

CHEM60001:
Advanced Chemistry Topics 1 – Pericyclic
Reactions

LECTURE 6
Cycloaddition, Cheletropic & Group Transfer
Reactions

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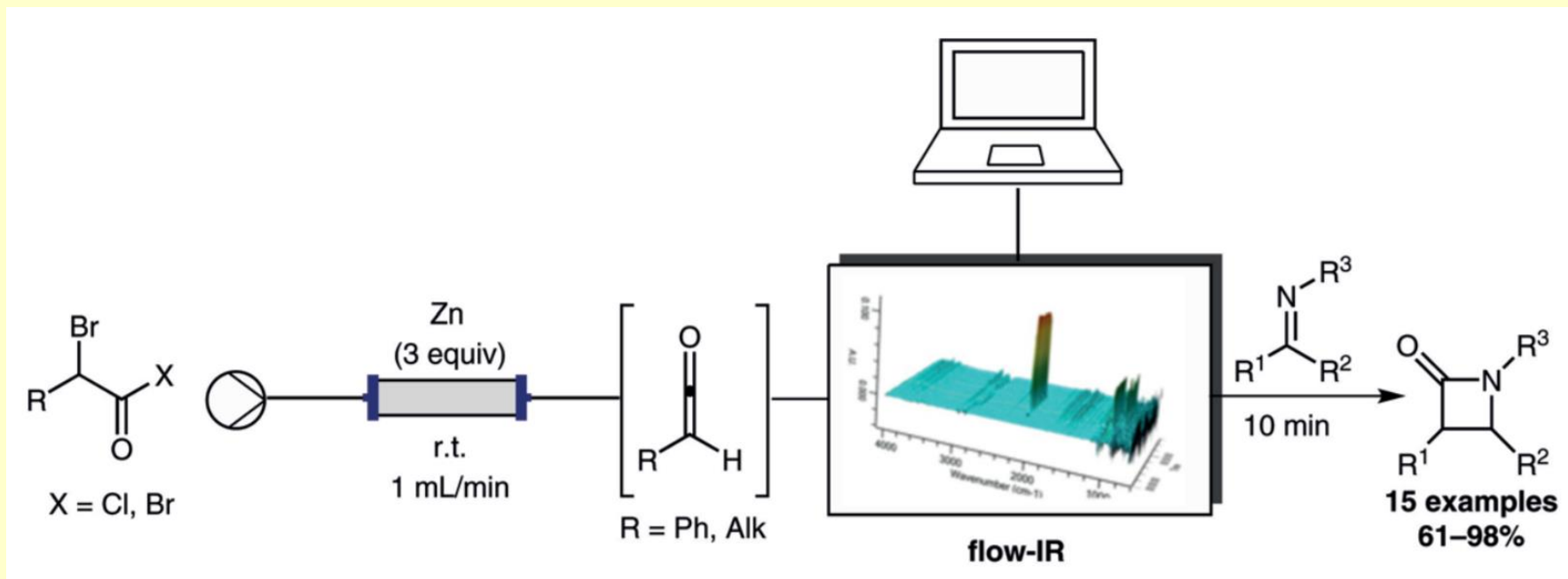
Format & scope of lecture 6

- ***[2+2]-cycloaddition reactions***
 - Ketene cycloaddition reactions
- ***Cheletropic reactions***
 - Carbene & SO₂ extrusion reactions
- ***Group transfer reactions***
 - Alder ene reactions
 - Conia ene & carbonyl ene reactions
 - Syn-elimination reactions

Key further reading:

- **BOOK**: Clayden, Greeves & Warren, *Organic Chemistry*, 2nd Ed.,
 - **Chapter 34** – pericyclic reactions 1 - cycloadditions
- **WEB**: Pericyclic Reactions - https://www.stereolectronics.org/webPR/PR_home.html
 - **Chapter 3** – Other concerted [m+n] cycloadditions

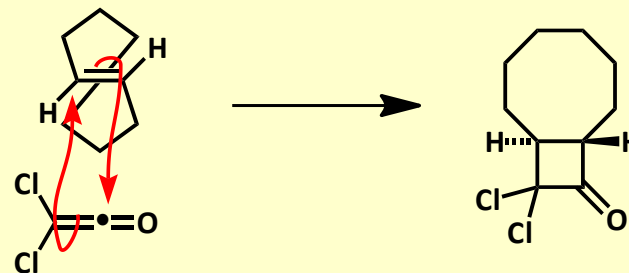
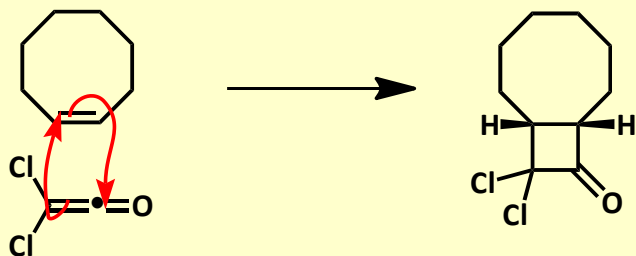
Ketene [2+2] cycloaddition reactions



Mono-substituted ketenes are generally highly reactive and difficult to isolate, but flow conditions allow for efficient formation. *NB.* Characteristic carbonyl stretch @ 2100 cm^{-1}

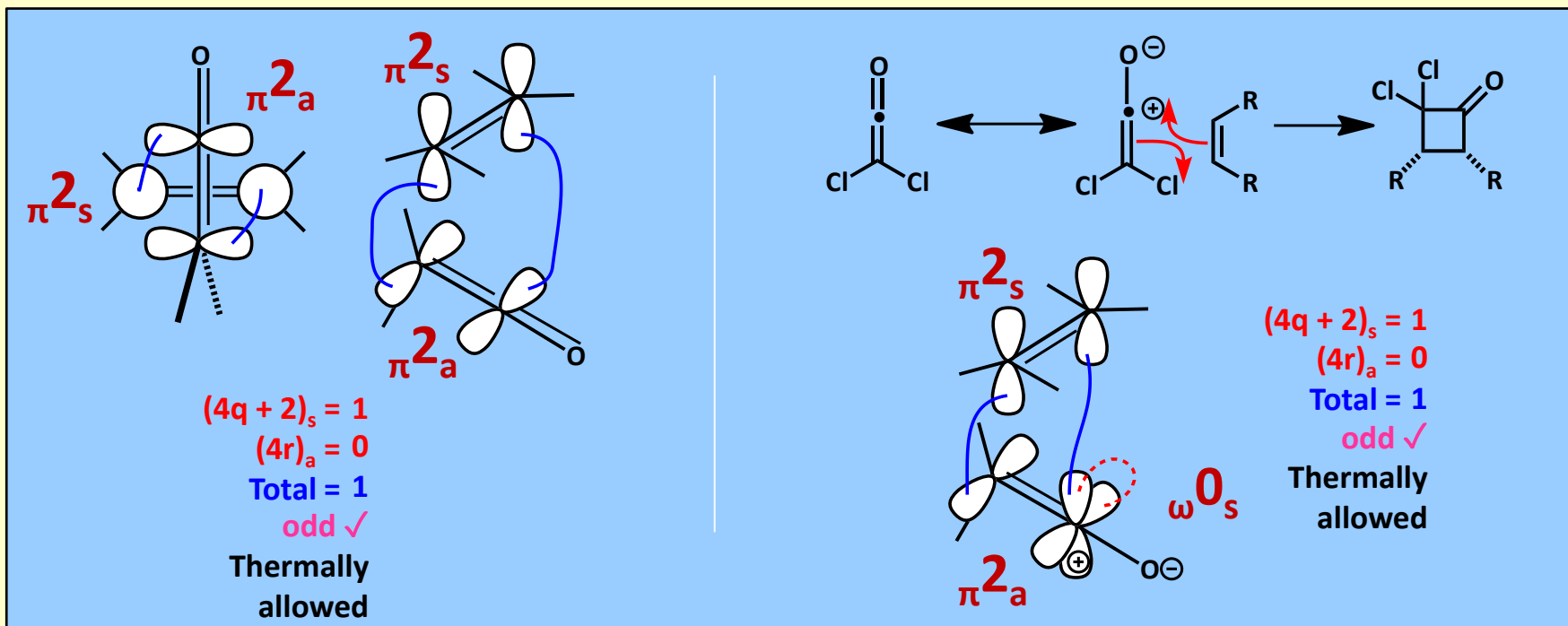
Cycloadditions: ketene [2+2] (W-H approach)

Ketenes undergo (thermal) [2+2]-cycloadditions with alkenes to generate cyclobutanones:



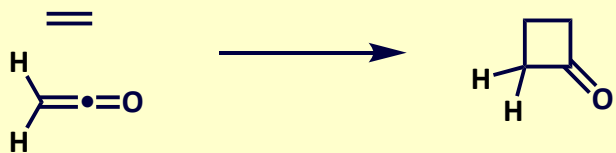
Two W-H explanations:

- (1) orbitals of the ketene are used as an antarafacial component (geometrically difficult)
- (2) treat ketene as a vinyl cation (geometrically better, but requires communication between orthogonal p-orbitals)

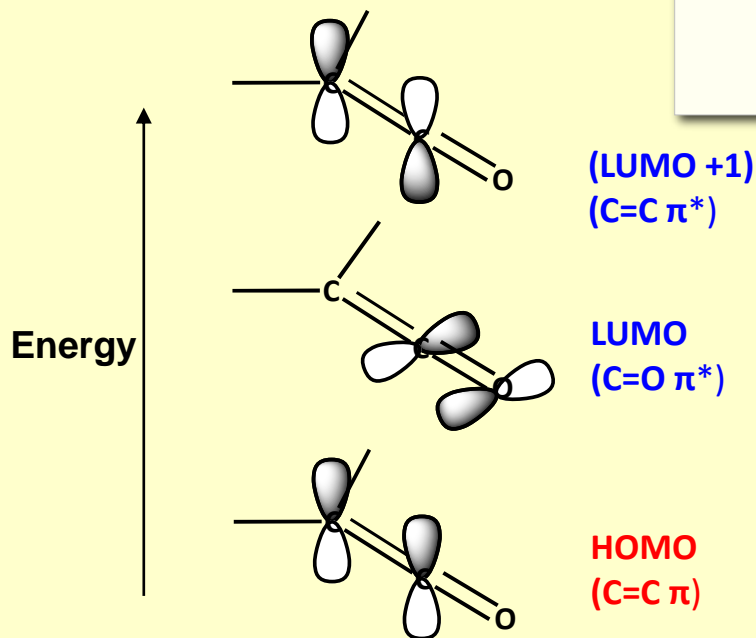


Cycloadditions: ketene [2+2] (FMO approach)

Ketenes undergo (thermal) [2+2]-cycloadditions with alkenes to generate cyclobutanones:



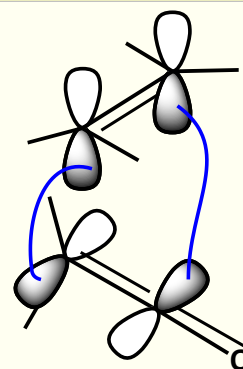
Ketene MOs:



Primary overlap:

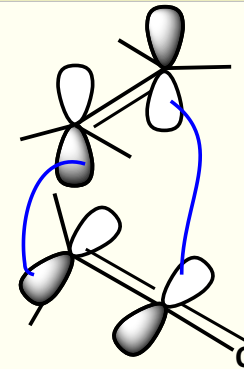
HOMO alkene (C=C π)

(LUMO +1) ketene (C=C π^*)



LUMO alkene (C=C π^*)

HOMO ketene (C=C π)

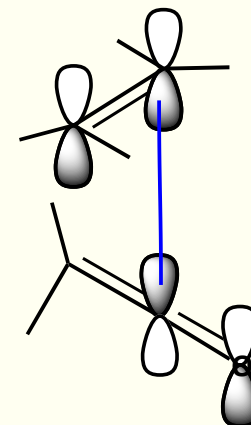


constructive overlap ✓

Secondary overlap:

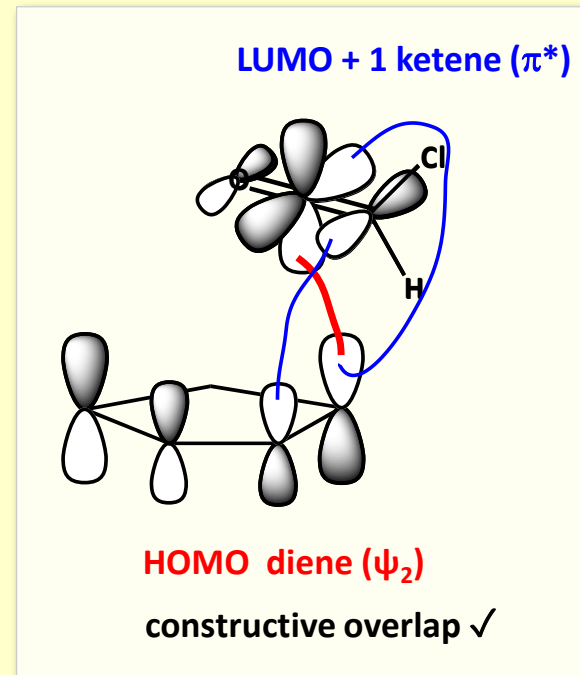
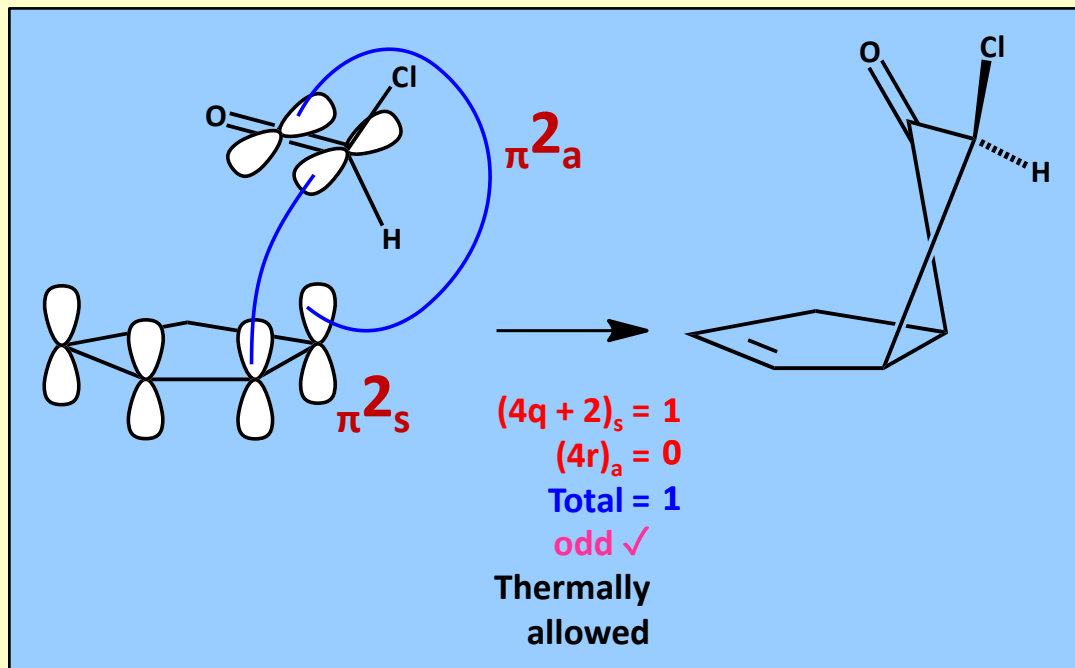
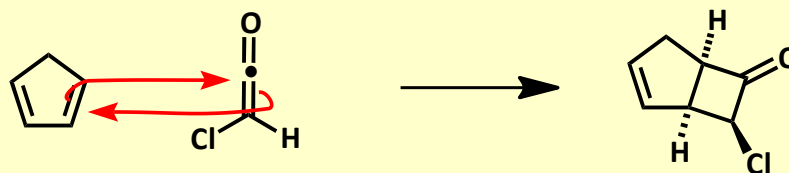
HOMO alkene (C=C π)

LUMO ketene (C=O π^*)



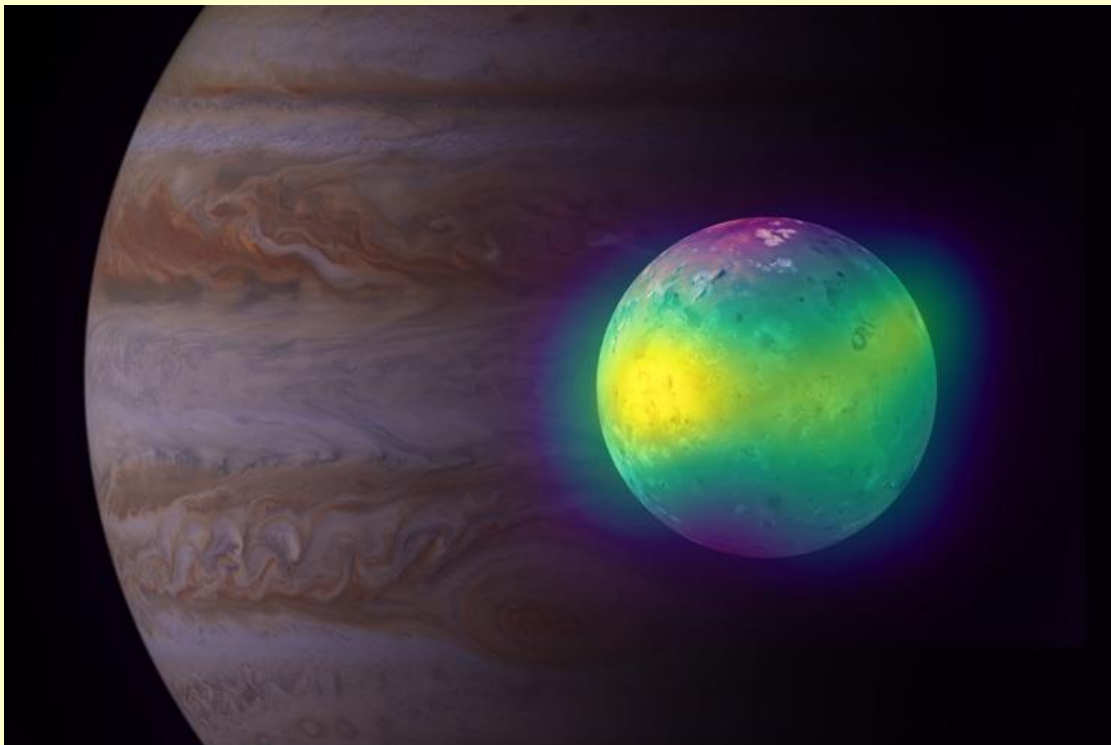
With ketenes it is probable that the low-lying C=O π^* orbital is involved in secondary orbital overlap; other cumulated π systems which contain a central sp -hybridised carbon atom (e.g. allenes, vinyl cations) also readily undergo [2+2] cycloaddition

Cycloadditions: *unsymmetric ketene* [2+2]



- With an unsymmetrical ketene, the larger ketene substituent will point away from the plane of the alkene.
- As for other cycloadditions, regioselectivity can be predicted from polarity considerations (*i.e.* resonance & “arrow-pushing” arguments), or from looking at FMO coefficients.
- In reactions of unsymmetrical alkenes the less sterically demanding C=O part of the ketene will be oriented above the larger alkene substituents.

Cheletropic reactions



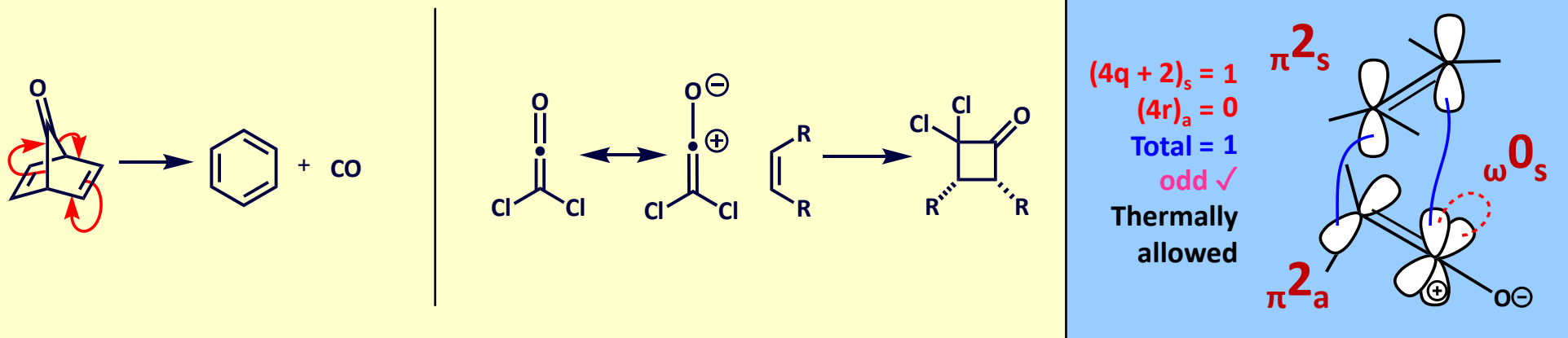
Sulfur dioxide (SO_2) participates readily in cheletropic reactions with dienes and trienes.

SO_2 is found at ~ 1 ppm concentration in the earth's atmosphere, but the atmosphere of Io, a natural satellite of Jupiter, is 90% sulfur dioxide.

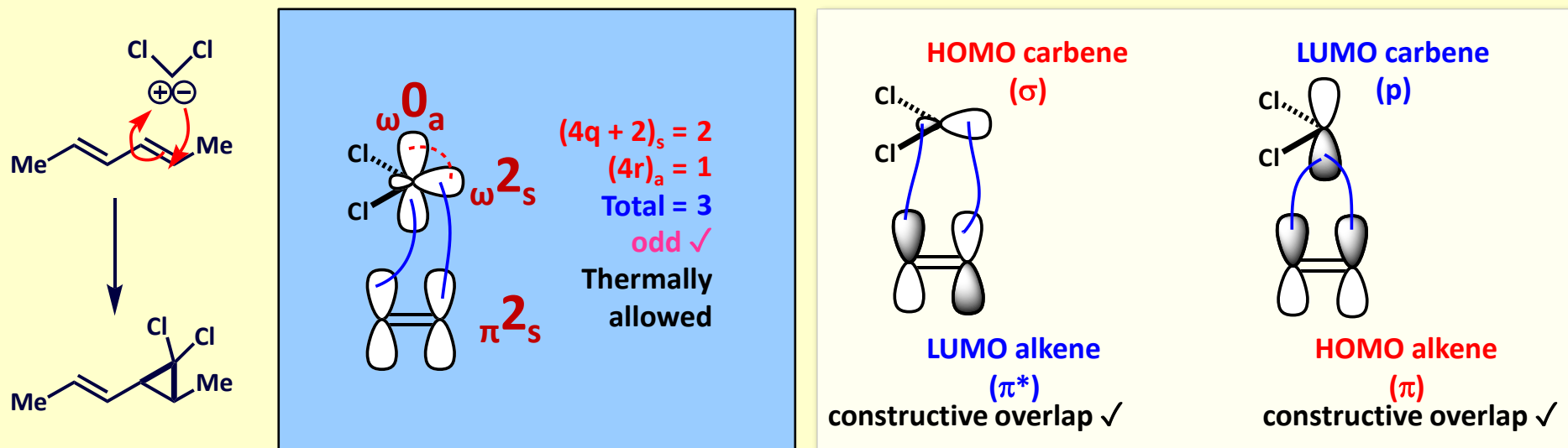
This is a composite image of Io and Jupiter in which sulfur dioxide plumes from Io's volcanoes are seen in yellow (Jupiter image from the Cassini spacecraft, Io image from the Alma telescope in Chile).

Cheletropic reactions – singlet carbene [2+1]

A sub-class of cycloaddition/cycloreversion reactions in which the two σ – bonds are made or broken to the same atom (compare with ketenes as vinyl cations)



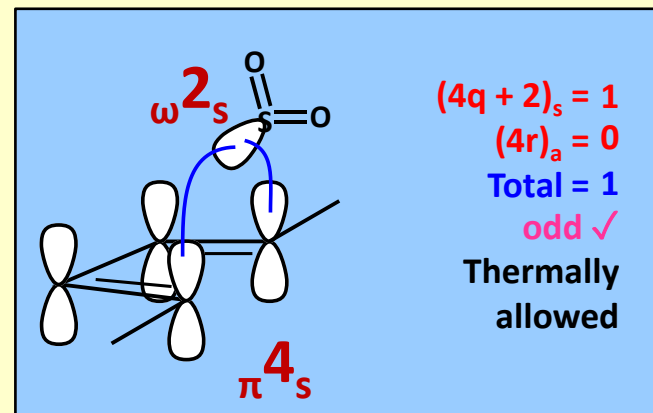
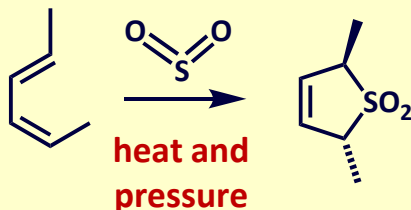
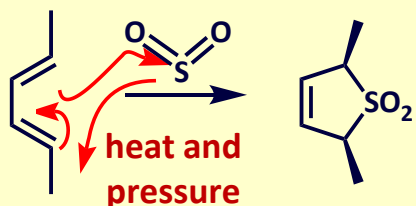
Addition of singlet carbenes (stereospecific) is most important; side on approach necessary:



W-H approach

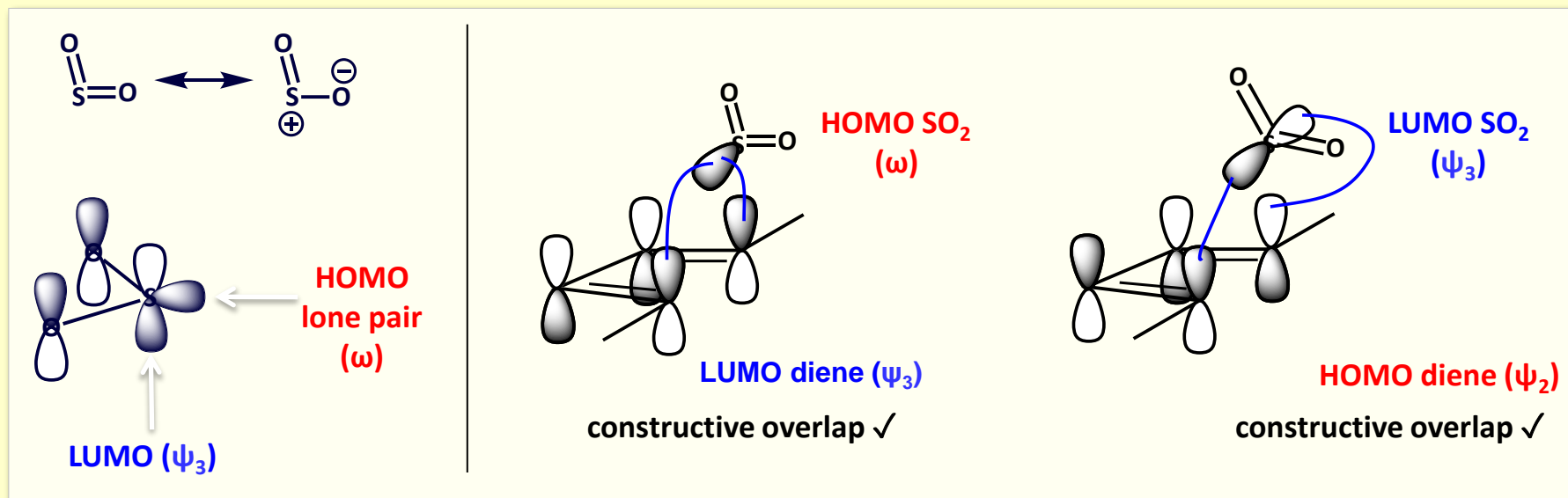
FMO approach

Cheletropic reactions: *sulfur dioxide & polyenes*



W-H approach

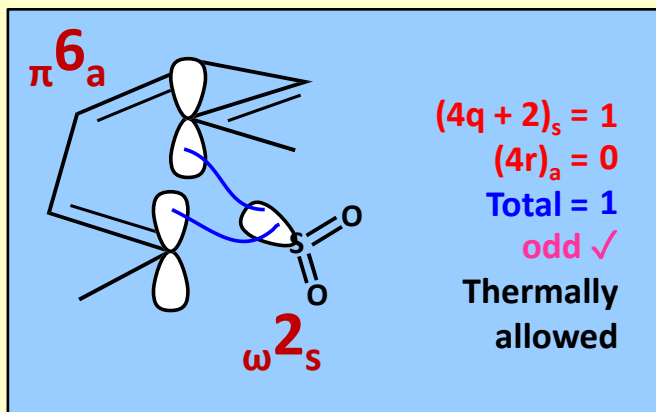
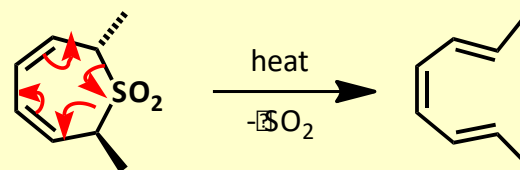
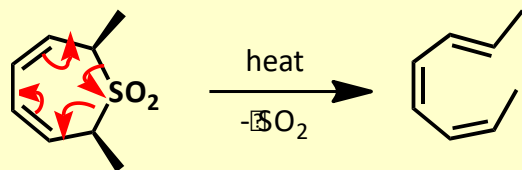
The addition of sulfur dioxide to polyenes is a reversible process



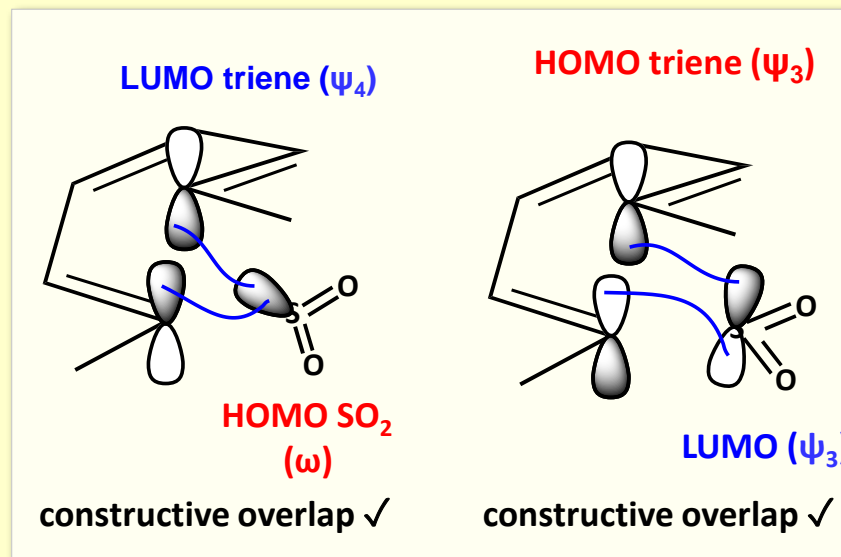
FMO approach

Cheletropic reactions: *sulfur dioxide & polyenes*

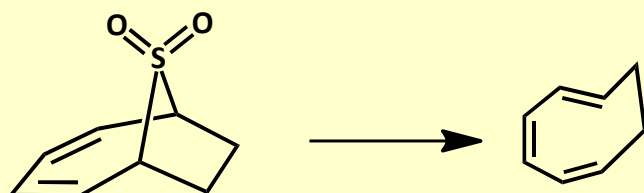
With trienes the extrusion process dominates but considering the reverse process, the reaction must be *antarafacial* with respect to the triene component:



W-H approach



FMO approach

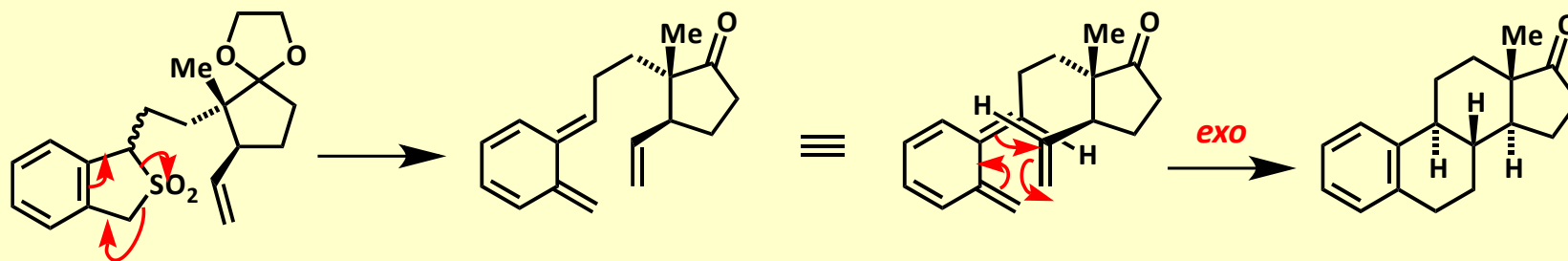


too strained; ca. 10^4 times less reactive than

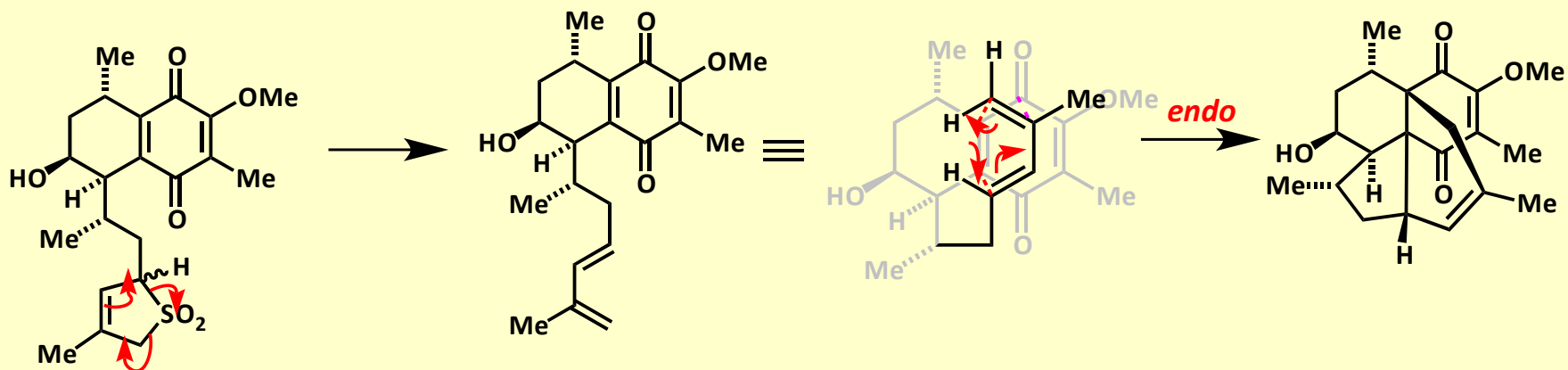
Cheletropic reactions: *sulfur dioxide* & *polyenes*

- **The cheletropic extrusion of SO_2 is often used in synthesis to unmask a diene, as a prelude to a Diels-Alder or other cycloaddition.**

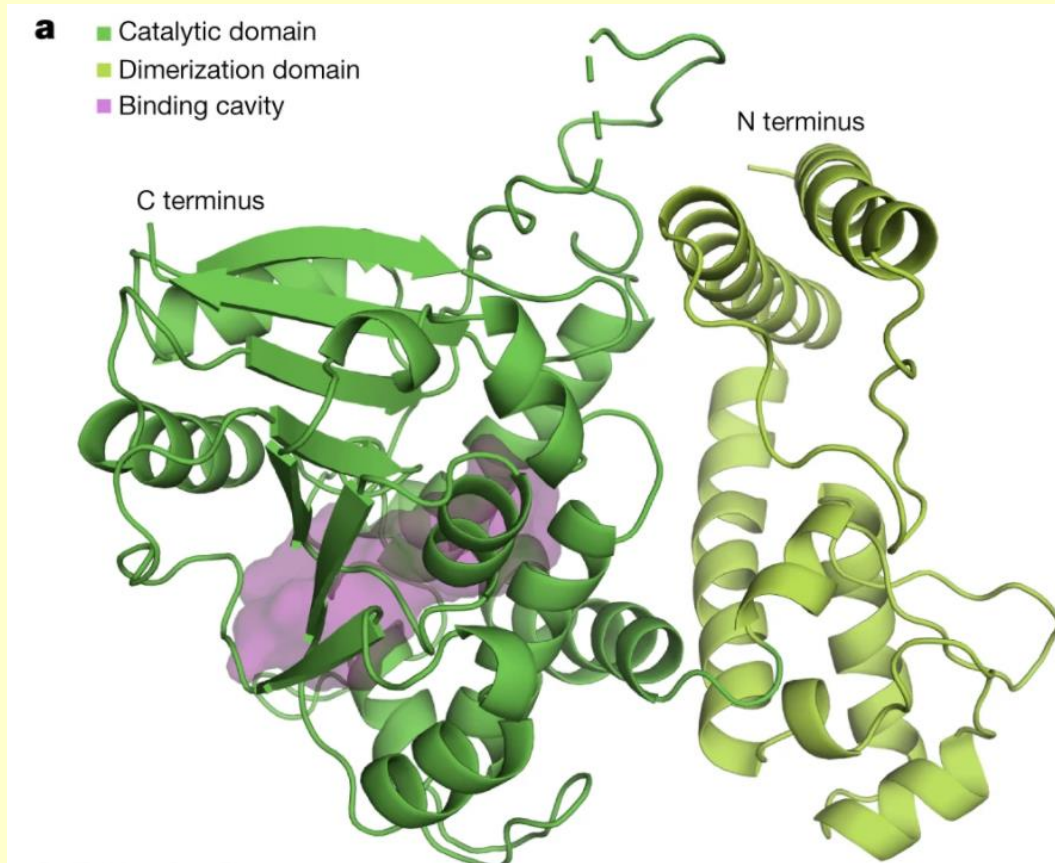
- Application in the synthesis of estrone (a human steroid):
 - Nicolaou *J. Org. Chem.* **1979**, *45*, 1463 [DOI]



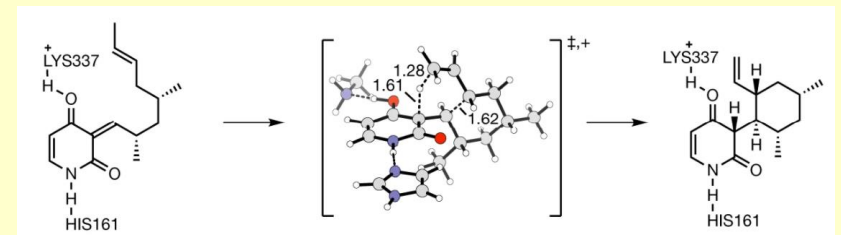
- Application in the synthesis of columbiasin (a coral-derived diterpene natural product):
 - Nicolaou *Angew. Chem. Int. Ed.* **2001**, *40*, 2482 [DOI]



Group transfer reactions



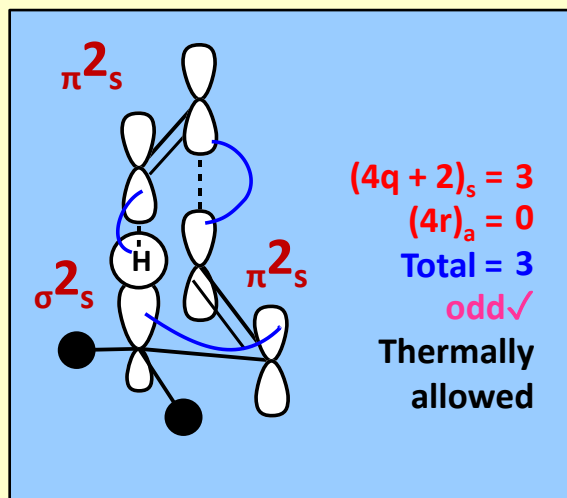
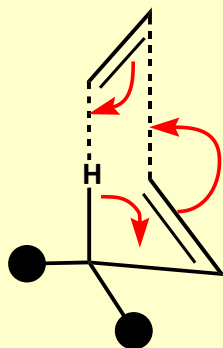
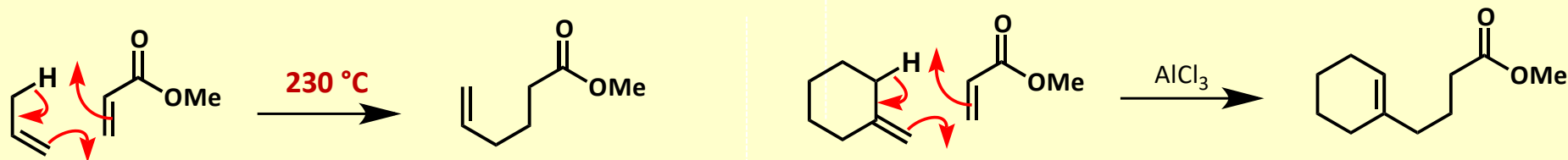
The enzyme PdxI catalyses an Alder-ene reaction *en route* to the natural antibiotic and antioxidant natural product – pyridoxatin. A crystal structure has been obtained of the product complexed into the active site of this enzyme – see: PDB: [7BQL](https://www.rcsb.org/structure/7BQL)



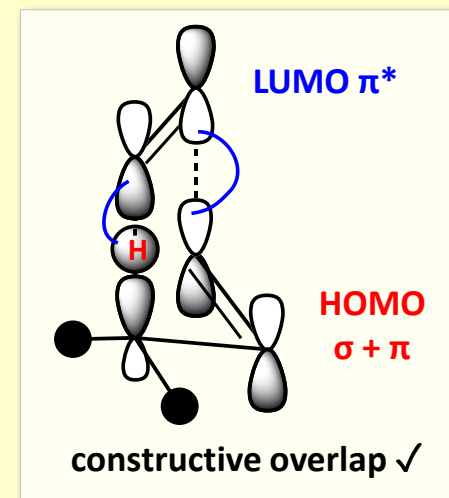
Group transfer reactions

- **Group Transfer Pericyclic Reactions** – a mix of a *sigmatropic rearrangement* and a *cycloaddition*
 - Bimolecular, so not sigmatropic rearrangements, and no ring is formed so they are not cycloadditions

- **The Alder-ene reaction:**



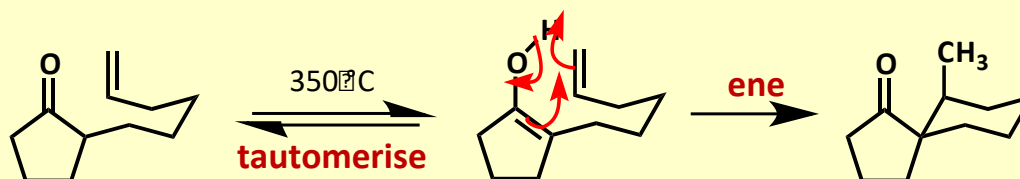
W-H approach



FMO approach

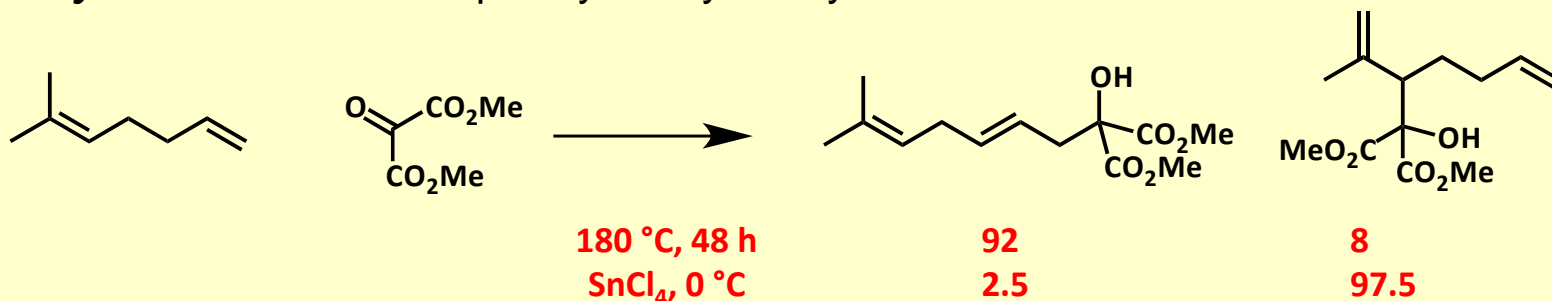
- **The Conia-ene reaction:**

- Enol as 'ene' component:

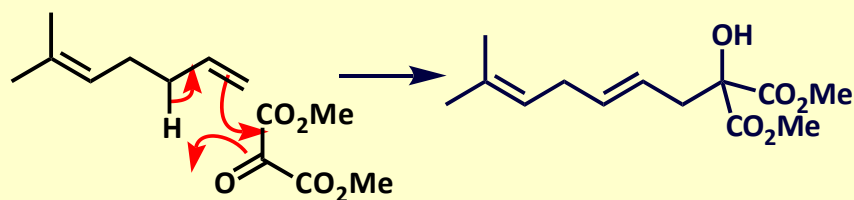


Group transfer reactions

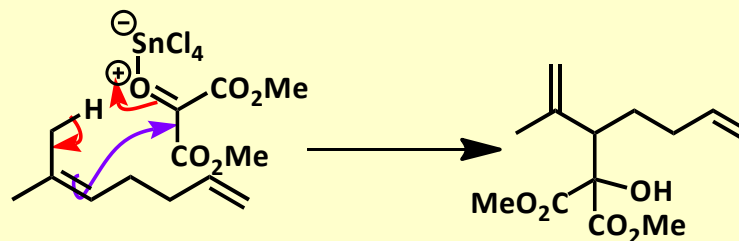
- The Carbonyl-ene reaction** - frequently catalysed by Lewis acids:



*In thermal carbonyl ene reactions
sterics are important*



*In Lewis acid-catalysed reactions the
enophile develops significant +ive charge*



- Retro-ene and retro-group transfer reactions are common**

