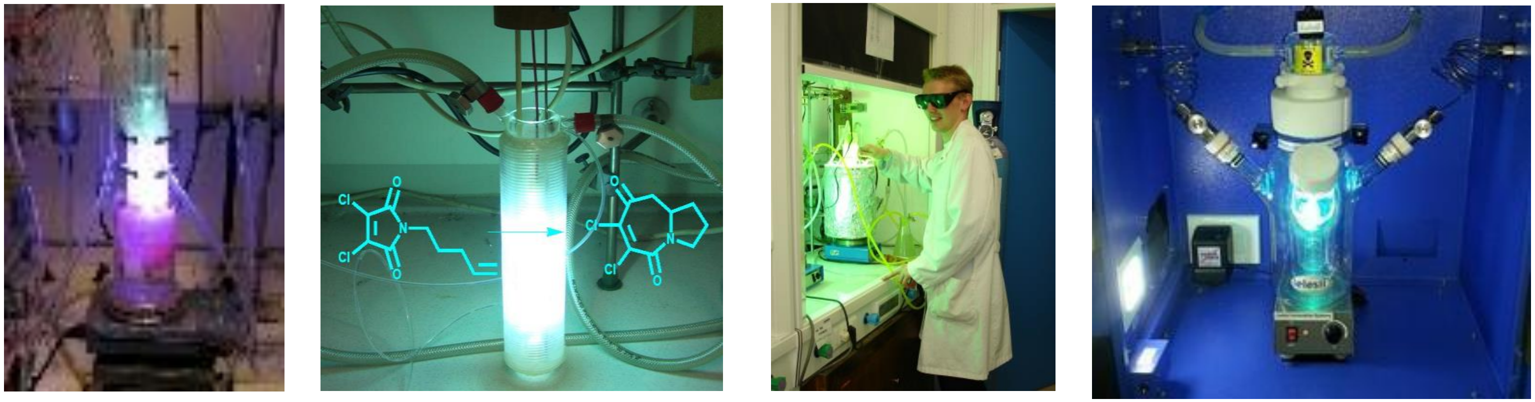


M2 Chimie Organique 2023-24

Synthetic Organic Photochemistry

Lecture Course by

Pr. David J. Aitken

Université Paris-Saclay, Orsay, France

PROGRAMME

Theory & practice of organic photochemistry

Photooxygenation

Photochemistry of alkenes and dienes

Photochemistry of enones

Photochemistry of carbonyls

Photochemistry of diazo compounds

Asymmetric photochemical synthesis

Recommended Reading

A. Albini & M. Fagnoni, Eds.
Handbook of Synthetic Photochemistry
Wiley, 2010

A. G. Griesbeck & J. Mattay, Eds.
Synthetic Organic Photochemistry
Marcel Dekker, 2005

W. Horspool & F. Lenci, Eds.
CRC Handbook of Organic Photochemistry and Photobiology
2nd Edn. CRC Press, 2003

P. Klán & J. Wirz
Photochemistry of Organic Compounds
Wiley, 2009

Organic Photochemistry: Theory & Practice

Introduction

A. Fundamentals

A.1 Generation of an excited state
A.2 Evolution of an excited state
A.3 Electronic energy transfer: photosensitization

B. Practical Aspects

B.1 Light sources
B.2 Solvents and solutions
B.3 Apparatus

INTRODUCTION

The importance of the interaction between light and matter has been known since ancient times, and is still of prime importance today

For living systems, there are benefits:

— vision; photosynthesis

But there are also negative effects:

— skin cancer; atmospheric polluants

Present-day applications of organic photochemistry are found in:

— medicine; biology; energy storage and conversion; environemental science …

A Short History of Organic Photochemistry

Ancient history: ***sunlight is beneficial for life, but more of a mythology than a science***

18th century: ***first deliberate (inorganic) photochemical reactions: observation of photosynthesis***

“I fully ascertained the influence of light in the production of dephlogisticated air in water by means of a green substance”
Experiments and Observations on Different Kinds of Air, 1790.

Joseph Priestley (1733-1804)

« La lumière est-elle une modification du calorique, ou bien le calorique est-il une modification de la lumière ? C'est sur quoi il est impossible de prononcer dans l'état actuel de nos connaissances. »
Traité Élémentaire de Chimie, 1789.

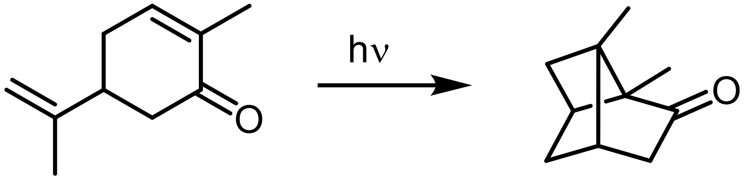
Antoine-Laurent de Lavoisier (1743-1794)

A Short History of Organic Photochemistry

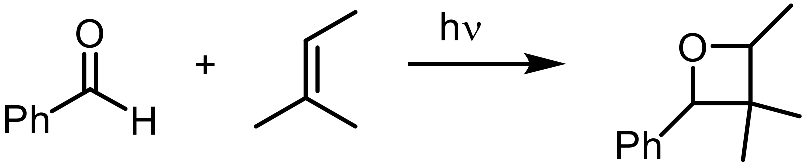
19th century: ***photoreactions of santonin (Cannizzaro); olefin isomerization (Perkin); photodimers (Fritzsche, Liebermann); halogenation Schramm); photoreduction of carbonyls (Klinger)…***

Early 20th century: ***prototype [2+2] photocycloadditions***

Ciamician & Silber (1908)
photocarvone



Paternò & Chieffi (1909)
carbonyls + olefins → oxetanes



Since 1950: ***much fuller appreciation of the synthetic potential of organic photochemistry; exponential increase in applications in the literature (Europe – America – Asia)***

Importance in Organic Synthesis

Objective : transformation of one substance into another

$$\mathbf{A} \xrightarrow{\boldsymbol{R}} \mathbf{B}$$

$$\mathbf{A} + \mathbf{B} \xrightarrow{\boldsymbol{R}} \mathbf{C}$$

Keywords: ***selectivity; efficiency; economy***

In a photochemical transformation, the reagent ***R*** is a photon

Advantages : selective excitation of only one part of the molecule
acquisition of a significant amount of energy without heating

Limitations : requirement of a chromophore
Appropriate apparatus required; scale-up is not a trivial matter

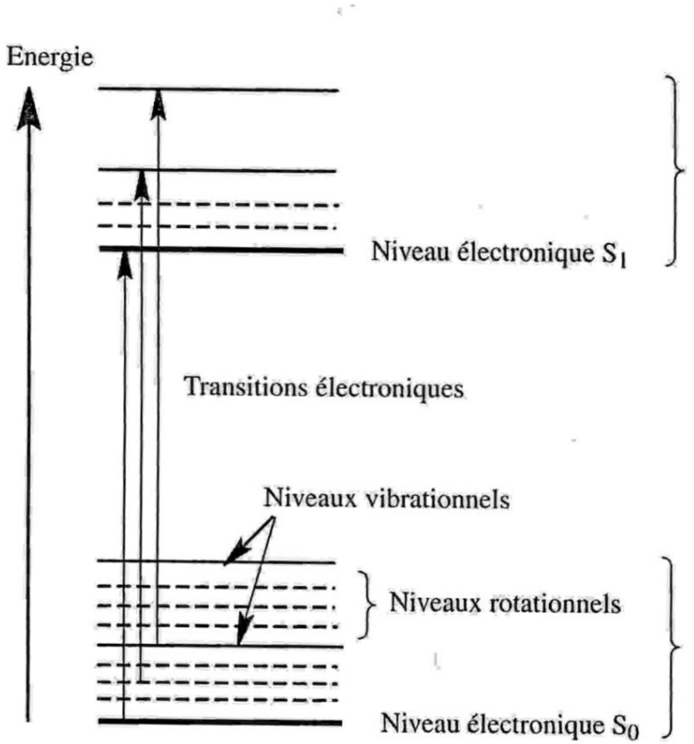
A. FUNDAMENTALS

1. Generation of an Excited State

Total energy of a molecule

Born-Oppenheimer
Approximation

$$E_{tot} = E_n + E_r + E_v + E_e$$

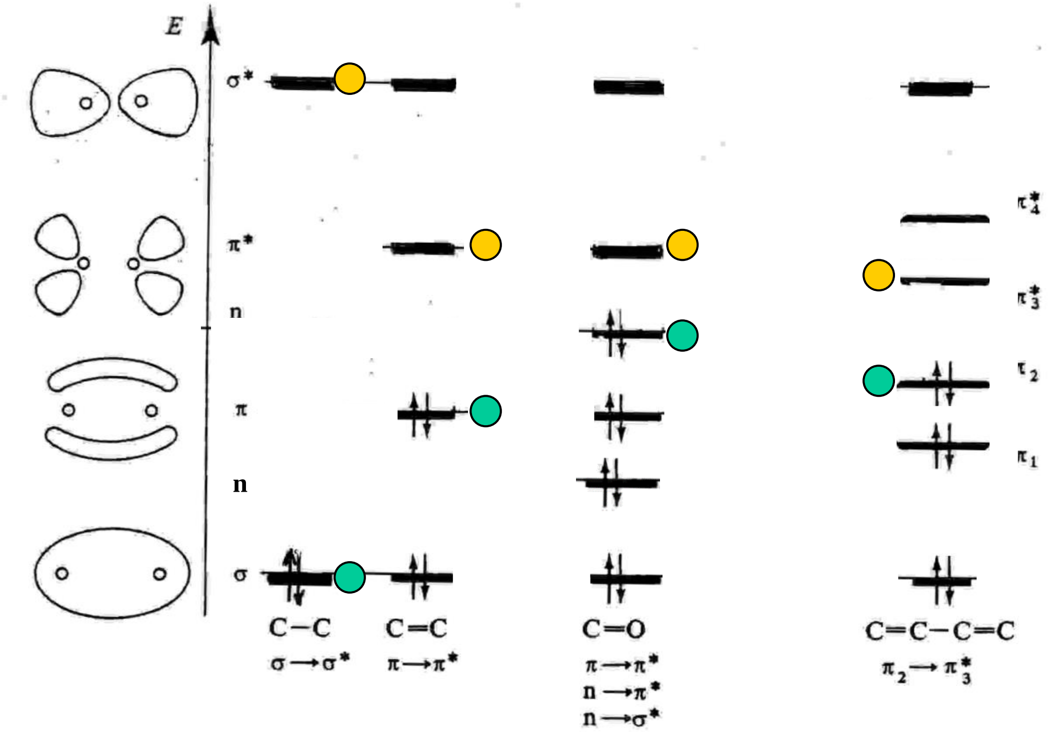


excited state

ground state

Figure 1 - Diagramme énergétique réunissant les niveaux de rotation, de vibration, et électroniques d'une molécule

Electronic configuration and molecular orbitals (respecting de Pauli’s exclusion principle)



🟡 LUMO

🟢 HOMO

For any molecule in its **ground state**, the total spin S = 0

Multiplicity = 2S + 1 → Multiplicity in the ground state = 1

Electronic ground state: **singlet; S_0**

Electronic Absorption

Collision photon—molecule, resulting in transfer of all the energy

$$\boxed{E = h\nu = hc/\lambda}$$

$c = \nu\lambda = 3{,}0 \times 10^{8}$ m.s^{-1}
$h = 6{,}6 \times 10^{-34}$ J.s^{-1}

Energy range: 200-700 nm (UV-vis)

Duration of the absorption process: 10^{-15} s
(Franck-Condon principle: no other changes in the system during the process)

The energy acquired by the molecule is used to promote an electron form a low-energy orbital to a higher-energy orbital
(typically HOMO → LUMO)

Conservation of spin ($\Delta S = 0$) during the absorption process

The molecule is obtained in a **singlet excited state: S_1**

In this excited state, de Pauli's exclusion principle no longer applies → *possible evolution to a same-spin configuration*

In this state, total spin $S = 1$
multiplicity $= 2S + 1 = 3$
triplet excited state: T_1

Transition $S_1 \rightarrow T_1$:
Intersystem crossing (ISC)

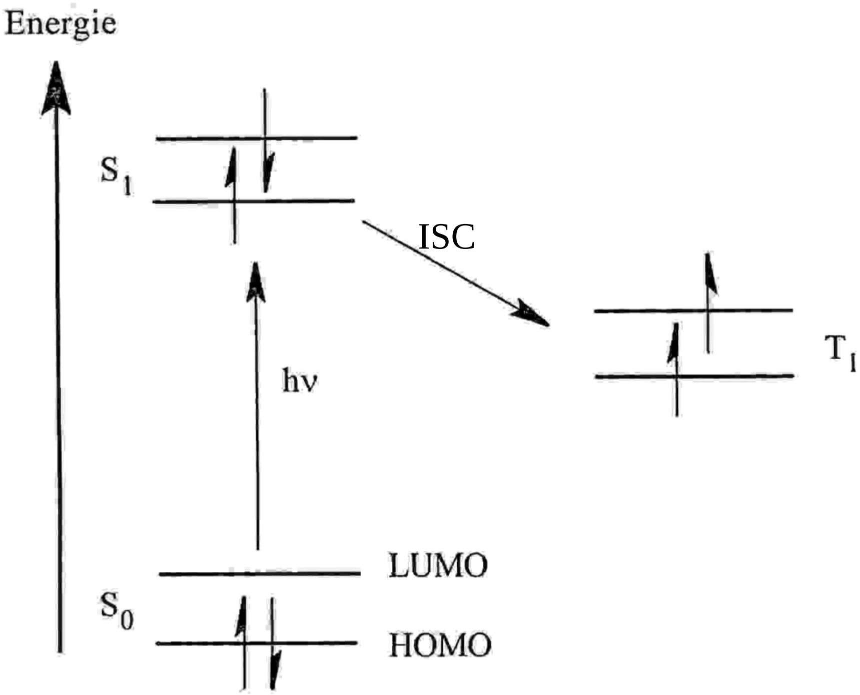
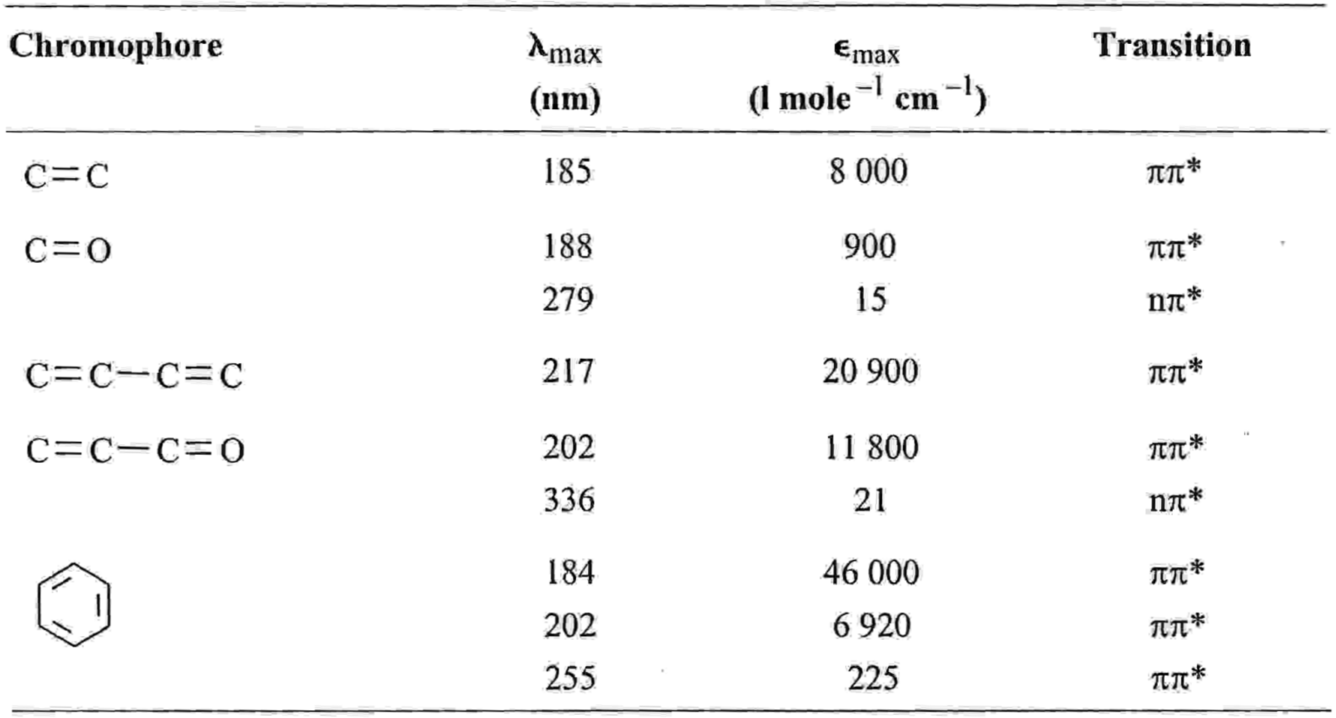


Figure 3 - Diagramme énergétique indiquant les premiers états excités singulet et triplet

The direct transition $S_0 \rightarrow T_1$ does not occur by absorption

Electronic absorption energies

Characterized (λ_{max} , ε_{max}) by the chromophore



Chromophore	λ_{max} (nm)	ϵ_{max} (l mole^{-1} cm^{-1})	Transition
$C{=}C$	185	8 000	$\pi\pi^*$
$C{=}O$	188	900	$\pi\pi^*$
	279	15	$n\pi^*$
$C{=}C{-}C{=}C$	217	20 900	$\pi\pi^*$
$C{=}C{-}C{=}O$	202	11 800	$\pi\pi^*$
	336	21	$n\pi^*$
	184	46 000	$\pi\pi^*$
	202	6 920	$\pi\pi^*$
	255	225	$\pi\pi^*$

2. Evolution of an Excited State

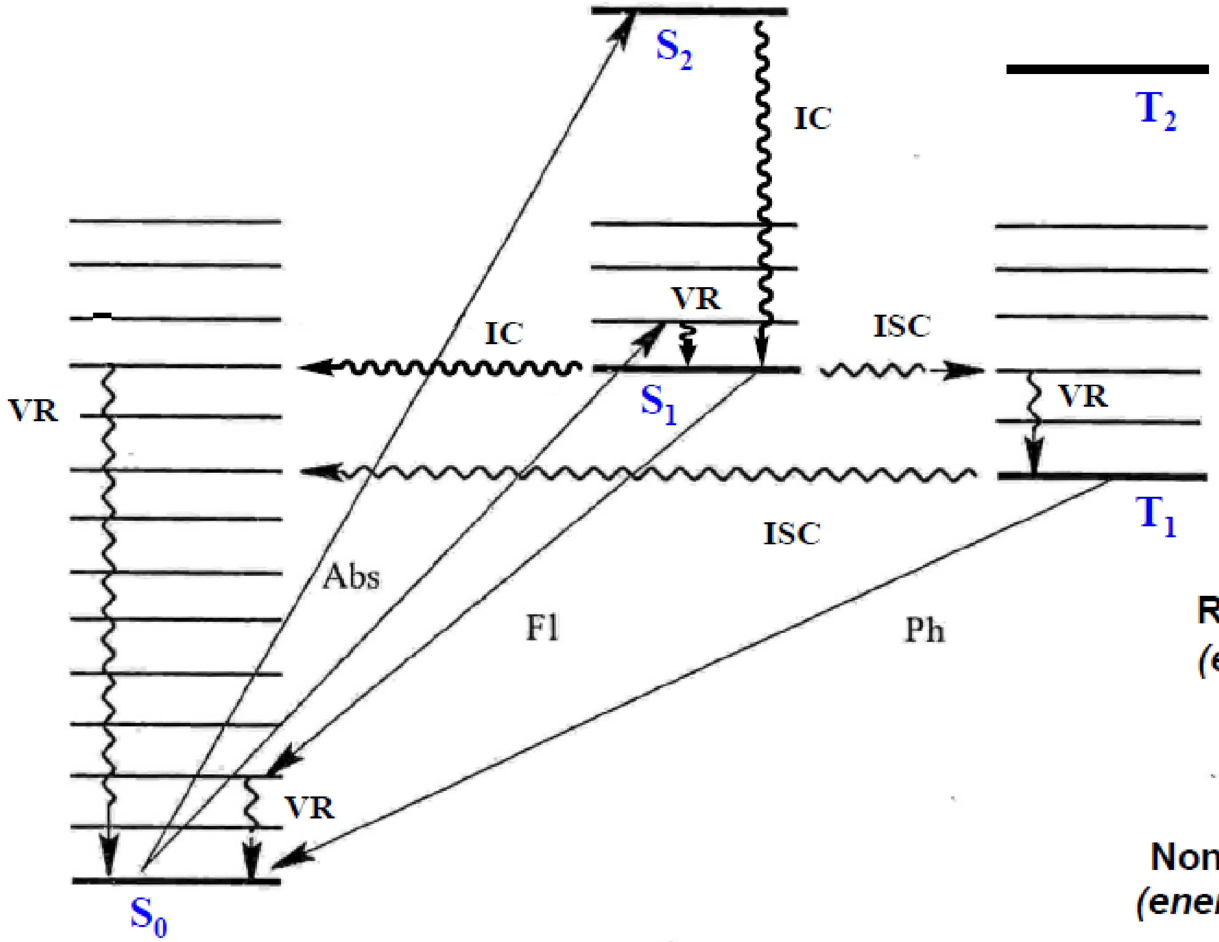


Diagramme de Perrin-Jablonski

Radiative process ⟶
(emission of a photon)

Fl = fluorescence
Ph = phosphorescence

Non-radiative process ⇝
(energy dissipation as heat)

ISC = intersystem crossing
IC = internal conversion
VR = vibrational relaxation

Process	Transition	Time (sec)
Absorption	$S_0 \rightarrow S_n$	$\sim 10^{-15}$
Internal Conversion	$S_n \rightarrow S_1$	$10^{-14} - 10^{-11}$
	$S_1 \rightarrow S_0$	$10^{-7} - 10^{-5}$
Vibrational Relaxation	$S_n \rightarrow S_n$	$10^{-12} - 10^{-10}$
Intersystem crossing	$S_1 \rightarrow T_1$	$10^{-11} - 10^{-6}$
	$T_1 \rightarrow S_0$	$10^{-3} - 100$
Fluorescence	$S_1 \rightarrow S_0$	$10^{-9} - 10^{-6}$
Phosphorescence	$T_1 \rightarrow S_0$	$10^{-3} - 100$

Overview

Radiative process ***light* → *light***

Non-radiative process ***light* → *heat***

Organic synthesis ***light* → *chemical reaction***

3. Electronic Energy Transfer: Photosensitization

The transition $S_1 \rightarrow T_1$ cannot occur by absorption (change of spin)
Alternative way of achieving this: *photosensitization*

Transfer of electronic energy from one molecule to another:

$$\textbf{sens* + A} \rightarrow \textbf{sens + A*}$$

Conditions apply: - E (A*) ≤ E (sens*)

- global conservation of spin:

$$^3\textbf{sens* + }^1\textbf{A} \rightarrow {}^1\textbf{sens + }^3\textbf{A*}$$

The molecule A is acquired in its T_1 state *without* having absorbed a photon. The overall process begins with absorption by sens:

$$^1\textbf{sens*} \overset{h\nu}{\rightarrow} {}^1\textbf{sens*} \overset{\text{ISC}}{\rightarrow} {}^3\textbf{sens*}$$

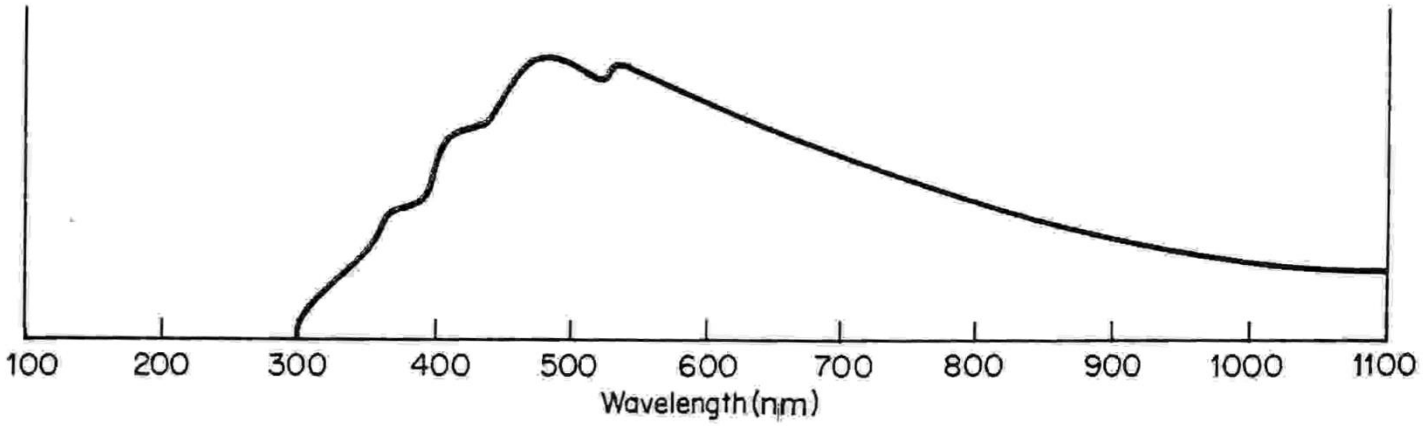
An ideal photosensitizer:

- *is obtained efficiently in its own T_1 state*
- *has a long-lived T_1 state*
- *does not react with the molecule it sensitizes*

B. PRATICAL ASPECTS

1. Light Sources

Solar emission spectrum (as detected on Earth)



Multi-wavelength emission spectrum – Hg vapor lamp

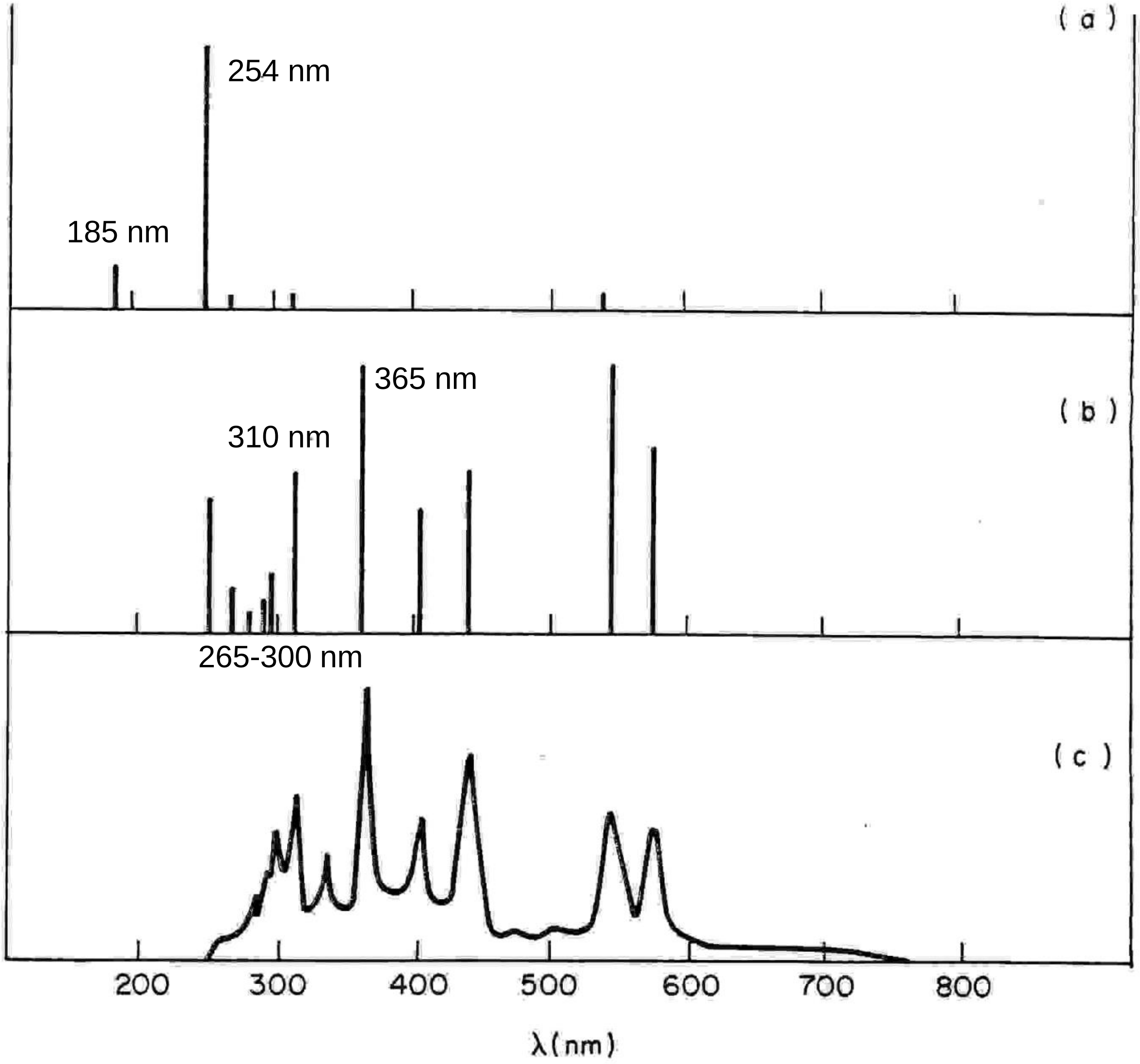
low pressure
(0,005 à 0,1 atm)

medium pressure
(1 à 10 atm)

200 – 500 W
heating

(super)high pressure
(100 à 200 atm)

considerable heating



Temperature

Advantage of a photochemical reaction:

Conduct a chemical transformation in a selective manner, through the acquisition of a significant quantity of energy by one functional group. Thermal energy acquisition is not function-selective

Combining thermal and photochemical activation is generally counter-intuitive

At the “hottest”, a photochemical reaction is conducted at room temp.

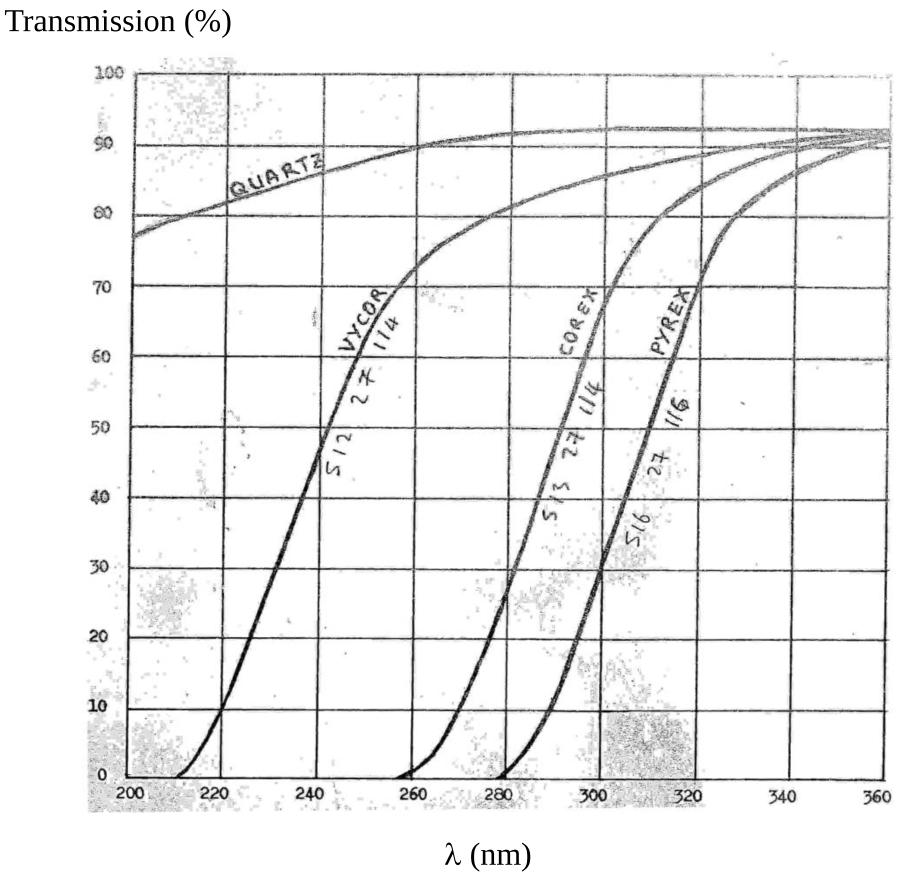
If the light source is also a source of heat, cooling system may be necessary

Filters

Often, irradiation with light of a particular wavelength (or wavelength range) is required.To remove unwanted wavelengths, a filter is used.

Two types of filter : solid filters, liquid filters

Solid filters



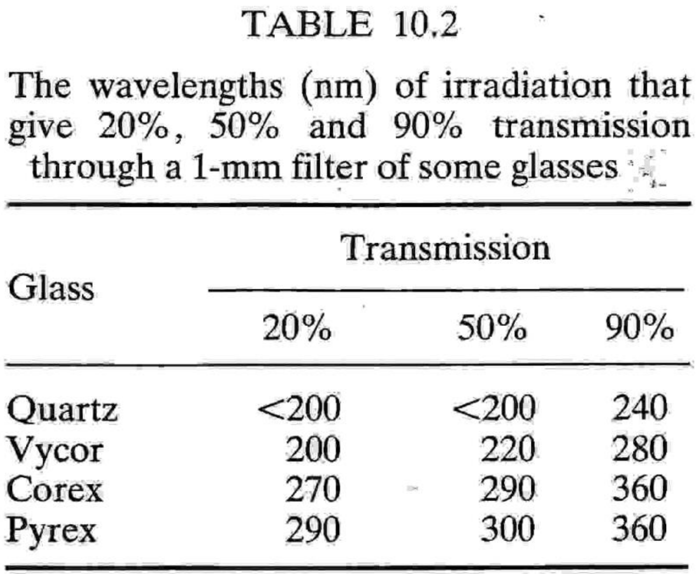


TABLE 10.2

The wavelengths (nm) of irradiation that give 20%, 50% and 90% transmission through a 1-mm filter of some glasses

Glass	Transmission		
	20%	50%	90%
Quartz	<200	<200	240
Vycor	200	220	280
Corex	270	290	360
Pyrex	290	300	360

Liquid filters

Aqueous solutions of mineral salts/complexes

Upper and/or lower wavelength cut-offs are available

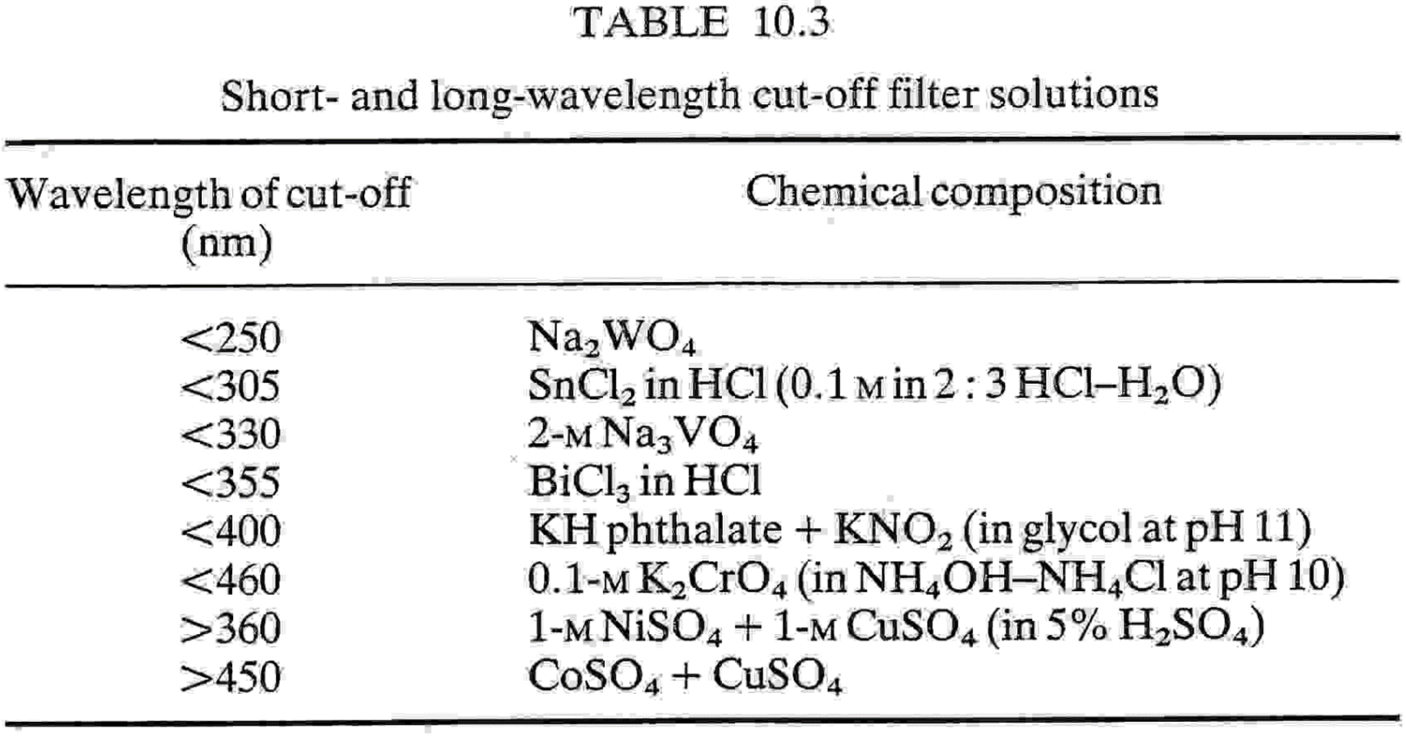


TABLE 10.3

Short- and long-wavelength cut-off filter solutions

Wavelength of cut-off (nm)	Chemical composition
<250	Na_2WO_4
<305	$SnCl_2$ in HCl (0.1 M in 2 : 3 HCl–H_2O)
<330	2-M Na_3VO_4
<355	$BiCl_3$ in HCl
<400	KH phthalate + KNO_2 (in glycol at pH 11)
<460	0.1-M K_2CrO_4 (in NH_4OH–NH_4Cl at pH 10)
>360	1-M $NiSO_4$ + 1-M $CuSO_4$ (in 5% H_2SO_4)
>450	$CoSO_4$ + $CuSO_4$

2. Solvents and solutions

In general, photochemical reactions are conducted in solution.
A successful reaction depends on:

a) Choice of solvent

Clear solution (not turbid)
If the solvent is inert, it should be transparent
If the solvent is also a sensitizer, it should absorb

b) Solvent purity

Usual solvent purification procedures (no stabilizers, peroxides, …)
Deoxygenation of the solution (except in photooxygenations)

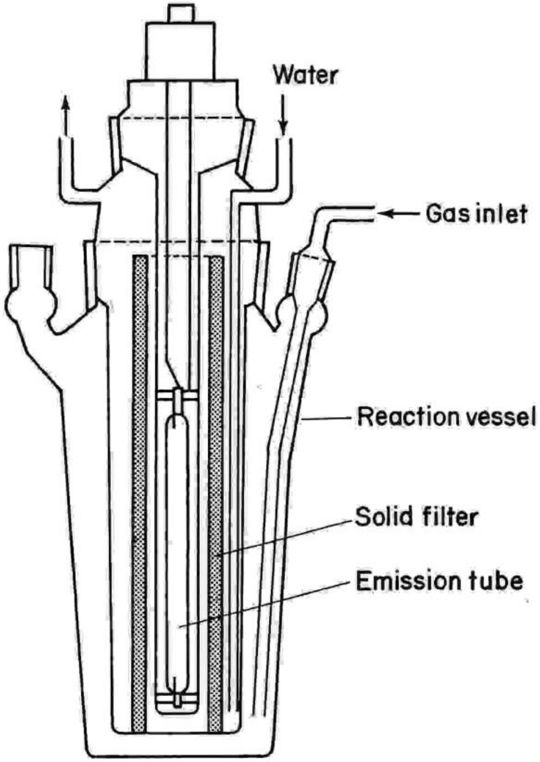
c) Concentration

Generally 1 – 100 mM. Dilute for unimolecular reactions, concentrated for bimolecular reactions

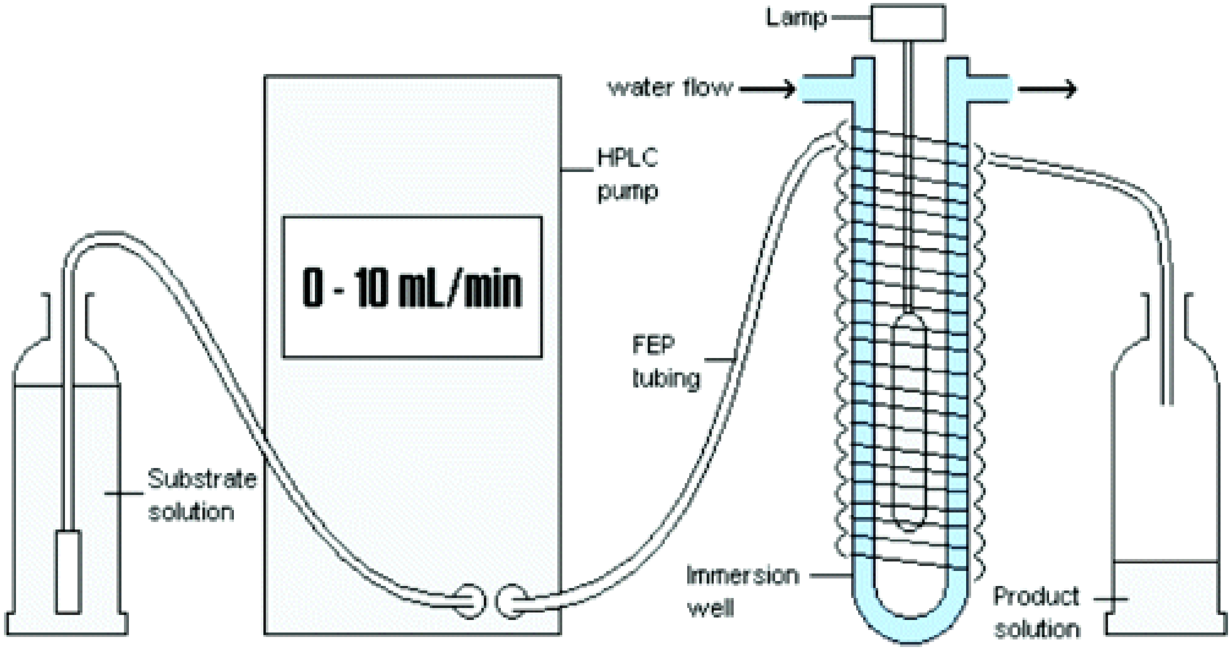
3. Apparatus

External irradiation reactors

Immersion reactors



Continuous flow reactors

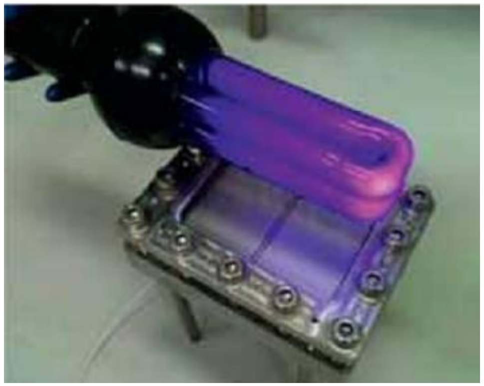


FEP (fluorinated ethylene propylene) tubing: 0.7 mm ø
Reactor: 5 cm × 30 cm
Lamp: 400 W Hg-vapor

> 500 g product in 24 h

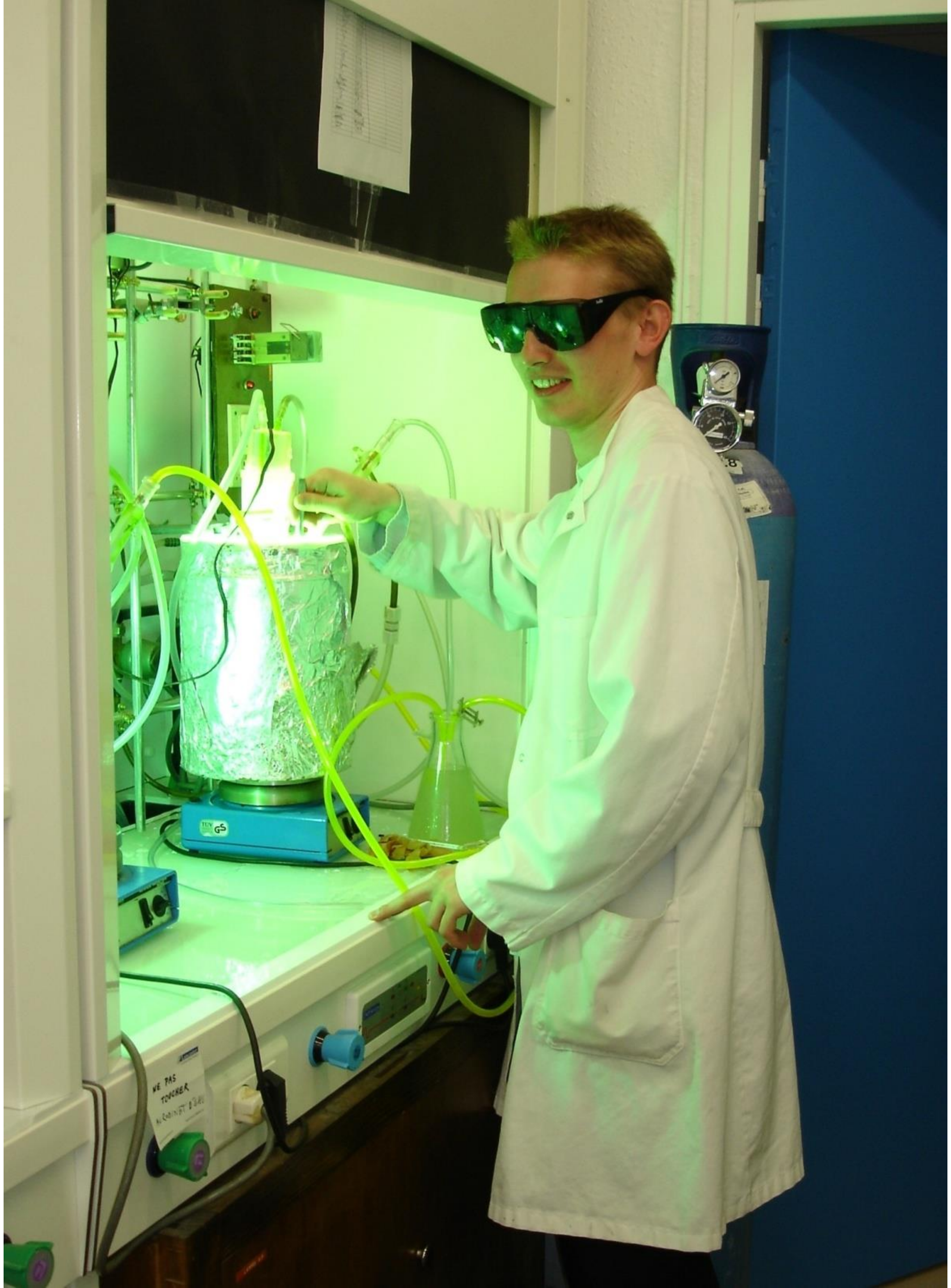
Microreactors

Micro-size channel
1 mm × 0.1 mm × 2 m long
(volume 0.2 ml)



”Black light”
λ_{max} 352 nm; 15 W

LED array
λ_{max} 365 nm; 6 × 250 mW


NE PAS
TOUCHER

Photooxygenation

Introduction

A. <u>Generation of singlet oxygen</u>

B. <u>Reactions of singlet oxygen with alkenes</u>

1. **Allylic addition:**
   formation of allylic hydroperoxides
2. **2+2 Cycloaddition:**
   formation of dioxetanes
3. **4+2 Cycloaddition:**
   formation of endoperoxides

INTRODUCTION

Photooxygenation is sometimes considered to be a destructive process for synthetic and natural organic compounds

— degradation of plastics
— degradation of biological materials

The reactive species is **singlet oxygen**

Some dates for singlet oxgyen

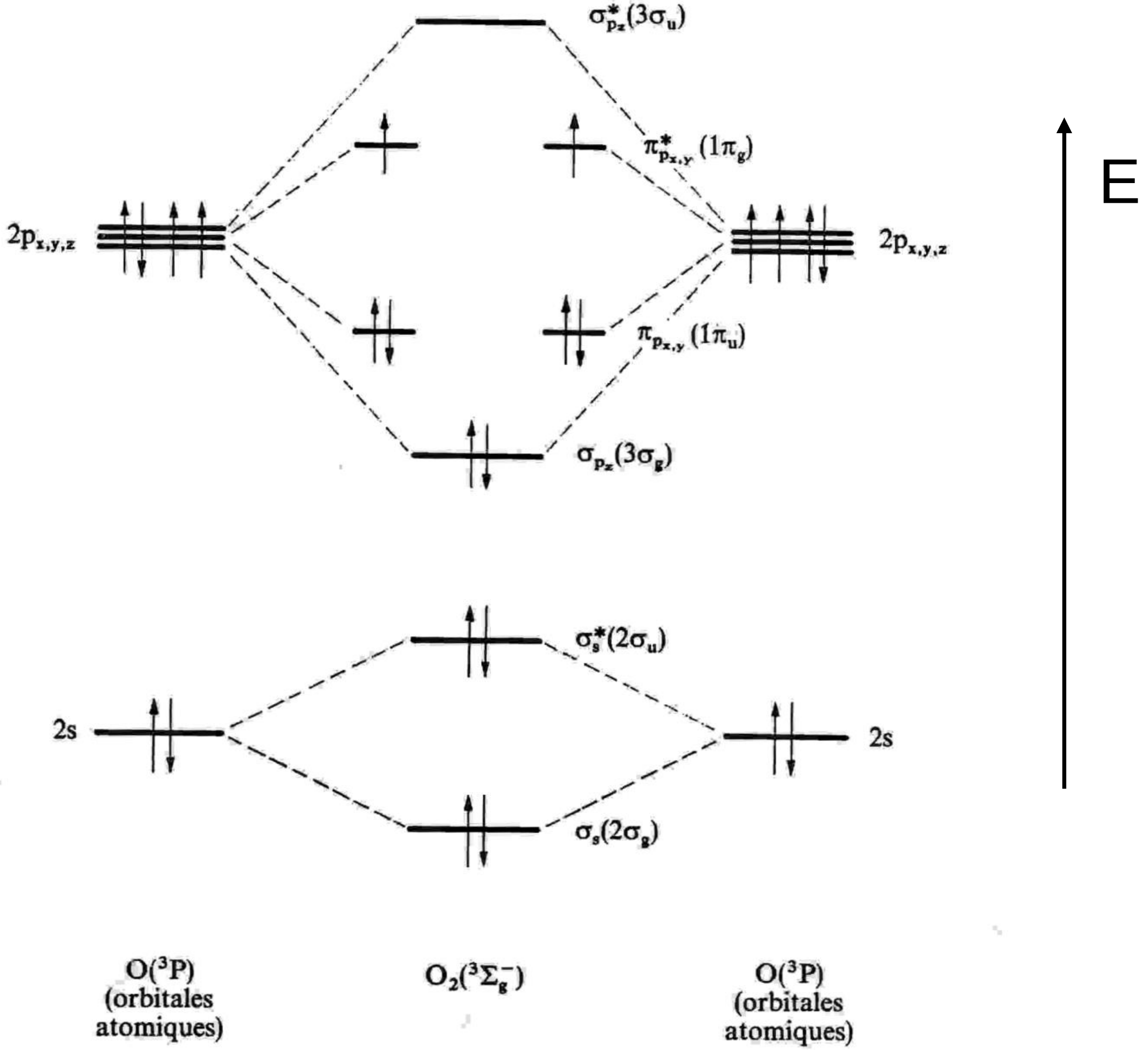
1924 – discovery by astrophysicists
1963 – shown to be the reactive species in photooxygenations
2000 – industrial production: 10 tons/year

A. GENERATION OF SINGLET OXYGEN

1. Electronic states of dioxygen

Molecular orbitals of dioxygen

The electronic ground state is a **triplet**



The first two excited states of dioxygen

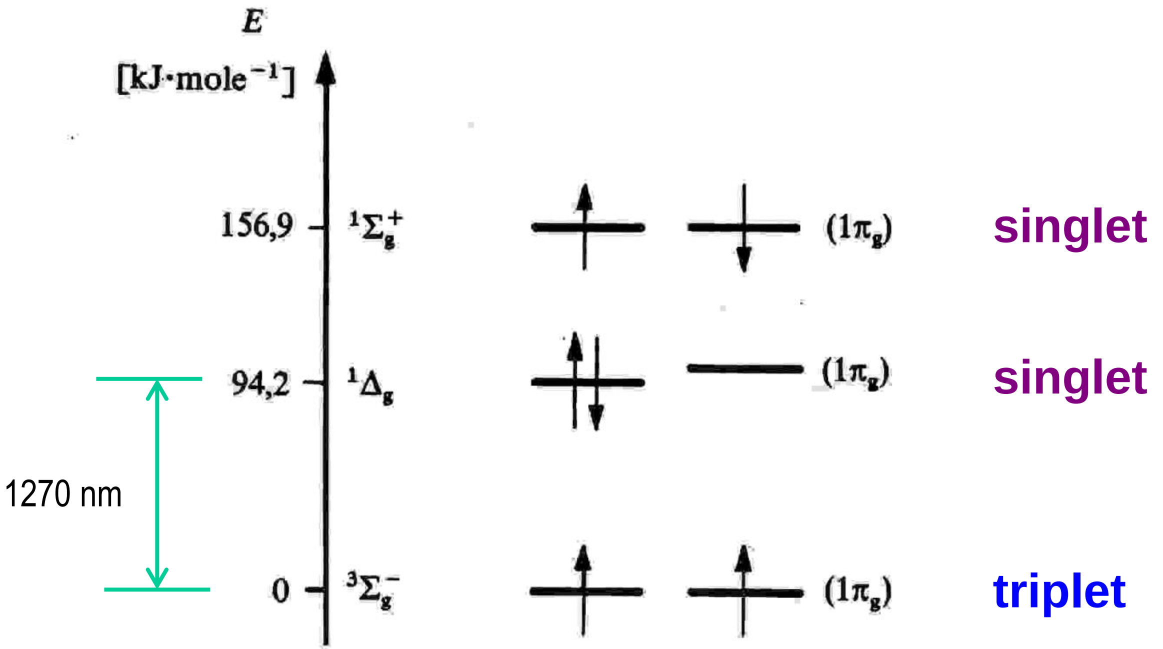


Fig. 11.2 Représentation simplifiée de l'occupation électronique des orbitales $1\pi_g$ ($\pi^*_{p_{x,y}}$) dans l'état fondamental et dans les deux premiers états excités de l'oxygène moléculaire.

Lifetime	$^1\Sigma_g$	$^1\Delta_g$
in gas phase	~ 10 s	72 min
in solution	10^{-12} s	10^{-2} -10^{-6} s

In photooxygenation reactions, the $^1\Delta_g$ state is implicated.

Singlet oxygen: $^1O_2$

2. Production of Singlet Oxygen

chemical methods

— $H_2O_2 + NaOCl \rightarrow {}^1O_2 + H_2O + NaCl$

— decomposition of endoperoxides

electric discharge

In an oxygen plasma $\rightarrow$ ${}^1O_2 + O + O_3$

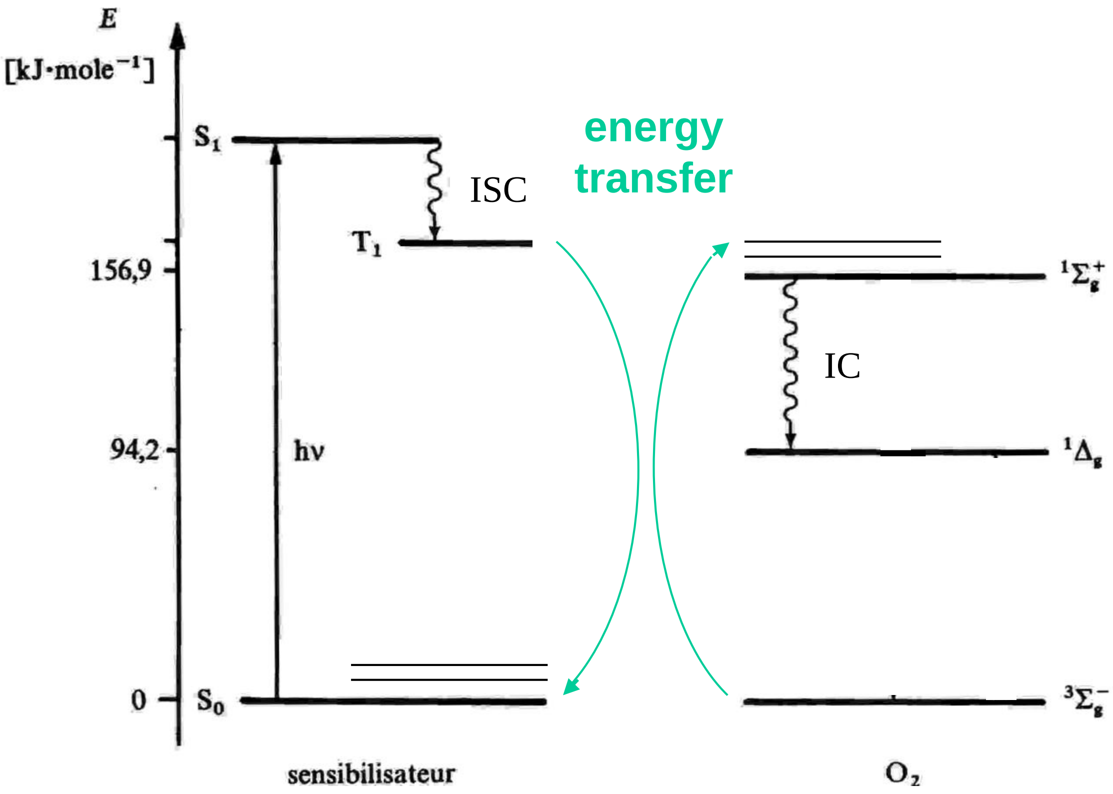
photolysis of ozone $O_3 \xrightarrow{h\nu} {}^1O_2 + O$

photochemically

problem: excitation from the ground state (triplet) to the excited state (singlet) by absorption of a photon *does not occur*

solution : photosensitization

Production of singlet oxygen by photosensitization



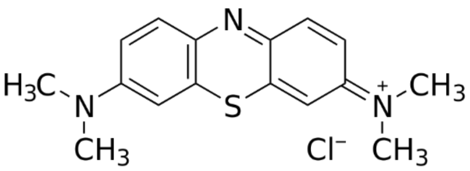
$$\text{sens } (S_0) \xrightarrow{h\nu} \text{sens* } (S_1) \xrightarrow{\text{ISC}} \text{sens* } (T_1)$$

$$\text{sens* } (T_1) + {}^3O_2 \ (T_0) \xrightarrow[\text{transfer}]{\text{energy}} \text{sens } (S_0) + {}^1O_2 \ (S_1)$$

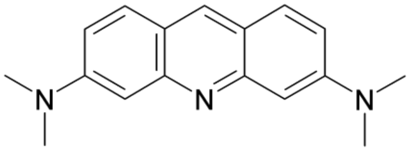
Conservation of total spin : two triplets (↑↑ + ↓↓) become two singlets (↑↓ + ↑↓)

Photosensitizers for the production of $^1O_2$

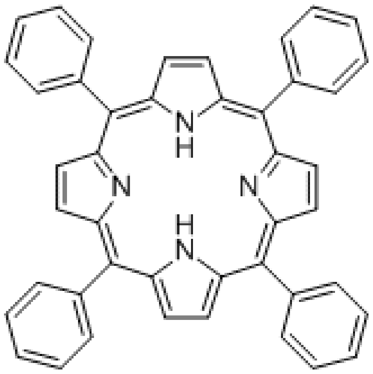
- inorganic substances: TiO_2, CdS, …
- organic compounds:



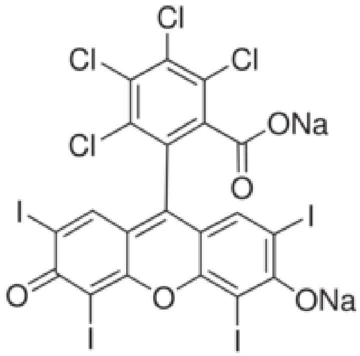
Methylene blue



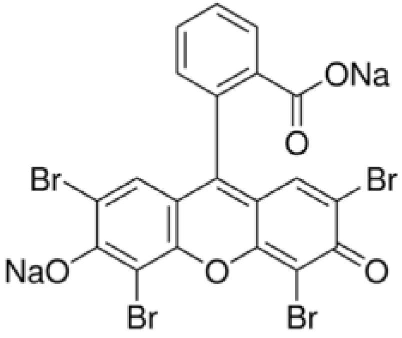
Acridine orange



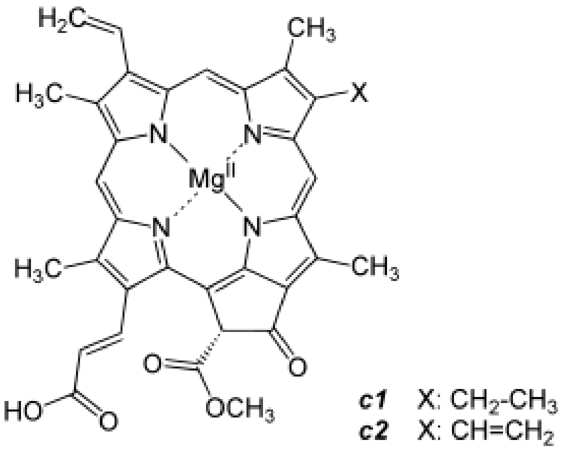
Tetraphenylporphyrin (TPP)



Rose Bengal



Eosin Y



Chlorophyll

Photosensitized oxidation

Implicates electron transfer

$$\underset{\textit{acceptor}}{{}^3\text{sens}^*} \quad + \quad \underset{\textit{donor}}{\text{D}} \quad \longrightarrow \quad \text{sens}^{\overset{-}{\bullet}} \quad + \quad \text{D}^{\overset{+}{\bullet}} \qquad \textit{electron transfer}$$

$$\textit{then} \quad \text{sens}^{\overset{-}{\bullet}} \quad + \quad {}^3\text{O}_2 \quad \longrightarrow \quad \text{sens} \quad + \quad \text{O}_2^{\overset{-}{\bullet}} \qquad \text{superoxide anion}$$

Efficiency depends on the nature of the donor and the sensitizer

Numerous photo-oxidation reactions implicating electron transfer exist:

oxidation of alkenes → carbonyls, epoxides
reactions with amines → imines, iminiums
aromatic compounds → benzylic oxidation

In this lecture course we will deal only with reactions involving energy transfer: photooxygenations

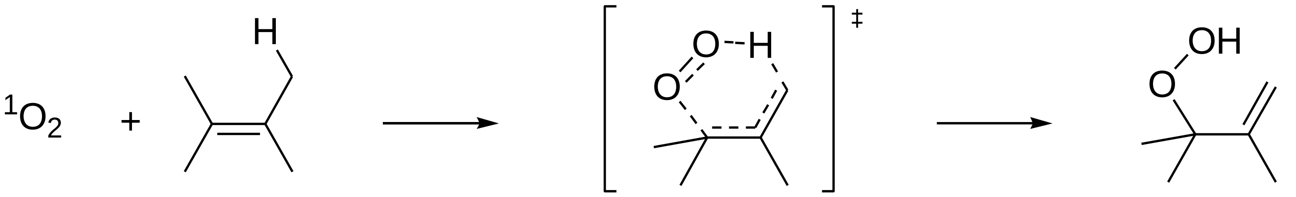
$${}^3\text{sens}^* \quad + \quad {}^3\text{O}_2 \quad \longrightarrow \quad \text{sens} \quad + \quad {}^1\text{O}_2 \quad \xrightarrow[\text{compound}]{\text{organic}} \quad \begin{array}{c}\text{oxygenated}\\ \text{product}\end{array}$$

B. REACTIONS OF SINGLET OXYGEN WITH ALKENES

1. Allylic addition: formation of allylic hydroperoxides

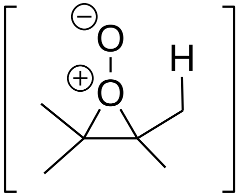
This reaction involves alkenes which have at least one hydrogen atom in an **allylic position**

General scheme:



allylic hydroperoxide

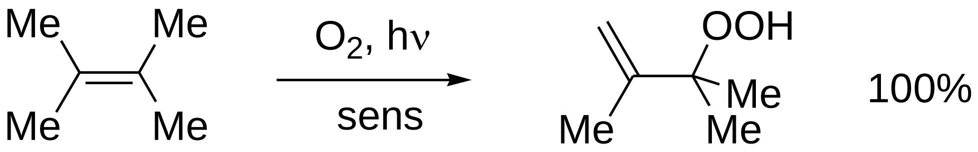
Several mechanisms are possible, still a subject of debate (*e.g.* via a perepoxide intermediate?)

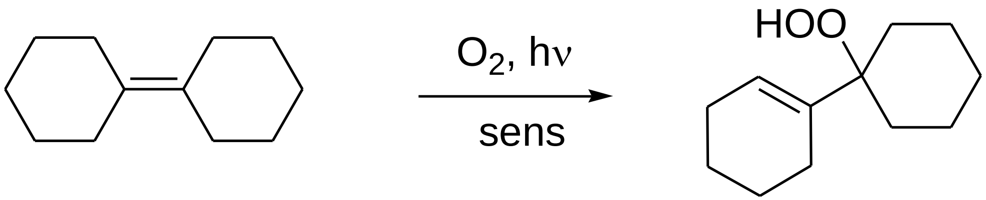


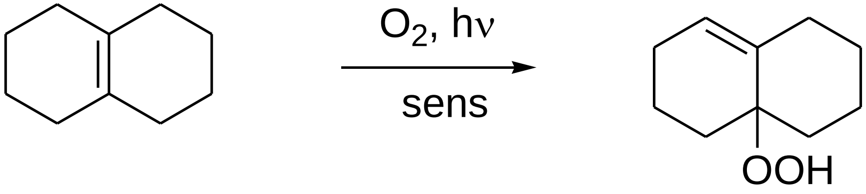
Here, we will assume a concerted process; “ene” reaction

Allylic Addition Reactions

Examples:





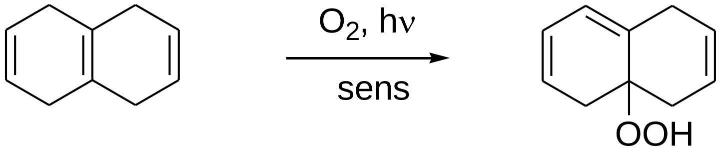


Allylic Addition Reactions

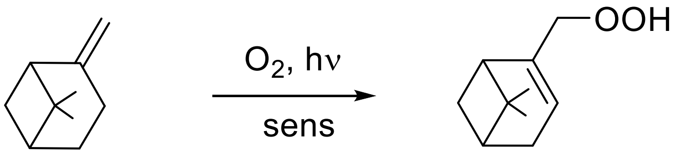
Regioselectivity Issues

Depending on the nature of the alkene

Singlet oxygen preferentially attacks the most-substituted double bonds

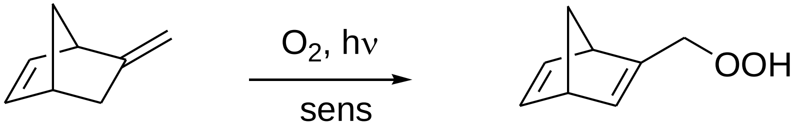


Terminal alkenes react slowly



slow reaction

Exceptions exist, *e.g.* ring strain constraints (Bredt's rule)

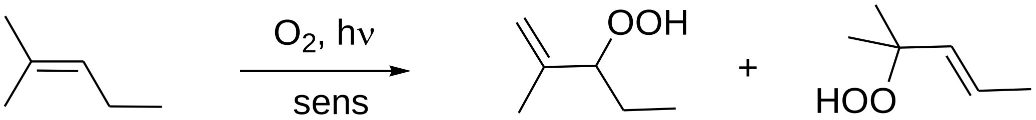


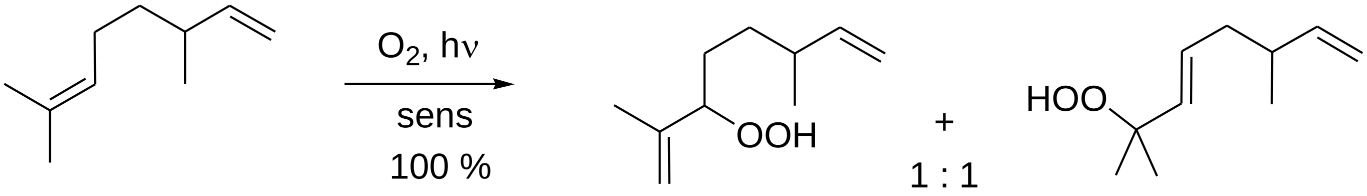
Allylic Addition Reactions

Regioselectivity Issues

Depending on the nature of the allylic carbon

Little differentiation if any between methyl and methylene carbons; methine carbons often react more slowly, but this is due to steric hindrance rather than a lack of intrinsic reactivity





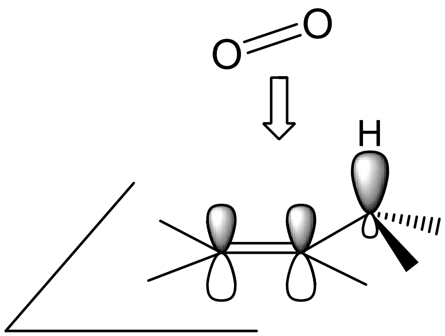
Allylic Addition Reactions

Regioselectivity Issues

Depending on geometrical or steric constraints

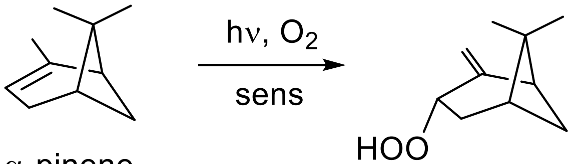
The concerted mechanism imposes regioselectitivity and/or stereoselectivity when complex/rigid alkenes are used

— arrival of $^1O_2$ and transfer of allylic-H occur on the same face of the alkene
— allylic-H transfer requires parallel alignment of C–H σ-bond and the alkene π orbital



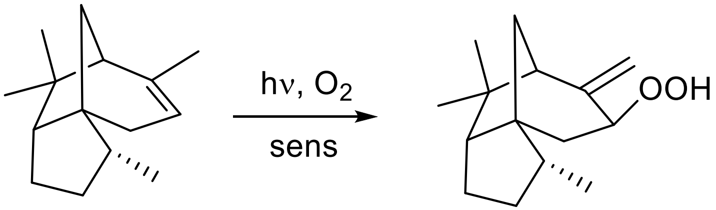
Allylic Addition Reactions

Regioselectivity Issues



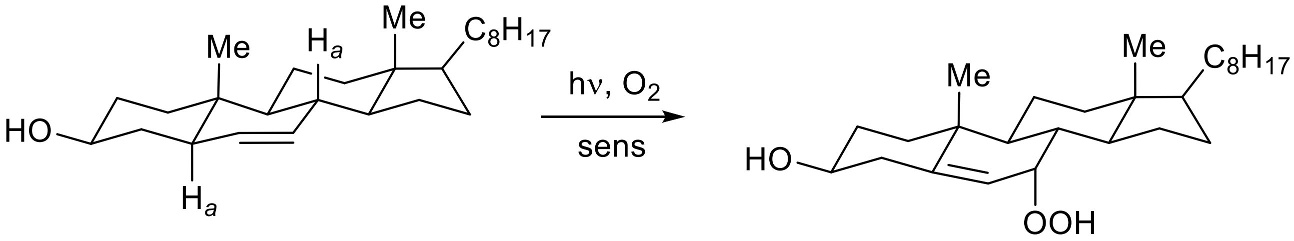
α-pinene

single product



cedrene

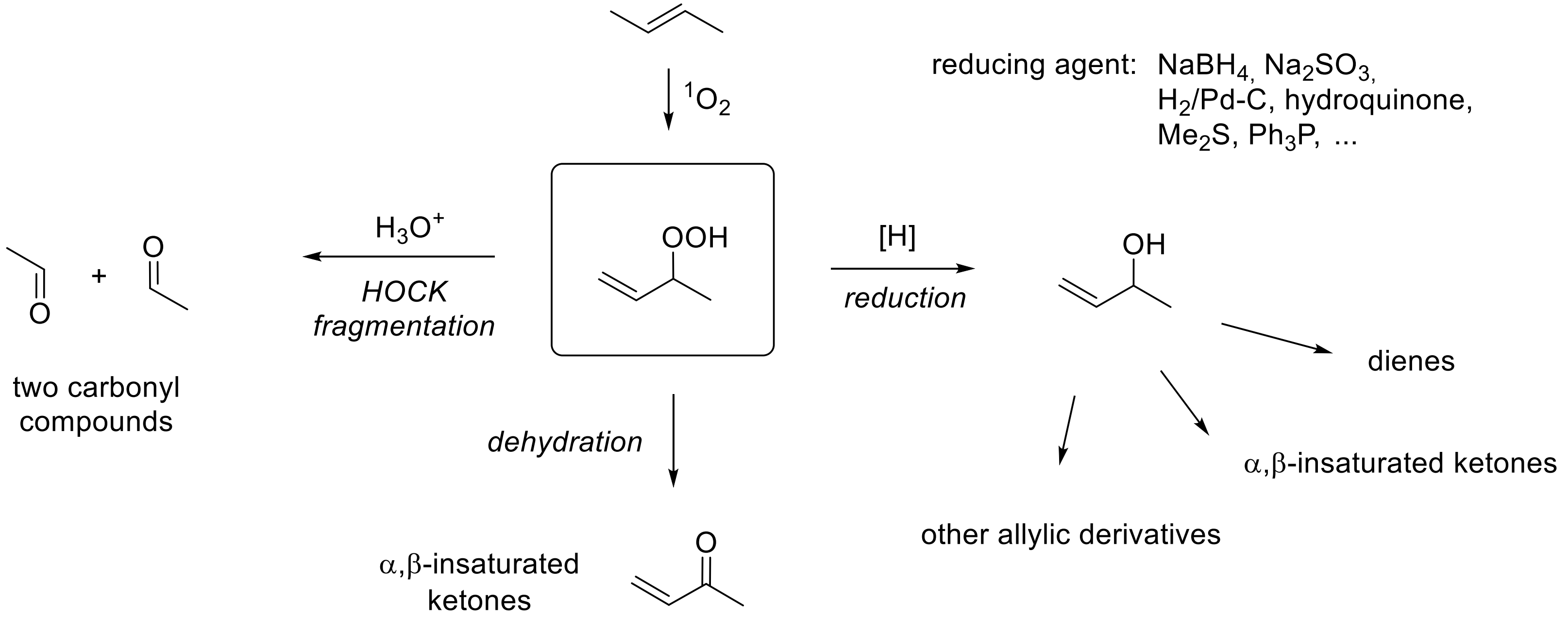
single product



3β-hydroxy-5α-cholest-6-ene

single product

Transformation of allylic hydroperoxides



reducing agent: $NaBH_4$, Na_2SO_3,
H_2/Pd-C, hydroquinone,
Me_2S, Ph_3P, ...

two carbonyl compounds

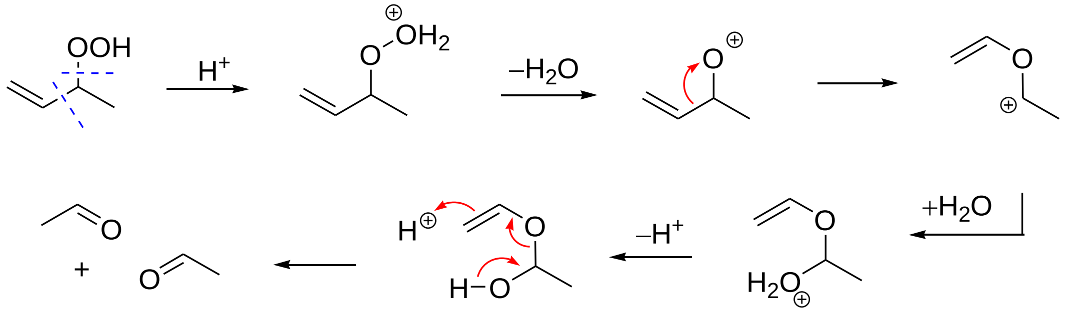
dienes

α,β-insaturated ketones

other allylic derivatives

α,β-insaturated ketones

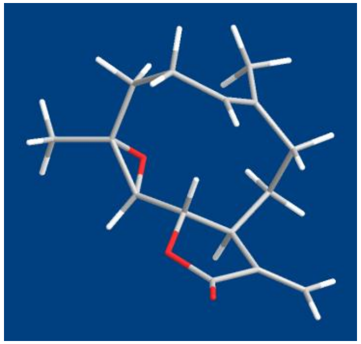
Mechanism of the HOCK fragmentation

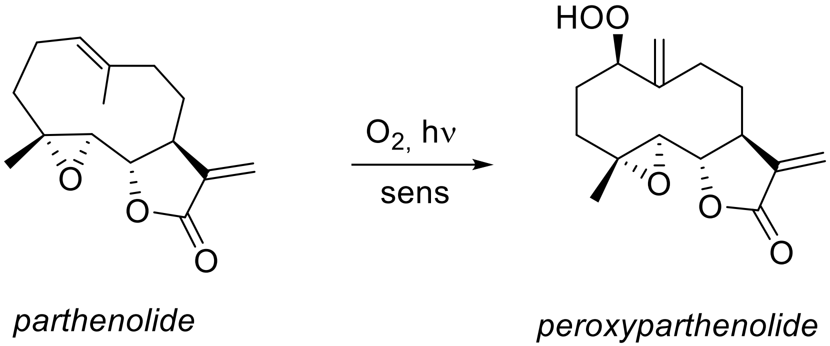


Examples in organic synthesis

- ***Synthesis of peroxyparthenolide*** *cytotoxic component of Magnolia leaves*

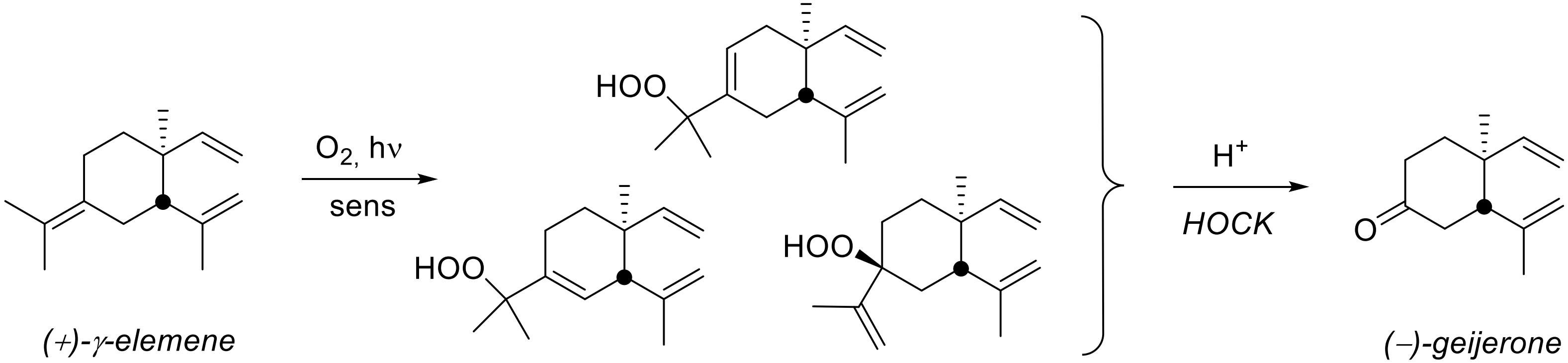
  Tetrahedron Lett. **1977**, 1973





- ***Synthesis of (–)-geijerone*** *sesquiterpene from juniper*

  Helv. Chim. Acta **1972**, *55*, 2429

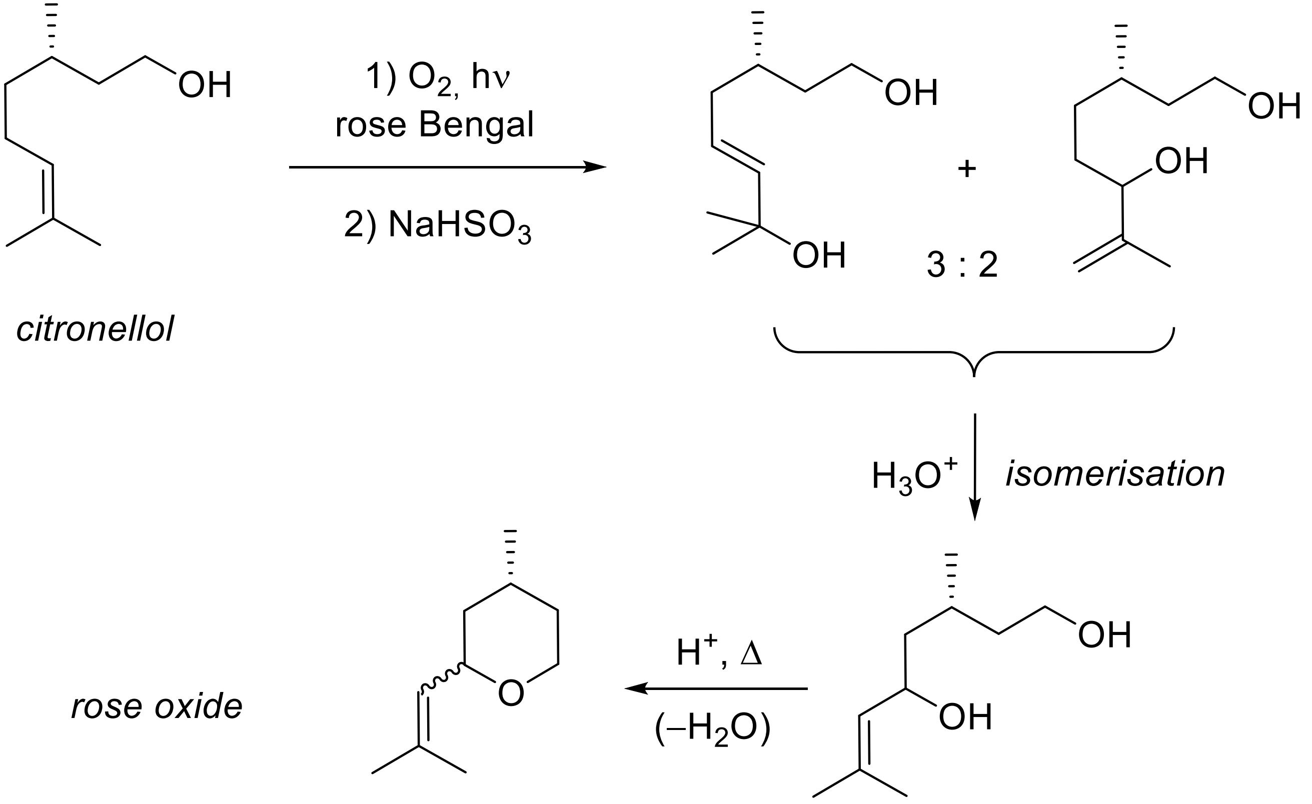


Examples in organic synthesis

- ***Synthesis of rose oxide***

  Sol. Energy Eng. **2001,** *123,* 171

Fragrance found in roses and rose oil
(also in fruits and white wines).
High value in perfume industry

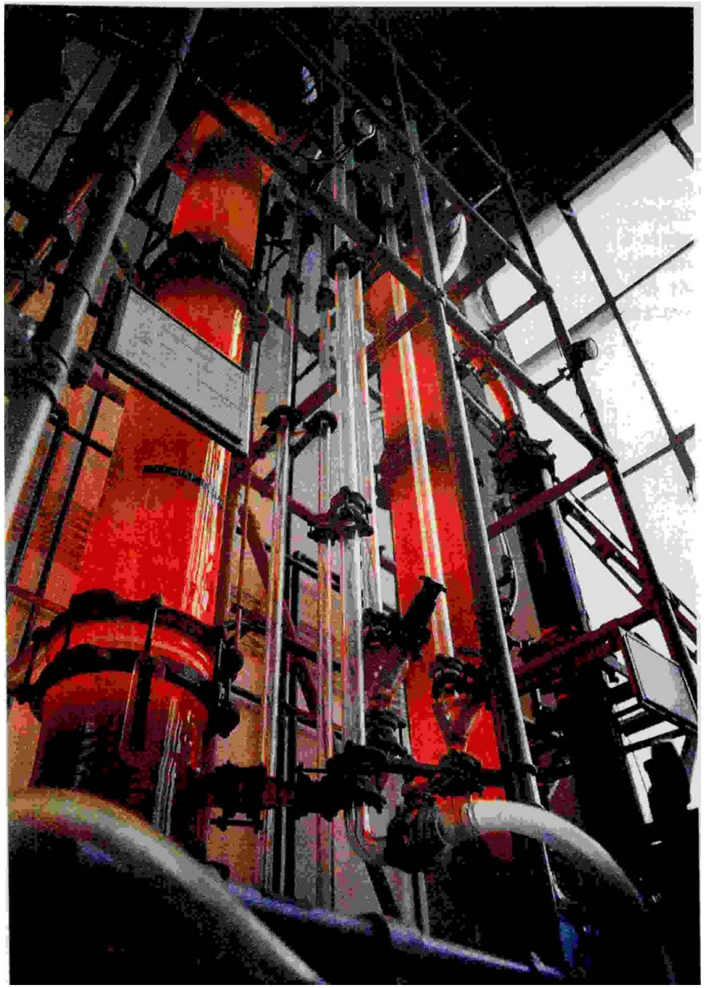


- ***Industrial synthesis of rose oxide***

Photo : Dragoco (Germany)

Cylindrical immersion photoreactors,
each is 3 m high, with 5 kW light source

Production: several tons / year

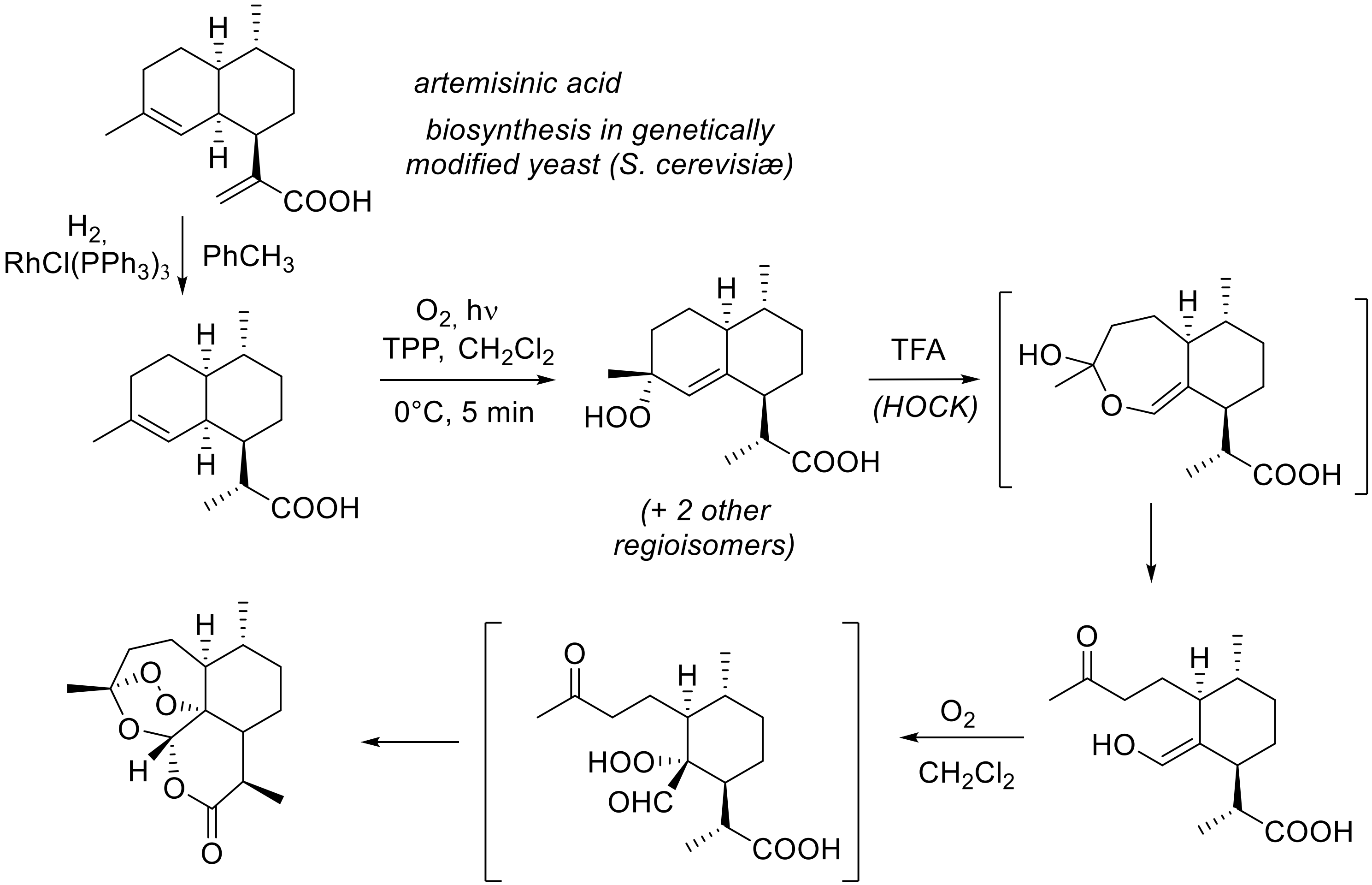


Examples in organic synthesis

- ***Synthesis of artemisinin***

  Angew. Chem. Int. Ed. **2012,** *51,* 1706

sesquiterpene from Artemisia annua, antimalarial activity



artemisinic acid

biosynthesis in genetically modified yeast (S. cerevisiæ)

H_2, $RhCl(PPh_3)_3$ $PhCH_3$

O_2, hν TPP, CH_2Cl_2 0°C, 5 min

(+ 2 other regioisomers)

TFA *(HOCK)*

O_2 CH_2Cl_2

artemisinin

- ***Industrial synthesis of artemisinin***

Sanofi, in cooperation with *The Bill and Melinda Gates Foundation*, has established an industrial production of artimisenin.

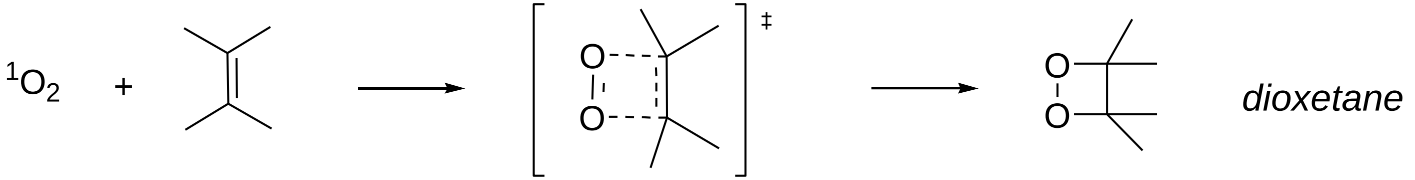
Output:
35 tons in 2013,
60 tons in 2014.

Photo : Sanofi factory at Garessio (Italy)

2. 2+2 Cycloaddition: formation of dioxetanes

This reaction involves alkenes

General scheme:



Several mechanisms are possible, still a matter of debate
Here, we assume a concerted process

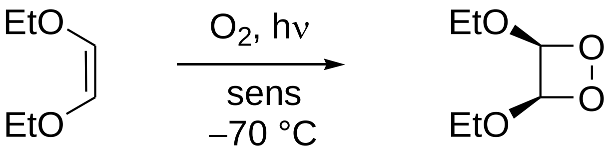
Singlet oxygen + alkene:
Allylic addition or 2+2 cycloaddition?

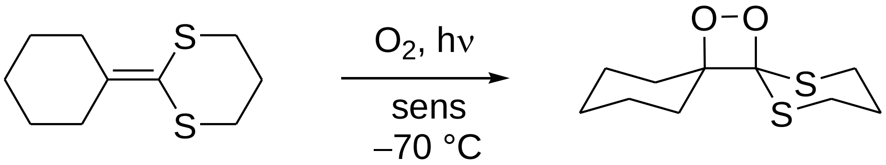
As a general rule the allylic hydroperoxidation prevails.
However, 2+2 cycloaddition is favored in the following cases:

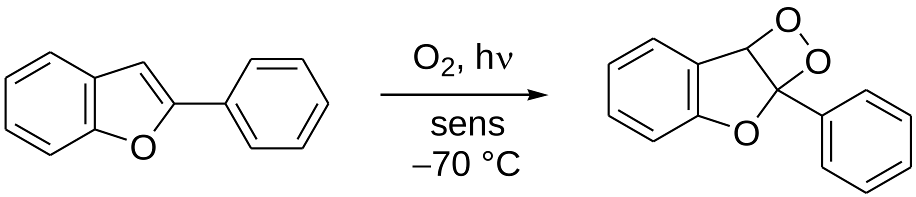
- absence of an available allylic H
- the alkene is electron-rich due to the presence of one or more heteroatom (O, S, N)
- reaction conditions of low temperature and/or protic solvent

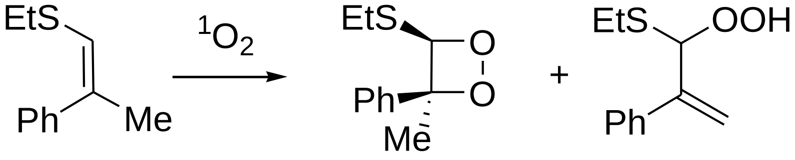
2+2 Cycloaddition Reactions

Examples:

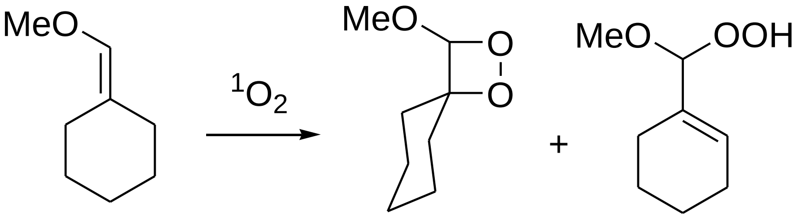








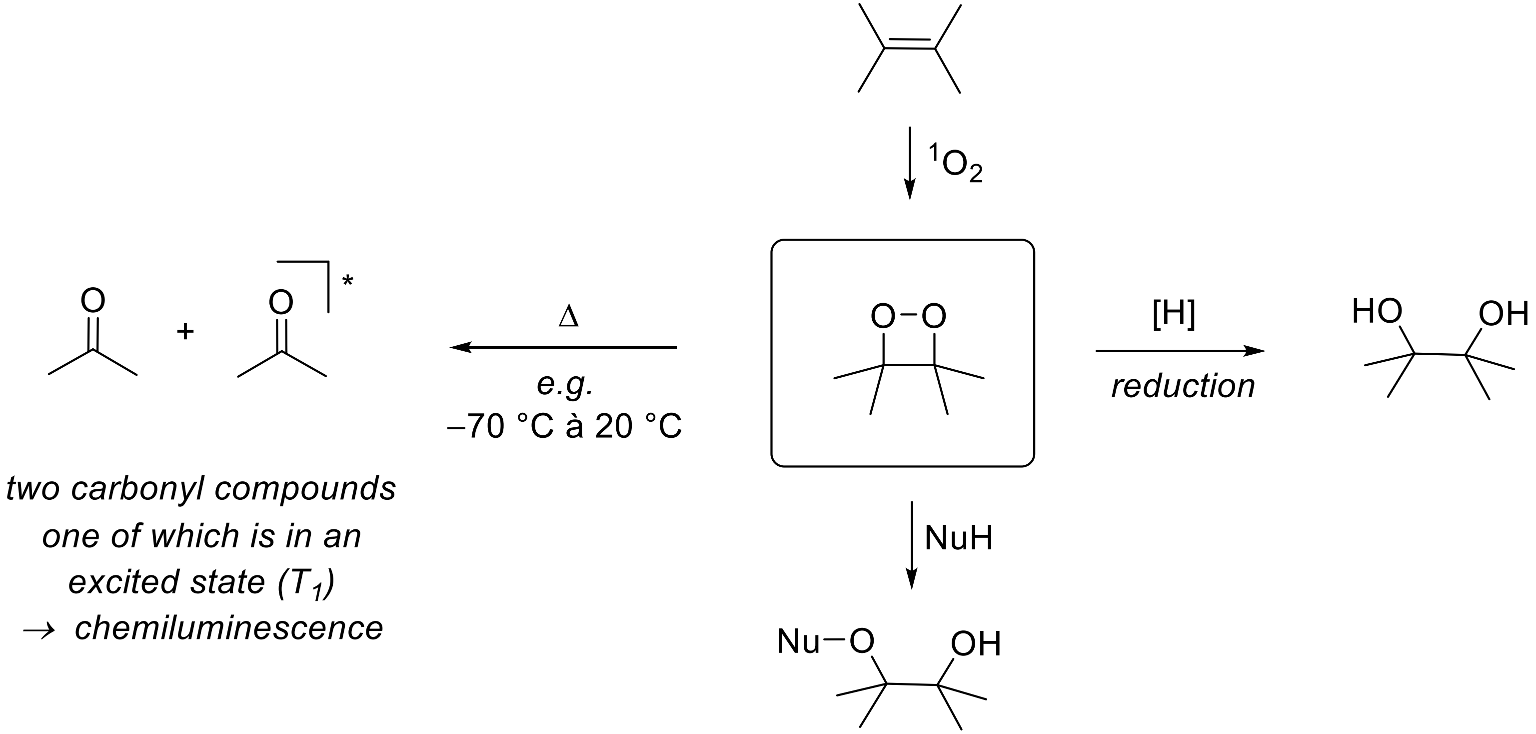
MeOH, 20 °C	95 : 5
CH_2Cl_2, 20 °C	20 : 80



MeOH, –80 °C	85 : 15
C_6H_6, 20 °C	3 : 97

Transformation of dioxetanes

Some dioxetanes are stable at room temperature, others undergo thermal decomposition

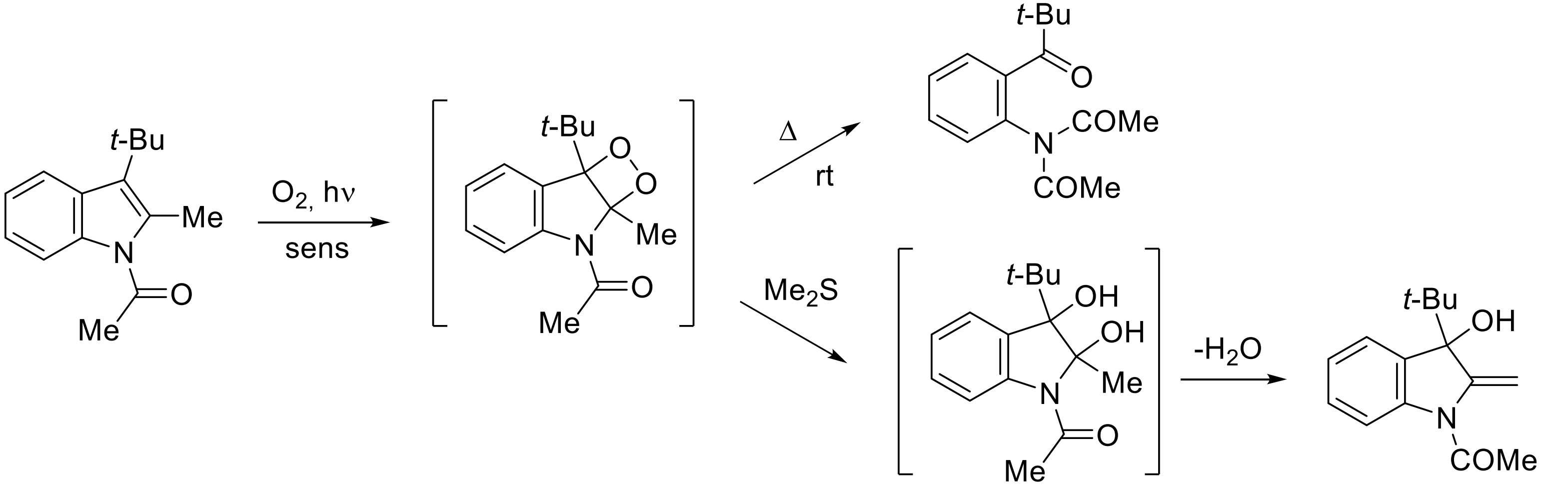


two carbonyl compounds one of which is in an excited state (T_1)
→ chemiluminescence

Examples in organic synthesis

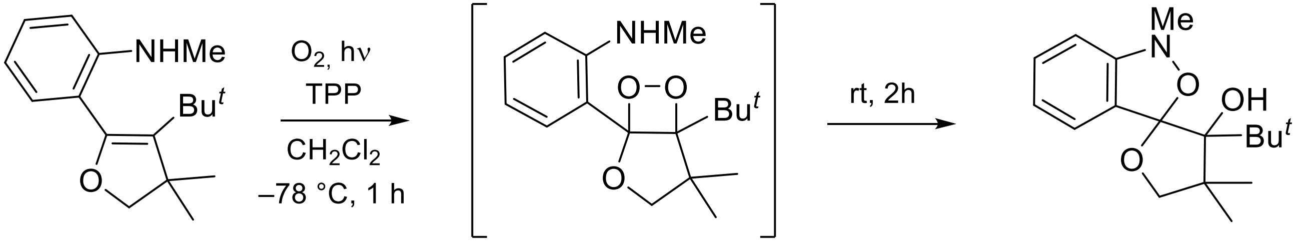
- ***Photooxygenation of indoles***

  J. Org. Chem. **1993,** *58,* 47



- ***Formation of spiroacetals***

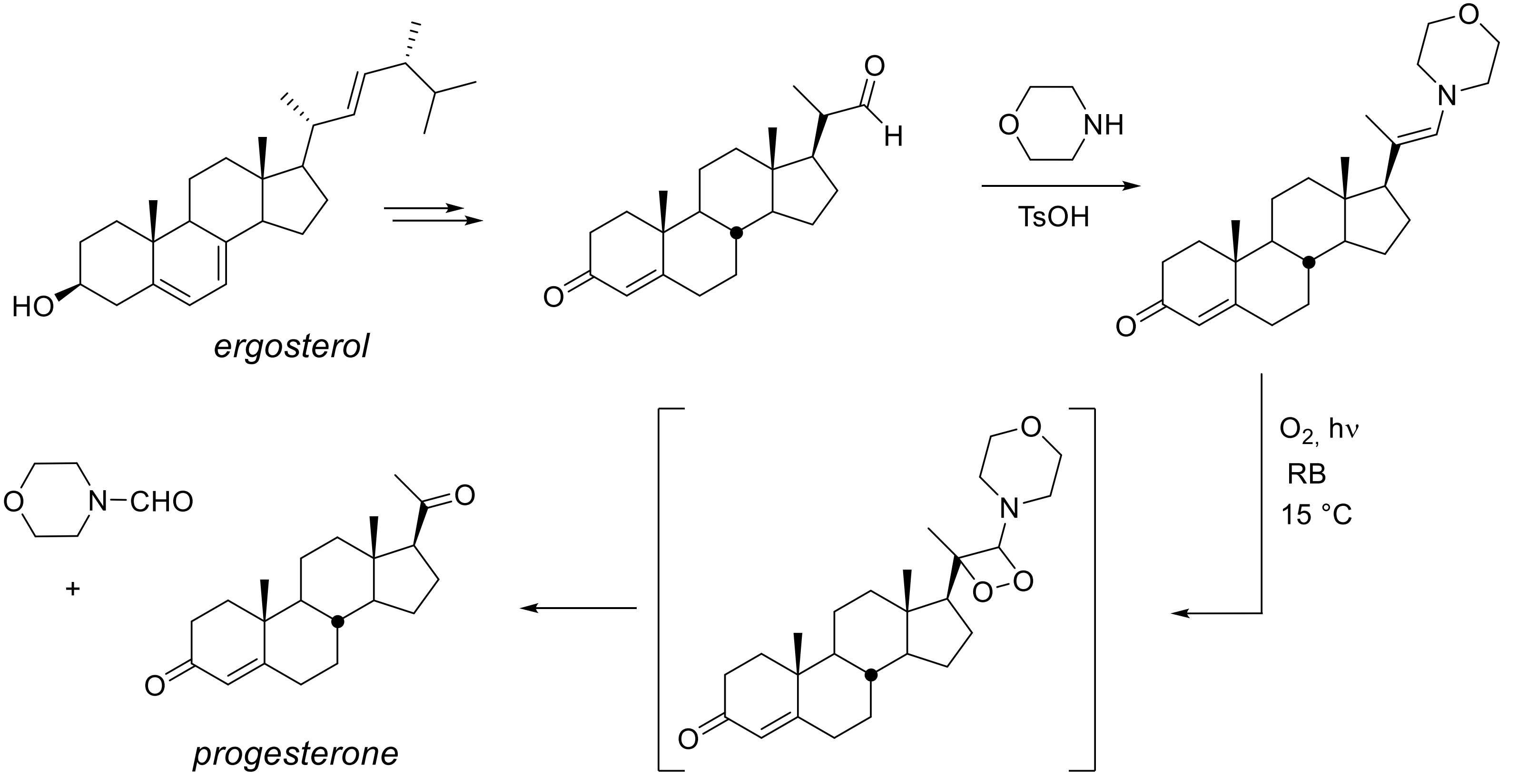
  Chem. Commun. **1998,** 2319



Examples in organic synthesis

- ***Synthesis of progesterone***

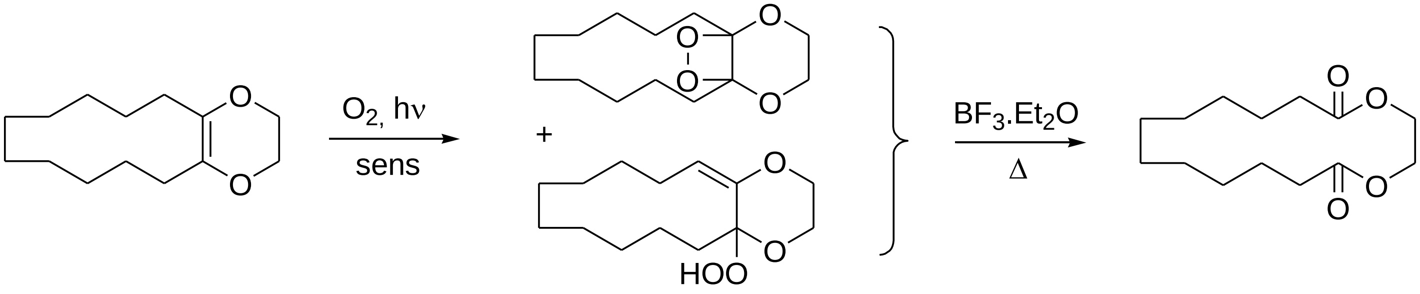
  Tetrahedron Lett. **1968,** 3271



Examples in organic synthesis

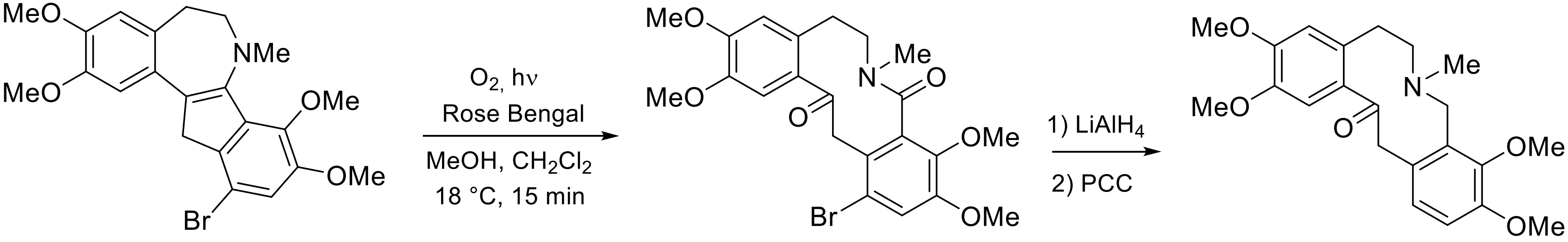
- ***A macrocyclic bis(lactone)*** *intermediate for the synthesis of musk-like fragrances*

  Patent (Firmenich), **1977,** CH 589642



- ***Synthesis of muramine*** *a protopine alkaloid: a family with a unique 10-membered amino-ketone ring*

  J. Org. Chem. **2007,** *72*, 7301

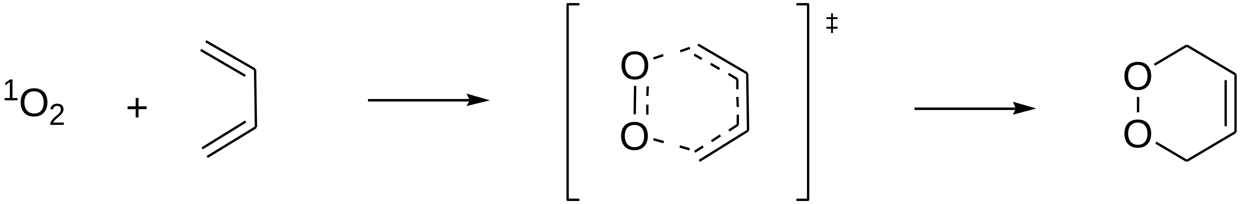


muramine

3. 4+2 Cycloaddition reactions: formation of endoperoxides

This reaction involves *cis*-1,3-dienes

General scheme:

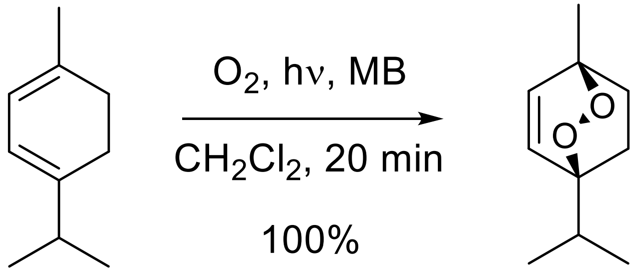


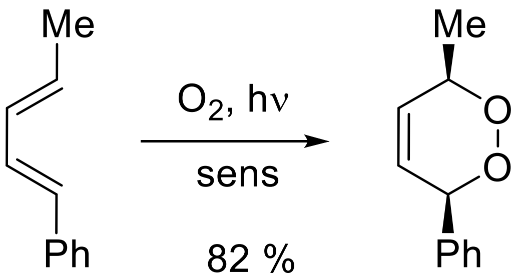
endoperoxide

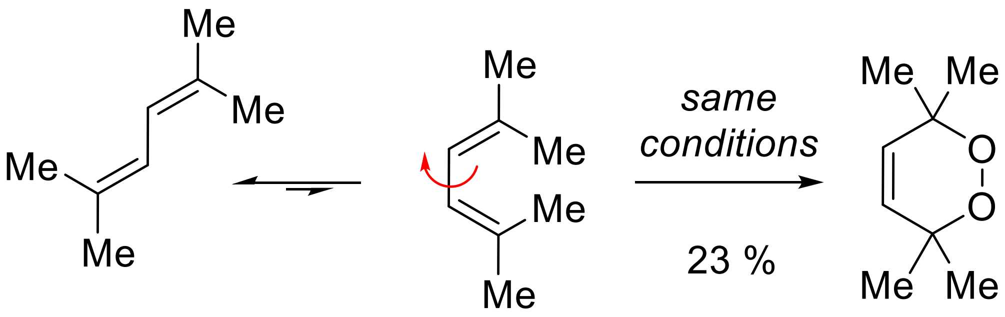
Concerted process (*cf Diels-Alder reaction*)

4+2 Cycloaddition Reactions

Examples :



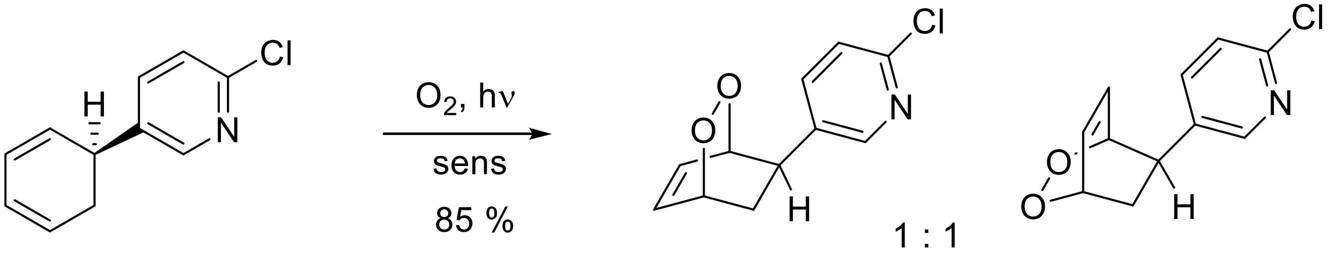


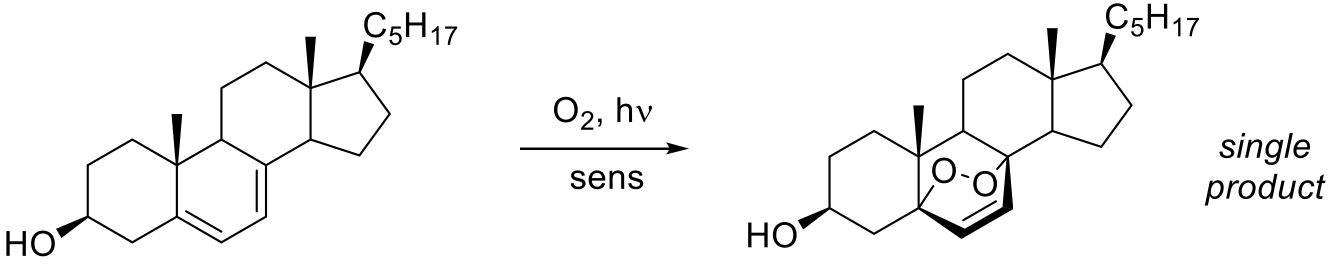


4+2 Cycloaddition Reactions

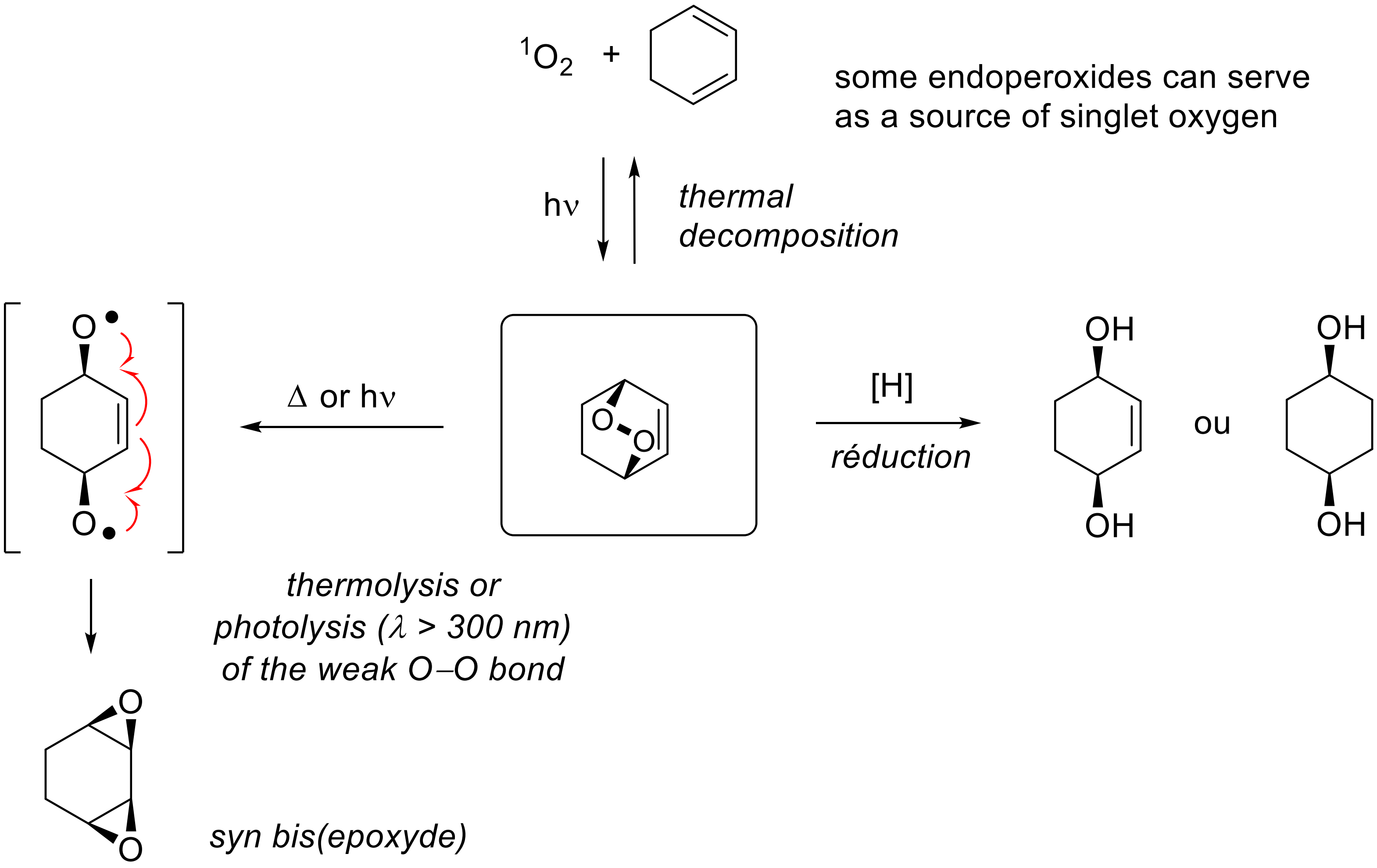
Stereoselectivity Issues

Diastereoselectivity is variable, and depends largely on whether steric constraints are present in the 1,3-diene





Transformation of endoperoxides



$^1O_2$ +

some endoperoxides can serve
as a source of singlet oxygen

hν

thermal
decomposition

Δ or hν

[H]

réduction

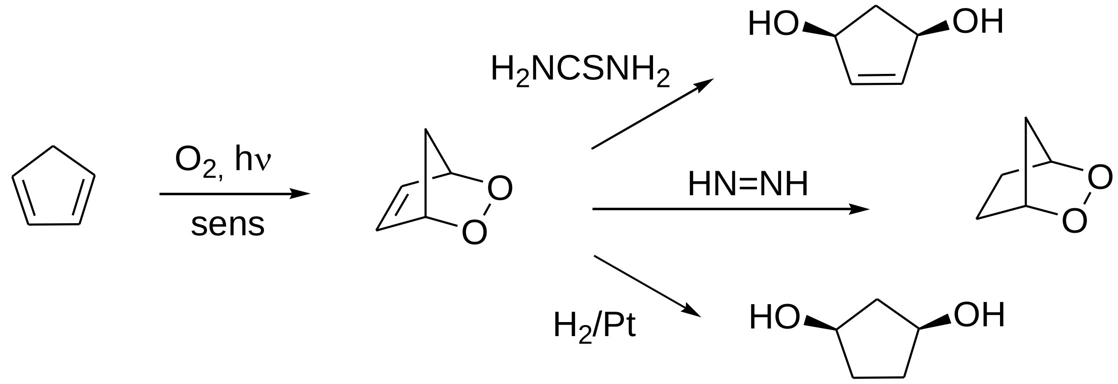
ou

thermolysis or
photolysis (λ > 300 nm)
of the weak O–O bond

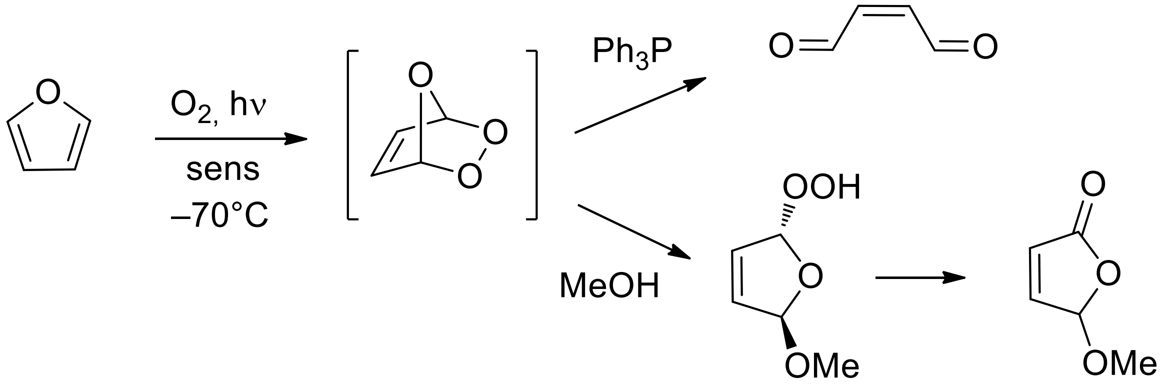
syn bis(epoxyde)

Reactions with other cyclic diene systems

Cyclopentadienes



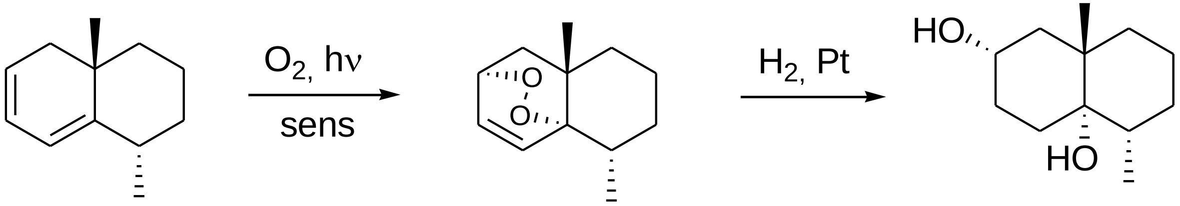
Furans



Examples in organic synthesis

- ***Synthesis of cybullol*** *fungal metabolite from a bird's nest*

  Can. J. Chem. **1976**, *54*, 3276

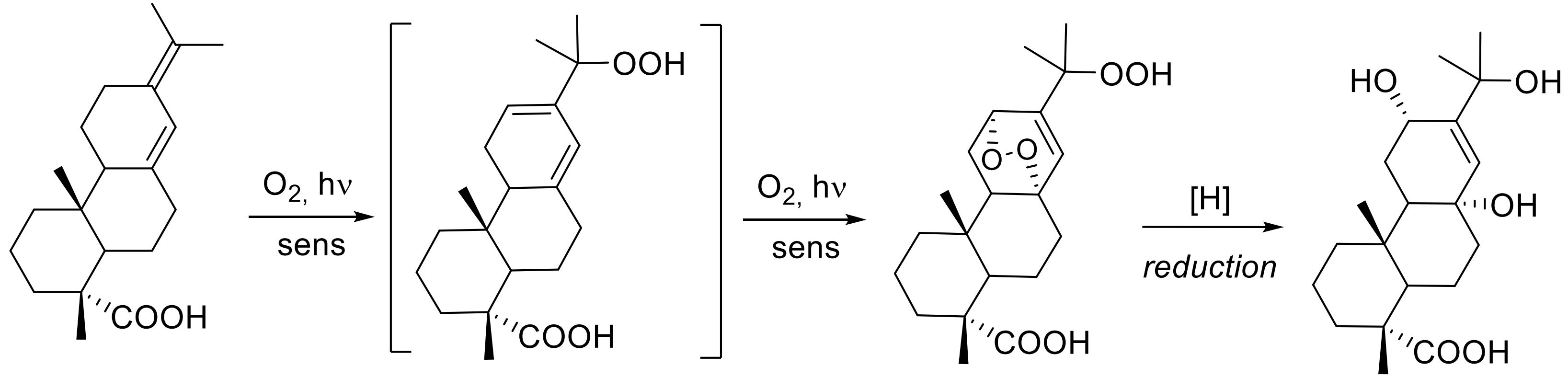


(±)

(±)-*cybullol*

- ***Oxygenation of neoabietic acid*** *constituent of pine resin*

  J. Am. Chem. Soc. **1961**, *83*, 2563

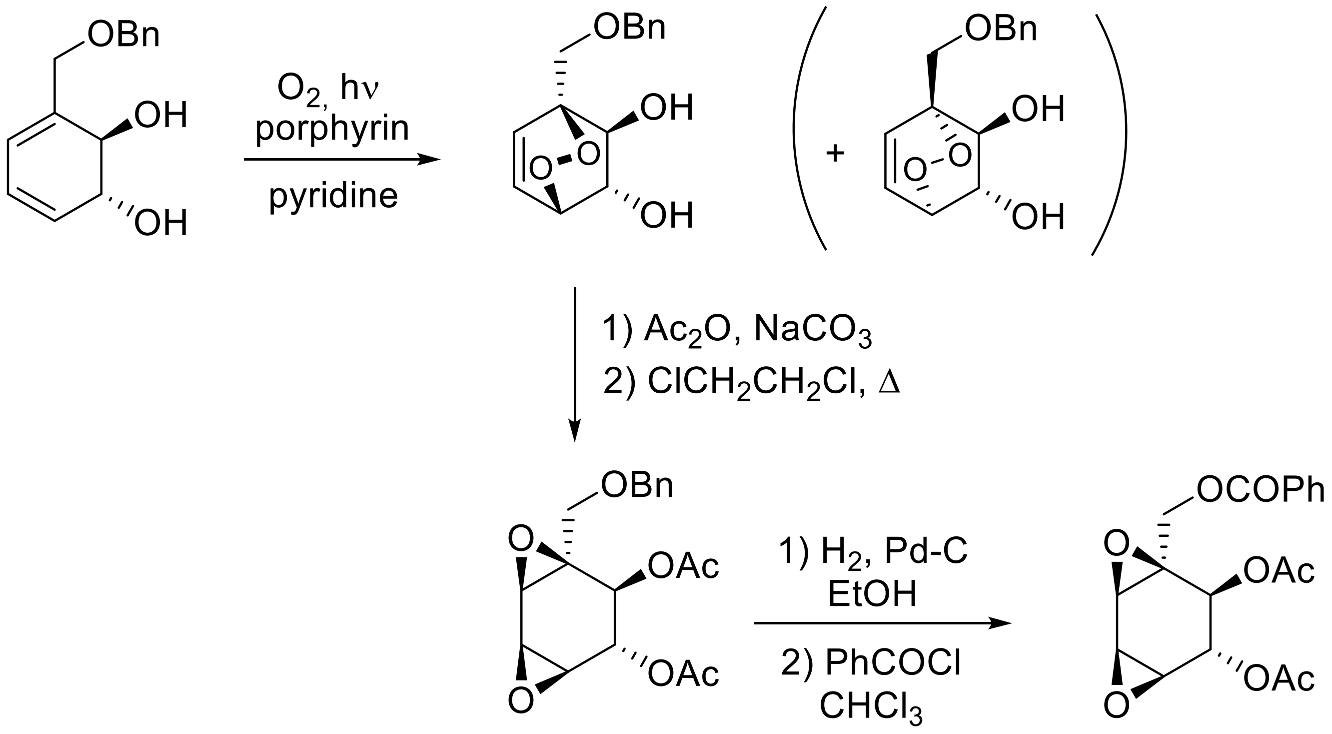


neoabietic acid

Examples in organic synthesis

- ***Synthesis of crotepoxide*** *cytotoxic constituent of peppercorns*

J. Am. Chem. Soc. **1976**, *98*, 634



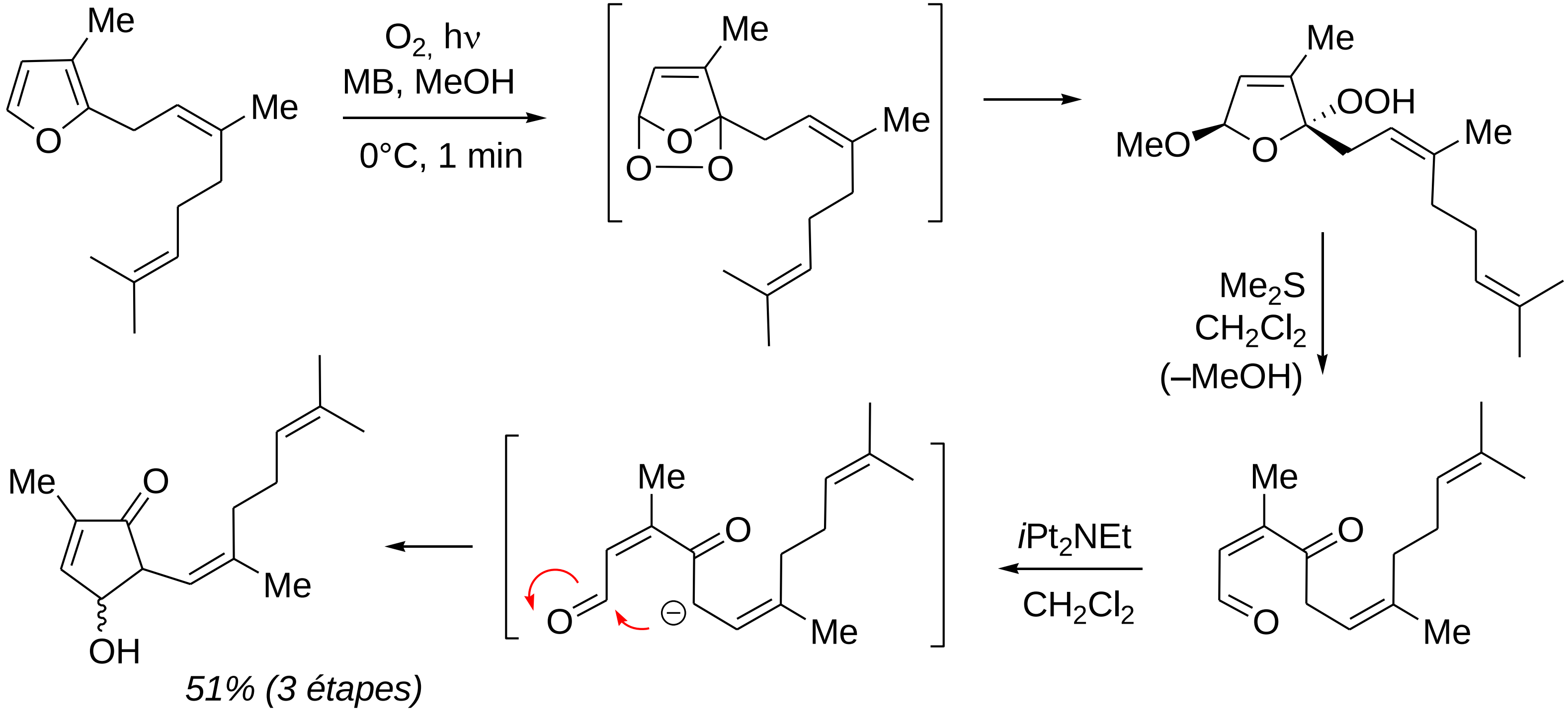
(±)-crotepoxide

Examples in organic synthesis

- ***Biomimetic synthesis of litseaverticillol B***

Org. Lett. **2004**, *6*, 2039

sesquiterpene family with anti-HIV activity,
isolated racemic from the bush Litsea verticillata



51% (3 étapes)

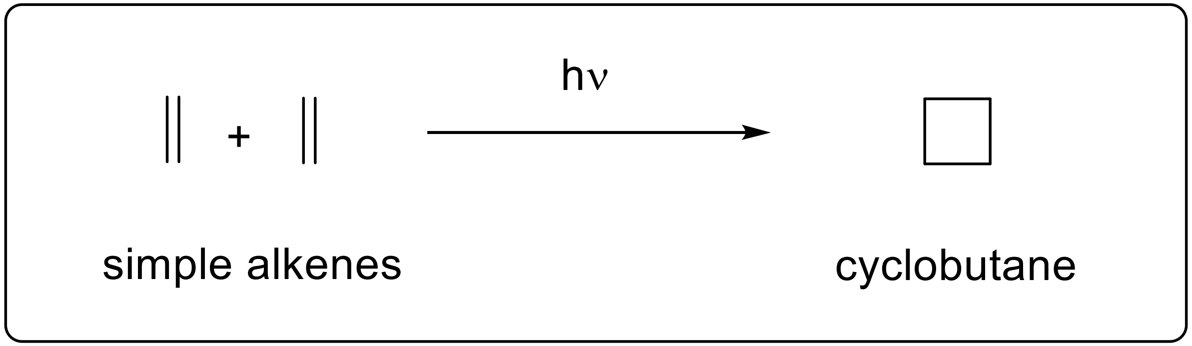
(±)-litseaverticillol B
(and a diasteréoisomer)

Photochemistry of Alkenes and Dienes

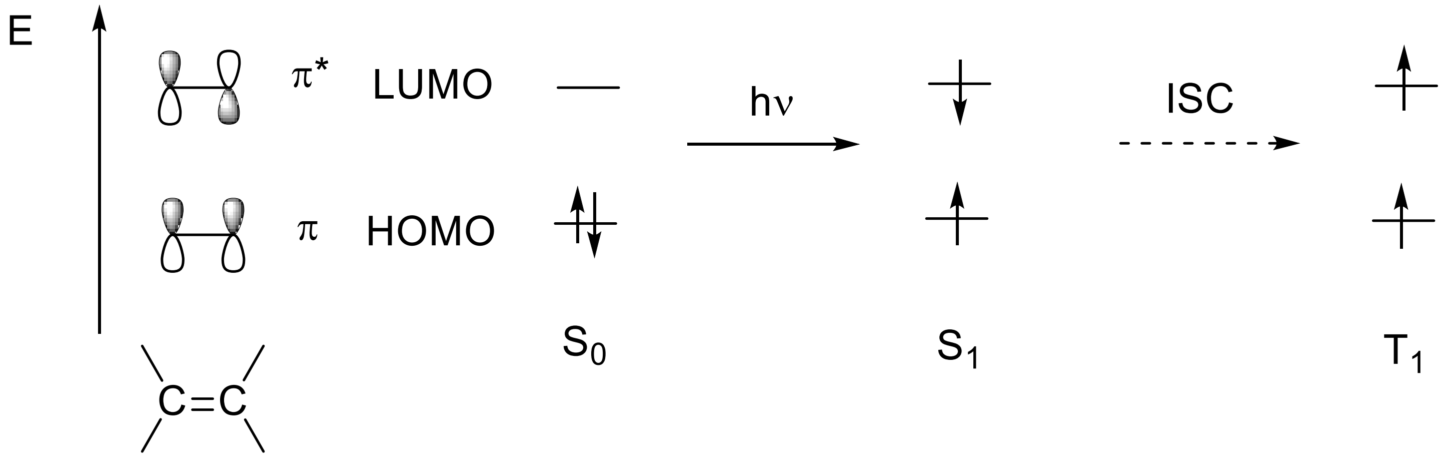
A. [2+2] Photocycloadditions of Simple Alkenes

B. Photochemical [2+2] Electrocyclizations of Dienes

A. PHOTOCHEMICAL [2+2] CYCLOADDITIONS OF ALKENES



Photoactivation of alkenes

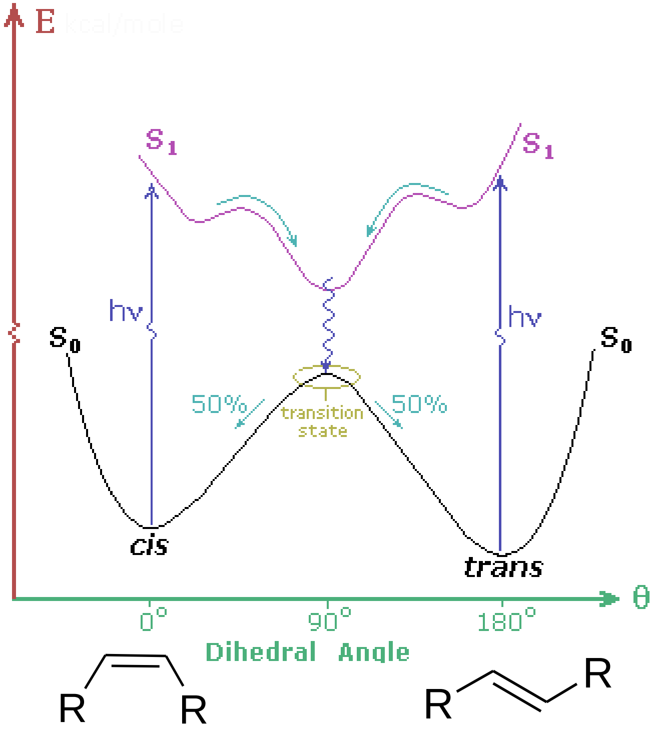


The transition $\pi \rightarrow \pi^*$ is implicated

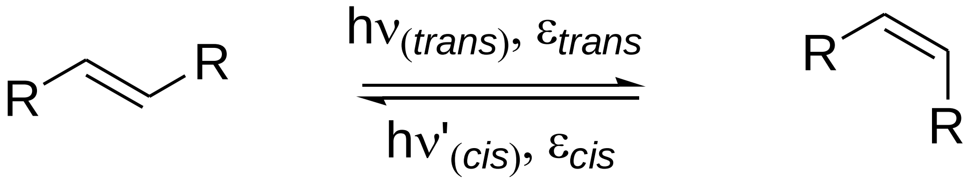
For simple alkenes: λ_{max} = 180-200 nm ($\varepsilon \sim 10^4$)

Photoisomerization of alkenes

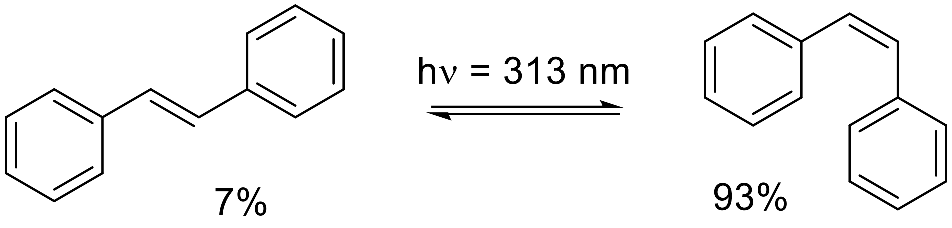
- Rapid “vertical” absorption of the photon; the geometry of the S_1 excited state is the same as that of S_0.
- Rapid rotation → “non vertical” S_1 state with less energy.
- Internal conversion (IC) $S_1 \rightarrow S_0$ to the transition state of *cis* / *trans* interconversion.



The **photostationary equilibrium** is *not* determined by theromodynamic stability, it is determined by the relative rates of removal of the *cis* and *trans* isomers due to absorption.



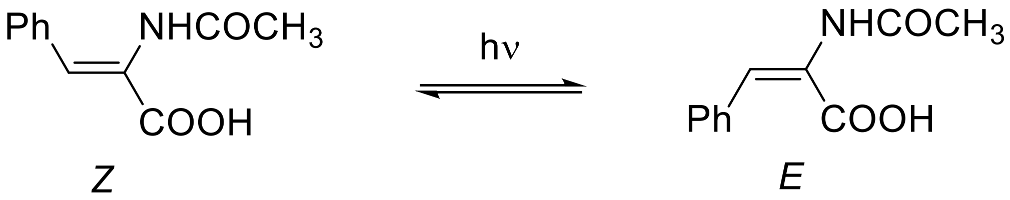
Examples:



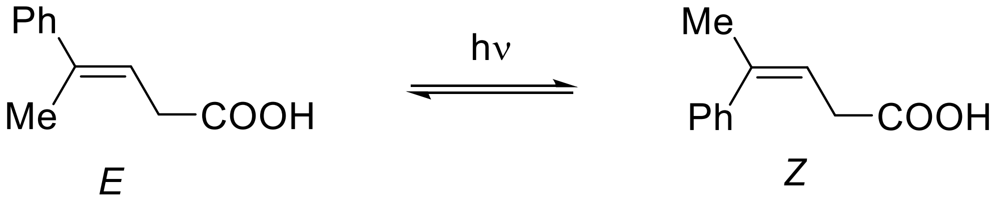
photoisomerization
of stilbene

at 313 nm:

ε_{cis} = 2 300 $\mathrm{l.mol^{-1}.cm^{-1}}$
ε_{trans} = 16 300 $\mathrm{l.mol^{-1}.cm^{-1}}$

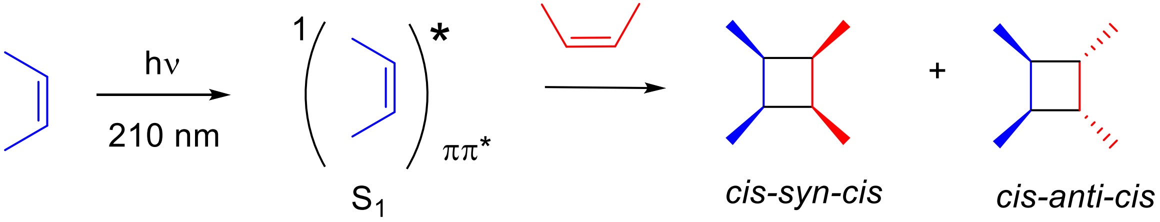


E:Z 3:1



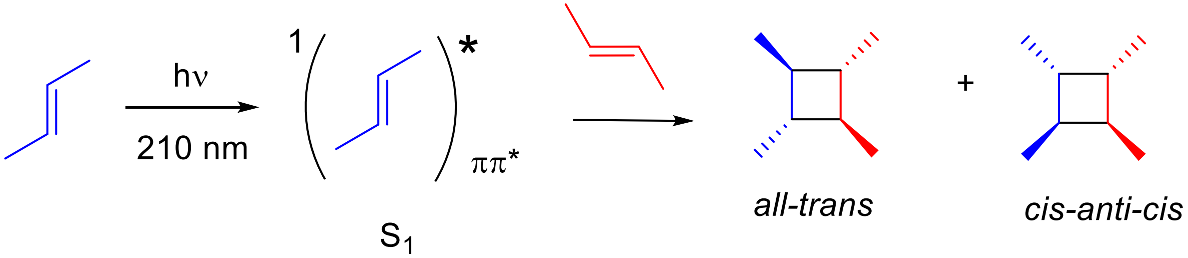
E:Z 1:1

Photodimerization of alkenes



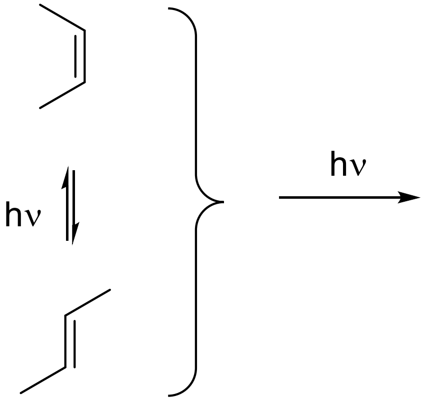
cis-syn-cis + *cis-anti-cis*

(concerted)



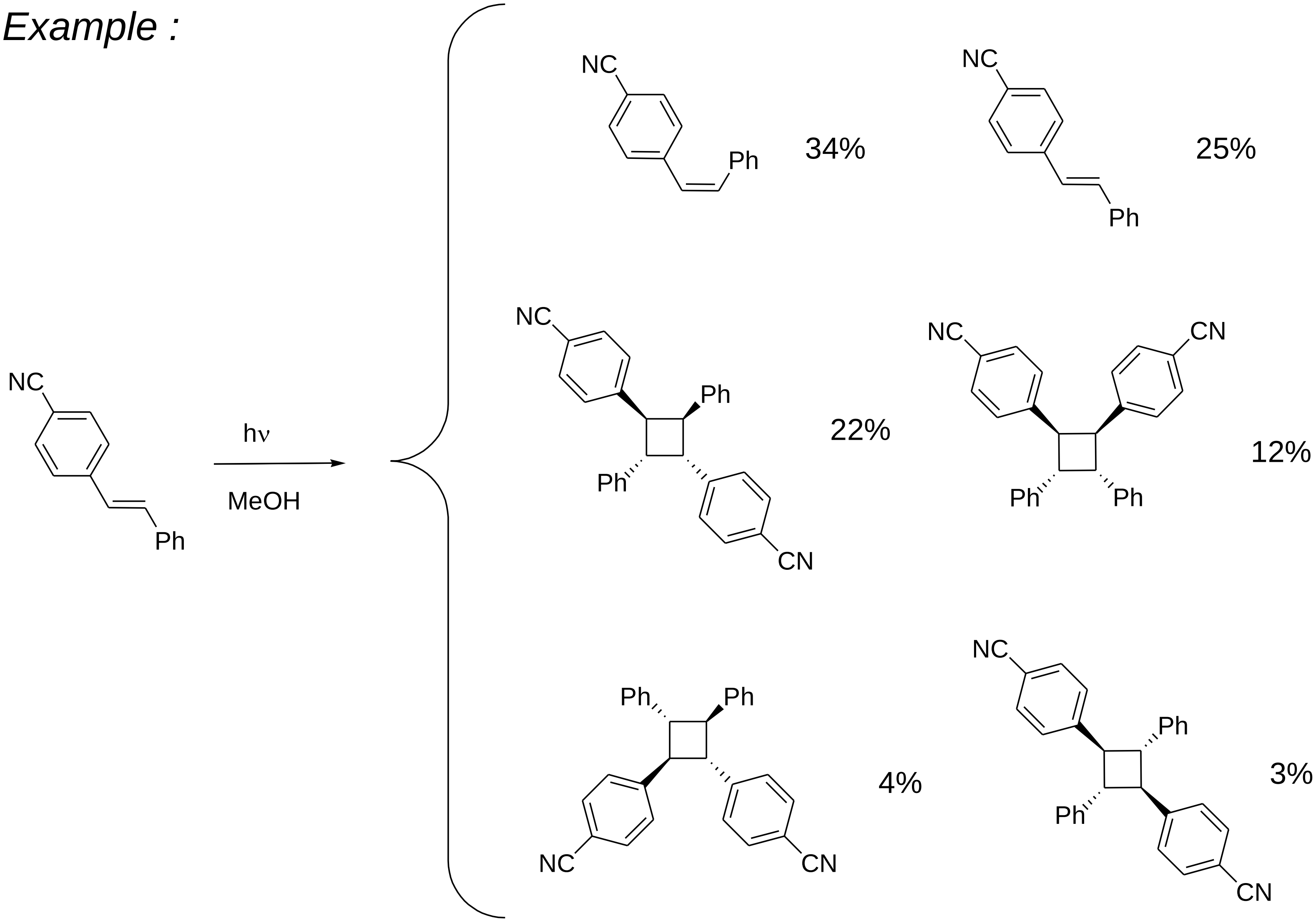
all-trans + *cis-anti-cis*

(concerted)



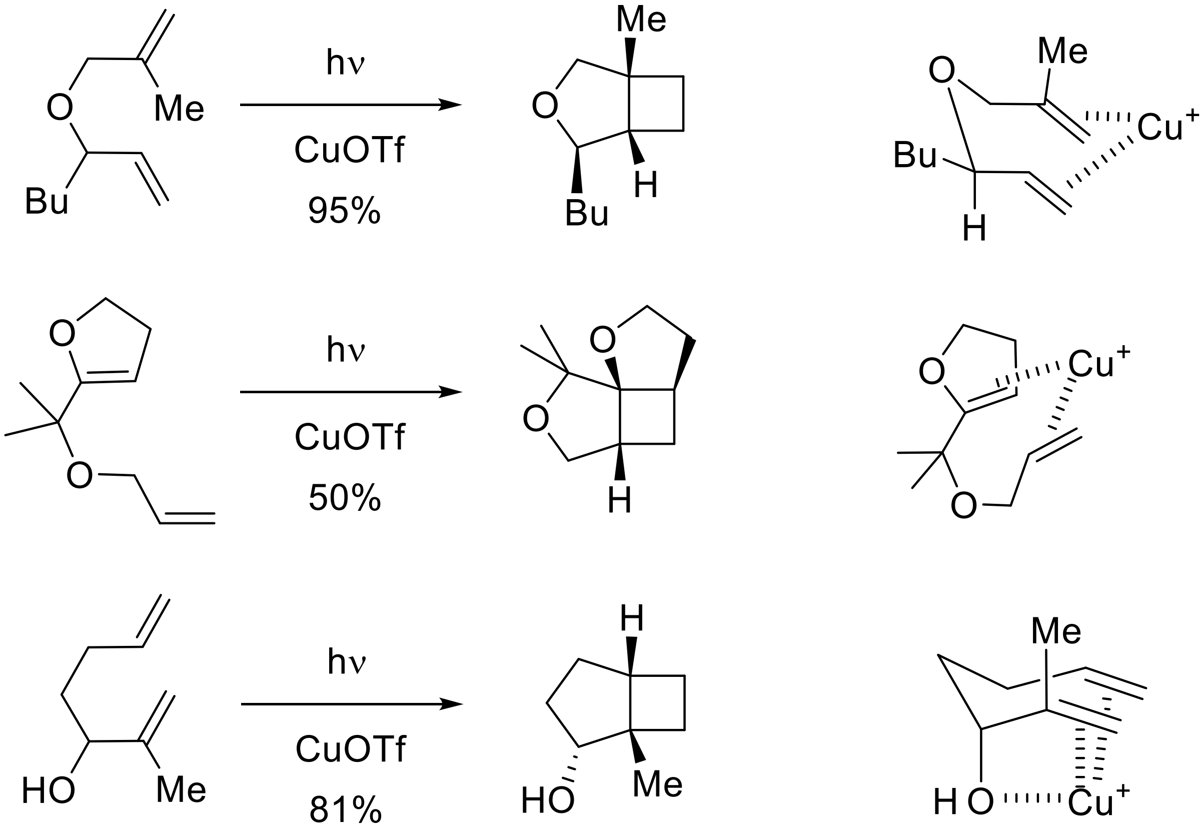
photodimeres
mixtures of stereoisomers

Example :

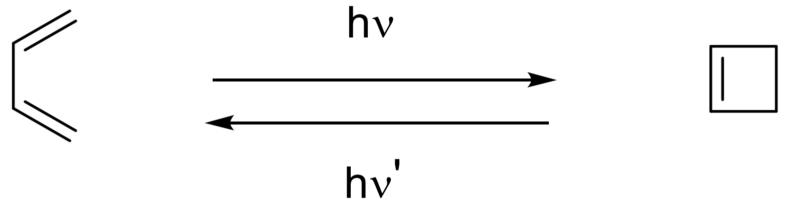

NC
Ph
hν
MeOH
NC
Ph
34%
NC
Ph
25%
NC
Ph
Ph
CN
22%
NC
CN
Ph
Ph
12%
Ph
Ph
NC
CN
4%
NC
Ph
Ph
CN
3%

Intramolecular photodimerization of alkenes

Usually carried out in the presence of a copper(I) salt, *e.g.* CuOTf



B. PHOTOCHEMICAL [2+2] ELECTROCYCLIZATIONS OF DIENES



cis-1,3-diene

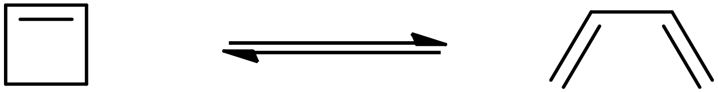
cyclobutene

Frontier orbital theory

Electrocyclic reactions are concerted.

Their course is predicted by the **Woodward-Hoffmann** rules.

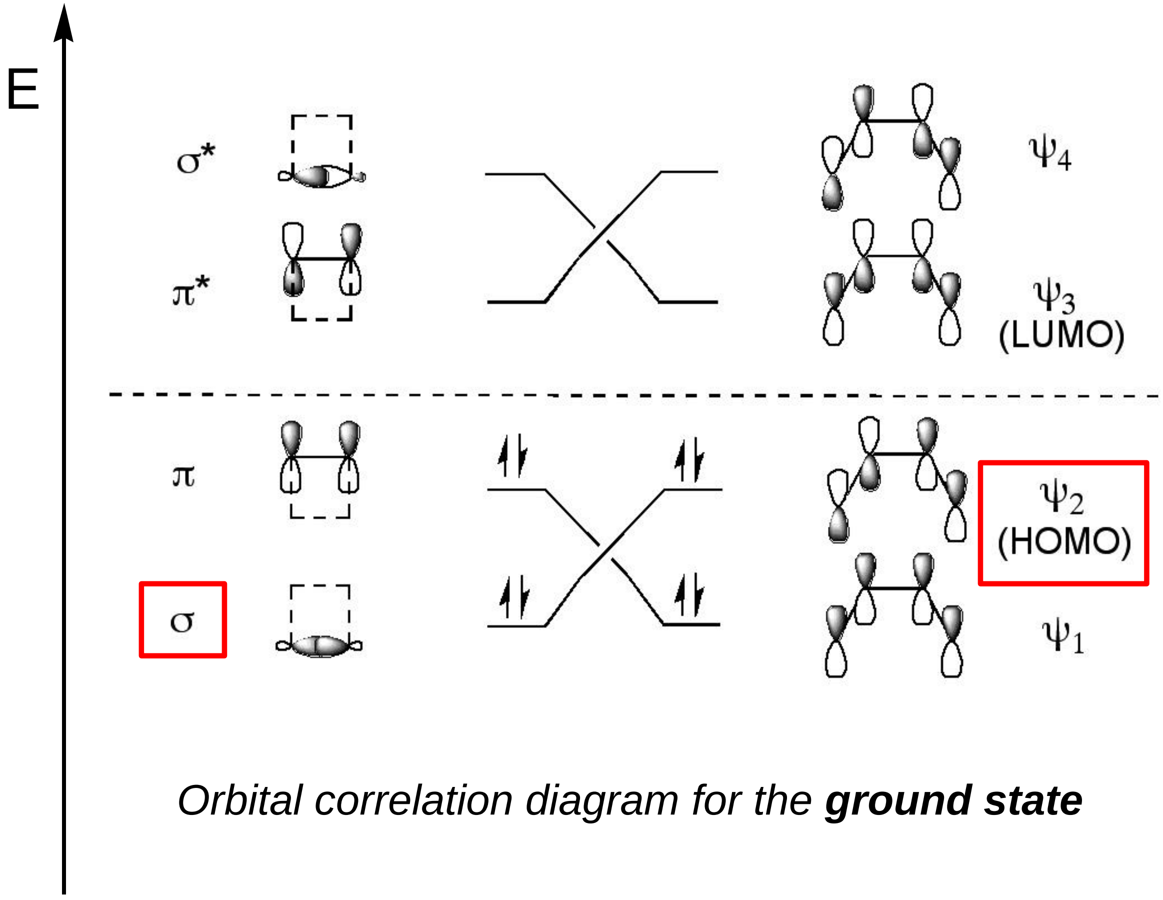
These rules propose that the energy barriers for pericyclic reactions are governed by the ***conservation of orbital symmetry***, which allows maximum orbital overlap in the transition state.
Reactions are “allowed” if the energy barrier is low or “forbidden” if the energy barrier is high.
A “forbidden” reaction may occur, but requires more activiation energy.



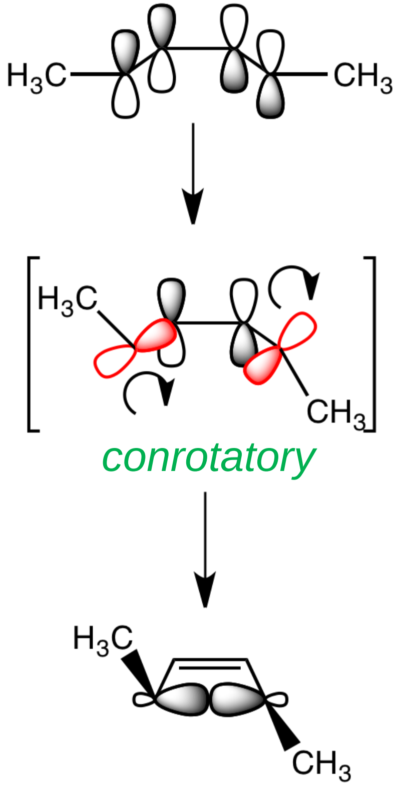
The σ bond of the cyclobutene is formed (or broken) in a manner which conserves of the symmetry of the diene HOMO.

Thermal **reactions**

Ring opening and ring closure proceed via a **conrotatory** process.

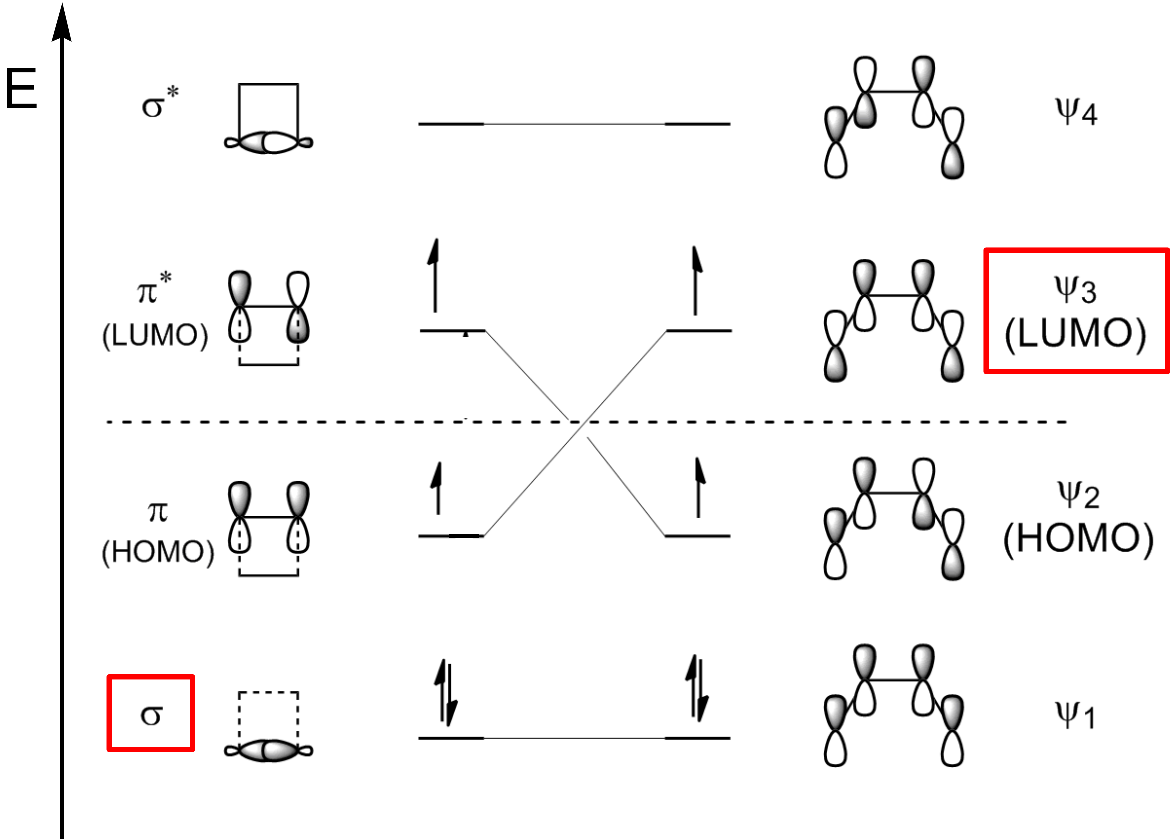


Orbital correlation diagram for the ***ground state***

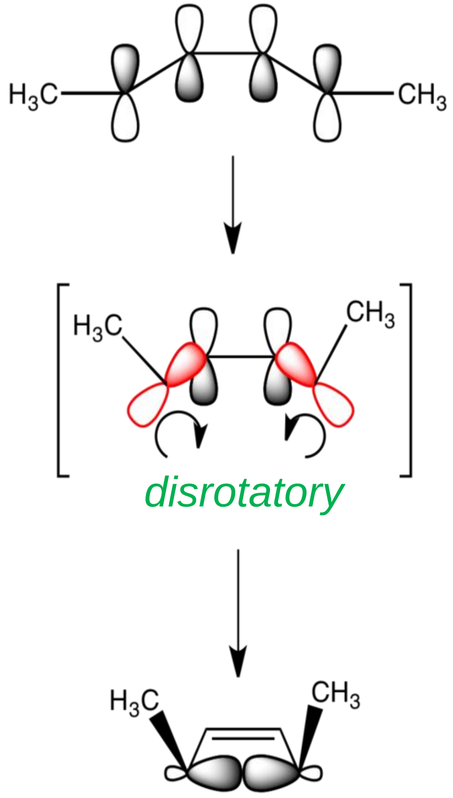


Photochemical reactions

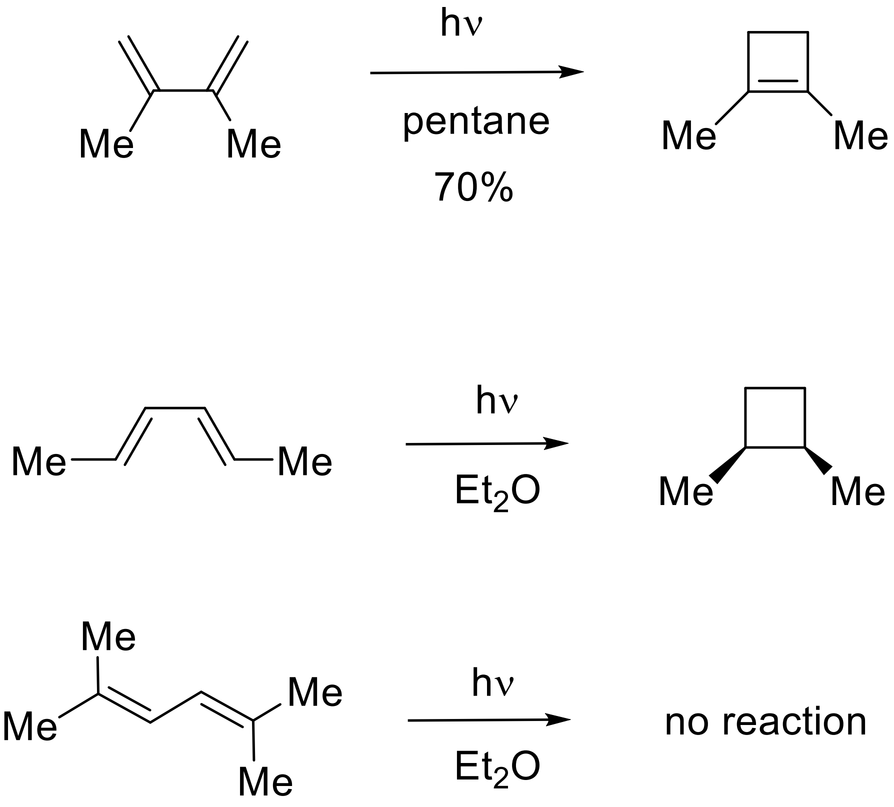
Ring opening and ring closure proceed via a **disrotatory** process.



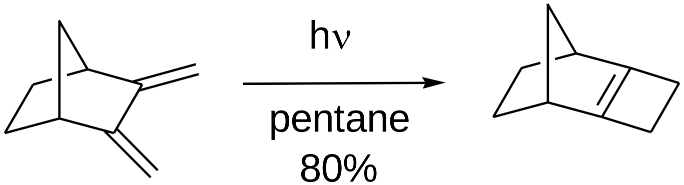
Orbital correlation diagram for the ***excited state***

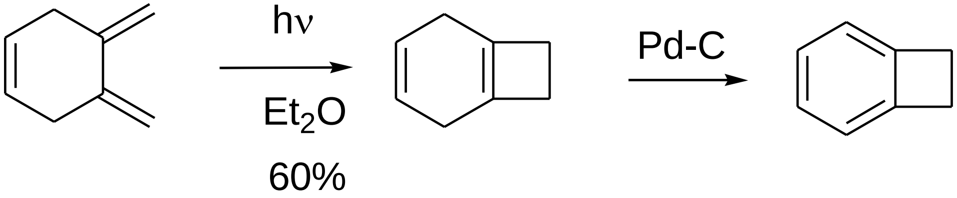


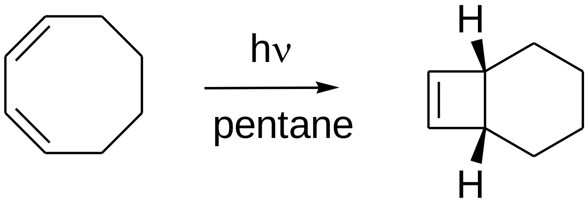
Reactions of acyclic dienes

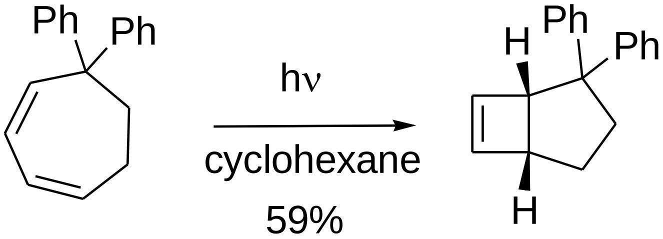


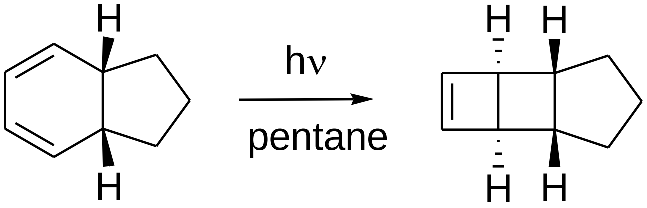
Reactions of carbocyclic dienes



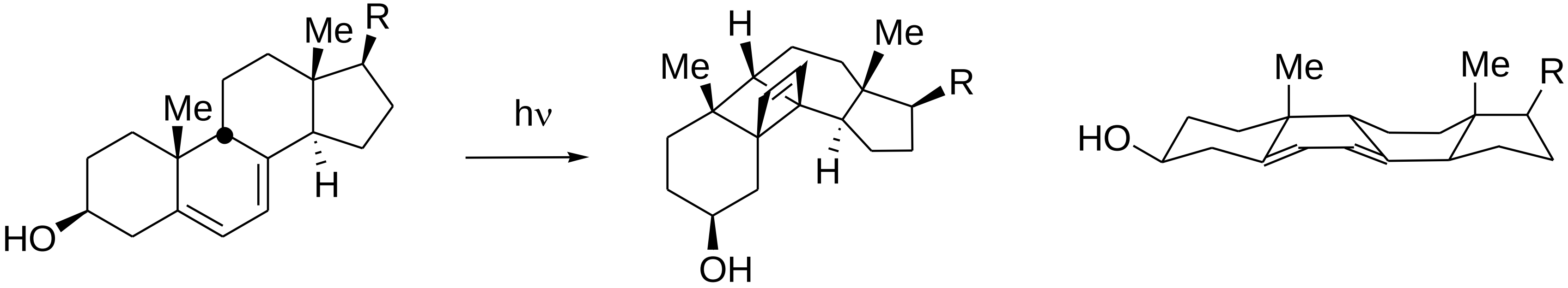


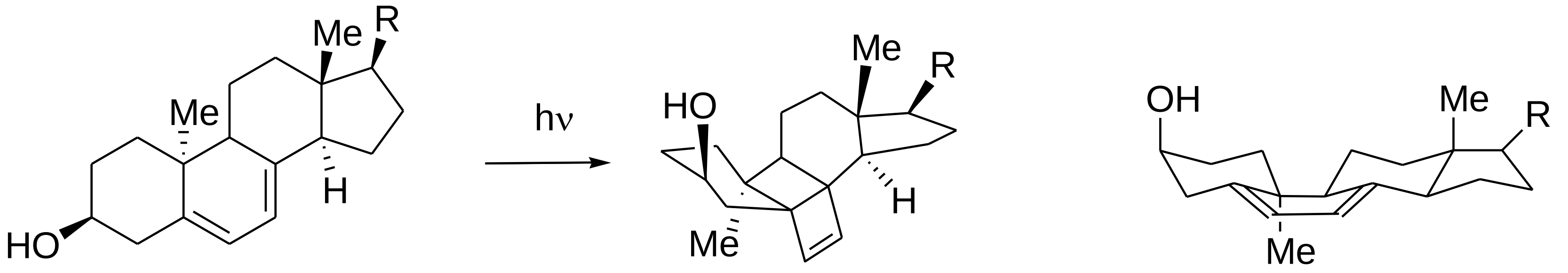




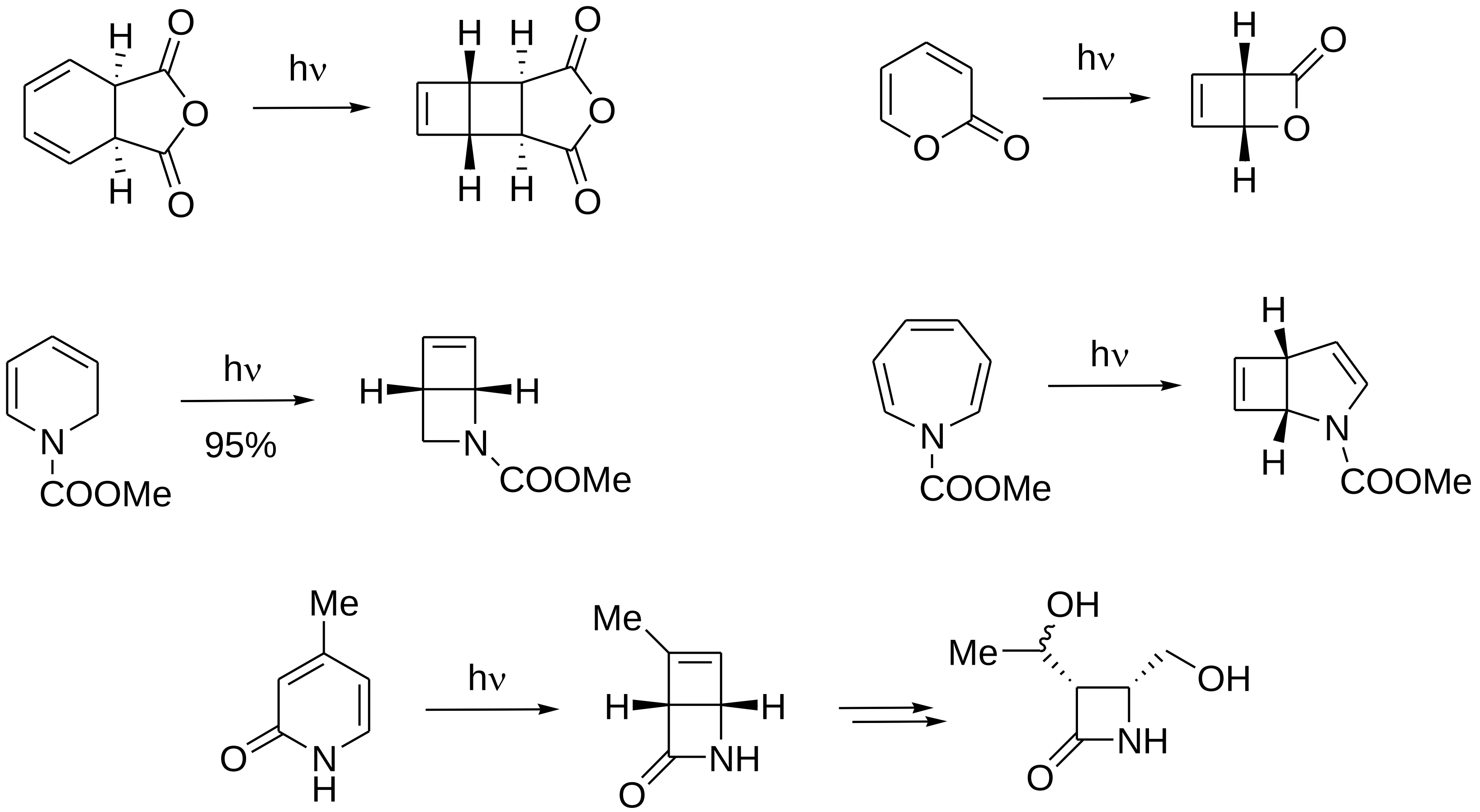


Reactions of carbocyclic dienes





Reactions of heterocyclic dienes



Photochemistry of Enones

A. Introduction

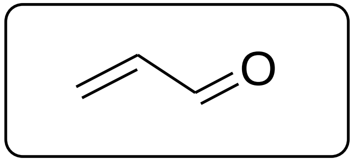
B. [2+2] Photocycloadditions between Enones and Alkenes

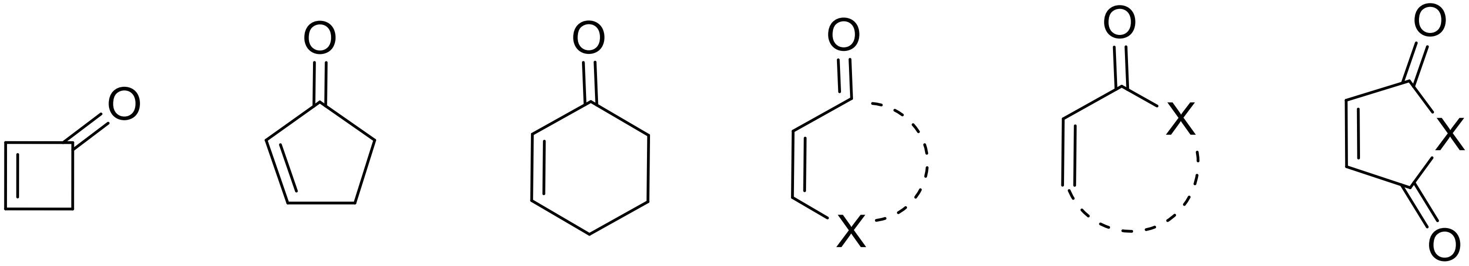
1. Intermolecular reactions
2. Intramolecular reactions
3. Reactions using β-dicarbonyls
4. Reactions using other enone systems

C. Examples of Applications in Organic Synthesis

A. INTRODUCTION

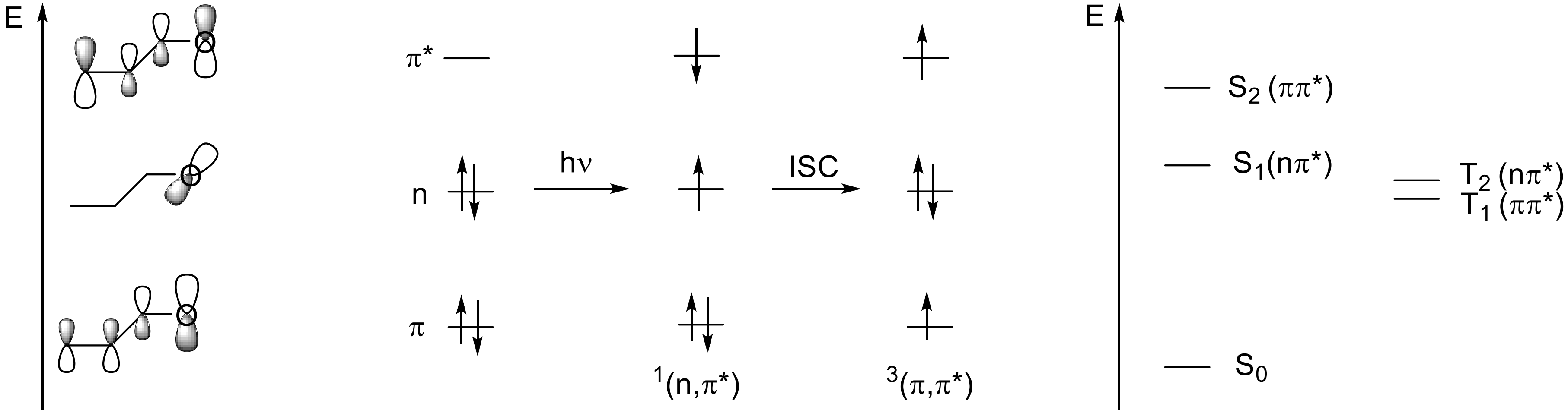
Enone:

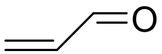




X = O, NR, ...

Photoactivation of enones



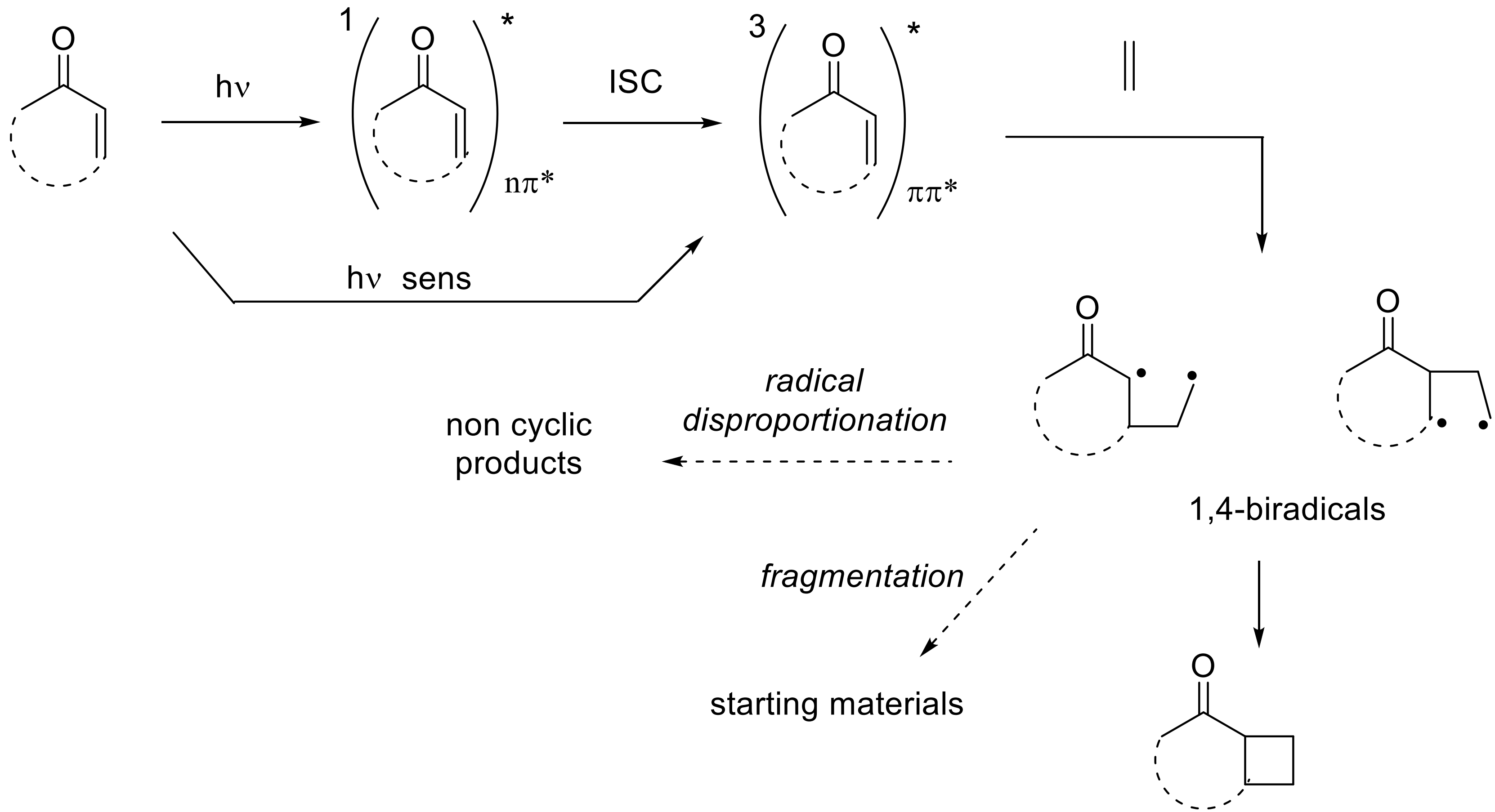


The transition $\mathbf{n \rightarrow \pi^*}$ is implicated

For enones : λ_{max} = 310-340 nm ($\varepsilon \sim 10^2$)

Inter-system crossing is efficient, leading to the $T_1(\boldsymbol{\pi\ \pi^*})$ excited state

Mechanism of the [2+2] photocycloaddition of enones



radical disproportionation

non cyclic products

1,4-biradicals

fragmentation

starting materials

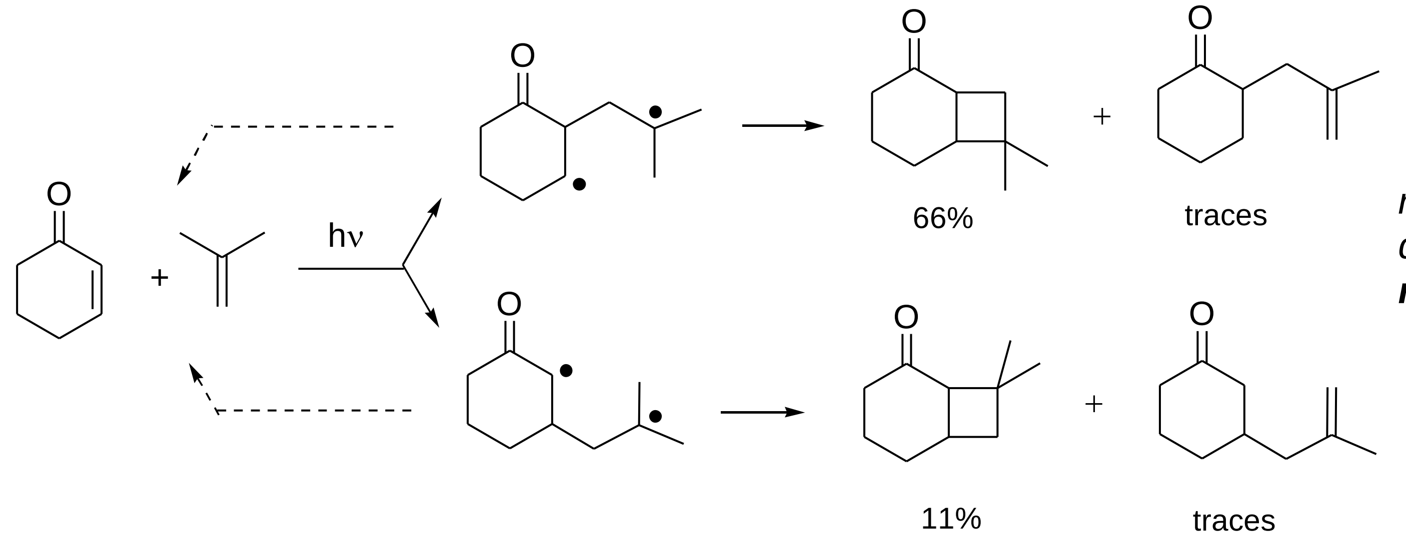
B. [2+2] PHOTOCYCLOADDTIONS BETWEEN ENONES AND ALKENES

In order to control selectivity, only the enone is photoactivated

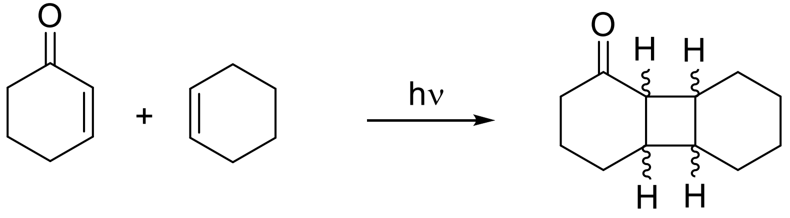
The alkene remains in its electronic ground state throughout the reaction process

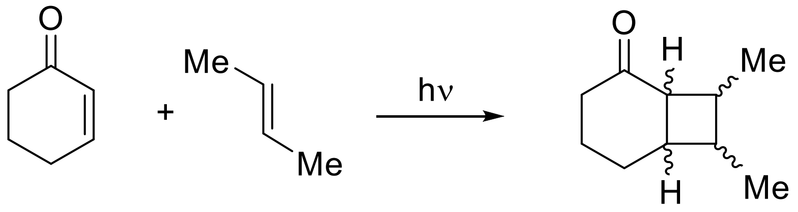
1. Intermolecular Reactions

Case study examples :



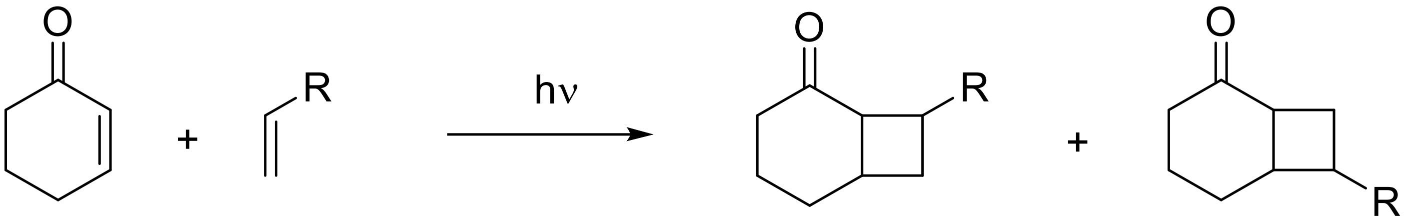
raises the question de ***regioselectivity***





raises the question of ***stereoselectivity***

Regioselectivity



H-H

head-to-head

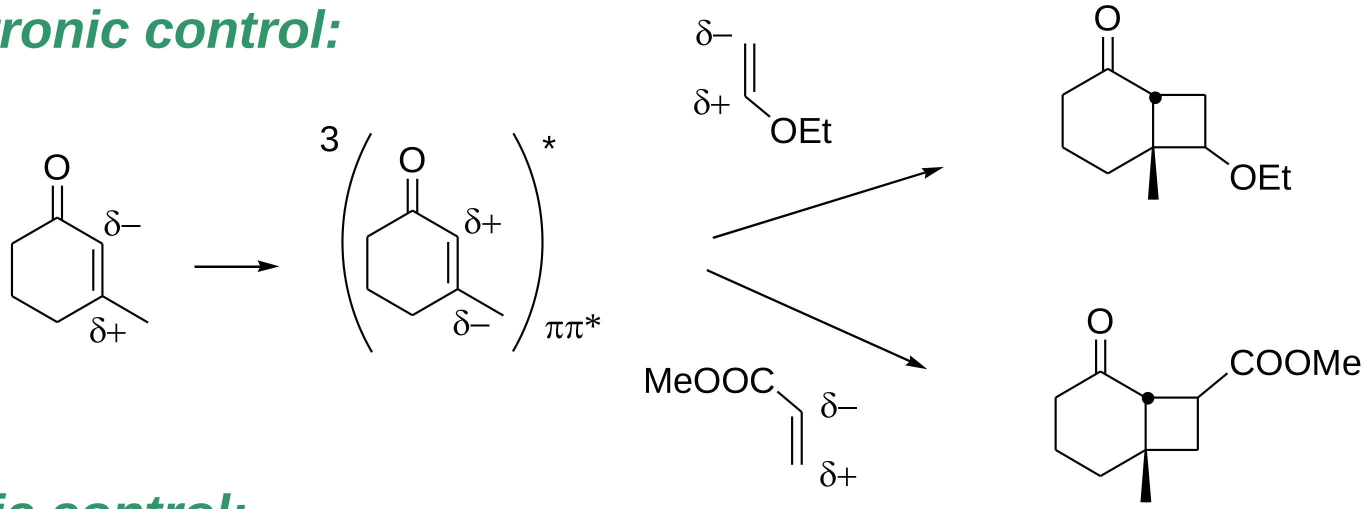
H-T

head-to-tail

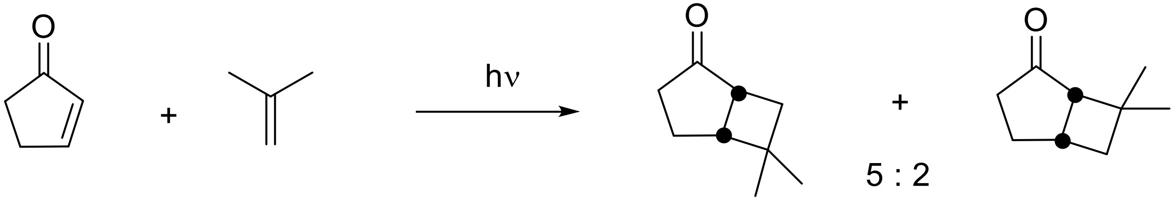
How can regioselectivity be controlled?

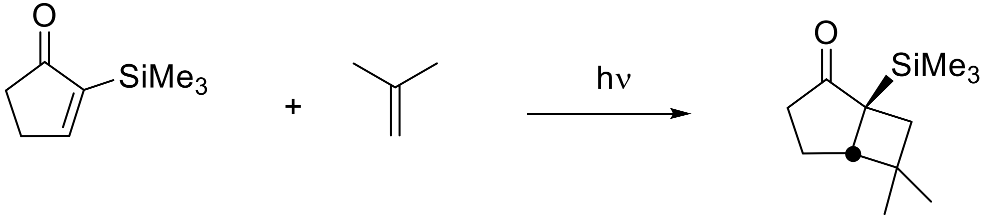
Regioselectivity

Electronic control:



Steric control:



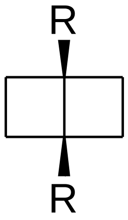


(only product)

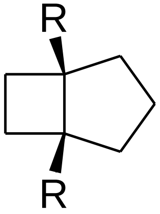
Stereoselectivity

Ring junction:

4:4 : *cis* exclusively



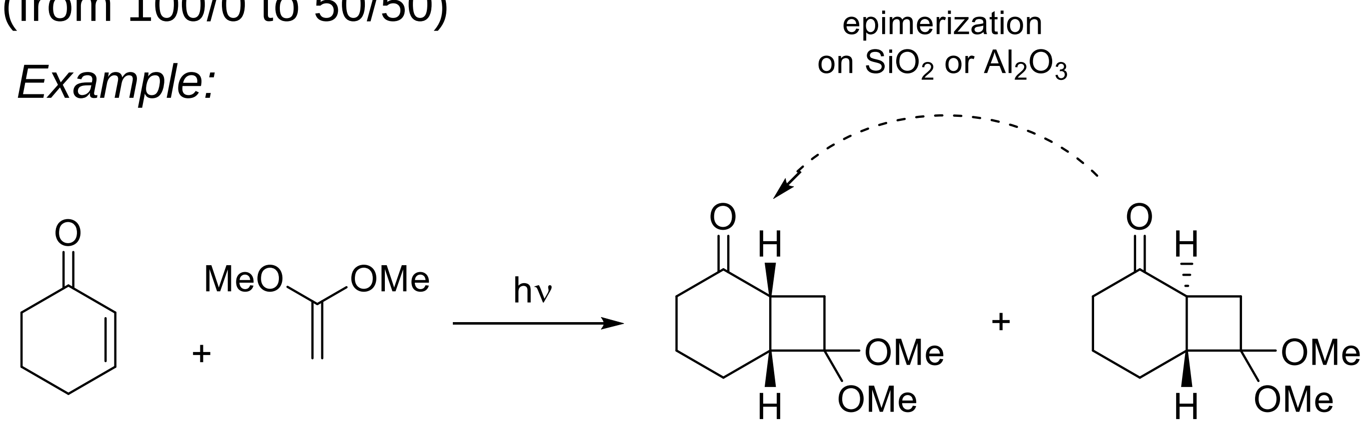
4:5 : *cis* exclusively



4:6 : *cis/trans* variable

(from 100/0 to 50/50)

Example:

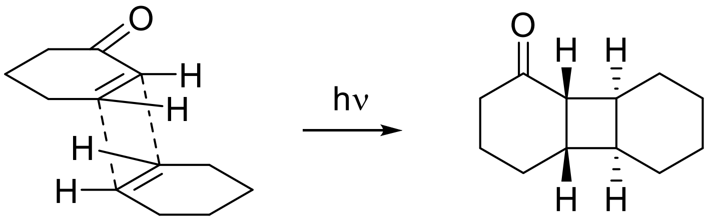


cis
major

trans
minor

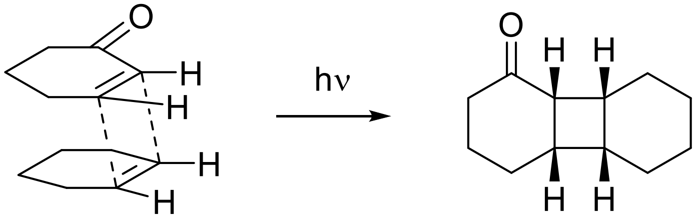
Stereoselectivity

endo / exo approach selectivity:



exo approch

cis-anti-cis

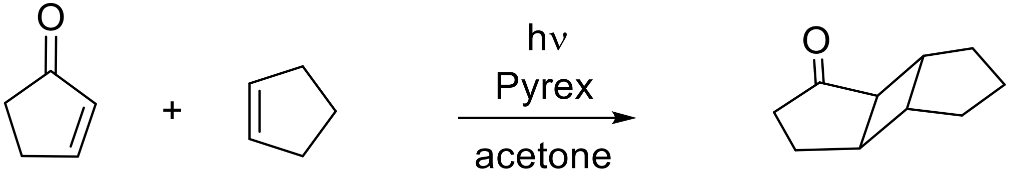


endo approch

cis-syn-cis

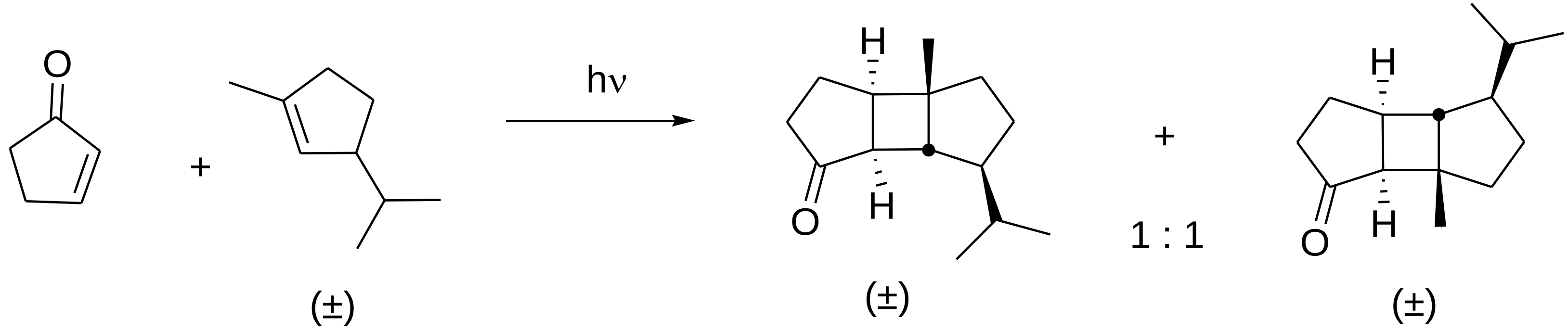
sterically favored

Example:



cis-anti-cis
unique stereoisomer

Example:



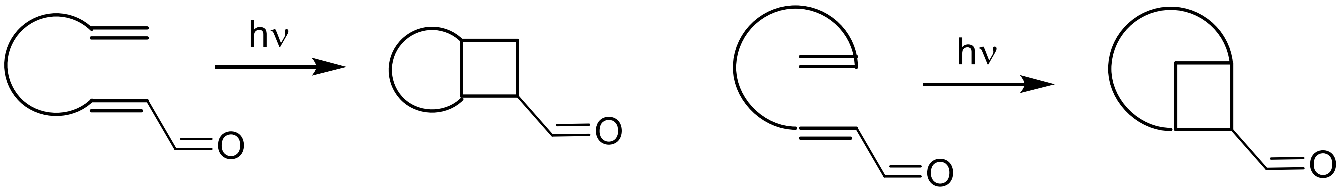
No regioselectivity H-H : H-T

Complete *cis-anti-cis* stereoselectivity
4:5 ring junction and *exo*/*endo*

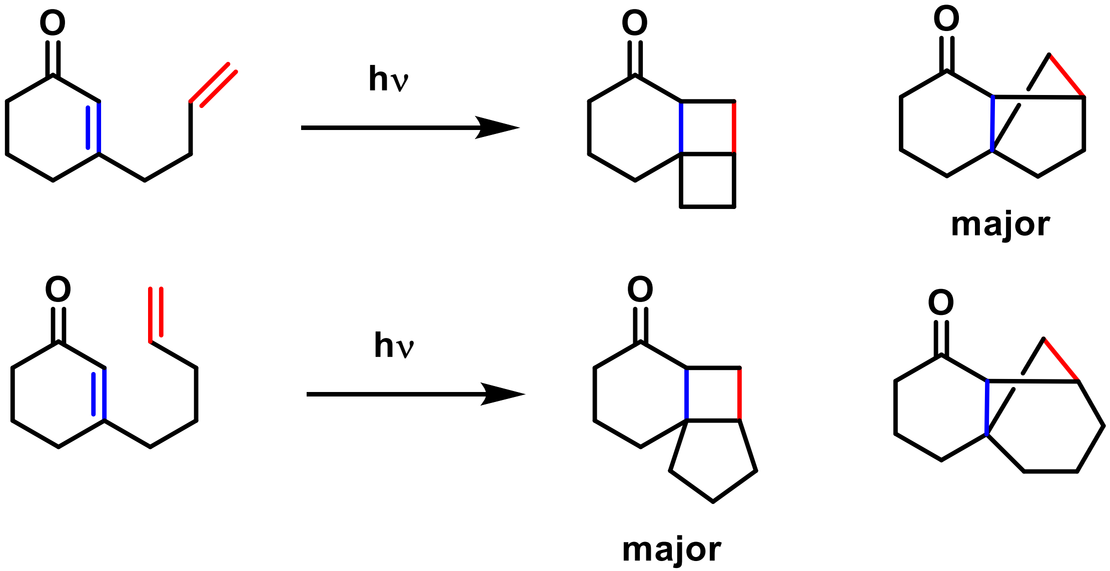
Complete *exo* stereoselectivity
steric bulk of the *iso*-propyl substituent

2. Intramolecular Reactions

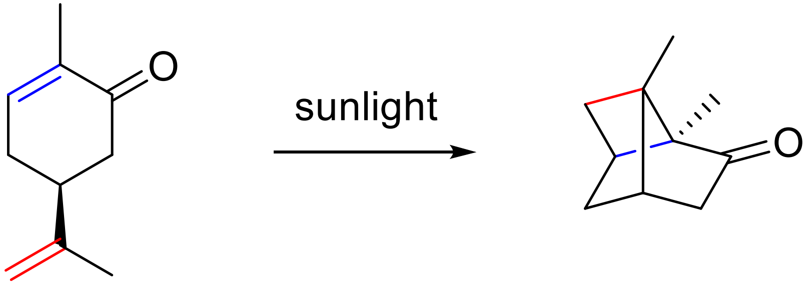
two
possibilites :



Rule of fives:

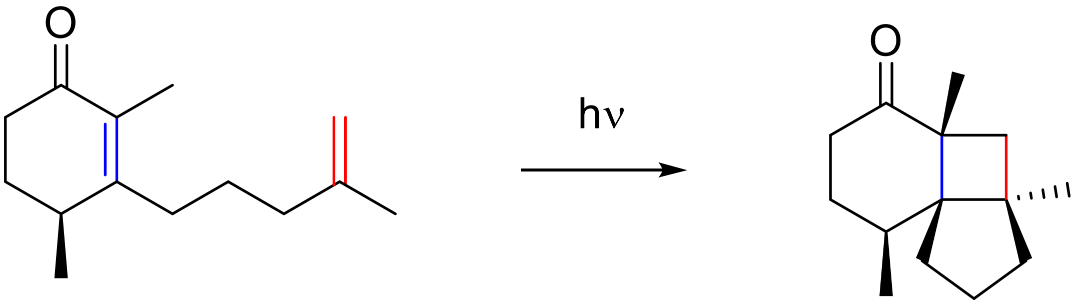


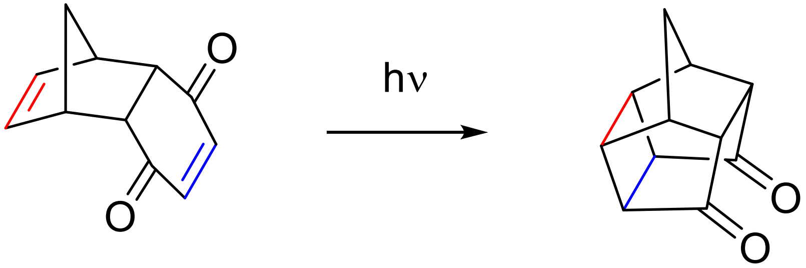
Examples:



carvone

photocarvone
(Ciamician, 1908)

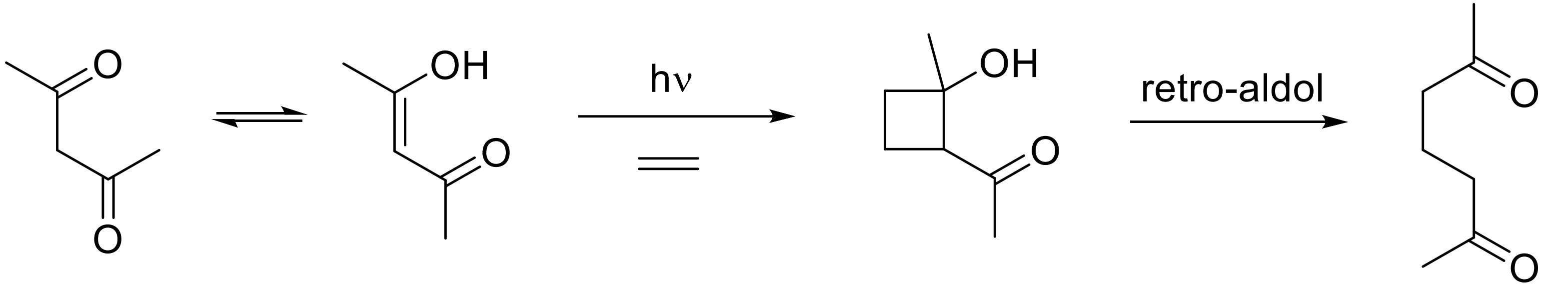




3. Reactions using β-dicarbonyls

De Mayo reaction

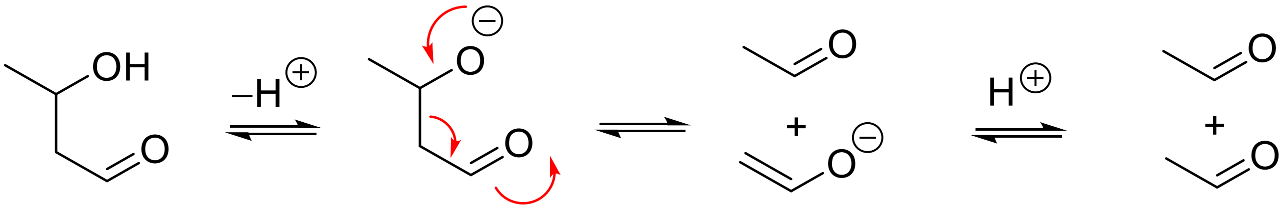
The enol form of a β-dicarbonyl is a β-hydroxy-enone



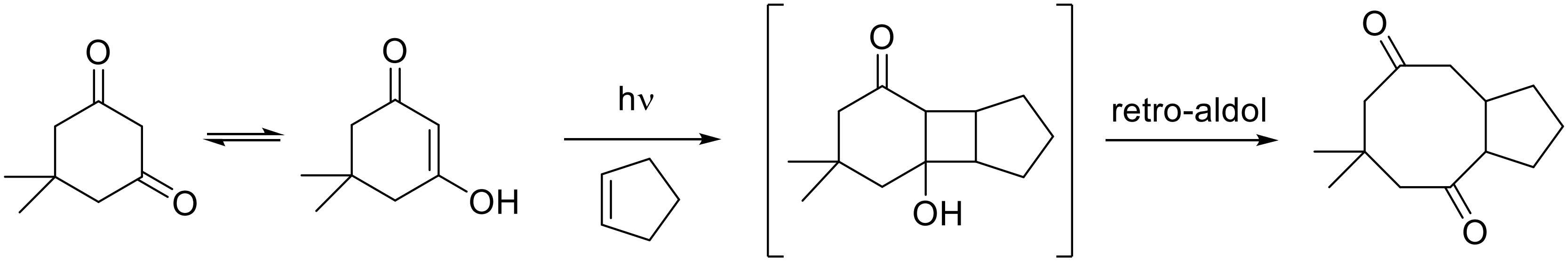
1,3-dicarbonyl

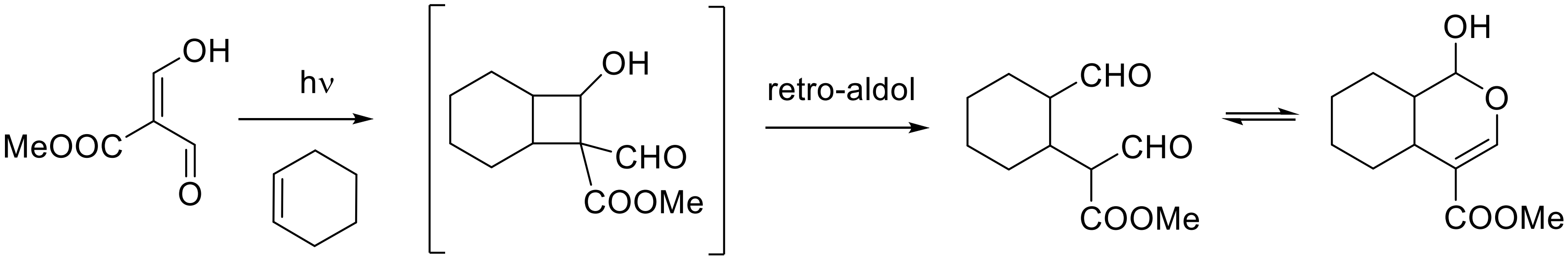
2-acylcyclobutanol
(aldol)

1,5-dicarbonyl



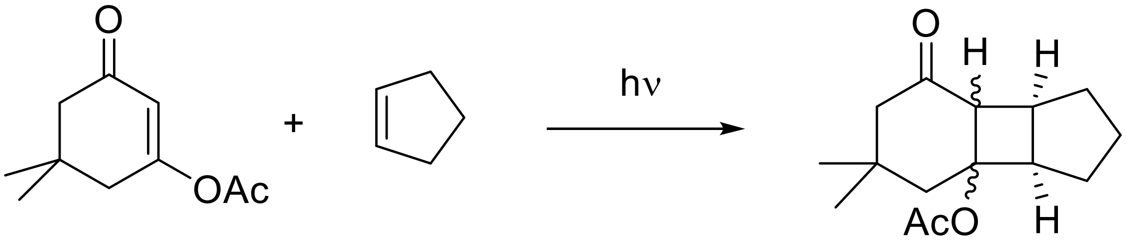
Examples:

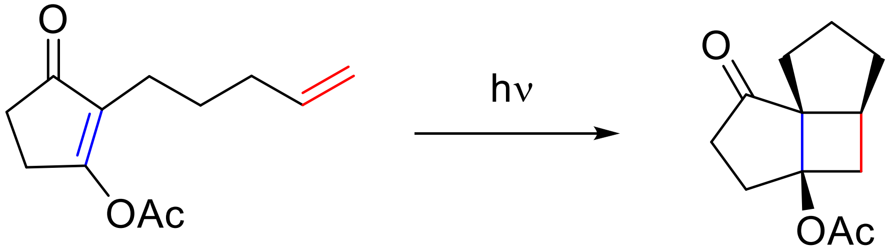

O
O
O
OH
hν
O
OH
retro-aldol
O
O


OH
MeOOC
O
hν
OH
CHO
COOMe
retro-aldol
CHO
CHO
COOMe
OH
O
COOMe

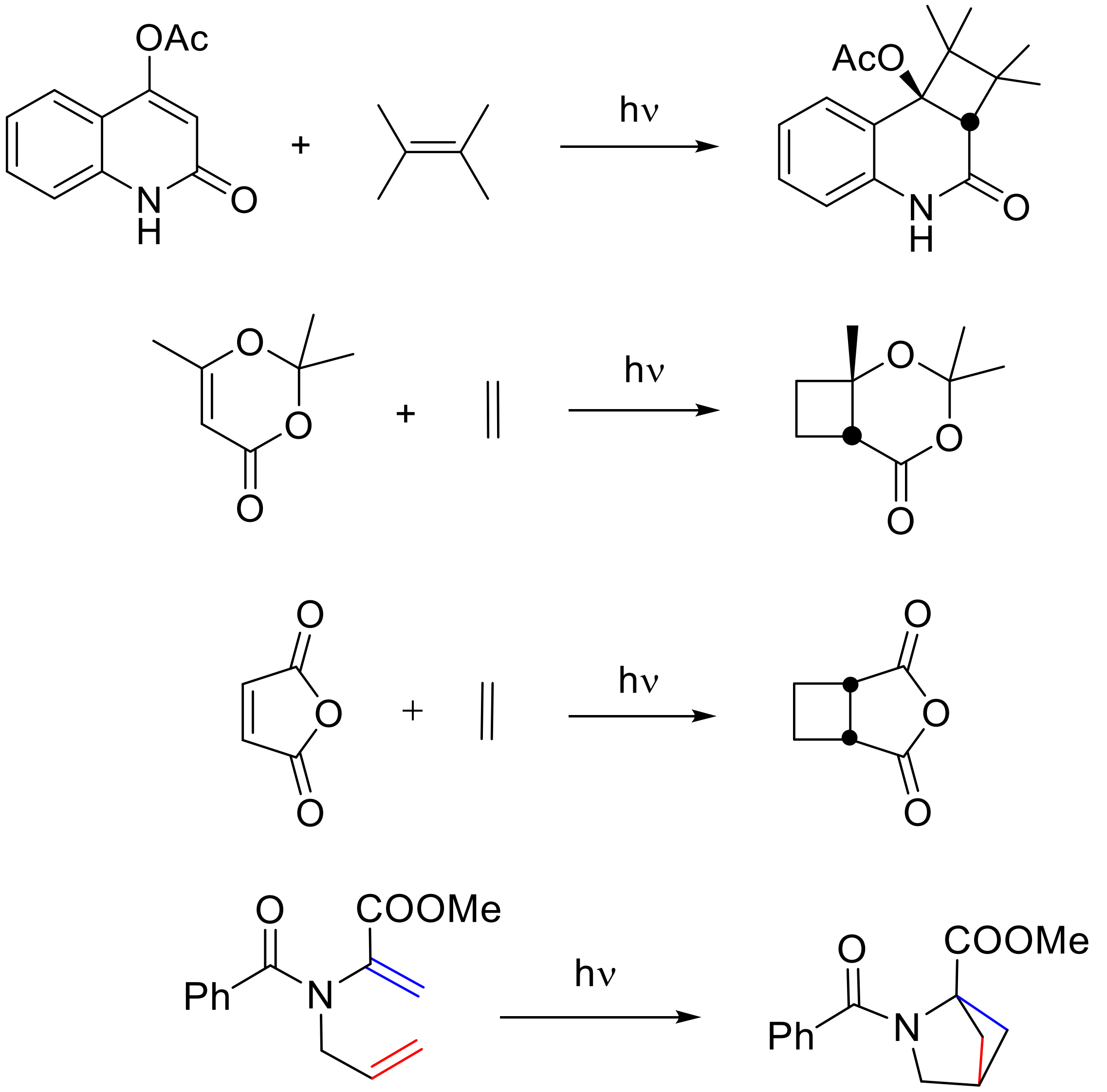
When the aldol is protected, no retro-aldol reaction occurs

Examples:





4. Reactions using other enone systems

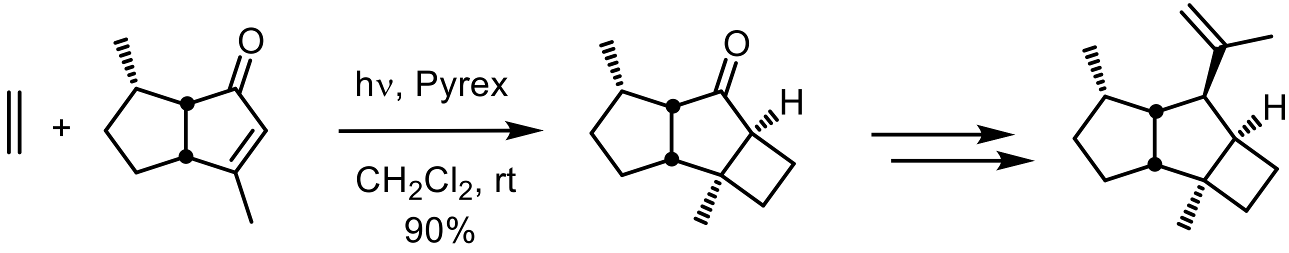


C. EXAMPLES OF APPLICATIONS IN ORGANIC SYNTHESIS

• *Synthesis of (±)-kelsoene*

natural product from a marine sponge

Synthesis **2001**, 2138

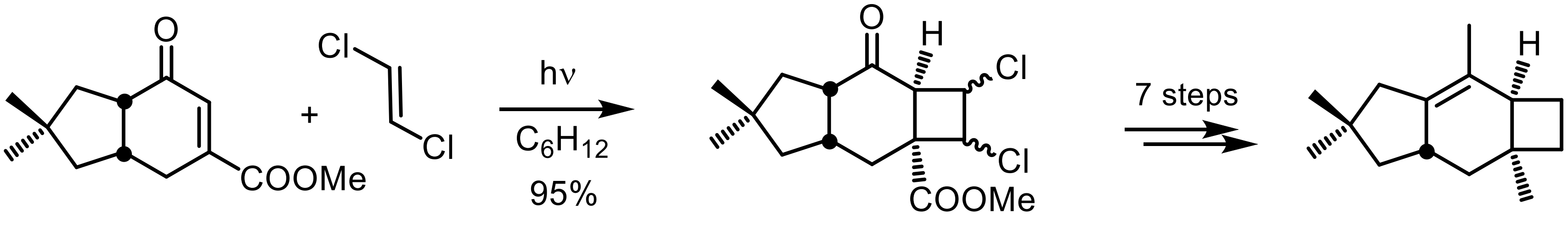


(±)-kelsoene

• *Synthesis of (±)-sterpurene*

sesquiterpene metabolite from the fungus which causes silver leaf disease

Tetrahedron Lett. **2002**, *43*, 703

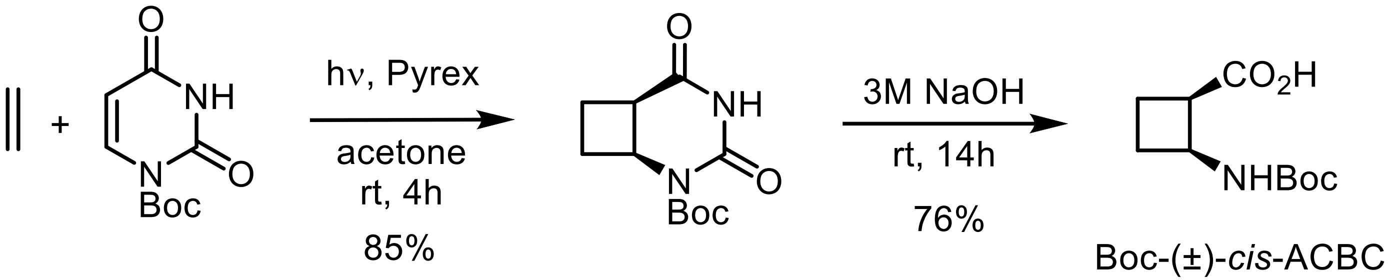


(±)-sterpurene

- ***Synthesis of a cyclobutane β-aminoacid***

Amino Acids **2011**, *41*, 587

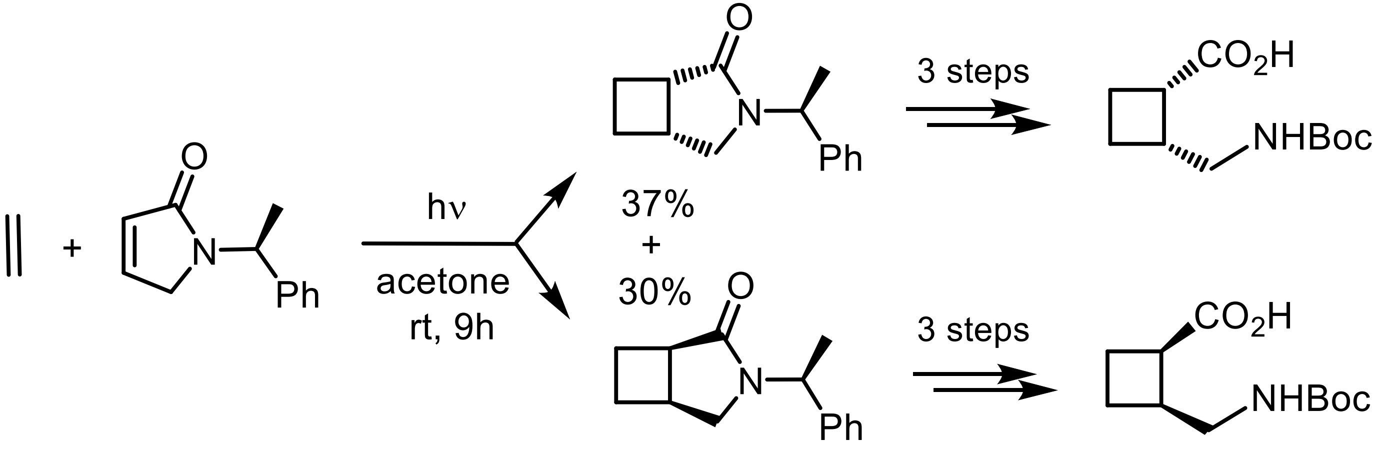
building block for helical peptide foldamers



- ***Synthesis of a cyclobutane γ-aminoacid***

Tetrahedron **2013**, *69*, 3571

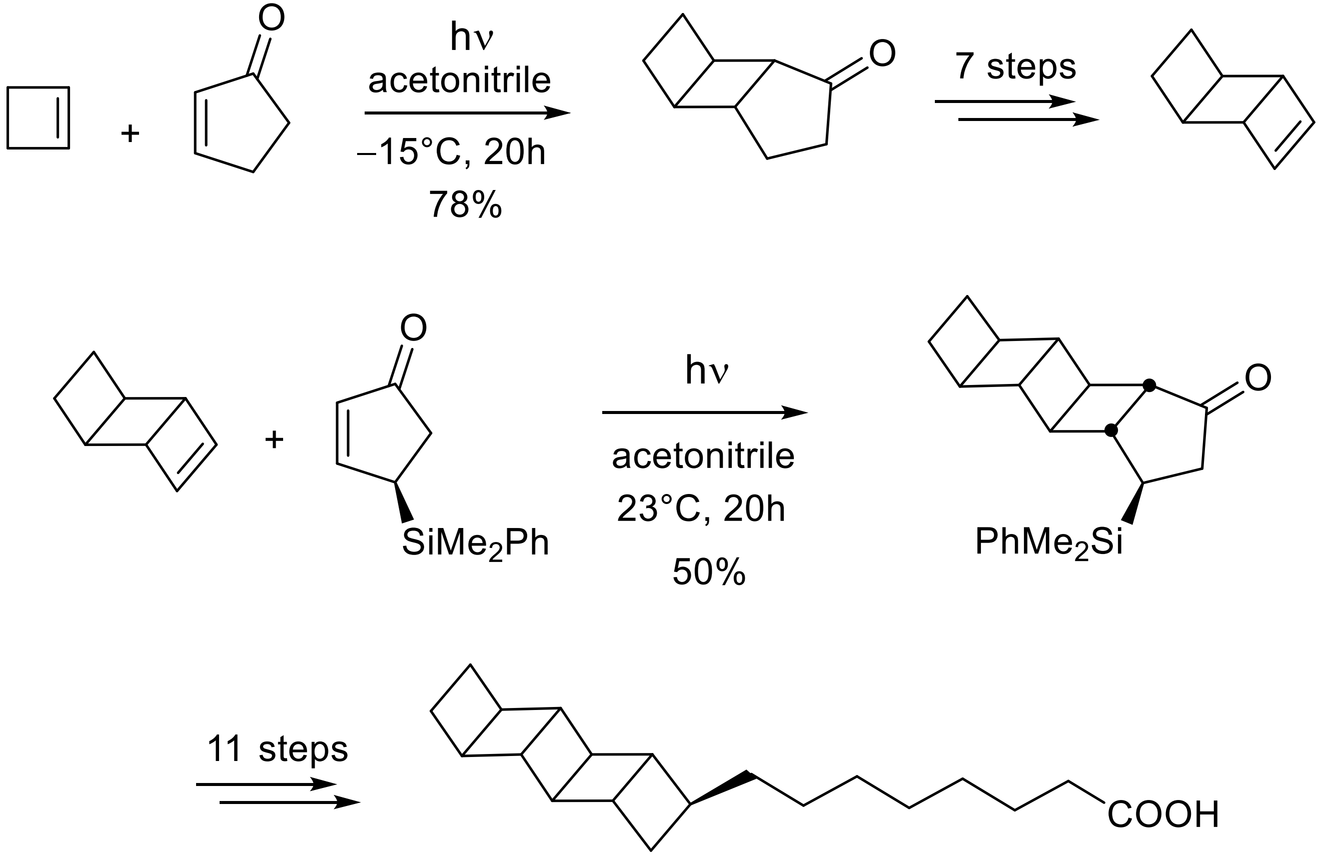
analog of the neurotransmitter GABA



• *Synthesis of (+)-pentacycloanammoxic acid*

J. Am. Chem. Soc. **2006**, *128*, 3118

an unusual fatty acid found in the anaerobic microbe Candidatus Brocadia anammoxidans

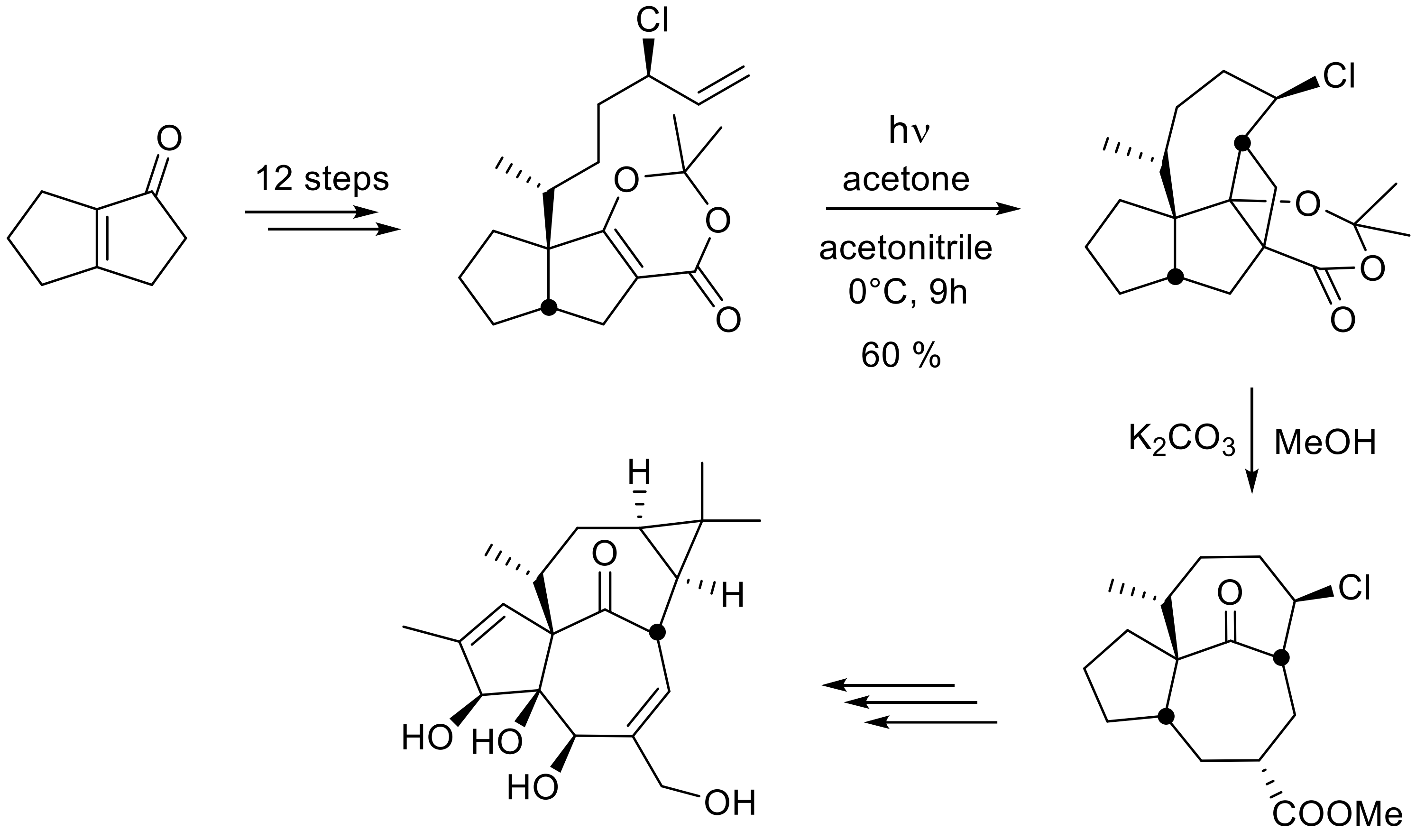


(+)-pentacycloanammoxic acid

- ***Synthesis of (±)-ingenol***

J. Am. Chem. Soc. **2002**, *124*, 9726

diterpene found in milkweed; its mebutate ester is used as a drug to treat actinic keratosis

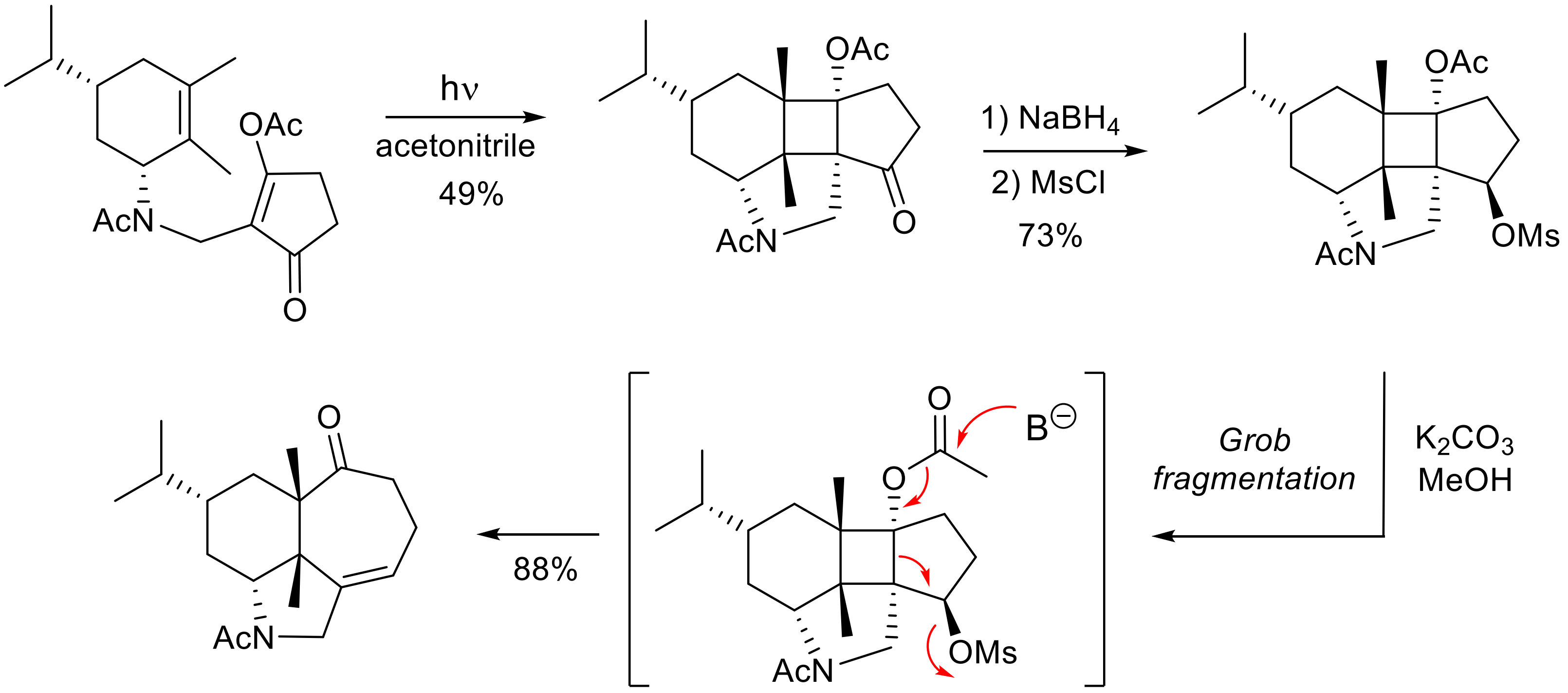


(±)-ingenol

- ***Synthesis of the tricyclic core of Calyciphylline alkaloids***

Org. Lett. **2011**, *13*, 1812

Calyciphylline-type *Daphniphyllum* alkaloids share a common [5-6-7] tricyclic core



Calyciphylline alkaloid
[5-6-7] tricyclic core

Photochemistry of Carbonyls

Introduction

1. Norrish-I: α-Cleavage reactions

1.1 Hydrogen transfer reactions

1.2 Ring expansion reactions

2. Norrish-II: Intramolecular γ-hydrogen abstraction

2.1 Fragmentation of acyclic ketones

2.2 Yang cyclization reactions

2.3 Photoenolisation

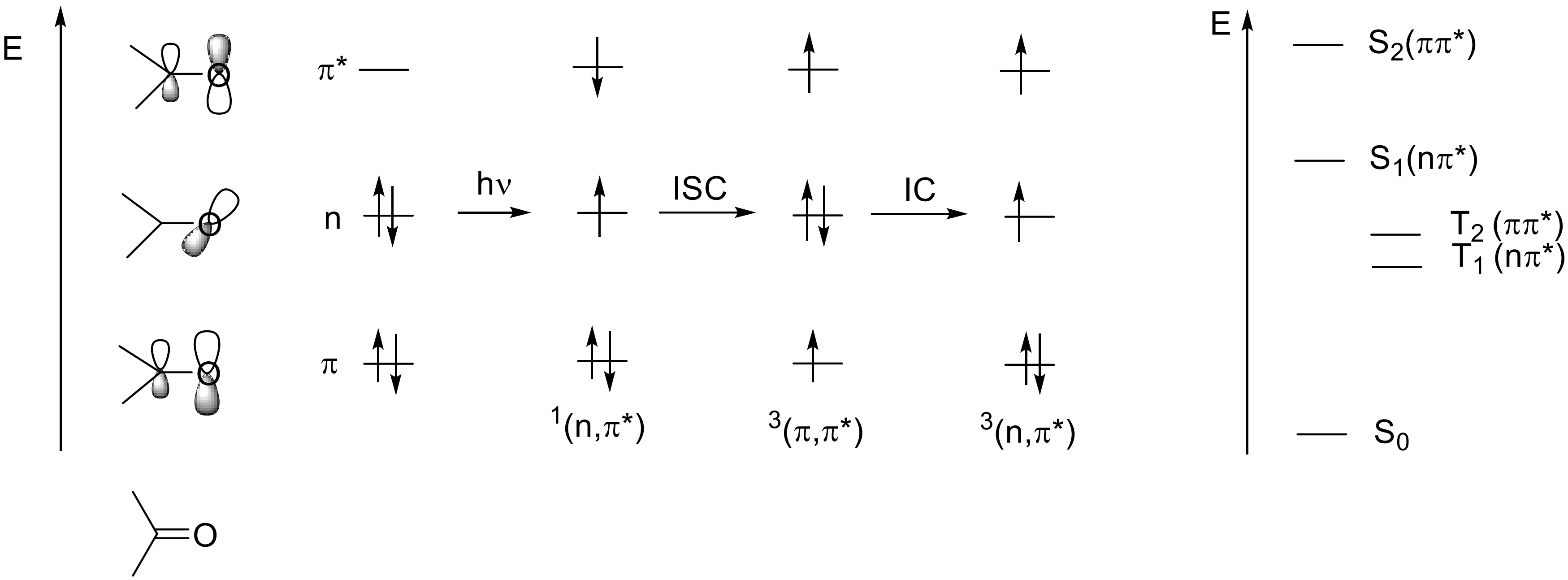
3. Reactions with alkenes: the Paternò-Büchi reaction

3.1 Intermolecular reactions

3.2 Intramolecular reactions

Introduction

Photoactivation :



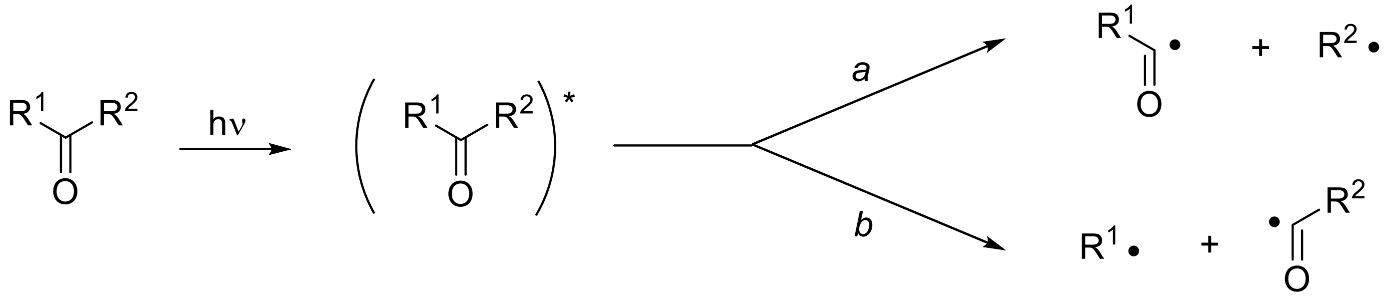
The transition **n → π*** plays a key role in carbonyl photochemistry

saturated aldehydes and ketones: λ_{max} = 280-300 nm ; ε ~ 20

α,β-insaturated or aromatic aldehydes and ketones: λ_{max} = 300-350 nm ; ε ~ 100

1. Norrish-I: α-Cleavage Reactions

Primary photochemical process:



When $R^1 \neq R^2$, two paths *a* and *b*, are possible.
The preferred path involves cleavage of the weaker bond, and/or formation of the more stable alkyl radical

Remarks :

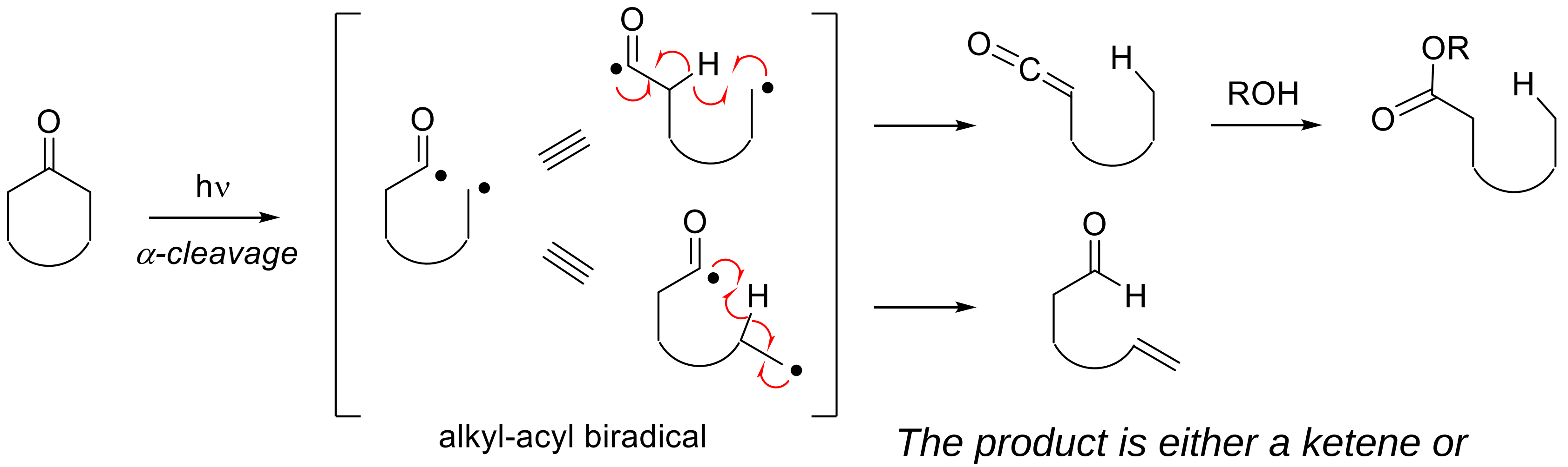
For aldehydes (R^1 = H), path *a* is always followed (formation of $H^\bullet$ disfavored)

α-Cleavage is rare for aromatics: $E(\lambda_{max}) < E(C\text{-}C)$

Most synthetically useful for cyclic aliphatic ketones

Most frequent evolution of radicals: recombination to give starting materal

1.1. Hydrogen Transfer Reactions

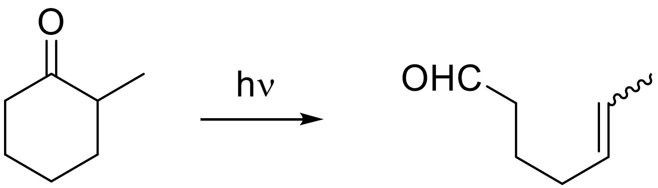


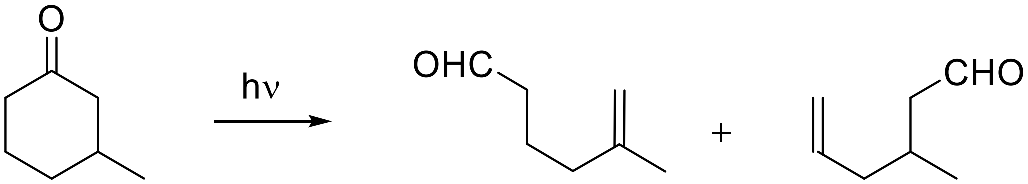
The product is either a ketene or an unsaturated aldehyde

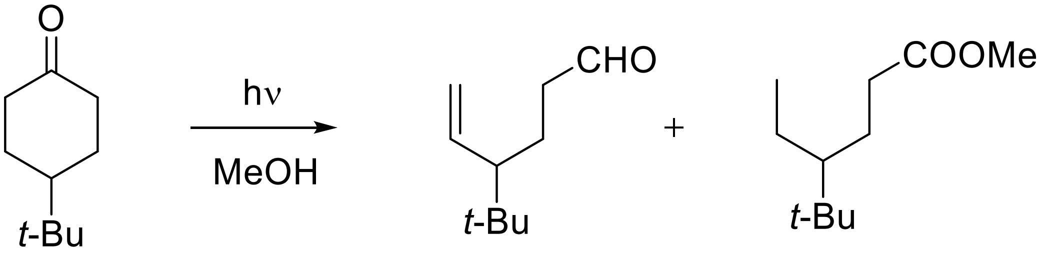
When a ketene is formed, it generally reacts with the (protic) solvent to give a carboxylic acid or ester.

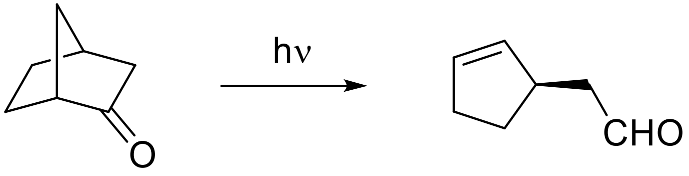
This **secondary process** is often observed for cyclopentanones and cyclohexanones (after the α-cleavage primary process).

Examples :

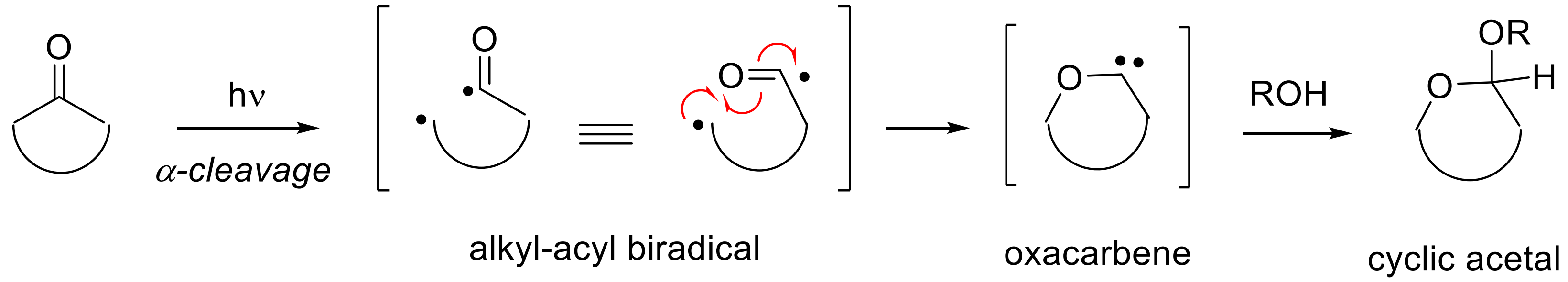








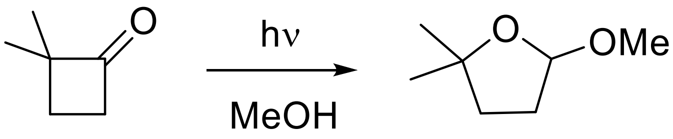
1.2. Ring Expansion Reactions

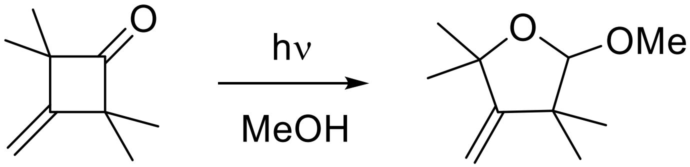


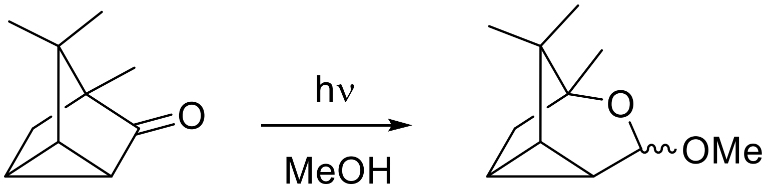
The oxacarbene generally reacts with the (protic) solvent to give a cyclic acetal.

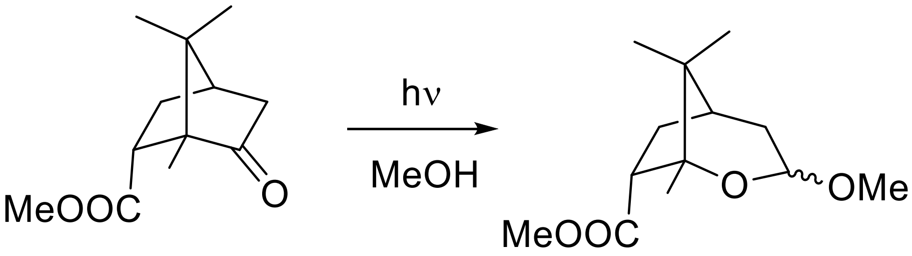
This **secondary process** is often observed for small-ring and/or strained bicyclic ketones.

Examples :


O
hν
MeOH
O
OMe


O
hν
MeOH
O
OMe


O
hν
MeOH
O
OMe

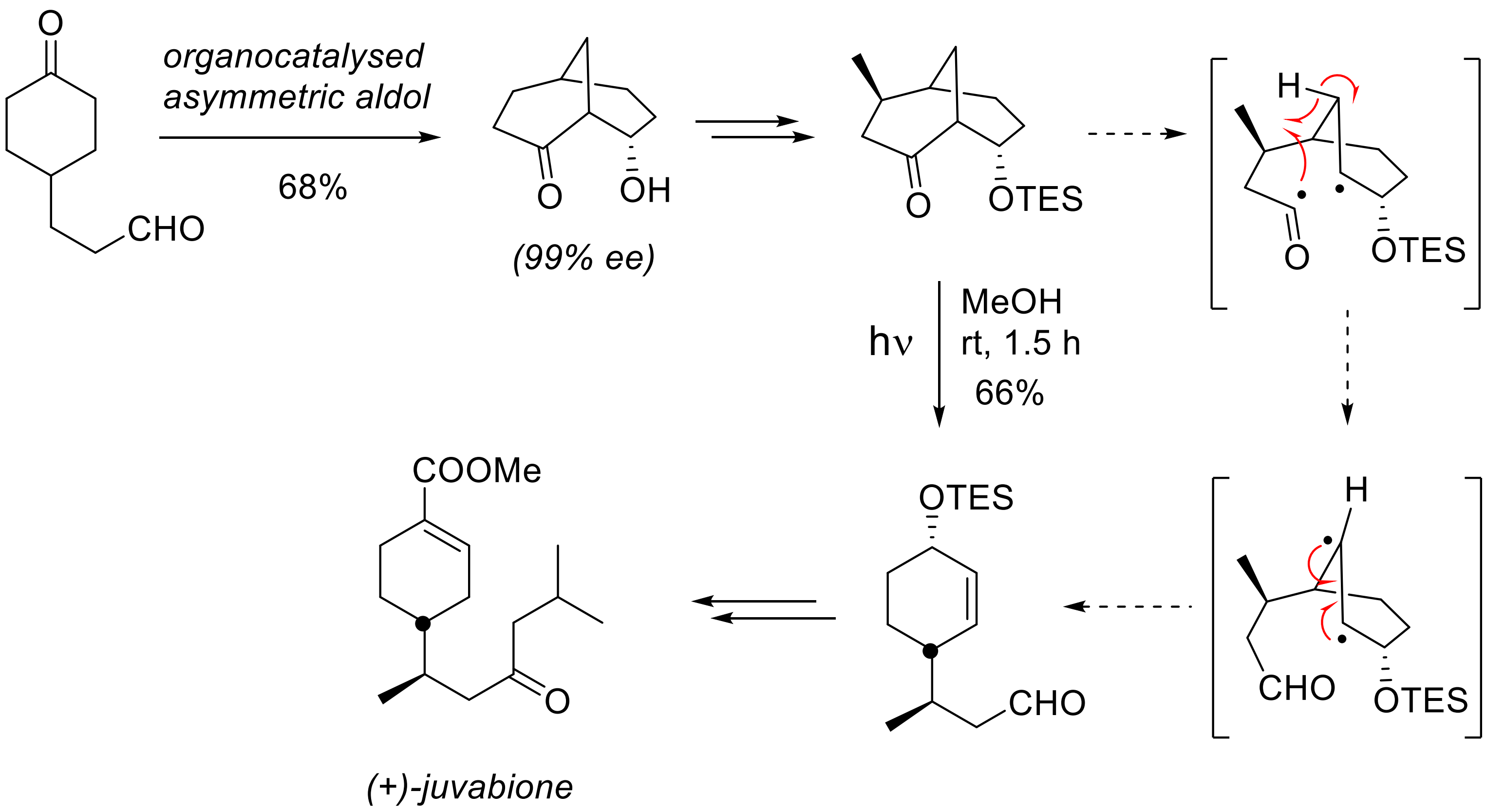

MeOOC
O
hν
MeOH
O
OMe
MeOOC

Examples in organic synthesis

- ***Synthesis of (+)-juvabione***

  Chem. Commun. **2007,** 1175

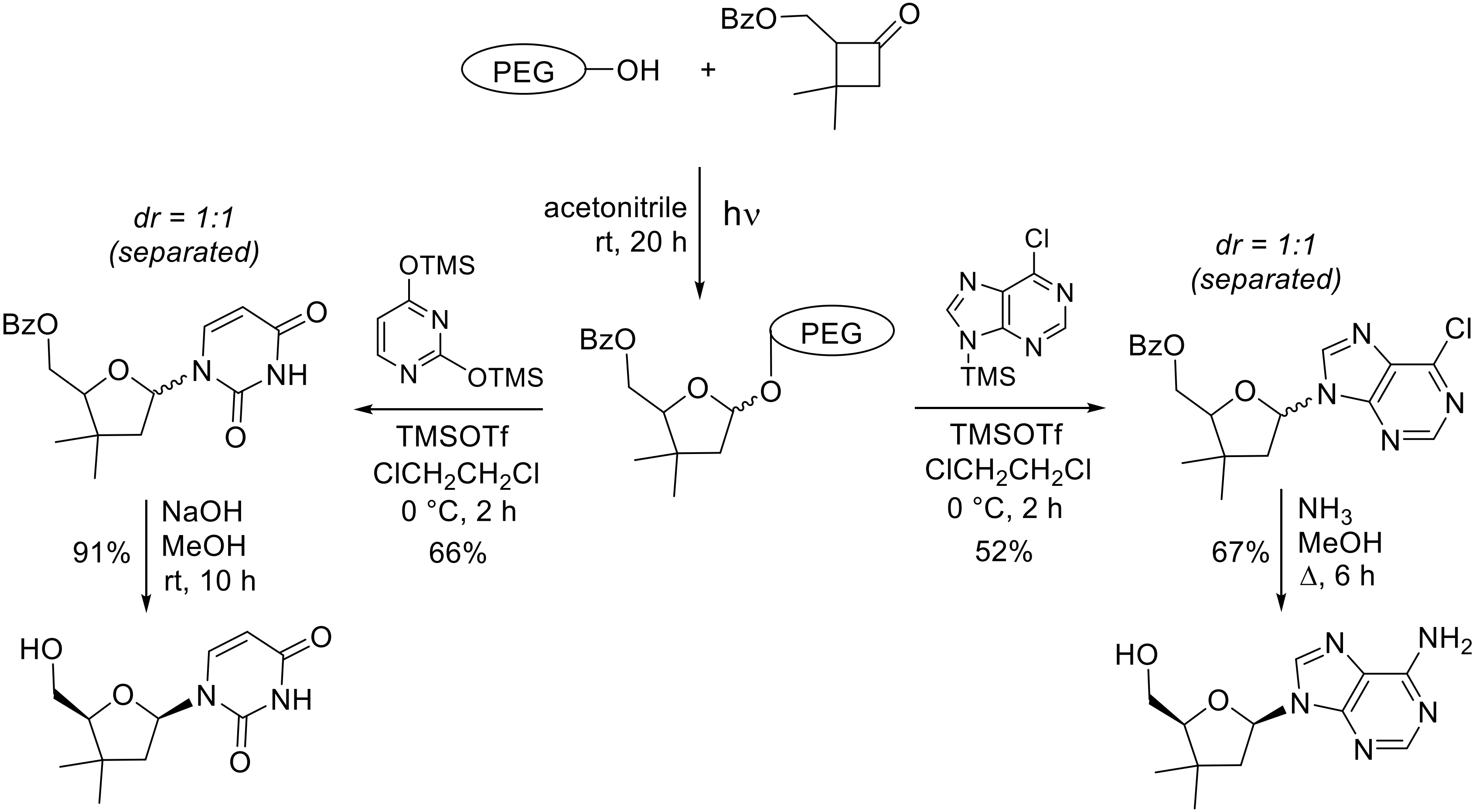
natural sesquiterpene exhibiting insect juvenile hormone activity



Examples in organic synthesis

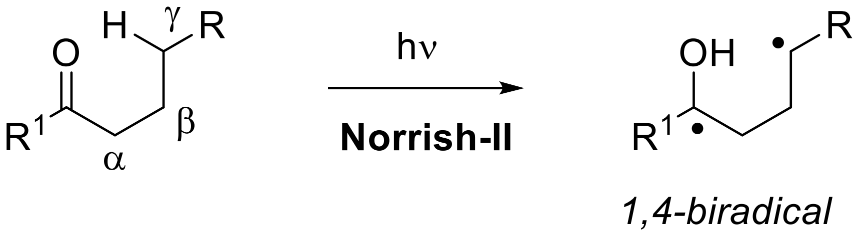
- ***Synthesis of analogues of nucleosides***

Org. Lett. **2002,** *4,* 4415



2. Norrish-II: γ-Hydrogen Abstraction

Primary photochemical process:



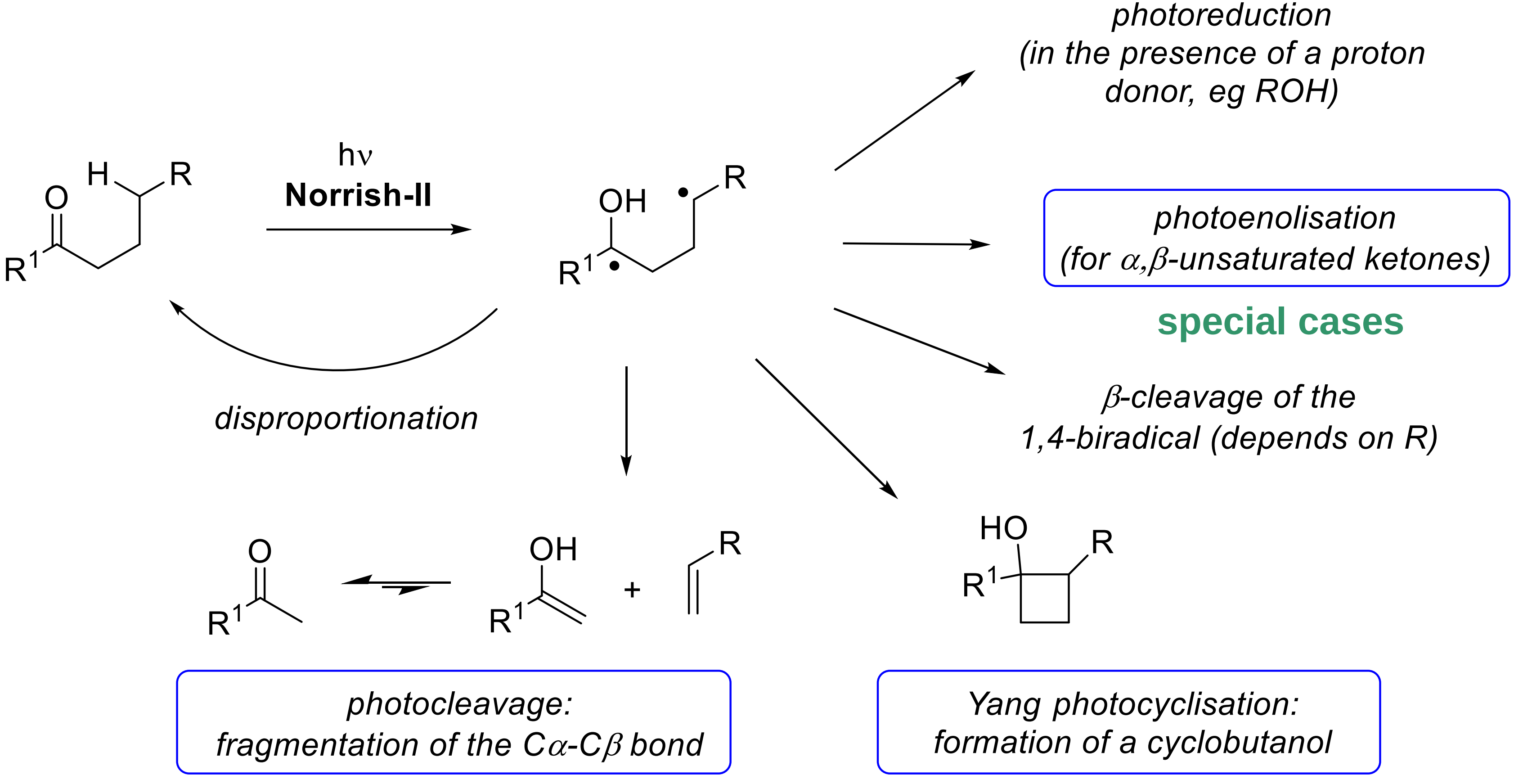
If a hydrogen atom at the γ-position is accessible, the Norrish-II process is favored for many ketone and aldehydes

Remarks:

Often observed for acyclic ketones (possible for cyclic ketones too)

Abstraction of β- or δ- hydrogens is much less common

Secondary processes:



photoreduction
(in the presence of a proton donor, eg ROH)

photoenolisation
(for α,β-unsaturated ketones)

β-cleavage of the 1,4-biradical (depends on R)

special cases

disproportionation

photocleavage:
fragmentation of the Cα-Cβ bond

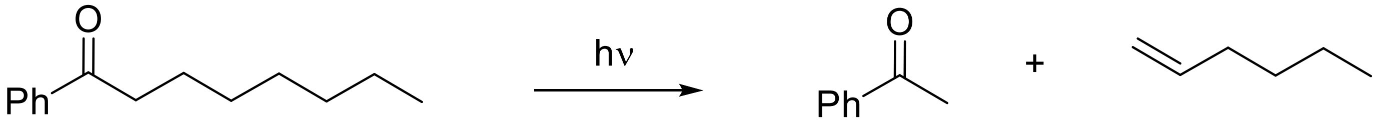
particularly for acyclic ketones

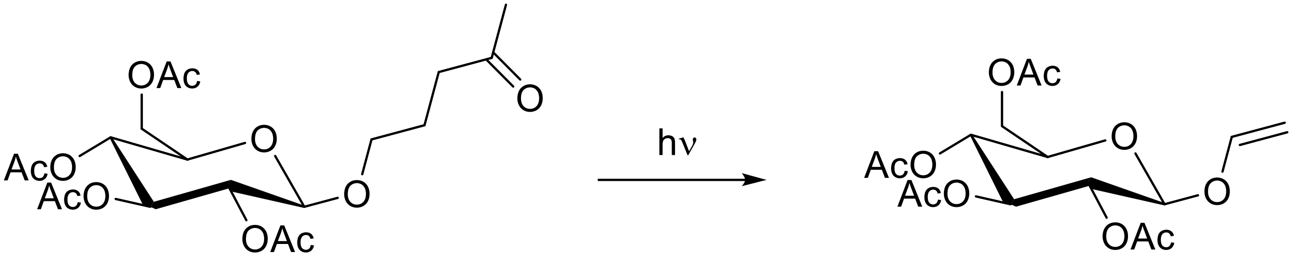
Yang photocyclisation:
formation of a cyclobutanol

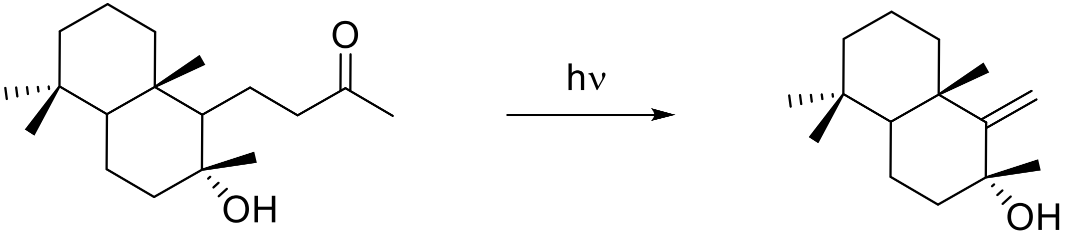
particularly for cyclic ketones

2.1. Fragmentation of Acyclic Ketones

Examples:



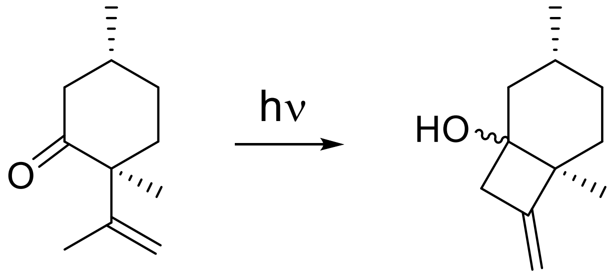


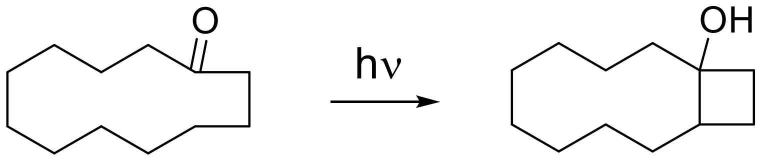


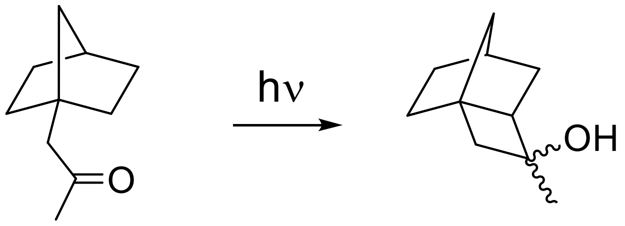
2.2. Yang Cyclisation Reactions

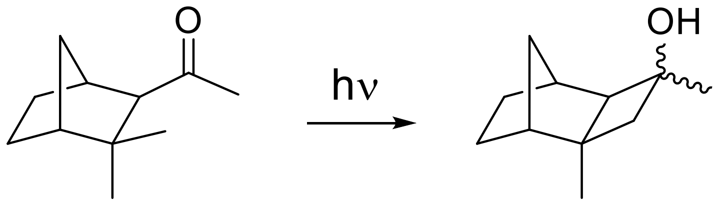
2.2.1 Formation of cyclobutanols

Examples:



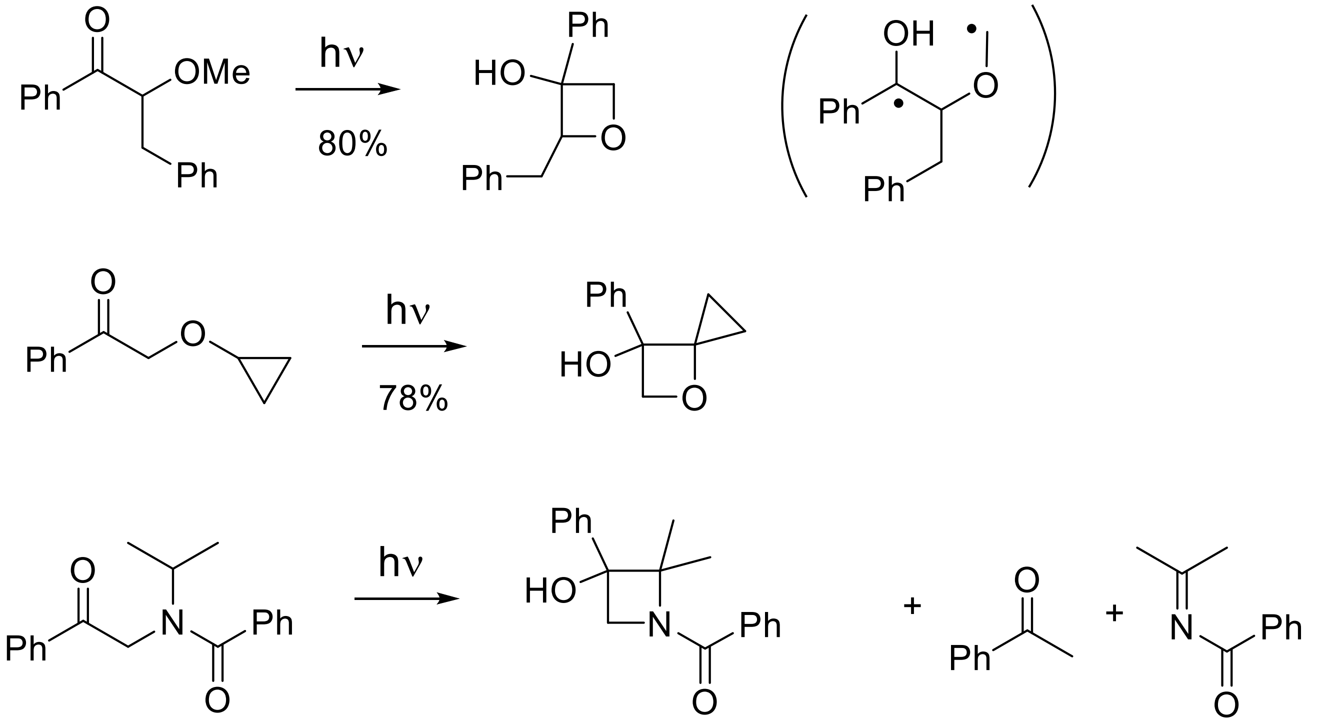






2.2.2 Formation of 4-membered ring heterocyclic alcohols

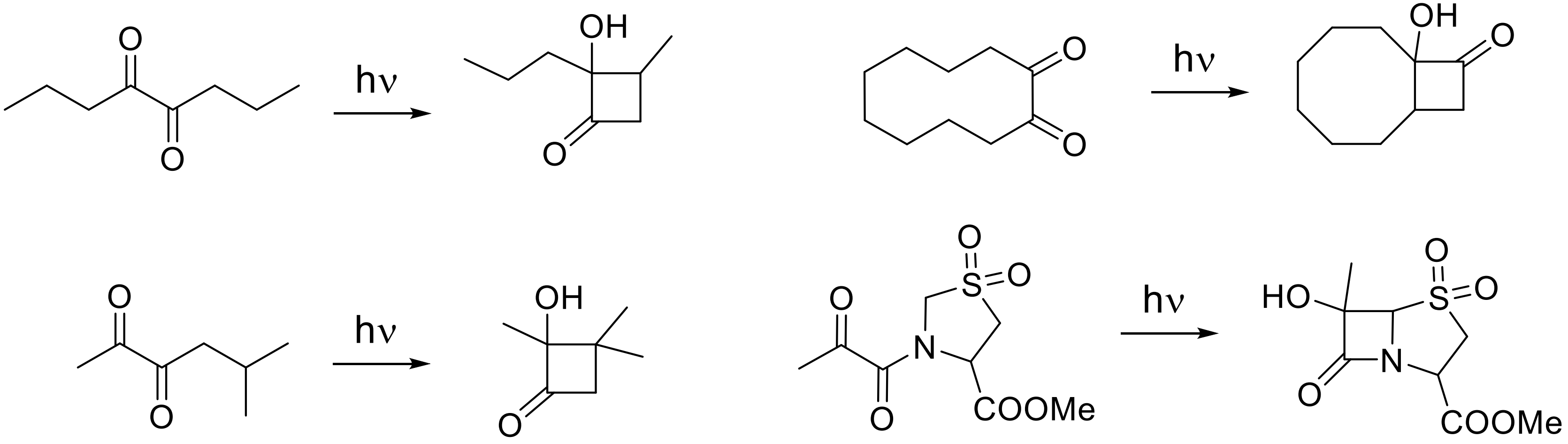
Examples:



2.2.3 Formation of 2-hydroxycyclobutanones

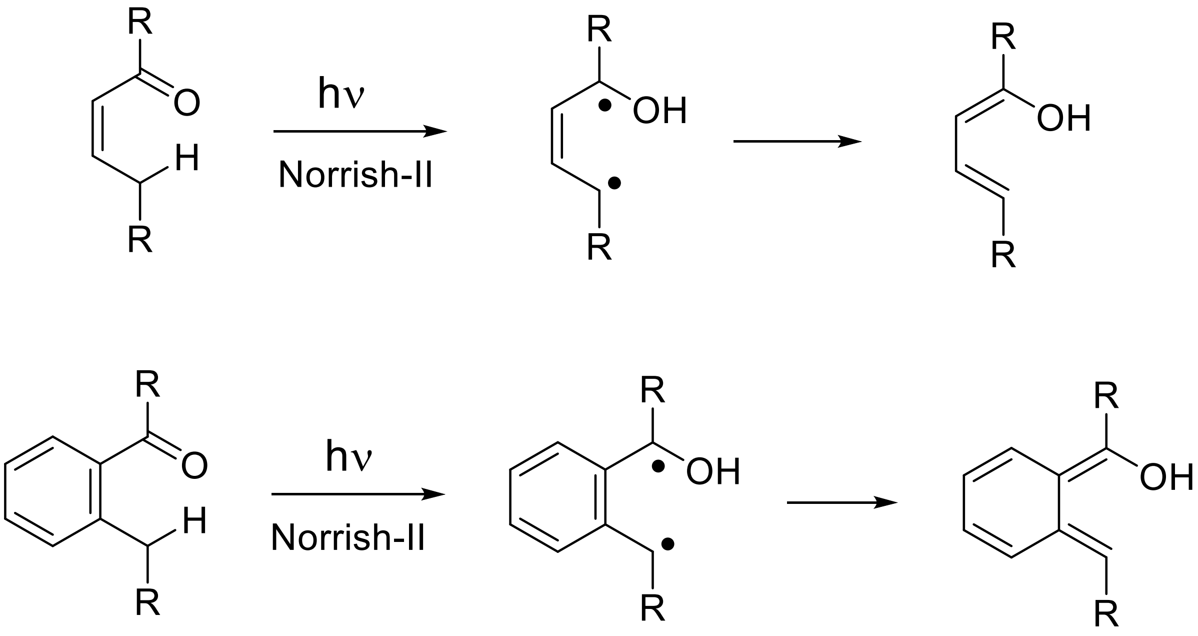
The substrates are α-diketones: λ_{max} ~ 400 nm

Examples:

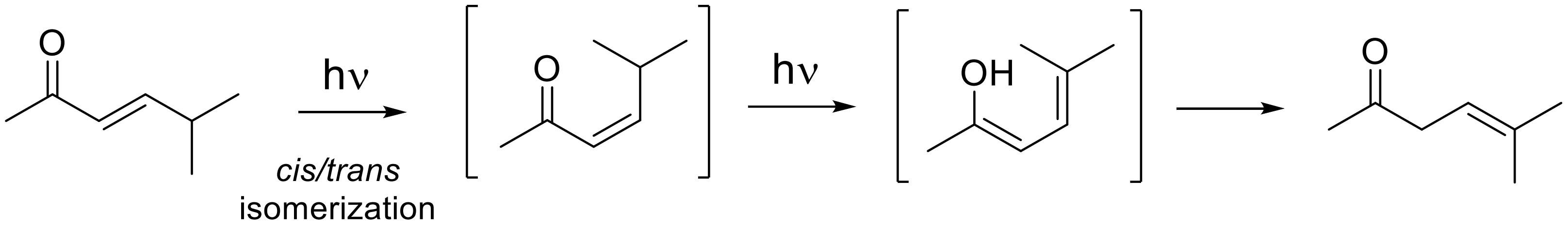


2.3. Photoenolisation

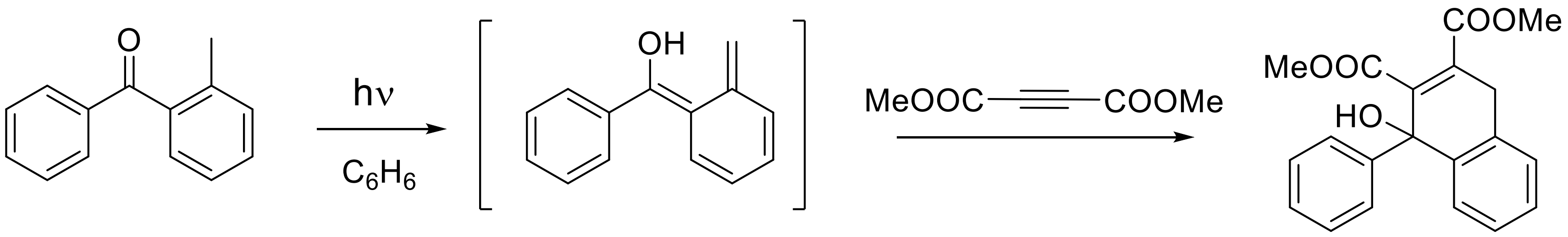
This **secondary process** can only occur with α,β-insaturated ketones or *ortho*-substituted aromatic ketones (following the Norrish-II primary process)



2.3.1 Photodeconjugation



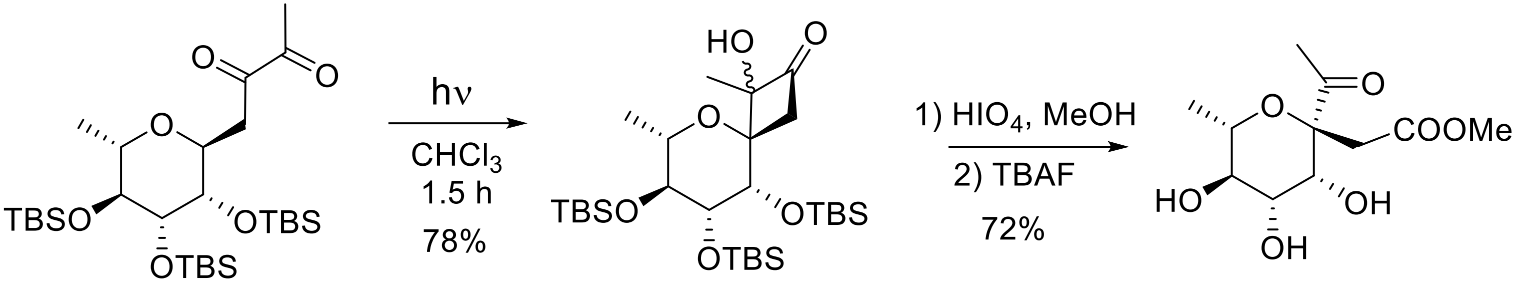
2.3.2 Tandem Norrish-II / 4+2 Cycloaddition



Examples in organic synthesis

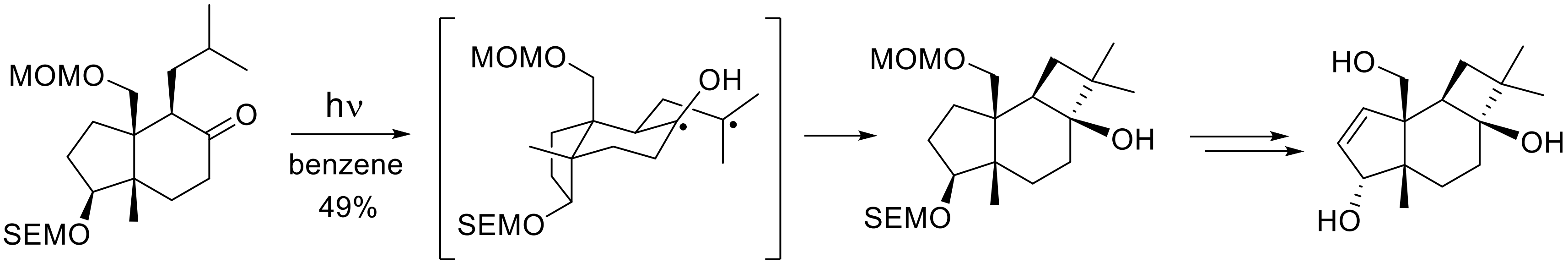
- ***Novel C-ketoside derivative*** *sugar-fused γ-keto ester building block*

J. Org. Chem. **2008**, *73*, 3384



- ***Synthesis of (–)-punctaporonin A*** *an antibiotic metabolite from the dung fungus Poronia punctata*

J. Am Chem. Soc. **1987,** *109*, 3017



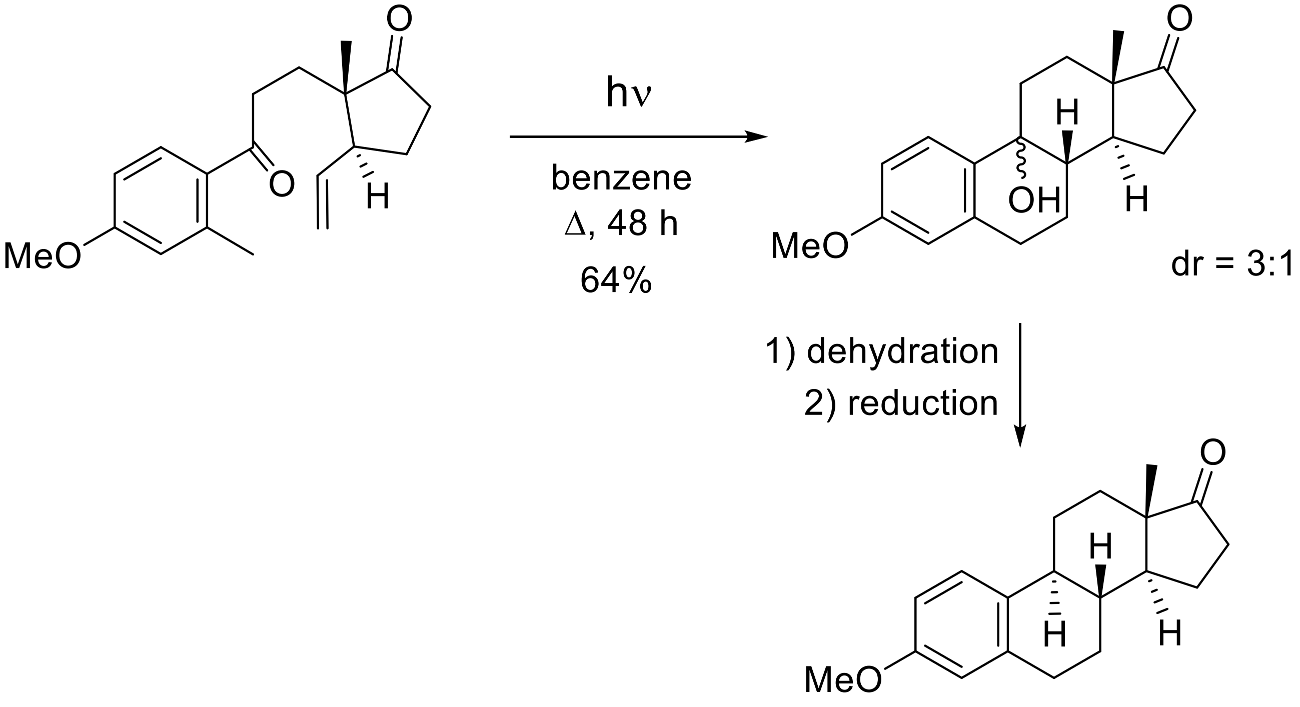
(–)-punctaporonin A

Examples in organic synthesis

- ***Synthesis of estrone methyl ether***

Ann. Chem. **1981,** 2335

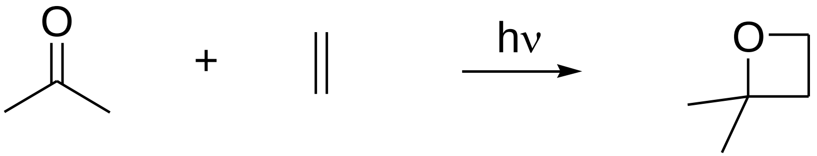
synthetic estrogen, precursor of mestranol (oral contraceptive)



estrone methyl ether

3. Reactions With Alkenes:
The Paternò-Büchi Reaction

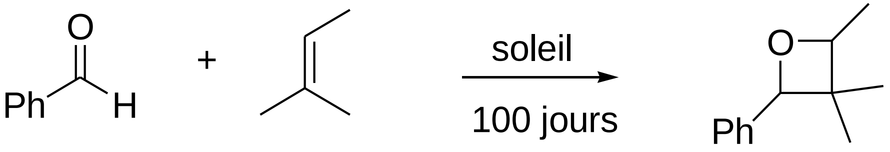
Introduction:



2+2 Photocycloaddition to provide an oxetane

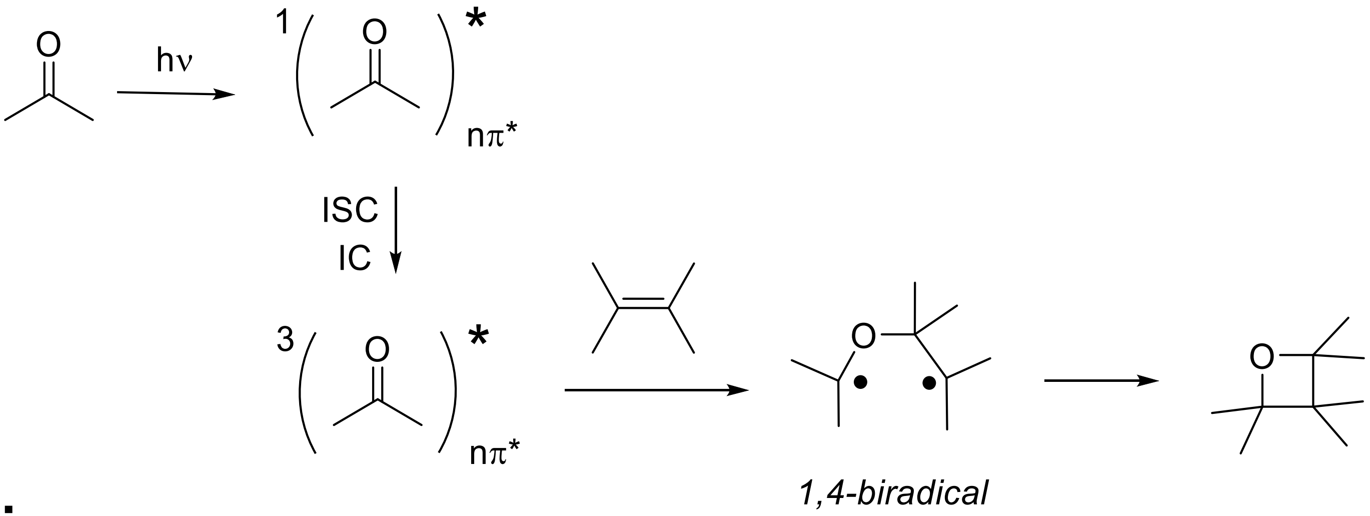
Historically:

- 1st exemple described by Paternò & Chieffi (1909)



- Important developments by Büchi (1950s)

Mechanism:



Remarks:

E ^{3}(n→π*) C=O < E ^{3}(π→π*) C=C
otherwise, energy transfer can be observed (photosensitization of the alkene)

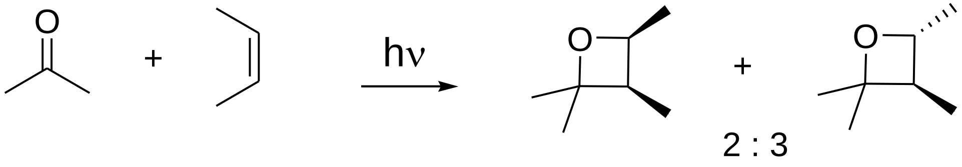
Non-concerted reaction: the first step is the attack of the electrophilic oxygen on the more electron-rich center of the alkene, to generate a 1,4-biradical intermediate → regioselectivity depends also on the 1,4-biradical stability
→ stereosélectivity is variable

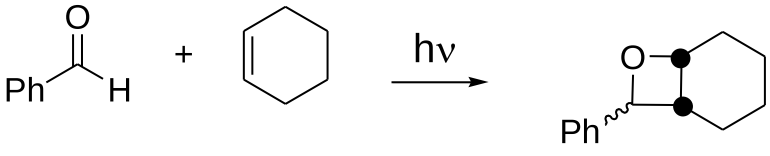
The alkene reagent can be used in excess (it is not photoactivated)

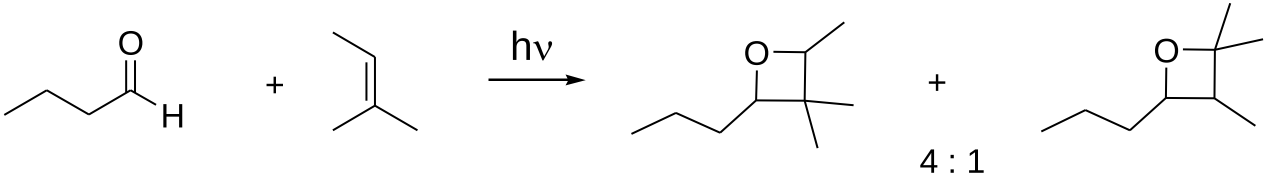
3.1. Intermolecular Reactions

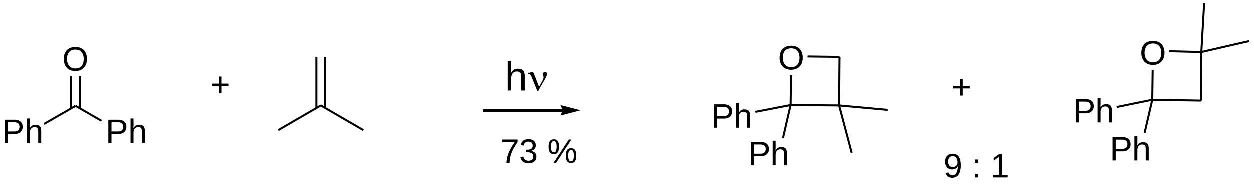
3.1.1 Reactions with simple alkenes

Examples:



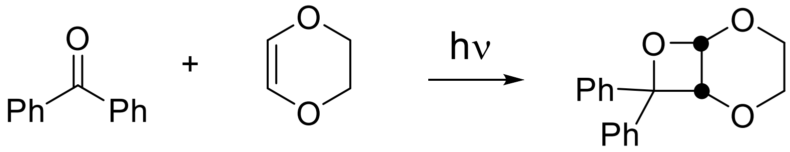


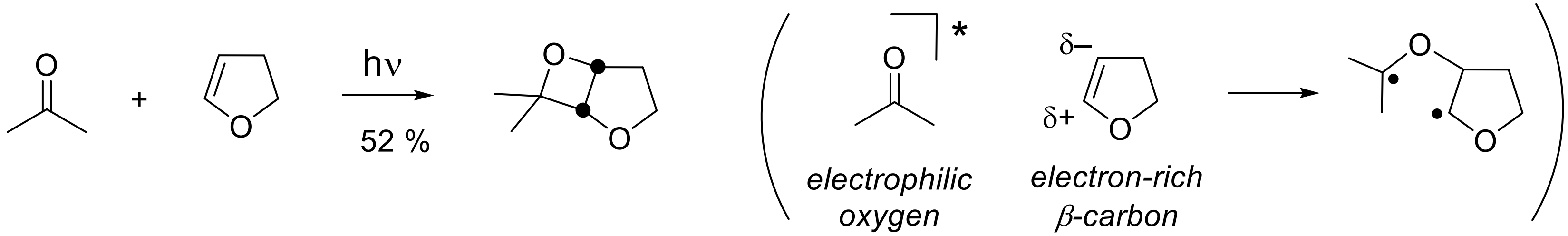


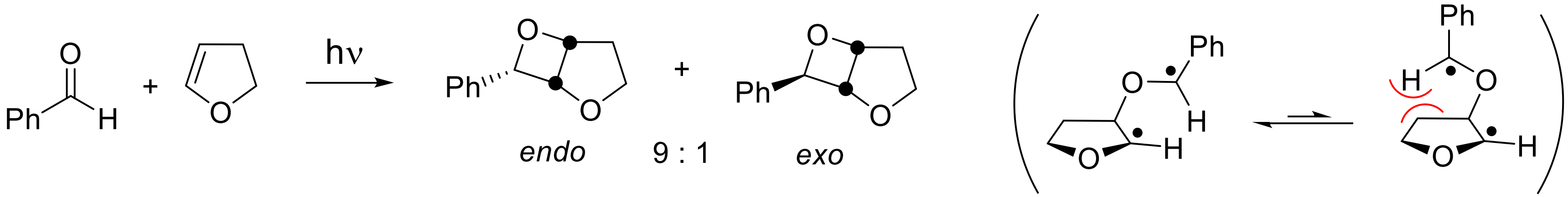


3.1.2 Reactions with electron-rich alkenes

Examples:

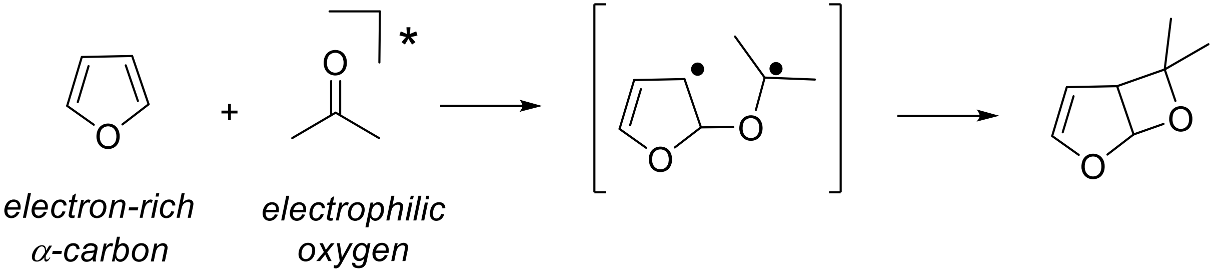






3.1.3 Reactions with furans

The oxygen attacks the α-carbon of the furan



The product is a cyclic acetal. The remaining alkene (an enol ether) may react further, but in general this is much slower.

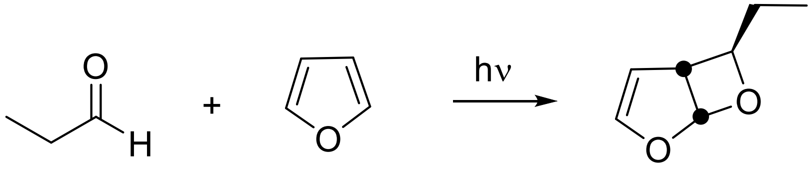
Remarks:

Aldehydes and aromatic ketones are good carbonyl partners

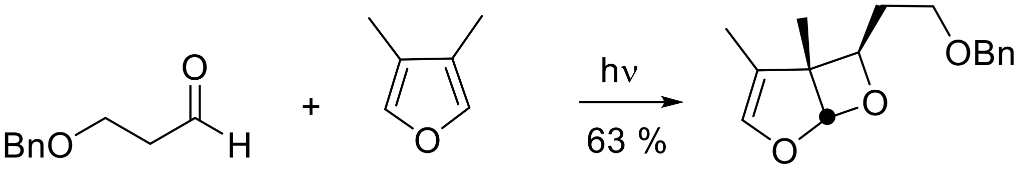
Regioselectivity is the opposite of that observed with enol ether alkenes

Stereosélectivity is usually good, with a preference for the *exo* product

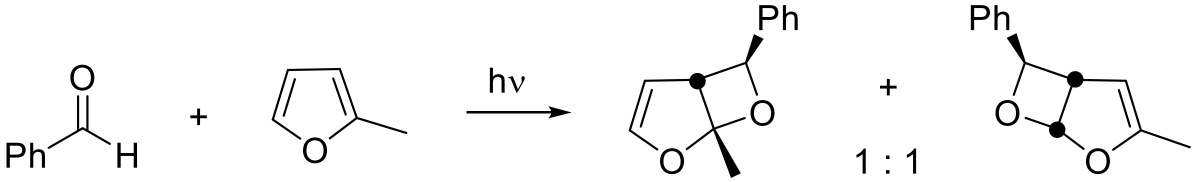
Examples:



only product

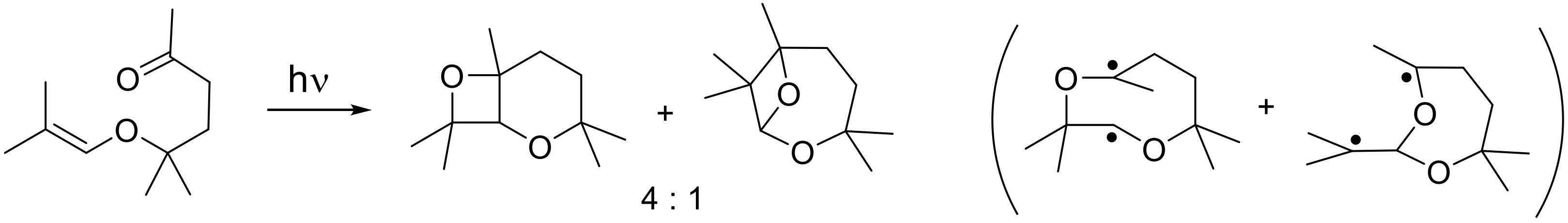


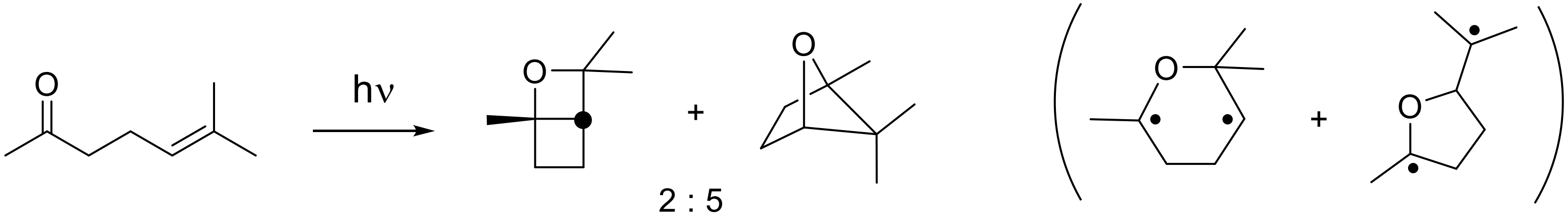
only product

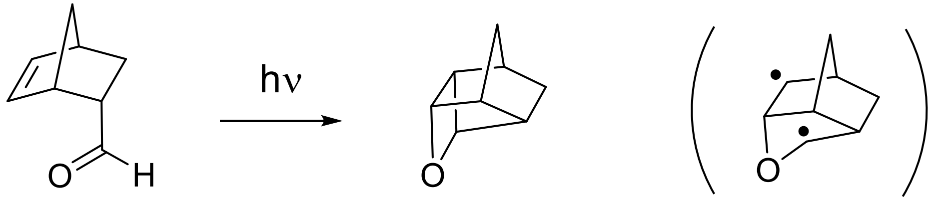


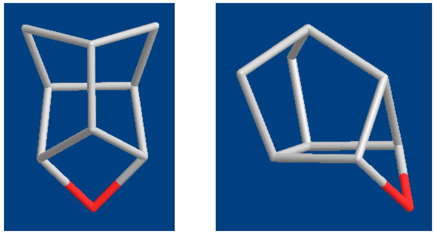
3.2 Intramolecular Reactions

Examples:







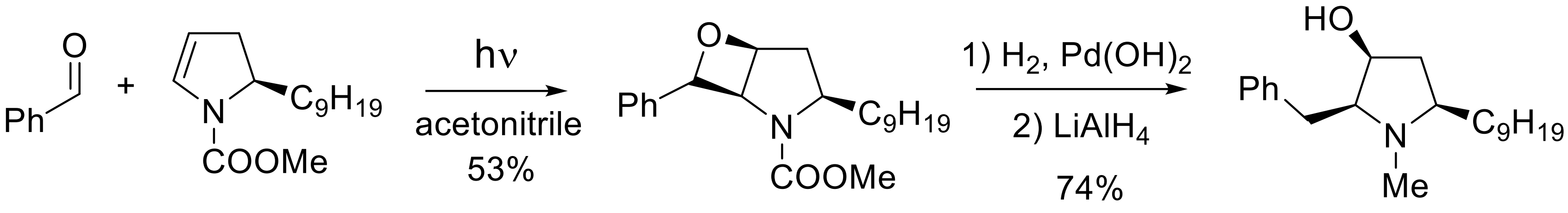


Examples in organic synthesis

- ***Synthesis of (+)-preussin***

  Chem. Eur. J. **2000,** 3838

pyrrolidine alkaloid with antifungal and immunsuppressant activities

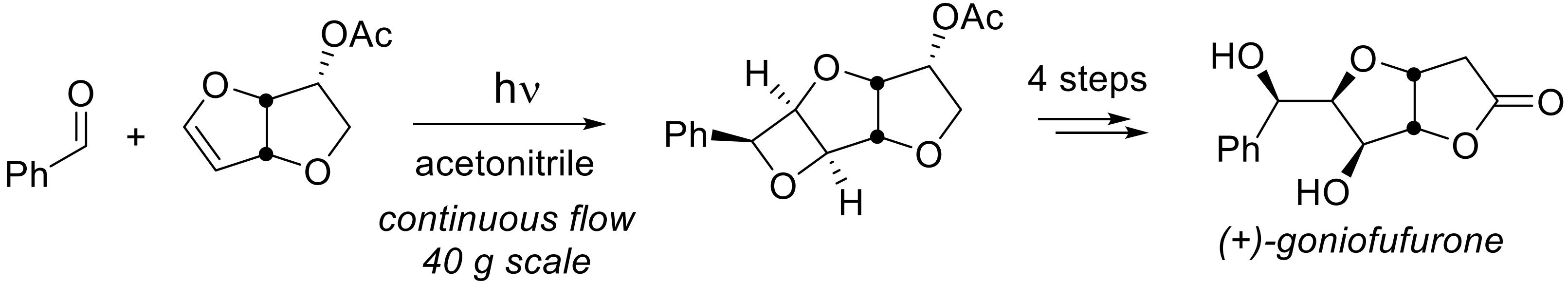


(+)-preussin

- ***Large scale synthesis of (+)-goniofufurone***

  Org. Lett. **2016**, *18*, 968

Cytotoxic metabolite from Goniothalamus trees

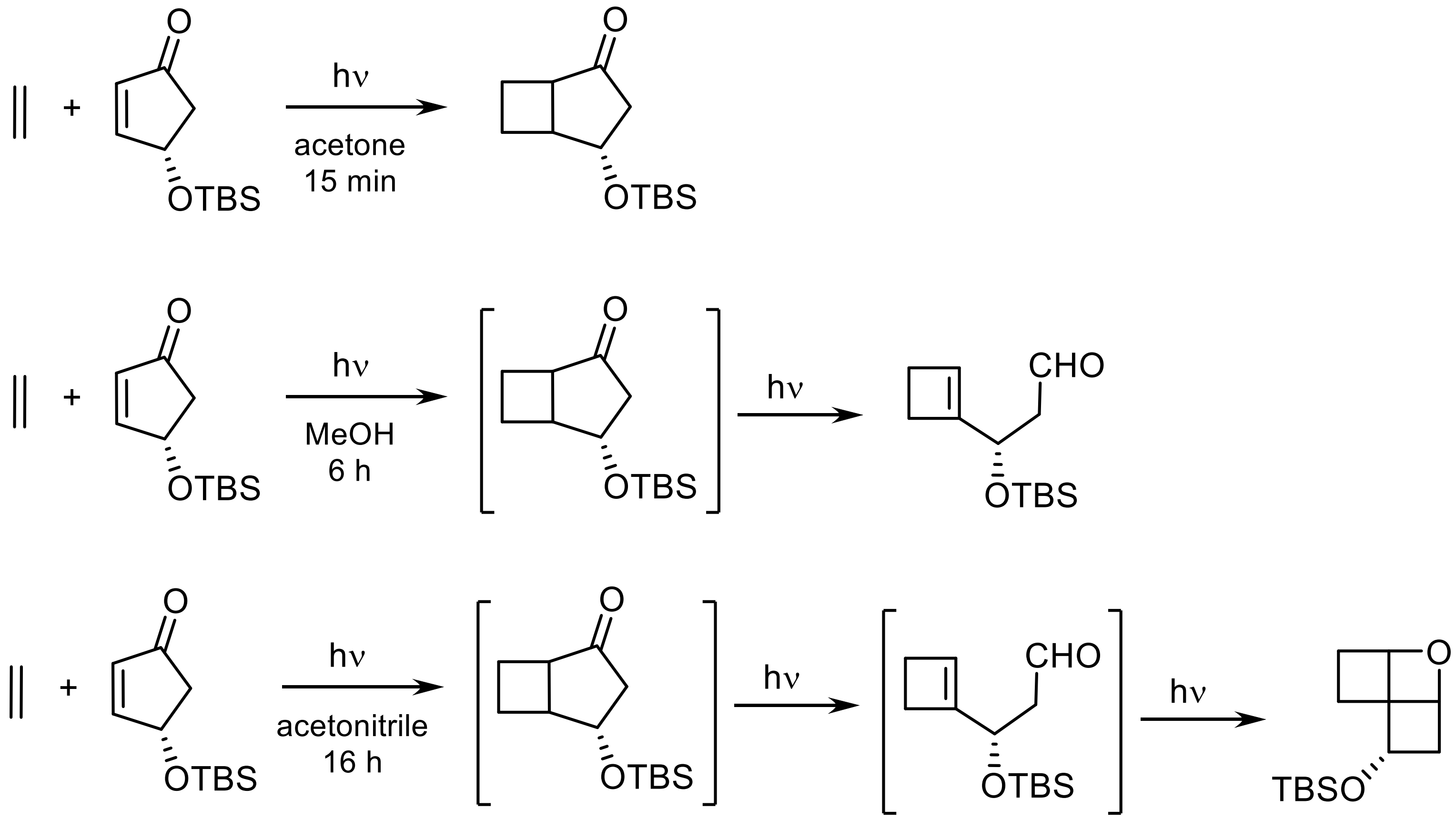


(+)-goniofufurone

Examples in organic synthesis

- ***Tandem and cascade photo-reactions for molecular diversity***

Angew. Chem. Int. Ed. **2018**, *57*, 6592



Photochemistry of azo and diazo compounds

A. Azo compounds

1. Formation of azo compounds
2. Photo-isomerization
3. Photo-elimination of N_2

B. Diazoalkanes

1. Formation of diazoalkanes
2. Photochemical reactivity of diazoalkanes

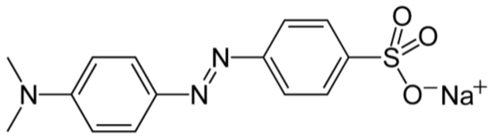
C. α-Diazoketones

1. Formation of α-diazoketones
2. Photochemical reactions of α-diazoketones

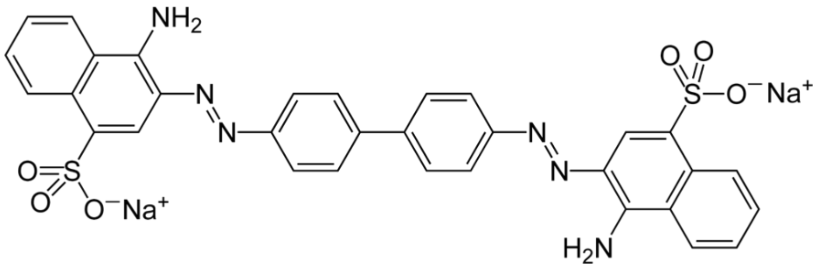
A. AZO COMPOUNDS

Exist in *Z* or *E* forms

Azo dyes are well known

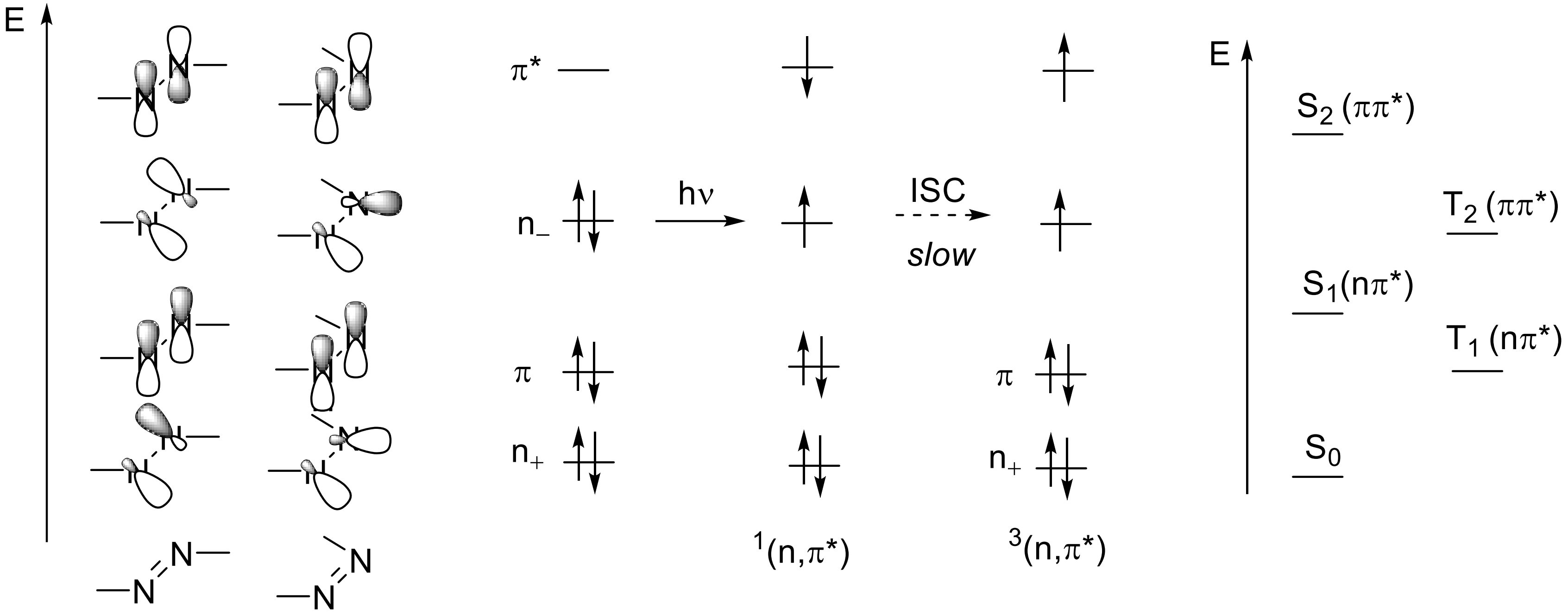


Methyl Orange



Congo Red

Photoactivation of azo compounds



The transition **n → π*** is implicated

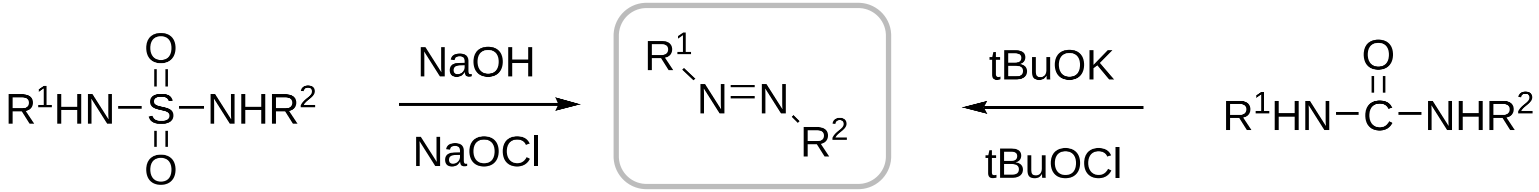
RN=NR λ_{max} = 350-380 nm ($\varepsilon \sim 10^1$ *trans*, 10^2 *cis*)

ArN=NAr λ_{max} = 420-460 nm ($\varepsilon \sim 10^2$ *trans*, 10^3 *cis*)

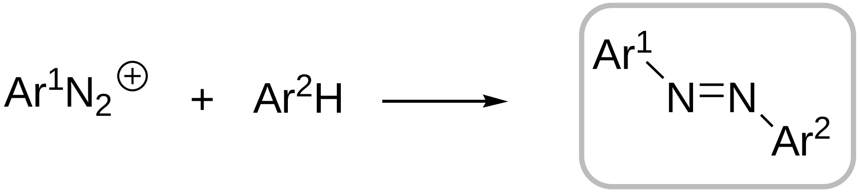
1. Formation of azo compounds

a) Acyclic

- oxidation of sulfamides or ureas (extrusion of SO_2 or CO):



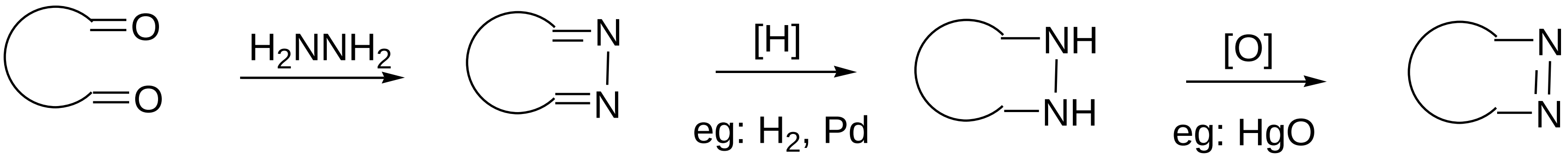
- via diazonium salts:



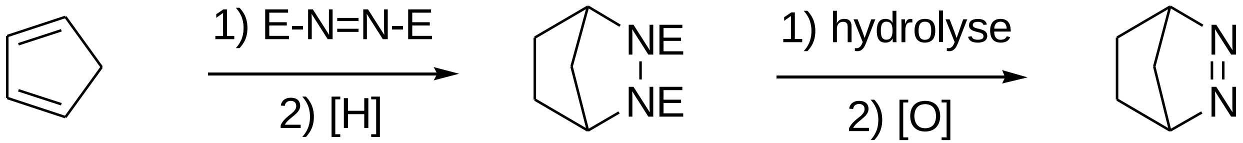
These syntheses generally give the *trans* isomers

b) Cyclic

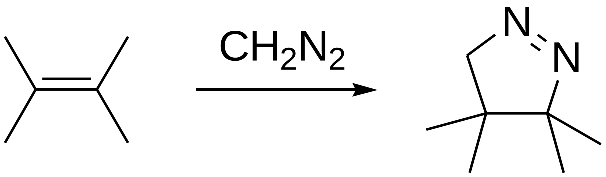
- from dicarbonyl compounds:



- via azodicarboxylates:

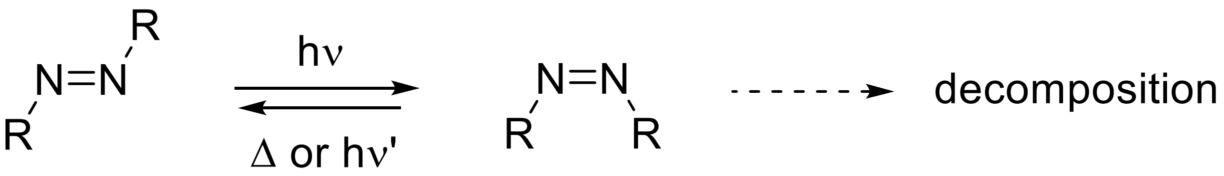


- diazomethane + alkene:



2. Photo-isomerization

This is a common phenomenon for acyclic compounds



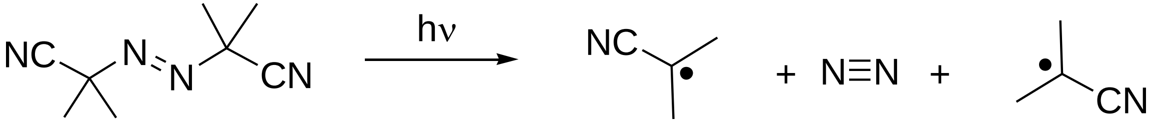
For alkyl derivatives, the *cis* isomer may not be stable.

Aryl derivatives are more stable.

Numerous applications of *cis/trans* isomerisation:
Photo-manipulation of molecular architecture, photo-switches, …

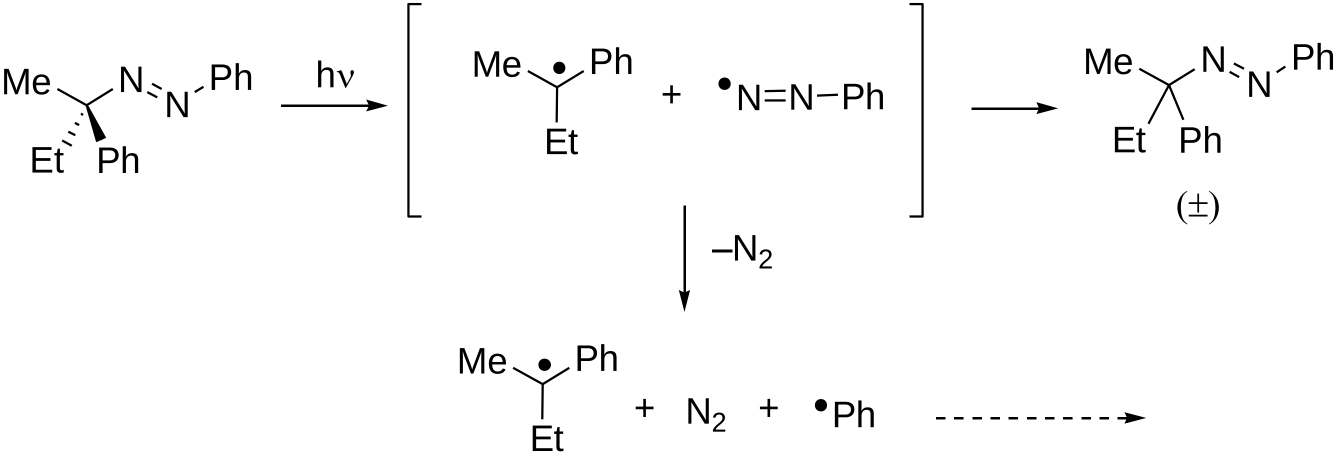
3. Photo-elimination of N_2

Electronic excitation is followed by fragmentation to give two (alkyl) radicals and a molecule of N_2.



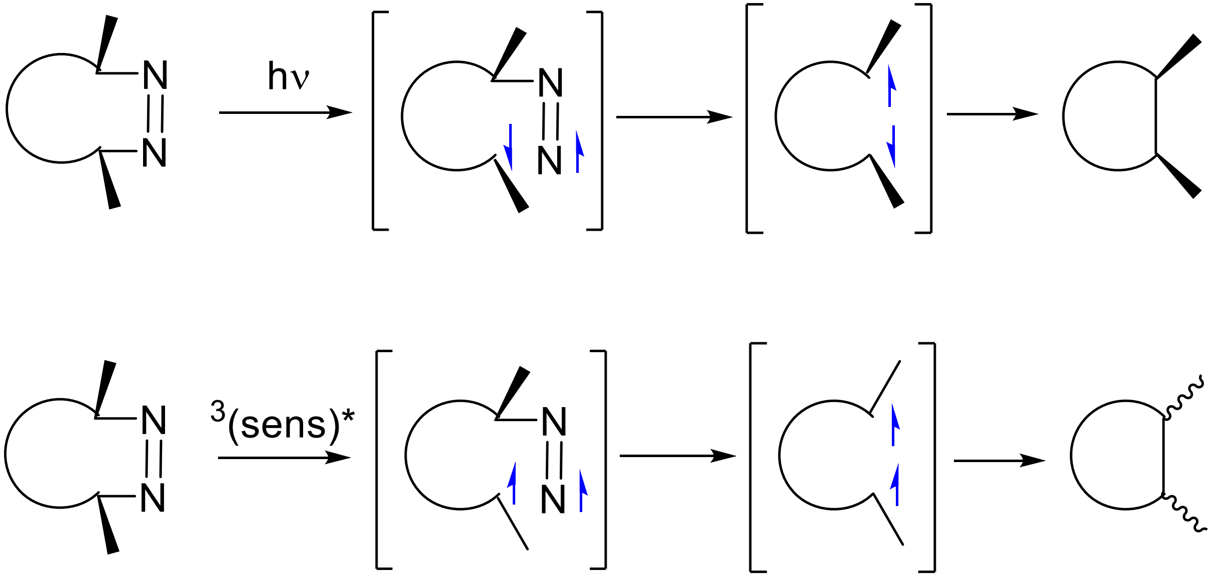
azobisisobutyronitrile (AIBN), an initiator of radical reactions

Non-concerted mechanism:



Photoelimination of N_2 is most useful for cyclic azo compounds

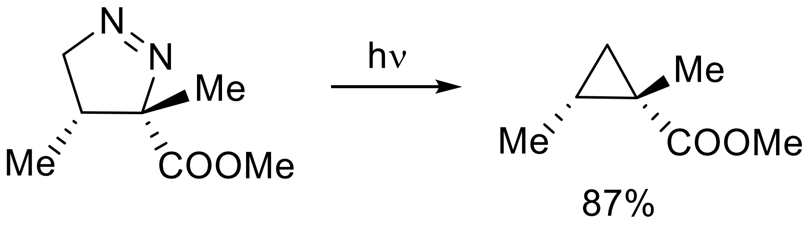
Stereochemistry:

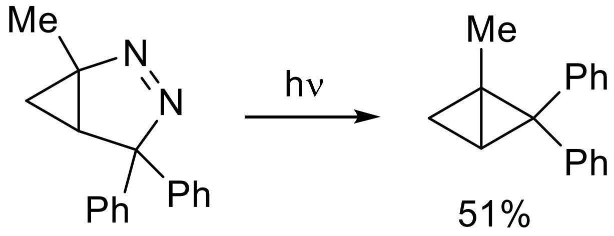


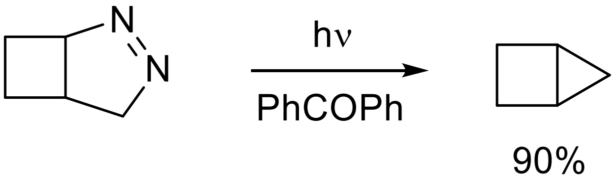
(and/or other products)

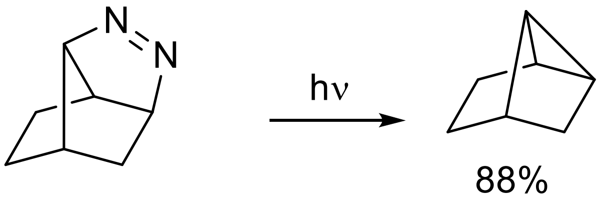
(and/or other products)

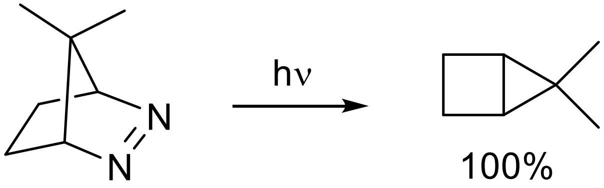
Formation of cyclopropanes

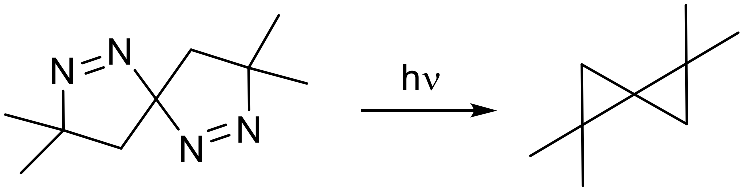






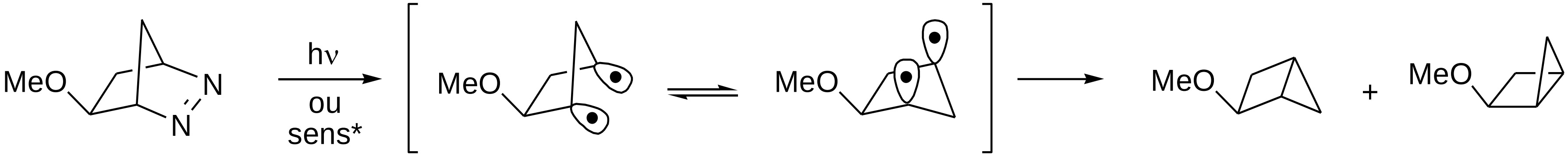


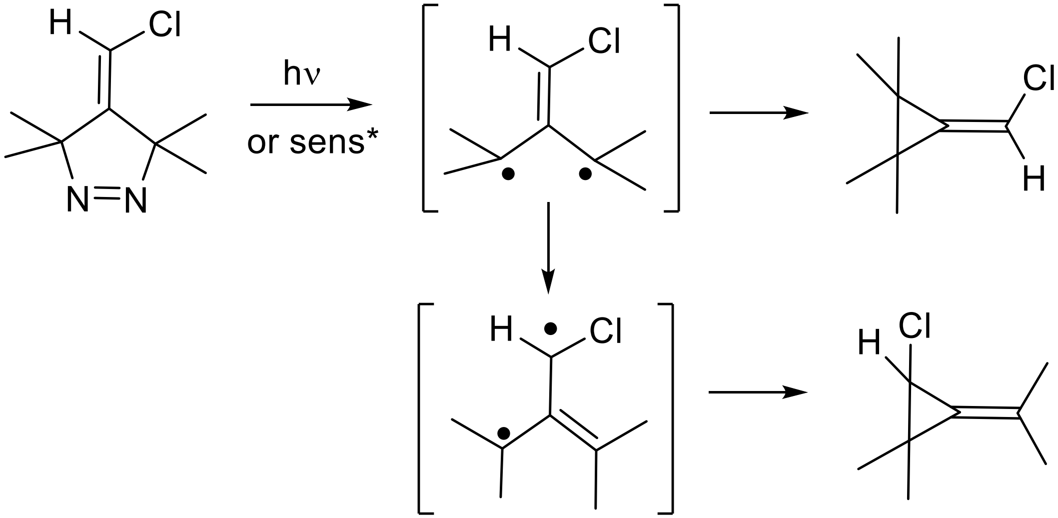




Formation of cyclopropanes

Some consequences of the radical mechanism

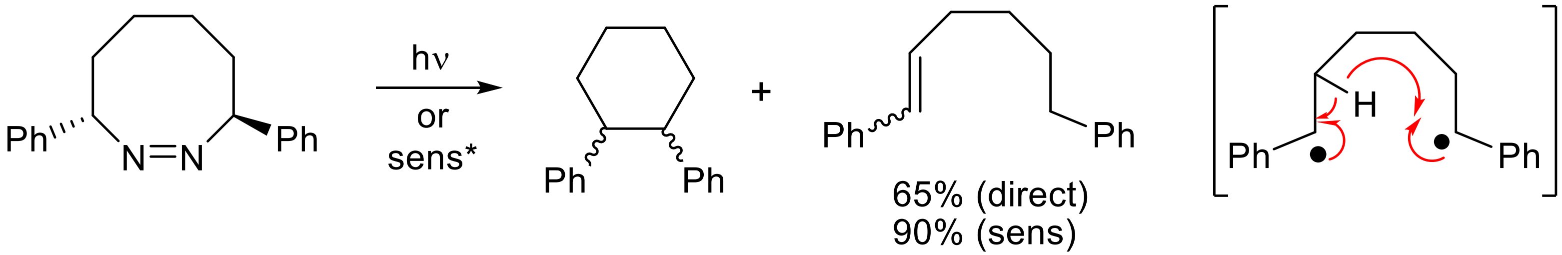


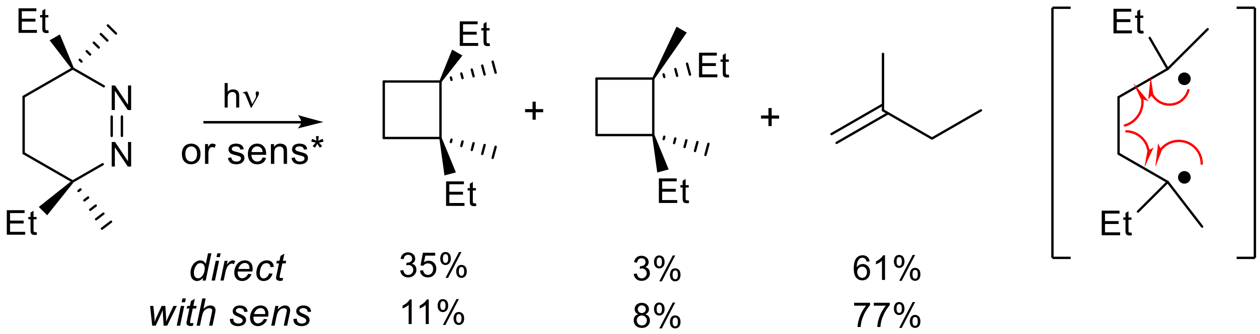


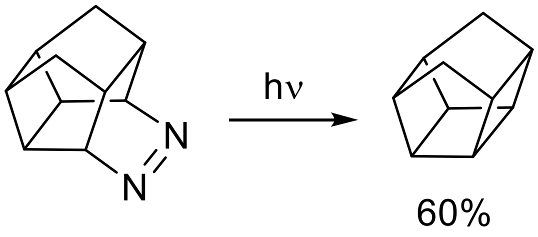
direct	with sens (PhCOPh)
80%	25%
20%	75%

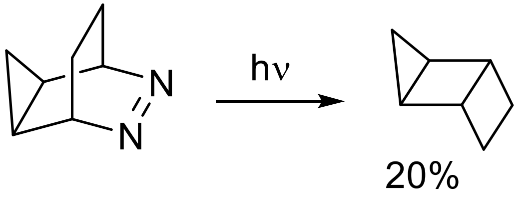
Formation of other ring systems

Les useful than for cyclopropanes
Fragmentations or rearrangements compete





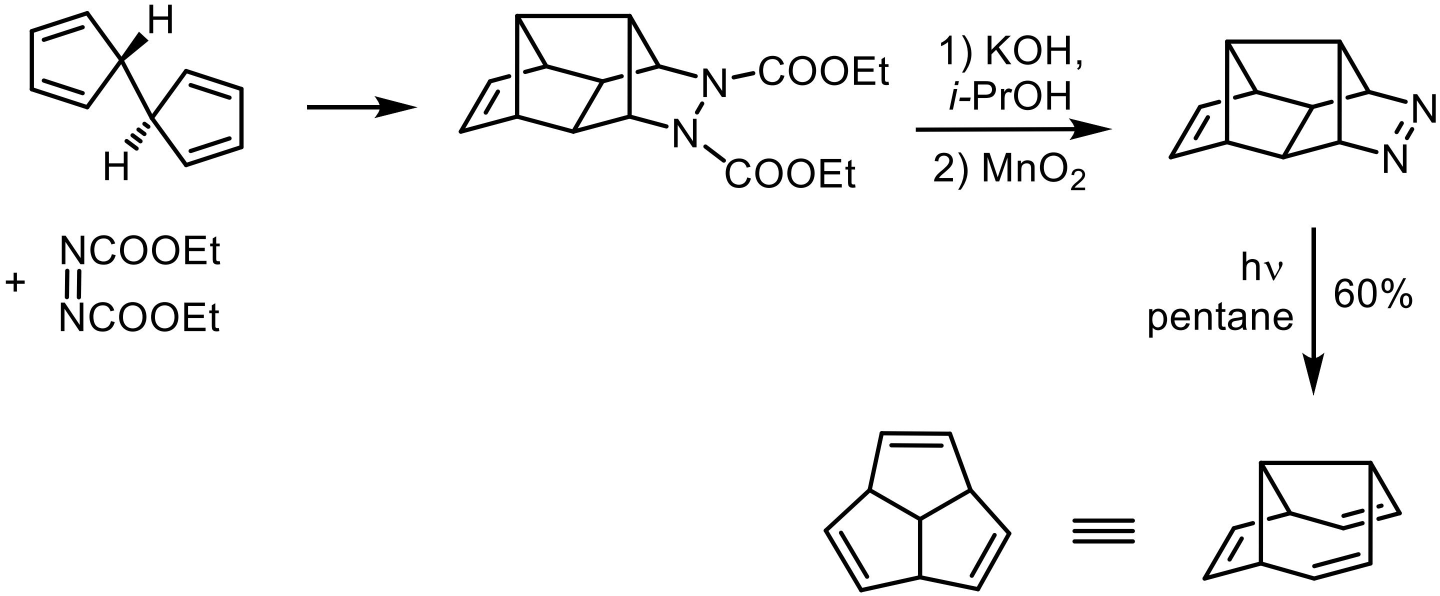




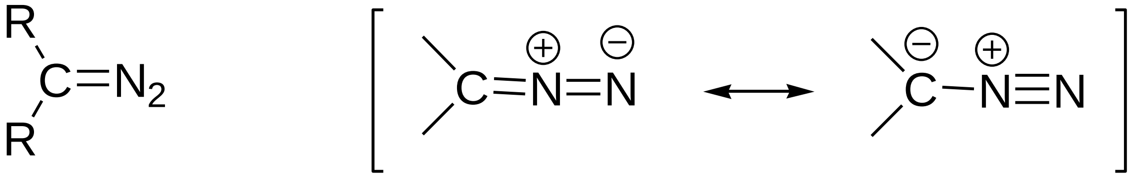
Examples in organic synthesis

- ***Synthesis of triquinacene*** *an unusual hydrocarbon*

  Tetrahedron Lett. **1974,** 2433

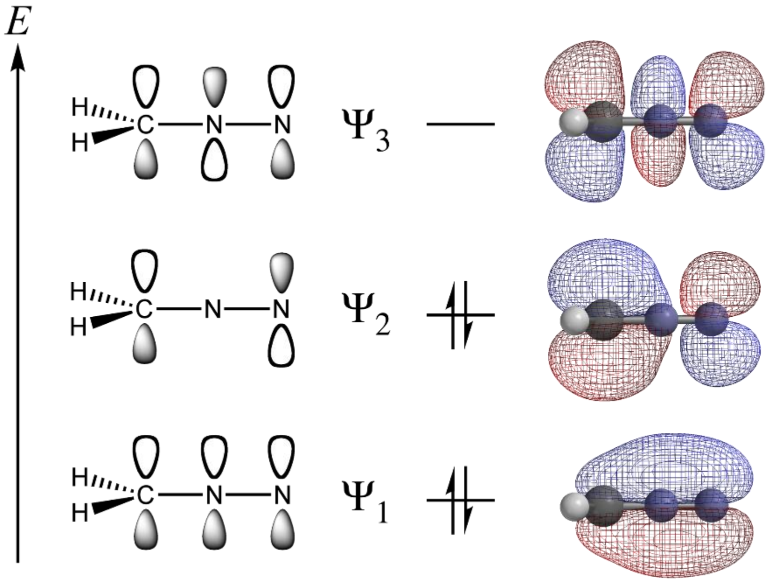


B. DIAZOALKANES



Highly reactive; may present a risk of explosion

Photoactivation of diazoalkanes

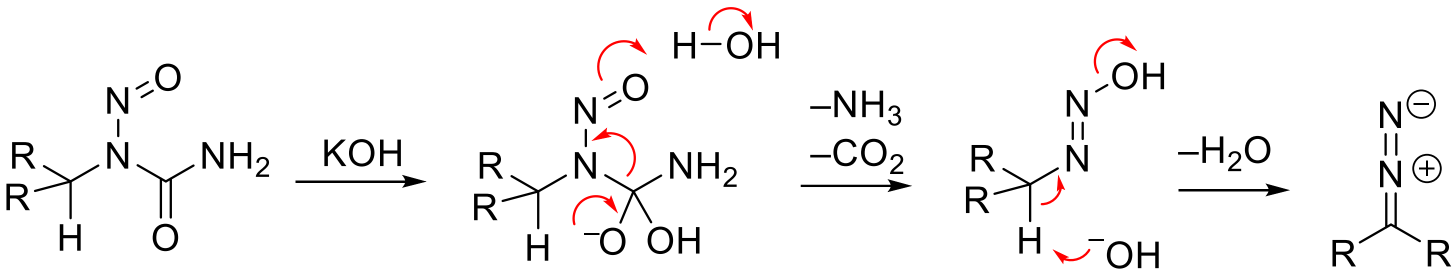


The energy required for the **HOMO → LUMO** transition is low

λ_{max} = 400-500 nm ; ε ~ 10 (alkyle) – 100 (aryle)

1. Formation of diazoalkanes

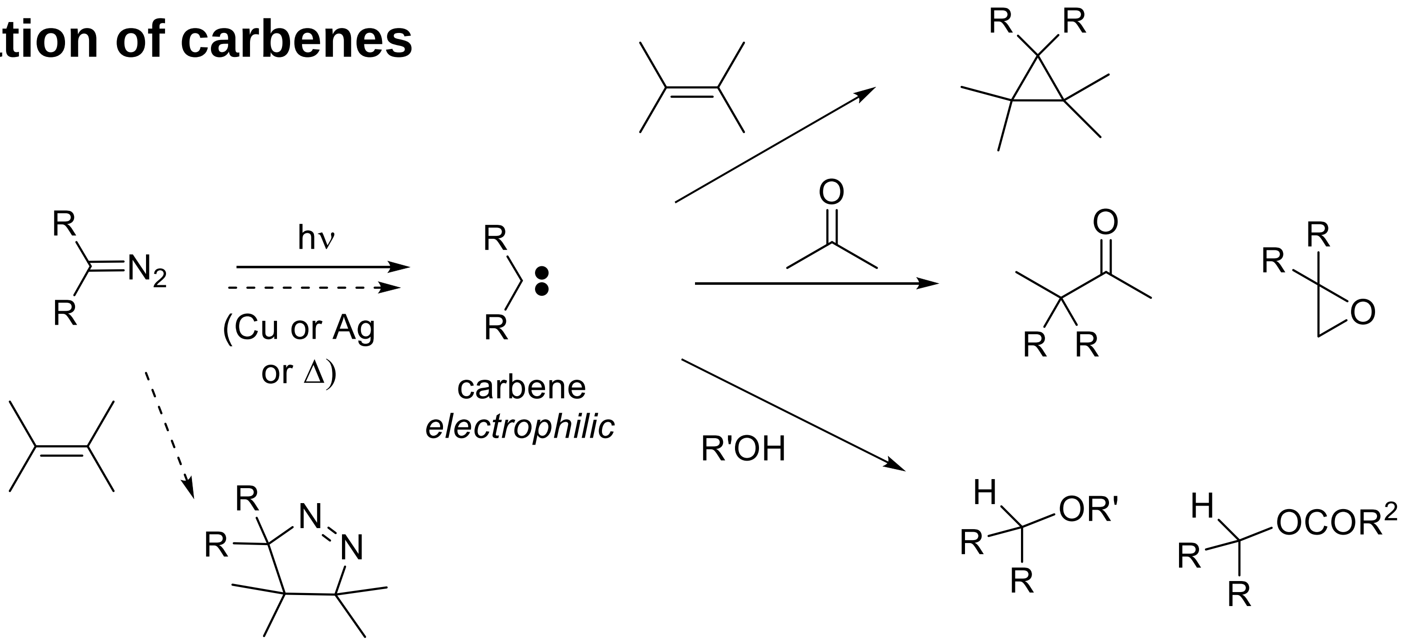
— from *N*-nitrosoureas or *N*-nitrosoamides:



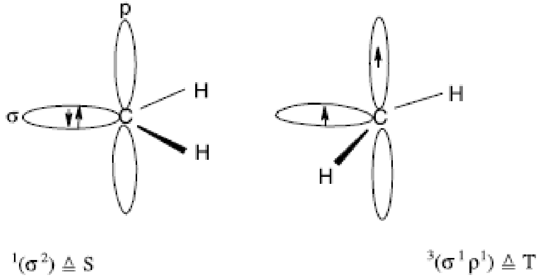
In general, diazoalkanes are prepared in ether solution and used immediately

2. Photochemical reactivity of diazoalkanes

Formation of carbenes

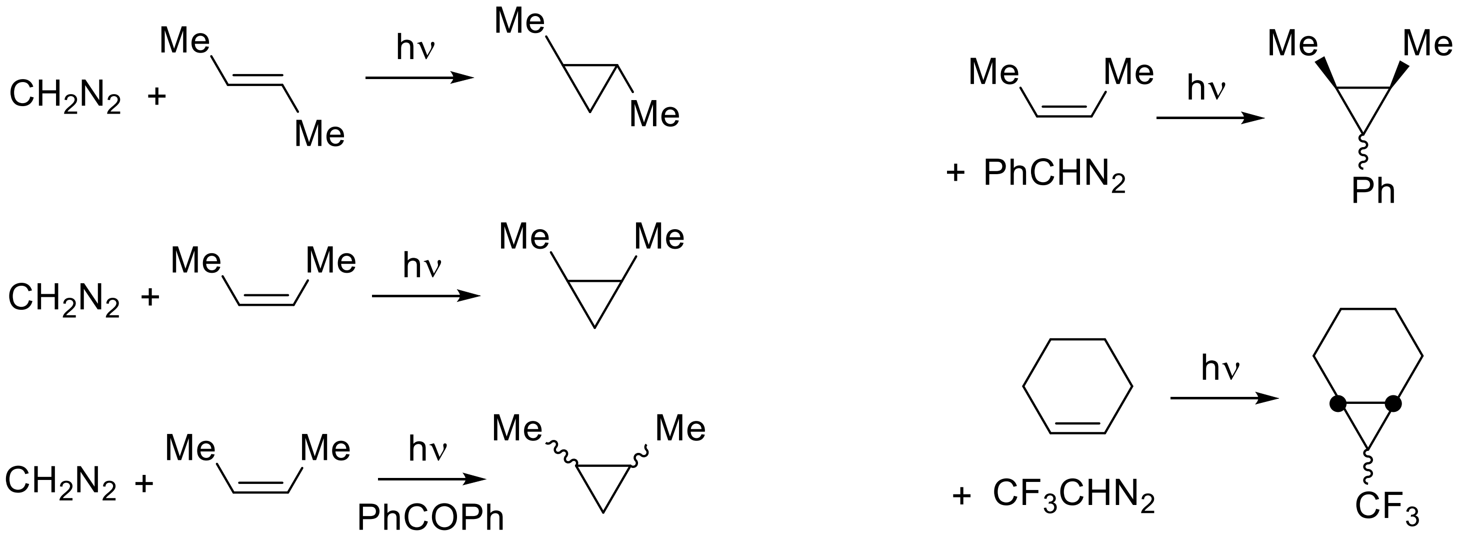


Direct photochemical excitation gives S_1 then loss of N_2 gives the singlet carbene.
This may react as such, or convert to triplet carbene before reacting.
The triplet carbene may also be generated by photosensitization.



Reactions with alkenes – formation of cyclopropanes

Intermolecular reactions are useful

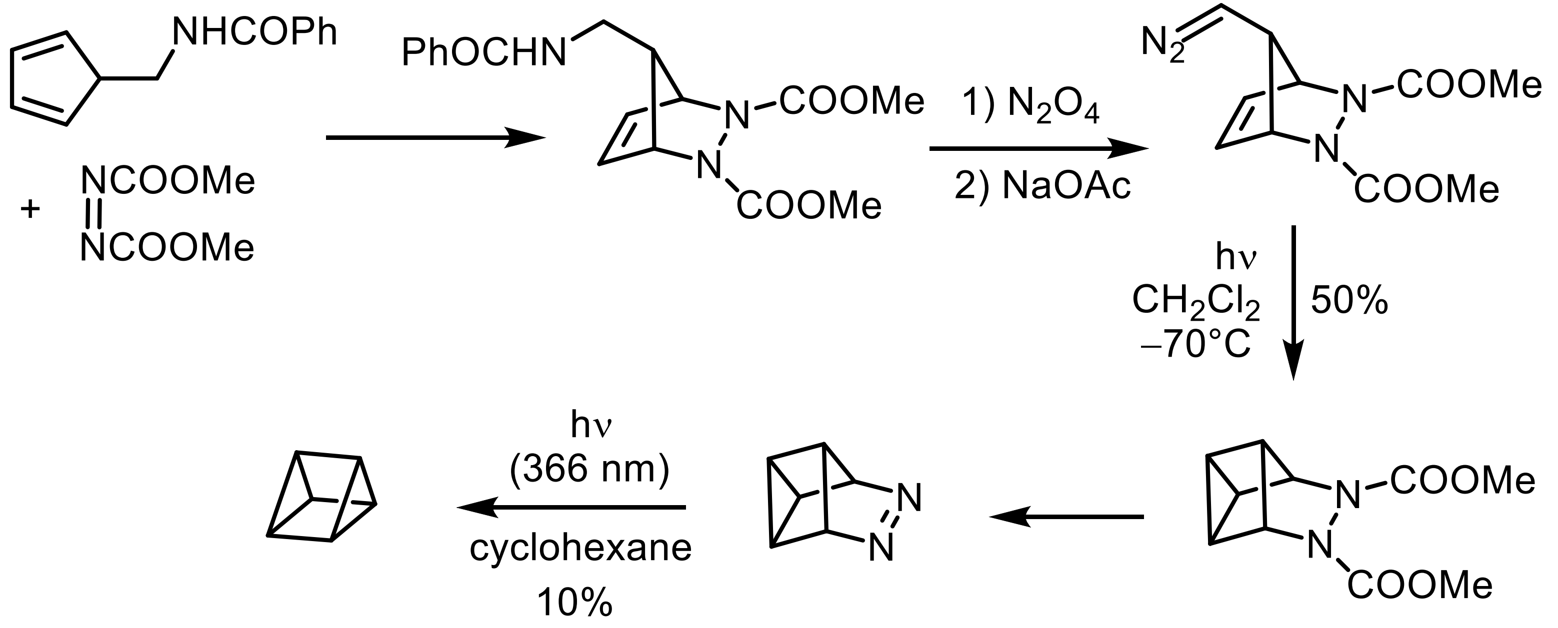


Intramolecular reactions do not always proceed so well;
other reactions may compete, such as C-H insertions, rearrangements, …

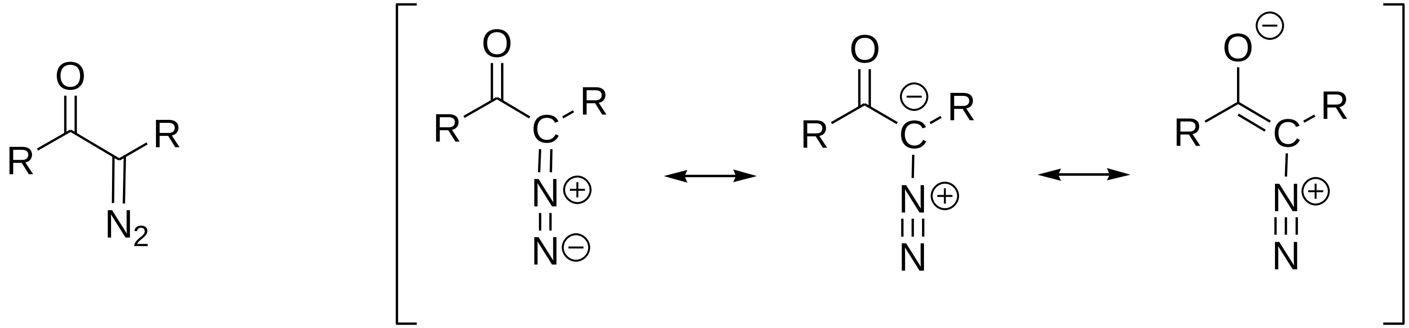
Examples in organic synthesis

- ***Synthesis of prismane*** *a valence isomer of benzene*

J. Am. Chem. Soc. **1973**, *95*, 7813; *J. Am. Chem. Soc.* **1976**, *98*, 4320



3. α-DIAZOKETONES



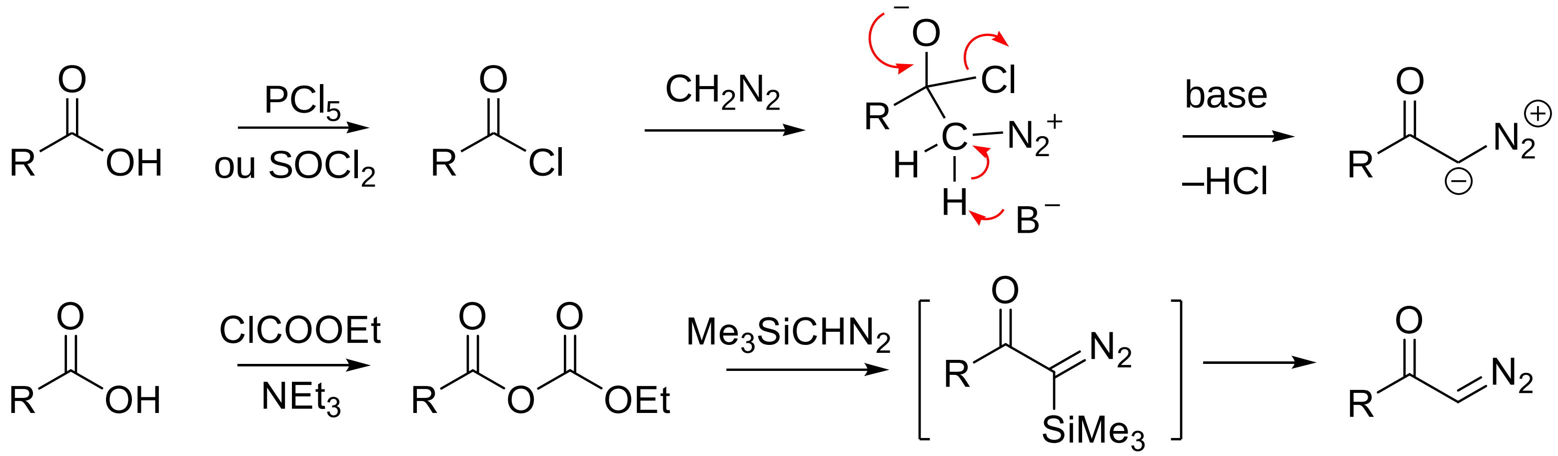
Much more stable that azoalkanes

The **π → σ*** excitation gives S_1 (preferred)
λ_{max} = 270-320 nm ($\varepsilon \sim 10^1$)

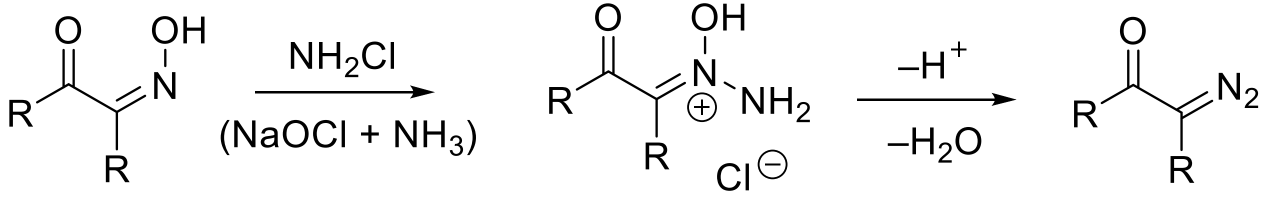
The **π → π*** excitation gives S_2 (may lead to competing reactions)
λ_{max} = 240-270 nm ($\varepsilon \sim 10^2$-10^3)

1. Formation of α-diazoketones

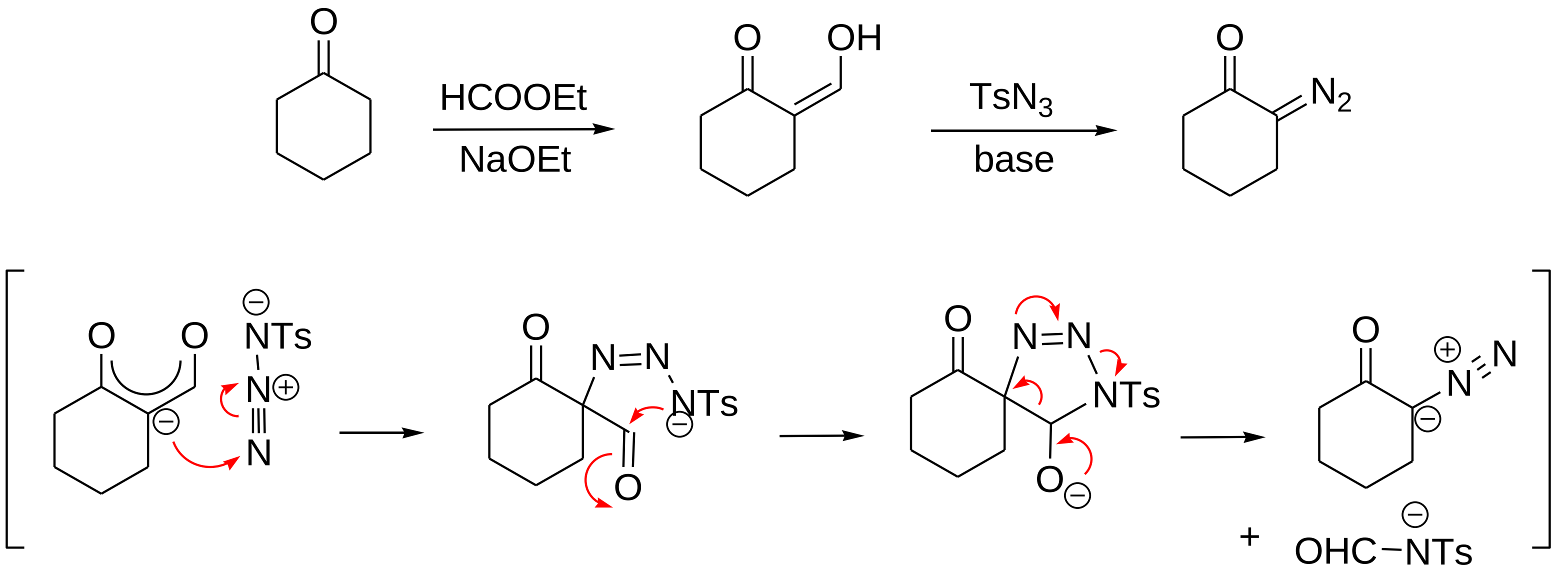
— from a carboxylic acid via an anhydride (***acyclic only***)



— from an α-oximinoketone (Forster reaction)

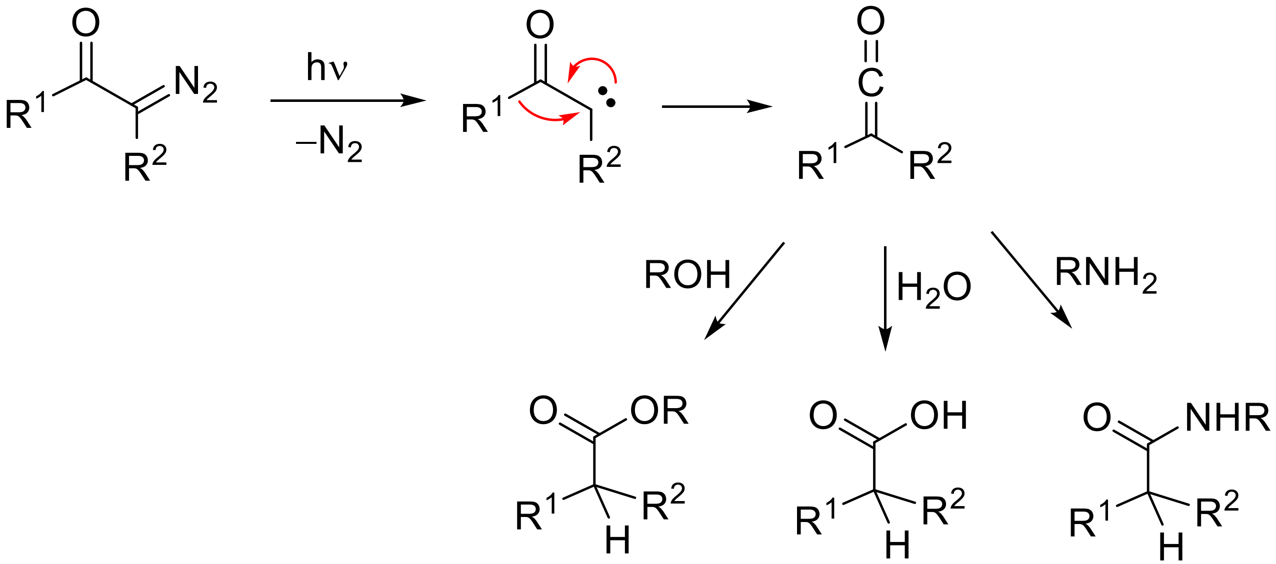


— diazo-transfer reaction (***cyclic only***)



2. Photochemical reactions of α-diazoketones

Following photochemical excitation, loss of N_2 gives the carbene.
This rearranges to become a ketene.
The ketene reacts with any available nucleophile (which may be the solvent)

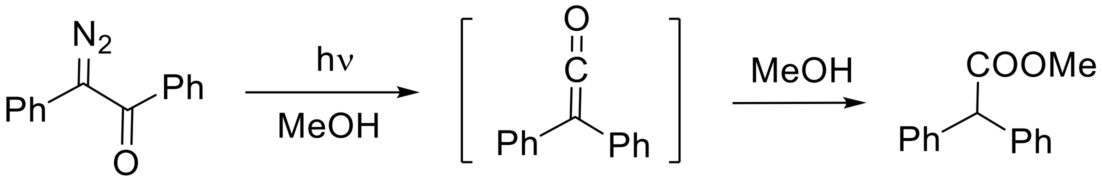


Migratory aptitude **(R^1)**

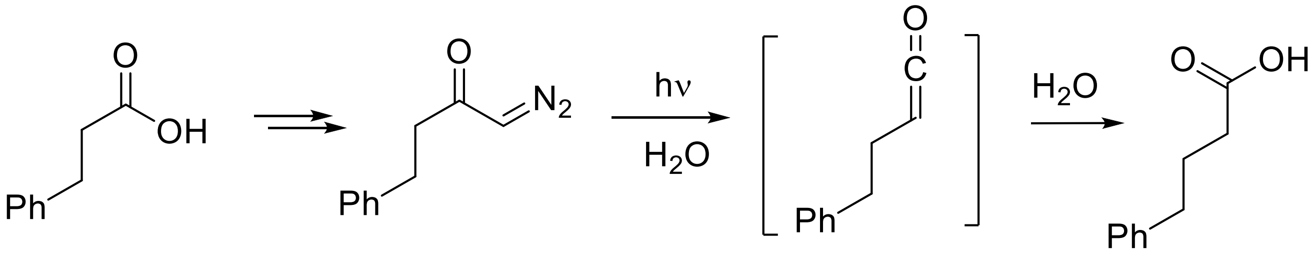
Depends largely on structural / conformational constraints.
Many groups can migrate; general ranking H > alkyl > aryl > SR > OR > NR_2

a) Acyclic

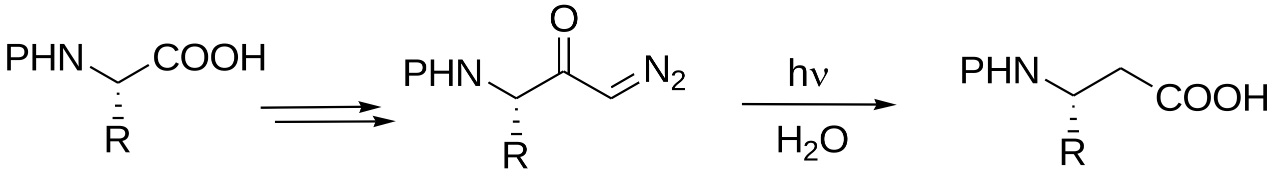
Internal diazo group – *shortening of main chain, side chain creation*



Terminal diazo group – *chain extension*



Arndt-Eistert homologation of α-amino acids

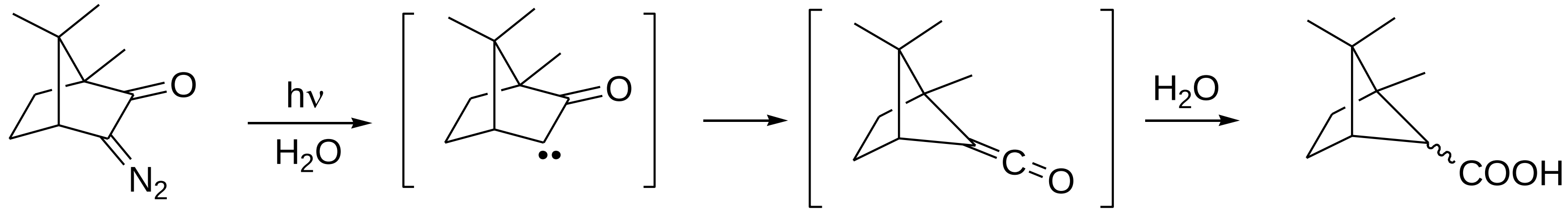


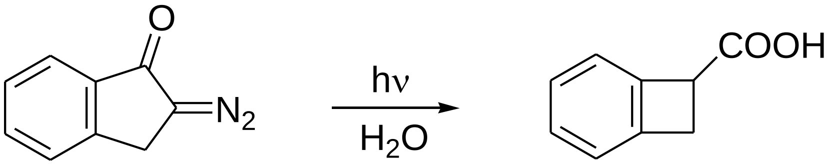
α-amino acid *β-amino acid*

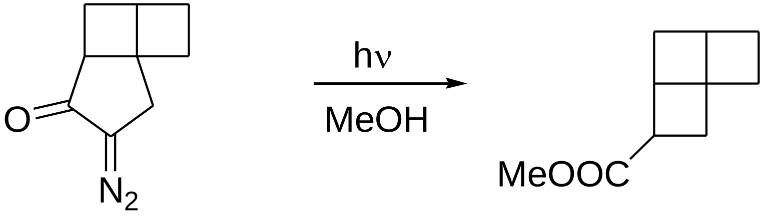
b) Cyclic

Ring contraction, even with rings that are already small

Wolff rearrangement

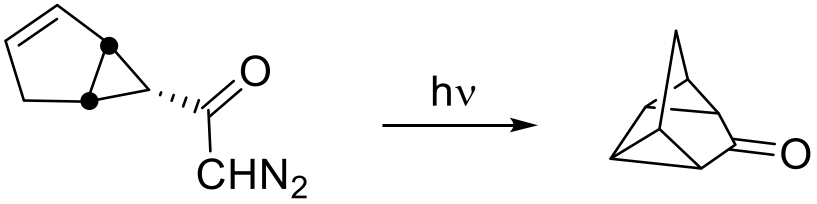




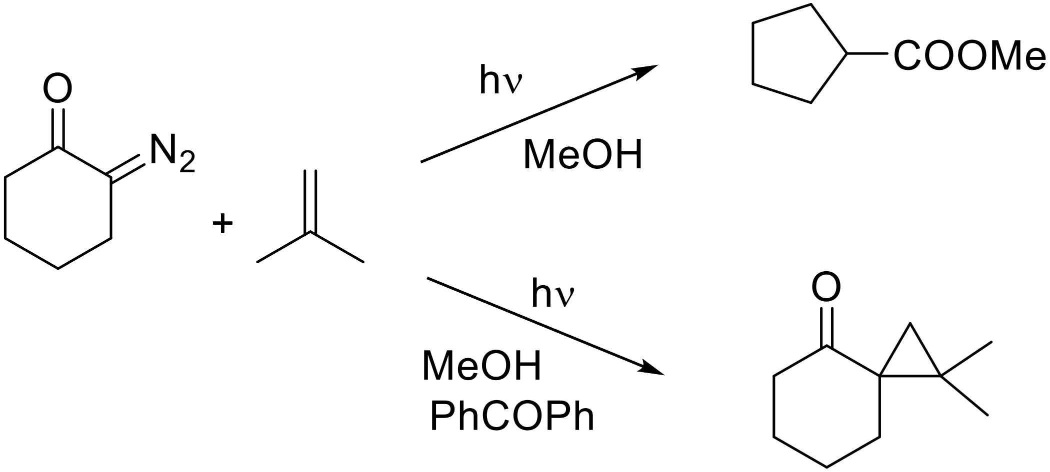


Wolff rearrangement v. carbene addition

— **intramolecular** *: addition generally predominates*



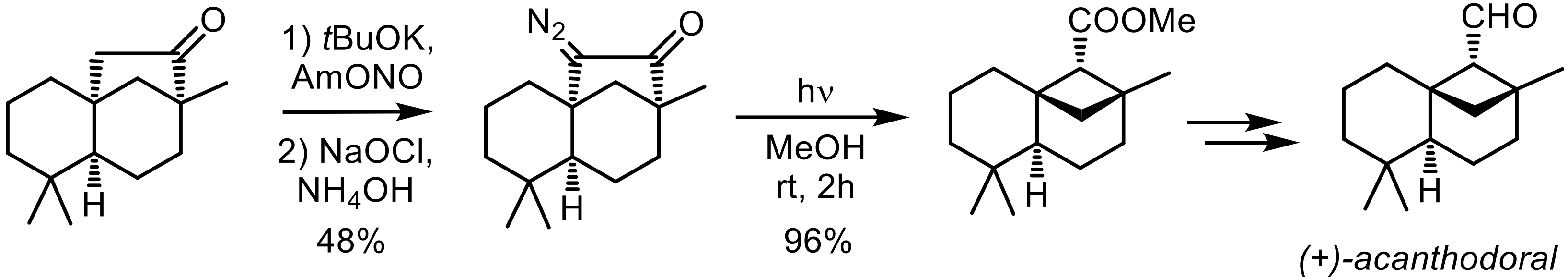
— **intermolecular**: *depends on the multiplicity of the carbene*



Examples in organic synthesis

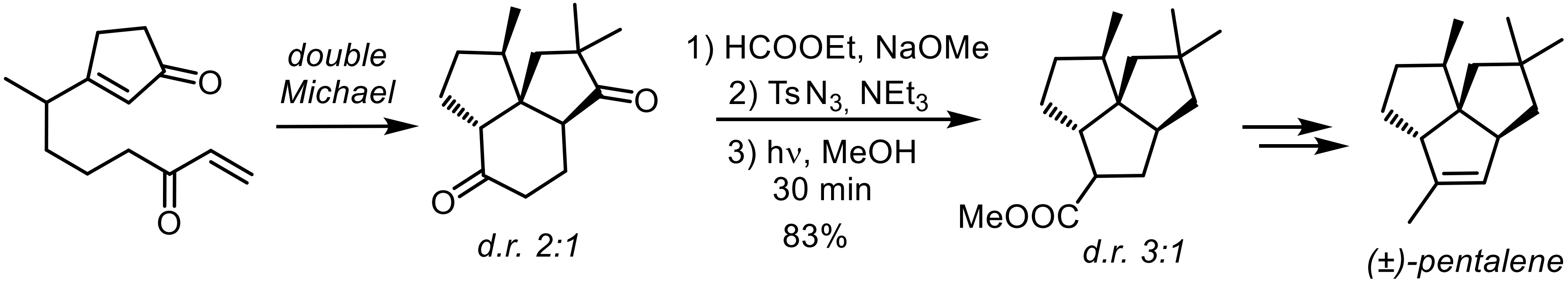
- ***Synthesis of (+)-acanthodoral*** *antibiotic sesquiterpene from the sea slug Acanthodoris nanaimoensis*

  Org. Lett. **2004, 6,** 537



- ***Synthesis of (±)-pentalene*** *angular triquinane sesquiterpene from Streptomyces broth*

  JCS Perkin Trans. 1. **1988,** 2963

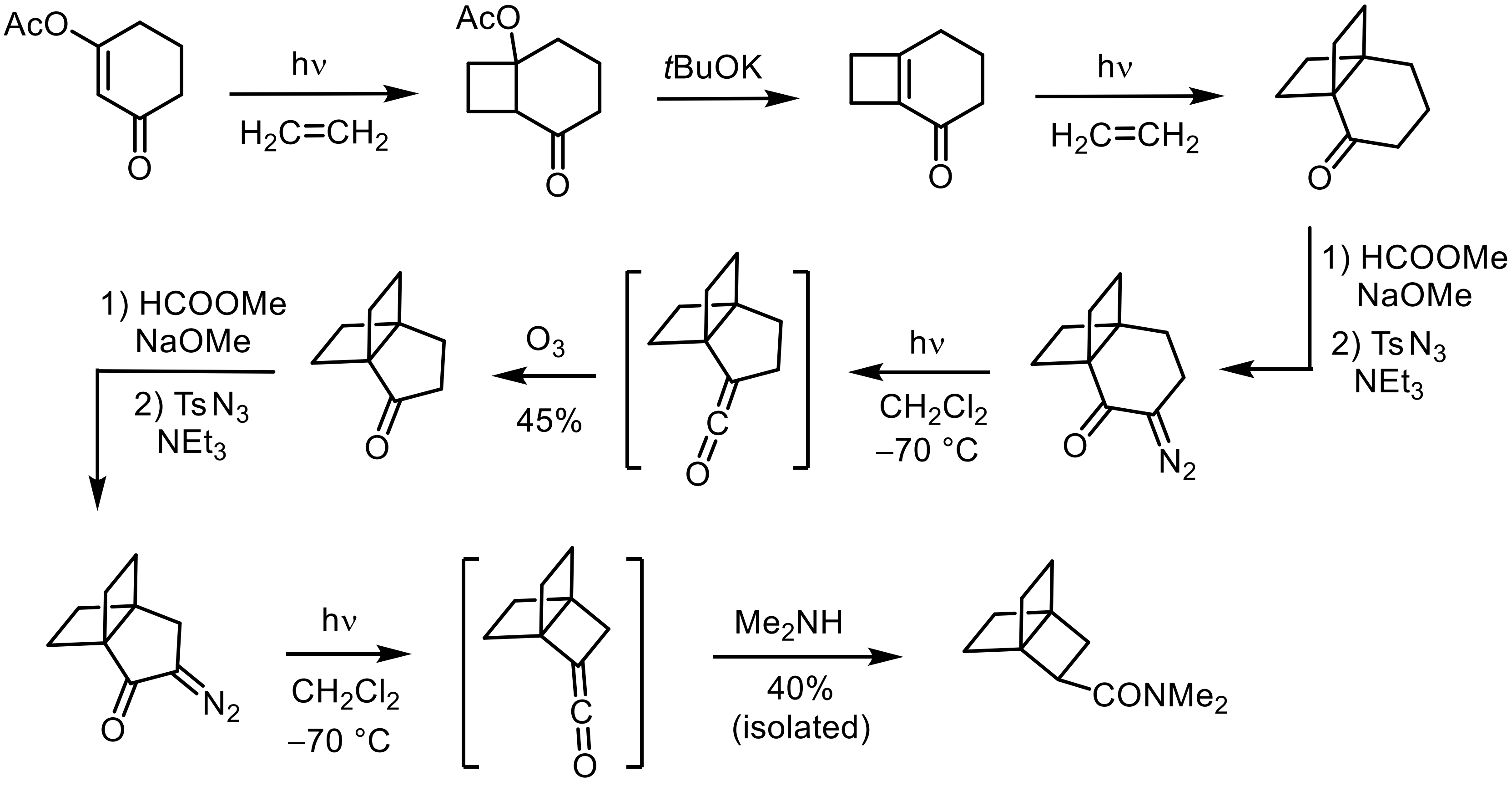


Examples in organic synthesis

- ***The first synthesis of a [2.2.2]propellane***

  J. Am. Chem. Soc. **1973,** *95*, 7508

a (very) highly strained molecular skeleton

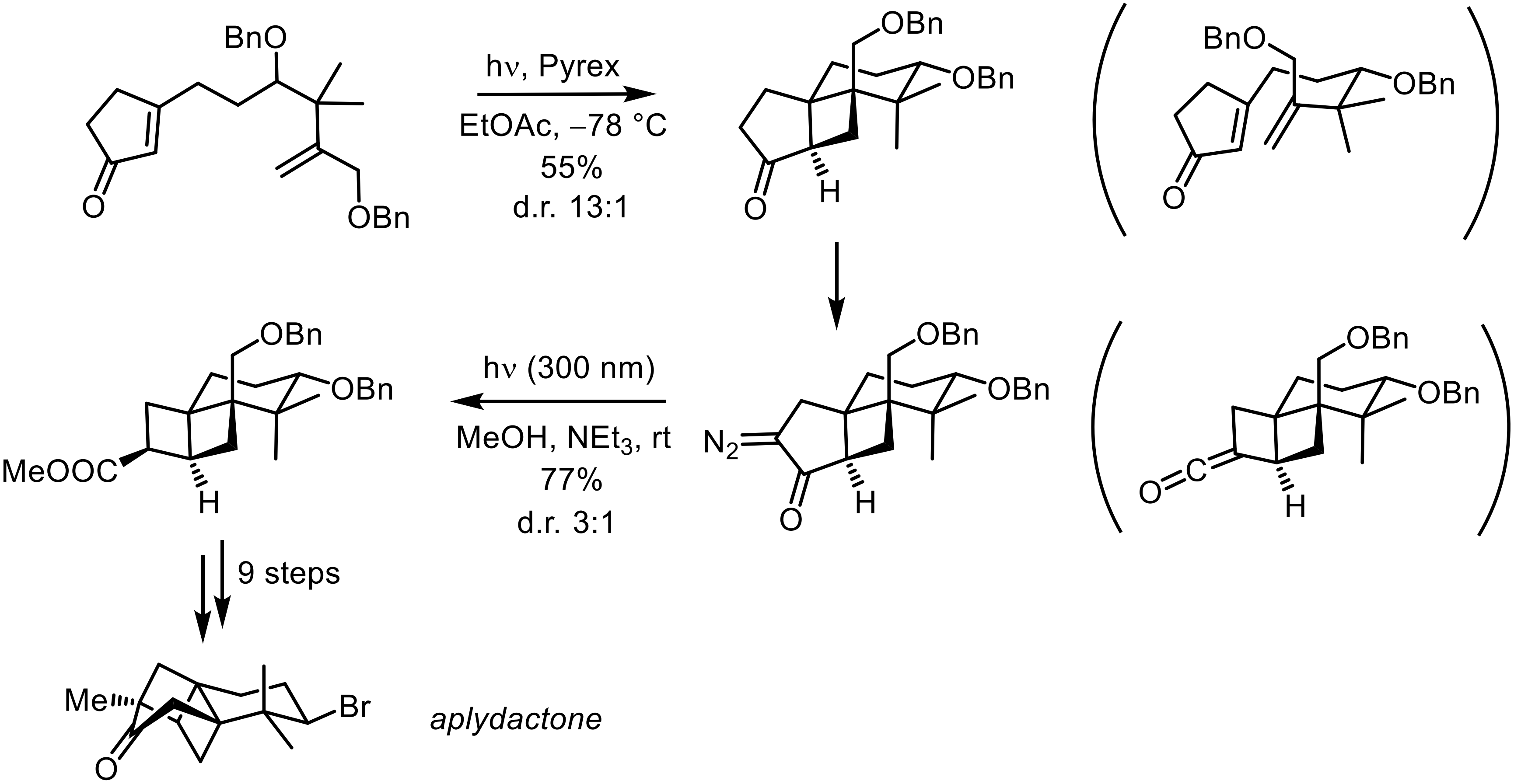


Examples in organic synthesis

- ***Synthesis of (±)-aplydactone***

  Angew. Chem. Int. Ed. **2016,** *55*, 11251

sesquiterpenoid isolated form the sea hare Aplysia dactylomela



aplydactone

Asymmetric Photochemical Synthesis

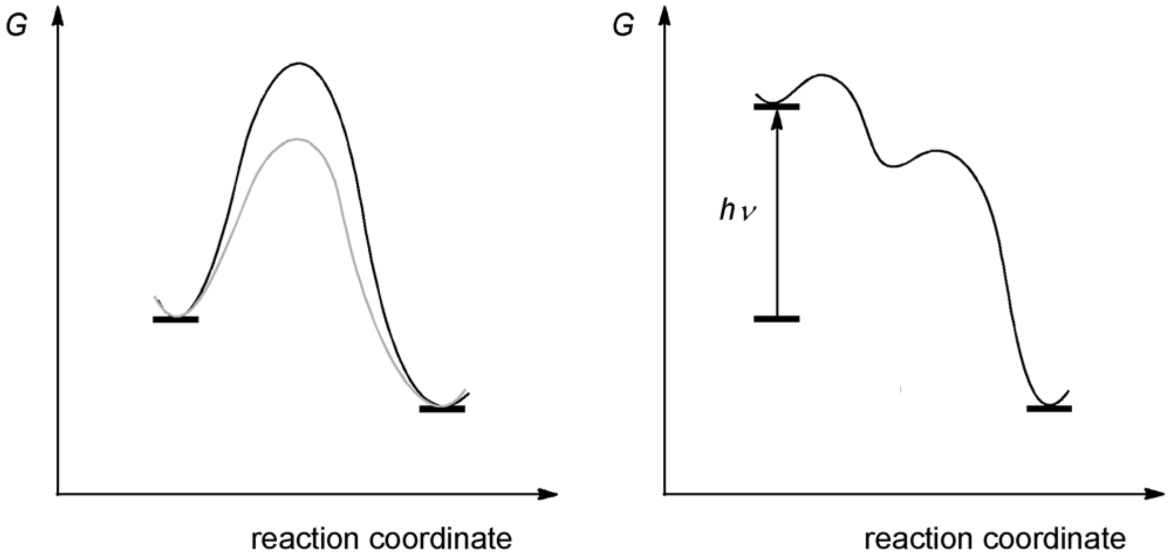
Photochirogenesis: The light-induced formation of chiral non-racemic molecules from achiral substrates

Intrinsically challenging!

The electronically excited state of a molecule is highly reactive and has a short lifetime.

The intra or intermolecular interactions required for delivery of chiral information are less efficient in the excited state than in the ground state.

To achieve an enantioselective photochemical reaction, it must be ensured that the substrate molecule already resides in a chiral environment during the excitation step.



Energy diagrams of a thermal reaction (left) and a photochemical reaction (right).

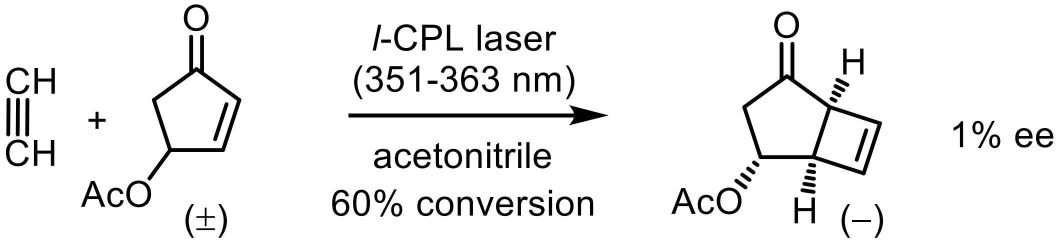
Circularly polarized light

One hypothesis for homochirality on Earth

Enantioselective photodestruction
Photoderacemization
Enantioselective photochemical synthesis

Depends on the anisotropy factor $g = (\varepsilon_1 - \varepsilon_2) / \varepsilon$
(relative difference of molar extinction coefficients of enantiomers 1 and 2 for *l*-CPL or *r*-CPL at the given wavelength)

For most organic molecules g is very low ($< 10^{-2}$)



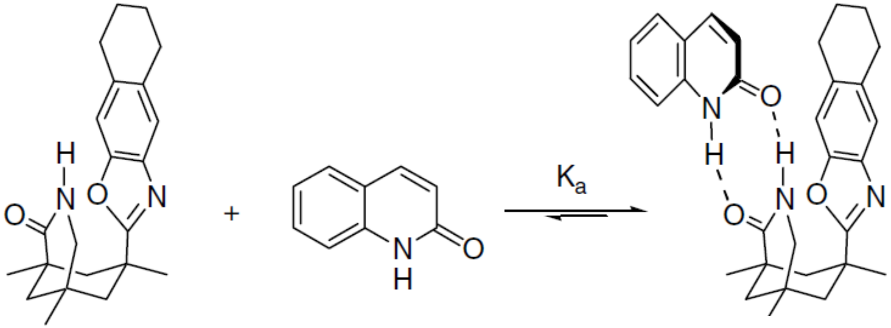
1. Chiral host-guest complexes

Principle : sufficiently strong interactions between host and guest in the ground state are retained (long enough) in the short-lived the excited state

Small hosts

With a small host stereodifferentiation is achieved due to the shielding role of part of the template.

The host may be designed to serve as a sensitizer, to avoid competition from non-templated (racemic) reaction.

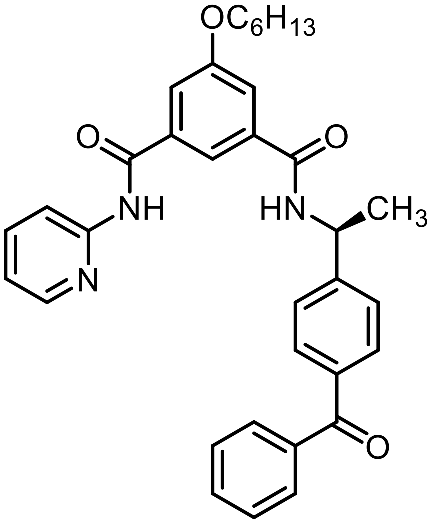


$K_a = 500\ M^{-1}$ (30 °C, toluene)

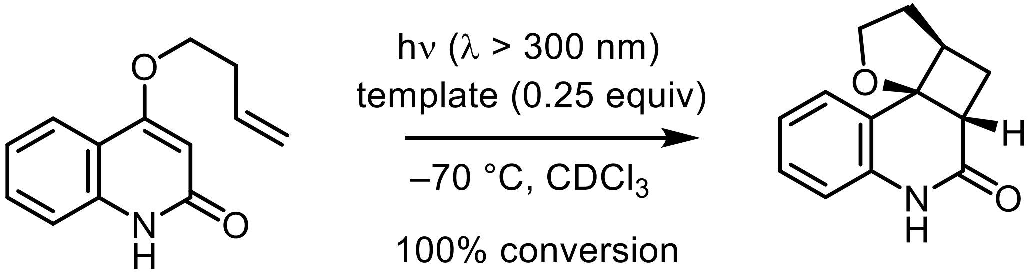
Chiral pyridine-isophthalate template

Intramolecular [2+2] photocycloaddition

Krische, *J. Org. Chem.* **2003**, *68,* 15



The template bears a benzophenone sensitizer.
Best selectivity at –70 °C.
Sub-stoichiometic amount of template used.

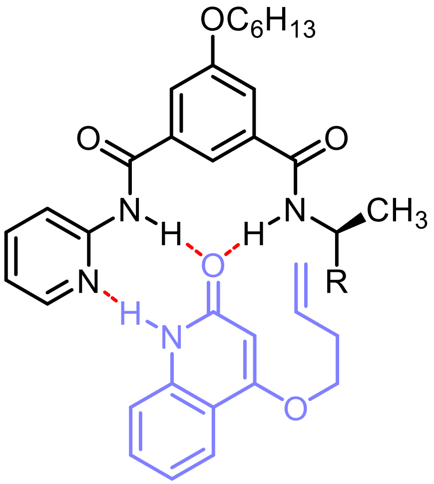


hν (λ > 300 nm)
template (0.25 equiv)

–70 °C, $CDCl_3$

100% conversion

20% ee

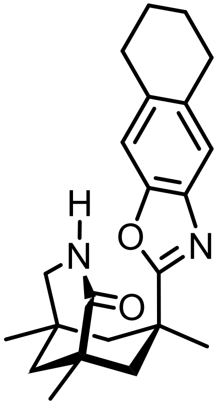


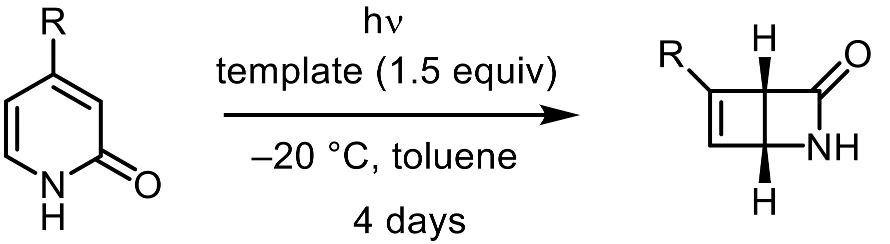
Kemp triacid lactam template

Photochemical [2+2] electrocyclization

Bach, *Org. Lett.* **2001**, *3,* 601

At low temperature, enantioselectivity was higher (tighter binding) but reactions were slower.





hν

template (1.5 equiv)

–20 °C, toluene

4 days

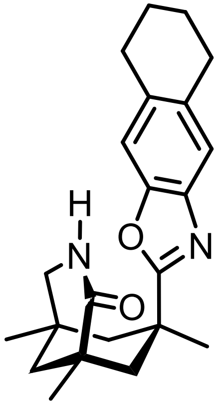
R = H, OMe, OBn

up to 51% yield
20-23% ee

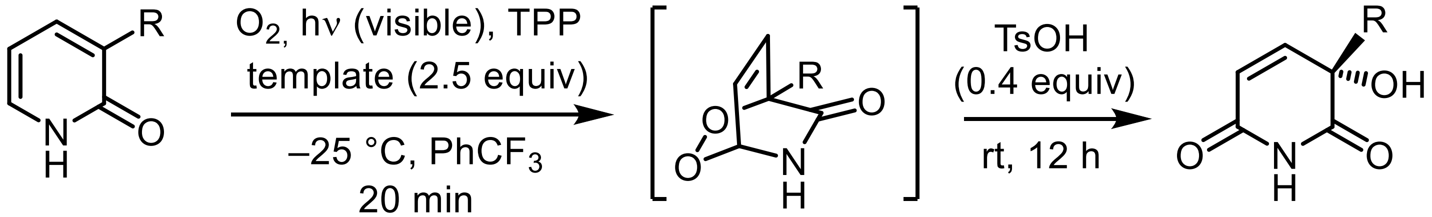
Kemp triacid lactam template

Singlet oxygen [4+2] cycloaddition

Bach, *Chem. Commun.* **2012**, *48*, 10195



One-pot reaction followed by acid-catalyzed Kornblum-DeLaMare rearrangement.

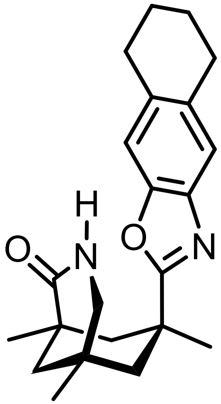


R = Me, Et, Bn

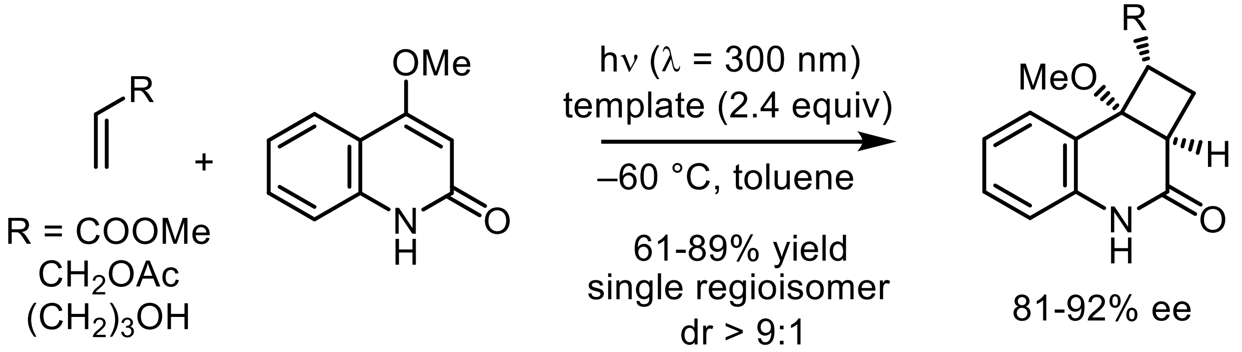
73-99% yield
69-90% ee

Kemp triacid lactam template

Intermolecular [2+2] photocycloaddition



Bach, *J. Am. Chem. Soc.* **2002**, *124*, 7983



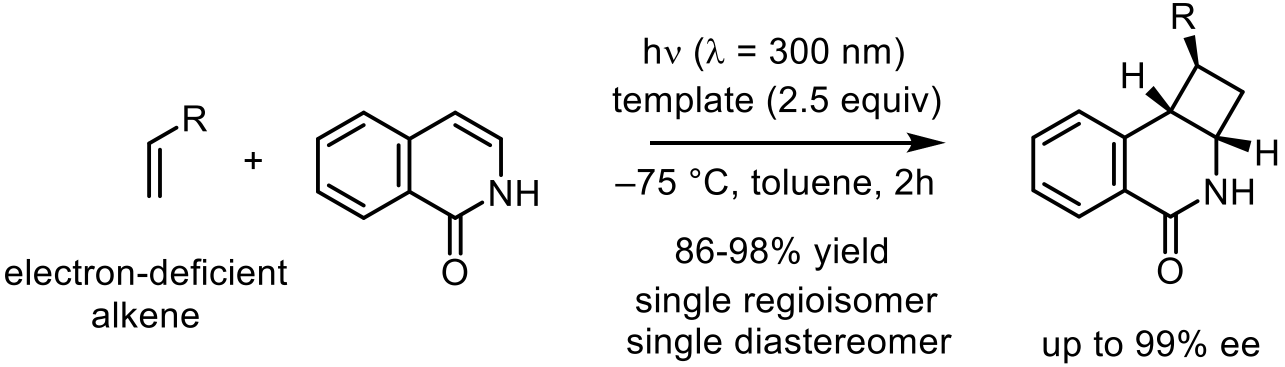
R = COOMe
CH_2OAc
$(CH_2)_3OH$

hν (λ = 300 nm)
template (2.4 equiv)
–60 °C, toluene

61-89% yield
single regioisomer
dr > 9:1

81-92% ee

Bach, *J. Am. Chem. Soc.* **2013**, *135*, 14948



electron-deficient
alkene

hν (λ = 300 nm)
template (2.5 equiv)
–75 °C, toluene, 2h

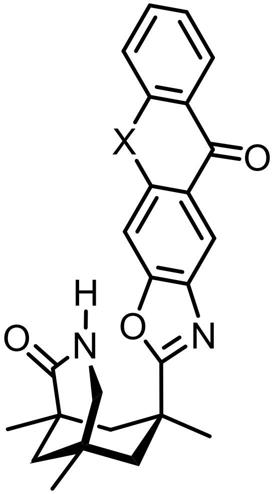
86-98% yield
single regioisomer
single diastereomer

up to 99% ee

Kemp triacid lactam template

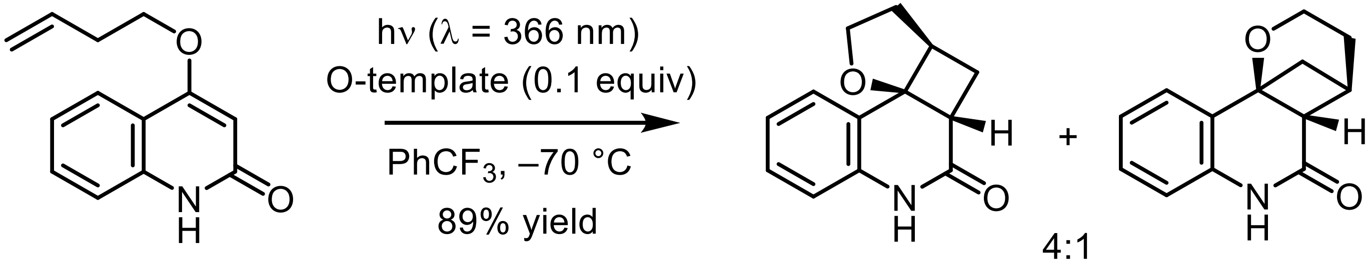
Intramolecular [2+2] photocycloaddition

Xanthone or thioxanthone templates acts as sensitizers
Wavelength selected appropriately



X = O, S

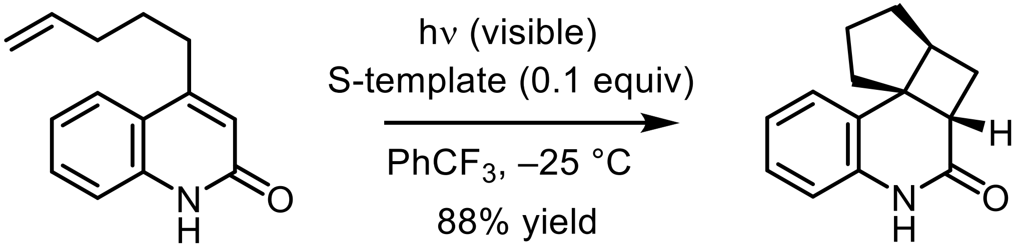
Bach, *Angew. Chem. Int. Ed.* **2009**, *48*, 6640



hν (λ = 366 nm)
O-template (0.1 equiv)
PhCF$_3$, –70 °C
89% yield

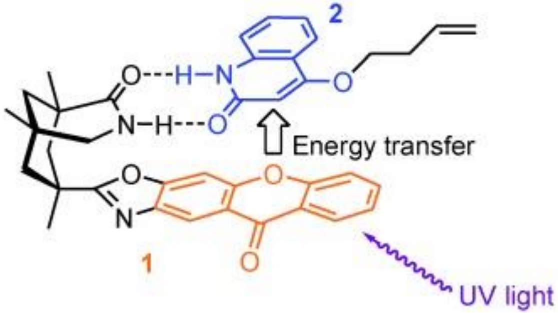
> 90% ee 4:1 > 90% ee

Bach, *Angew. Chem. Int. Ed.* **2014**, *53*, 4368



hν (visible)
S-template (0.1 equiv)
PhCF$_3$, –25 °C
88% yield

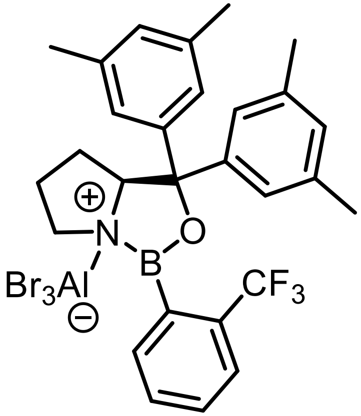
90% ee

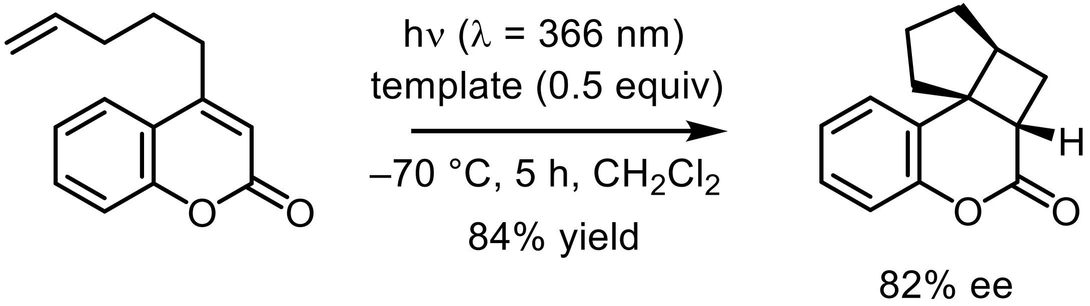


Chiral oxazaborolidine template

Intramolecular [2+2] photocycloaddition

Bach, *Angew. Chem. Int. Ed.* **2010**, *49*, 7782

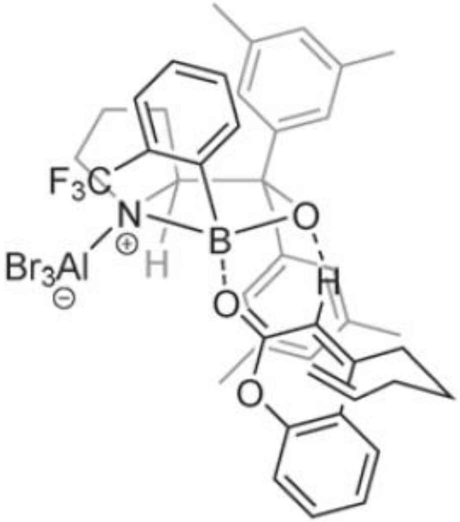




Without the template, yield = 28% (racemic)

Template has two effects:

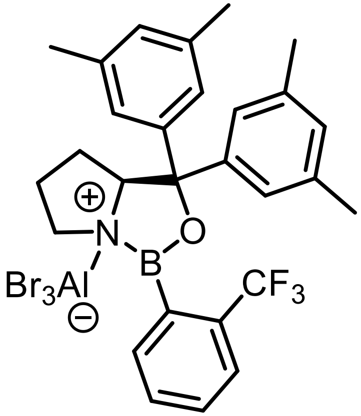
- binding provides asymmetric environment
- Lewis Acid behavior induces a bathochromic shift and increases S1 lifetime (and thus T1 population after ISC)

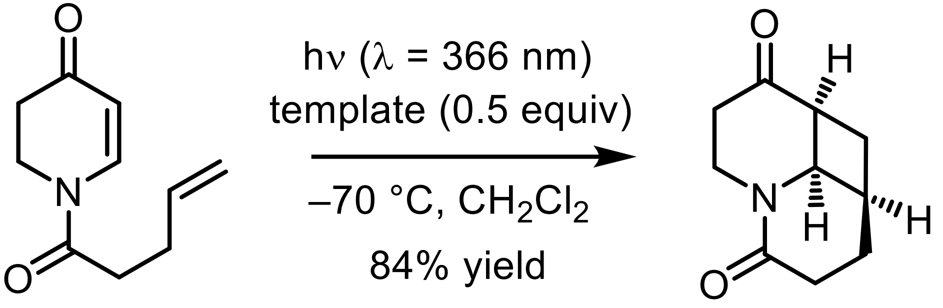


Chiral oxazaborolidine template

Intramolecular [2+2] photocycloaddition

Bach, *Science* **2013**, *342,* 840



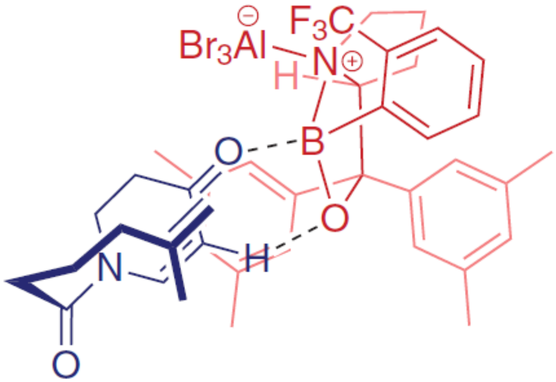

hν (λ = 366 nm)
template (0.5 equiv)
–70 °C, CH_2Cl_2
84% yield

88% ee

Without the template, the reaction proceeds at λ = 366 nm (ε = 70) via n → π* then ISC.

Template has two effects:

- binding provides asymmetric environment
- Lewis Acid behavior induces a *large* bathochromic shift (Δλ 50 nm); absorption at λ = 366 is π → π* (ε = 10^4). Light is therefore almost exclusively absorbed by the complex



Large hosts

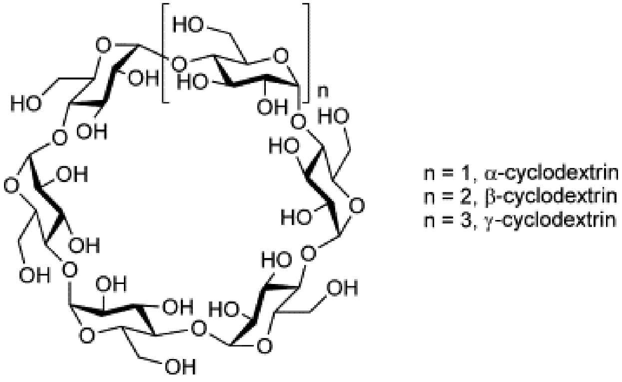
The host is a relatively large molecular structure and behaves as a molecular flask: the guest is at least partly enclosed by the host and party isolated from the external environment.

Template types include: cucurbitils; self-assembled cages, bowls, cavitands

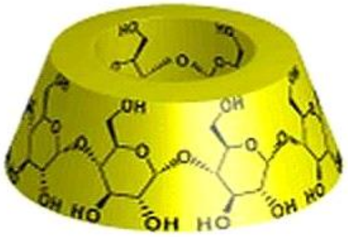
Cyclodextrins

Readily available (produced enzymatically from starch), variable size, inherent chirality, photochemically inert.

Toroid (truncated cone) shape. Smaller face (primary hydroxy groups), larger face (2° hydroxyl groups), hydrophobic cavity.



n = 1, α-cyclodextrin
n = 2, β-cyclodextrin
n = 3, γ-cyclodextrin

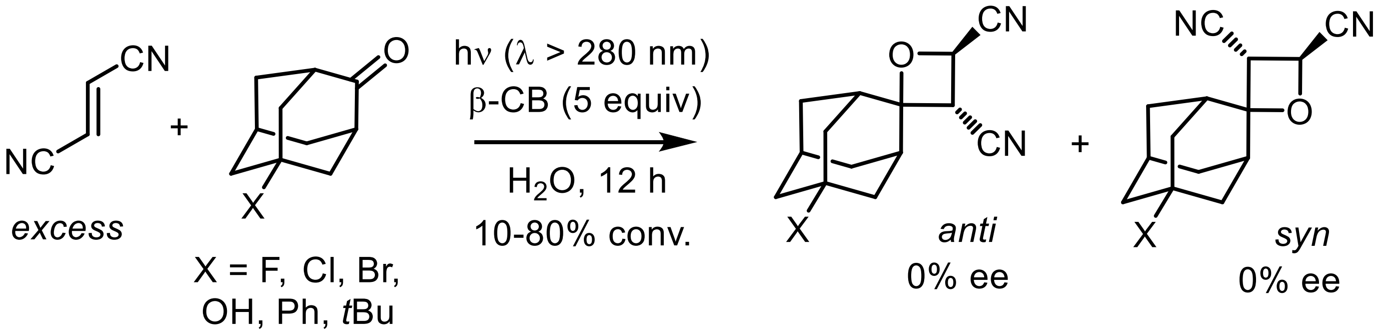


β-CD

Cyclodextrins

Paternò-Büchi reaction

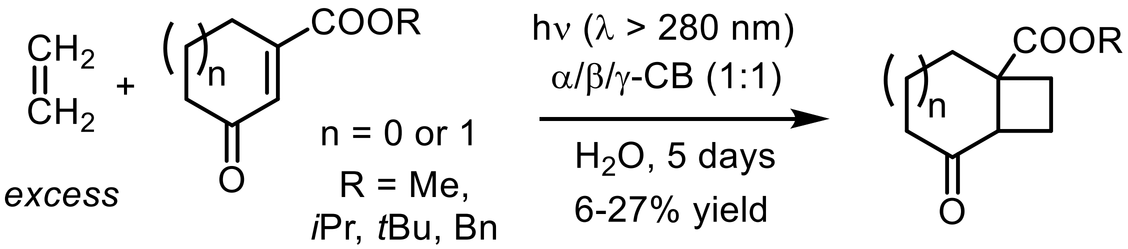
Turro, *J. Am. Chem. Soc.* **1990**, *112*, 1202



Without β-CB *anti/syn* = 60/40
With β-CD *anti/syn* = 20/80

Intermolecular [2+2] photocycloaddition

Kakiuchi, *Chirality* **2006**, *18*, 217



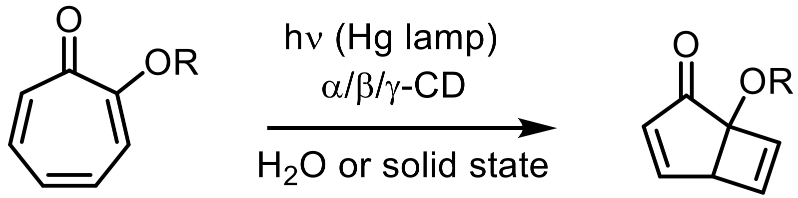
Best result 8% ee
α-CB; n = 0; R = Me

Cyclodextrins

Photochemical [2+2] electrocyclizations

Ramamurthy, *Tetrahedron* **2000**, *56,* 7003

Irradiation in aqueous solution with CDs gave photoproducts with negligible ee.
Irradiation of solid state CD complexes gave photoproducts with ee up to 33%.
Cavity size effect for R = Me: α-CD → 5% ee; β-CD → 28% ee; γ-CD → 0% ee.



hν (Hg lamp)
α/β/γ-CD

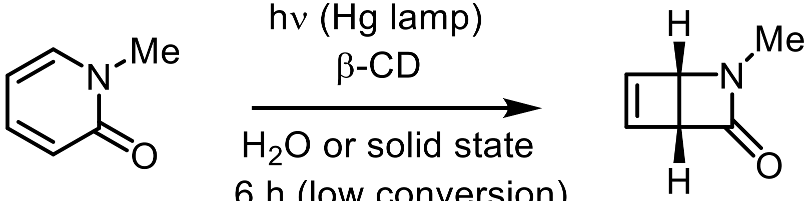
H_2O or solid state
1-8 days

R = various alkyl

yields not reported

host:guest ratio
α-CD (1:1)
β-CD (1:2)
γ-CD (1:2)

Ramamurthy, *Tetrahedron Lett.* **2002**, *43,* 9335



hν (Hg lamp)
β-CD

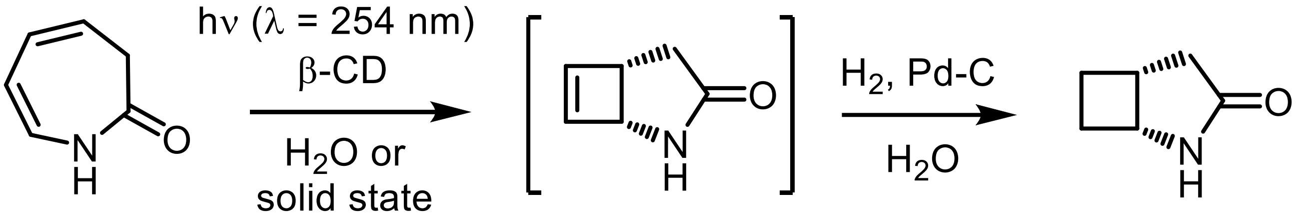
H_2O or solid state
6 h (low conversion)

In solution: ee < 5%
In solid state: ee = 60% ee

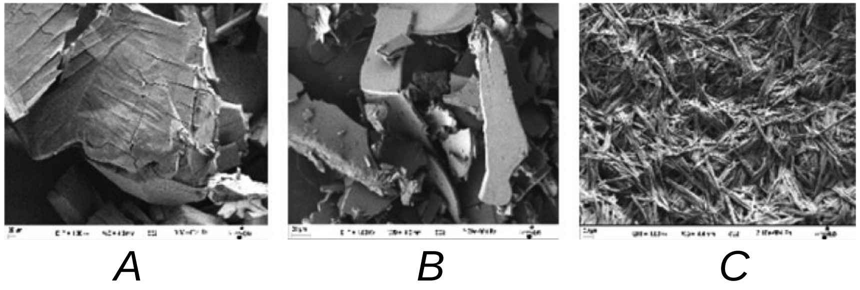
Cyclodextrins

Photochemical [2+2] electrocyclizations

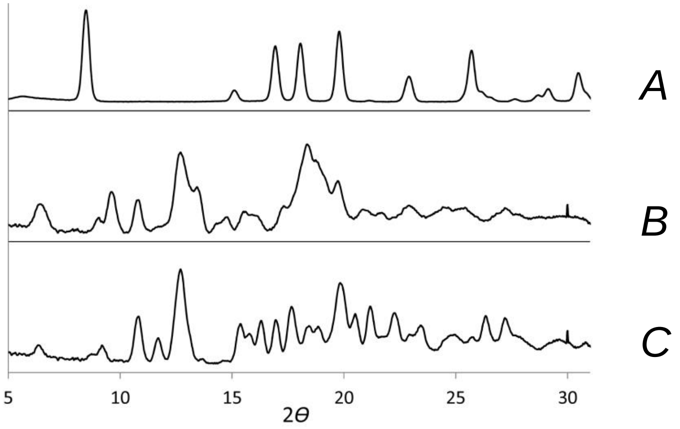
Aitken, *J. Org. Chem.* **2017**, *82*, 9832



Solution state: isolated yield 65%, ee = 0%
Solid state 1:1 complex (suspension, film): isolated yield 78%, ee 45%



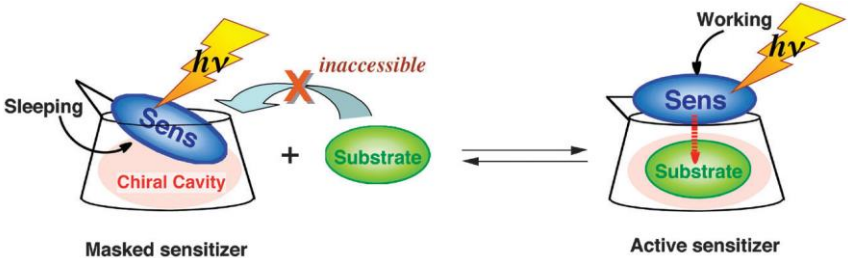
A: solid azepinone
B: solid β-CD
C: azepinone:β-CD 1:1 complex



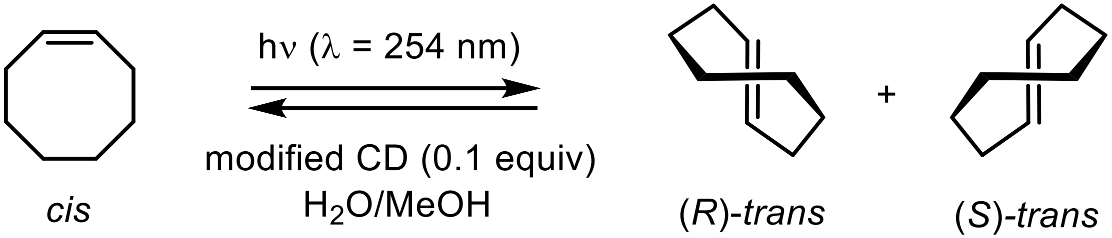
Cyclodextrins bearing sensitizers

Alkene *cis/trans* photoisomerization

Inoue, *J. Org. Chem.* **2000**, *65*, 8041



trans-cyclooctene is
a chiral molecule



cis

hν (λ = 254 nm)

modified CD (0.1 equiv)
H_2O/MeOH

(*R*)-*trans*

(*S*)-*trans*

R = H
R = *o*-OMe
R = *m*-OMe
R = *p*-OMe
R = *m*-CO_2Me

6-*O*-benzoate esters of α/β/γ-CDs as hosts

In the photostationary state, the *trans/cis* ratio was 0.4–0.8
(*c.f.* 0.25 for conventional benzoate sensitizations in hydrocarbon solvents)

Cavity size effect: α-CD → 3% ee; β-CD → 46% ee; γ-CD → 5% ee.

2. Solid state reactions

Principle : substrates form single crystals (of appropriate size and quality) which have a **chiral space group**. The chiral packing is equivalent to an asymmetric reaction cavity.

There are 230 space groups, of which 65 are chiral.
The is no general understanding of the relationship between molecular structure and crystal structure.
The vast majority of achiral compounds do *not* crystallize in chiral space groups; it is virtually impossible to predict when a substance will do so.

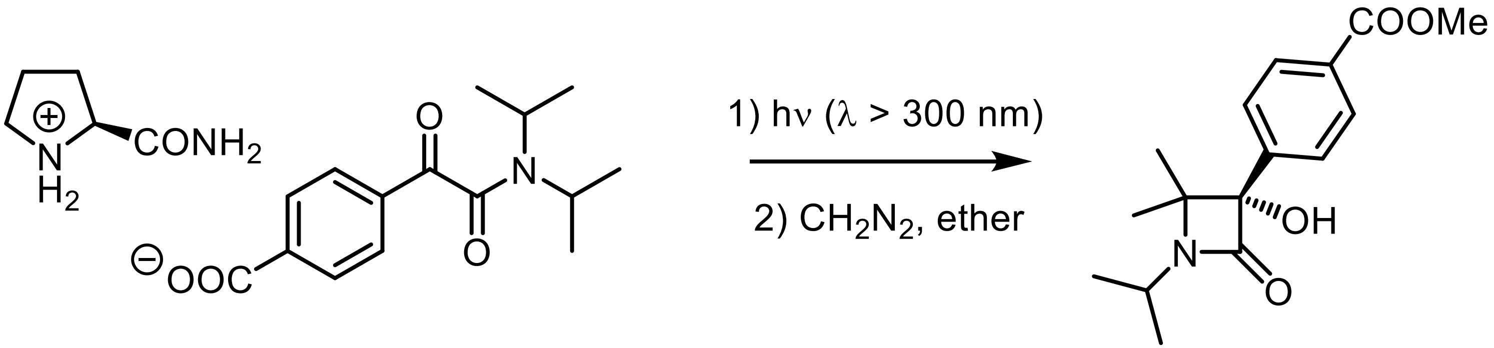
A common approach to *guarantee* a chiral space group is to associate (non covalently) the substrate with an optically pure chiral auxiliary. Such compounds are required to crystallize in chiral space groups.

In the footsteps of Louis Pasteur (1853)
Resolution of racemic tartaric acid via formation of diastereoisomeric salts with cinchonicine followed by fractional crystallization

Cocrystallized as a chiral salt

Norrish-II / Yang cyclization

Scheffer, *Synthesis* **2001**, 1253



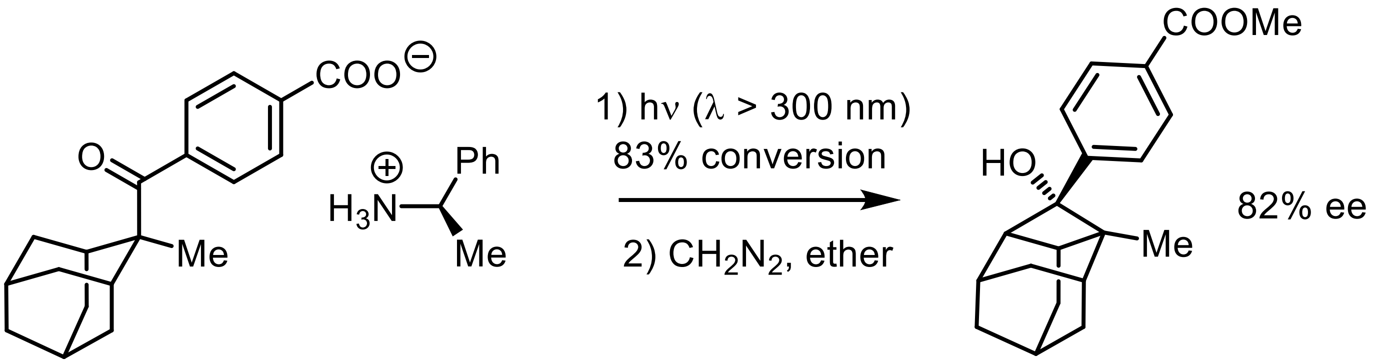
Crystallized from methanol
(space group not determined)

crystals suspended in hexane (500 mg scale): 99% ee, 91% yield
pure solid state: 99% ee
solution in acetonitrile: 7% ee

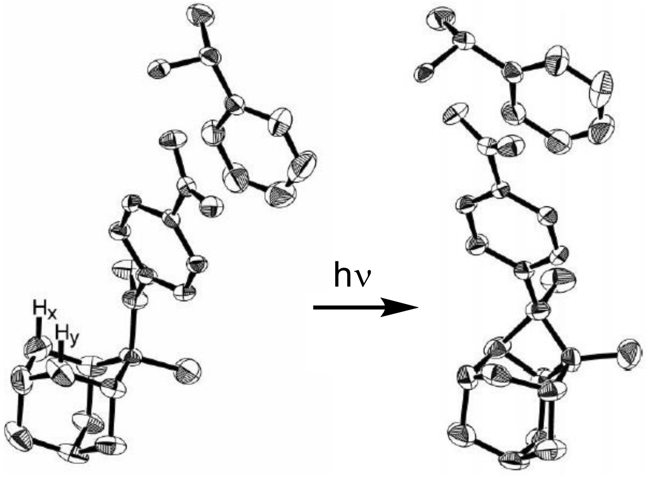
Cocrystallized as a chiral salt

Norrish-II / Yang cyclization

Scheffer, *Can. J. Chem.* **2001**, *79*, 349



The single (homochiral) conformation in the crystal allows selective abstraction of one of the two enantiotopic hydrogens

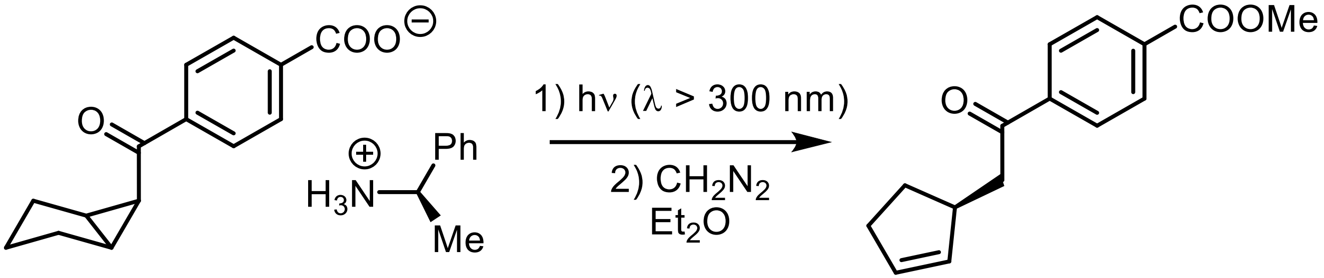


X-ray structure of the same crystal before and after irradiation (space group $P2_12_12_1$)

Cocrystallized as a chiral salt

Norrish-II / α,β-fragmentation

Xia, *Tetrahedron* **2009**, *65*, 9952

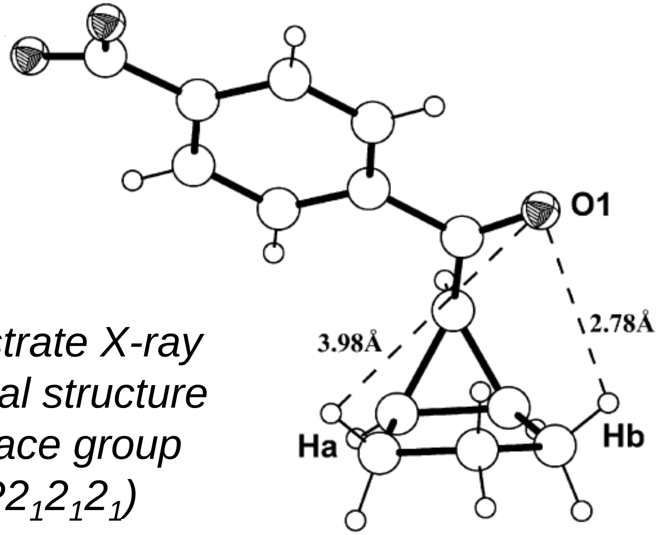


conv (%)	ee (%)
41	90
79	67
95	55

Crystals (5 mg) crushed between Pyrex microscope slides, irradiated on both sides (450 W Hg lamp)

As conversion increased, ee decreased; possibly due to breakdown in crystal lattice order as product replaces substrate.

Irradiation in CH_3CN solution: ee = 0%

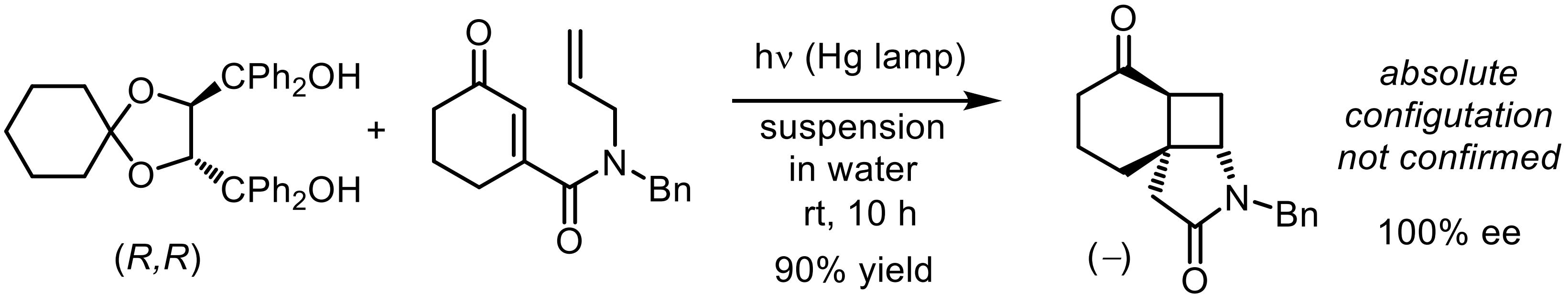


substrate X-ray crystal structure (space group $P2_12_12_1$)

Cocrystallized with a chiral non-racemic molecule

Intramolecular [2+2] photocycloaddition

Toda, *Chem. Commun.* **1995**, 621



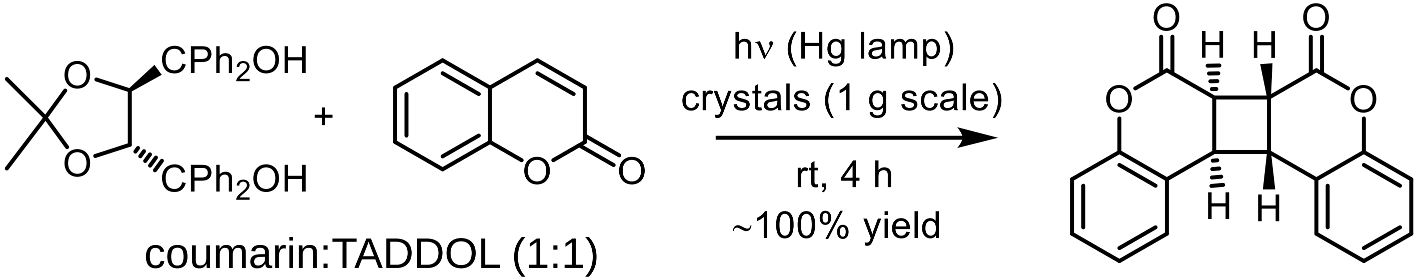
2:1 inclusion complex crystallized from ether

crystals irradiated as a suspension in water (2 g scale)

Cocrystallized with a chiral non-racemic molecule

Intermolecular [2+2] photocycloaddition (dimerization)

Toda, *Angew. Chem. Int. Ed.* **1999**, *38,* 3523



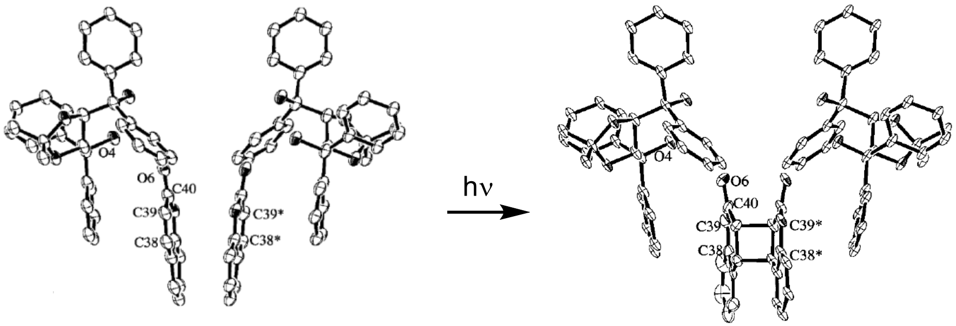
coumarin:TADDOL (1:1)
crystallized from EtOAc/hexane

exclusively
HH, *cis-anti-cis*

96% ee

Coumarin dimerization in solution is inefficient and gives regio/stereo mixtures
Coumarin crystals do not photodimerize (unfavorable packing)

X-ray structure of the same crystal before and after irradiation (space group C2)

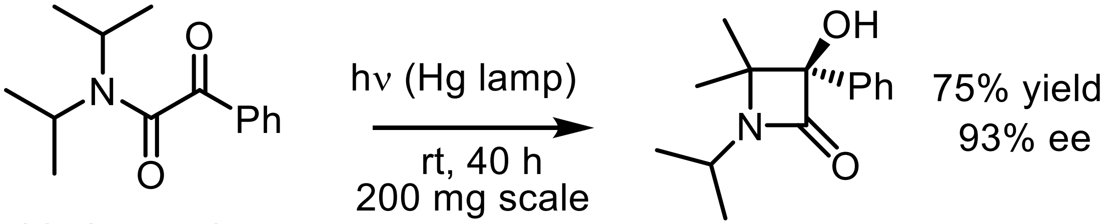


Chiral crystals from achiral molecules

Norrish-II / Yang cyclization

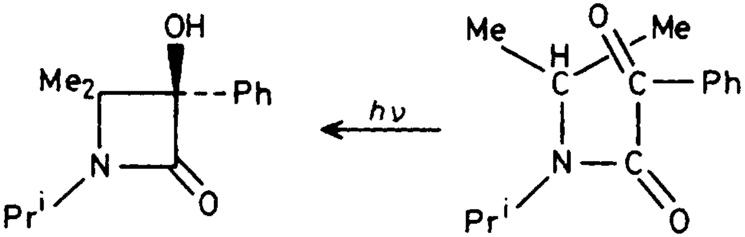
Toda, *Chem. Commun.* **1987**, 1413

“Absolute asymmetric synthesis”



chiral crystals

Chiral crystals (5-10 mg) of the achiral glyoxylamide grown from benzene
Space group $P2_12_12_1$



(1)

(+)-(2)

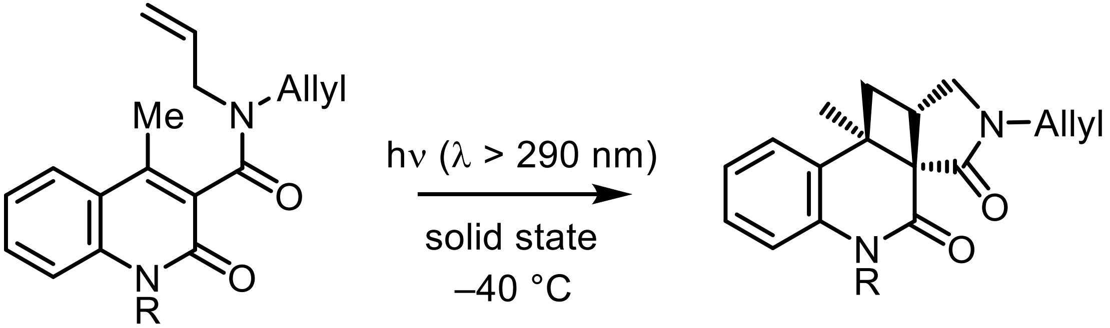
in (+)-crystal

Chiral crystals from achiral molecules

Intramolecular [2+2] photocycloaddition

Sakamoto, *Org. Lett.* **2011**, *13*, 6168

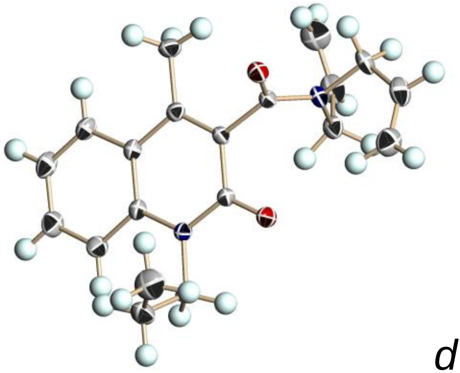
"Absolute asymmetric synthesis"

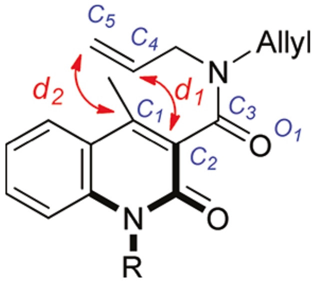


R	space group	conv (%)	yield (%)	ee (%)
Me	*P*bca	43	86	0
Et	$P2_1/c$	38	76	0
Pr	$\boldsymbol{P2_1}$	**67**	**92**	**95**

Crystallized from $CHCl_3$/hexane

In the crystal, all substrates adopt a near-perpendicular conformation between the quinolone ring and the amide plane





d_1 = 3.4-3.9 Å, d_2 = 4.1-5.8 Å