Substituição

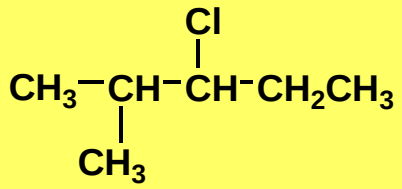
Haletos de alquila

Nomenclatura

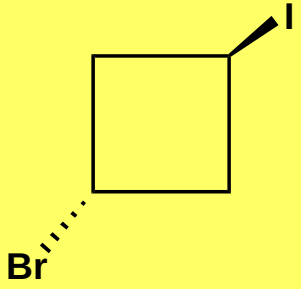
IUPAC - adicione fluoro-
cloro-
bromo-
iodo-

} ao nome do alcano

exemplos:

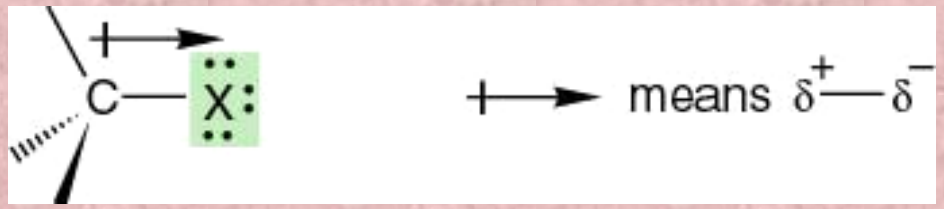


3-metil-3-cloro-hexano



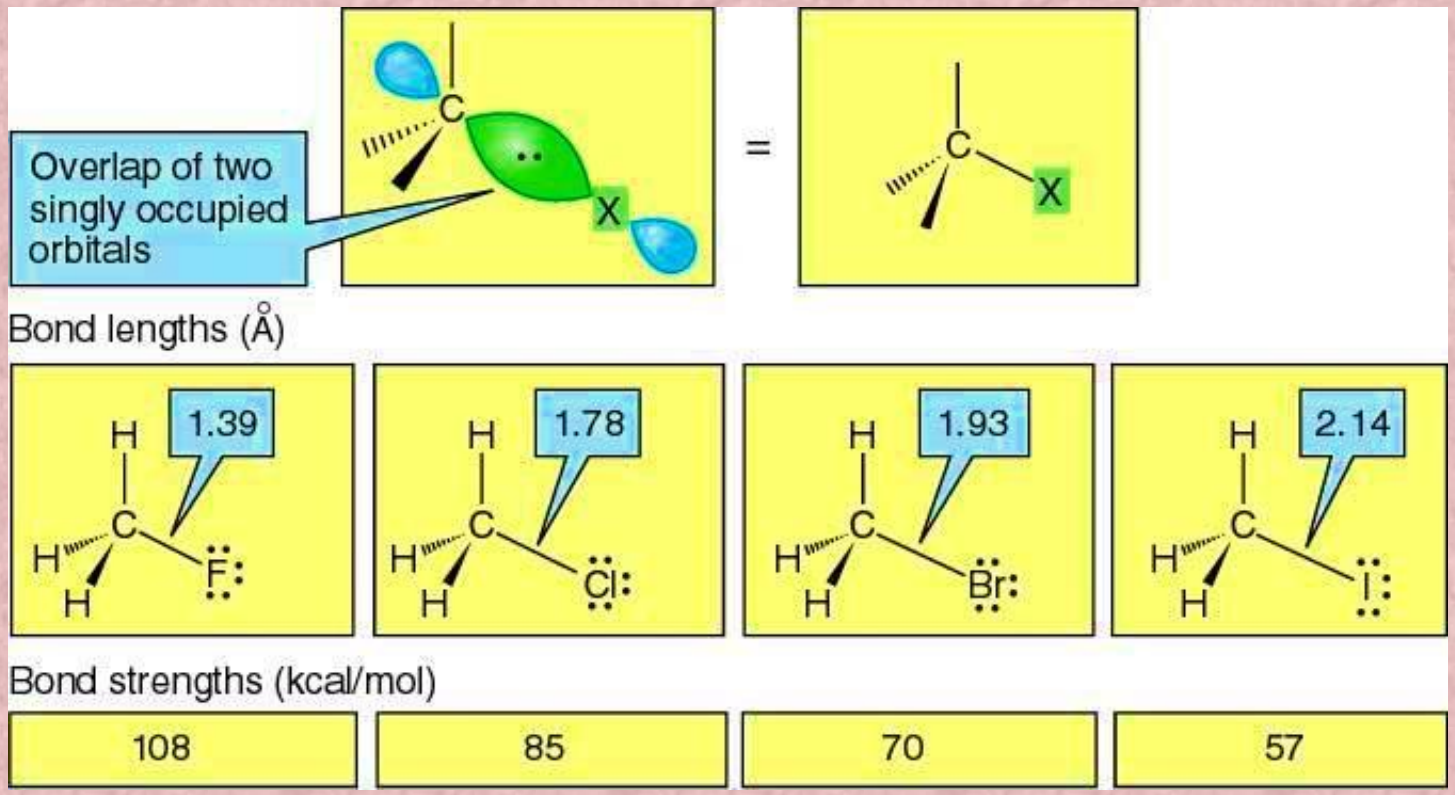
Trans-1-bromo-3-iodociclobutano

C. structure/properties



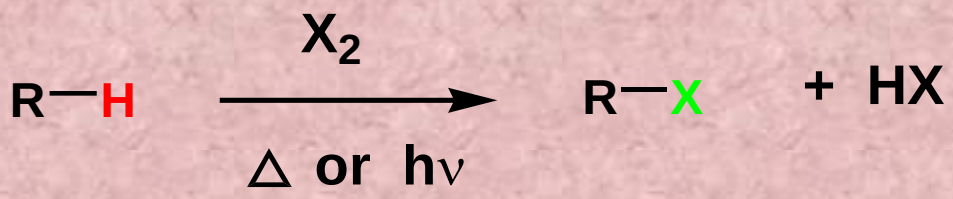
X = F
= Cl
= Br
= I

increasing electronegativity



Preparation - we will see many other ways in the future!

1. Free radical halogenation-



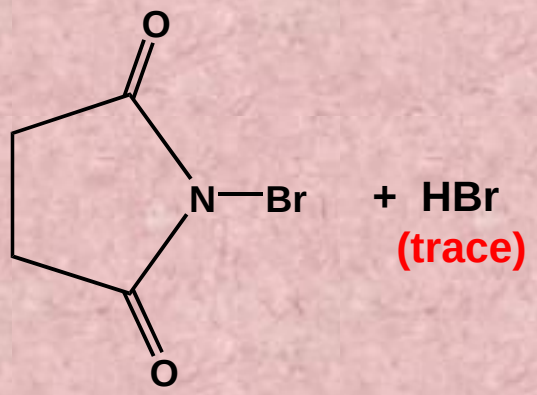
BUT

- poor selectivity 1° versus 2° versus 3°
- little control often di, tri, etc. proctucts formed

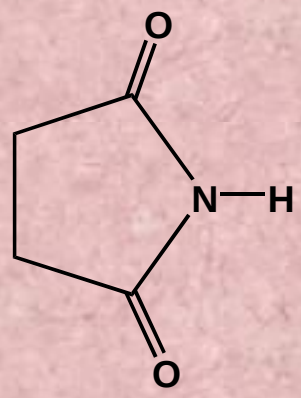
BUT

2. allylic bromination - a special case

- We need only a small amount of Br_2 so



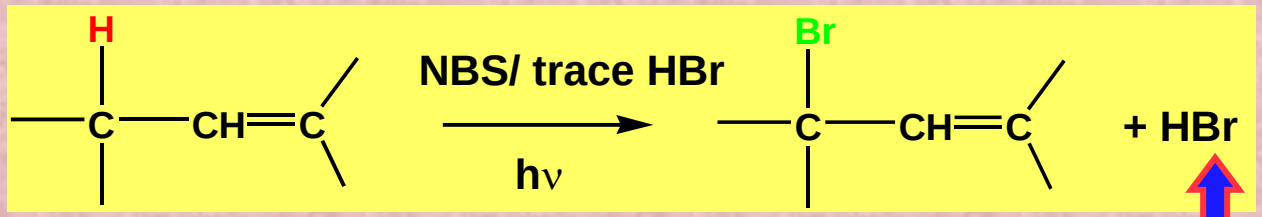
+ HBr (trace)



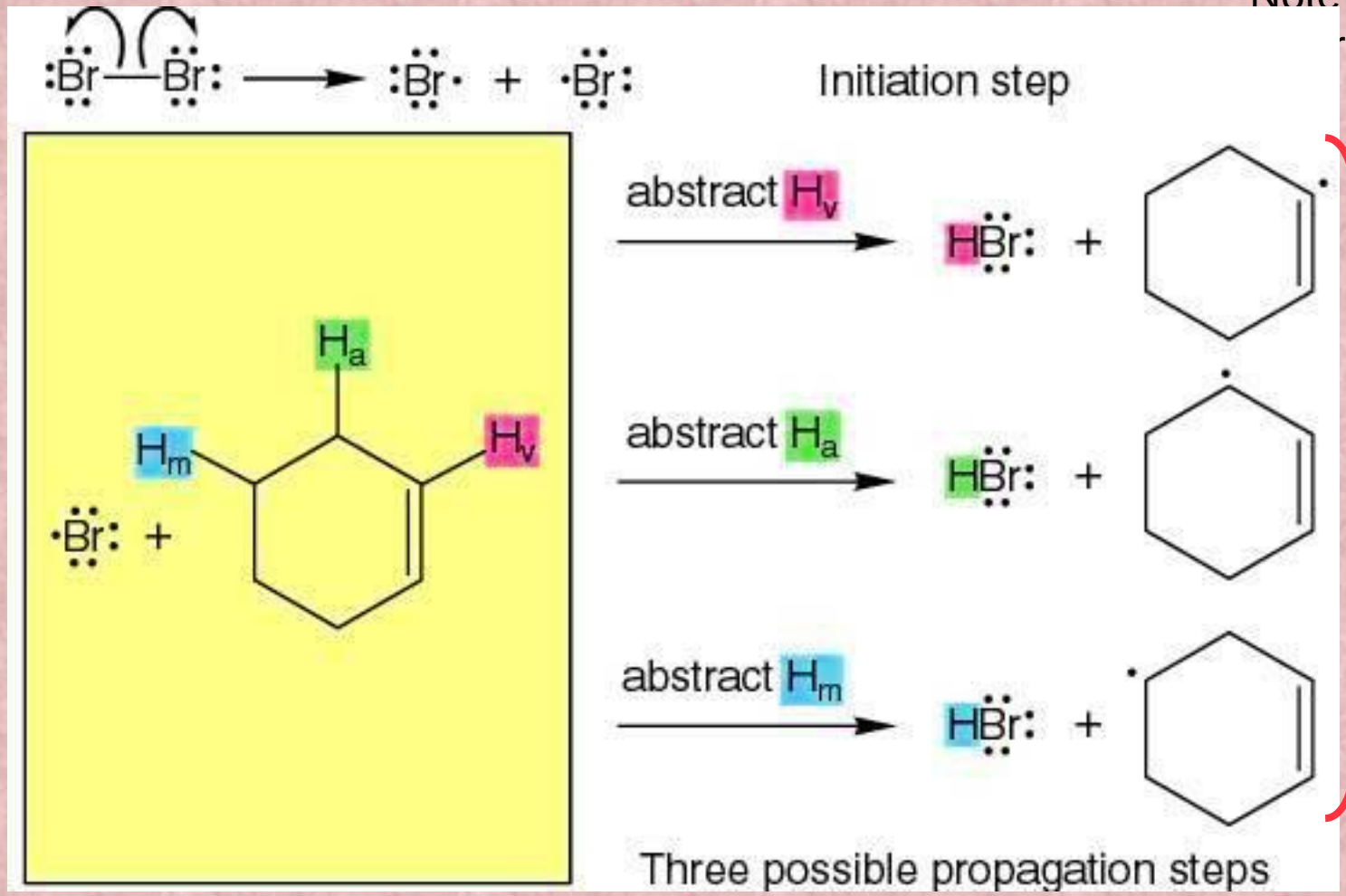
+ Br_2 (small amts)

N- bromosuccinimide (NBS)

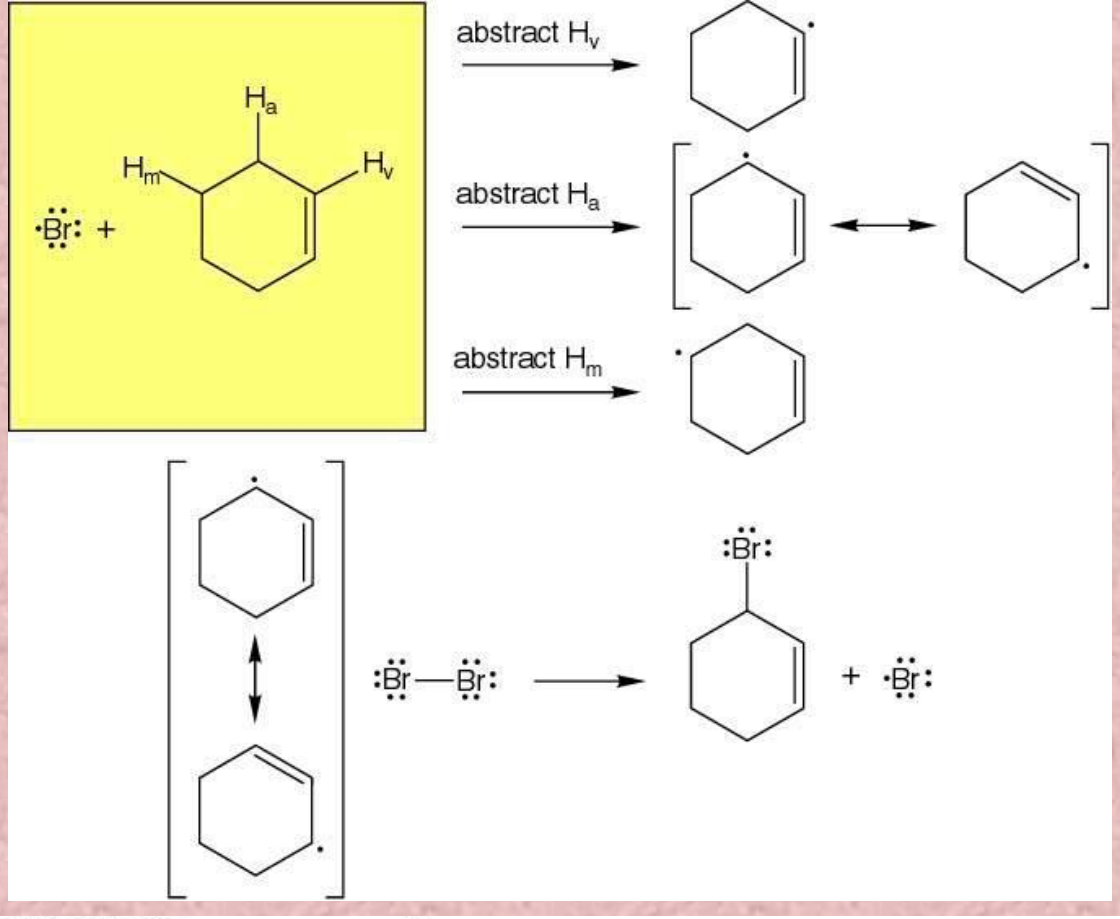
a. overall reaction



Note that the product
reactant



First
Propagation
Step

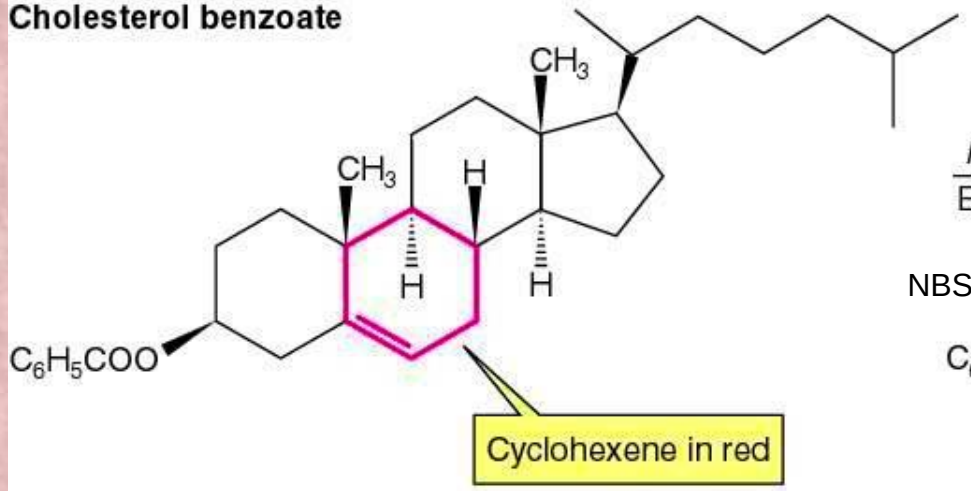


First propagation step

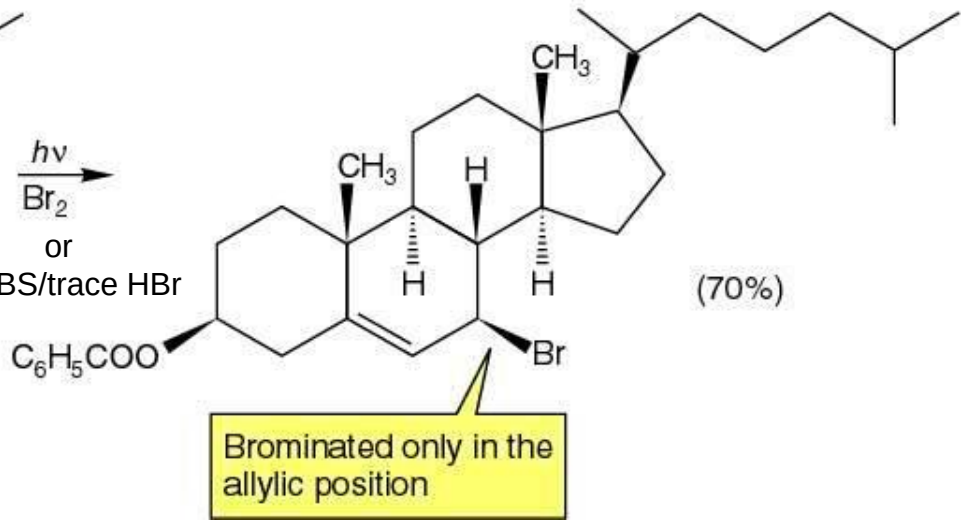
Second propagation step

EXAMPLE

Cholesterol benzoate



$h\nu$
Br_2
or
NBS/trace HBr

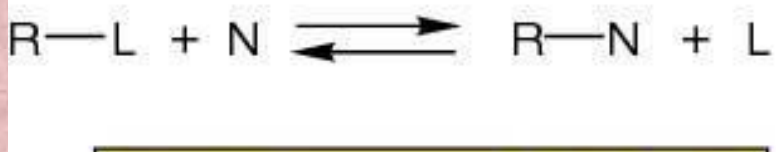


(70%)

Reactions of alkyl halides - **substitution**

1. general reaction

The general case



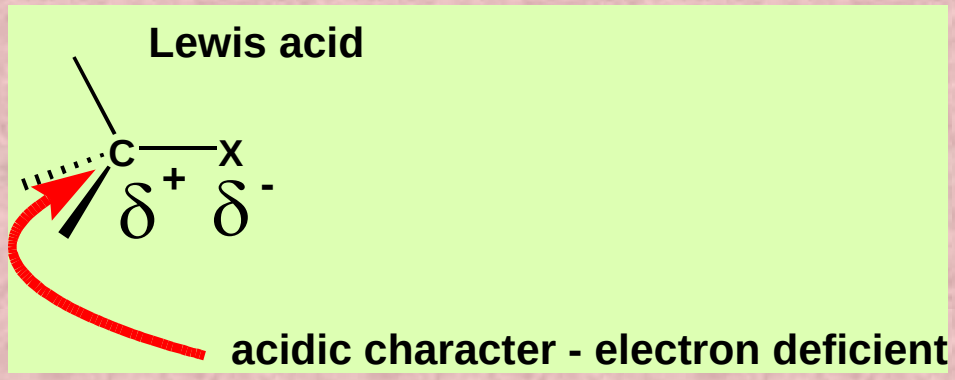
R =

H_3C Methyl group	$(CH_3)_2CH$ Isopropyl group
CH_3CH_2 Ethyl group	$(CH_3)_3C$ *tert*-Butyl group

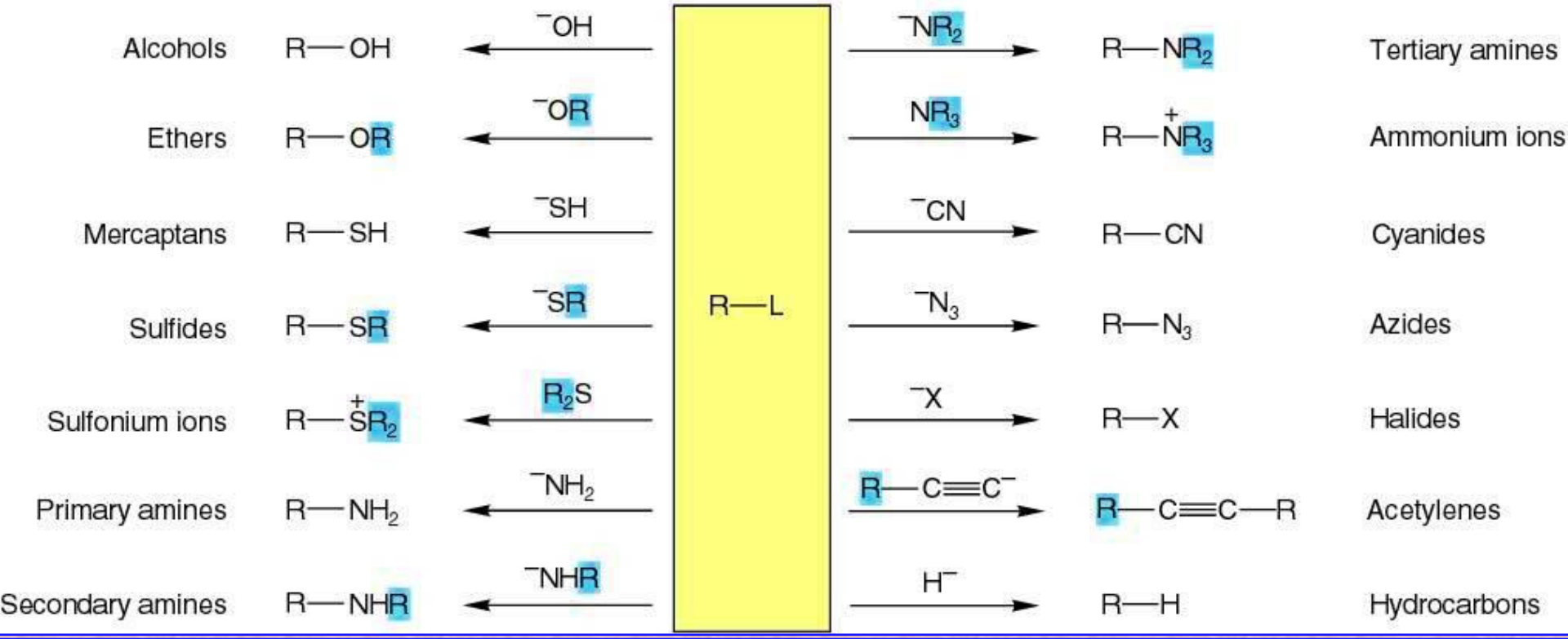
N = nucleophile - electron rich - Lewis base

R-L = electrophile - electron poor - Lewis acid

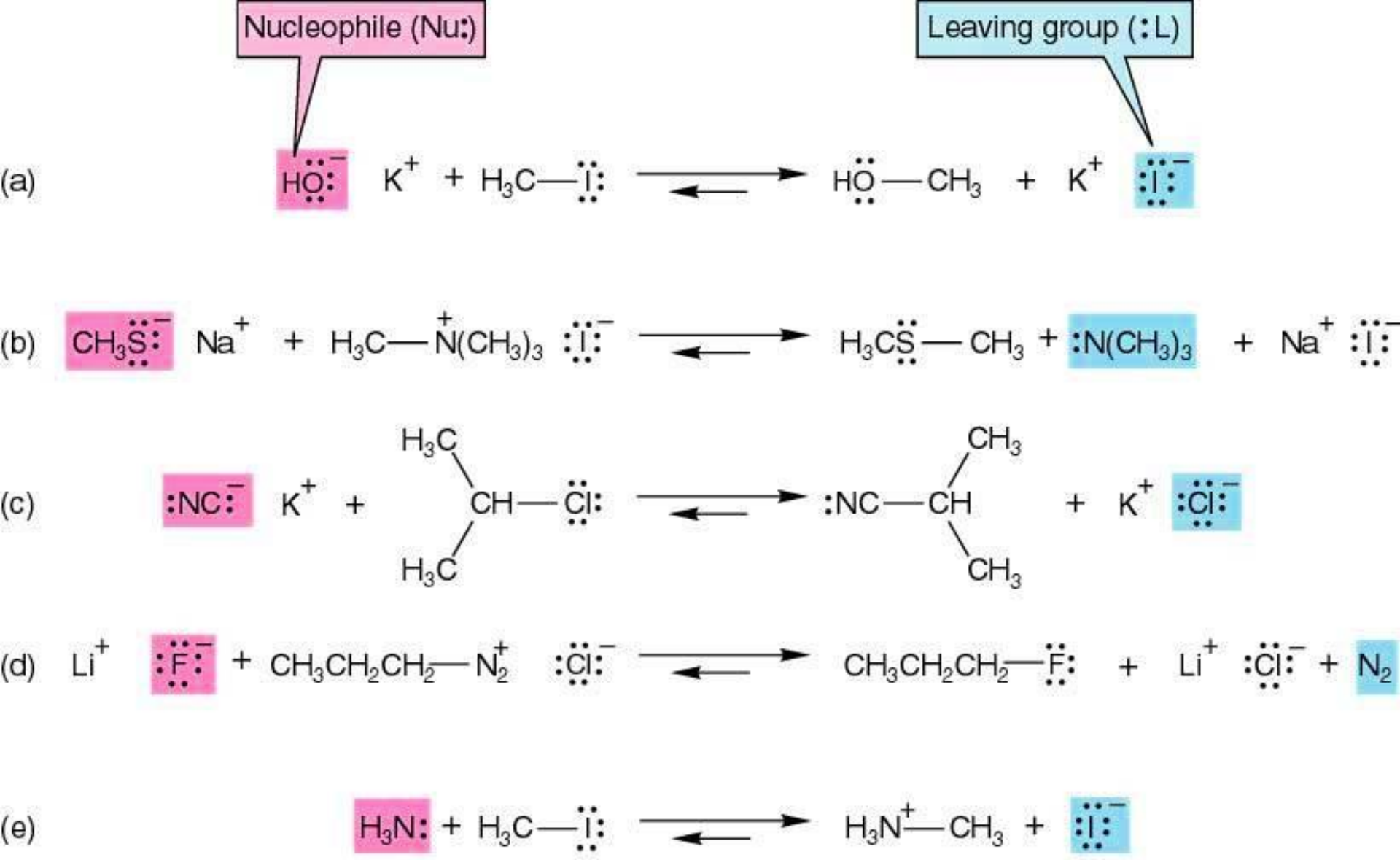
L = leaving group - must form a stable species (weak base e.g. X^-)

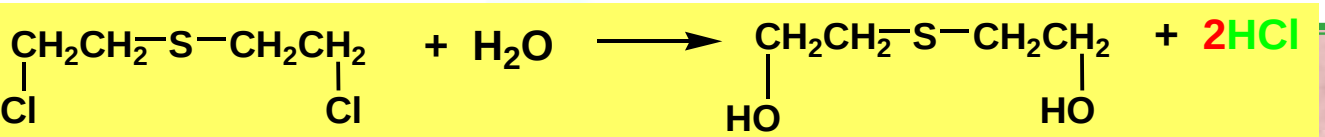


general examples:



(L is not always X^- in these examples)





mustard gas
WW1

specific examples

Reaction mechanism - there are two: First we will look at

S_N2 - substitution nucleophilc bimolecular

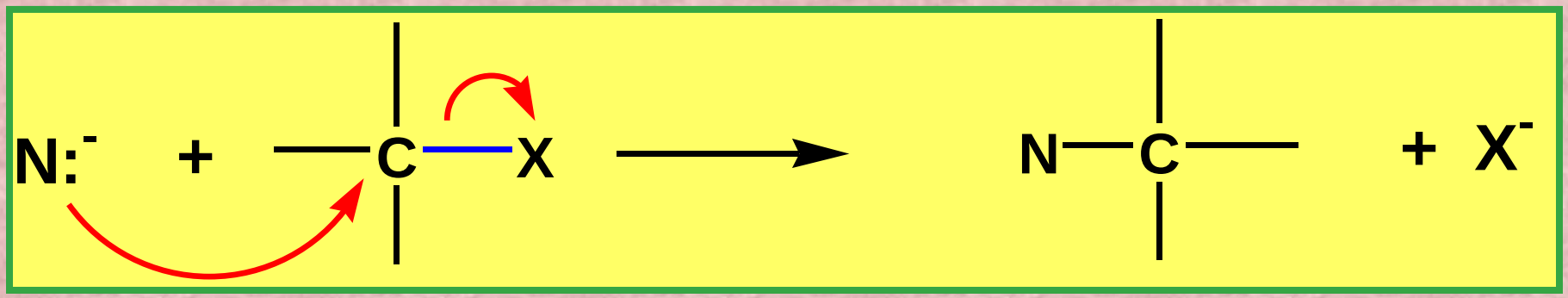
1. Rate law:

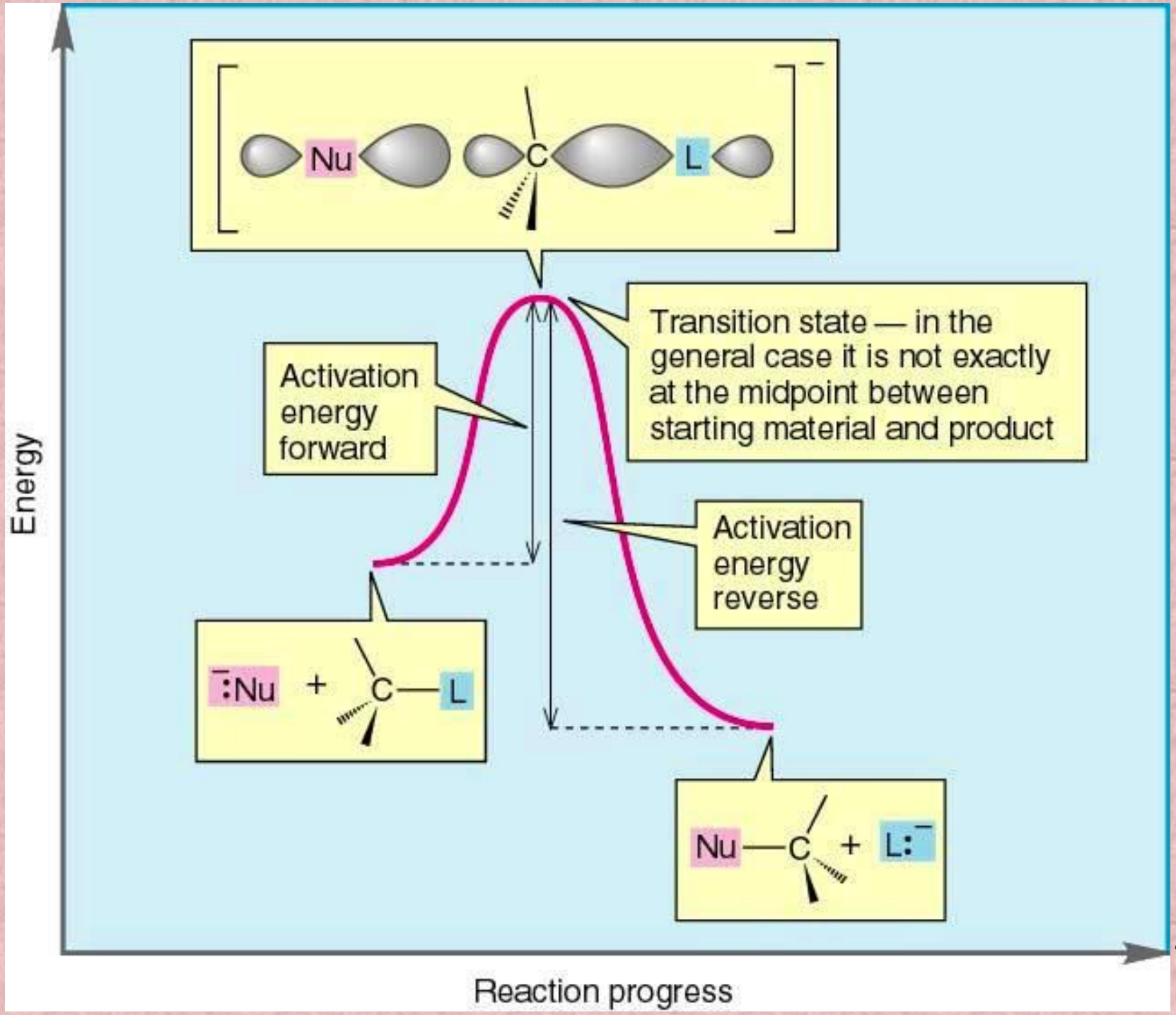
rate = k[R-L][N] ie dependent on both

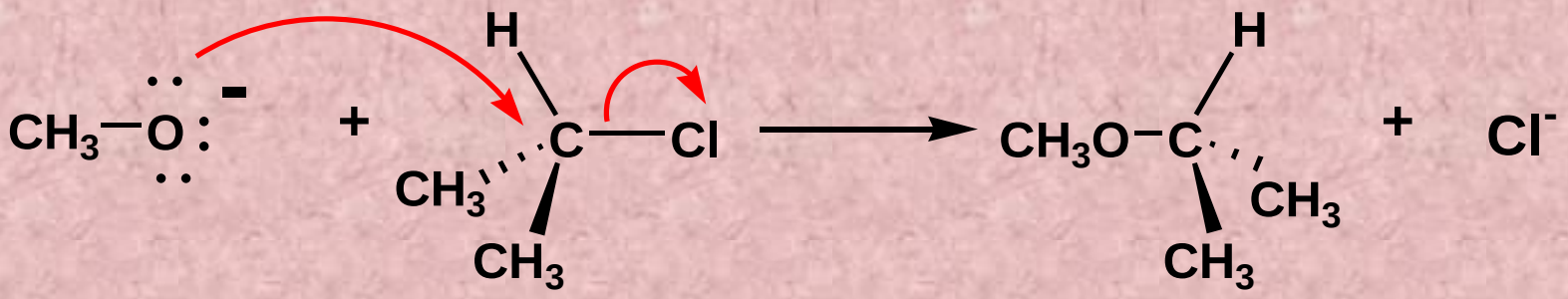
Dado empírico

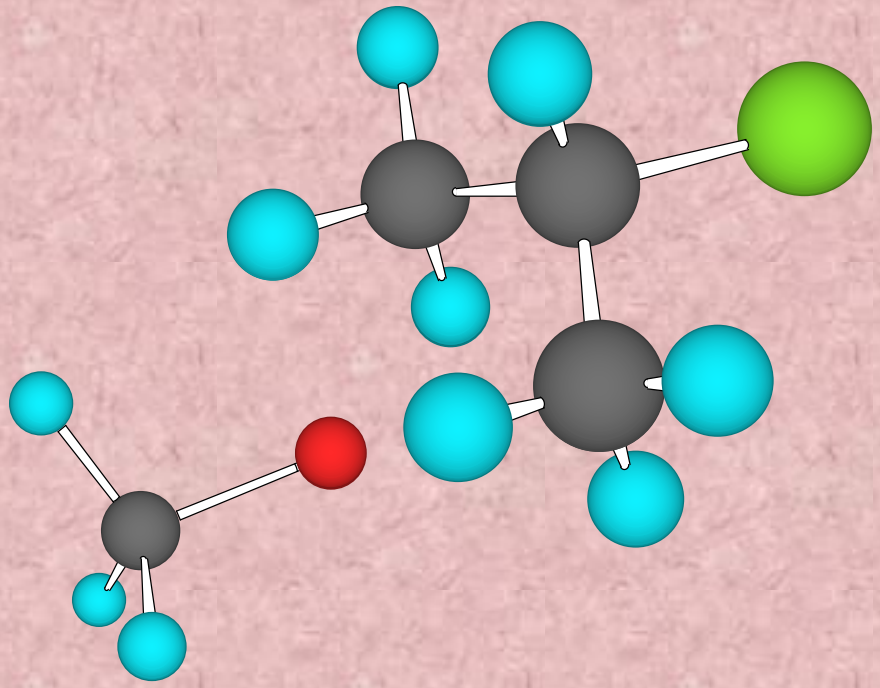
concen. of nucleophile and electrophile

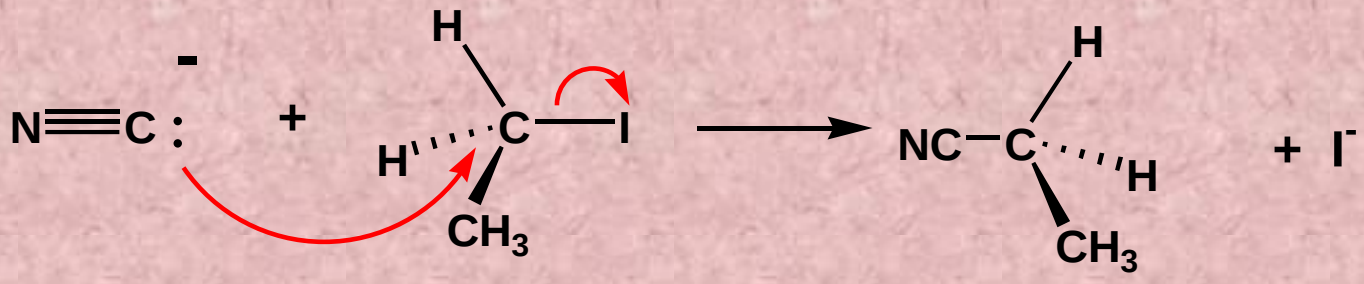
2. Mechanism - one step:



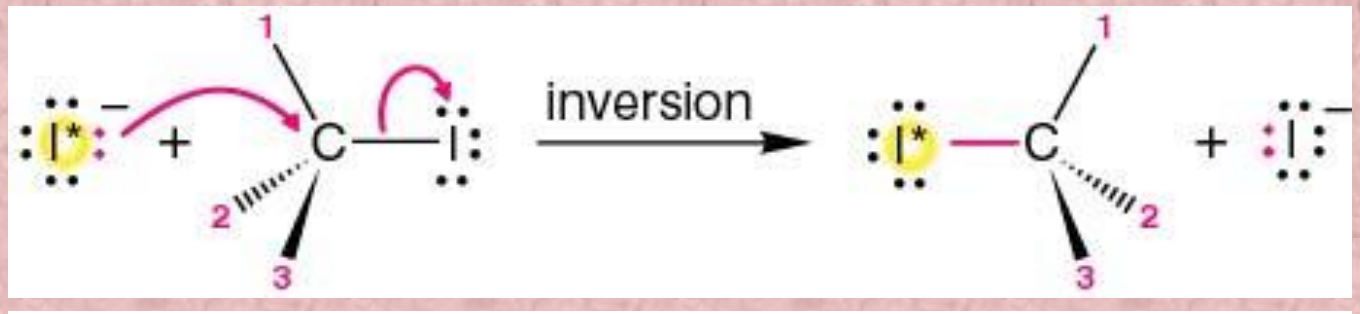

Nu
C
L
−
Transition state — in the general case it is not exactly at the midpoint between starting material and product
Activation energy forward
Activation energy reverse
:Nu
+
C
L
Nu
C
+
L:
−
Energy
Reaction progress

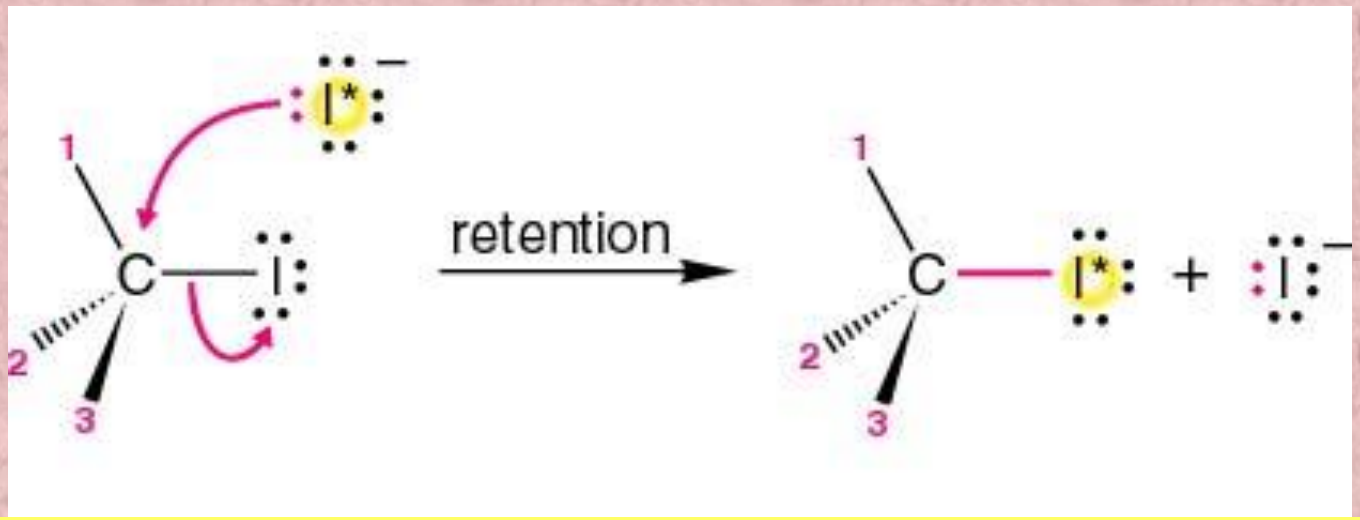

CH3—O:
-
+
H
C
Cl
CH3
CH3
CH3O—C
CH3
CH3
+
Cl-



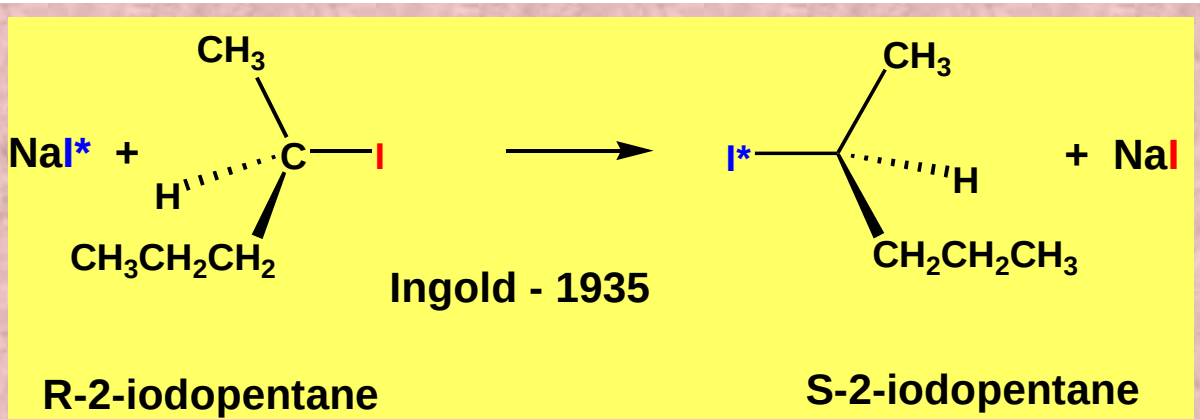

N≡C:
-
+
H
C
I
H
CH3
NC—C
H
H
CH3
+ I-

Stereochemistry in S_N2 mechanism:





Experimentally - **always get inversion - backside attack**



R-2-iodopentane **S-2-iodopentane**

Effect of nucleophile

The stronger the base - in general - the stronger the nucleophile.

Examples:

H_2O: versus $HO^{:-}$

CH_3OH: versus $CH_3O^{:-}$

H_3N: versus $NH_2^{:-}$

Basicity factors

a. electronegativity of atom that contains the lone pair

b. inductive effects of substituents on lone pair

c. resonance effects - delocalization of lone pair

There is one major exception to this factors:

The size of the orbital and polarizability

Nucleophilicity increases going from bottom to top row in Periodic Table.

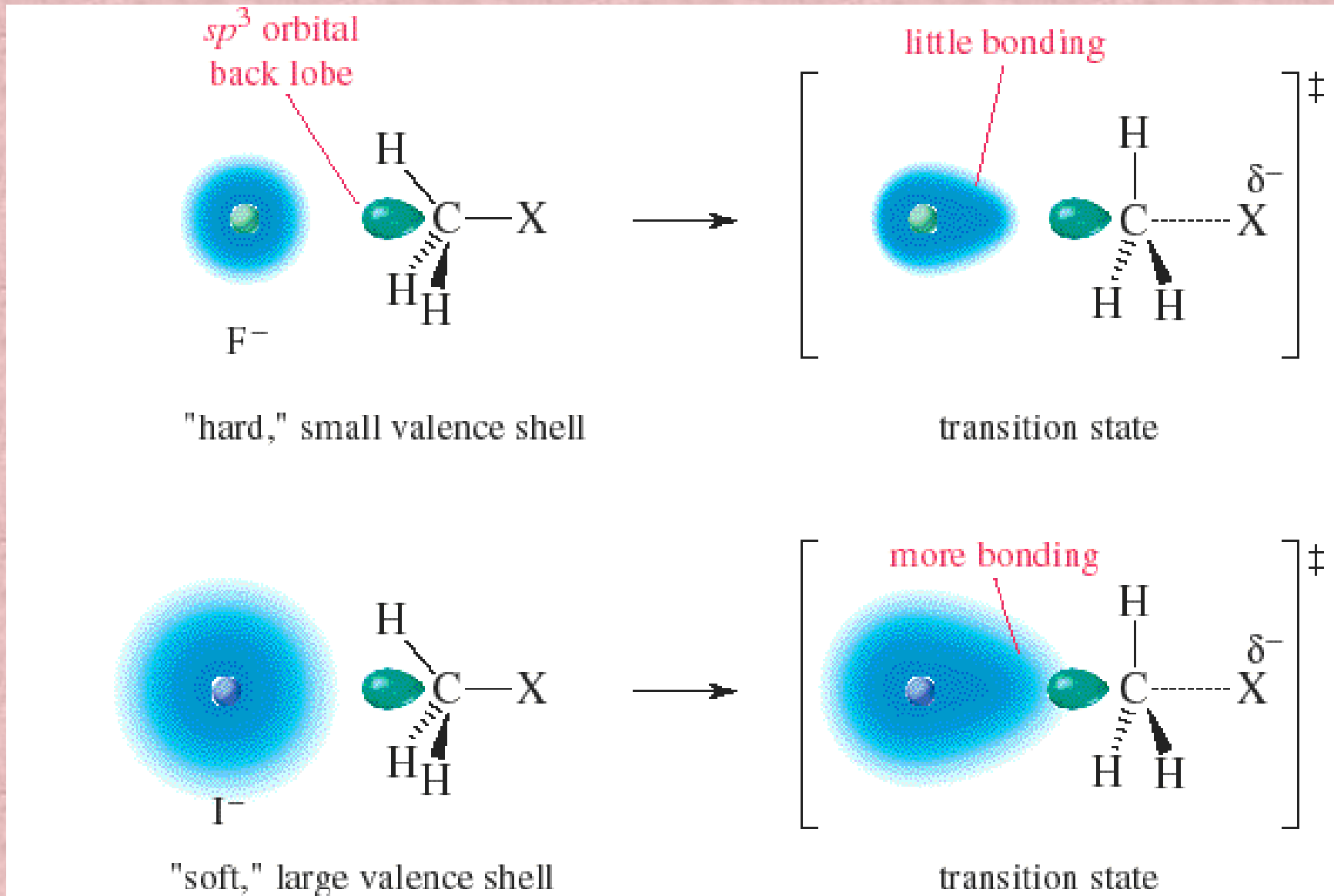
The size of the orbital and polarizability

Nucleophilicity increases going from bottom to top row in Periodic Table.

$(CH_3CH_2)_2S > (CH_3CH_2)_2O$

$(CH_3)_3P > (CH_3)_3N$

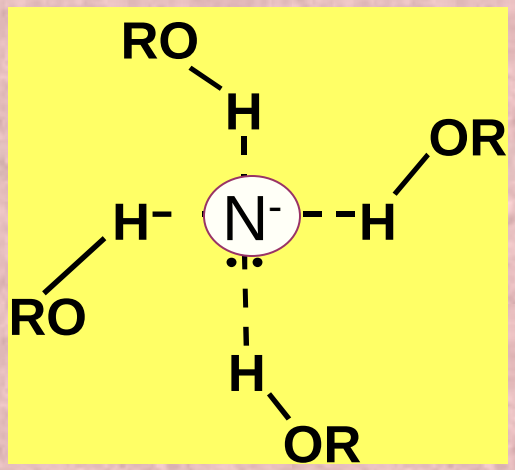
$I^- > Br^- > Cl^- > F^-$



solvent effects on nucleophilicity

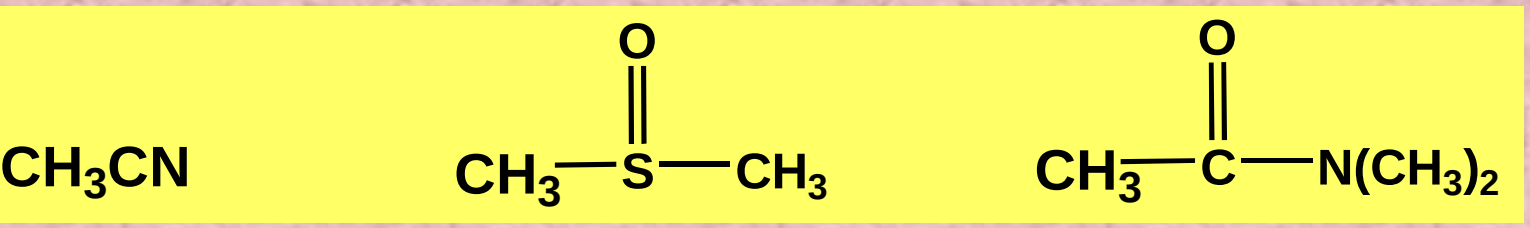
In general, nucleophiles are polar or ionic molecules so we need a **polar solvent** to solvate them.

a. protic solvents, ie H_2O, ROH, etc.



Hydrogen bonding decreases nucleophilicity - particularily for small nucleophiles

b. polar, **aprotic solvents** - very high bp.



Acetonitrile DMSO DMF

Leaving group effects:

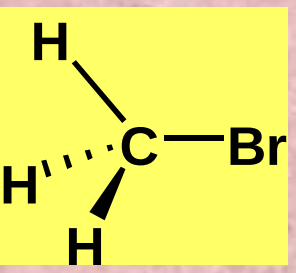
The R-L bond should be as weak as possible,
therefore,L should be as stable as possible.
In other words, L should have:
a. an electron withdrawing group o atom
connected to L
b. a polarizable atom connected to
c. as weakly basic as possible

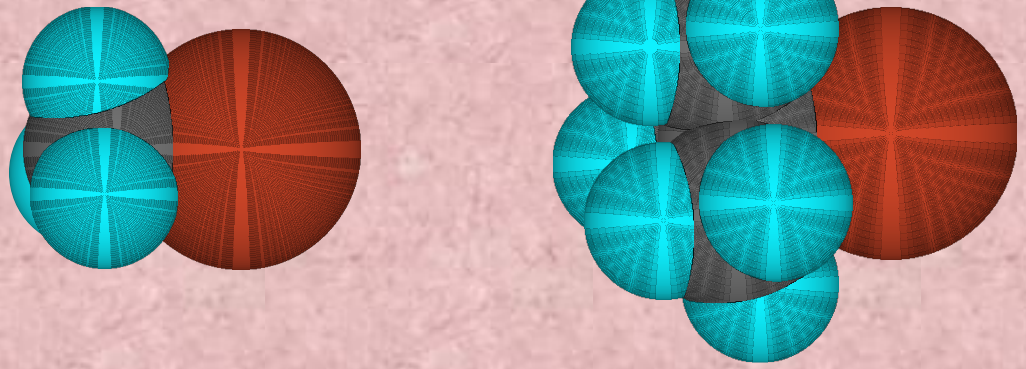
Acid	pK_a	Leaving Group	Name
		Good Leaving Groups	
HI	−10	^{-}I	Iodide
HBr	− 9	^{-}Br	Bromide
HCl	− 7	^{-}Cl	Chloride
$HOSO_2R$	− 6.5	$^{-}OSO_2R$	Sulfonate
H_3O^+	− 1.7	OH_2	Water
		Bad Leaving Groups	
HF	+ 3.2	^{-}F	Fluoride
H_2S	+ 7.0	^{-}SH	Thiolate
HCN	+ 9.2	^{-}CN	Cyanide
H_2O	+15.7	^{-}OH	Hydroxide
HOR	+16–18	^{-}OR	Alkoxide

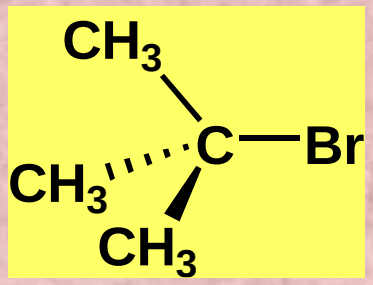
Effects in R - the alkyl group - primarily steric:

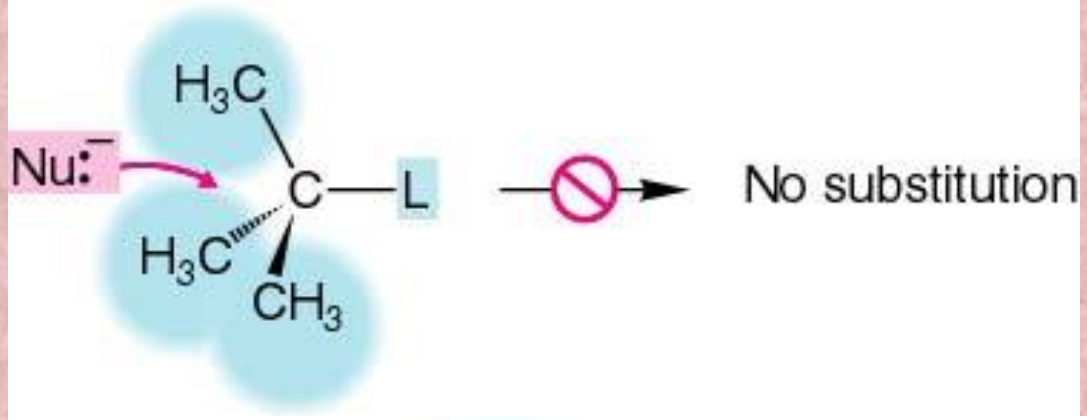
R	Relative rates
CH_3-	1.0
CH_3CH_2-	0.033
$CH_3CH_2CH_2$-	0.013
$(CH_3)_2CH$-	8.3×10^{-4}
$(CH_3)_3CCH_2$-	2×10^{-7}
$(CH_3)_3C$-	$<<10^{-7}$

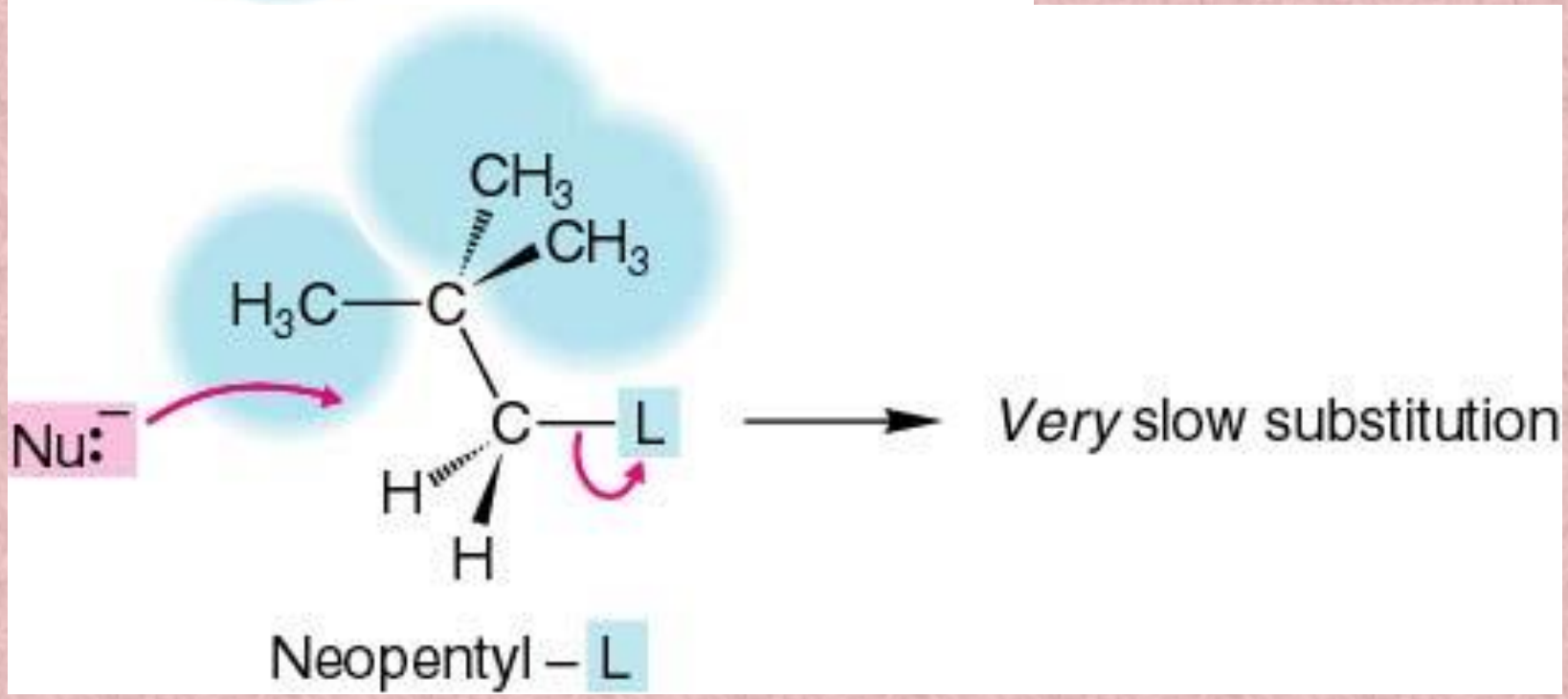
Space-filling model











So for any R-L compound, the relative rates of S_N2:

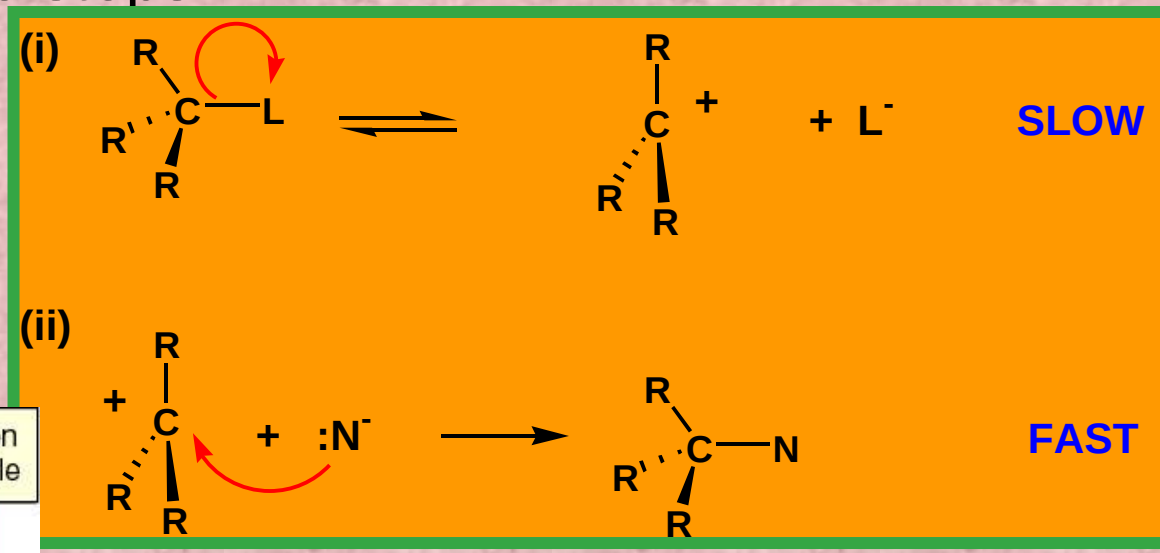
CH_3- > 1° > 2° > 3°

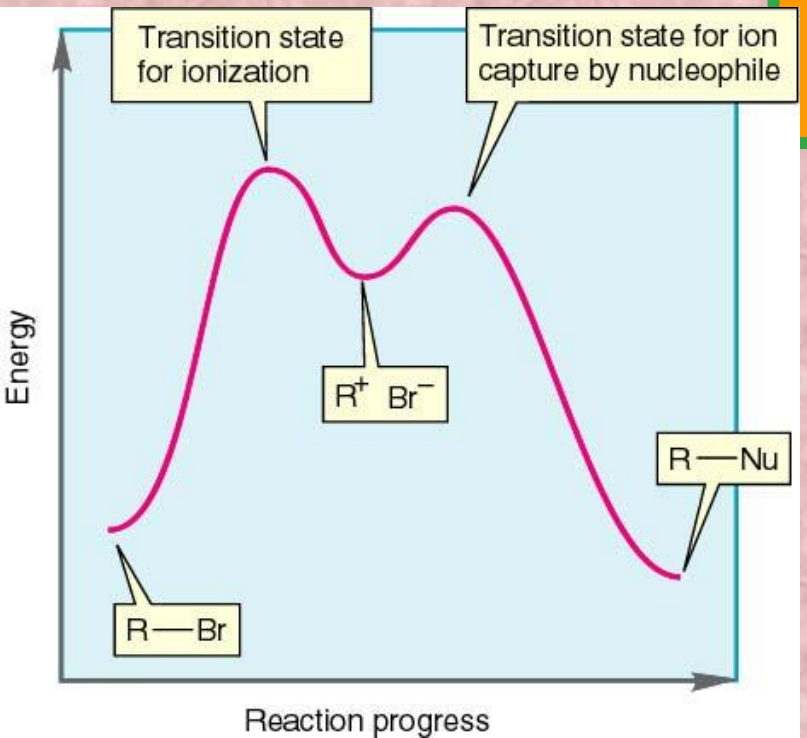
S_N1 - substitution nucleophilic unimolecular

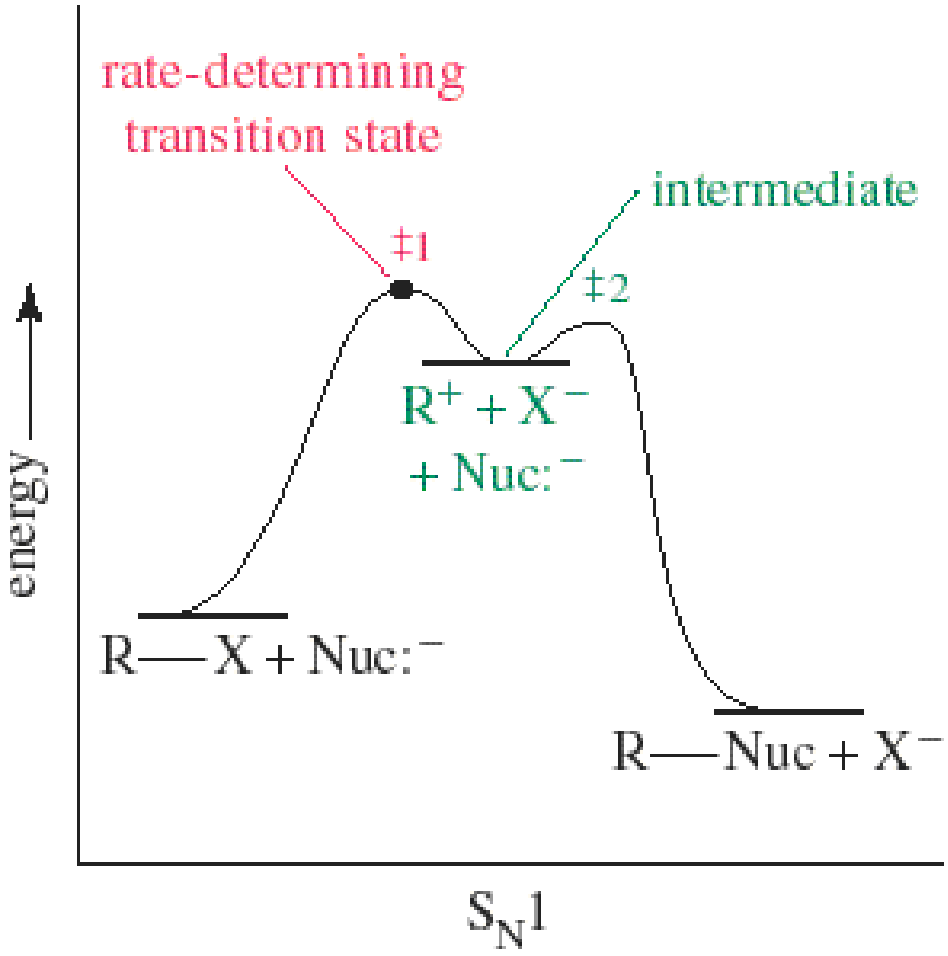
1. rate law:

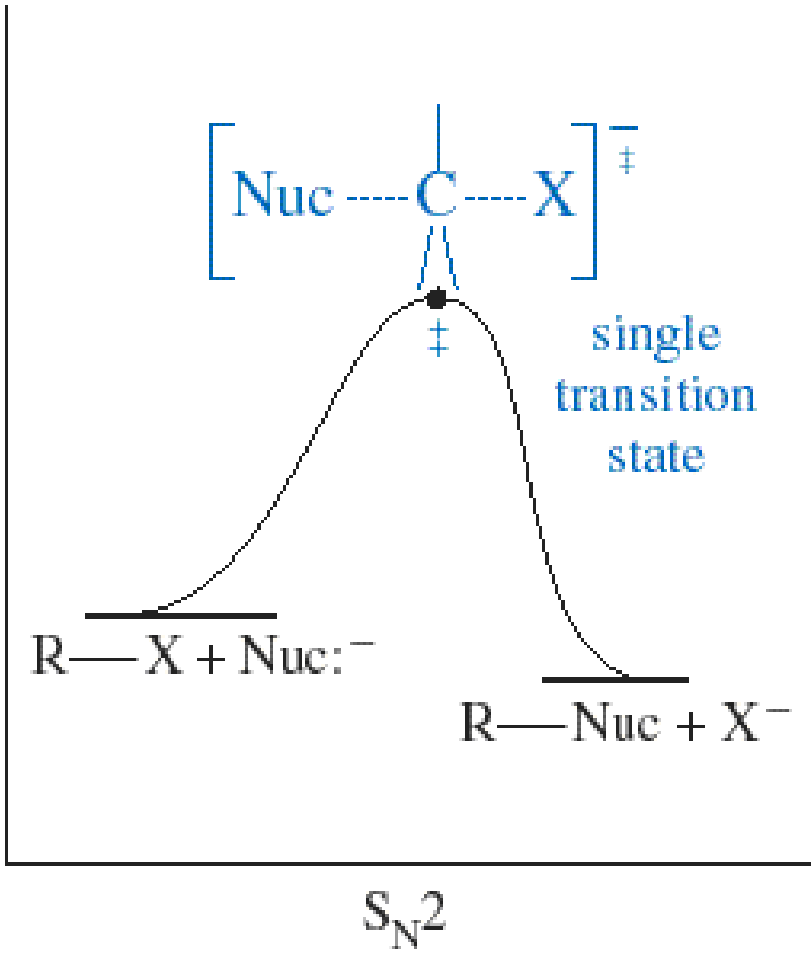
rate = k[R-L] not dependent upon the conc. of N:!

2. mechanism - two steps:

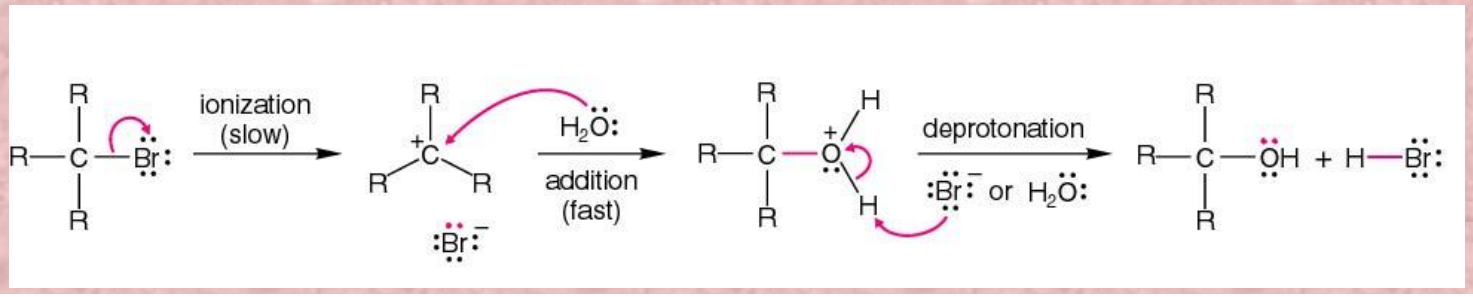


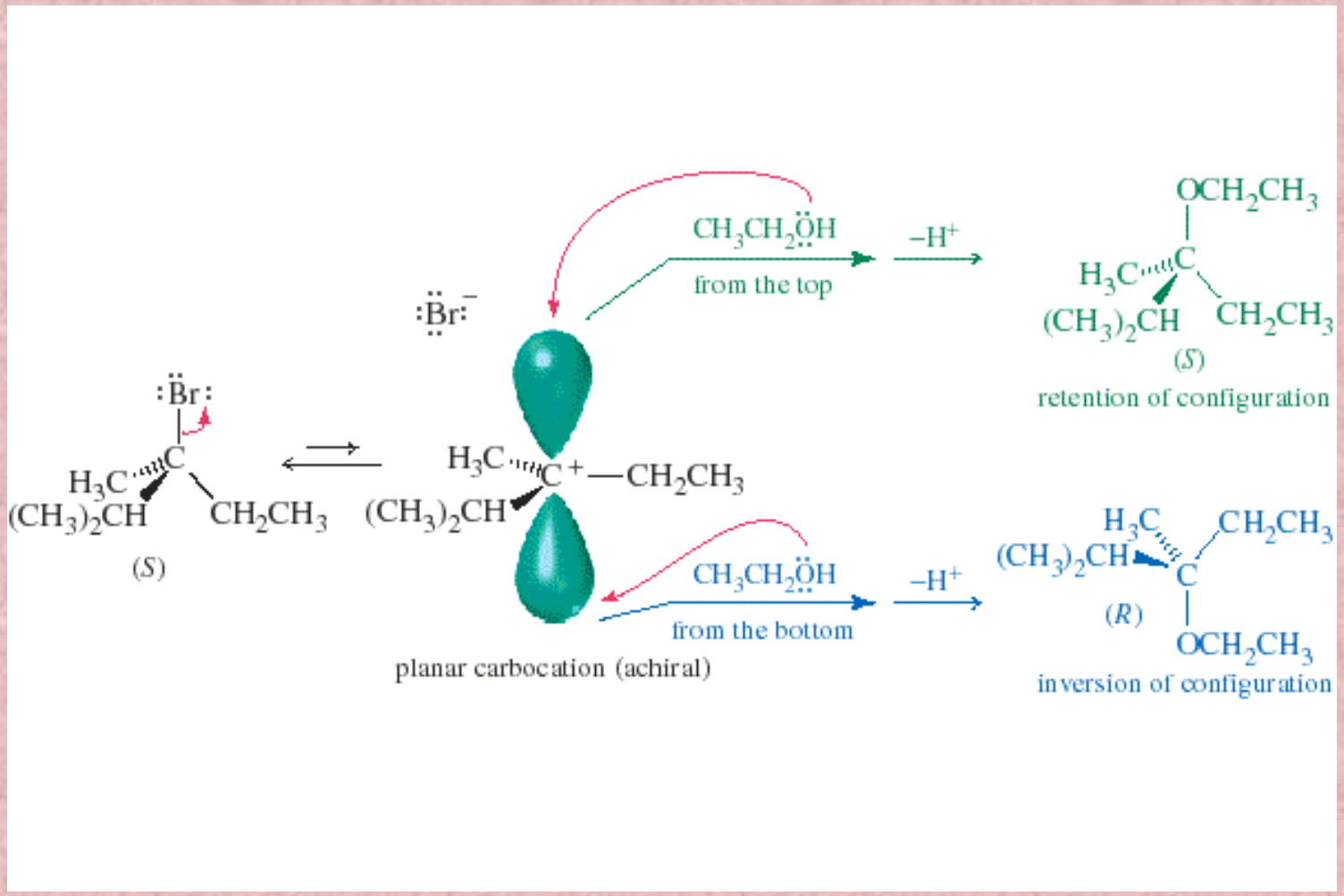



rate-determining
transition state
intermediate
‡1
‡2
energy
R⁺ + X⁻
+ Nuc:⁻
R—X + Nuc:⁻
R—Nuc + X⁻
SN1


Nuc ----- C ----- X
‡
single
transition
state
R—X + Nuc:⁻
R—Nuc + X⁻
SN2

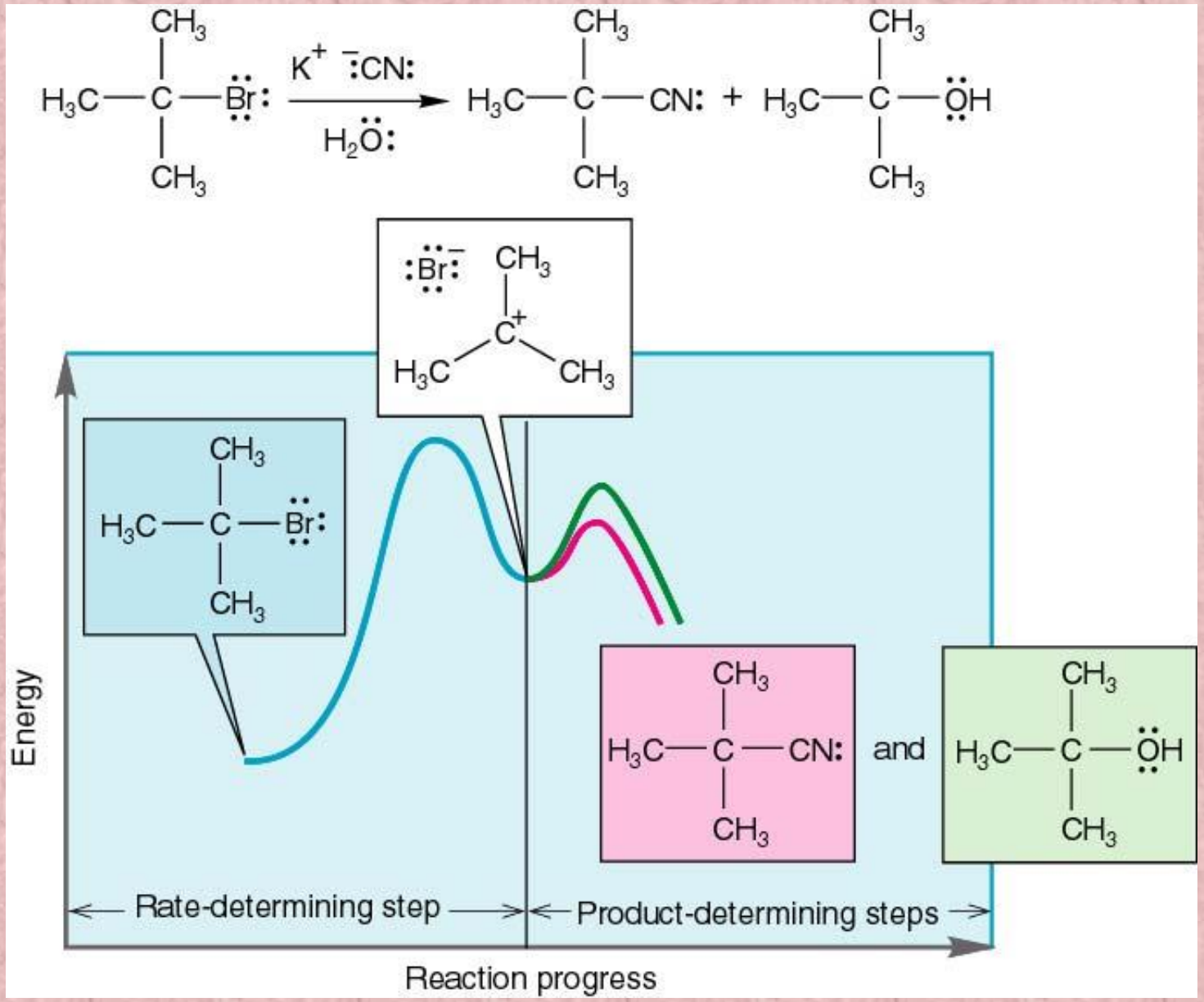
stereochemistry - racemization



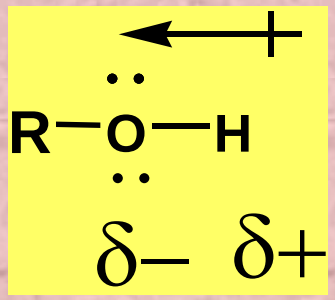


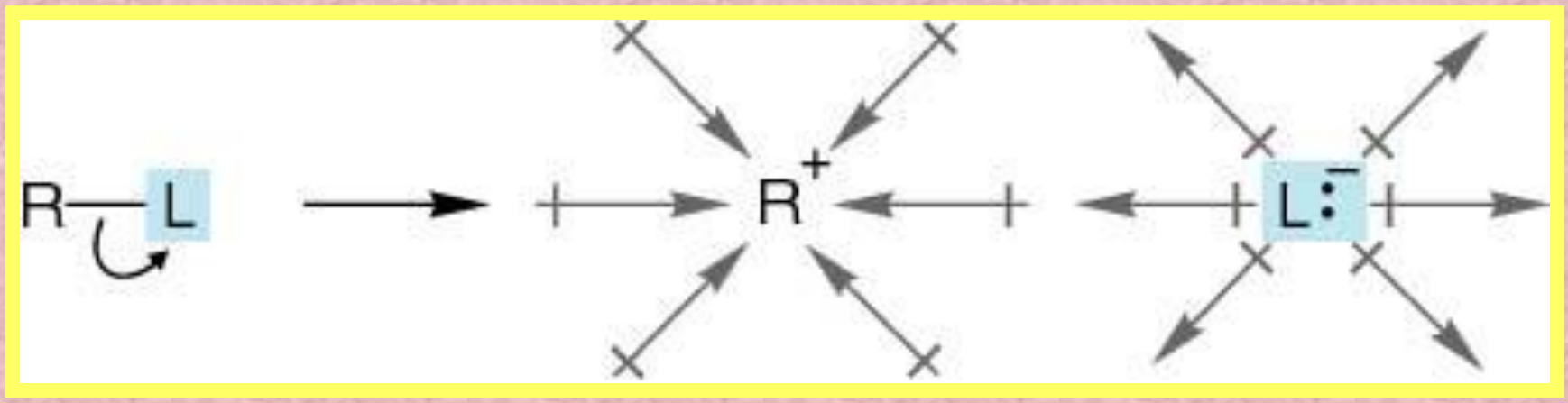
effect of nucleophiles -

to a first approximation - **none**



solvents - we need a very polar solvent to stabilize the carbocation - water and alcohols are good

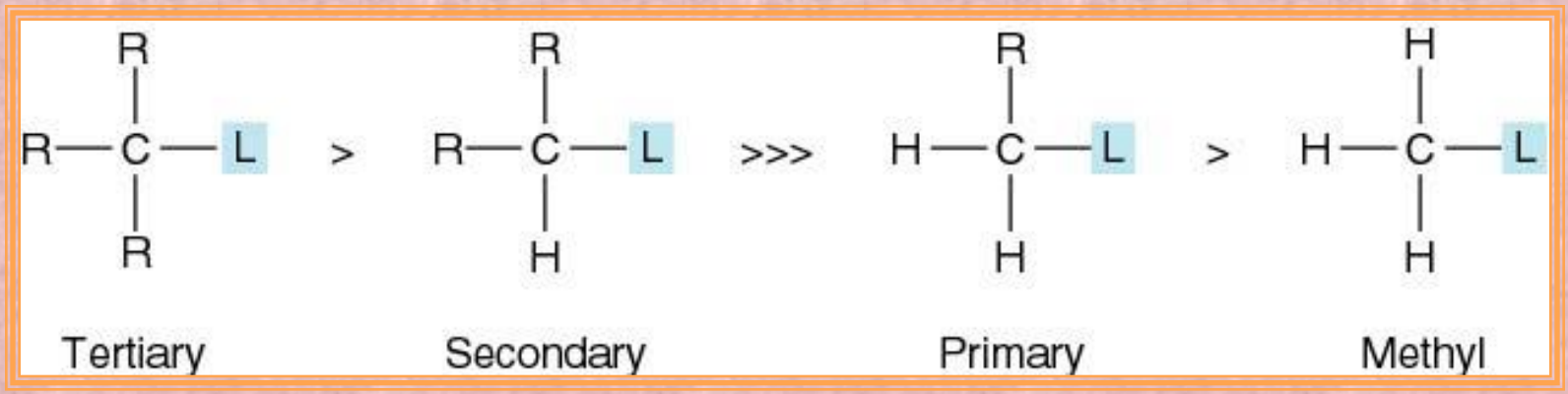




Leaving group effects - same as for S_N2 (weak R-L, stable L^-)

Effects in the alkyl group, R - primarily determined by the stability of the carbocation, R^+.

- R^+ is unstabile - therefore, endothermic step
  - late transition state resembles R^+
  - stabilize R^+, stabilize transition state, faster reaction
  - destabilize R^+, destabilize transition state, slower reaction

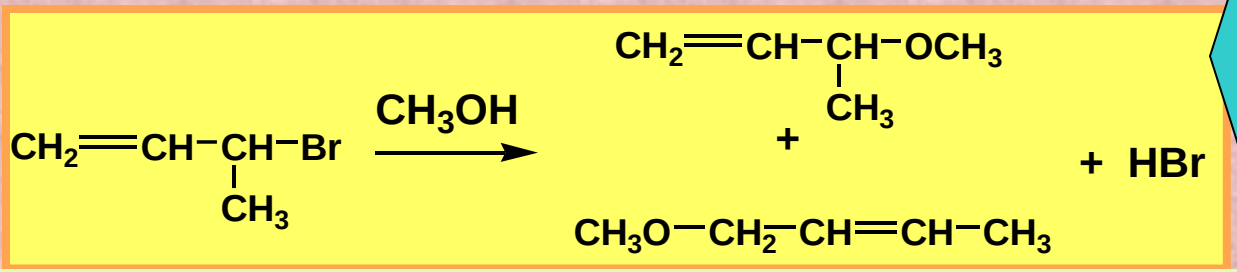


Steric argument: R-L = sp^3 but R^+ sp^2 hybridized

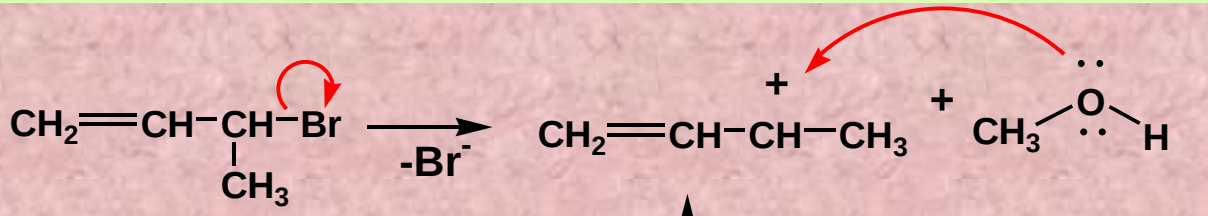
Electronic argument:

Recall hyperconjugation and resonance

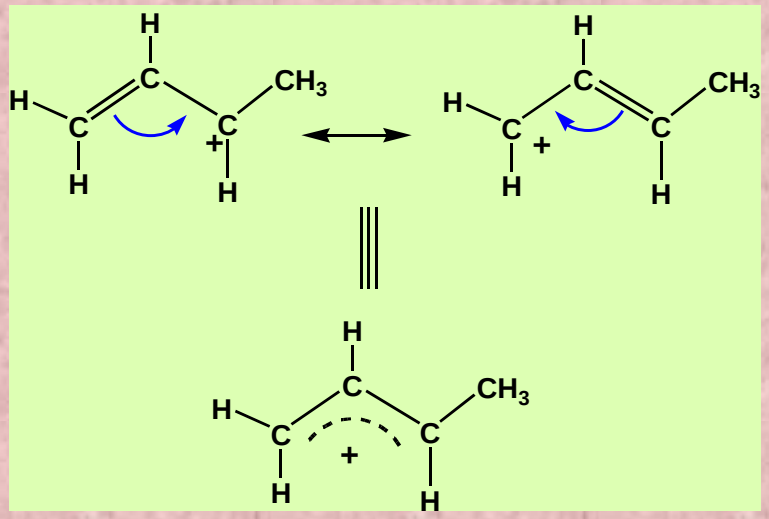
A special case - allylic substitution:



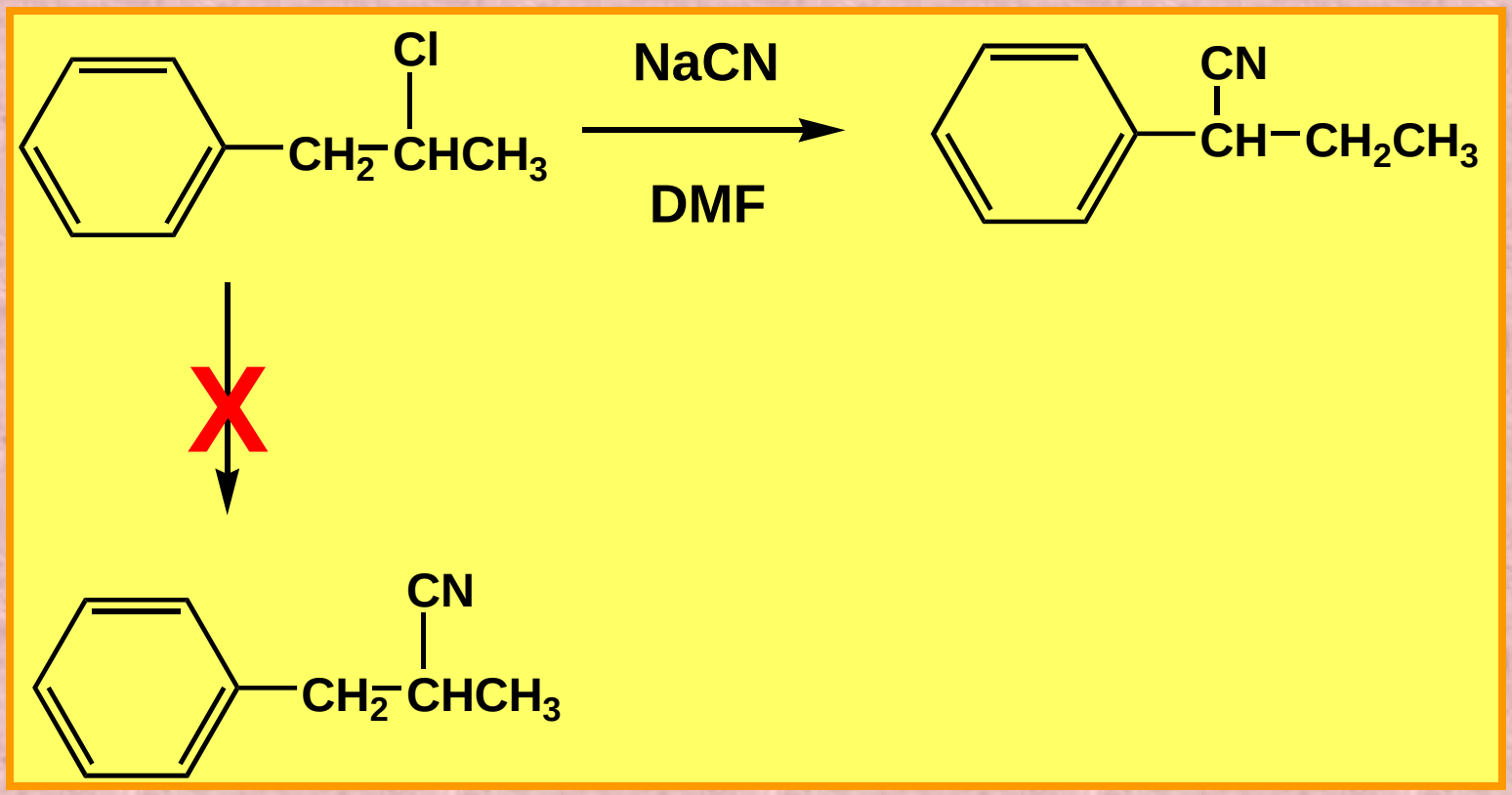
mechanism - consistent with carbocation intermediate:

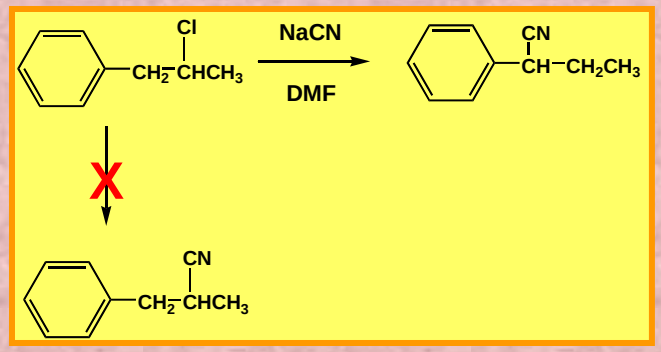


allyl carbocation:

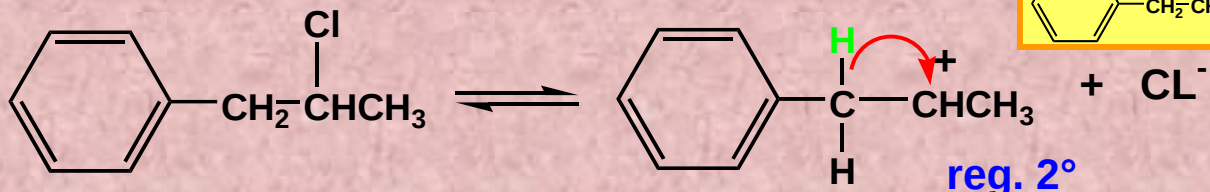


Rearrangements from a carbocation -
Primarily a 1,2-H shift to form a more stable carbocation.



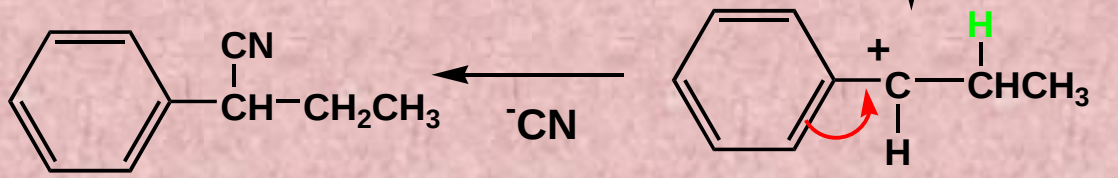


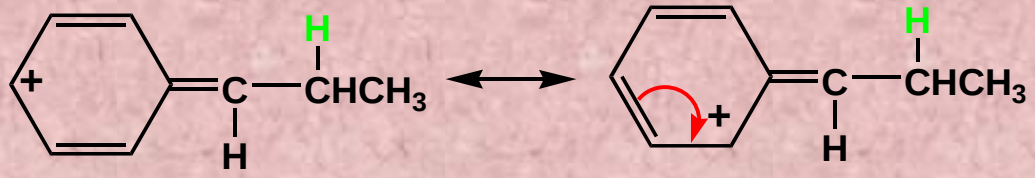
mechanism:



reg. 2° carbocation

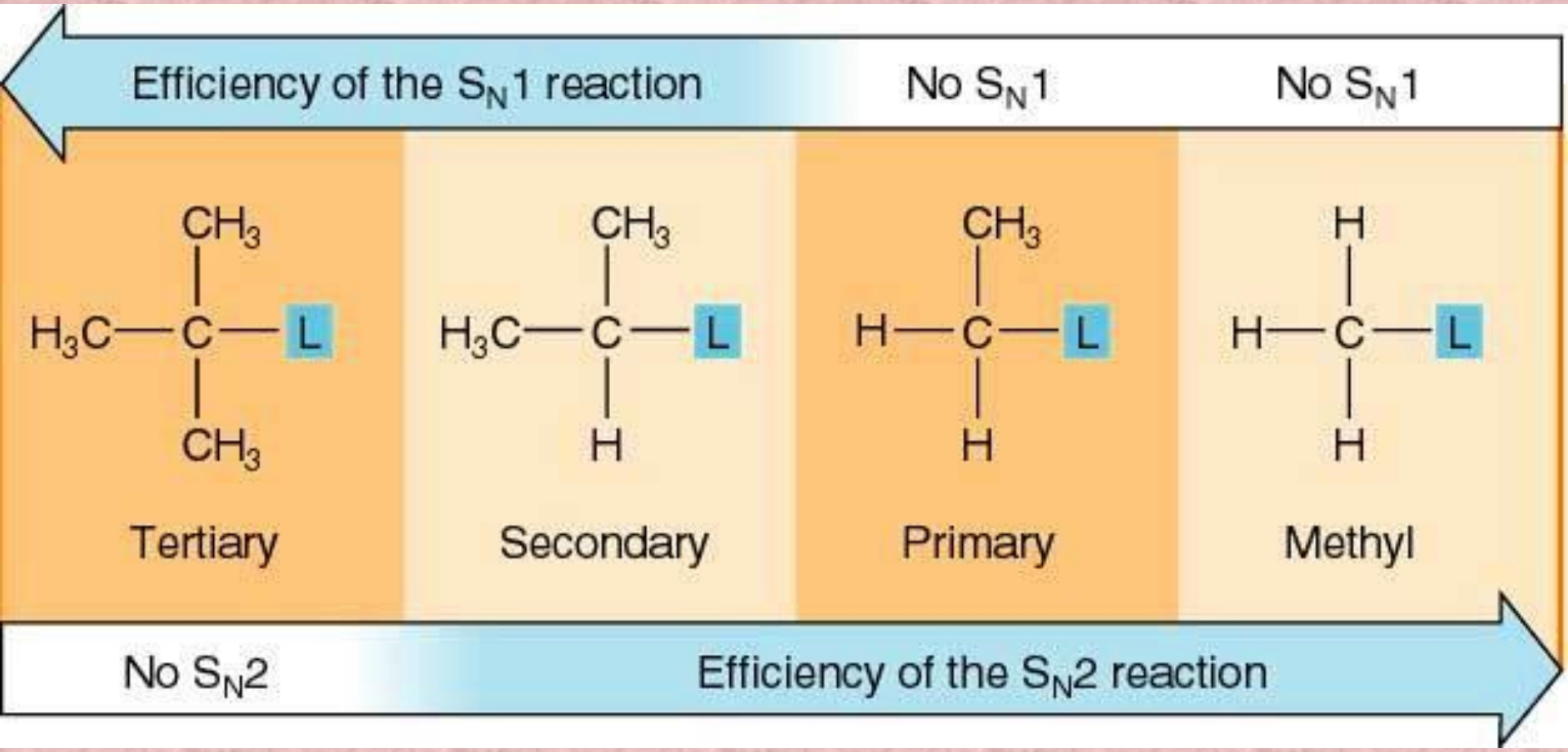
1,2 -H shift





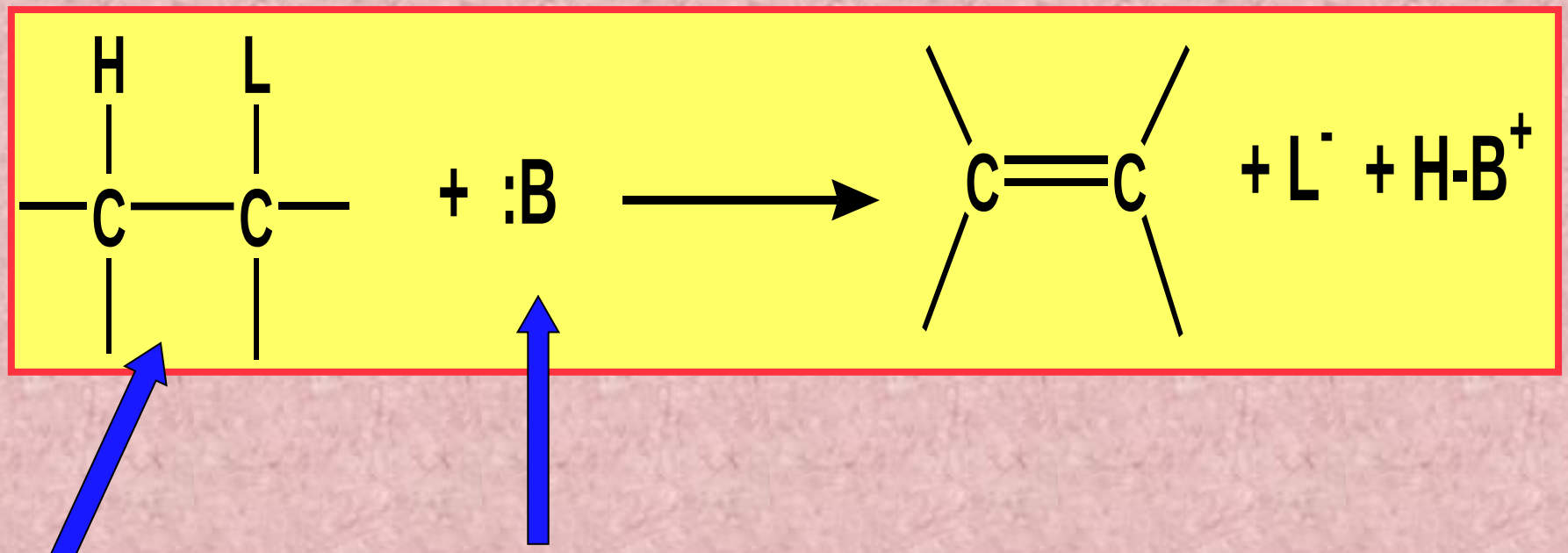
benzyl carbocation - stabilized by resonance

Difference between S_N1 and S_N2 - **PRIMARILY** the structure of R



- solvent polarity
- strength of R-L bond

H. Elimination reactions - general reaction scheme:



acid

base

L = leaving group
B = base

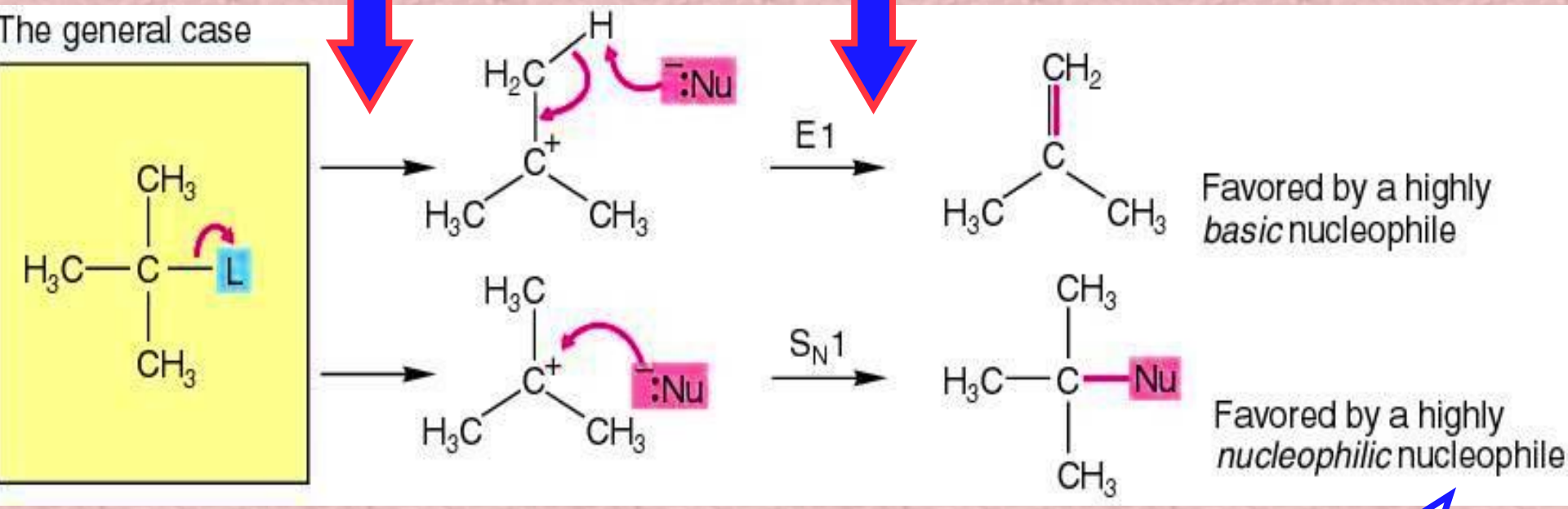
There are actually three mechanisms for this reaction

I. E1 - elimination unimolecular - proceeds just like S_N1- first step forms carbocation - -

1. mechanism:

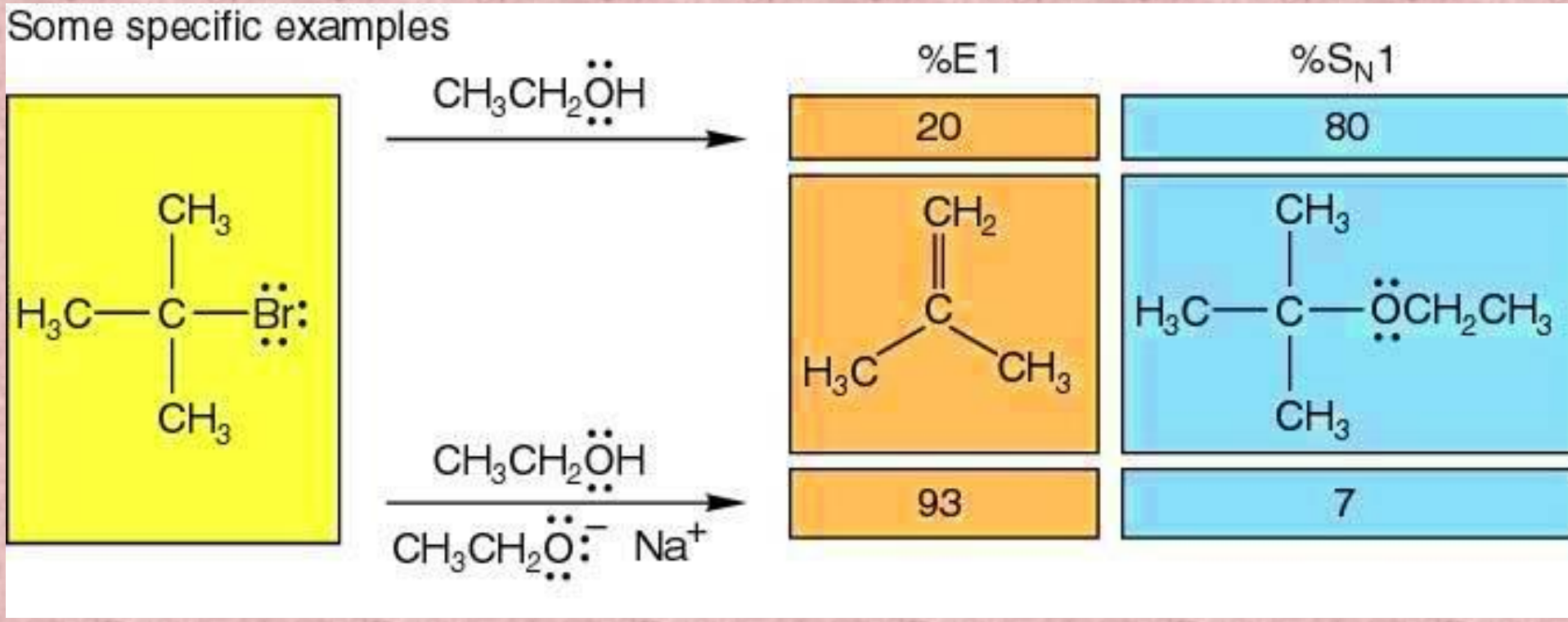
rate determining slow step

fast step

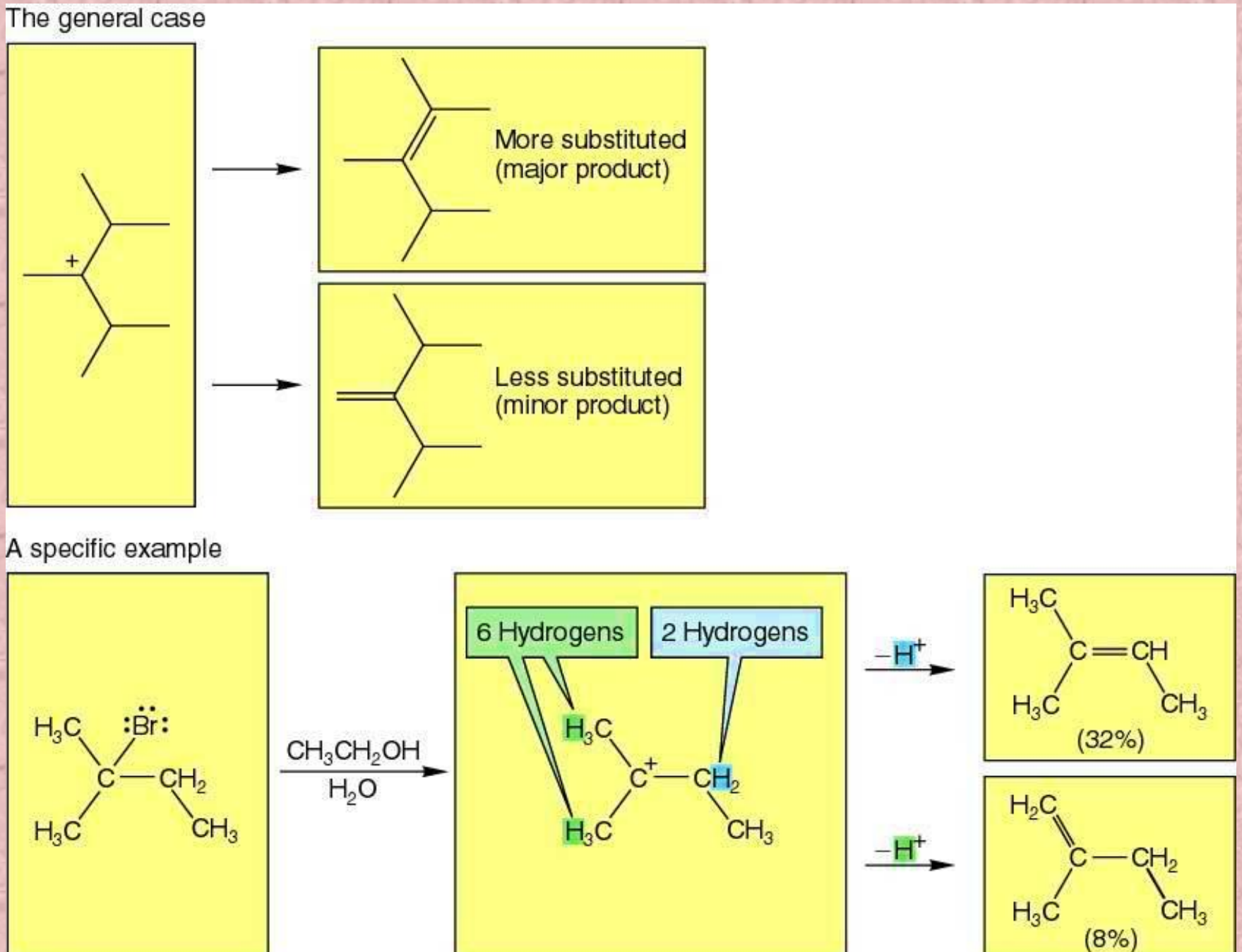


Note: potential competition with S_N1 reaction

In **GENERAL** E1 is favored by a strong base, e.g.

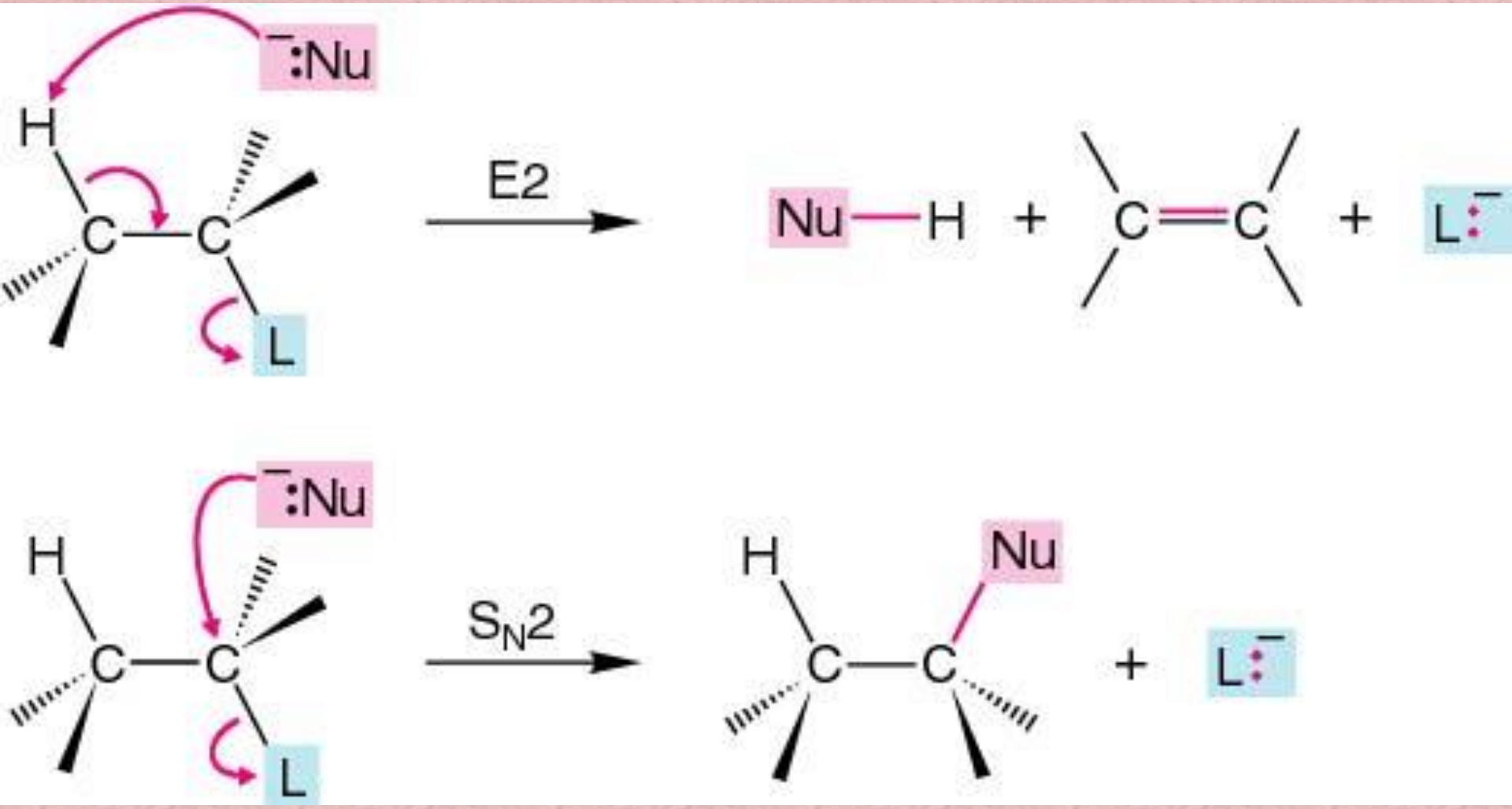


2. Orientation: the most substituted(most stable) olefin is formed

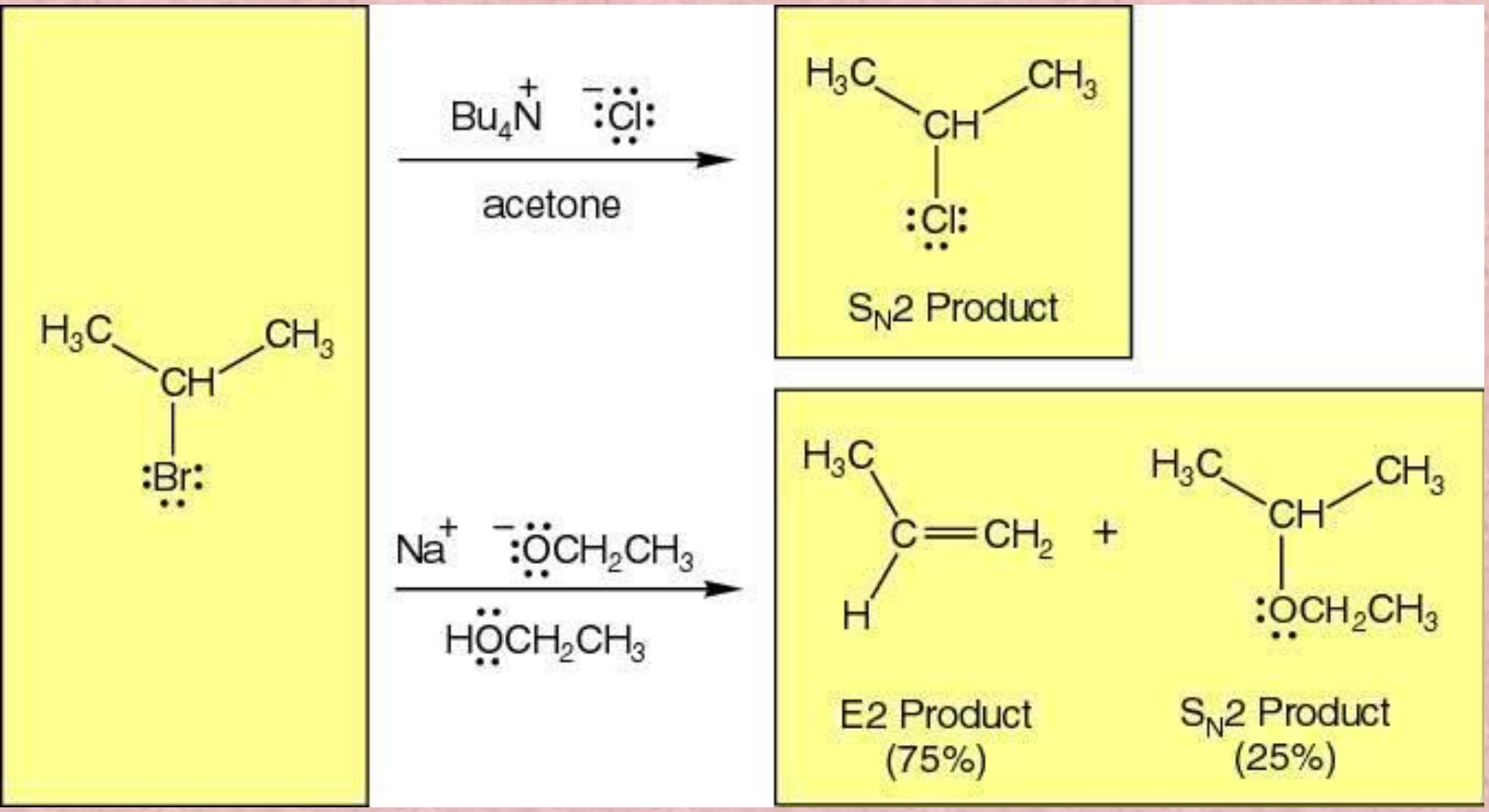


J. E2 - elimination bimolecular - one step just like S_N2

1. mechanism:

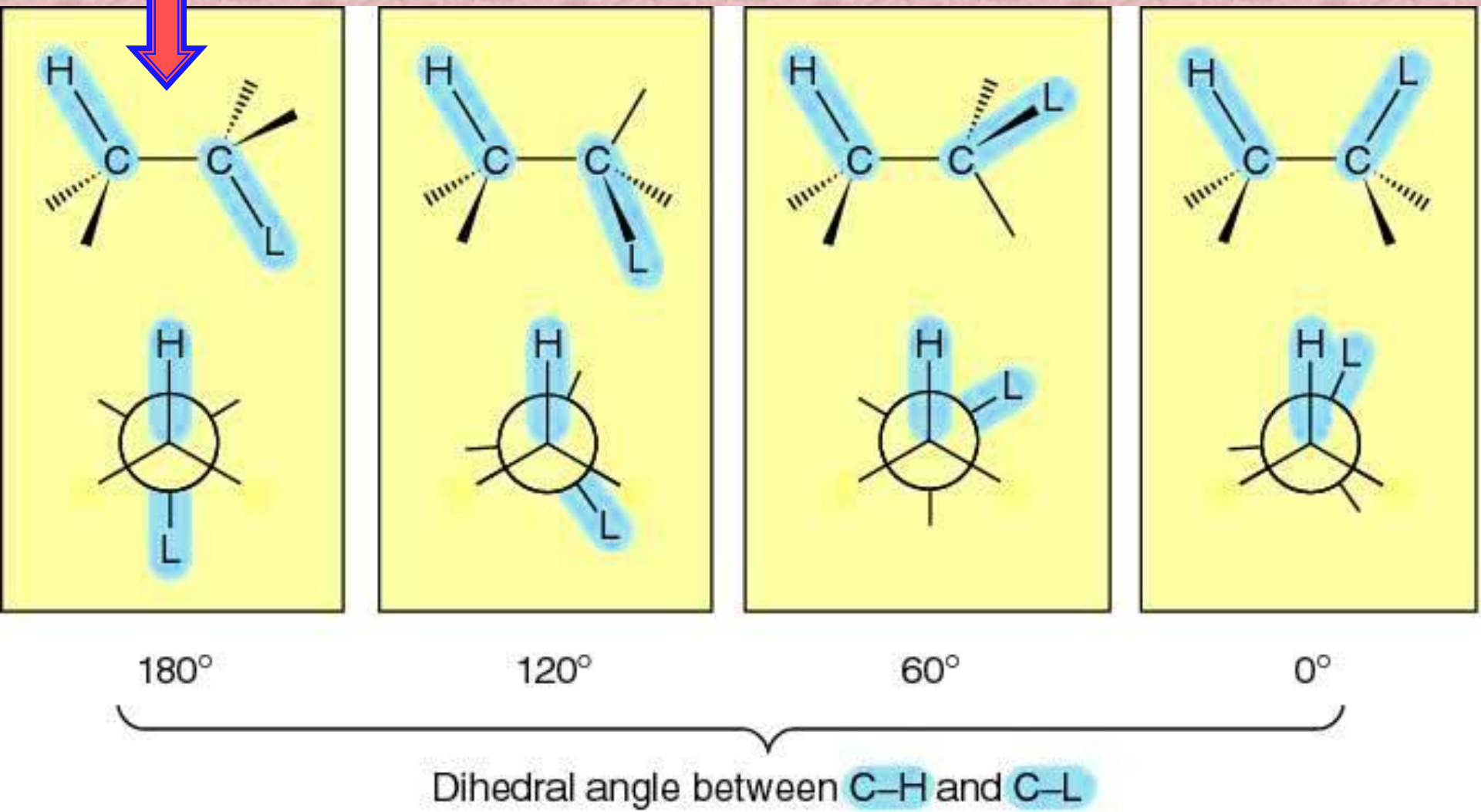


Strong bases are needed for E2 - but there is competition with S_N2



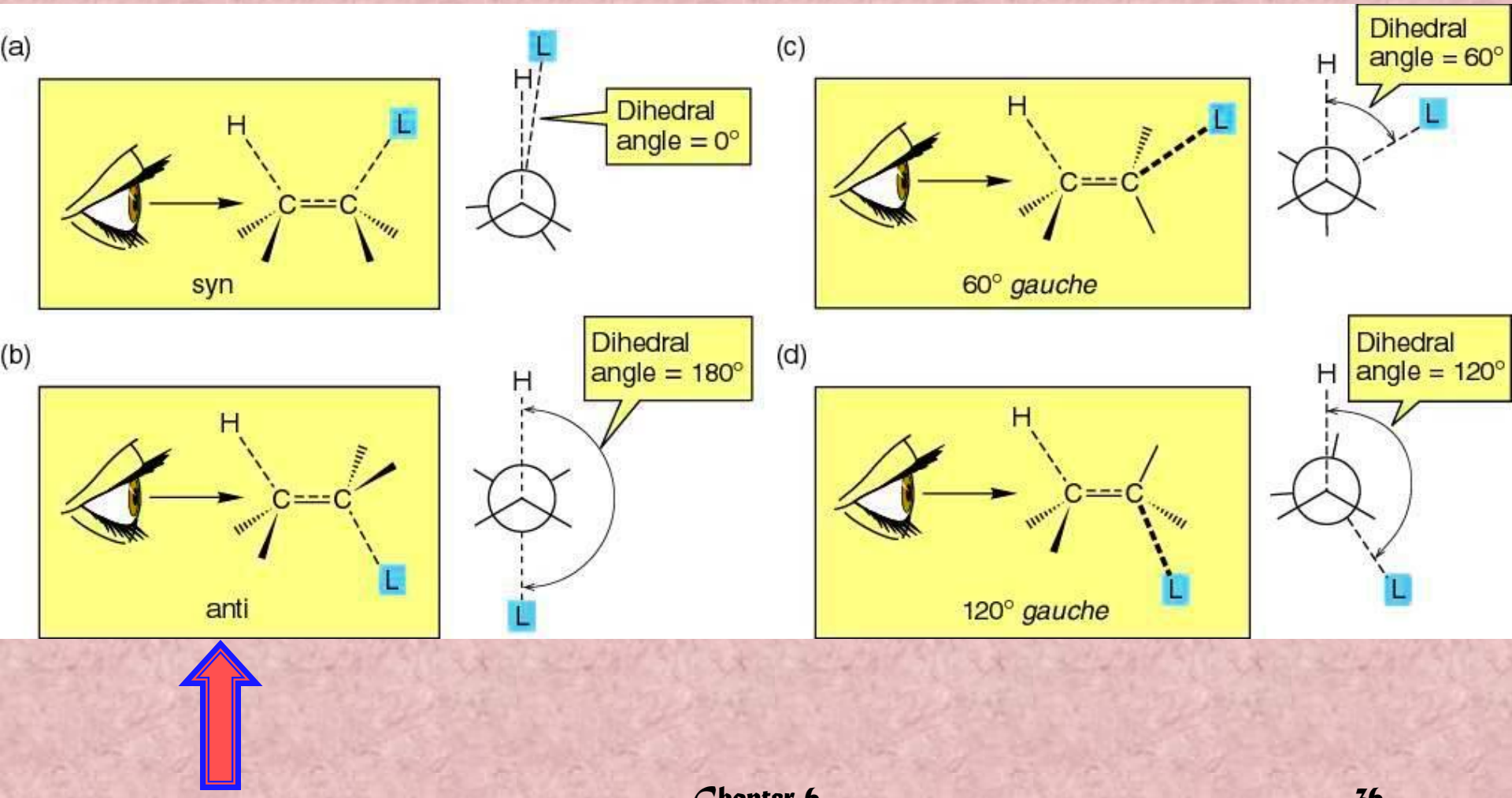
2. Stereochemistry - (there is none for E1- forms an achiral carbocation) - but for E2 -

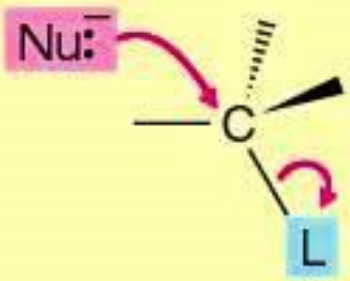
anti-peri-planar stereochemistry



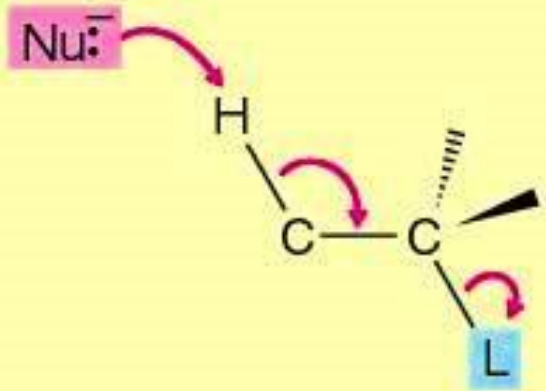
2. Stereochemistry - (there is none for E1- forms an achiral carbocation) - but for E2 -

anti-peri-planar stereochemistry

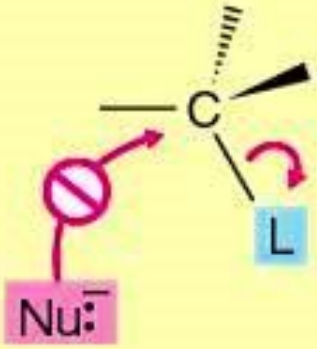




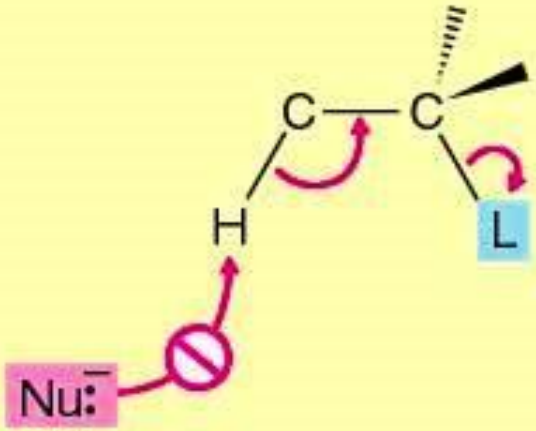
The favored backside displacement in the S_N2 reaction



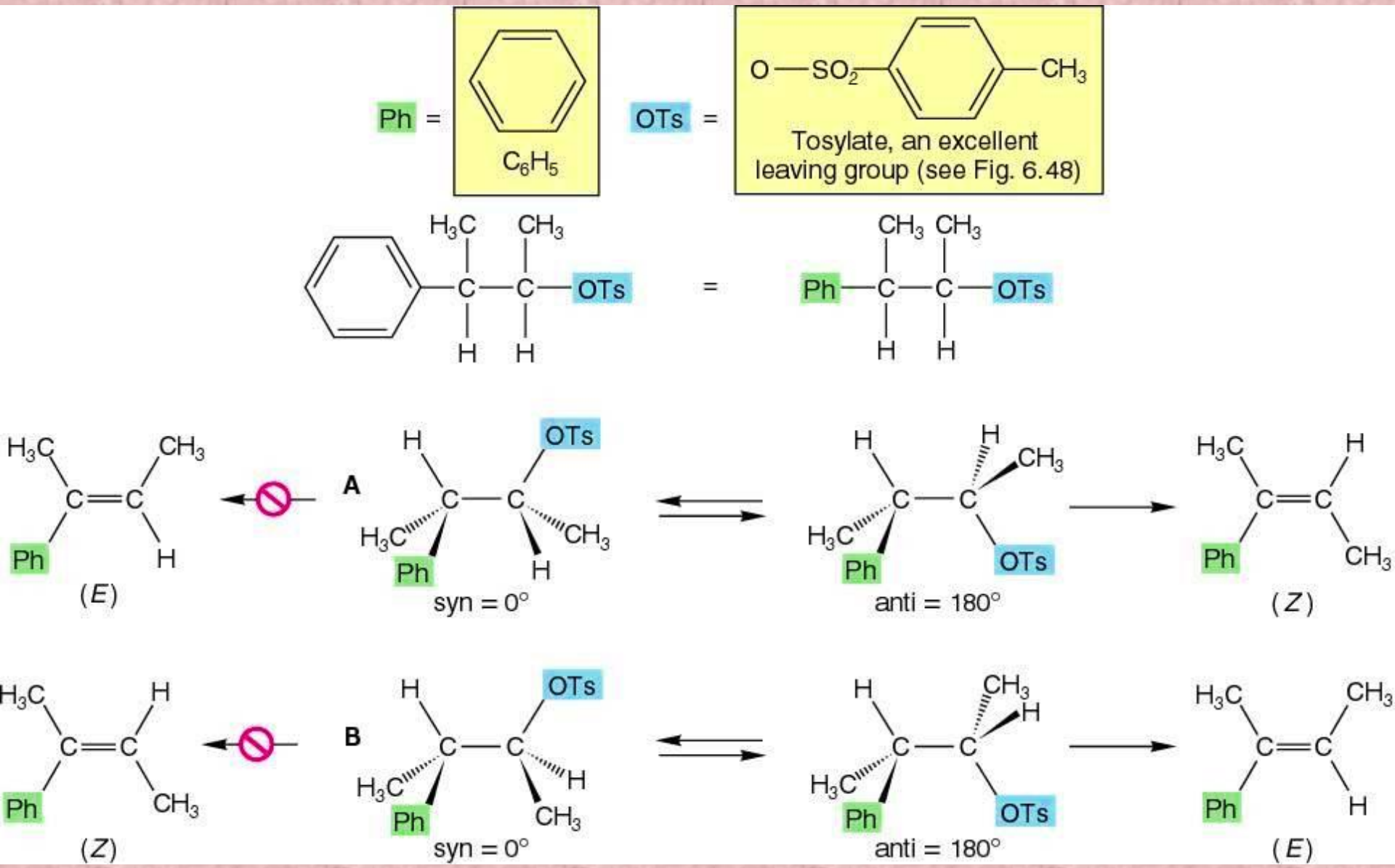
The 180° E2 reaction: the electrons in the C–H bond displace the leaving group from the rear



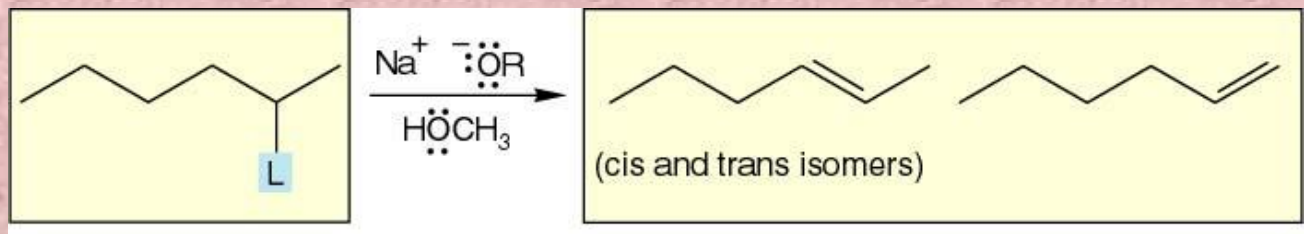
The disfavored frontside S_N2 displacement



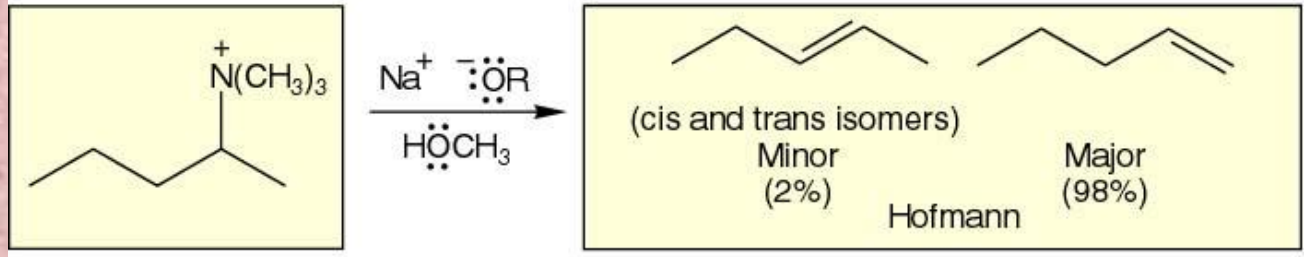
The 0° E2 mimics the frontside S_N2 reaction: the electrons in the C–H bond displace the leaving group from the front


Ph = C6H5
OTs = O—SO2—CH3
Tosylate, an excellent leaving group (see Fig. 6.48)
H3C CH3
C C OTs
H H
=
CH3 CH3
Ph C C OTs
H H
H3C CH3
C=C
Ph H
(E)
A
H OTs
C C
H3C CH3
Ph H
syn = 0°
H H
C CH3
H3C C OTs
Ph
anti = 180°
H3C H
C=C
Ph CH3
(Z)
H3C H
C=C
Ph CH3
(Z)
B
H OTs
C C
H3C H
Ph CH3
syn = 0°
H CH3
C H
H3C C OTs
Ph
anti = 180°
H3C CH3
C=C
Ph H
(E)

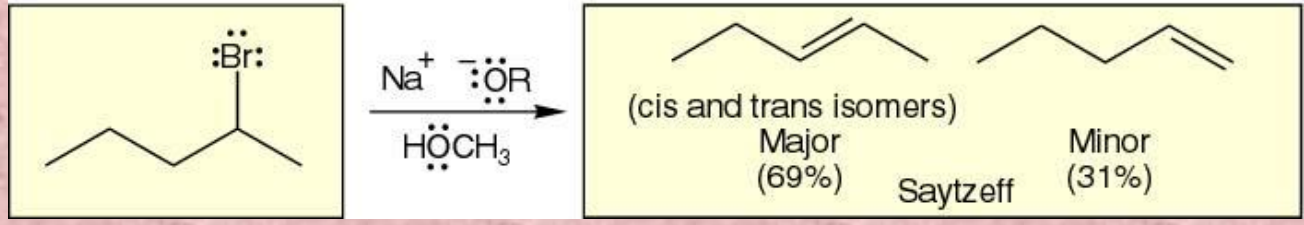
3. **Orientation** - mainly follows the **Saytzeff rule** (most substituted olefin) - HOWEVER - there is another pattern!
The **Hofmann orientation** - the least substituted olefin is formed:



Hofmann rule

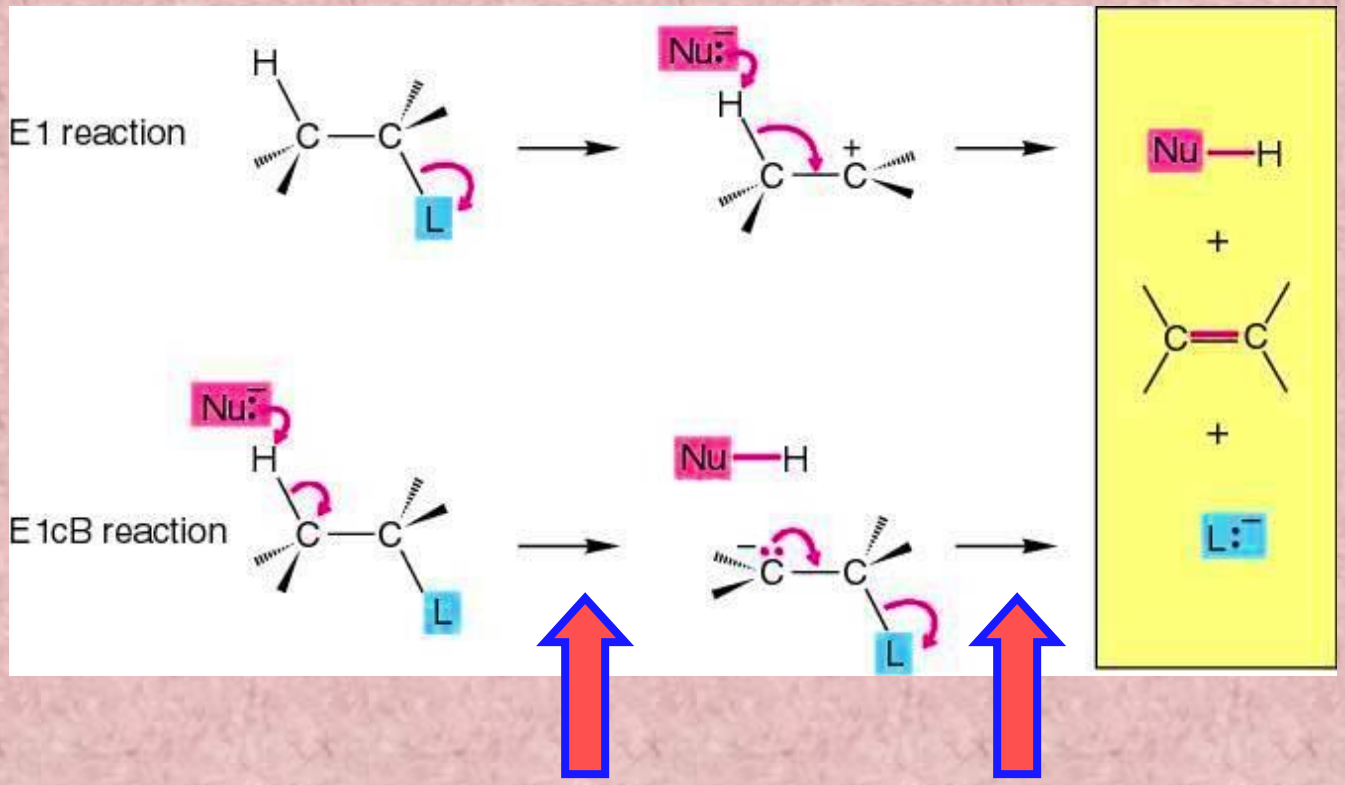


Saytzeff rule



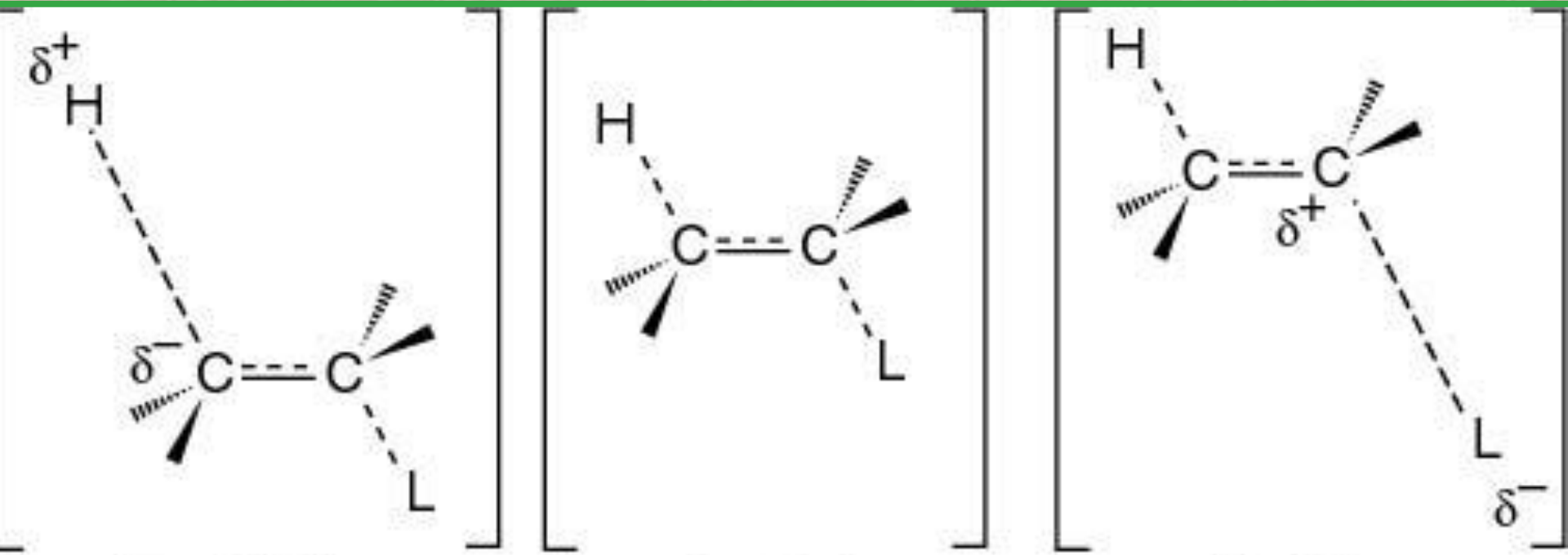
The difference in orientation here is related to the nature of the leaving group, L…

The orientational preference for the Hofmann rule is derived from a change in the nature of the E2 mechanism. Let us first look at the third mechanism - E1cB - elimination unimolecular carbon base:



There is a spectrum of reaction mechanisms!!

The transition states look like:



E1cB-Like | Central | E1-Like

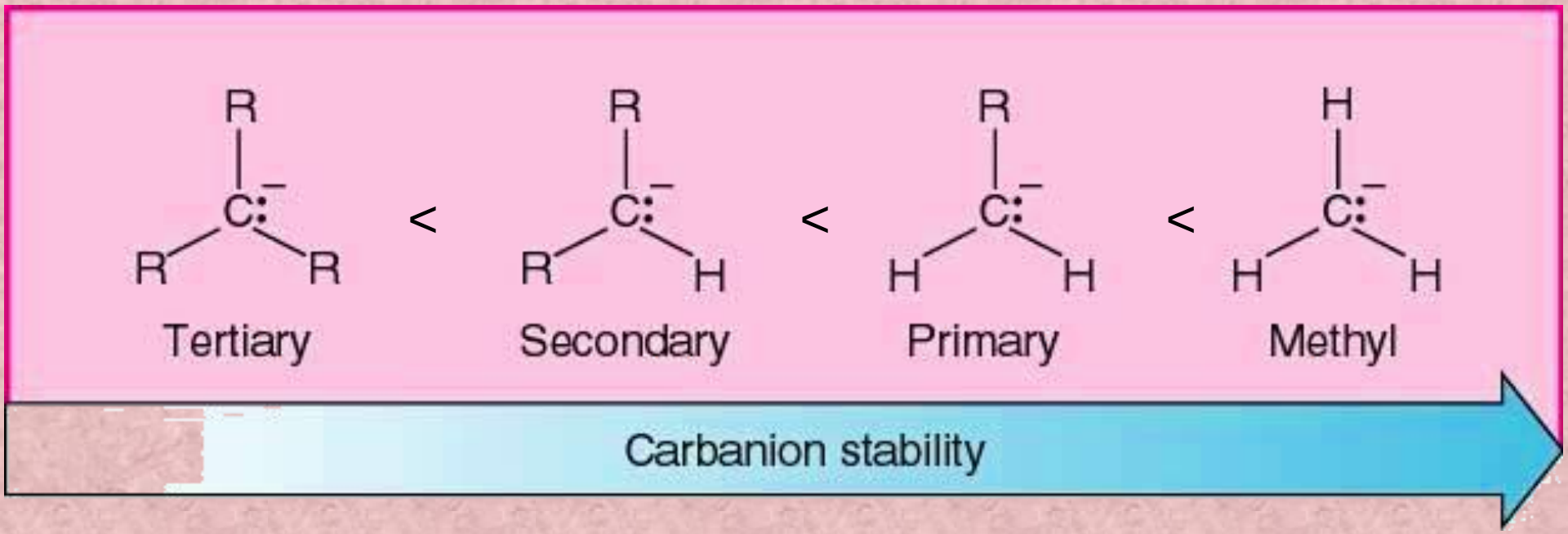
Hofmann | “pure” E1cb | E2 | “pure” E1 | Saytzeff

So if **L** is a strongly electron withdrawing group -

e. g. **-F or -N(NMe)$_3$**

then a E1cB or E2 with”E1cB-like” character is favored.

NOW REMEMBER - that the stability of carbanions is:



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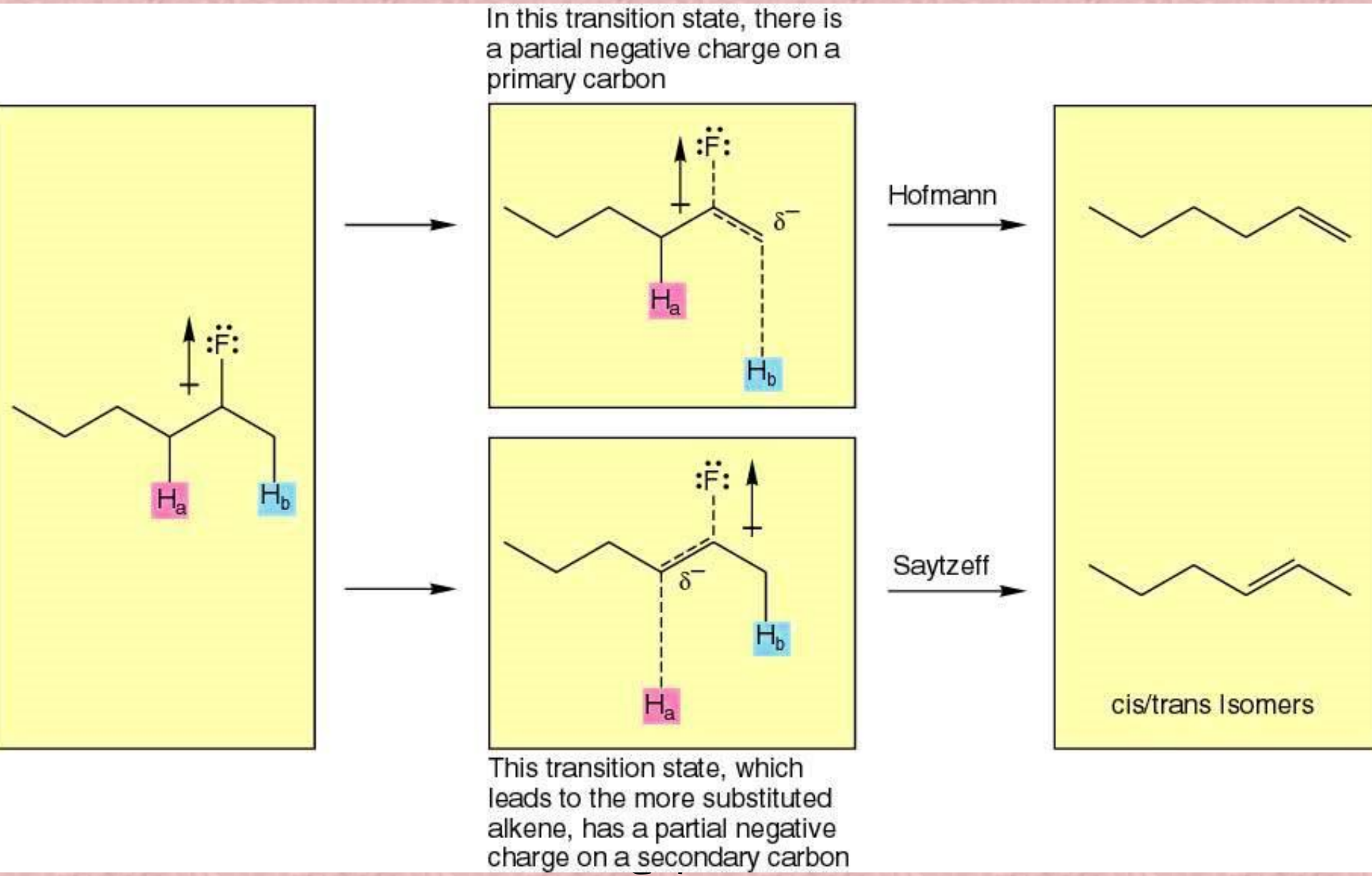

S_N1

https://www.youtube.com/watch?v=JmcVgE2WKBE

S_N2

https://www.youtube.com/watch?v=h5xvaP6bIZI&feature=youtu.be&t=66

Universidade de Surrey

https://www.youtube.com/watch?v=TnY1S5IdVqI

isomeria

https://www.youtube.com/watch?v=RBtgAz70_JY

- Overall Summary

- $CH_3—X$ $RCH_2—X$ $(R_2C)CH—X$ $(R_3)C—X$

SN2	Mainly SN2 Except with a hindered strong base and then E2	Mainly SN2 wiht weak base (I^-,CN^-,RCO_2^-) Mainly E2 with strong bases	No SN2 In solvolysis gives SN1/E1 Low T SN1 With strong bases E2 dominates