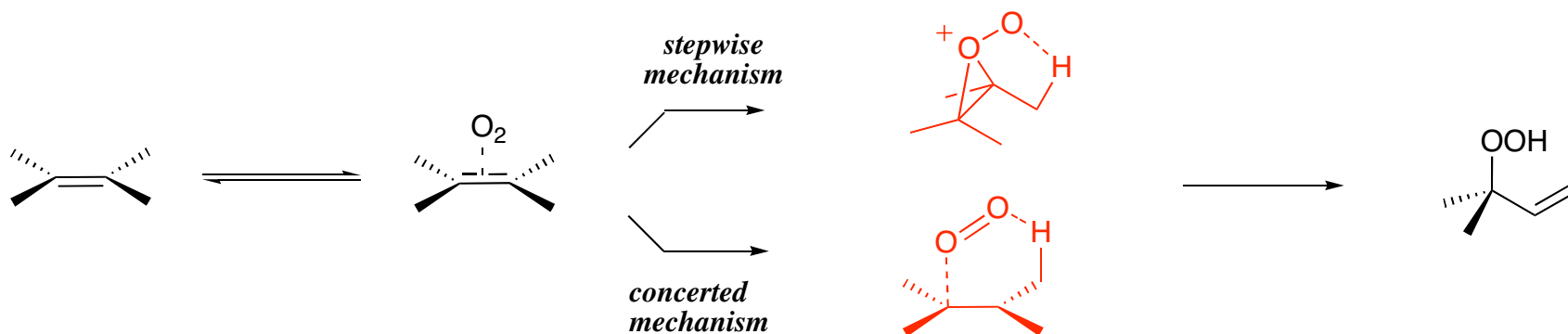


Singlet Oxygen Ene Reaction



By Pavel Nagorny
Evans Group Friday Seminars

Table of Contents:

- Discovery of singlet oxygen
- Generation and physical properties
- Overview of reactivity
- The singlet oxygen ene reaction
 - Mechanism
 - Cis Effect
 - Steric and Electronic Effects
 - Oxidation of Indoles
 - Directed Ene
 - Chiral Auxiliaries
 - Enantioselective Ene
 - Conclusion

References:

Reviews:

Clennan, E. L. *Tetrahedron*, **2000**, *56*, 9151-9179.

Orfanopoulos, M. *Tetrahedron*, **2000**, *56*, 1959-1615

Adam, W. *ACIEE*, **1996**, *35*, 477-494

Wasserman, H. H. *Tetrahedron*, **1981**, *37*, 1825-1852.

Monographs:

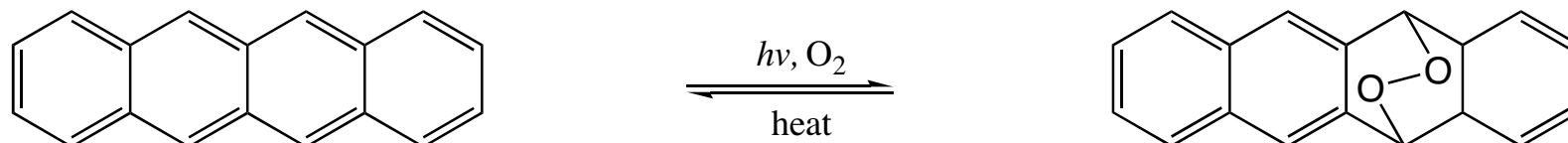
Frimer, A. A. *Singlet O₂*, CRC: Boca Raton, FL, 1985.

Wasserman, H. H.; Murray, R. W. In *Singlet Oxygen*, Wasserman, H.H., Ed.; Academic: New York, 1979; Vol. 40.

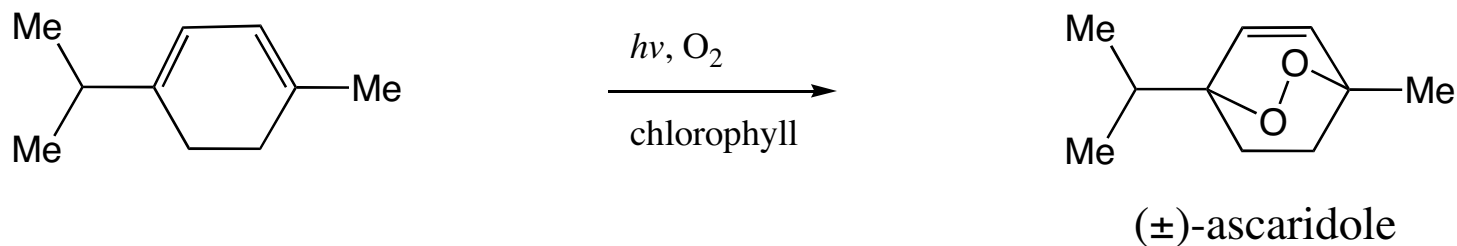
Shaap, A.P. In *Singlet Molecular Oxygen*, VanderWerf, C.A., Ed.; Dowden, Hutchinson & Ross: Stroudsburg, Pennsylvania, 1976; 5.

Discovery and First Use in Organic Synthesis

- The earliest description was made by Fritzsche in 1867



- In 1931 Kautsky and coworkers reported first evidence for metastable, reactive state of molecular oxygen
- In 1954 Schenck and Ziegler reported the first use of singlet oxygen in organic synthesis of (±)-ascaridole



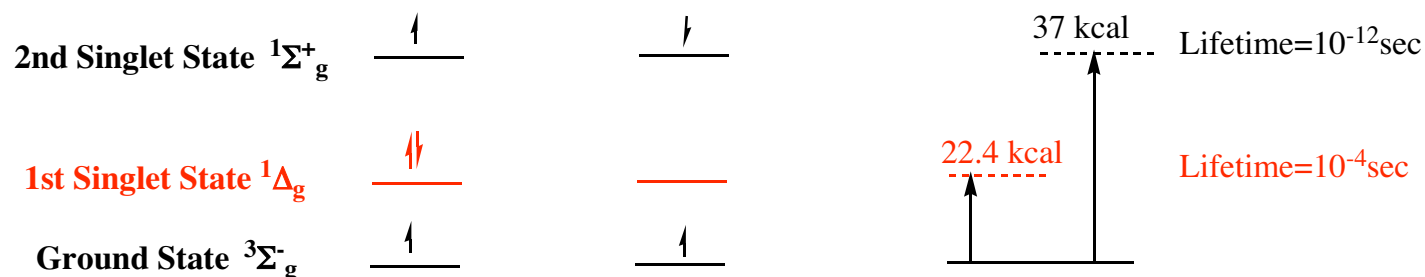
Fritzsche, M. *Compt. Rend.* **1867**, *64*, 1035-1037

Kautsky, H.; de Bruijn H. *Naturwissenschaften* **1931**, *19*, 1043

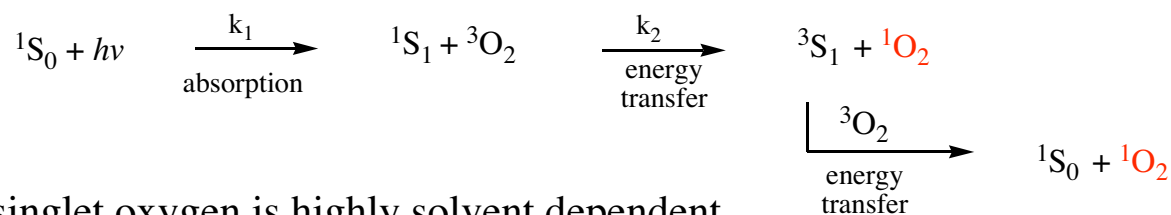
Schenck G. O.; Ziegler K. *Naturwissenschaften* **1954**, *32*, 157

Physical Properties

- Singlet oxygen is the first excited state of O_2 lying 22.4 kcal/mol above the ground triplet state



- The intersystem crossing $^3\Sigma_g^- \rightarrow ^1\Delta_g$ could be achieved by photosensitization with a dye



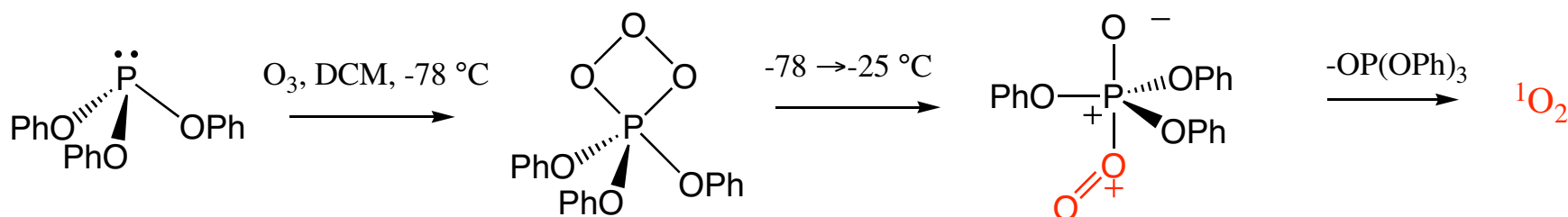
- The lifetime of the singlet oxygen is highly solvent dependent

Solvent	Lifetime ($\times 10^{-6}$ s)	Deuterated Solvent	Lifetime ($\times 10^{-6}$ s)
Chloroform	220	Chloroform	800
Benzene	24	Benzene	700
Ethanol	12	Ethanol	230

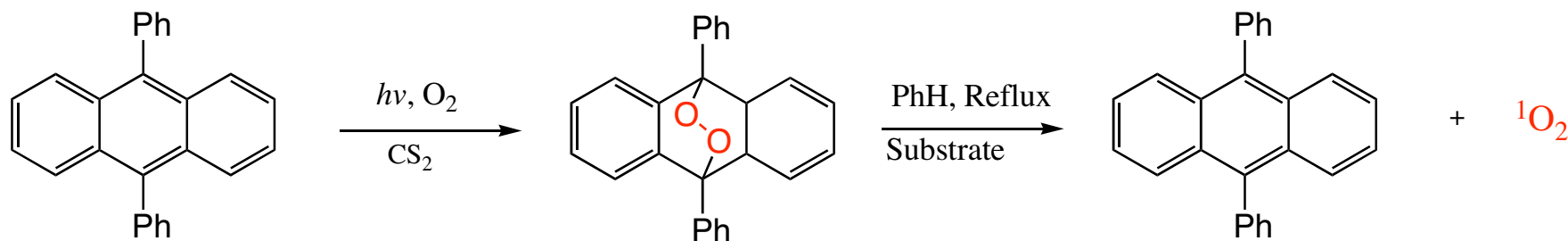
Singlet Oxygen Generation

- Photosensitization with Rose-Bengal, Methelene Blue or tetraphenyl porphyrine (TPP) is the preferred method. However, to avoid side-photoreactions, other methods could be used

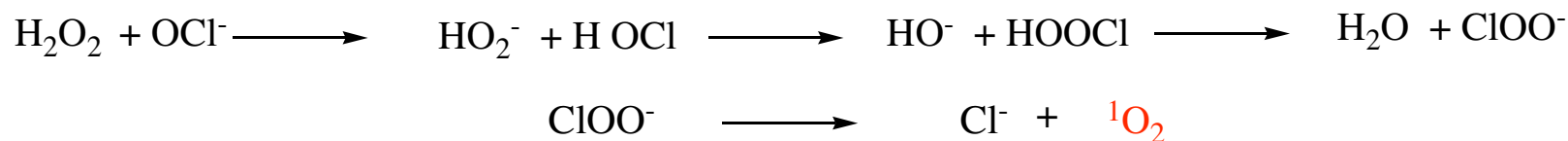
a) Murray Method: thermal decomposition of ozone-phosphite adducts



b) Thermal decomposition of aromatic endoperoxides

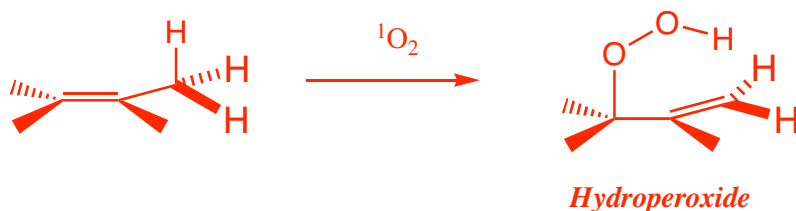


c) Decomposition of hydrogen peroxide with bleach

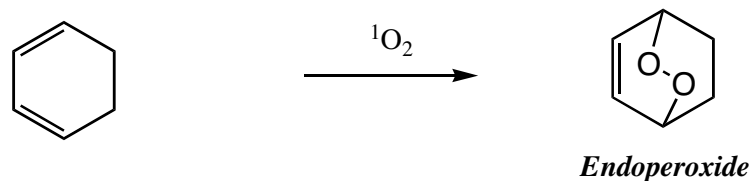


Different Reaction Modes

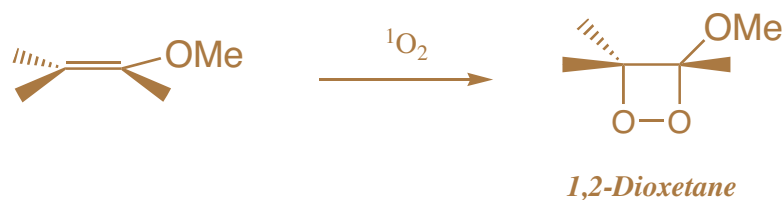
- Schenck Ene Reaction



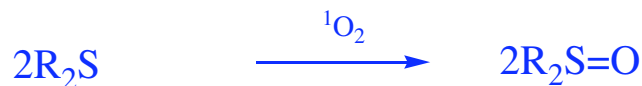
- [4+2] Cycloaddition





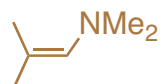
- [2+2] Cycloaddition



- Oxidation of heteroatoms



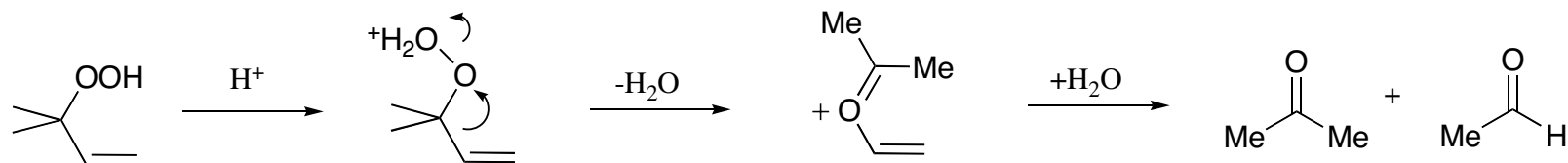
Reaction Rate Constants in $CHCl_3$

Compound	Rate ($\times 10^6 \text{ M}^{-1}\text{s}^{-1}$)
	25
	1.0
1-methylcyclohexene	0.16
5-methoxyindole	2.2
α -Pinene	0.002
2-methyl-2-pentene	0.83
Cyclopentadiene	43
1,3-cyclohexadiene	3.1
Isoprene	0.02
2,5-dimethylfuran	233
Furan	11
Imidazole	40
2,5-diphenyloxazole	1.5
diethyl sulfide	7.0
	460

Ene Reaction: Introduction

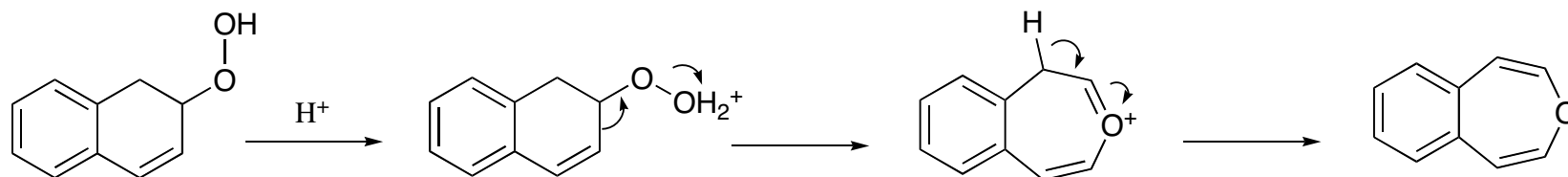
- The ene reaction with singlet oxygen was discovered in 1943 by Schenck
- Schenk ene reaction has been highly used in organic synthesis
- The products of the ene reaction--allylic hydroperoxides can undergo a number of different transformations

a) Hock-Cleavage



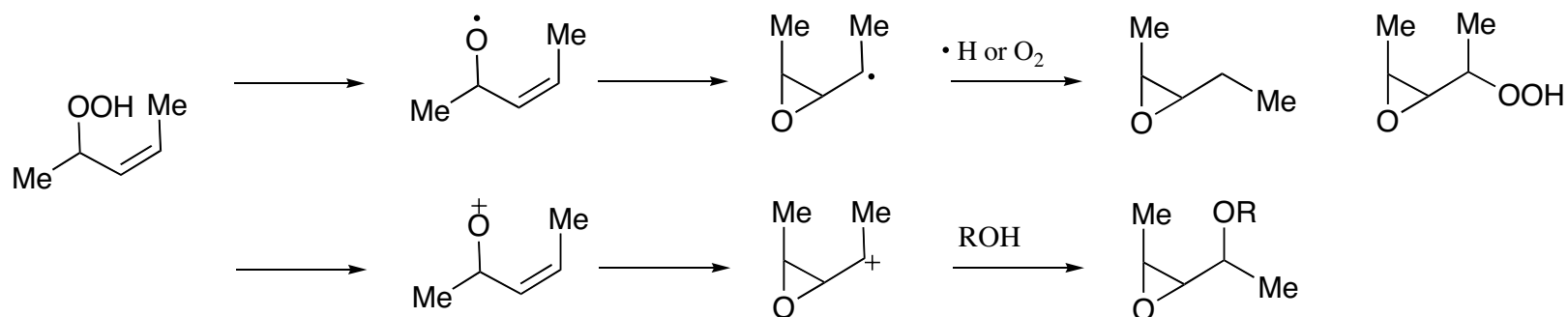
cyclobutyl > aryl > vinyl > hydrogen > cyclopentyl \cong cyclohexyl \gg alkyl

b) Fragmentation to Divinyl Ethers

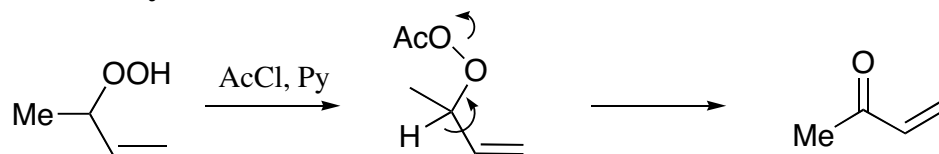


Ene Reaction: Hydroperoxides

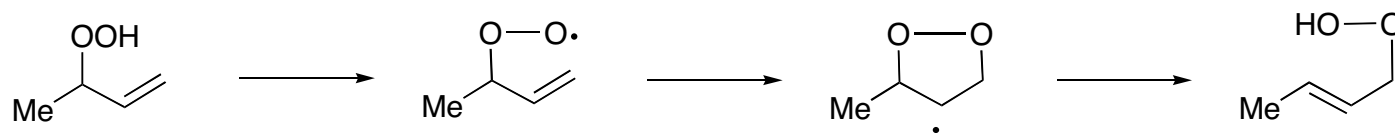
c) Rearrangement to epoxides



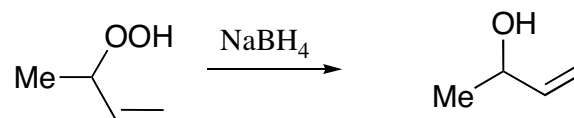
d) Kornblum-DeLaMare Dehydration



e) 1,5-Isomerization

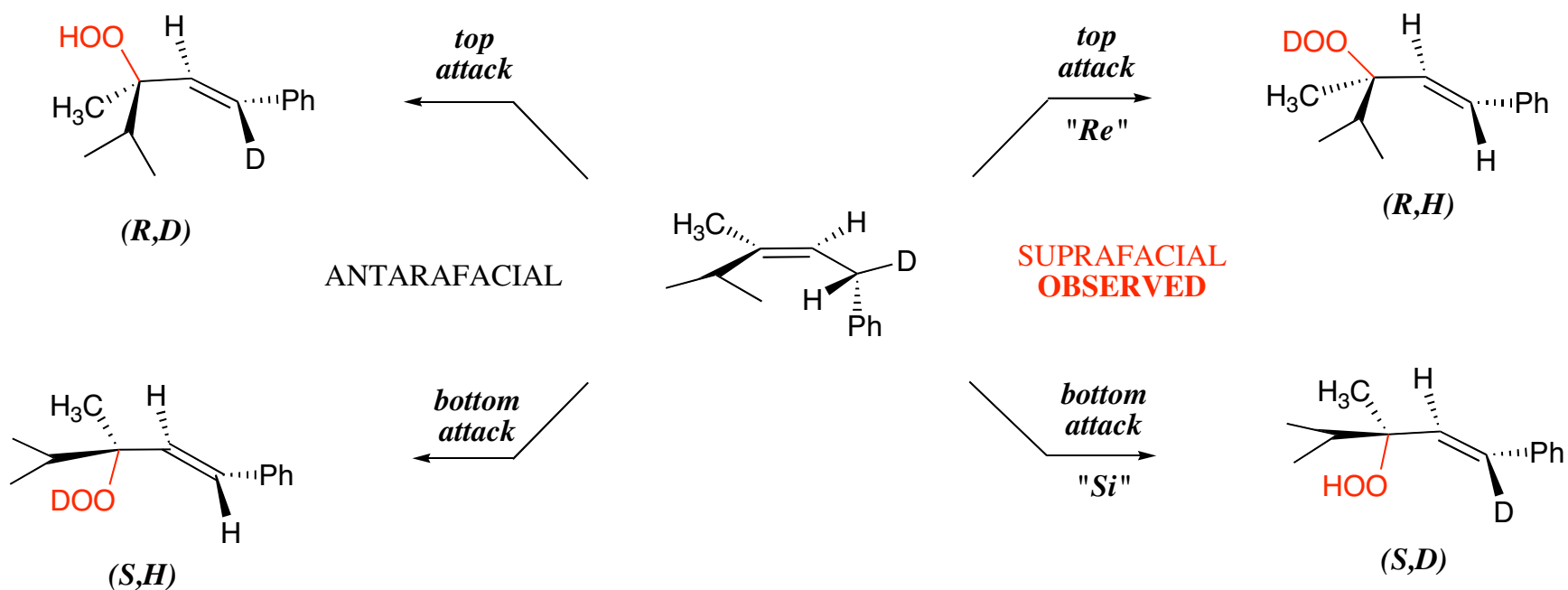


f) Reduction to an alcohol



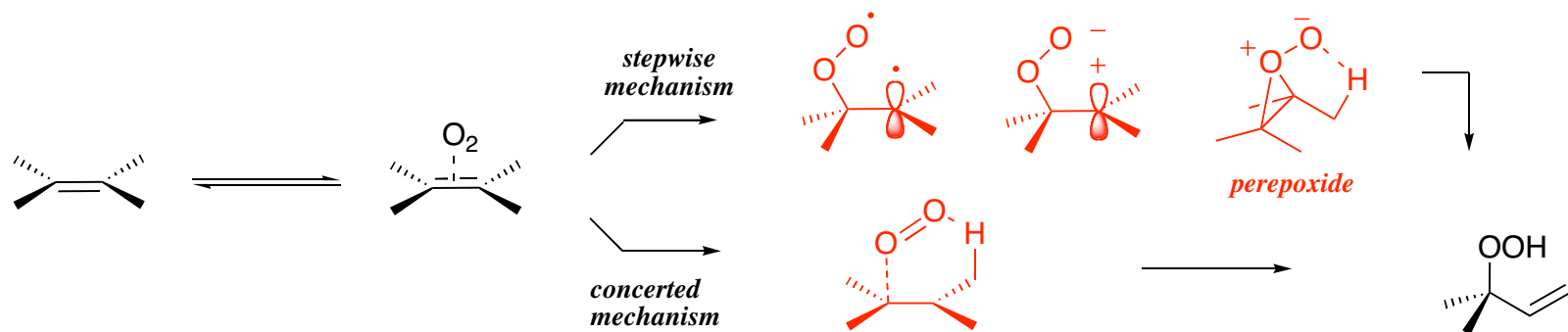
Ene Reaction: Mechanism

- Singlet oxygen ene reaction is suprafacial

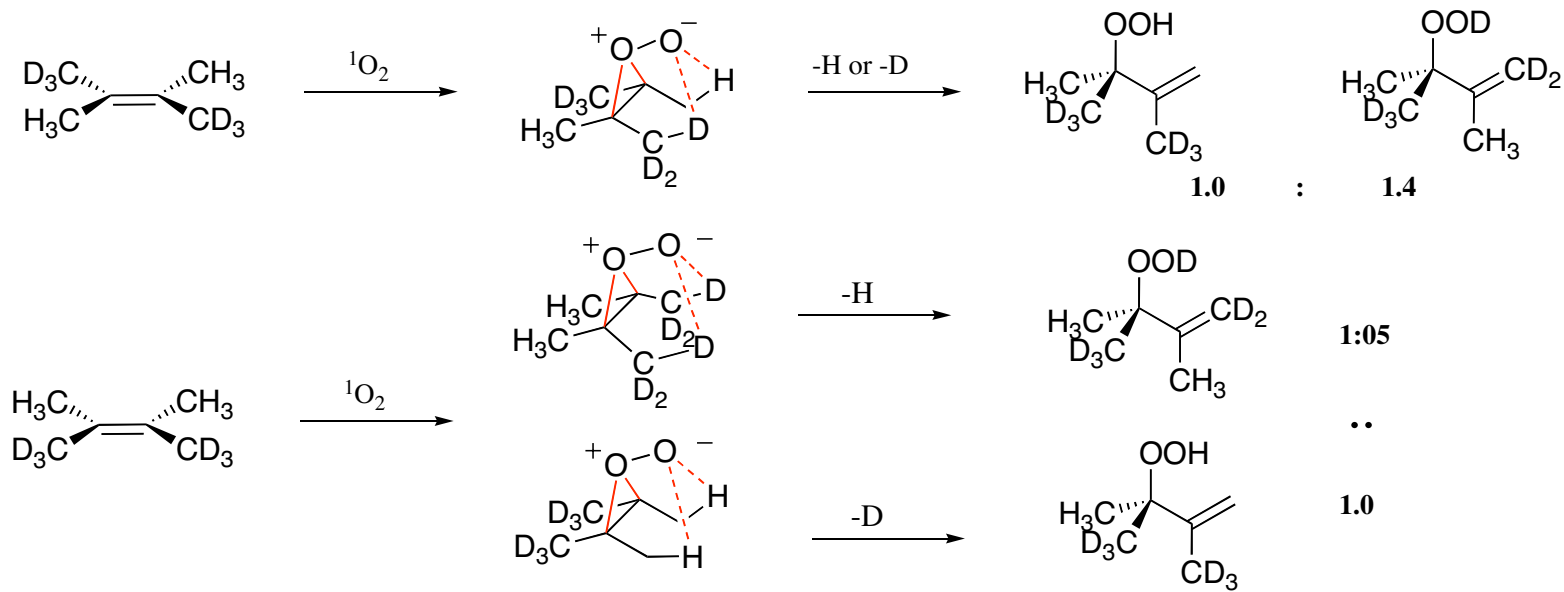


- Benzylic position is oxidized with 86% selectivity

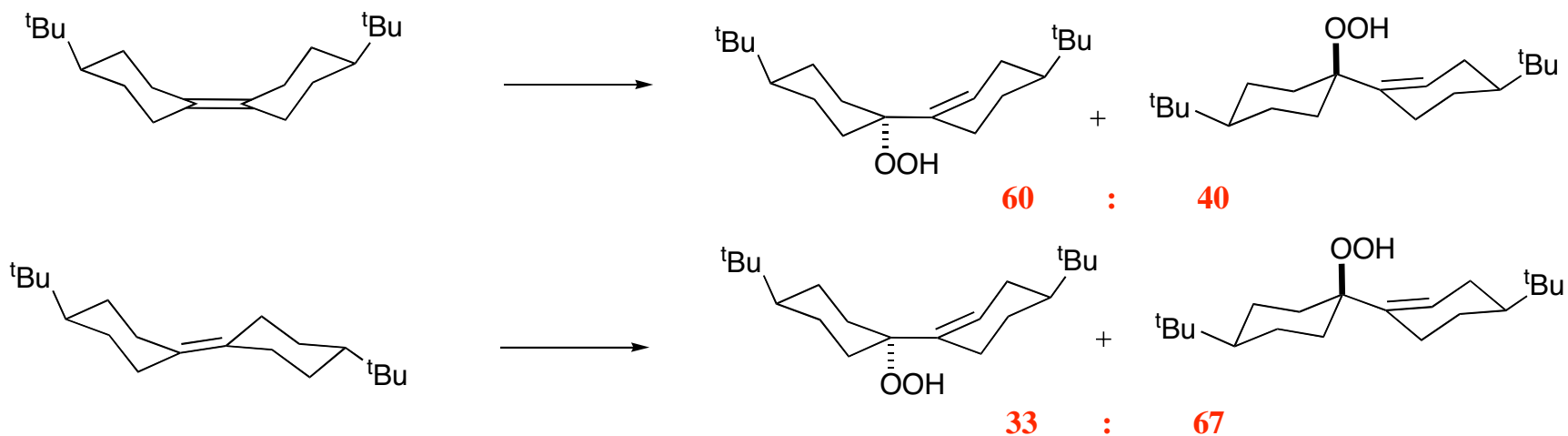
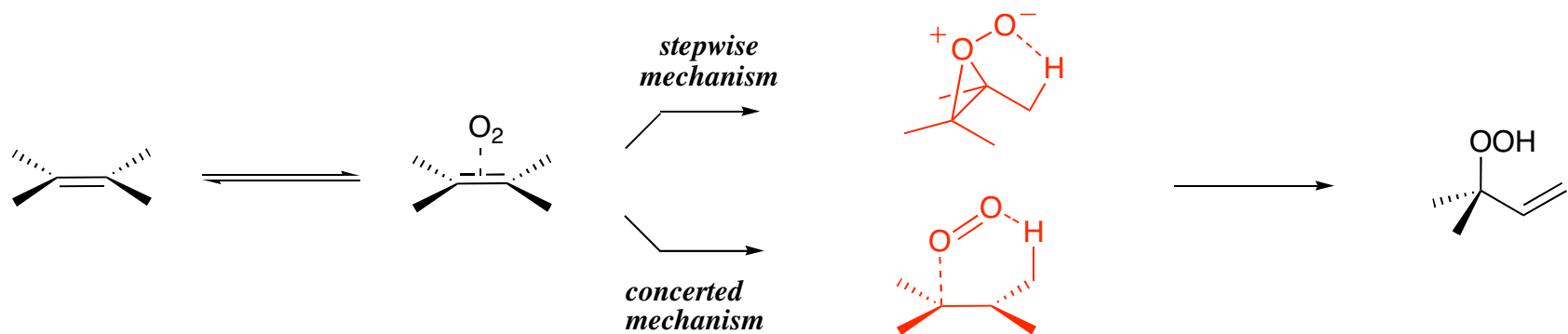
Ene Reaction: Mechanism



- Absence of the Markovnikov directing effects rules out the zwitterion and diradical intermediates
- The kinetic isotope effect studies support the peroxide intermediate showing that the hydrogen abstraction is not the rate determining step



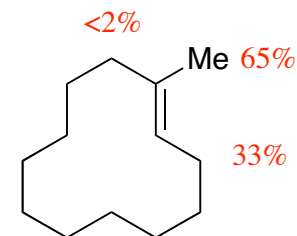
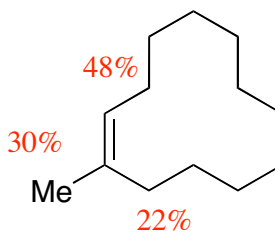
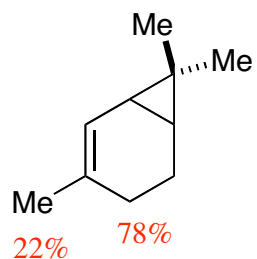
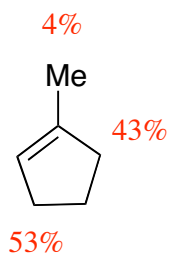
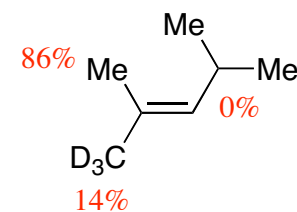
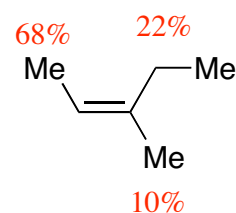
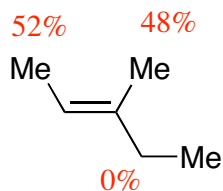
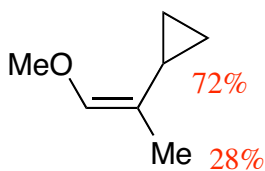
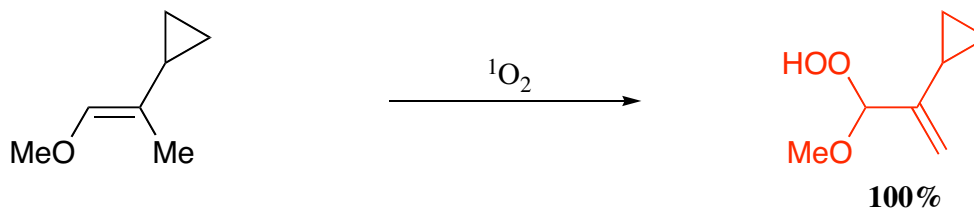
Ene Reaction: Mechanism



- The activation energy for the ene reaction is estimated to be 1.3 kcal/mol
- Calculations based on cyclohexane A values would give >99:1 ratio for the products of the concerted mechanism

Ene Reaction: "Cis Effect"

- Singlet oxygen abstracts hydrogen from the most congested side of an olefine. It is known as the "Cis Effect"



Conia, *Tet. Lett.*, **1977**, 2517-2520

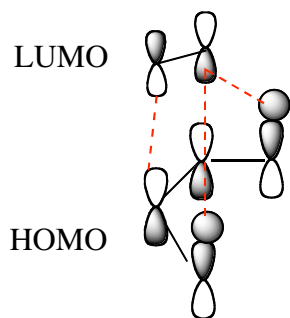
Foote, *Tet. Lett.*, **1978**, 3227-3230

Clennan, *Tetrahedron*, **2000**, 56, 9151-9179

Orfanopoulos, *Tetrahedron*, **2000**, 56, 1595-1615

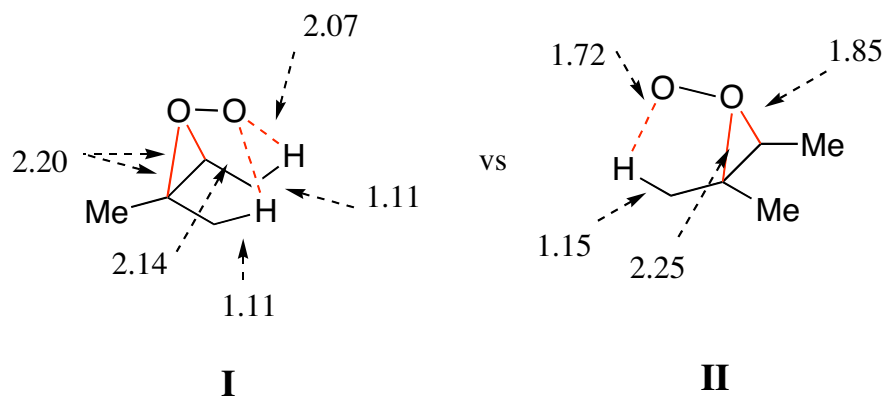
Ene Reaction: "Cis effect" Explanation

Stephenson/Fukui Model



Overlap is maximized on the more congested side

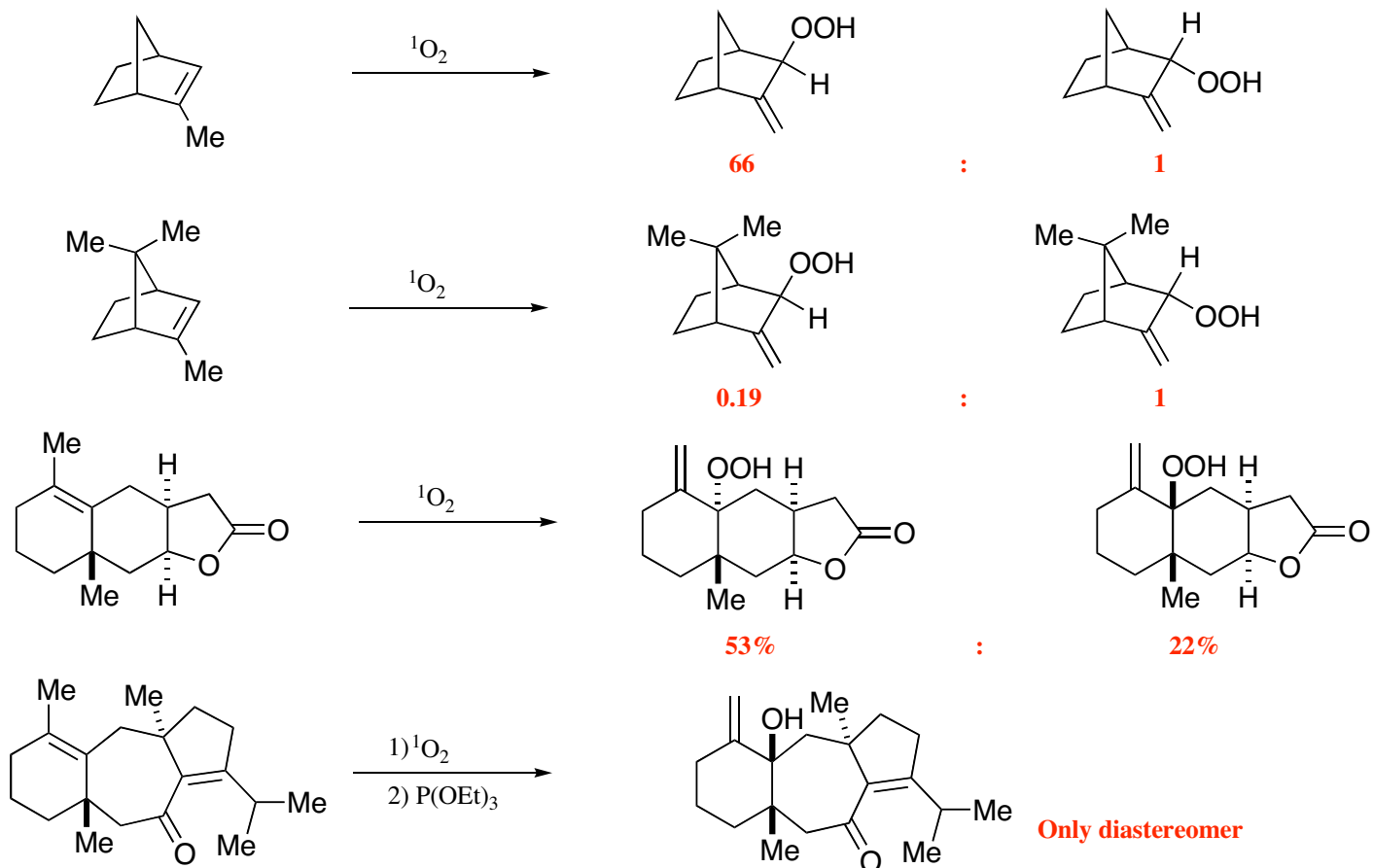
Houk Model



- CCSD calculations gave 2.8 kcal/mol energy difference
- II is a late transition state compared to I
- II involves an asynchronous attack on olefinic carbons so that II is more polar than I

Ene Reaction: Steric Effect

- Singlet oxygen ene reactions are sensitive to the steric effects. Oxygen approaches the olefine from the least sterically hindered side.

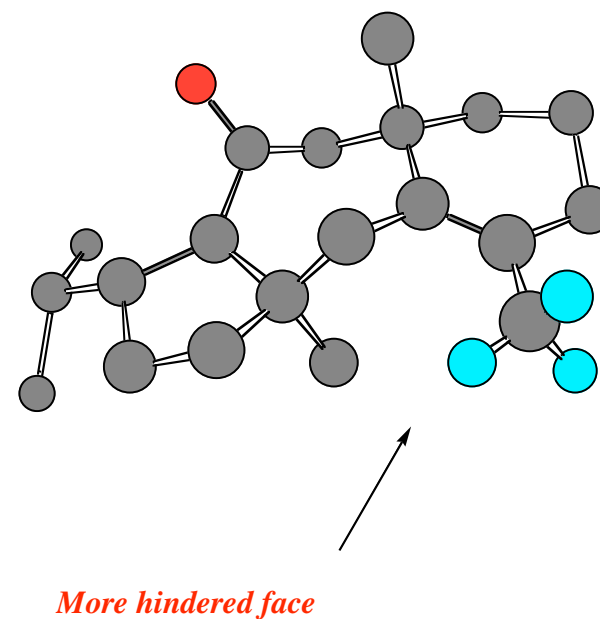
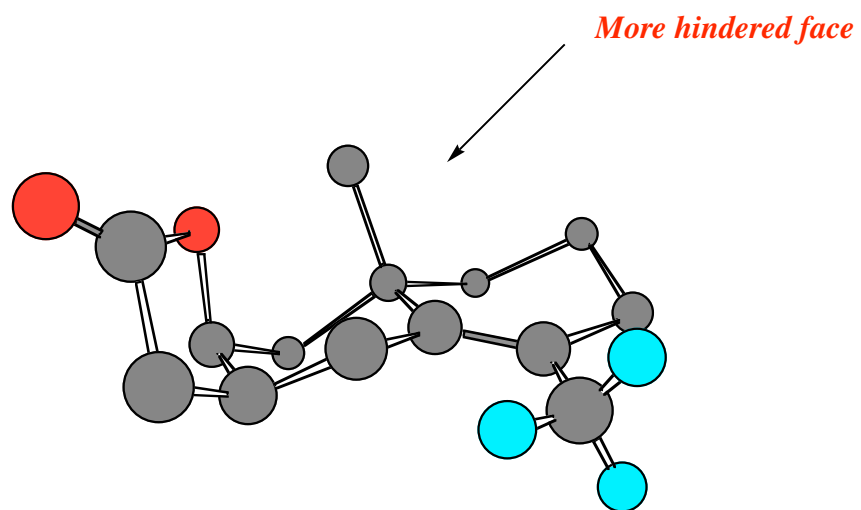
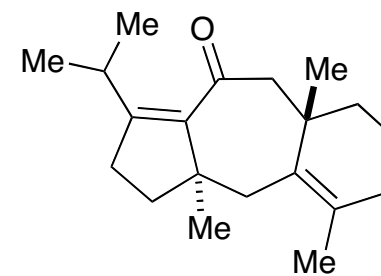
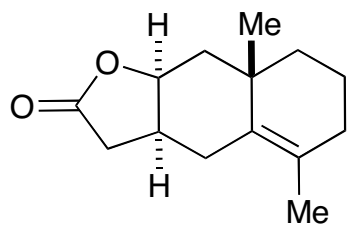


Clennan, *Tetrahedron*, **2000**, 9151-9179

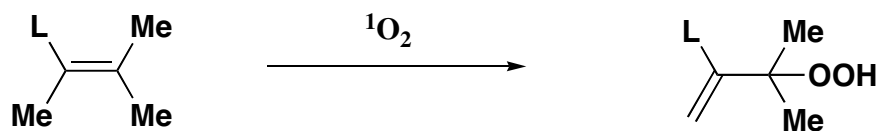
Jefford, *JACS*, **1972**, *94*, 8904-8905

Paquette, *Synth. Commun.* **1986**, *16*, 1275-1283

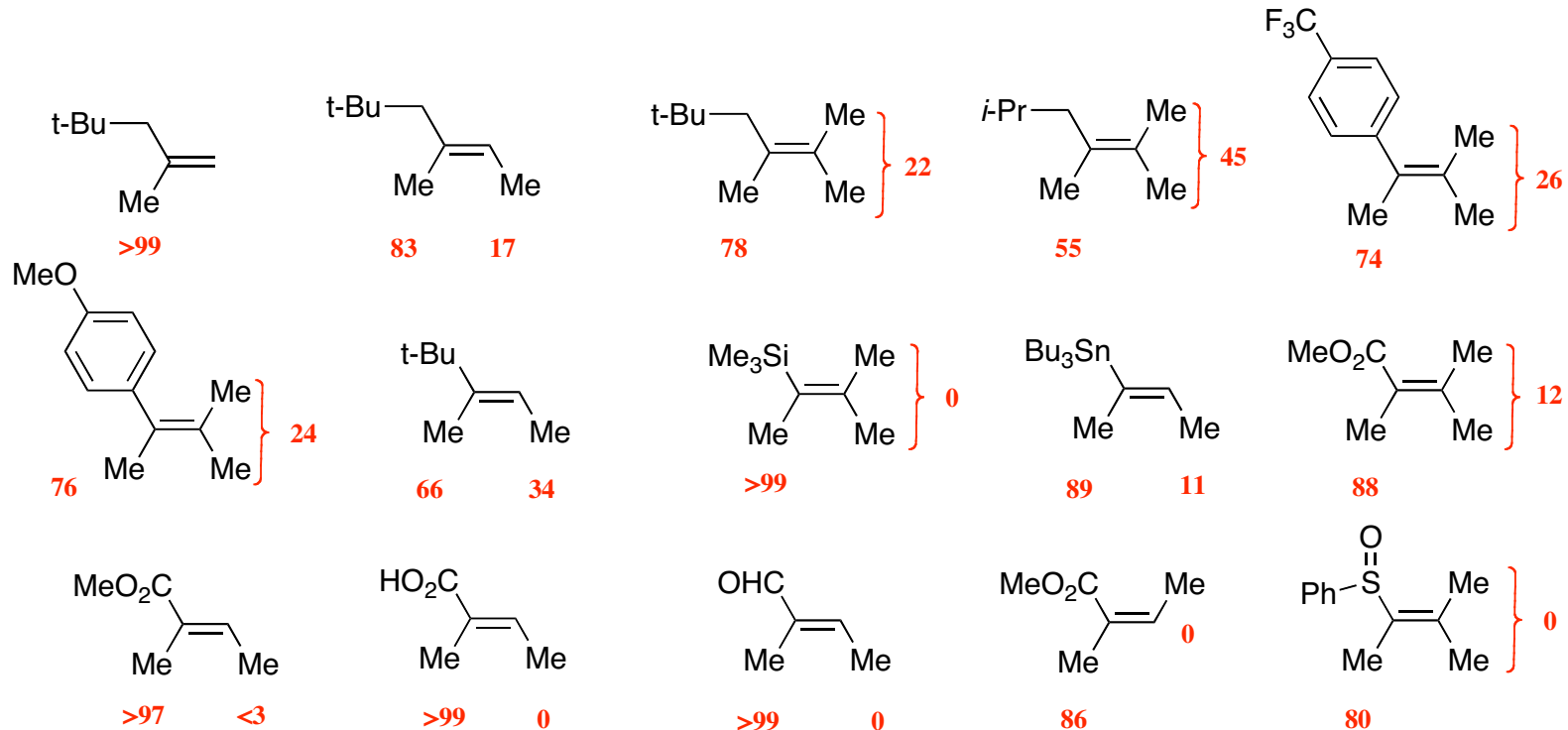
Ene Reaction: Steric Effect



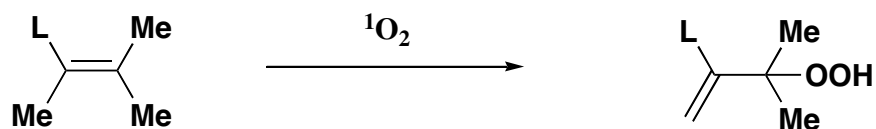
Ene Reaction: Geminal Group Effect



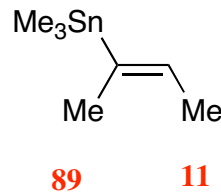
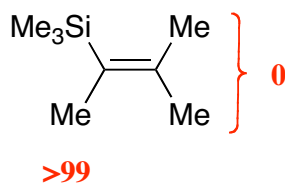
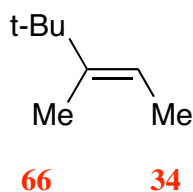
L = -C(O)R, -COOR, -COOH, -S(O)Ph, -CH₂SPh, -CH₂S(O)Ph, -CH=N^tBu, -CN, -C(O)NH₂,
 -SiR₃, -SnR₃, -*t*Bu, -*i*Pr, -Ph



Ene Reaction: Geminal Group Effect



- Both steric and electronic effects were invoked to explain the geminal group directing effect
- Stereoelectronic effects are working opposite to the steric effects



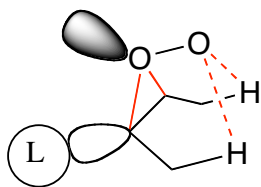
Steric Effects:



Electronic Effects:

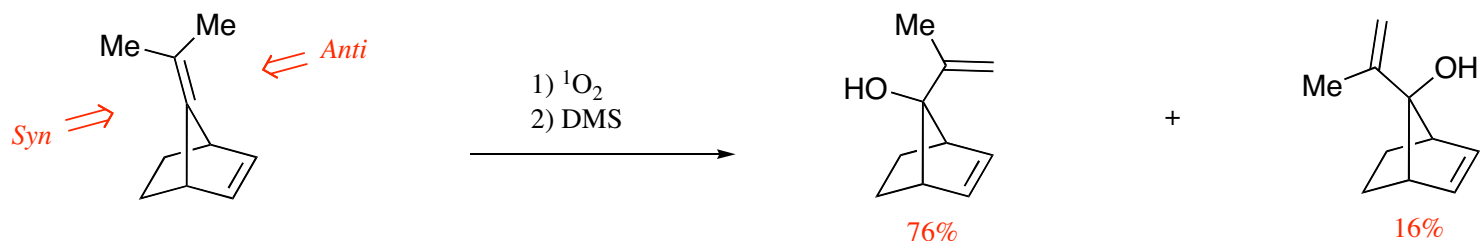


- MO interactions could explain selectivity in some cases



- HOMO of the peroxide is a linear combination of the $n(\text{O})$ and $\sigma(\text{C-L})$
- HOMO is antibonding in nature
- Any substituent that reduces the energy between $n(\text{O})$ and $\sigma(\text{C-L})$ would increase the antibonding interaction and favor cleavage of the adjacent C-O bond

Ene Reaction: Stereoelectronic Effects

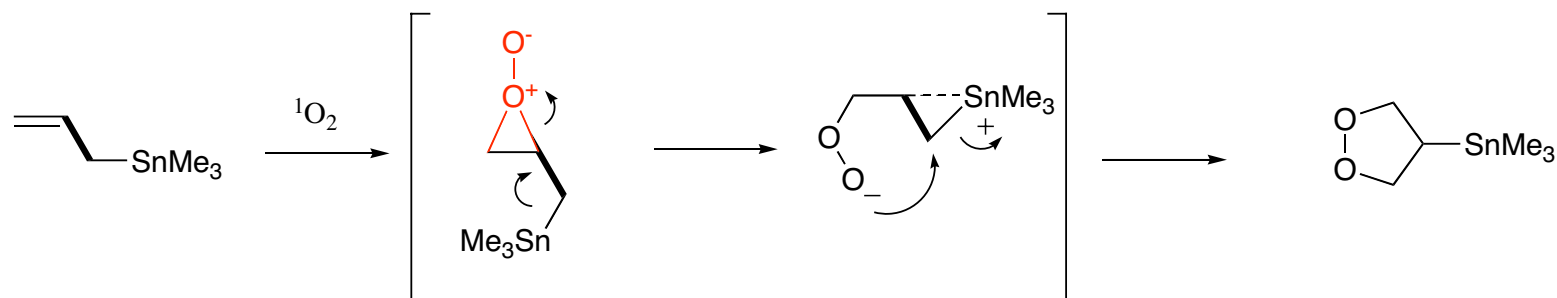
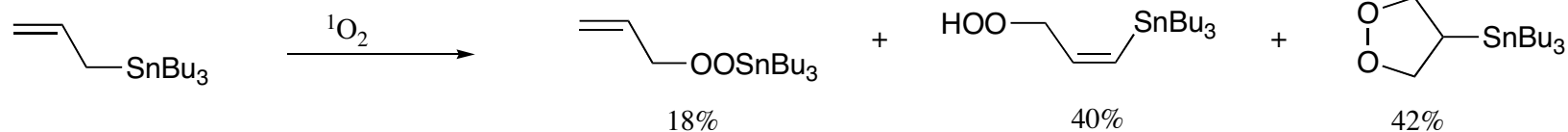
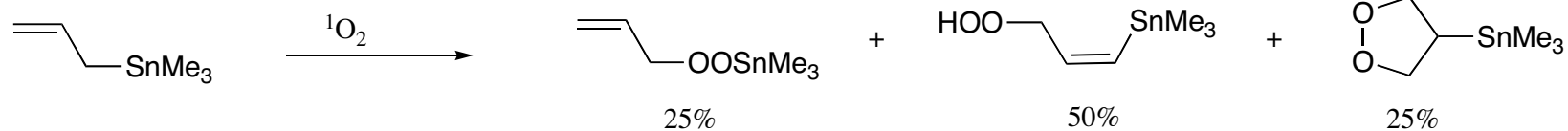
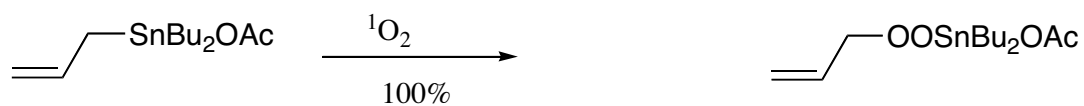
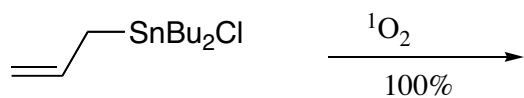


Anti/Syn	80/20	79/21	48/52	46/54	49/41
k(M⁻¹s⁻¹)	1.36×10^5	4.28×10^6	9.63×10^4	5.24×10^4	

- Mukai proposed that π -orbital distortion arising from the mixing of the isopropylidene π -orbital with a lying σ -orbital is responsible for the effect above
- Paquette and coworkers pointed out that the experimental results are consistent with anchimeric π -electron density donation to the developing anti-perepoxide
- Later, Houk and coworkers proposed that the effect above results from the electrostatic repulsion of singlet oxygen and π cloud of the aromatic ring

Mukai, *JACS*, **1978**, 6509-6510
 Paquette, *JACS*, **1978**, 6510-6512
 Houk, *JOC*, **1993**, 4625-4628

Ene Reaction: Electronic Effects



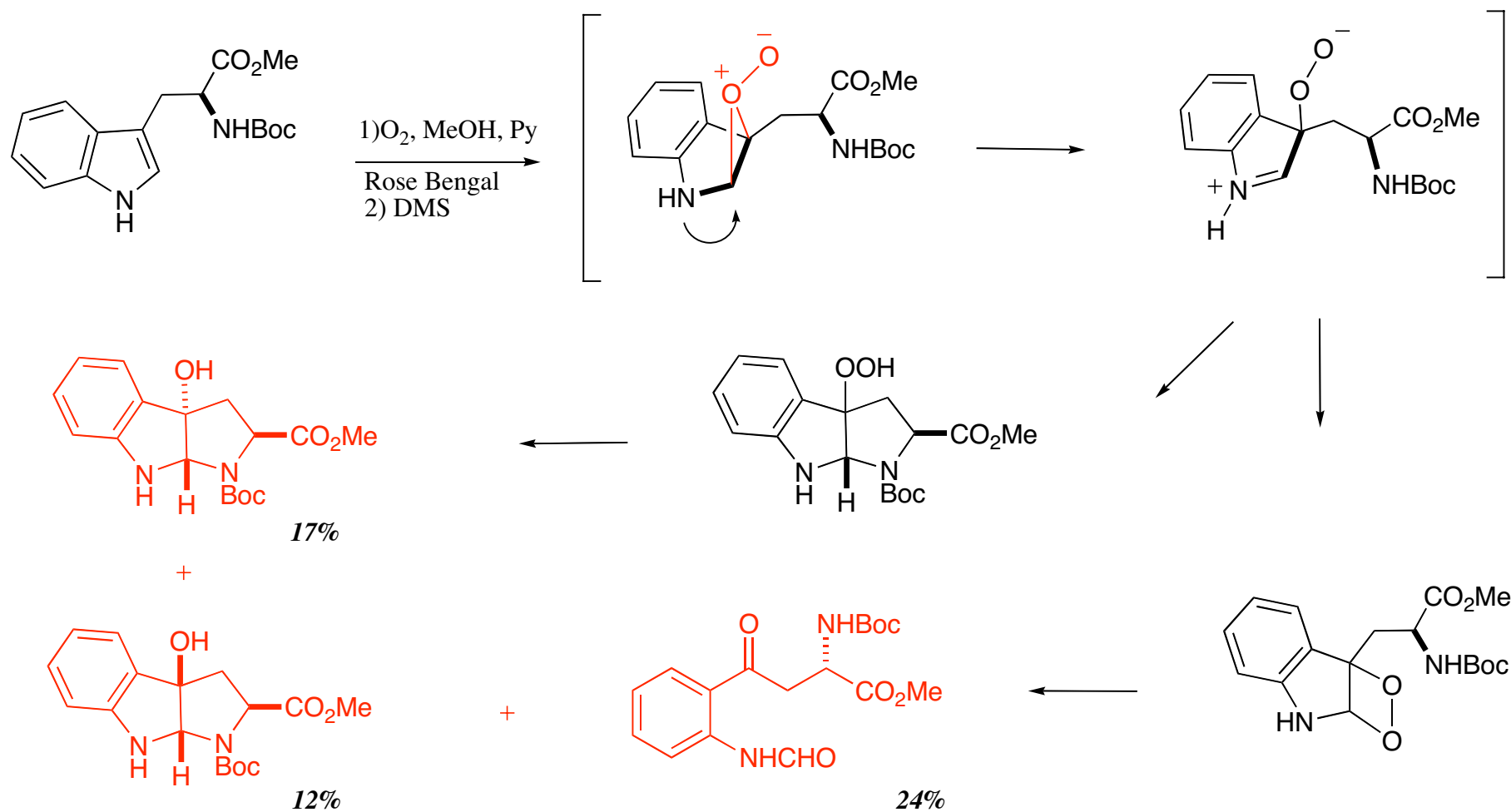
Dang, Davies, *Tet. Lett.*, **1991**, 32, 1745-1784

Dang, Davies, *J. Chem. Soc. Perkin Trans, 2*, **1992**, 1095-1101

Dang, Davies, *J. Organomet. Chem.*, **1992**, 430, 287-289

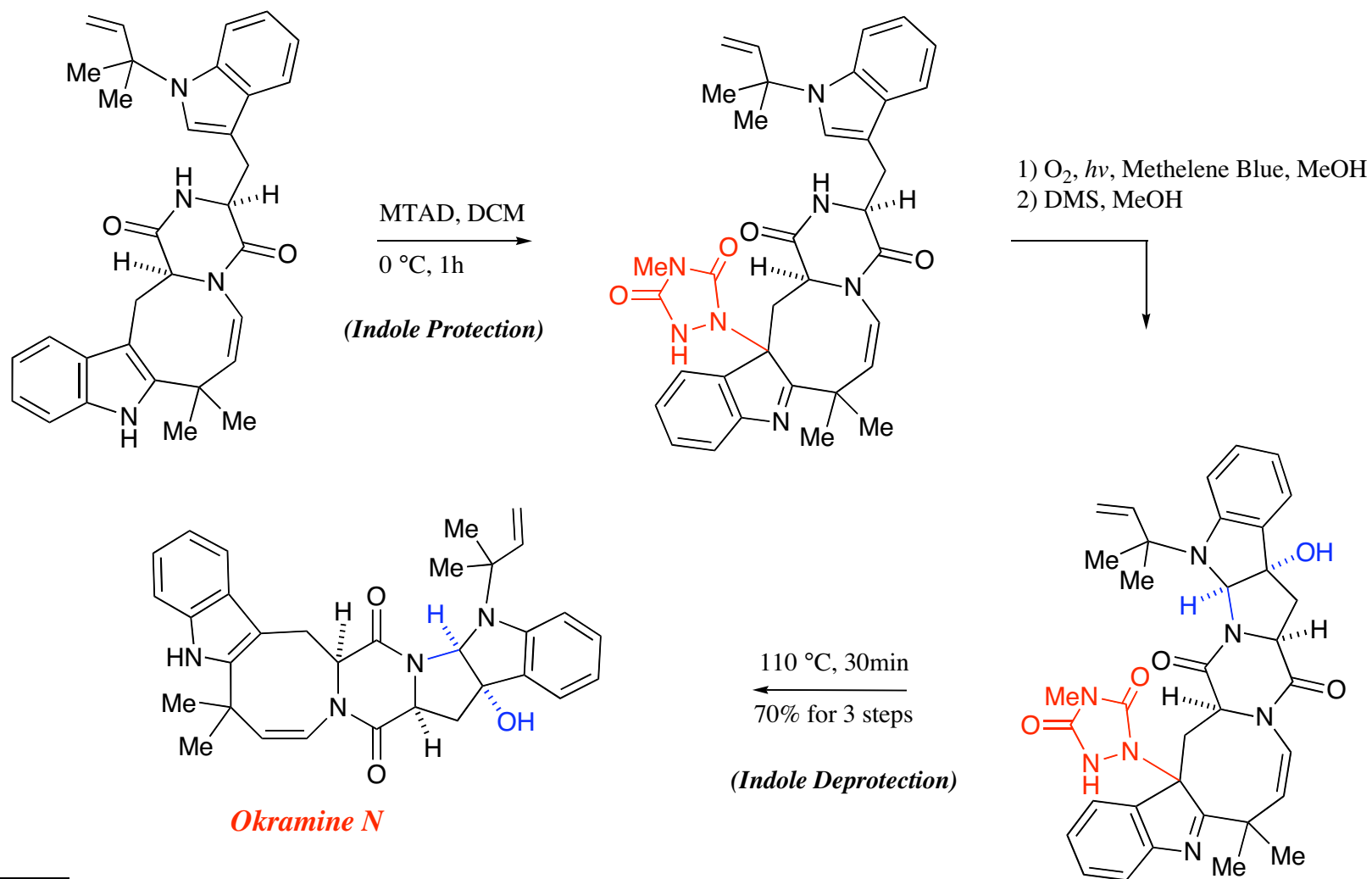
Ene Reaction: Oxidation of Indoles

- Photooxygenation of indoles is well studied in connection with the metabolism of tryptophan and its derivatives



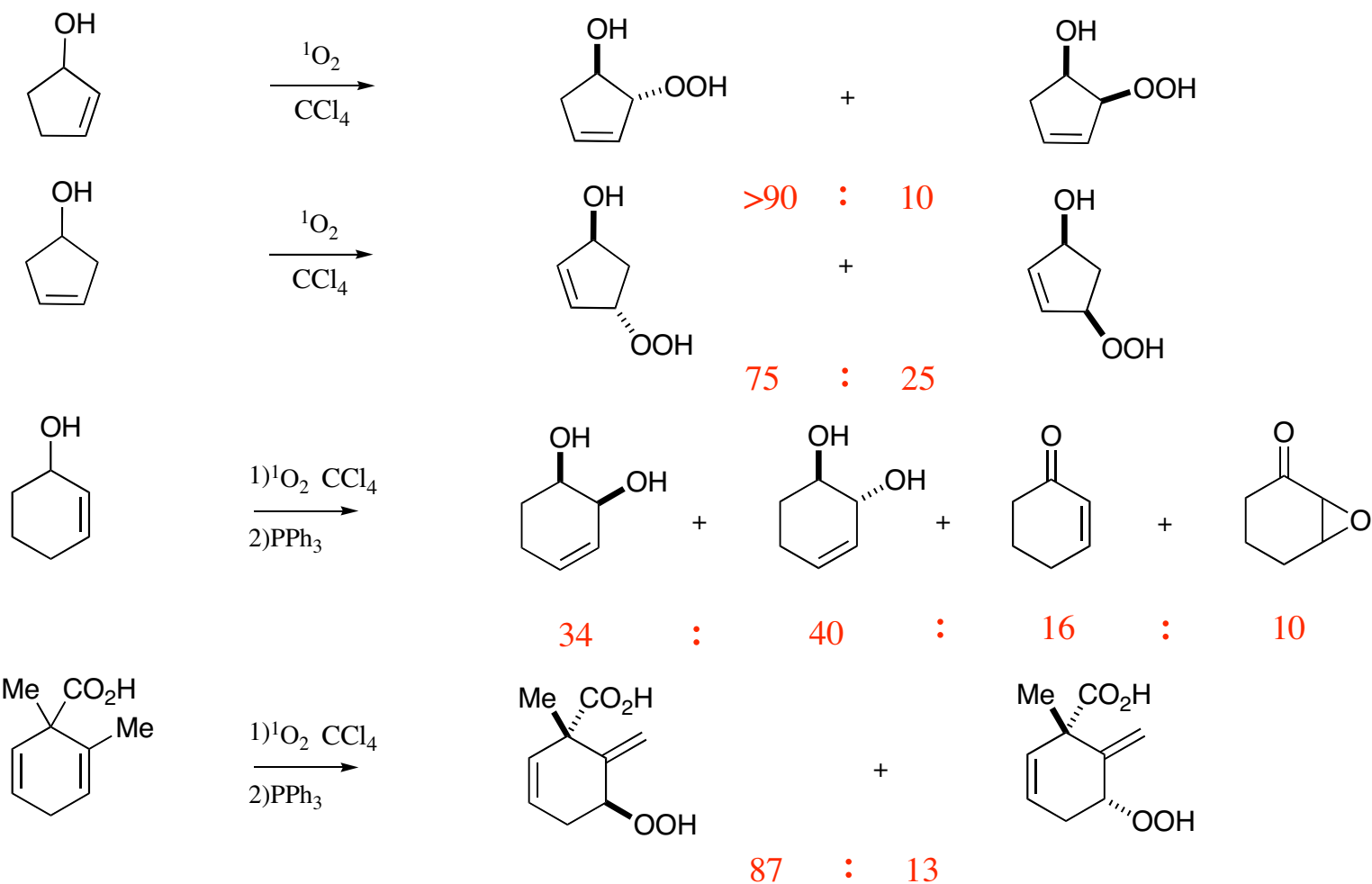
Ene Reaction: Okramine N by E. J. Corey

- The photooxygenation of indole was employed in one of the final stages of the Okramine N synthesis



Ene Reaction: Hydrogen Bonding

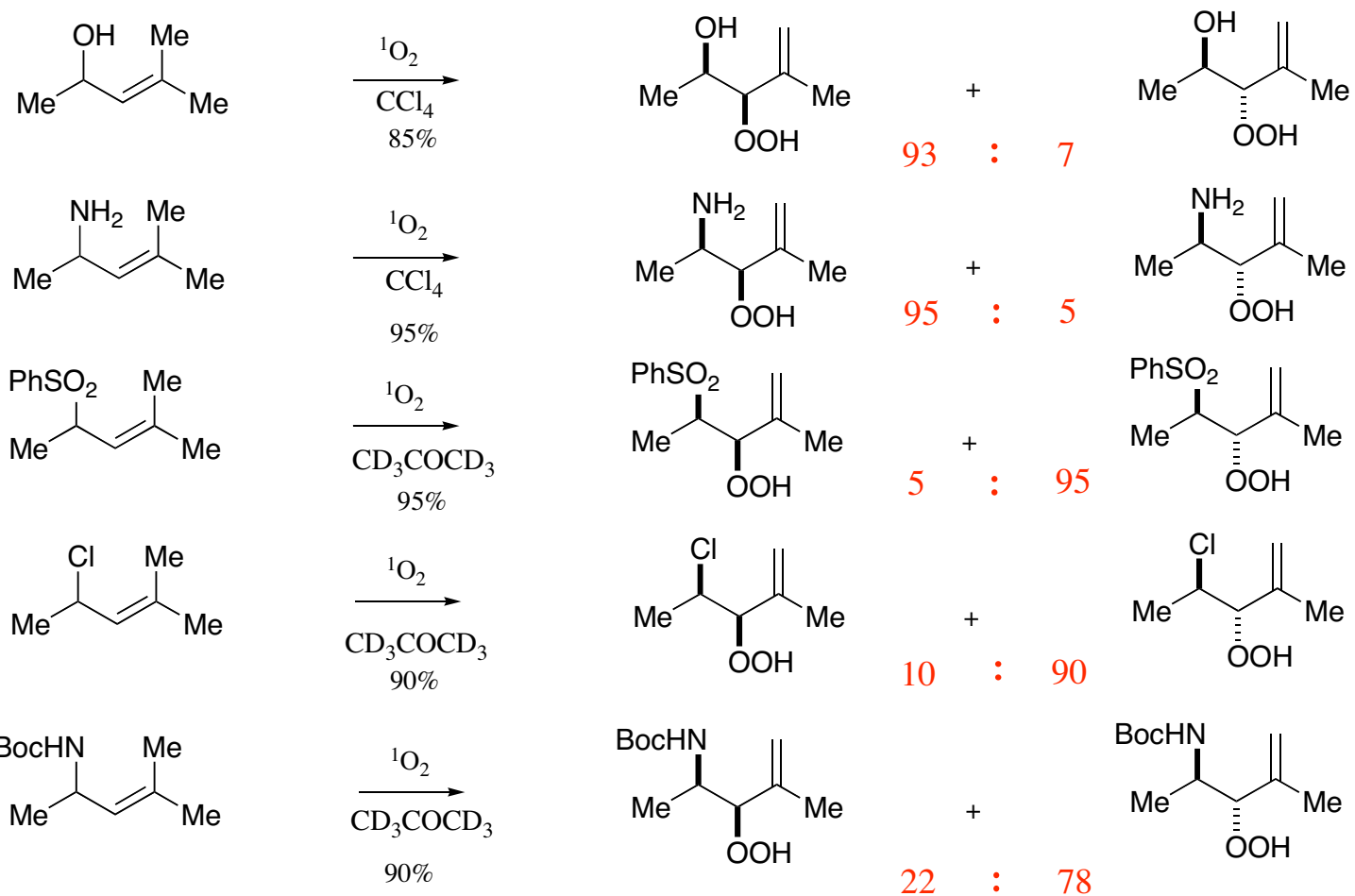
- Adam and coworkers have investigated the possibility of directed ene reaction



Adam, *Acc. Chem. Res.* **1999**, 32, 703-710
 Adam, *JACS*, **1996**, 118, 1899-1905
 Adam, *Angew. Chem. Int. Ed.* **1996**, 35, 477-494

Ene Reaction: Hydrogen Bonding

- For acyclic compounds, the hydrogen bonding coupled to A1,3 strain promoted conformational bias can produce synthetically useful diastereoselectivities



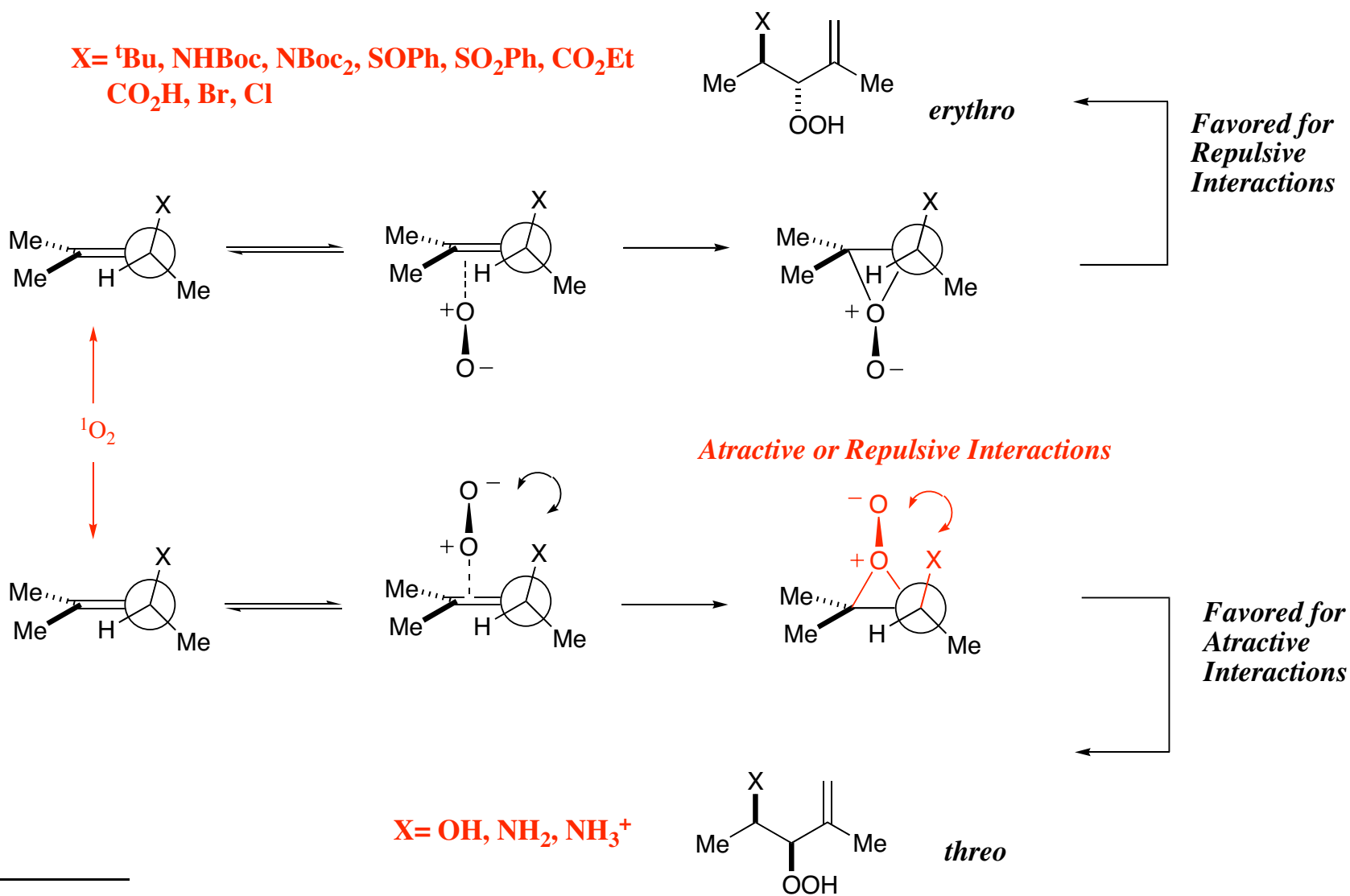
Adam, *Acc. Chem. Res.* **1999**, 32, 703-710

Adam, *JACS*, **1996**, 118, 1899-1905

Adam, *Angew. Chem. Int. Ed.* **1996**, 35, 477-494

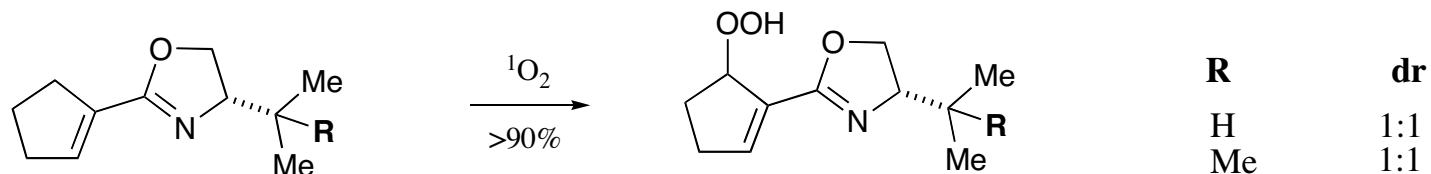
Ene Reaction: Hydrogen Bonding

X = ^tBu, NHBoc, NBoc₂, SPh, SO₂Ph, CO₂Et, CO₂H, Br, Cl

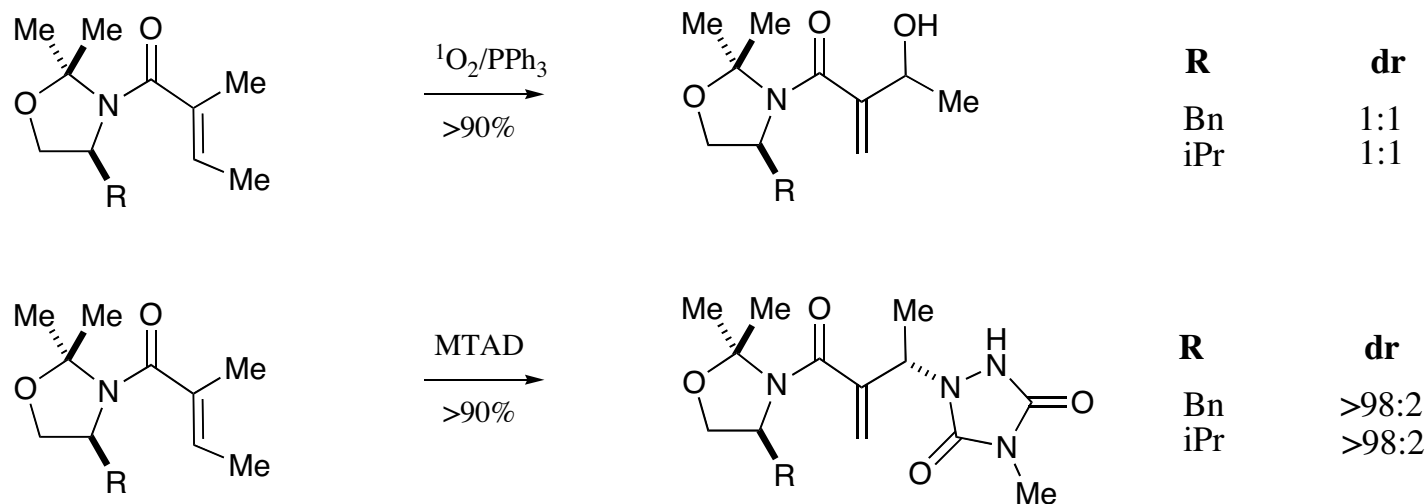


Ene Reaction: Chiral Auxiliaries

- The first attempt to use chiral auxiliary was made by Ensley and coworkers, and was unsuccessful

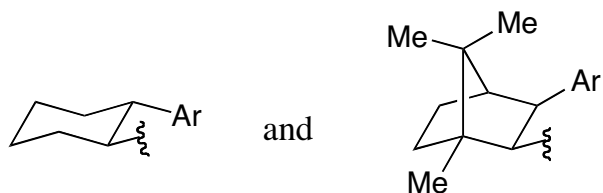
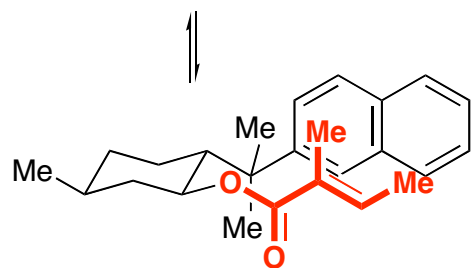
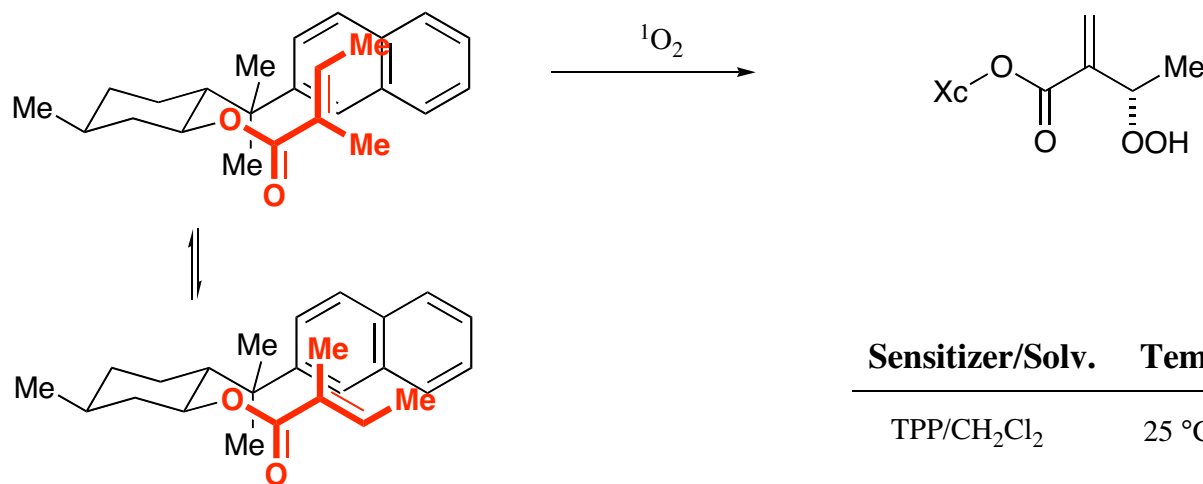


- Adams and coworkers investigated similar auxiliaries for singlet oxygen and MTAD ene reactions



Ene Reaction: Chiral Auxiliaries

- Dussault has demonstrated that 8-arylmethyl auxiliaries could give acceptable diastereoselectivity in singlet oxygen reaction

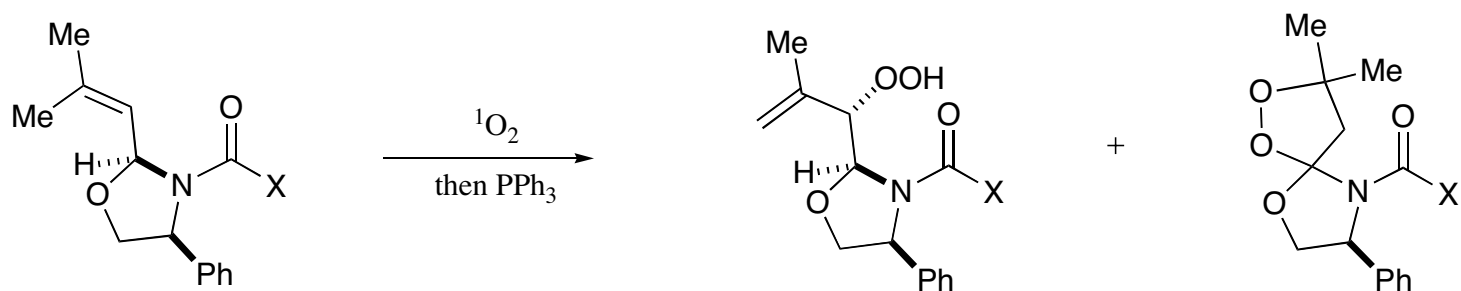


did not give any selectivity

Sensitizer/Solv.	Temp.	Yield	dr
TPP/CH ₂ Cl ₂	25 °C	82	1:2.3
TPP/CCl ₄	25 °C	87	1:2.3
RB/MeCN	25 °C	94	1:2.3
RB/MeOH	-30 °C	89	1:3.3
TPP/CH ₂ Cl ₂	-45 °C	83	1:3.3
TPP/CH₂Cl₂	-60 °C	86	1:4.5

Ene Reaction: Chiral Auxiliaries

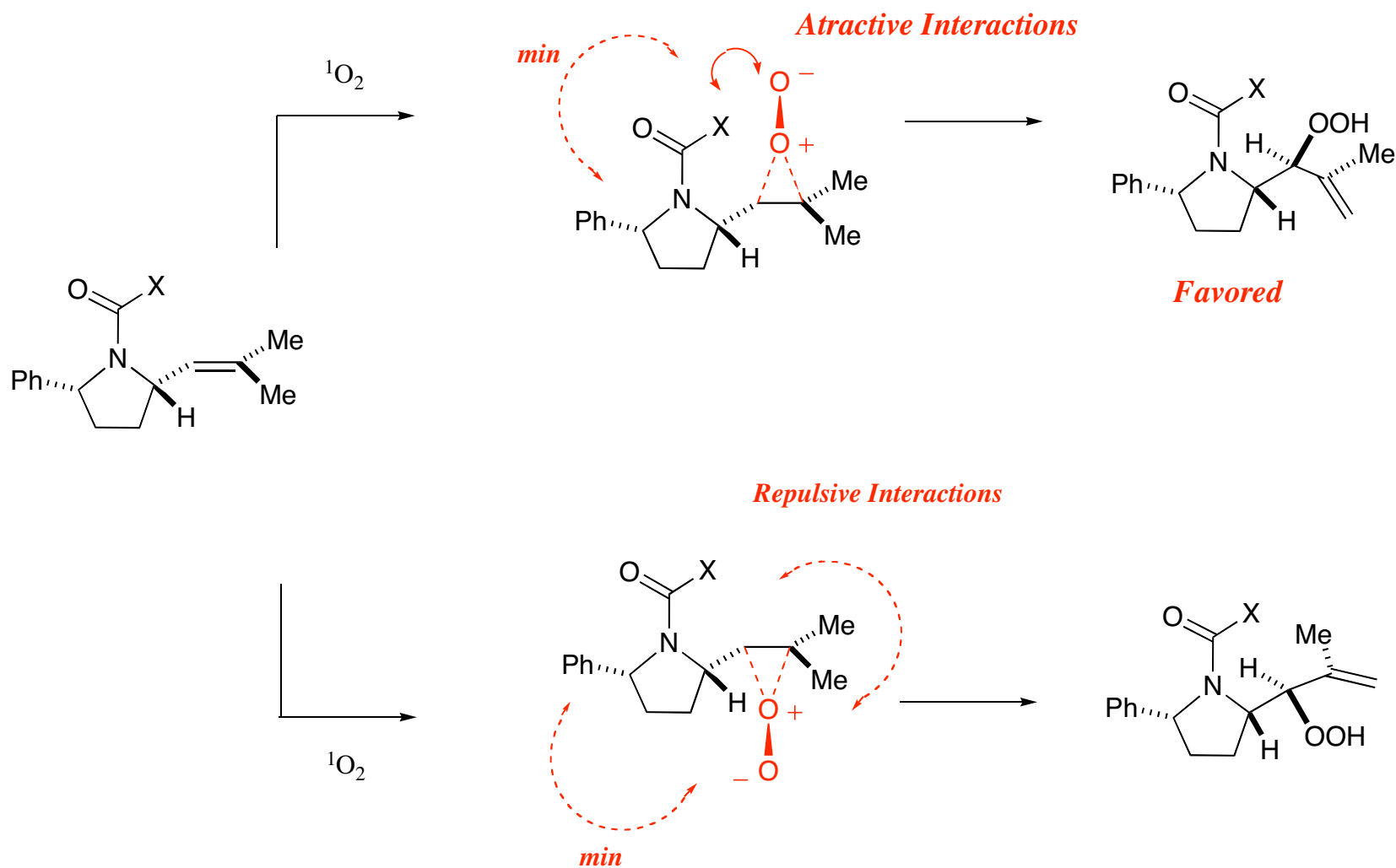
- Adam has attempted to construct an oxazole-based system with hydrogen directing ability to mimic the oxidation of allylic alcohols



X	Solvent	Temp.	Time	Mass Balance	Regioselectivity	dr
-OtBu	CCl_4	-5	20	92%	75:25	25:75
-Ph	CDCl_3	-5	23	86%	86:14	45:55
-NHPH	CDCl_3	-5	4	>95%	93:7	94:6
-NHPH	<i>d6</i> -acetone	-10	40	72%	96:4	85:15
-NH <i>p</i> -(NO ₂)Ph	CDCl_3	-10	28	85	96:4	>95:5
-NMePh	CDCl_3	-10	48	90	70:30	41:59

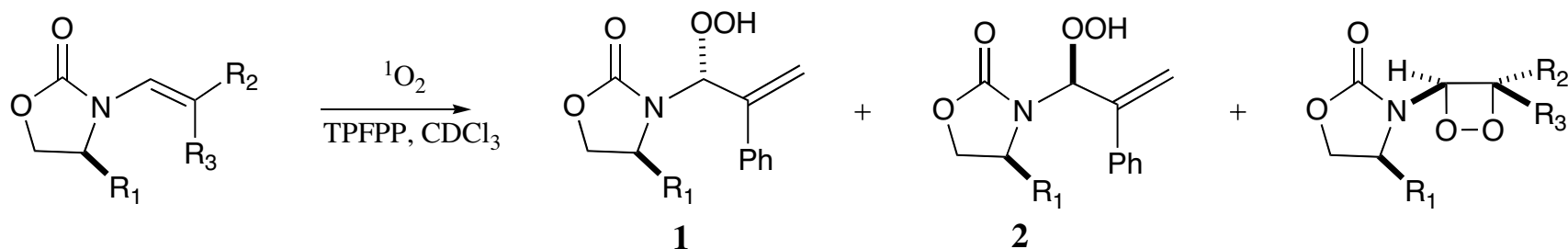
Ene Reaction: Chiral Auxiliaries

- Adam has attempted to construct an oxazole-based system with hydrogen directing ability to mimic the oxidation of allylic alcohols



Ene Reaction: Chiral Auxiliaries

- Adam has used oxazolidinone auxiliary to perform diastereoselective $^1\text{O}_2$ ene and [2+2] reactions

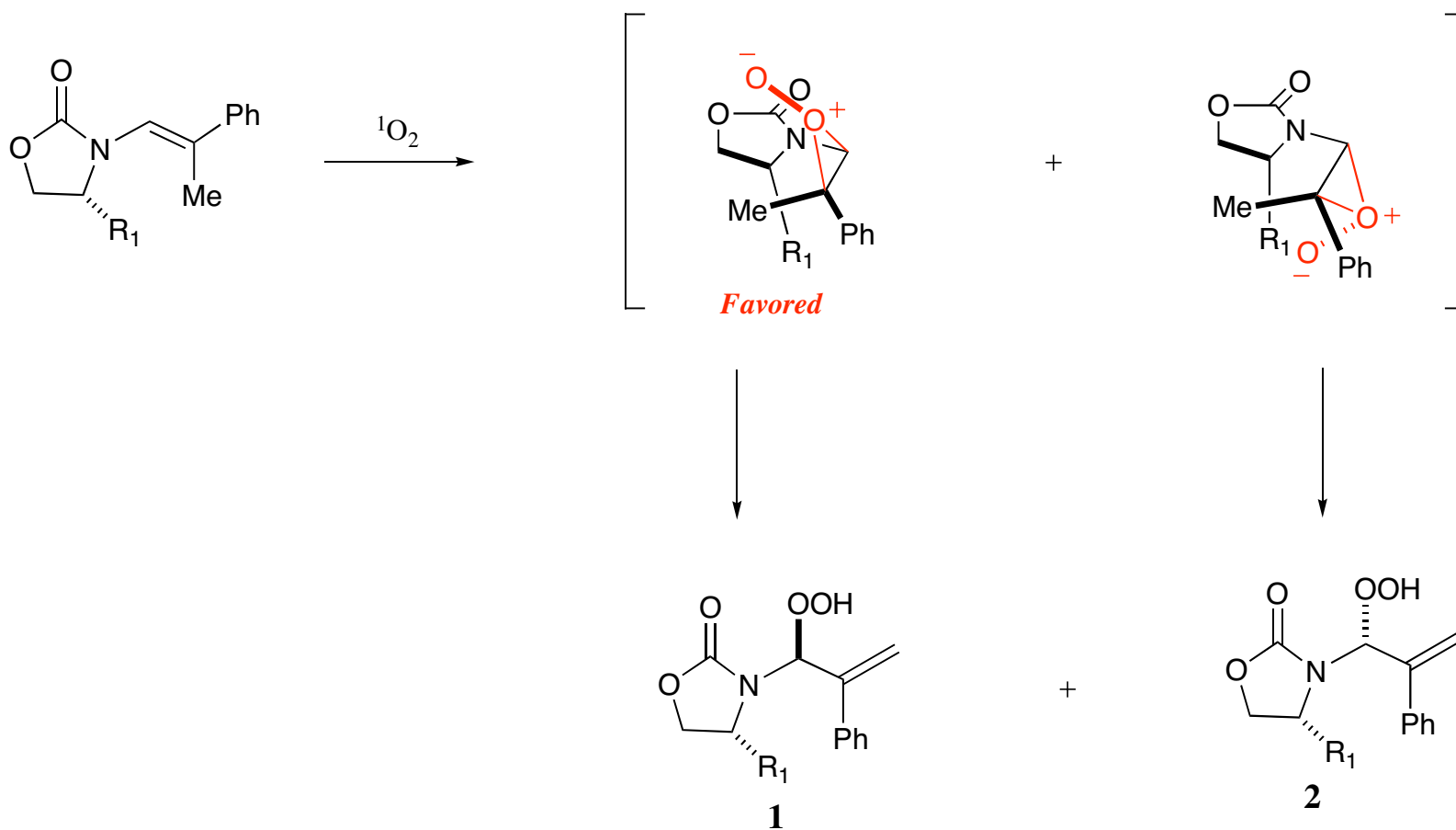


TPFPP=5,10,15,20-tetrakis(pentafluorophenyl)porphine

R_1	R_2	R_3	[2+2]:ene	1:2	[2+2] dr
(<i>S</i>)- <i>t</i> Bu	(<i>R</i>)-Ph(Me)CH	Ph	>95:5	-	<5:95
(<i>R</i>)- <i>i</i> Pr	<i>i</i> Pr	Ph	>95:5	-	>95:5
(<i>R</i>)-Me	Me	Ph	80:20	53:47	>95:5
(<i>R</i>)- <i>i</i> Pr	Me	Ph	75:25	56:44	>95:5
(<i>R</i>)-Me	Ph	Me	16:84	88:12	nd
(<i>R</i>)- <i>i</i> Pr	Ph	Me	36:64	83:17	nd
(<i>S</i>)-Ph	Ph	Me	8:92	71:29	nd
(<i>S</i>)- <i>t</i> Bu	Ph	Me	23:77	91:9	nd

Ene Reaction: Chiral Auxiliaries

- Both the mode of reaction and diastereoselectivity of the ene reaction strongly depend on the double bond geometry
- Ene reaction is favored when the "cis effect" is operational



Ene Reaction: Conclusion

- Singlet oxygen ene reaction is one of the highly investigated processes in organic chemistry
- There are certain trends of oxidation ("cis effect", "geminal effect", etc.) that could be used with a to predict the outcome of the ene reaction
- Ene singlet oxygen reaction could be performed diastereo- and enantioselectively although some further advancements in this area is required

