INTRODUCTION TO CHEMISTRY

CML-101

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Syllabus and References

Syllabus: Determination of reaction mechanism: kinetic methods, isotope effects, intermediate trapping, the stereo chemical outcome in reactions (NGP and elimination reaction)

References

1. Solomons's Organic Chemistry, Global Edition Paperback – 1 January 2017 by T. W. Graham Solomons, Craig B. Fryhle, Scott A. Snyder.

2. Organic Chemistry 2nd Ed. (J. Clayden, N. Greeves and S. Warren, Oxford University Press, 2012, ISBN 978-0-19-927029-3).

3. Guidebook to Mechanism in Organic Chemistry (6th Edition) by Peter Sykes.

Nucleophilic Substitution Reaction

Nucleophilic Substitution

$$Y^{\ominus} + R\!-\!X \longrightarrow R\!-\!Y + X^{\ominus}$$

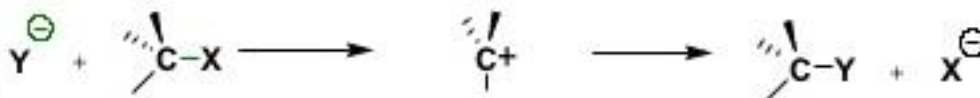R = aliphatic as well as aromatic

Nucleophile + Substrate ⟶ Product + Leaving group

Nucleophilic Substitution Reaction

Nucleophilic Substitution

S$_N$1

S: Substitution
N: Nucleophilic
1: unimolecular

S$_N$2
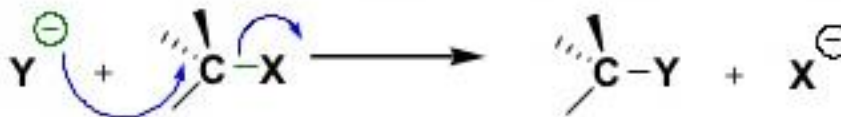
S: Substitution
N: Nucleophilic
2: Bimolecular
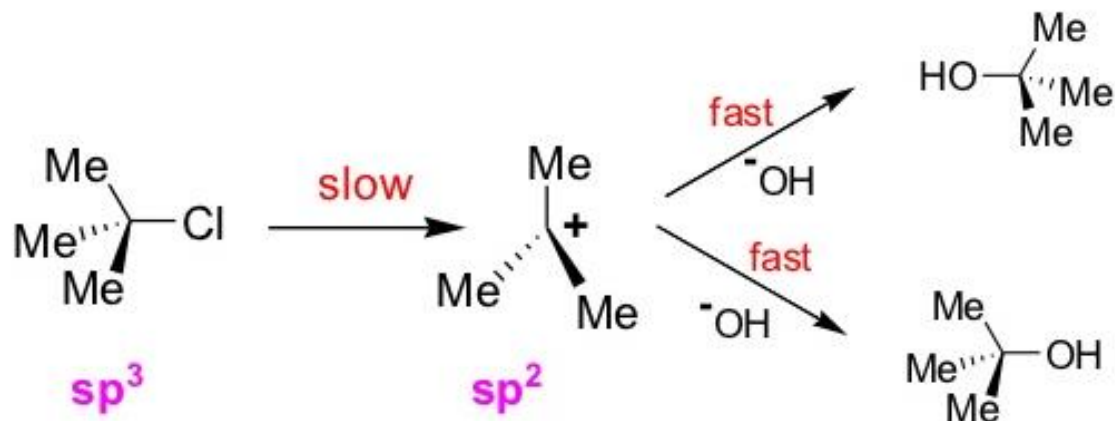
leaving group goes first and nucleophile comes later

nucleophile attacks and leaving group goes simultaneously

Nucleophilic Substitution Reaction (SN1)
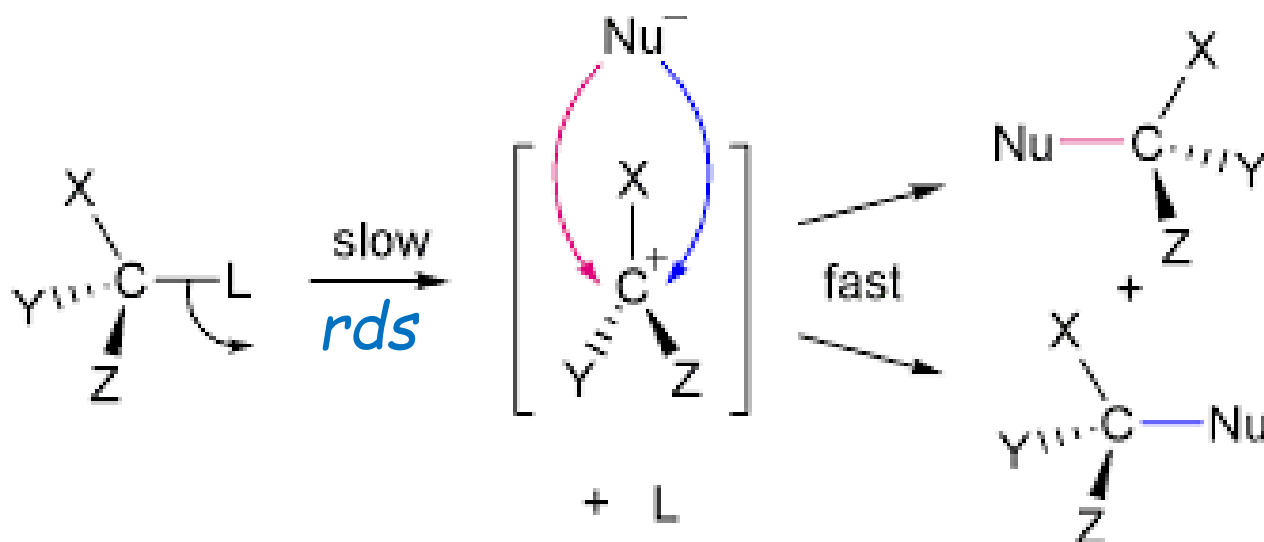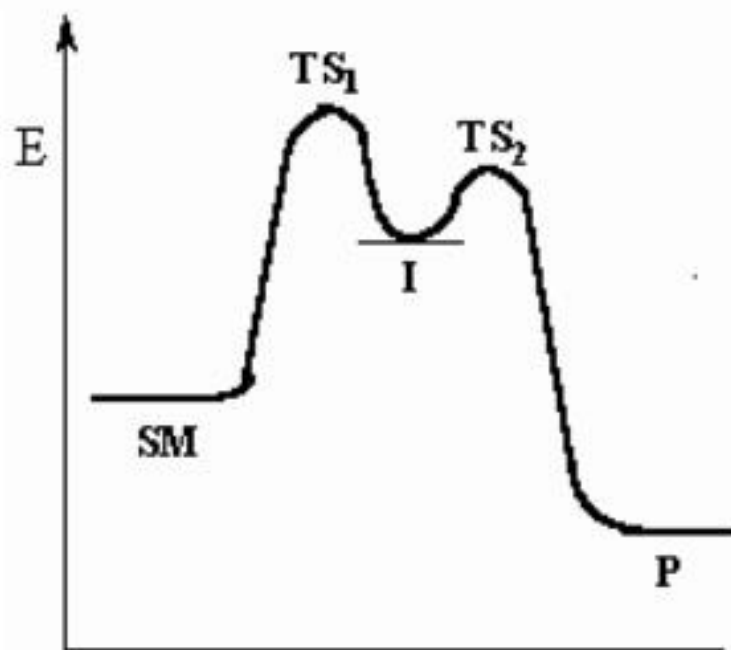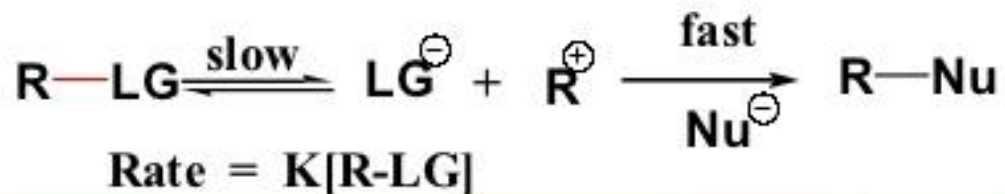

Rate = k_1[t-BuCl] or independent of [OH-]

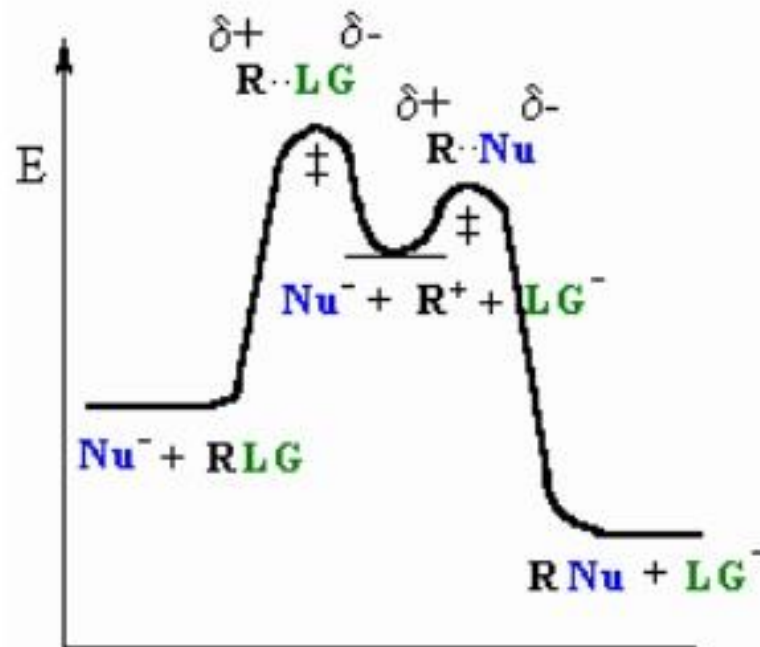# Nucleophilic Substitution Reaction (S_N1)

Reaction profile for S_N1 reaction

$$R—LG \underset{}{\overset{slow}{\rightleftharpoons}} LG^{\ominus} + R^{\oplus} \xrightarrow[Nu^{\ominus}]{fast} R—Nu$$

$$Rate = K[R\text{-}LG]$$
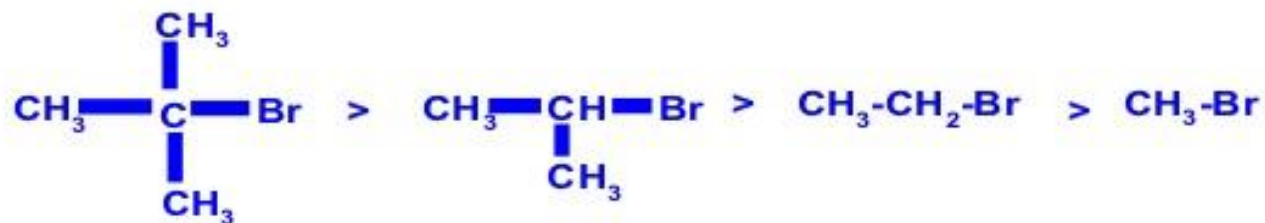

Reaction Coordinate

Reaction Coordinate

Nucleophilic Substitution Reaction (Sɴ1)

tertiary   secondary   primary
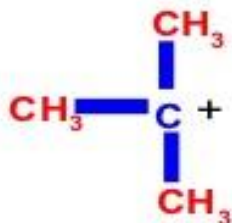
tertiary carbocation (very stable)
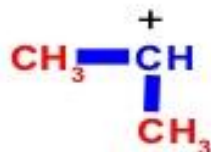
secondary carbocation

primary carbocation (unstable)

very unstable carbocation

three methyl groups

two methyl groups

one methyl group

no methyl groups

$$CH_3Br \quad + \quad HO^- \quad \longrightarrow \quad CH_3OH \quad + \quad Br^-$$

bromomethane   **methanol**

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Obtained experimentally:

$$rate = k \text{ [alkyl halide][nucleophile]}$$

the rate constant

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Rate law includes both the alkyl halide and the nucleophile, a second-order process

Nucleophilic Substitution Reaction (SN2)
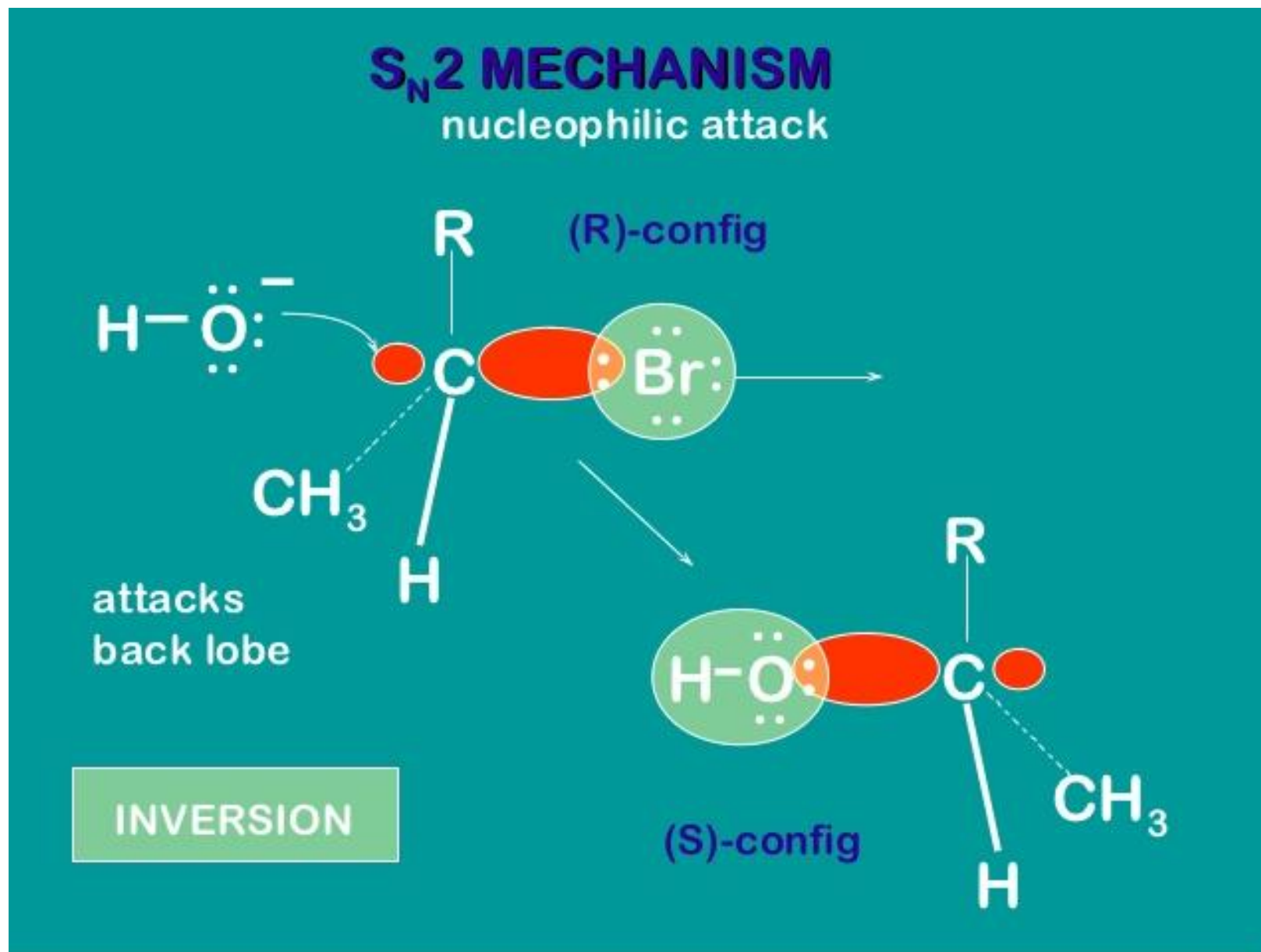
Stereochemistry of S_N2
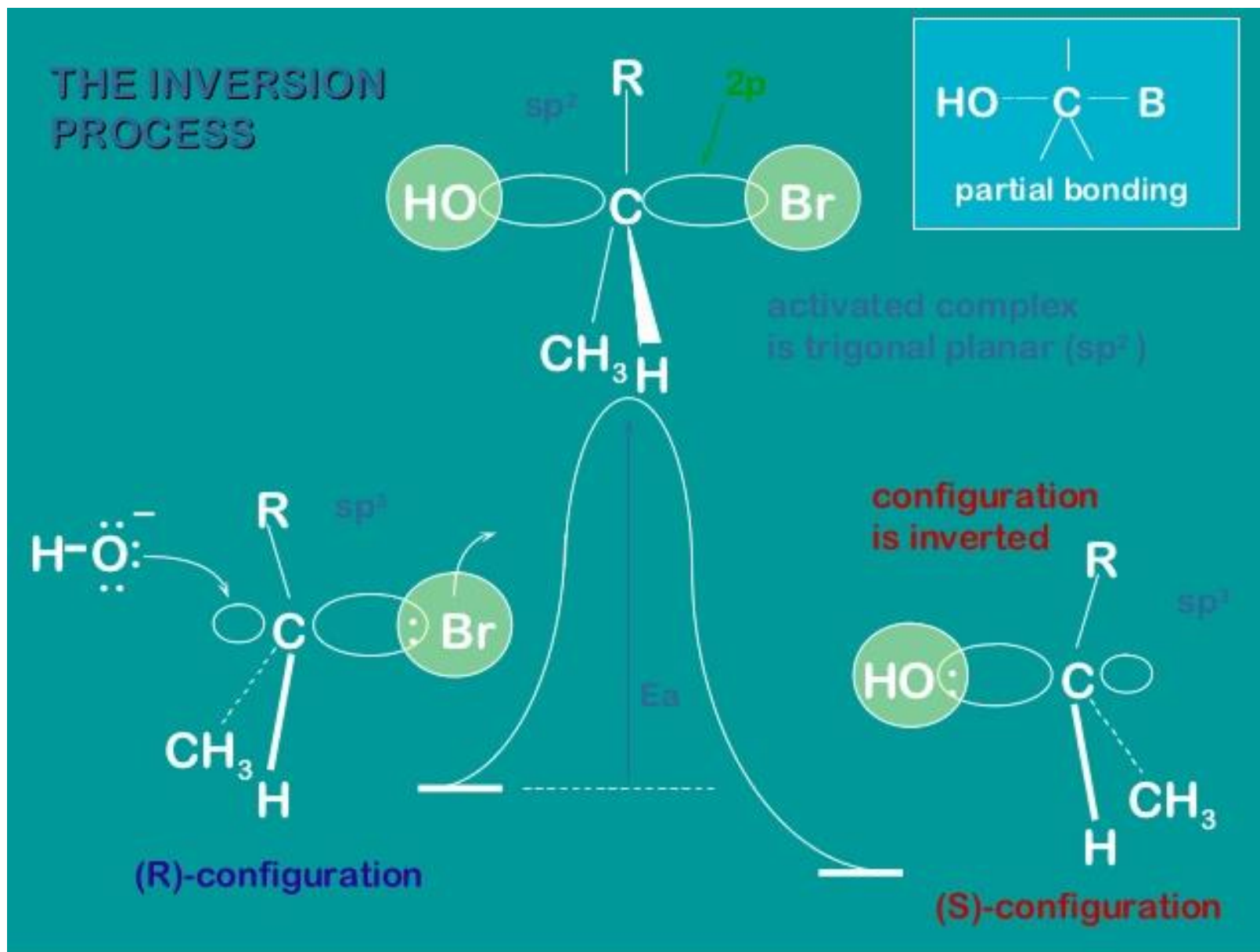
Walden inversion
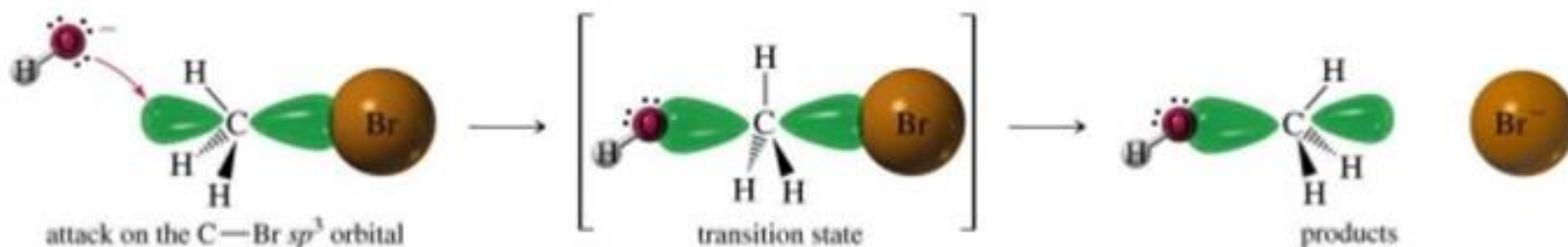
attack on the C—Br sp^3 orbital

transition state

products

HO:⁻ inversion HO— :Br:⁻

S$_N$2 Reaction: substrate structure

KI in Acetone at 25°

	k_{rel}
CH_3-Br	150
CH_3-CH_2-Br	1

CH_3-CH-Br
    |
   CH_3
	0.008

CH_3
   |
CH_3-C—Br
   |
   CH_3
	unreactive!

S$_N$2 or   S$_N$1?

S$_N$2
- Primary or methyl
- Strong nucleophile
- Polar aprotic solvent
- Rate = k [halide] [Nuc]
- Inversion
- No rearrangements

S$_N$1
- Tertiary
- Weak nucleophile (may also be solvent)
- Polar protic solvent, silver salts
- Rate = k [halide]
- Racemization
- Rearranged products

=>

Nucleophilic Substitution Reaction (SNi)

1-Phenyl ethanol

T.S

- Cl⁻

-H⁺

SO₂ +

1-Phenyl ethyl chloride
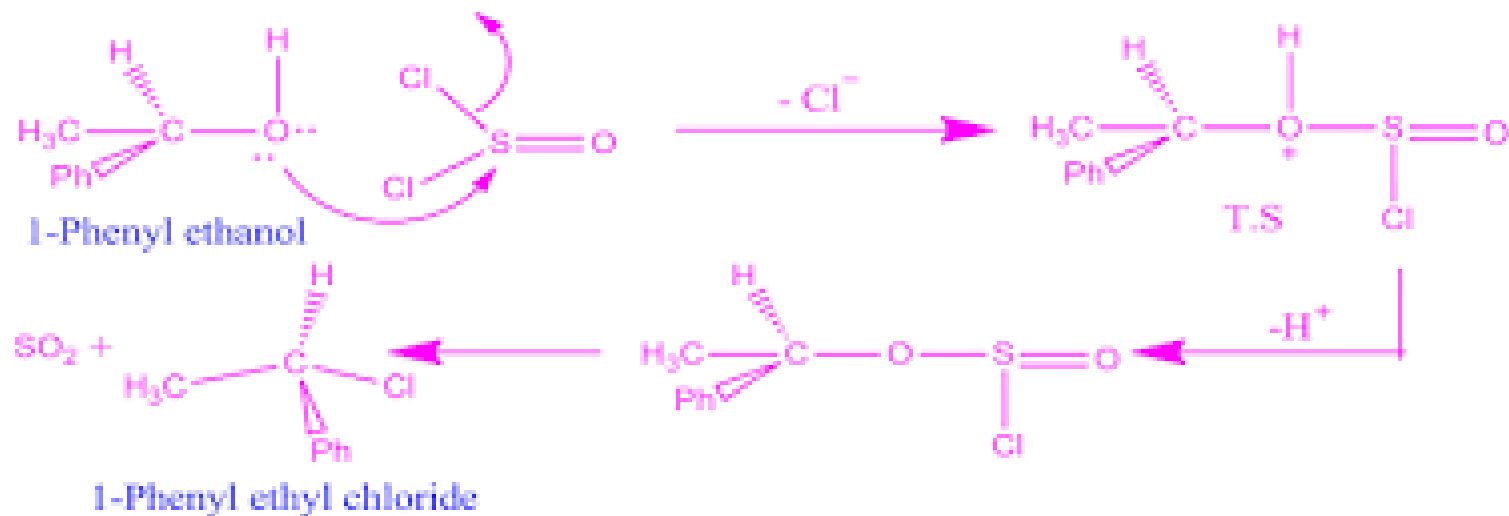
Neighboring Group Participation (Anchimeric Assistance)

Neighboring groups can accelerate substitution reactions

(1) Neighboring group participation (NGP, also known as anchimeric assistance) has been defined as the interaction of a reaction centre with a lone pair of electrons in an atom or the electrons present in a sigma bond or pi bond contained within the parent molecule.

(2) When NGP is in operation it is normal for the reaction rate to be increased by many folds.

(3) It is also possible for the stereochemistry of the reaction to be abnormal (or unexpected) when compared with a normal reaction.

(4) While it is possible for neighboring groups to influence many reactions in organic chemistry (e.g. the reaction of a diene such as 1,3-cyclohexadiene with maleic anhydride normally gives the endo isomer because of a secondary effect {overlap of the carbonyl group p orbitals with the transition state in the Diels-Alder reaction})

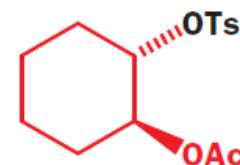# Neighboring groups can accelerate substitution reactions
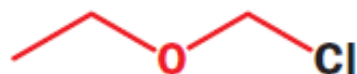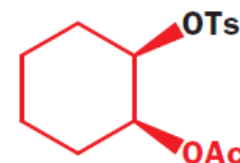

PhS⟋⟍⟋Cl

reacts with water
600 times faster than

⟋⟍⟋Cl

Ph⟋⟍⟋OTs

reacts with CF$_3$CO$_2$H
3000 times faster than

⟋⟍OTs

TsO⟍ (norbornene)

reacts with acetic acid
10^{11} times faster than

TsO⟍ (norbornane)

⟍⟍OTs / OAc (trans cyclohexane)

reacts with acetic acid
670 times faster than

⟍OTs / OAc (cis cyclohexane)

⟋⟍O⟋⟍Cl   reacts with nucleophiles 10^6 times as fast as   ⟋⟍⟋⟍Cl
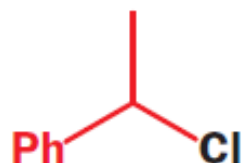
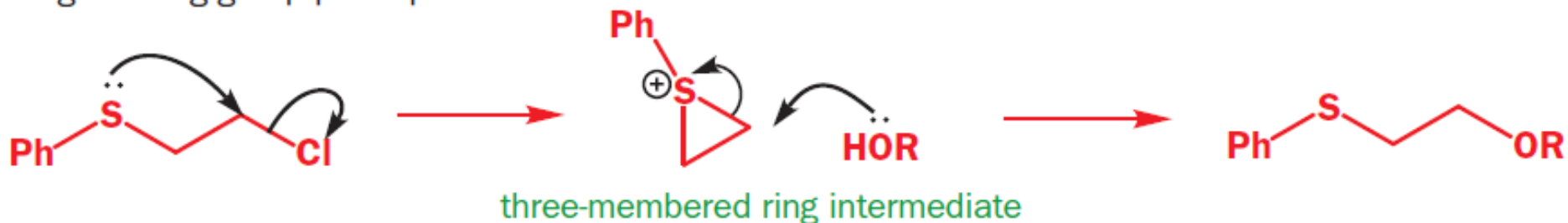Ph⟍Cl (isopropyl)   reacts with nucleophiles 10^5 times as fast as   ⟍Cl (isopropyl)

Why??

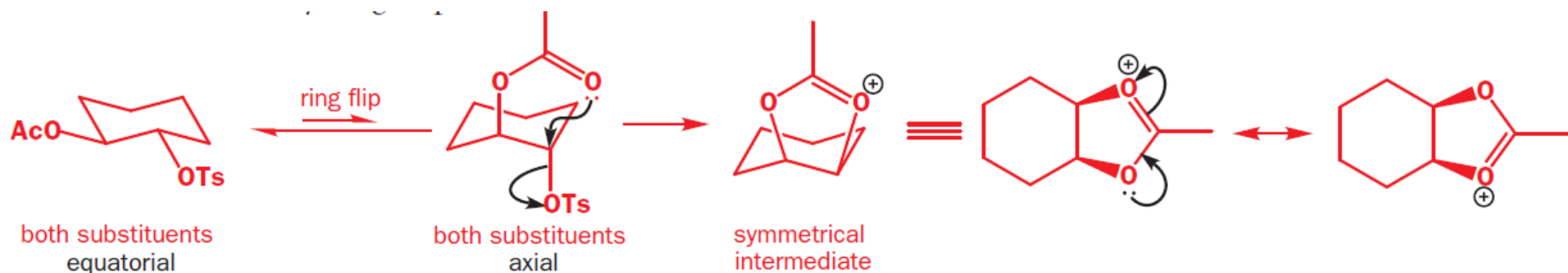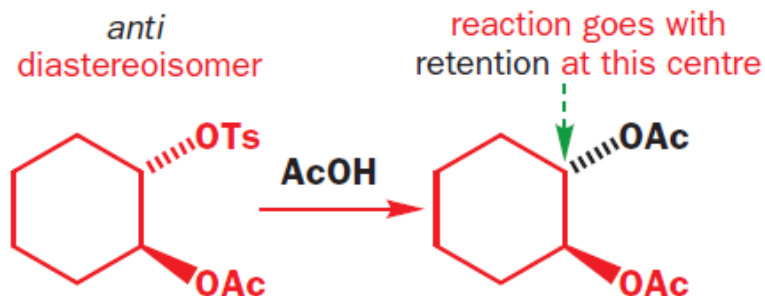# Neighboring groups can accelerate substitution reactions

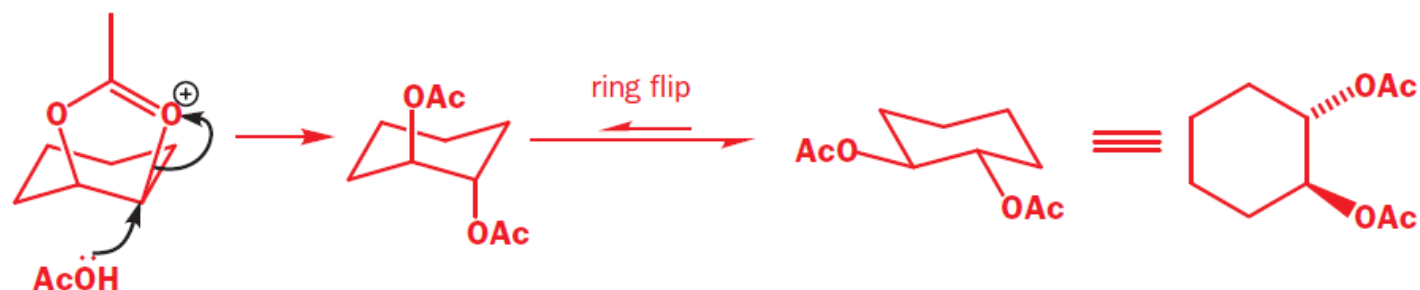π-bonded cationic intermediate
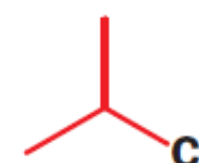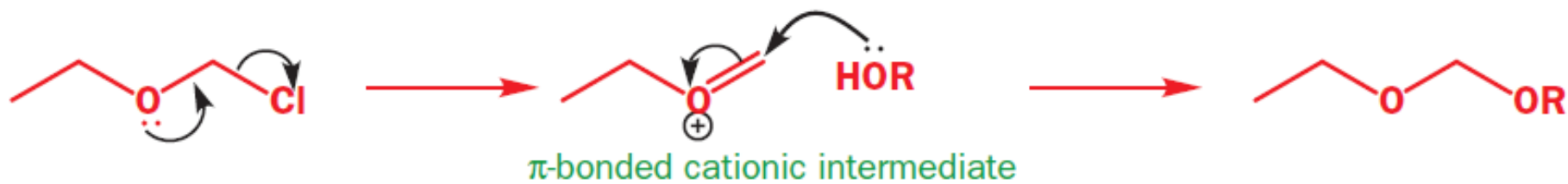
neighbouring group participation of a sulfide

three-membered ring intermediate

OAc group can act as a NGP
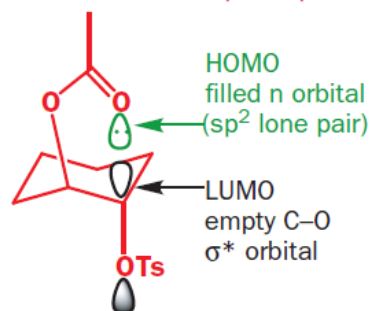
OAc group can't act as a NGP here because of its orientation

syn diastereoisomer

reaction goes with inversion at this centre

AcOH

ring flip

S_N2

HÖAc
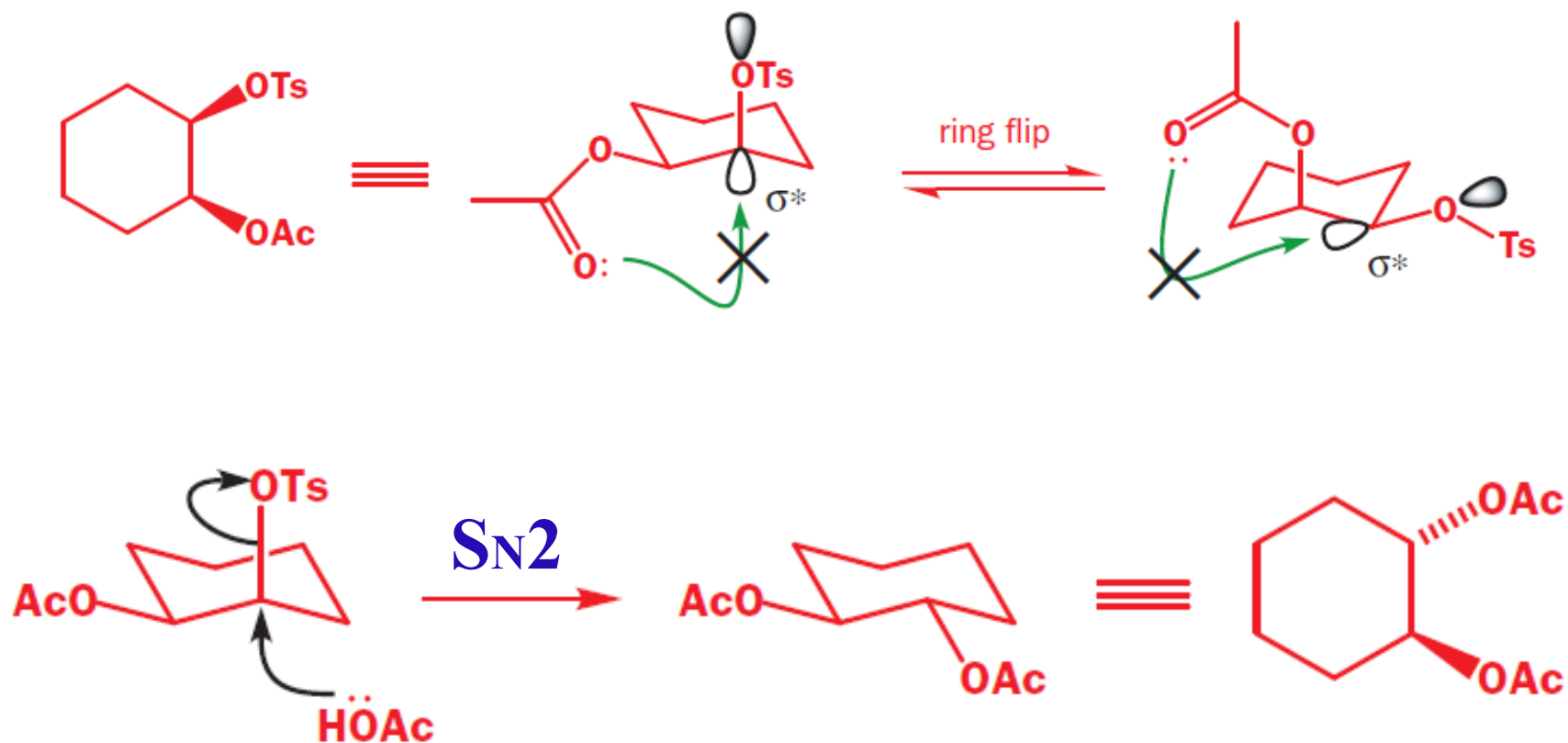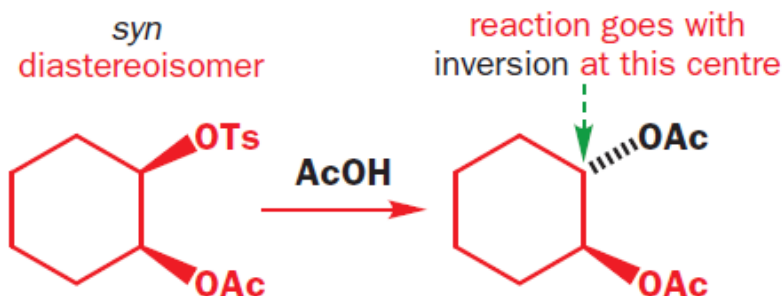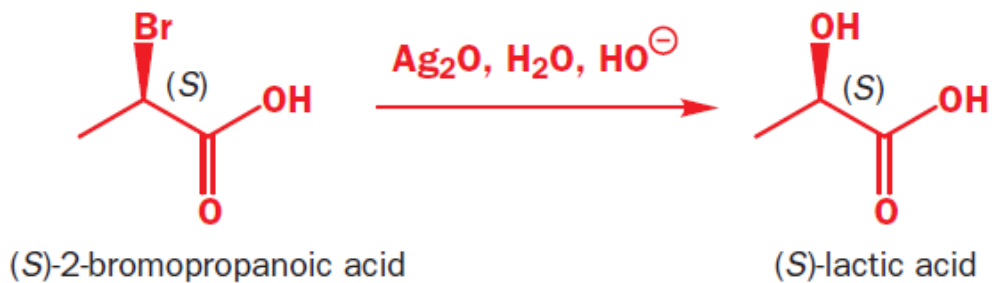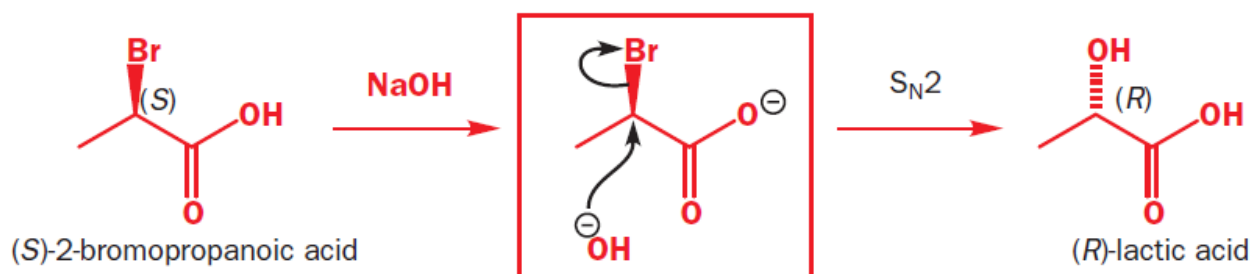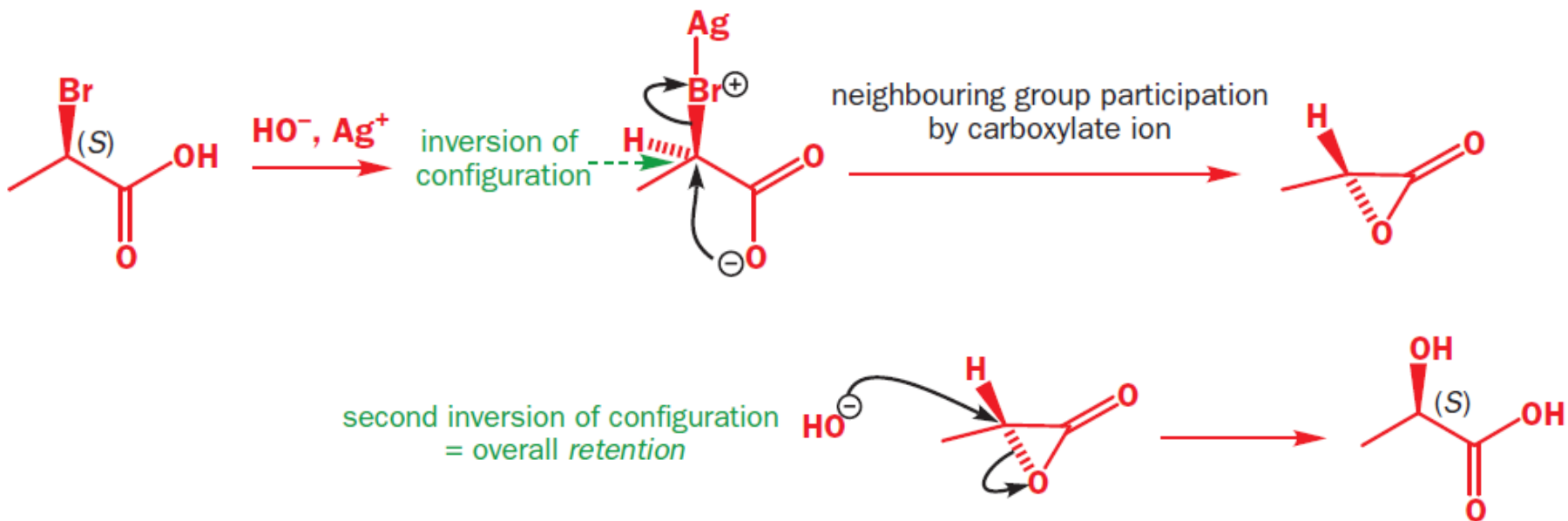
If you see a substitution reaction at a stereogenic saturated carbon atom that goes with retention of stereochemistry, look for neighboring group participation!
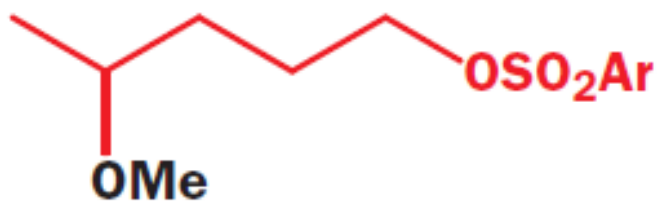
reacts with ROH
4000 times faster than

5-membered ring intermediate

TsO H Vs H OTs

TsO H Vs TsO H
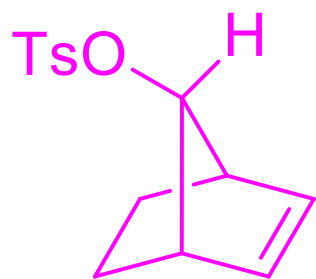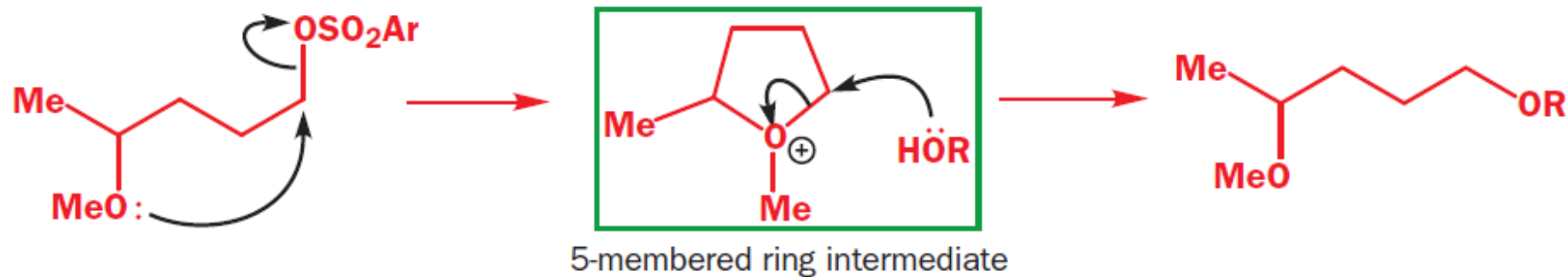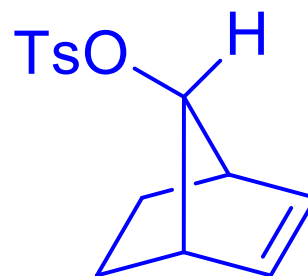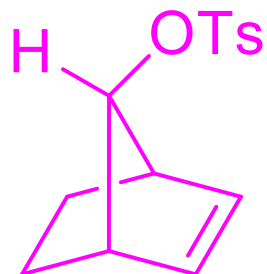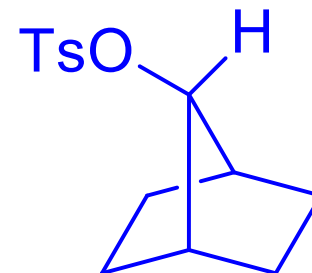
π electrons of a C=C double bond can participate.   NGP by an alkene

TsO

AcOH

just one way of representing
the intermediate cation

AcO

orbitals involved in π-participation
LUMO: empty σ* orbital
Ts
O
HOMO:
filled π orbiral
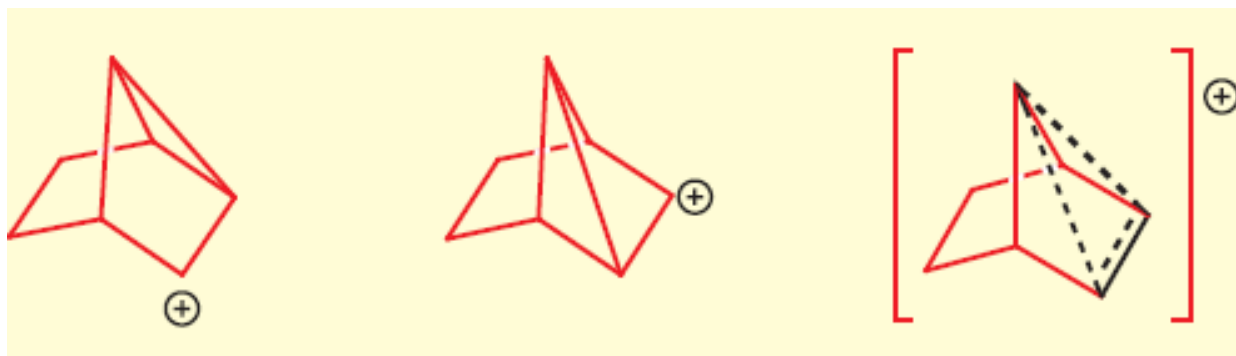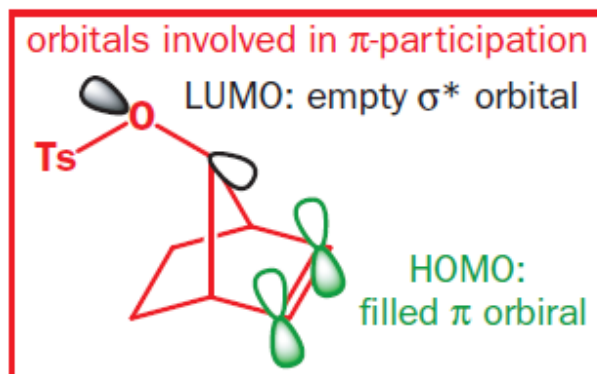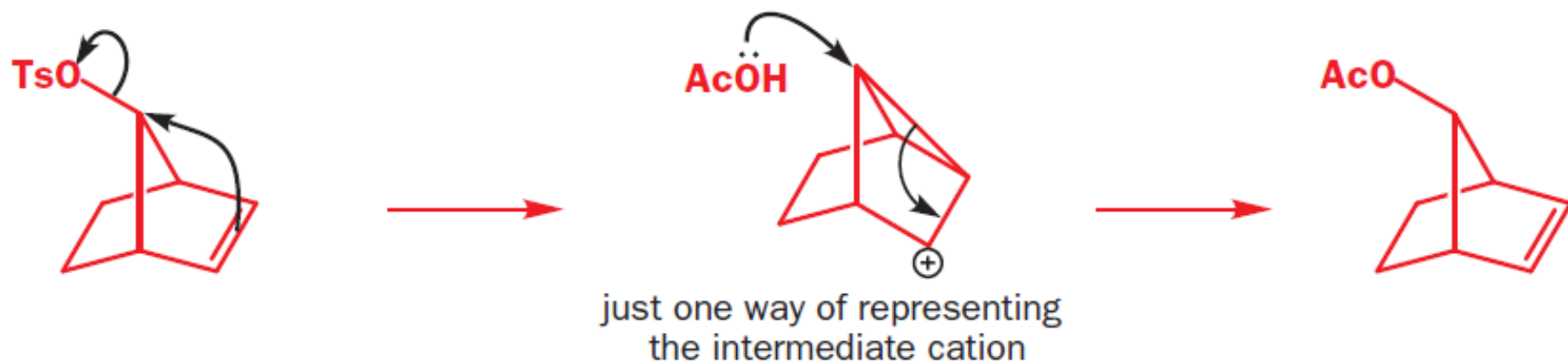
Aryl participation
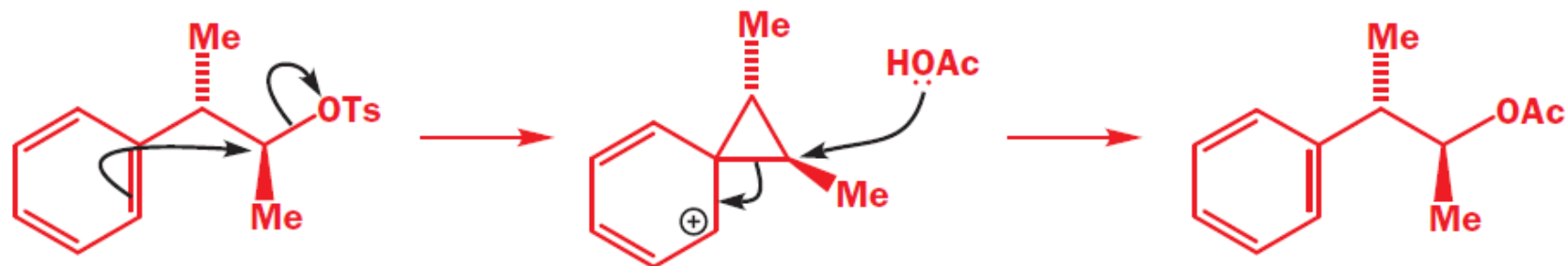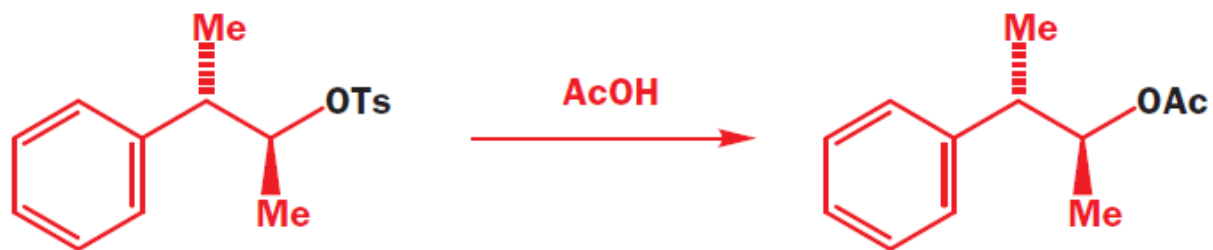
turn the molecule over – it's the same

the delocalized phenonium ion
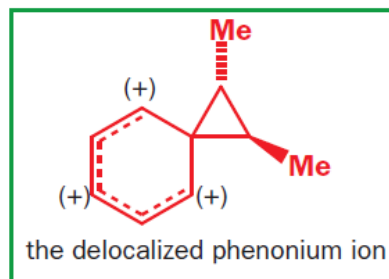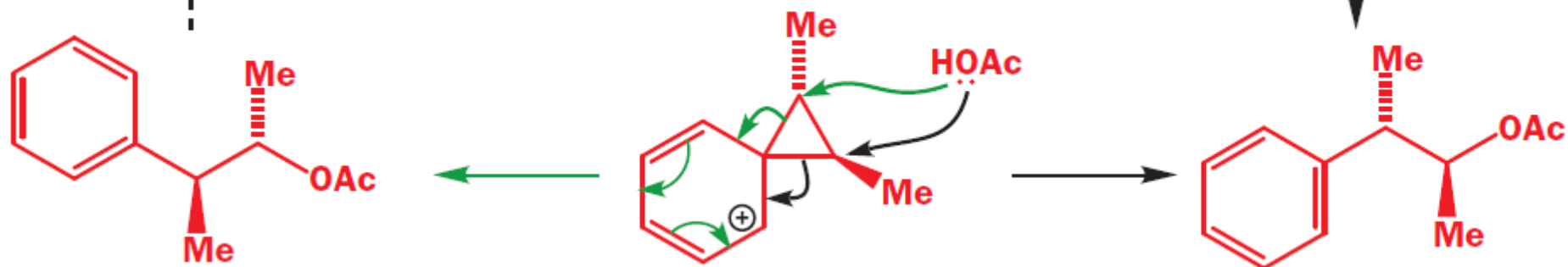
start with this enantiomer of tosylate . . . we get this phenonium ion . . . and therefore this enantiomer of product
whichever end the acid attacks
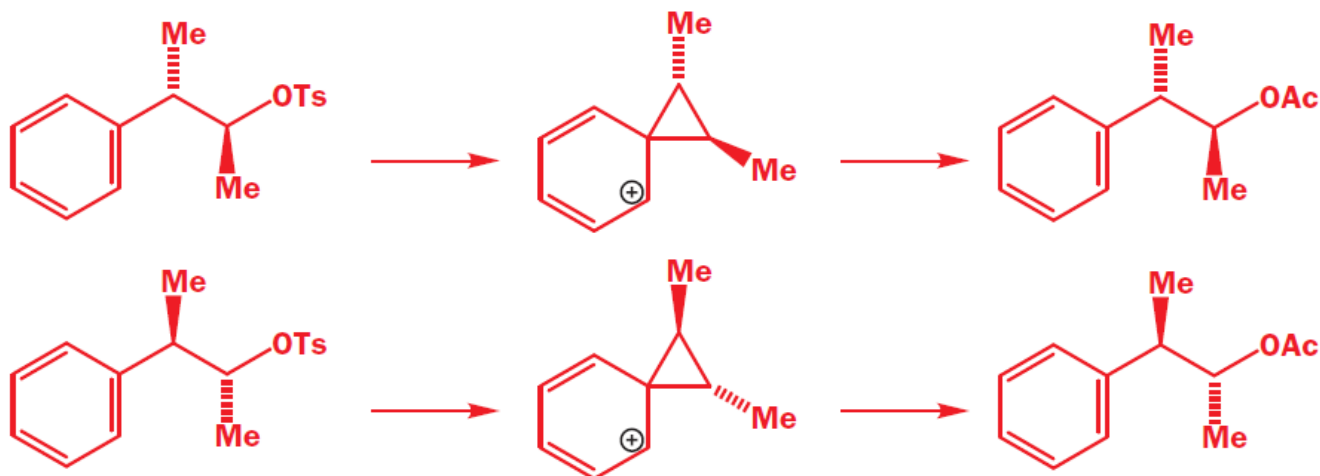
start with either enantiomer . . . we get the same achiral phenonium ion . . . and therefore racemic product

50% attack at A

turn molecule over - they are indentical

50% attack at B

racemic mixture of two enantiomers

NaOH, H₂O

Et_2N ... Cl → HO ... NEt_2

57% yield

3 Me, Et_2N, 2, Cl, 1 → HO, NEt_2 (+), 1, 2, 3, Me → HO, NEt_2, 1, 2 Me, 3

good nucleophile
bad leaving group

slow substitution at secondary centre with external nucleophile

good leaving group from primary or secondary centre

Me, Et_2N, Cl, good leaving group → NEt_2 (+), HO, Me → HO, NEt_2, Me

fast S$_N$2 at primary centre with external nucleophile

strong nucleophile attacks primary centre

weak nucleophile attacks secondary cation

NR_2, HO, R^1 ← S$_N$2 ← R_2N (+), R^1, HO ⇌ R_2N, R^1 (+), H₂O: → S$_N$1 → OH, R_2N, R^1

Proof of phenyl group participation in NGP: Isotope Labelling experiment
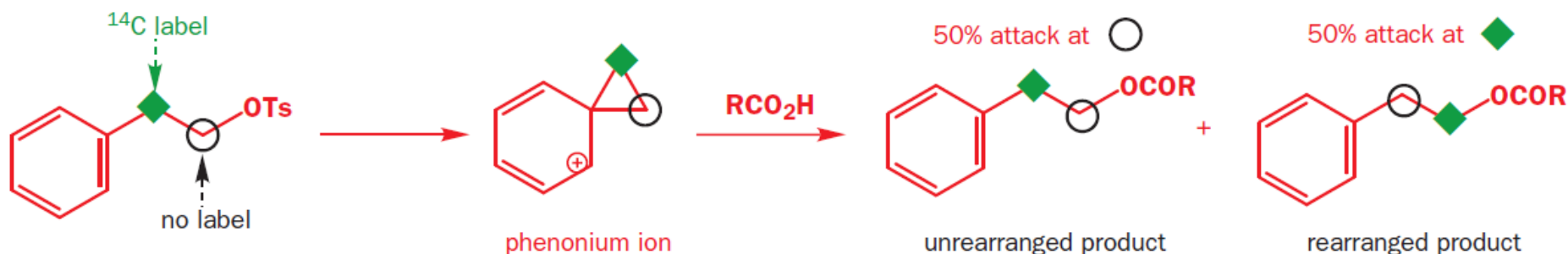
Rearrangements occur when a participating group ends up bonded to a different atom

Because the intermediates in these examples are symmetrical, 50% of the time one substituent ends up moving from one carbon atom to another during the reaction. This is clearer in the following example: the starting material is prepared such that the carbon atom carrying the phenyl group is an unusual isotope—carbon-14. This doesn't affect the chemistry, but means that the two carbon atoms are easily distinguishable. Reacting the compound with trifluoroacetic acid scrambles the label between the two positions: the intermediate is symmetrical and, in the 50% of reactions with the nucleophile that take place at the labelled carbon atom, the phenyl ends up migrating to the unlabeled carbon atom in a rearrangement reaction

Stereochemical Outcome of NGP

threo d or l

(+)

(-)

erythro d or l

Meso
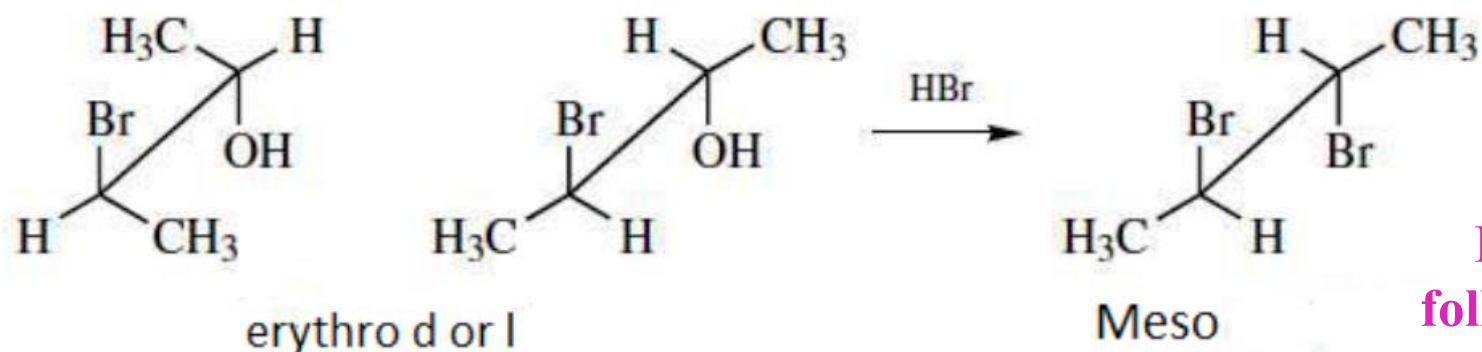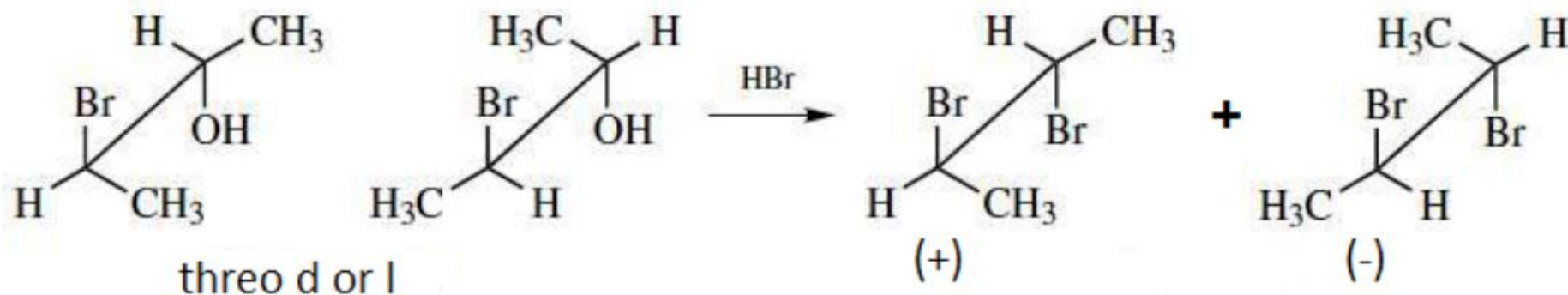
Explain the following facts...

Inversion at Carbon 2
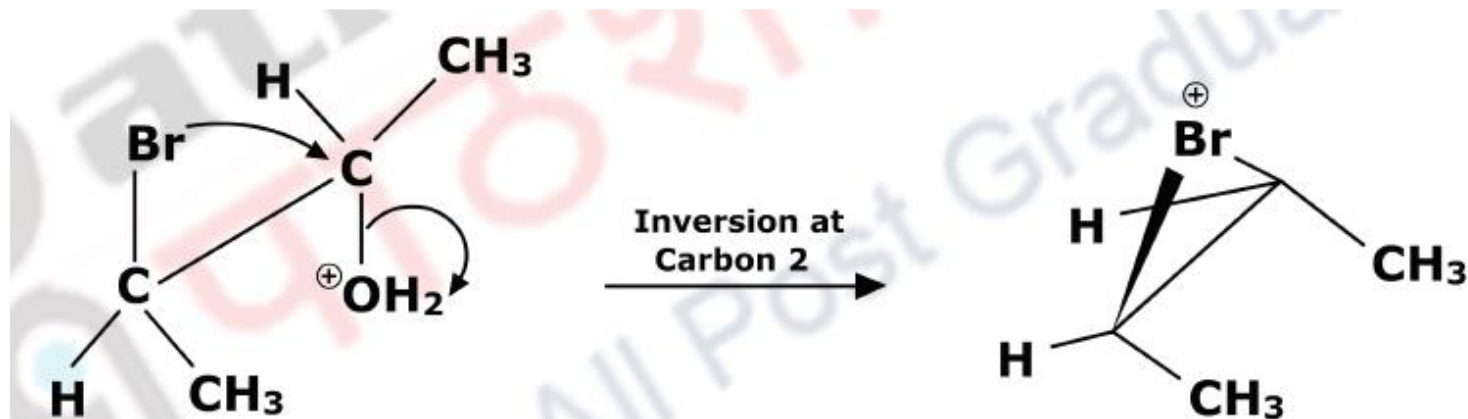
Kinetic isotope effects

Isotope Effects – *all about ZPE$_{GS}$ and ZPE$_{TS}$*

√ Kinetic isotope effects arise from the relative difference of ZPE at the GS and TS for H and D. This situation occurs when bond breaking, rehybridization, etc.

D_0 = dissociation energy

D_e = hypothetical dissociation energy

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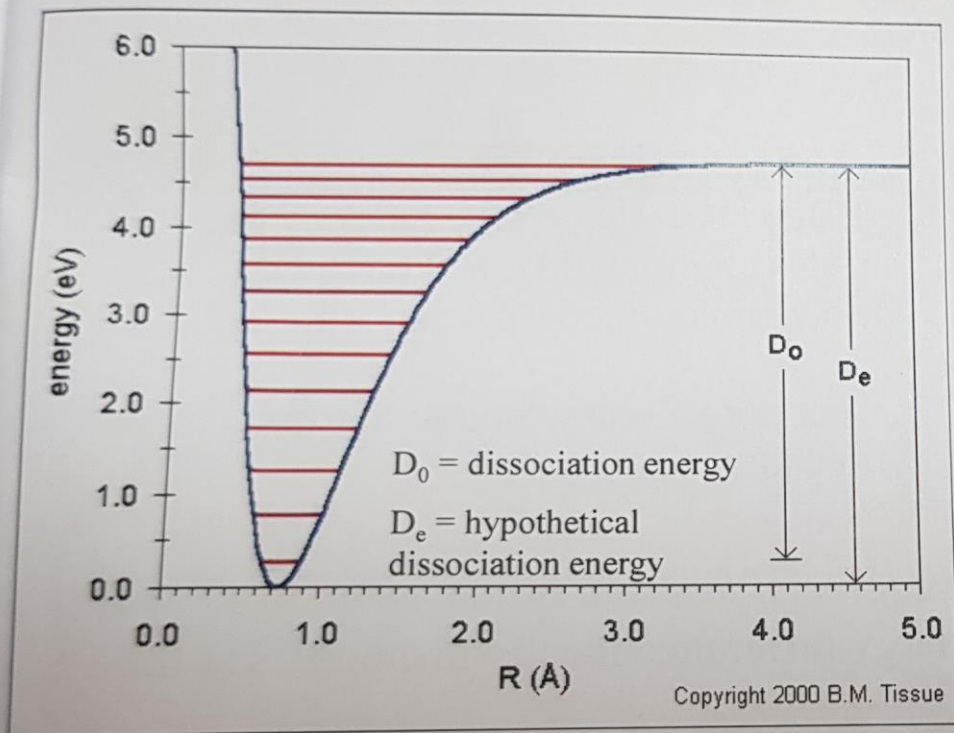
√ The energy is a set of **vibrational energy** levels. This energy varies as a function of the internuclear distance.

√ Vibrational energy at each energy level: $E = h\nu(\nu + 1/2)$ (vibrational quantum number, $\nu = 0, 1, 2..$); $\nu = \sqrt{k/\mu}/(2\pi)$ (**molecular frequency**), where μ is the reduced mass $= m_1m_2/(m_1+m_2)$, $k =$ force constant (m is large, ν decreases; k is high, ν increases).

√ cf) $E = h\nu$; The energy required for excitement of a molecular vibration, which corresponds to **IR stretching frequency** of a C-H/D bond ~ ν, frequency is also proportional to bonding strength (k, bond stiffness).

√ Based on this equation, at $\nu = 0$ the vibrational energy of the molecules (99% at 298 K at E_0; $\Delta G = -RT\ln K$; $\nu = 0, 1$) is called zero point energy (E_0).

4

Isotope Effects

√ We can utilize the equation for vibrational energy levels to calculate E_0 for C-H and C-D.

√ $E_0 = h\nu(\nu + 1/2)$, when $\nu = 0$, $E_0 = 0.5h\nu$

√ Thus, E_0 (H) $= 0.5h\nu = 0.5$ (3000 cm^{-1}) = 1500 cm^{-1}

   E_0 (D) $= 0.5h\nu = 0.5$ (2200 cm^{-1}) = 1100 cm^{-1}

√ Then, $\Delta E_0 = 400$ cm^{-1} (bond dissociation energy difference) ~ **1.15 kcal/mol of activation energy difference** (more greater for the C-D bond dissociation)

√ $k_H = A_He^{-Ea(H)/RT}$; $k_D = A_De^{-Ea(D)/RT}$, therefore, **product ratio = k_H/k_D**
    $= e^{\Delta E/RT} = e^{[1150/(300K\ 1.98)]}$ (when $A_H = A_D$) ~ **7**

√ Based on this calculation, the maximum for the isotope effect k_H/k_D involving C-H bonds is about **7** at r.t. However, proton tunneling effect gives sometimes $k_H/k_D > 20$ (*vide infra*).
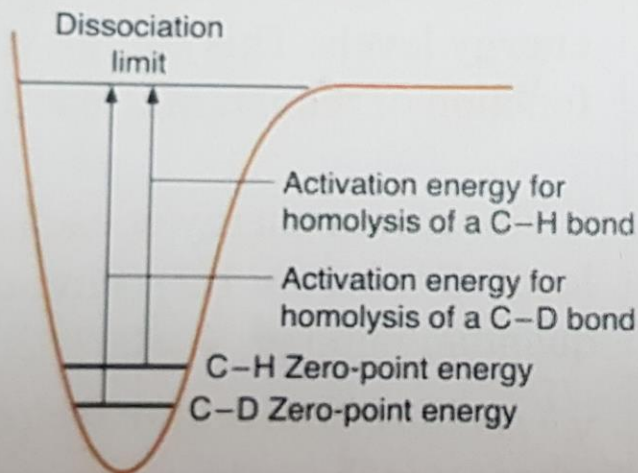
√ Let's derive the KIE (k_H/k_D) corresponding to 1.15 kcal/mol of ΔE (Hint: KIE ~ product ratio under kinetic control)!

Primary kinetic isotope effects

Primary Kinetic Isotope Effects

√ **PKIE** is observed when the isotope is directly involved in the **bond breaking or formation**, which is the rate-limiting step.

Dissociation limit

Activation energy for homolysis of a C–H bond

Activation energy for homolysis of a C–D bond

C–H Zero-point energy
C–D Zero-point energy

• The bond dissociation energies (BDE) for C-H and C-D differ by ca. 1.15 kcal/mol (400 cm^{-1}) based on the vibration model shown left.

• For purely unimolecular thermal reactions, $k_H/k_D \sim 7$.

√ As the reaction proceeds, *a vibration degree of freedom is converted to a translational degree of freedom.* The energy difference ideally disappears at the T.S (dissociation limit).

√ Thus, *the TS has the almost same energy for H/D species.* Since the D-labeled molecule has the *lower zero point energy*, it requires higher activation energy (PKIE).
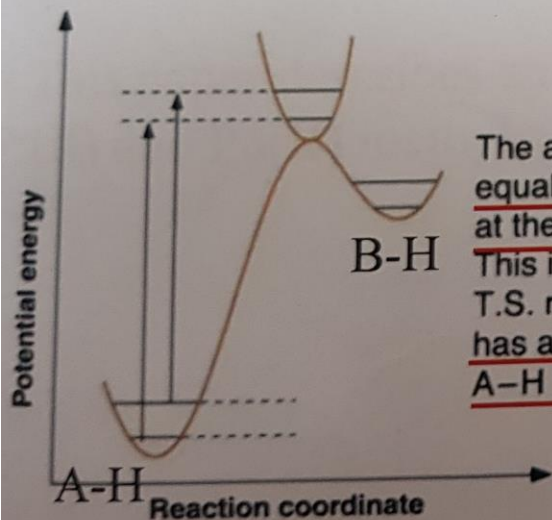
Cases of KIE ~ 1.0 (non-linear transition states)

√ *Very* **early** TS resembles reactants, while *very* **late** TS is close to products.

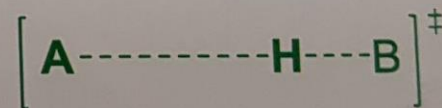*no big difference of activation energies due to no dissociation limit.*
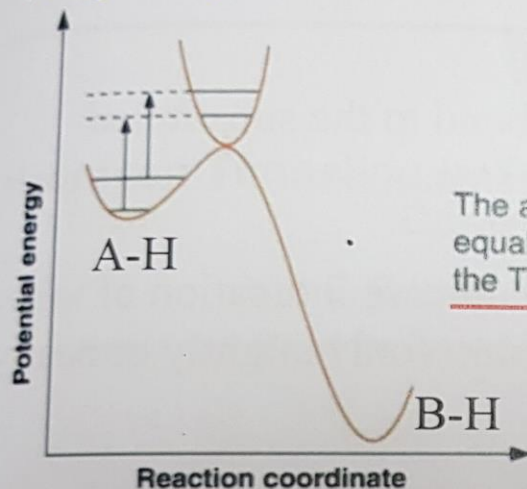
Potential energy

A-H

B-H

Reaction coordinate

The activation energies are roughly equal because the symmetric stretch at the T.S. is similar to the A--H stretch.

$$\left[A\text{-}\text{-}\text{-}H\text{-}\text{-}\text{-}\text{-}\text{-}\text{-}\text{-}\text{-}\text{-}B \right]^{\ddagger}$$

Potential energy

B-H

A-H

Reaction coordinate

The activation energies are roughly equal because the symmetric stretch at the T.S. is similar to the A−H stretch. This is due to symmetric stretch at the T.S. resembling the B−H bond, which has a similar force constant to the A−H bond.
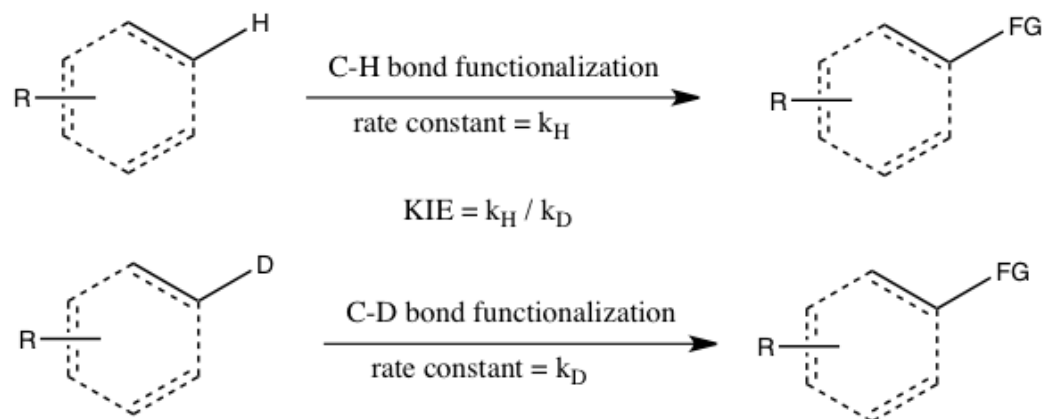
$$k_{(A\text{-}H)} \sim k_{(B\text{-}H)}$$

$$\left[A\text{-}\text{-}\text{-}\text{-}\text{-}\text{-}\text{-}\text{-}\text{-}H\text{-}\text{-}\text{-}B \right]^{\ddagger}$$
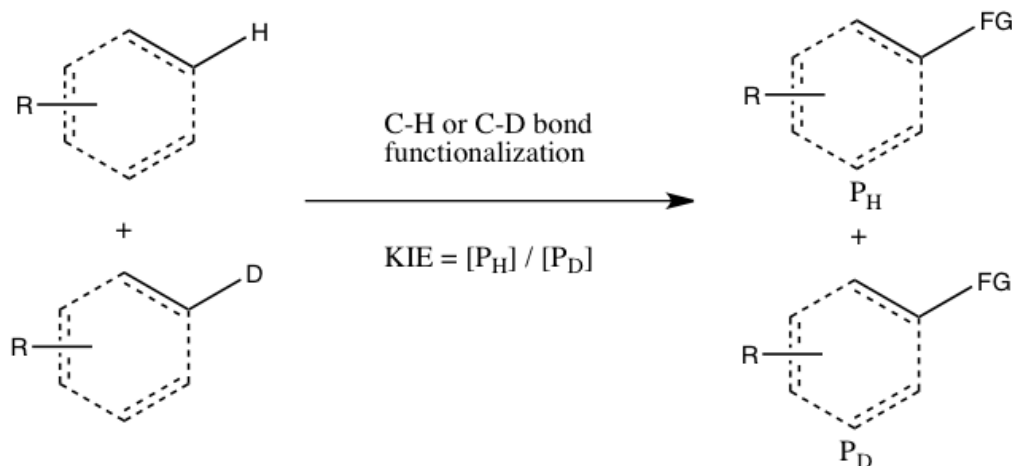
7

√ Let's understand what k (force constant) means in KIE analysis!

Primary kinetic isotope effects

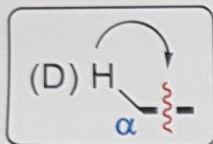## KIE determined from absolute rates of two parallel reactions

C-H bond functionalization
rate constant = k_H

$KIE = k_H / k_D$

C-D bond functionalization
rate constant = k_D

KIE determined from an intermolecular competition

C-H or C-D bond functionalization

$KIE = [P_H] / [P_D]$

+

P_H

+

P_D

Secondary kinetic isotope effects

Secondary KIE (SKIE) Effects

√ SKIE is usually seen in the cases that C-H(D) is on a molecule undergoes *bond changes* or *rehybridization, but itself is not broken* during the rate-limiting step. *Just tightening or loosening of a C-H at the TS.*

√ SKIE is usually smaller than PKIE and in the range of $k_H/k_D = 0.7 \sim 1.5$.

√ ***Normal*** $(k_H/k_D > 1)$ is observed in reactions that the hybridization state changes in such direction: *from sp³ to sp² to sp.*

Rationalization: C-H(D) bending vibration becomes more easy or less resistive with increasing "s" character. C-H bond is longer than C-D bond, so the freeing of vibration has a large amplitude.

In-plane bend | Out-of-plane bend

1350 cm⁻¹ | 1350 cm⁻¹ | sp³ Higher energy (large k)

1350 cm⁻¹ | 800 cm⁻¹ | sp² Lower energy (low k)

√ When sp³ is rehydridized to sp² (**s character increases**), where **out-of-plane C-H(D)** bending vibration becomes easy (weaken), **C-H(D) bond relatively labile** (lower energy ~ 800 cm⁻¹). **Thus, ΔZPE_{TS} is less than ΔZPE_{GS} and more than ΔZPE_{int},** giving rise to a normal KIE.
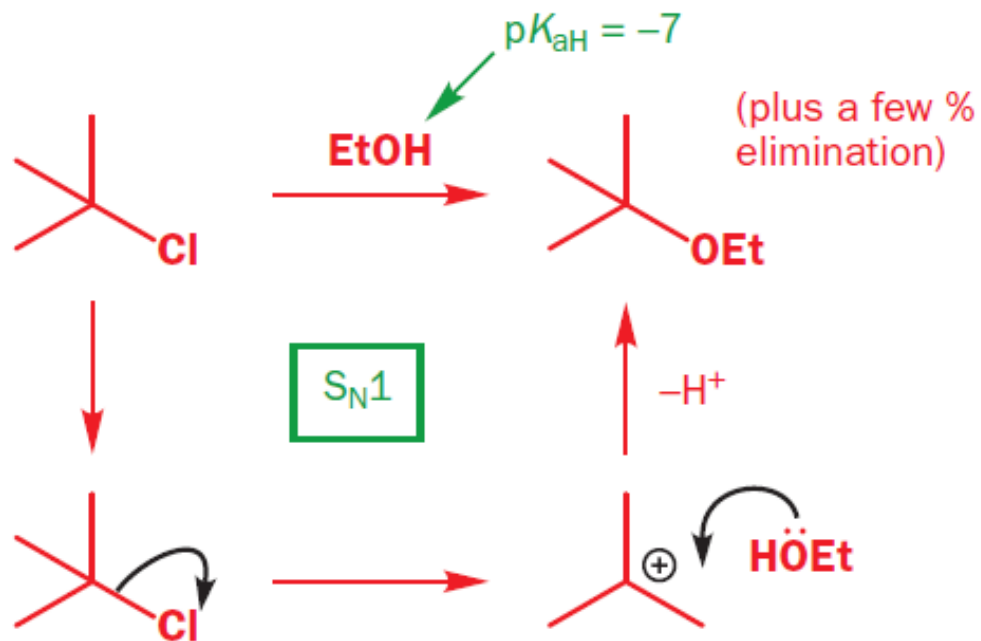
16

# Secondary kinetic isotope effects

Normal α-SKIE Effects

A.

less ΔZPE_{TS} *(mixed character)*

Potential energy well of a mix of sp^2 and sp^3 character at the T.S.

Larger activation energy for the C–D bond

Potential energy well for out-of-plane bend at an sp^2 center *(sp^2 character)*

Potential energy well for the out-of-plane bend at an sp^3 center

more ΔZPE_{GS} *(sp^3 character)*

Potential energy (y-axis)

Reaction coordinate (x-axis)

S_N1 reaction:

(D)H, HO — OCH$_3$, OCH$_3$ — sp^3

$\xrightarrow{H^+}$

(D)H ⊕ — OCH$_3$, OCH$_3$ — sp^2

$k_H/k_D = 1.18$

Elimination Reaction

Nucleophile Affects Elimination Versus Substitution
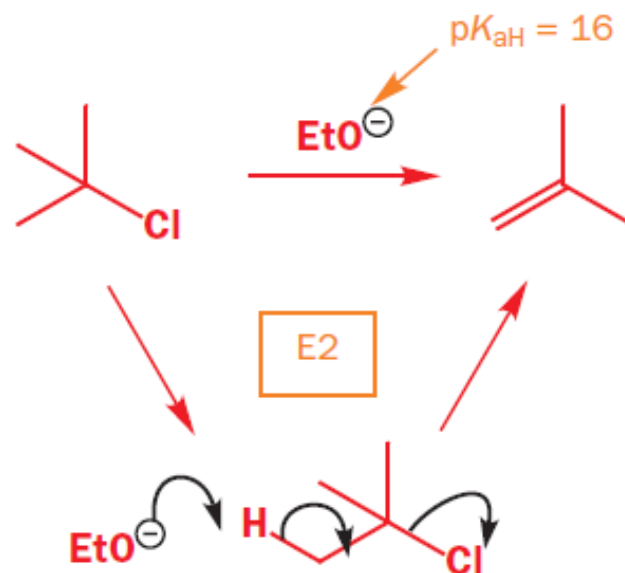
Comparing the E1, E2, and E1cB Mechanisms

E1	E2	E1cB
Two steps	**One** step	**Two** steps
1) C–LG breaks	C–H breaks, C–C (pi) forms	1) C–H breaks
2) C–H breaks C–C (pi) forms	C–LG breaks, all at same time	2) C–LG breaks C–C (pi) forms
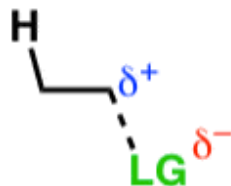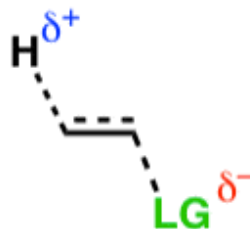
| **Carbocation** intermediate	**No** intermediate (concerted)	**Carbanion** intermediate
Carbocation stabilized by electron **donating** groups		Carbanion stabilized by electron **withdrawing** groups
Assisted by **good** leaving groups		Assisted by **poor** leaving groups
No strict requirement on stereochemistry of C–H and C–LG	C–H and C–LG are **anti**	No strict requirement on stereochemistry of C–H and C–LG
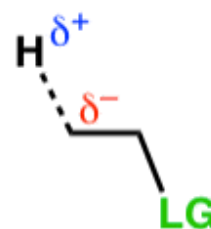
E1 Versus E2

general mechanism for E1 elimination

rate = k[alkyl halide]
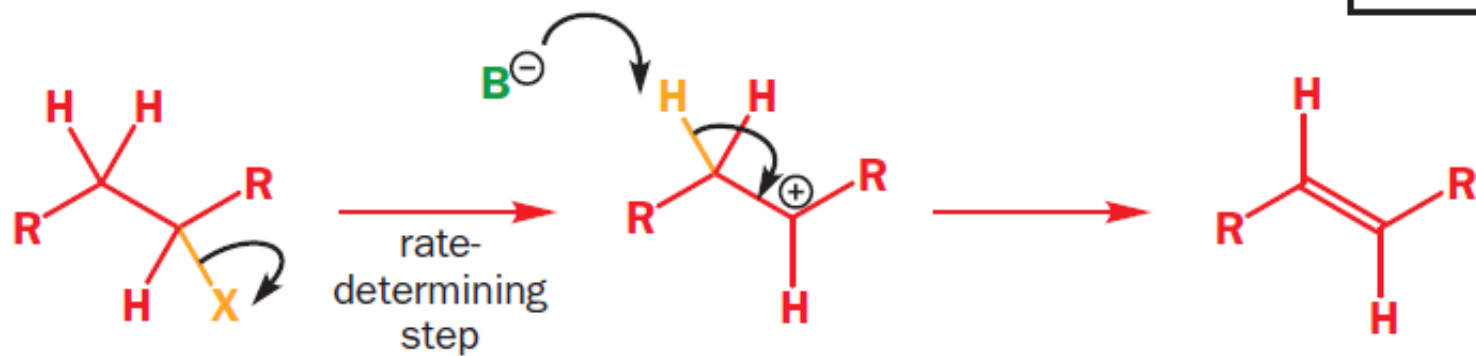
general mechanism for E2 elimination
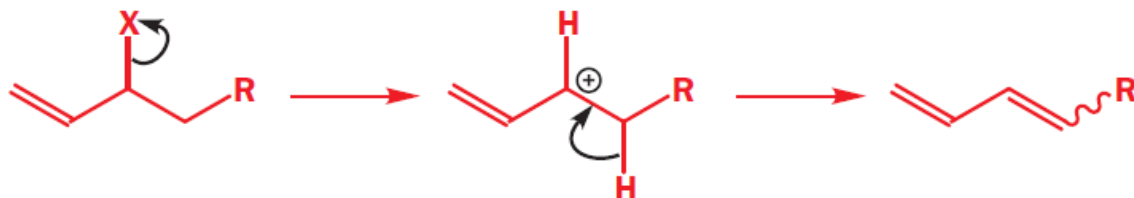
rate = k[B⁻][alkyl halide]

substrates that readily eliminate by E1
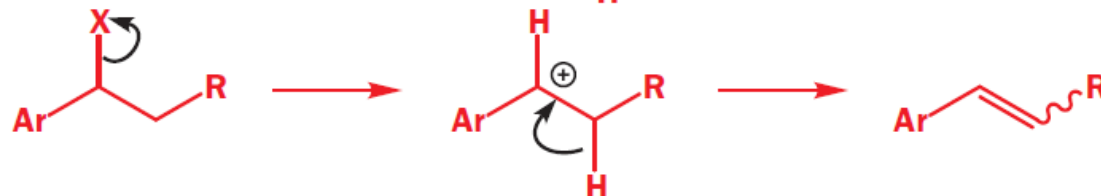
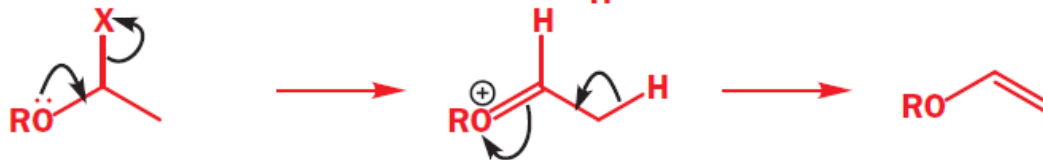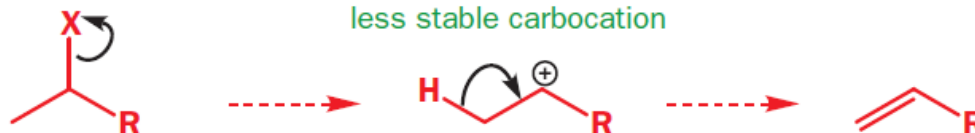stabilized carbocations

tertiary
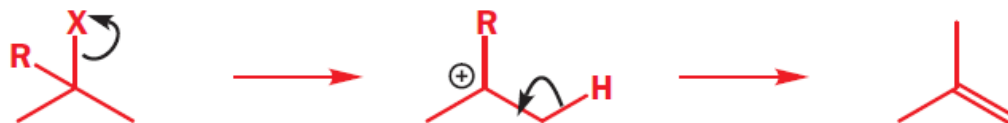
allylic

benzylic

α-hetero substituted

substrates that may eliminate by E1

less stable carbocation
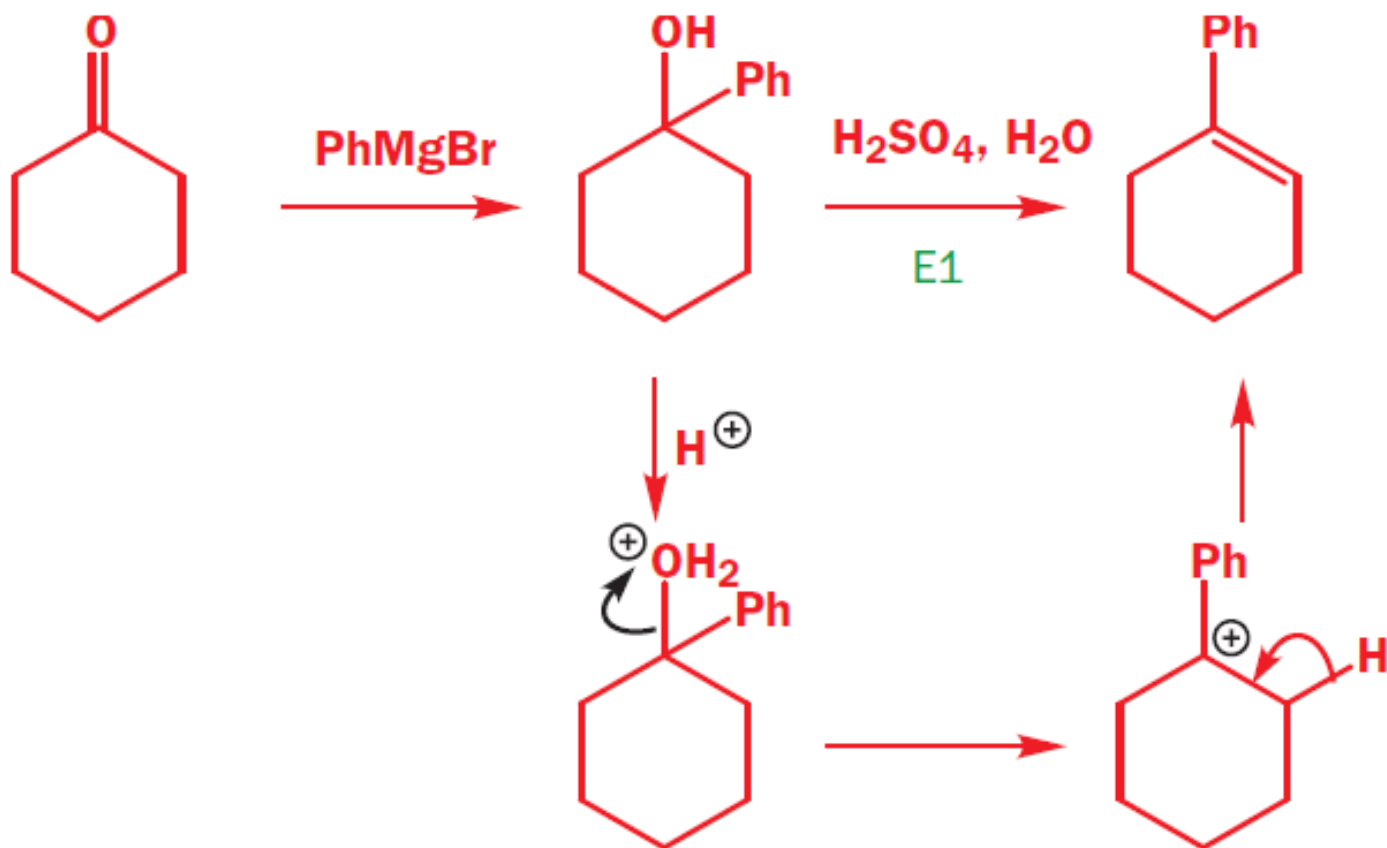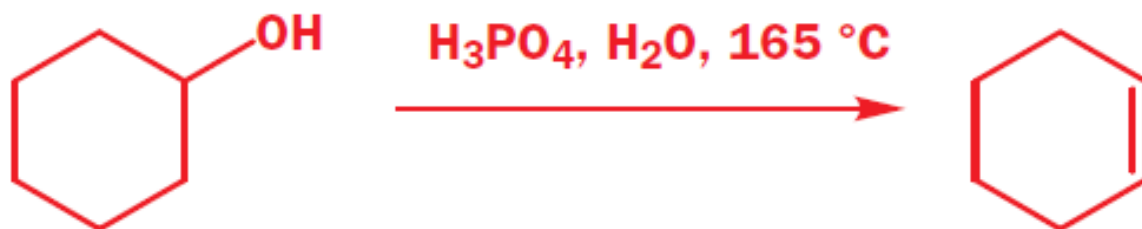
secondary

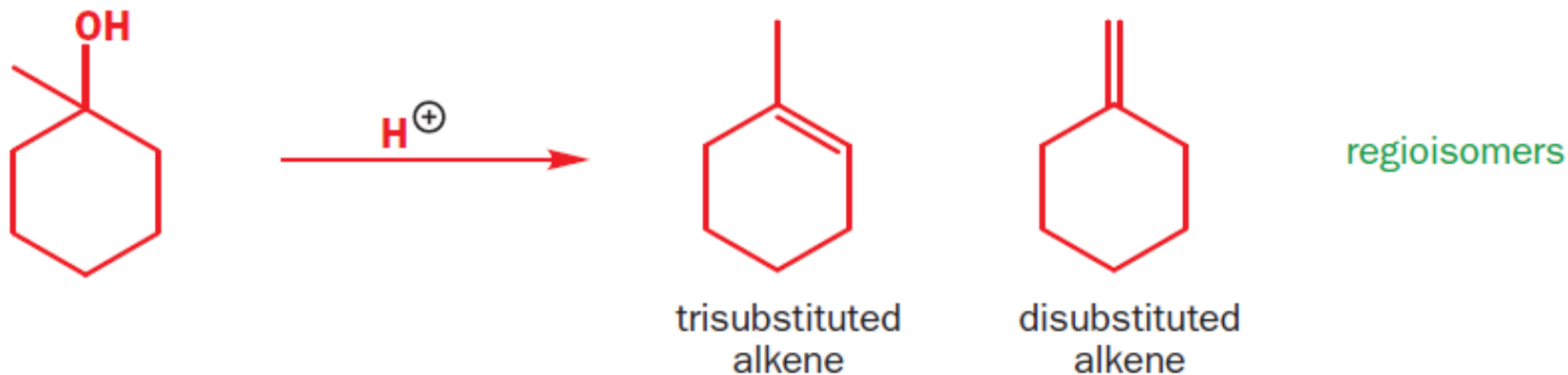substrates that never eliminate by E1

unstable carbocation
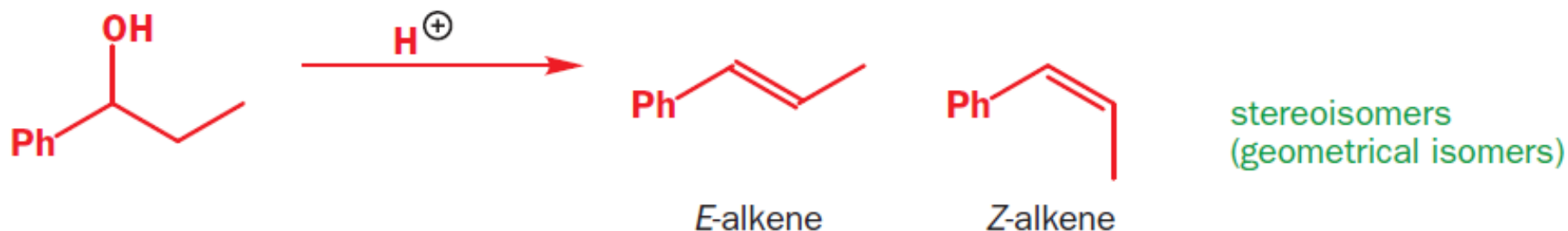
primary

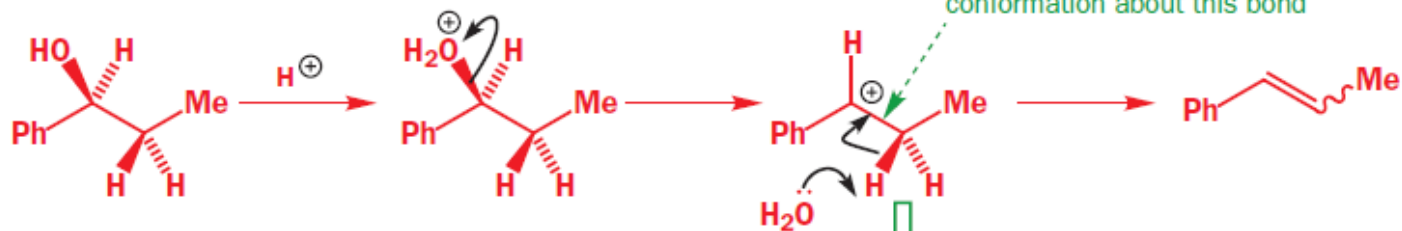may also eliminate by E2

Example of E1

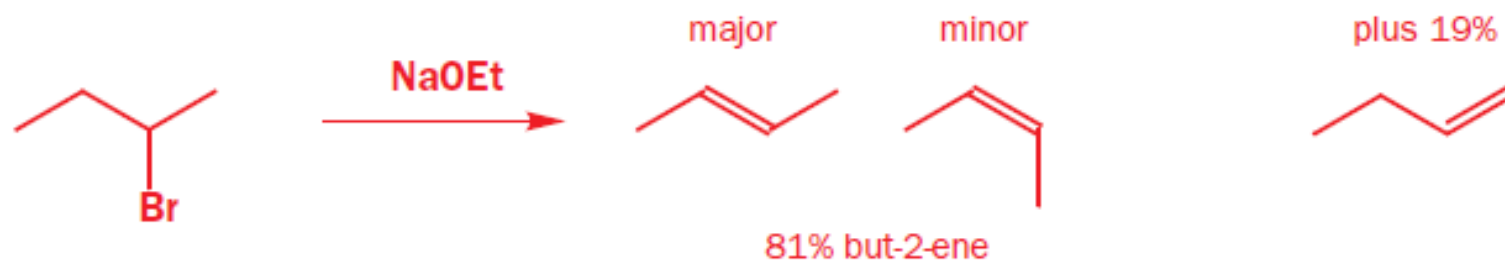# E1 can be stereoselective

two regioisomeric alkenes possible

trisubstituted alkene

disubstituted alkene

regioisomers

two stereoisomeric alkenes possible

E-alkene

Z-alkene

stereoisomers
(geometrical isomers)

stereoselective formation of an *E*-alkene

geometry of product depends on conformation about this bond

conformations of the intermediate cation with C–H and vacant p orbital aligned parallel

lower energy transition state

higher energy transition state

higher energy intermediate: steric hindrance

lower energy intermediate

E-alkene formed faster

Z-alkene formed more slowly

energy

towards *E*-alkene

towards *Z*-alkene

reaction coordinate

E2 eliminations have anti-periplanar transition states

NaOEt

major   minor   plus 19%

81% but-2-ene

H and Br must be anti-periplanar for E2 elimination:
two possible conformations

minor

two methyl groups
syn-coplanar (gauche) -
more hindered

two methyl groups
anti-periplanar – less
hindered

major
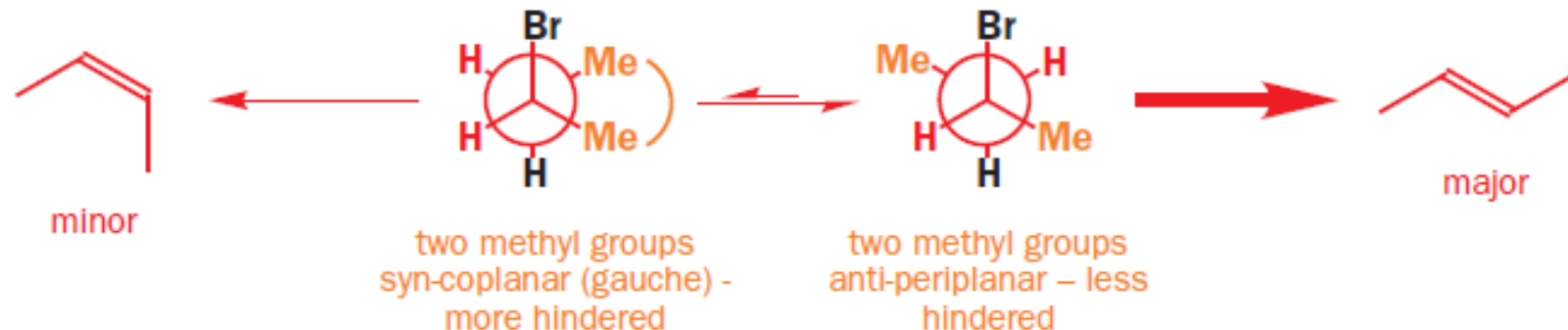
E2 eliminations from cyclohexanes

ring inversion

⊖ OR

equatorial X is anti-periplanar
only to C–C bonds
and cannot be eliminated by an
E2 mechanism

axial X is anti-periplanar to C–H
bonds, so E2 elimination is
possible
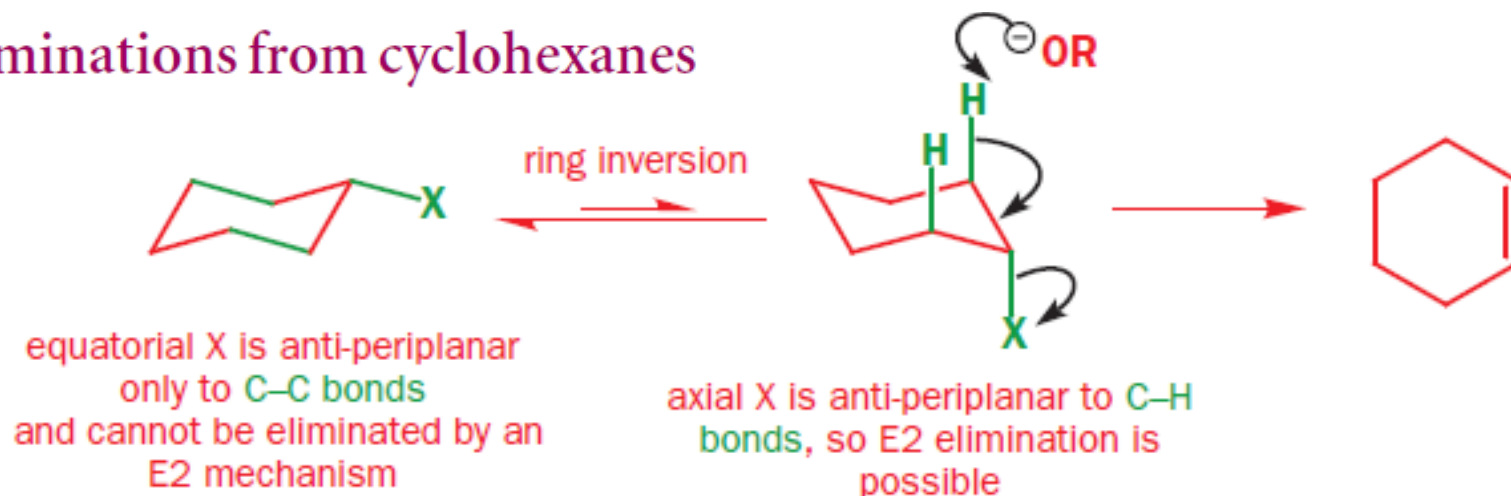
E2 Reaction

this diastereoisomer   eliminates to give this alkene (*E*)

NaOH

redraw

HO⁻

only this proton can
be attacked by HO⁻

H and Br must be
anti-periplanar

this diastereoisomer   eliminates to give this alkene (*Z*)

NaOH

redraw

slower reaction because of
gauche interactions in
reactive conformation

HO⁻

only this proton can
be attacked by HO⁻

H and Br must be
anti-periplanar
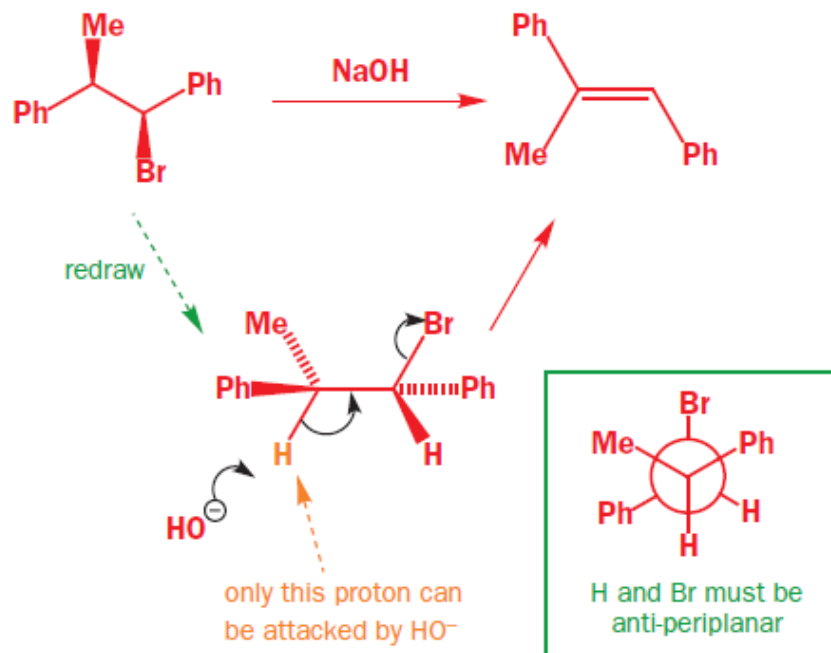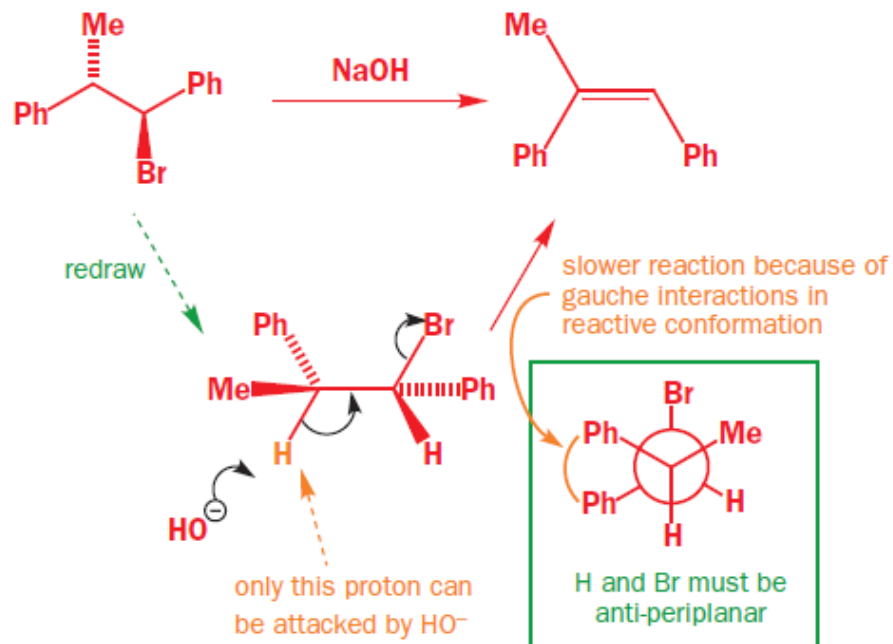
E2 eliminations can be stereospecific

Example of stereoselective and stereospecific reactions

● **Stereoselective or stereospecific?**

- Stereoselective reactions give one predominant product because the reaction pathway has a choice. Either the pathway of lower activation energy is preferred (kinetic control) or the more stable product (thermodynamic control)

- Stereospecific reactions lead to the production of a single isomer as a direct result of the mechanism of the reaction and the stereochemistry of the starting material. There is no choice. The reaction gives a different diastereoisomer of the product from each stereoisomer of the starting material
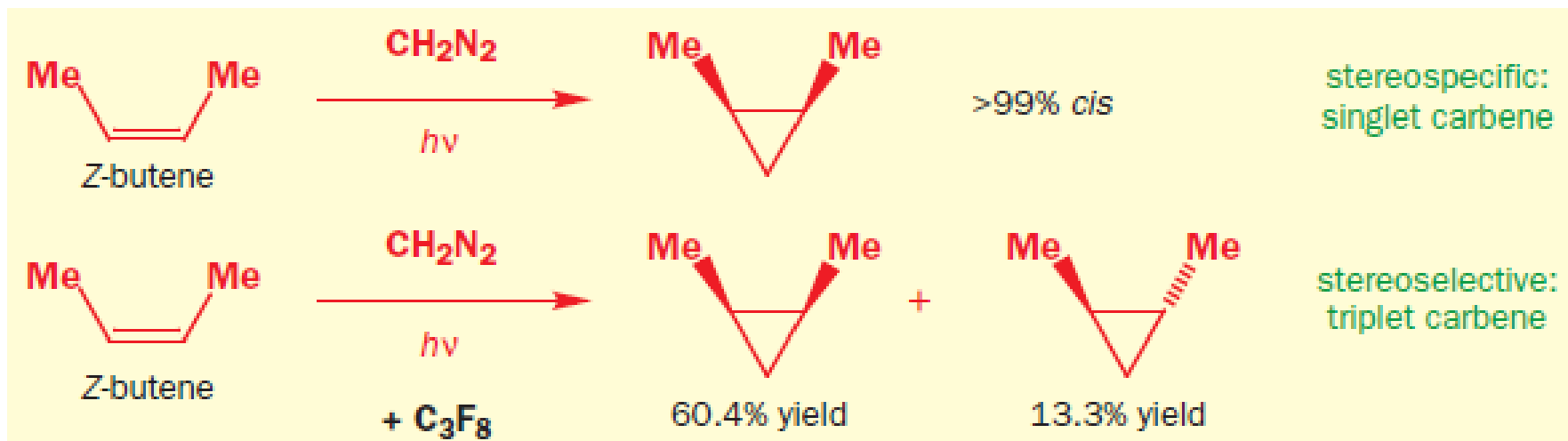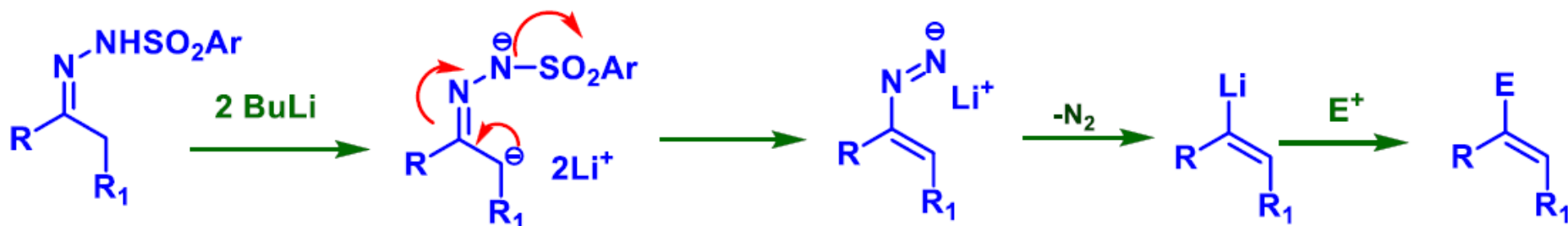
E1CB Reactions

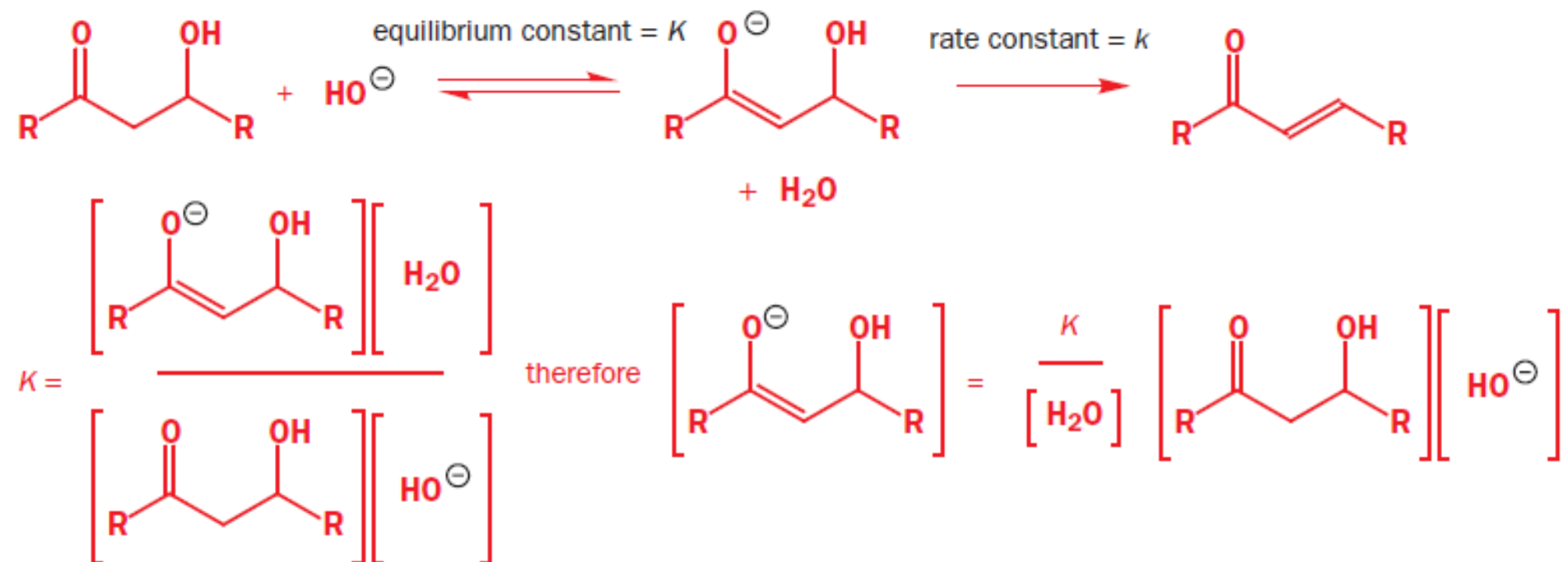## Anion-stabilizing groups allow another mechanism—E1cB

the E1cB mechanism

fast, reversible deprotonation

stabilized anionic intermediate

rate-determining step

MsCl, Et₃N

Et₃N:

Shapiro reaction

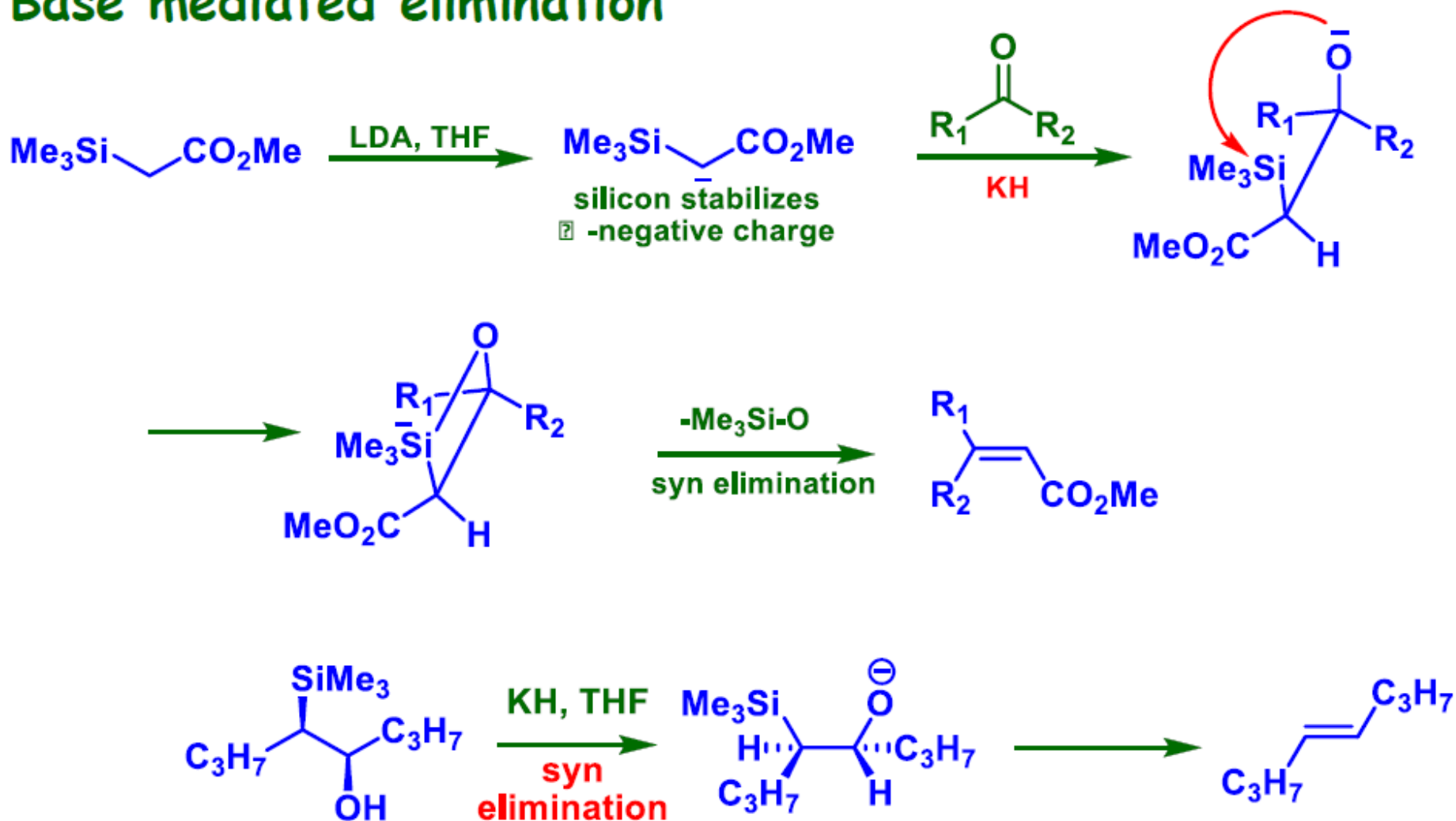
2 BuLi

-N₂

E⁺
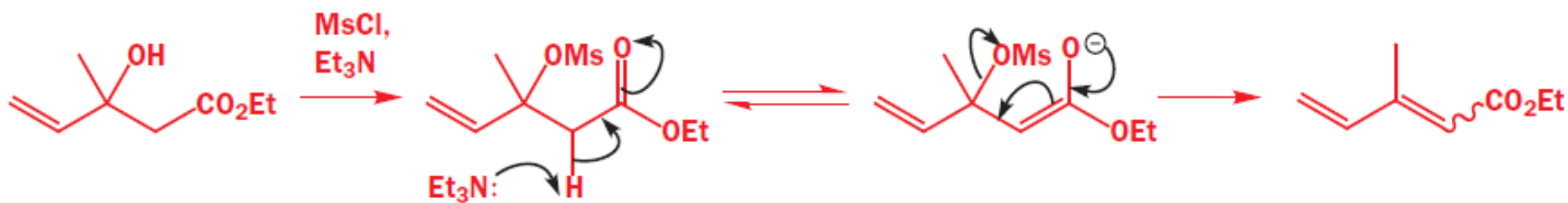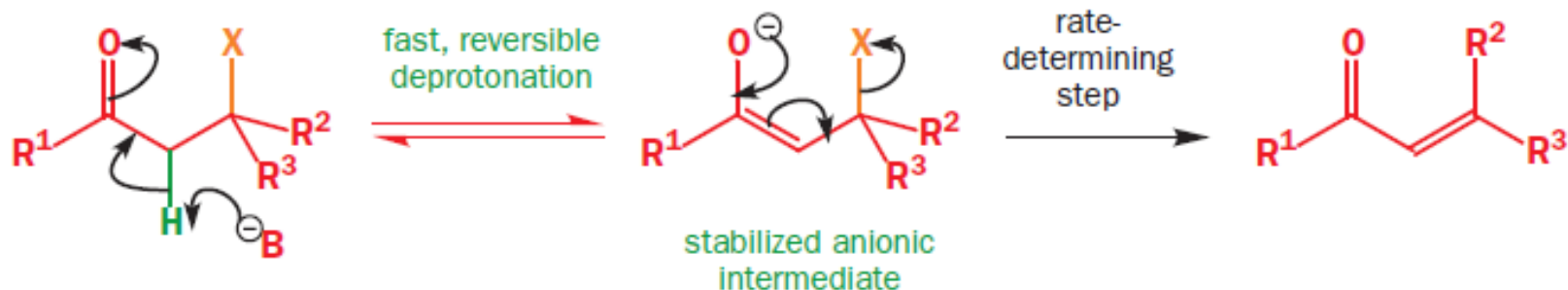
E1CB Reactions: rate equation

The rate is proportional to the concentration of the anion, and we now have an expression for that concentration. We can simplify it further because the concentration of water is constant.
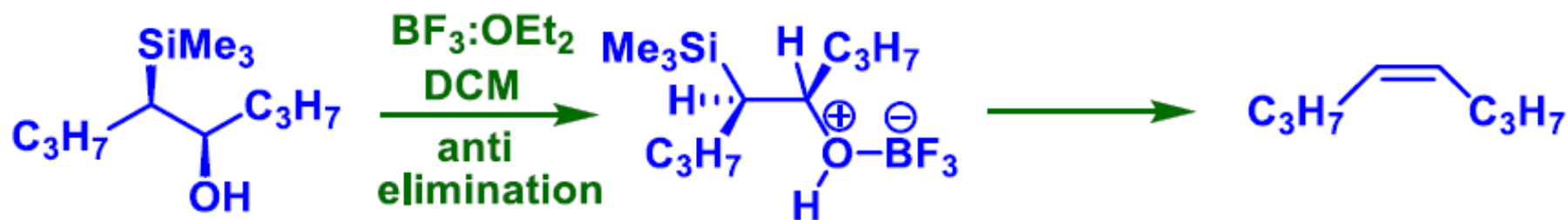
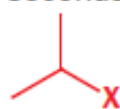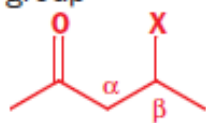# Peterson Olefination: Base mediated
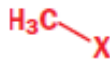
Base mediated elimination

Peterson Olefination: Acid mediated

Summarize: Substitution and Elimination Reactions

	Poor nucleophile (e.g. H_2O, ROH)[a]	Weakly basic nucleophile (e.g. I^-, RS^-)	Strongly basic, unhindered nucleophile (e.g. RO^-)	Strongly basic, hindered nucleophile (e.g. DBU, DBN, t-BuO$^-$)
methyl H_3C—X	no reaction	S_N2	S_N2	S_N2
primary (unhindered)	no reaction	S_N2	S_N2	E2
primary (hindered)	no reaction	S_N2	E2	E2
secondary	S_N1, E1 (slow)	S_N2	E2	E2
tertiary	E1 or S_N1	S_N1, E1	E2	E2
β to anion-stabilizing group	E1cB	E1cB	E1cB	E1cB

[a] Acid conditions.