

CHEM60001:
Advanced Chemistry Topics 1 – Pericyclic
Reactions

LECTURE 5
Cycloaddition Reactions

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Format & scope of lecture 5

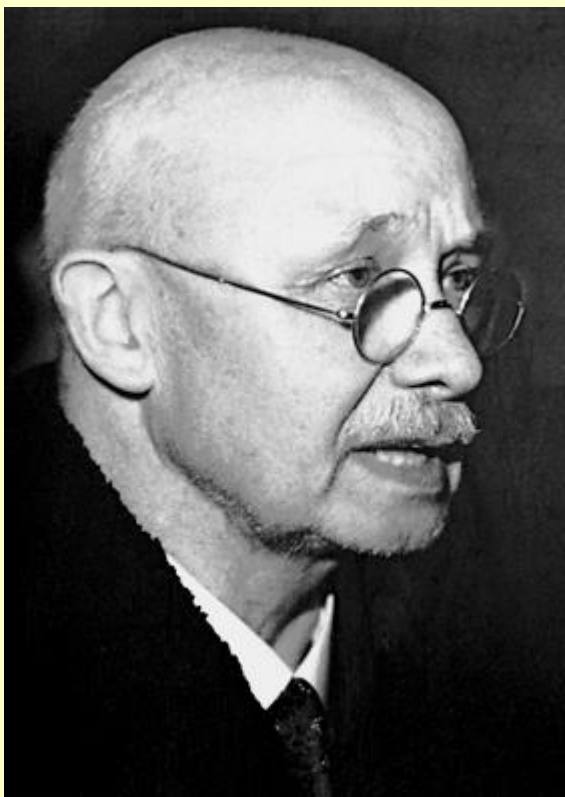
- **Cycloaddition reactions**
 - Diels-Alder reaction
 - Rates
 - Regioselectivity
 - Stereoselectivity – the *endo* 'rule'
 - 1,3-Dipolar cycloadditions
 - Ozonolysis
 - Azomethine ylides
 - Nitrones in synthesis

Key further reading:

- **BOOK:** Clayden, Greeves & Warren, *Organic Chemistry*, 2nd Ed.,
 - [Chapter 34](#) – pericyclic reactions 1 - cycloadditions
- **WEB:** Pericyclic Reactions - https://www.stereoelectronics.org/webPR/PR_home.html
 - [Chapter 2](#) – The $[4\pi+2\pi]$ cycloaddition (Diels-Alder reaction)

The Diels-Alder reaction

Nobel Prize 1950 – The [4+2] cycloaddition reaction:



Otto Diels (1876-1954)



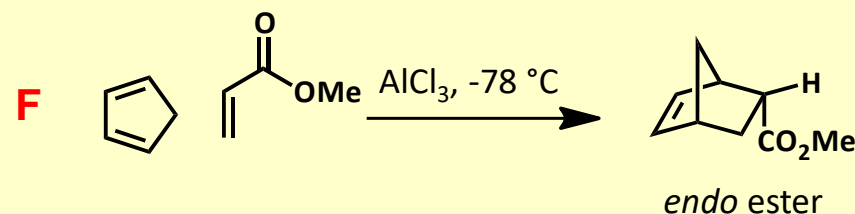
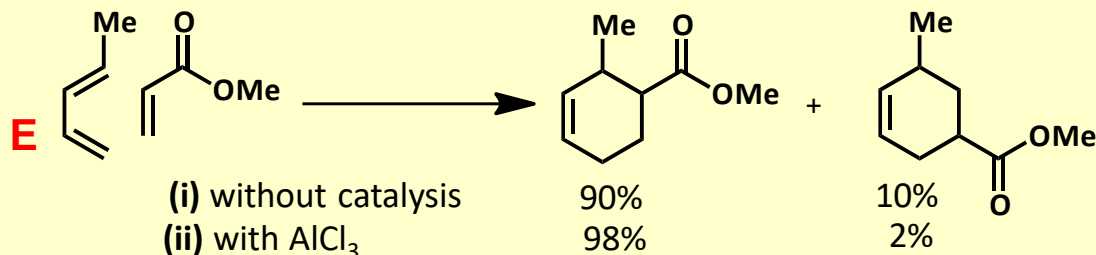
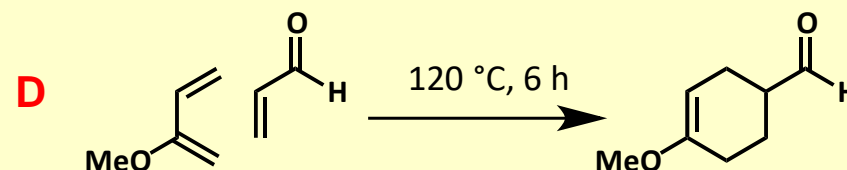
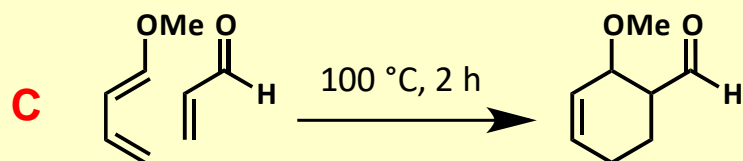
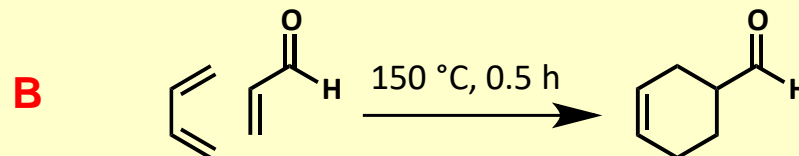
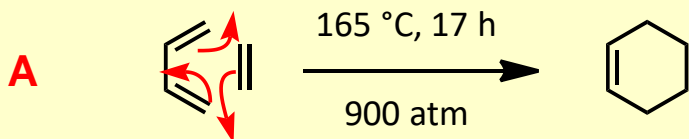
Kurt Alder (1902-1958)

IMAGES: https://en.wikipedia.org/wiki/Otto_Diels and https://en.wikipedia.org/wiki/Kurt_Alder

The Diels-Alder reaction - *summary*

Overall synthetic characteristics - summary:

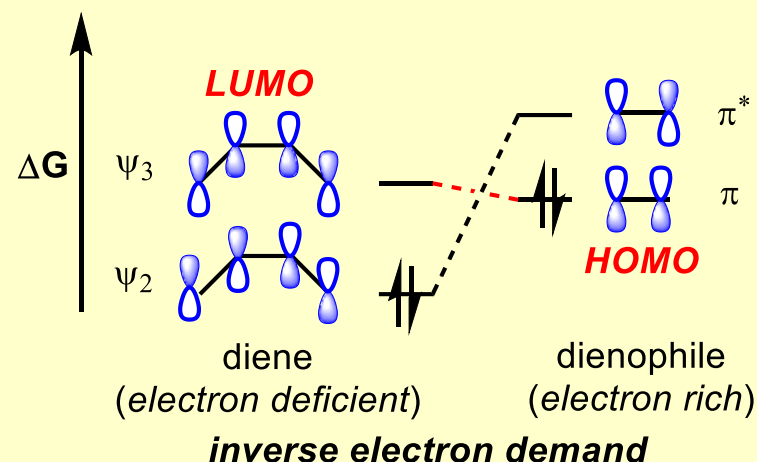
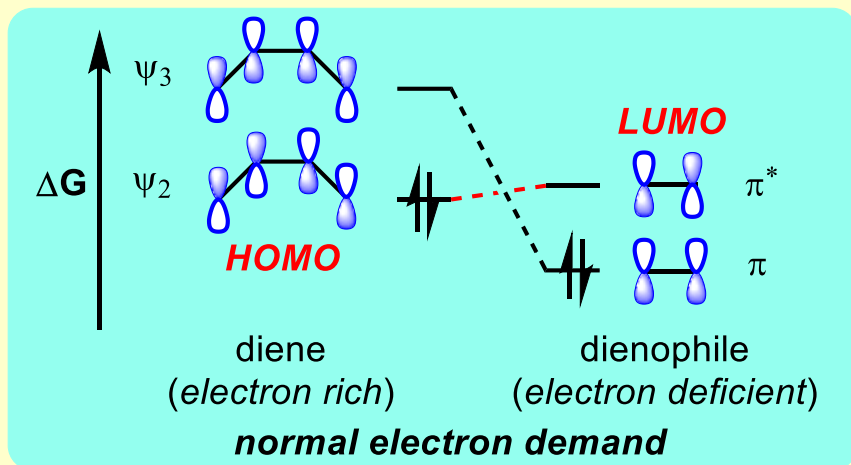
- Reaction rates: dependent on the HOMO-LUMO energy gap
 - Therefore varies as a function of reaction partner electronics
 - 'Normal' electron demand: accelerated by having an EDG on the diene & an EWG on the dienophile (cf. **A** vs. **B** vs. **C/D**)
 - 'Inverse' electron demand: accelerated by having 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 π -conjugated alkene dienophiles) (see: **F**)



The Diels-Alder reaction – *rate of reaction*

Reaction rates:

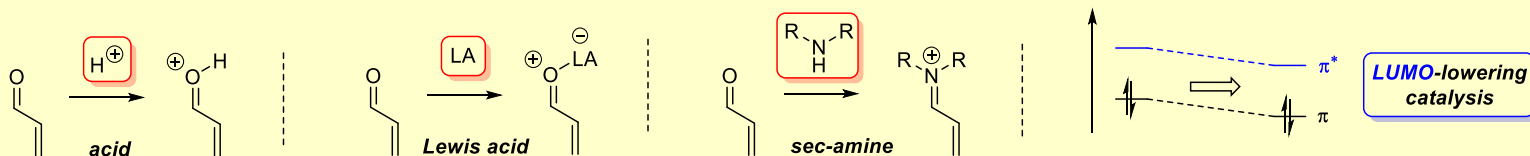
- Reactivity is controlled by the relative energies of the FMOs
- The key interaction is between the HOMO of one reactant and the LUMO of the other reactant
 - the closer the two interacting orbitals are in energy the faster the reaction rate (*cf.* Klopman-Salem equation, lecture 1)
 - consequently,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



- Recall from Lecture 1:
-
-

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

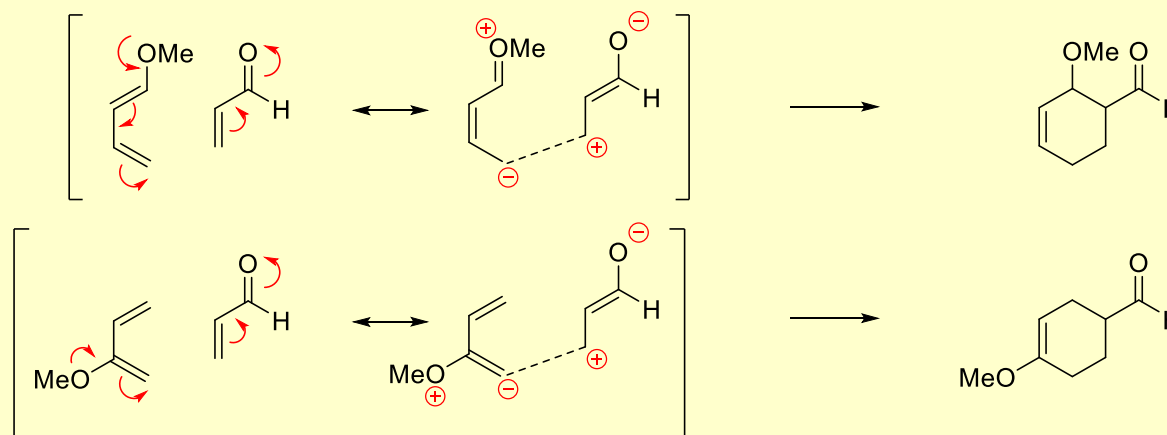
- Catalysis of 'normal' electron demand Diels-Alder reactions is generally by 'LUMO-lowering' catalysis':
 - *i.e.*, interaction of catalyst with a carbonyl conjugated to an alkene in the dienophile



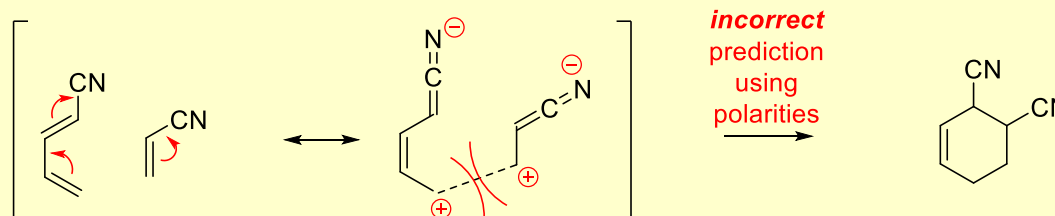
The Diels-Alder reaction - *regioselectivity*

Regioselectivity – the simple but approximate method using polarities

- The regioselectivity of Diels-Alder reactions is controlled by the *relative sizes of the coefficients on the reaction-controlling HOMO and LUMO orbitals*.
- For most synthetically useful D-A reactions, the outcome can also be predicted/rationalised by considering the resonance-based polarities of the two partners, e.g.



- However, sometimes simple consideration of *polarities* (predicted using resonance principles) does NOT give the correct prediction.
- These 'exceptions' are generally reactions with large HOMO-LUMO energy differences (*i.e.* ones with slow rates/low yields), e.g.

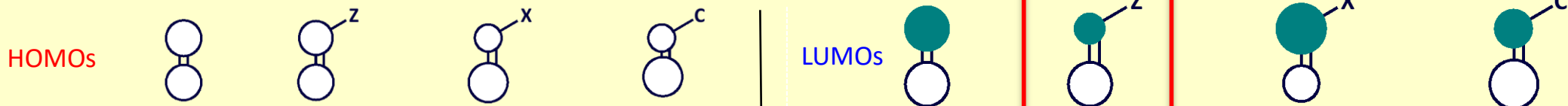


The Diels-Alder reaction - *regioselectivity*

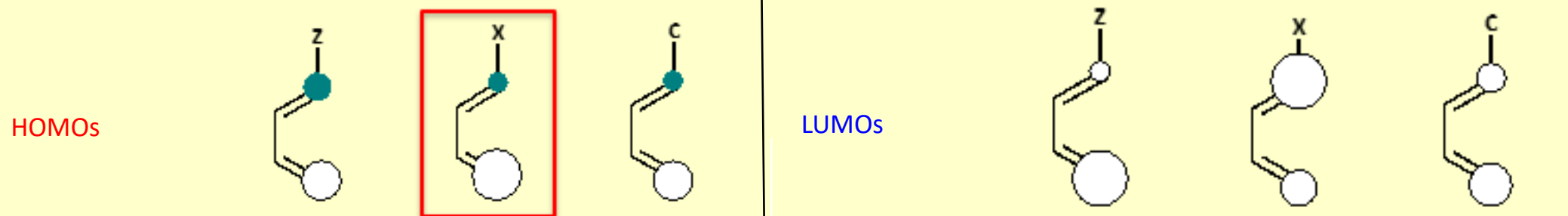
Regioselectivity – the less intuitive but reliable method using FMO orbital coefficients

- If we calculate (or can estimate) the *relative sizes of the coefficients on the reaction-controlling HOMO and LUMO* orbitals then we can predict regioselectivities reliably.
- We are looking to match large-large and small-small coefficients.
- Z = EWG (e.g. CO₂Me), X = EDG (e.g. OMe), C = conjugating group (vinyl, phenyl)

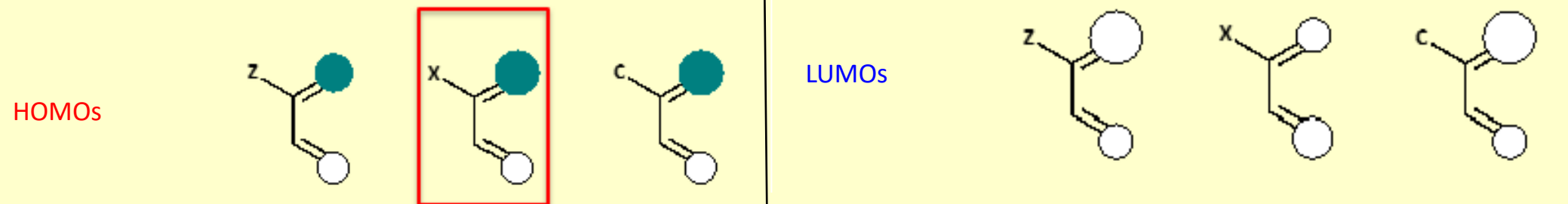
Substituted dienophile orbital coefficients



1-Substituted diene orbital coefficients



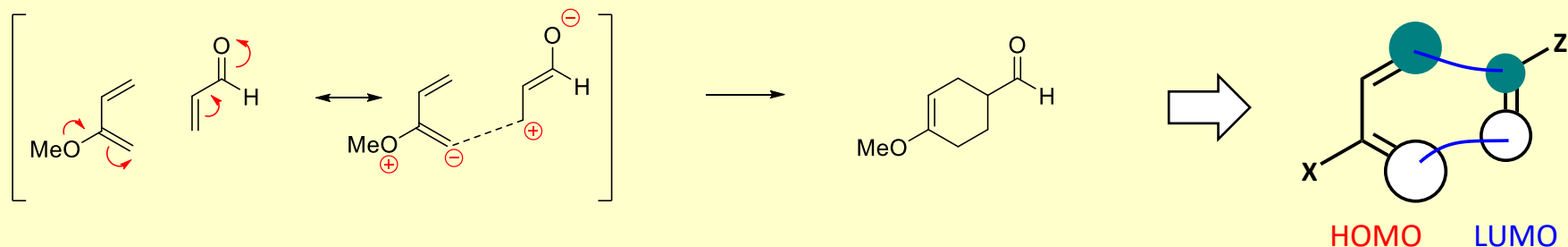
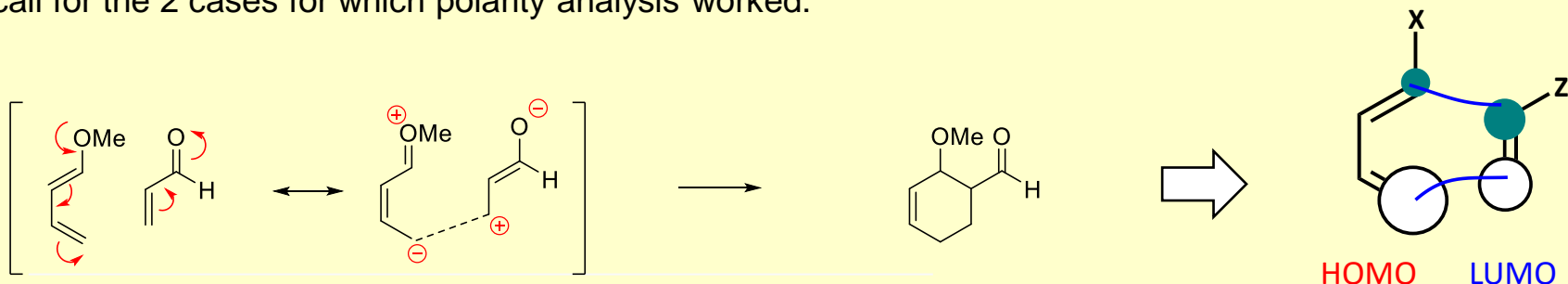
2-Substituted diene orbital coefficients



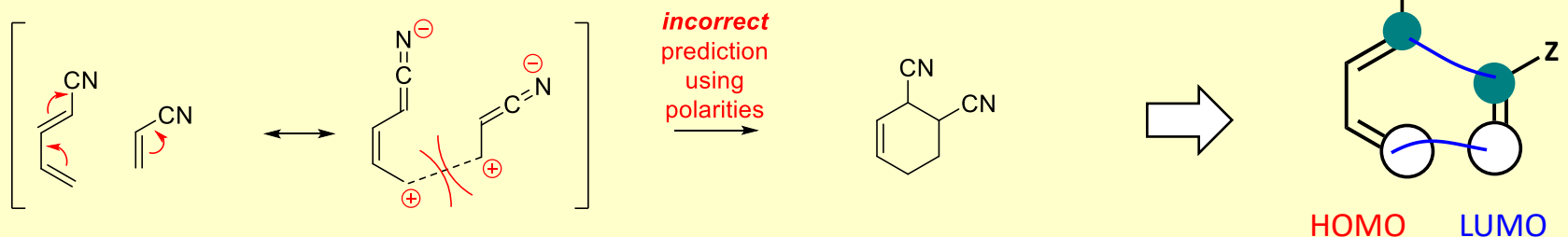
The Diels-Alder reaction – *regioselectivity*

Regioselectivity – the less intuitive but most reliable method using FMO orbital coefficients

- We can now re-analyse the three Diels-Alder reactions we examined previously using the polarity approach.
- Recall for the 2 cases for which polarity analysis worked:



- ...and for the case where polarity analysis failed:

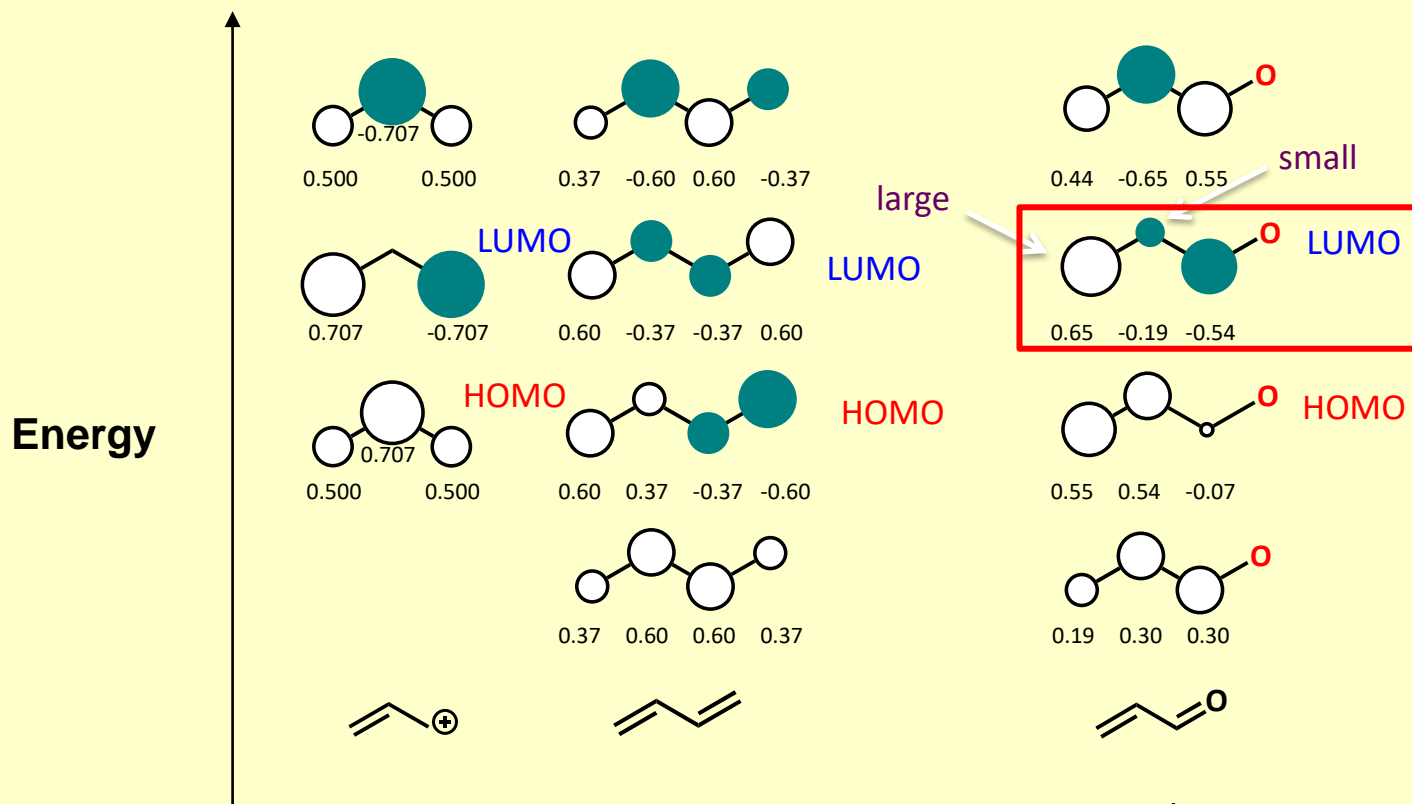


- ...the FMO orbital coefficient method correctly predicts the regiochemical outcome.

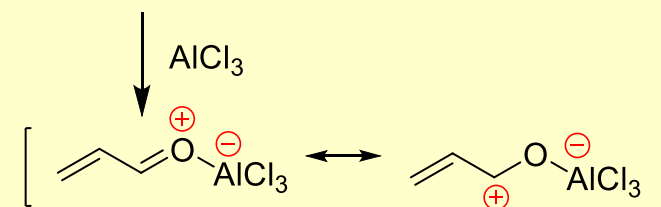
Diels-Alder regioselectivity – dienophile polarity

- **Estimating orbital coefficients:**

- How does an EWG substituent on a dienophile change orbital coefficients?
- Consider *acrolein* as an average of allyl cation and butadiene:



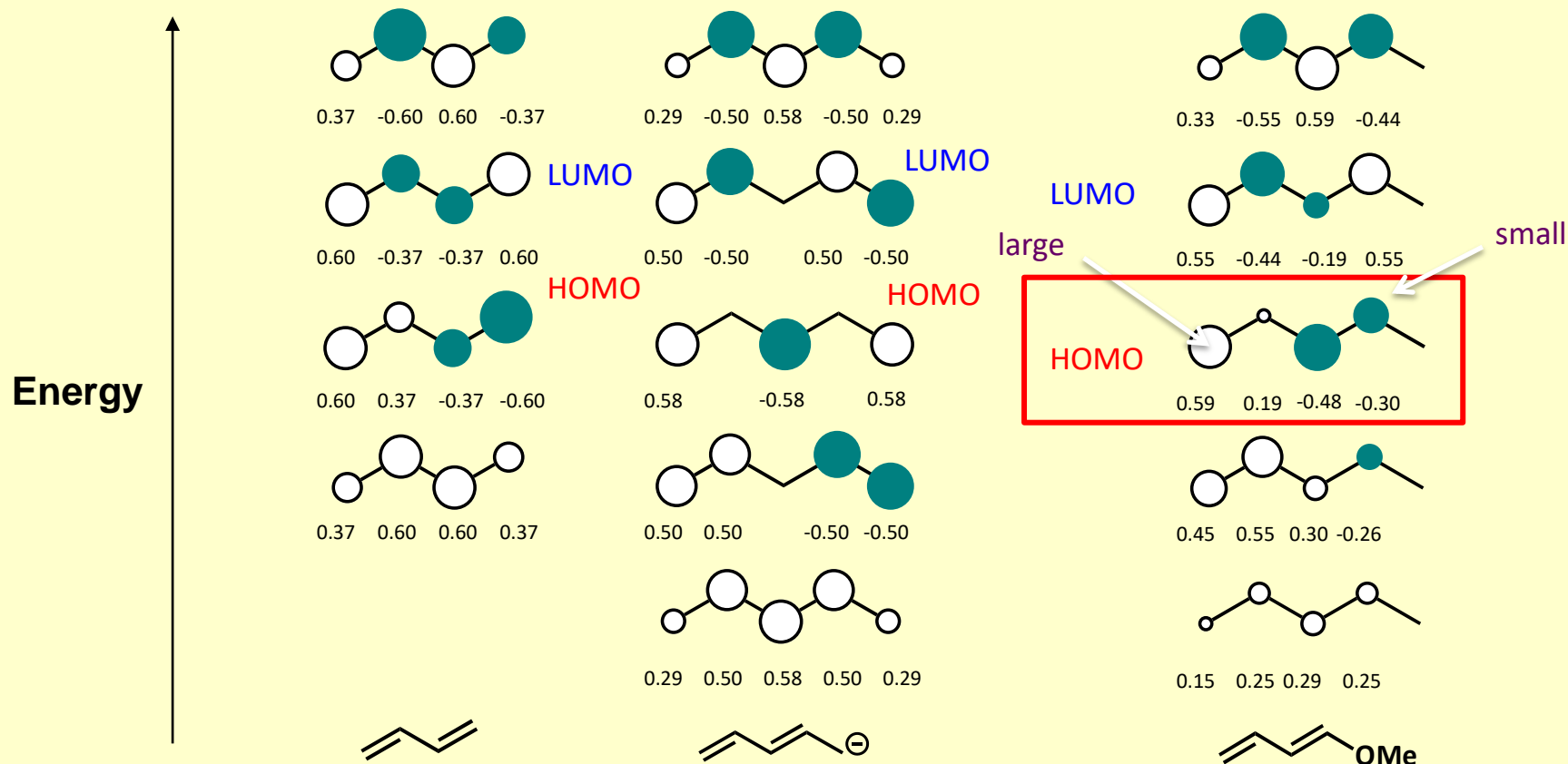
- In the presence of a Lewis acid (e.g. AlCl_3) acrolein will have more allyl cation character and hence the C-terminus coefficient of the LUMO will be larger, leading to greater selectivity (as well as a higher rate).



Diels-Alder regioselectivity – diene polarity

- **Estimating orbital coefficients:**

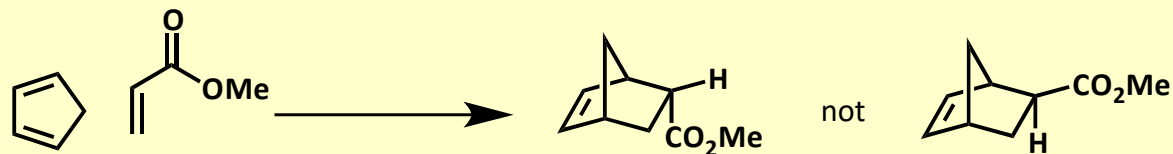
- How does an EDG substituent on a diene change orbital coefficients?
- consider *1-methoxybutadiene* as an average of butadiene and a pentadienyl anion:



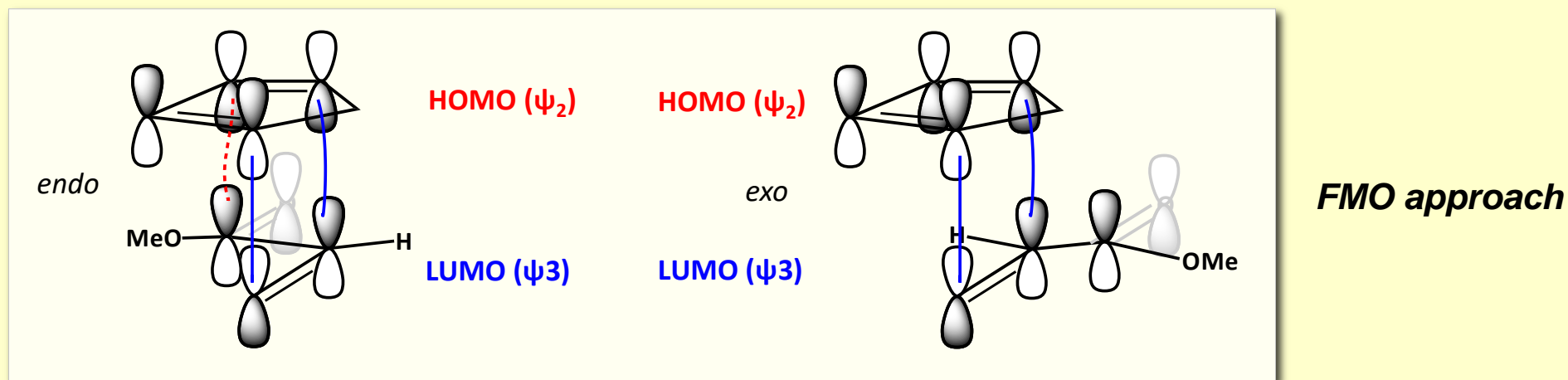
- HOMO of diene has a large orbital coefficient at the end of the diene.

The Diels-Alder reaction - *stereoselectivity*

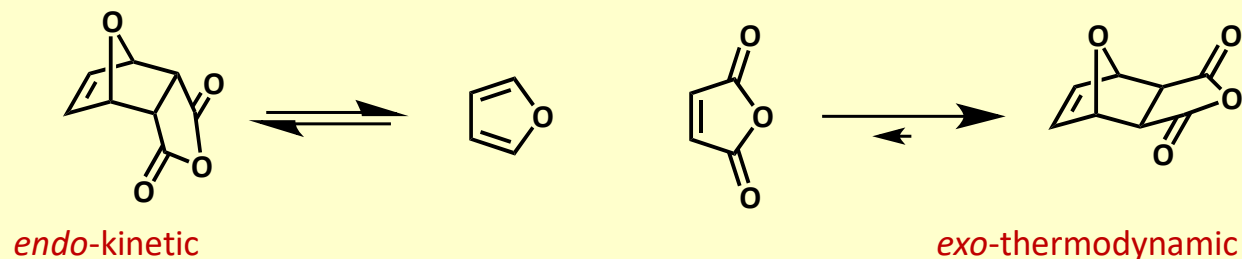
- The *endo*-product is generally the major with dienophiles containing π -conjugation (e.g. a Z substituent)



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

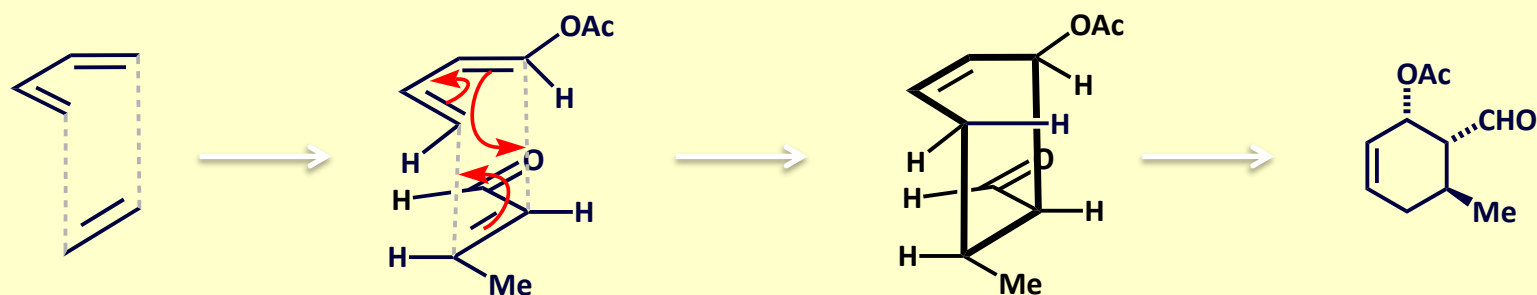
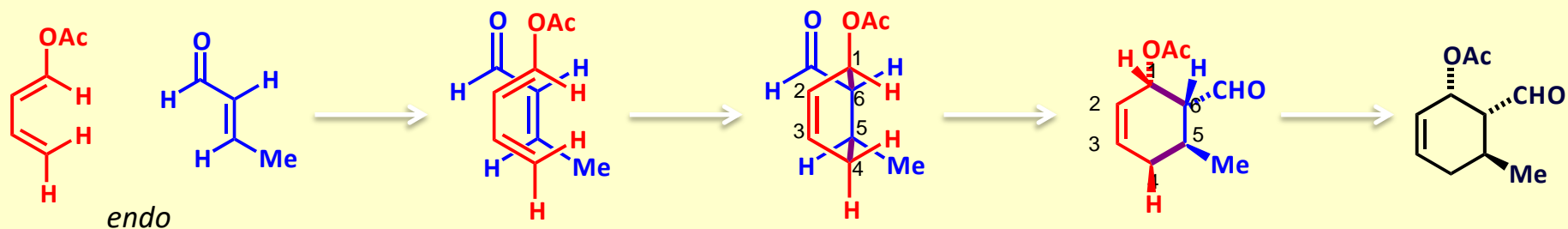
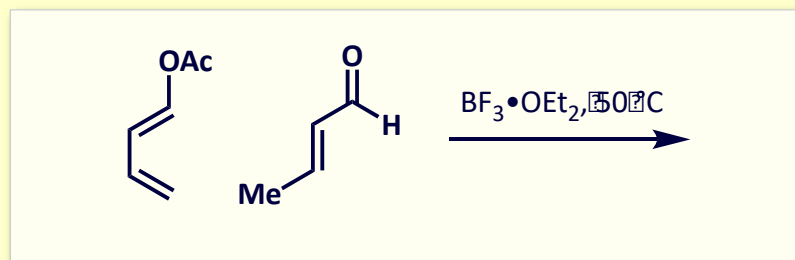


- Reversibility (as in D-A reactions with furan) can lead to the thermodynamically preferred *exo* adduct



The Diels-Alder reaction - *stereoselectivity*

- Drawing and working out stereochemistry for Diels-Alder reactions



Draw diene and dienophile in appropriate 3D arrangement

Decorate with substituents & draw arrows to form bonds

Draw product in 3D-arrangement like starting materials

Rotate to flat and transcribe stereochemistry

The 1,3-Dipolar cycloaddition reaction

"In 2000 I was the Dean at LMU and was moderating the Festkolloquium on the occasion of Rolf's 80th birthday. Looking in the audience with distinguished guests, I commented that we have an Olah reagent, a Wittig-Horner reaction, a Hünig base, a Schlosser base, and so on. I do not remember all the other prominent chemists who were in the audience. And then I asked the question, "Has anybody heard of a Huisgen reagent or Huisgen reaction?" and gave the answer, "It is due to your perfectionism that nobody knows about such a reaction, dear Professor Huisgen, because from the beginning you have created the term "1,3-Dipolar Cycloaddition." I then continued that this term is misleading anyway, because most "1,3-dipoles" do not really have 1,3-dipolar character and suggested to speak about "Huisgen reactions" instead. Unsuccessful: The term "1,3-Dipolar Cycloaddition" is so firmly established and "Huisgen reaction" will not be able to replace it." Herbert Mayr

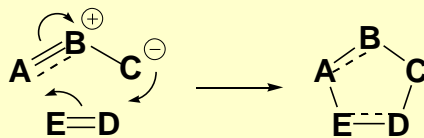


Rolf Huisgen (1920-2020)

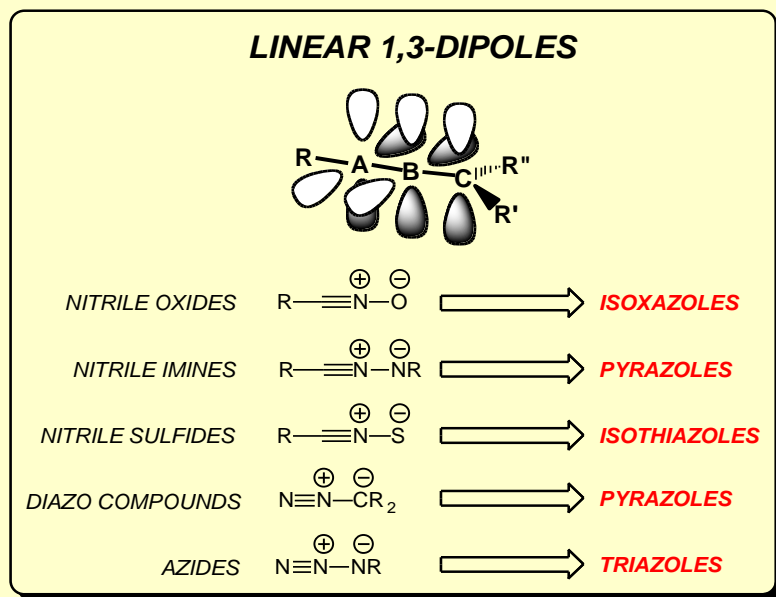
1,3-Dipolar cycloaddition reactions - *summary*

Overall synthetic characteristics - summary:

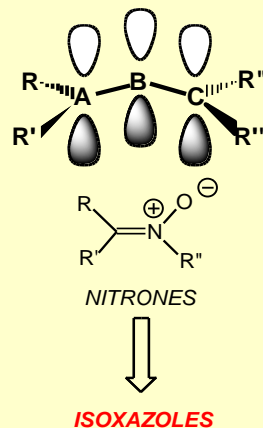
- **1,3-Dipolar cycloadditions are 6 electron [$\pi_{4s} + \pi_{2s}$] concerted pericyclic reactions:**
 - sometimes referred to as [3+2]-cycloadditions – this refers to the number of ATOMS (not electrons)



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



TRIGONAL 1,3-DIPOLES

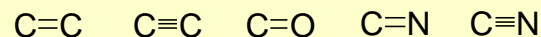


notes

- 3 atom/4 π electron species
- central atom \neq C
- always have formal charges
- charges @ 1,2- NOT 1,3-positions
- linear are: sp-sp-sp²
- trigonal are sp²-sp²-sp²
- no correlation between reactivity & geometry
- retrosynthetic 'signature' is ≥ 2 adjacent heteroatoms in the ring

- **Most multiple bonds can act as dipolarophiles:**

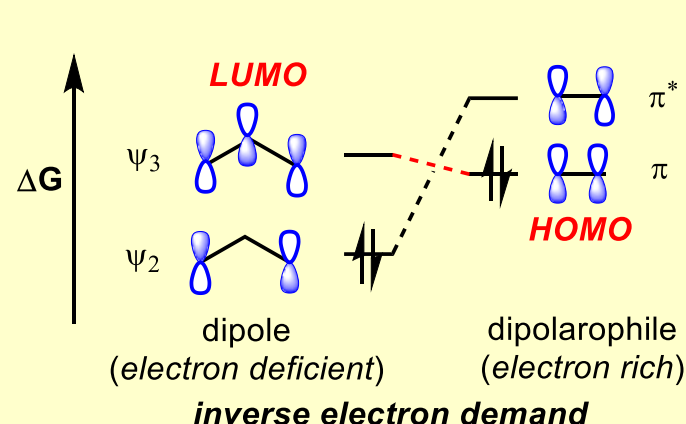
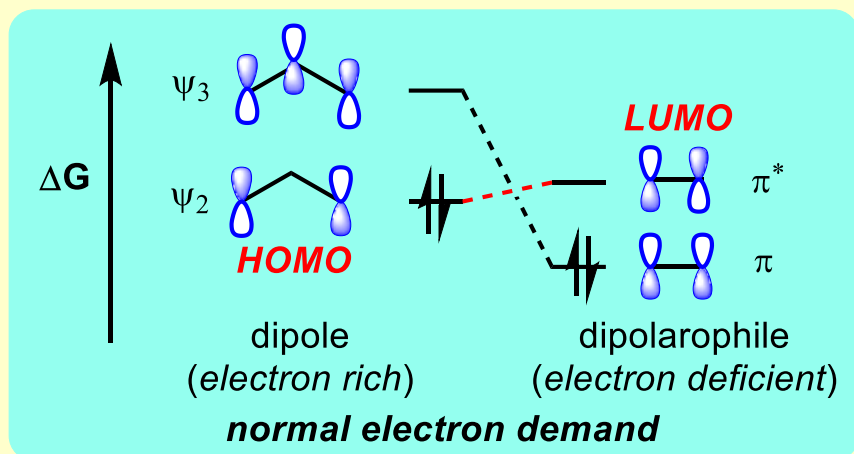
- BUT normally a C=C bond...



1,3-Dipolar cycloaddition reactions – *rates of reaction*

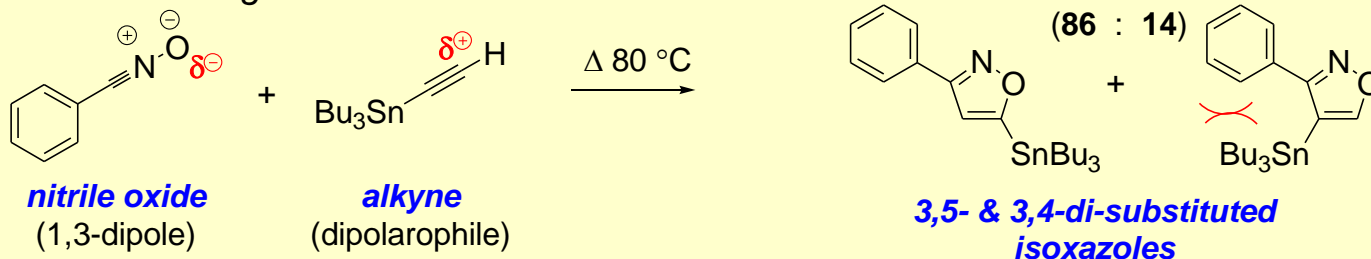
Reaction rates:

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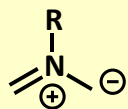
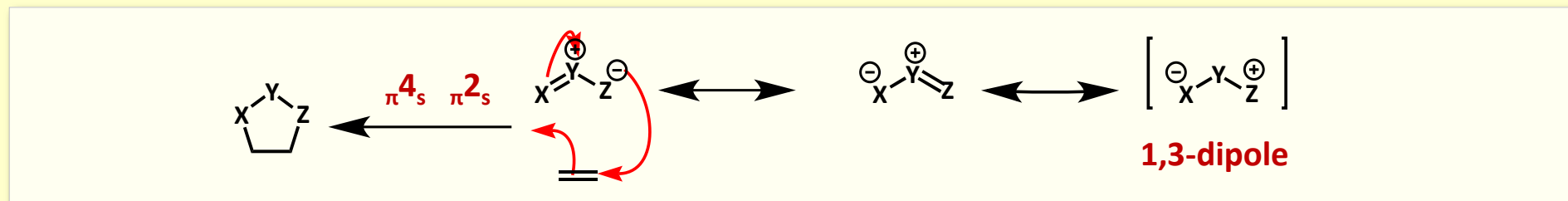
Regiochemistry:

- Controlled by the coefficients of the FMOs, but like for the Diels-Alder reaction, can be approximated by examining the polarity of the components
- However, sterics can override e.g.:

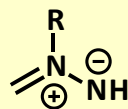


1,3-Dipolar cycloaddition reactions – 1,3-dipoles

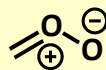
■ sp²-hybridized central atom



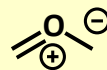
azomethine ylid



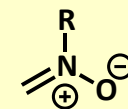
azomethine imine



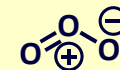
carbonyl oxide



carbonyl ylid

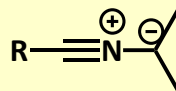
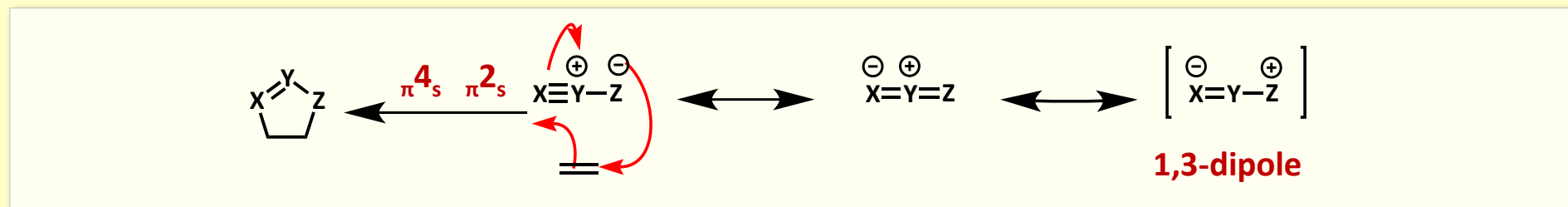


nitrone

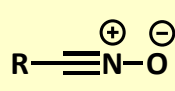


ozone

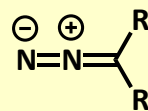
■ sp-hybridized central atom



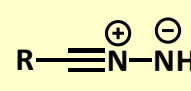
nitrile ylids



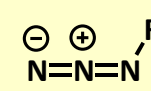
nitrile oxides



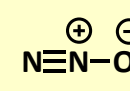
diazoalkanes



nitrile imines

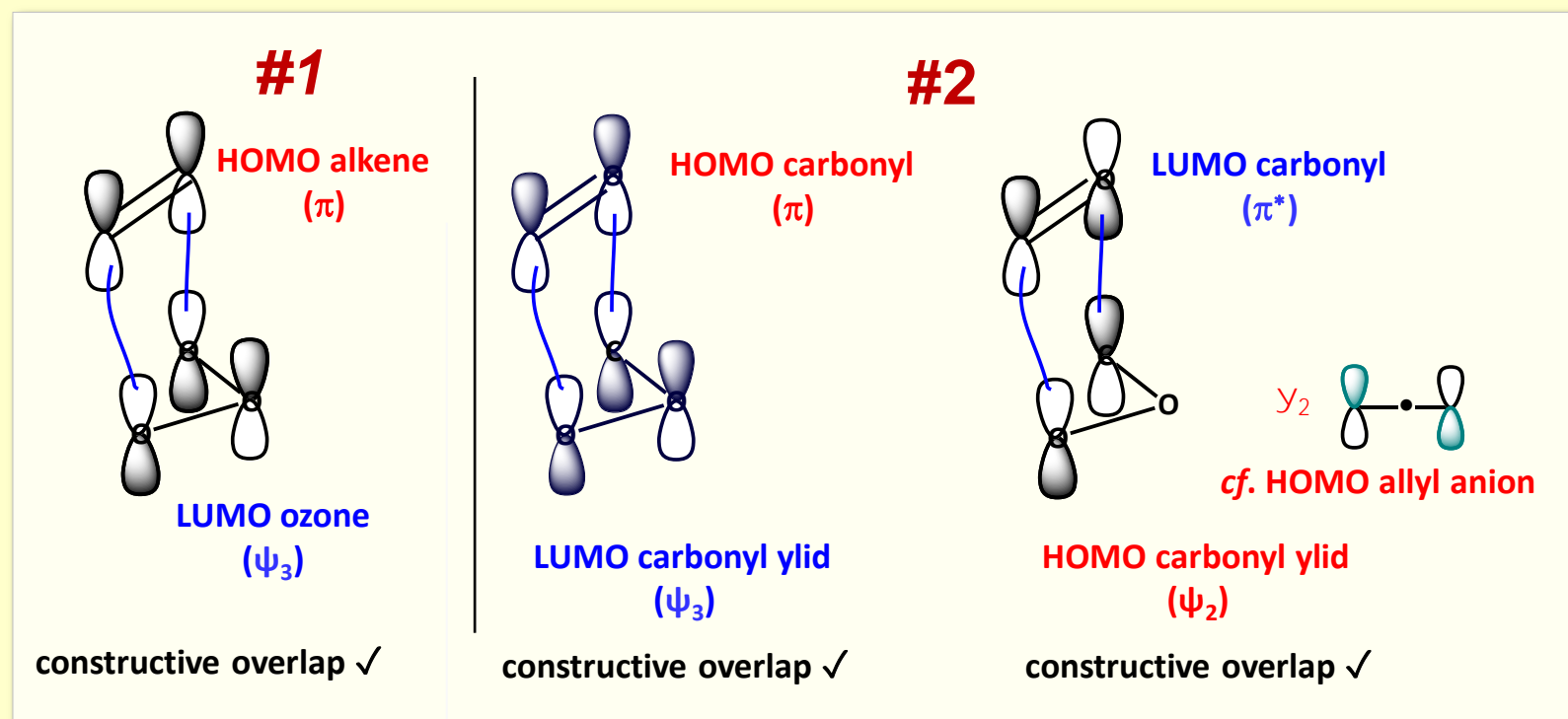
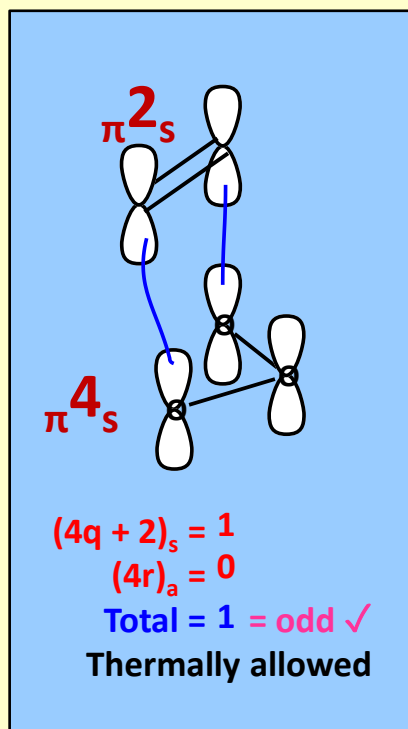
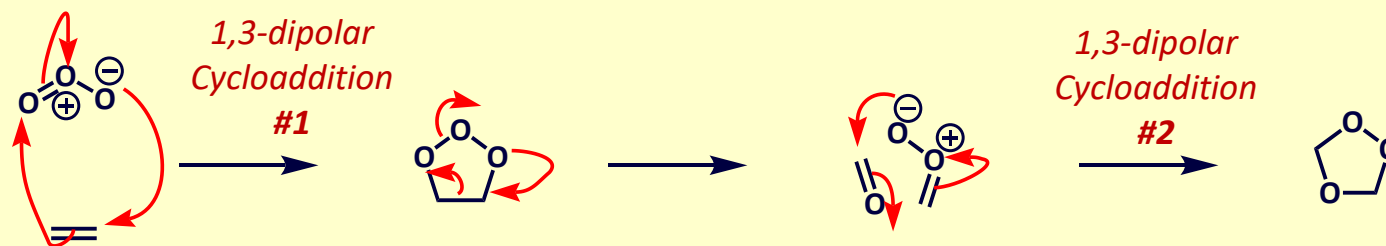


alkyl azides



nitrous oxide

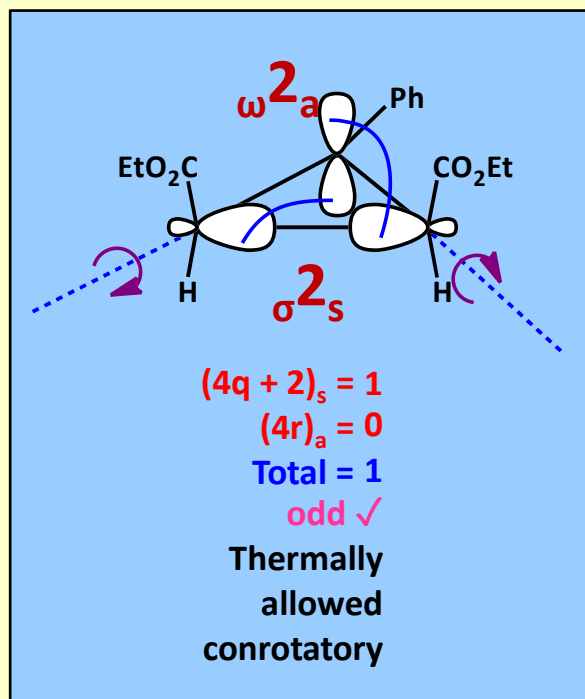
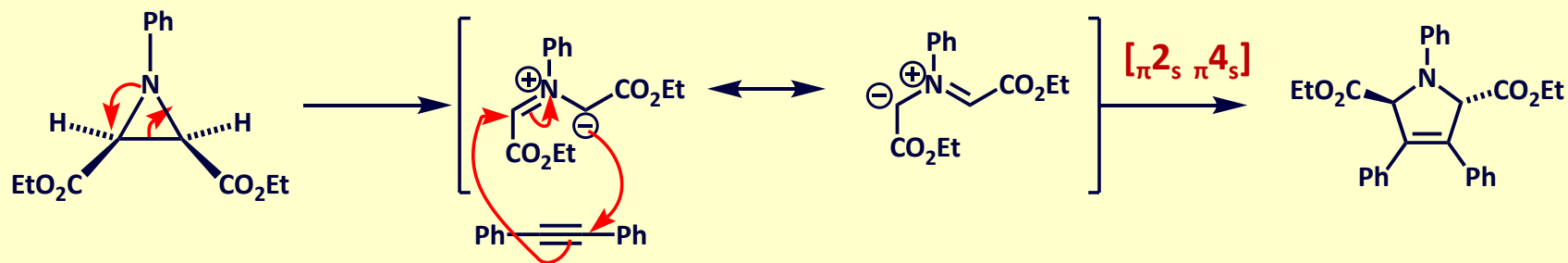
1,3-Dipolar cycloaddition: *ozonolysis*



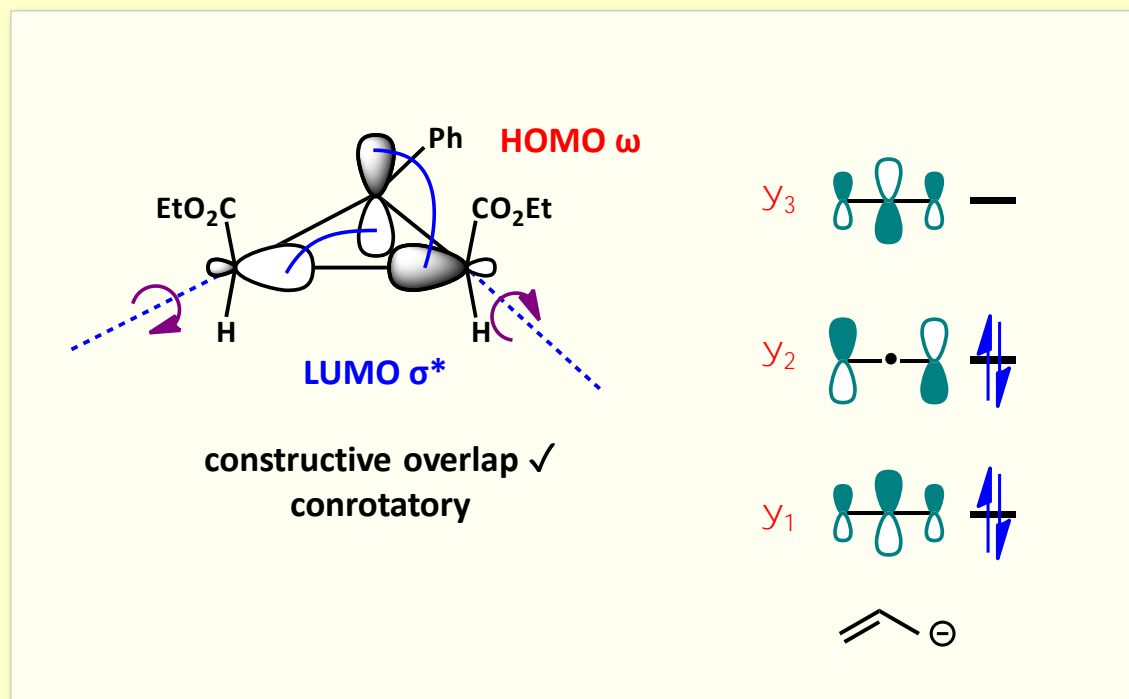
W-H approach

FMO approach

1,3-Dipolar cycloaddition: *azomethine ylid formation* ¹⁸



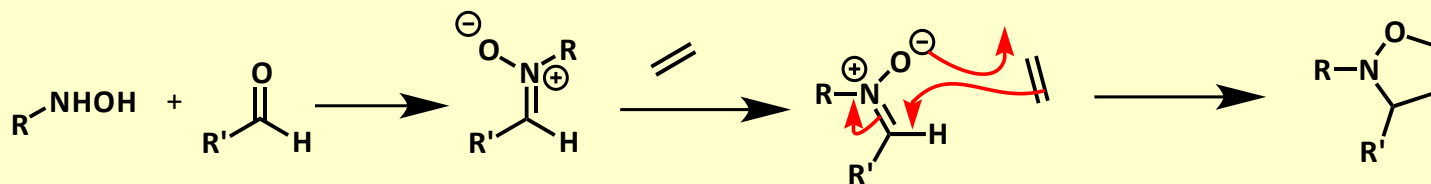
W-H approach



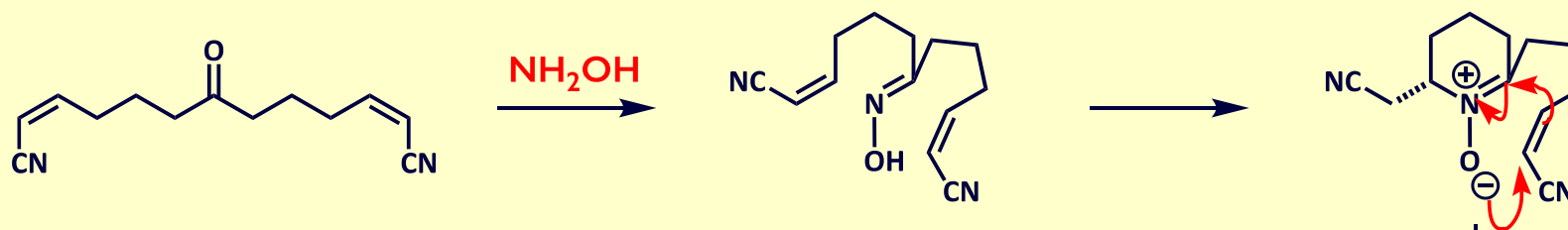
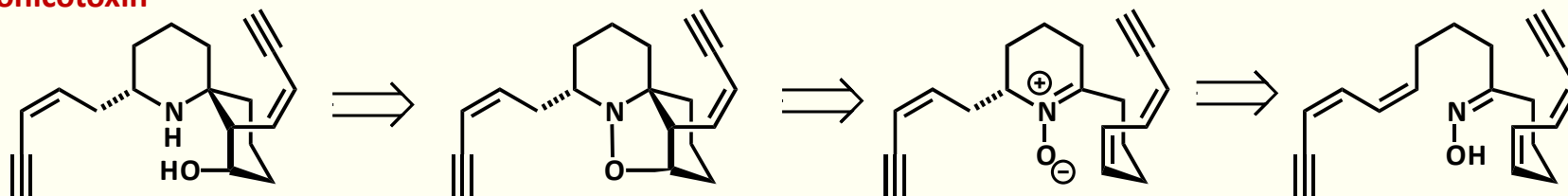
FMO approach

1,3-Dipolar cycloadditions in synthesis - *nitrones*

- Nitrones are readily formed between aldehydes and substituted hydroxylamines



Histrionicotoxin



Fuchs *J. Am. Chem. Soc.* **2006**, *128*, 12656 [[DOI](#)]

