

***CHEM95002:***  
***Orbitals in Organic Chemistry - Pericyclics***

***LECTURE 7 Cycloaddition Reactions***

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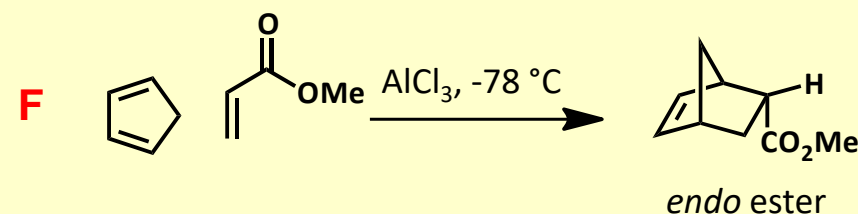
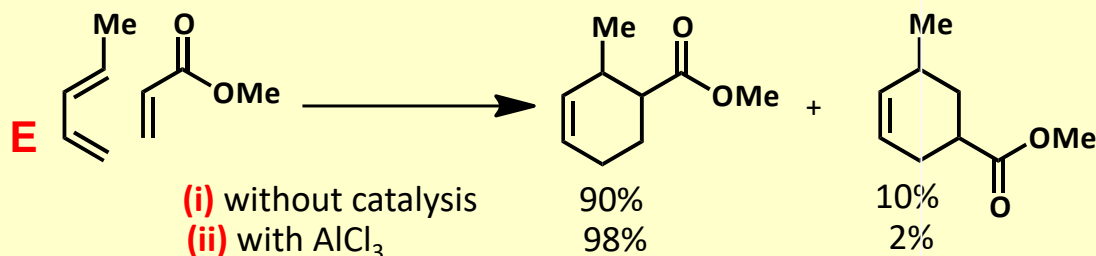
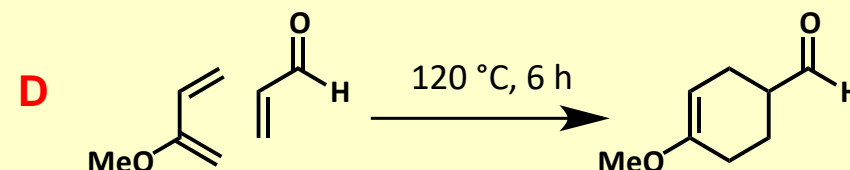
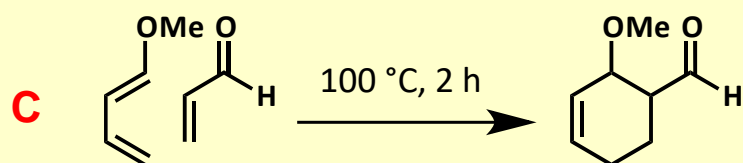
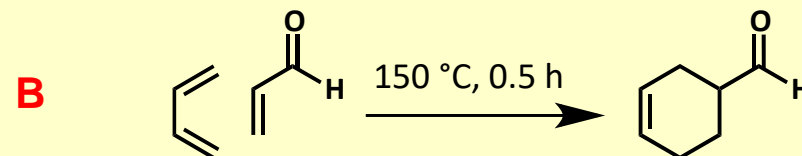
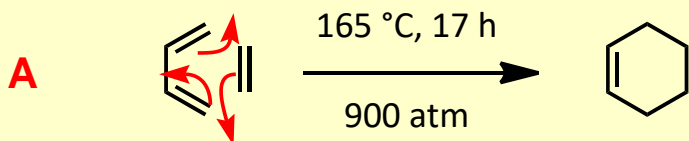
# Format & scope of lecture 7

- **Cycloaddition reactions**
  - Diels-Alder reaction
    - Rates
    - Regioselectivity
    - Stereoselectivity – the *endo* 'rule'
  - 1,3-Dipolar cycloadditions
    - Ozonolysis

# Cycloaddition: *the Diels-Alder reaction*

## Overall synthetic characteristics - summary:

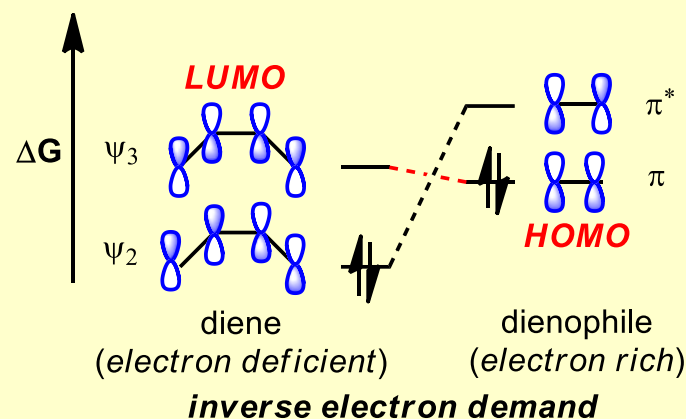
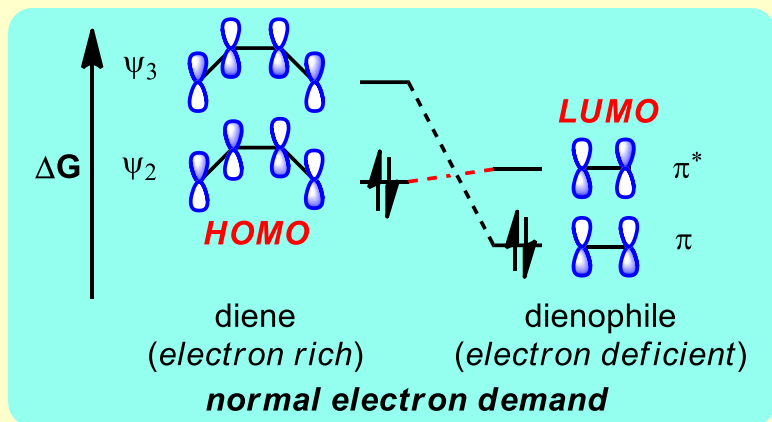
- Reaction rates: dependent on the HOMO-LUMO energy gap
  - Therefore varies as a function of reaction partner electronics
    - 'Normal' electron demand: accelerated by having an EDG on the diene & an EWG on the dienophile (cf. **A** vs. **B** vs. **C/D**)
    - 'Inverse' electron demand: accelerated by having an EWG on the diene & an EDG on the dienophile
- Reaction regioselectivity: dependent on the coefficients (=sizes) of the HOMO & LUMO reacting orbitals
  - can usually be anticipated by considering the 'polarisation' of the reaction partners
  - *ortho* and *para* products tend to predominate (cf. **Ei** vs **Eii**)
  - rate & selectivity often increased by catalysis
- Reaction stereoselectivity: dependent on secondary orbital interactions
  - *endo* products formed preferentially for normal electron demand reactions (i.e. involving EWG  $\pi$ -conjugated alkene dienophiles) (see: **F**)



# Diels-Alder reactivity – *HOMO-LUMO* matching

## Reaction rates:

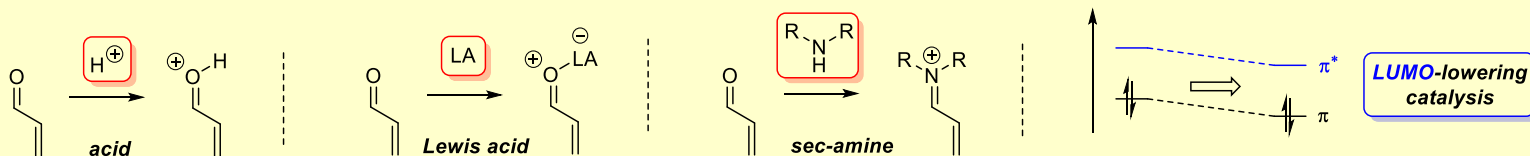
- Reactivity is controlled by the relative energies of the FMOs
- The key interaction is between the HOMO of one reactant and the LUMO of the other reactant
  - the closer the two interacting orbitals are in energy the faster the reaction rate (cf. Klopman-Salem equation, lecture 1, slides 7/8)
  - consequently, 2 important types can be identified:



- Recall from Lecture 1 (slides 9/10):
- 
- 

EWG (Z-substituents) lower HOMO & LUMO energies  
 EDG (X-substituents) raise HOMO & LUMO energies  
 conjugating systems (C-substituents) raise HOMO & lower LUMO

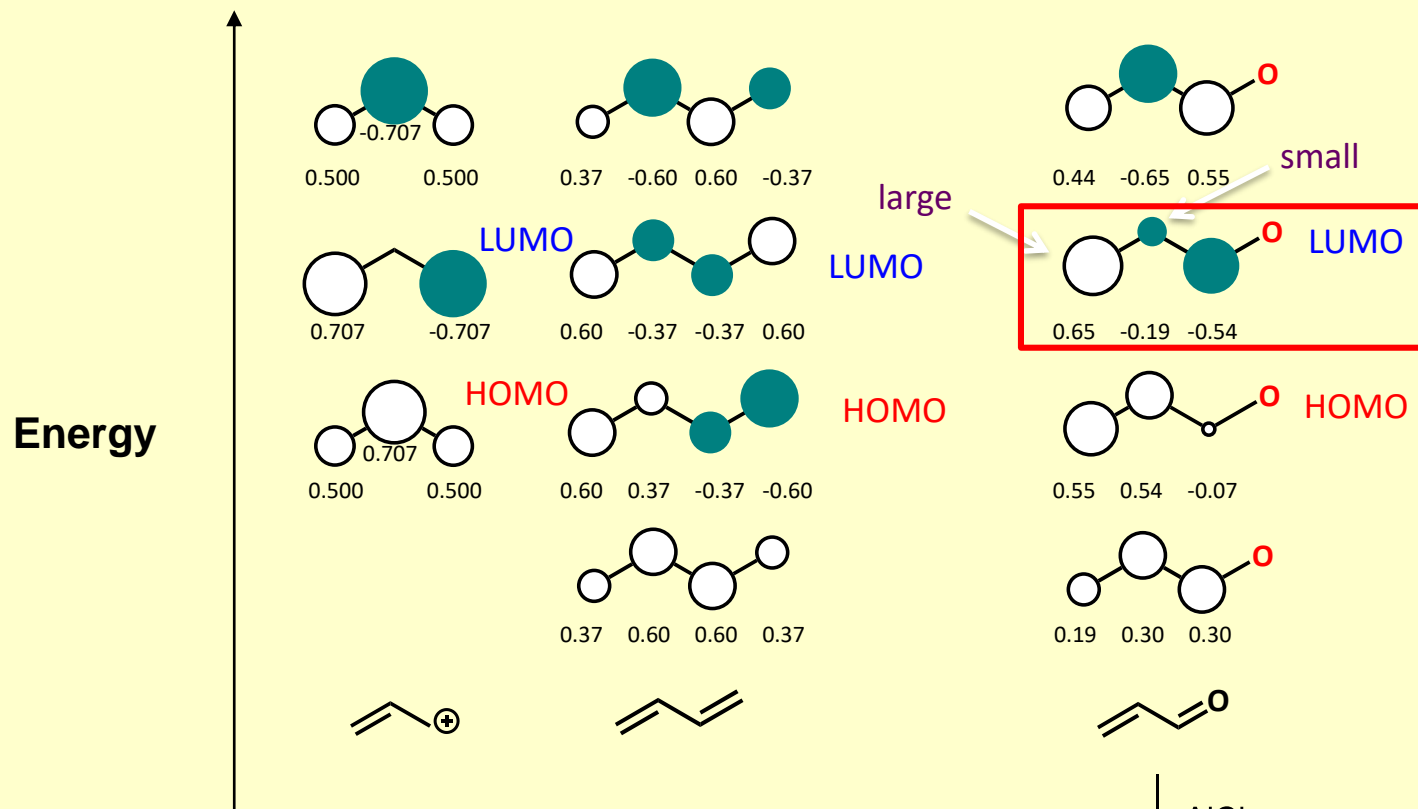
- Catalysis of 'normal' electron demand Diels-Alder reactions is generally by 'LUMO-lowering' catalysis':
  - i.e. interaction of catalyst with a carbonyl conjugated to an alkene in the dienophile



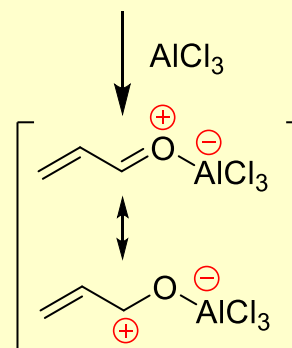
# Diels-Alder regioselectivity – dienophile polarity

Can we understand how substitution on dienophile with an EWG changes orbital coefficients?

- Consider *acrolein* as an average of allyl cation and butadiene:



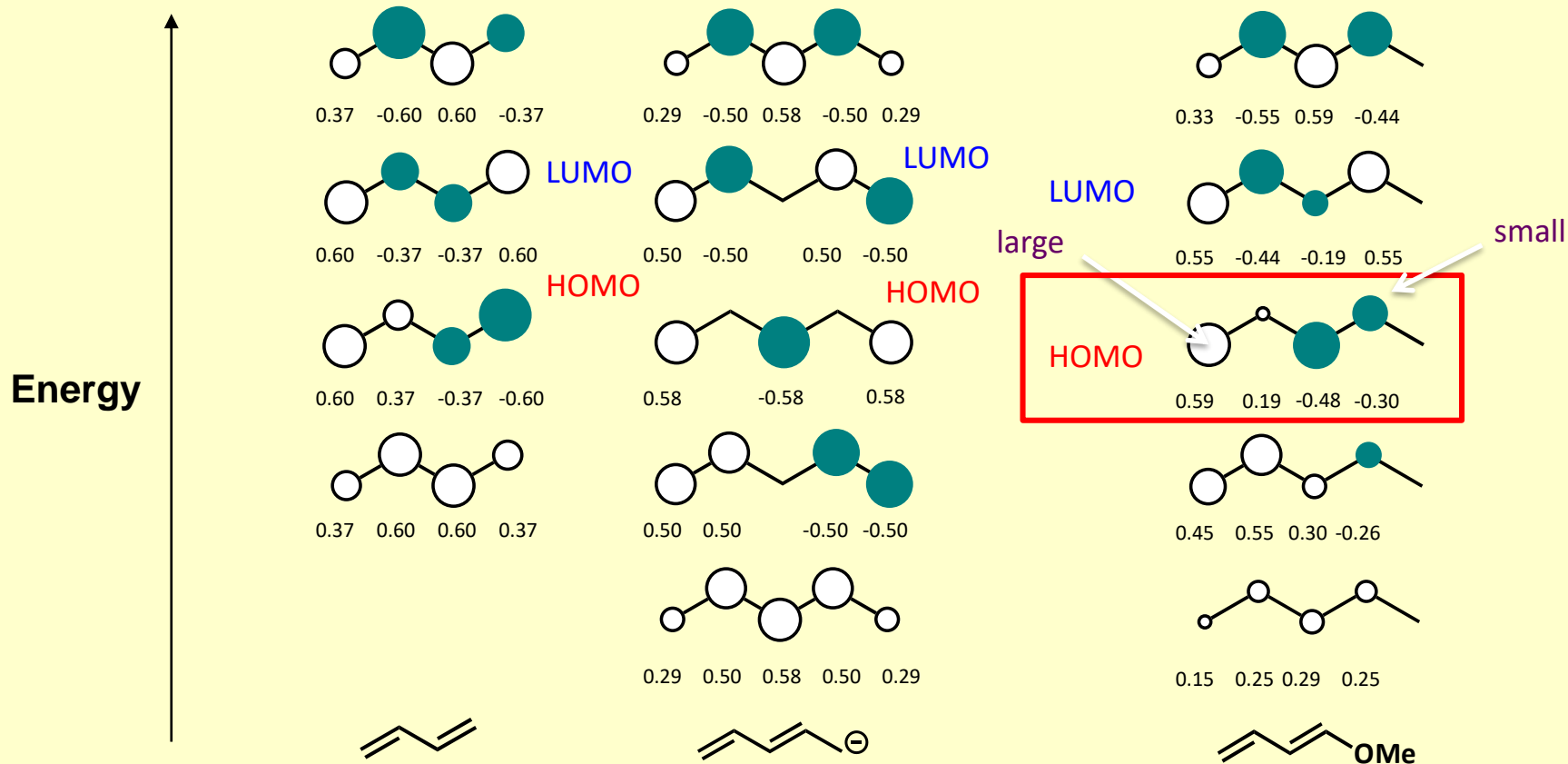
- In the presence of a Lewis acid (e.g.  $\text{AlCl}_3$ ) acrolein will have more allyl cation character and hence the C-terminus coefficient of the LUMO will be larger, leading to greater selectivity (as well as higher rate).



# Diels-Alder regioselectivity – diene polarity

Similarly, the effect on orbital coefficients of substituting the diene with electron donating groups

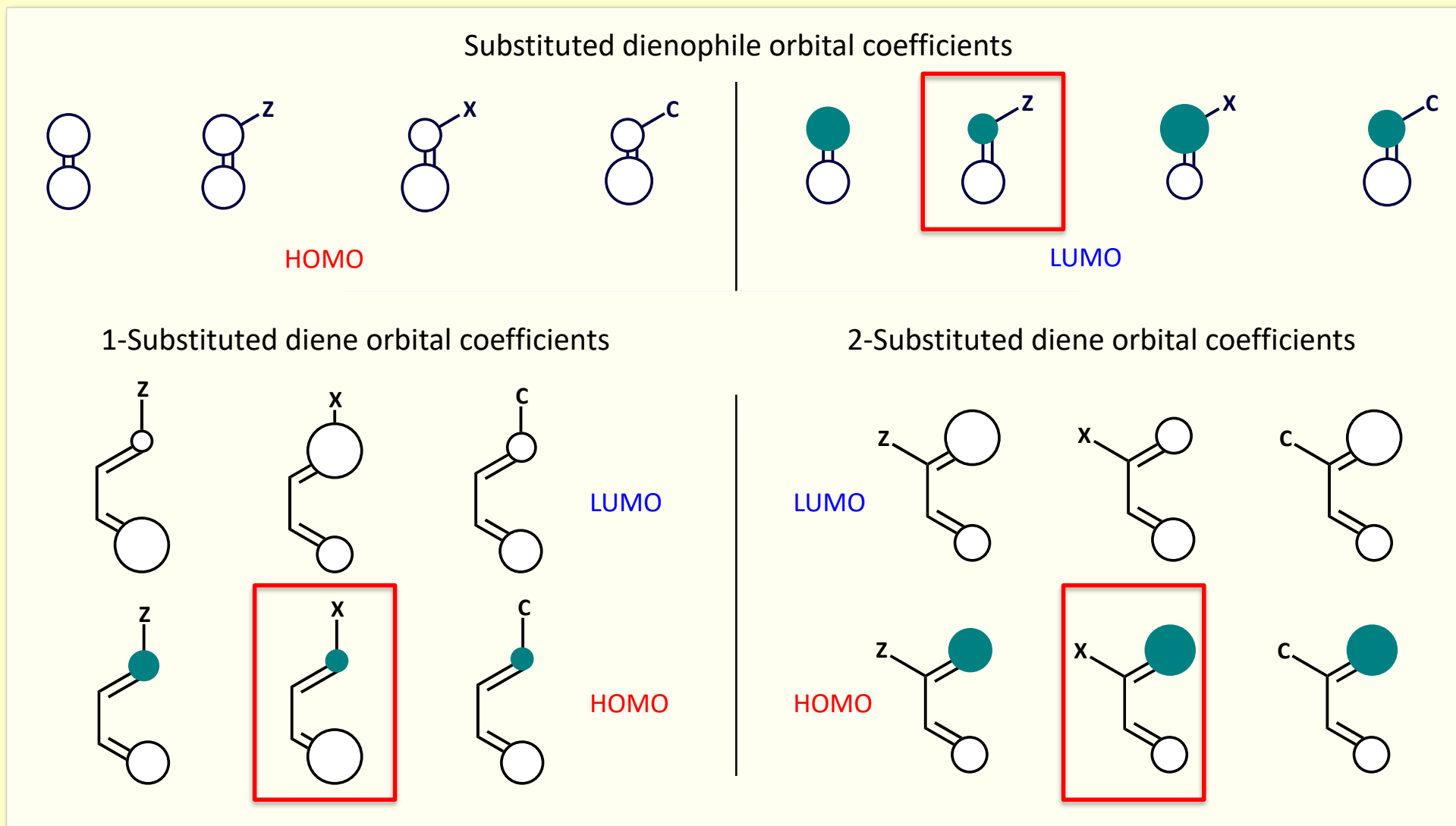
- consider 1-methoxybutadiene as an average of butadiene and a pentadienyl anion:



- HOMO of diene has a large orbital coefficient at the end of the diene.

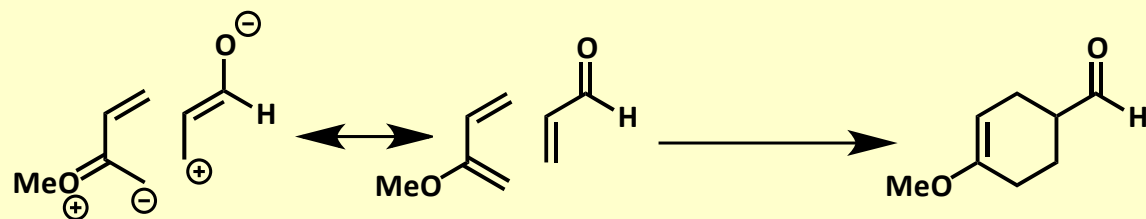
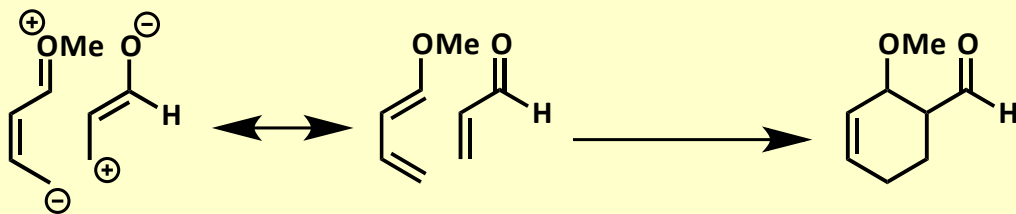
# Diels-Alder regioselectivity - *summary*

- Large-large and small-small overlap is best
- Z = EWG (e.g. CO<sub>2</sub>Me), X = EDG (e.g. OMe), C = conjugating group (vinyl, phenyl)

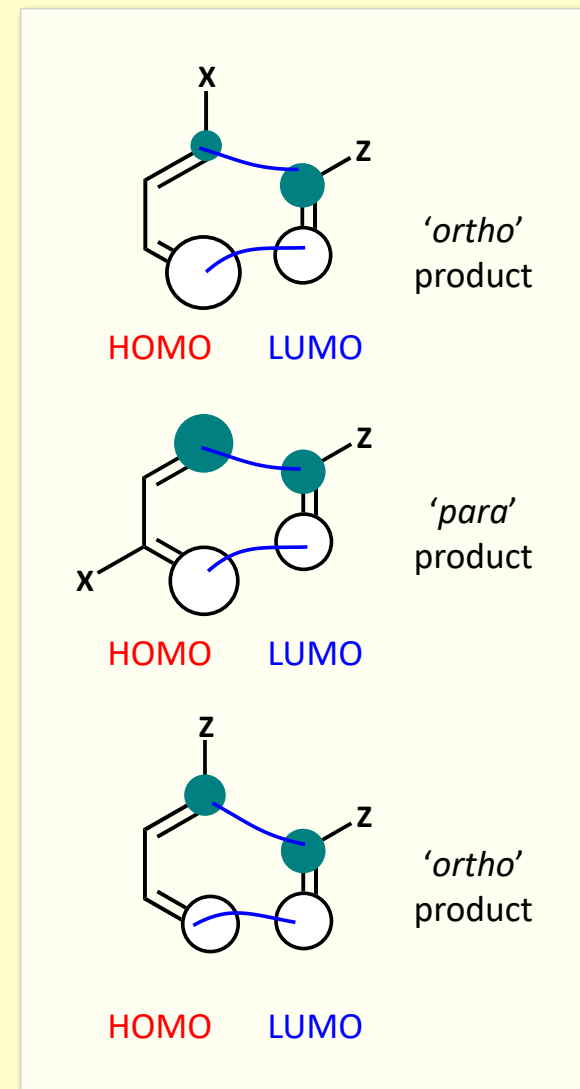
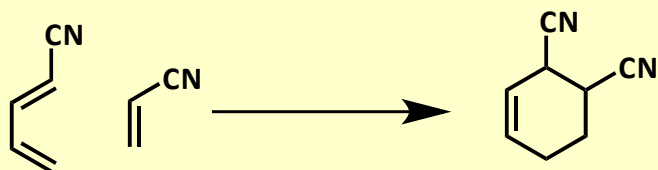


# Diels-Alder regioselectivity – *in practice* ...

- Fortunately, for most synthetically useful D-A reactions, resonance-based polarity will correctly predict regioselectivity:



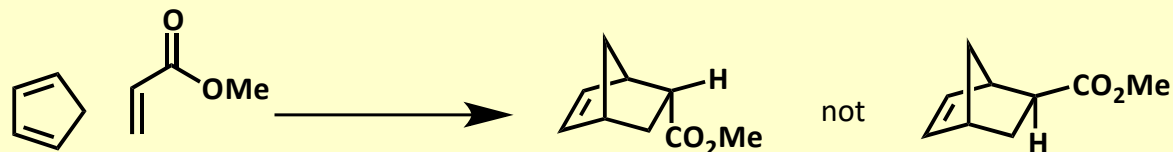
- BUT, not always. Sometimes, only the orbital coefficient approach correctly predicts the outcome.
  - However, these 'exceptions' are generally poor reactions from a HOMO-LUMO energy matching perspective (*i.e.* slow rates), e.g.



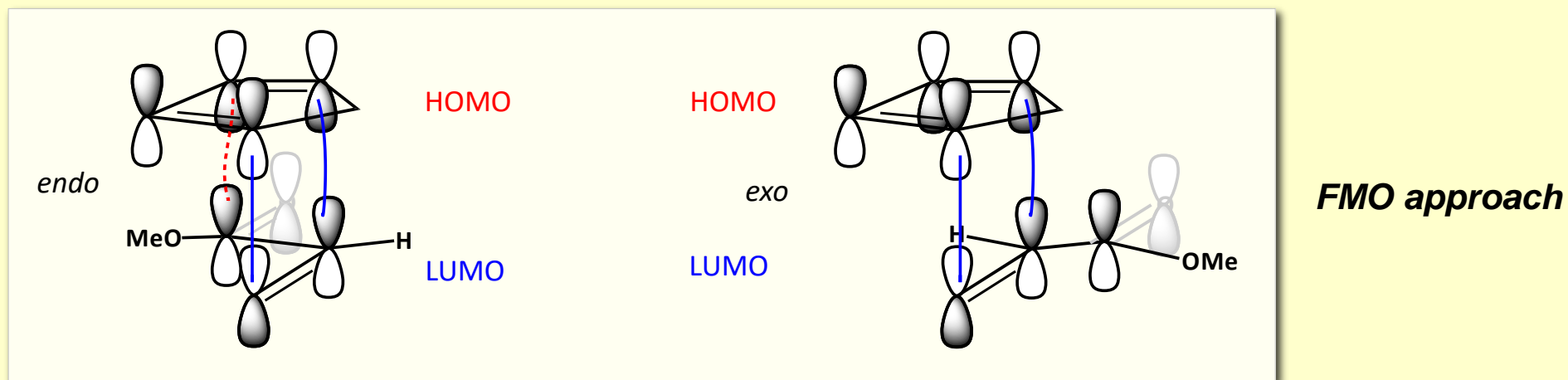


# Diels-Alder stereoselectivity

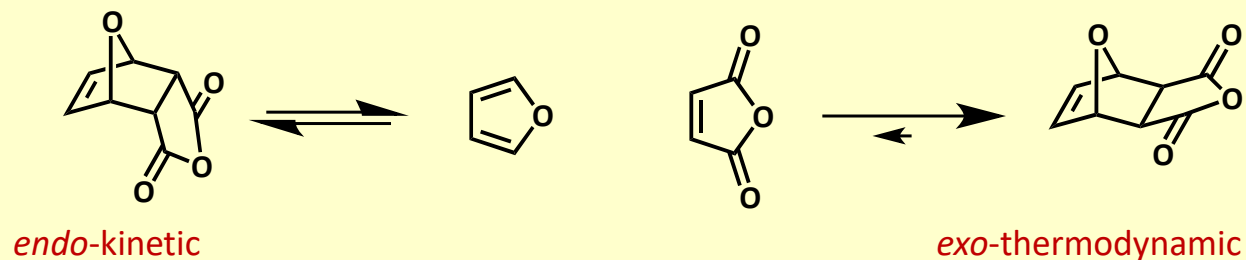
- The *endo*-product is generally the major with dienophiles containing  $\pi$ -conjugation (e.g. a Z substituent)



- Secondary orbital overlap is a simple explanation for the kinetic preference for the *endo*-adduct

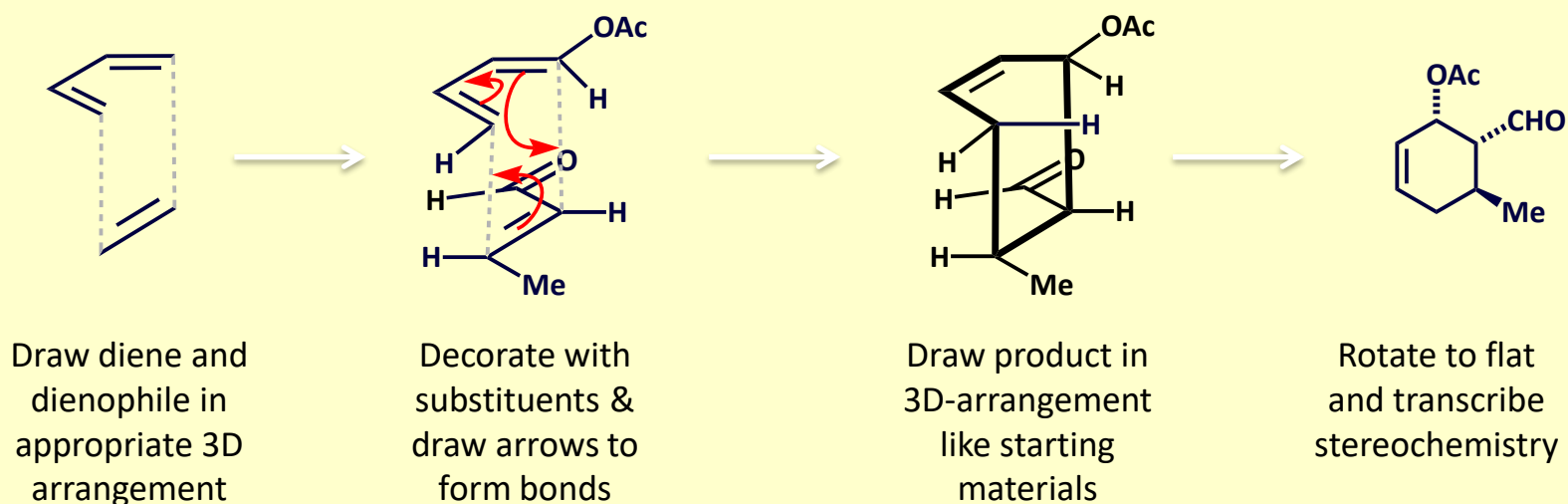
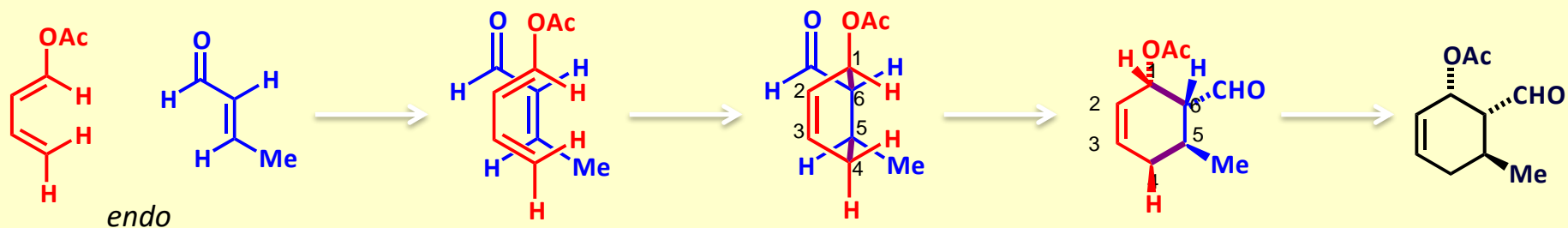
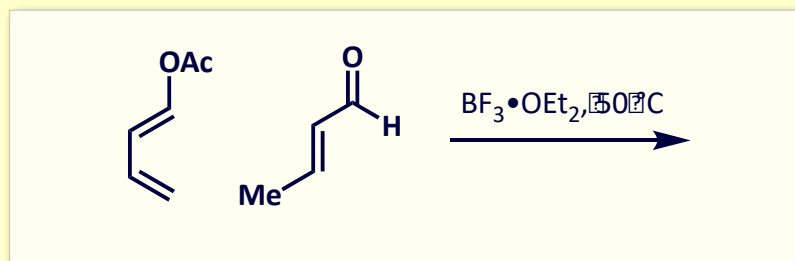


- Reversibility (as in D-A reactions with furan) can lead to the thermodynamically preferred *exo* adduct



# Diels-Alder stereoselectivity

- Drawing and working out stereochemistry for Diels-Alder reactions



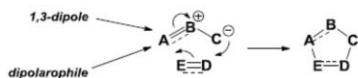
# 1,3-Dipolar cycloadditions

## RECALL: Heteroaromatics Lectures

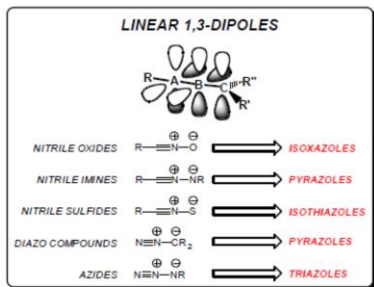
- Prof. Donald Craig, lectures 2 & 3:

### Cycloaddition Reactions – 1,3-dipolar cycloadditions: 5-membered rings

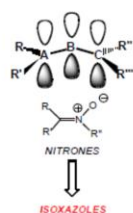
- 1,3-Dipolar cycloadditions are 6-electron [ $4_s+2_s$ ] concerted pericyclic reactions:
  - sometimes referred to as [3+2]-cycloadditions – this refers to the number of ATOMS (not electrons)



- There are 2 main classes of dipoles used in 1,3-dipolar cycloadditions:



### TRIGONAL 1,3-DIPOLES



#### notes

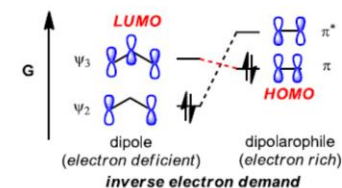
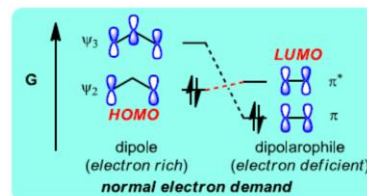
- 3 atom/4 $\pi$  electron species
- central atom  $\neq$  C
- always have formal charges
- charges @ 1,2- NOT 1,3-positions
- linear are: sp-sp-sp<sup>2</sup>
- trigonal are sp<sup>2</sup>-sp<sup>2</sup>-sp<sup>2</sup>
- no correlation between reactivity & geometry
- products have  $\geq 2$  adjacent heteroatoms in the ring

- Most multiple bonds can act as dipolarophiles:

- BUT usually a C-C double or triple bond...

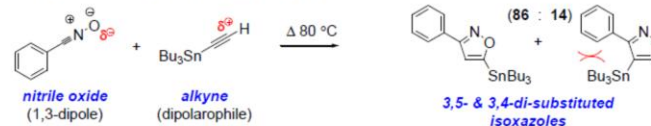
### Cycloaddition Reactions – 1,3-dipolar cycloadditions: reactivity and regioselectivity

- Reactivity** is controlled by relative energies of Frontier Molecular Orbitals (FMOs: more on this from Alan Spivey later this term)
  - the key interaction is between the Highest Occupied Molecular Orbital (HOMO) of one reactant and the Lowest Unoccupied (i.e. empty) Molecular Orbital (LUMO) of the other reactant
    - the closer the two interacting orbitals are in energy the faster the reaction rate
    - consequently, two important types can be identified:



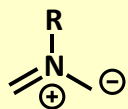
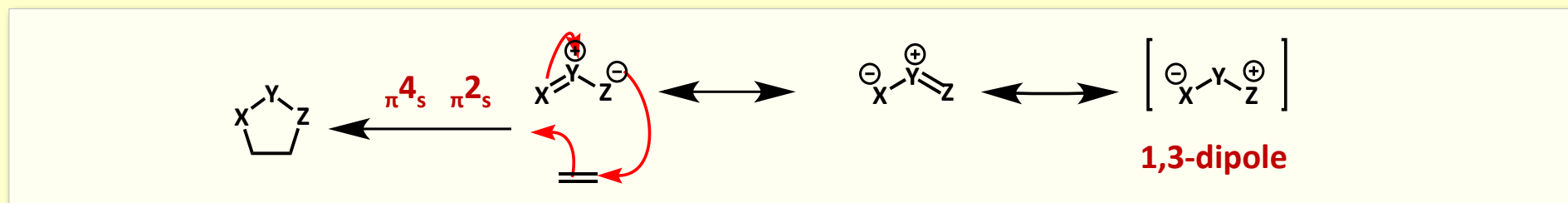
- Regiochemistry** is controlled by:

- the polarity of the frontier molecular orbitals (as for hetero-Diels-Alder regioselectivity, see later)
- BUT, sterics can dominate electronic effects, e.g.:

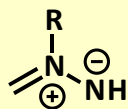


# 1,3-Dipolar cycloadditions

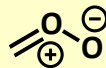
## ■ sp<sup>2</sup>-hybridized central atom



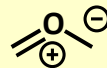
azomethine ylid



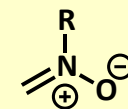
azomethine imine



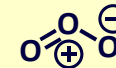
carbonyl oxide



carbonyl ylid

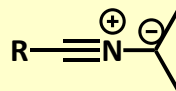
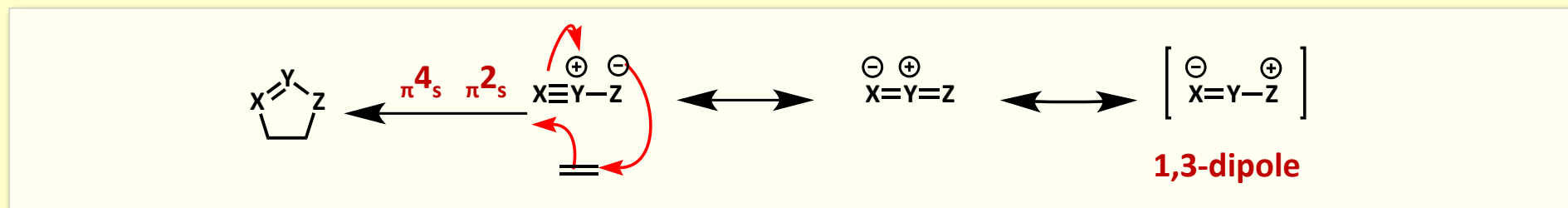


nitrone

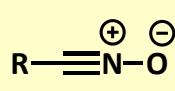


ozone

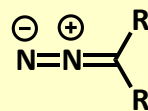
## ■ sp-hybridized central atom



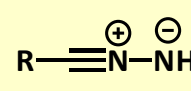
nitrile ylids



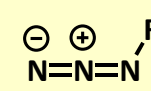
nitrile oxides



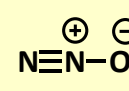
diazoalkanes



nitrile imines

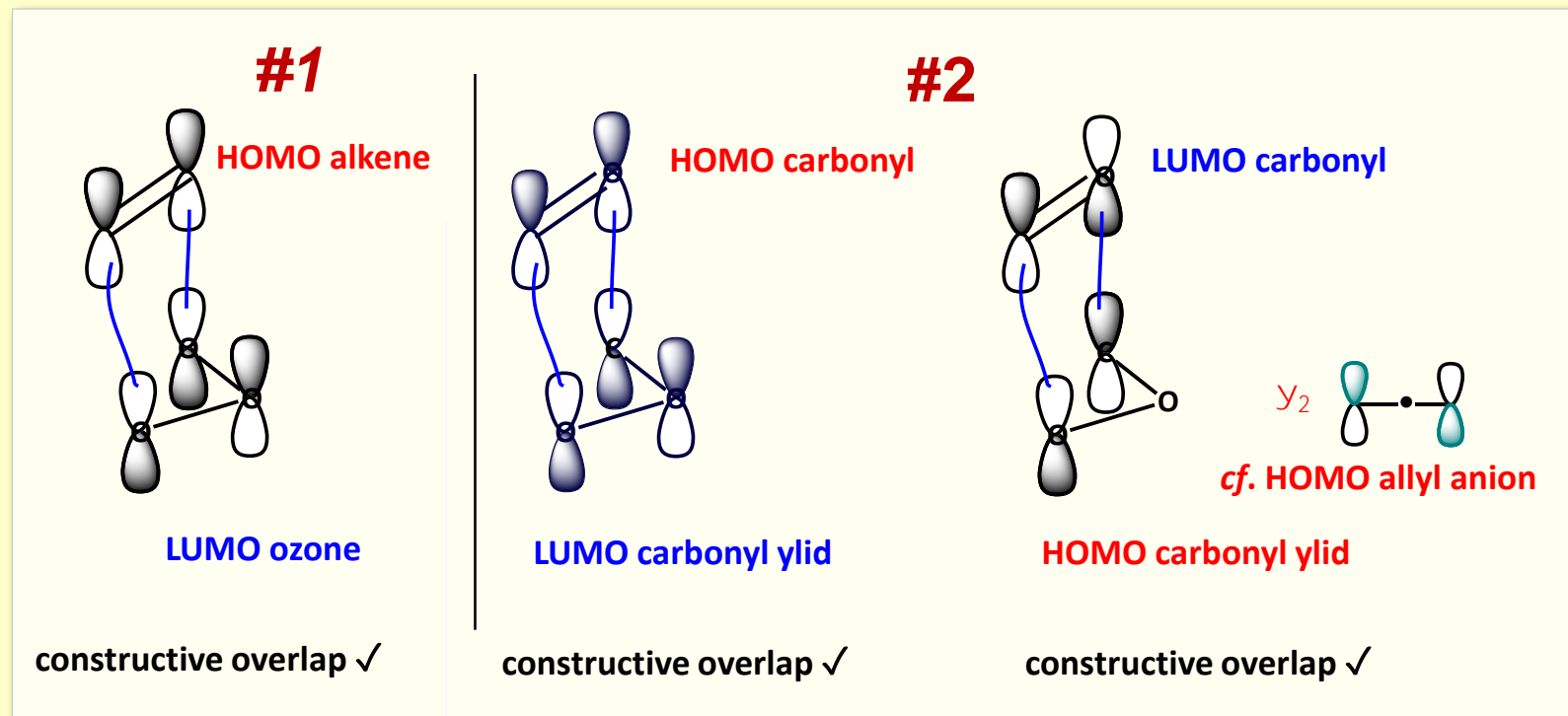
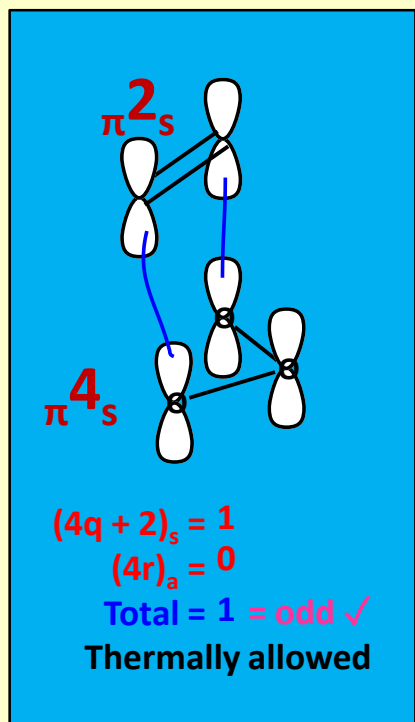
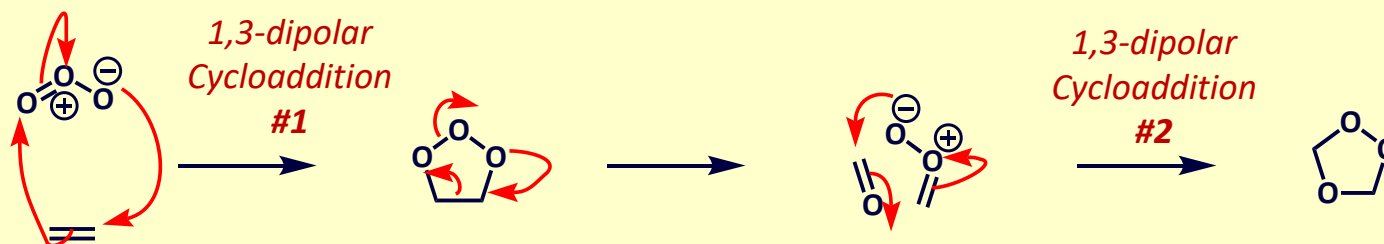


alkyl azides



nitrous oxide

# 1,3-Dipolar cycloaddition: *ozonolysis*



*W-H approach*

*FMO approach*