Concerted Reactions

- up to now via polar intermediates
- slight difference in polarity of SM and transition intermediates
- through cyclic transition structutes
- thermal x photochemical excitation
- no intermediate
- *Concerted Pericyclic Reactions*
    - Cycloaddition Reactions
    - Unimolecular Rearrangements
    - Elimination Reactions

Mechanism and stereochemistry

- R. B. Woodward and R. Hoffmann, *The Conservation of Orbital Symmetry*, Academic Press, New York,1970.

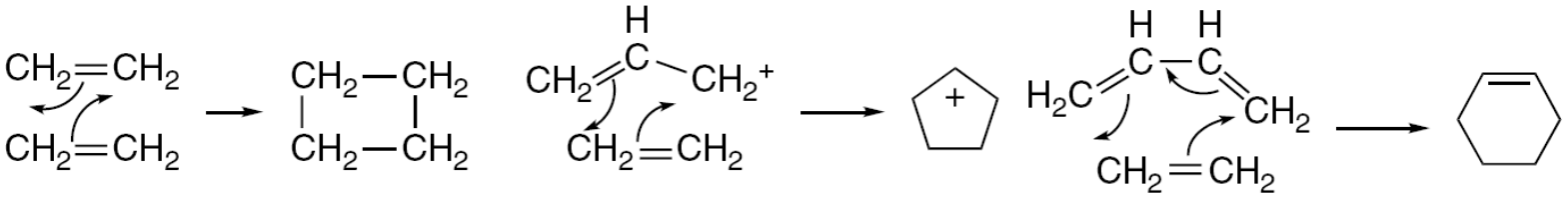
TS with certain orbital alignments:

- energetically favorable TS (allowed)
- high-enengy TS (forbidden)

Note: Stabilized TS share electronic features with aromatic systems (Huckel x Mobius)

Cycloaddition Reactions

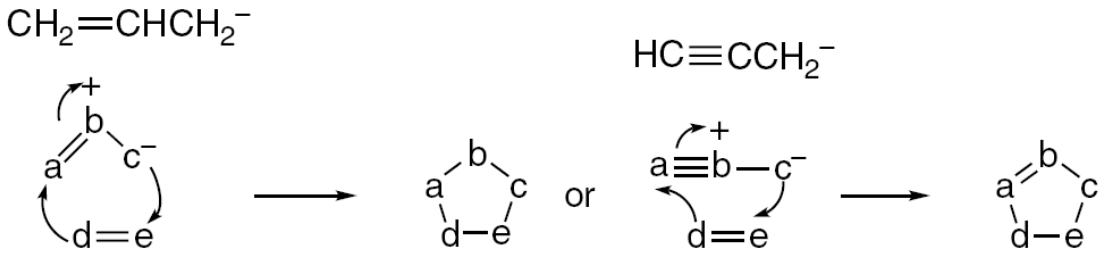
- combination of two molecules
- reorganization π-electron system
- two new σ-bonds are formed



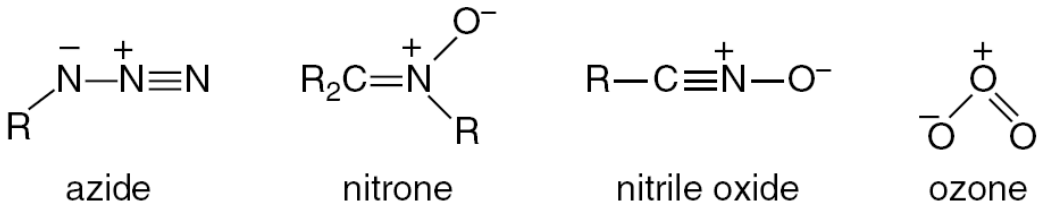
- cycloadditions can be characterized by
  - number of π-electrons involved: [4+2], [2+2]

[4+2]

- Diels-Alder Reactions
- 1,3-Dipolar Cycloaddition

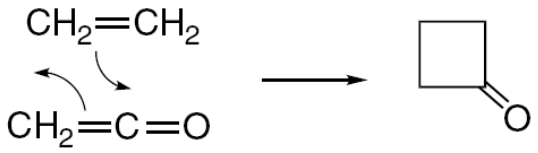


Cycloaddition Reactions

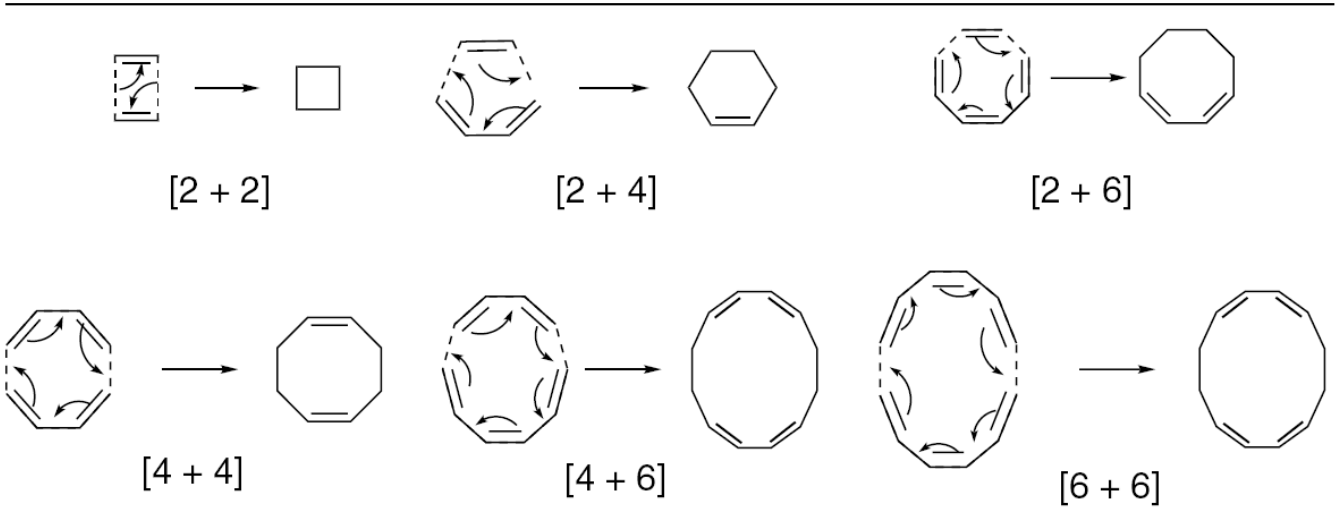


[2+2]

- ketenes



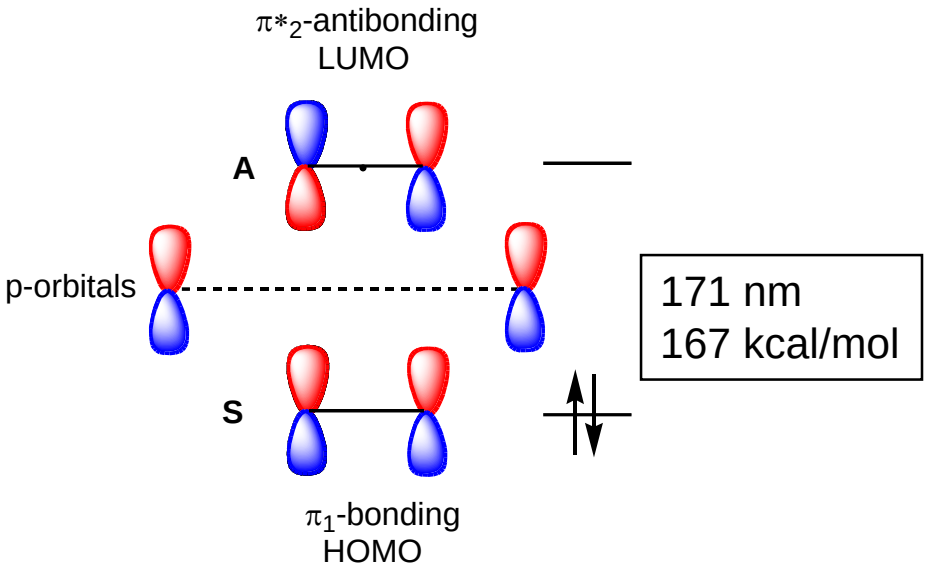
[6+2], [6+4], atd.



Cycloaddition Reactions

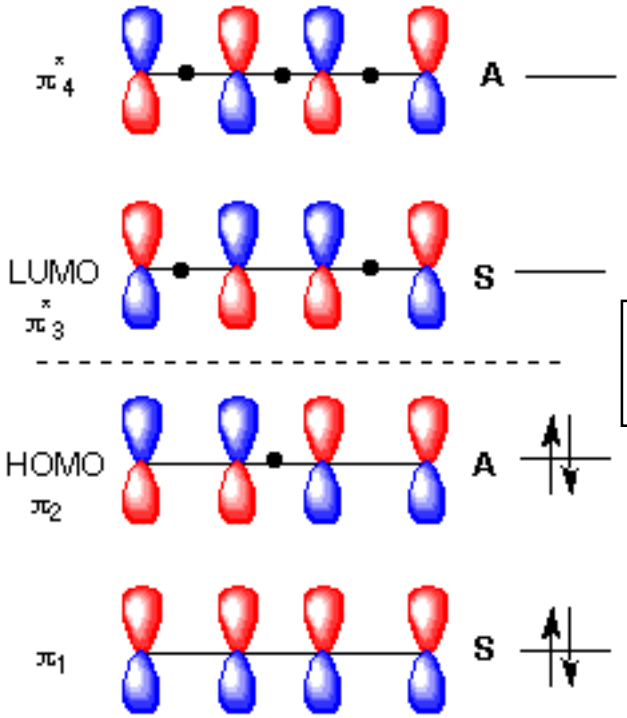
- Woodward, Hoffmann
  - FMO (HOMO x LUMO)

- ethylene



171 nm
167 kcal/mol

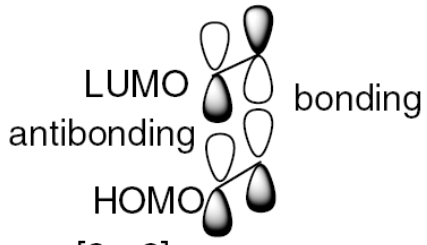
- 1,3-butadiene



214 nm
133 kcal/mol

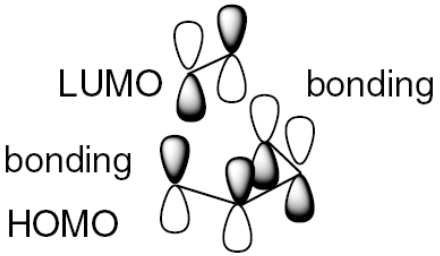
Cycloaddition Reactions

- requirement for bonding interaction



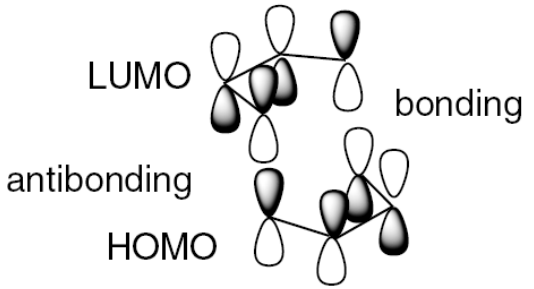
[2 + 2]

unfavorable, forbidden



[2 + 4]

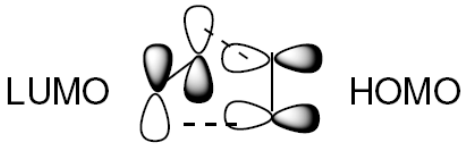
favorable, allowed



[4 + 4]

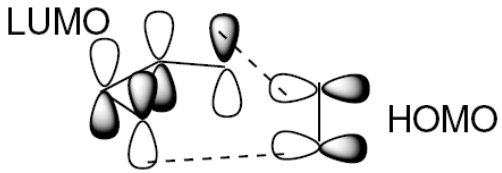
unfavorable, forbidden

- second aspect – mode of addition (Huckel x Mobius system):
  - face to face (suprafacial) - *s*
  - opposite faces (antarafacial) - *a*



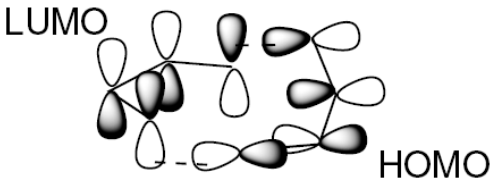
$[\pi 2_a + \pi 2_s]$

allowed



$[\pi 4_a + \pi 2_s]$

forbidden



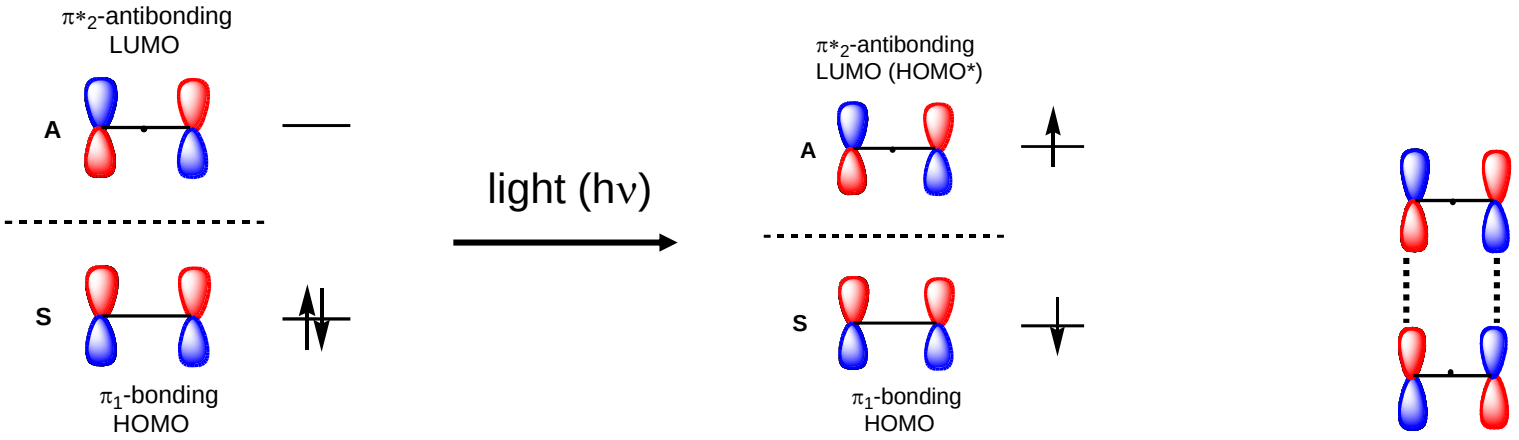
$[\pi 4_a + \pi 4_s]$

allowed

Cycloaddition Reactions

Orbital symmetry rules

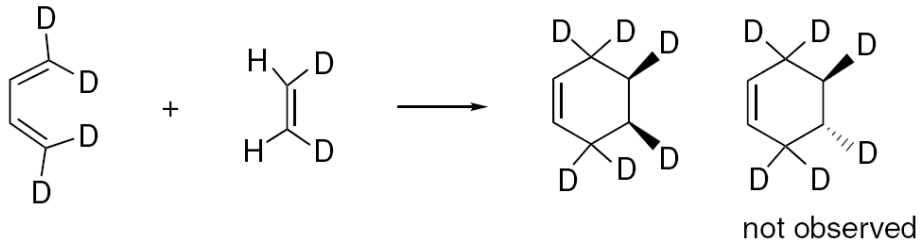
$m+n$	Orbital Symmetry Rules for $m+n$ Cycloaddition Supra/supra	Supra/antara	Antara/antara
$4n$	Forbidden	Allowed	Forbidden
$4n+2$	Allowed	Forbidden	Allowed



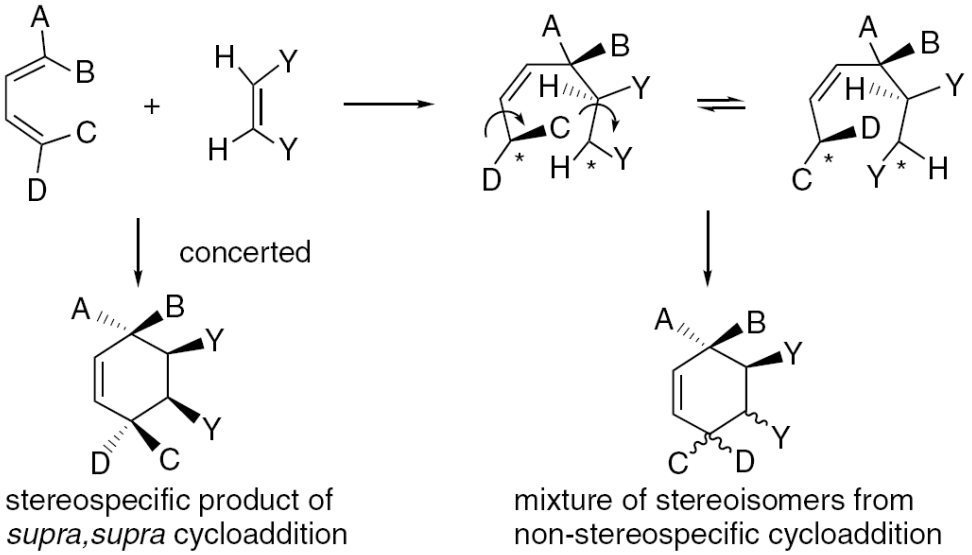
Cycloaddition Reactions

Diels-Alder Reactions, [4+2]

- reorganization π-electron system (*synchronous*)
- two new σ-bonds are formed
- *s*-cis conformation
- *syn* (suprafacial) addition
  – highly stereospecific



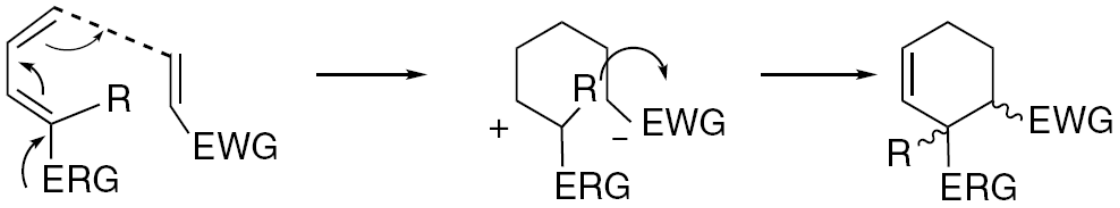
- also *asynchronous process*
  (asymmetrical alkenes and dienes)



Cycloaddition Reactions

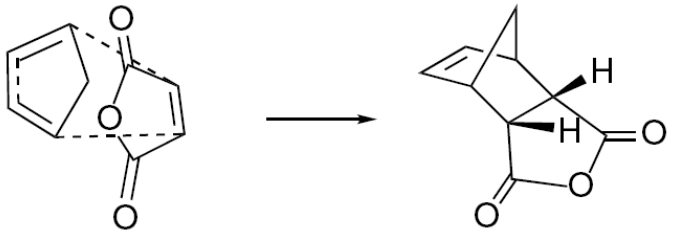
Diels-Alder Reactions, [4+2]

- electronic character
  strongly electrophilic dienophile and strongly nucleophilic diene



- *endo* TS x *exo TS*
  Alder rule (endo TS) – EWG on the dienophile

endo *exo*



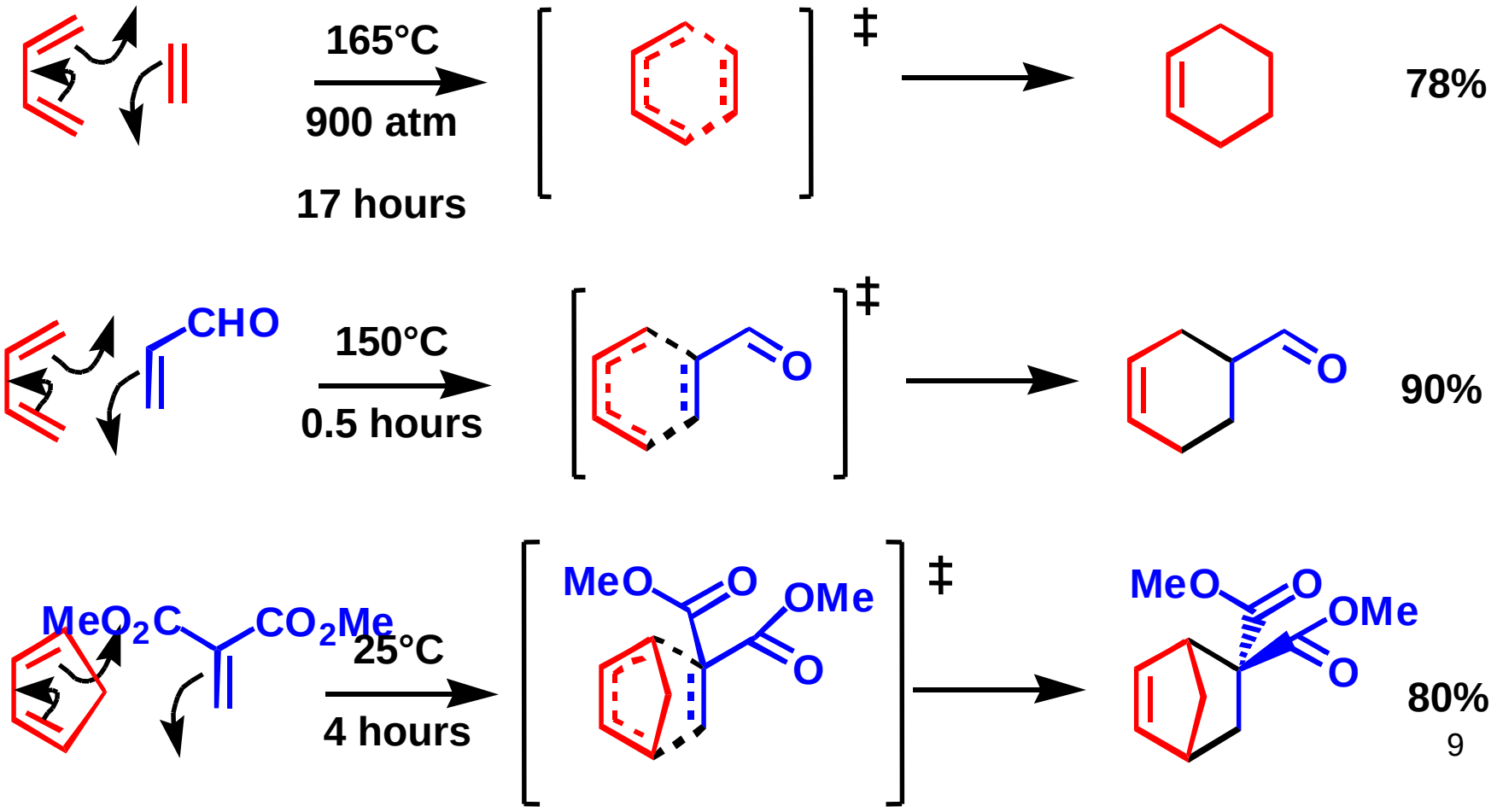
endo addition

- kinetic x thermodynamic

Cycloaddition Reactions

Diels-Alder Reactions, [4+2]

- substituent effect – reactivity



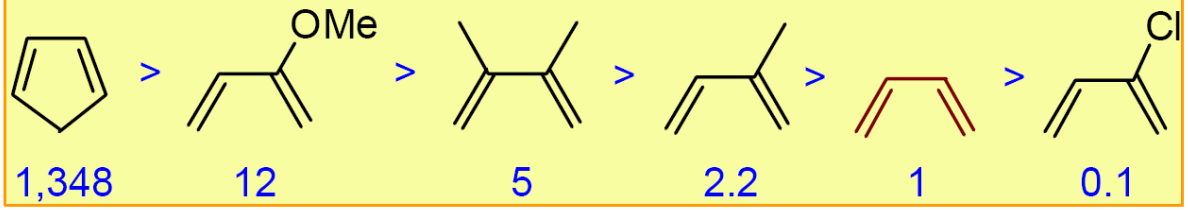
Cycloaddition Reactions

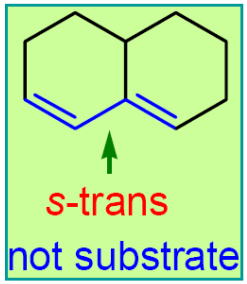
Diels-Alder Reactions, [4+2]

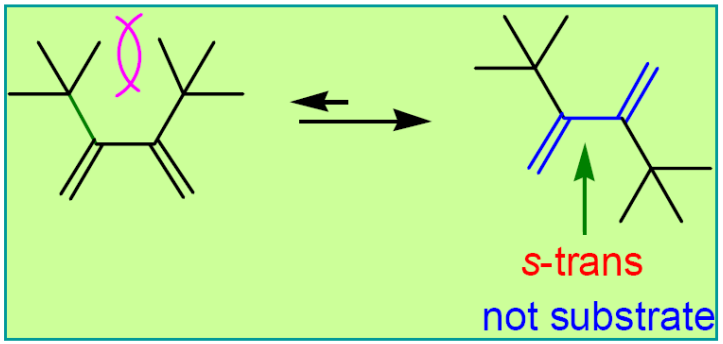
- substituent effect - reactivity

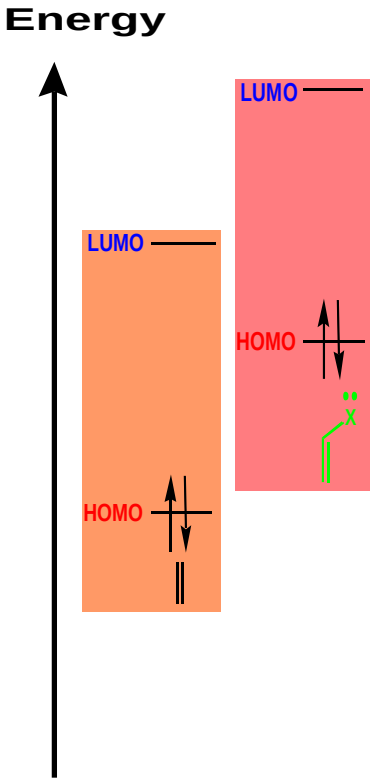
Diene

Reactivity toward maleic anhydride:









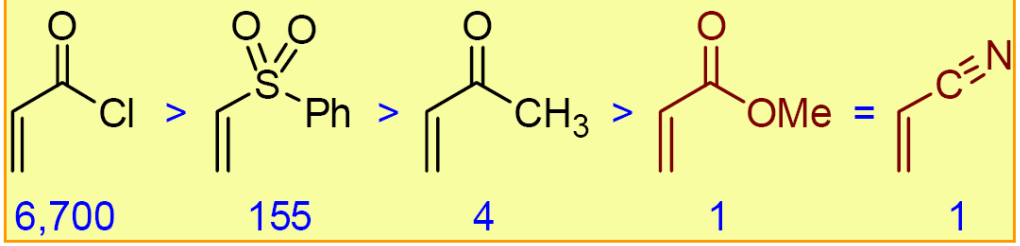
Cycloaddition Reactions

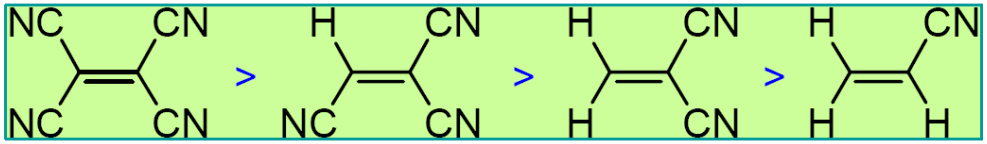
Diels-Alder Reactions, [4+2]

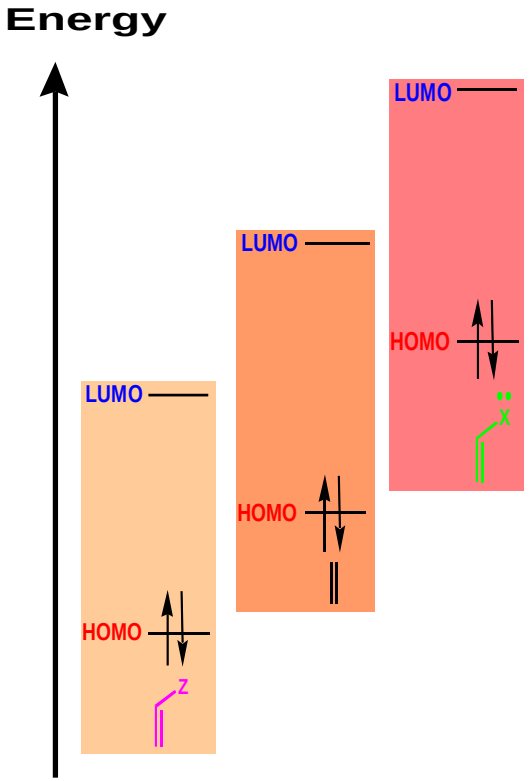
- substituent effect - reactivity

Dienophile

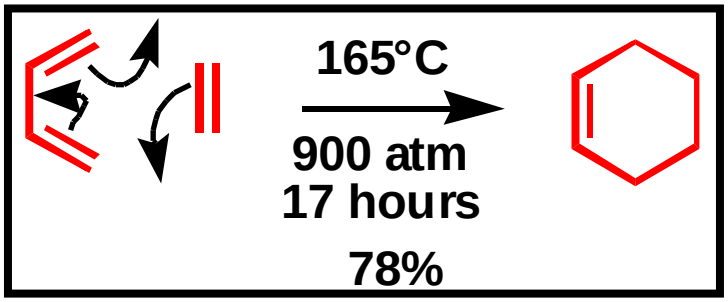
Reactivity toward cyclopentadiene:

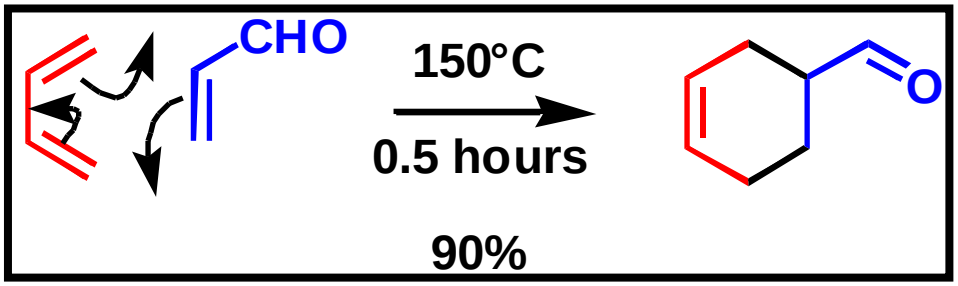


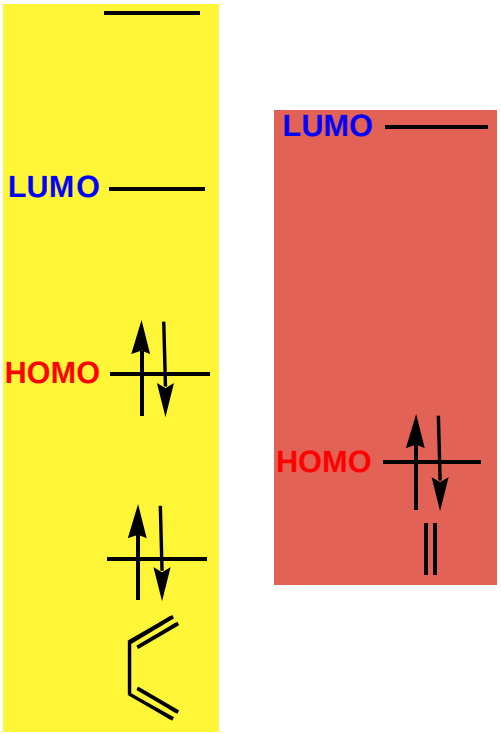


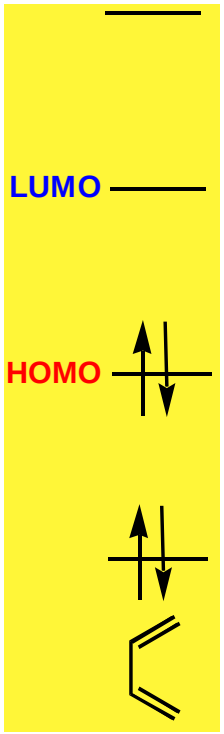


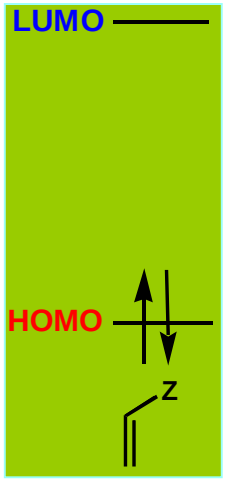
Cycloaddition Reactions







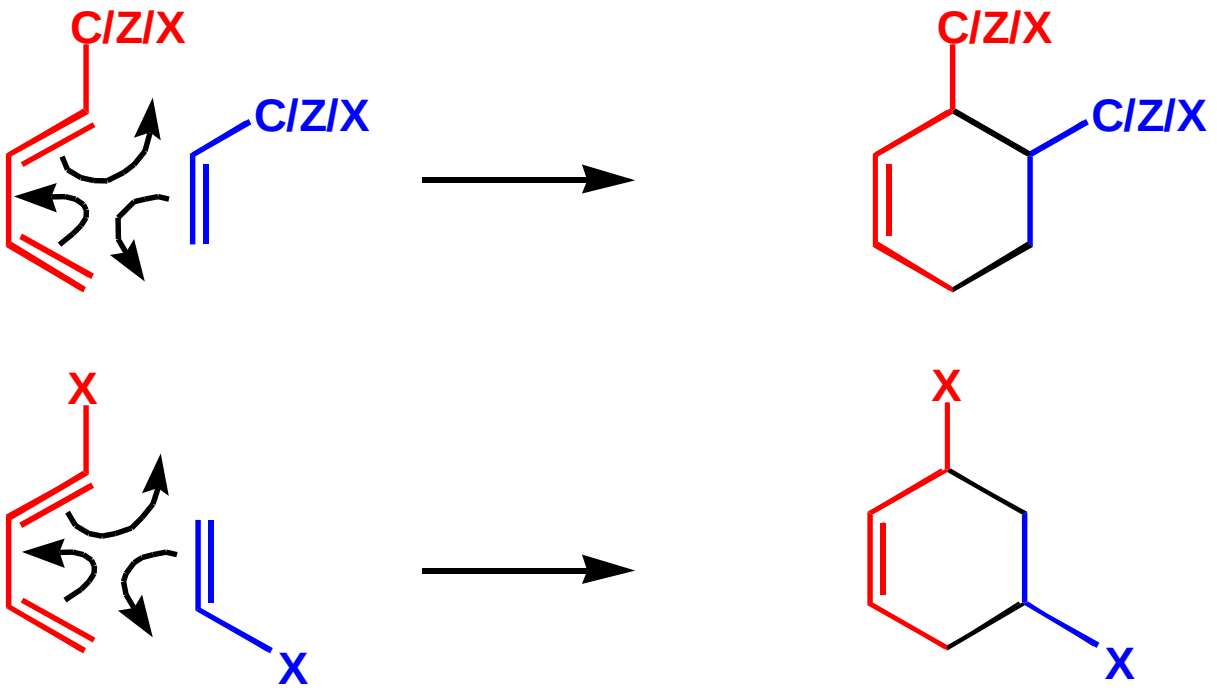




Cycloaddition Reactions

Diels-Alder Reactions, [4+2]

- substituent effect – **regioselectivity**
  Summary



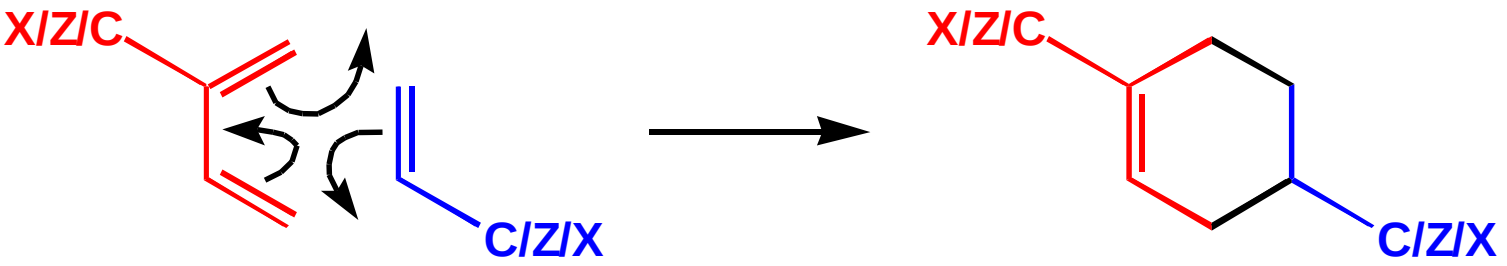
Except

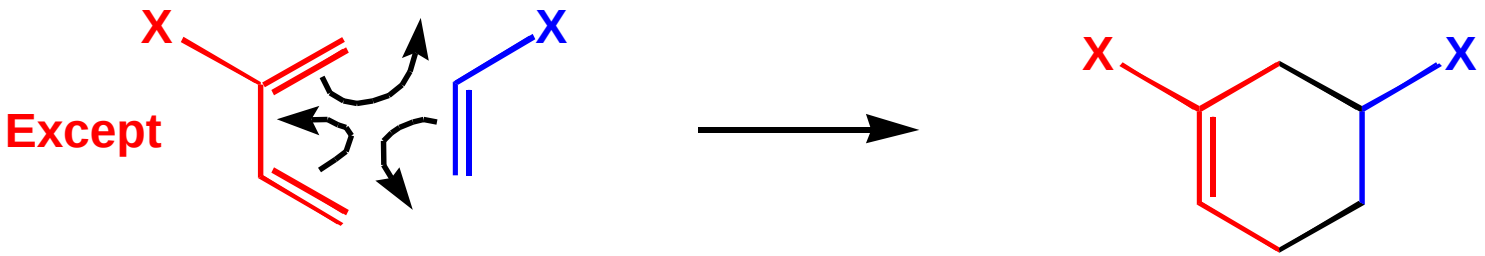
C = Extending Conjugation
Z = Electron Withdrawing Group
X = Electron Donating Group

Cycloaddition Reactions

Diels-Alder Reactions, [4+2]

- substituent effect – **regioselectivity**
  Summary (cont.)



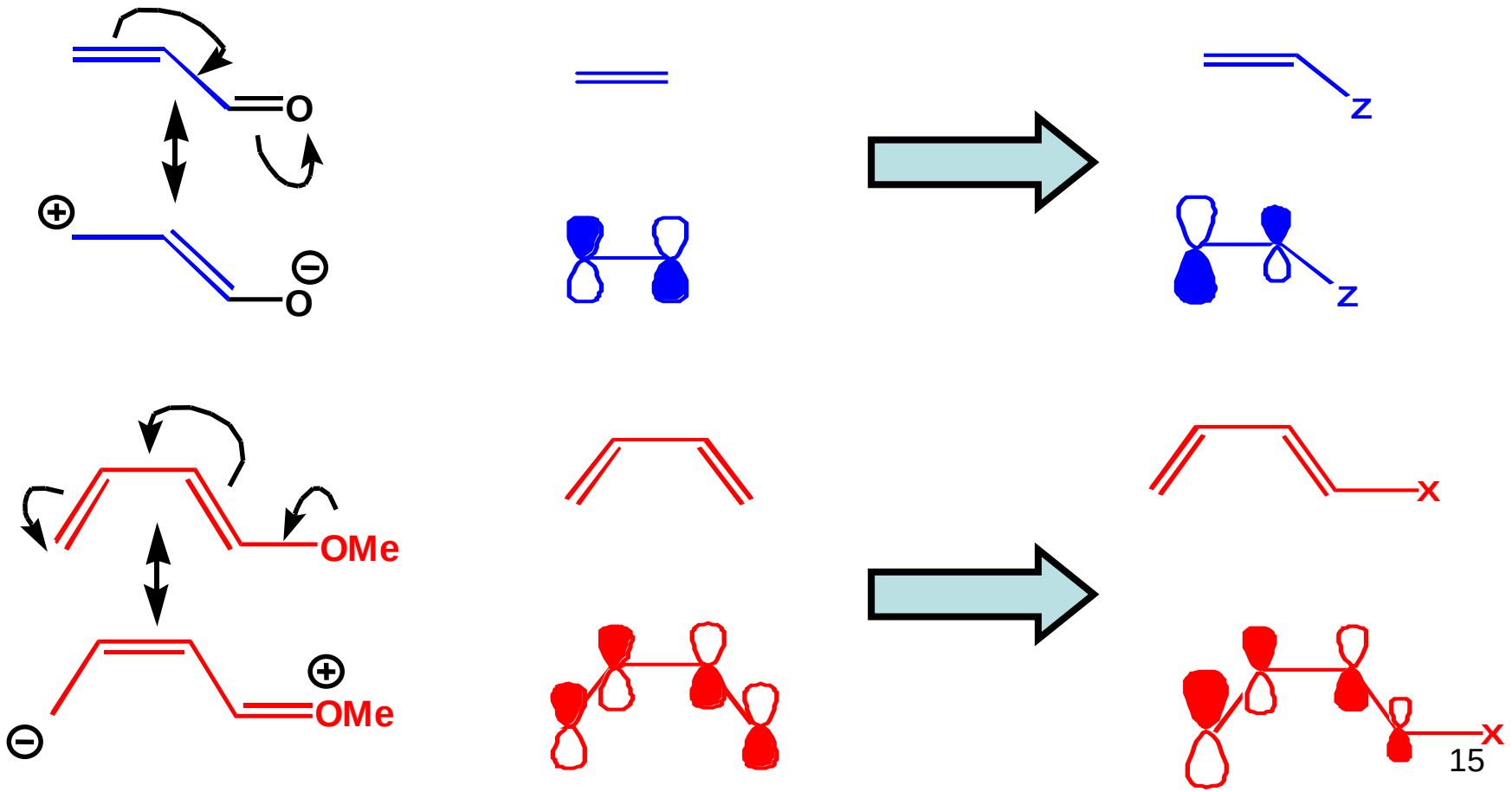


C = Extending Conjugation
Z = Electron Withdrawing Group
X = Electron Donating Group

Cycloaddition Reactions

Diels-Alder Reactions, [4+2]

- substituent effect – desymmetrisation of orbitals

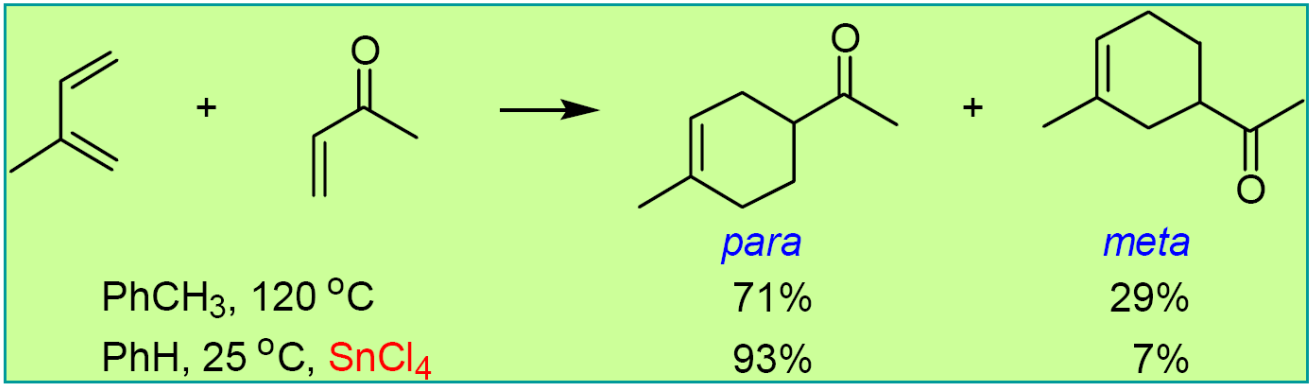


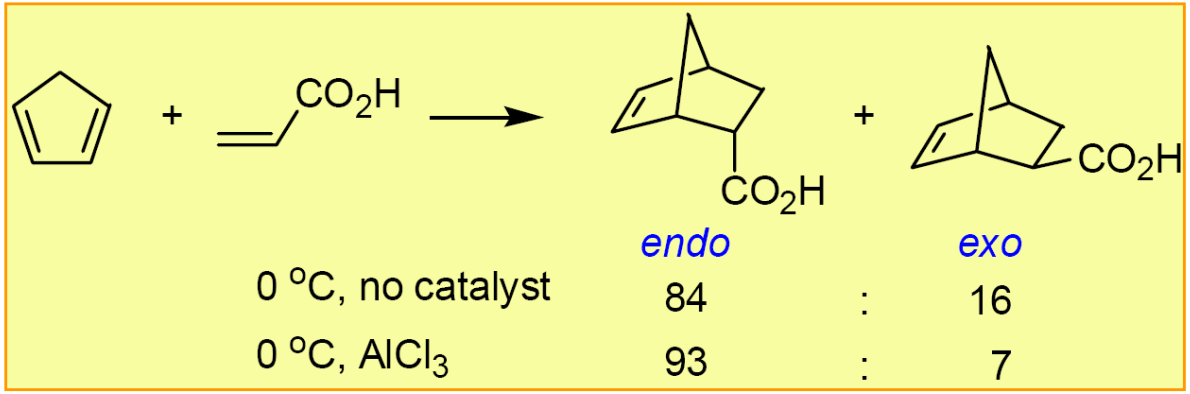
Cycloaddition Reactions

Diels-Alder Reactions, [4+2]

Stereoselectivity

- LA - enhanced selectivity ($SnCl_4$, $AlCl_3$, $LiClO_4$)

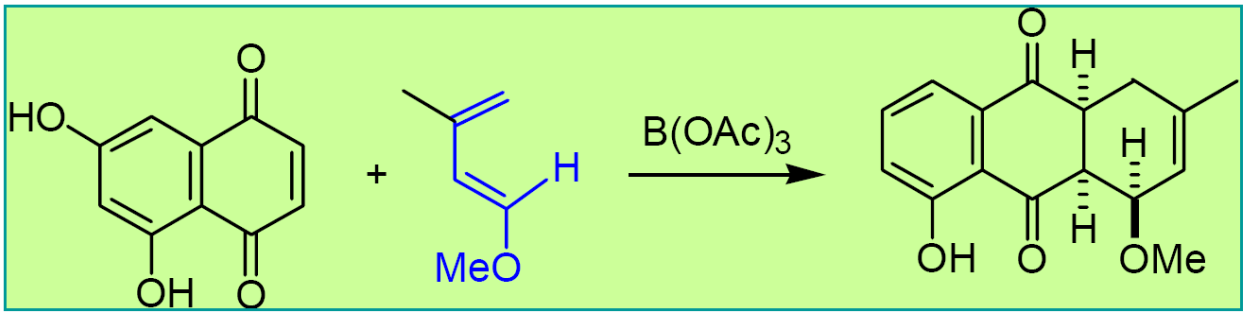


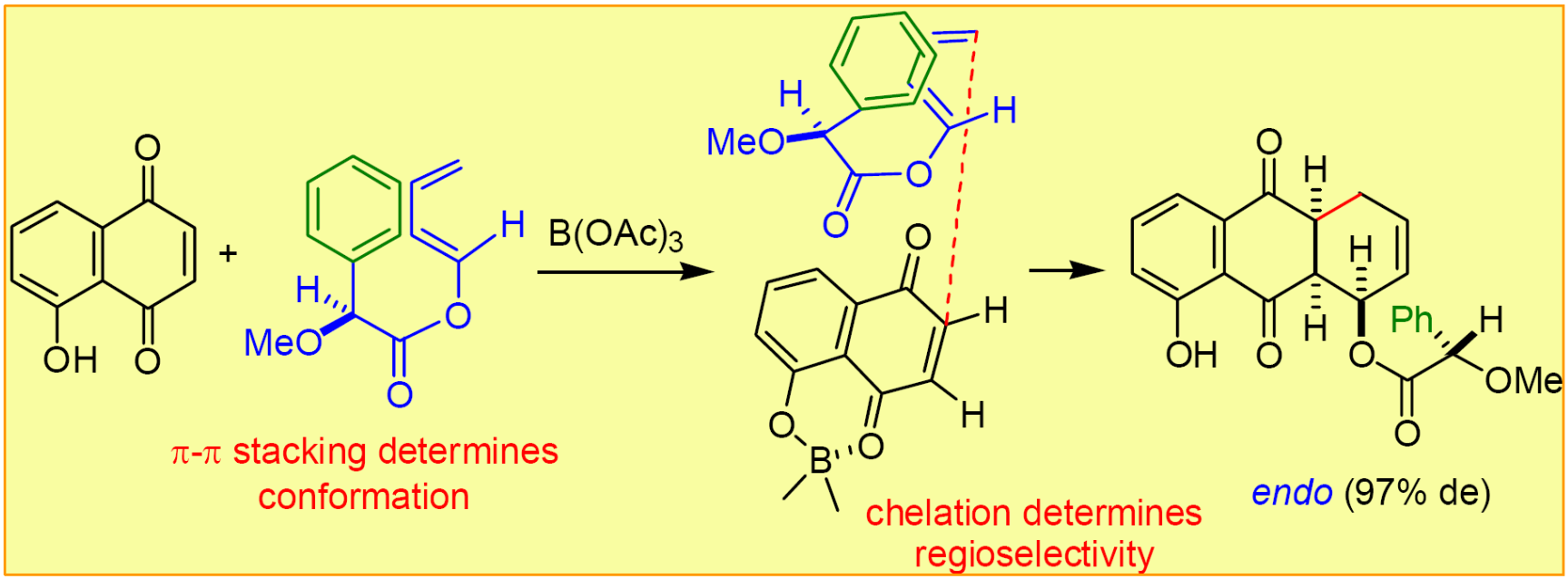


Cycloaddition Reactions

Diels-Alder Reactions, [4+2]

Stereoselectivity (LA)



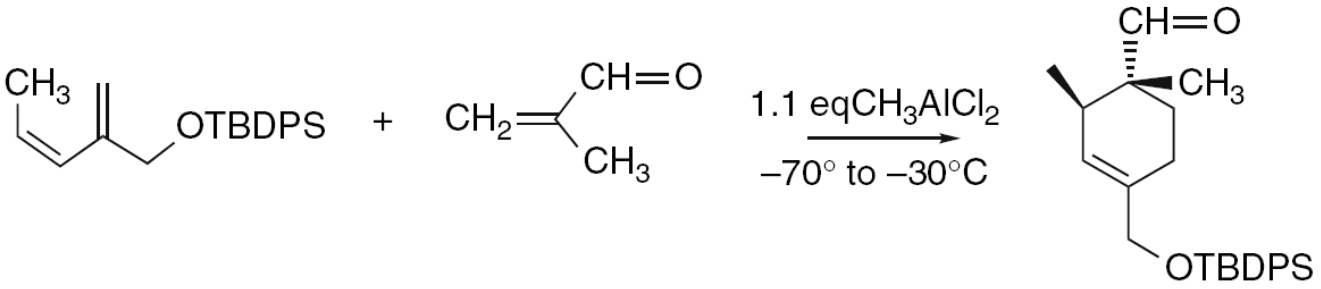


Cycloaddition Reactions

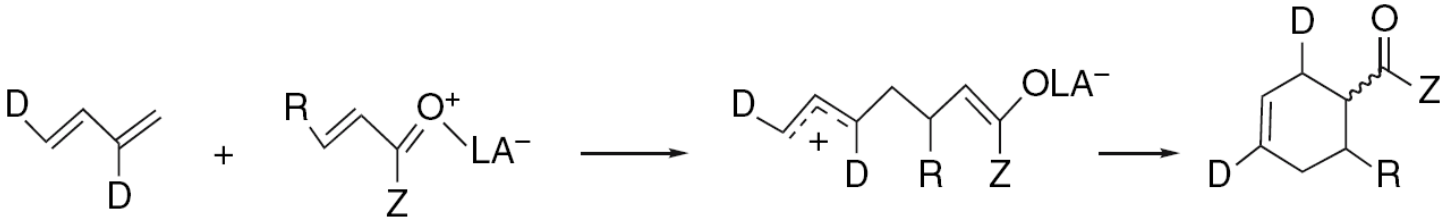
Diels-Alder Reactions, [4+2]

Stereoselectivity

- LA - enhanced selectivity
  (CH_3AlCl_2 for *Z*-dienes)



- strong LA

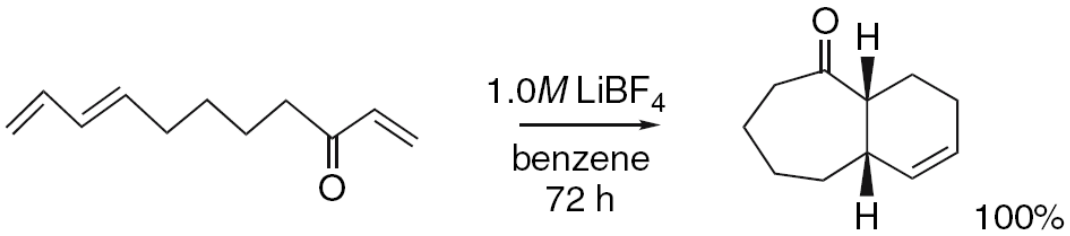


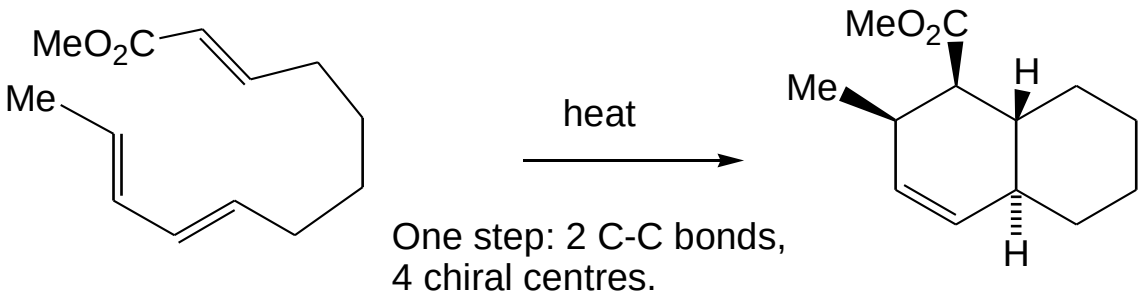
Cycloaddition Reactions

Diels-Alder Reactions, [4+2]

Stereoselectivity

- intramolecular





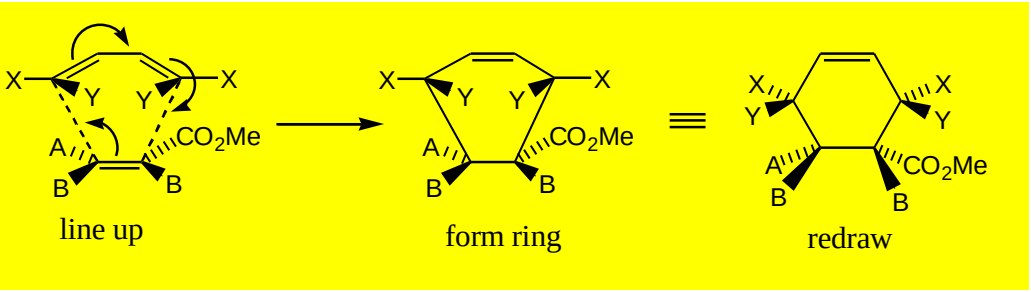
One step: 2 C-C bonds,
4 chiral centres.

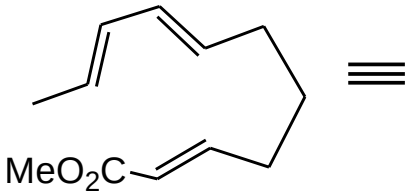
Cycloaddition Reactions

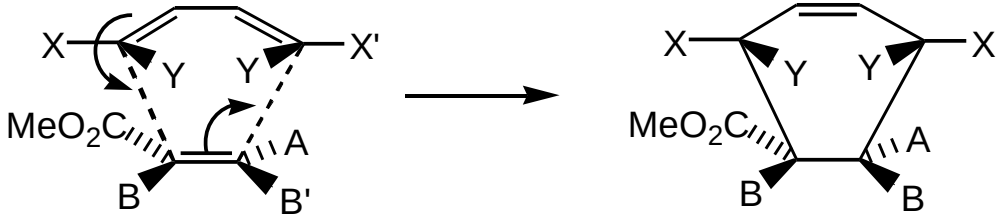
Diels-Alder Reactions, [4+2]

Stereoselectivity

- intramolecular



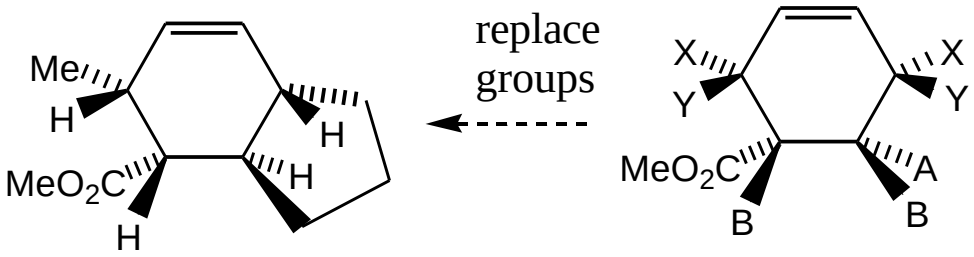




(Y=H, X=Me, X'-B' is three carbon bond, A, B=H)

- strong LA

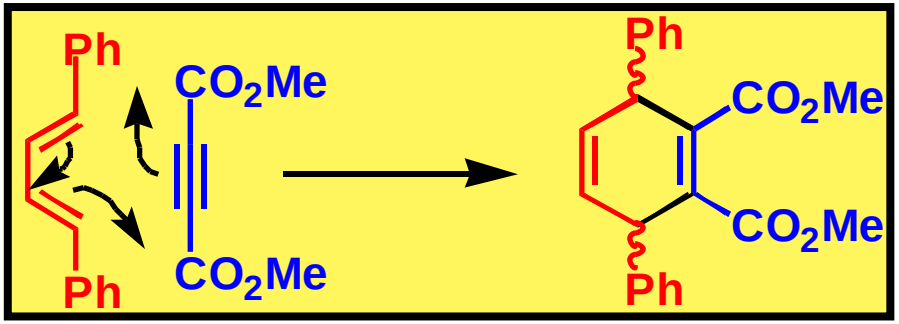
Remember:
try to redraw the molecule as few times as possible as each will result in a higher chance of errors slipping in.

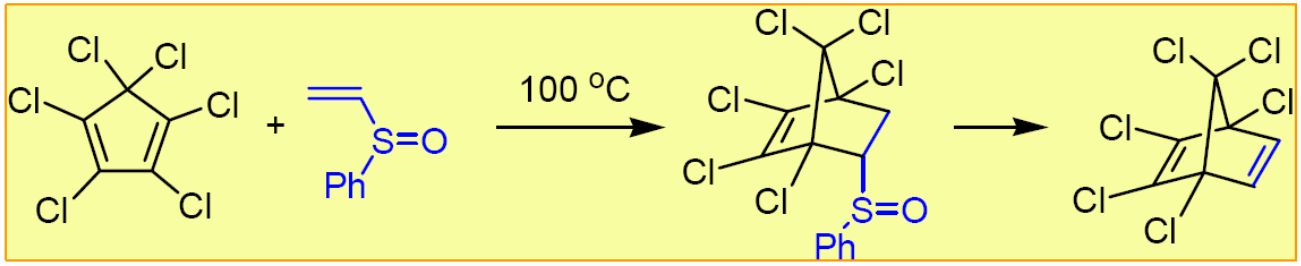


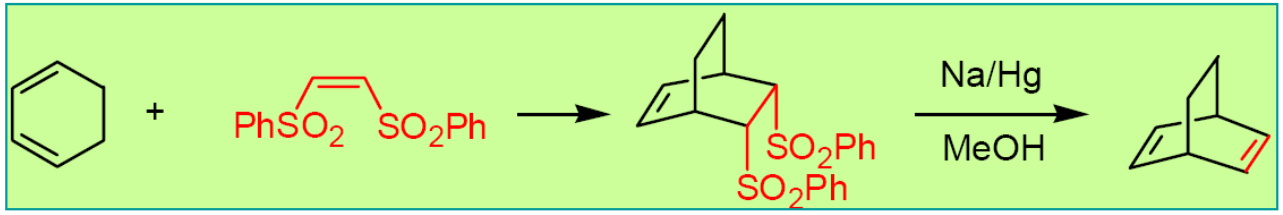
Cycloaddition Reactions

Diels-Alder Reactions, [4+2]

Acetylene equivalents





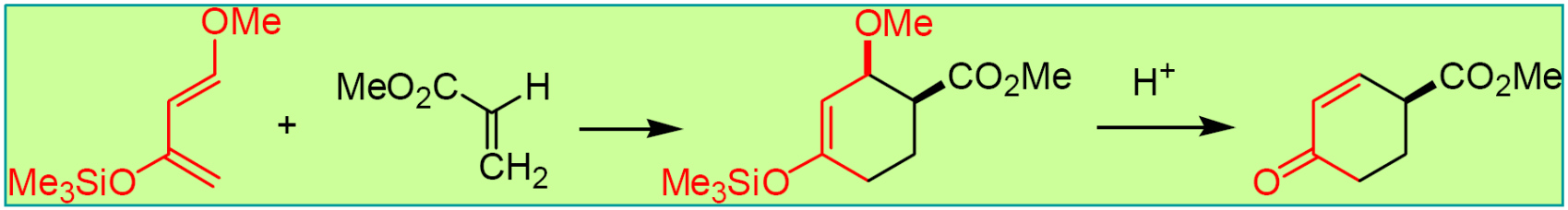


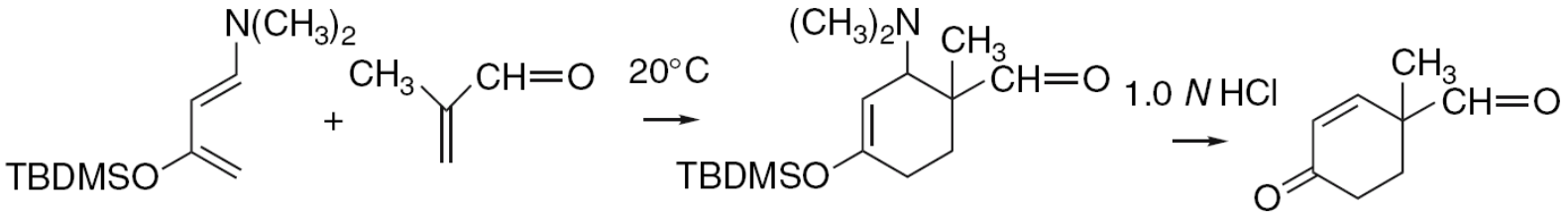
Cycloaddition Reactions

Diels-Alder Reactions, [4+2]

Applications

- Danishefsky´s diene



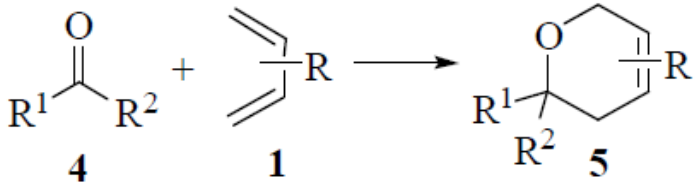


Cycloaddition Reactions

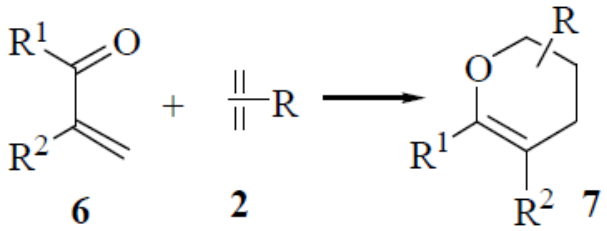
Hetero Diels-Alder Reactions, [4+2]

- ketones, imines
- normal NED HDA vs. IED HDA

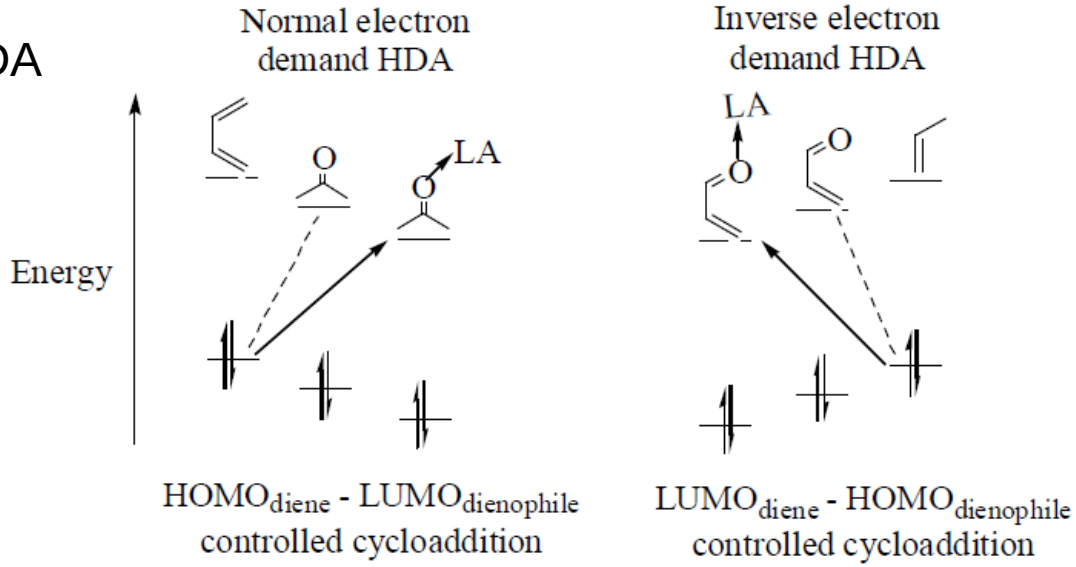
Normal electron demand



Inverse electron demand



- LA-promoted HDA

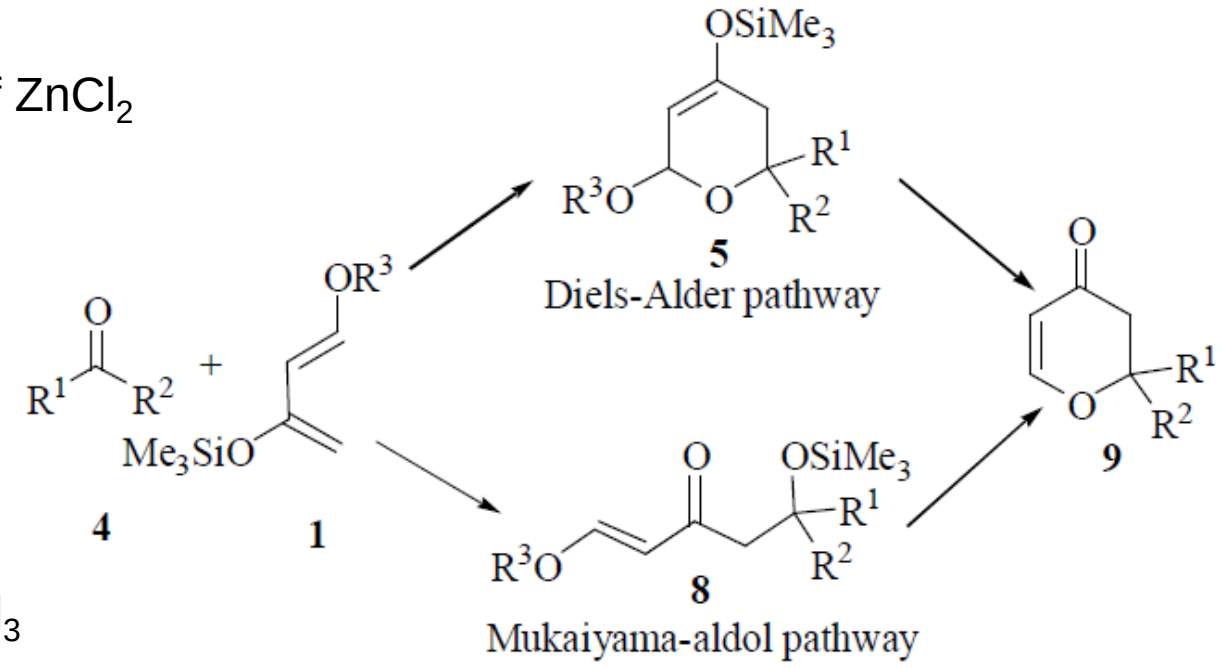


Cycloaddition Reactions

Hetero Diels-Alder Reactions, [4+2]

- Ketones: oxa-HDA reaction
- Mechanism: a) DA cycloaddition (traditional)
  b) Mukaiyama-aldol reaction + cyclization step

in presence of $ZnCl_2$

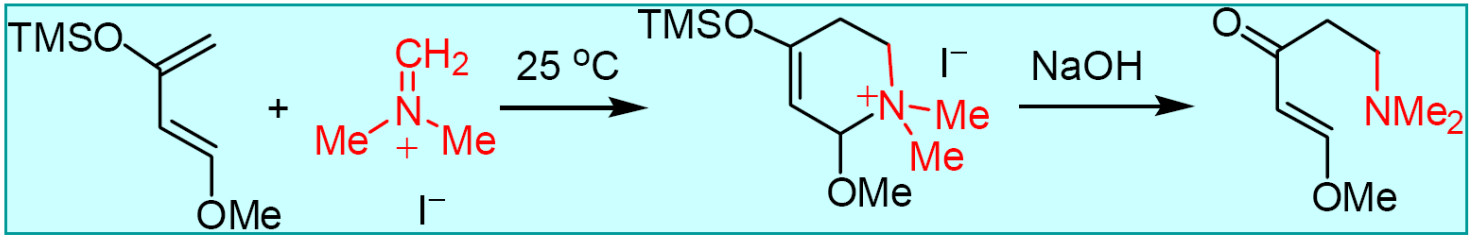


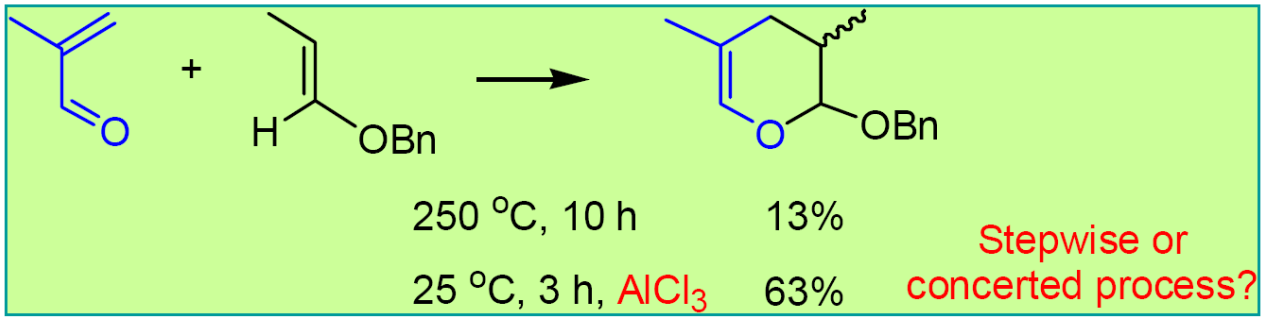
with BF_3, $AlCl_3$

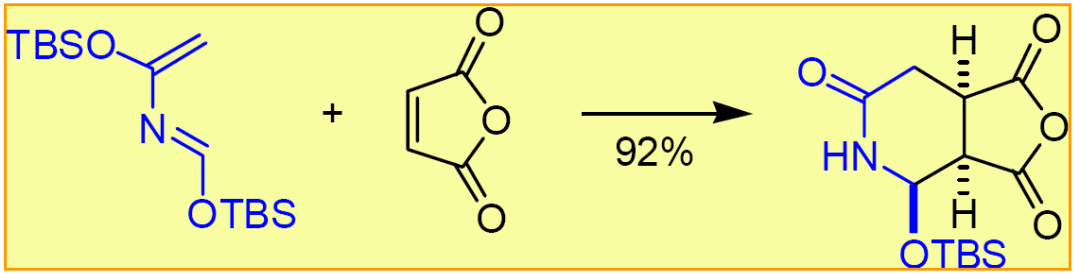
Cycloaddition Reactions

Hetero Diels-Alder Reactions, [4+2]

Other examples





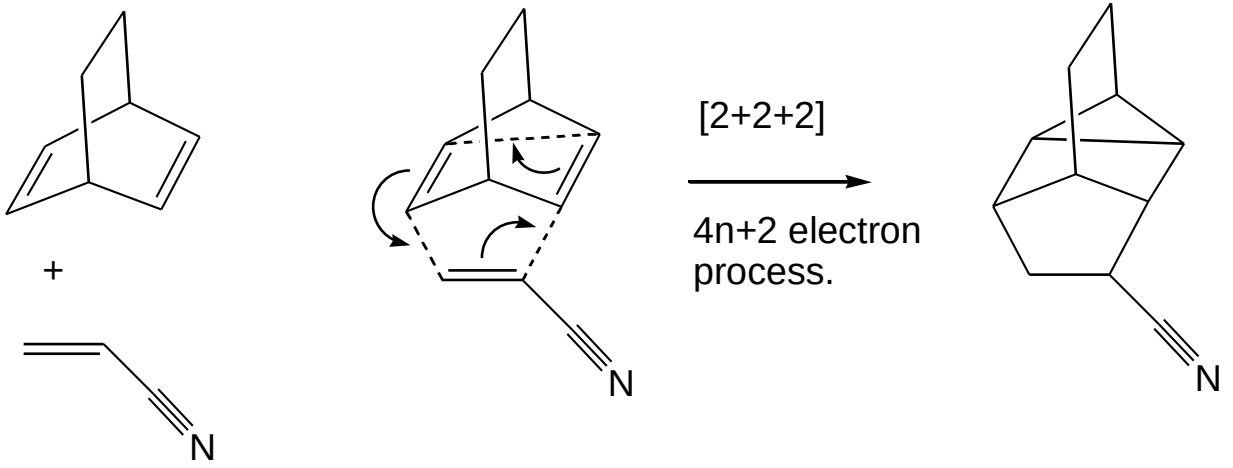


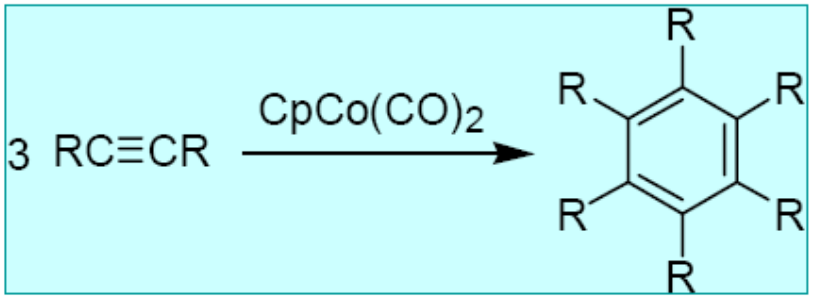
Cycloaddition Reactions

Diels-Alder Reactions, [4+2]

Three component Cycloadditions

- 3-body collision is unlikely





Cycloaddition Reactions

1,3-Dipolar cycloadditions, [4+2]

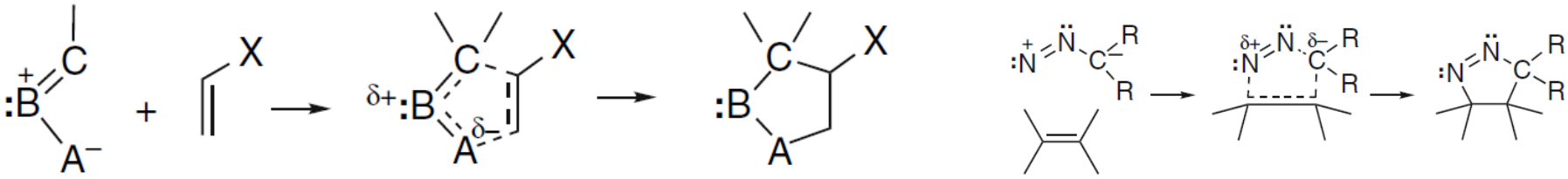
1,3-Dipoles

- π-electronic system similar to allyl and propargyl anions consisting of two filled and one empty orbital
- at least one charge-separated resonance structure with opposite charges in 1,3 relationship
- not highly polar

Dipolarophile

- usually alkene or alkyne
- other multiply bonded FG - imine, azo and nitroso
- low sensitivity towards polarity of solvent

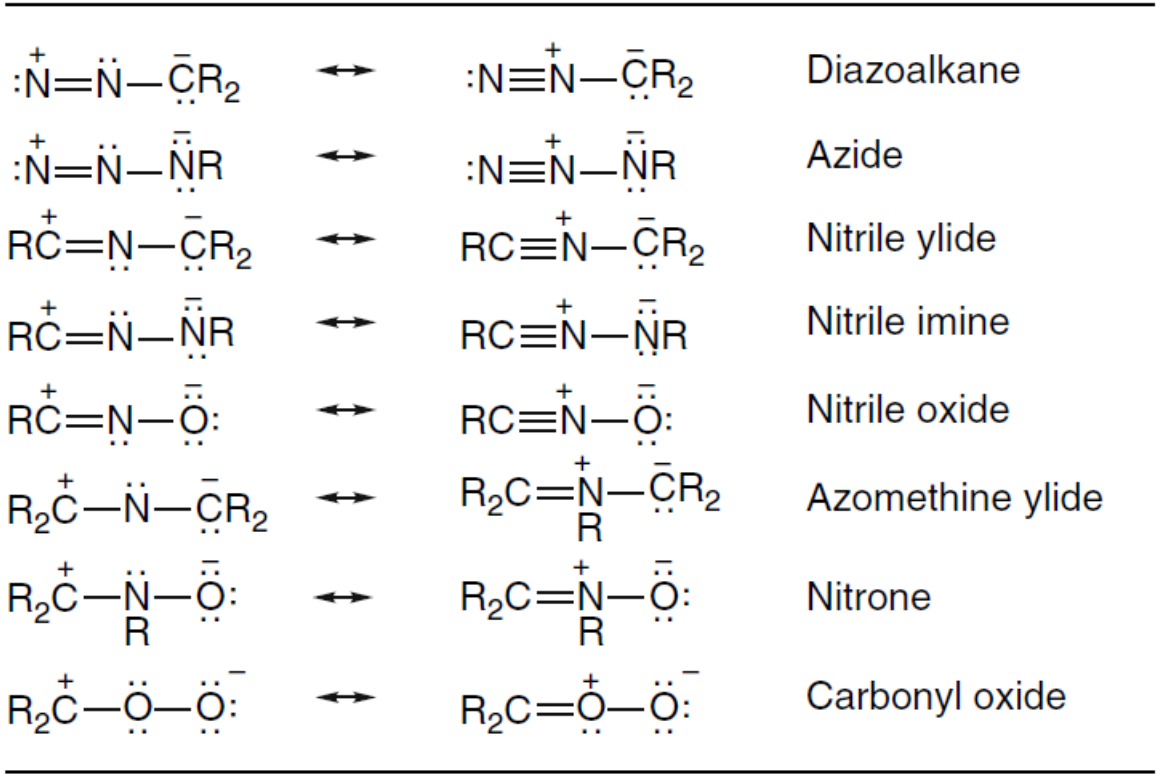
General scheme



Cycloaddition Reactions

1,3-Dipolar cycloadditions, [4+2]

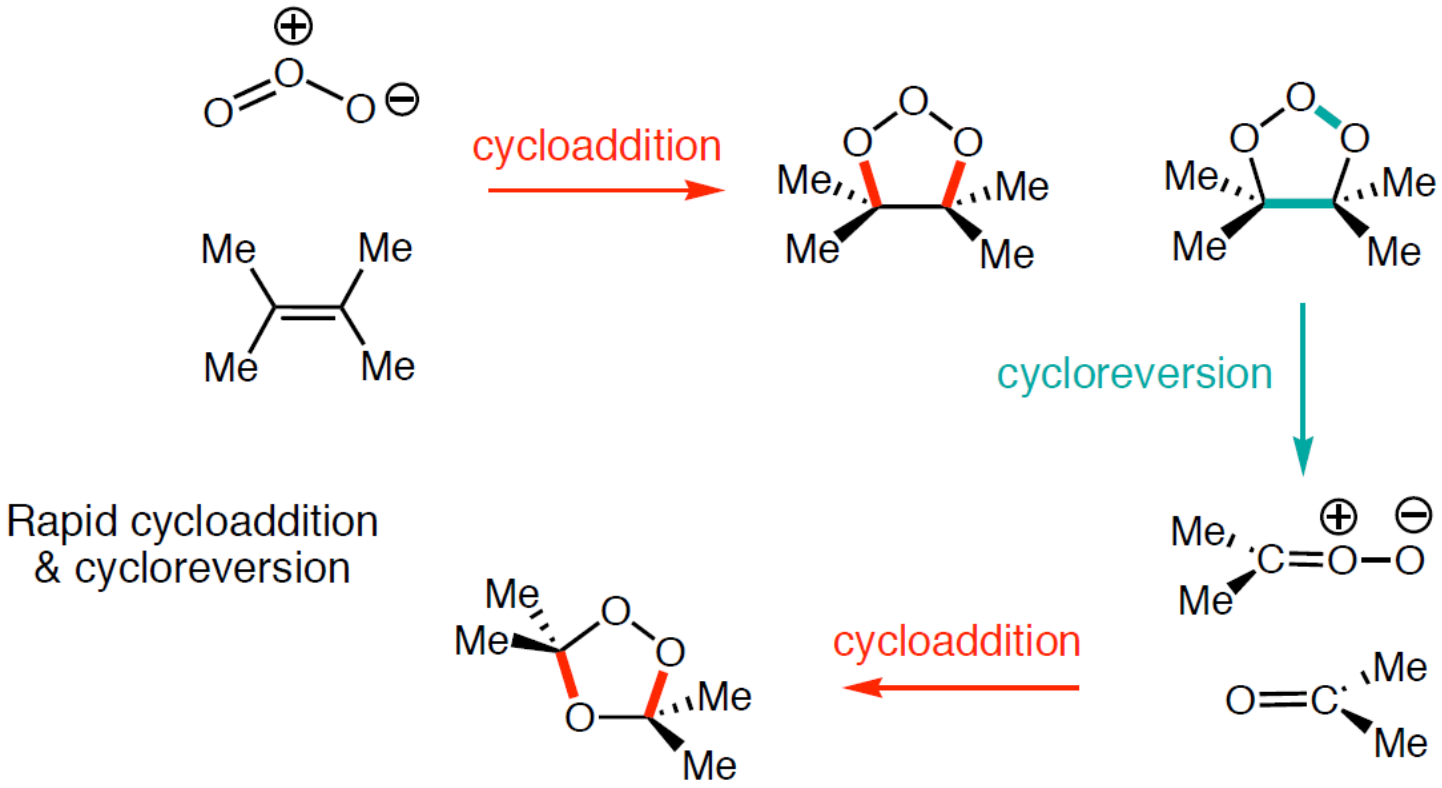
1,3-Dipoles



Cycloaddition Reactions

1,3-Dipolar cycloadditions, [4+2]

Ozonolysis



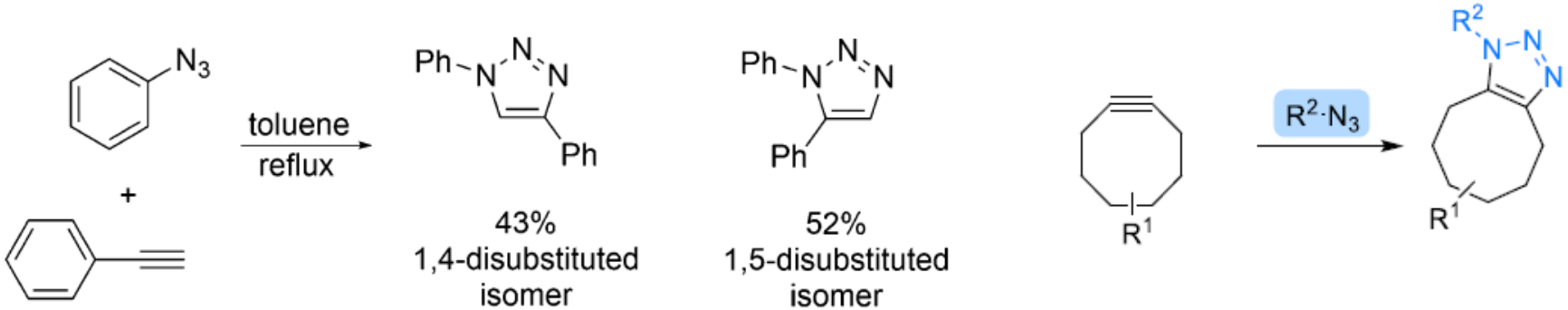
Criegee, R. "Mechanism of Ozonolysis." *Angew. Chem., Int. Ed.* **1975** *14,* 745.

Cycloaddition Reactions

1,3-Dipolar Cycloadditions: Azide-Alkyne Cycloaddition

- thermal conditions (AAC) – mixtures of 1,4- and 1,5-disubstituted 1,2,3-triazoles
- CuAAC (Cu(I)X, terminal alkynes) – Sharpless, 1,4-regiomers
- RuAAC oppose regioselectivity (also internal alkynes) – Fokin, 1,5-regiomers
- Strain promoted AAC

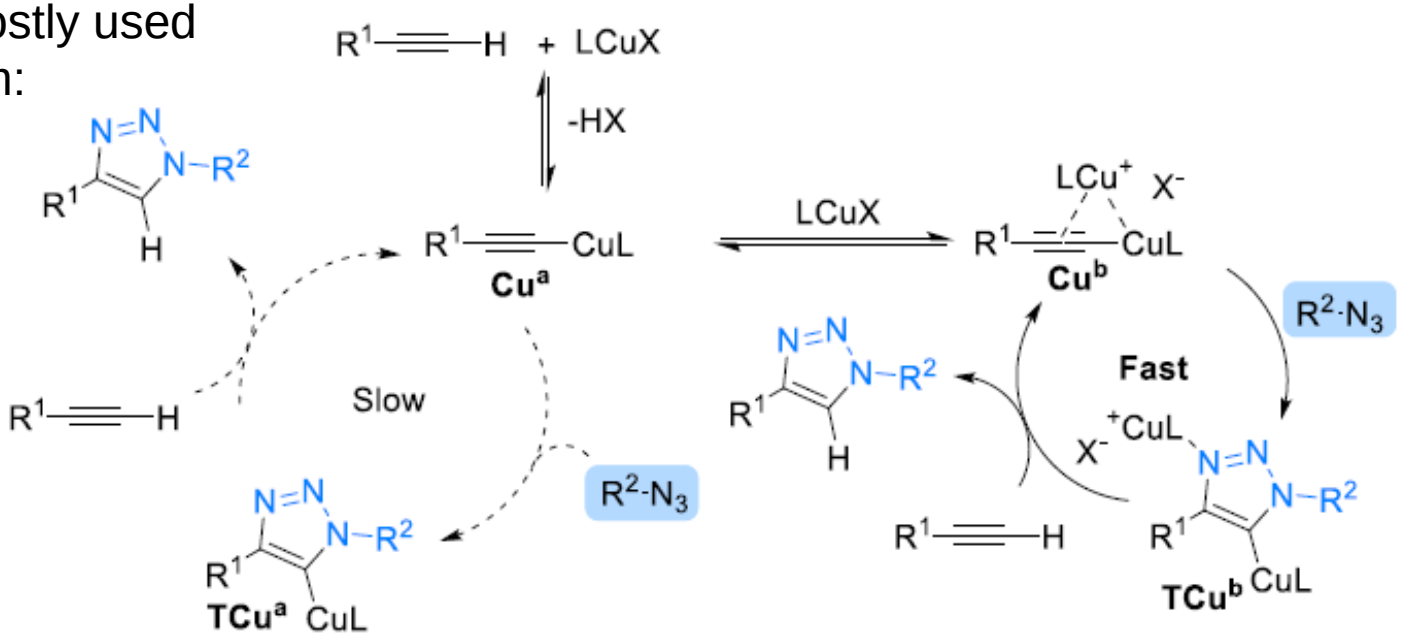
Examples



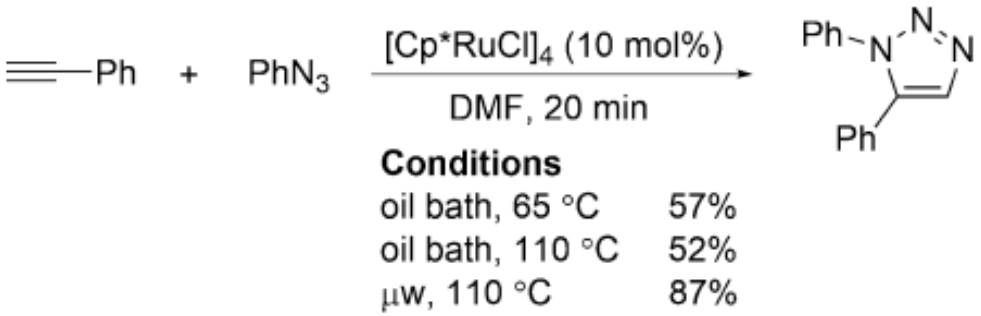
Cycloaddition Reactions

1,3-Dipolar Cycloadditions: Azide-Alkyne Cycloaddition

- CuAAC mostly used
- Mechanism:



- *Versus*

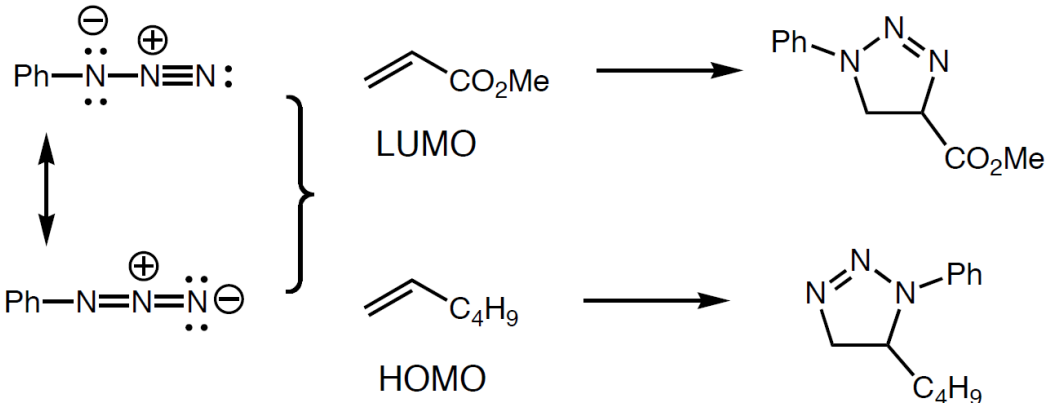


Cycloaddition Reactions

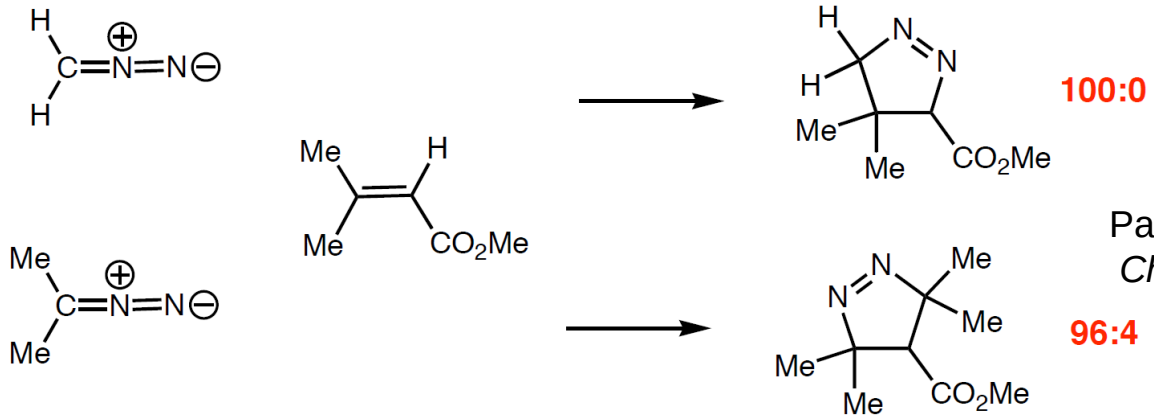
1,3-Dipolar cycloadditions, [4+2]

Regioselectivity

- dominant frontier orbitals
- the specific set of reaction partners defines the dominant FO



- steric effects alter regioselectivity



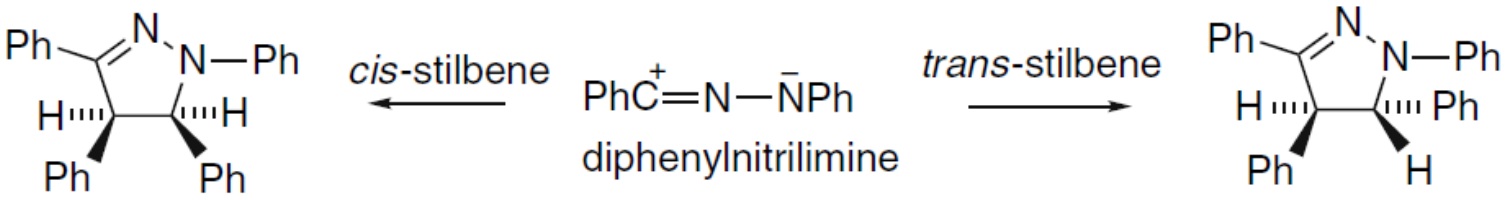
Padwa A. *1,3-Dipolar Cycloaddition Chemistry*, Wiley, 1984, Vol. 1.-2.

Cycloaddition Reactions

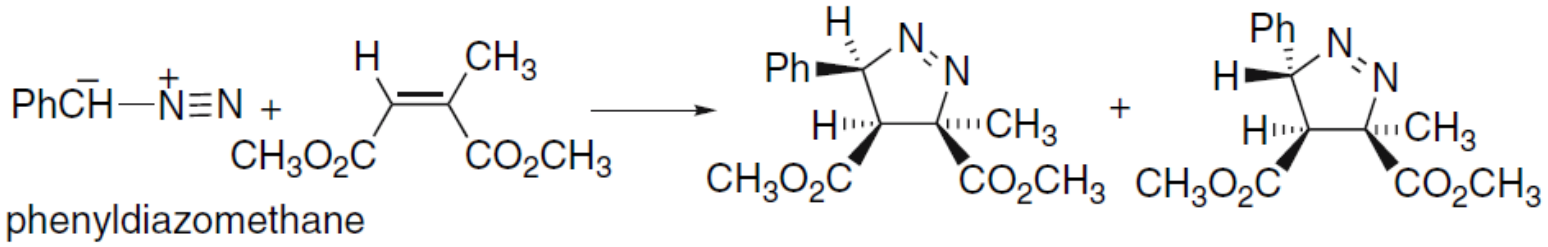
1,3-Dipolar cycloadditions, [4+2]

Stereochemistry

- stereospecific *syn* addition with respect to dipolarophile (*suprafacial*)



- some 1,3-dipoles give two possible stereoisomers by *syn* addition
- two differing orientations of reacting molecules that are analogous to the *endo* and *exo* TS in D-A reactions

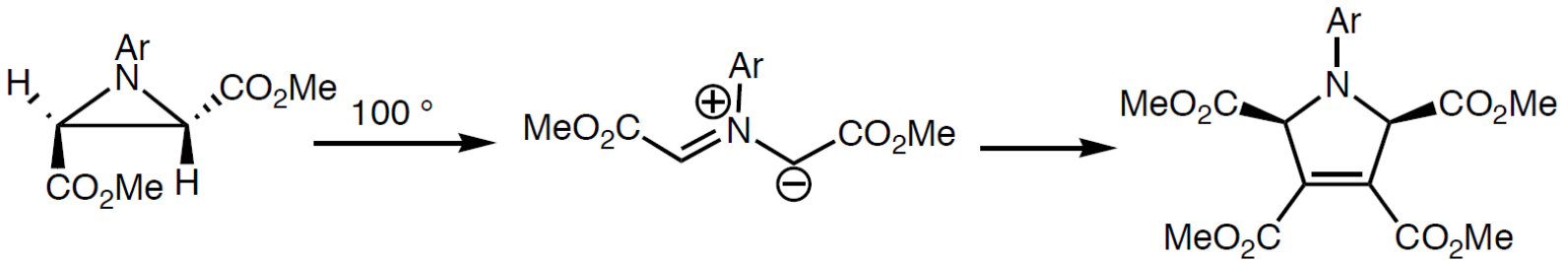


Cycloaddition Reactions

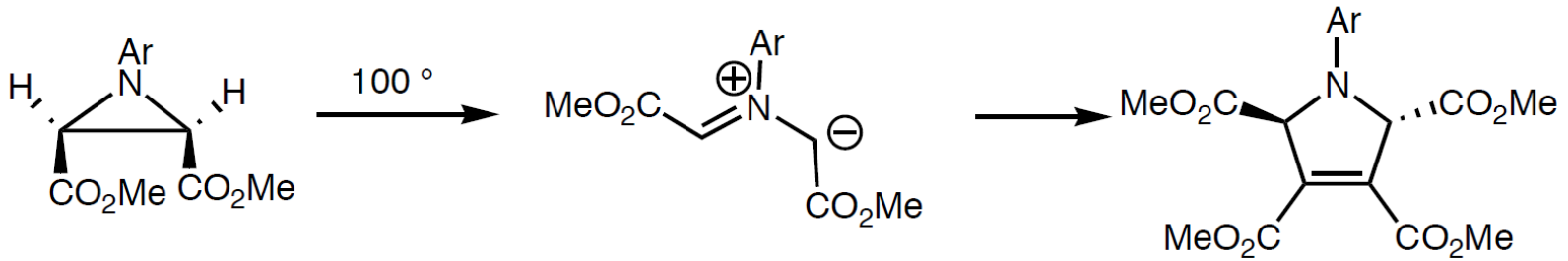
1,3-Dipolar cycloadditions, [4+2]

Stereoselectivity

Reaction Diastereoselectivity Huisgen et al, *Angew.Chem. Int. Ed.* **1969**, *8*, 604



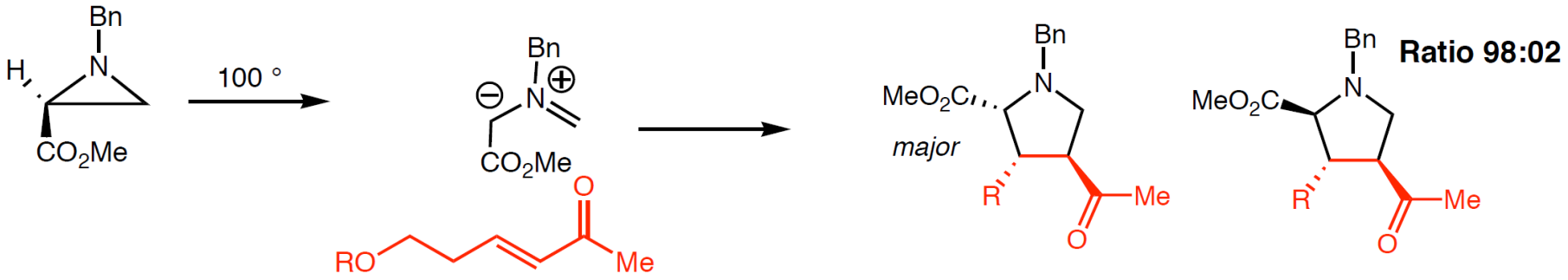
conrotation



Cycloaddition Reactions

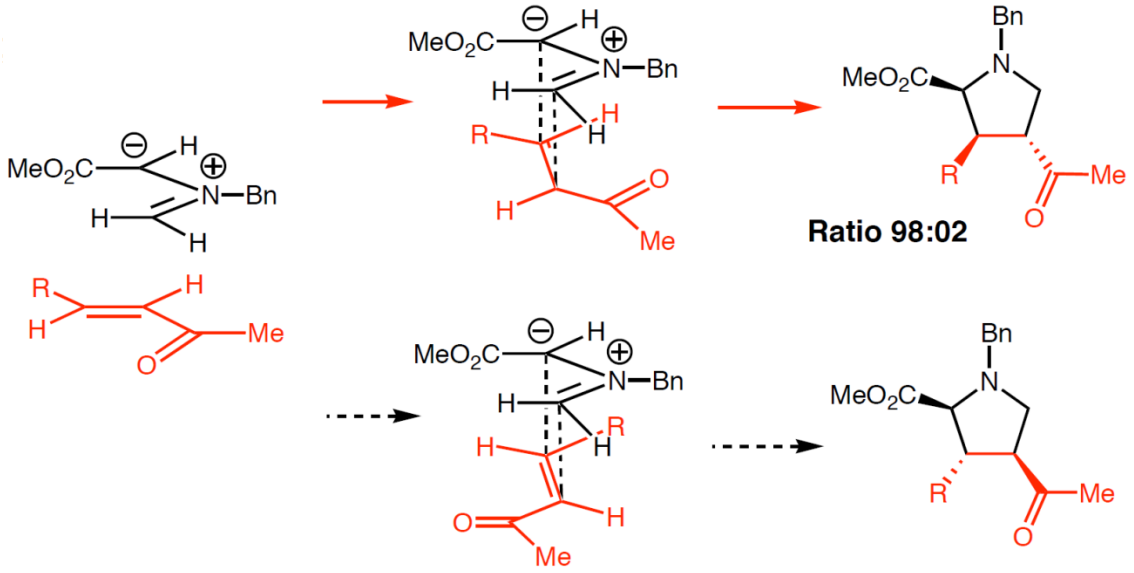
1,3-Dipolar cycloadditions, [4+2]

Stereoselectivity



DeShong, *JOC* **1985**, 50, 2309

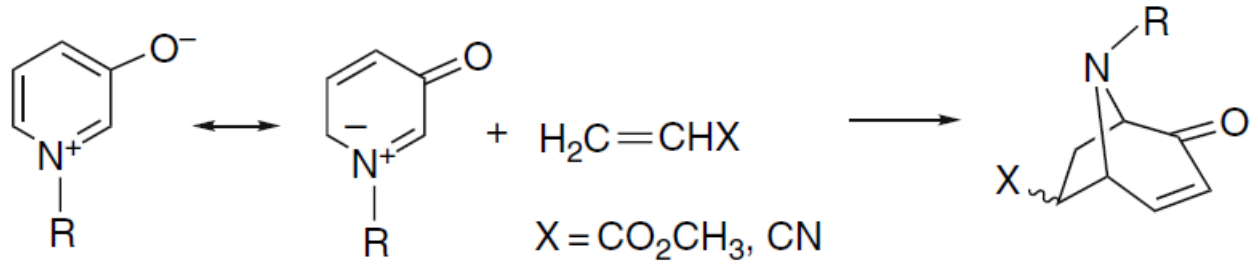
- relative orientation of reactants in TS analysis

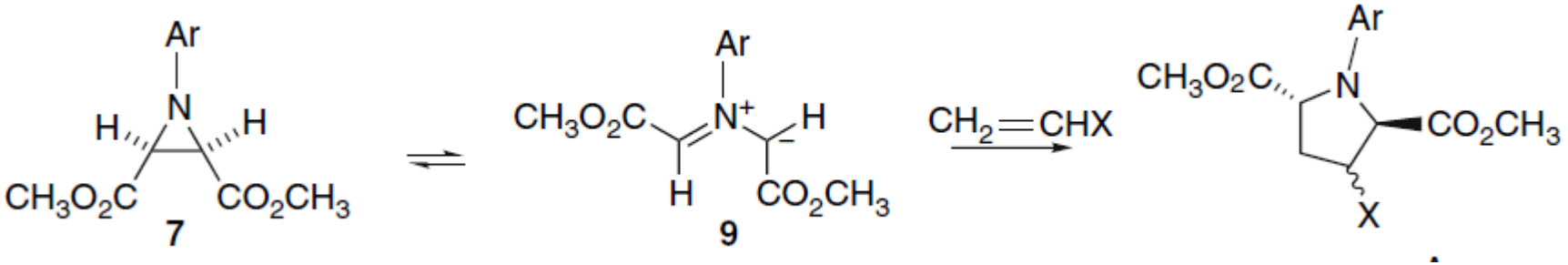


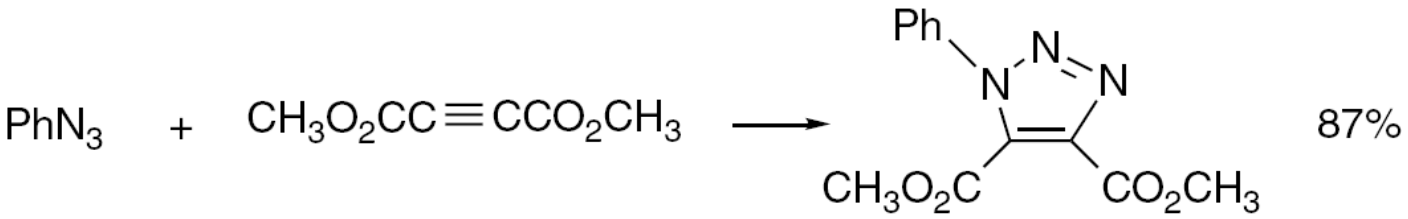
Cycloaddition Reactions

1,3-Dipolar cycloadditions, [4+2]

Examples



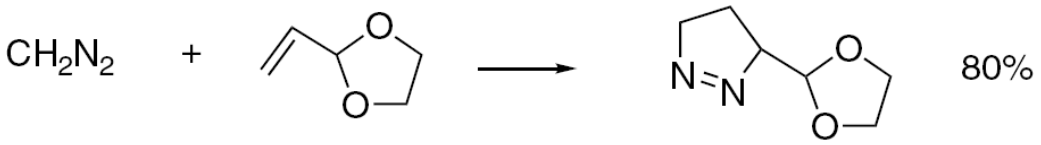


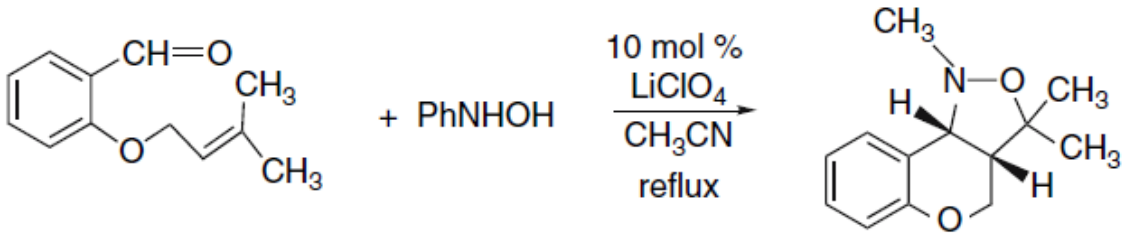


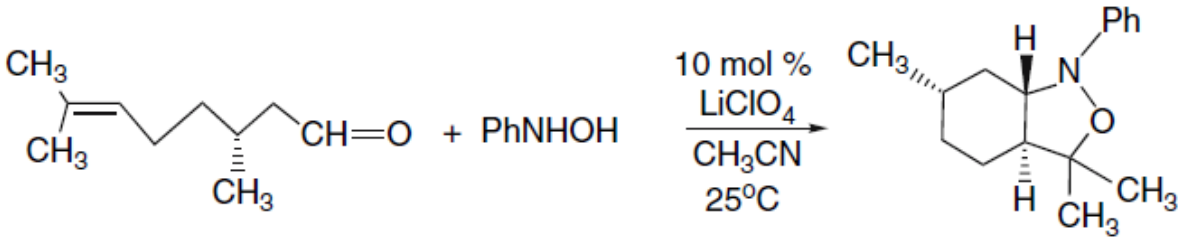
Cycloaddition Reactions

1,3-dipolar cycloadditions, [4+2]

Other examples







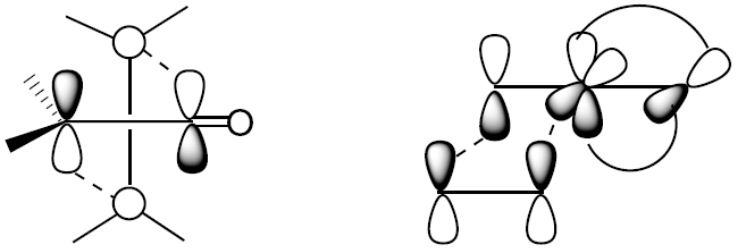
Cycloaddition Reactions

[2+2] Cycloadditions

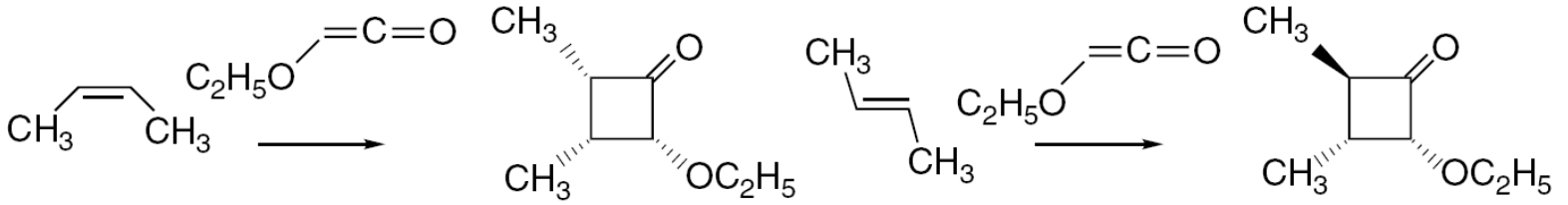
Ketenes + alkenes

- [$2\pi_s$ + 2 π_s] forbidden
- [$2\pi_a$ + $2\pi_s$] allowed
- also [2πs +(2 πs + 2 πs)]

	Orbital Symmetry Rules for $m+n$ Cycloaddition	
$m+n$	Supra/supra	Supra/antara
$4n$	Forbidden	Allowed
$4n+2$	Allowed	Forbidden



- C-2 and C-3 usually *syn (*for *E*- or *Z*- alkenes*)*



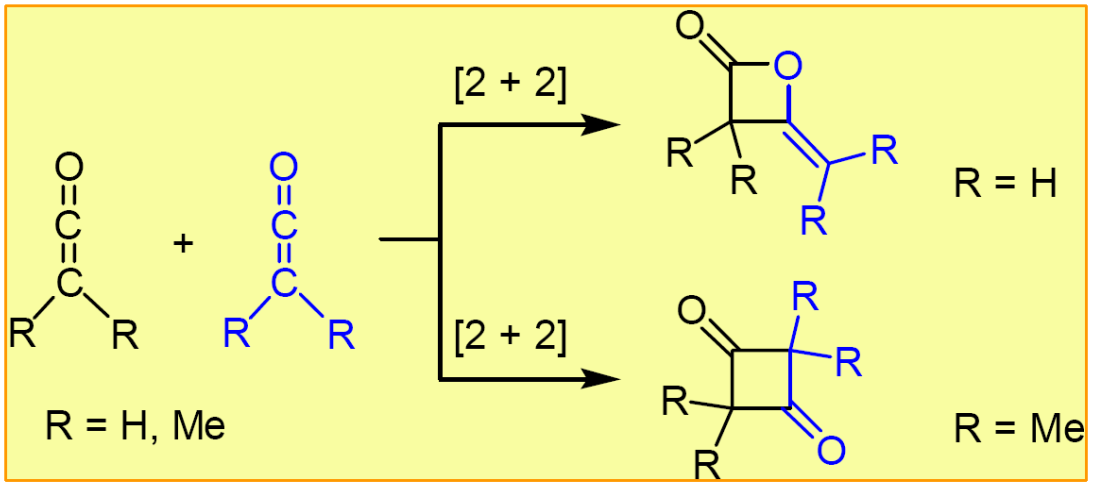
Cycloaddition Reactions

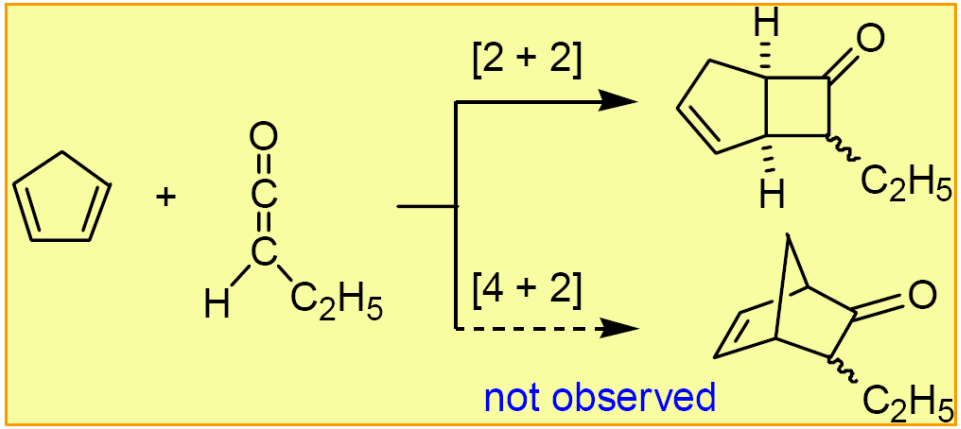
[2+2] Cycloadditions

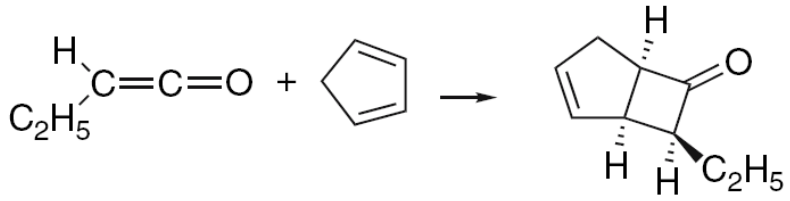
Ketenes + alkenes

- ketenes
  (highly reactive)

- ketenes formed *in situ*
  ($RCOCl + R_3N$)



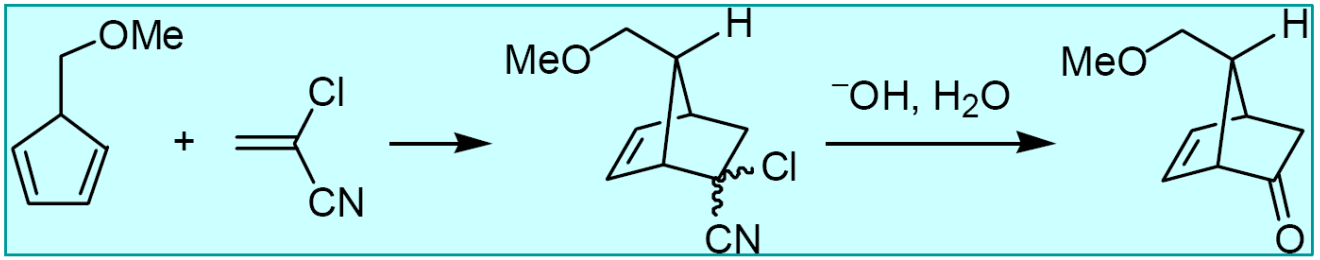


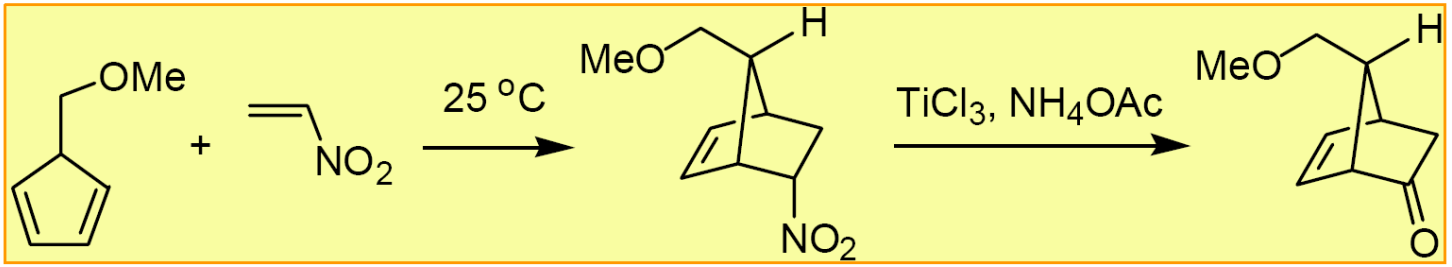


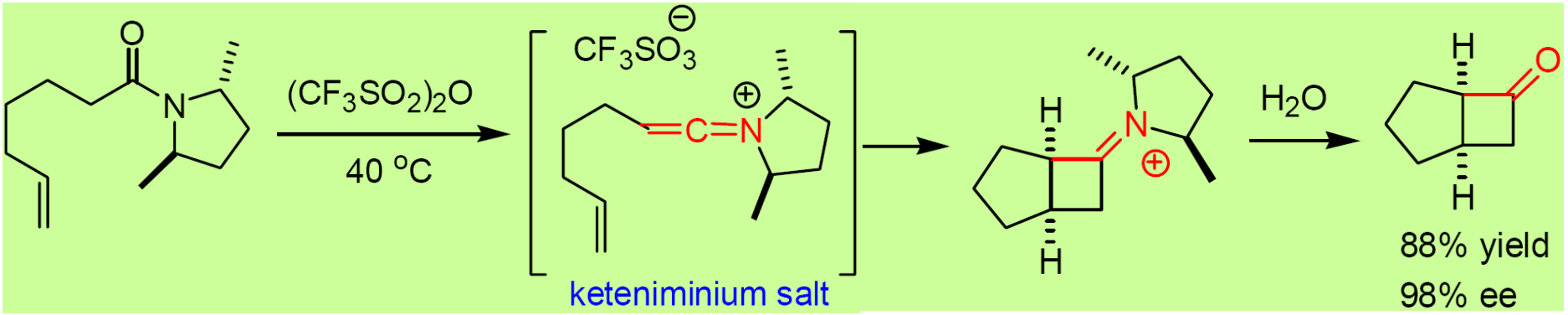
Cycloaddition Reactions

[2+2] Cycloadditions

Ketene equivalents





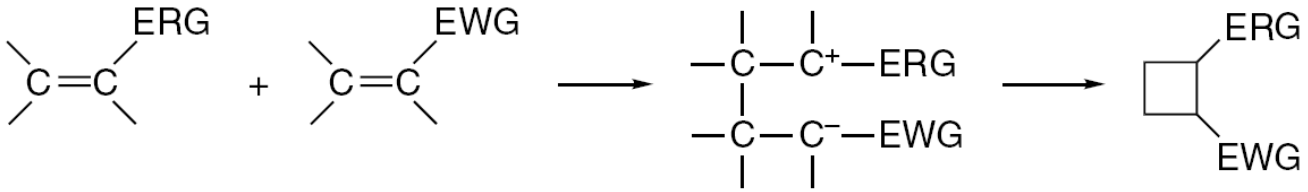


Cycloaddition Reactions

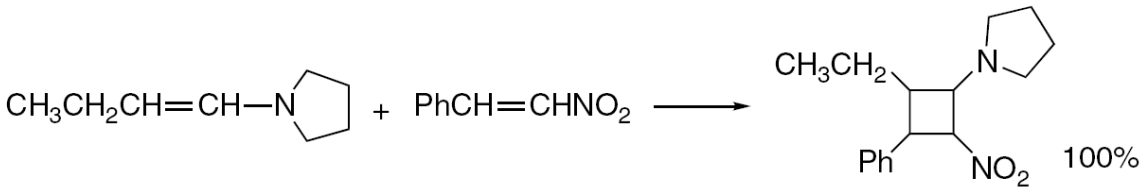
[2+2] Cycloadditions

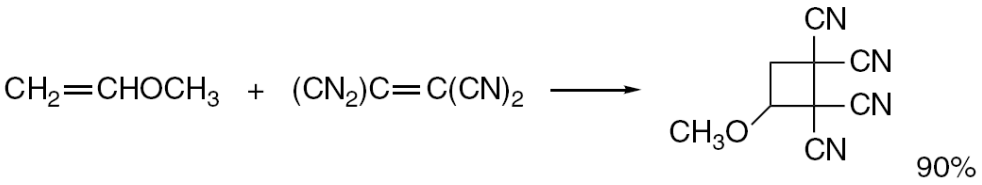
Alkene + alkene

- electron-rich alkene (enamine or vinyl ether)
- electron-poor alkene (nitro- or polycyanoalkene)



Examples





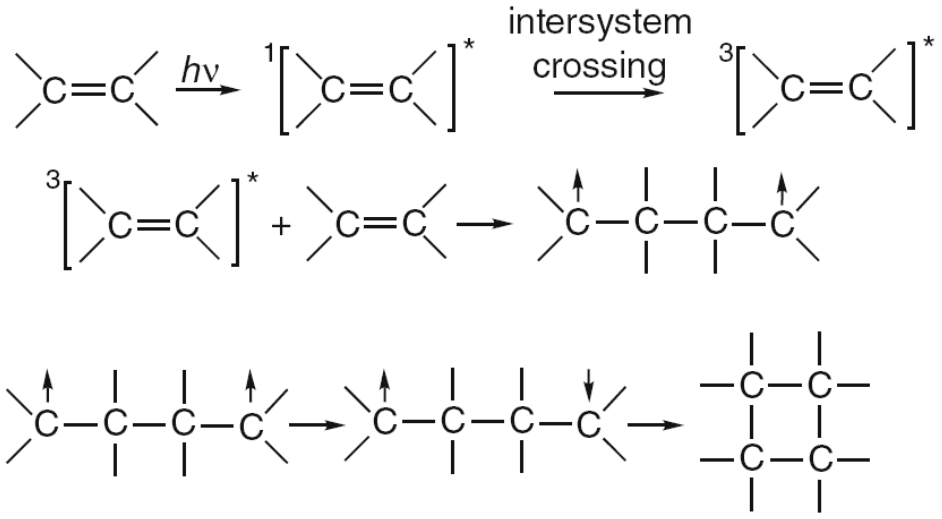
Cycloaddition Reactions

[2+2] Cycloadditions: Photochemical process

Alkenes, dienes

- often complementar to thermal cycloadditions
- mostly not concerted process (1,4-diradical)
- not stereospecific

- Mechanism:
  singlet – triplet – biradical formation – spin inversion – product formation

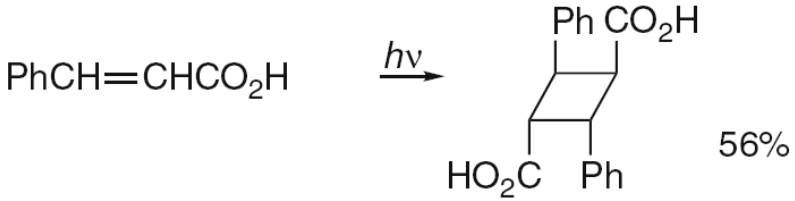


Cycloaddition Reactions

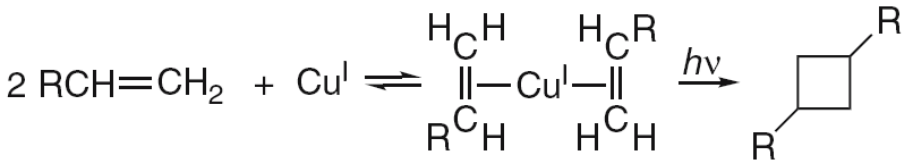
[2+2] Cycloadditions: Photochemical process

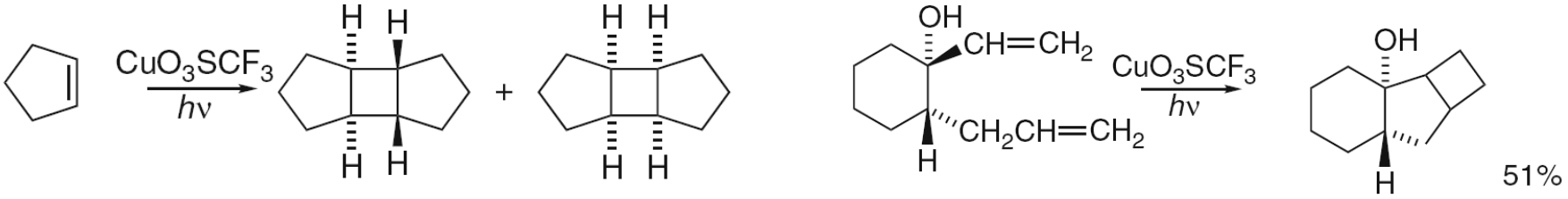
Alkenes, Dienes

- intermolecular photocycloadditions of alkenes (little preparative use)
- dienes (more used) – $PhCOCH_3$, PhCOPh, $CH_3COCOCH_3$
- crystaline state – best yields
- solution – *cis-trans* isomerization



- Cu(I) salts (2:1 ratio of alkene:Cu)



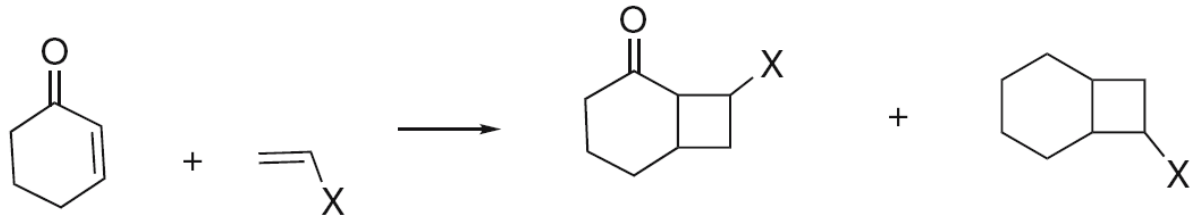


Cycloaddition Reactions

[2+2] Cycloadditions: Photochemical process

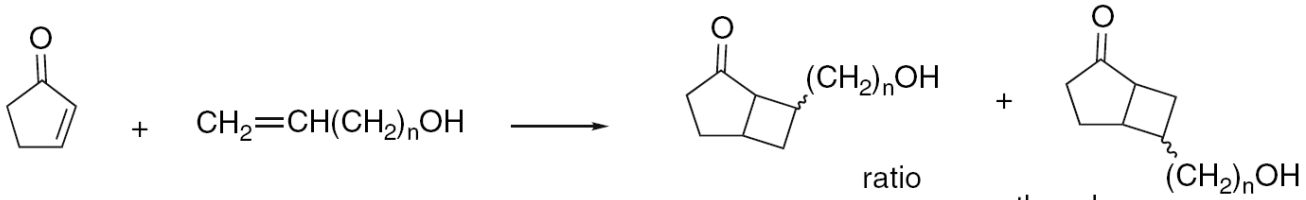
Enones

- especially cyclic enones
- photoaddition via 1,4-diradical intermediates
- not stereospecific, also less regioselective (head-to-head, head-to-tail)



X = CN	76:24
X = OC_2H_5	19:28

- H-bonding



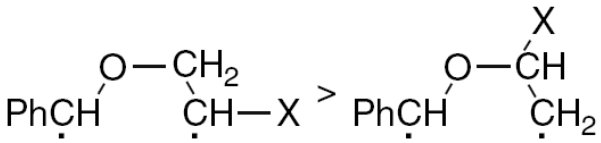
n	yield	ratio hexane	ratio methanol
1	84	71:26	33:67
2	86	65:35	34:66
3	79	60:40	32:68

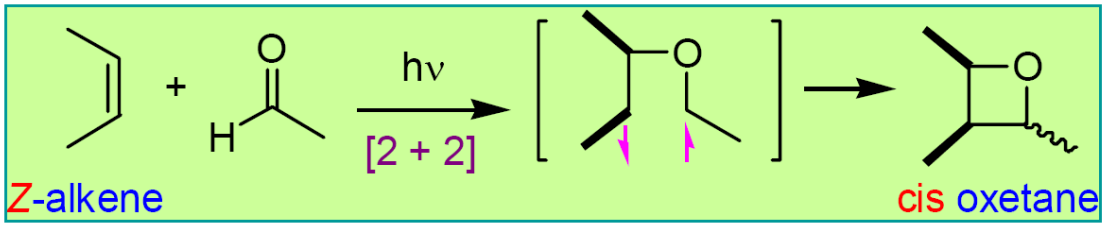
Cycloaddition Reactions

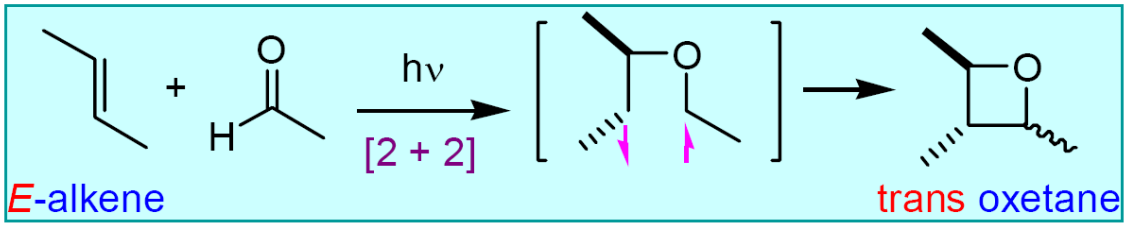
[2+2] Cycloadditions: Photochemical process

Carbonyls + alkenes

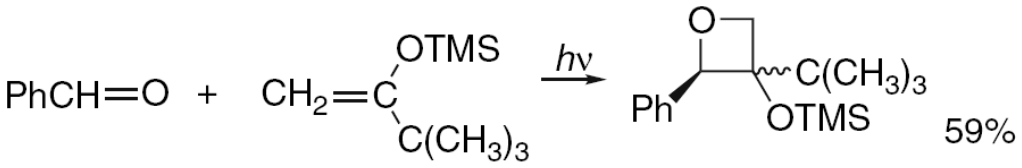
- formation of oxetanes (*Paterno-Büchi reaction*)
- stereospecific (not for aromatic ketones)
- regioselectivity (diradical formation)







Example



Cycloaddition Reactions

[2+2] Cycloadditions: Photochemical process

Carbonyls + alkenes

Examples