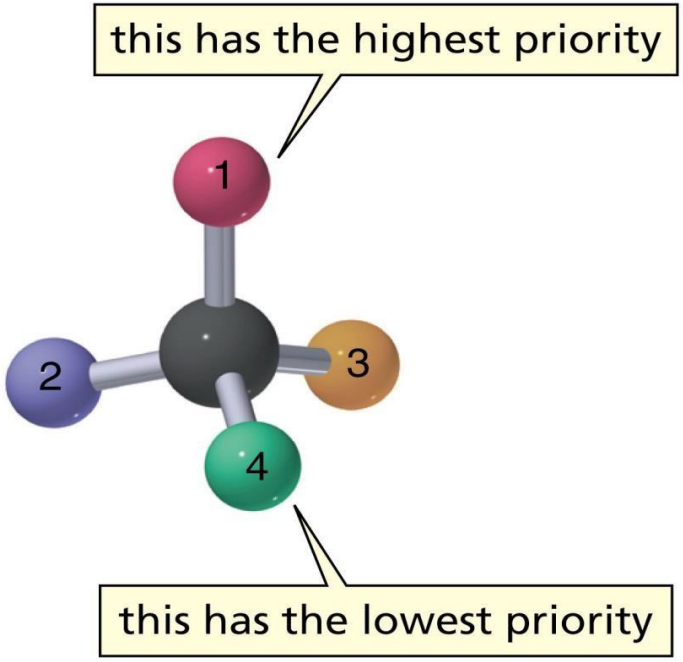
Stereochemistry

The *R,S* system of nomenclature Rank

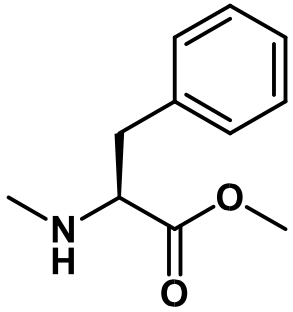
the groups (atoms) bonded to the chirality centre



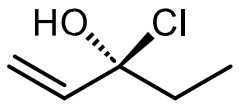
Q: Assign (*R*) or (*S*) configurations to each of the following compounds

Stereochemistry

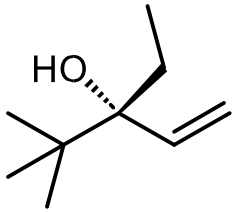
(i)



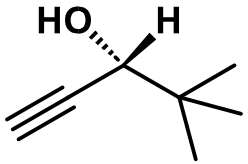
(ii)



(iii)

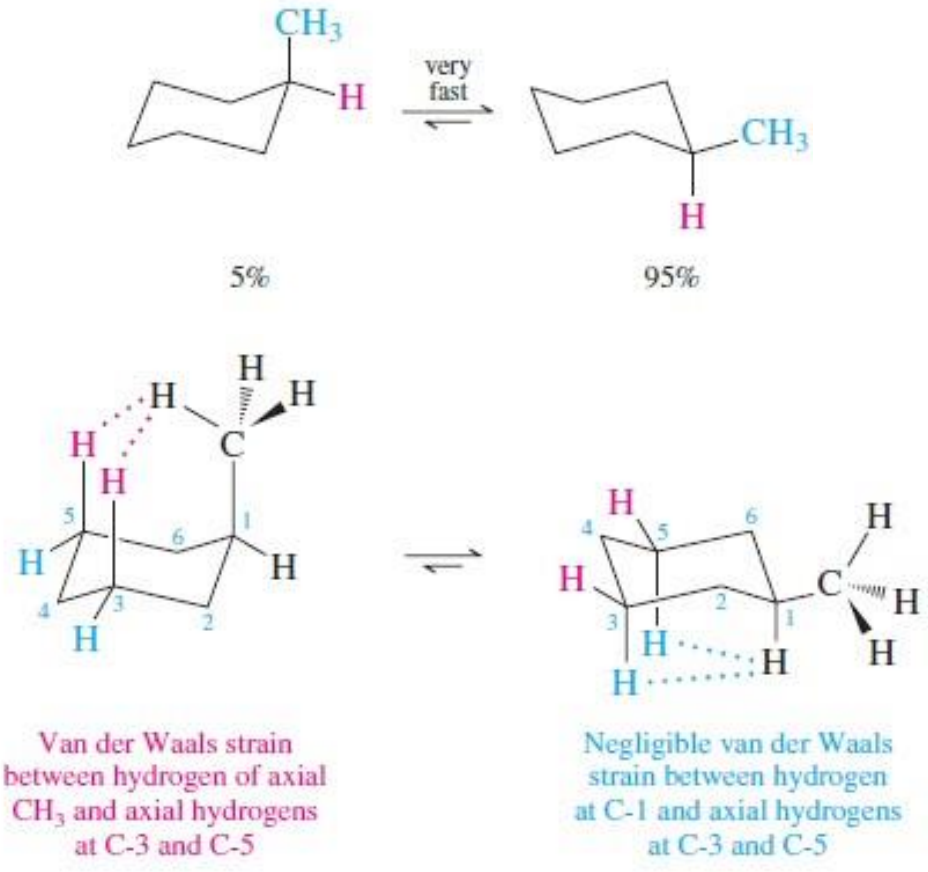


(iv)



- In substituted cyclohexanes, the most stable conformer keeps the bulky substituent in the equatorial position

Stereochemistry



Specific rotation

- Each optically active compound has a characteristic specific rotation

$$[\alpha]_{\lambda}^{T} = \frac{\alpha}{l.c}$$

T is the temp in °C

□ is the wavelength of light □ is the measured rotation in degrees ***l*** is the path length in decimeters (10 cm) ***c*** is the concentration in grams per mL

Specific rotation

- A racemic mixture, which contain an equimolar amount of the two enantiomers is optically inactive

□□□□□

Percentage optical purity =

$[(moles\ of\ one\ enantiomer - moles\ of\ the\ other\ enantiomer)/(moles\ of\ one\ enatiomer + moles\ of\ the\ other\ enantiomer)] * 100\ \%$

$= (\boldsymbol{observed\ specific\ rotation\ of\ the\ sample/specific\ rotation\ of\ the\ pure\ enantiomer}) * \mathbf{100}\%$

Enantiomeric excess (*ee*) = The excess of one enantiomer over the other in a mixture of enantiomers

Calculation of *ee*

Q: The observed specific rotation of a chiral compound is +7.00°. The specific rotation of the pure enantiomer is +28.00°. Calculate the percentage optical purity, the enantiomeric excess (*ee*) and the total % of this enantiomer in the sample.

$$Percentage\ optical\ purity = (+7.00^o/+28.00^o) * 100$$

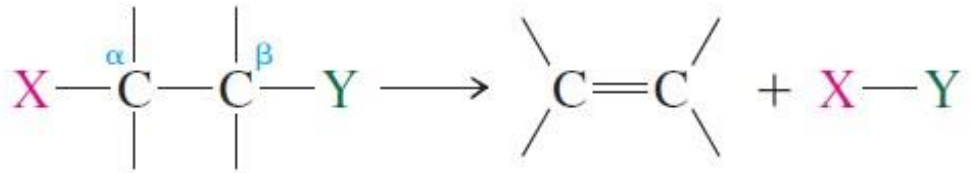
$$= 25\%$$

Therefore, the sample consists of **75% of the racemic form** and an excess of 25% of the pure enantiomer. The 75% racemic mixture is composed of an equimolar amount of the two enantiomers (37.5% each)

Therefore, *ee* of the particular enantiomer = 25%

Total % of the particular enantiomer in the sample = 37.5% + 25% = 62.5%

Elimination reactions



- There are three possible mechanistic routes for elimination reactions ✓ ***E1***, ***E2*** and ***E1cB***

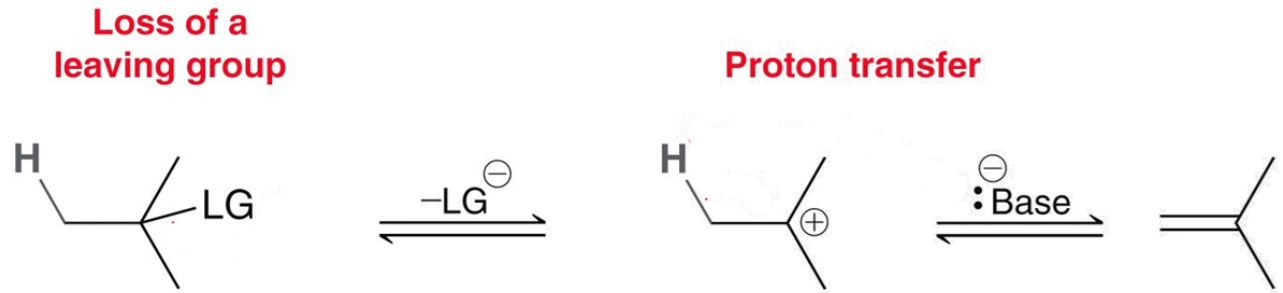
  - ✓ ***E1*****:** two-step process, carbocation intermediate is involved; rate depends on the stability of the carbocation ($3^o > 2^o > 1^o$)

- ✓ ***E2*:** single-step process, no intermediate; rate depends on the concentration of both the substrate and the base; rate trends of substrates depend on the structure and partial charge development in the transition state (usually, $3^o > 2^o > 1^o$)

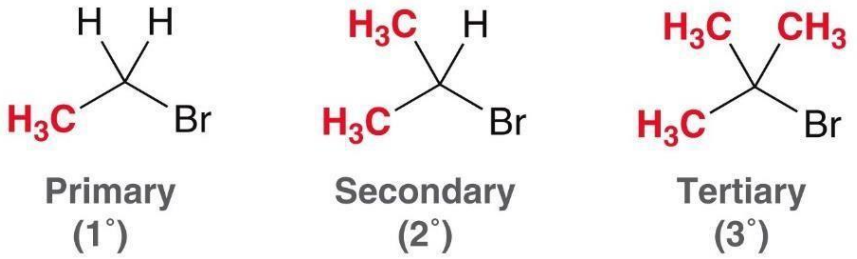
- ✓ ***E1cB*:** deprotonation happens prior to removal of the leaving group!, carbanion stabilising groups are required; rate depends on removal of the leaving group (the second step)

elimination

E1



❖ **More stable carbocations form more quickly, hence reaction rates are in the order:**



1° < 2° < 3° alkyl halides

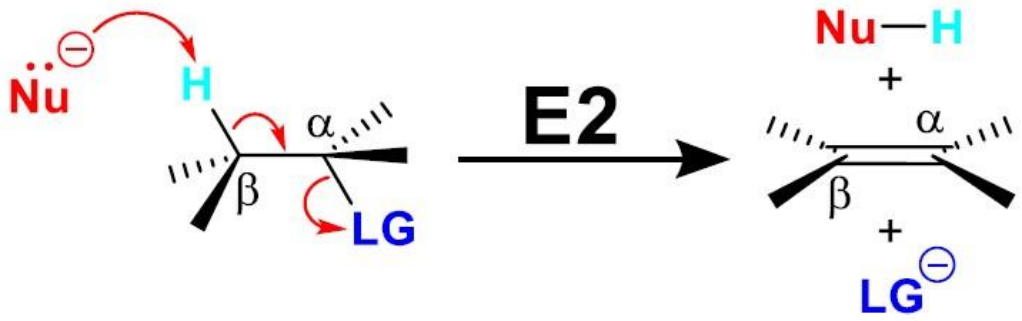
elimination

Increasing stability of the intermediate carbocation

NOTE: ***This is the similar to S_N1. For S_N1, primary alkyl halides react far slower than tertiary alkyl halides***

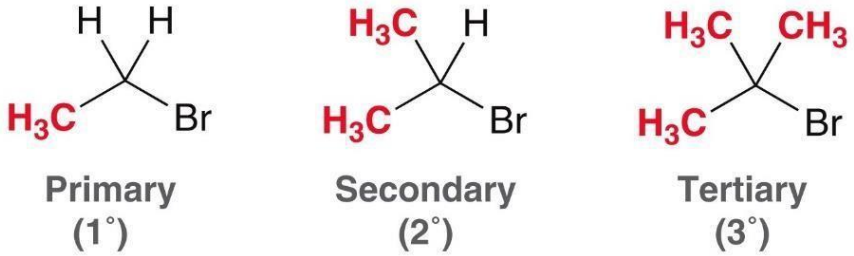
✓ **So *E1* competes with S_N1 and will generally result in a mixture of products**

E2



❖ ***E2*** **elimination rates generally follow the following order:**

elimination



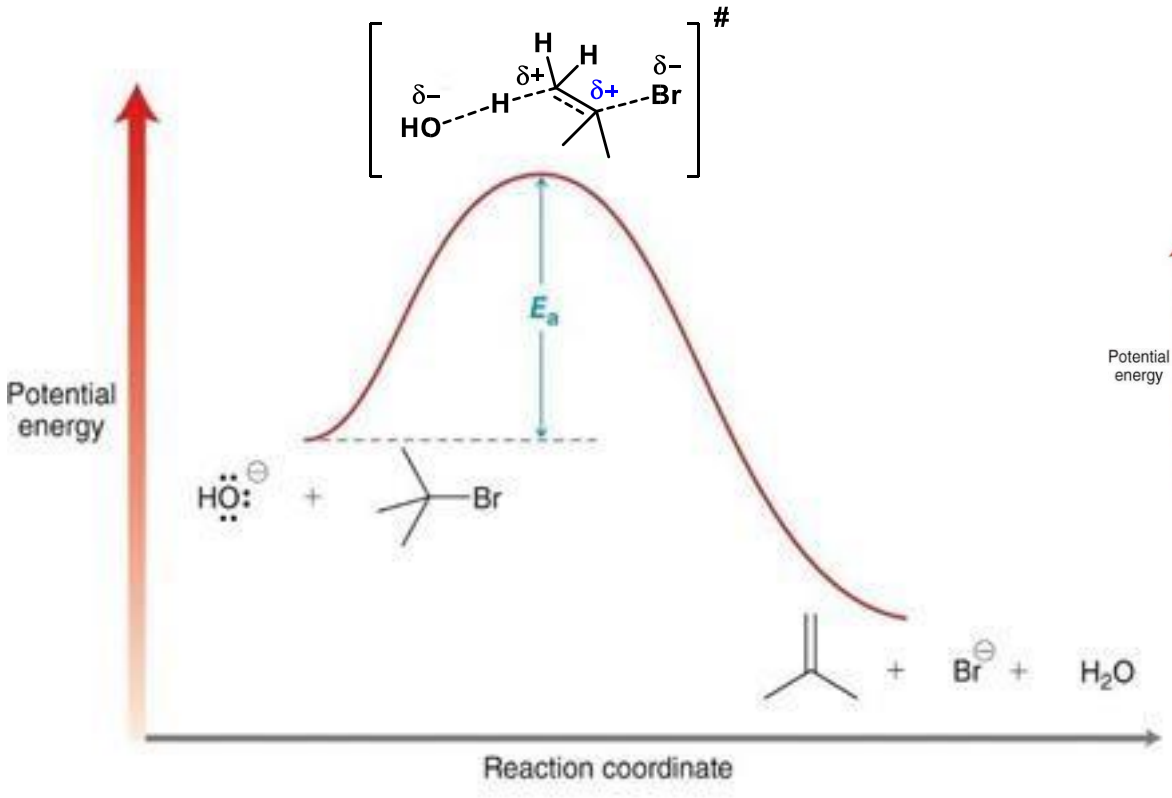
1□ < 2□ < 3□ alkyl halides

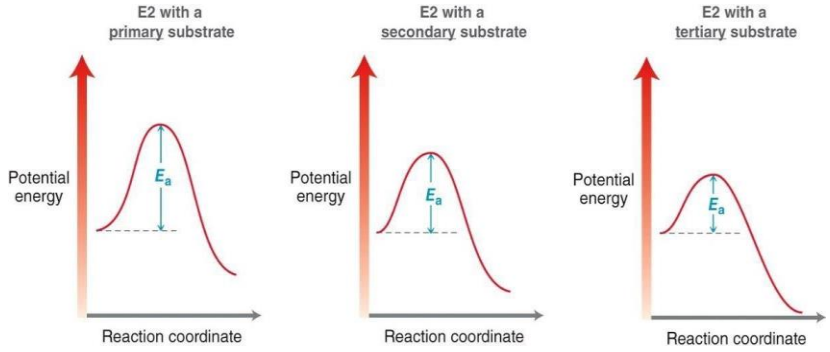
- ✓ **Same as that of *E1***
- ✓ ***Opposite to S_N2***

E2

- ✓ **It is the transition state that determines the rate of the *E2* reaction**

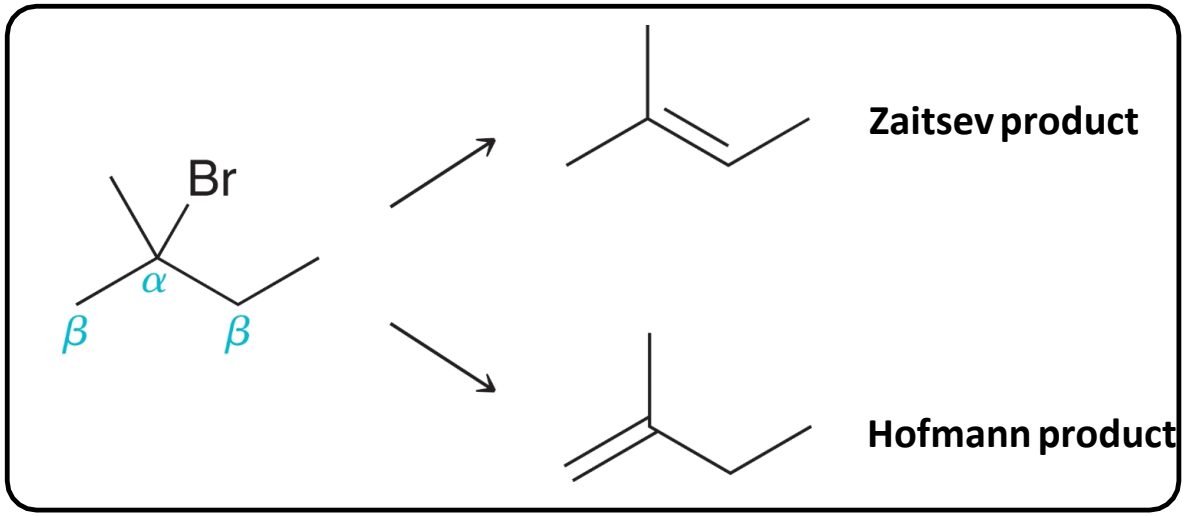
elimination





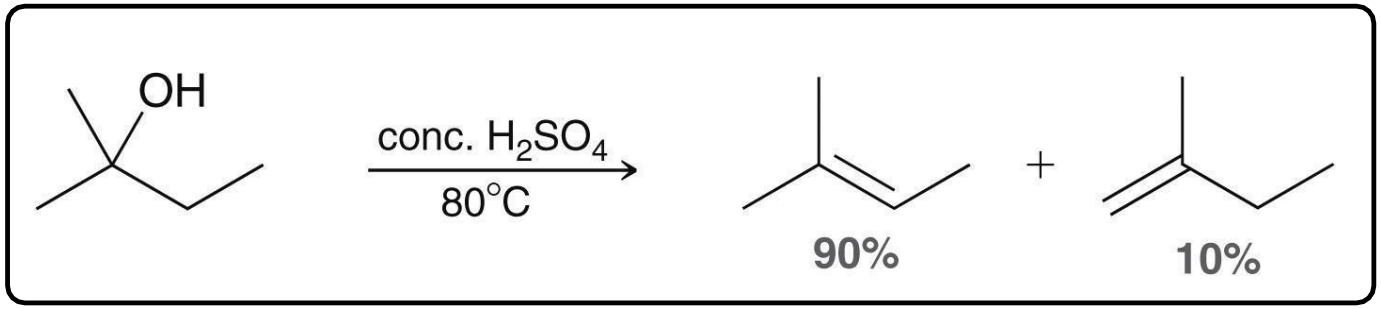
***Regioselectivity in* elimination reactions**

- **Regioselectivity:** Preference of locations in reactions (producing isomers)
  - In elimination reactions, **if different β sites are available**, deprotonation may yield different alkenes
    - ✓ ***Zaitsev*** **product**: more substituted alkene
    - ✓ ***Hofmann*** **product**: less substituted alkene



Regioselectivity in elimination reactions

- ***E1*** reactions produce the **Zaitsev product** (more substituted alkene) predominantly



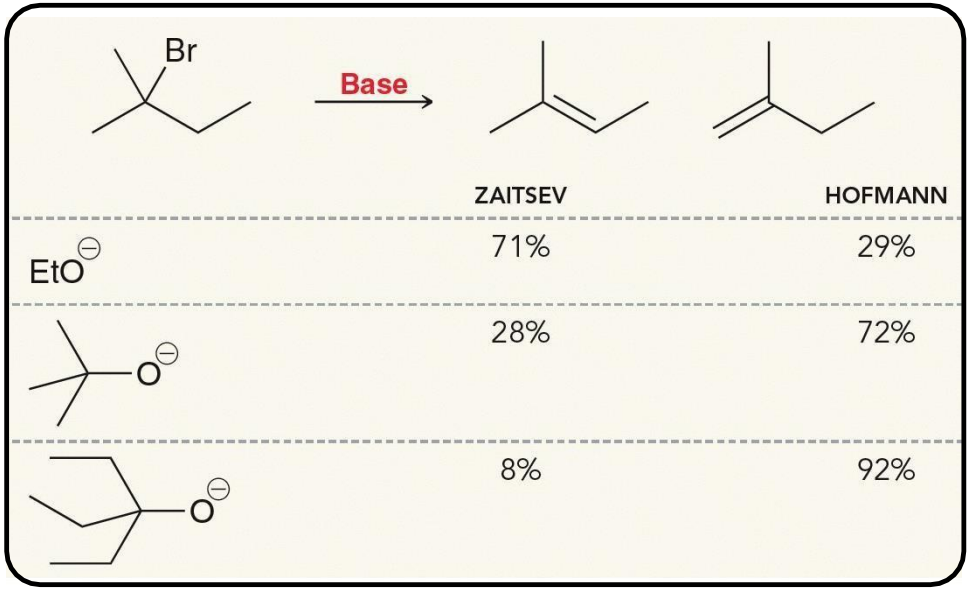
This is because the most highly substituted alkene is **thermodynamically the most stable alkene**.

Also, the **transition state leading to the most highly substituted alkene is of lower energy** (in

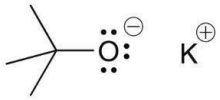
both *E1* and *E2*).

Regioselectivity in elimination reactions

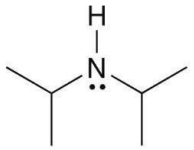
- ***E2*** regioselectivity depends on the base
  - Sterically hindered bases generate the Hofmann product



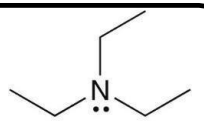
Sterically hindered base
➔ Hoffmann



Potassium *tert*-butoxide (*t*-BuOK)

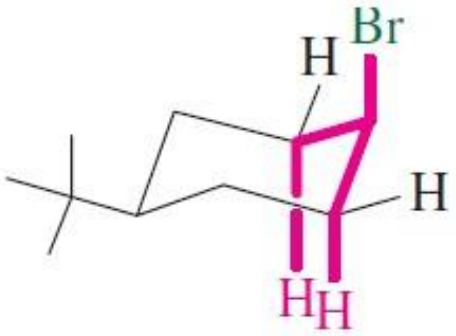


Diisopropylamine

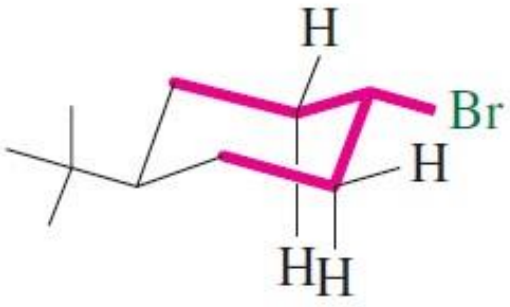


Triethylamine

E2 requires anti-coplanar orientation of leaving groups



cis-4-*tert*-Butylcyclohexyl bromide
(faster E2 rate:
H and Br are anti coplanar)



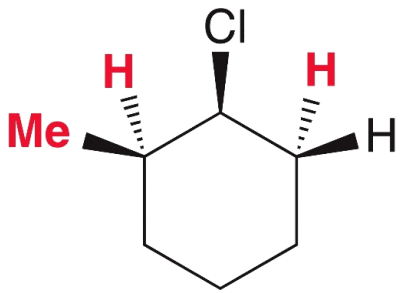
trans-4-*tert*-Butylcyclohexyl bromide
(slower E2 rate:
no H atoms anti to Br)

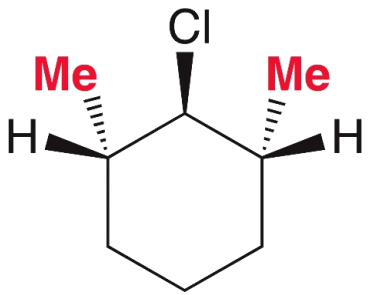
- The π bond formation is best achieved when the four atoms of the **H-C-C-X** unit lie in the same plane in the transition state. **This is because the developing π bond requires the p orbitals**

E2 requires anti-coplanar orientation of leaving groups

to be in coplanar orientation.

Which of the following molecules will **NOT** be able to undergo an ***E2*** elimination reaction? Explain.

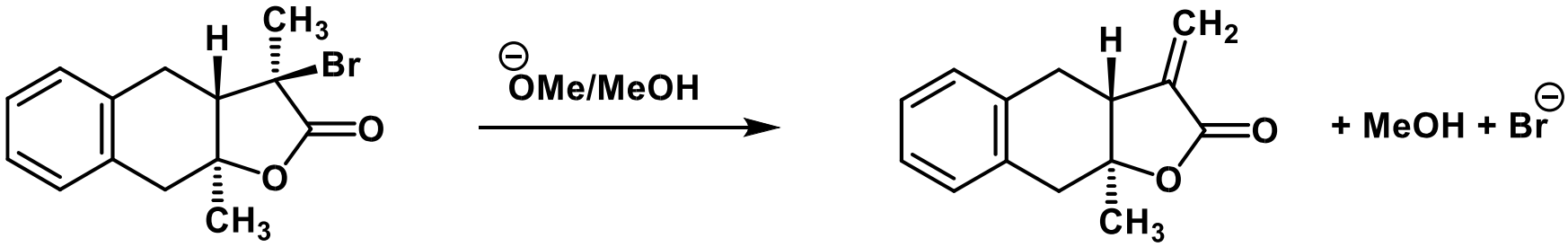




You must draw the chair conformers to understand the difference and to answer this properly

E2 requires anti-coplanar orientation of leaving groups

Explain why the following reaction gives thermodynamically less stable Hofmann product?

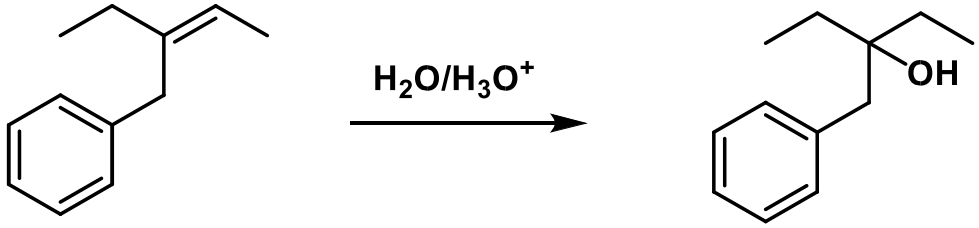


Regioselectivity of addition reactions

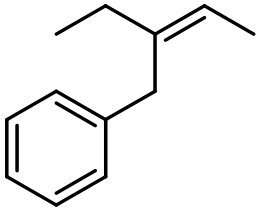
- **Electrophilic addition to unsymmetrical alkenes is regioselective**

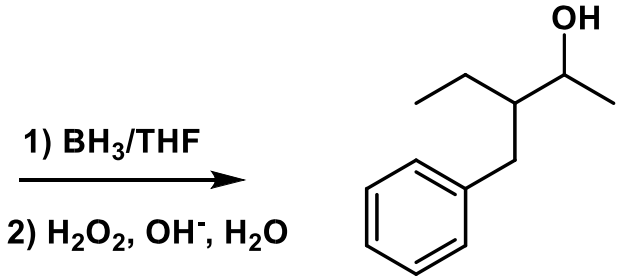
Markovnikov's rule

  - The regioselectivity is determined by the **stability** of the carbocation intermediate

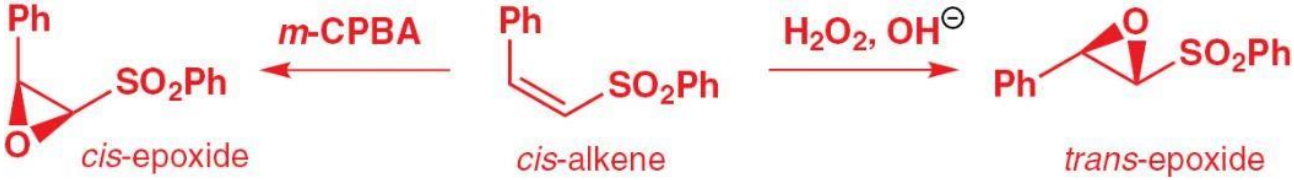


- **We can make the other regio isomer of the alcohol by hydroboration-oxidation reaction**



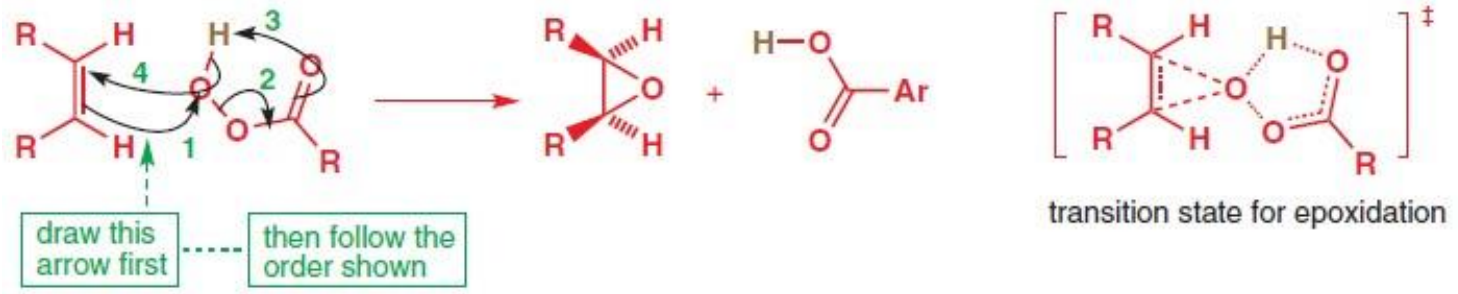


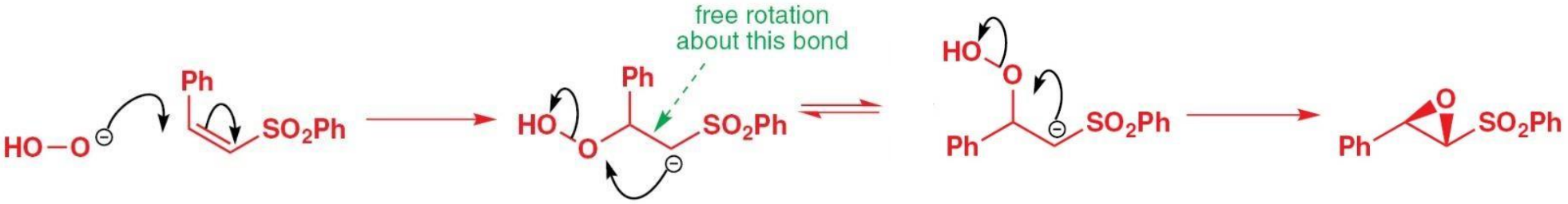
Stereochemistry of epoxidation reactions



(A)

(B





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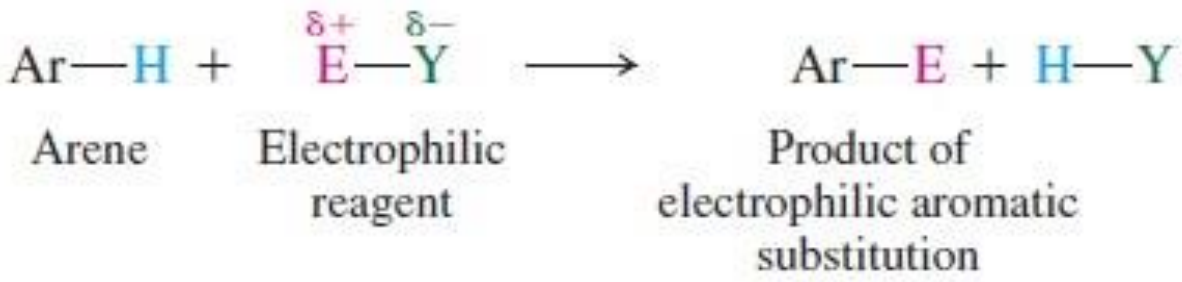
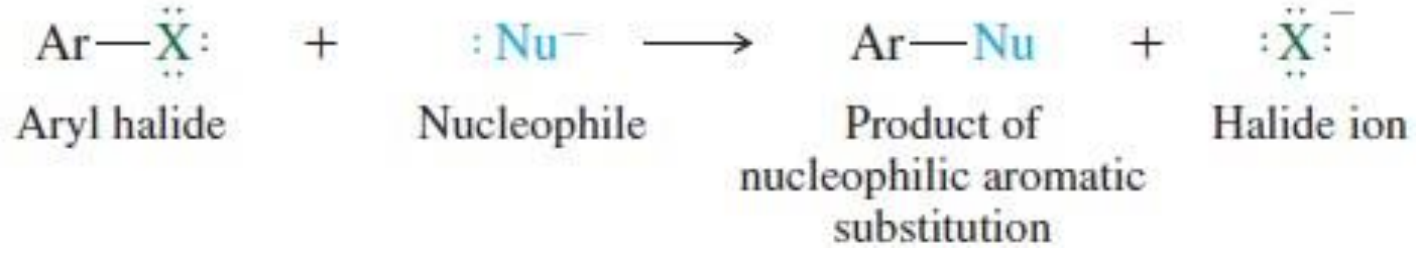
Reactions of aromatic compounds

- Aromatic compounds undergo **electrophilic substitution reactions**

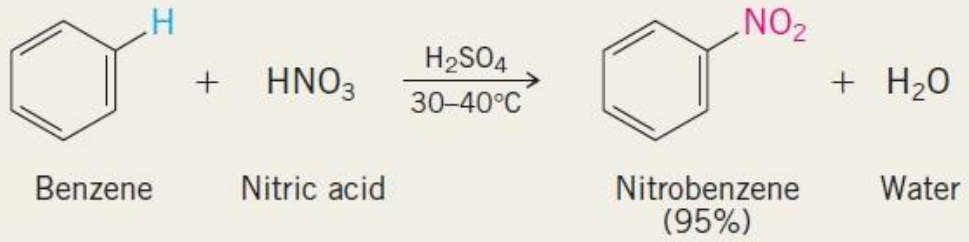
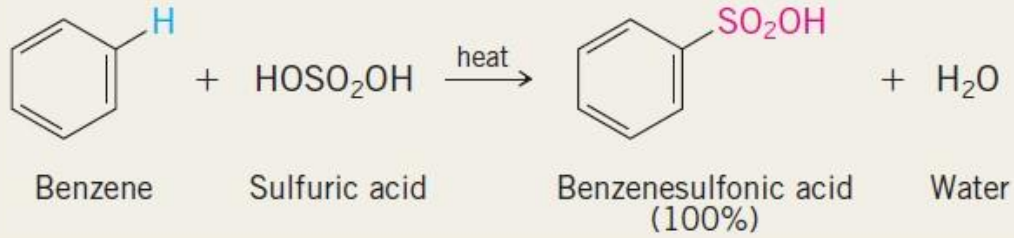
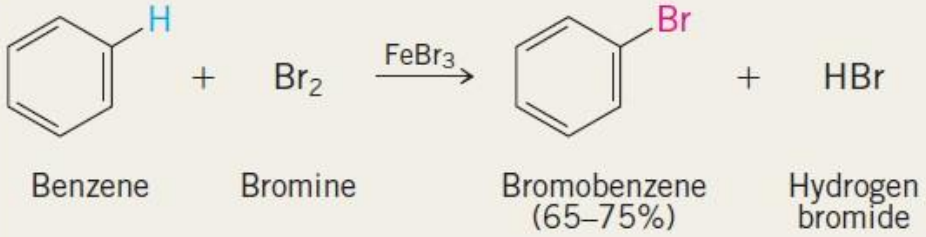


- Under certain conditions they may undergo nucleophilic substitution reactions as well



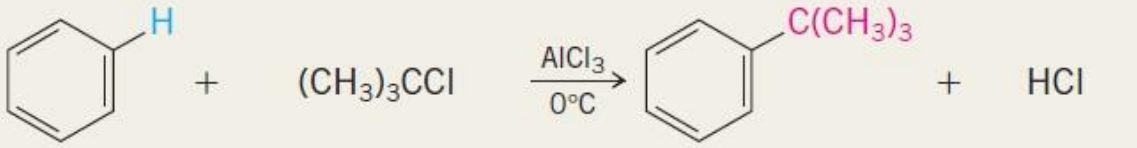
ASSIGNMENT MENTOR

Electrophilic aromatic substitution reactions

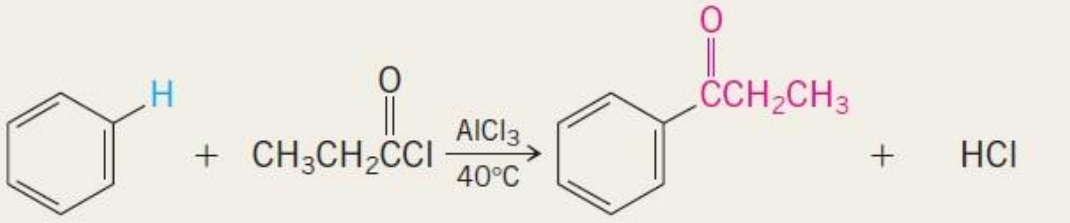
Reaction and comments	Equation
1. **Nitration** Warming benzene with a mixture of nitric acid and sulfuric acid gives nitrobenzene. A nitro group (—NO_2) replaces one of the ring hydrogens.	
2. **Sulfonation** Treatment of benzene with hot concentrated sulfuric acid gives benzenesulfonic acid. A sulfonic acid group (—SO_2OH) replaces one of the ring hydrogens.	
3. **Halogenation** Bromine reacts with benzene in the presence of iron(III) bromide as a catalyst to give bromobenzene. Chlorine reacts similarly in the presence of iron(III) chloride to give chlorobenzene.	

Electrophilic aromatic substitution reactions

4. **Friedel–Crafts alkylation** Alkyl halides react with benzene in the presence of aluminum chloride to yield alkylbenzenes.



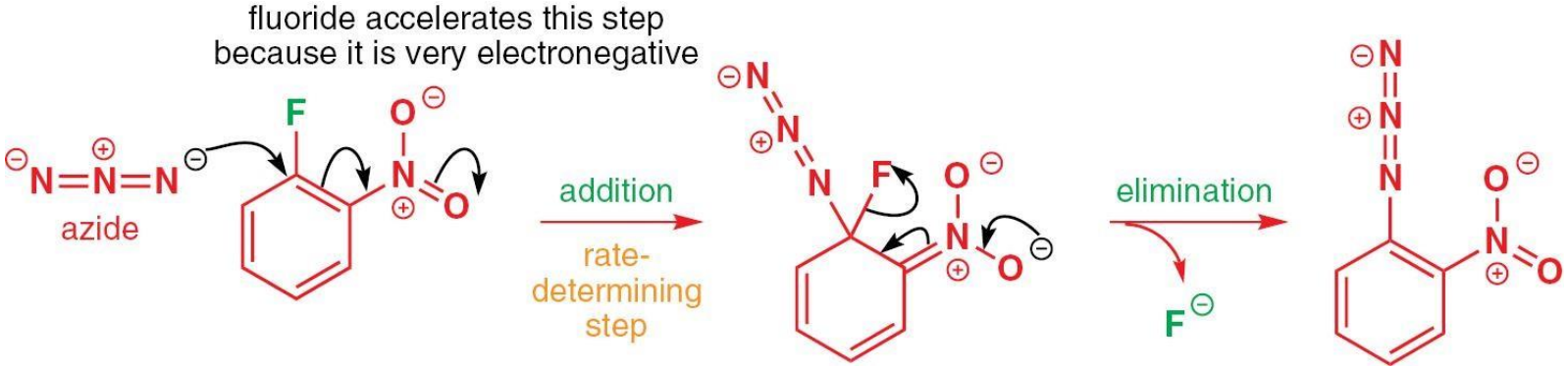
5. **Friedel–Crafts acylation** An analogous reaction occurs when acyl halides react with benzene in the presence of aluminum chloride. The products are aryl ketones.



Nucleophilic aromatic substitution

1) The addition-elimination mechanism

- Nucleophilic aromatic substitution is a **two-step process**, with **addition-elimination** sequence
- The **addition step** is the **rate-determining step** (slow) because it **disturbs the aromaticity**
- **F** being electronegative accelerates the first step because of its **inductive effect**, and **stabilises the anionic intermediate**

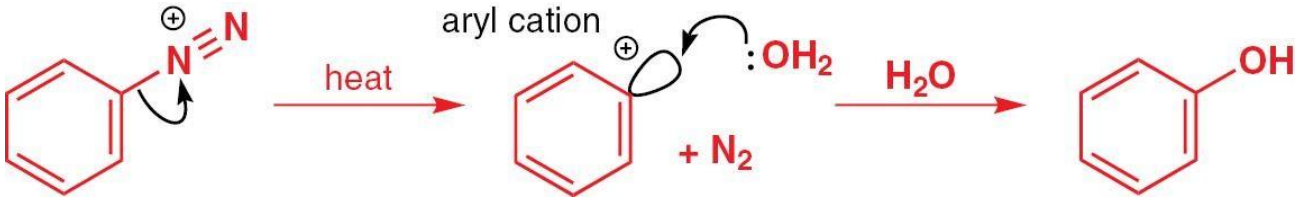


Nucleophilic aromatic substitution

Not the rate-determining step

2) The S_N1 mechanism!

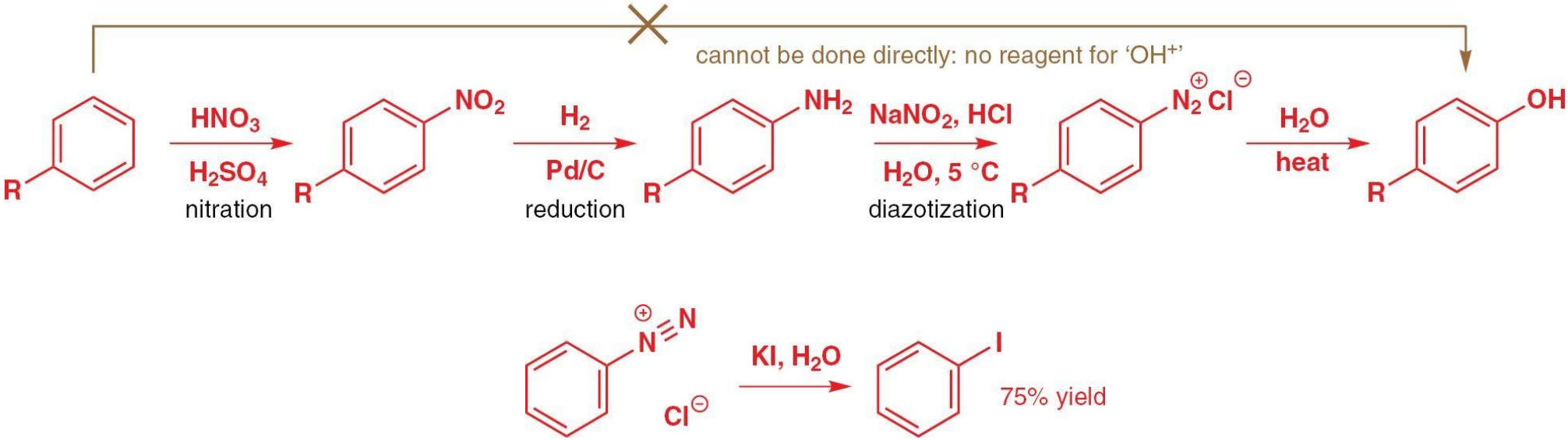
- Diazonium compounds can undergo S_N1 mechanism



- Diazonium compounds can undergo S_N1 mechanism

- **Diazotisation is useful to introduce functional groups in aromatic compounds**

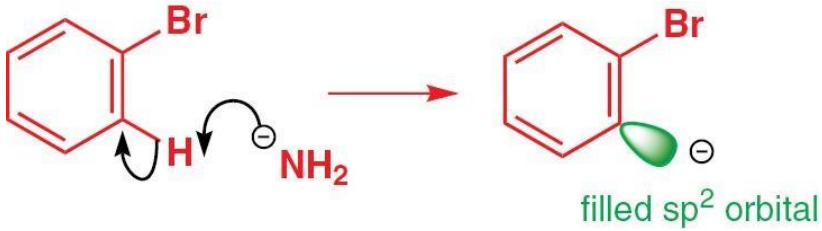
Nucleophilic aromatic substitution



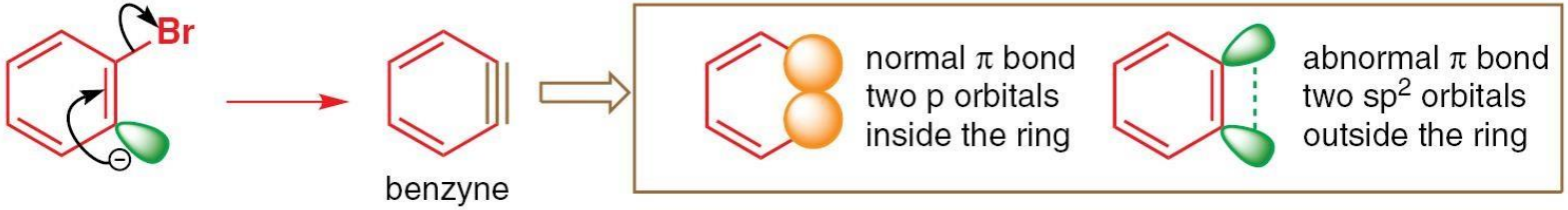
3)The benzyne mechanism (elimination-addition mechanism)

- A strong base such as $NaNH_2$ can deprotonate aromatic ring at **position ortho to a halide**

Nucleophilic aromatic substitution

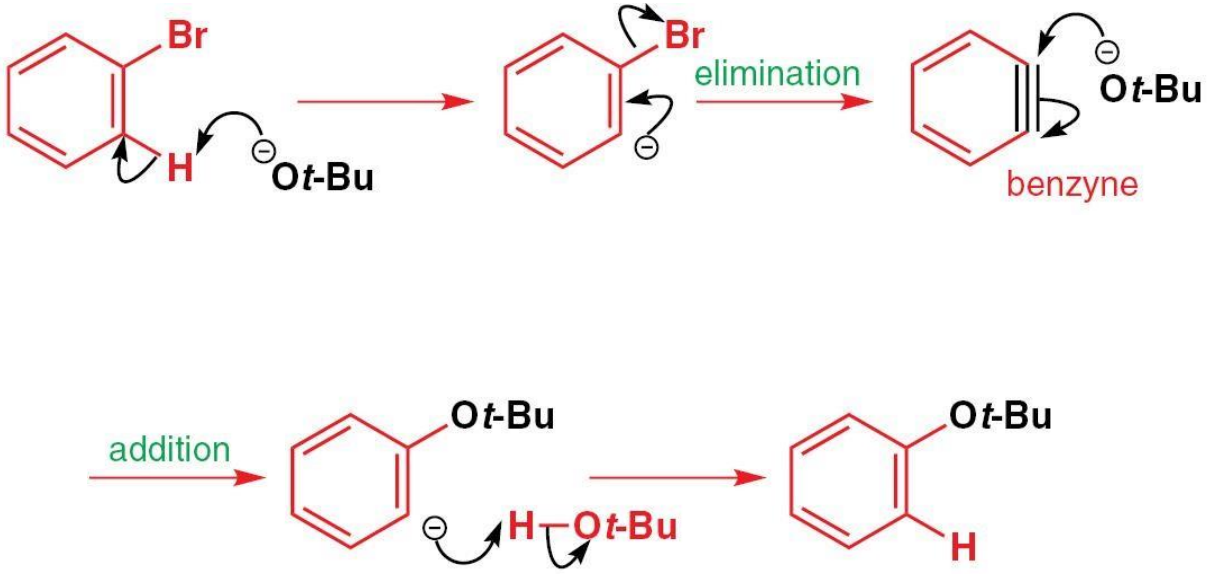


- The next step is the loss of bromide in an elimination



The benzyne mechanism (elimination-addition mechanism)

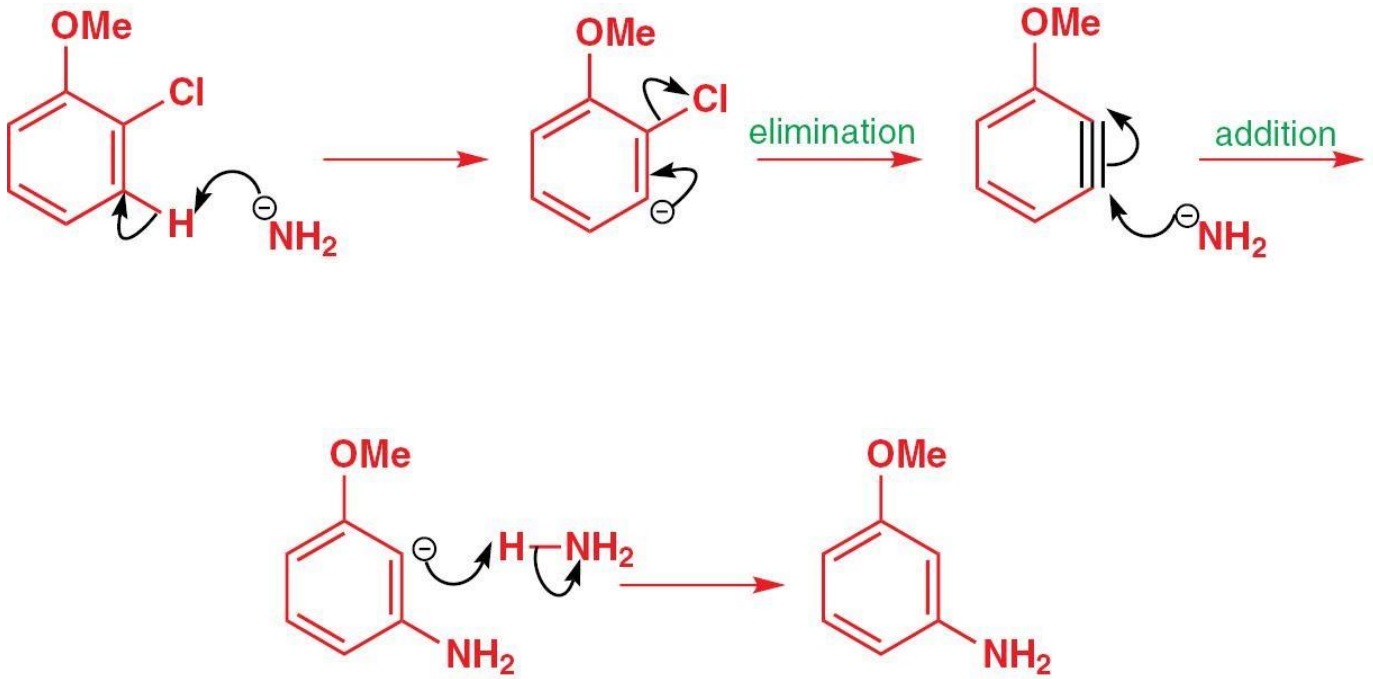
Nucleophilic aromatic substitution



The benzyne mechanism (elimination-addition mechanism)

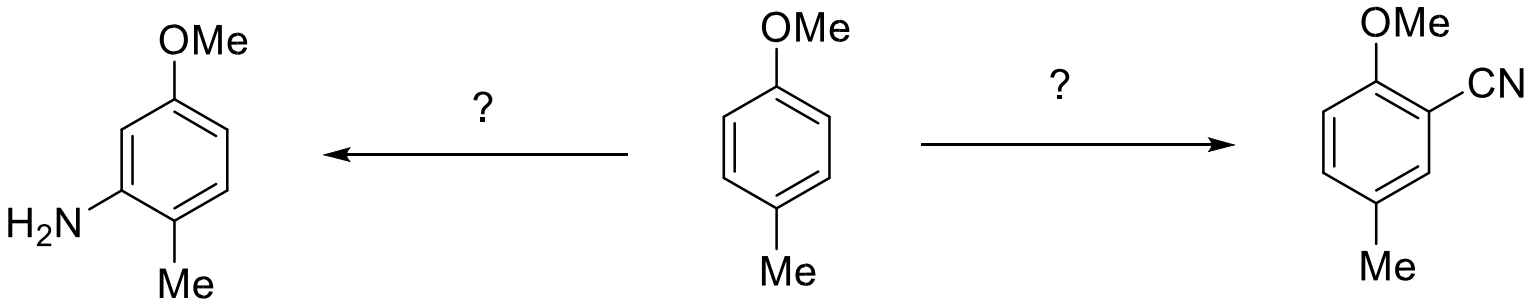
- Note the *meta*-substitution below,

Nucleophilic aromatic substitution



Q: How would you carry out these two conversions?

Nucleophilic aromatic substitution



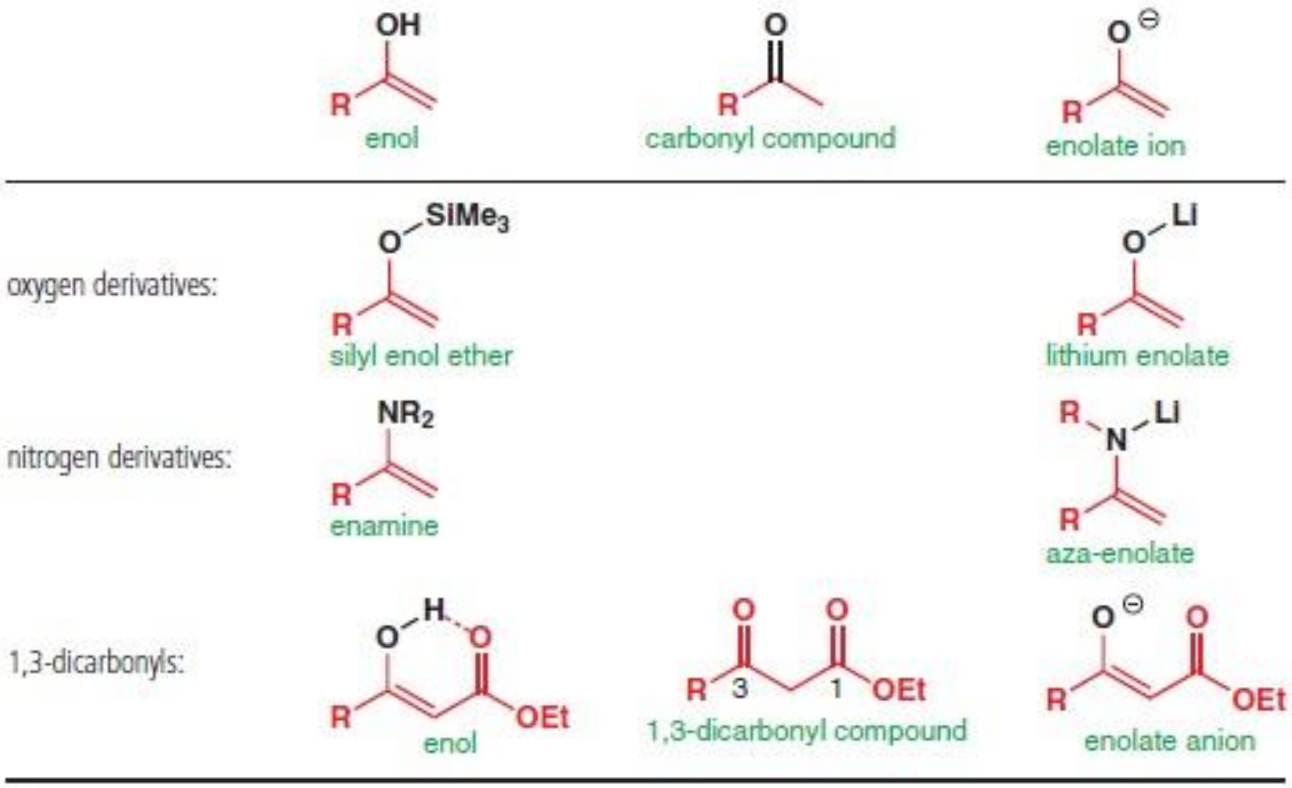
Enolate chemistry

Stable enol/enolate equivalents: They have the reactivity of enols/enolates but are stable enough to be prepared in good yields from the carbonyl compound without any aldol reaction!

used in an **alkylation reaction**

new carbon-carbon bond.

Important specific enol equivalents

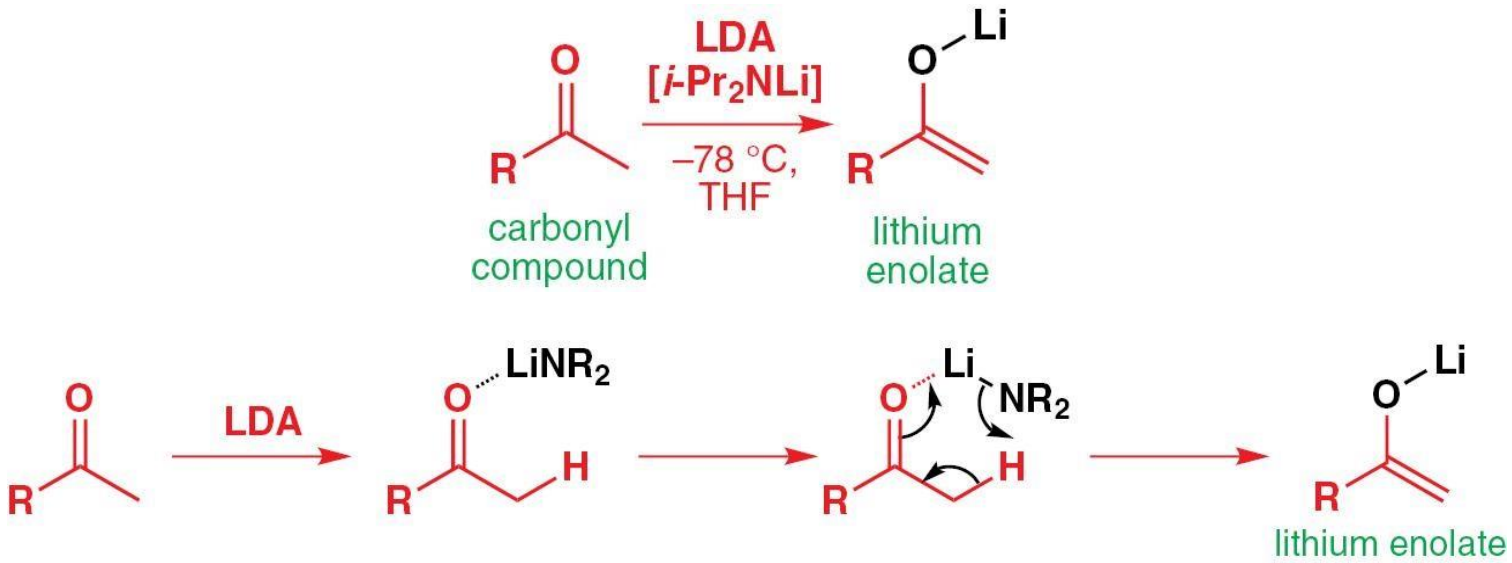


Once enolates or enols are generated, they are usually with an alkyl halide to form a The enolate acts as a nucleophile.

Lithium enolates

Preparation

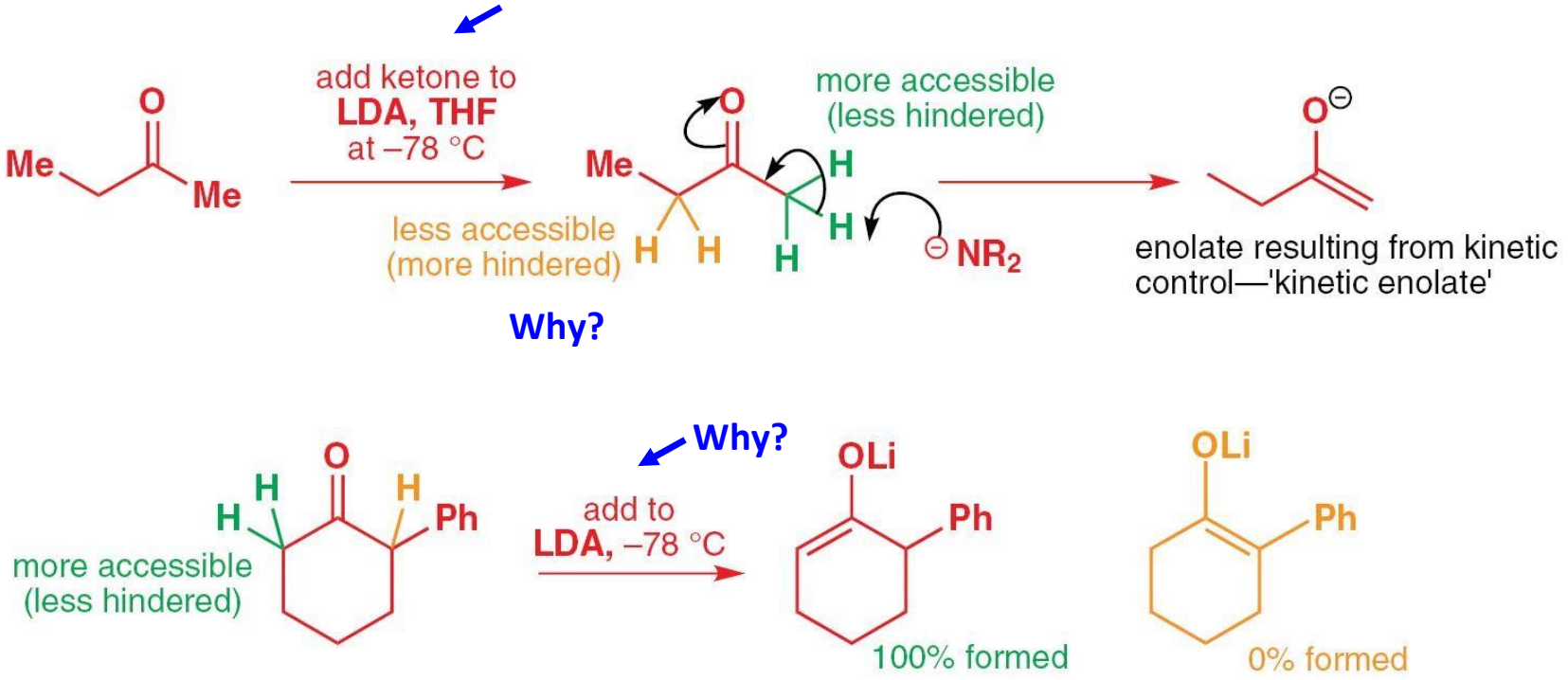
- Carbonyl compound is treated with LDA in THF at low temperature



- This reaction is so **quick** that the partially formed lithium enolate cannot attack the carbonyl compound. So, we don't get a self-condensation reaction

Lithium enolates

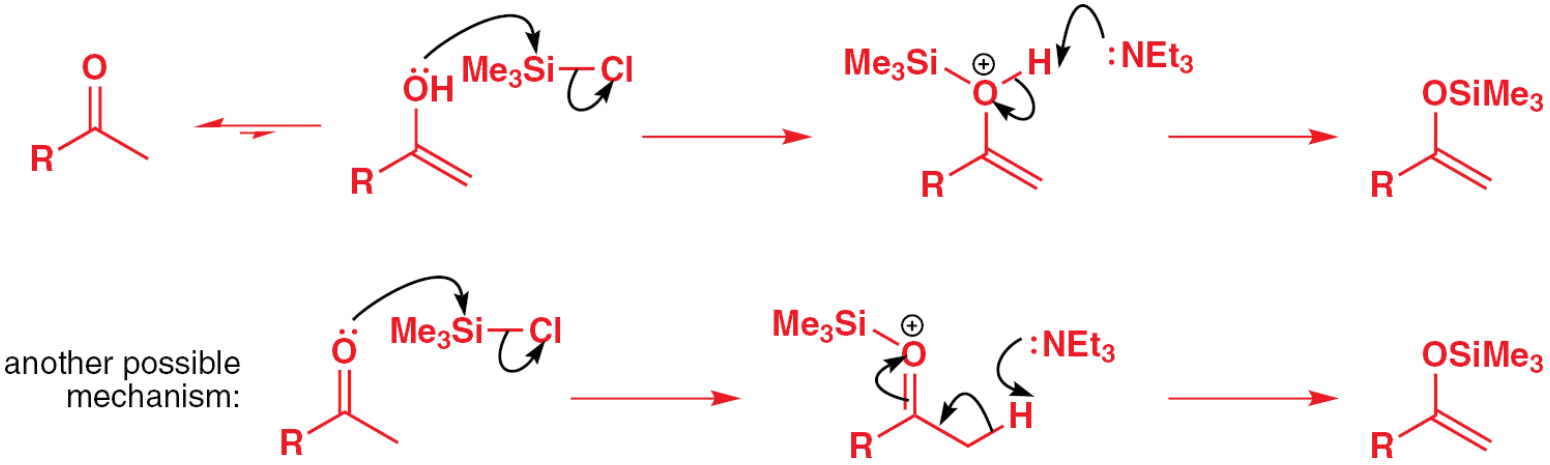
LDA at low temperature → **Kinetically controlled enolate formation**



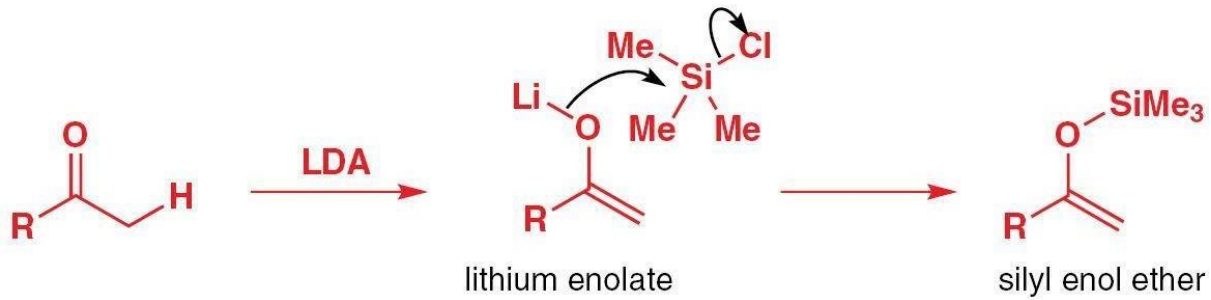
It is important to note that **reaction conditions** (type of base, temperature, relative proportion of reagents etc.) play a crucial role in the **thermodynamic vs. kinetic control** of enolate formation

Silyl enol ethers

- **TMS-Cl and a mild base (e.g. triethyl amine)**

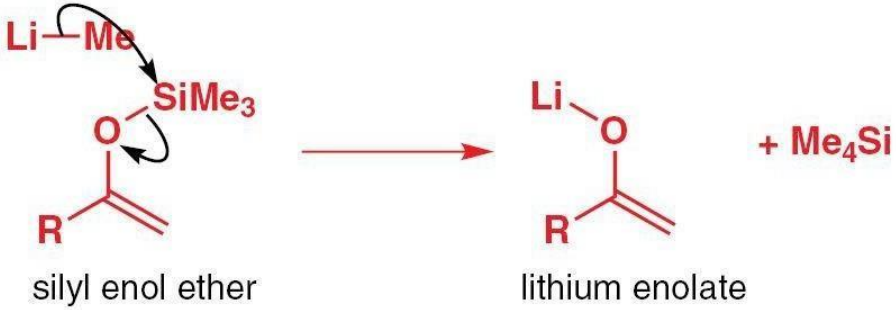


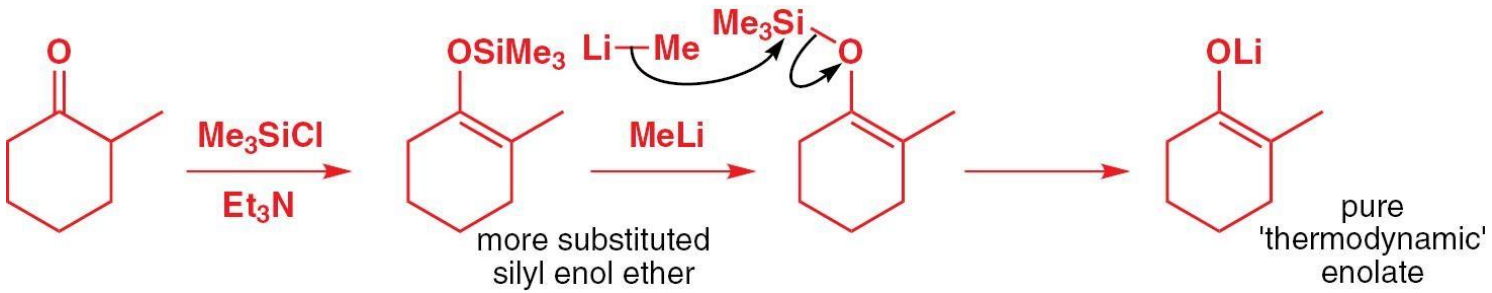
- **From lithium enolates**



Silyl enol ethers

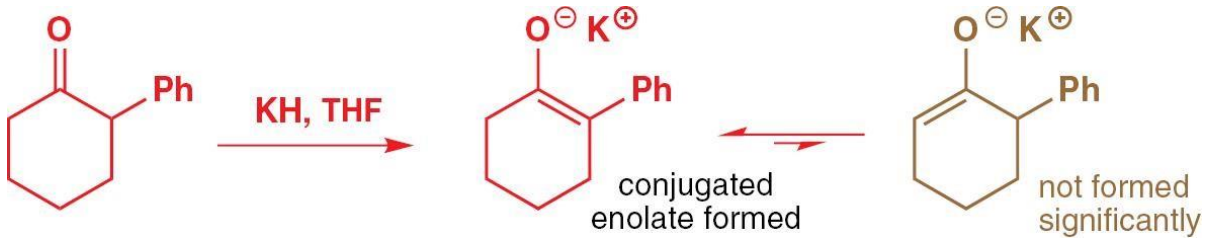
- Silyl enol ethers can be converted to lithium enolates by treatment with **methyl lithium** (= a method to generate thermodynamic enolates)





Note that the silyl enol ether formation is under thermodynamic control. Unlike lithium enolates, the silyl enol ethers can be purified and fully regiochemically pure enolates can be formed

Thermodynamically controlled enolates

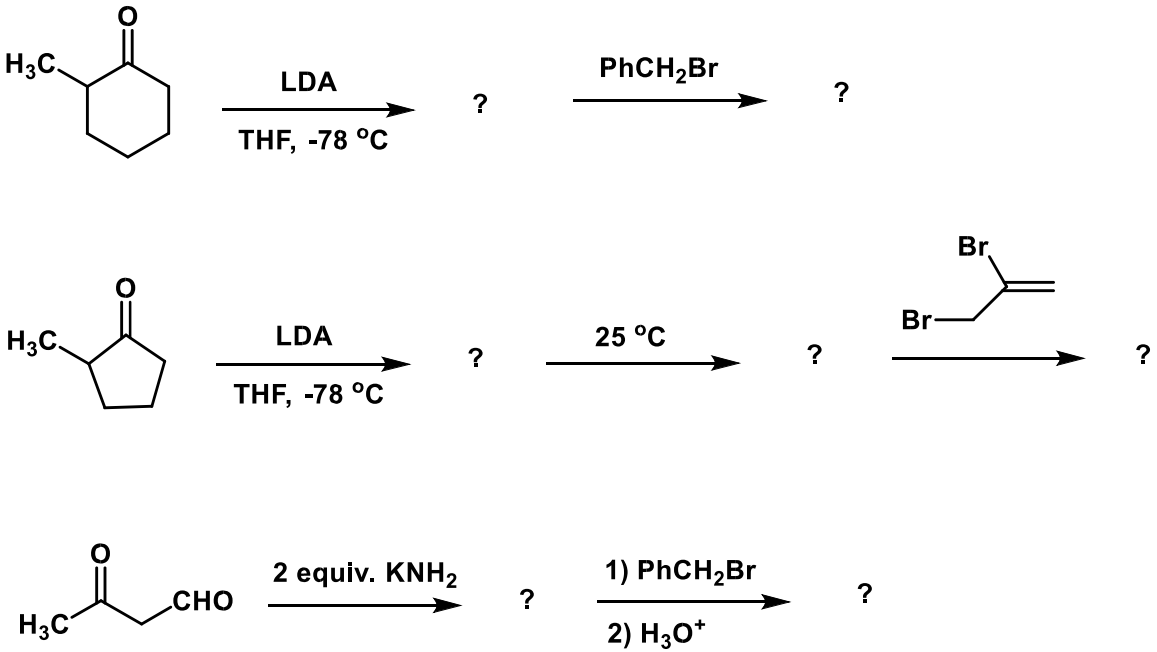


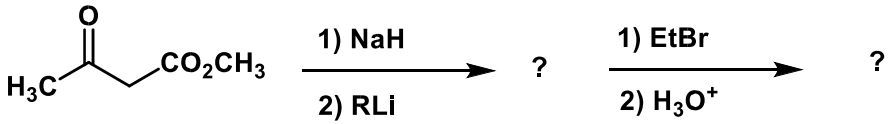
ASSIGNMENT MENTOR

- Reaction conditions that lead to a chemical equilibrium will generate thermodynamic products

Enolate chemistry

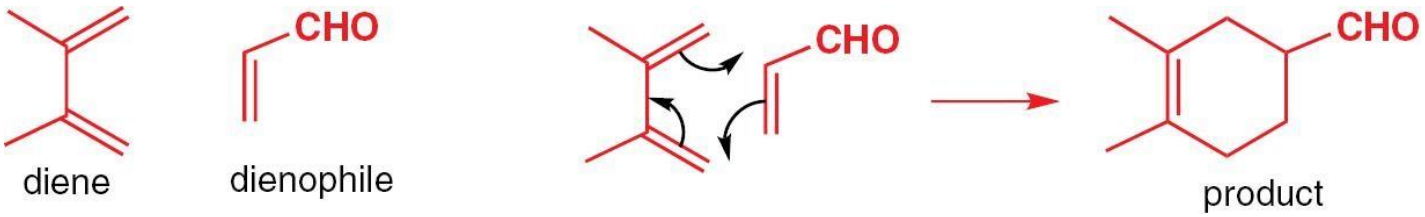
Q. Predict the products formed in the reactions below



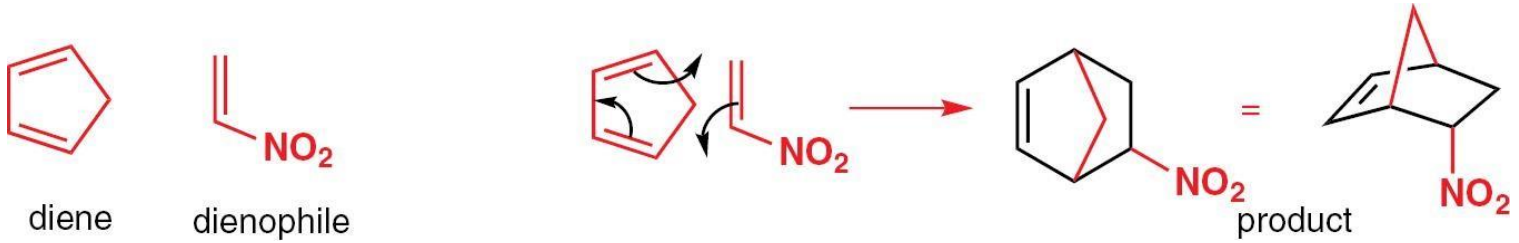

O
H3C
CO2CH3
1) NaH
2) RLi
?
1) EtBr
2) H3O+
?

The Diels-Alder reaction

- The Diels-Alder reaction occurs between a **conjugated diene** and an alkene, called a **dienophile**

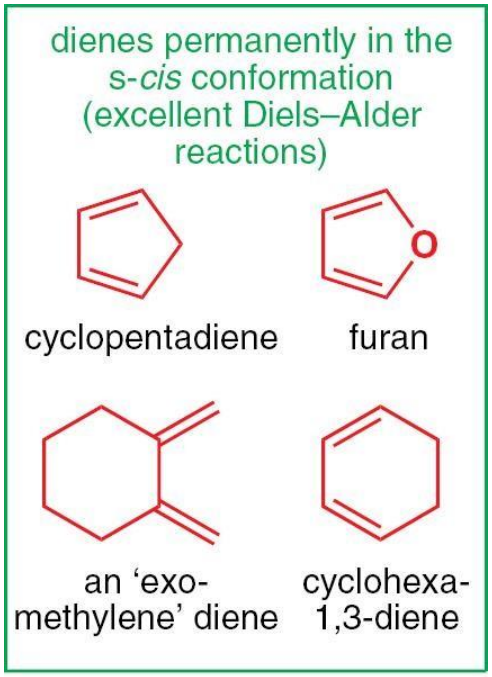


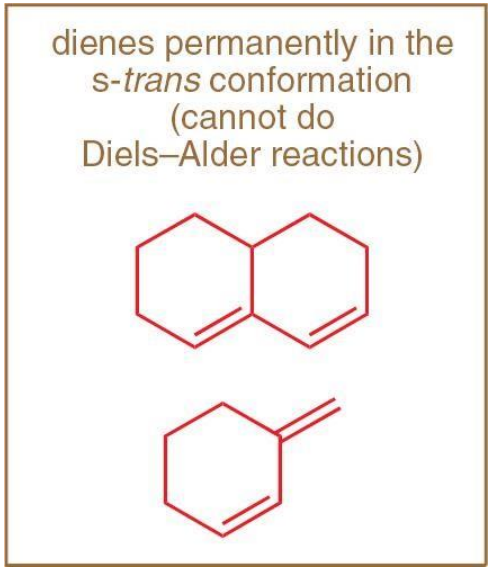
Here is an example with a **cyclic diene** and a nitroalkene



The Diels-Alder reaction

- The diene must have **s-*cis*** conformation for Diels-Alder reaction to take place

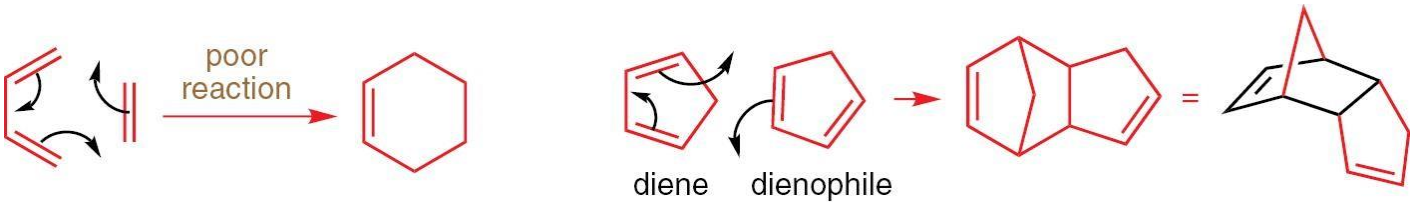




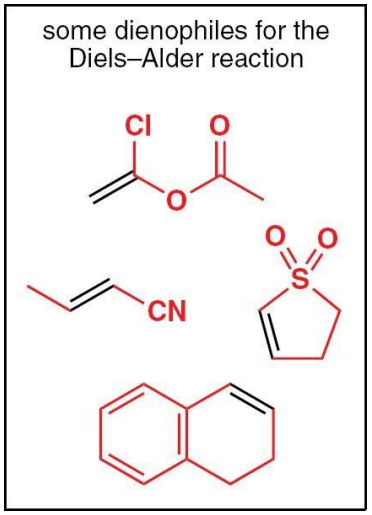
- The **dienophile**

The Diels-Alder reaction

- The dienophiles usually have **electron withdrawing groups** conjugated to the alkene

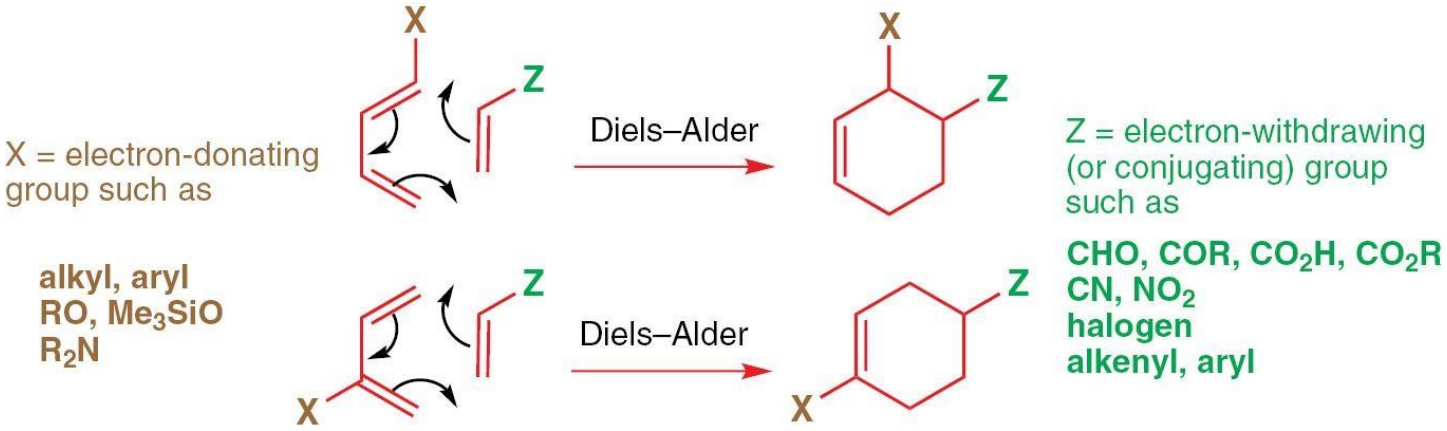


- Alkenes that undergo the DA reaction are:
  - Conjugated carbonyl compounds
  - Nitro compounds
  - nitrile compounds
  - *Others include:*
  - Sulfones, aryl alkenes, vinyl ethers and esters, haloalkenes and dienes



Regioselectivity in Diels-Alder reaction

- **the substitution pattern on the diene affects the regioselectivity**



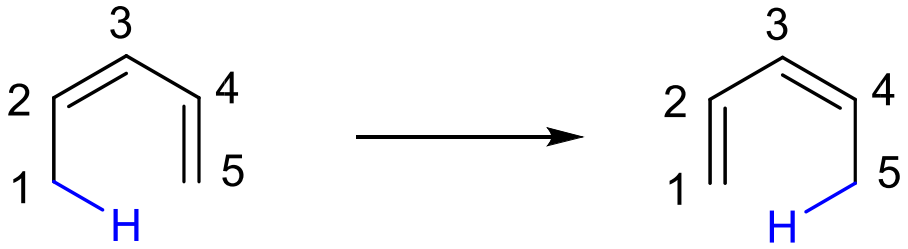
Sigmatropic rearrangements

- **A useful mnemonic**

  If you prefer a rule to remember, try this one

  - The Diels–Alder reaction is a cycloaddition with an aromatic transition state that is *ortho* and *para* directing *(Use with caution!)*

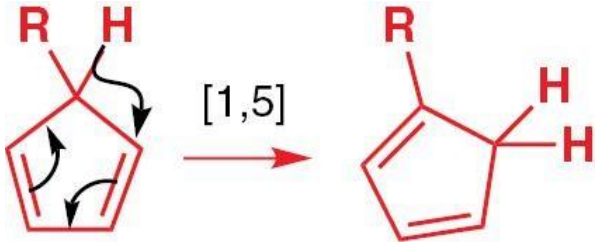
[1,5]-sigmatropic hydrogen shifts



➢ Cyclopentadienes undergo [1,5]-sigmatropic hydrogen shifts.

Sigmatropic rearrangements

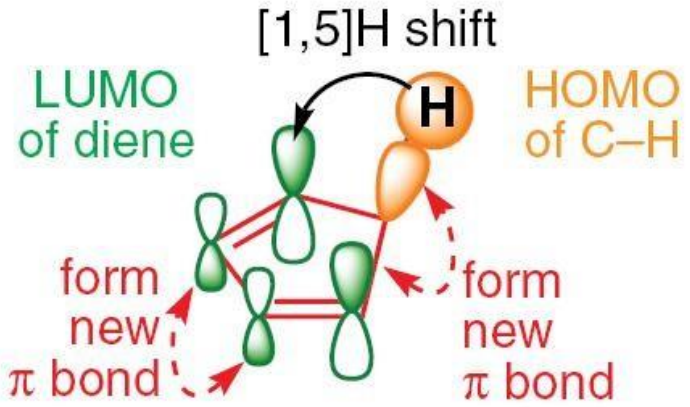
- If a cyclopentadiene is used as a diene starting material of a Diels-Alder reaction, **there will be a problem**



- **Orbital description of [1,5]-sigmatropic hydrogen shifts**
  - [1,5]-sigmatropic hydrogen shifts are **suprafacial**, **symmetry allowed** and take place **easily**

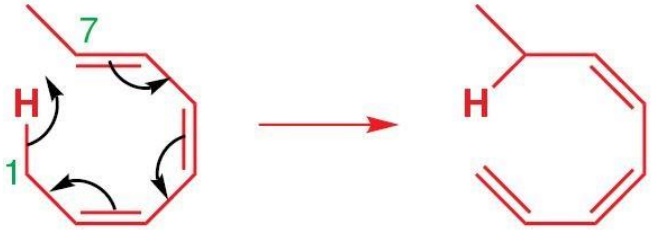
Sigmatropic rearrangements

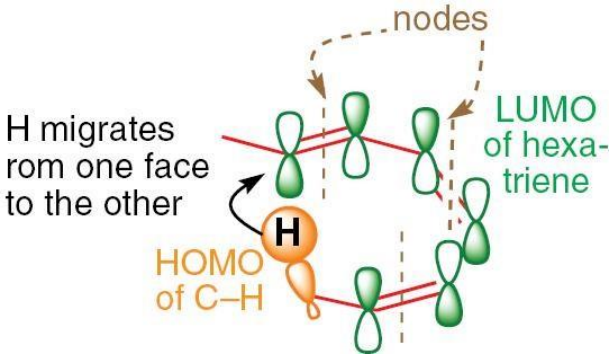
❖ **Orbital**



➢ One $(4q+2)_s$ component and no $(4r)_a$ component.
Allowed as per WoodwardHoffmann rule.
description of [1,7]-sigmatropic hydrogen shifts

allowed and possible antarafacial [1,7]H shift



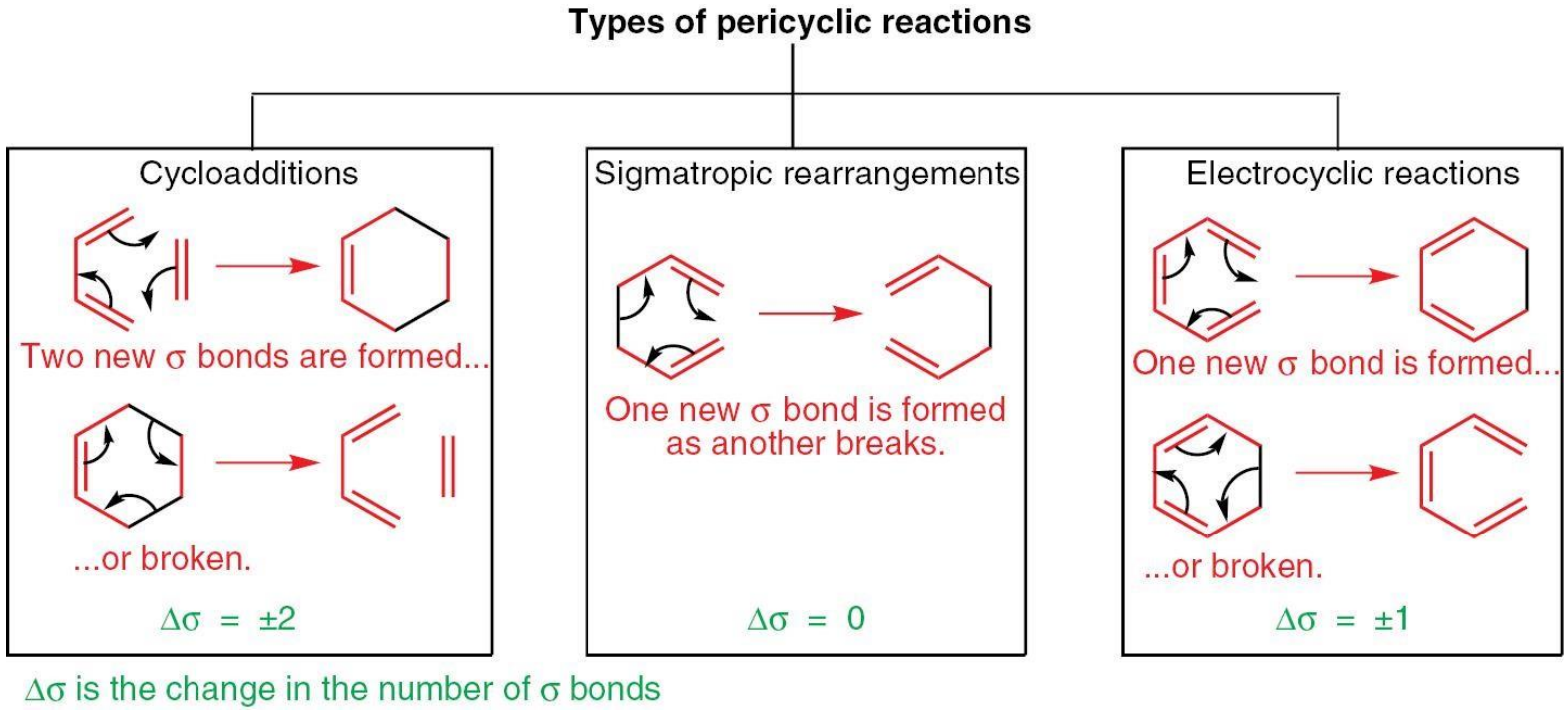


Sigmatropic rearrangements

- The **antarafacial interaction** here is symmetry allowed. Also, the **long chain is flexible enough to allow the antarafacial migration**

Electrocyclic reactions

- **In an electrocyclic reaction, a ring is always broken or formed. One sigma bond is either broken or formed**



ASSIGNMENT MENTOR

Electrocyclic reactions

- **When both orbitals at the ends of the conjugated system rotate in the same direction :- Conrotatory**

- **When the orbitals at the ends of the conjugated system rotate in opposite direction :- Disrotatory**

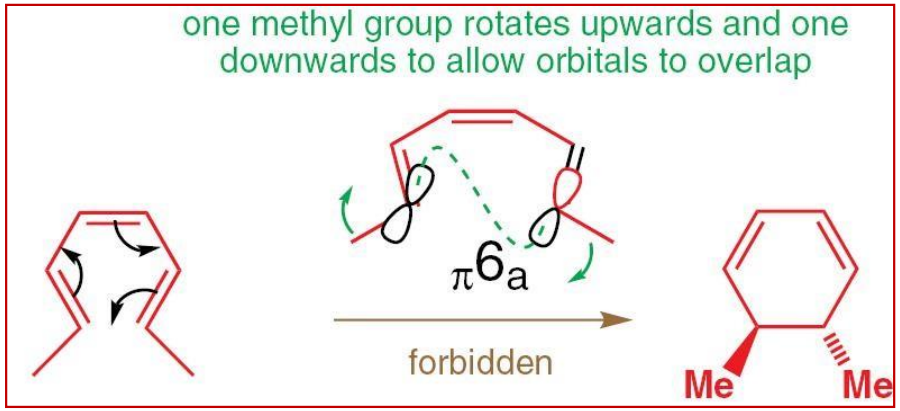
❖ The rules for electrocyclic reactions

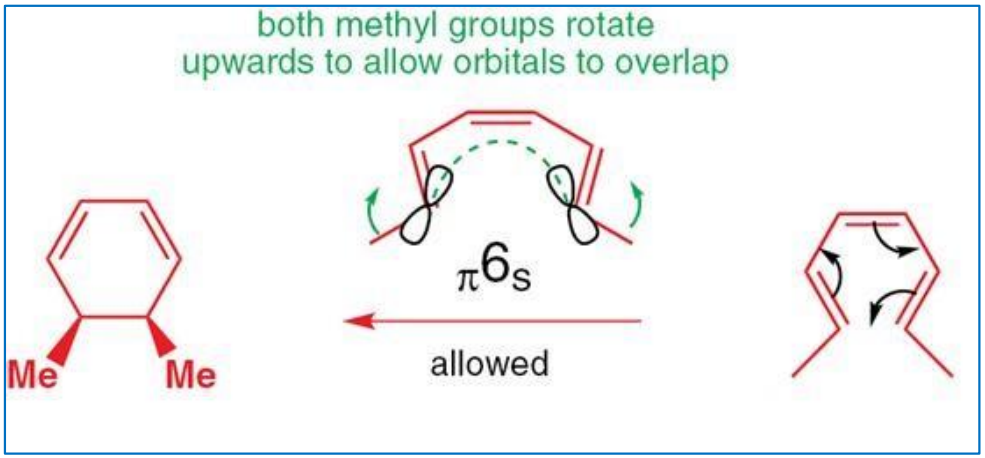
- **All *electrocyclic* reactions are allowed**
- Thermal *electrocyclic* reactions involving **(4n+2) π** electrons are ***disrotatory***
- Thermal *electrocyclic* reactions involving **(4n) π** electrons are ***conrotatory***
- In **photochemical conditions** the above two rules are just **reversed**

Electrocyclic reactions

- When there are **substituents** at the ends of the double bonds, the ***con***- and ***dis-rotations*** have different **stereochemical outcome**

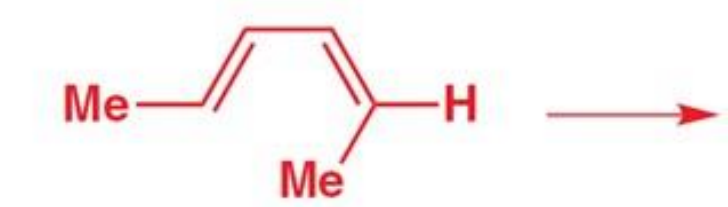
Electrocyclic reactions





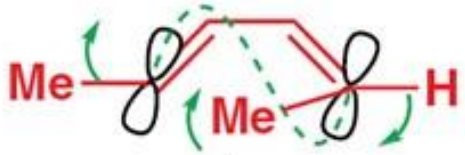
Predict the product and its stereochemistry

Electrocyclic reactions



only this geometrical isomer…

both methyl groups rotate upwards
to allow orbitals to overlap

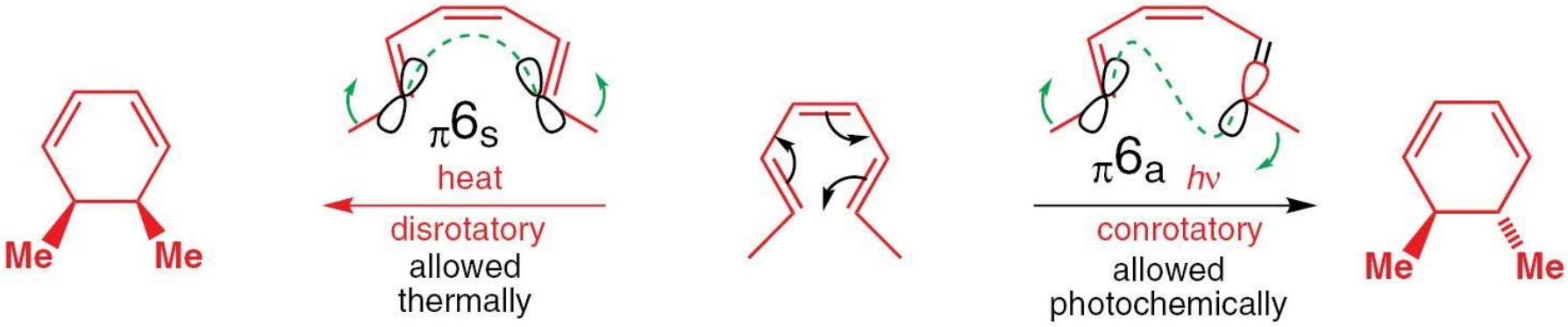


π^4_a

...can give this diastereoisomer

Electrocyclic reactions

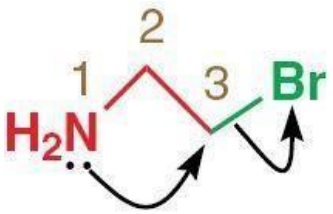
- Under **photochemical conditions** the electrocyclic reaction follows the **opposite rule** as that of the thermal reactions



Saturated heterocycles

- **Cyclisation reactions can be classified by a simple system:**
  - **[1]** Ring size
  - **[2]** Whether the bond that breaks is **inside** (***endo***) or **outside** (***exo***) the new ring
  - **[3]** Whether the **electrophile** is ***sp*** (**digonal**), ***sp*$_2$** (**trigonal**) or ***sp*$_3$** (**tetrahedral**) atom

For example:



3-*exo*-*tet*

ASSIGNMENT MENTOR

Saturated heterocycles

The ring being formed has **three members**; the breaking C–Br bond is **outside** the new ring (***exo***); the C carrying Br is a **tetrahedral** (sp^3) atom (***tet***)

The Baldwin's rules

All *exo*-tet cyclisations are **favoured**

All *exo*-trig cyclisations are **favoured**

5 & 6 *endo*-tet cyclisations are **disfavoured**

3 & 4 & 5 *endo*-trig cyclisations are **disfavoured**

6 & 7 *endo*-trig cyclisations are **favoured**

All *endo*-dig cyclisations are **favoured**

Saturated heterocycles

Q. Classify the following cyclisations reactions based on Baldwin's rules, and predict whether the reactions are favoured or disfavoured