

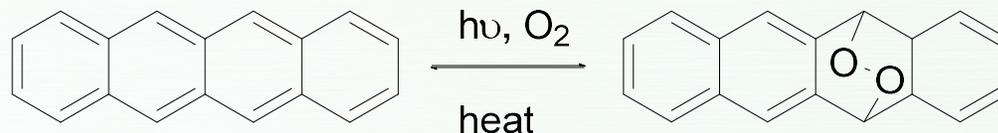
Singlet Oxygen

Laura Calvo Parra
Denmark Group Meeting
February 21, 2017

Presentation Outline

- I. Introduction
- II. Electronic transitions
- III. Photosensitizers
- IV. Schenk-Ene reaction
- V. [4+2] and [2+2] cycloadditions
- VI. Synthetic applications

Early Discoveries



» Fritzsche, 1867

- * First observed singlet oxygen reaction
- * Tetracene + oxygen

» Lewis, 1924

- * Molecular oxygen is a triplet state biradical species
- * Measured magnetic susceptibility of ethylene, formaldehyde, and molecular oxygen

» Kautsky, 1931

- * First evidence of metastable & reactive state of molecular oxygen

Early Discoveries

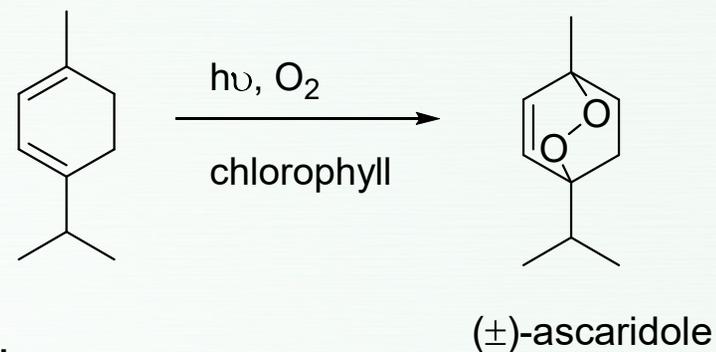
» Schenk and Ziegler, 1954

» First use of singlet oxygen in organic synthesis

» Foote, 1968

* Oxygen-sensitizer complex vs. singlet oxygen

* Comparison of photooxidation and chemical methods of singlet oxygen generation



Diatomic Oxygen

» Essential for life ...
sometimes

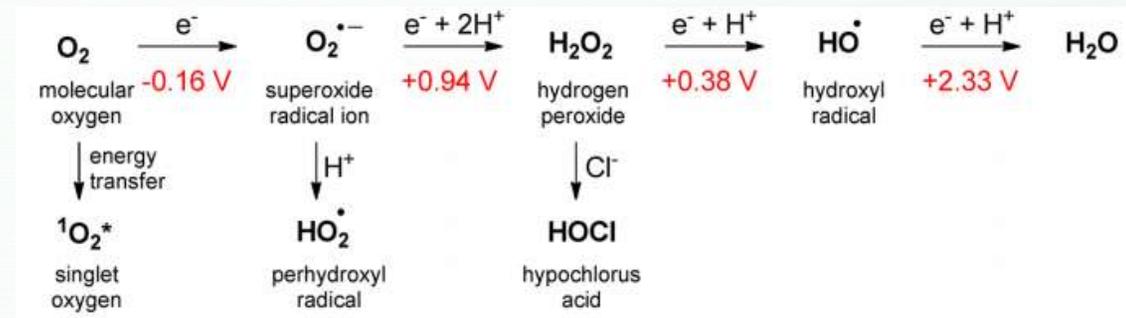
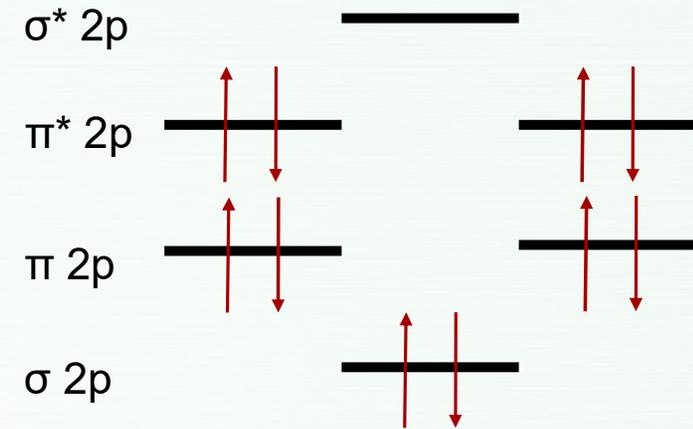
* Reactive species

- ROS
- ROI
- RNS

* Oxidative stress

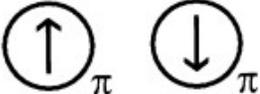
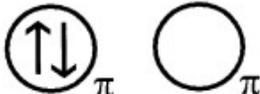
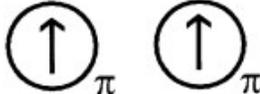
» ROS reactivity

* 1 or 2 electron process



Diatomic Oxygen

- » Paramagnetic & biradical species
- » Spin restriction limits reactivity
 - * Oxygen usually accepts 1 electron at a time
- » Mulliken – reasoned there would exist three orbitals closely related in energy
 1. The Σ triplet - $O_2(^3\Sigma_g^-)$
 2. The Δ singlet - $O_2(^1\Delta_g)$
 3. The Σ singlet - $O_2(^1\Sigma_g^+)$

State	Orbital Assignment
$^1\Sigma_g^+$	
$^1\Delta_g$	
$^3\Sigma_g^-$	

Singlet = molecular electronic state such that all electrons are spin paired

Triplet = molecular electronic state such that the electrons are *not* spin paired

Diatomic Oxygen

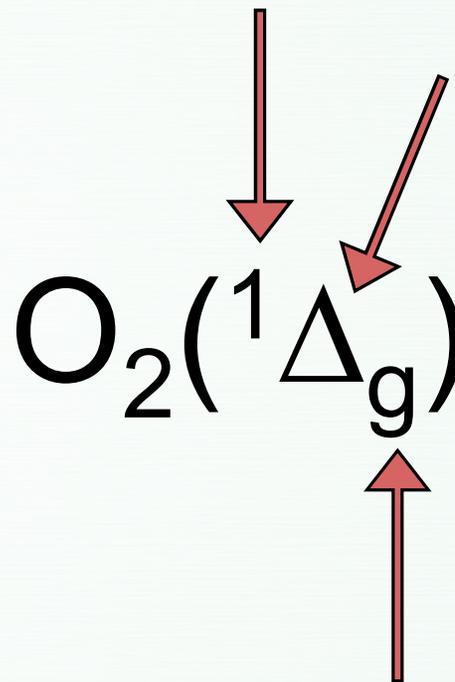
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* Multiplicity

- 1 = singlet
- 3 = triplet

* Orbital angular momentum

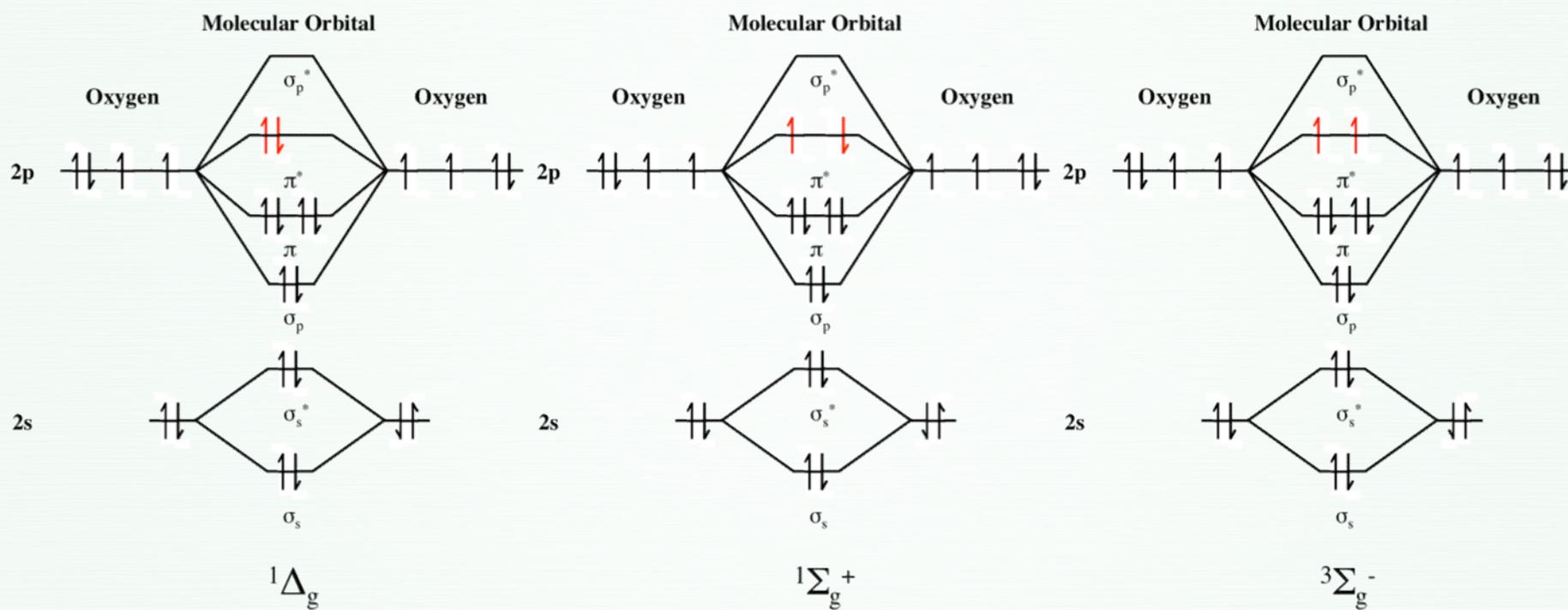
- $\Sigma, M_L = 0$
- $\Delta, M_L = 2$



* Symmetry

- Pair parity

Diatomic Oxygen



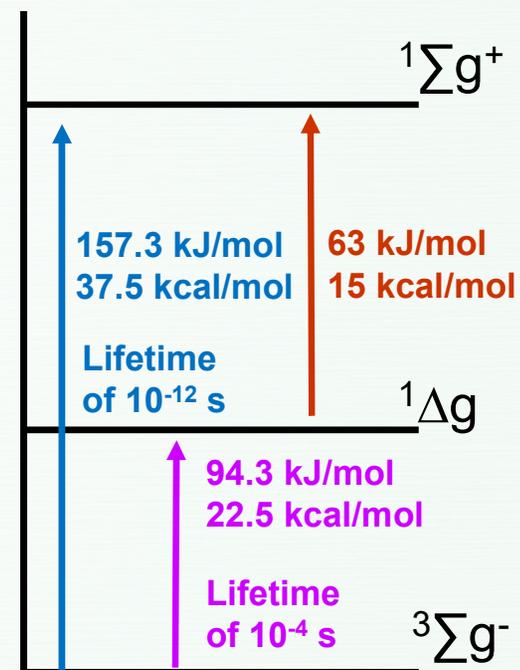
Reactivity: Singlet vs. Triplet Oxygen

Singlet oxygen $O_2(^1\Delta)$

- * Excited state
- * Powerful electrophile
- * 2 electron processes

Triplet oxygen $O_2(^3\Sigma)$

- * Ground state
- * Powerful oxidant
- * 1 electron processes



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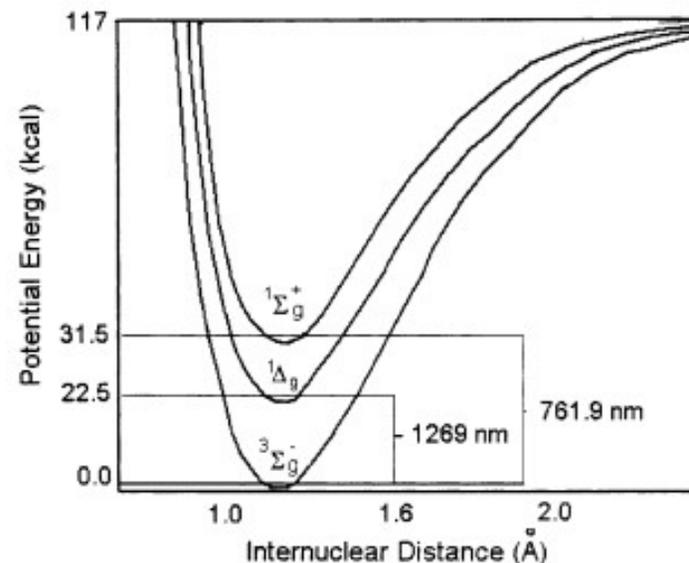
Electronic Transitions

» Intersystem crossing (ISC)

- * Radiationless process involving a transition between electronic states with different spin multiplicity
 - Singlet \rightarrow triplet transition is spin forbidden \therefore $^1\text{O}_2$ species are relatively “long” lived species

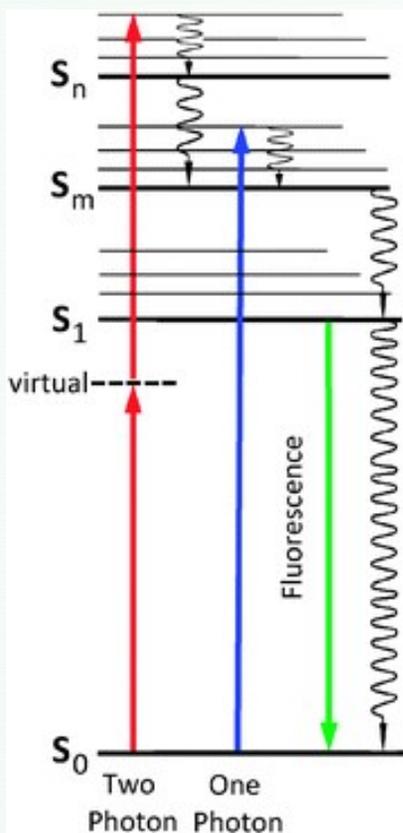
» Internal conversion

- * Radiationless process involving a transition between electronic states with the same spin multiplicity



Zero point energy = also referred to as ground state energy; the energy of the ground state species

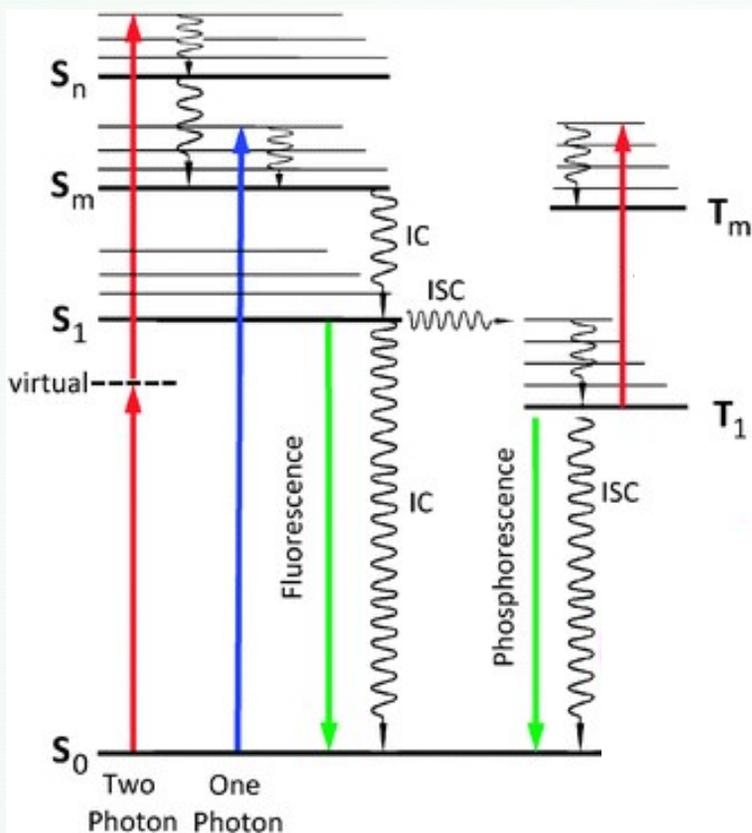
The S_n and T_n States



Fluorescence = electronic decay accompanied by emission of a photon

Phosphorescence = forbidden electronic decay – no immediate photonic release, and latter not of original intensity

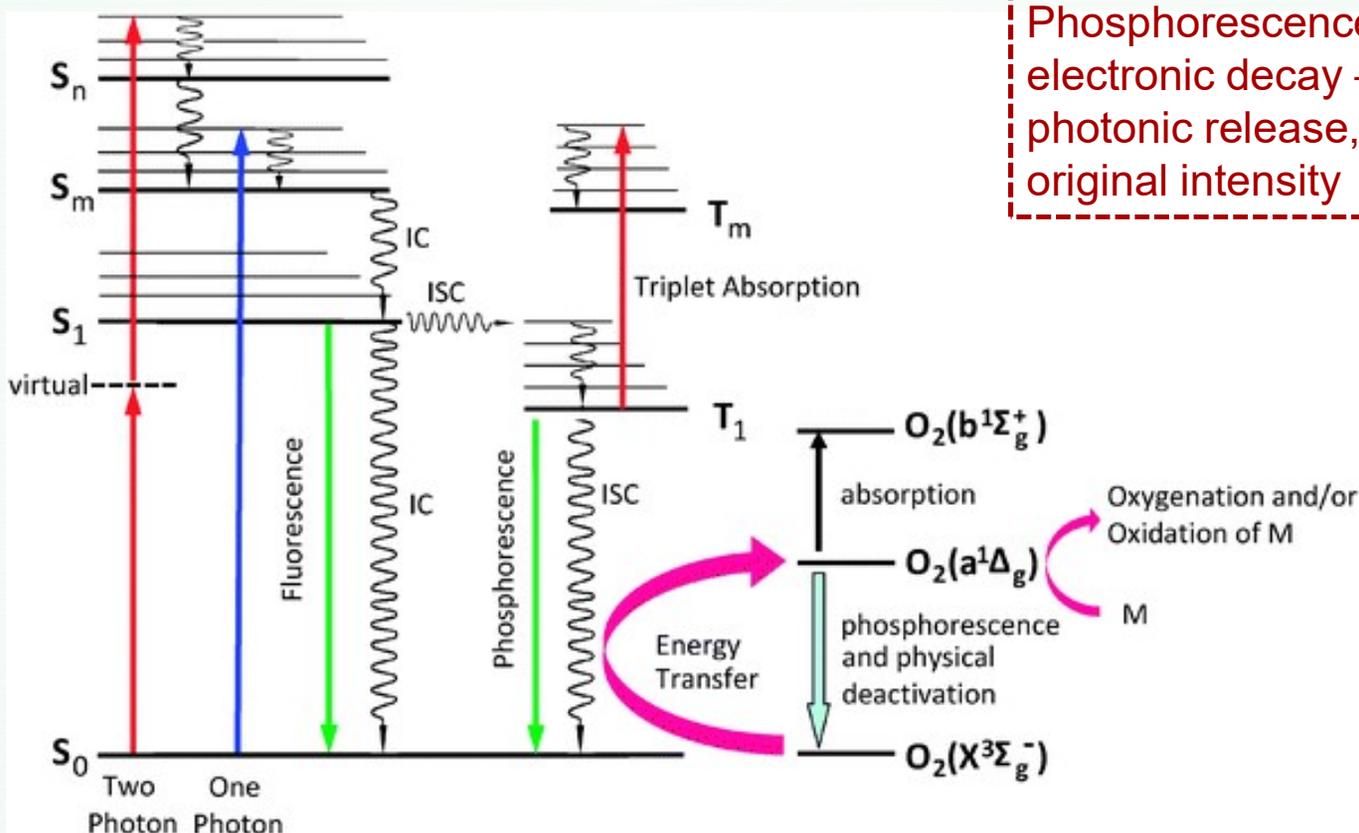
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The S_n and T_n States



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Reactivity of the T_1 state

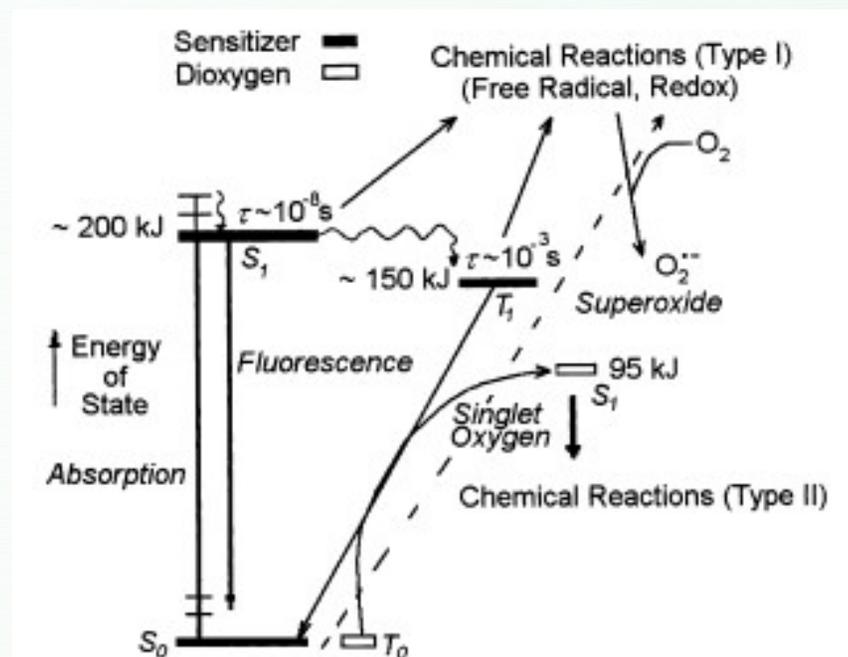
» Mechanisms

* Type I

- Electron transfer from excited photosensitizer to a substrate, producing free radicals
- Radicals react with oxygen to form a ROS

* Type II

- Energy transfer during a collision between the excited photosensitizer and molecular oxygen



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Photosensitizers

» Reagents

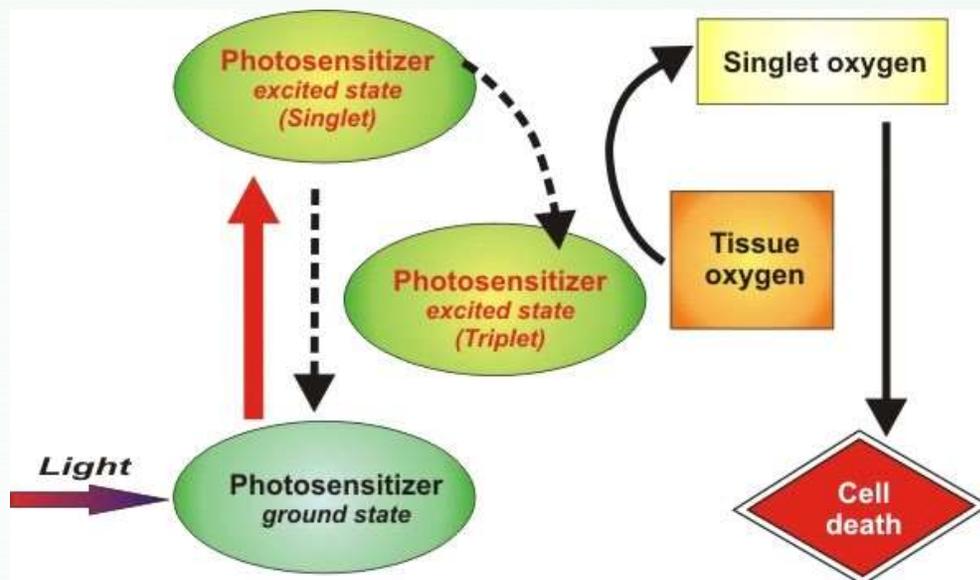
- * Oxygen
- * Light
- * Photosensitizer

» Procedure

- * Shine the light

» Requirements

- * Strong absorption coefficient in the spectral region of the excitation light
- * Excited triplet state with sufficient energy to carry out energy transfer to ground state oxygen
- * High quantum yield of the triplet state
- * High photostability



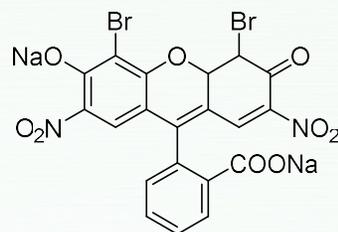
Photosensitizers

» Organic dyes & aromatic hydrocarbons

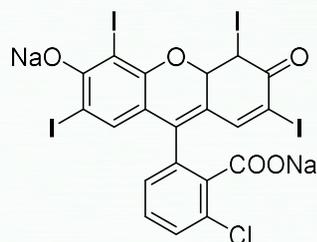
* Methylene blue, eosin, rose bengal, etc.

» Porphyrins and phthalocyanines

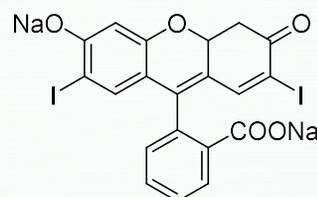
* Often found in biological systems
* Wide range of absorption
* Long-lived triplet states
* Tunable



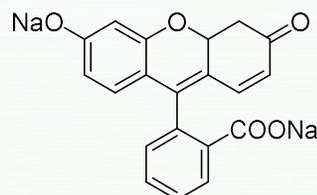
Eosin blue



Rose bengal



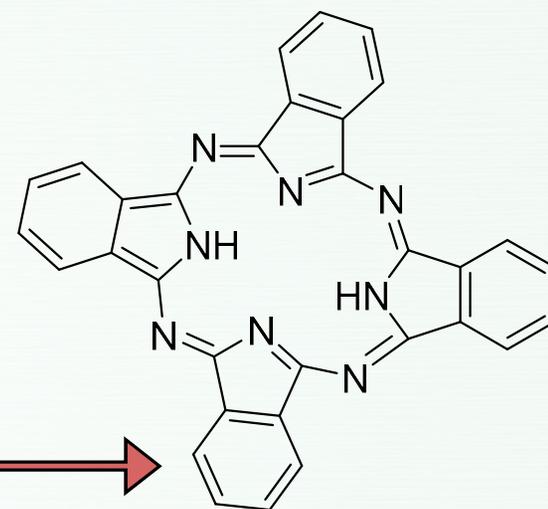
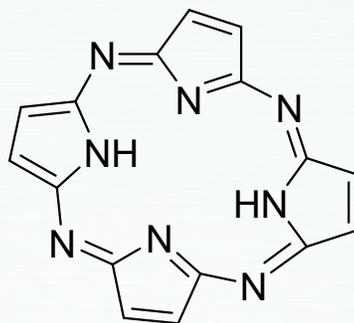
Erythrosin B



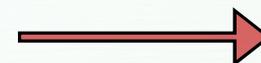
Fluorescein

Photosensitizers

- » Organic dyes & aromatic hydrocarbons
 - * Methylene blue, eosin, rose bengal, etc.
- » Porphyrins and phthalocyanines
 - * Often found in biological systems
 - * Wide range of absorption
 - * Long-lived triplet states
 - * Tunable



Extended conjugation



$$E = \frac{h\nu}{\lambda}$$

Photosensitizers

» Immobilized photosensitizers

* Photodynamic antimicrobial chemotherapy (PACT)

- Uses a photosensitizer that associates with the microorganism and is then activated
- Upon activation, ROS are created and the microorganism is inactivated
- Alternative to traditional antibiotics

» Photobleaching/autodegradation

» Singlet oxygen can react with photosensitizers, reducing degree of conjugation

- * Less conjugation \Rightarrow weaker absorption \Rightarrow loss of photosensitizing abilities

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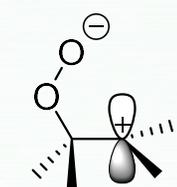
The ene reaction: Introduction

- » First singlet oxygen ene reaction published in 1948 by Schenck
- » Reaction of an olefin and singlet oxygen to generate a hydroperoxide

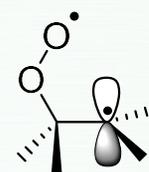
- * Reduce hydroperoxides to allylic alcohols

- » Two proposed mechanisms

- * Concerted
- * Step-wise

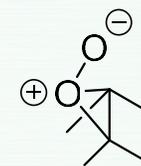


Zwitterion

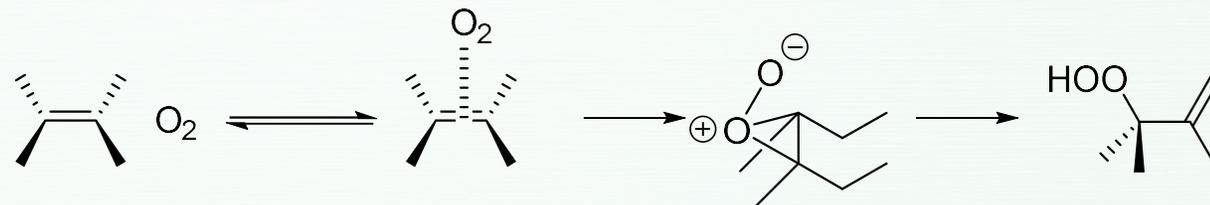


Radical

Perepoxide



Exciplex



The ene reaction: Reaction Control

- » Synthetic utility of the singlet oxygen-ene reaction based upon the following factors:
 - * Mechanistic constraints
 - Reaction follows suprafacial attack
 - * Electronic perturbations
 - Cis effect
 - Electronically withdrawing groups
 - * Steric perturbations
 - Anti-cis effect

The ene reaction: The *cis* Effect

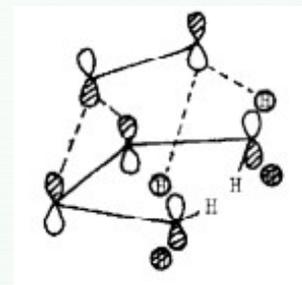
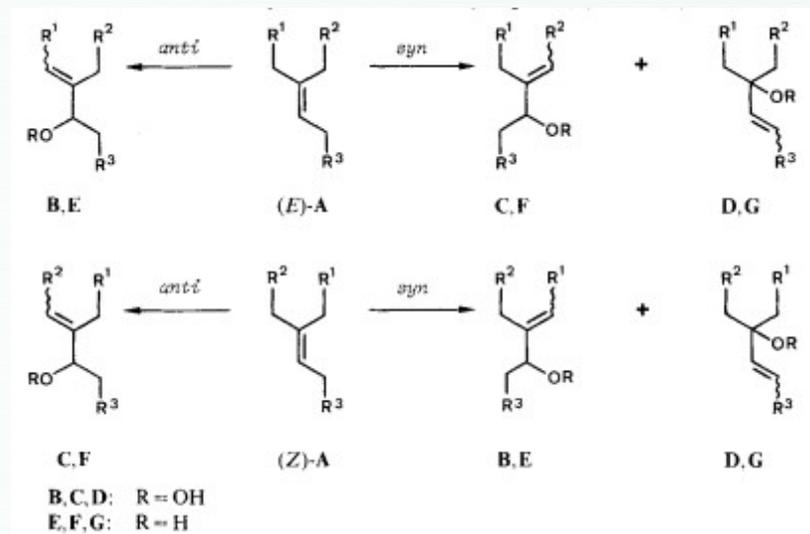
» Explanations

* Shulte-Elte

- Product distribution from *Z* and *E* olefins (R1 and R3)
 - *E* olefins
 - Only *syn* addition
 - *Z* olefins
 - Mainly *syn* addition

* Stephenson

- Interaction between LUMO of $^1\text{O}_2$ and butene-like HOMO of the olefin stabilizes TS



The ene reaction: The *cis* Effect

» Explanations

* Shuster

- Entropy of activation values
- Hammond postulate

* Houk

- Allylic C-H bond must be perpendicular to the plane of the olefin
- Rotation barriers of methyl groups; lower barrier \Rightarrow higher reactivity

Table 1. Reaction of $^1\text{O}_2$ with various olefins

Olefin	Solvent	$\Delta H^{\ddagger a}$ (kcal/mol)	$\Delta S^{\ddagger b}$ (e.u.)	$\Delta S_{\text{norm}}^{\ddagger}$ (e.u.)	k_p^b ($\text{M}^{-1} \text{s}^{-1}$)
	CS_2	0.5	-23	-30	2.2×10^7
	CS_2	0.7	-30	-31 ^c	7.2×10^5
	$(\text{CD}_3)_2\text{CO}$	1.1	-27	-28 ^c	1.3×10^6
	CS_2	1.6	-32	-35	4.8×10^4
	CS_2	2.0	-31	-34	3.9×10^4
	CS_2	1.2	-32	-35	5.8×10^4

The ene reaction: The *cis* Effect

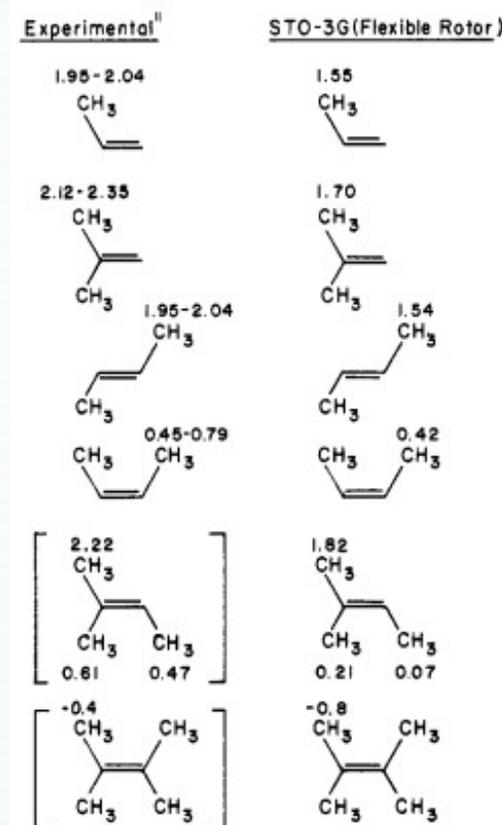
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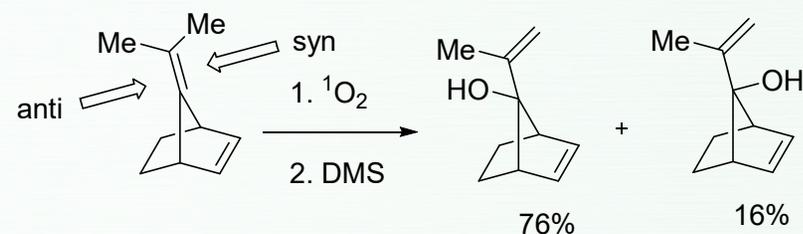
Hurst, J.; McDonald, D.; Schuster, G.; *J. Am. Chem. Soc.*, **1982**, *104*, 2065-2067.

Houk, K; Williams, J.; Mitchell, P.; Yamaguchi, K.; *J. Am. Chem. Soc.*, **1981**, *103*, 949-951.

The ene reaction: EWGs and EDGs

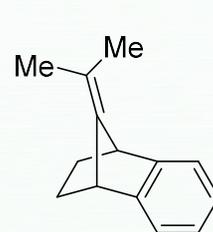
» Paquette

- » Anchimeric π electron density is donated to the developing peroxide

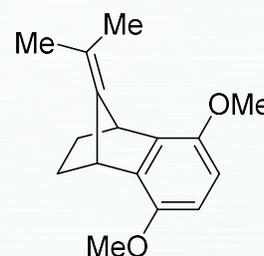


» Houk

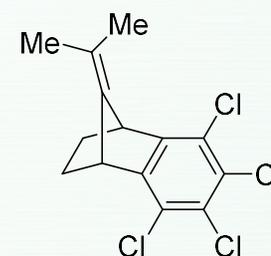
- » There exists electrostatic repulsion between the π electron cloud of the aromatic ring and singlet oxygen



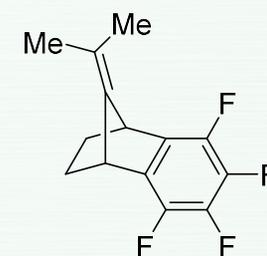
Anti/Syn 80/20



79/21



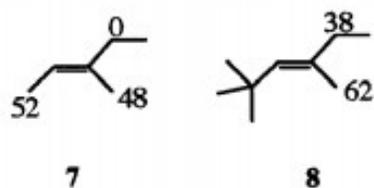
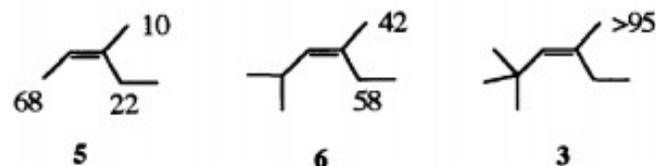
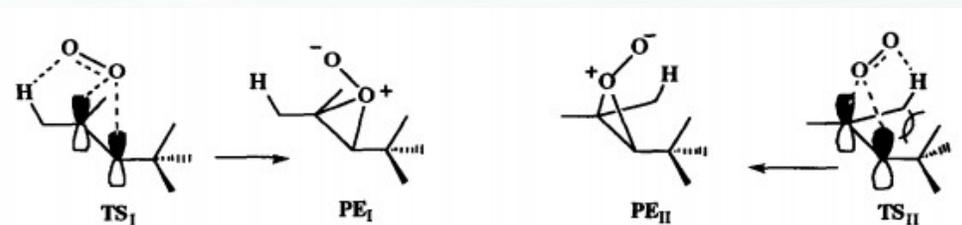
48/52



46/54

The ene reaction: The Anti-*cis* Effect

- » Olefins are known to violate the *cis* “rule”
- » Allylic H accessibility
 - Disubstituted side of an olefin has 2 accessible allylic hydrogens
 - Monosubstituted side of the olefin has 1 accessible allylic hydrogen
- » Main argument is sterics



The ene reaction: Mechanistic Studies

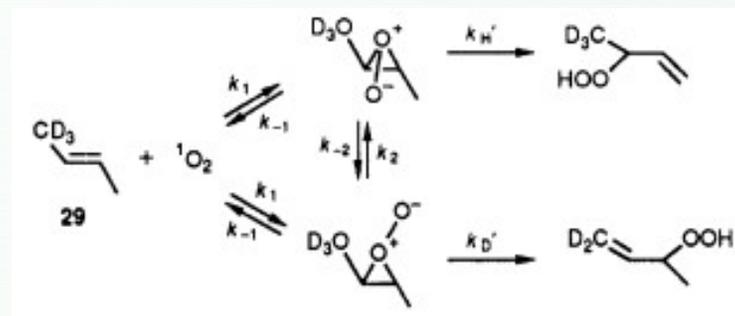
» Step-wise mechanism (Beak)

- * Studied kinetic isotope effects of the ene reaction
- * Observed variable kinetic isotope effects
 - Large KIEs \Rightarrow concerted synchronous
 - Small KIEs \Rightarrow step-wise
- * KIE distribution
 - Equilibrating intermediates
 - Substrate-intermediate equilibrium

Investigation of the Mechanisms of Ene Reactions of Carbonyl Enophiles by Intermolecular and Intramolecular Hydrogen-Deuterium Isotope Effects: Partitioning of Reaction Intermediates

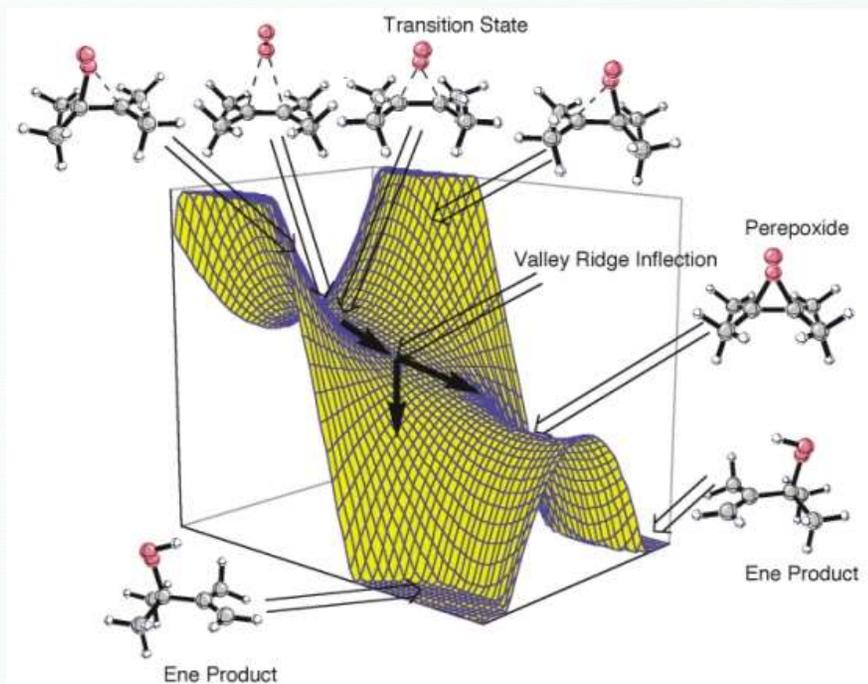
Zhiguo Song and Peter Beak*

Contribution from the Department of Chemistry, University of Illinois at Urbana-Champaign, Urbana, Illinois 61801. Received April 13, 1990



The ene reaction: Mechanistic Studies

- » Concerted mechanism – gas phase
 - » 2 step no intermediate
 - » No discrete energy minimum *but* rather an inflection point
- » Step-wise mechanism – in solvent
 - » Discrete perepoxide intermediate
 - » Intermediate has high degree of charge separation
- » Acevedo (2010)
 - » Perepoxide species stabilized in solvent – not a stationary point in the gas phase

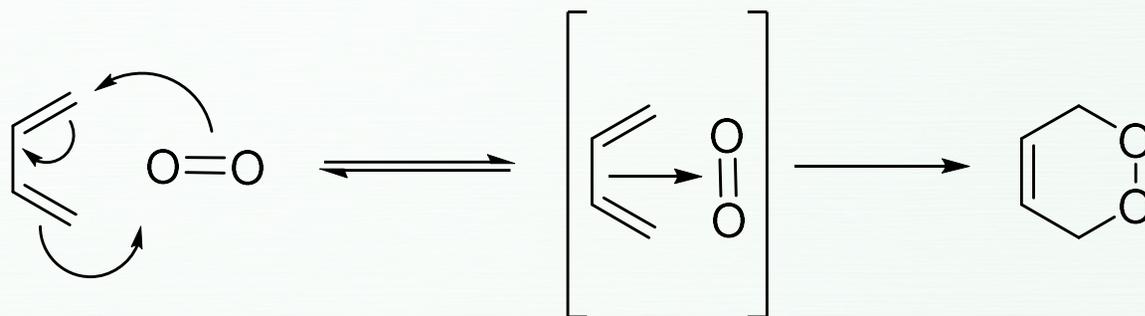


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[4+2] cycloaddition: Introduction

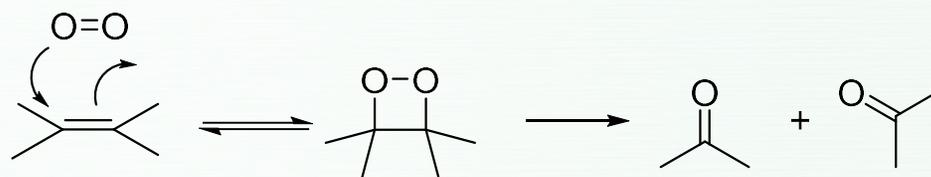
- » Reaction of an electron rich *s-cis* diene and singlet oxygen to generate an endoperoxide
- » [4+2] cycloadditions are reversible – product may undergo retro [4+2]
 - » Extrusion of oxygen gas
- » Suprafacial process
- » Exciplex intermediate



[2+2] cycloaddition: Introduction

» Reaction of an electron rich alkene and singlet oxygen to generate dioxetanes

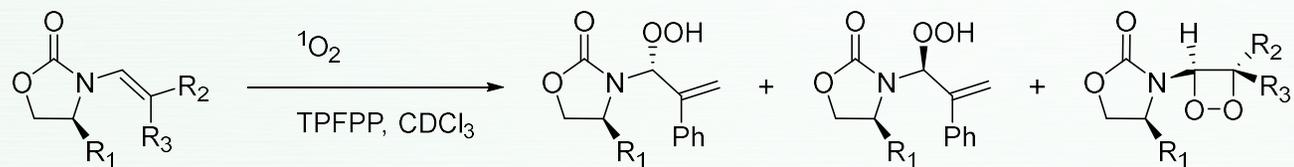
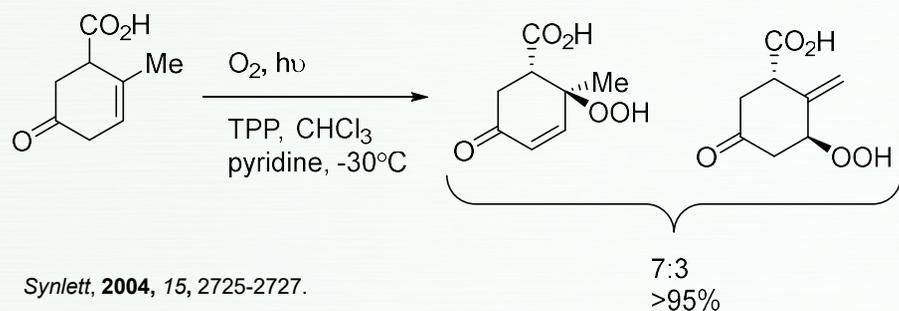
- * Formation of dioxetane is rate limiting
- * Product distribution may vary
 - Ene and [4+2] reactions could contaminate the [2+2] pathway
 - Dioxetane formation favoured when:
 - There are no allylic hydrogens
 - The allylic hydrogen can't attain the desired orthogonality
 - Heteroatom biases singlet oxygen toward the side with no allylic hydrogens



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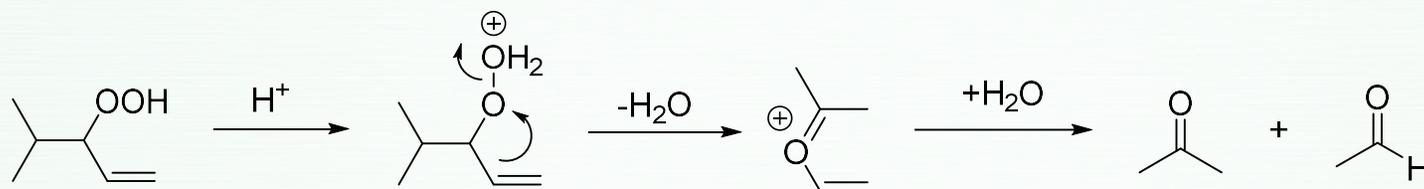
Synthetic Applications



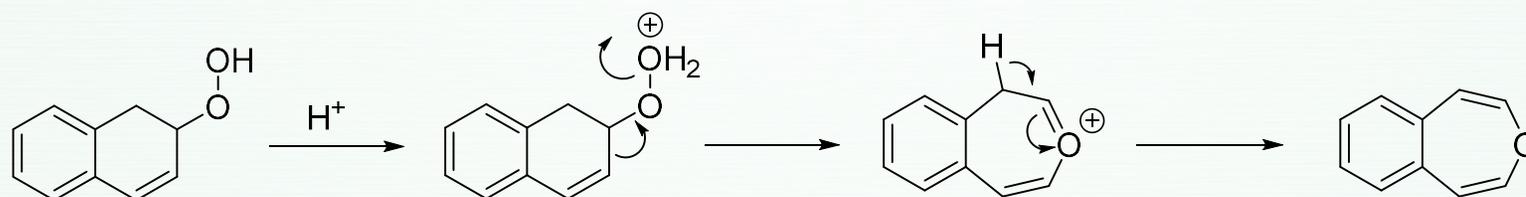
J. Org. Chem., **2004**, *69*, 1704-1716.

Synthetic Applications

» Hock cleavage

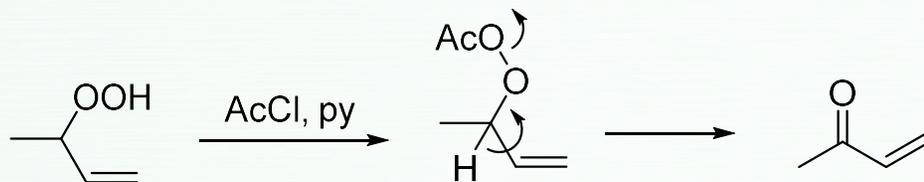


» Fragmentation to divinyl ethers

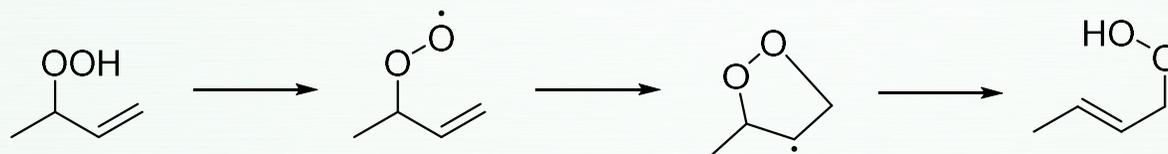


Synthetic Applications

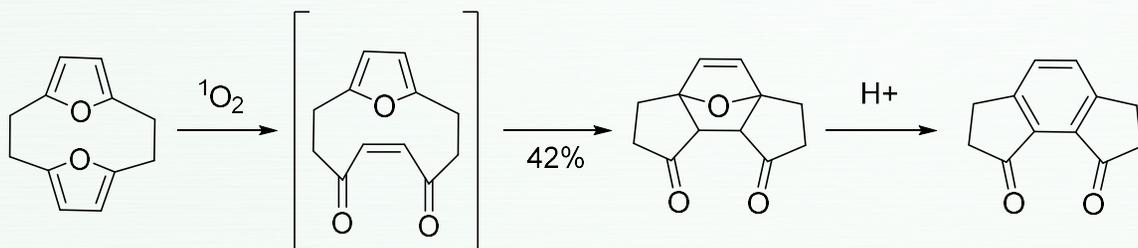
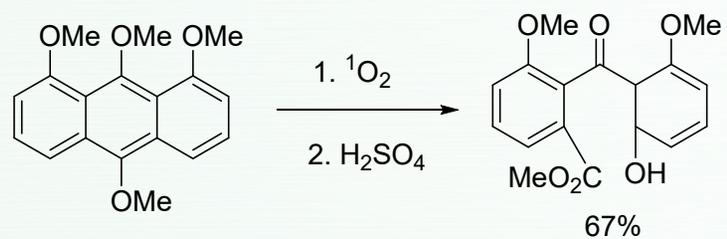
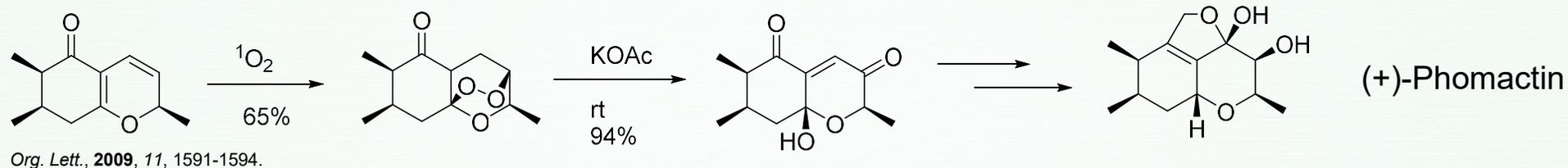
» Kornblum



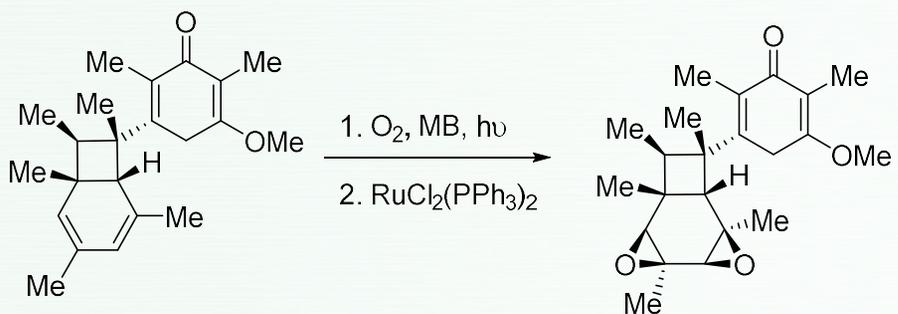
» 1,5-isomerization



Synthetic Applications

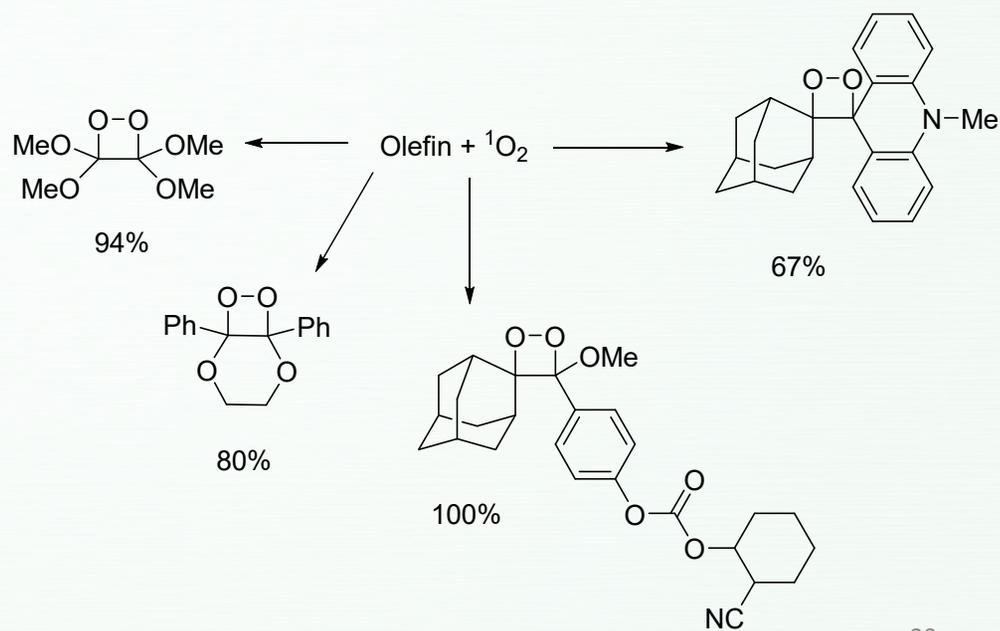


Synthetic Applications



Org. Lett., **2005**, *7*, 2901-2903.

Elsyapyrone A



Handbook of Synthetic Photochemistry

The Singlet Oxygen Strategy

- » Society based out of Europe
- » Seeks to further understand and use oxygen in a beneficial manner
 - * Methodology development
 - * Biological processes
 - * Materials chemistry

