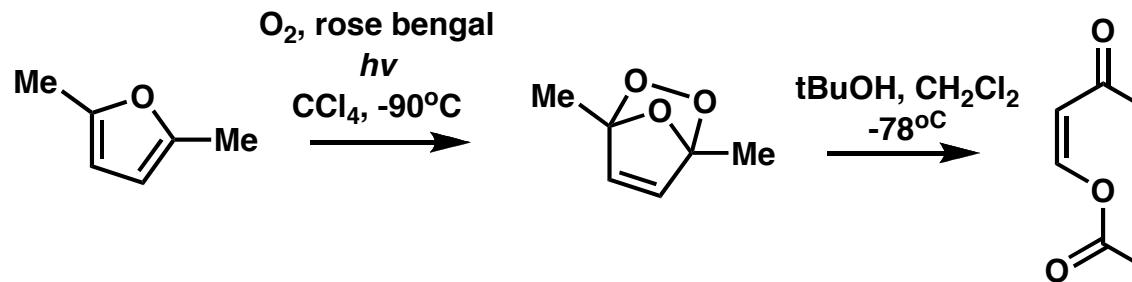
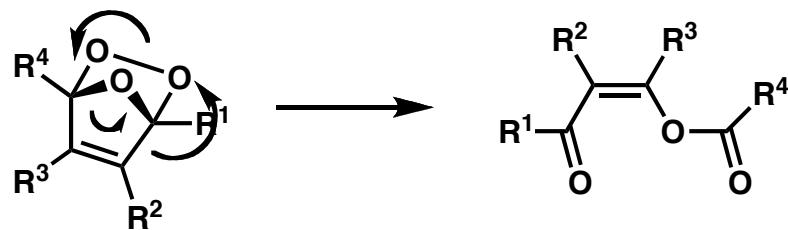
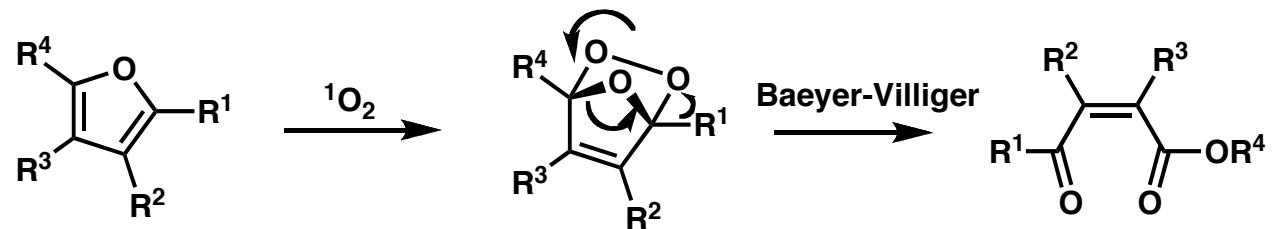
# *Heterocycles as Cycloaddition Substrates*

**Furans:**



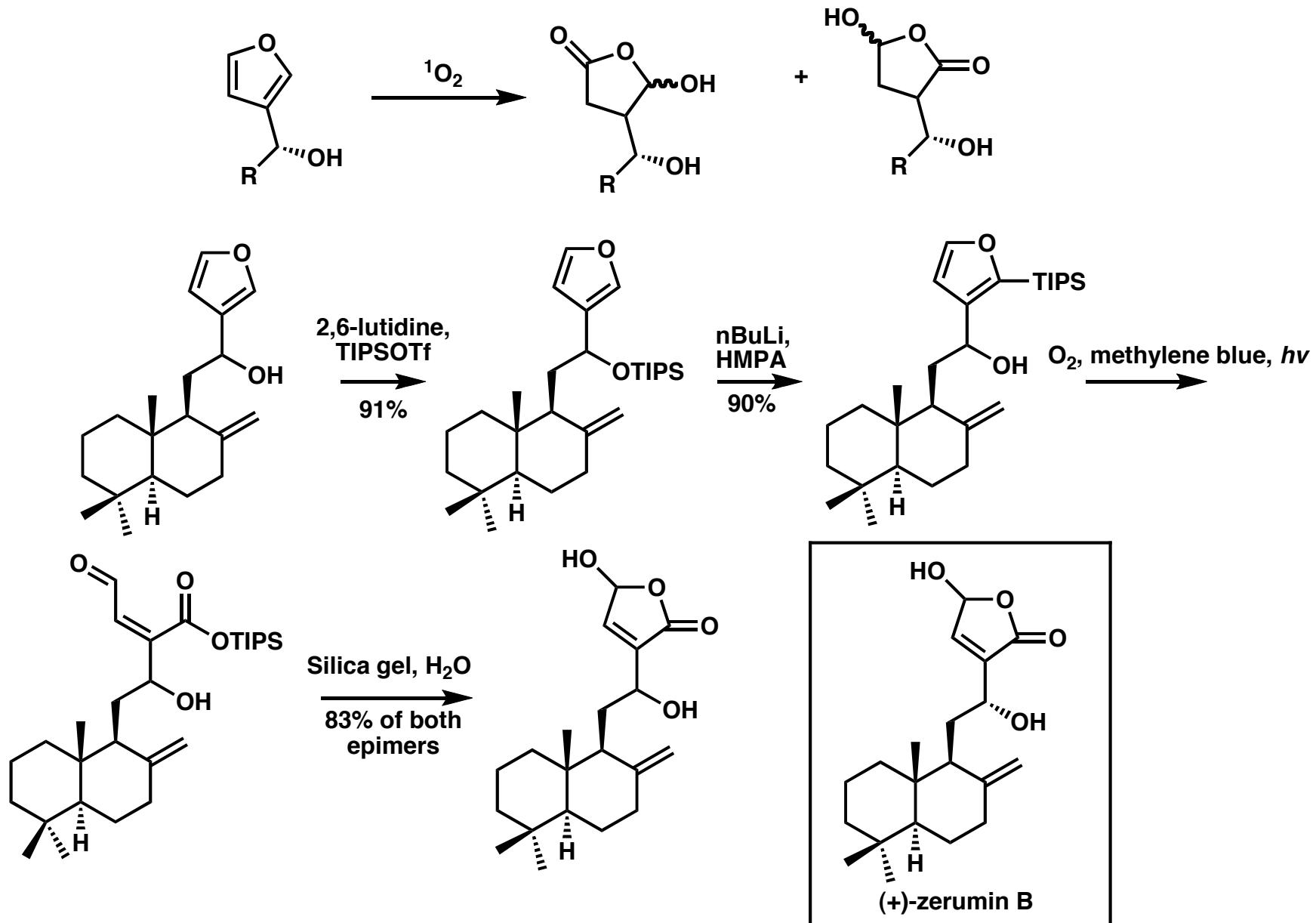
# *Heterocycles as Cycloaddition Substrates*

Furans:



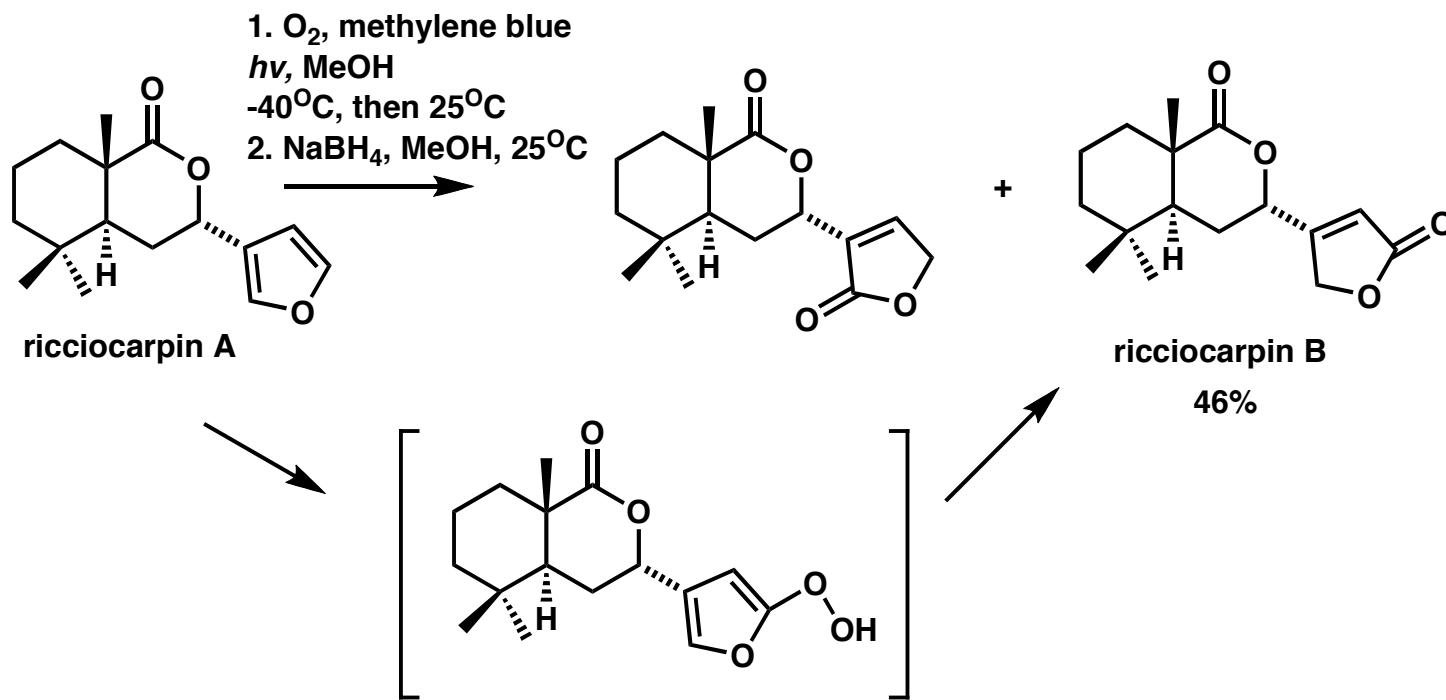
Gollnick, K.; Griesbeck, A. *Tetrahedron*, 41, 2057 (1985).  
Adam, W.; Rodriguez, A. *Tetrahedron Lett*, 22, 3509 (1981).

## *Manipulating Ozonide Cleavage*

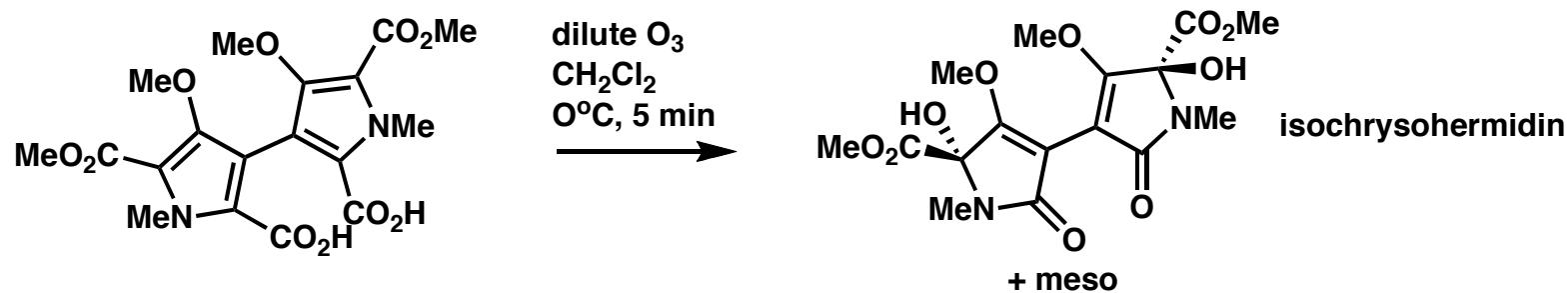


Margaros, I; Vassilikogiannakis, G. *J. Org. Chem.* 73, 2021 (2008).

# $^1O_2 [4+2]$ Cycloadditions in Natural Product Synthesis

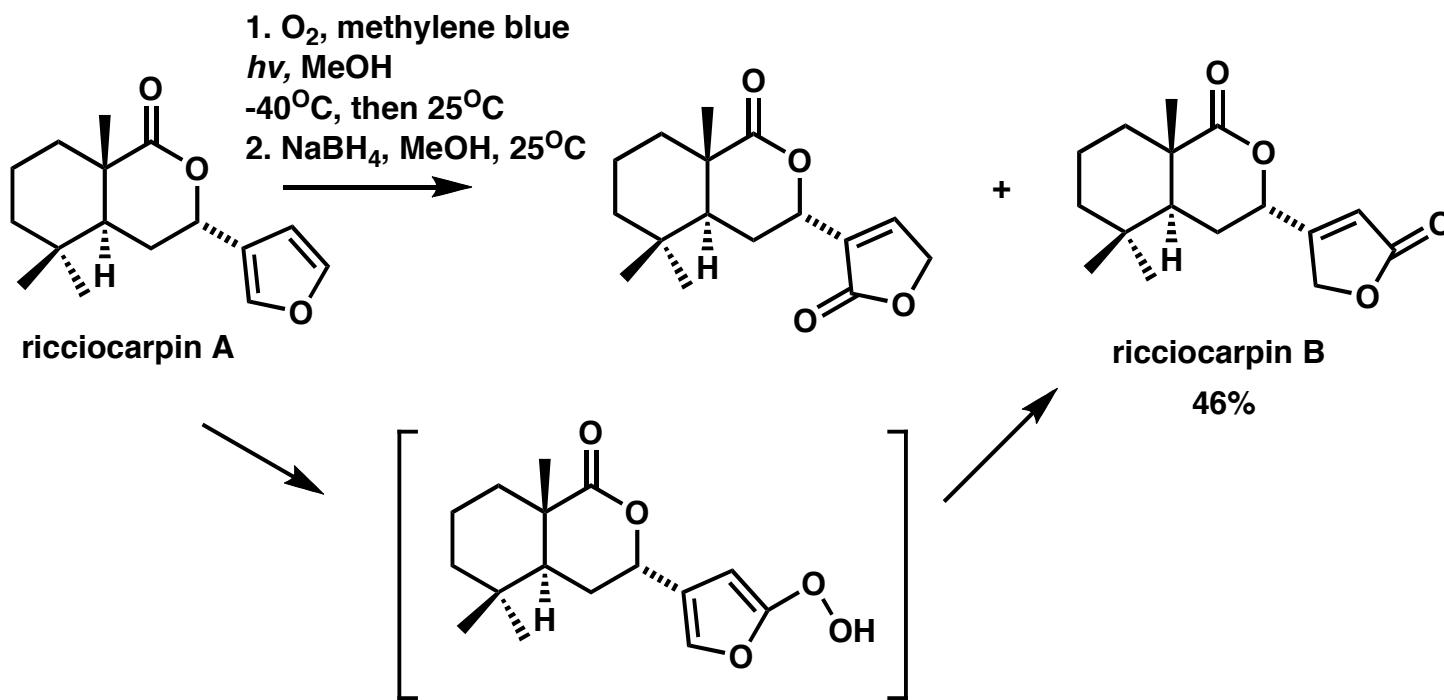


Held, C; Frohlich, R.; Metz, P. *Angew. Chem. Int. Ed.* 40, 1058 (2001).

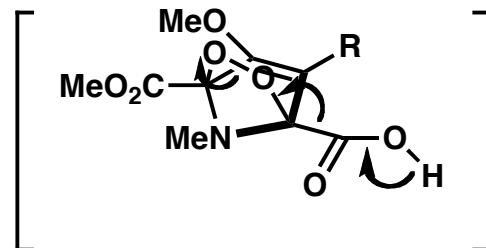


Wasserman, H.H.; Rotello, V.M.; Frechette, R.; DiSimone, R.B.; Yoo, J.U.; Baldino, C.M. *Tetrahedron*. 53, 8731 (1997).

# $^1O_2$ [4+2] Cycloadditions in Natural Product Synthesis

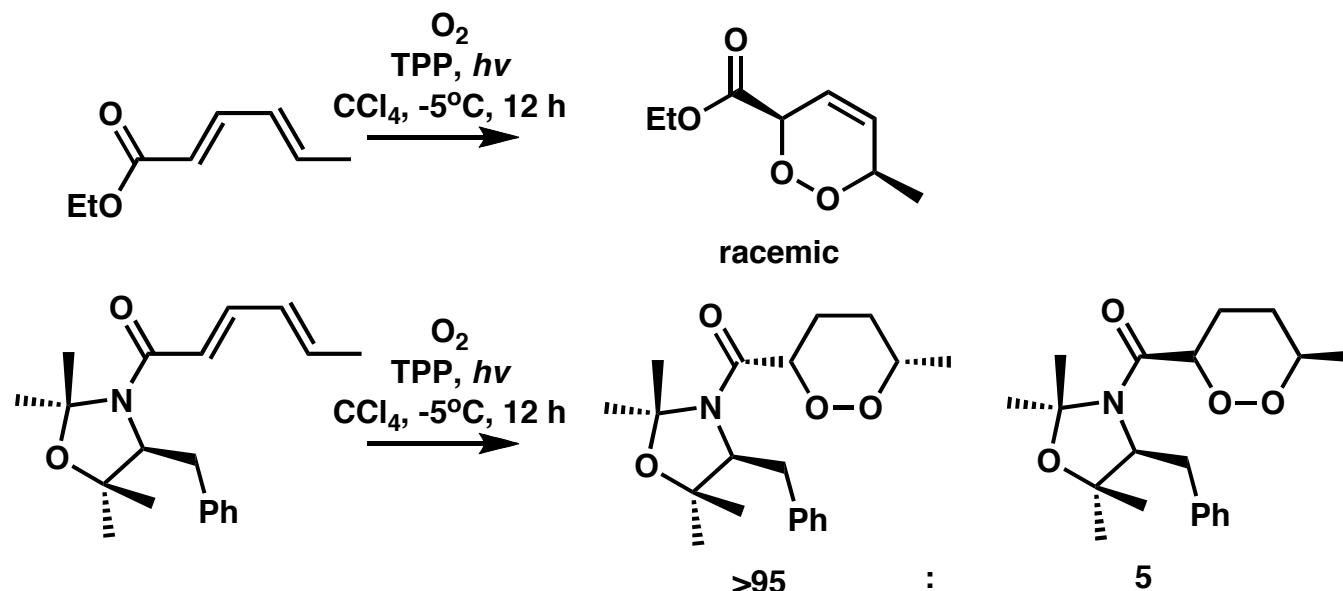


Held, C; Frohlich, R.; Metz, P. *Angew. Chem. Int. Ed.* 40, 1058 (2001).

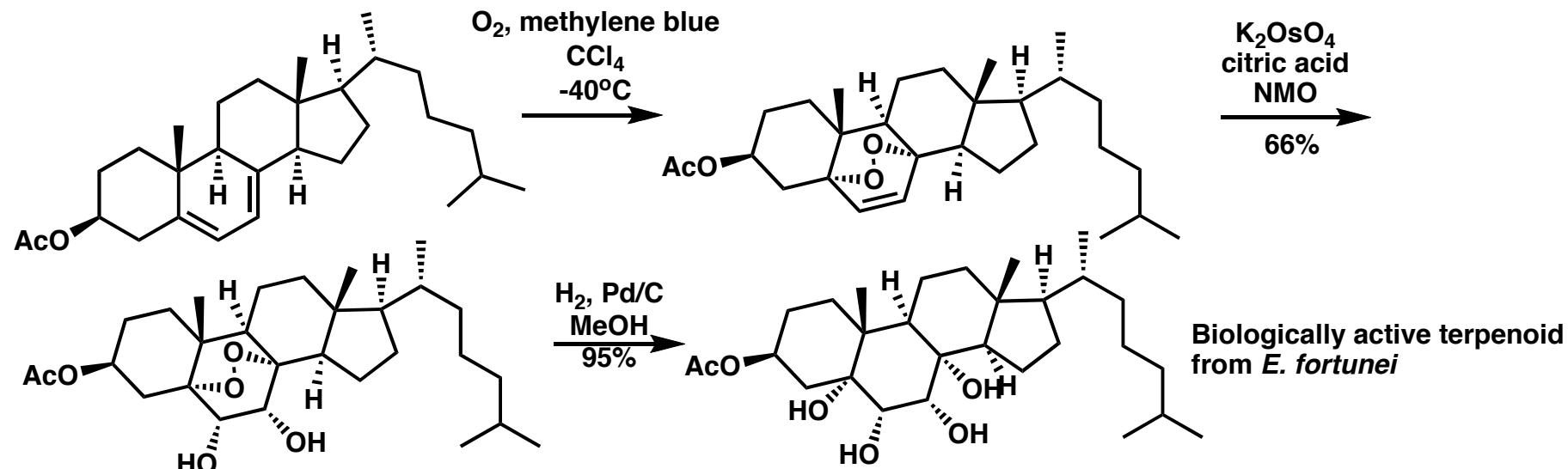


Wasserman, H.H.; Rotello, V.M.; Frechette, R.; DiSimone, R.B.; Yoo, J.U.; Baldino, C.M. *Tetrahedron*. 53, 8731 (1997).

# Steric Effects in the $^1\text{O}_2$ [4+2] Cycloaddition Reaction



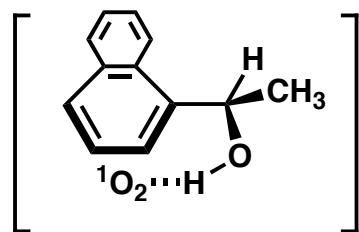
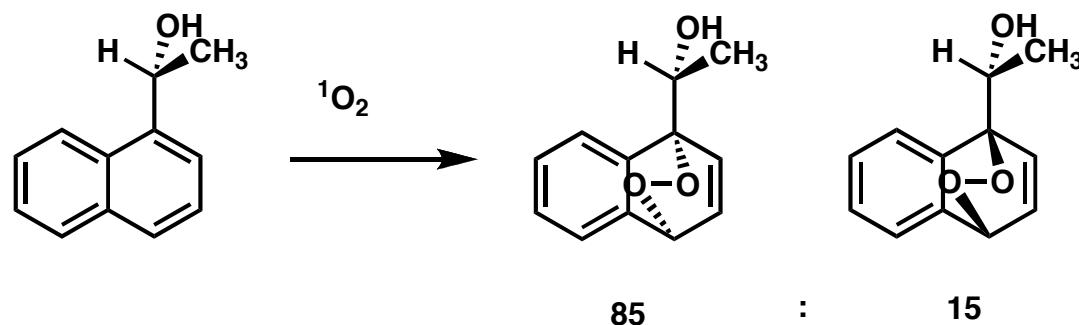
Adam, W.; Gthlein, M.; Peters, E.M.; Peters, K.; Wirth, T. *J. Am. Chem. Soc.* 120, 4091 (1998).



Valente, P.; Avery, T.D.; Taylor, D.K.; Tiekkink, E.R.T. *J. Org. Chem.* ASAP doi: 10.1021/jo8020506

## *Directing Effects by Hydrogen Bonds in [4+2] Reactions*

-Hydrogen-bond directed [4+2] cycloadditions have been known to occur, but they are infrequent due to the reactivity of singlet oxygen as a dienophile.

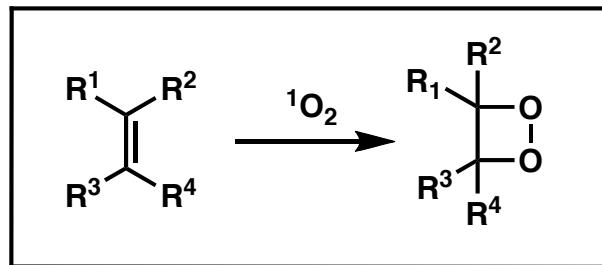


Adam, W.; Prein, M. *J. Am. Chem. Soc.* 115, 3766 (1993).

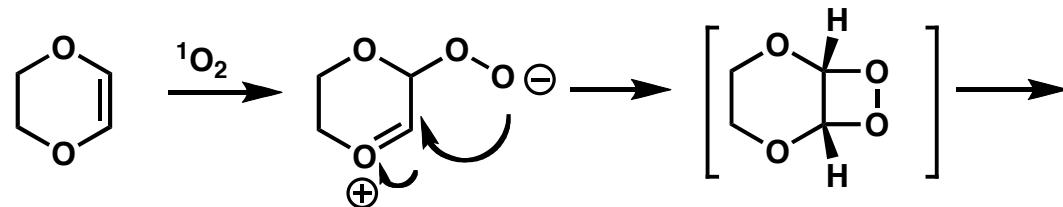
Adam, W; Peters, E.M.; Peters, K.; Prein, M.; von Schnerring, H.G. *J. Am. Chem. Soc.* 117, 6686 (1995).

Adam, W.; Prein, M. *Acc. Chem. Res.* 29, 275 (1996).

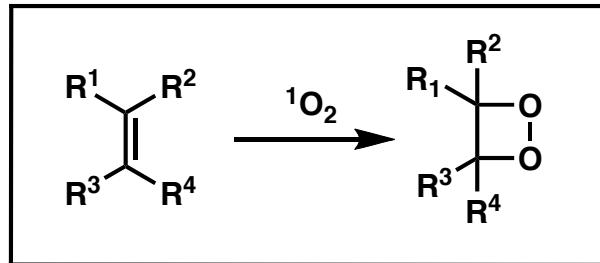
## $^1O_2$ [2+2] Cycloadditions



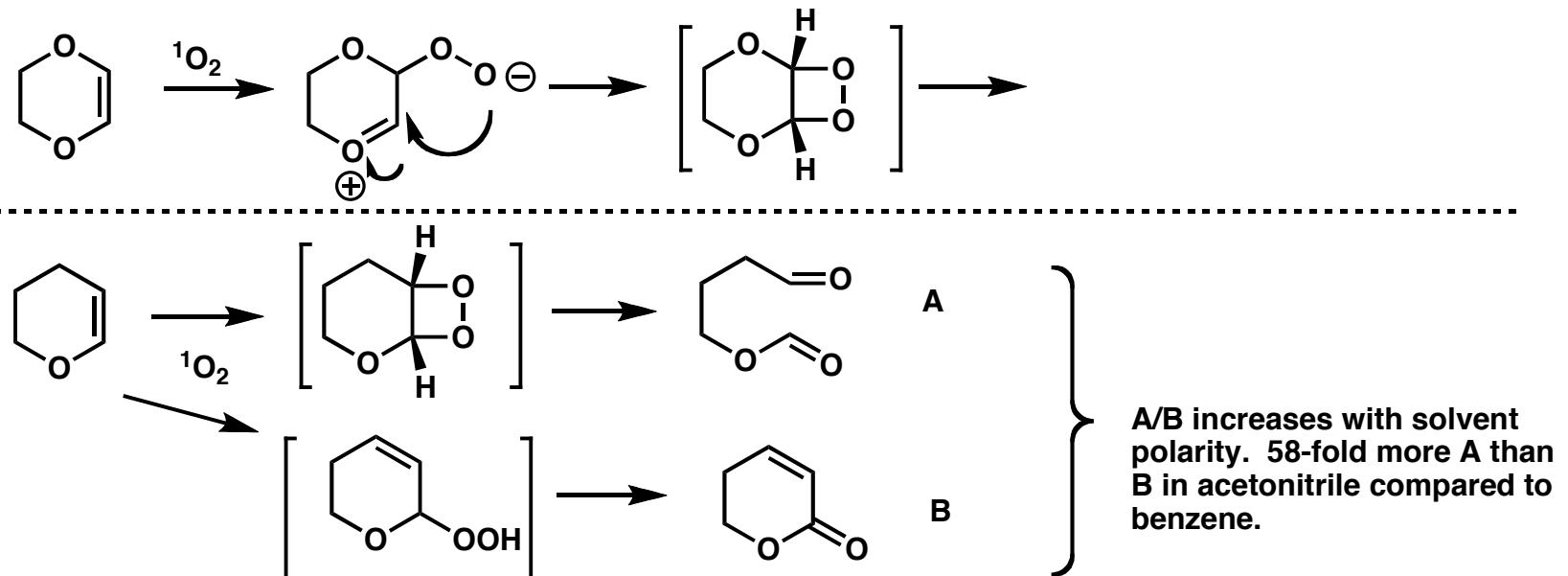
1. Not necessarily stereospecific.
2. Increasing solvent polarity favors dioxetane formation when other  $^1O_2$  reaction pathways exist.
3. Pathway more favorable with electron-rich olefins.



## $^1O_2$ [2+2] Cycloadditions



1. Not necessarily stereospecific.
2. Increasing solvent polarity favors dioxetane formation when other  $^1O_2$  reaction pathways exist.
3. Pathway more favorable with electron-rich olefins.

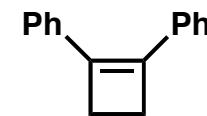
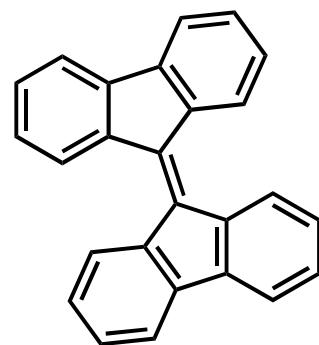
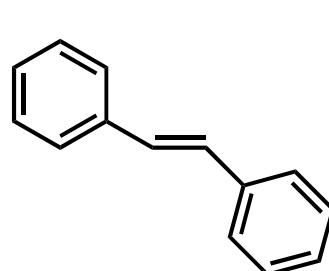
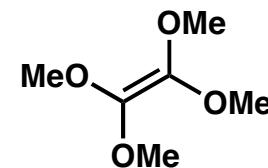
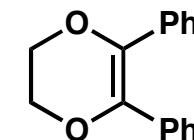
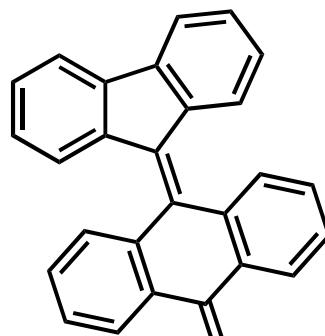
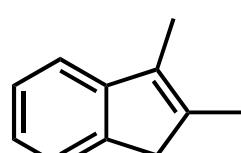
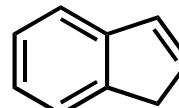
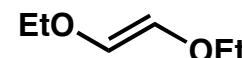
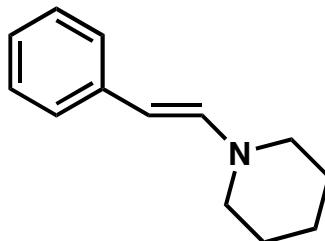
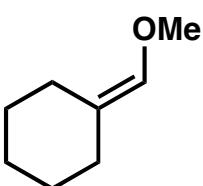


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## *Substrates for $^1O_2$ [2+2] Cycloadditions*



Fenical, W.; Kearns, D.R.; Radlick, P. *J. Am. Chem. Soc.* 91, 3396 (1969).

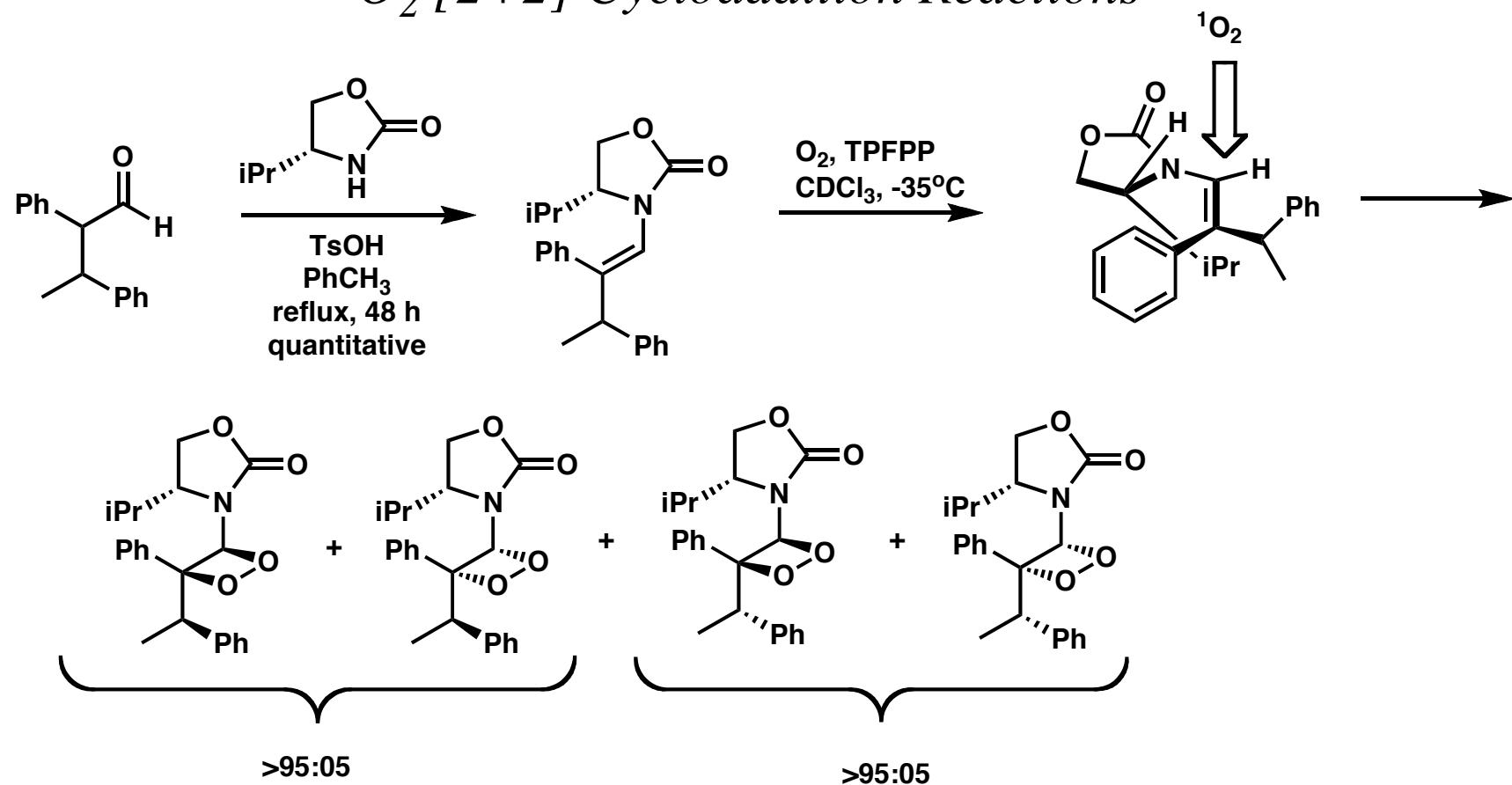
Foote, C.S.; Lin, J.W.-P. *Tetrahedron Lett.*, 3267 (1968).

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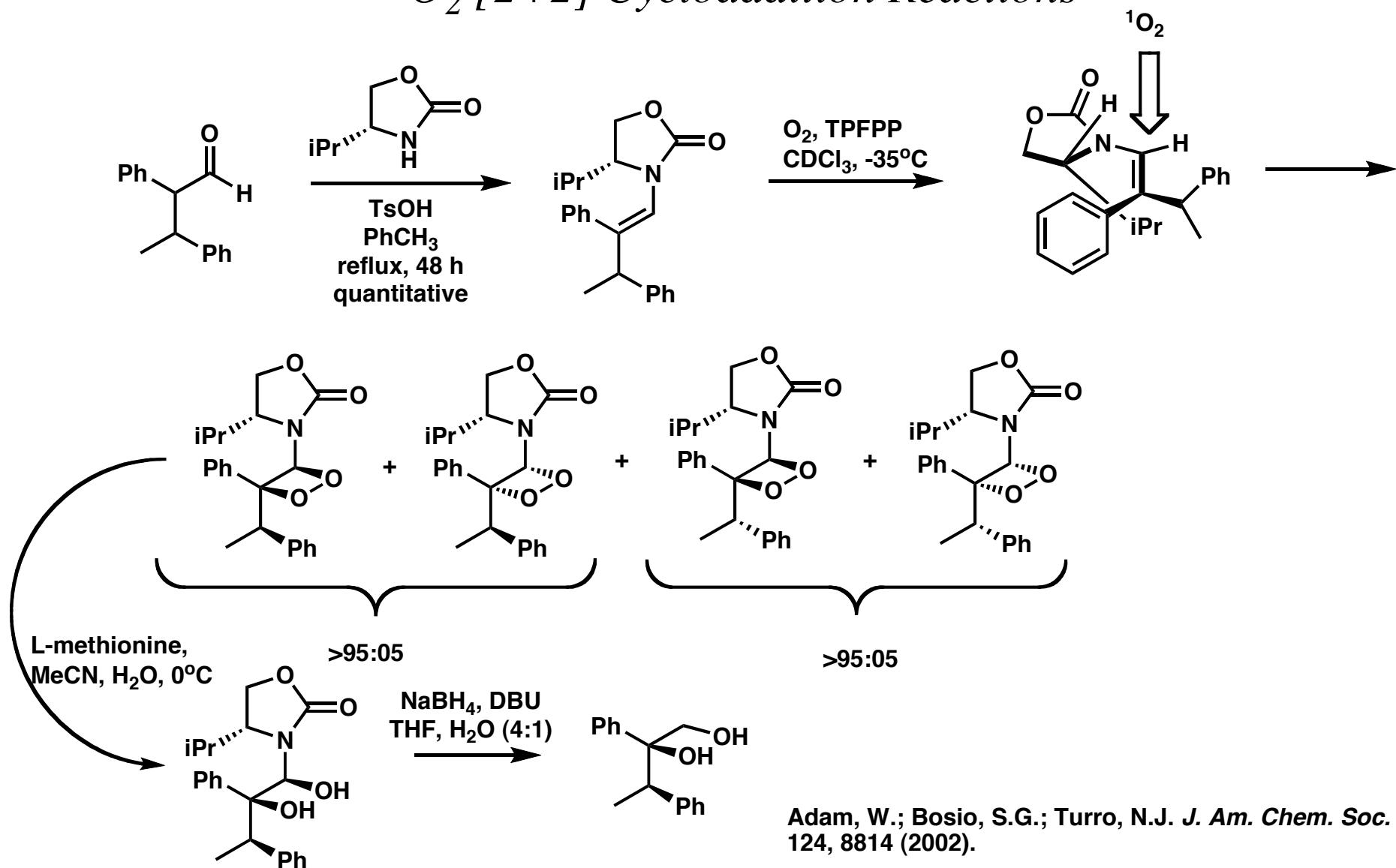
Richardson, W.H.; Hodge, V. *J. Org. Chem.* 35, 1216 (1970).

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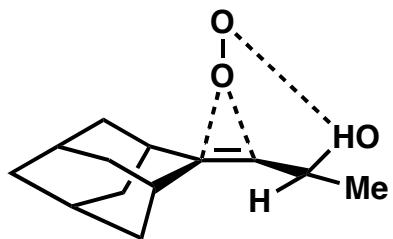
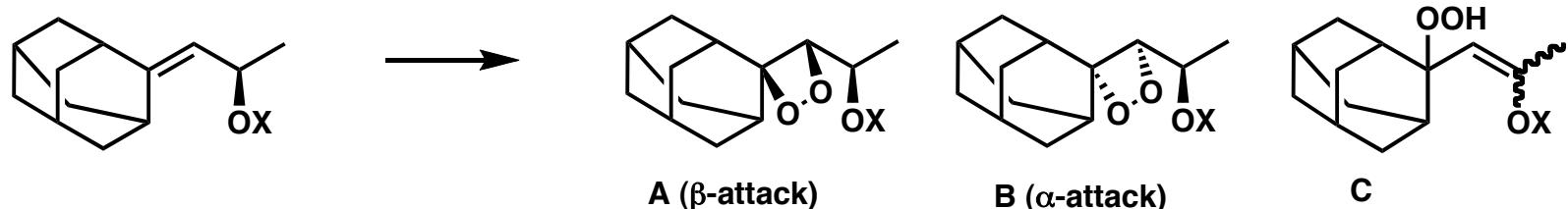
*Evans-Based Chiral Auxiliary Toward  
 $^1\text{O}_2$  [2+2] Cycloaddition Reactions*



*Evans-Based Chiral Auxiliary Toward  
 $^1O_2$  [2+2] Cycloaddition Reactions*



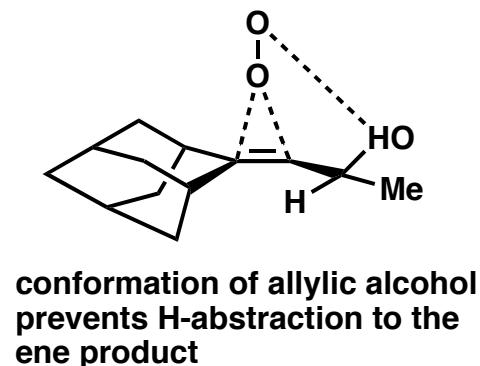
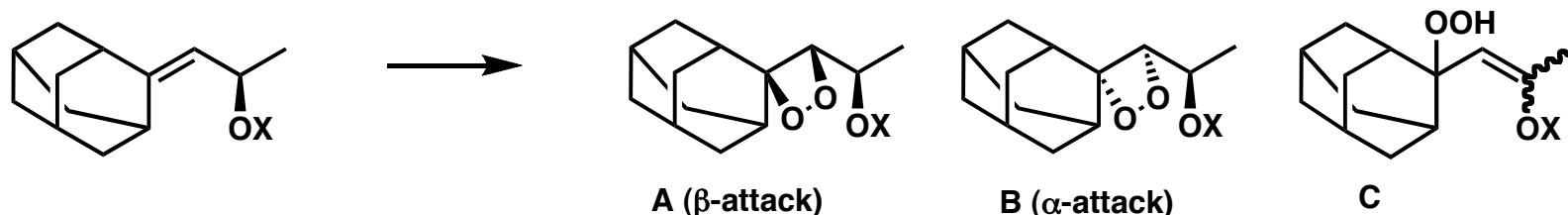
## Hydrogen Bonding Effects in [2+2] Reactions



conformation of allylic alcohol  
prevents H-abstraction to the  
ene product

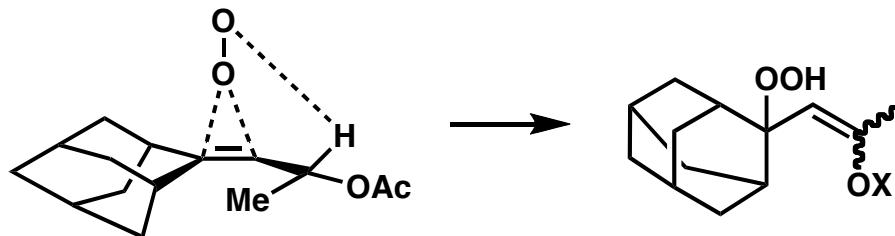
X	Solvent	A:B	[2+2]:ene
H	CDCl <sub>3</sub>	>95:5	47:53
H	CD <sub>3</sub> OD/CCl <sub>4</sub>	89:11	>95:5
OAc	CDCl <sub>3</sub>	N/A	<5:95
OAc	CD <sub>3</sub> OD	N/A	<5:95

## Hydrogen Bonding Effects in [2+2] Reactions



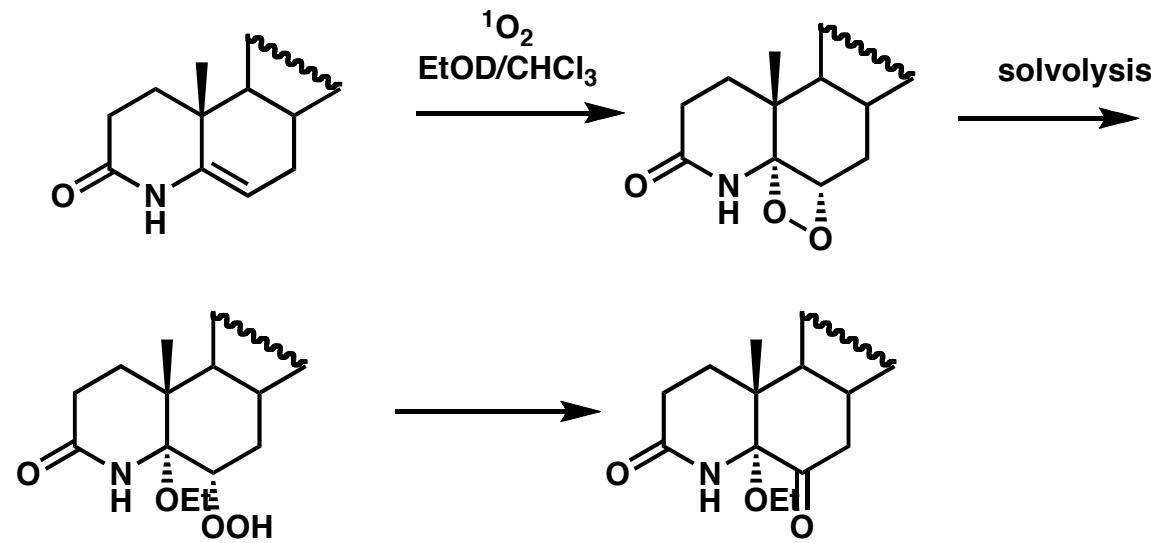
X	Solvent	A:B	[2+2]:ene
H	CDCl <sub>3</sub>	>95:5	47:53
H	CD <sub>3</sub> OD/CCl <sub>4</sub>	89:11	>95:5
OAc	CDCl <sub>3</sub>	N/A	<5:95
OAc	CD <sub>3</sub> OD	N/A	<5:95

-Increasing solvent polarity favors more polar transition state of [2+2] cycloaddition.

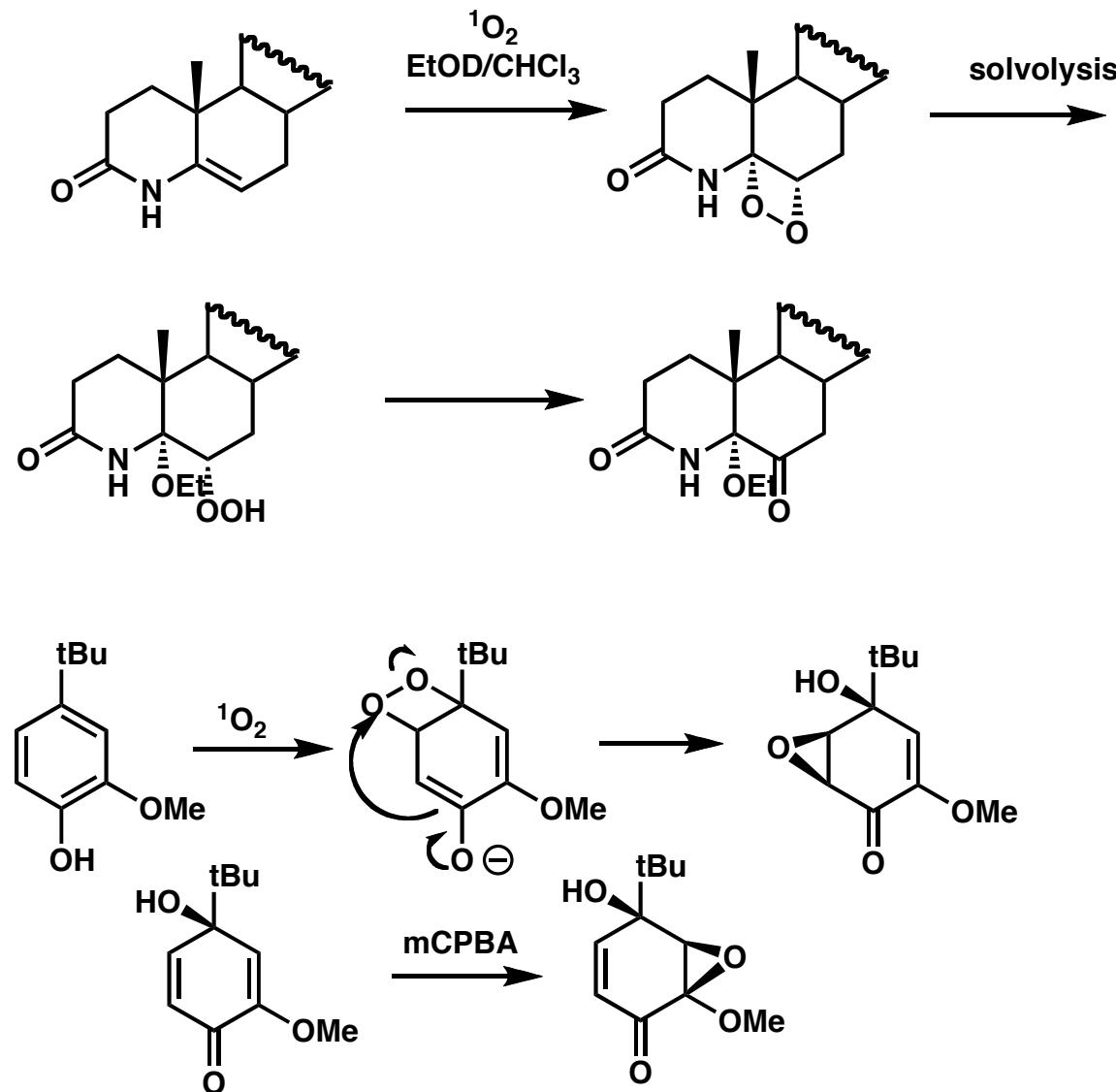


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## *Other Modes of Reactivity of Dioxetanes*

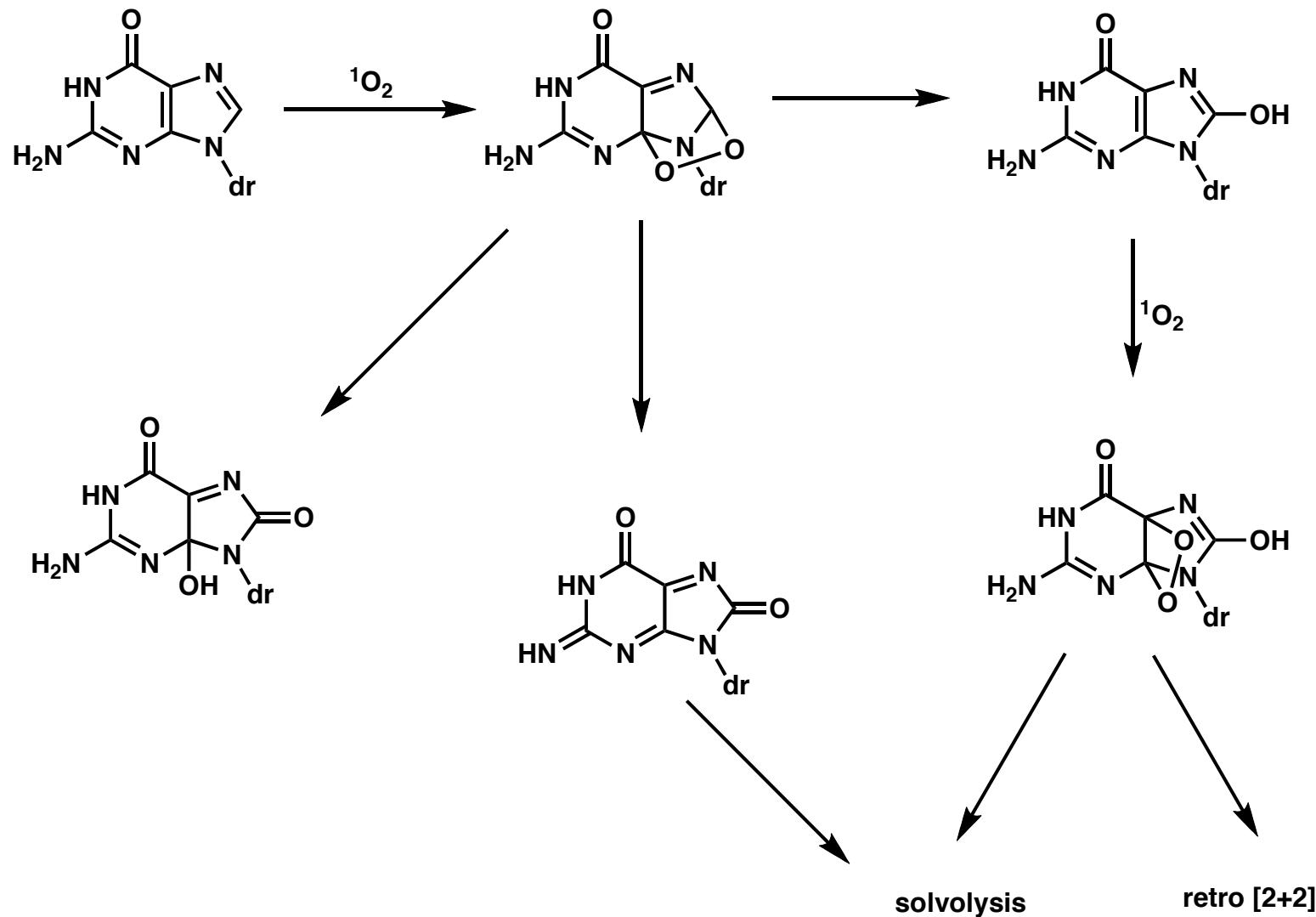


## *Other Modes of Reactivity of Dioxetanes*



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# $^1\text{O}_2$ Effects on DNA



Ravanat, J.-L.; Martinez, G.R.; Medeiros, M.H.G.; di Mascio, P.; Cadet, J. *Tetrahedron*, 62, 10709 (2006).