# Advanced Organic Chemistry

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## Chapter 6

# Organic Reactions and Their Mechanisms

## 6.1 Substitution Reaction

In a substitution reaction, a functional group in a particular chemical compound is replaced by another group.

| Reagent | Substrate | Reactive intermediate | Type of organic substitution |
|---|---|---|---|
| Nucleophilic | Aliphatic | Carbocation | Aliphatic nucleophilic substitution |
| Electrophilic | Aromatic | Carbanion | Aromatic electrophilic substitution |
| | | Free radical | Free radical substitution |

- The electrophilic and nucleophilic substitution reactions are of prime importance.
- Detailed understanding of a reaction type helps to predict the product outcome in a reaction. It also is helpful for optimizing a reaction with regard to variables such as temperature and choice of solvent.

# I. Aliphatic Nucleophilic Substitution

## A. General description

$$R{-}L + Nu: \rightarrow R{-}Nu + L:$$

- Nucleophilic substitution reactions can carry out at a *saturated aliphatic carbon* or at other *unsaturated carbon* centre.
- Charge type:

*Type a* $R{-}I + OH^- \longrightarrow R{-}OH + I^-$

*Type b* $R{-}I + NMe_3 \longrightarrow R{-}\overset{+}{N}Me_3 + I^-$

*Type c* $R{-}\overset{+}{N}Me_3 + OH^- \longrightarrow R{-}OH + NMe_3$

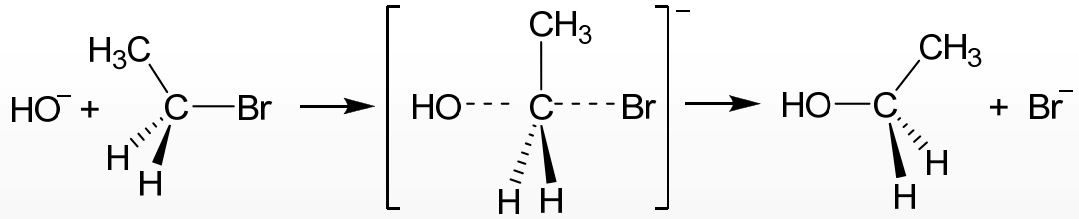
*Type d* $R{-}\overset{+}{N}Me_3 + H_2S \longrightarrow R{-}\overset{+}{S}H_2 + NMe_3$

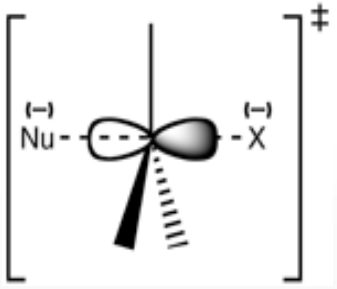
All necleophiles are Lewis bases.

Solvolysis: solvent used as a necleophile.
Alkylattion: nucleophilic substitution at an alkyl carbon.
Acylation: nucleophilic substitution at an acyl carbon.

## B. Nucleophilic Substitution Mechanisms at Saturated Carbon Centres

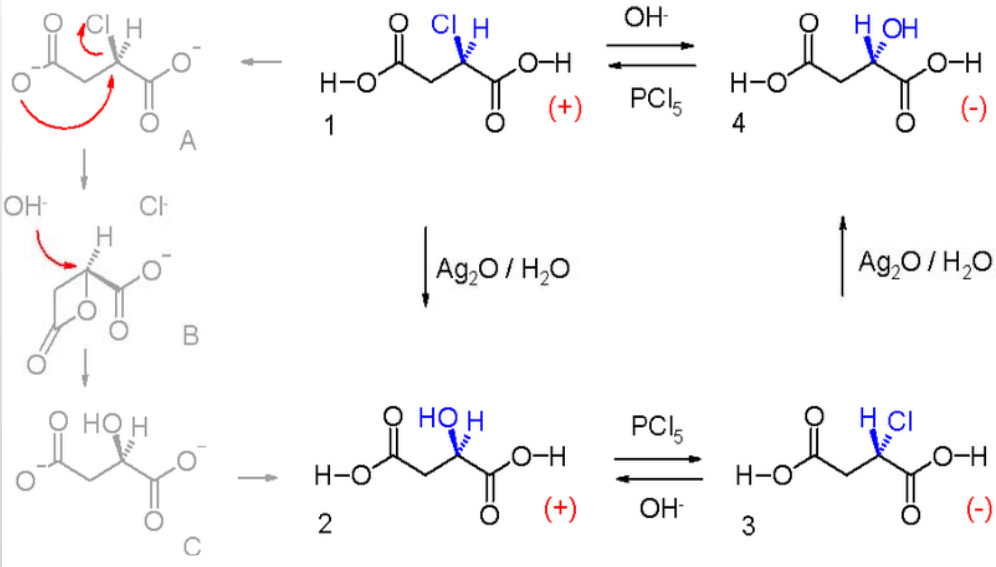
- Bimolecular Nucleophilic Substitution ($S_N2$)




Structure of the $S_N2$ transition state

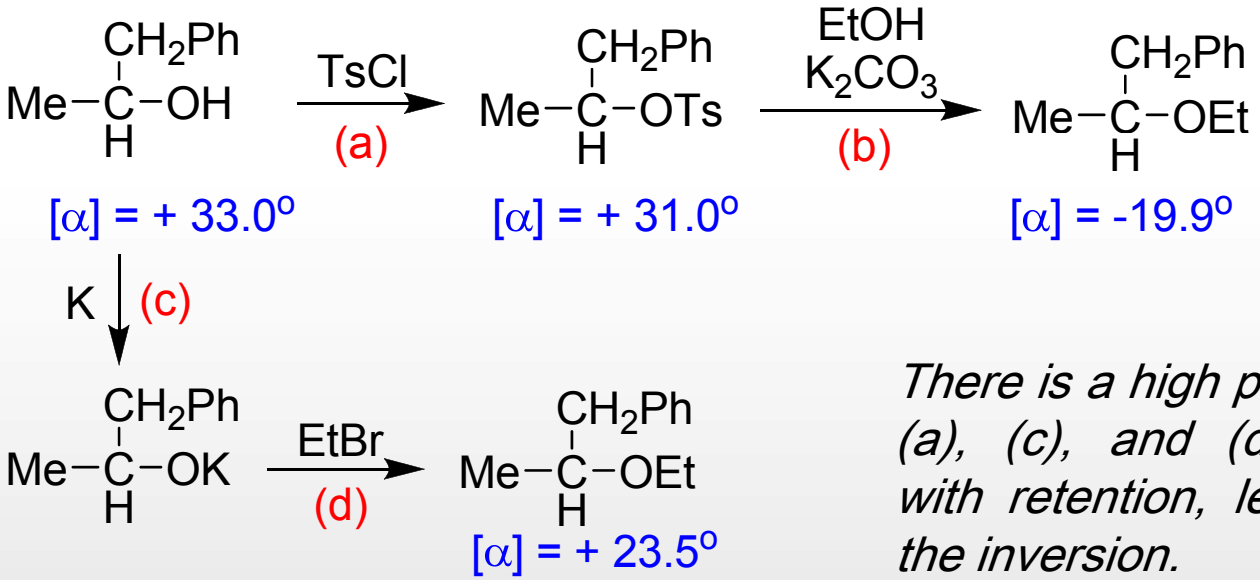
☞ The kinetic evidence: Rate = $k$ [RX][Nu]




### Walden inversion:

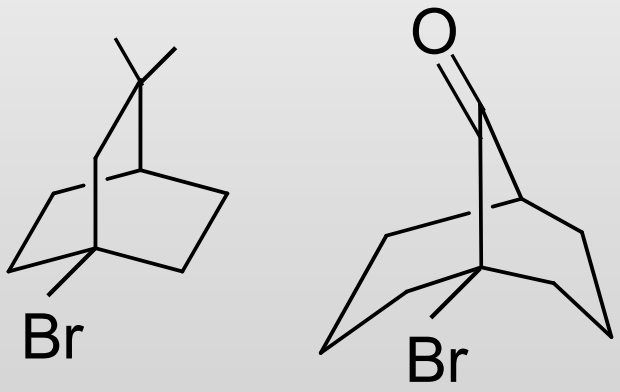
(+)-chlorosuccinic acid 1 was converted to (+) malic acid 2 by action of $Ag_2O$ in water with retention of configuration, in the next step the OH was replaced by Cl to 3 by reaction with $PCl_5$.

Philips (1923)

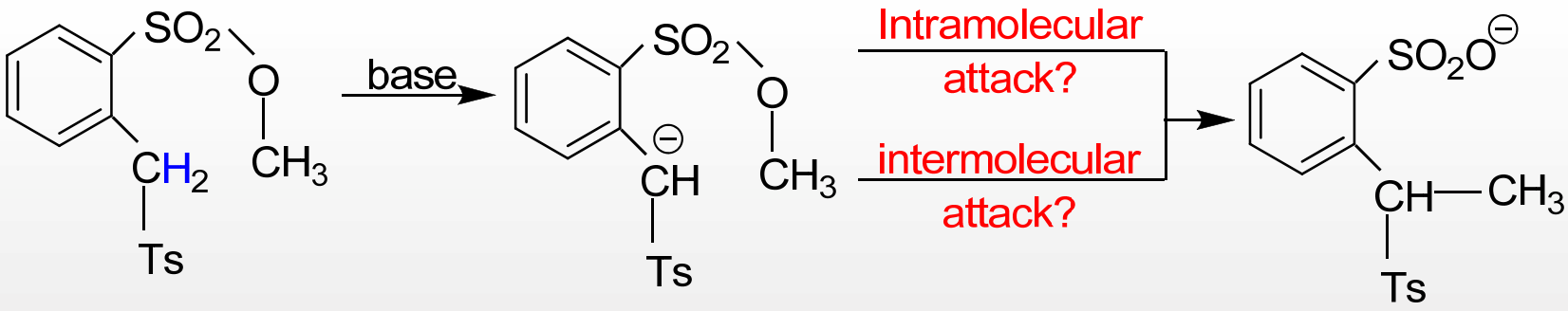



*There is a high probability that (a), (c), and (d) proceeded with retention, leaving (b) as the inversion.*

☞ Examples of unsuccessful reaction attempts at bridgeheads under SN2 conditions ($^-$OEt and $I^-$ used as an nucleophile, respectively). In these cases, open-chain analogs underwent the reactions readily.

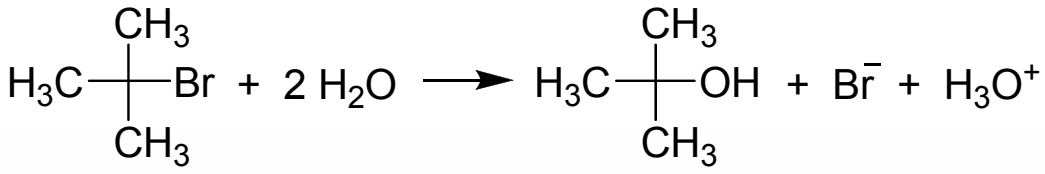


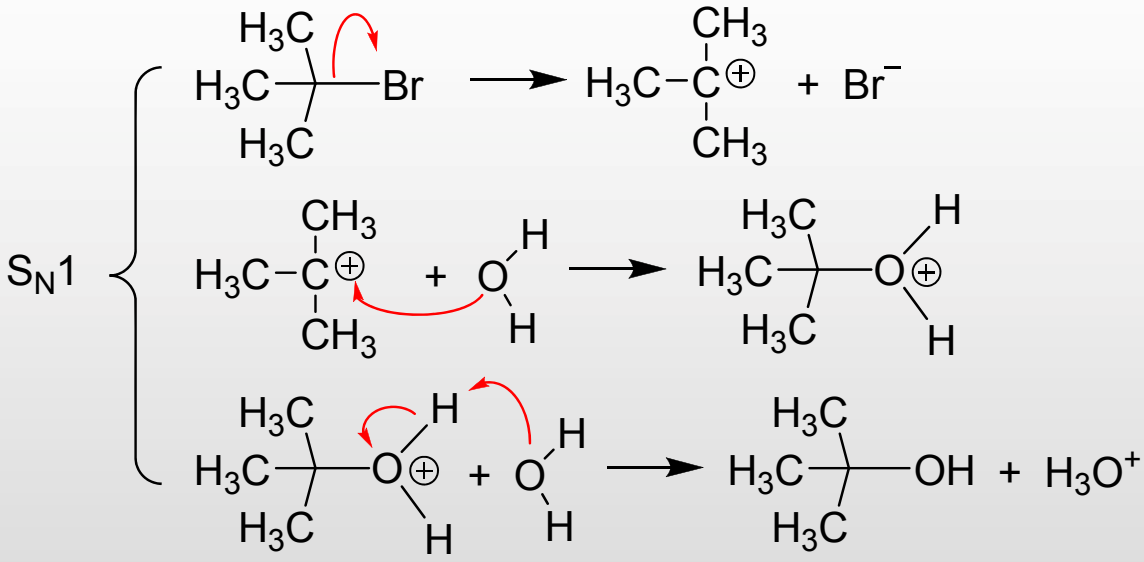
## Eschenmoser et al.




- The negatively charged carbon attacks the methyl group of another molecule rather than the nearby one in the same molecule, that is, the reaction is intermolecular and not intramolecular. The transition state in an $S_N2$ reaction must be linear.

- Unimolecular Nucleophilic Substitution ($S_N1$)






☞ Reaction kinetics:

rate = $k$ [RX]

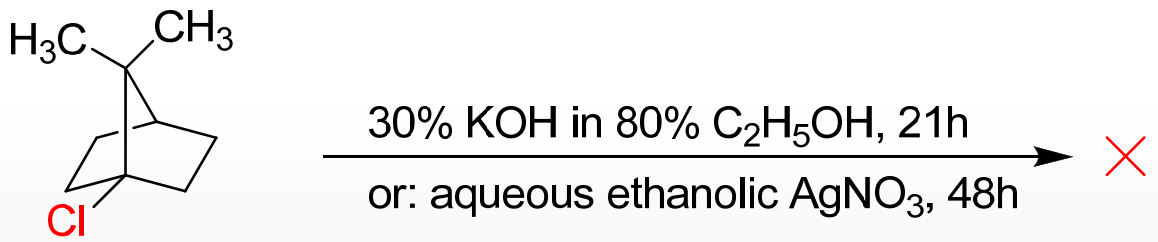
*Ionization of the substrate is the rate-determinating step.*

*t*-BuCl → *t*-Bu$^+$ + Cl$^-$

630 kJ/mol (in gas phase)
84 kJ/mol (in water)

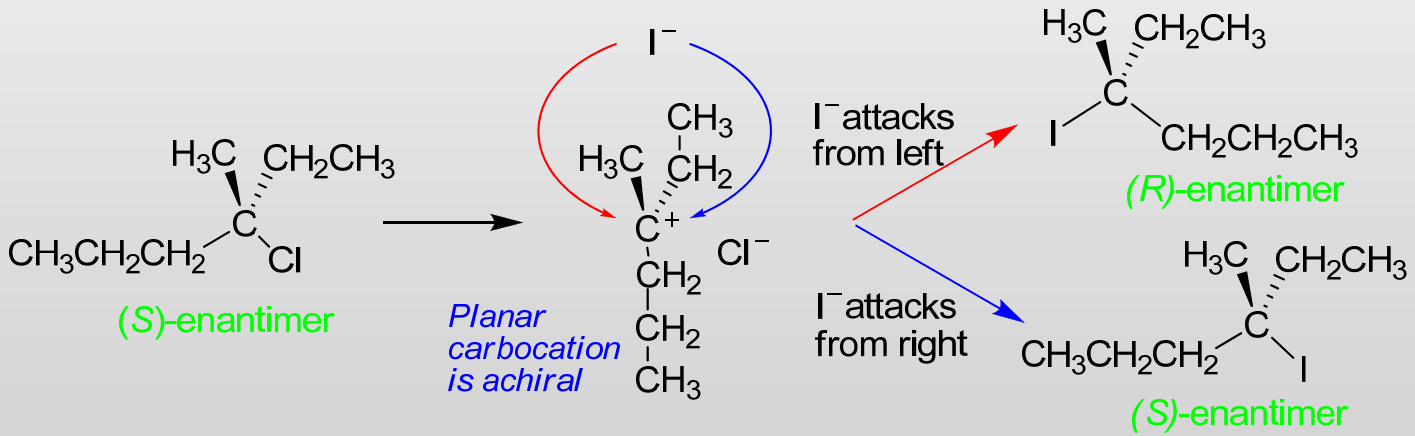
☞ Salt effect and common-ion effect: An increase in ionic strength of the solution usually increases the rate of an $S_N1$ reaction. A common ion will depress the $S_N1$ rate.

Steric factor: The reactions run under SN1 conditions fail or proceed very slowly at the bridgehead position of [2,2,1](norbornyl) systems.

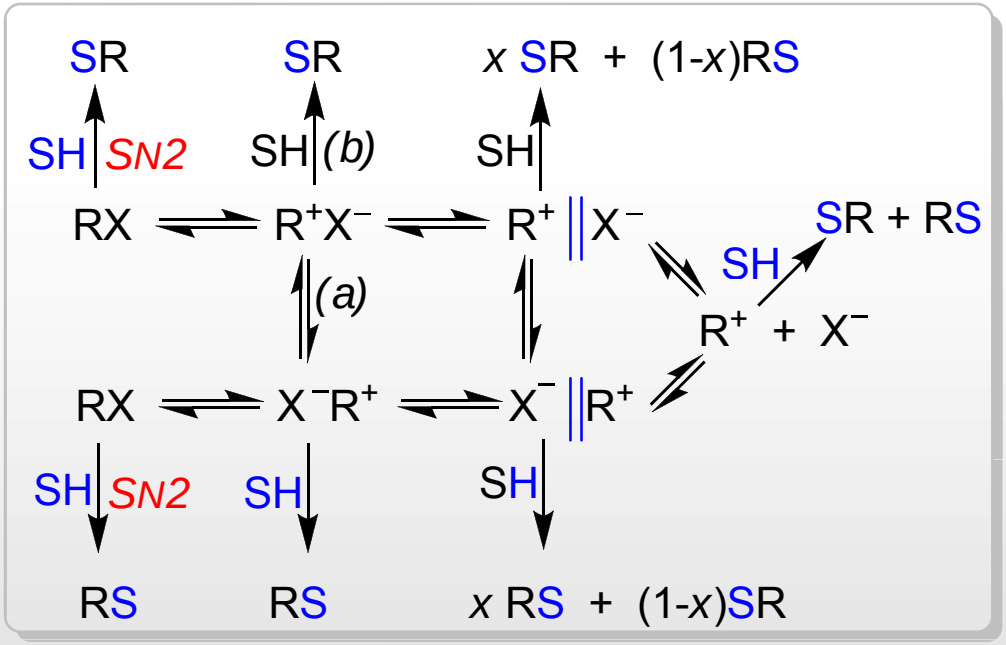



1-chloroapocamphane

➢ Stereochemistry: An excess of inversion is usually observed, as the leaving group can remain in proximity to the carbocation intermediate for a short time and block nucleophilic attack.



## ➢ Ion Pairs in the SN1 Mechanism




A complete picture of the possibilities for solvolysis in a solvent SH (ignoring the possibilities of elimination or rearrangement). RS and SR represent enantiomers; *x* = some fraction.

i. SN2 process: a complete inversion

ii. Intimate ion pair $R^+X^-$: total inversion if *(a)* does not take place or to a combination of inversion and racemization if there is competition between *(a)* and *(b)*.

iii. Solvent-separated $R^+\|X^-$: more racemization (perhaps total)

iv. Free $R^+$: complete racemization

v. The difference: SN1 and SN2 mechanisms is in the timing of the steps.

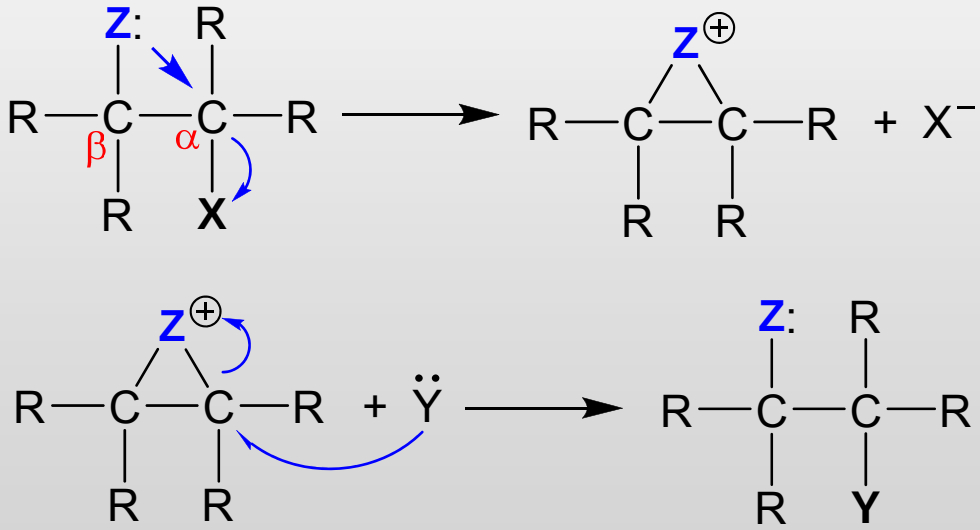
- **The Neighboring-Group Mechanism**

OBSERVATION with certain substrates:

i. The rate of reaction is greater than expected,

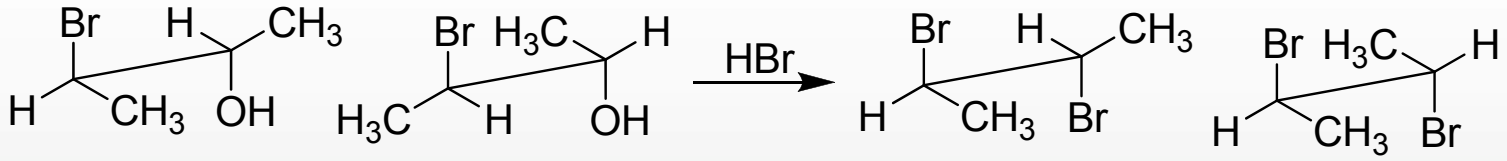
ii. The configuration at a chiral carbon is retained and not inverted or racemerized.

The *neighboring-group mechanism* consists essentially of two $S_N2$ substitutions, each causing an inversion so that the net result is retention of configuration.



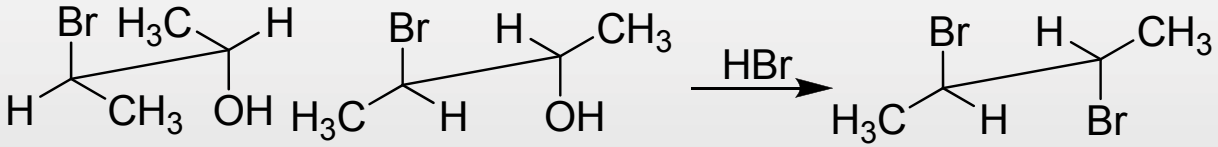
EVIDENCE:

(i) Configurational retention. Note that both products are optically inactive and so cannot be told apart by differences in rotation. The *meso* and *dl* dibromides have different boiling points and indexes of refraction and were identified by these properties.




threo *dl* pair

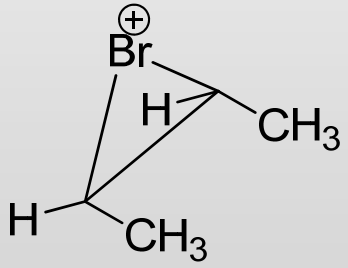
*dl* pair




erythro *dl* pair

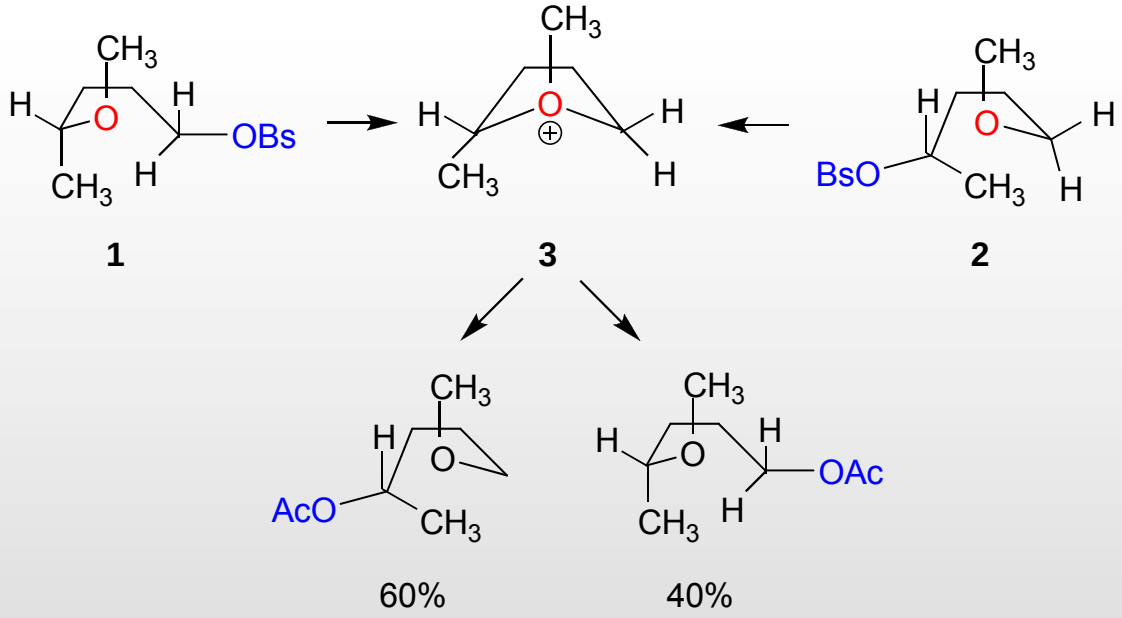
*meso*

➢ Even more convincing evidence: either of the two threo isomers alone gave not just one of the enantiomeric dibromides, but the *dl* pair.




A bromonium ion

(iii) Acetolysis of both 4-methoxy-pentyl brosylate **1** and 5-methoxy-2-pentyl brosylate **2**: the same mixture of products. In this case the intermediate **3** is common to both substrates.

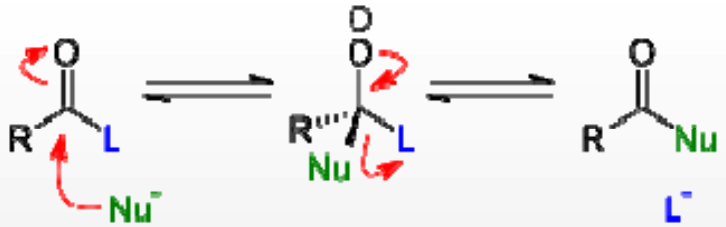



☞ Important neighboring groups: $COO^-$, COOR, COAr, OCOR, OR, OH, $O^-$, $NH_2$, NHR, $NR_2$, NHCOR, SH, SR, $S^-$, I, Br, Cl.

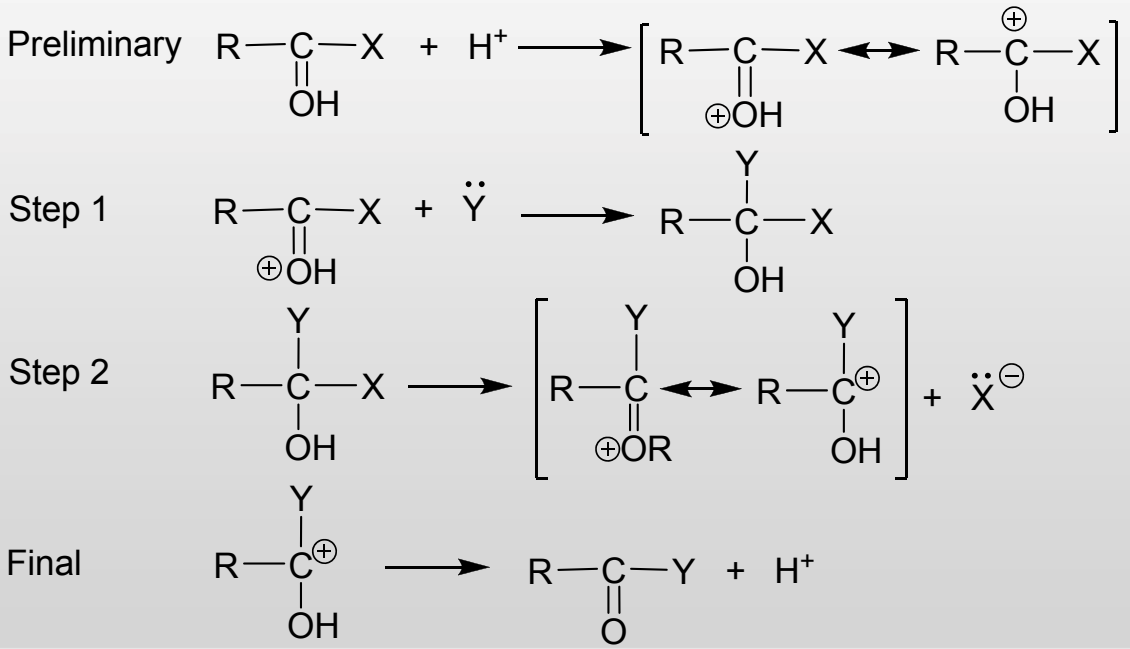
☞ The effectiveness: I > Br > Cl.

## C. Nucleophilic Substitution at an Aliphatic Trigonal Carbon. The Tetrahedral Mechanism

Acyl substitution is basically a two-step nucleophilic addition and elimination reaction. Both reaction steps are reversible reactions.




*When reactions are carried out in acid solution, there may also be a preliminary and a final step.*



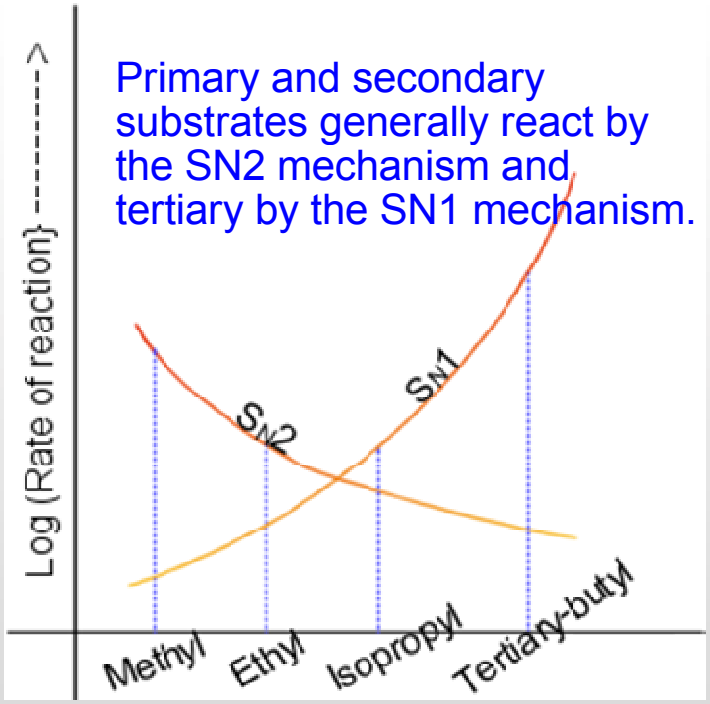
## D. Reactivity

- **The Effect of Substrate Structure**

➢ For the SN2 mechanism, branching at either the $\alpha$ or the $\beta$ carbon decreases the rate.

Table. Average relative SN2 rates for some alkyl substrates

| R | Relative rate | R | Relative rate |
|---|---|---|---|
| Methyl | 30 | Ispbutyl | 0.03 |
| Ethyl | 1 | Neopentyl | $10^{-5}$ |
| Propyl | 0.4 | Ally | 10 |
| Butyl | 0.4 | Benzyl | 120 |
| Isopropyl | 0.025 | | |




➢ Elimination is always a possible side reaction of nucleophilic substitutions of tertiary substrates (wherever a hydrogen is present).

➢ Substrates of the type RCOX are usually much *more* reactive than the corresponding $RCH_2X$. The mechanism here is always the tetrahedral one. Explanation:

i. The carbonyl carbon has a sizable partial positive charge.

ii. In an $S_N1$ reaction a $\sigma$ bond must break in the rate-determining step, which requires more energy than the shift of a pair of $\pi$ electrons, which is what happens in a tetrahedral mechanism.

iii. A trigonal carbon offers less steric hindrance to a nucleophile than a tetrahedral carbon.

➢ Unsturation at the $\beta$-carbon.

| Table. Relative rates for the $S_N1$ reaction between ROTs and ethanol at 25°C | | | |
|---|---|---|---|
| $CH_3CH_2$- | 0.26 | $PhCH_2$- | 100 |
| $(CH_3)_2CH$- | 0.69 | $Ph_2CH$- | ~ $10^5$ |
| $CH_2=CHCH_2$- | 8.6 | $Ph_3C$- | ~ $10^{10}$ |

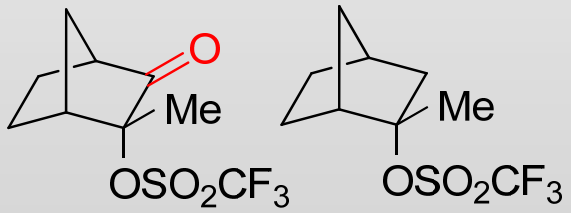
## NOTE

☞ In general, SN1 rates at allylic substrate are increased by any substituent in the 1 or 3 position that can stabilized the carbocation by resonance or hyperconjugation. Among these are alkyl, aryl, and halo groups.

☞ SN2 rates for allylic and benzylic systems are also increased, probably owing to resonance possibilities in the transition state.

➢ α-Substitution — resonance effect, field effect

| $ZCH_2X$ | SN1 relative rate |
|---|---|
| Z = RO, RS or $R_2N$- | Very rapid |
| Z = RCO, HCO, ROCO, $NH_2CO$, NC, $F_3C$ | Decreased compared to $CH_3X$ |

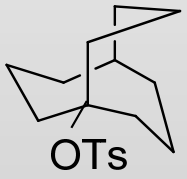



Relative rate: 1




$10^{7.3}$


Solvolytic rate ($k$) $4x10^{-17}$/s




$3x10^{6}$/s

Table. List of groups in approximately descending order of reactivity toward SN1 and SN2 reactions. (Z = RCO, HCO, ROCO, NC, or a similar group)

| SN1 reactivity | | SN2 reactivity | |
|---|---|---|---|
| $Ar_3CX$ | RCHDX | $Ar_3CX$ | $R_3CX$ |
| $Ar_2CHX$ | $RCHDCH_2X$ | $Ar_2CHX$ | $ZCH_2CH_2X$ |
| $ROCH_2X$, $RSCH_2X$, $R_2NCH_2X$ | C=CX | $ArCH_2X$ | $R_3CCH_2X$ |
| $R_3CX$ | $ZCH_2X$ | $ZCH_2X$ | C=CX |
| $C=CCH_2X$ | $ZCH_2CH_2X$ | $C=CCH_2X$ | ArX |
| $R_2CHX$ | ArX | $RCH_2X$ ~ RCHDX ~ $RCHDCH_2X$ | Bridgehead-X |
| $RCH_2X$ ~ $R_3CCH_2X$ | [2,2,1]bridgehead-X | $R_2CHX$ | |

- **The Effect of the Attacking Nucleophile**

➢ $S_N1$ rate: are independent of the identity of the nucleophile, since it does not appear in the rate-determining step.

➢ For $S_N2$ reactions in solution there are four principles that govern the effect of the nucleophile on the rate.

i. A nucleophile with a negative charge > its conjugate acid.
$OH^- > H_2O$, $NH_2^- > NH_3$

ii. In comparing nucleophiles whose attacking atom is in the same row of the periodic table, nucleophilicity is approximately in order of basicity. $NH_2^- > RO^- > OH^- > R_2NH > ArO^- > NH_3 > C_6H_5N > F^- > H_2O > ClO_4^-$; $R_3C^- > R_2N^- > RO^- > F^-$.

iii. Going down the periodic table, nucleophilicity increases, though basicity decreases. $I^- > Br^- > Cl^- > F^-$ (solvation, HSAB principle)

iv. The freer the nucleophile, the greater the rate.

Ex.: The rate of nucleophilic attack by $(EtOOC)_2CBu^-Na^+$ in benzene was increased by the addition of 1,2-dimethoxyethane.

NOTE:

i. The four rules given above do not always hold. One reason is that steric influences often play a part.

Basicity: $Me_3CO^-$ > $OH^-$ or $OEt^-$
Nucleophilicity: $Me_3CO^-$ < $OH^-$ or $OEt^-$

ii. Nucleophilicity order for $S_N2$ mechanism (in protonic solvents):

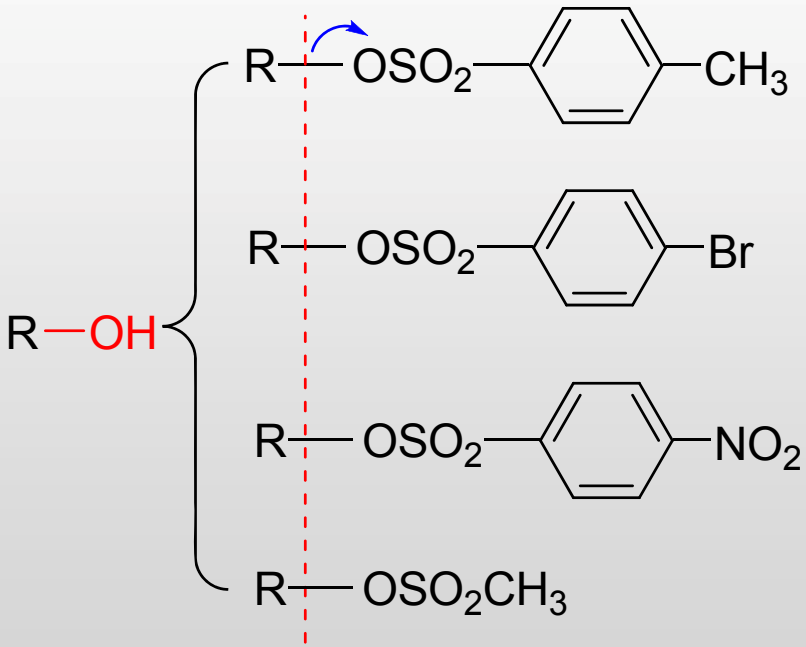
$RS^-$ > $Ar^-$ > $I^-$ > $CN^-$ > $OH^-$ > $N_3^-$ > $Br^-$ > $ArO^-$ > $Cl^-$ > $C_6H_5N$ > $^-OAc$ > $H_2O$.

iii. For substitution at a carbonyl carbon, the nucleophilicity order is not the same as it is at a saturated carbon, but follows the basicity order more closely.

$EtO^-$ > $MeO^-$ > $OH^-$ > $ArO^-$ > $N_3^-$ > $F^-$ > $H_2O$ > $Br^-$~ $I^-$

- **The Effect of the Leaving Group**

➢ At a saturated carbon. The leaving group comes off more easily the more stable it is as a free entity. This is usually inverse to its basicity, and the best leaving groups are the weakest bases. Thus iodide is the best leaving group among the halides and fluoride the poorest.




**ROTs**
*p*-Toluenesulfonates, Tosylates

**ROBs**
*p*-Bromobenzenesulfonates, Brosylates

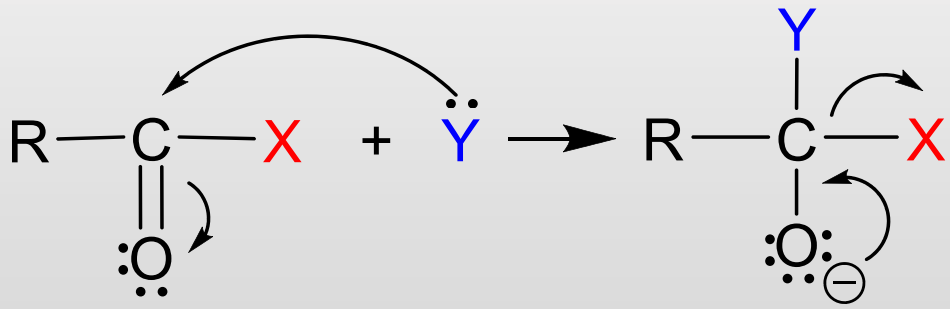
**RONs**
*p*-Nitrobenzenesulfonates, Nosylates

**ROMs**
Methanesulfonates, Mesylates

➢ At a carbonyl carbon. In the tetrahedral mechanism at a carbonyl carbon, the bond between the substrate and leaving group is still intact during the slow step. Nevertheless, the nature of the leaving group still affects the reactivity in two ways:

i. The greater the electron-withdrawing character of X, the greater the partial positive charge on carbonyl carbon and the more rapid the attack by a nucleophile.

ii. The nature of the leaving group affects the position of equilibrium. There is competition between X and Y as to which group leave:




RCOCl > RCOOCOR' > RCOOAr > RCOOR' > $RCONH_2$ > $RCOO^-$.

- **The Effect of the Reaction Medium**

| Table. Transition states for SN1 and for SN2 reactions of the four charge types | | |
|---|---|---|
| Reactants and transition states | Charge in the transition state relative to starting materials | How an increase in solvent polarity affects the rate |
| Type a $RX + Y^- \rightarrow Y^{\delta-}\cdots R\cdots X^{\delta-}$ | Dispersed | Small decrease |
| Type b $RX + Y \rightarrow Y^{\delta+}\cdots R\cdots X^{\delta-}$ | Increased | Large increase |
| Type c $RX^+ + Y^- \rightarrow Y^{\delta-}\cdots R\cdots X^{\delta+}$ | Decreased | Large decrease |
| Type d $RX^+ + Y \rightarrow Y^{\delta+}\cdots R\cdots X^{\delta+}$ | Dispersed | Small decrease |
| $RX \rightarrow R^{\delta+}\cdots X^{\delta-}$ | Increased | Large increase |
| $RX^+ \rightarrow R^{\delta+}\cdots X^{\delta+}$ | Dispersed | Small decrease |

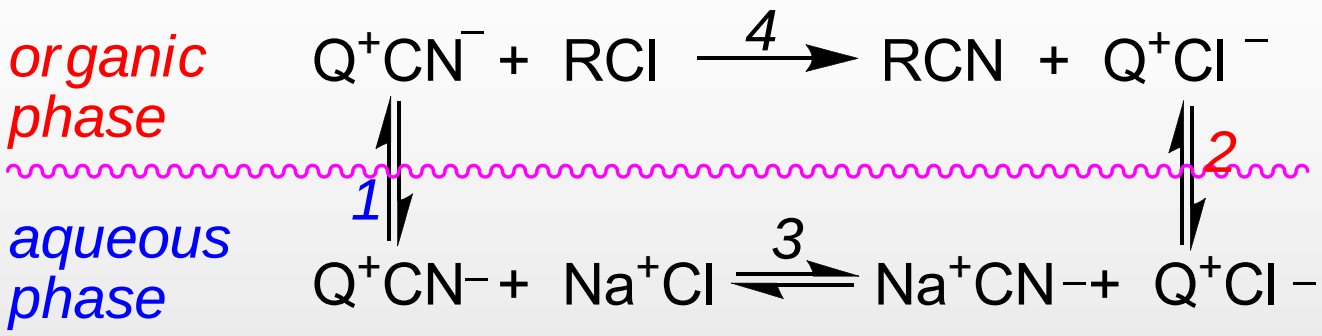
➢ When there is a greater charge in the transition state than in the starting compound, the more polar the solvent, the faster the reaction.

➢ Even for solvents with about the same polarity, there is a difference between protonic and aprotonic solvents. In *type a* and *b*, TS solvation: polar aprotonic solvents > prontonic solvents.

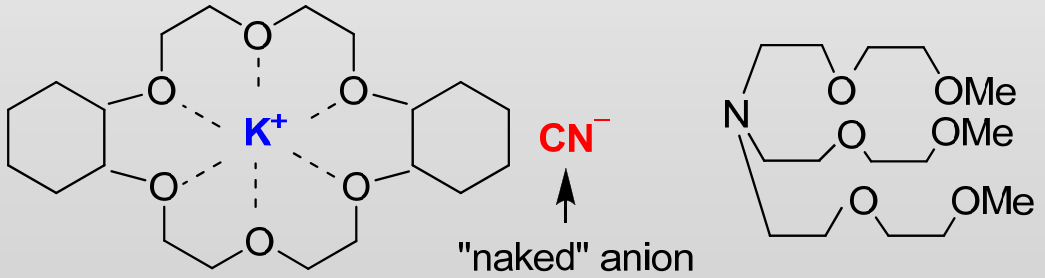
➢ It is quite possible for the same reaction to go by the SN1 in one solvent and the SN2 in another. (see: *J. Am. Chem. Soc*. 1961,**83**,618)

- **Phase Transfer Catalysis**

A difficulty that occasionally arises when carrying out nucleophilic substitution reactions is that the reactants do not mix.



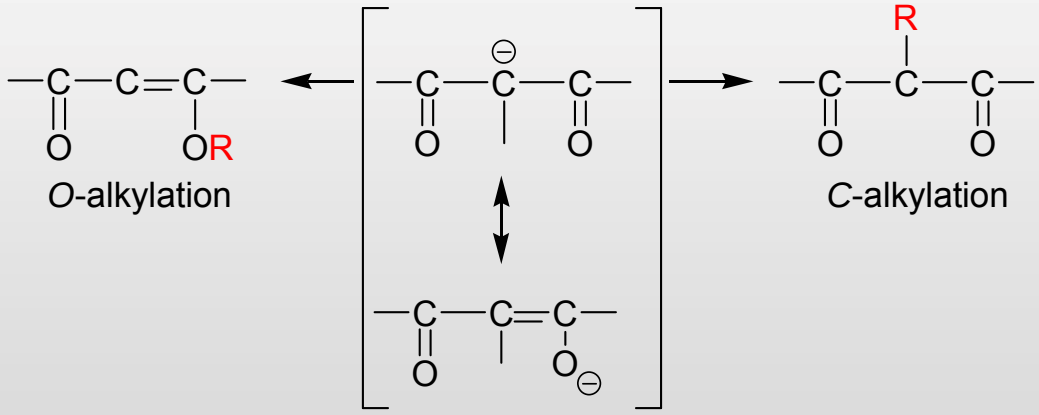

$Q^+ = R_4N^+$ or $R_4P^+$



- **Ambident Nucleophiles / Substrates. Regioselectivity**

➢ Ambident nucleophiles: Some nucleophiles have a pair of electrons on each of two or more atoms, or canonical forms can be drawn in which two or more atoms bear an unshared pair.

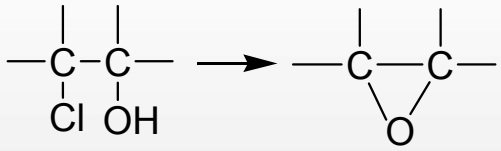
➢ Ambident substrates: Some substrates (e.g., 1,3-dichlrorbutane) can be attacked at two or more positions.



## E. Reactions

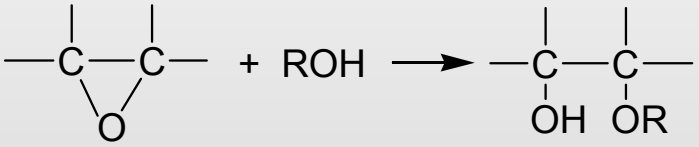
$RX + OH^- \rightarrow ROH$

$RX + OR'^- \rightarrow ROR'$



$R{-}OSO2OR'' + OR' \rightarrow ROR'$

$2\ ROH \rightarrow ROR$



$R_3O^+ + R'OH \rightarrow ROR'$

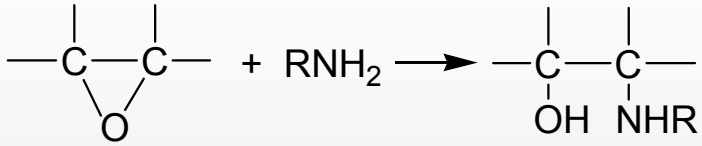
$RX + R'COO^- \rightarrow R'COOR$

$RX + OOH^- \rightarrow ROOH$

$RX + R'_2NH \rightarrow RR'_2N$

$RX + R'_3N \rightarrow RR'_3N^+X^-$

$RX + R'CONH^- \rightarrow RNHCOR'$



$RCOX + H_2O \rightarrow RCO_2H$

$RCOOCOR' + H_2O \rightarrow RCO_2H + R'CO_2H$

$RCO_2R' + H_2O \rightarrow RCO_2H + R'OH$

$RCONR' + H_2O \rightarrow RCO_2H + R'_2NH$ (R = H, alkyl, aryl)

$RCOX + R'OH \rightarrow RCO_2R'$

$RCOOCOR + R'OH \rightarrow RCO_2R'$

$RCOOH + R''OH \rightarrow RCO_2R'' + R'OH$

$RCOX + R'COO^- \rightarrow RCOOCOR'$

$RCOX + H_2O_2 \rightarrow RCO_3H$

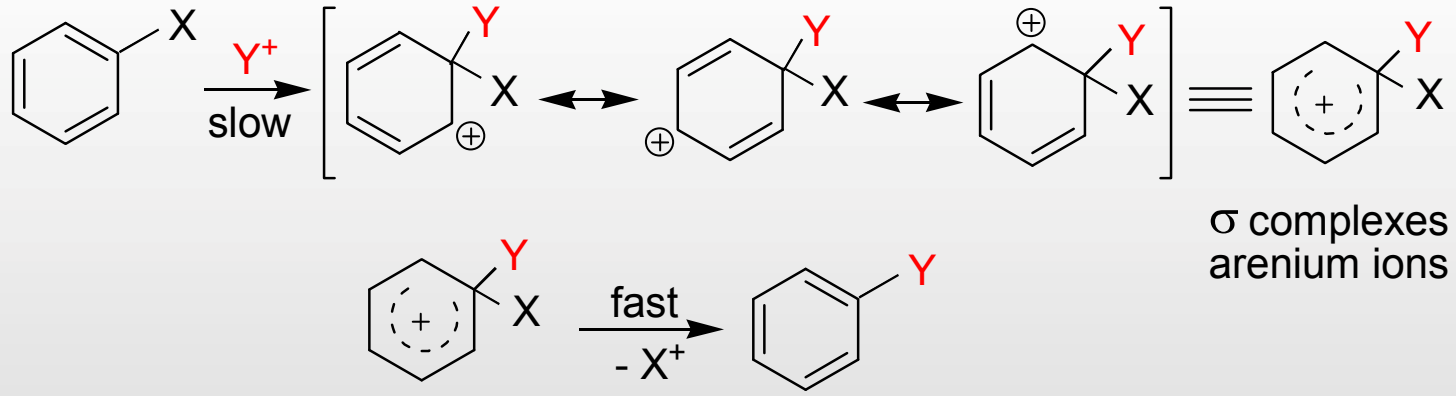
## II. Aromatic Electrophilic Substitution

◆ Most substitution at an aliphatic carbon are nucleophilic. In aromatic systems the situation is reversed, because the high electron density at the aromatic ring attracts positive species and not negative ones. In electrophilic substitutions the attacking species is a positive ion or the positive end of a dipole or induced dipole. The leaving group must necessarily depart without its electron pair.

◆ In nucleophilic substitutions, the chief leaving groups are those best able to carry the unshared pair: Br–, $H_2O$, OTs–, etc., that is, the weakest bases. In electrophilic substitutions the most important leaving groups are those that can best exist without the pair of electrons necessary to fill the outer shell, that is, the weakest Lewis acids. The most common leaving group in electrophilic aromatic substitutions is the proton ($H^+$).

## A. The Arenium Ion Mechanism

➢ In the arenium ion mechanism the attacking species may be produced in various ways, but what happens to the aromatic ring is basically the same in all cases. For this reason most attention in the study of this mechanism centers around the identity of the attacking entity and how it is produced.




The attacking species
is not an ion but a dipole.

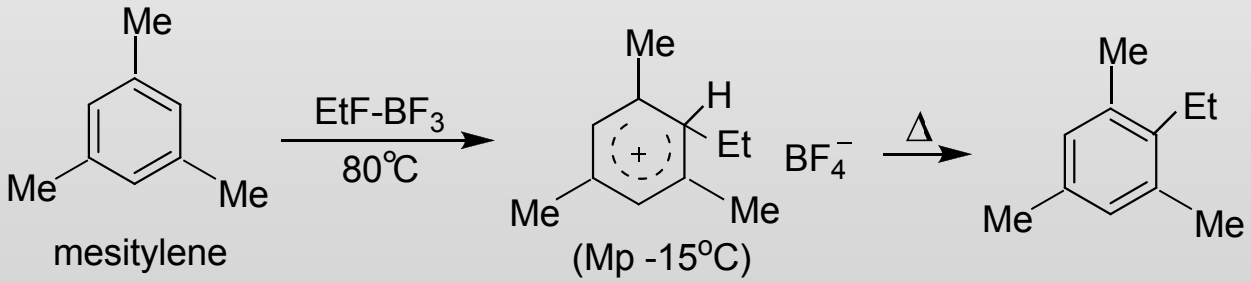
## Evidence:

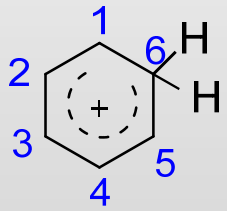
### i. No isotope effects

If the hydrogen ion departs before the arrival of the electrophile or if the arrival and departure are simultaneous, there should be a substantial isotope effect (i.e., deuterated substrates should undergo substitution more slowly than nondeuterated compounds) because, in each case, the C—H bond is broken in the rate-determining step.

*However, in the arenium ion mechanism, the C—H bond is not broken in the rate-determining step, so no isotope effect should be found.*

### ii. Isolation of arenium ion intermediates

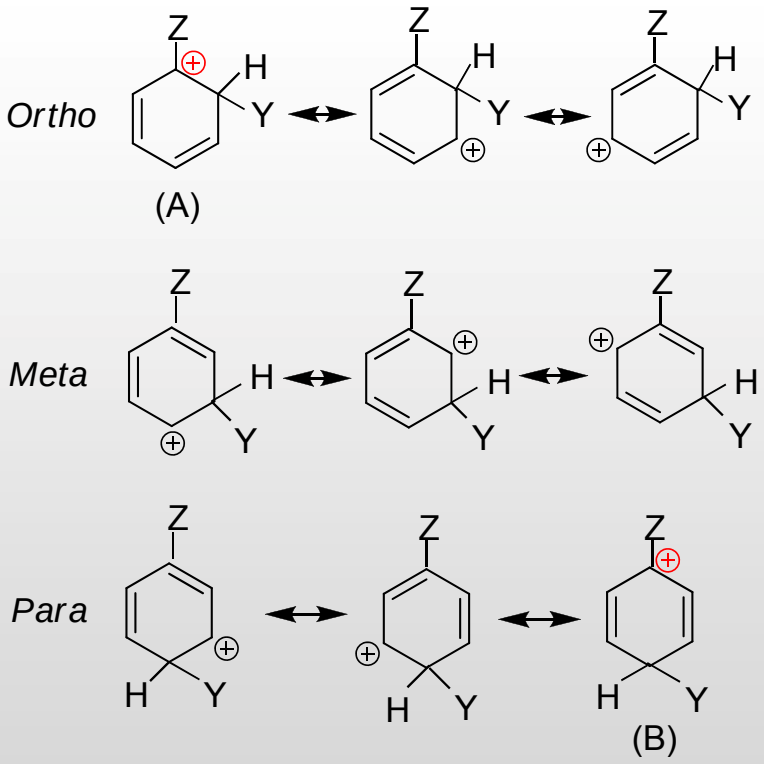


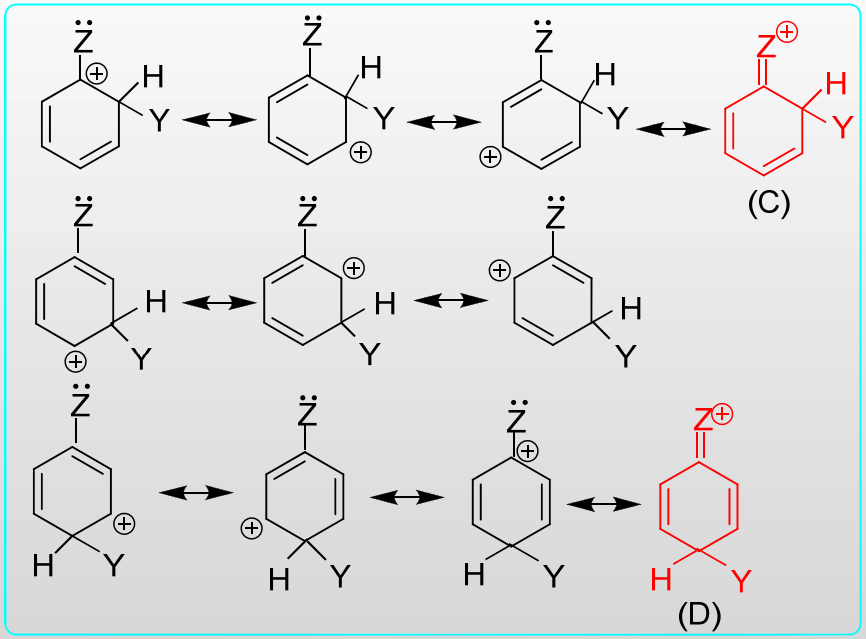

Benzenonium ion in $HF\text{-}SbF_5\text{-}SO_2ClF\text{-}SO_2F_2$ at -134°C

## B. Orientation and Reactivity

### ➢ Monosubstituted Benzene Rings




Some substituents have a pair of electrons (usually unshared) that may be contributed toward the ring.



## Three Types of Groups:

i. Groups that contain an unshared pair of electrons on the atom connected to the ring.

$O^-$, $NR_2$, NHR, $NH_2$, OH, OR, NHCOR, OCOR, SR, the four halogens, and SH (except for the case of thiophenols electrophiles usually attack the sulfur rather than the ring).

☞ Cl, Br, and I deactivate the ring, but they direct ortho-para.

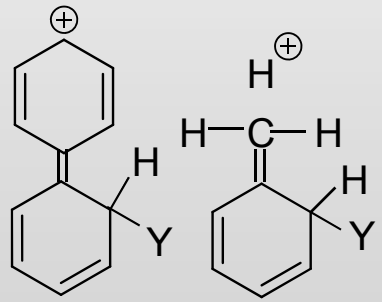
ii. Groups that lack an unshared pair on the atom connected to the ring and that are *–I*.

Approximate deactivating ability: $NR_3^+$> $NO_2$ > $CF_3$ > CN > $SO_3H$ > CHO > COR > COOH > COOR > $CONH_2$ > $CCl_3$ > $NH_3^+$.

☞ The $NH_3^+$ group is an anomaly, since this group directs *para* about as much as or a little more than it directs *meta*.

iii. Groups that lack an unshared pair on the atom connected to the ring and that are *ortho-para*-directing.

–R, –Ar, $–COO^-$ groups, which active the ring.



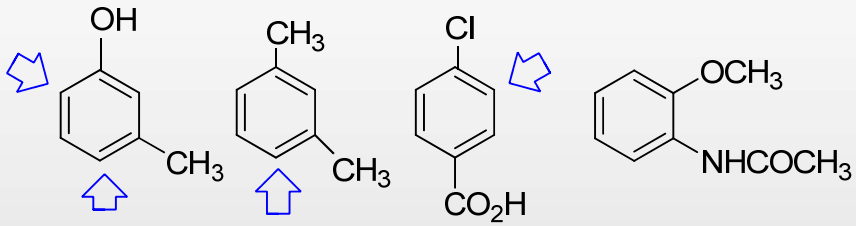

(E) (F)

## ➢ Orientation in Benzene Rings with More than One Substituent

### Generalization

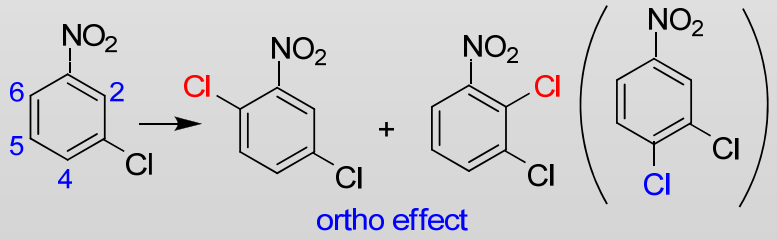
i. If a strong activating group competes with a weaker one or with a deactivating group, the former controls.

Directing order: $NH_2$, OH, $NR_2$, $O^-$ > OR, OCOR, NHCOR >, R, Ar > halogen > *meta*-directing groups.




ii. All other things being equal, a third group is least likely to enter between two groups in the *meta* relationship (steric hindrance).

iii. When a *meta*-directing group is *meta* to an *ortho-para*-directing group, the incoming group primarily goes *ortho* to the *meta*-directing group rather than *para*.

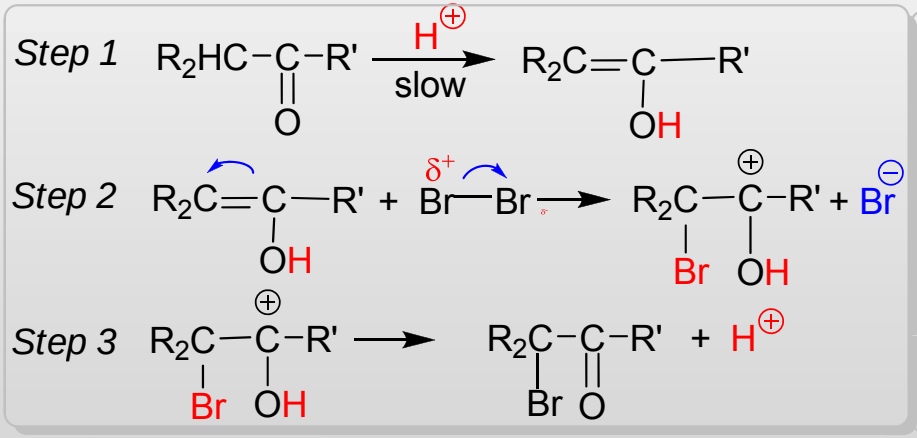


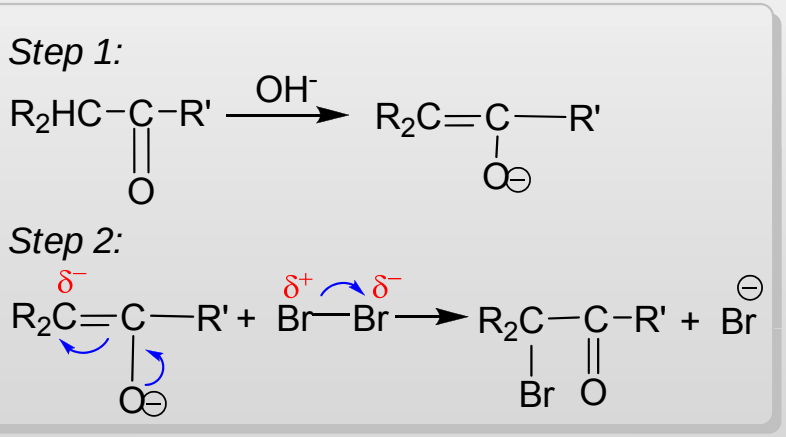
# III. Aliphatic Electrophilic Substitution

## MECHANISMS

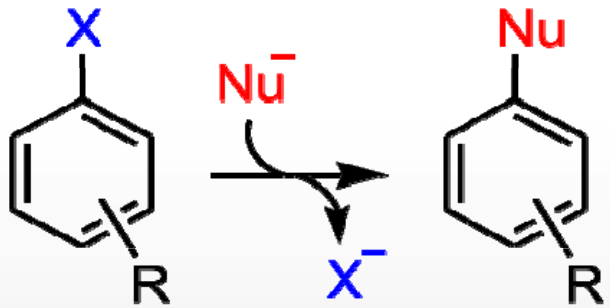
Aliphatic electrophilic substitution can be distinguish unimolecular and bimolecular (SE2). The bimolecular mechanisms are analogous to the SN2 mechanism in that the new bond forms as the old one breaks.

### Halogenation of Aldehydes and Ketones:



## IV. Aromatic Nucleophilic Substitution




X = halogen etc. Nu = nucleophile

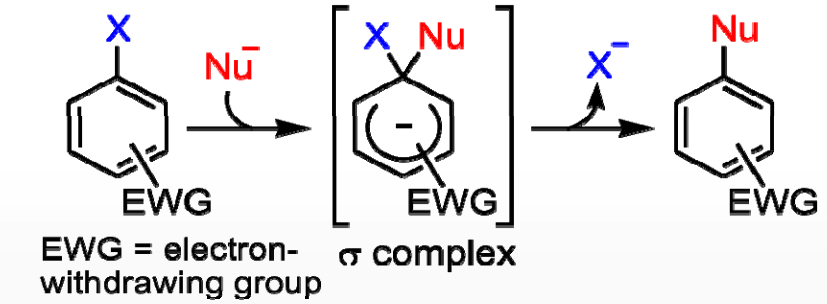
i. Reactions activated by electron-withdrawing groups *ortho* and *para* to the leaving group;

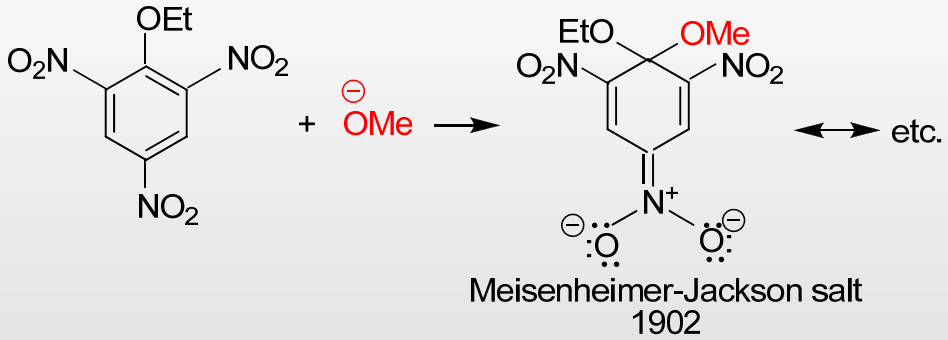
ii. Reactions catalyzed by very strong bases and proceeding through aryne intermediates; 苯炔

iii. Reactions initiated by electron donor;

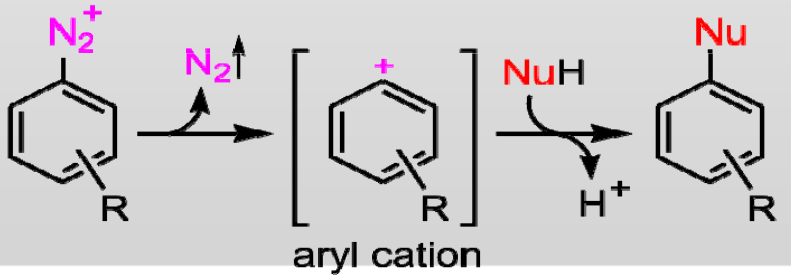
iv. Reactions in which the nitrogen of a diazonium salt is replaced by a nucleophile. 重氮盐

- the $S_NAr$ (addition-elimination) mechanism

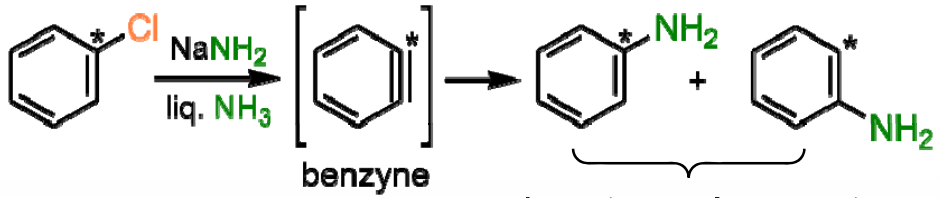



- the aromatic $S_N1$ mechanism



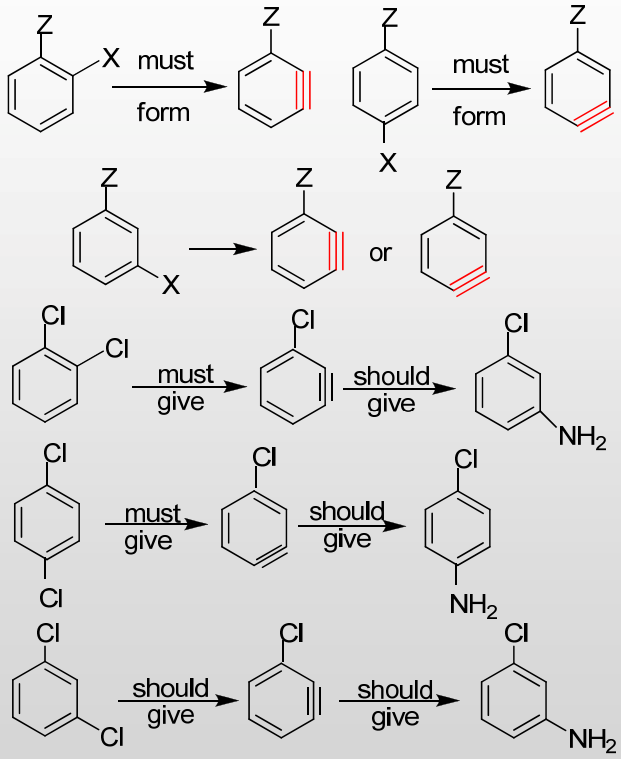
- The Benzyne Mechanism




Two factors affect the positions of the incoming group:

i. The direction in which the aryne forms.

ii. The aryne, once formed, can be attacked by two positions. The favored position for nucleophilic attack is the one that leads to the more stable carbanion intermediate, and this in turn also depends on the field effect of Z.



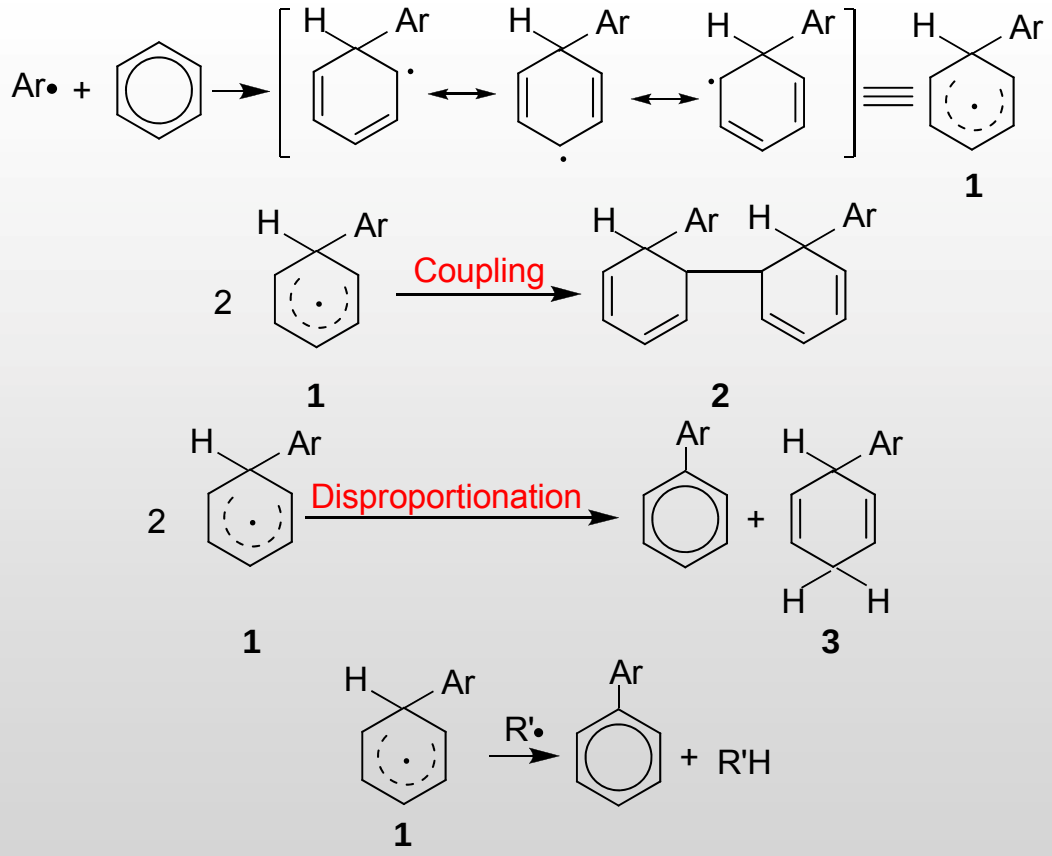
## V. Free-Radical Substitution

### Some general characteristics:

1. Reactions are fairly similar whether they are occurring in the vapor or liquid phase, though solvation of free radicals in solution does cause some differences.
2. They are largely unaffected by the presence of acids or bases or by changes in the polarity of solvents, except that nonpolar solvents may suppress competing ionic reactions.
3. They are initiated or accelerated by typical free-radical sources, such as the peroxides referred to, or by light.
4. Their rates are decreased or the reactions are suppressed entirely by substrates that scavenge free radicals, e.g., nitric oxide, molecular oxygen, or benzoquinone. These substances are called inhibitors.

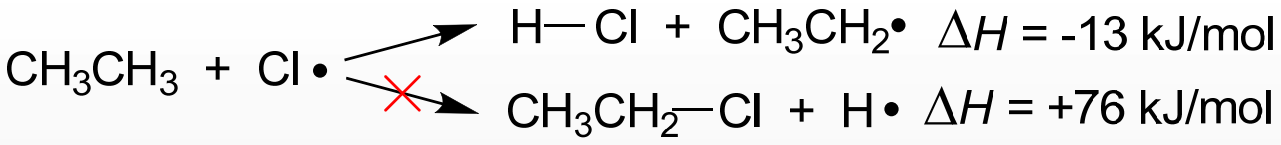
## Mechanisms at an Aromatic Substrate

In the first step, the radical attracts the ring in much the same way as would an electrophile or a nucleophile:



## ➢ Reactivity in Aliphatic Substrates

In a chain reaction, the step that determines what the product will be is most often an abstraction step. What is abstracted by a radical is nearly always univalent, it is hydrogen or halogen for organic compounds.




i. A univalent atom is much more exposed to attack by the incoming radical;
ii. In many cases abstraction of a univalent atom is energetically more favored.

**Table. Relative susceptibility to attack by Cl· of promary, secondary, and tertiary hydrogen in the gas phase**

| Temp./ °C | Primary | Secondary | Tertiary |
|---|---|---|---|
| 100 | 1 | 4.3 | 7.0 |
| 600 | 1 | 2.1 | 2.6 |

Temperature ↑ selectivity ↓

| Table . Relative substitution rates | | | | | | | |
|---|---|---|---|---|---|---|---|
| | $CH_3H$ | $CH_3CH_2$-H | $(CH_3)_2CH$–H | $(CH_3)_3C$–H | $PhCH_2$–H | $Ph_2CH$–H | $Ph_3C$–H |
| Br· | 0.0007 | 1 | 220 | 19400 | 64000 | $1.1\times10^6$ | $6.4\times10^6$ |
| Cl· | 0.004 | 1 | 4.3 | 6.0 | 1.3 | 2.6 | 9.5 |

| Compounds containing electron-withdrawing substituents | | |
|---|---|---|
| | | $CH_3—CH_2—COOH$ |
| $CH_3$· | 1 | 7.8 |
| Cl· | 1 | 0.03 |

Electrophilic radical: halogen atoms
Nucleophilic radical: Me•, t-butyl, benzyl, cyclopropyl

☞ When the substrate molecule contains a double bond, treatment with chlorine or bromine leads to addition rather than substitution.

☞ Vinylic hydrogens are practically never abstracted, allylic hydrogens are greatly preferred to other position of the molecule.

## ➢ Reactivity in Aromatic Substrates

Generalizations:

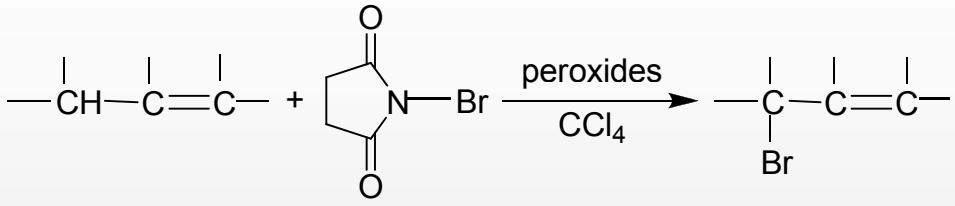
i. All substituents increase reactivity at *ortho* and *para* positions over that of benzene. There is no great difference between electron-donating and electron-withdrawing groups.

ii. Reactivity at *meta* positions is usually similar to that of benzene, perhaps slightly higher or lower. This fact, coupled with the preceding one, means that all substituents are activating and *ortho-para*-directing; none are deactivating or (chiefly) meta-directing.

iii. Reactivity at *ortho* position is usually somewhat greater than at *para* positions, except where a large group decreases *ortho* reactivity for steric reasons.

## Allylic Halogenation

Olefins can be halogenated in the allylic position by a number of reagents, of which N-bromosuccinimide (NBS) is by far the most common.




NBS (Wohl-Ziegler bromination)

## The Heck Reaction: Arylation and alkylation of olefins by organopalladium compounds.

$$R_2C{=}CH_2 + \text{“ArPdX”} \rightarrow R_2C{=}CH\text{-}Ar$$

“ArPdX” reagent can be generated in situ by treatment of an aryl bromide with a palladium-triarylphosphine complex.

The substrate can be simple olefin, or it can contain a variety of functional groups, such as ester, ether, carboxyl, phenolic, or cyano groups.

## 6.2 Addition to Multiple Bonds

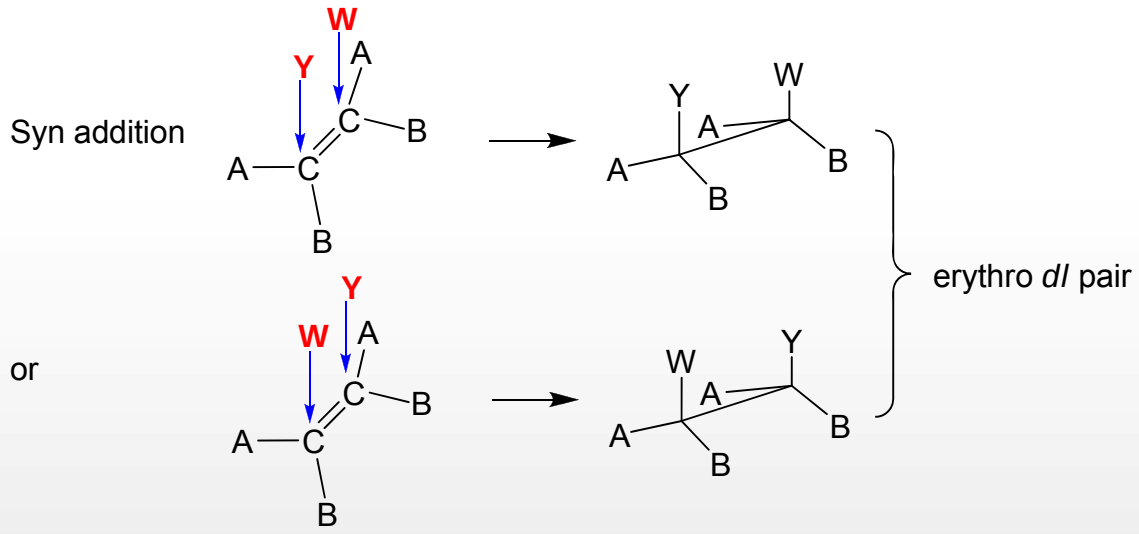
There are basically four ways in which addition to a double or triple bond can take place.

- A two-step process, with initial attack by a nucleophile, an electrophile, or a radical, and then second step consists of combination of the resulting intermediate with, respectively, a positive species, a negative species, or a neutral entity.
- A one-step mechanism, attack at the two carbon atoms of the double or triple bond is simultaneous.

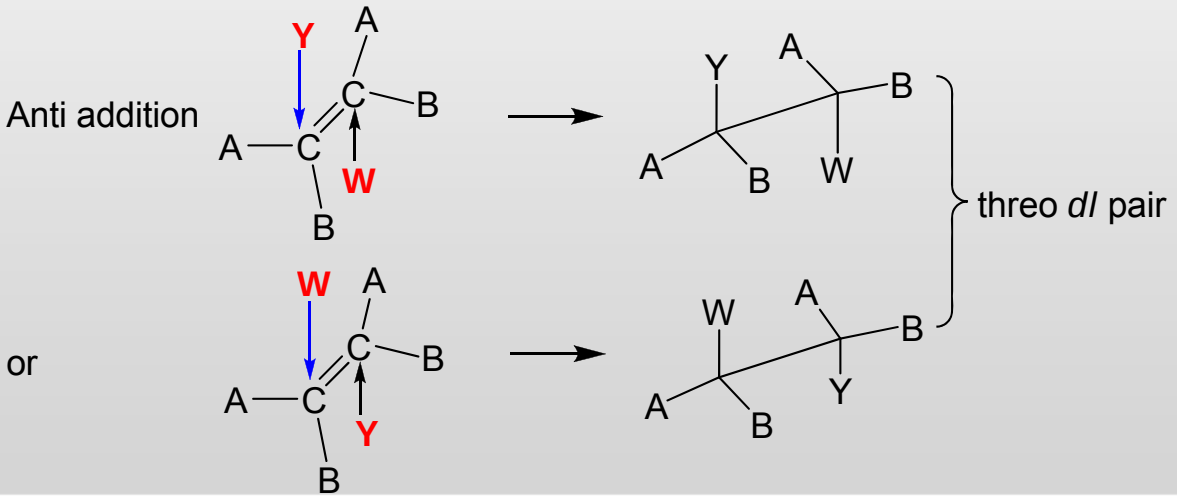
*Which of the four mechanisms is operating in any given case is determined by the nature of the substrate, the reagent, and the reaction conditions.*

# I. Stereochemistry

- Syn addition→ the erythro *dl* pair

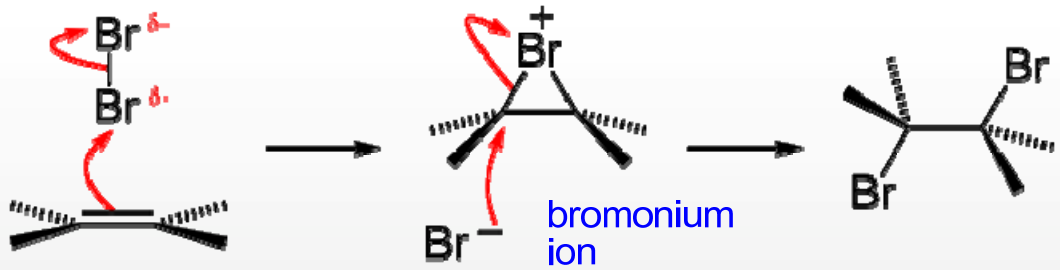



- Anti addition → the threo *dl* pair

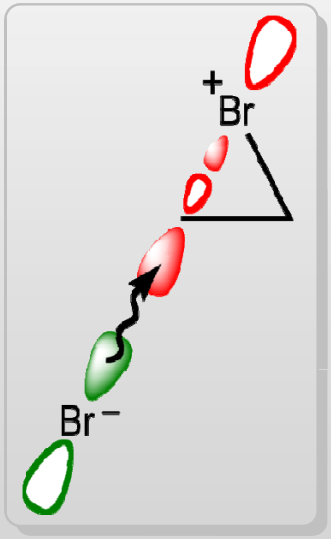


## II. Electrophilic Addition

There is much evidence that when the attack is by $Br^+$ (or a carrier of it), the bromonium ion is often an intermediate and the addition is anti.



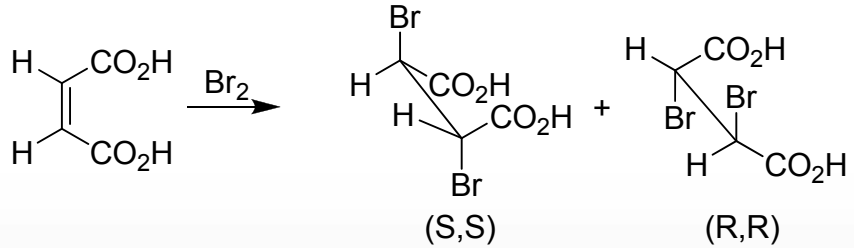

The atom is electrophilic at this time and attacks the negatively charged, high energy π-bond portion of the alkene's C=C bond. It forms for an instant a single σ-bond to *both* of the carbon atoms involved.

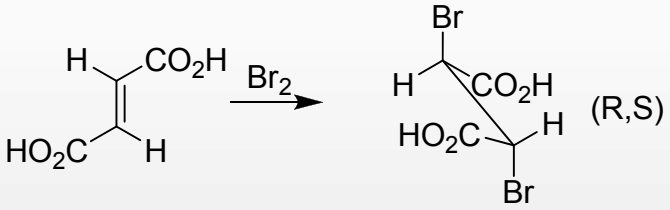


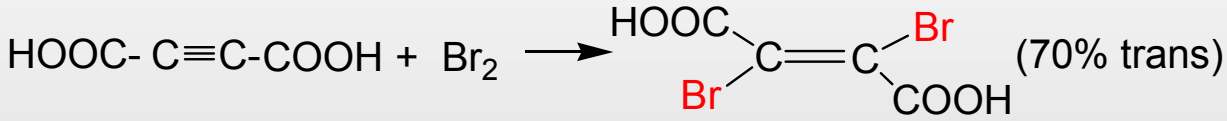

A bromide ion attacks the C–Br σ* antibonding molecular orbital of a bromonium ion.

The two halogens add in an anti addition fashion, and when the alkene is part of a cycle the dibromide adopts the trans configuration.

- Brominations of maleic acid and fumaric acid: stereospecific *trans*-addition:

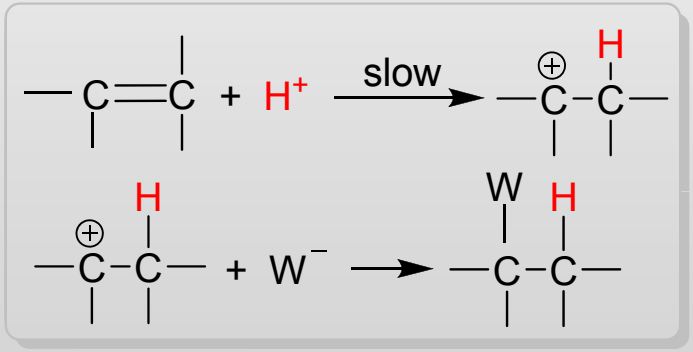



➢ When the electrophile is a proton:

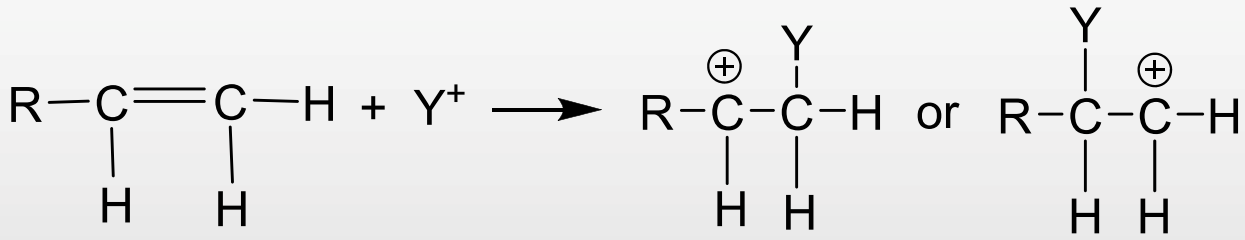
i. The reaction is general-acid, implying rate-determining proton transfer from the acid to the double bond.
ii. The existence of alkyl substituent effects.
iii. Open carbocations are prone to rearrange.



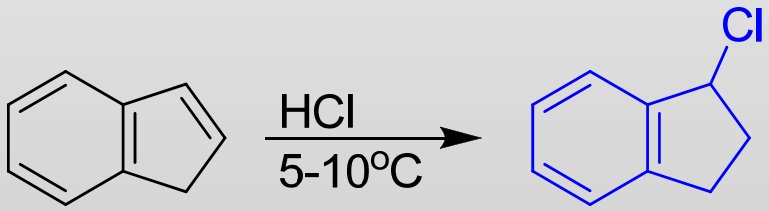
- The Reactivity Toward Electrophilic Addition:

$CCl_3CH=CH_2 < CHCl_2CH=CH_2 < CH_2ClCH=CH_2 < CH_3CH=CH_2$

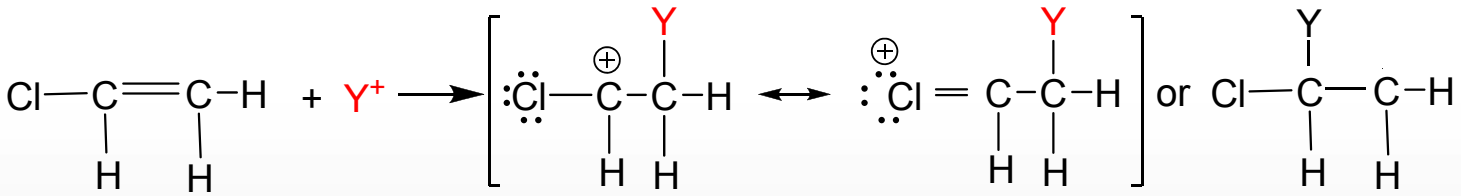
- Orientation — Markovnikov's rule: For electrophilic attack, the positive portion of the reagent goes to the side of the double or triple bond that has more hydrogens.

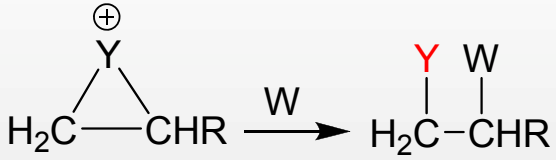



Hydrochlorination of indene with hydrochloric acid gas:

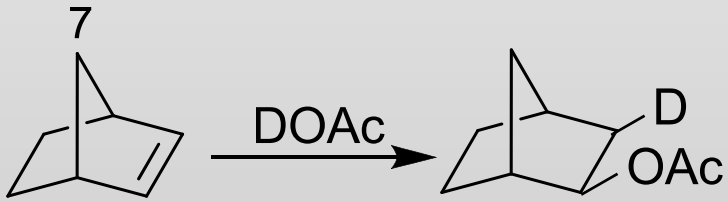


☞ Markovnikov's rule also applies for halogen substituents or the case where bromonium ions or other three-membered rings are intermediates.



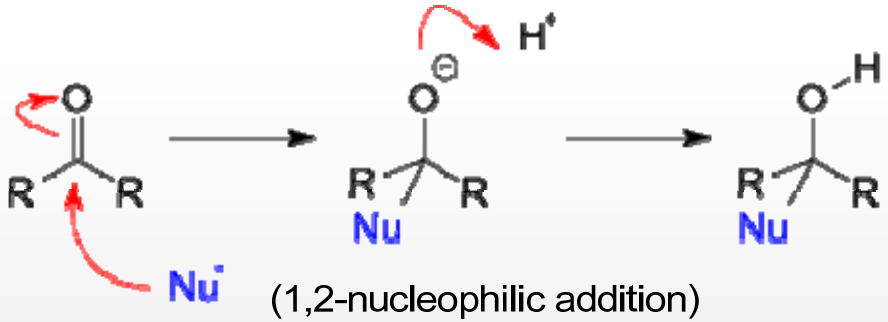




- Stereochemical Orientation Many electrophilic additions to norbornene and similar strained bicycloalkenes are syn addition, in these cases attack is always from the exo side. unless the exo side is blocked by substituents in the 7 position, in which case endo attack may predominate.



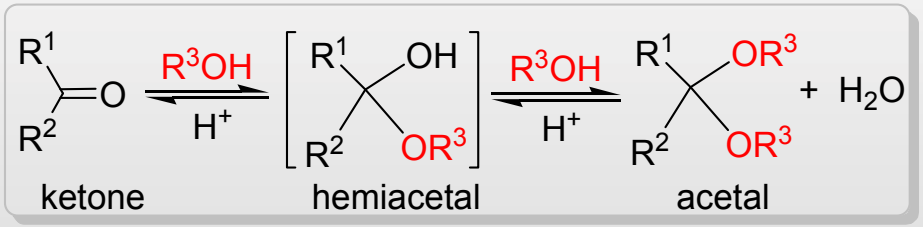
# III. Nucleophilic Addition

## A. Addition to Carbon-Hetero Multiple bonds

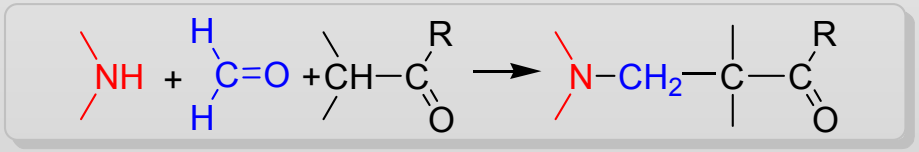



(1,2-nucleophilic addition)

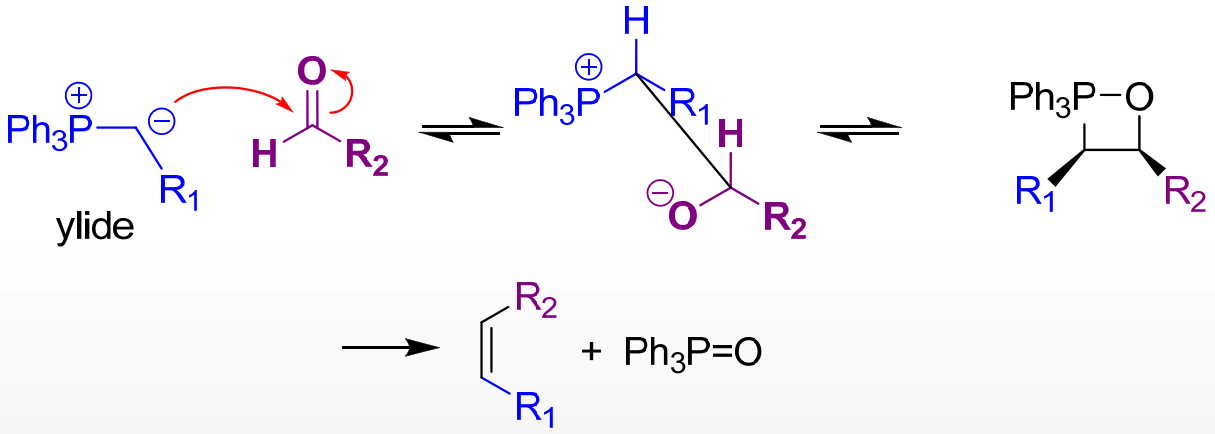
➢ With a carbonyl compound electrophiles, the Nu can be:



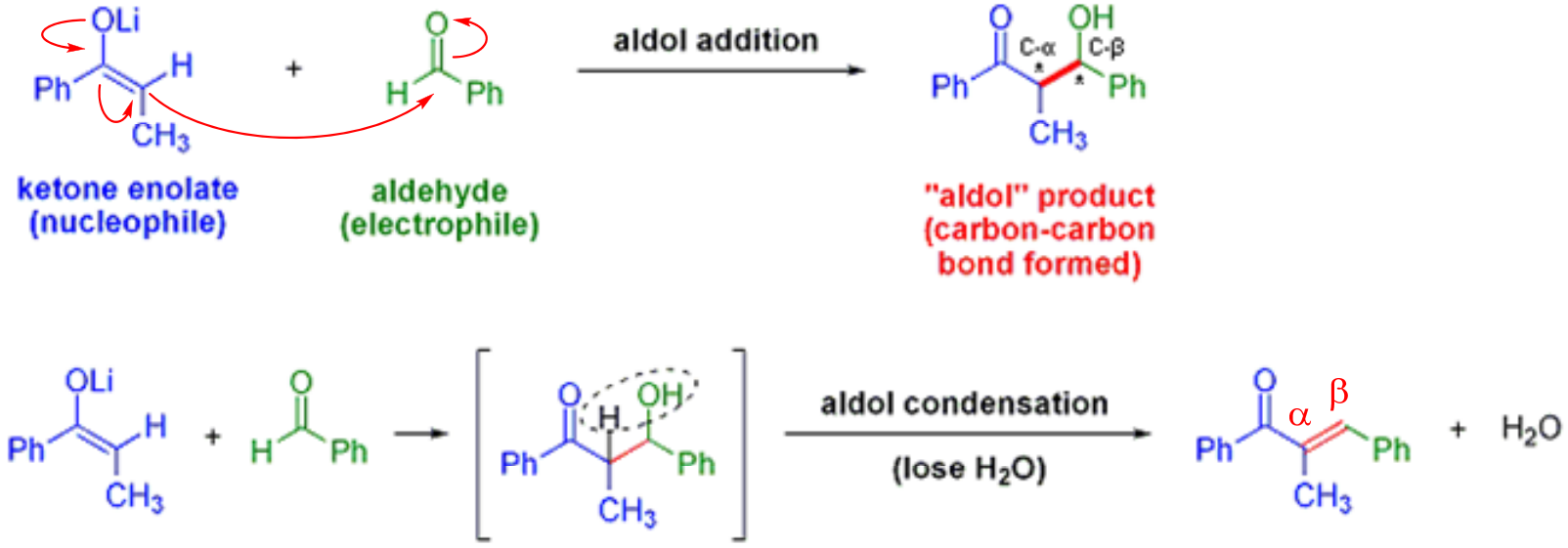

- an alcohol in acetalisation
- an amine in Mannich reaction
- ylides in Wittig reaction
- an enolate ion an aldol reaction
- an hydride in reduction
- an organometallic nucleophile (RMgX) in the Grignard reaction



# Wittig reaction

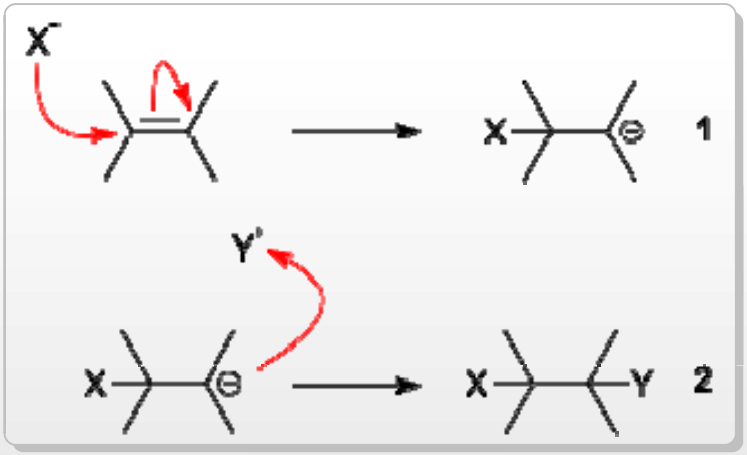


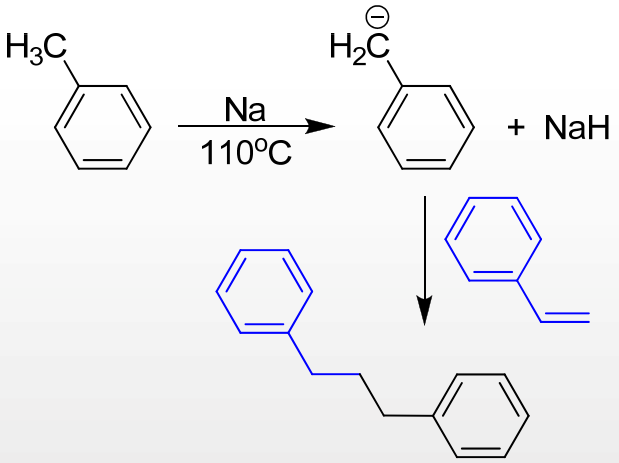

*a typical aldol reaction*



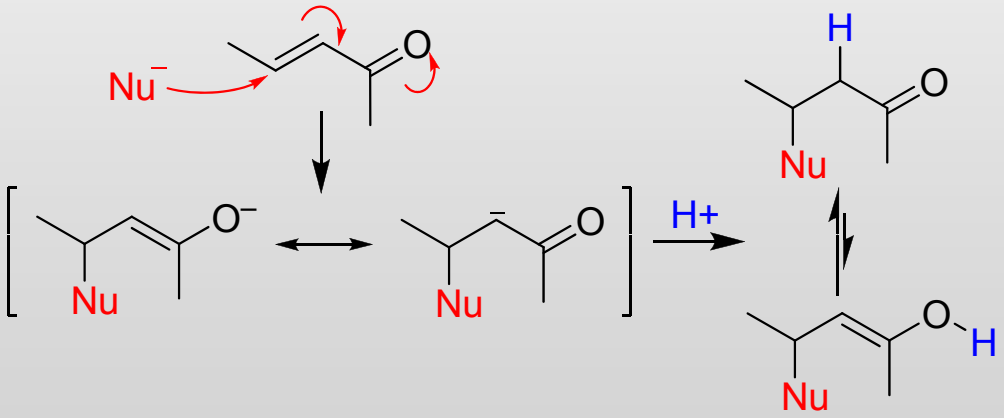
## B. Addition to Carbon-Carbon Double Bonds

Ordinary alkenes are not susceptible to a nucleophilic attack (apolar bond).

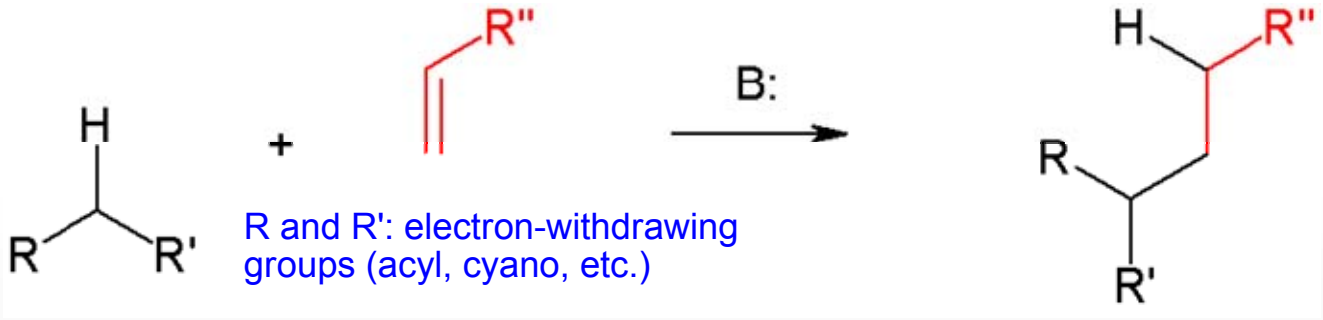


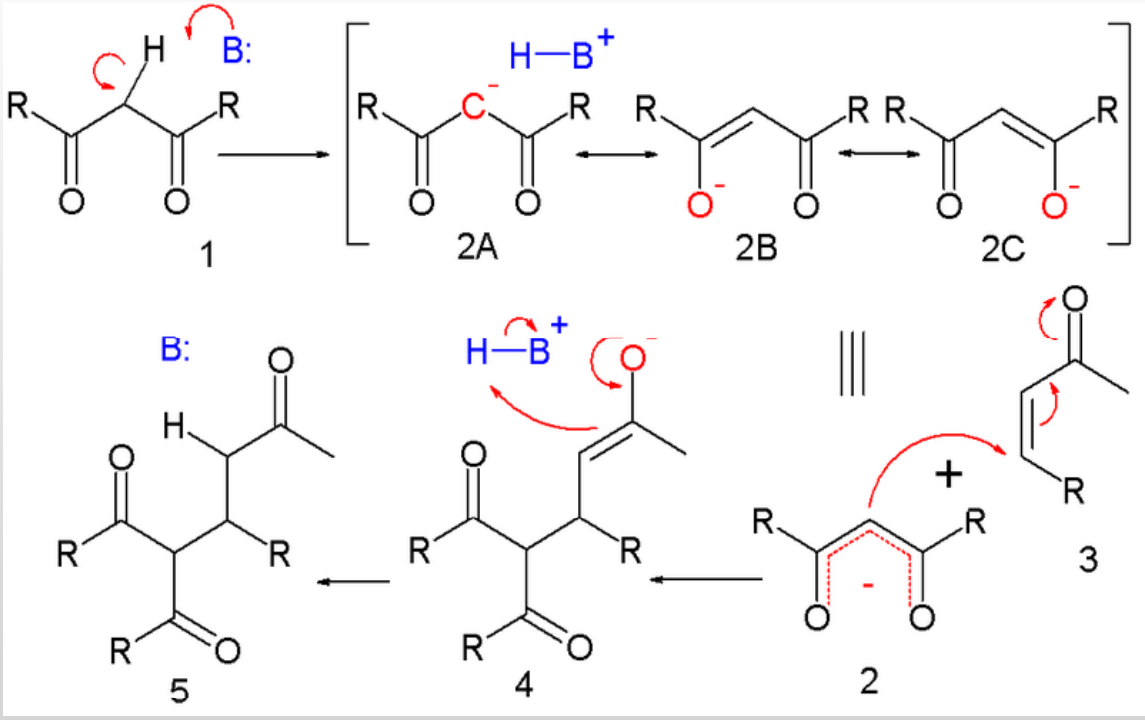

- Nucleophilic conjugate addition:



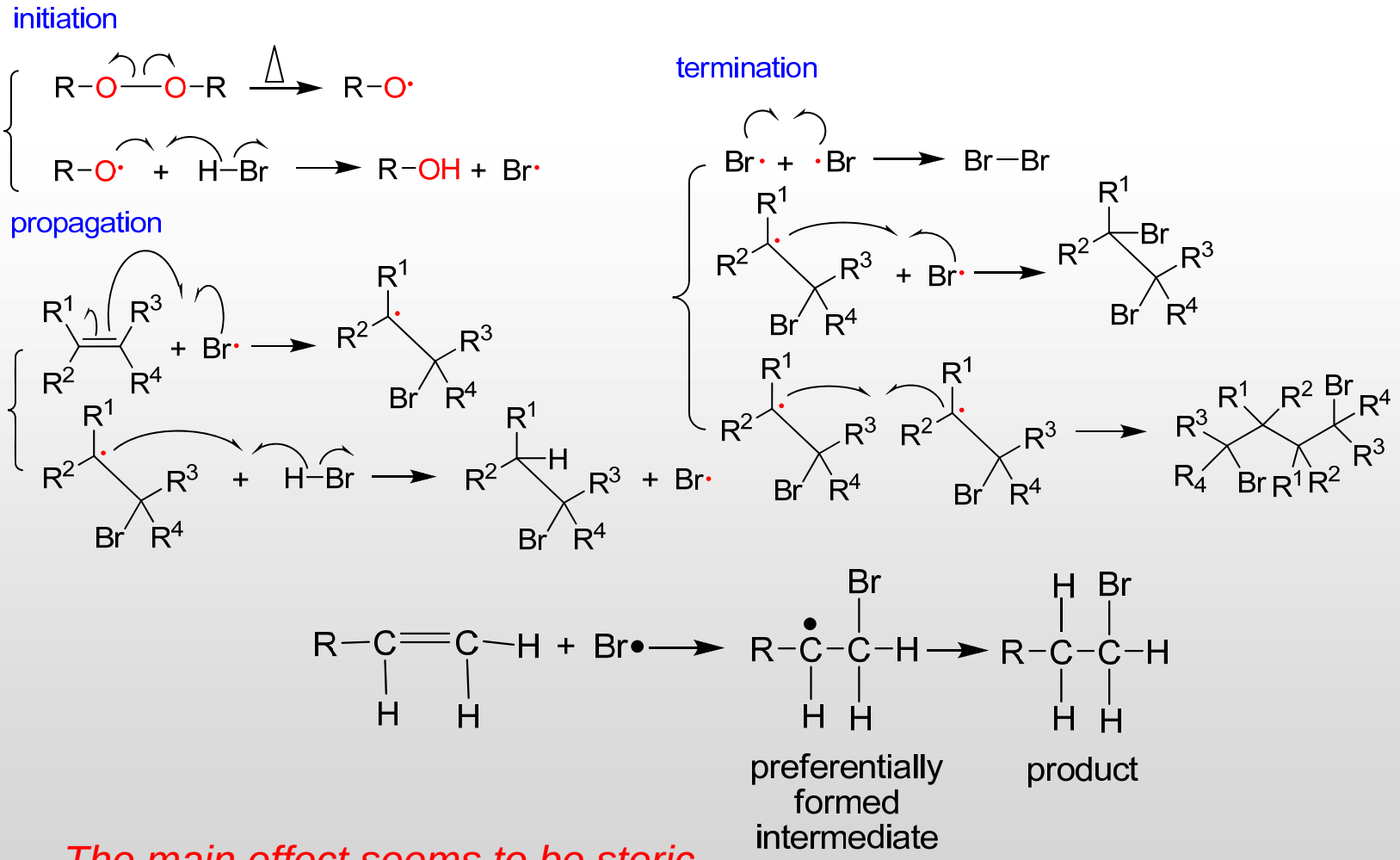
- Michael reaction




R and R': electron-withdrawing groups (acyl, cyano, etc.)

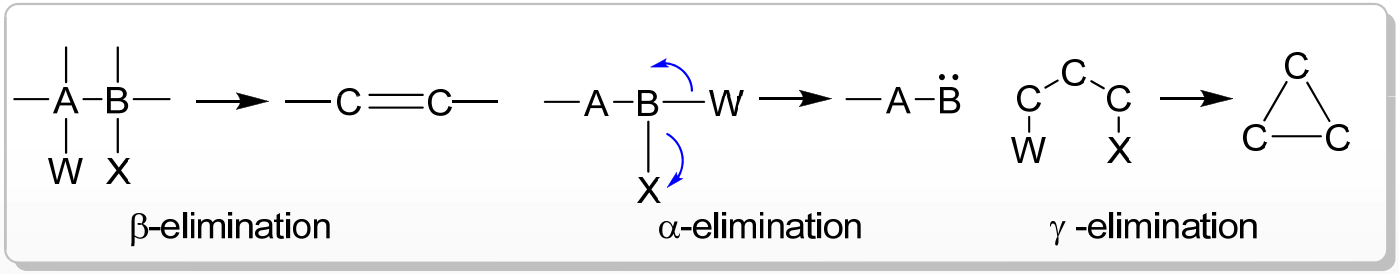


# IV. Free-radical Addition

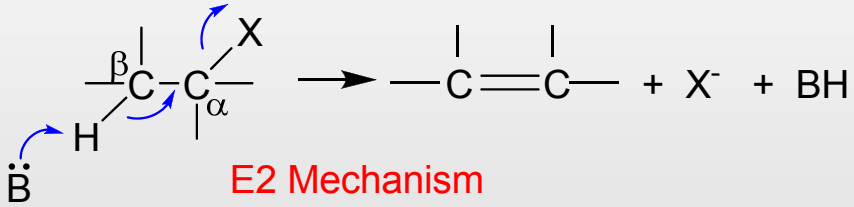


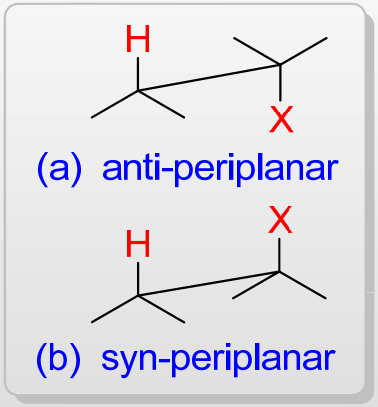

*The main effect seems to be steric.*

# 6.3 Elimination Reactions



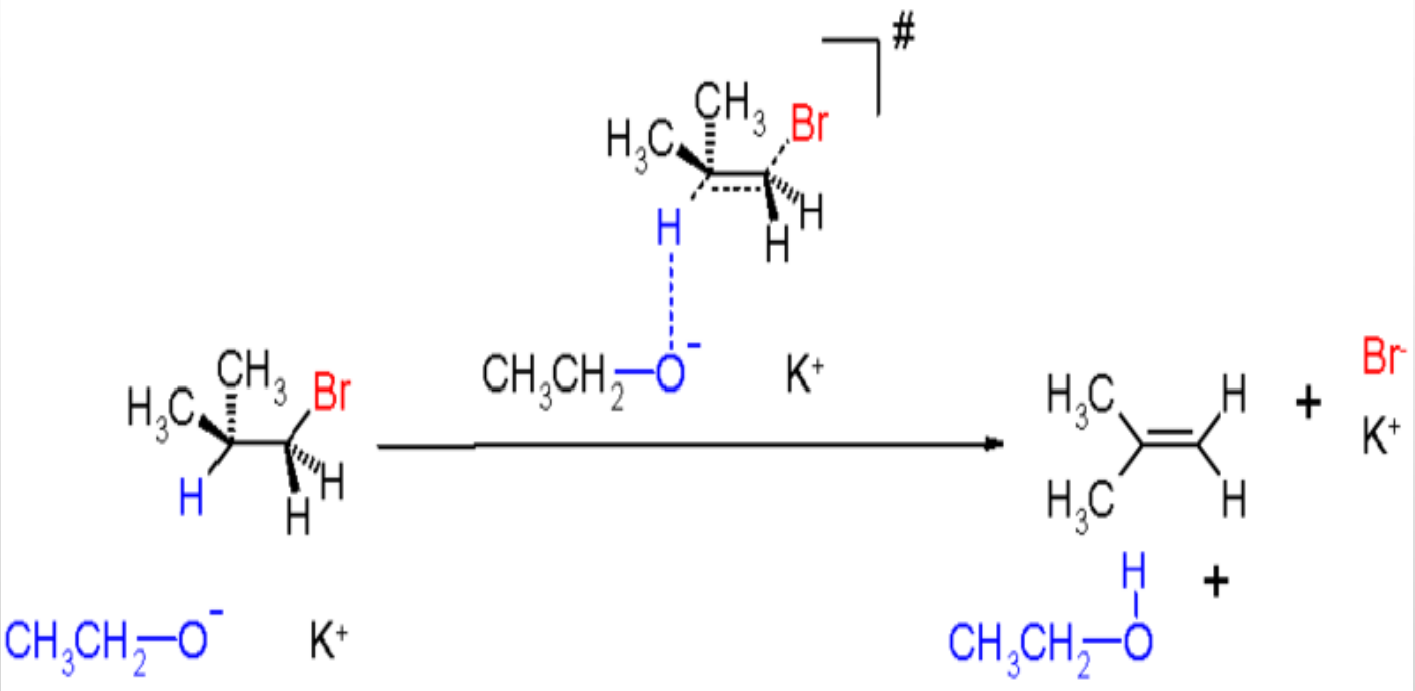

## I. E2 and E1 Mechanism

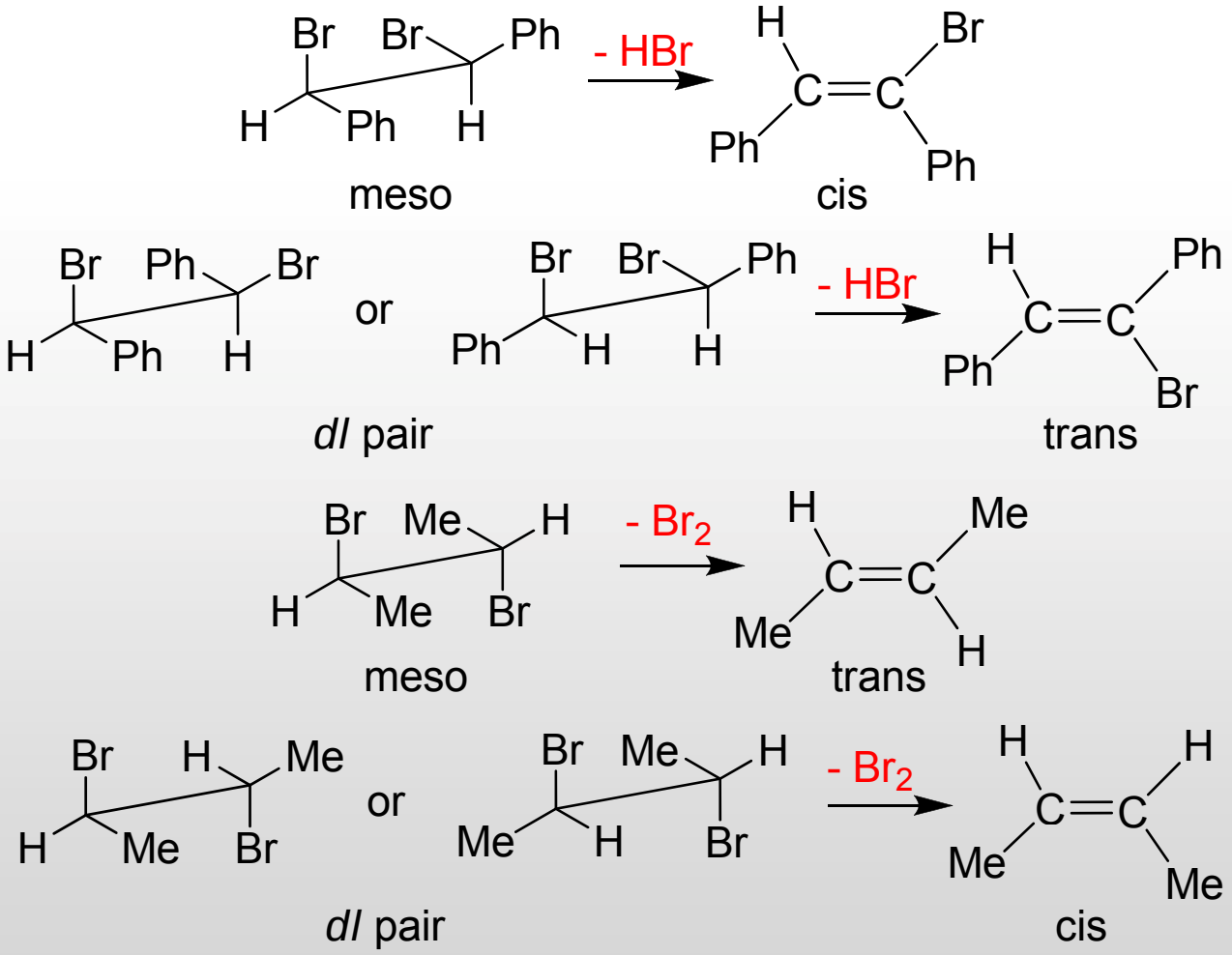


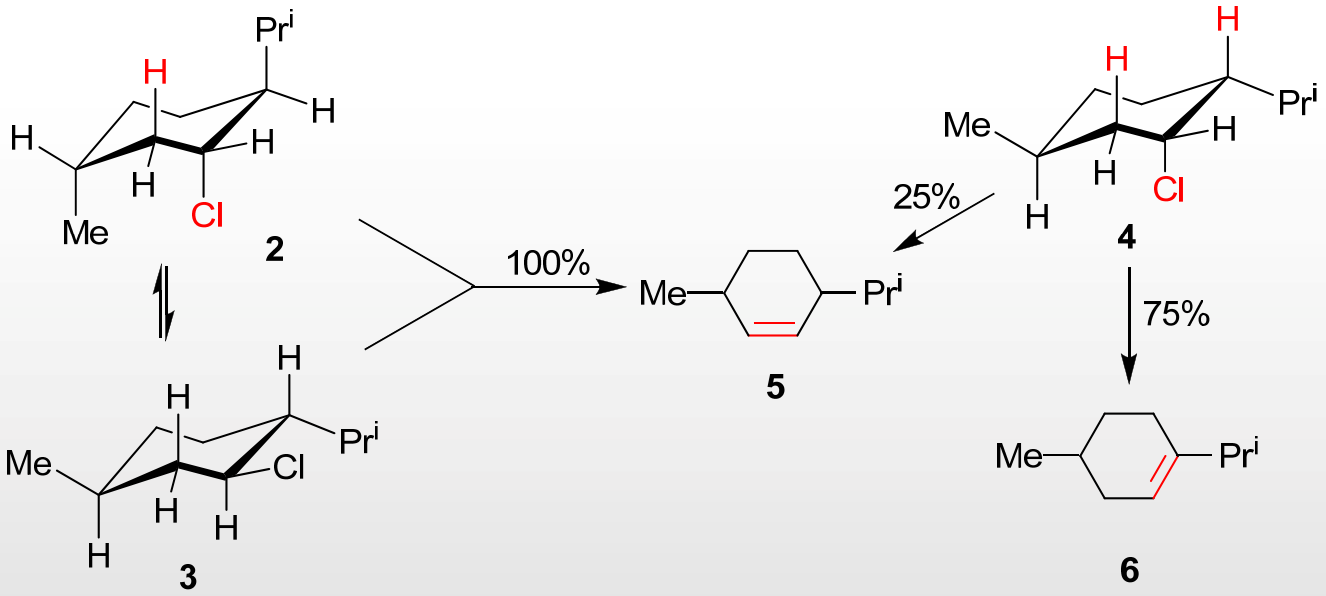

i. The proper second-order kinetics;
ii. An isotope effect: $k_D/k_H$ = 3~8;
iii. Stereochemistry — the E2 mechanism is stereospecific: the five atoms involved (including the base) in the transition state must be in one plane.

➢ *Anti* elimination is usually greatly favored over *syn* elimination, probably because **a** is a staggered conformation and the molecule requires less energy to reach this transition state than it does to reach the eclipsed transition state **b**.





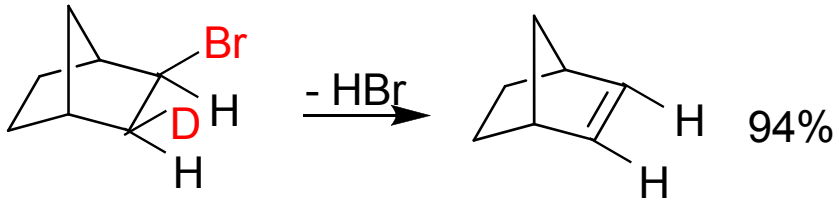
For a six-membered ring, anti-periplanarity of the leaving groups requires that they be diaxial even if this is the conformation of higher energy.

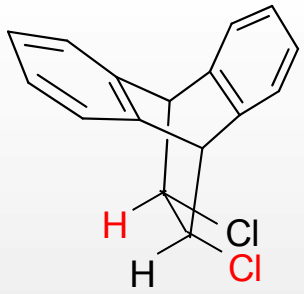



| | Relative rate | Product |
|---|---|---|
| cis-HOOCCH=CClCOOH | 1 | HOOC-C≡C-COOH |
| trans-HOOCCH=CClCOOH | 50 | |

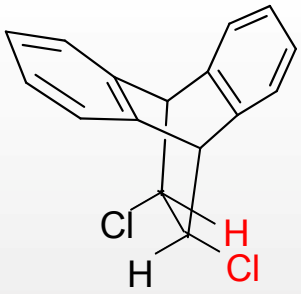
## ➢ syn-Elimination

The deuterated norbornyl bromide




cis-isomer



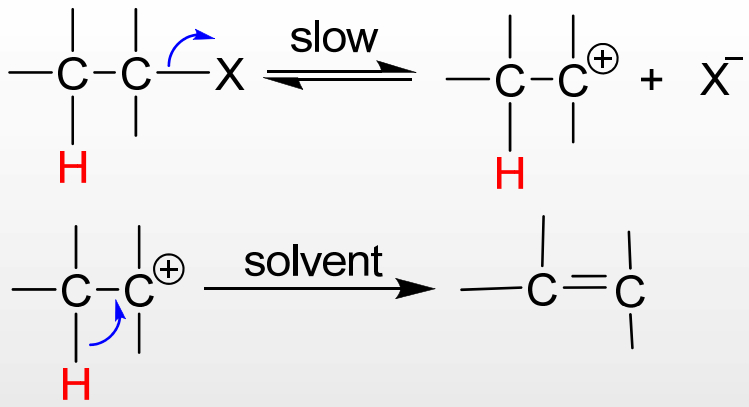

trans-isomer

cis-isomer: HCl elimination is much slower than from corresponding nonbridged compounds.
trans-isomer: Syn elimination can take place (dihedral angle about 0°); reached about eight times faster than cis-isomer.

a) Anti elimination requires a dihedral angle of 180°. When this angle cannot be achieved, anti elimination is greatly slowed or prevented entirely.
b) Anti elimination is generally favored in the E2 mechanism, but that steric (inability to form the anti-periplanar transition state), conformational, ion-pairing, and other factors cause syn elimination to intervene (and even predominate) in some cases.

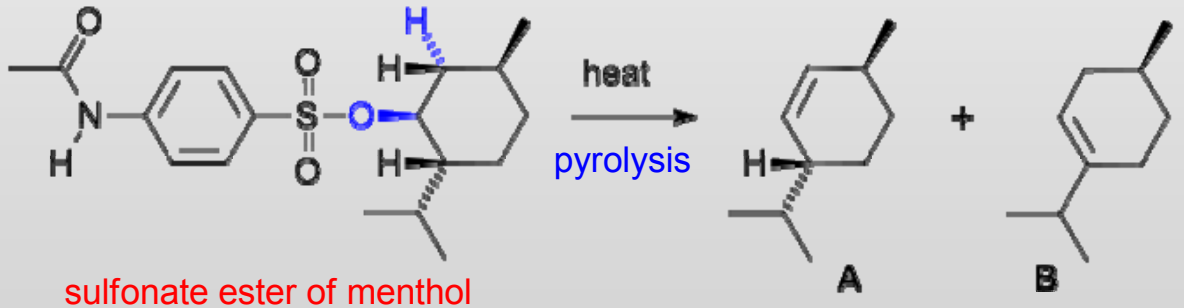
## The E1 Mechanism

The E1 mechanism is a two-step process, ionization of the substrate to give a carbocation that rapidly loses a β proton to a base, usually the solvent:



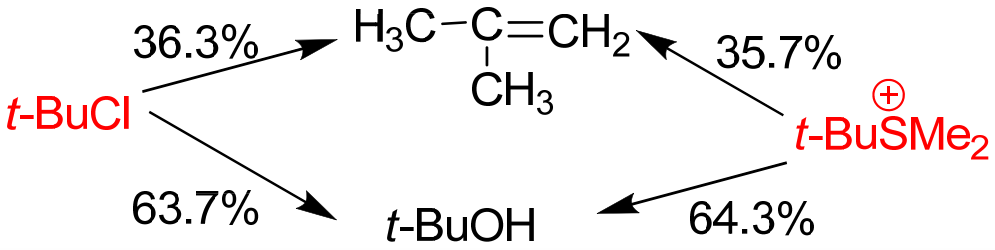

i. Tertiary and some secondary substituted alkyl halides.
ii. First order kinetics
iii. Reaction mostly occurs in complete absence of base or presence of only a weak base
iv. E1 are in competition with $S_N1$
v. No deuterium isotope effect
vi. No antiperiplanar requirement:

Example 1:




sulfonate ester of menthol

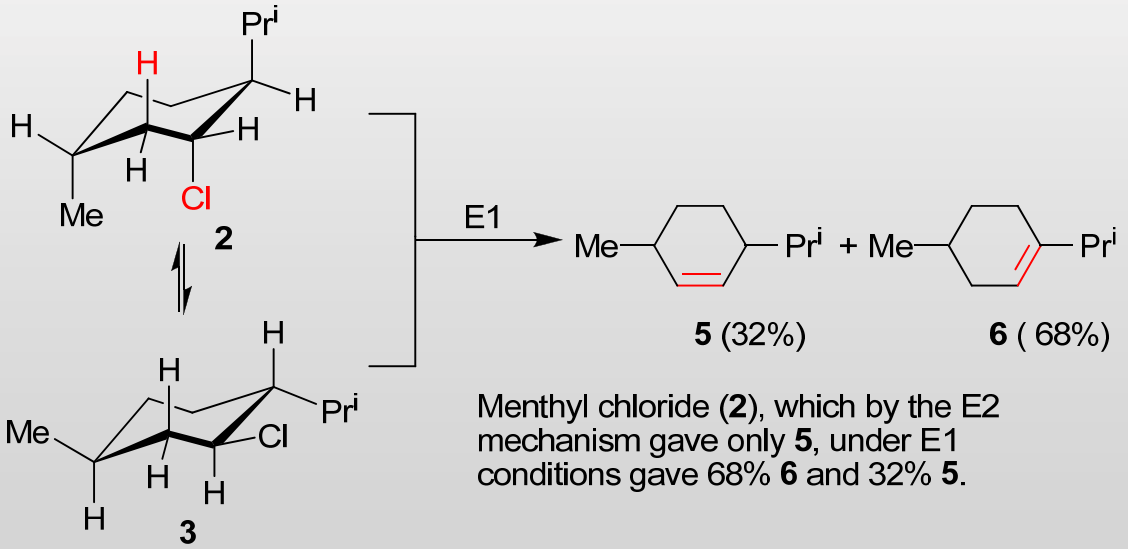
Example 2.




Solvolysis at 65.3°C in 80% aqueous ethanol.

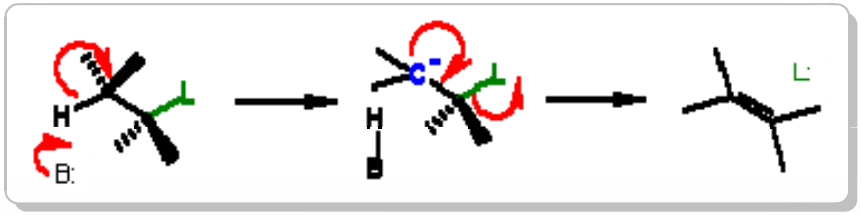
If this reaction had taken place by a second-order mechanism, the nucleophile would not be excepted to have the same ratio of preference for attack at the β hydrogen compared to attack at a *neutral* chloride as for attack at the β hydrogen compared to attack at a *positive* $SMe_2$ group.

Example 3.



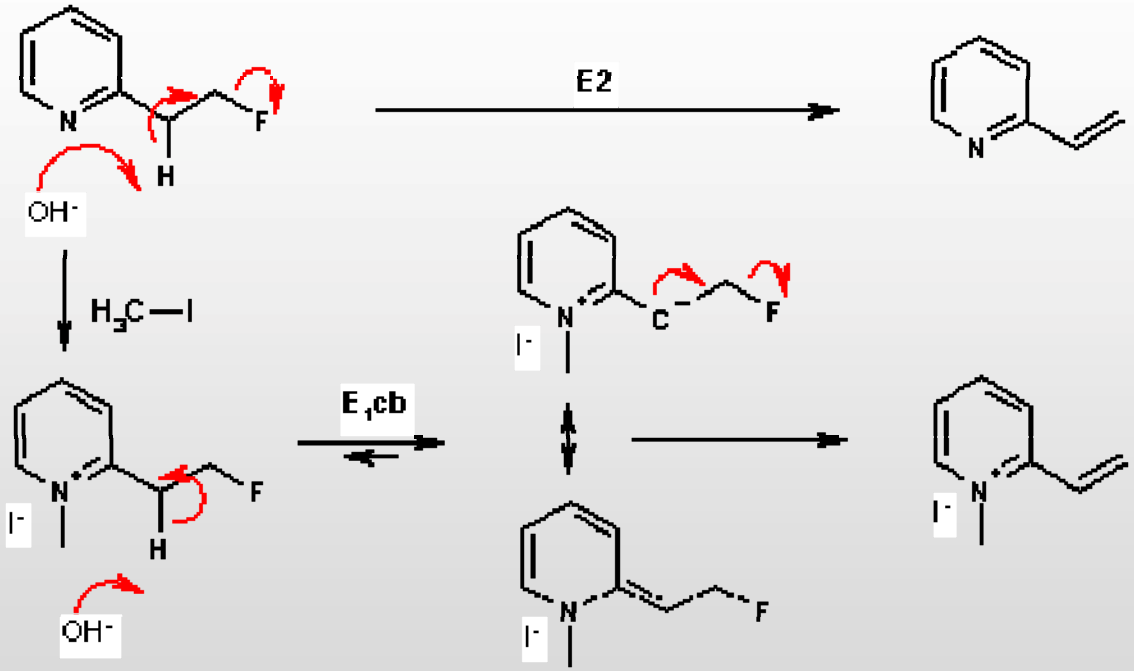

Menthyl chloride (**2**), which by the E2 mechanism gave only **5**, under E1 conditions gave 68% **6** and 32% **5**.

# II. E1cB Mechanism (Carbanion Mechanism)




$LCH_2CH_2OPh$

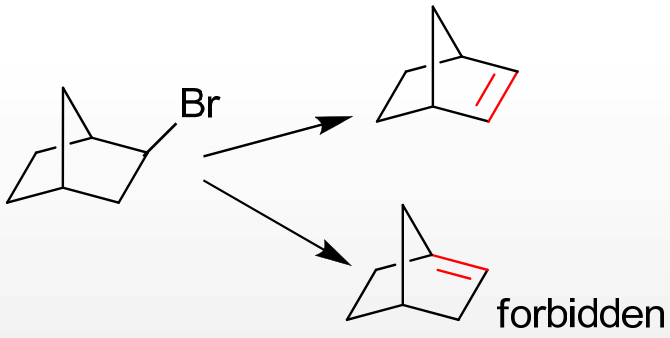
L = $NO_2$, $SMe_2^+$, $ArSO_2$, CN, COOR



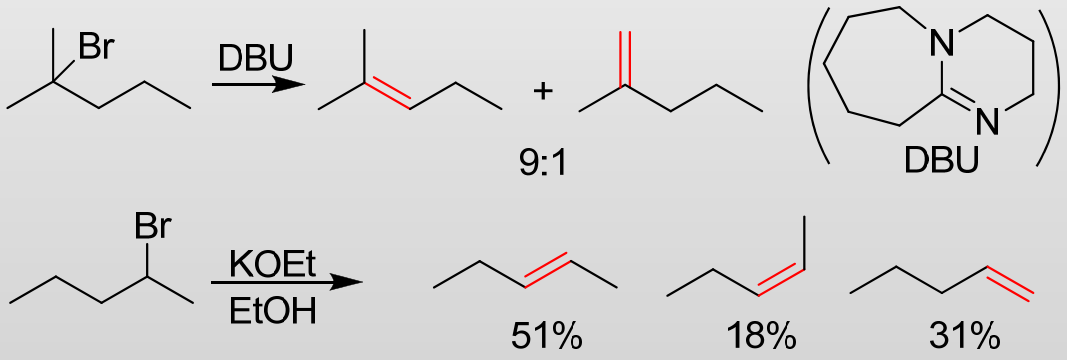

The E1cB reaction mechanism. Dehydration of 1-methyl-2-(2-fluoroethyl)pyridinium iodide).

## III. Orientation of the Double Bond

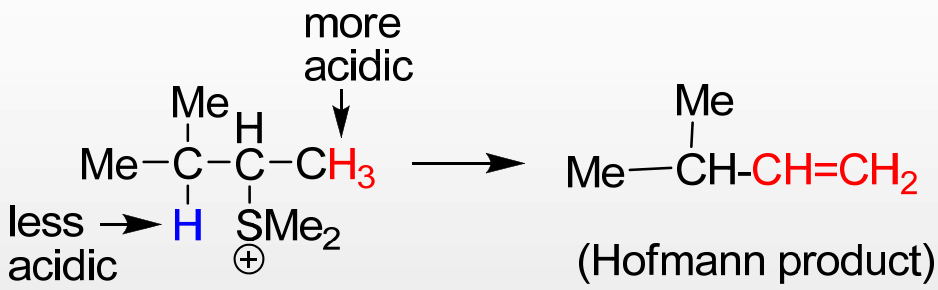
a. No matter what the mechanism, a double bond does not go to a bridgehead carbon unless the ring sizes are large enough (Bredt's rule).




b. Zaitsev's rule: the double bond goes mainly toward the most highly substituted carbon.



c. Elimination from compounds with charged nucleofuges, e.g., $NR_3^+$, $SR_2^+$ (those that come off as neutral mlecules), follow Hofmann's rule if the substrate is acyclic: *the double bond goes mainly toward the least highly substituted carbon*, but Zaitsev's rule if the leaving group is attached to a six-membered ring.




d. No matter what the mechanism, if there is a double bond (C=C or C=O) or an aromatic ring already in the molecule that can be in conjugation with the new double bond, the conjugated product usually predominates, sometimes even when the stereochemistry is unfavorable.

## IV. Reactivity

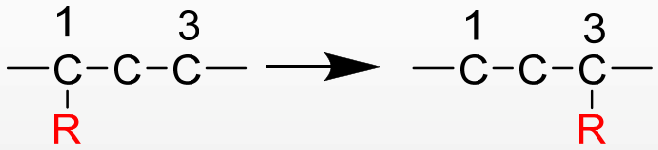
- Factors influencing the elimination reactivity:
  - Substrate structure
  - The attacking base
  - The leaving group
  - The medium
- Elimination Reaction *vs* Nucleophilic Substitution:

Substitution generally predominates and elimination occurs only during precise circumstances. Generally, elimination is favored over substitution when

- steric hindrance increases
- basicity increases
- temperature increases
- the steric bulk of the base increases ($KOBu^t$)
- the nucleophile is poor.

## 6.4 Rearrangement Reaction

In a rearrangement reaction a group moves from one atom to another in the same molecule. Most are migrations from an atom to an adjacent one (called 1,2 shift), but some are over longer distances.




➢ A rearrangement is not well represented by simple and discrete electron transfers. The actual mechanism of alkyl groups moving probably involves transfer of the moving alkyl group fluidly along a bond, not ionic bond-breaking and forming.

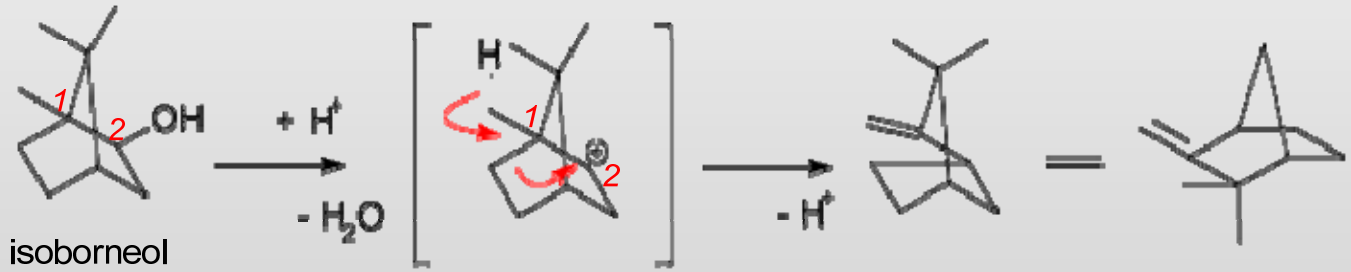
➢ Some key rearrangement reactions:

- 1,2-rearrangements
- pericyclic reactions
- olefin metathesis

- **Wagner-Meerwein rearrangement**

A Wagner-Meerwein rearrangement is a class of carbocation 1,2-rearrangement reactions in which a hydrogen, alkyl or aryl group migrates from one carbon to a neighboring carbon.

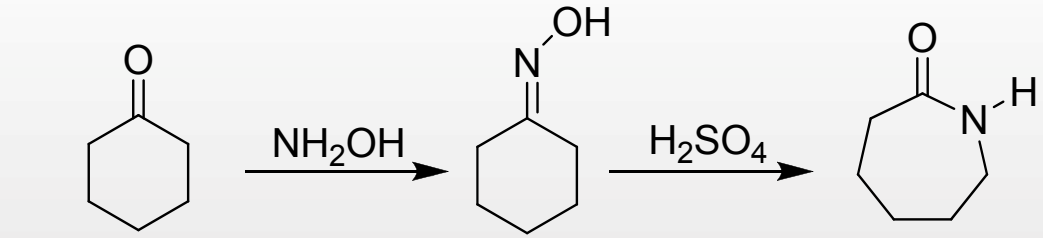
The rearrangement was first discovered in bicyclic terpenes:



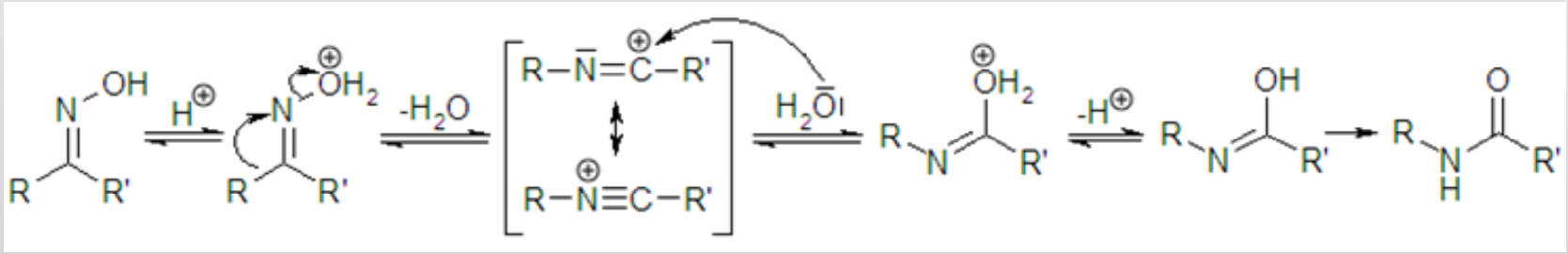
- **Beckmann rearrangement**

This is an acid-catalyzed rearrangement of an oxime to an amide. Cyclic oximes yield lactams.

The mechanism is generally believed to consist of an alkyl migration with expulsion of the hydroxyl group to form a nitrilium ion followed by hydrolysis:

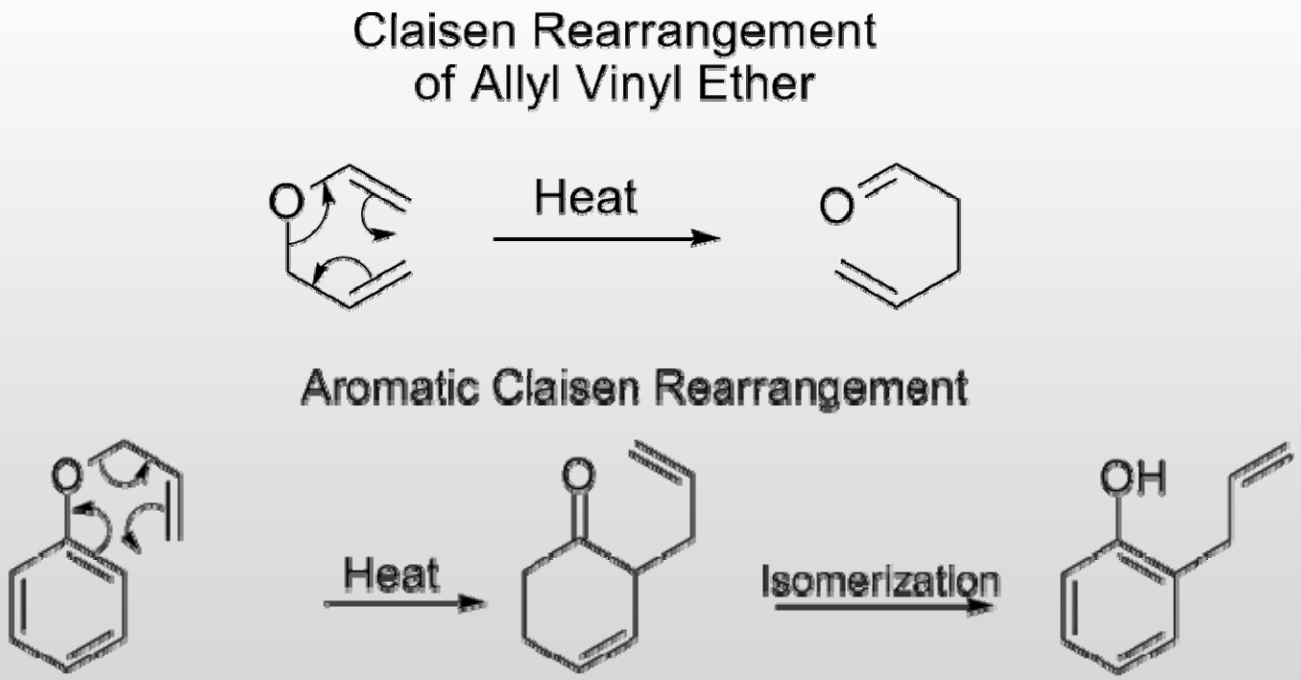



cyclohexanone cyclohexanoxime caprolactam

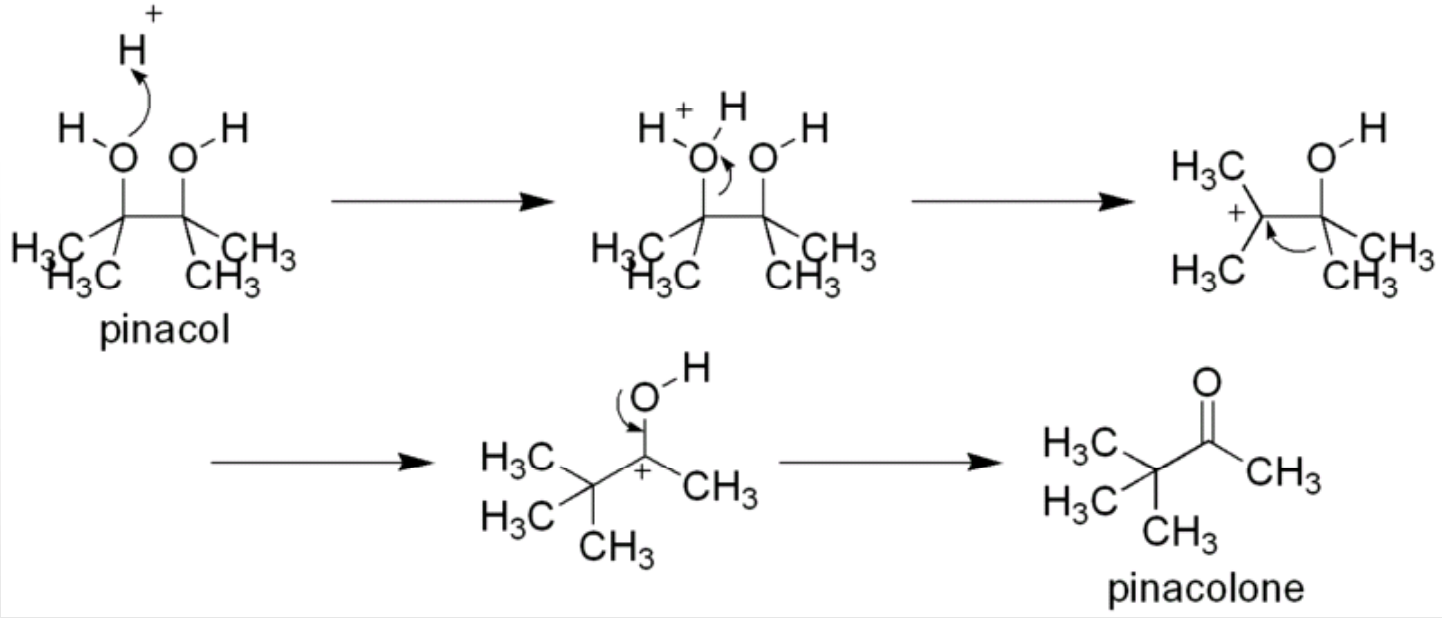


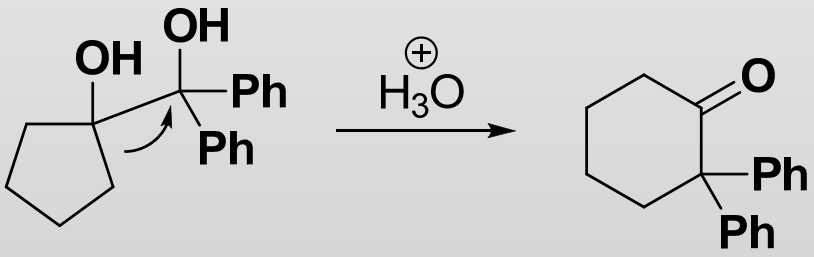
- **Claisen rearrangement**

The Claisen rearrangement is a powerful carbon-carbon bond-forming chemical reaction. The heating of an allyl vinyl ether will initiate a [3,3] rearrangement to give a γ, δ-unsaturated carbonyl.

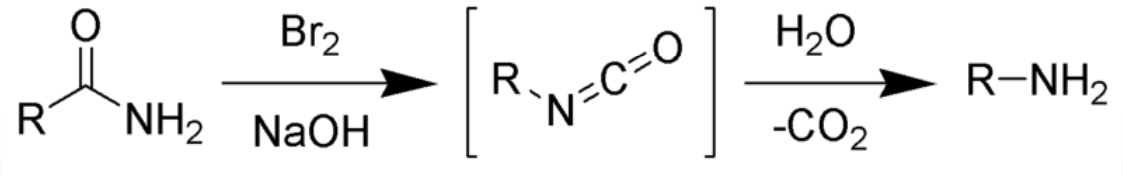


- **Pinacol Rearrangement**

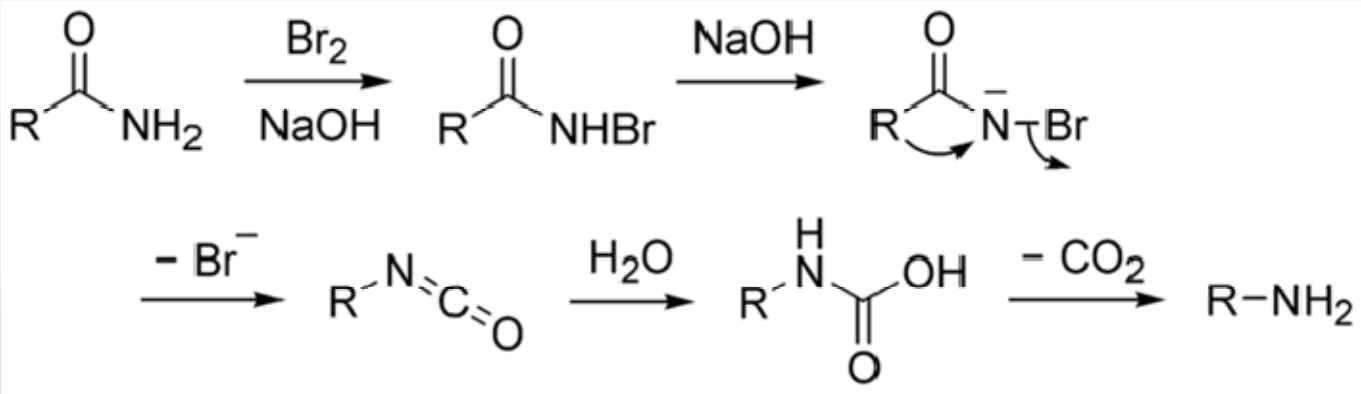


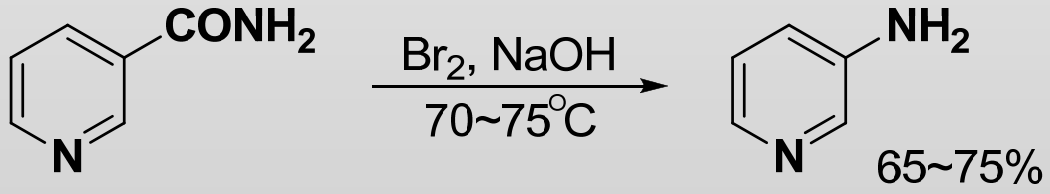



## Hofmann rearrangement




a primary amide isocyanate a primary amine

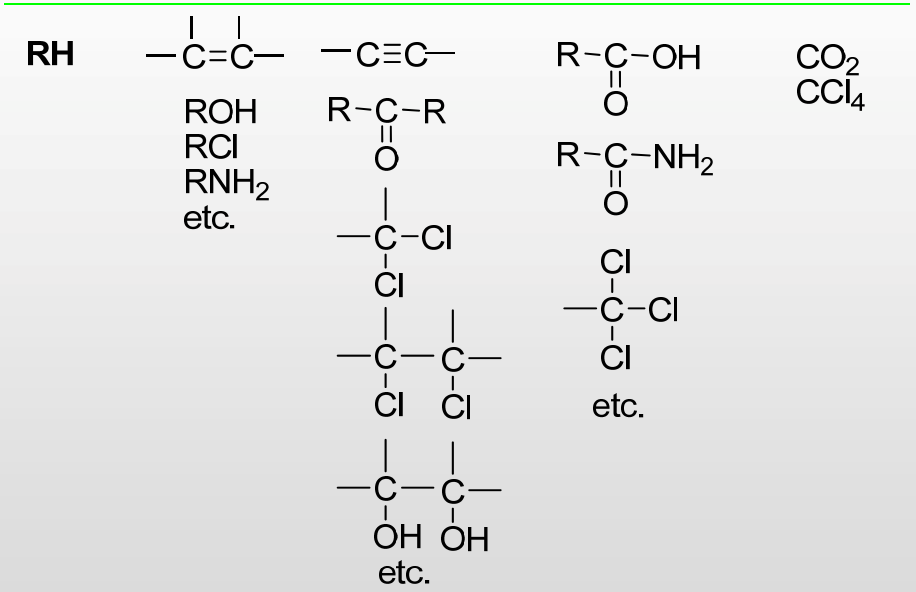


# 6.5 Organic Redox Reaction

In organic chemistry oxidations and reductions are different from ordinary redox reactions because many reactions carry the name but do not actually involve electron transfer in the electrochemical sense of the word.

- Categories or simple functional groups arranged according to oxidation state

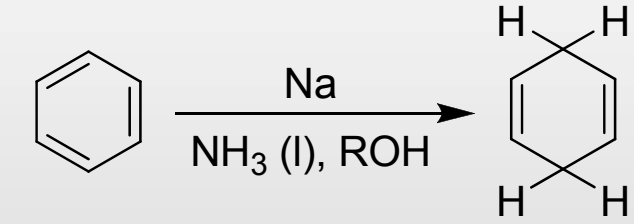


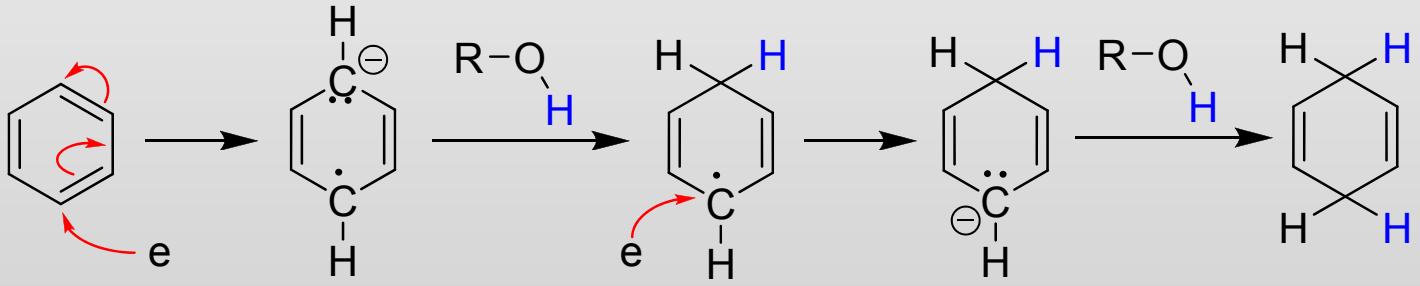
# I. Organic reductions

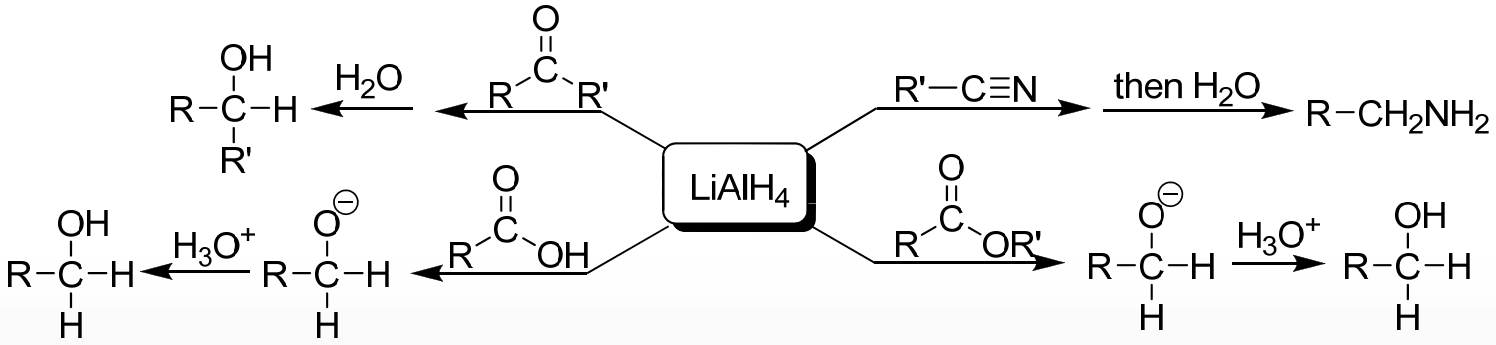
Several reaction mechanisms exist for organic reductions:

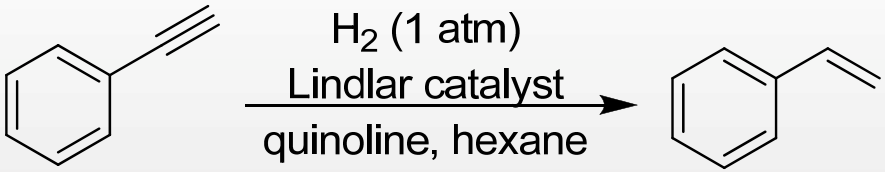
- Direct electron transfer in Birch reduction
- Hydride transfer in reductions, $LiAlH_4$
- Hydrogen reduction with a catalyst such as Lindlar catalyst
- Disproportionation reaction such as the Cannizzaro reaction

Birch reduction:



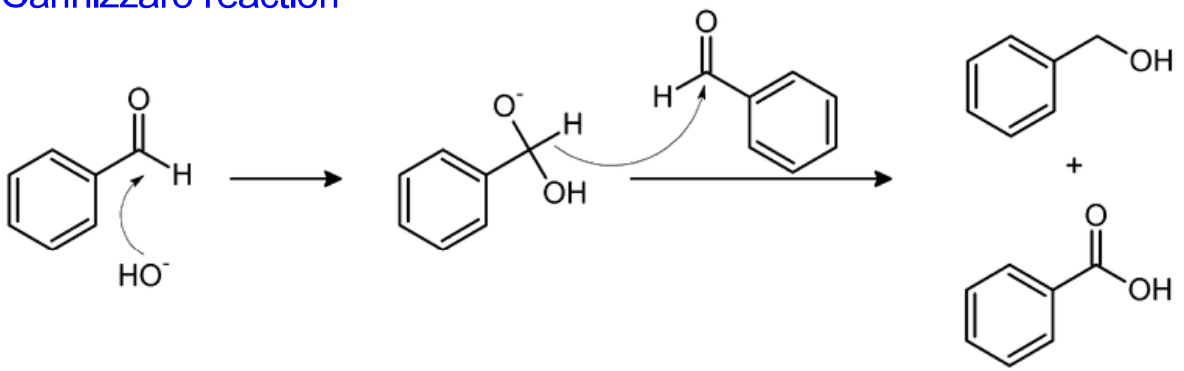






A Lindlar catalyst: consists of palladium deposited on calcium carbonate and treated with various forms of lead.

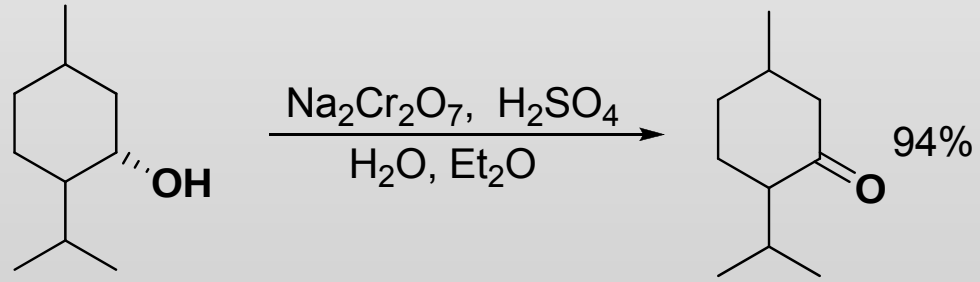
Cannizzaro reaction



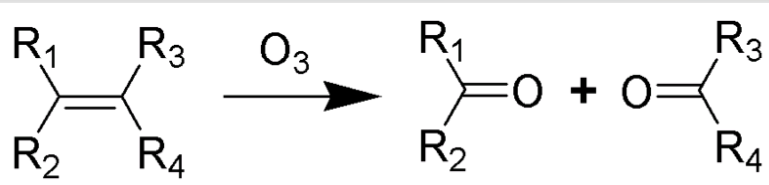
## II. Organic oxidations

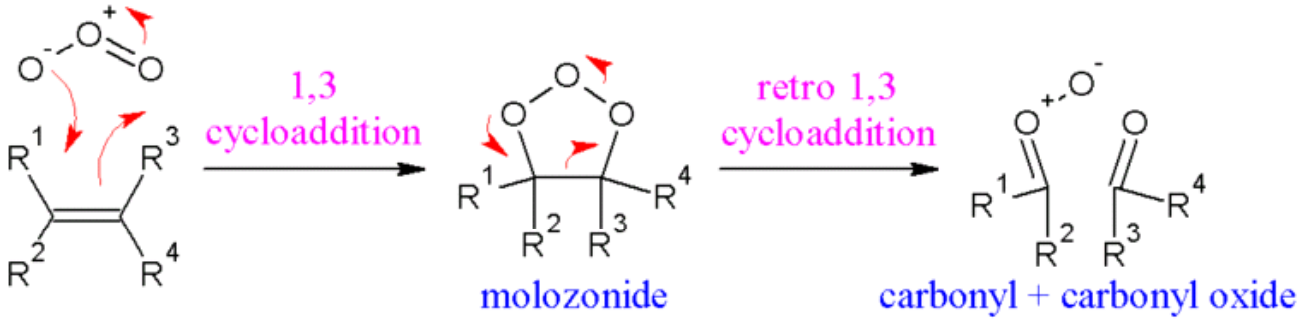
Several reaction mechanisms exist for organic oxidations:

- Single electron transfer;
- Oxidations through ester intermediates with chromic acid;
- Hydrogen atom transfer as in Free radical halogenation;
- Oxidation with oxygen (combustion);
- Oxidation involving ozone ($O_3$) in ozonolysis;
- Oxidations involving an elimination reaction mechanism such as the Swern oxidation;
- oxidation by nitroso radicals, fremy's salt or TEMPO.



Ozonolysis



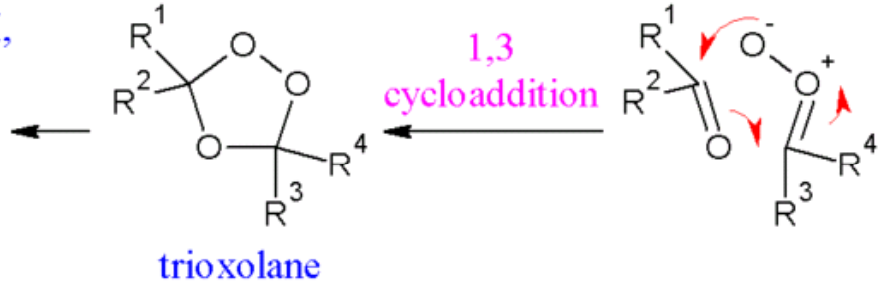




flip carbonyl

**Reductive Workup:-**

ketones ($R^N$ = alkyl, aryl)

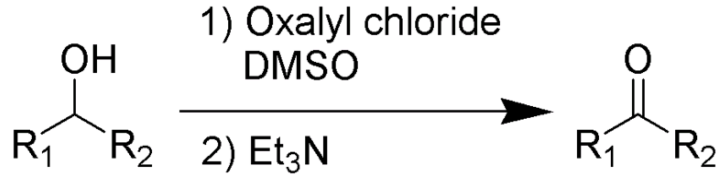
aldehydes ($R^1$ & $R^3$ =H, $R^2$ & $R^4$ =alkyl, aryl)



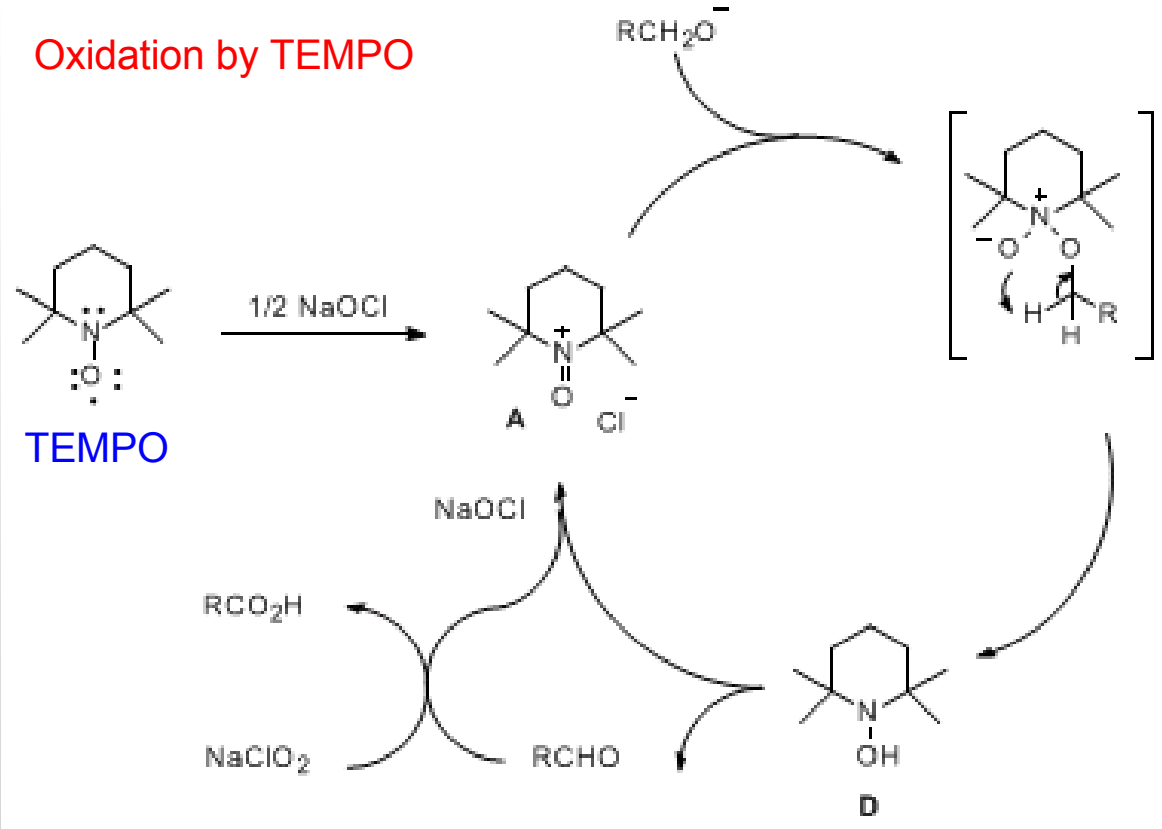

**Oxidative Workup:-**

acids ($R^1$ & $R^3$ =H, $R^2$ & $R^4$ =alkyl, aryl)

Swern oxidation




Oxidation by TEMPO



# Overview of Chapter 6

- 主要内容：脂肪族亲核取代、芳香族亲电取代；
- 亲核取代与消去反应底物、进攻试剂、反应条件基本相同，如何判断主要发生哪种反应？一般认为优先发生取代反应，当满足一个或几个以下条件时，发生消去反应：**a)** 位阻增加（包括底物和亲核试剂）、**b)** 强碱、**c)** 高温；
- **SN1, SN2, E1, E2, E1cB**；
- 加成和消去的**orientation**：一般反式（何时发生顺式？与环有关）、Markovnikov and Zaitsev rules；
- 苯环上亲电取代反应的定位与钝化活化；
- 取代与加成反应中的鎓离子（溴、氧等，中间体，邻基效应）