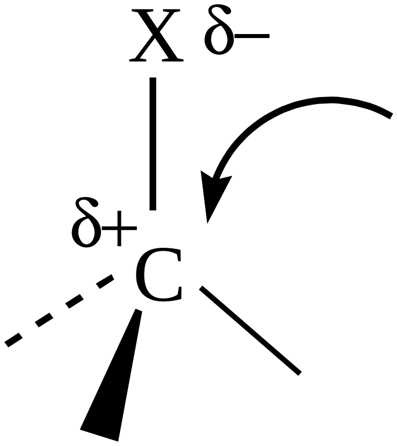
PHẢN ỨNG
THẾ THÂN HẠCH
& PHẢN ỨNG KHỬ

ALKYL HALIDE



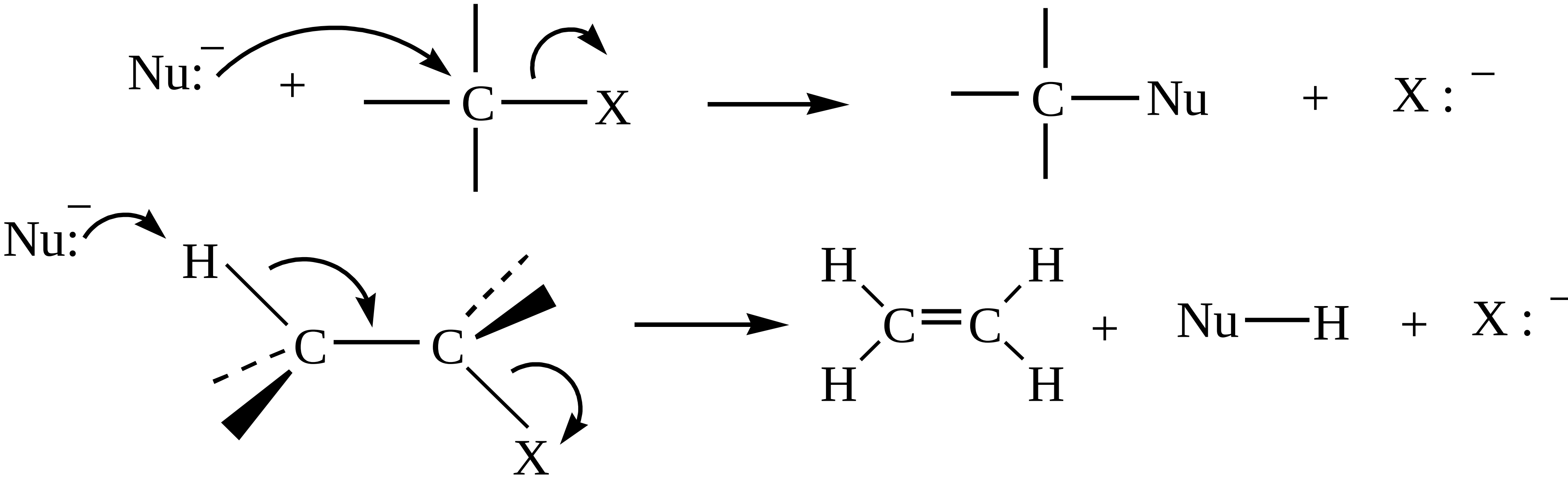
Tâm thân điện tử

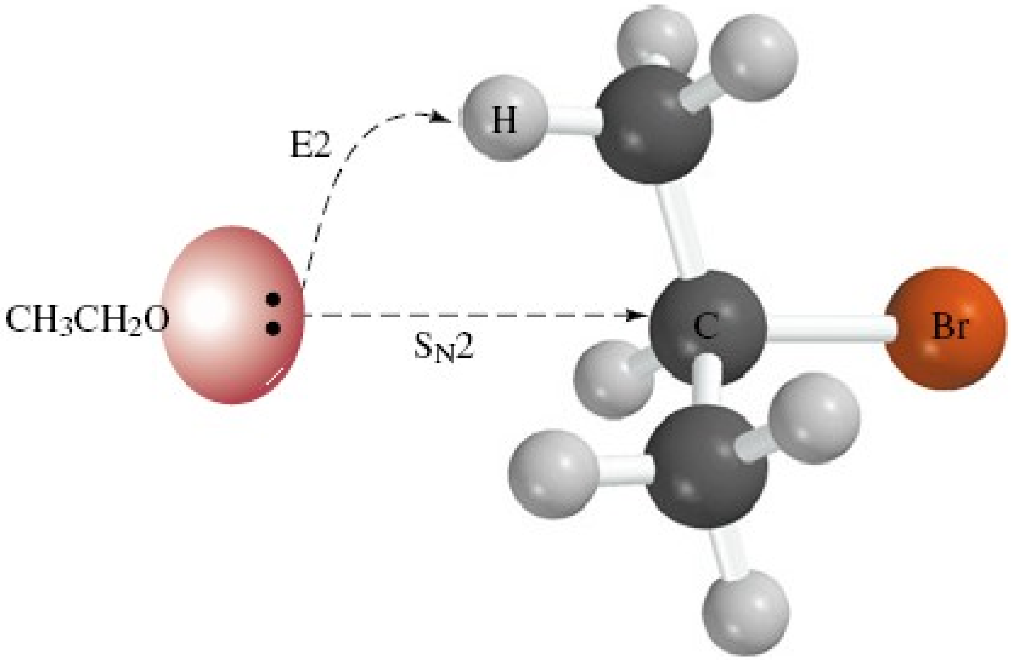
The strengths of the carbon-halogen bonds

C-H	413	C-F	467
		C-Cl	346
		C-Br	290
		C-I	228

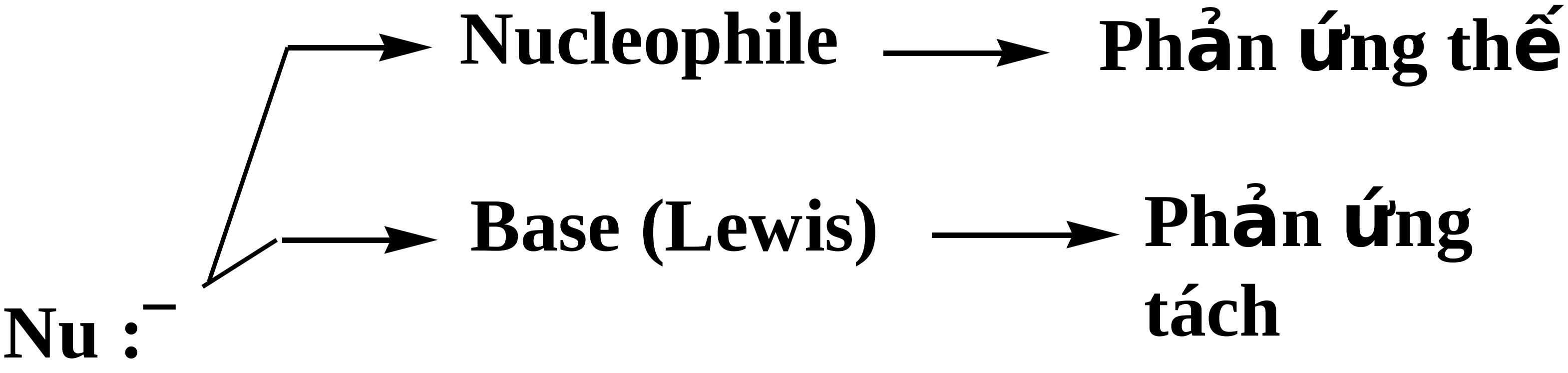
Rates of reaction: RCl < RBr < RI

SUBSTITUTION or ELIMINATION ?





TÍNH THÂN HẠCH VÀ TÍNH BASE



Nucleophile → Phản ứng thế

Base (Lewis) → Phản ứng tách

Nu :$^-$

(RO^-, H_2O, Br^-, NH_3,....)

- **Tính thân hạch**

  Ái lực đối với chất *thân điện tử*

- **Tính base**

  Ái lực đối với *proton*

TÍNH THÂN HẠCH VÀ TÍNH BASE

- **Các chất thân hạch có tâm thân hạch là các nguyên tố giống nhau: Tính thân hạch và tính base biến đổi song song với nhau.**

Ví dụ: tính base và tính thân hạch:

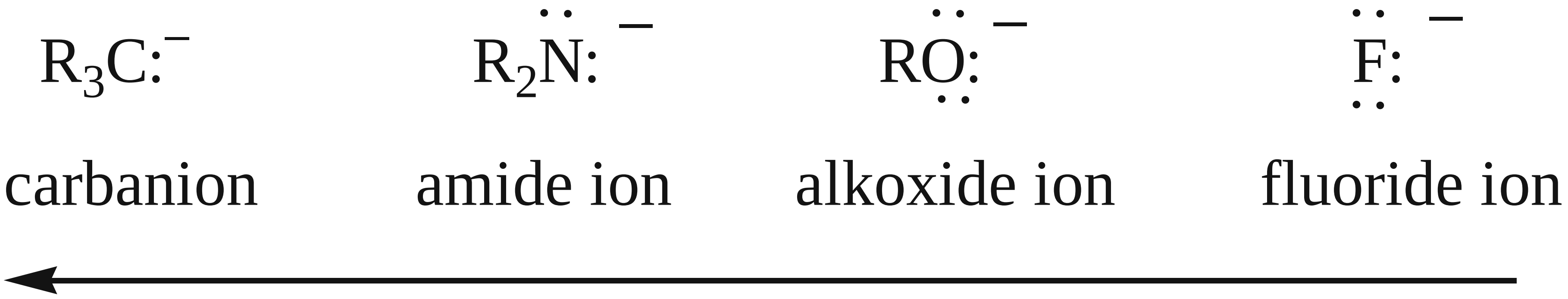
$$RO^- > HO^- >> RCO_2^- > ROH > H_2O$$

TÍNH THÂN HẠCH VÀ TÍNH BASE

☻ **Khi các tâm thân hạch khác nhau**

*** Trong cùng một chu kỳ**:

Các ion cùng điện tích: tính thân hạch và tính base biến thiên song song với nhau và cùng giảm dần từ trái sang phải.



$R_3C:^-$ $\quad R_2\ddot{N}:^-$ $\quad R\underset{\cdot\cdot}{\ddot{O}}:^-$ $\quad \underset{\cdot\cdot}{\ddot{F}}:^-$

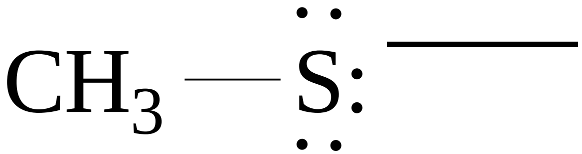
carbanion amide ion alkoxide ion fluoride ion

Tính thân hạch và tính base tăng

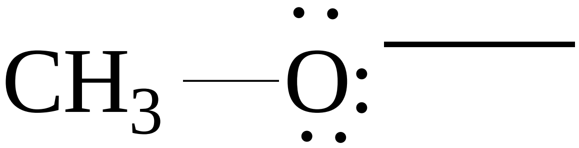
TÍNH THÂN HẠCH VÀ TÍNH BASE

* **Trong cùng một nhóm:**

Tính base và tính thân hạch biến đổi ngược với nhau.



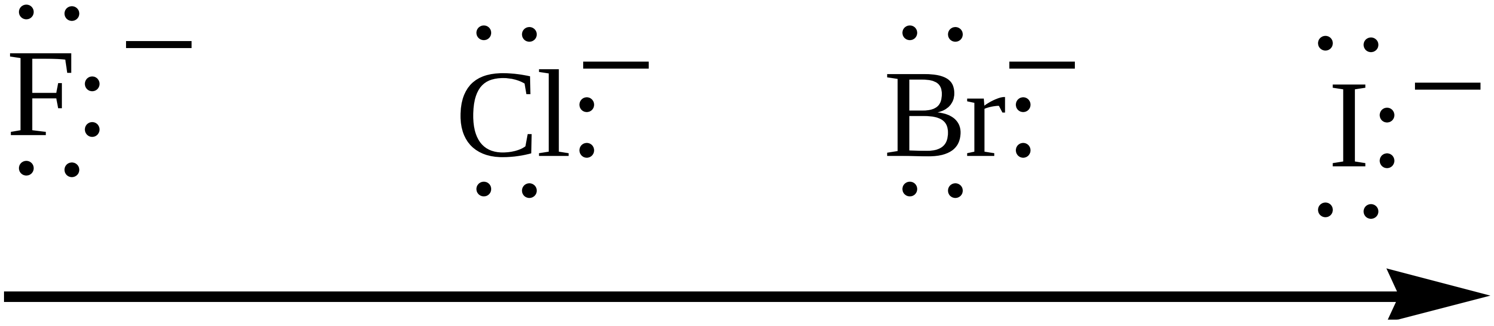
$CH_3-\overset{\cdot\cdot}{\underset{\cdot\cdot}{S}}:^{-}$



$CH_3-\overset{\cdot\cdot}{\underset{\cdot\cdot}{O}}:^{-}$

Tính thân hạch mạnh hơn
Tính base yếu hơn

Tính thân hạch yếu hơn
Tính base mạnh hơn



Tính thân hạch tăng, tính base giảm

- **Từ trên xuống bán kính nguyên tử tăng trong khi độ âm điện lại giảm.**
- **Khả năng bị solvat hóa bởi dung môi.**

TÍNH THÂN HẠCH VÀ TÍNH BASE

* Ảnh hưởng của điện tích ion

Dạng *anion* luôn có tính thân hạch *mạnh* hơn dạng *phân tử*

Ví dụ: $OH^- > H_2O$; $RO^- > ROH$

TÍNH THÂN HẠCH VÀ TÍNH BASE

*** Ảnh hưởng của yếu tố lập thể**

Kích thước càng lớn

► Tính thân hạch càng yếu

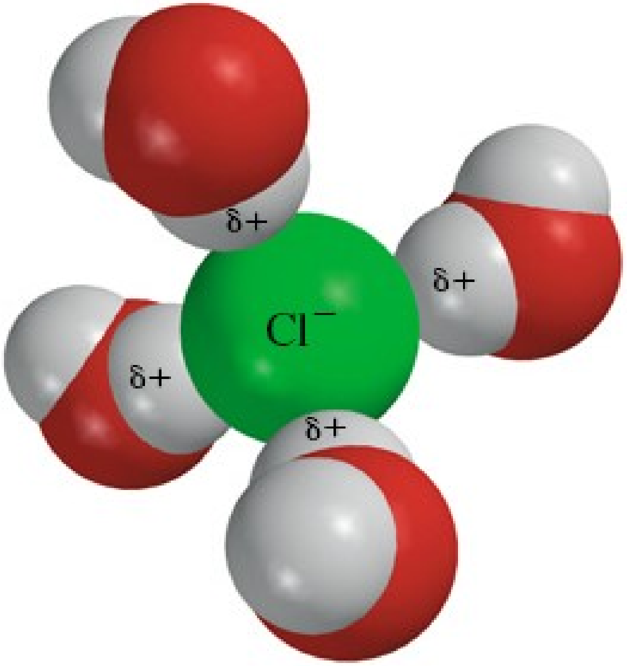
► Tính base càng mạnh

Tính base: $(CH_3)_3CO^- > CH_3CH_2O^-$

Tính thân hạch: $(CH_3)_3CO^- < CH_3CH_2O^-$

TÍNH THÂN HẠCH VÀ TÍNH BASE

* Ảnh hưởng của dung môi



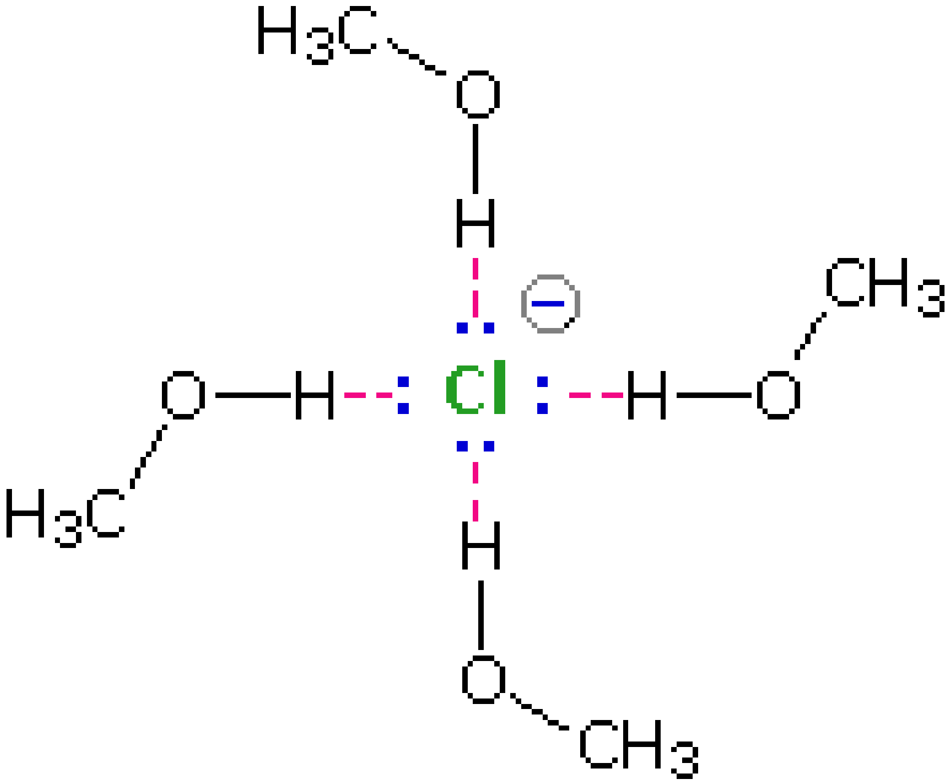


TABLE 8.6 Relative Rate of S_N1 Solvolysis of *tert*-Butyl Chloride as a Function of Solvent Polarity*

Solvent	Dielectric constant ϵ	Relative rate
Acetic acid	6	1
Methanol	33	4
Formic acid	58	5,000
Water	78	150,000

TABLE 8.7 Relative Rate of S_N2 Displacement of 1-Bromobutane by Azide in Various Solvents*

Solvent	Structural formula	Dielectric constant ϵ	Type of solvent	Relative rate
Methanol	CH_3OH	32.6	Polar protic	1
Water	H_2O	78.5	Polar protic	7
Dimethyl sulfoxide	$(CH_3)_2S{=}O$	48.9	Polar aprotic	1300
N,*N*-Dimethylformamide	$(CH_3)_2NCH{=}O$	36.7	Polar aprotic	2800
Acetonitrile	$CH_3C{\equiv}N$	37.5	Polar aprotic	5000

*Ratio of second-order rate constant for substitution in indicated solvent to that for substitution in methanol at 25°C.

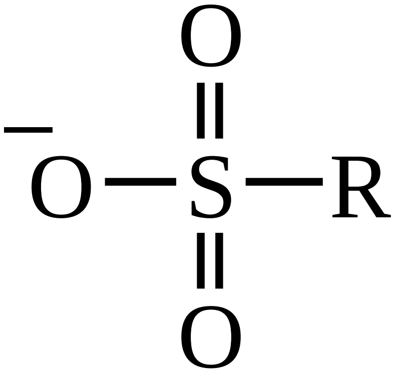
NHÓM XUẤT

- Được tách ra khỏi phân tử dưới dạng phân tử trung hòa điện hoặc ion âm.
- **Nhóm xuất tốt**: ion có khả năng bền vững hóa điện tích âm của nó: **base yếu**

Tính base: $F^- >> Cl^- > Br^- > I^-$

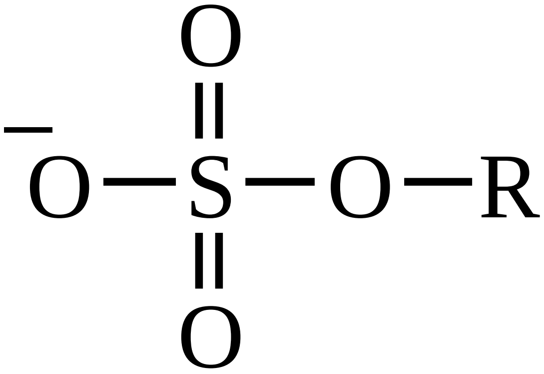
Khả năng xuất: $I^- > Br^- > Cl^- >> F^-$

NHÓM XUẤT TỐT



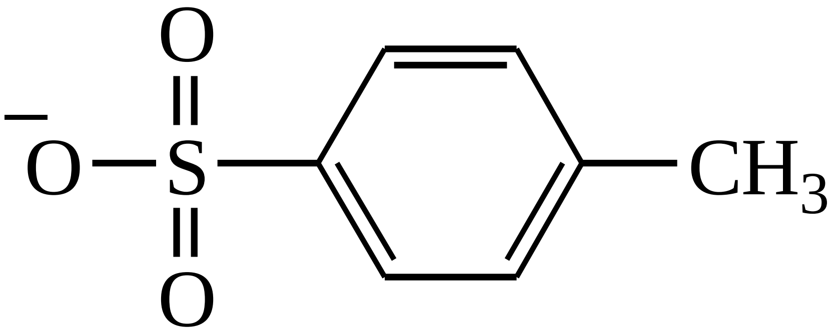
$${}^{-}O-\underset{\underset{O}{\|}}{\overset{\overset{O}{\|}}{S}}-R$$

Alkanesulfonate ion

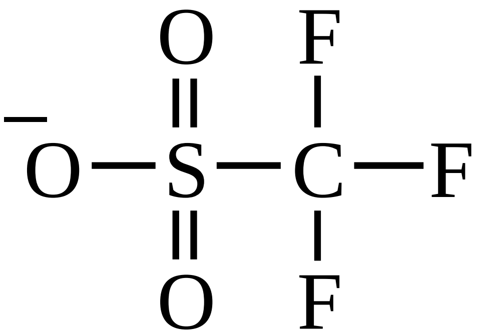


$${}^{-}O-\underset{\underset{O}{\|}}{\overset{\overset{O}{\|}}{S}}-O-R$$

Alkyl sulfate ion



p-Toluenesulfonate ion

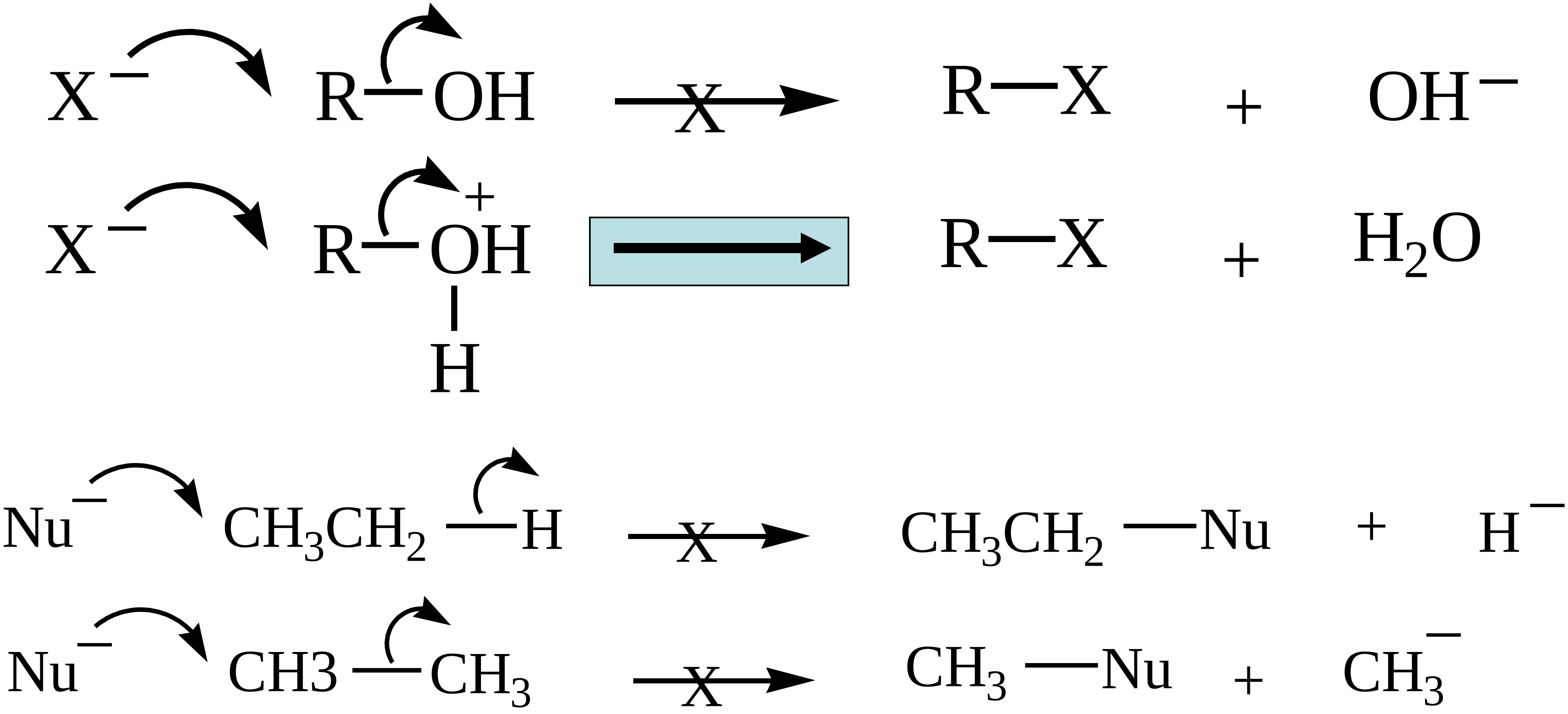


$${}^{-}O-\underset{\underset{O}{\|}}{\overset{\overset{O}{\|}}{S}}-\underset{\underset{F}{|}}{\overset{\overset{F}{|}}{C}}-F$$

Triflate ion

Ion có tính base mạnh: OH^- , H^-, R^-

► Nhóm xuất rất yếu



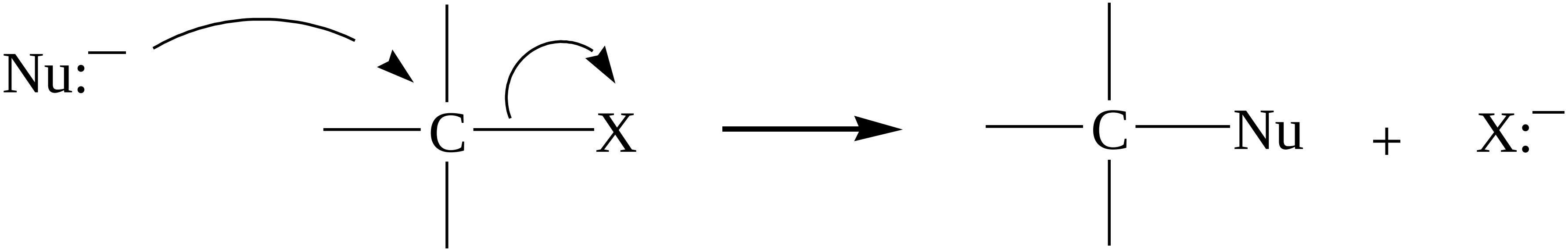
$$X^- \quad R-OH \not\longrightarrow R-X + OH^-$$

$$X^- \quad R-\overset{+}{O}H(-H) \longrightarrow R-X + H_2O$$

$$Nu^- \quad CH_3CH_2-H \not\longrightarrow CH_3CH_2-Nu + H^-$$

$$Nu^- \quad CH3-CH_3 \not\longrightarrow CH_3-Nu + CH_3^-$$

PHẢN ỨNG THẾ THÂN HẠCH
(NUCLEOPHILIC SUBSTITUTION)

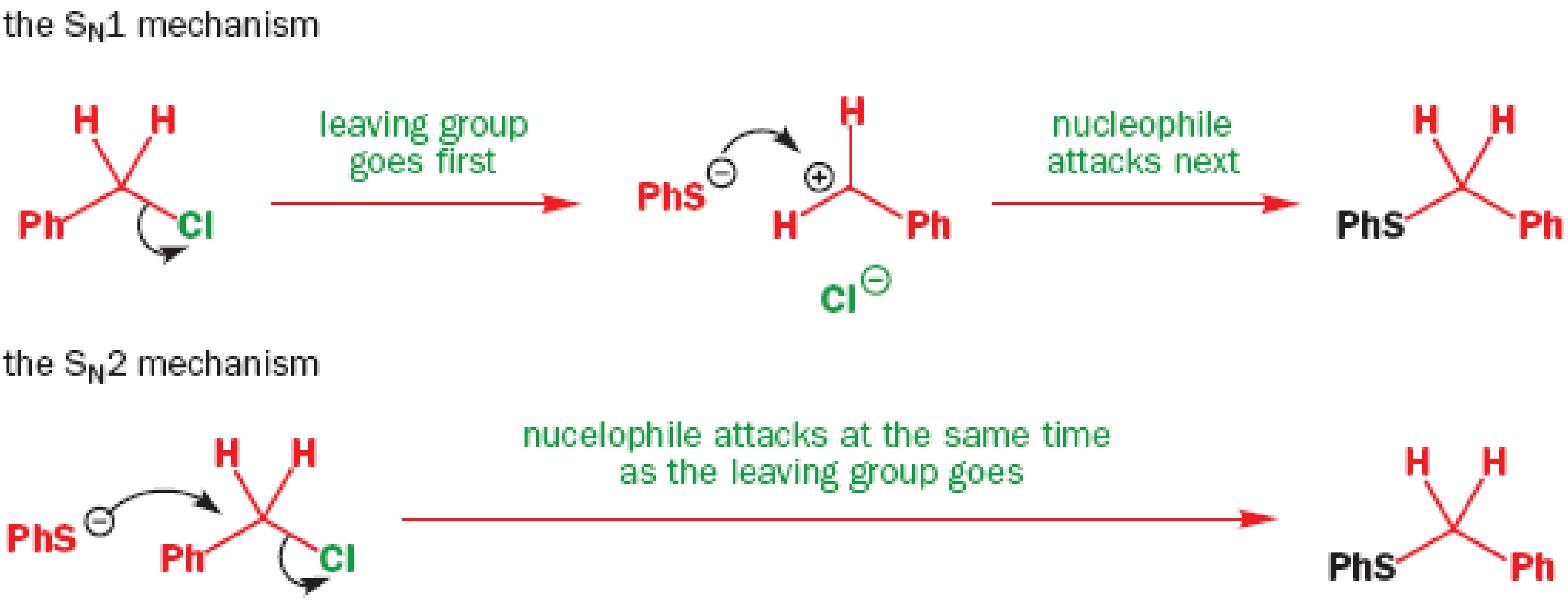


Nu: Chất thân hạch (Nucleophile)

X Nhóm xuất (Leaving group)

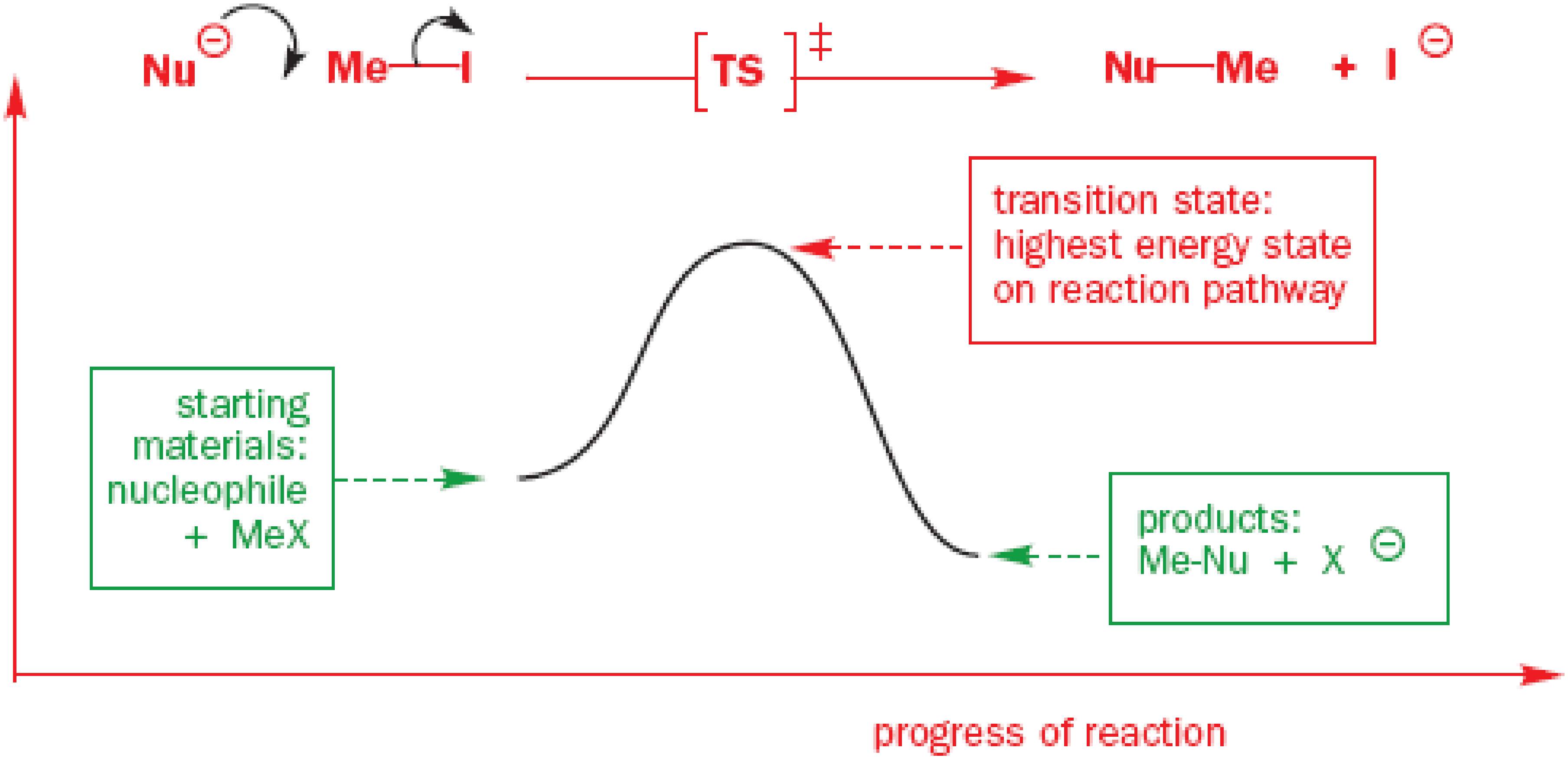
N N

PHẢN ỨNG THẾ THÂN HẠCH



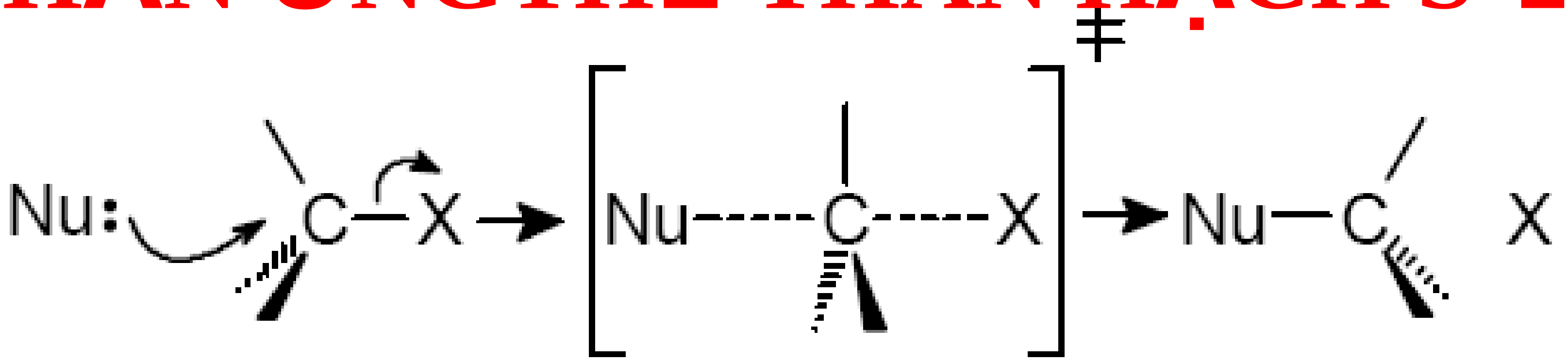
N

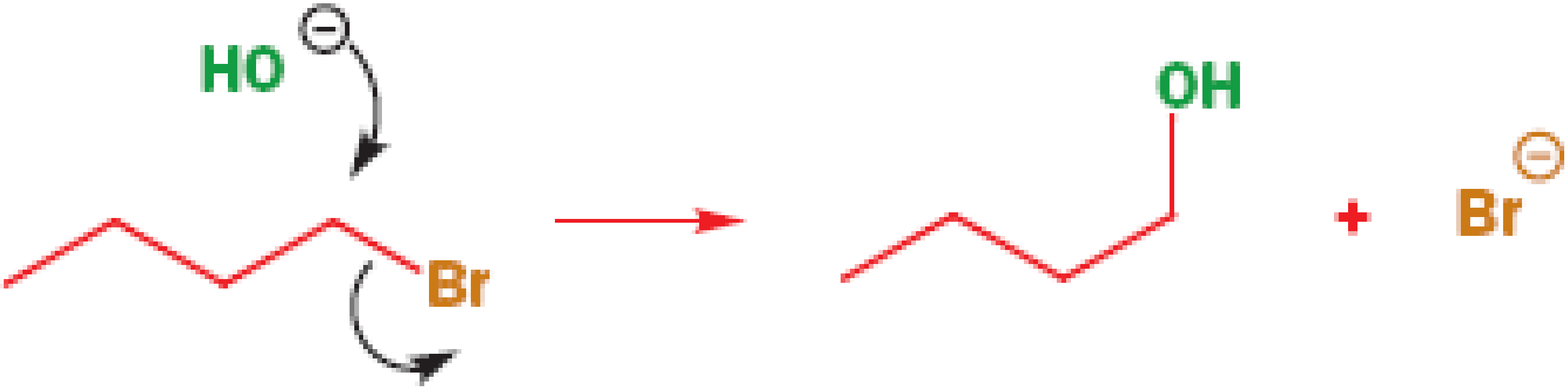
PHẢN ỨNGTHẾ THÂN HẠCH S 2



N

PHẢN ỨNGTHẾ THÂN HẠCH S 2

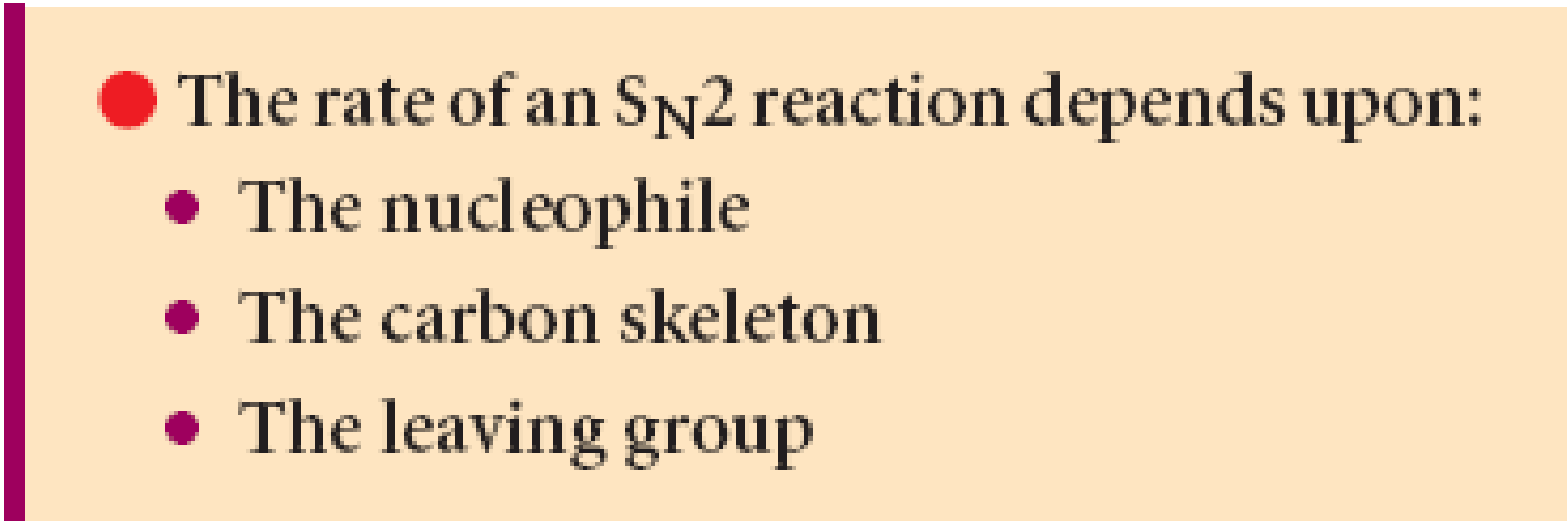


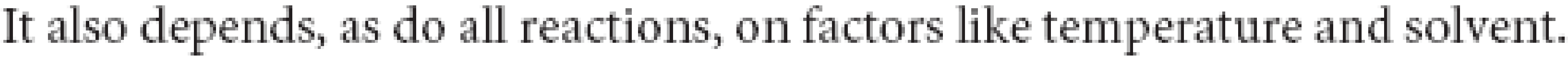


rate of reaction = $k[n\text{-BuBr}][\text{HO}^{-}]$

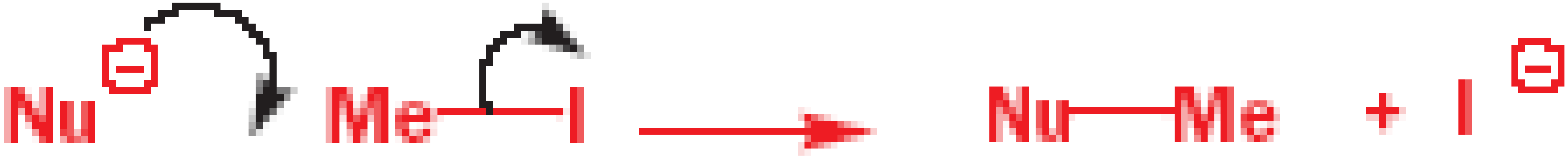
N

PHẢN ỨNGTHẾ THÂN HẠCH S 2


- The rate of an S_N2 reaction depends upon:
  - The nucleophile
  - The carbon skeleton
  - The leaving group


It also depends, as do all reactions, on factors like temperature and solvent.

CHẤT THÂN HẠCH



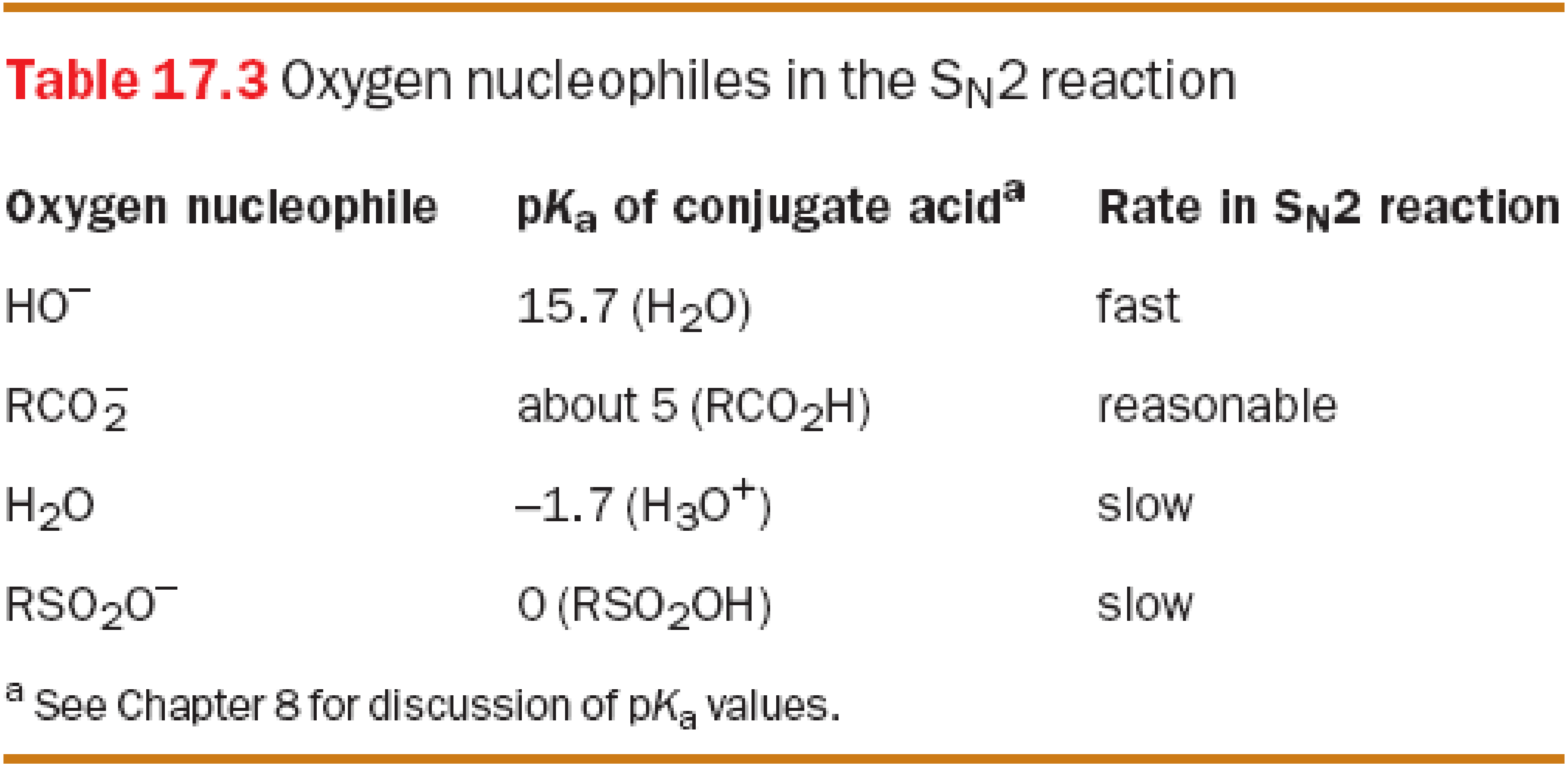


Table 17.3 Oxygen nucleophiles in the S_N2 reaction

Oxygen nucleophile	pK_a of conjugate acid[a]	Rate in S_N2 reaction
HO^-	15.7 (H_2O)	fast
RCO_2^-	about 5 (RCO_2H)	reasonable
H_2O	–1.7 (H_3O^+)	slow
RSO_2O^-	0 (RSO_2OH)	slow

[a] See Chapter 8 for discussion of pK_a values.

CHẤT THÂN HẠCH

- **Chất thân hạch càng mạnh, phản ứng xảy ra càng nhanh**
- **Độ mạnh tương đối của các chất thân hạch:**

$$CH_3Br \quad + \quad Nu:^{-} \xrightarrow[C_2H_5OH]{H_2O} CH_3Nu \quad + \quad Br^{-}$$

$$Nu = \quad HS^{-} > CN^{-} > I^{-} > CH_3O^{-} > HO^{-} > Cl^{-} > NH_3 > H_2O$$

NHÓM XUẤT

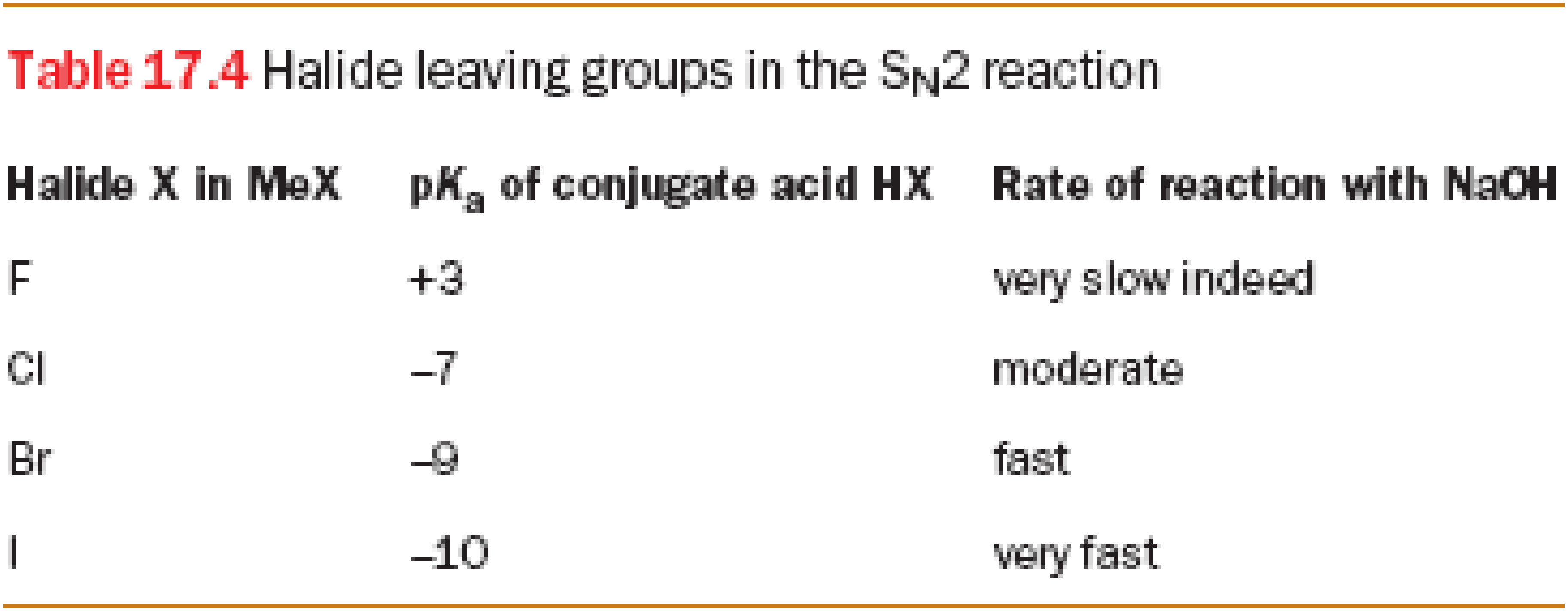


Table 17.4 Halide leaving groups in the S_N2 reaction

Halide X in MeX	pK_a of conjugate acid HX	Rate of reaction with NaOH
F	+3	very slow indeed
Cl	–7	moderate
Br	–9	fast
I	–10	very fast

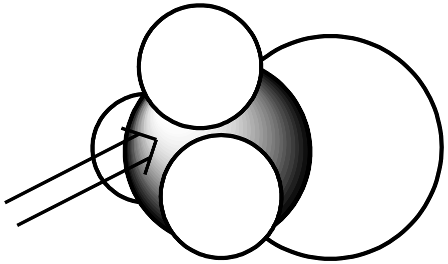
CẤU TRÚC ALKYL HALIDE

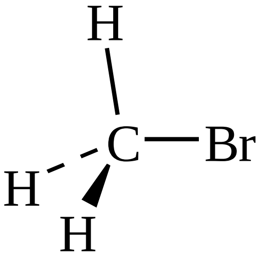
- Carbon mang nhóm thế cồng kềnh

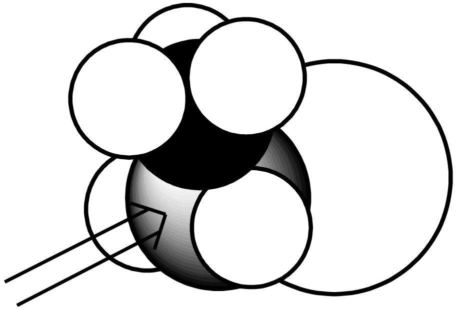
→Cản trở tác kích của chất thân hạch

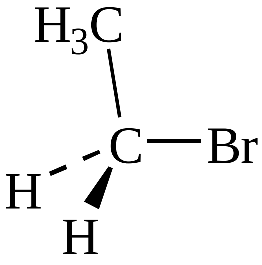
→Phản ứng càng chậm.

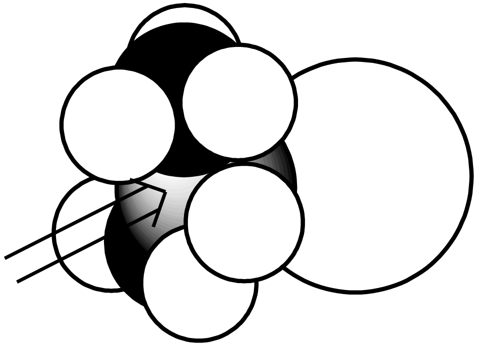
- Alkyl halide bậc 3°: không cho phản ứng thế S_N2.
- Tương tự, do chướng ngại lập thể, vinylic halide và aryl halide hoàn toàn không cho phản ứng thế S_N2.

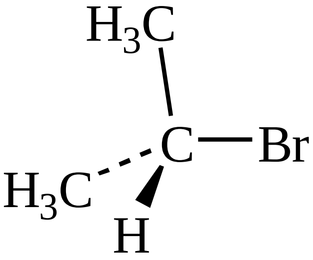


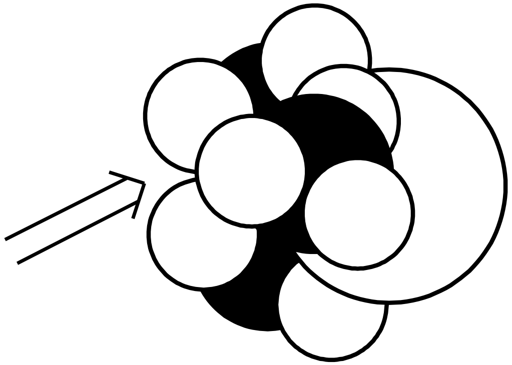

H
C
Br
H
H

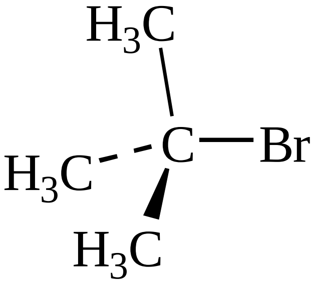



H_3C
C
Br
H
H

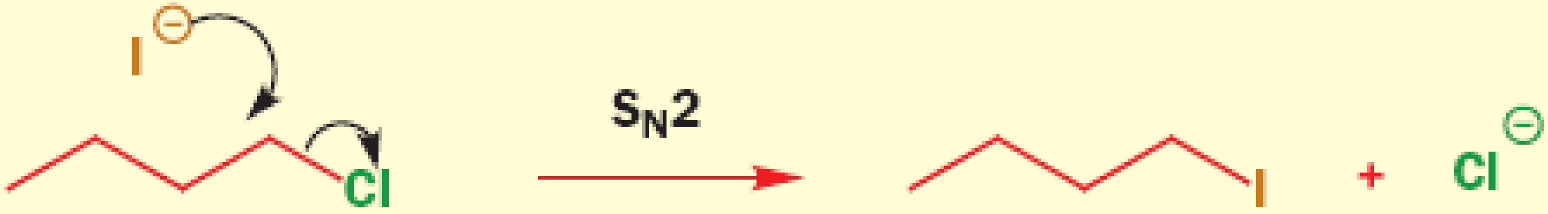


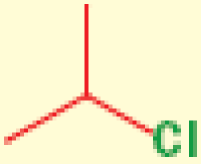
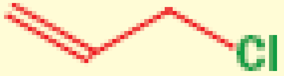
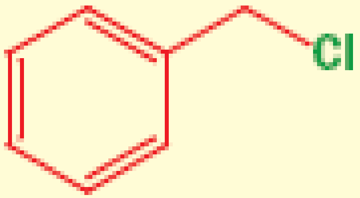
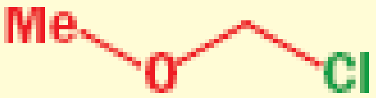
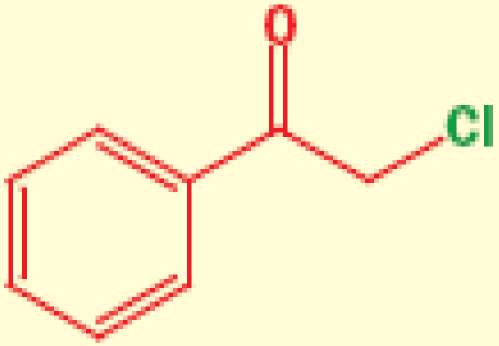

H_3C
C
Br
H_3C
H




H_3C
C
Br
H_3C
H_3C

Variation of rate with structure

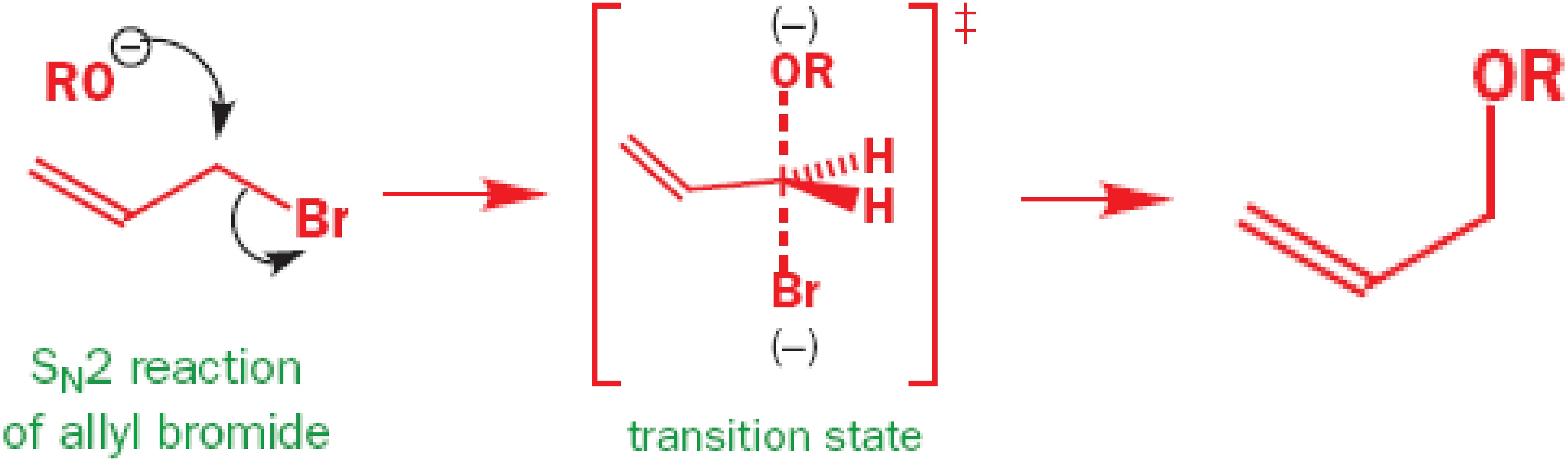


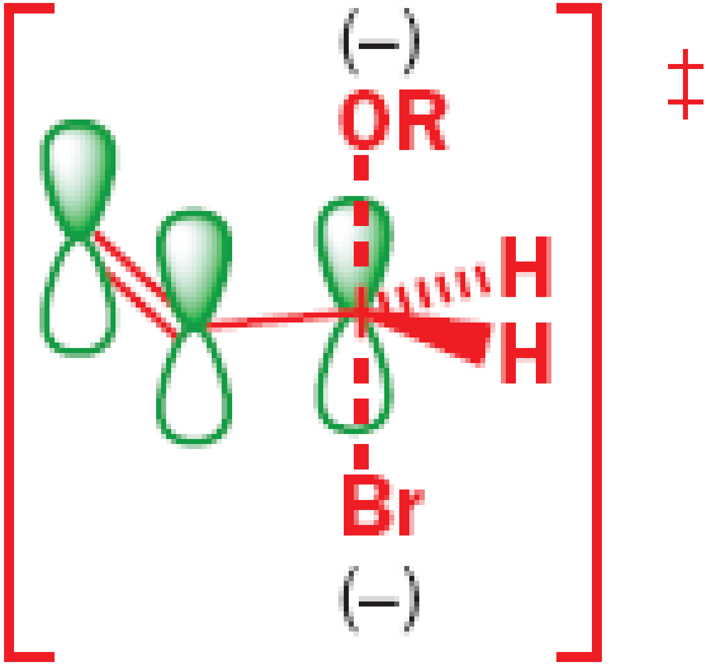
Alkyl chloride	Relative rate
Me—Cl	200
	0.02
	79
	200
	920
	100 000

CẤU TRÚC ALKYL HALIDE

- KHẢ NĂNG BỀN VỮNG HÓA

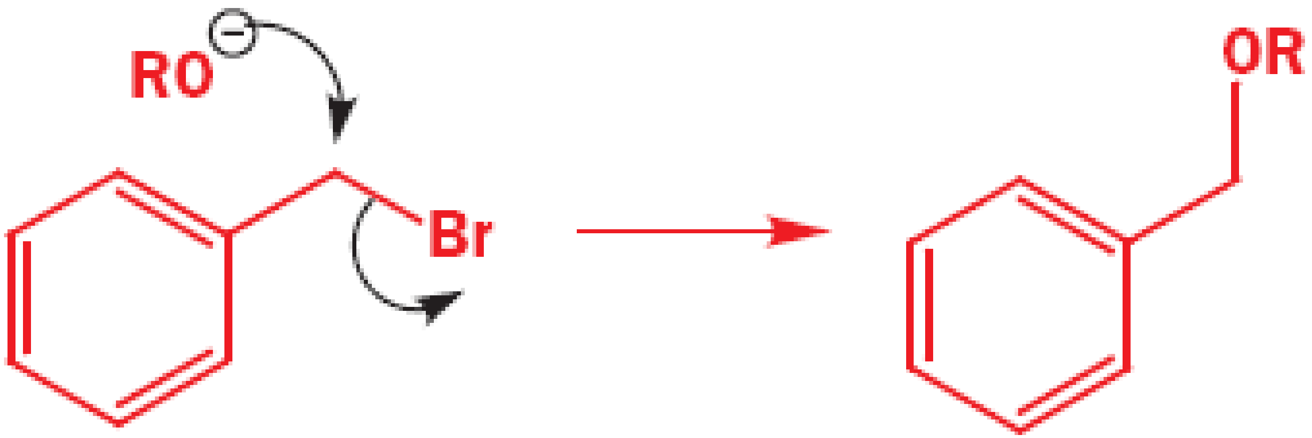
  TRẠNG THÁI CHUYỂN TIẾP
- CHƯỚNG NGẠI LẬP THỂ

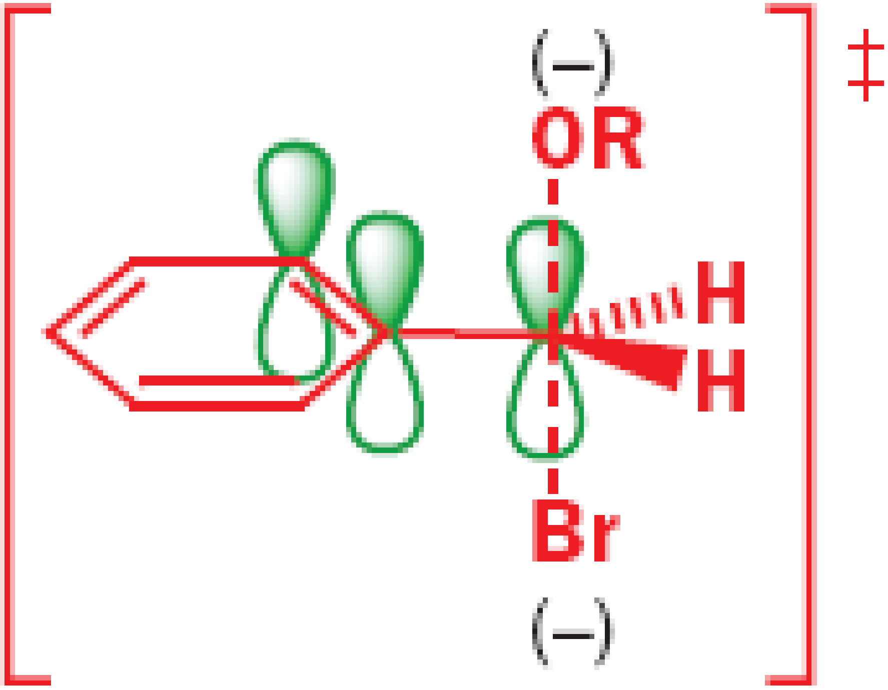




stabilization of the transition state by conjugation with the allylic π bond

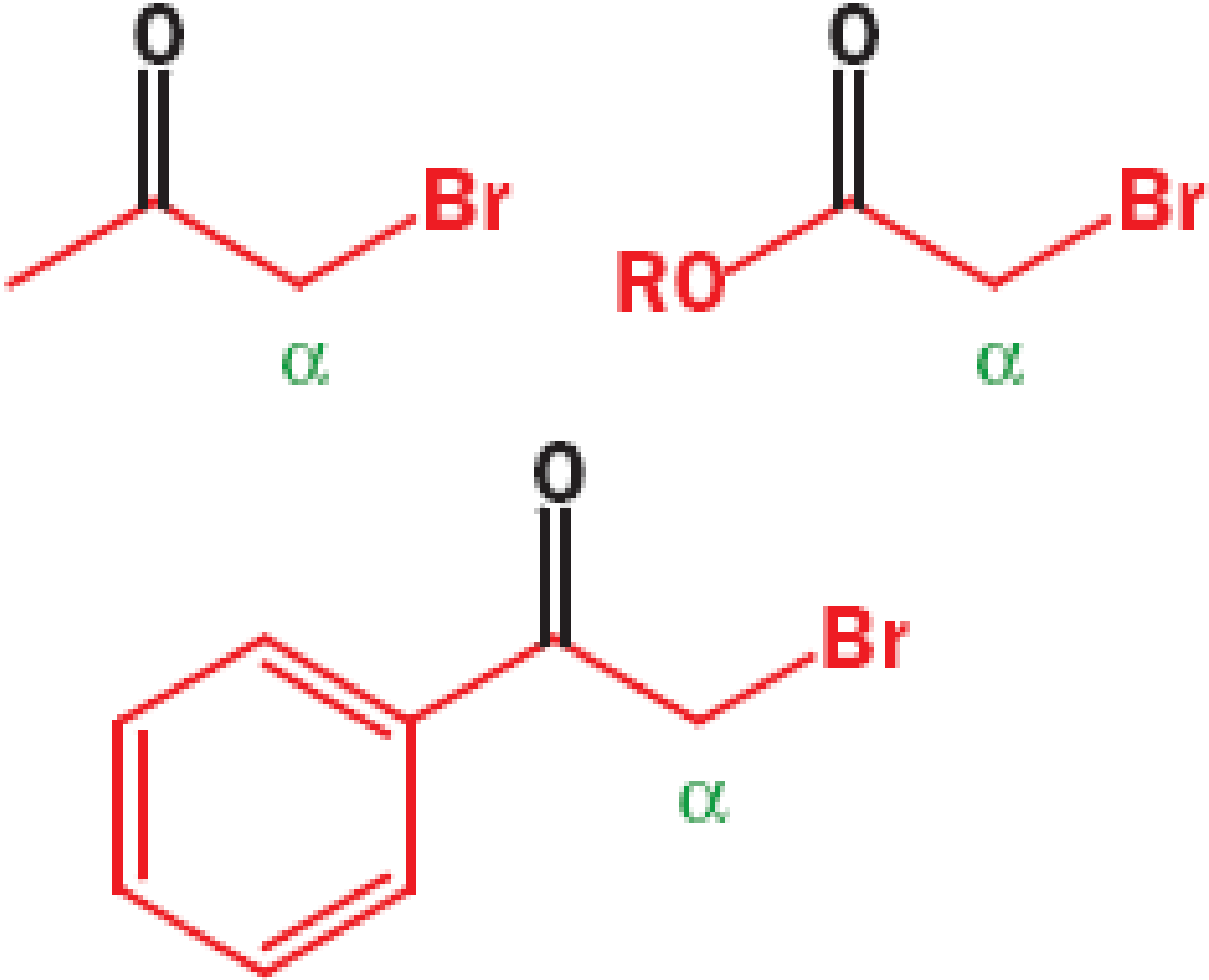
S_N2 reaction of benzyl bromide

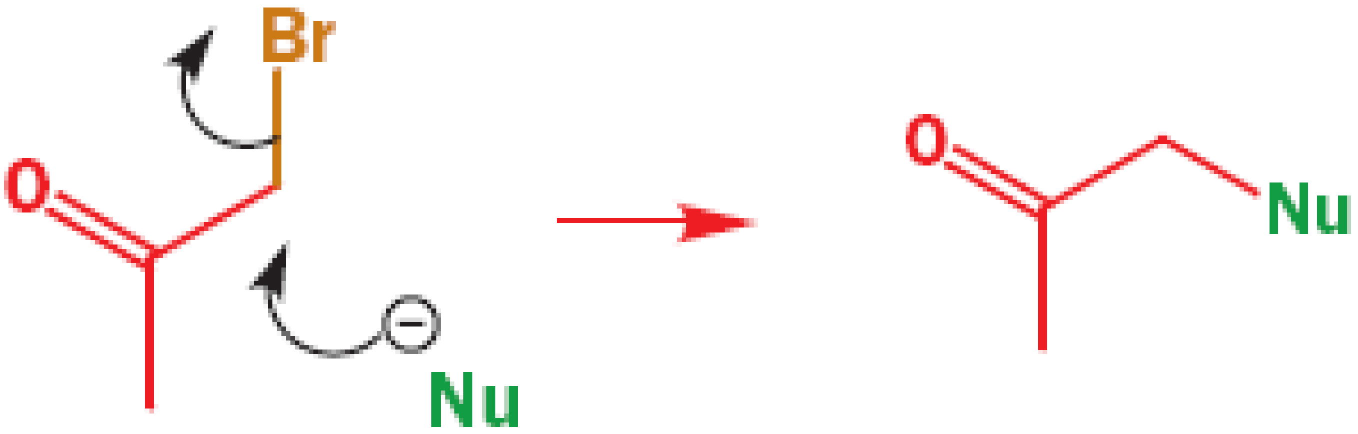


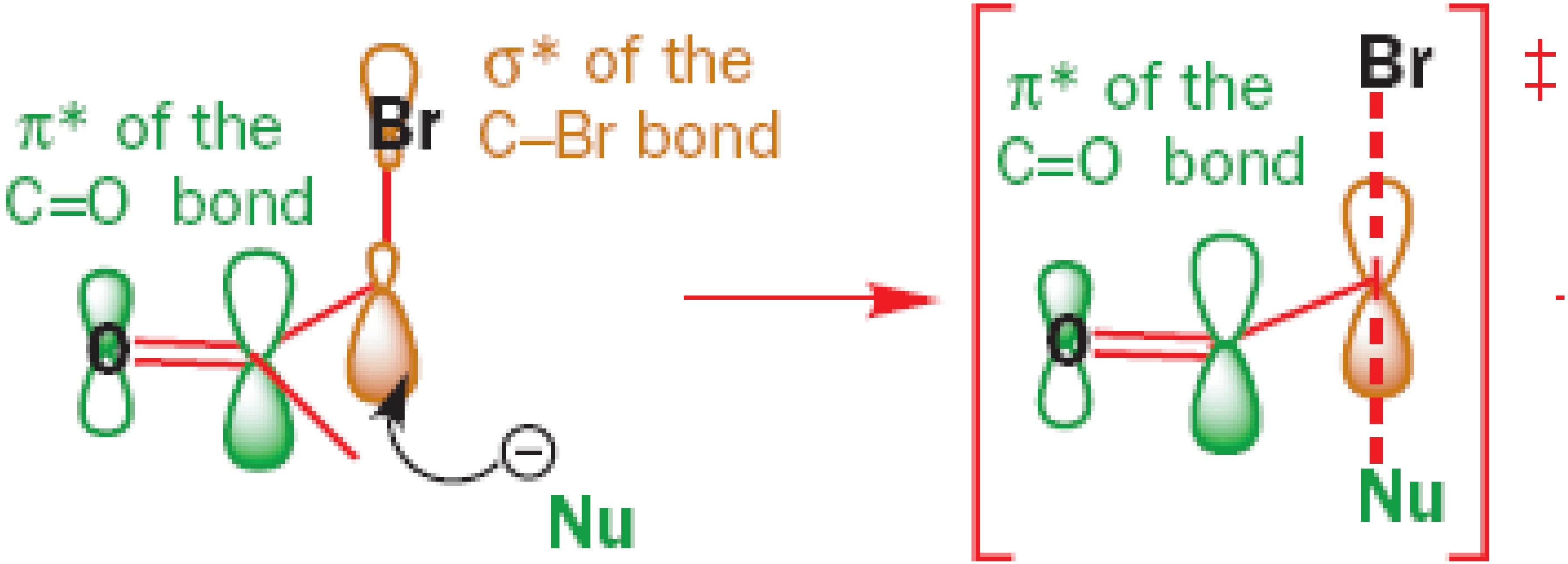


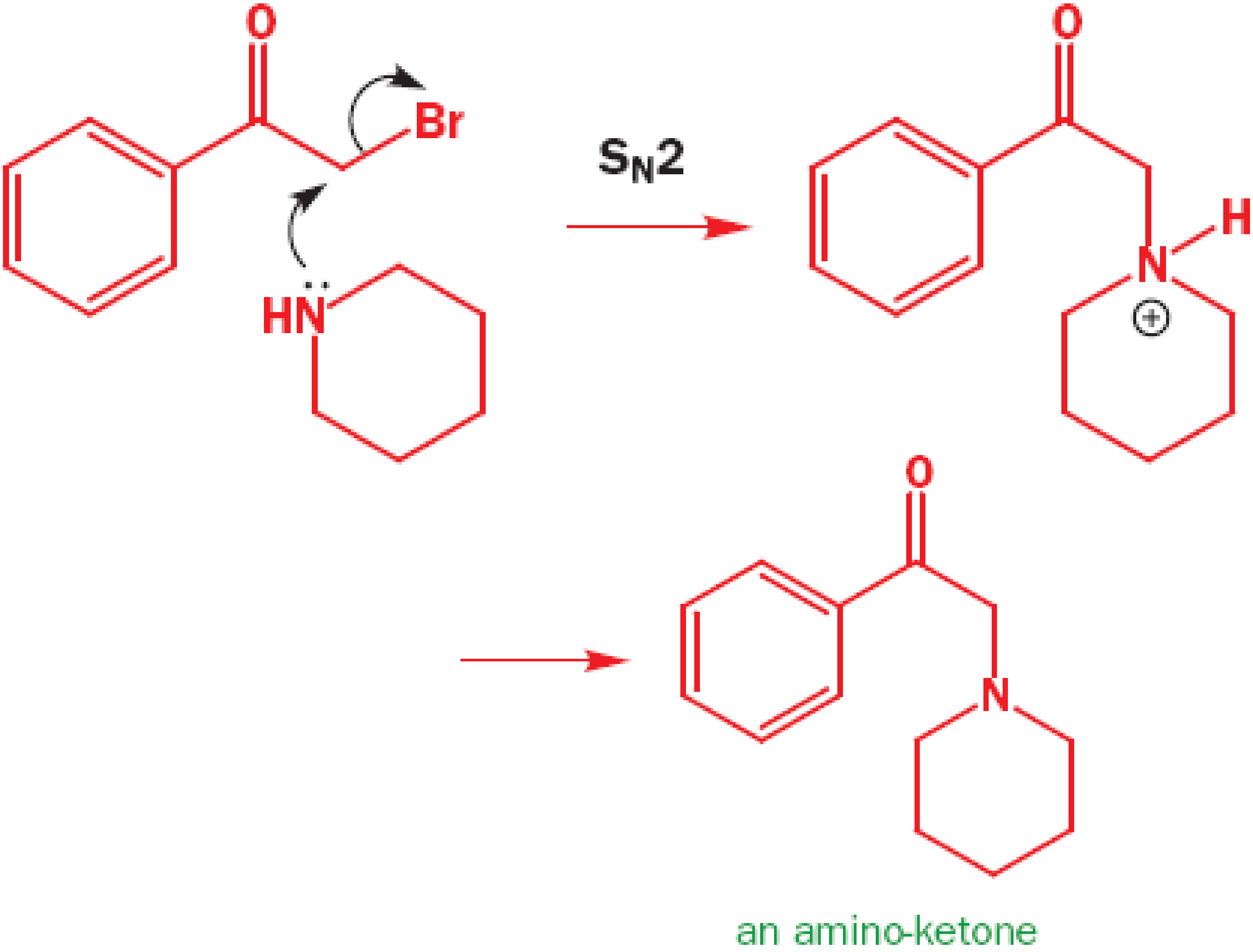
stabilization of the transition state by conjugation with the benzene ring (only two p orbitals shown in the benzene ring)

Reactive α-bromo carbonyl compounds

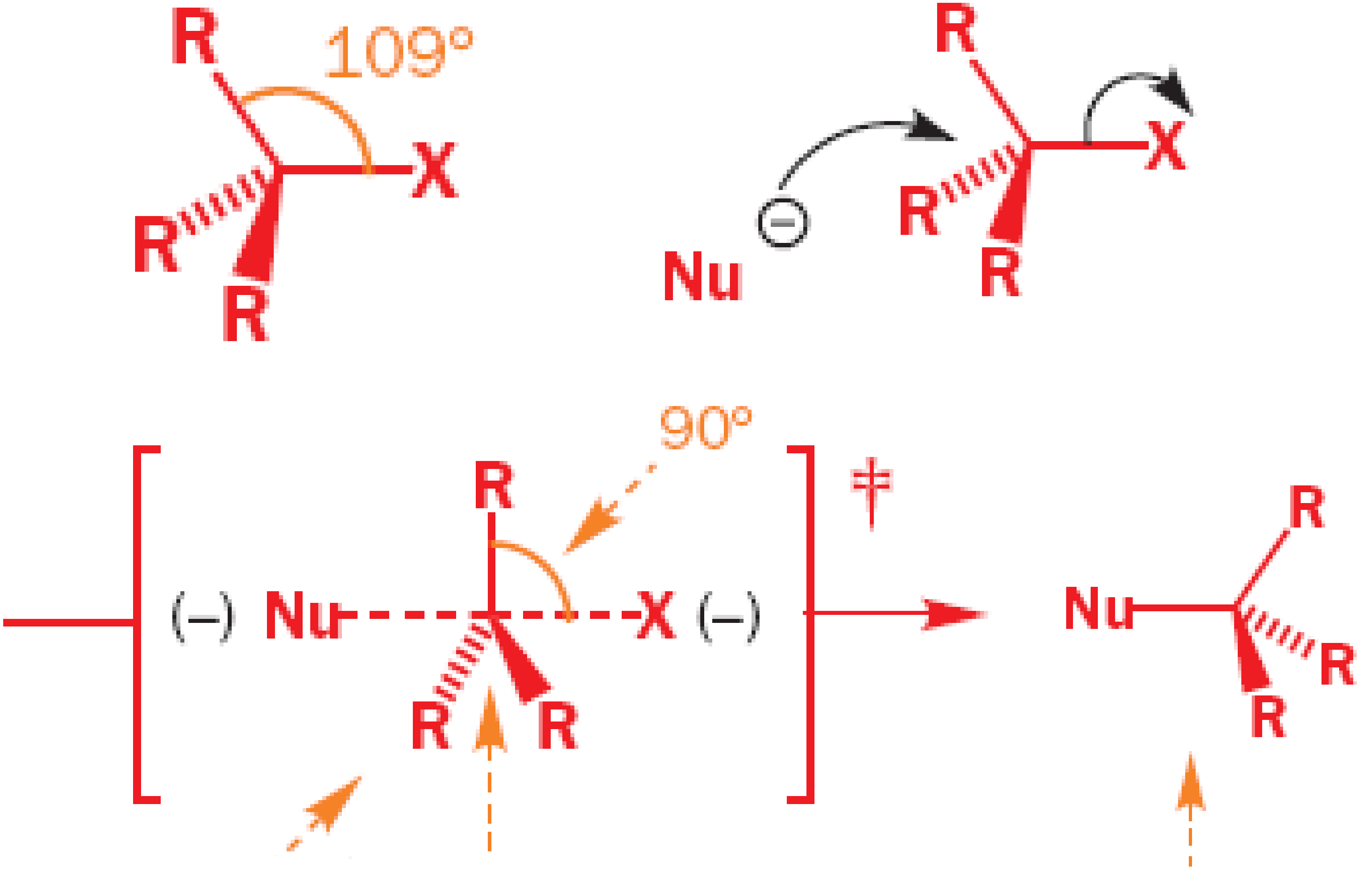



Br
O
Nu
O
Nu


π* of the
C=O bond
Br
σ* of the
C–Br bond
O
Nu
π* of the
C=O bond
Br
O
Nu
‡


O
Br
HN
S$_N$2
O
H
N
+
O
N
an amino-ketone

- **Alkyl bậc 1°: RCH –X: nhanh**

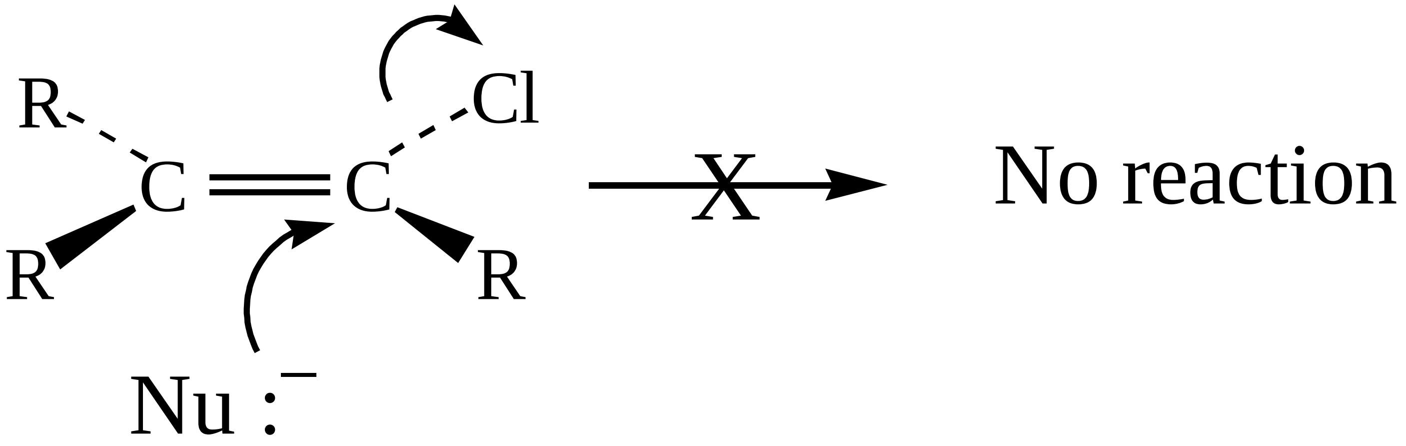


trigonal bipyramid –
three angles of 120°
six angles of 90°

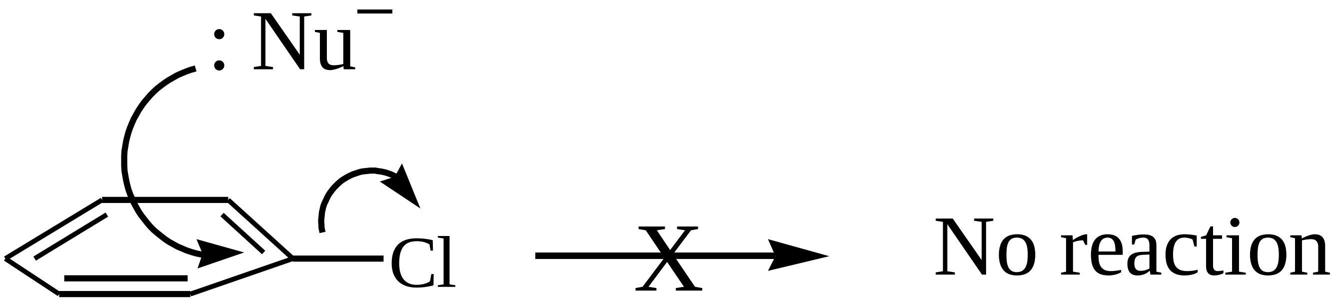
120°

tetrahedral –
all angles 109°

rate-determining step



Vinyl halide



Aryl halide

Ảnh hưởng của dung môi

- **Dung môi phân cực**
- Trong dung dịch: **chất thân hạch** và cả **tạp chất kích động** sẽ bị **solvat hóa**:

► Bền vững hóa trạng thái chuyển tiếp

→ Tăng vận tốc phản ứng.

► Cản trở sự tiếp cận tâm carbon thân điện tử của chất thân hạch

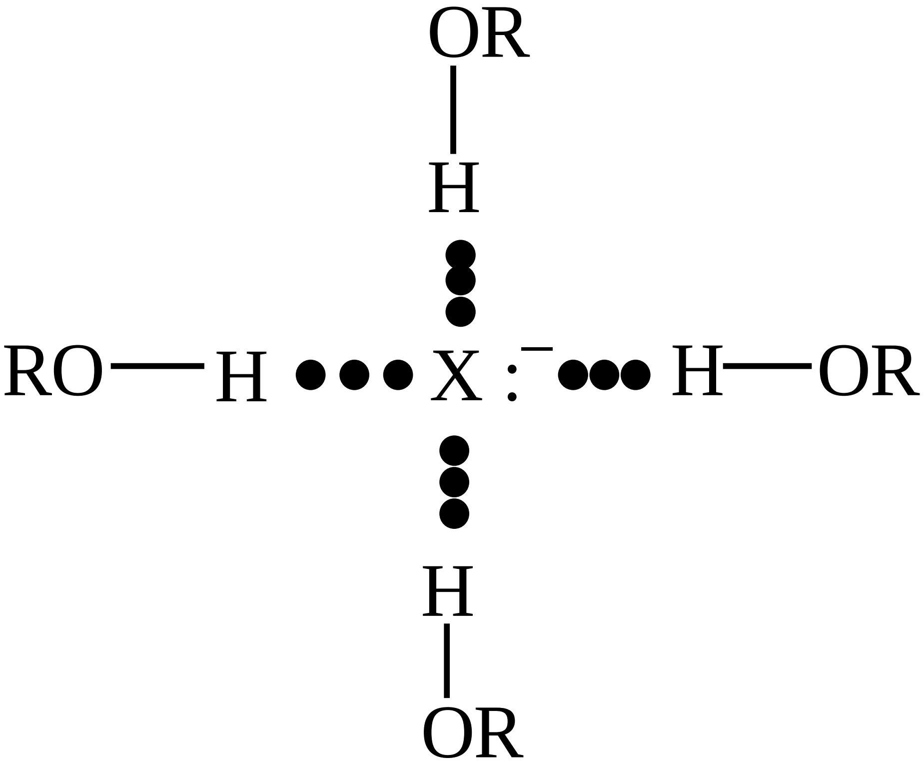
→ Giảm tốc độ phản ứng thế S_N2.

Ảnh hưởng của dung môi

Protonic solvents

Khả năng solvate hóa mạnh, đặc biệt với chất thân hạch là anion

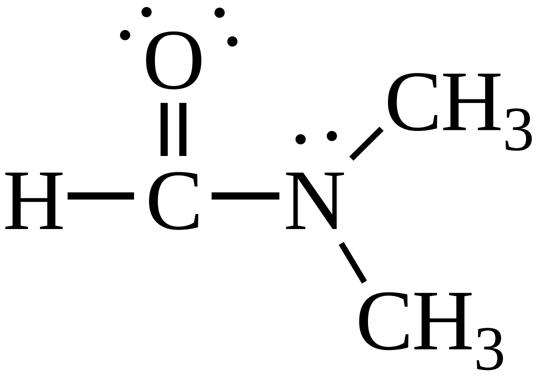
► **ít được sử dụng**



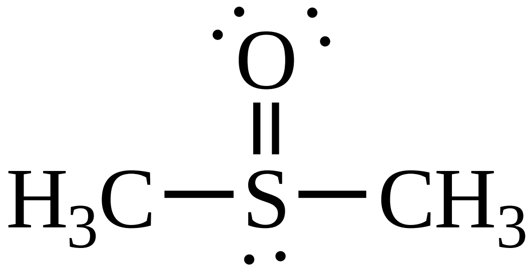
N

Dung môi trong phản ứng S 2

- **Solvate hóa tốt các cation kim loại**
- **Solvat hóa rất kém các anion**



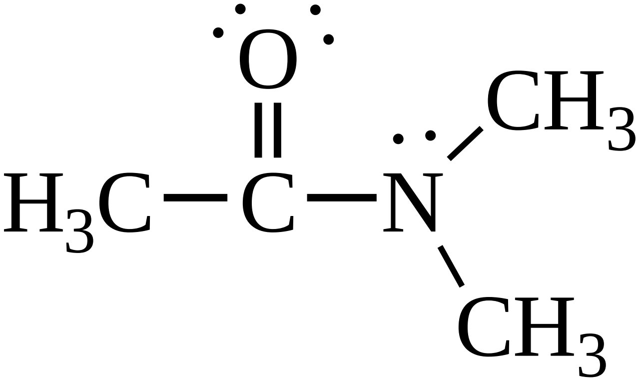
N,*N*-Dimethylformamide
(DMF)



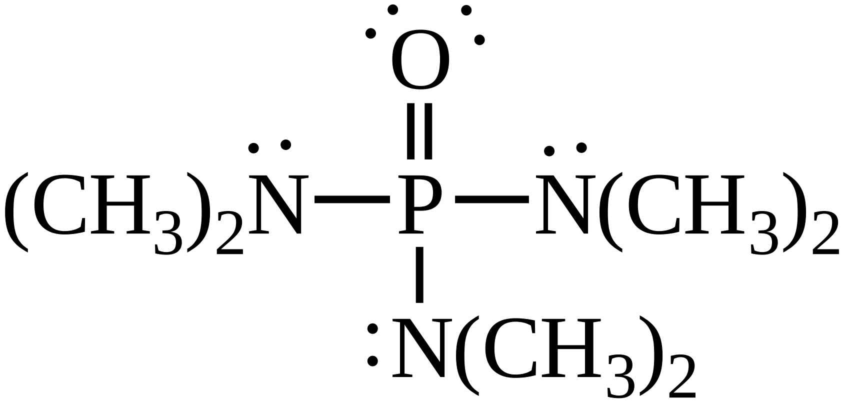
Dimethylsulfoxide
(DMSO)

N

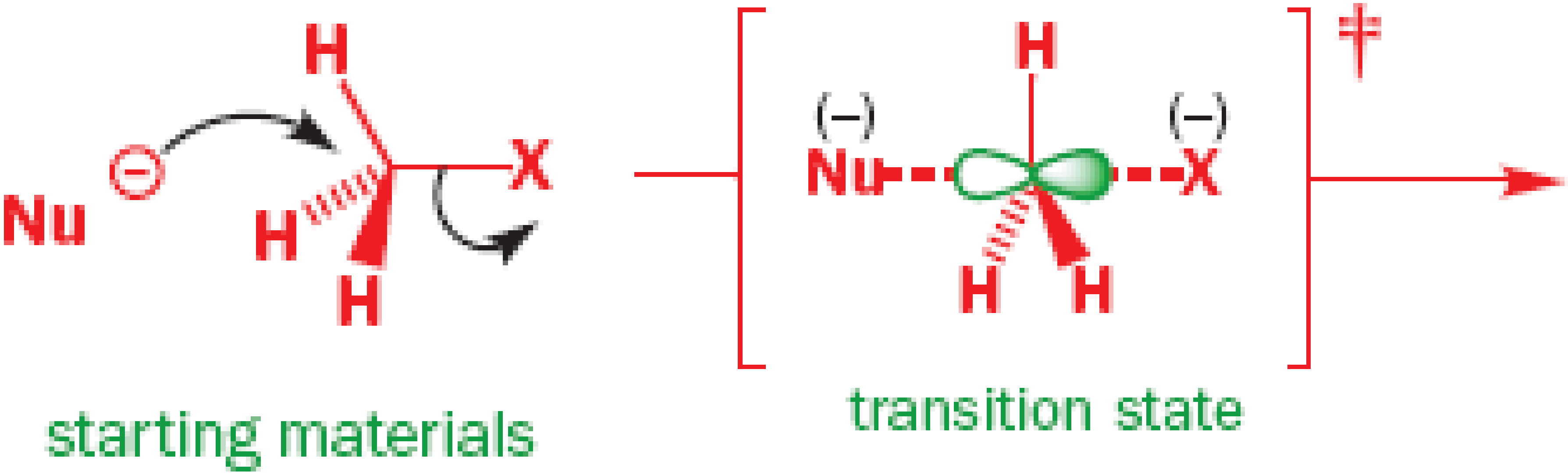
Dung môi trong phản ứng S 2



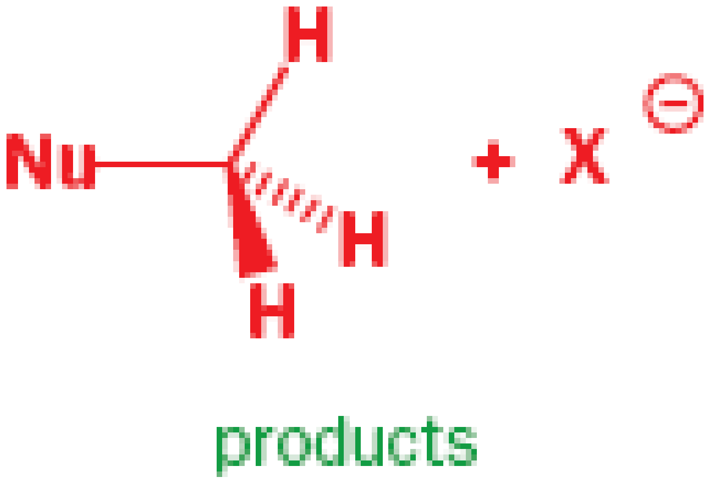
Dimethylacetamide
(DMA)



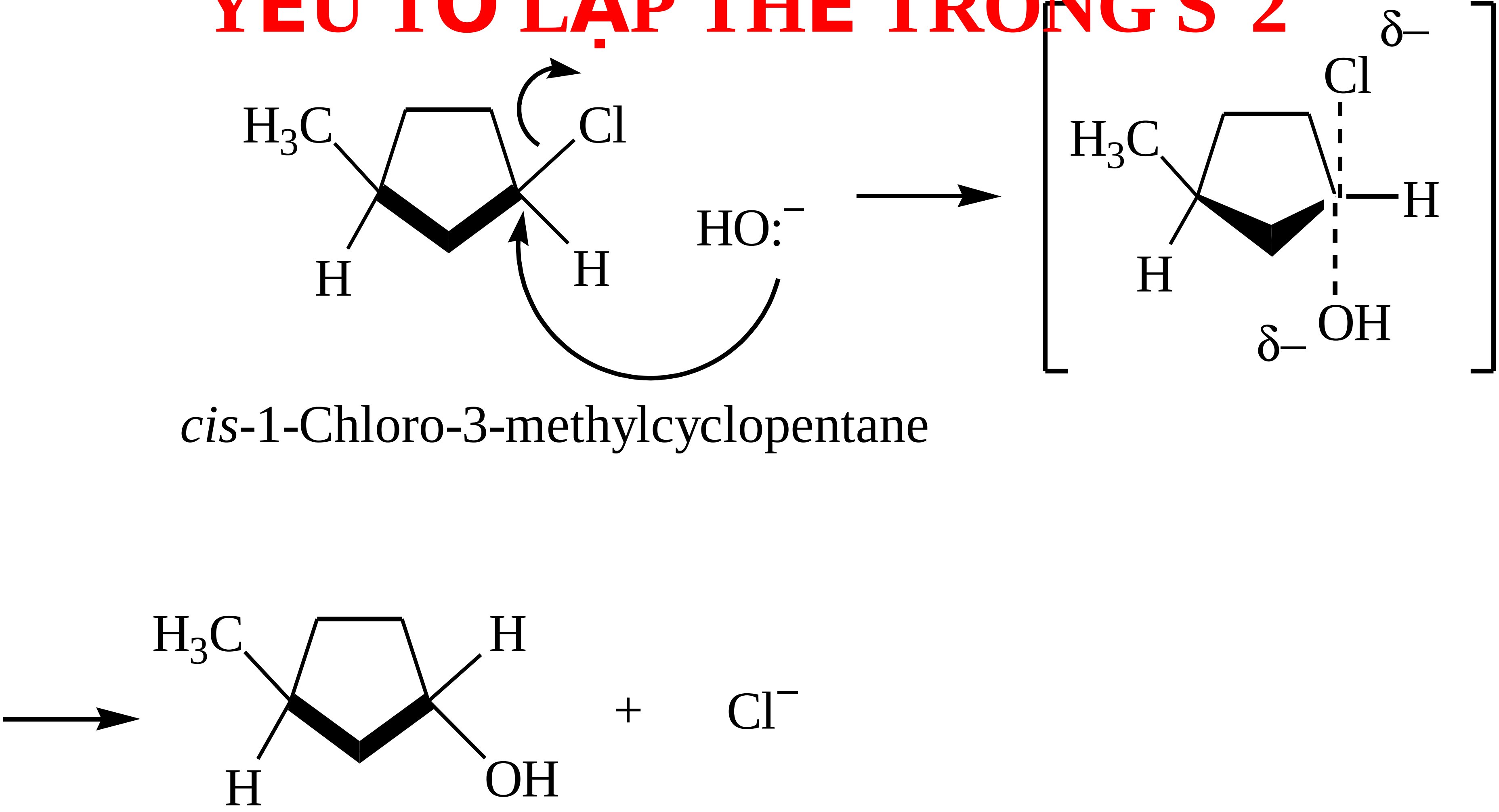
Hexamethylphosphoramide
(HMPA)



Sản phẩm tạo thành có sự đảo ngược cấu hình của nguyên tử carbon so với ban đầu



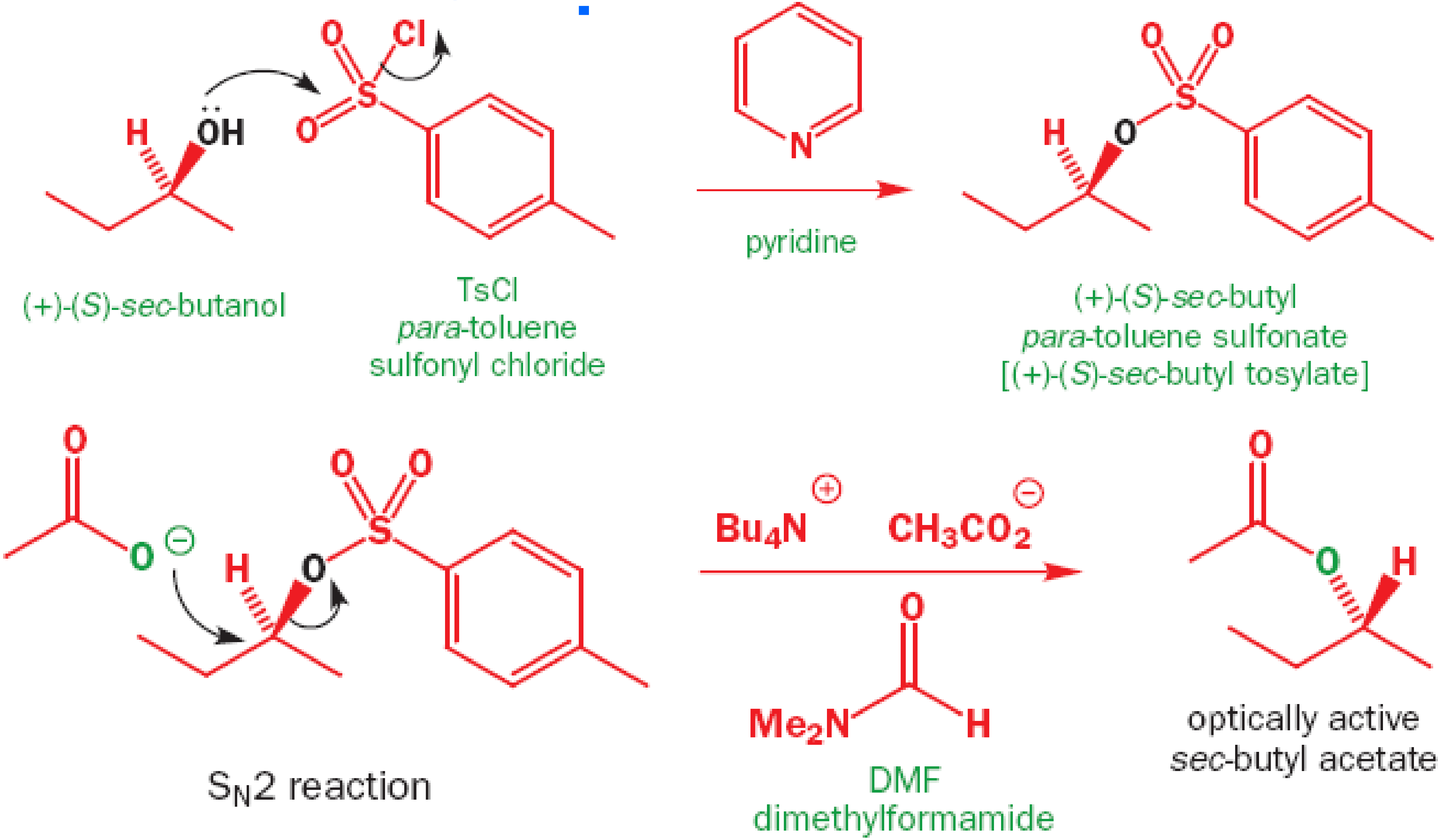
YẾU TỐ LẬP THỂ TRONG S 2



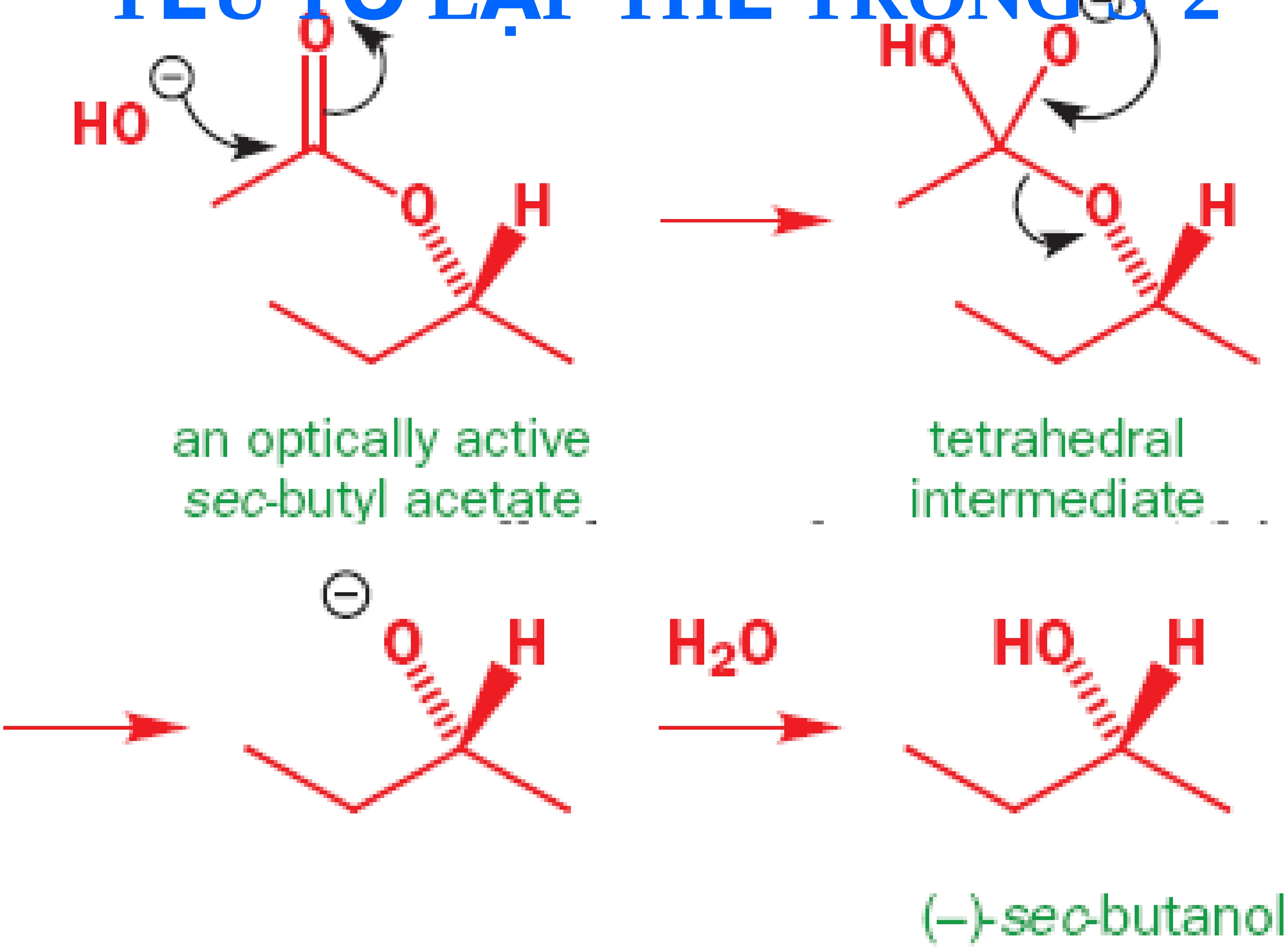
cis-1-Chloro-3-methylcyclopentane

trans-3-methylcyclopentanol

YẾU TỐ LẬP THỂ TRONG S 2



YẾU TỐ LẬP THỂ TRONG S 2

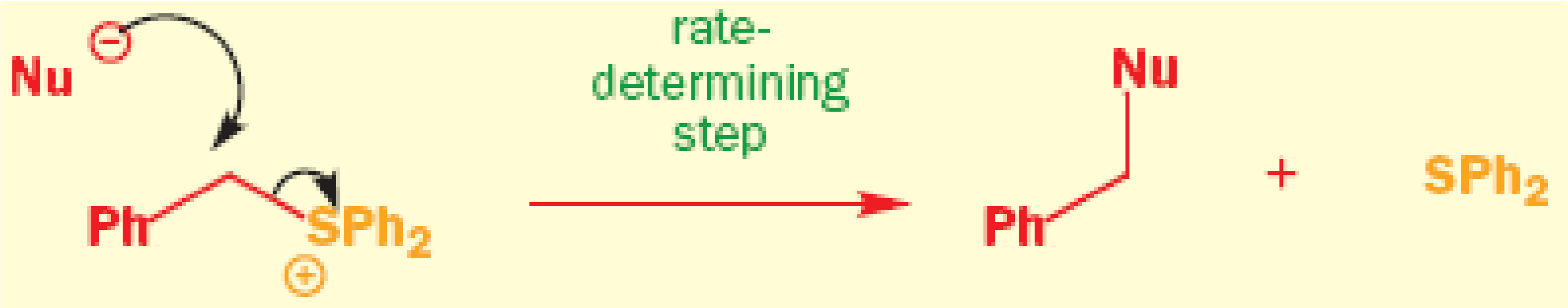


an optically active
sec-butyl acetate

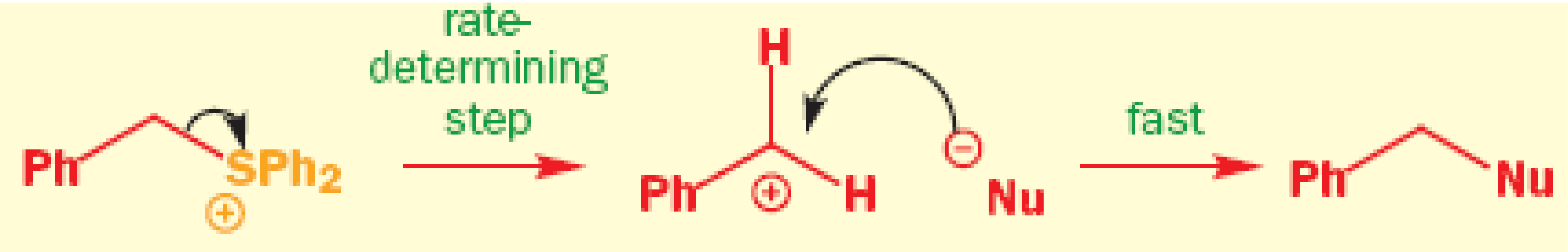
tetrahedral
intermediate

(–)-*sec*-butanol

the S_N2 mechanism

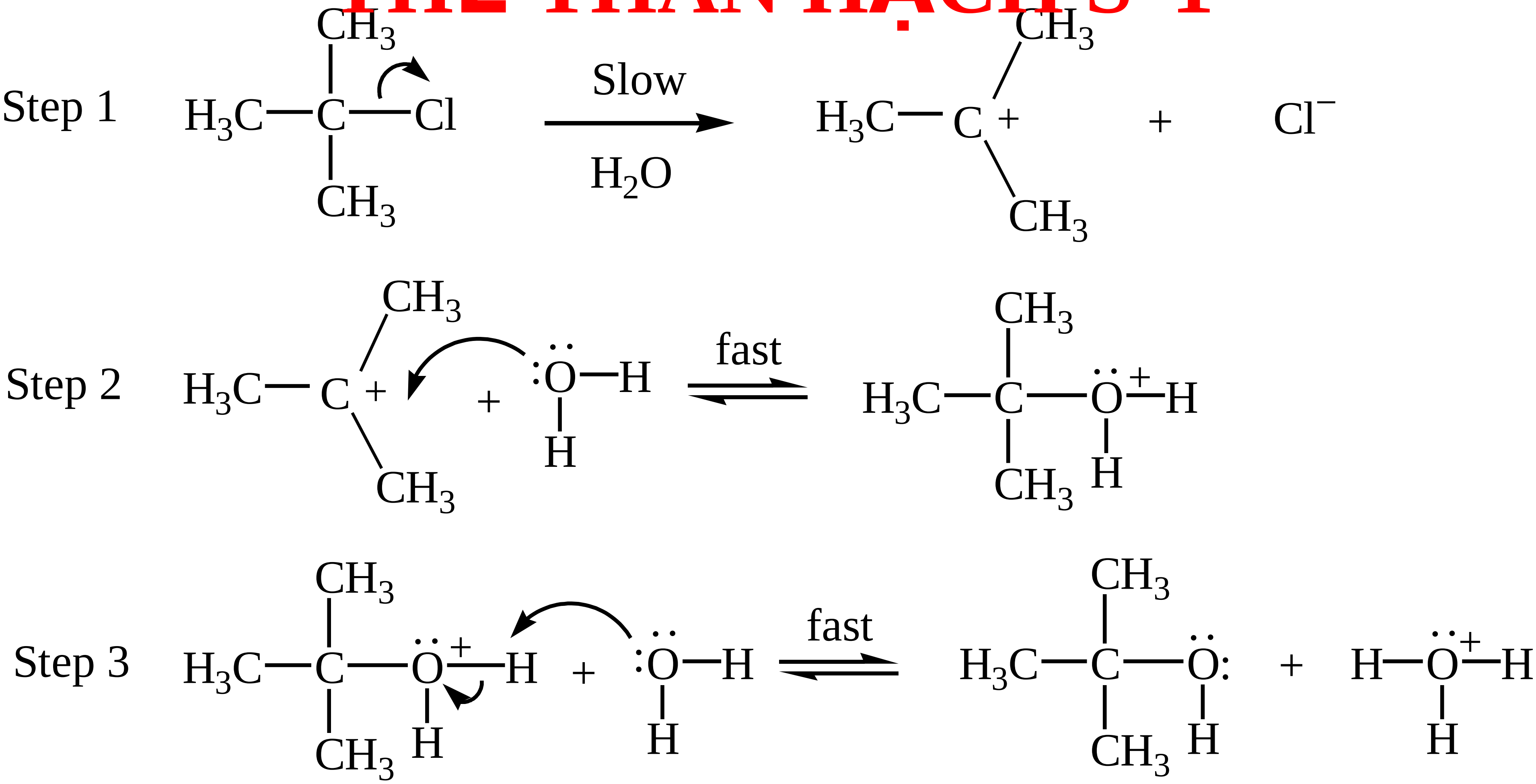


the S_N1 mechanism



N

THẾ THÂN HẠCH S 1



THẾ THÂN HẠCH S 1

stage 1: formation of the carbocation

stage 2: reaction of the carbocation

$$\text{rate} = k_1[t\text{-BuBr}]$$

- Chỉ phụ thuộc vào bản chất và nồng độ Ankyl Halide

Tốc độ phản ứng thế S 1

- Không phụ thuộc vào bản chất và nồng độ của chất thân hạch

stage 1: formation of the carbocation

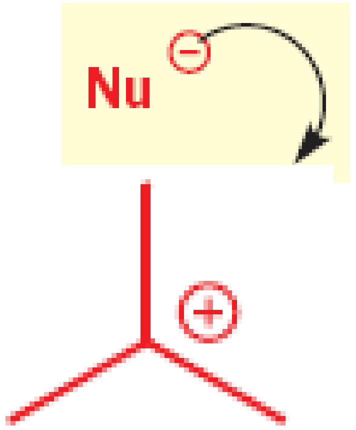


Table 17.3 Oxygen nucleophiles in the S_N2 reaction

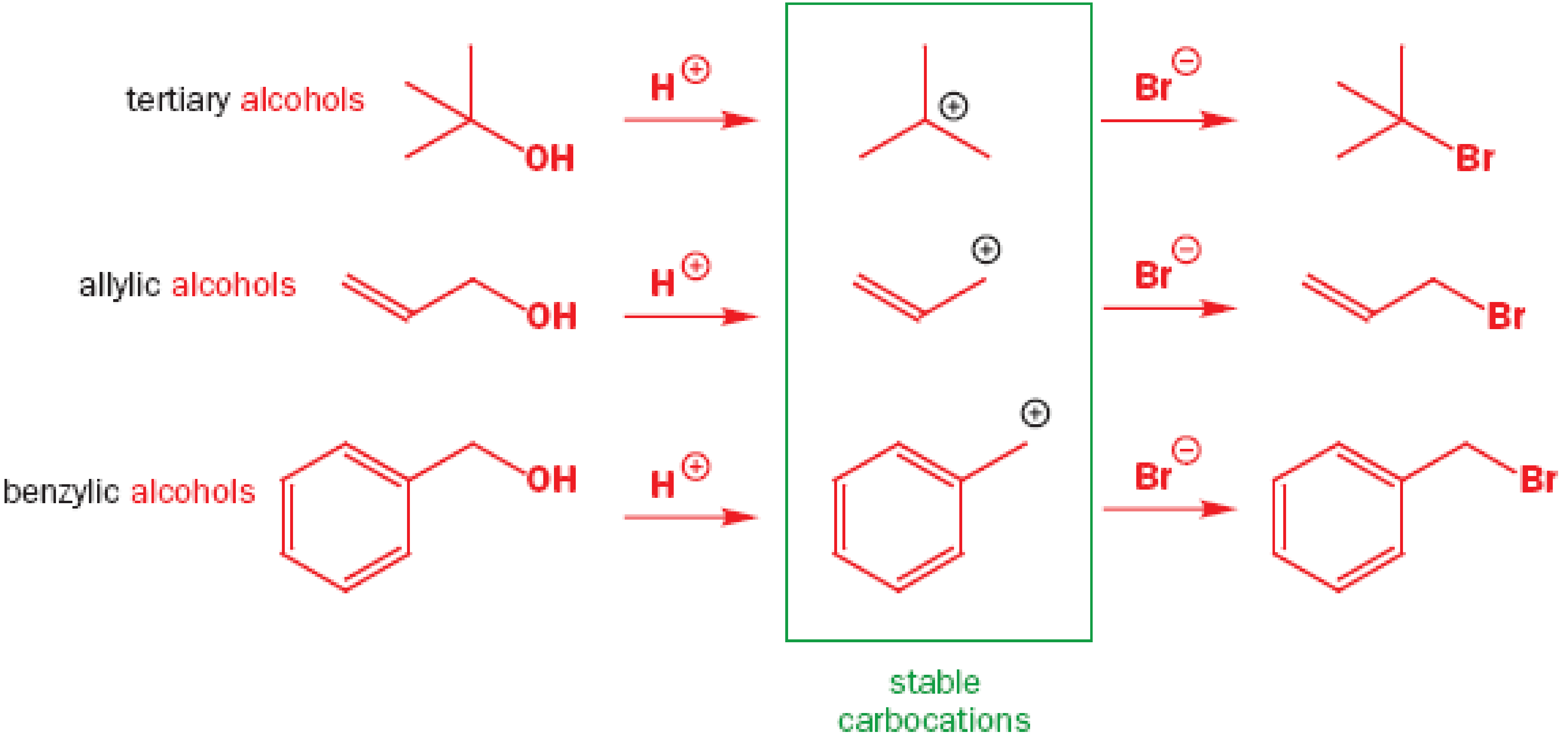
Oxygen nucleophile	**pK_a of conjugate acid**[a]	**Rate in S_N2 reaction**
HO^-	15.7 (H_2O)	fast
RCO_2^-	about 5 (RCO_2H)	reasonable
H_2O	–1.7 (H_3O^+)	slow
RSO_2O^-	0 (RSO_2OH)	slow

[a] See Chapter 8 for discussion of pK_a values.

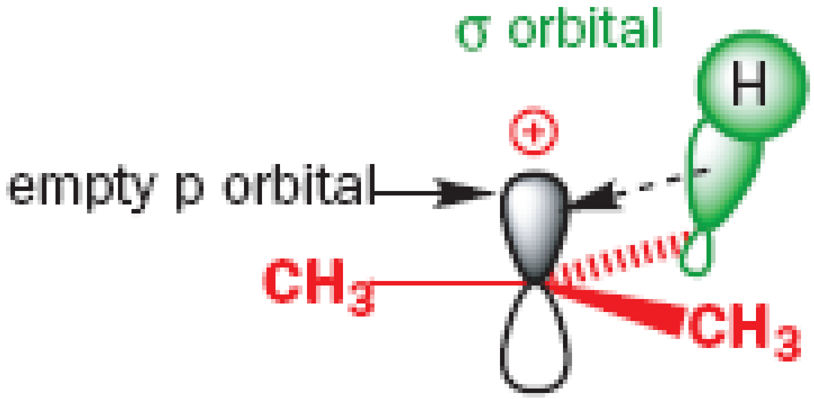
CẤU TRÚC ALKYL HALIDE

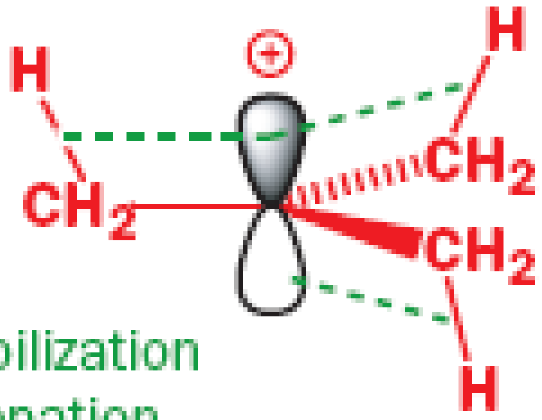
- **KHẢ NĂNG BỀN VỮNG HÓA ION CARBOCATION**
- **KHÔNG ẢNH HƯỞNG BỞI CHƯỚNG NGẠI LẬP THỂ**

Structure and stability of carbocations



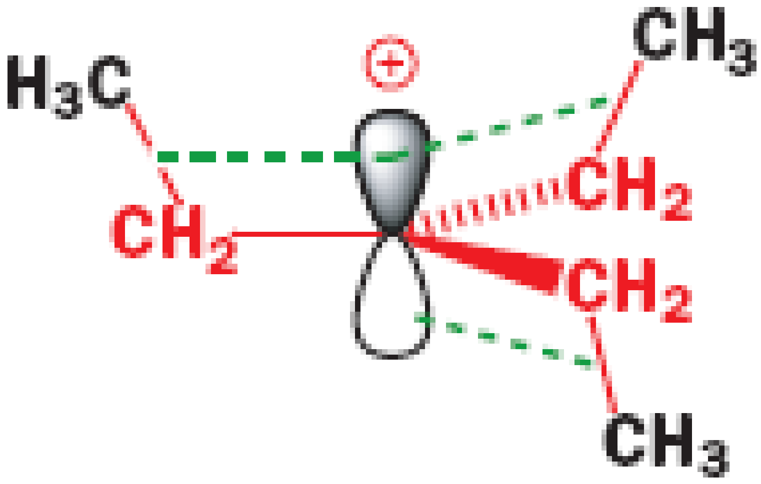
ALKYL CARBOCATION



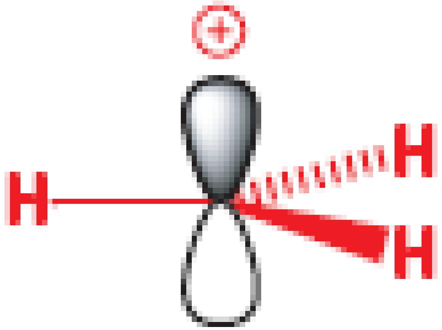


extra stabilization
from σ donation
into empty p orbital
of planar carbocation

ALKYL CARBOCATION



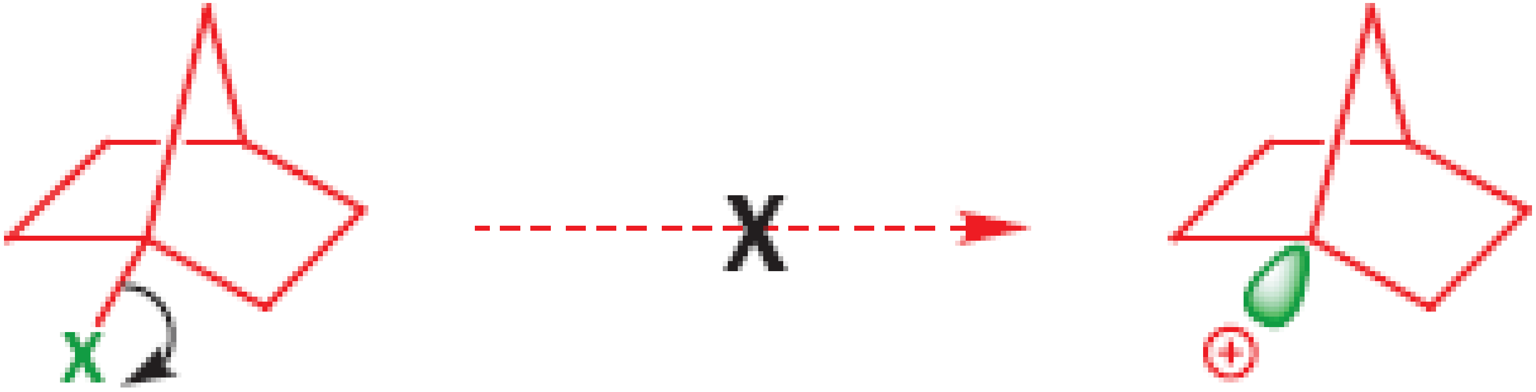
extra stabilization
from σ donation
into empty p orbital
of planar carbocation



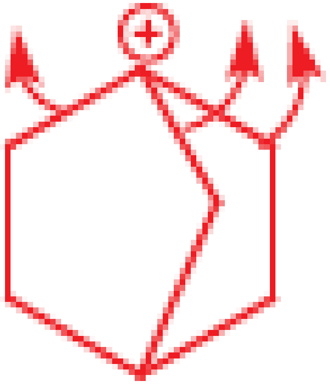
no stabilization: no electrons
to donate into empty p orbital

note: The C–H bonds are at
90° to the empty p orbital
and cannot interact with it

ALKYL CARBOCATION

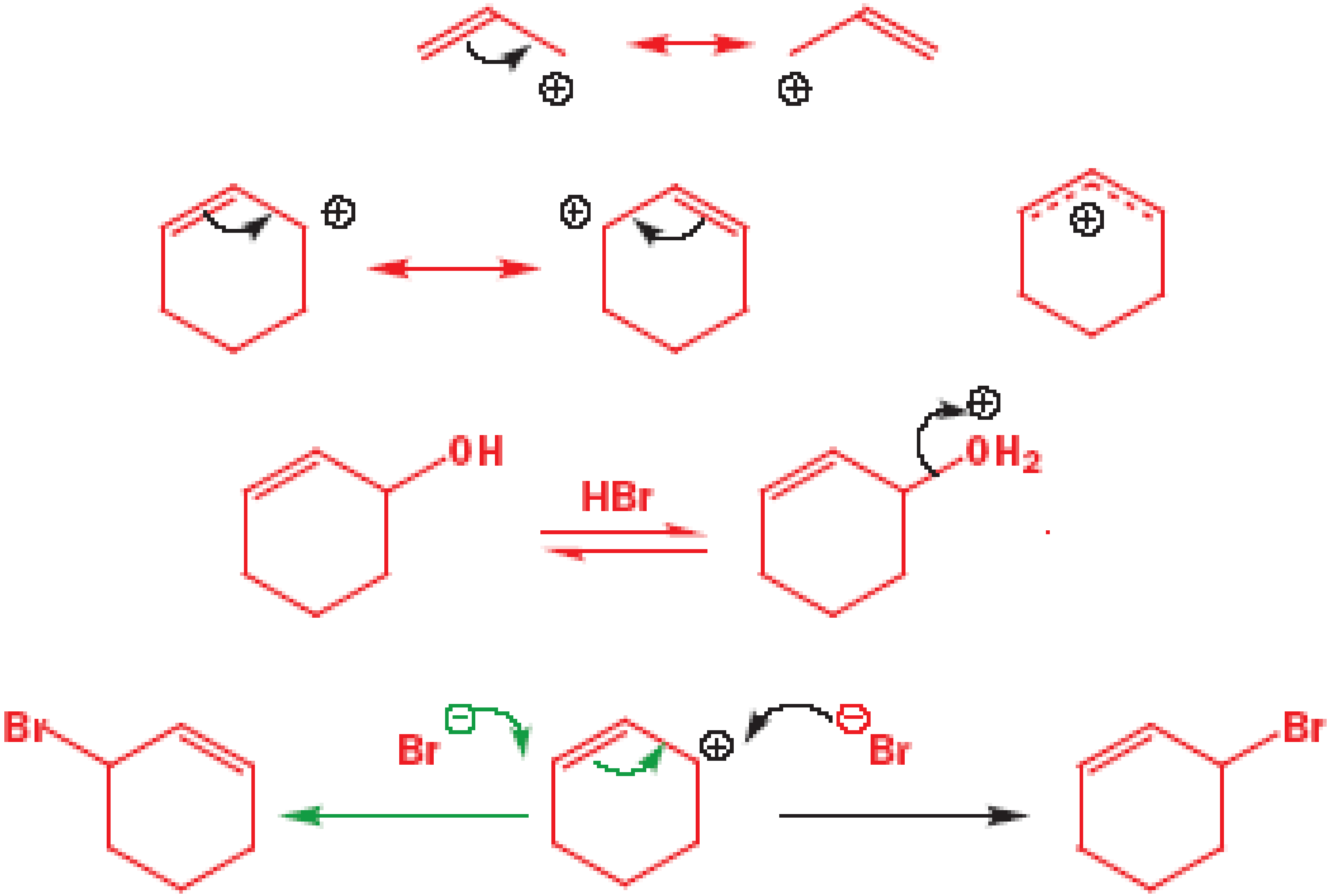


carbocation
would have to be
tetrahedral

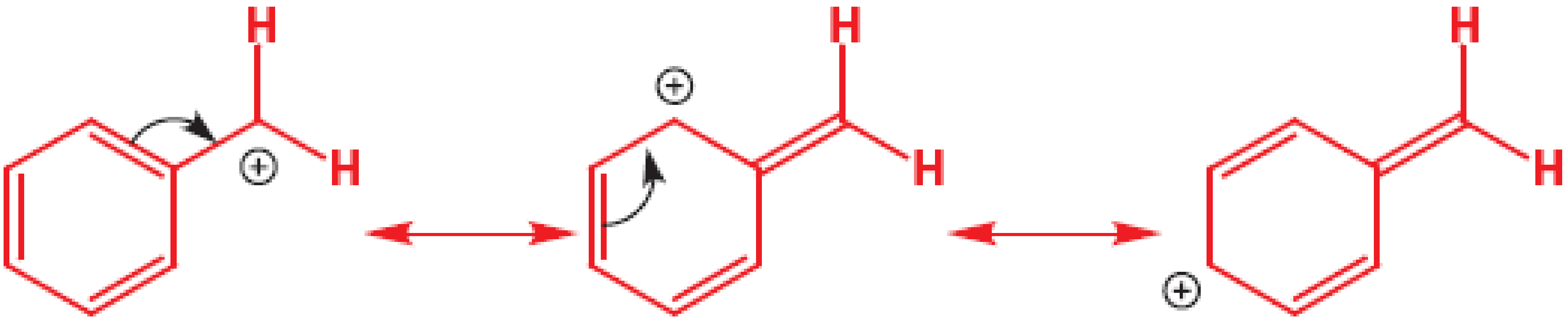


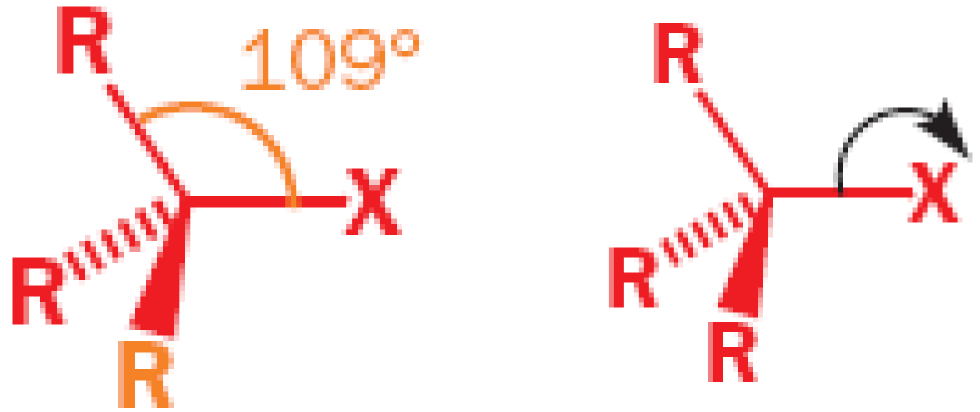
can't get planar because
of bicyclic structure

ALLYLIC CARBOCATION

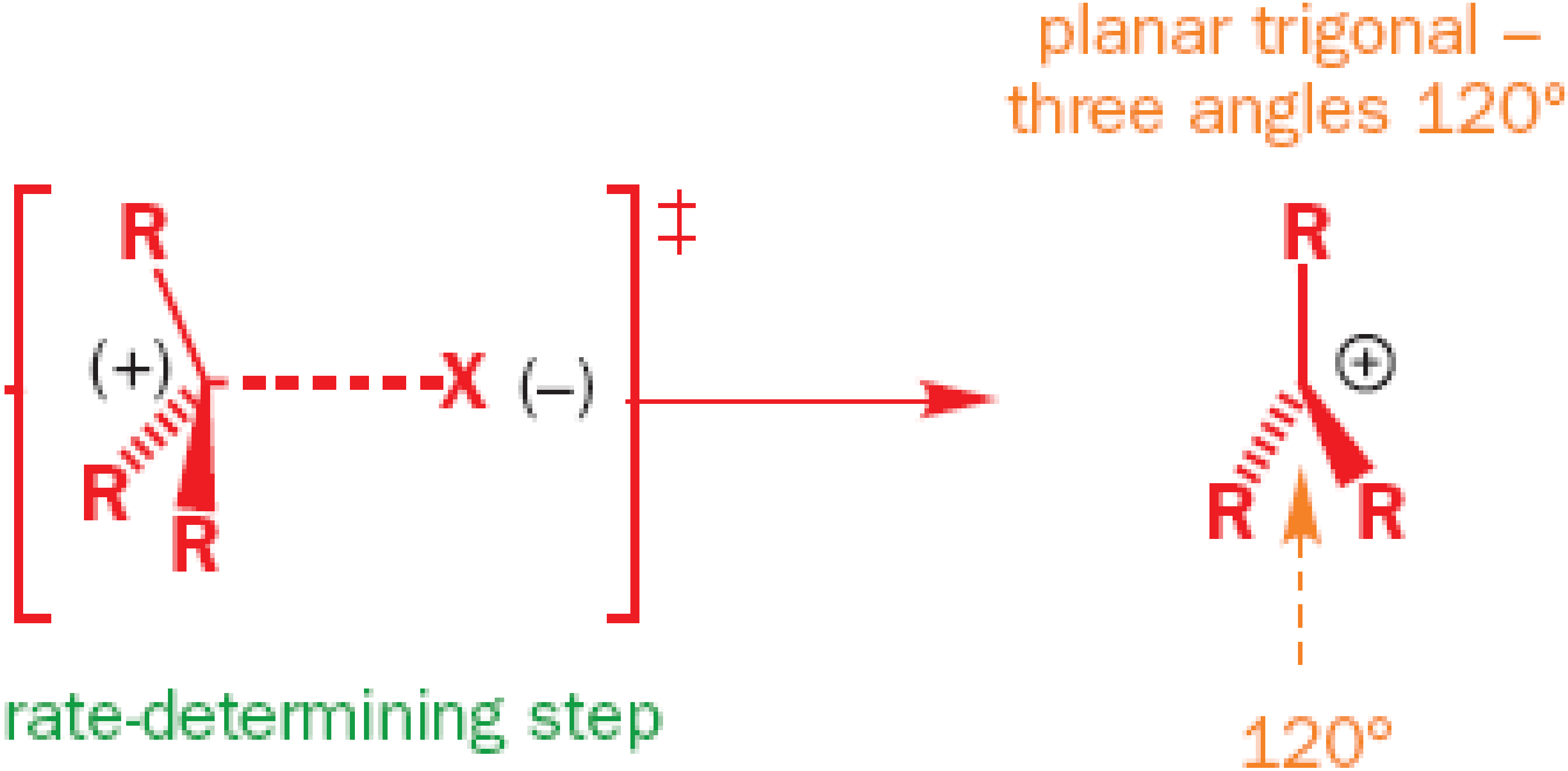


BENZYLIC CARBOCATION

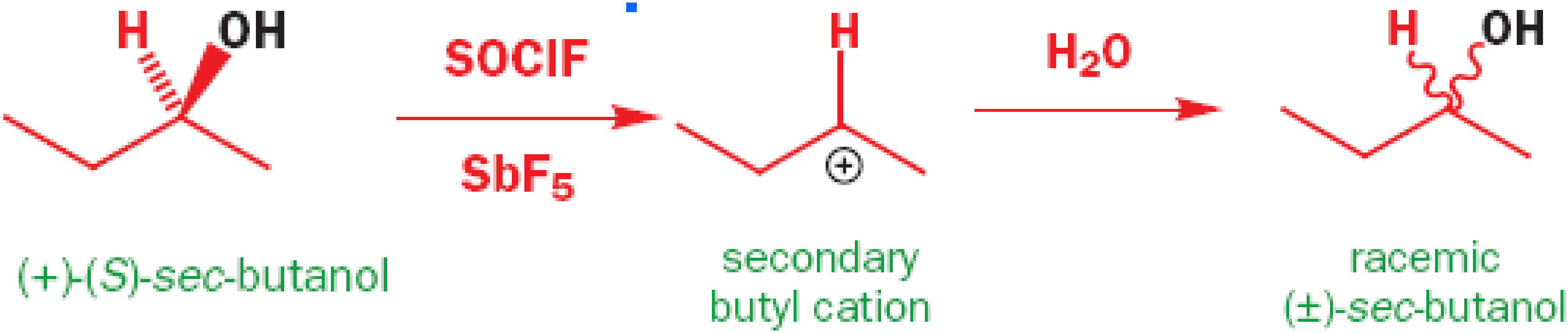


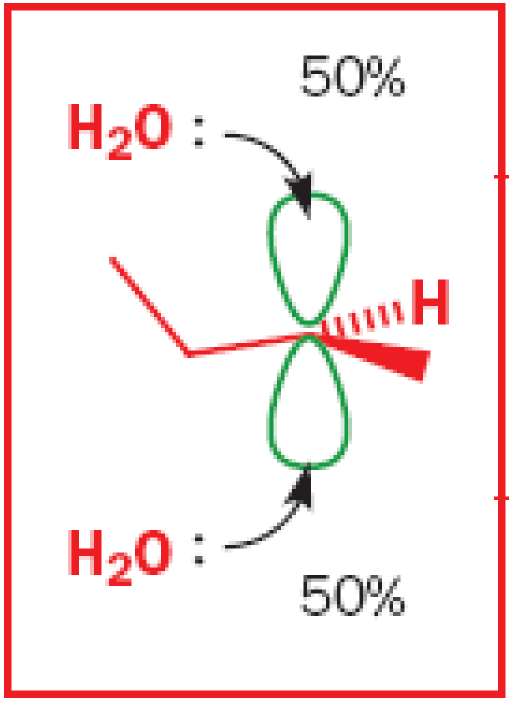


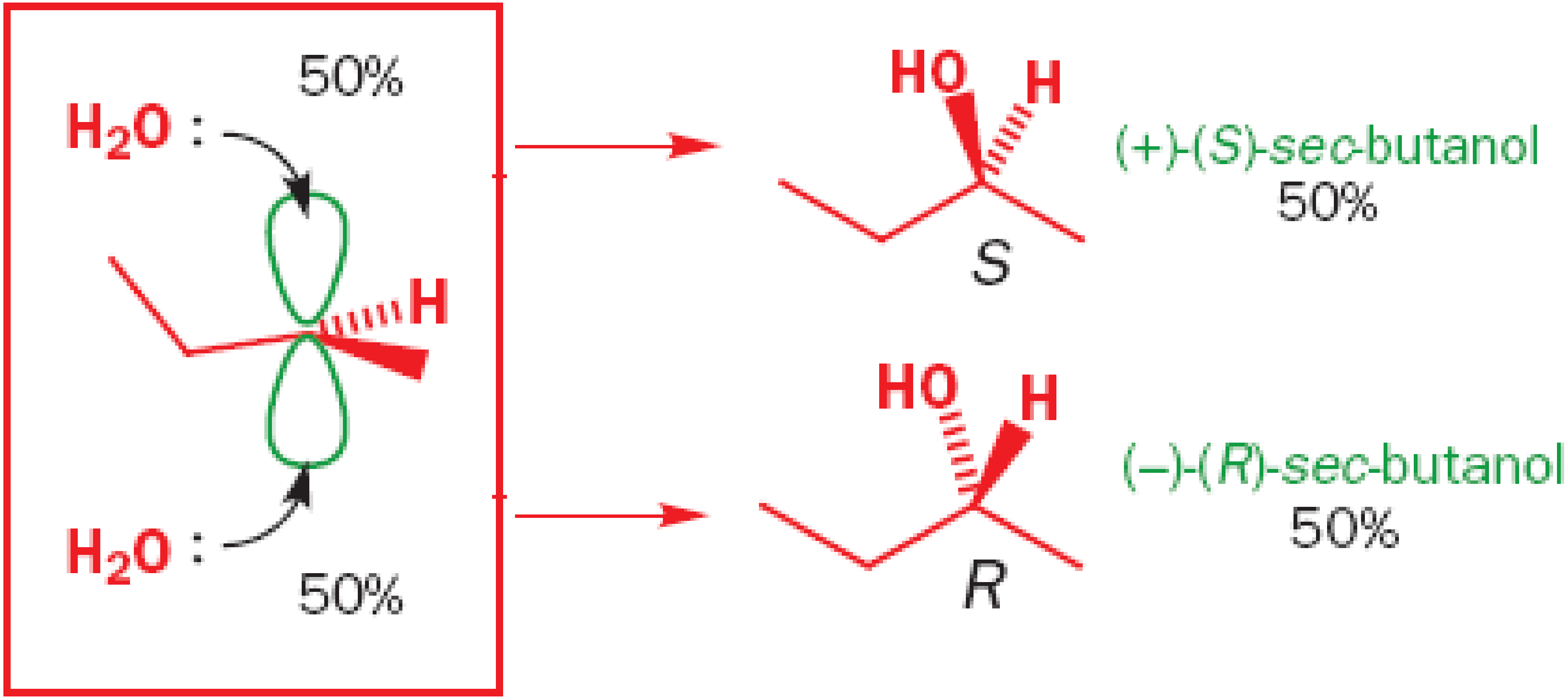
Không ảnh hưởng bởi chướng ngại lập thể.

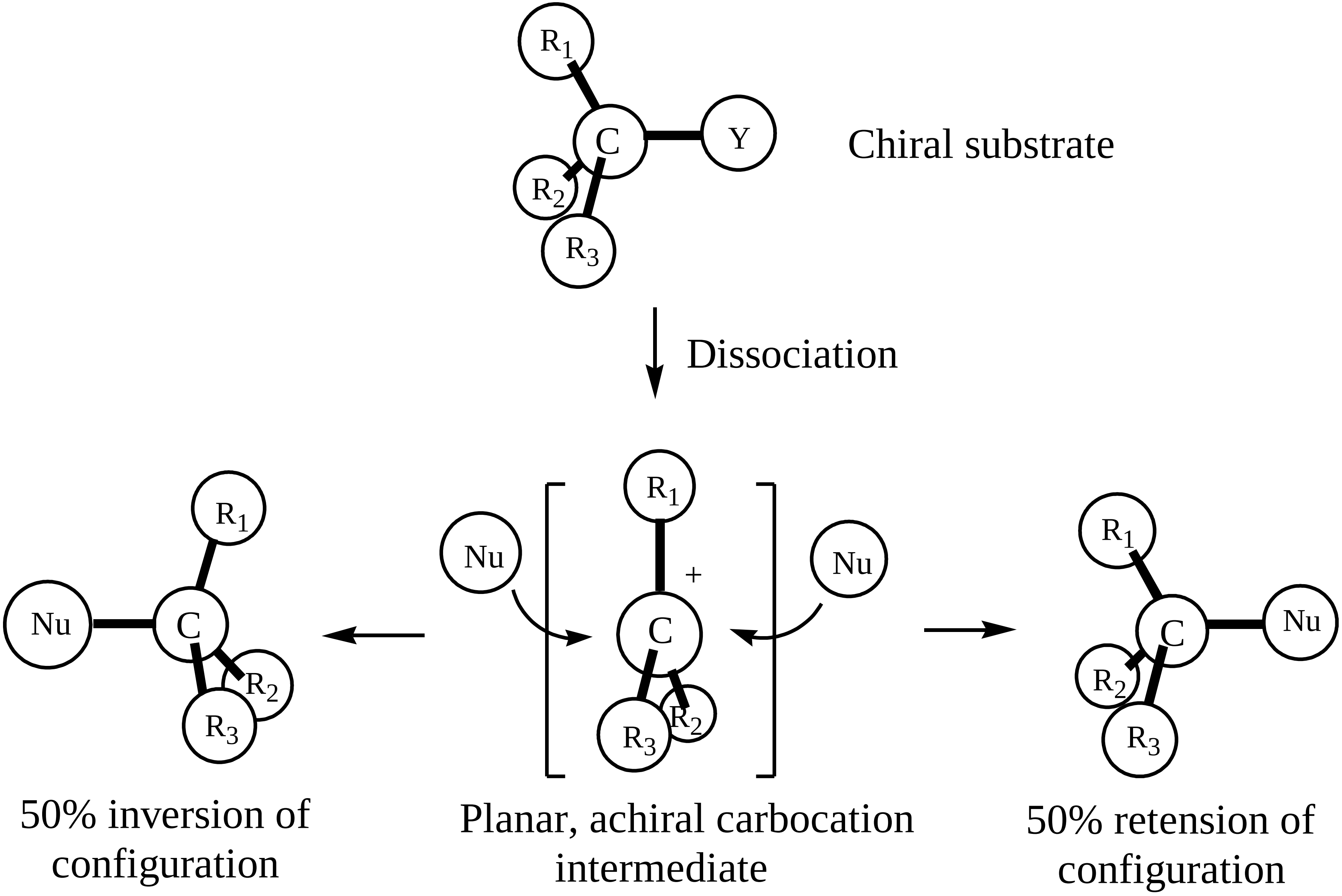


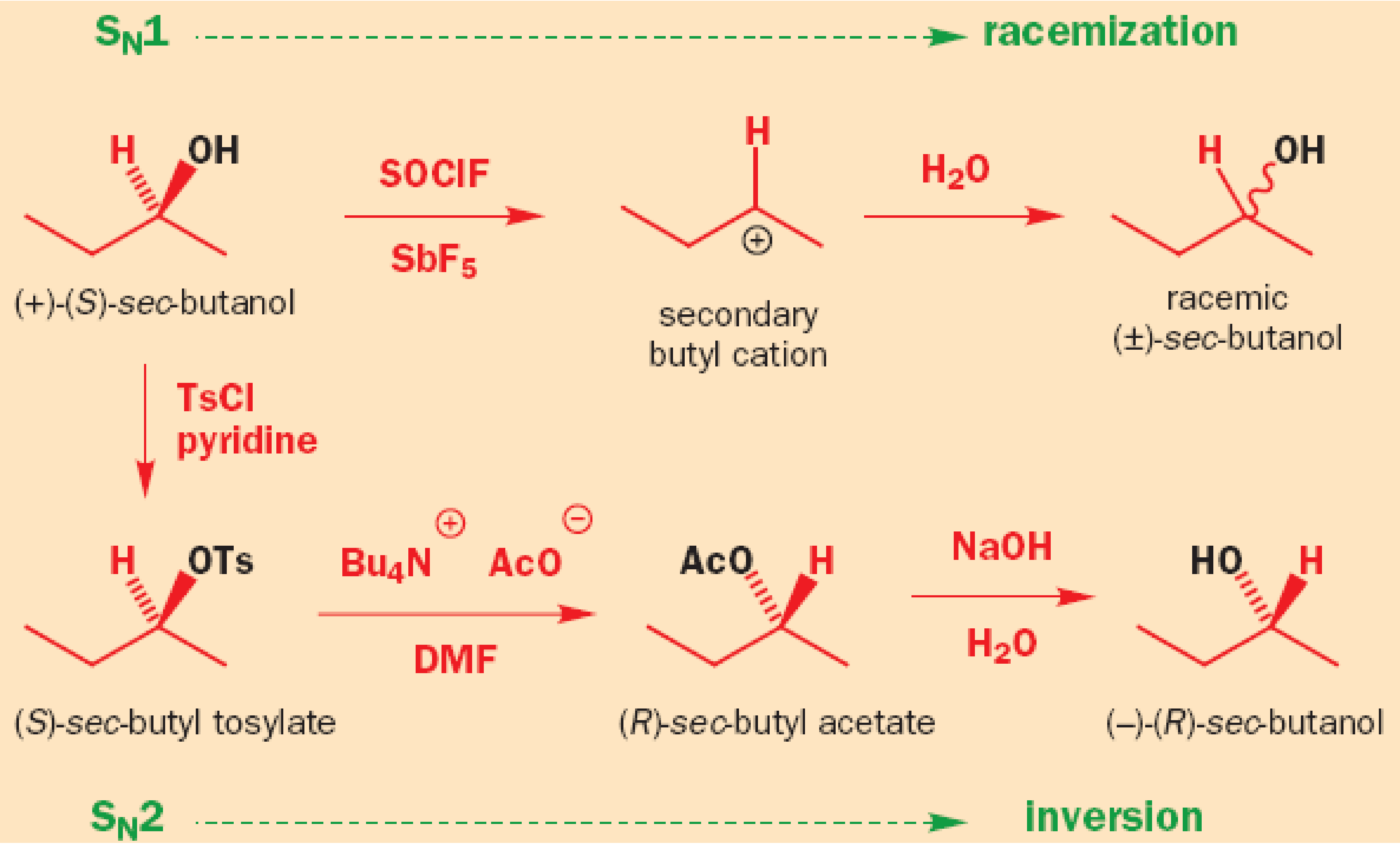
YẾU TỐ LẬP THỂ TRONG S 1






50%
H_2O :
H
H_2O :
50%
HO
H
S
(+)-(*S*)-*sec*-butanol
50%
HO
H
R
(–)-(*R*)-*sec*-butanol
50%


R1
C
Y
R2
R3
Chiral substrate
Dissociation
R1
Nu
C
R2
R3
Nu
R1
+
C
R3
R2
Nu
R1
C
Nu
R2
R3
50% inversion of configuration
Planar, achiral carbocation intermediate
50% retension of configuration


S_N1 - - - - - - - - - - - -► racemization
H
OH
SOClF
SbF_5
(+)-(*S*)-*sec*-butanol
H
⊕
secondary butyl cation
H_2O
H
OH
racemic (±)-*sec*-butanol
TsCl
pyridine
H
OTs
(*S*)-*sec*-butyl tosylate
$Bu_4\overset{\oplus}{N}$
$Ac\overset{\ominus}{O}$
DMF
AcO
H
(*R*)-*sec*-butyl acetate
NaOH
H_2O
HO
H
(–)-(*R*)-*sec*-butanol
S_N2 - - - - - - - - - - - -► inversion

Ảnh hưởng của dung môi

- **Protic solvents**: **tăng tốc độ ion hóa** của alkyl halide

N

► **Tăng vận tốc phản ứng thế S 1**

- Những dung môi loại này thường có **hằng số điện môi lớn**, tức có khả năng tách mạnh các ion dương và âm ra khỏi nhau

N N

SỰ CẠNH TRANH GIỮA S 1 và S 2

4 yếu tố quan trọng

- Cấu trúc của tác chất
- Nồng độ và độ mạnh của chất thân hạch
- Dung môi
- Bản chất của nhóm xuất

	SN^{1}	SN^{2}
R–X	**3°**	**Methyl > 1° > 2°**
Nu:	**Base Lewis yếu, các phân tử trung hòa hoặc các phân tử dung môi (sự dung môi giải)**	**BaseLewis mạnh, nồng độ cao**
Dung môi	**Phân cực, có proton (rượu, nước,…)**	**Phân cực, không có proton (DMF, DMSO,…)**

Nhóm xuất: Ảnh hưởng như nhau trong cả hai

S 1 *OR* S 2 ???

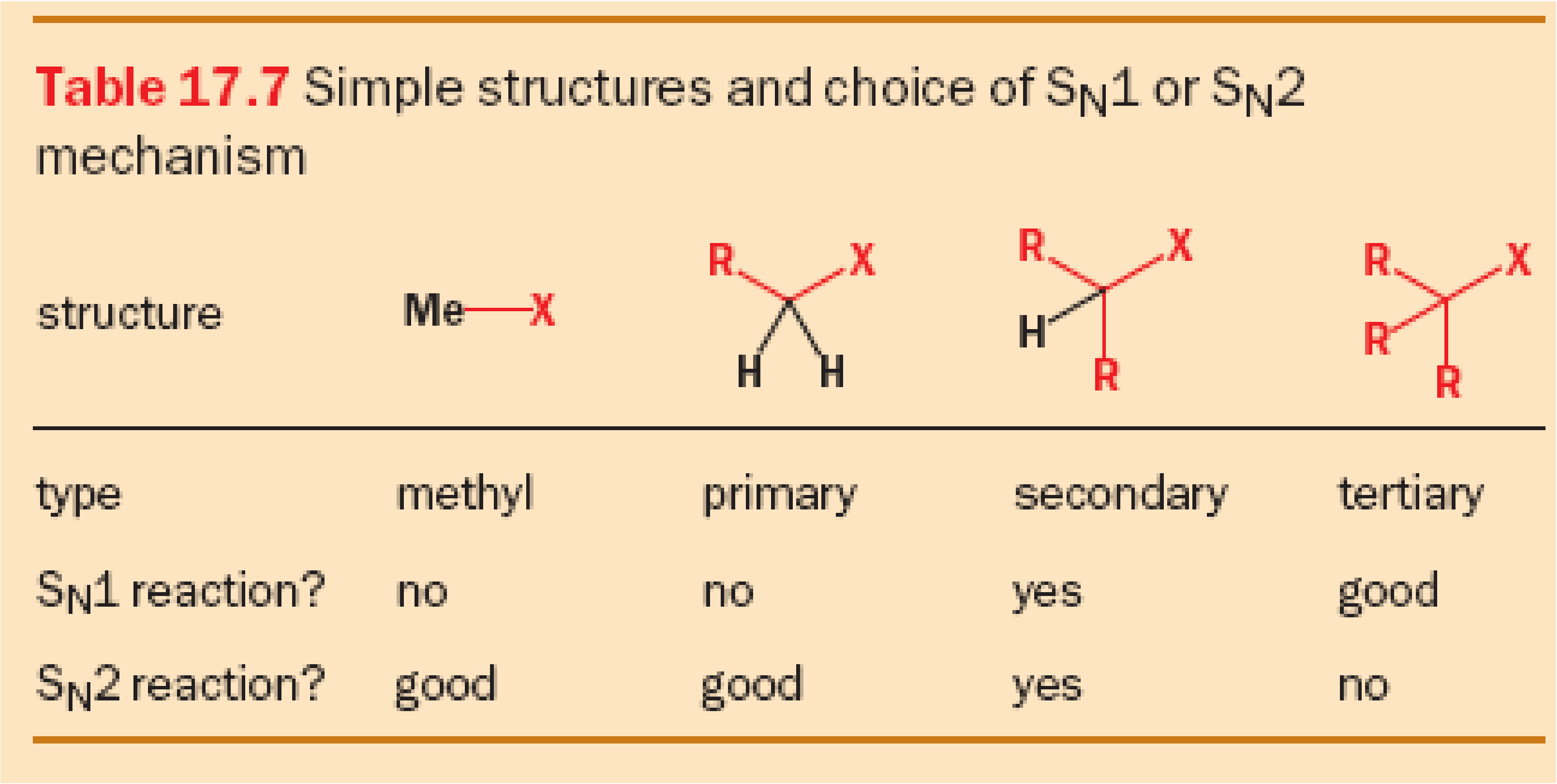
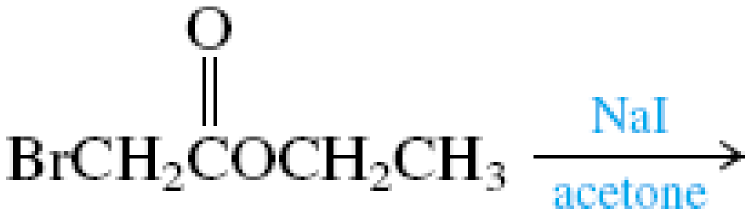
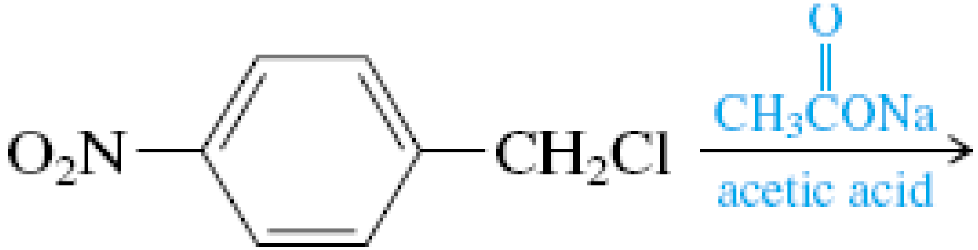


Table 17.7 Simple structures and choice of S_N1 or S_N2 mechanism

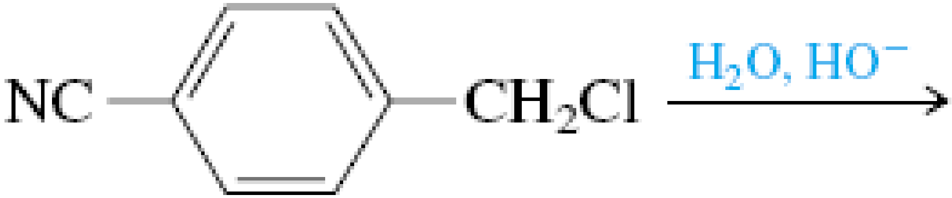
structure	Me—X			
type	methyl	primary	secondary	tertiary
S_N1 reaction?	no	no	yes	good
S_N2 reaction?	good	good	yes	no

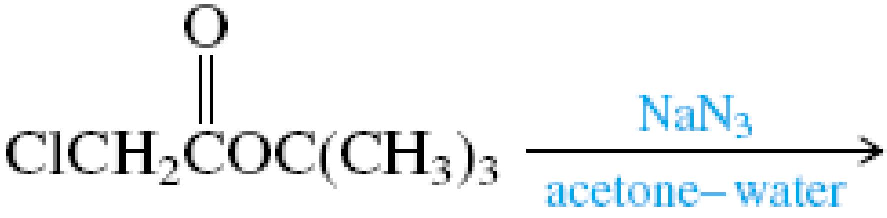
(a) 

$$BrCH_2\overset{\overset{\displaystyle O}{\|}}{C}OCH_2CH_3 \xrightarrow[\text{acetone}]{\text{NaI}}$$

(b) 

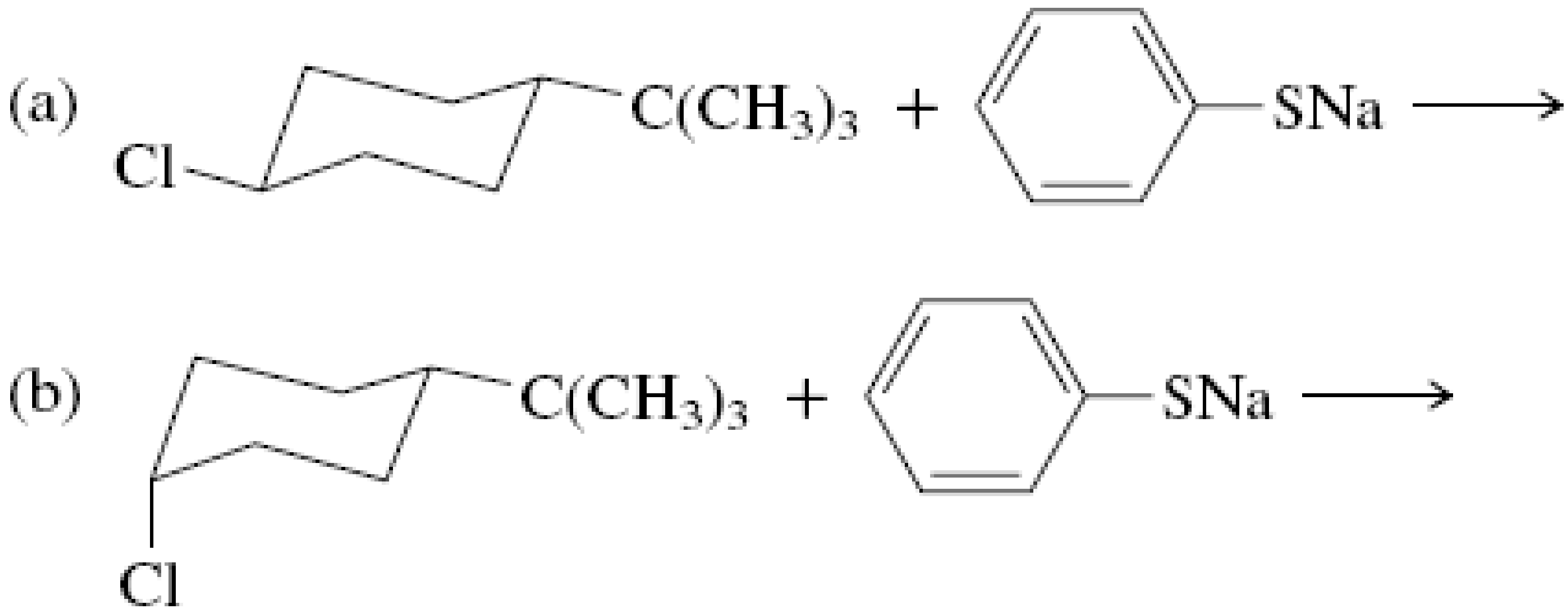
(c) $$CH_3CH_2OCH_2CH_2Br \xrightarrow[\text{ethanol–water}]{\text{NaCN}}$$

(d) 

(e) 

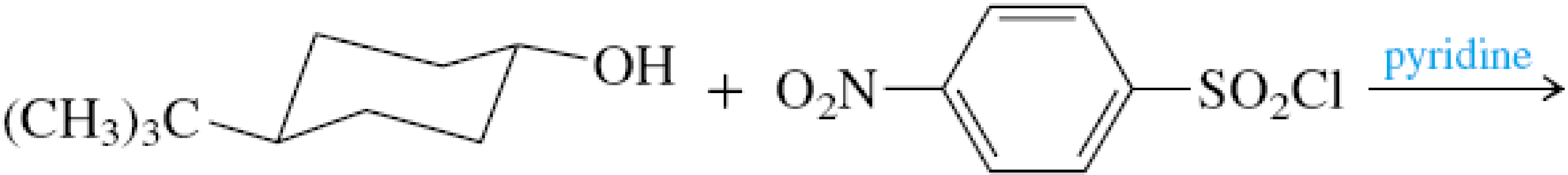
$$ClCH_2\overset{\overset{\displaystyle O}{\|}}{C}OC(CH_3)_3 \xrightarrow[\text{acetone–water}]{NaN_3}$$

Sản phẩm của (a) là đồng phân của sản phẩm (b). Phản ứng S_N1 Hay S_N2 ?

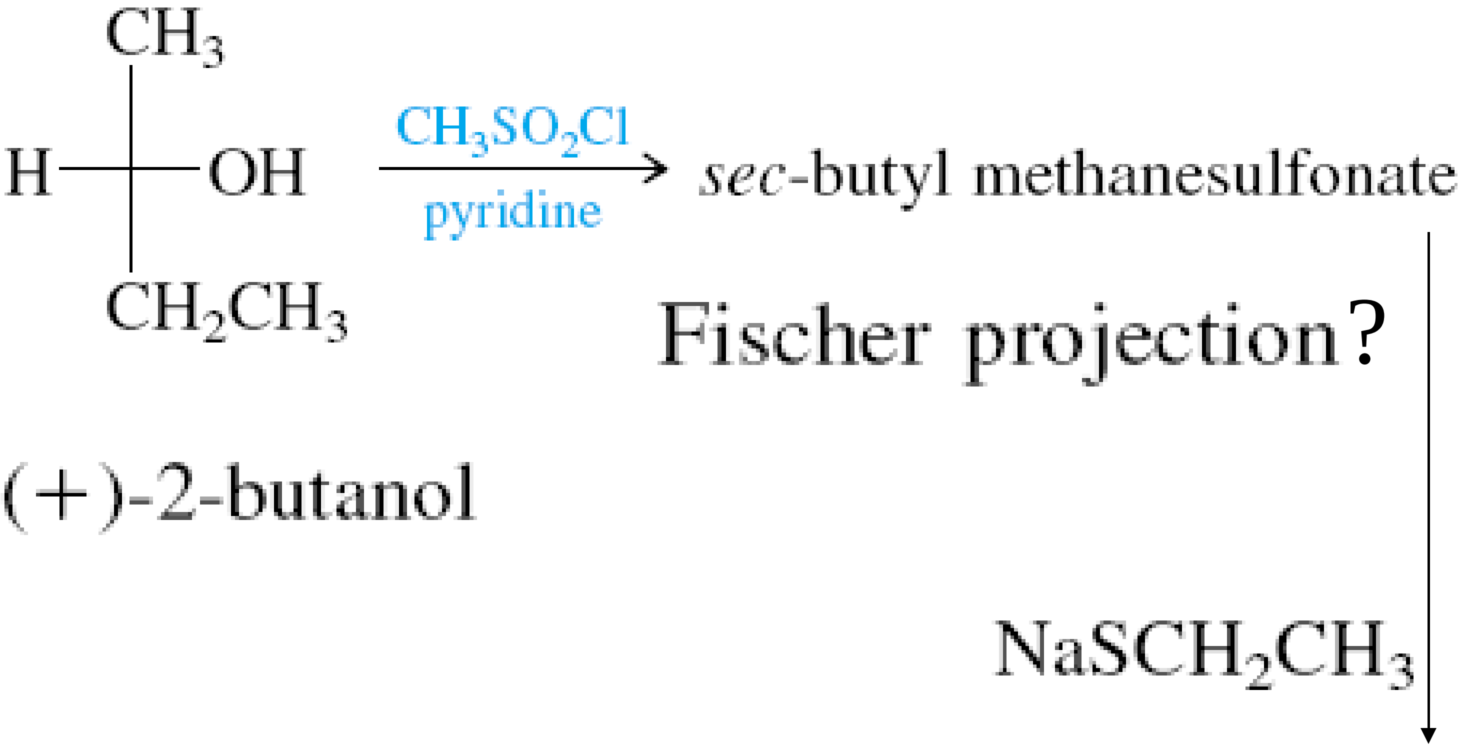


Sắp xếp các đồng phân có

Hóa học lập thể của A và B?



compound A $\xrightarrow[\text{acetone}]{\text{LiBr}}$ compound B



CH_3 / H—C—OH / CH_2CH_3 $\xrightarrow[\text{pyridine}]{CH_3SO_2Cl}$ *sec*-butyl methanesulfonate

Fischer projection?

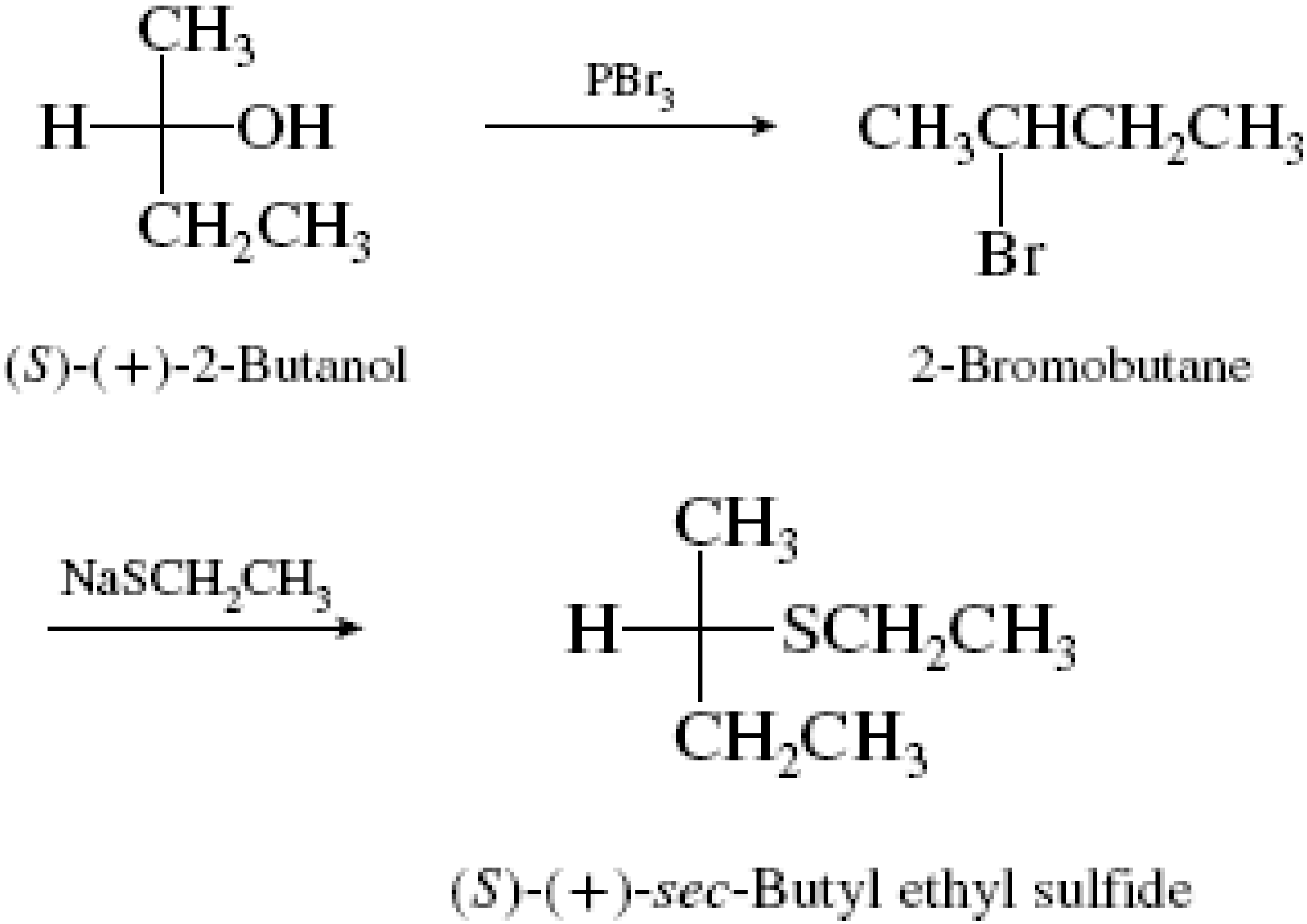
(*S*)-(+)-2-butanol

$NaSCH_2CH_3$

optical rotation α_D of −25°

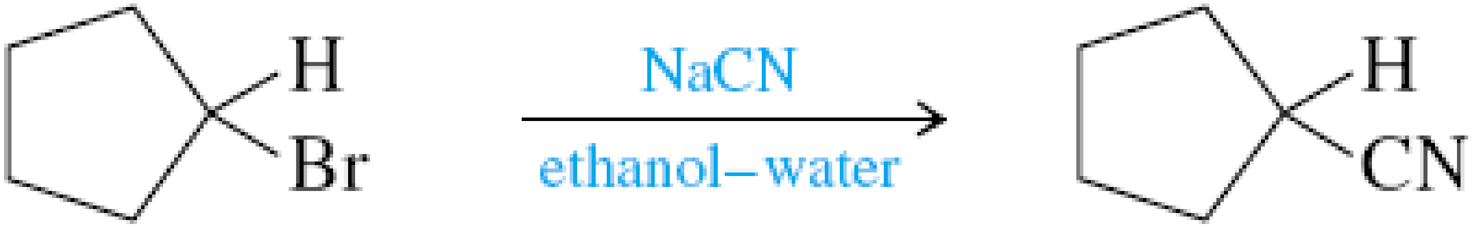
Fischer projection?

Hóa học lập thể của 2-Bromobutane?



Vận tốc phản ứng tăng khi dùng một lượng nhỏ NaI làm xúc tác.

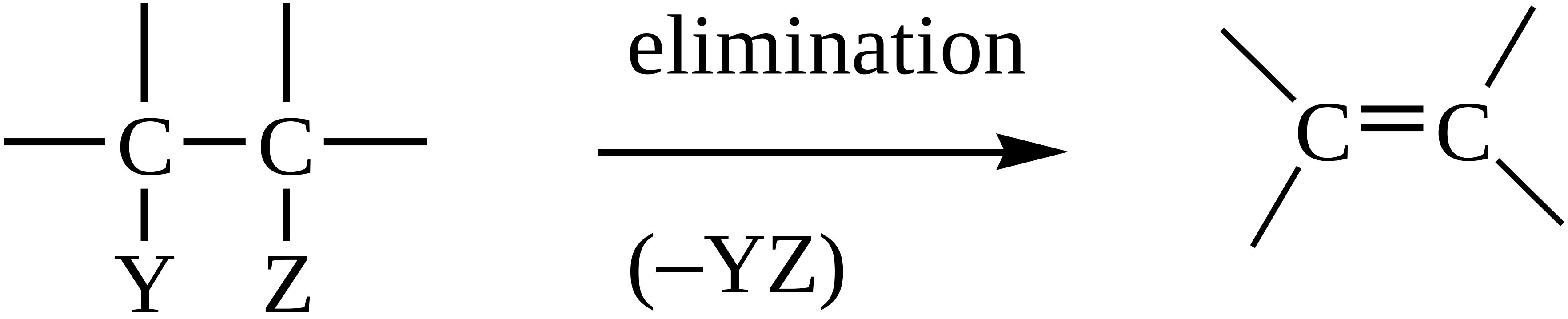
Giải thích?



Cyclopentyl bromide

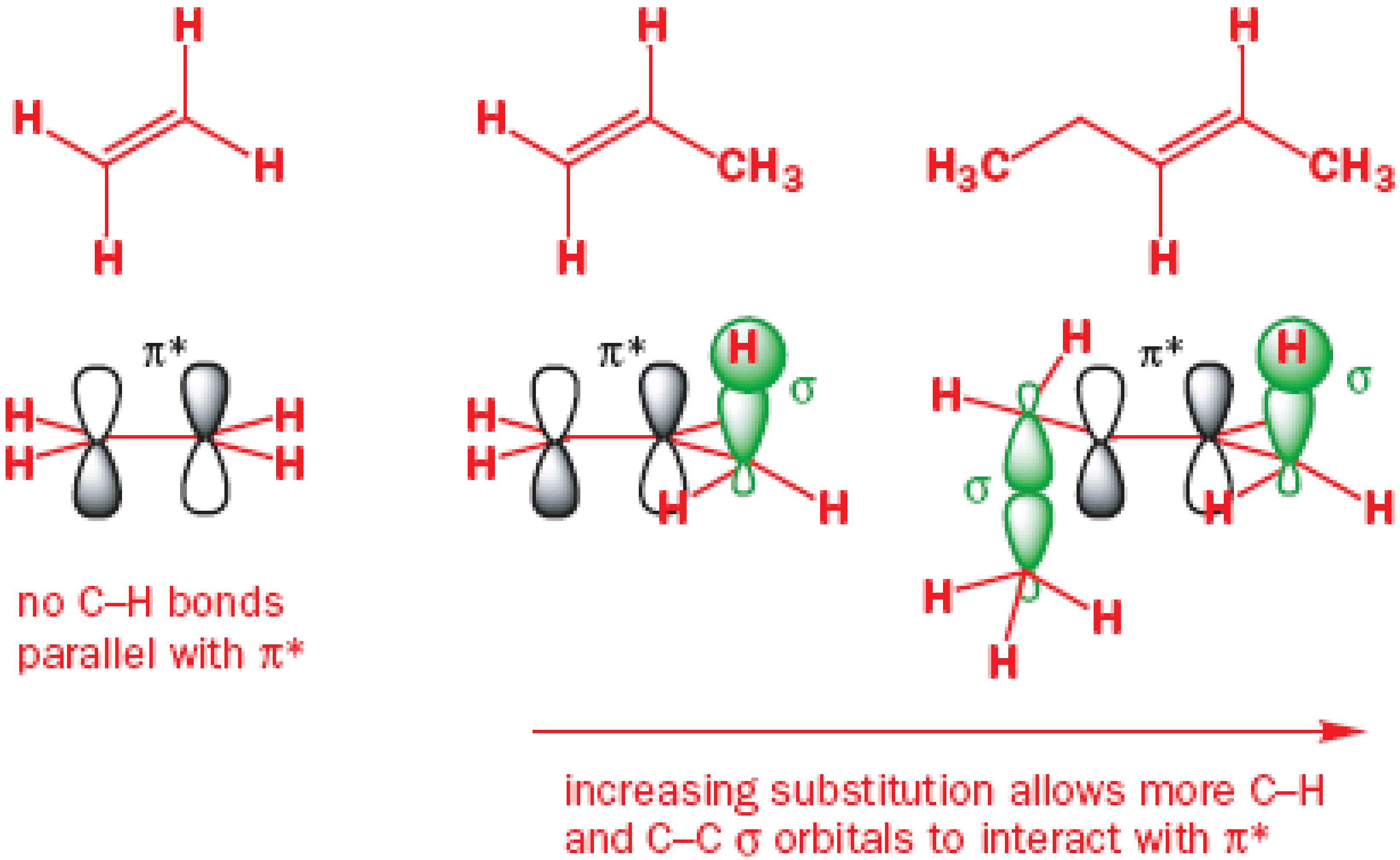
Cyclopentyl cyanide

PHẢN ỨNG TÁCH (KHỬ) (ELIMINATION REACTION)



- Phân tử bị loại: HX (dehydrohalogen hóa), nước (dehydrat hóa),…
- **Quy tắc Zaitsev**: sản phẩm chính tạo thành sẽ là alkene mang nhiều nhóm thế nhất

Độ bền của Alkene



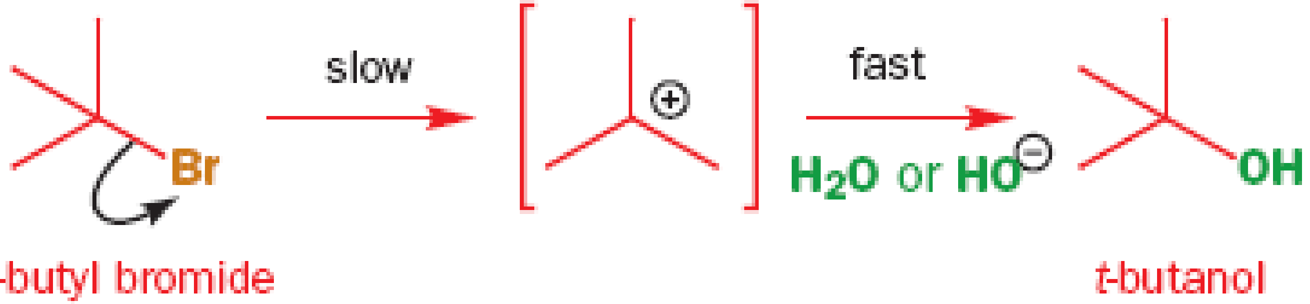
no C–H bonds parallel with π*

increasing substitution allows more C–H and C–C σ orbitals to interact with π*

PHẢN ỨNG TÁCH

nucleophilic substitution reactions of *t*-BuBr

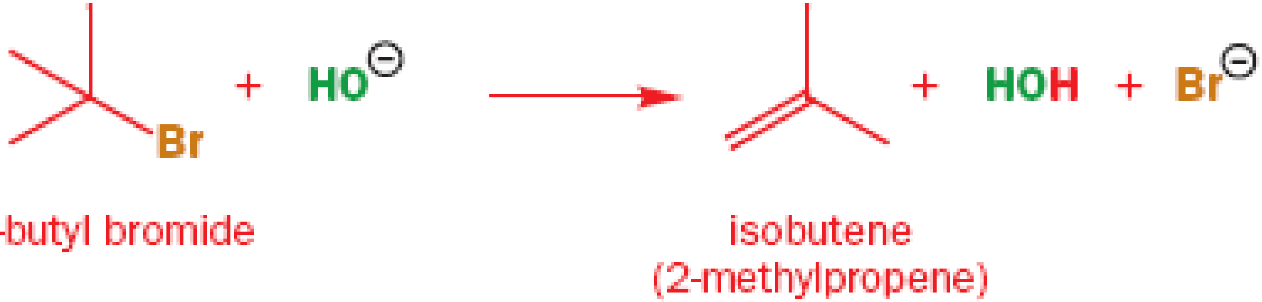
rate = *k*[*t*-BuBr]



reaction goes at the same rate whatever the nucleophile

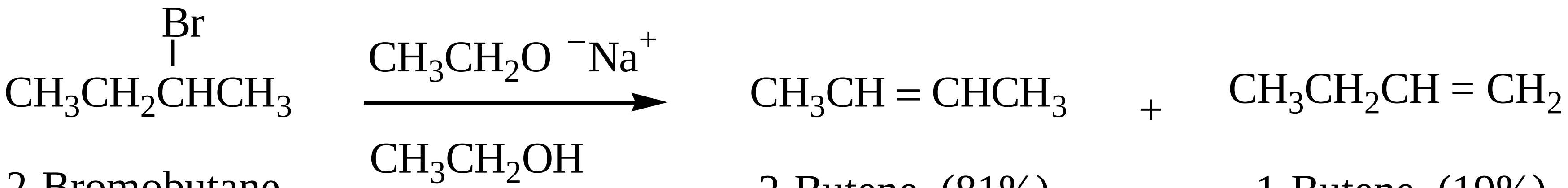
reaction of *t*-BuBr with concentrated solution of NaOH

rate = *k*[*t*-BuBr][HO^-]



elimination reaction forms alkene

PHẢN ỨNG TÁCH

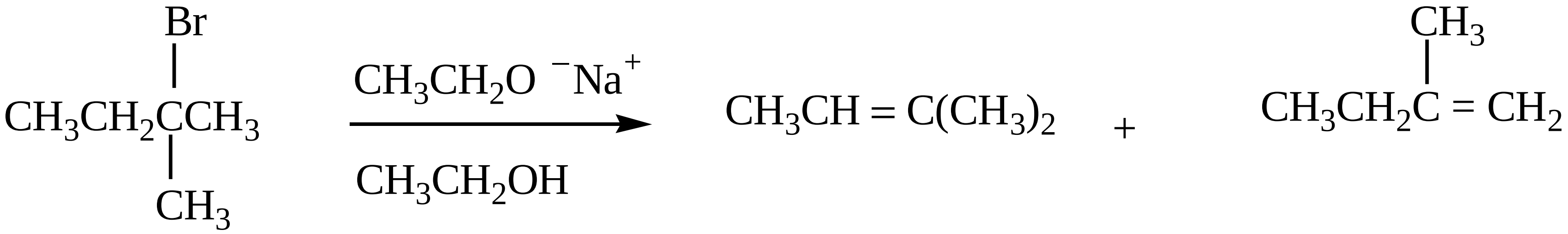


$$CH_3CH_2\overset{\overset{\displaystyle Br}{|}}{C}HCH_3 \xrightarrow[CH_3CH_2OH]{CH_3CH_2O^-Na^+} CH_3CH=CHCH_3 + CH_3CH_2CH=CH_2$$

2-Bromobutane

2-Butene (81%)

1-Butene (19%)



$$CH_3CH_2\underset{\underset{\displaystyle CH_3}{|}}{\overset{\overset{\displaystyle Br}{|}}{C}}CH_3 \xrightarrow[CH_3CH_2OH]{CH_3CH_2O^-Na^+} CH_3CH=C(CH_3)_2 + CH_3CH_2\overset{\overset{\displaystyle CH_3}{|}}{C}=CH_2$$

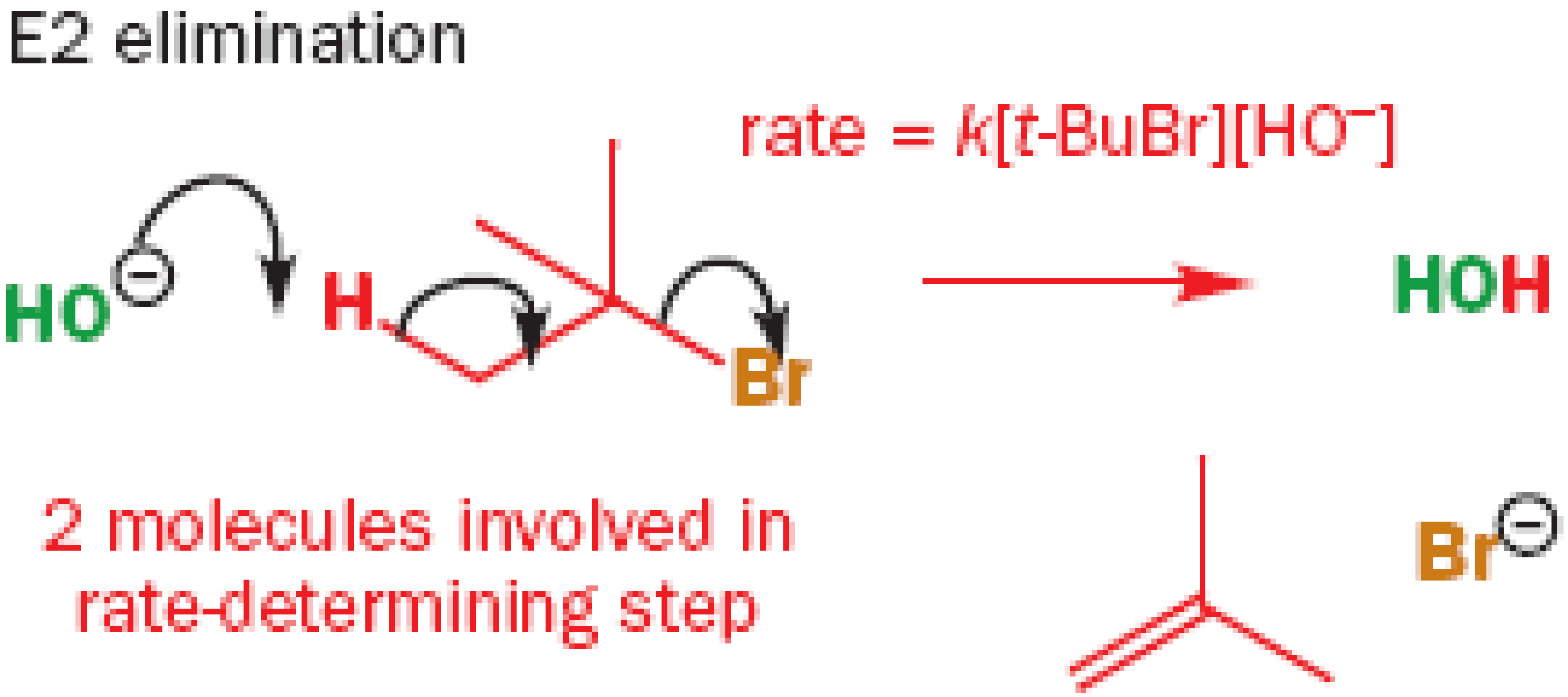
2-Bromo-2-methylbutane

2-Methyl-2-butene (70%)

2-Methyl-1-butene (30%)

Hai cơ chế: Tách E1 *và* Tách E2

PHẢN ỨNG TÁCH E2

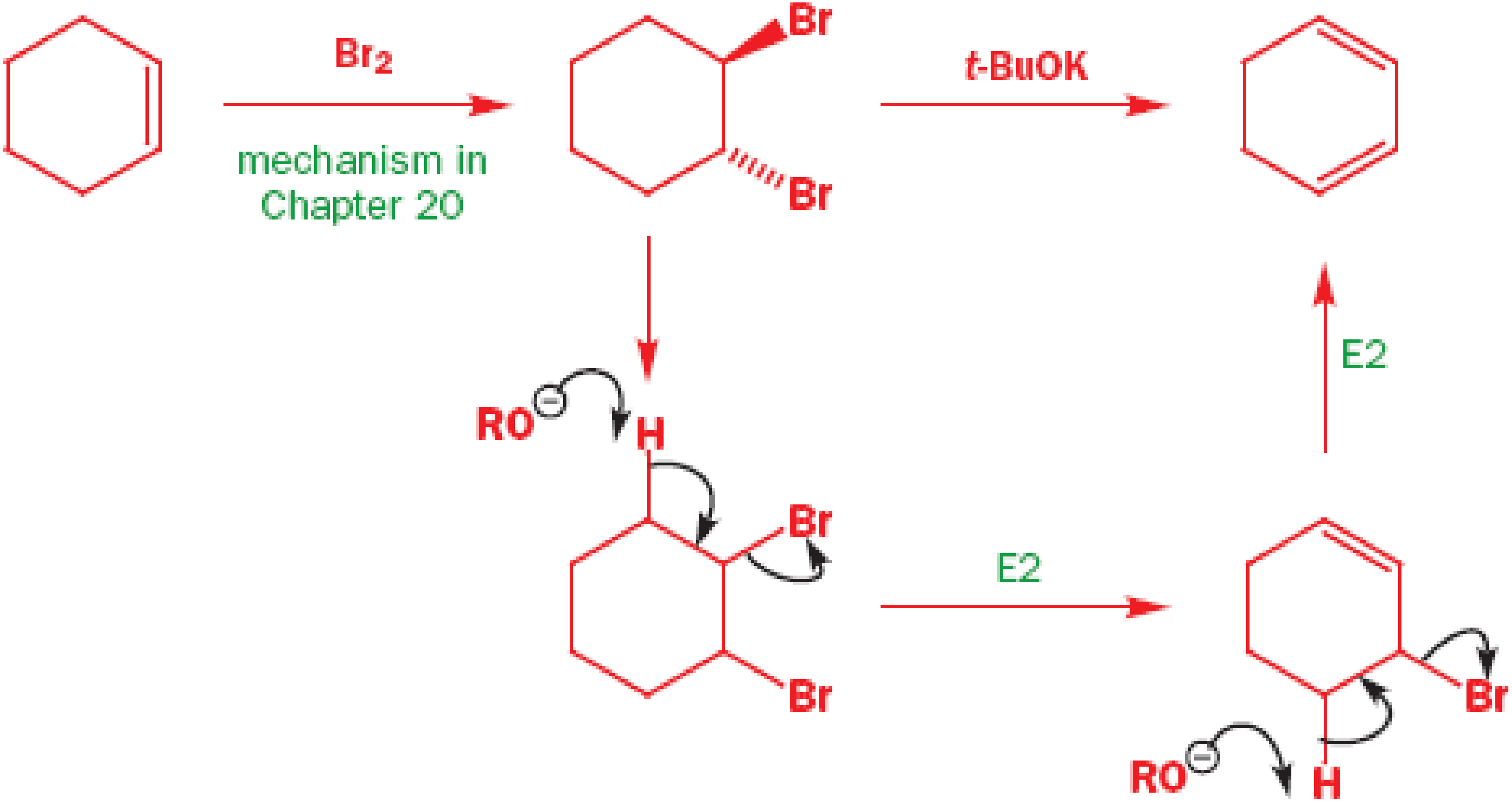

E2 elimination

rate = $k[t\text{-BuBr}][HO^-]$

2 molecules involved in rate-determining step

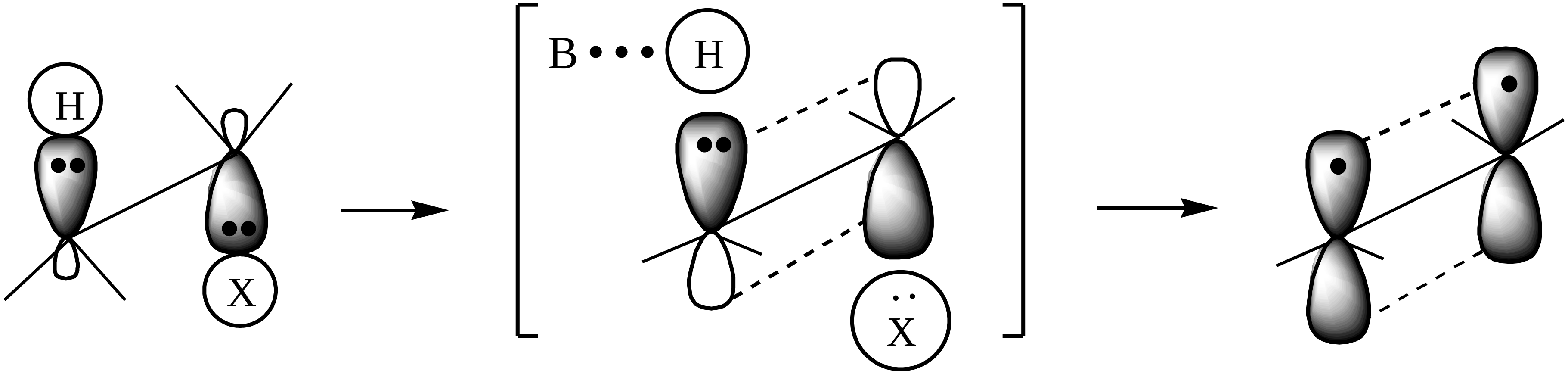
- *Cần sử dụng* ***Base mạnh*** ***và*** ***nồng độ base cao.***

synthesis of a diene by a double E2 elimination



YẾU TỐ LẬP THỂ TRONG E2

Nguyên tử **H**, hai nguyên tử **C** và nhóm xuất **X**: **anti periplanar**

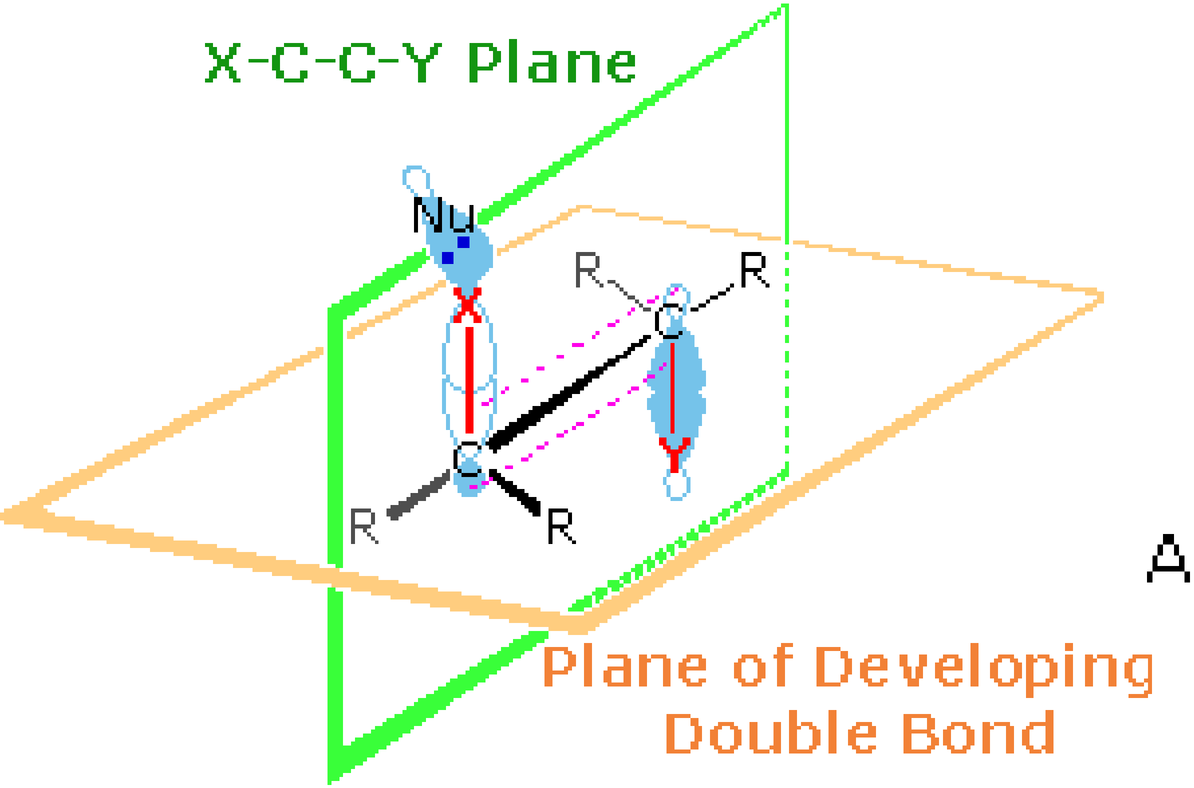


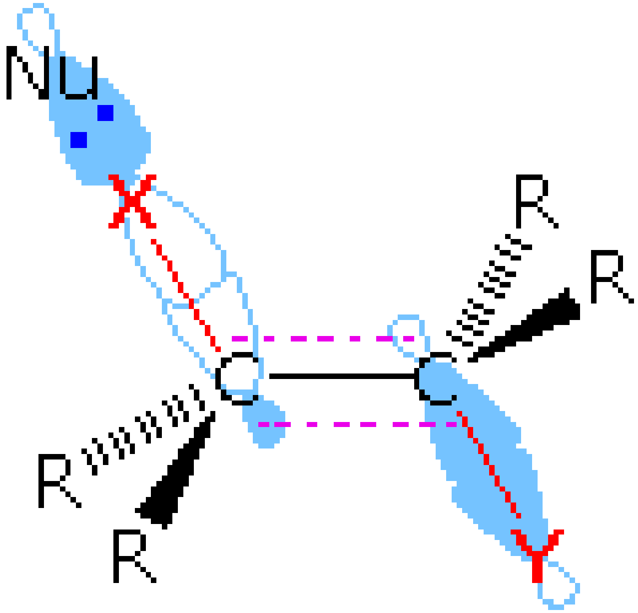
Anti periplanar

Anti transition state

Alkene

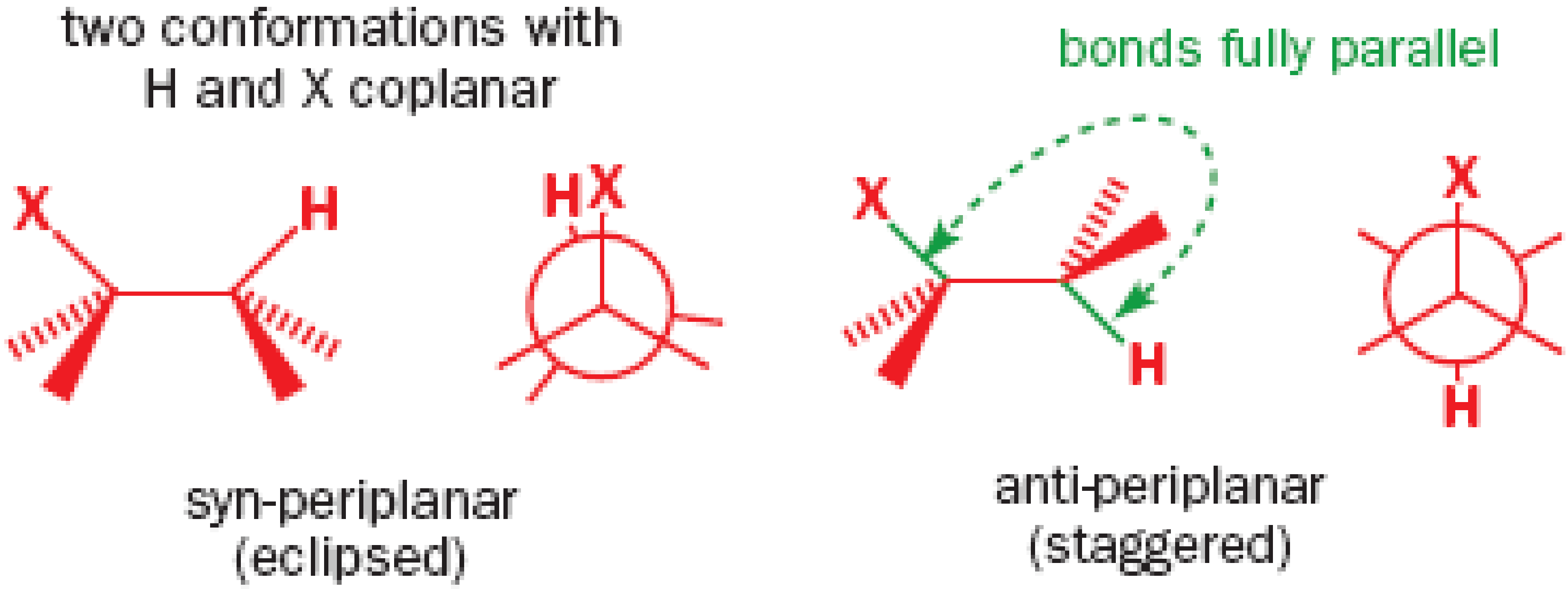
YẾU TỐ LẬP THỂ TRONG E2





Anti Orbital Interaction

YẾU TỐ LẬP THỂ TRONG E2



two conformations with
H and X coplanar

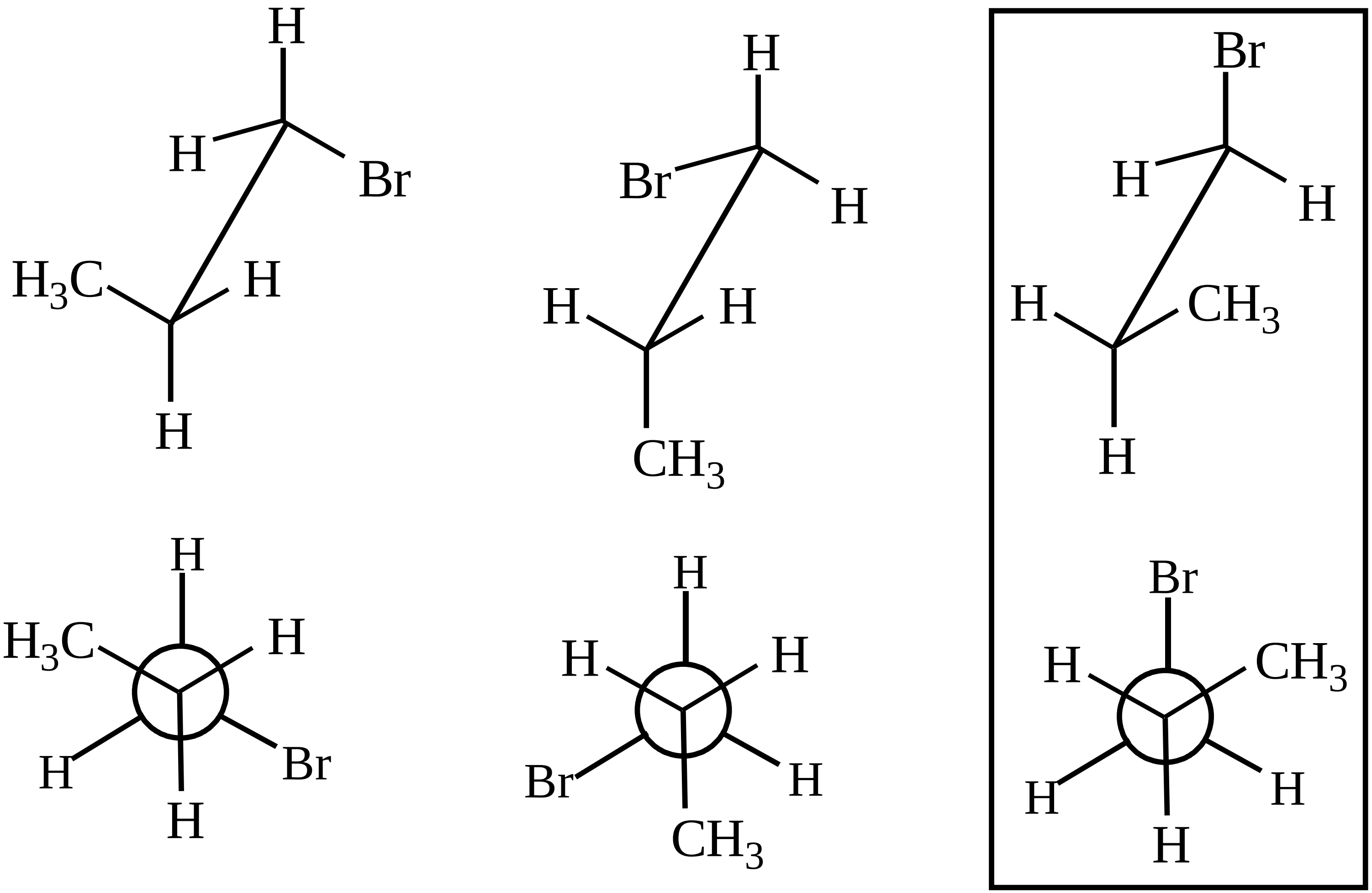
bonds fully parallel

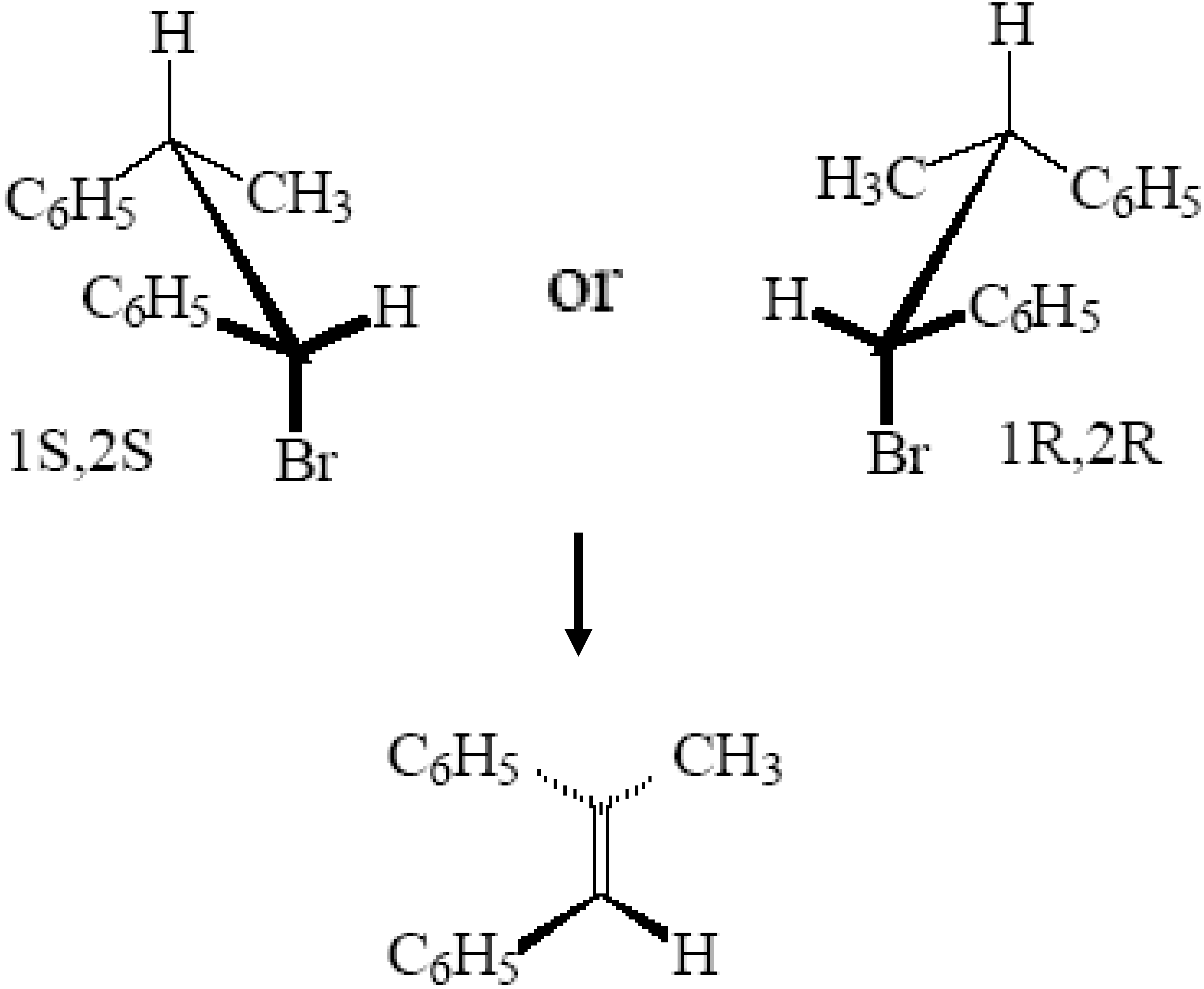
syn-periplanar
(eclipsed)

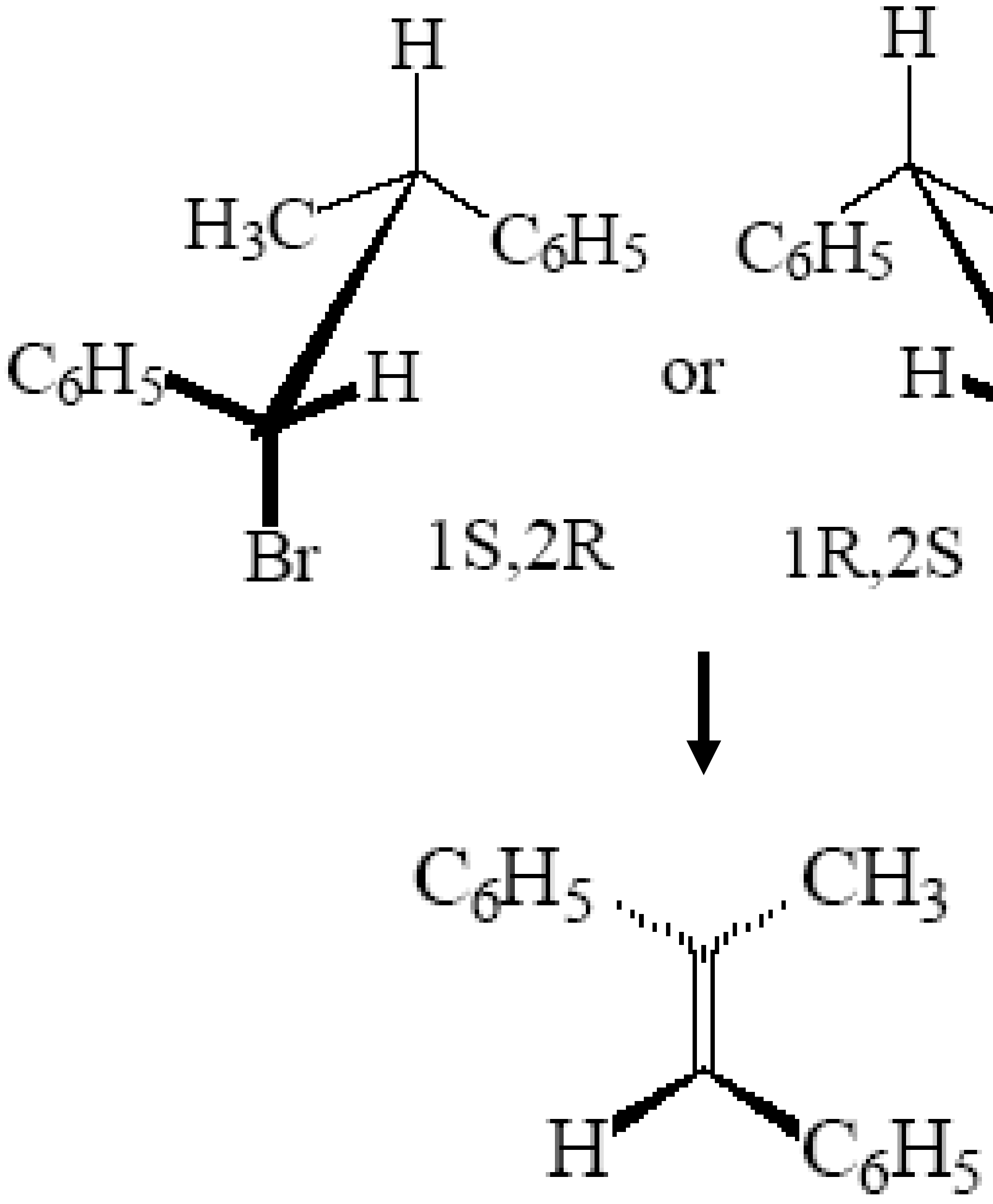
anti-periplanar
(staggered)

YẾU TỐ LẬP THỂ TRONG E2

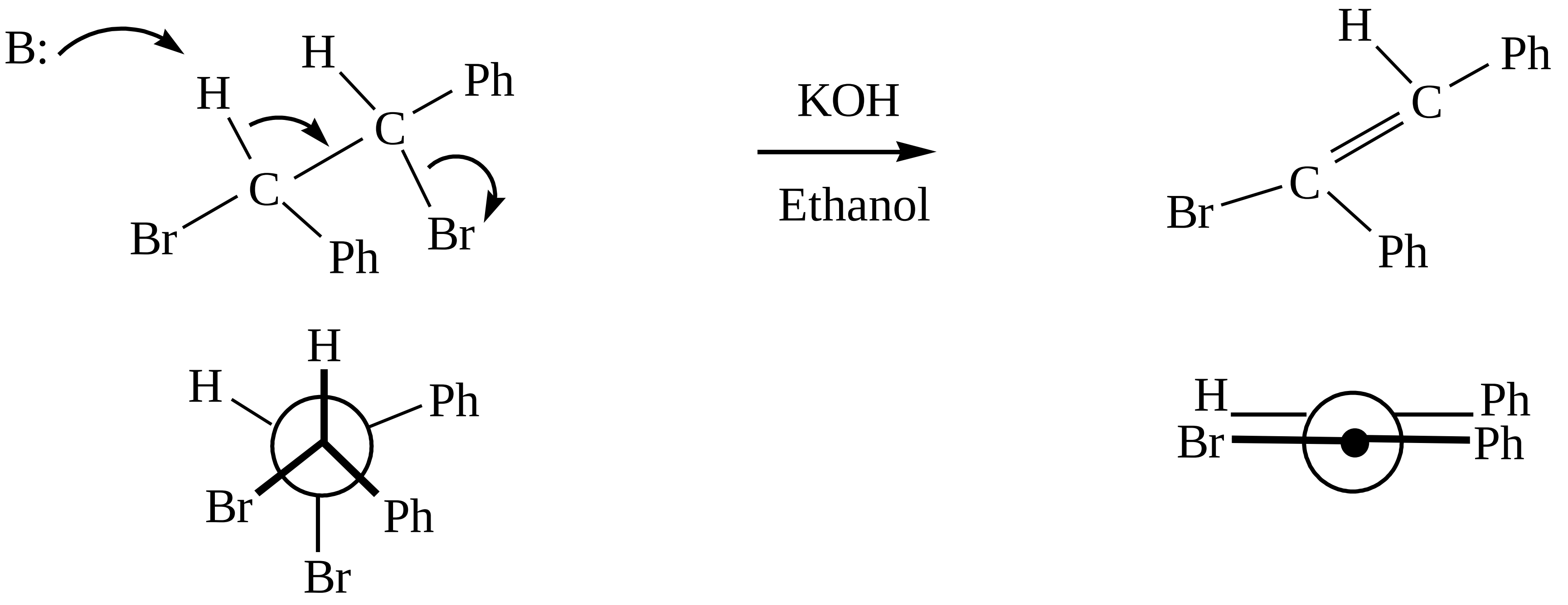
$$CH_3CH_2CH_2Br + {}^{t}BuOK \xrightarrow{{}^{t}BuOH} CH_3CH{=}CH_2$$




H
C6H5
CH3
C6H5
H
Br
1S,2S
or
H
H3C
C6H5
H
C6H5
Br
1R,2R
C6H5
CH3
C6H5
H


H
H3C
C6H5
C6H5
H
Br
1S,2R
or
H
C6H5
CH3
H
C6H5
Br
1R,2S
C6H5
CH3
H
C6H5

YẾU TỐ LẬP THỂ TRONG E2

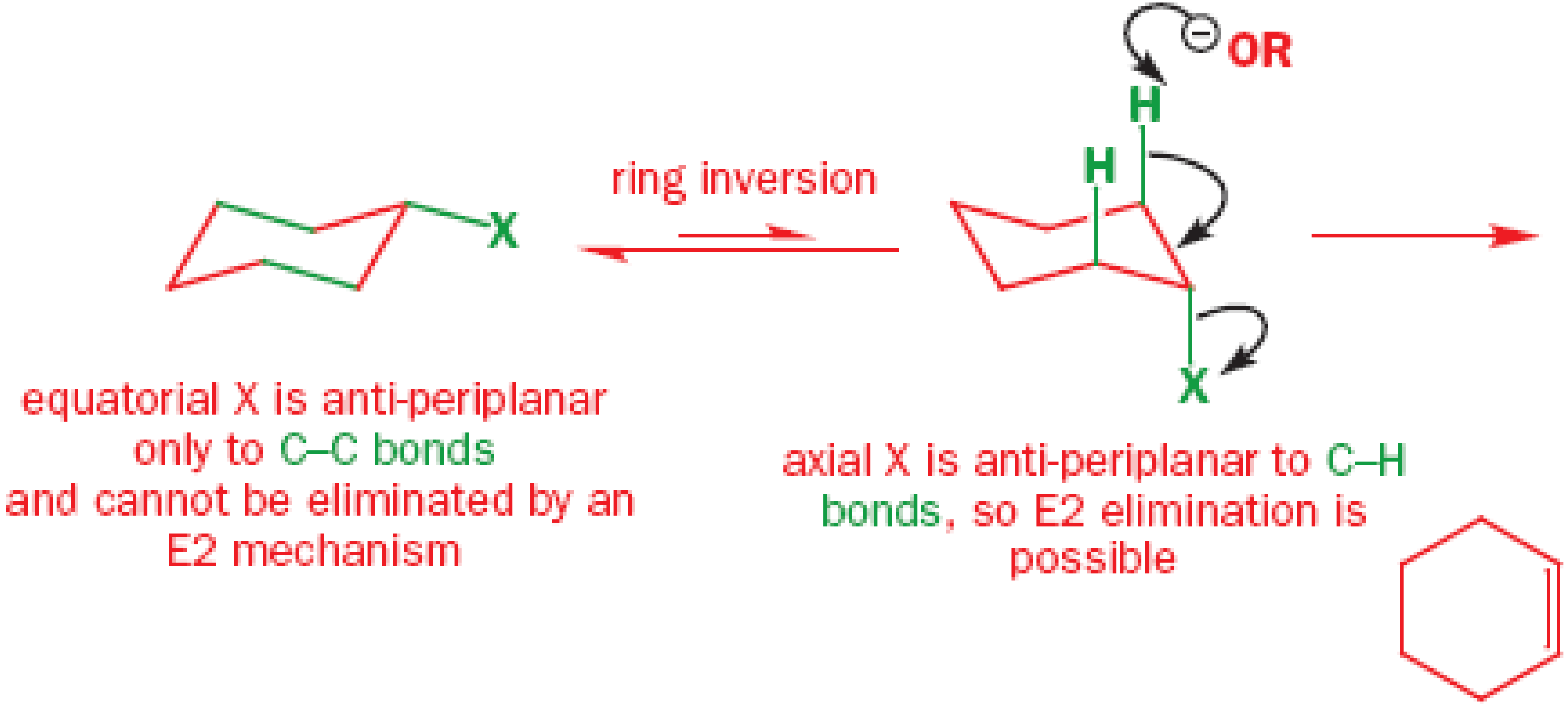


meso-1,2-Dibromo-1,2-diphenylethane

(E)-1-Bromo-1,2-diphenylethylene

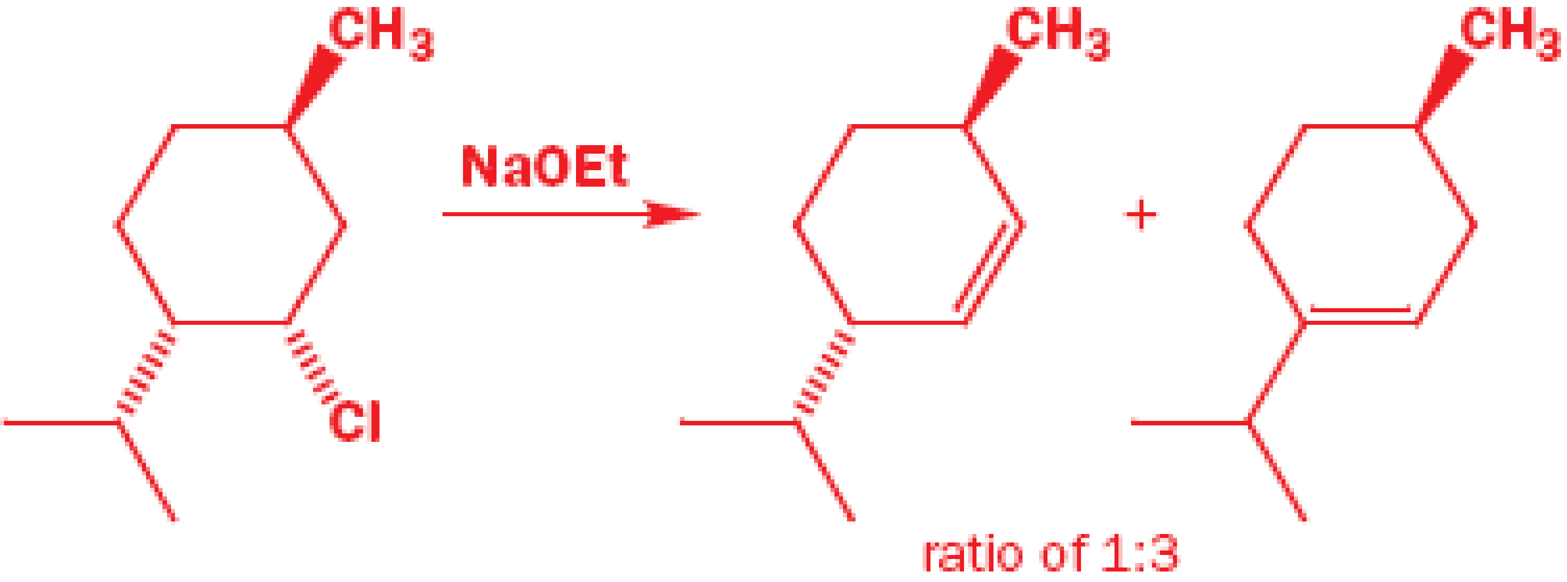
YẾU TỐ LẬP THỂ TRONG E2

Cyclohexyl halide: H và X đều ở vị trí **axial** và là ***trans*** đối với nhau

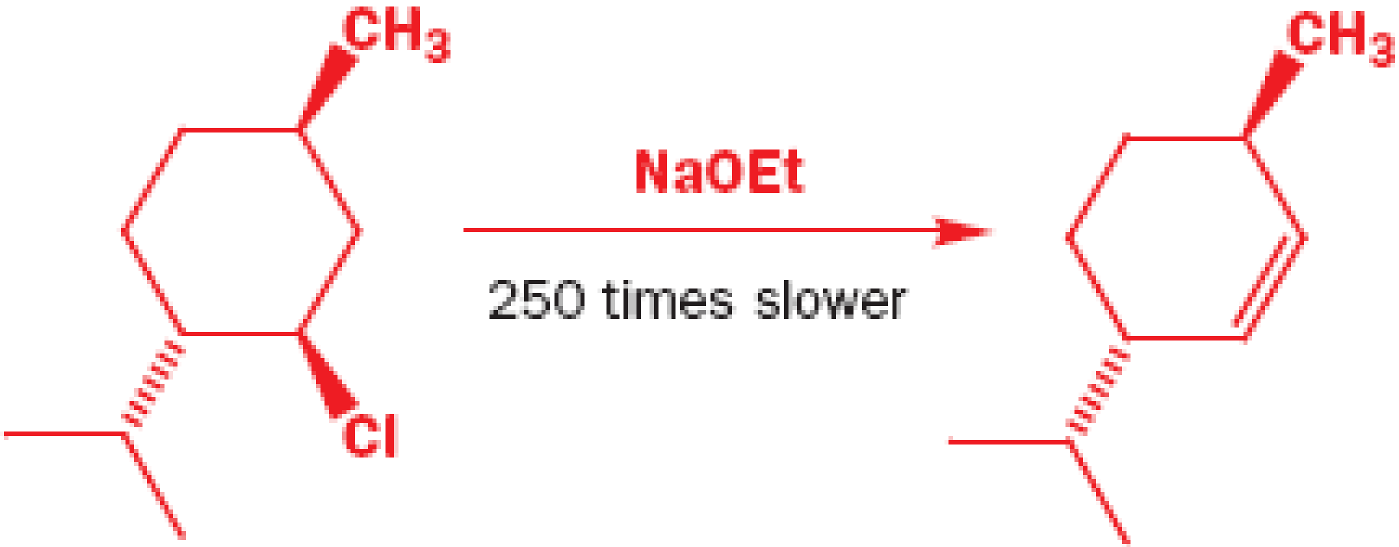


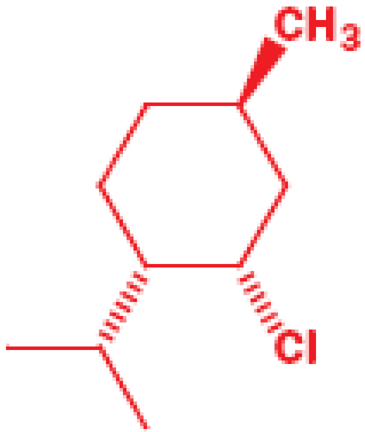
equatorial X is anti-periplanar only to C–C bonds and cannot be eliminated by an E2 mechanism

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

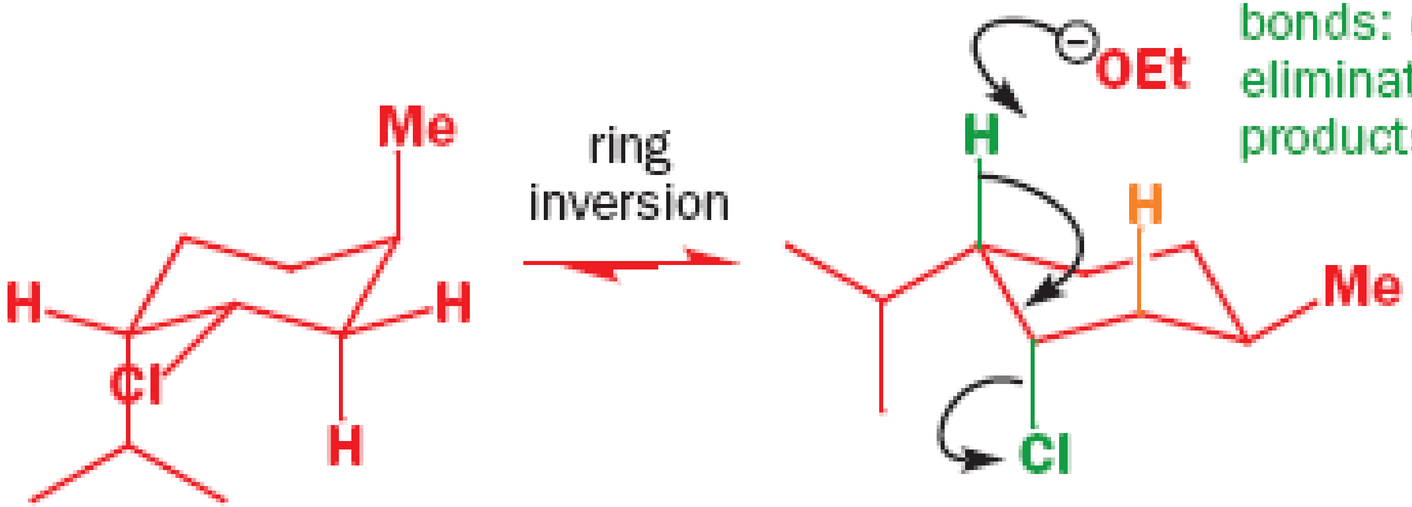


elimination of diastereoisomer B





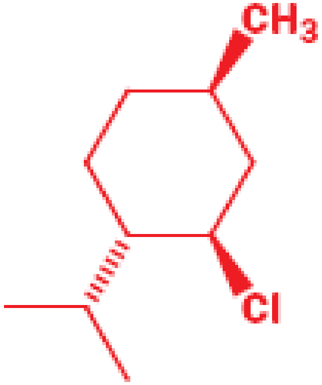
conformation of diastereoisomer A



two anti-periplanar C–H bonds: either can be eliminated to give different products

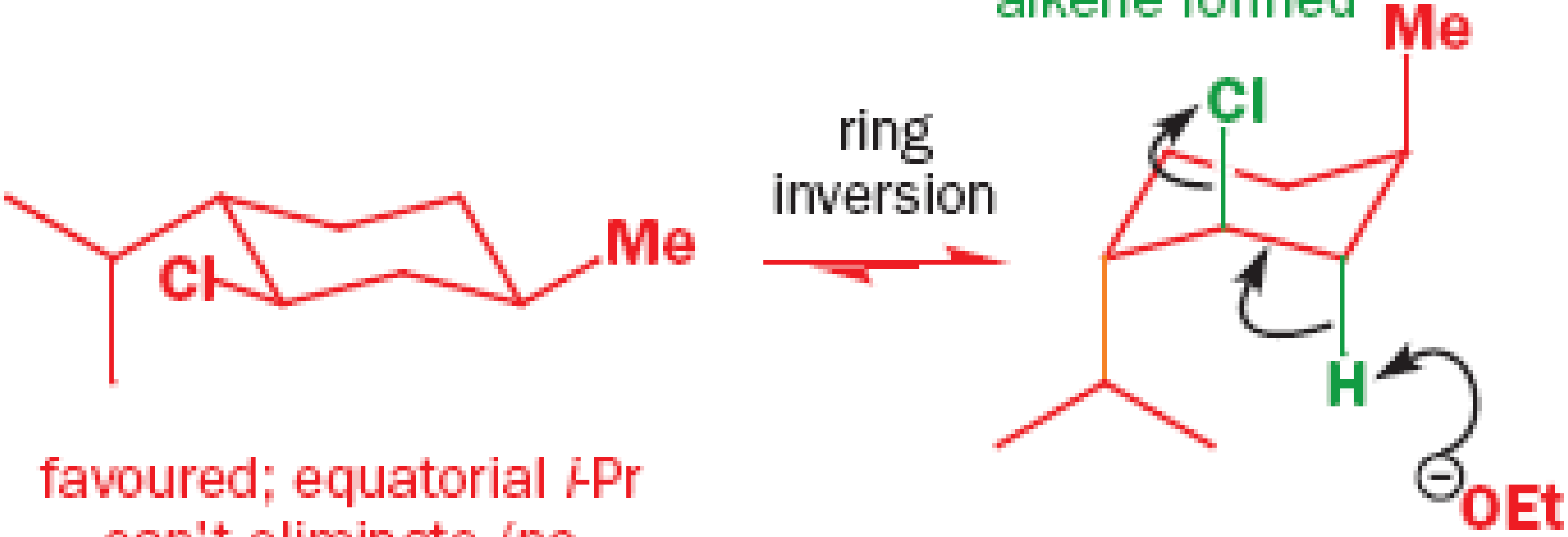
disfavoured; axial *i*-Pr can't eliminate (no anti-periplanar C–H bonds)

favoured; equatorial *i*-Pr



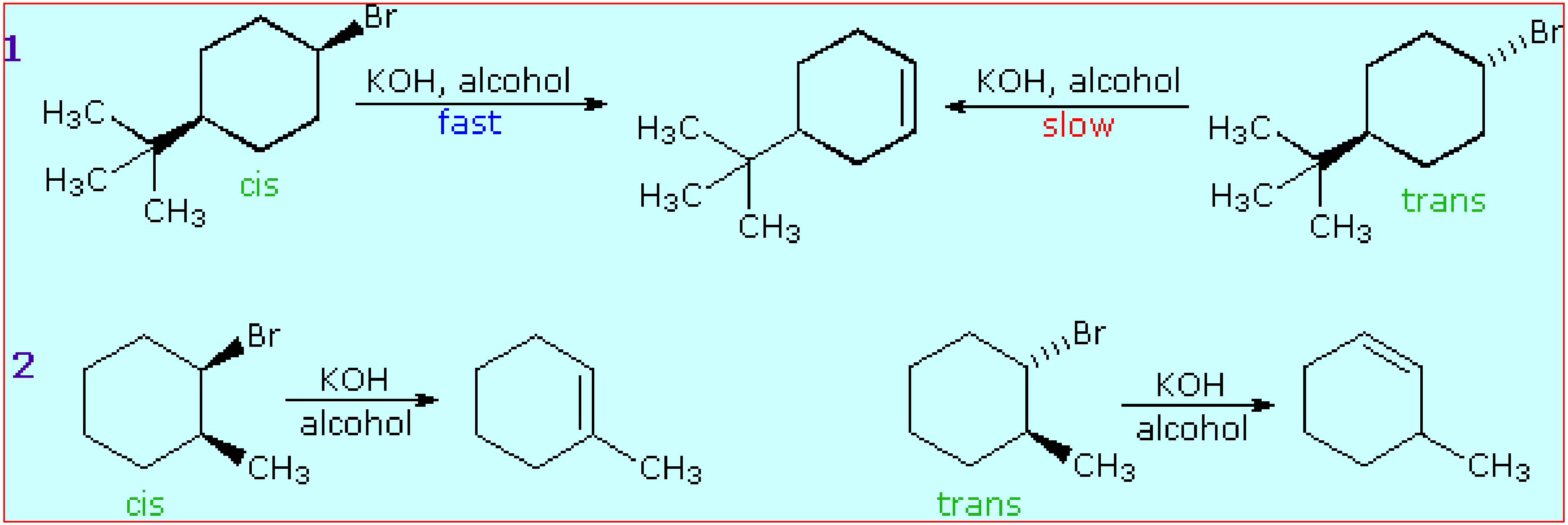
conformation of diastereoisomer B

one anti-periplanar C–H bond: single alkene formed

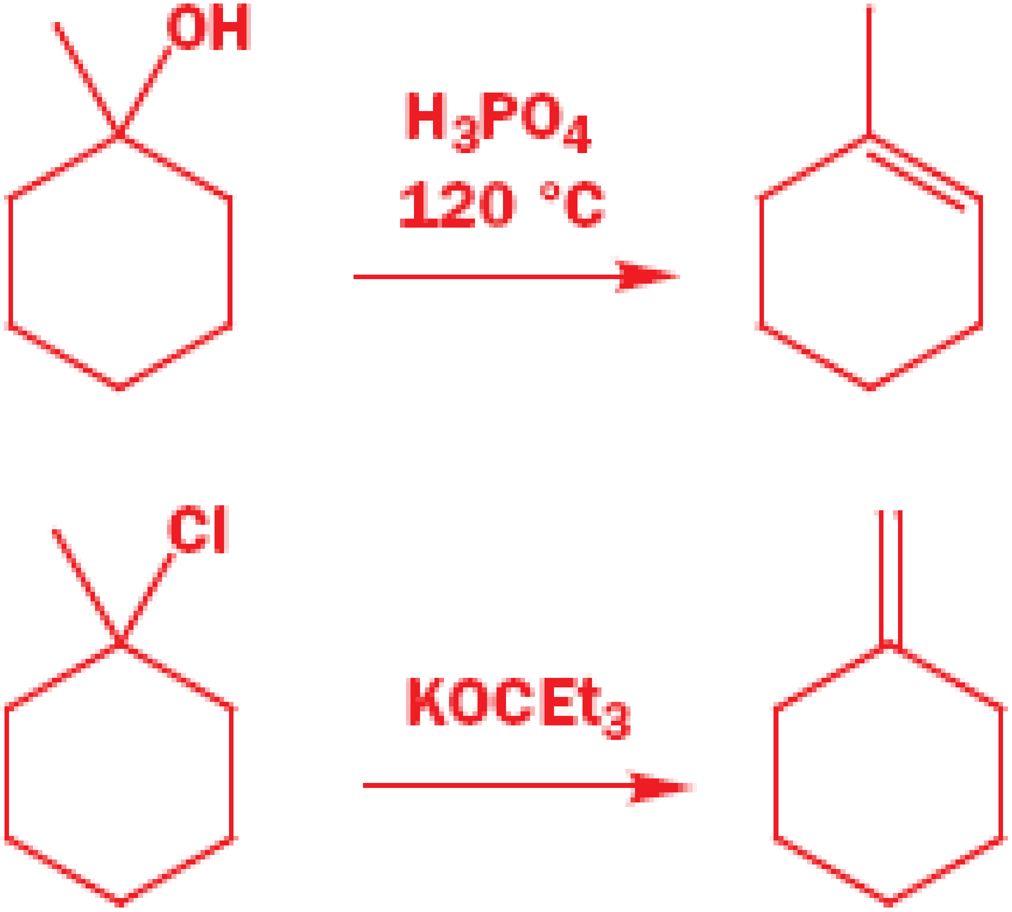


favoured; equatorial *i*-Pr can't eliminate (no anti-periplanar C–H bonds)

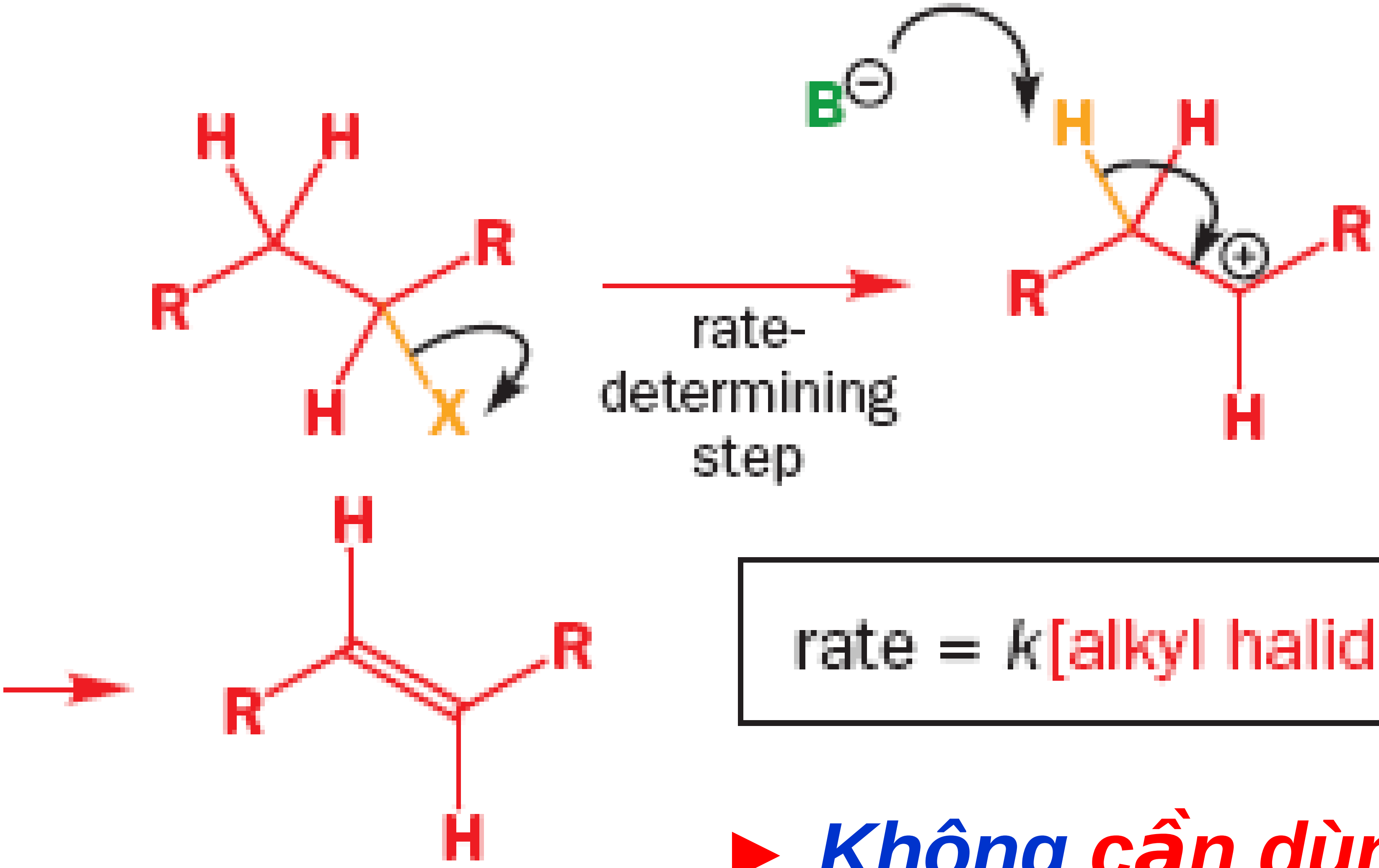
disfavoured: axial *i*-Pr


1
Br
H3C
H3C
CH3
cis
KOH, alcohol
fast
H3C
H3C
CH3
KOH, alcohol
slow
Br
H3C
H3C
CH3
trans
2
Br
CH3
cis
KOH
alcohol
CH3
Br
CH3
trans
KOH
alcohol
CH3

The regioselectivity of E2 eliminations



PHẢN ỨNG TÁCH E1



rate = *k*[alkyl halide]

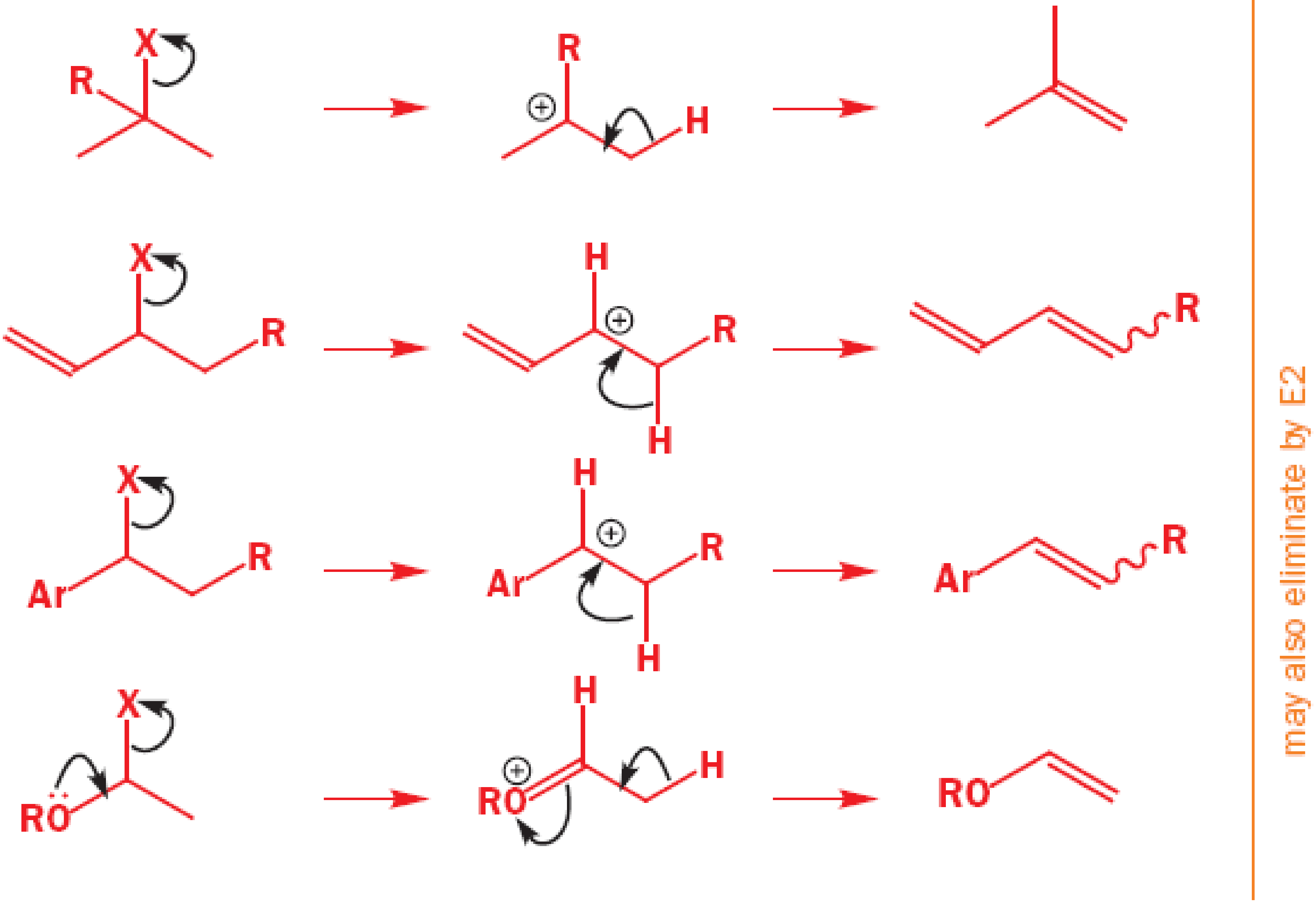
- ► ***Không cần dùng base mạnh***

PHẢN ỨNG TÁCH E1

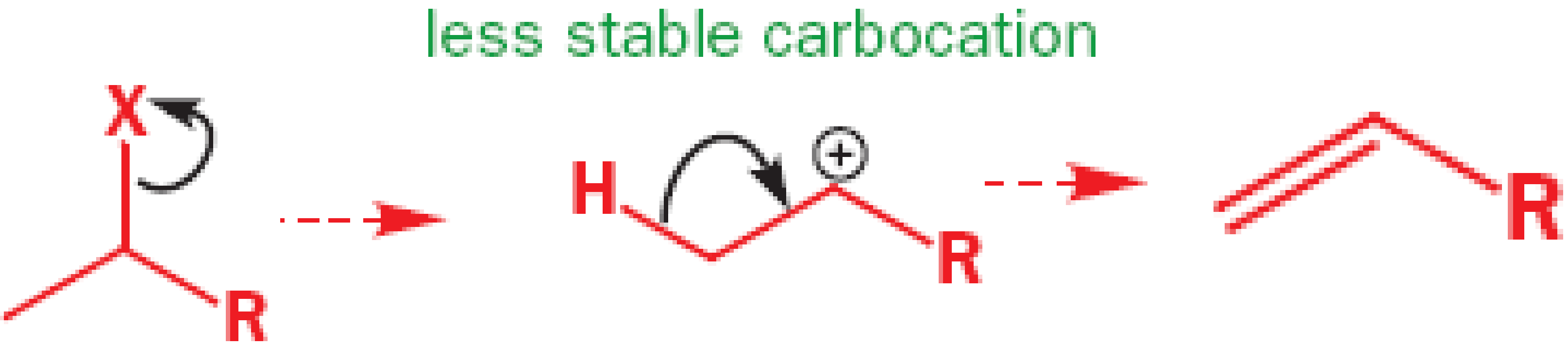
Chỉ xảy ra đối với những chất có thể ion hóa tạo thành carbocation bền vững:

- Alkyl halide bậc 3°
- Benzyl halide
- Allyl halide,…

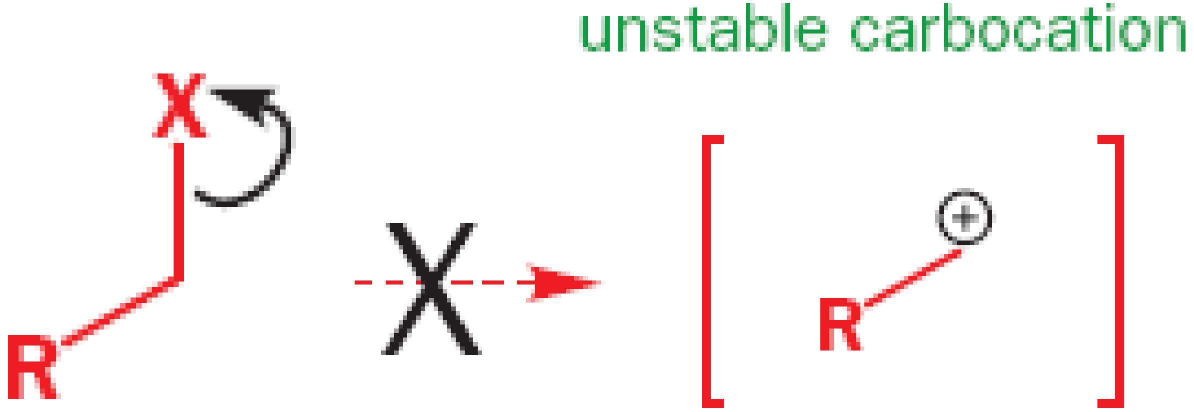
stabilized carbocation



substrates that may eliminate by E1

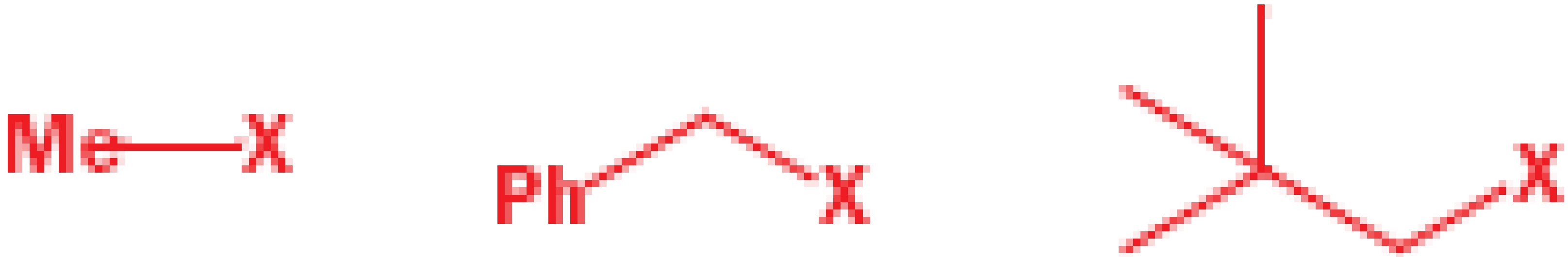


substrates that never eliminate by E1

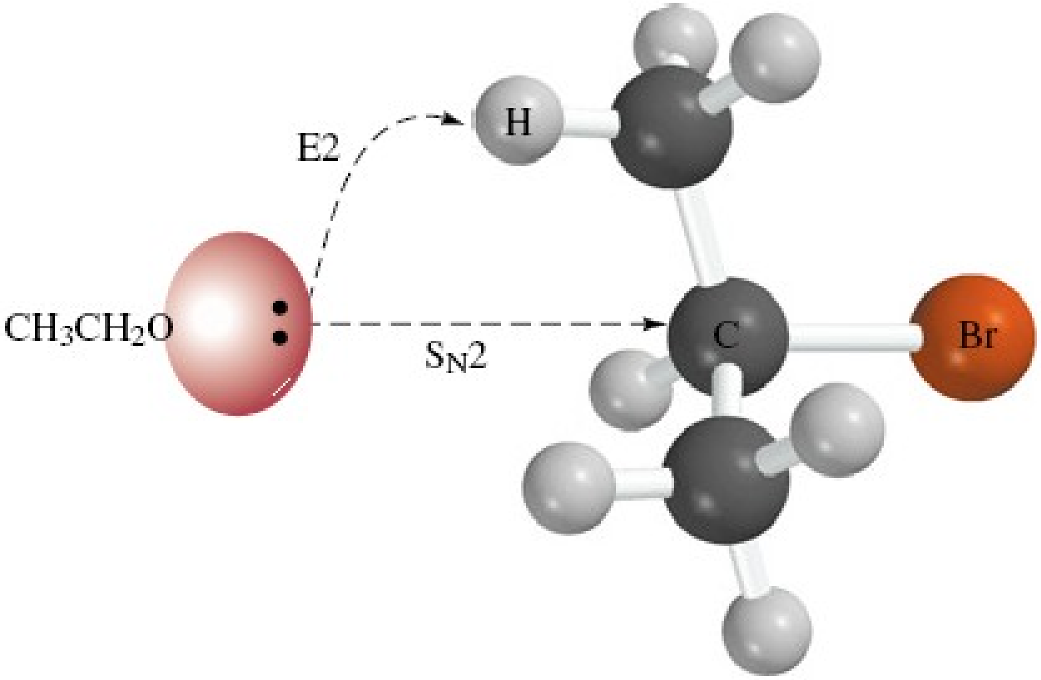


may also eliminate by E2

substrates that cannot eliminate by either mechanism



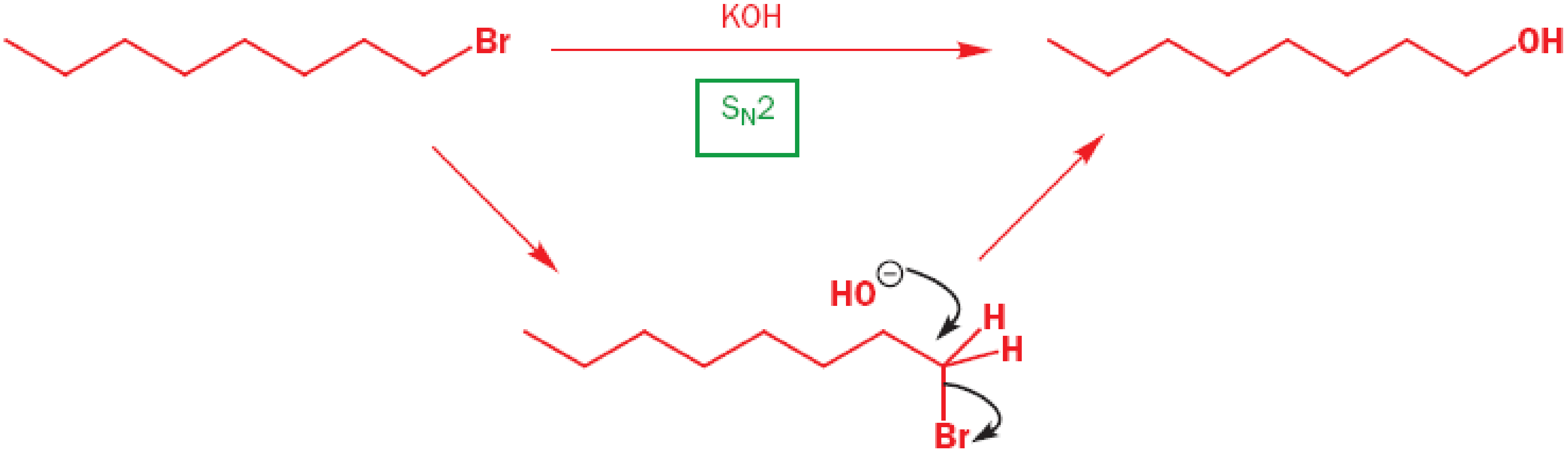
Phản ứng Thế hay Khử ?



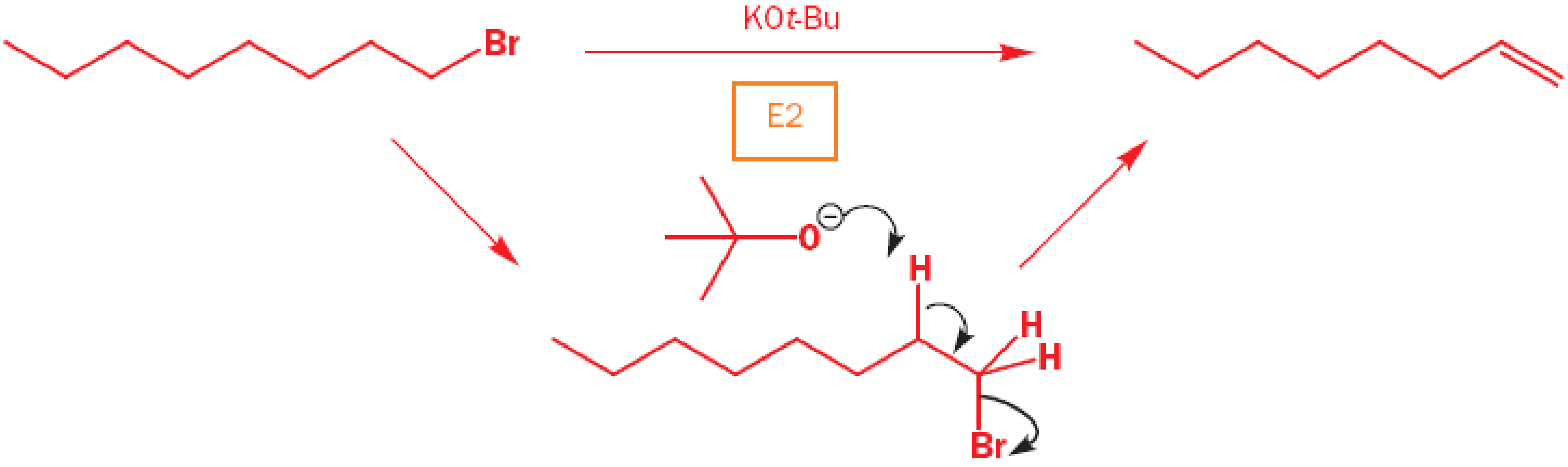
- Chướng ngại lập thể
- Tính base
- Nhiệt độ

CHƯỚNG NGẠI LẬP THỂ

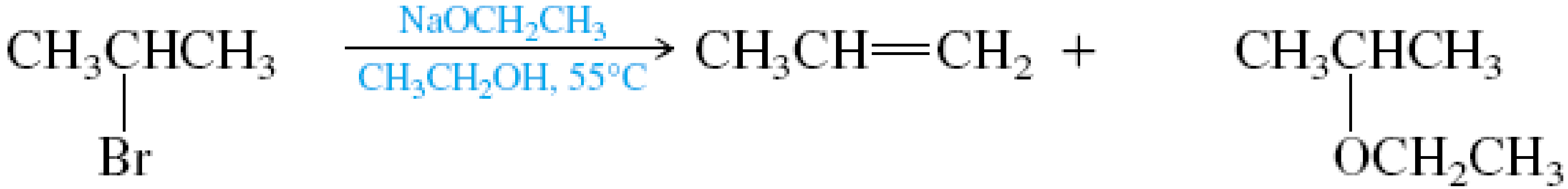
small nucleophile: substitution



large nucleophile: elimination

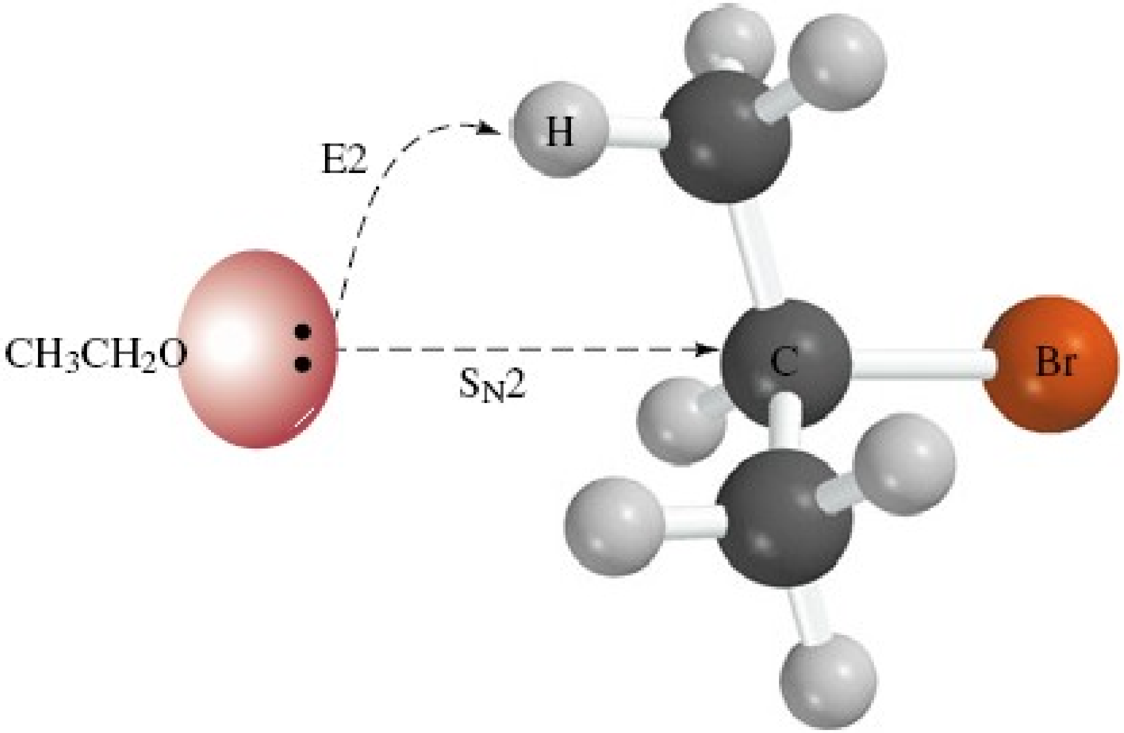


E2 hay S 2 ???

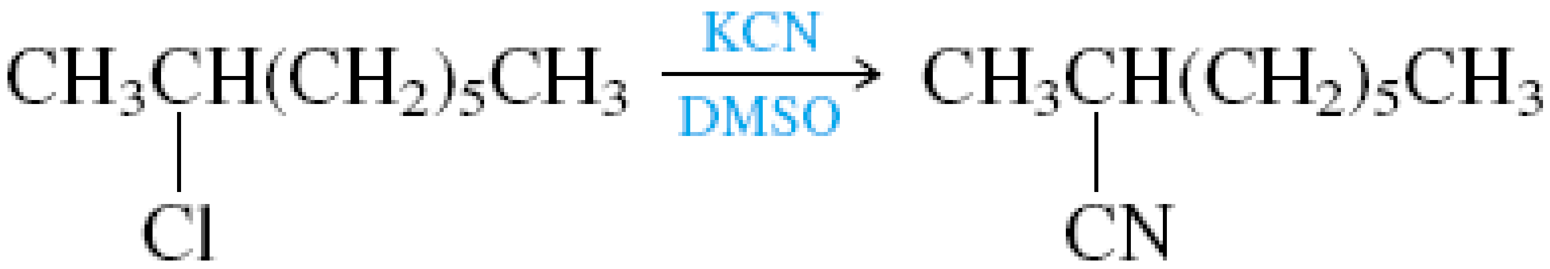


$$\underset{\mathrm{Br}}{\mathrm{CH_3CHCH_3}} \xrightarrow[\mathrm{CH_3CH_2OH,\ 55^{\circ}C}]{\mathrm{NaOCH_2CH_3}} \mathrm{CH_3CH{=}CH_2} + \underset{\mathrm{OCH_2CH_3}}{\mathrm{CH_3CHCH_3}}$$

Isopropyl bromide — Propene (87%) — Ethyl isopropyl ether (13%)



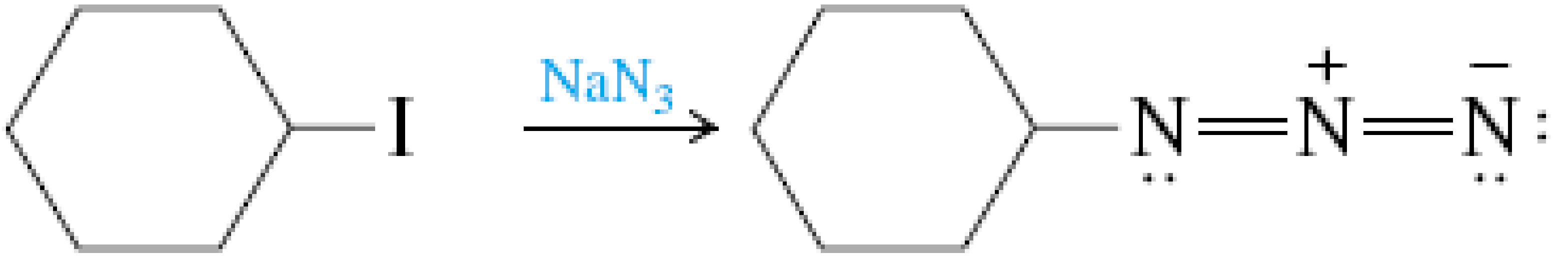
E2 hay S 2 ???



$$CH_3\underset{\underset{Cl}{|}}{C}H(CH_2)_5CH_3 \xrightarrow[DMSO]{KCN} CH_3\underset{\underset{CN}{|}}{C}H(CH_2)_5CH_3$$

2-Chlorooctane

2-Cyanooctane (70%)

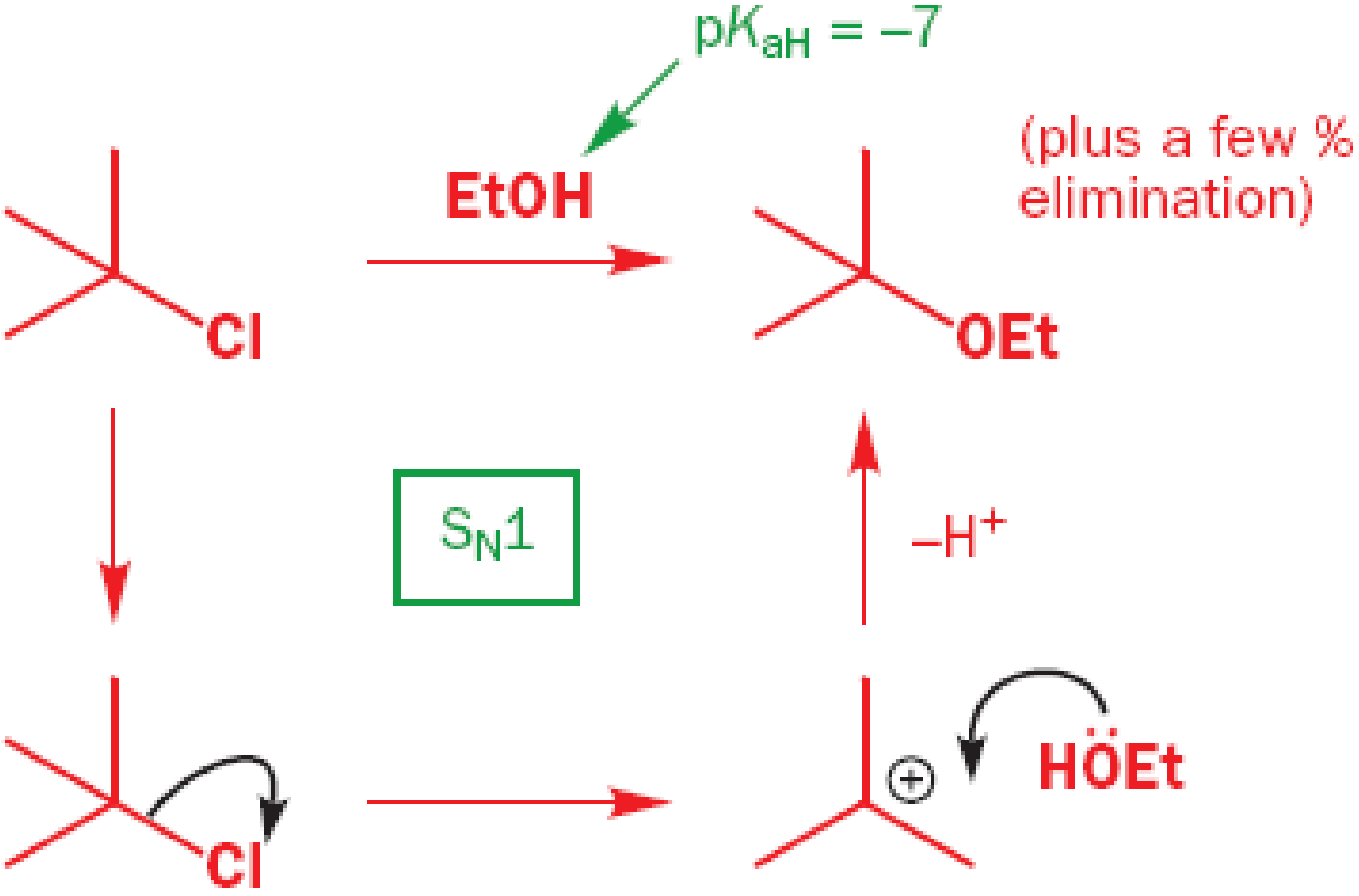


Cyclohexyl iodide

Cyclohexyl azide (75%)

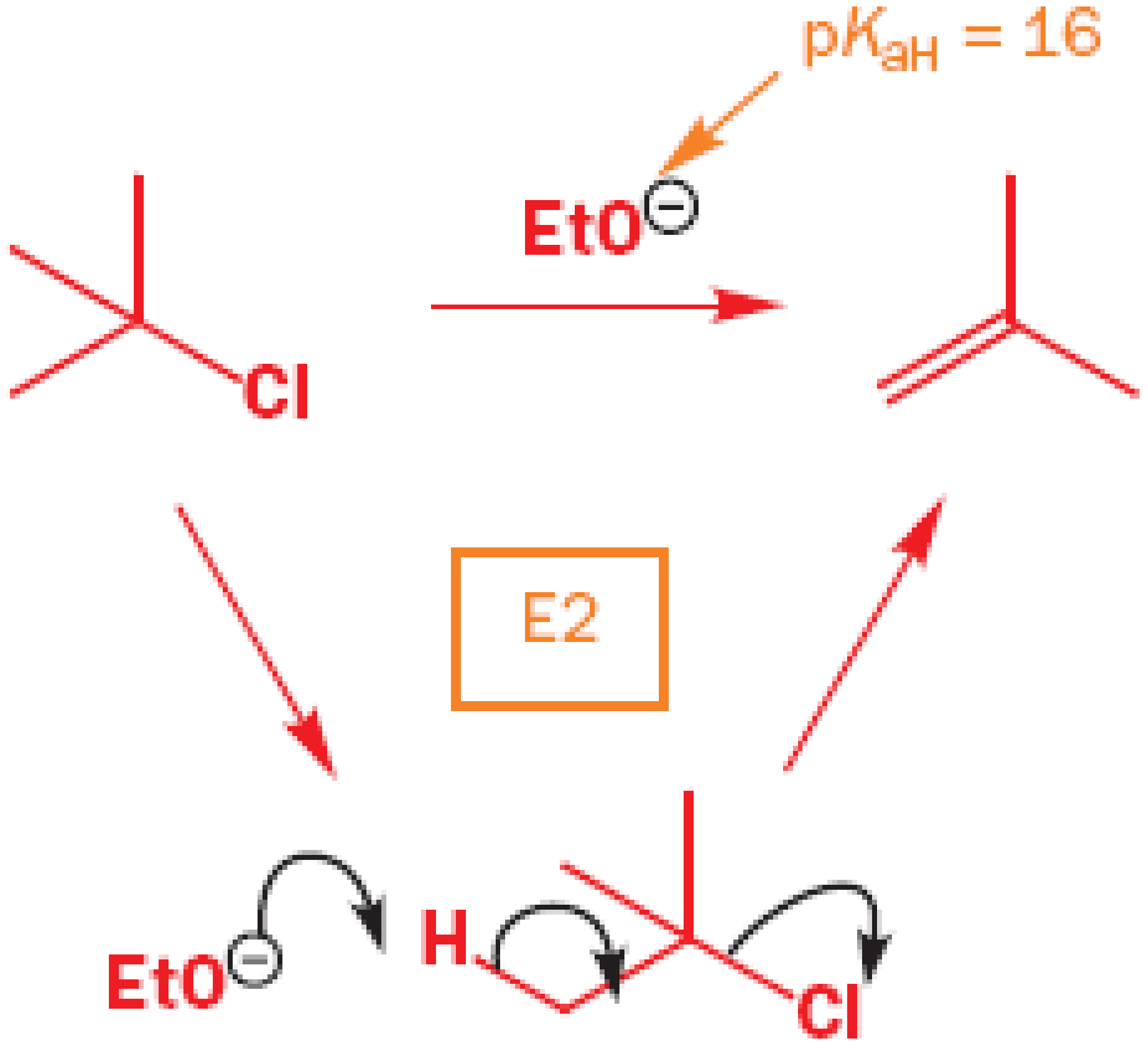
TÍNH BASE

weak base: substitution



TÍNH BASE

strong base: elimination



Nhiệt độ

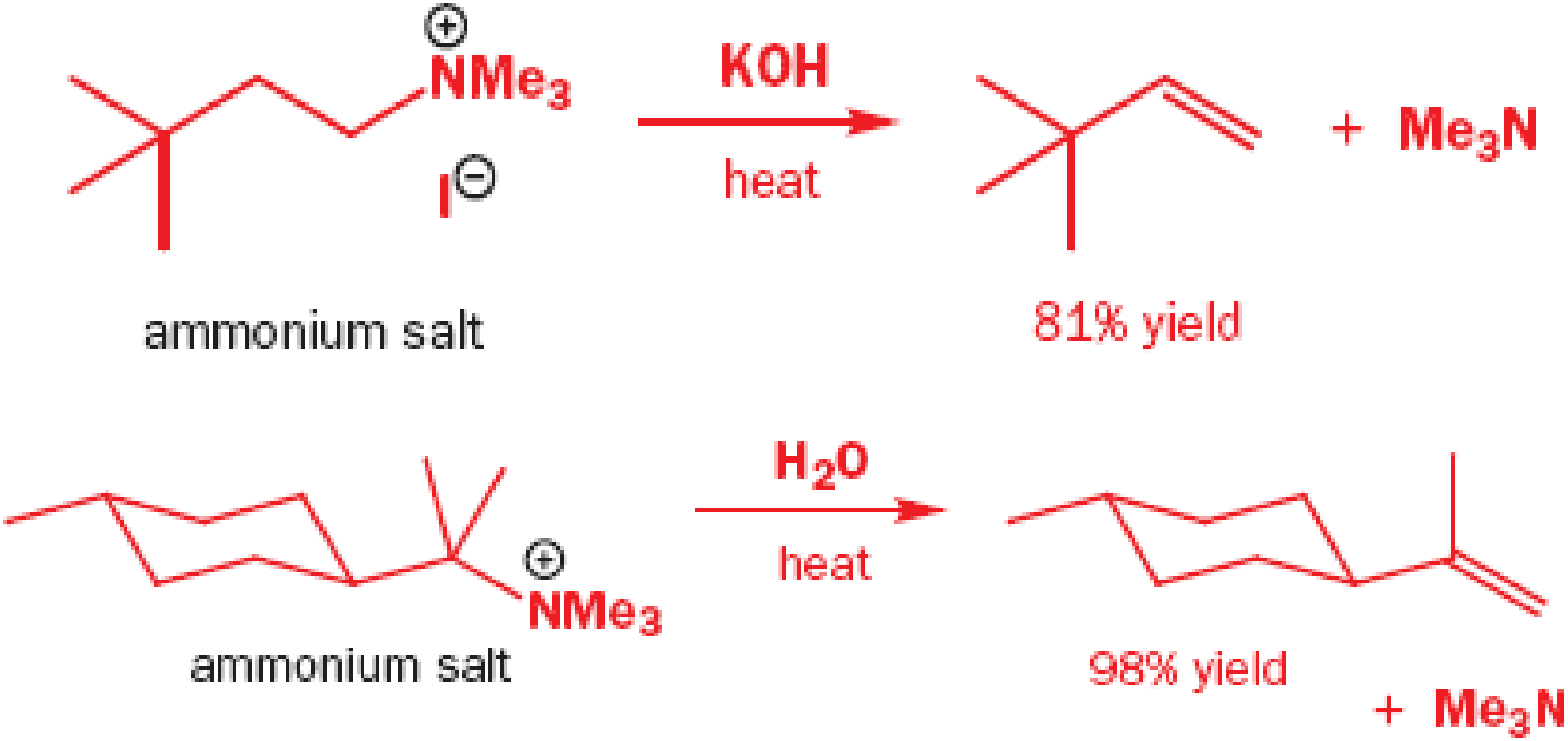
$$\Delta G = \Delta H - T\Delta S$$

Phản ứng tách: $\Delta S > 0$

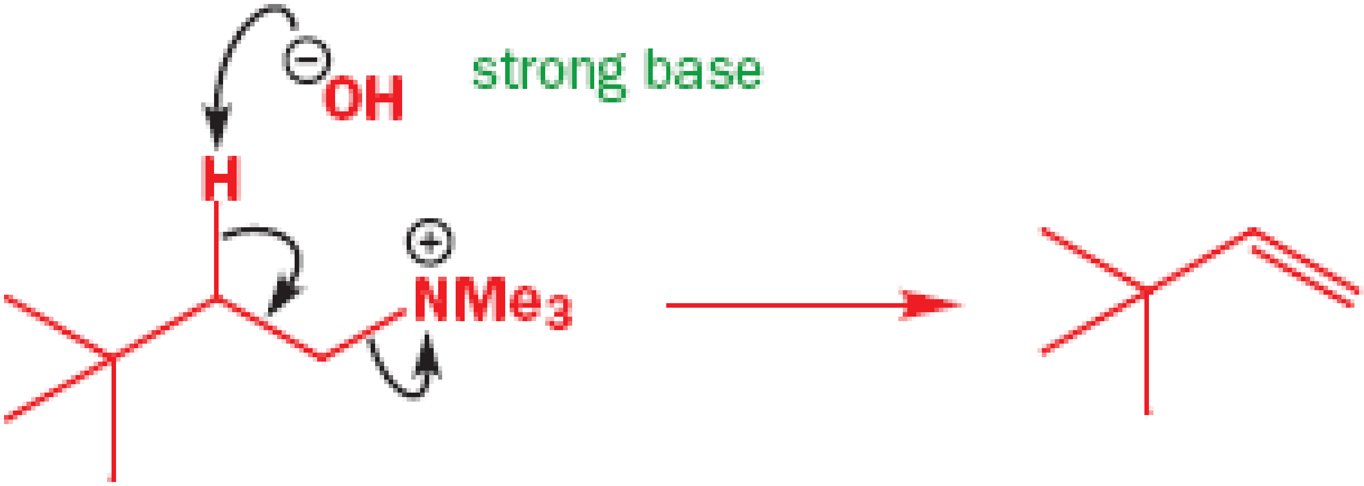
► **$\Delta G < 0$ khi T càng lớn**

► **Phản ứng tách cần nhiệt độ**

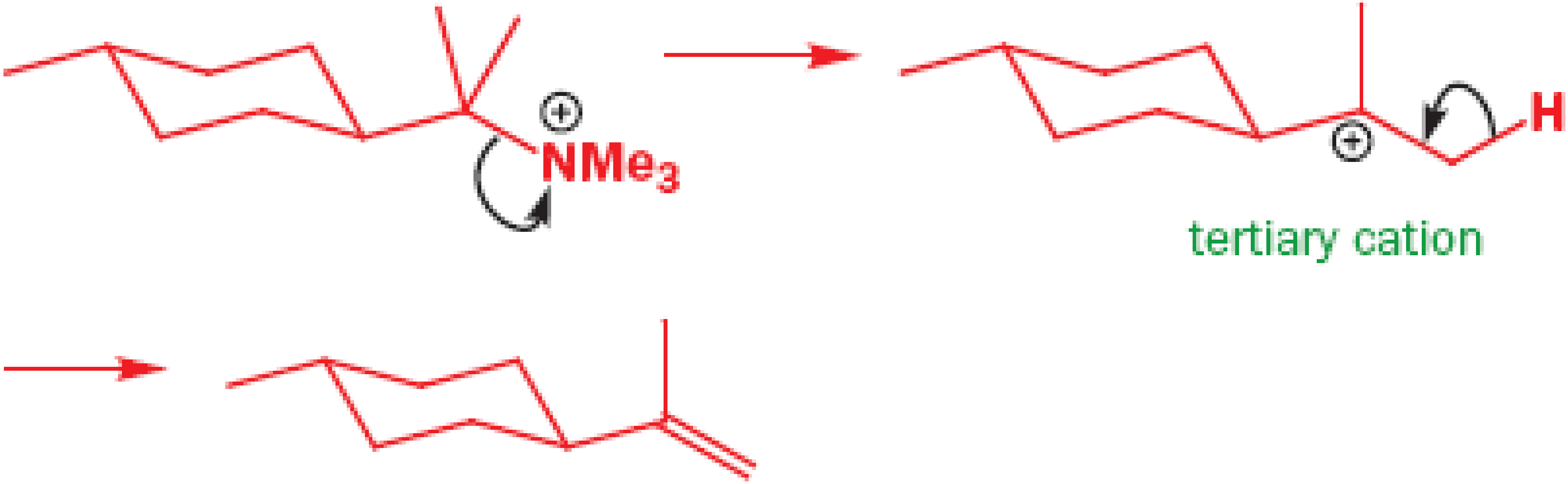
Nhóm xuất trong E2 và E1



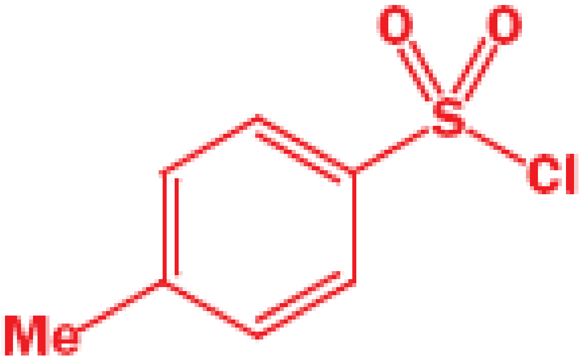
E2 elimination



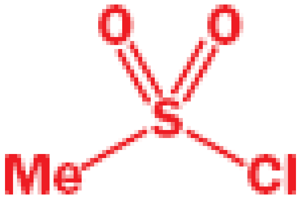
E1 elimination



Nhóm xuất trong E2 và E1

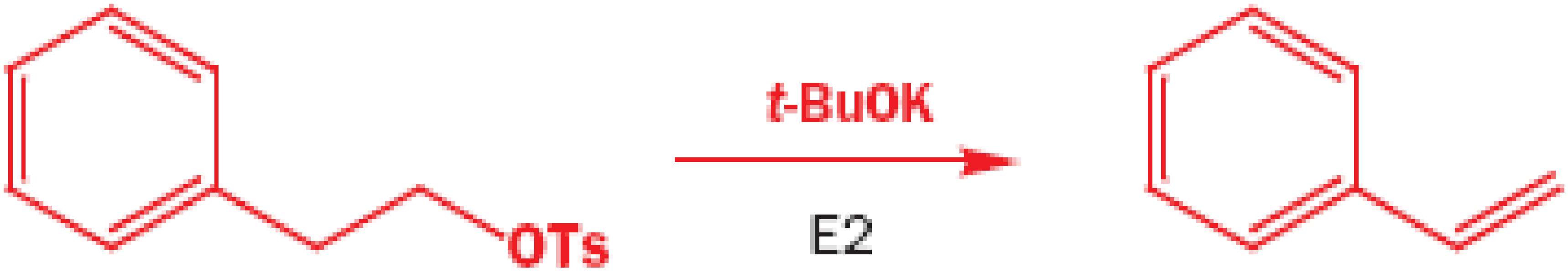


toluene-*para*-sulfonyl chloride
(tosyl chloride, TsCl)



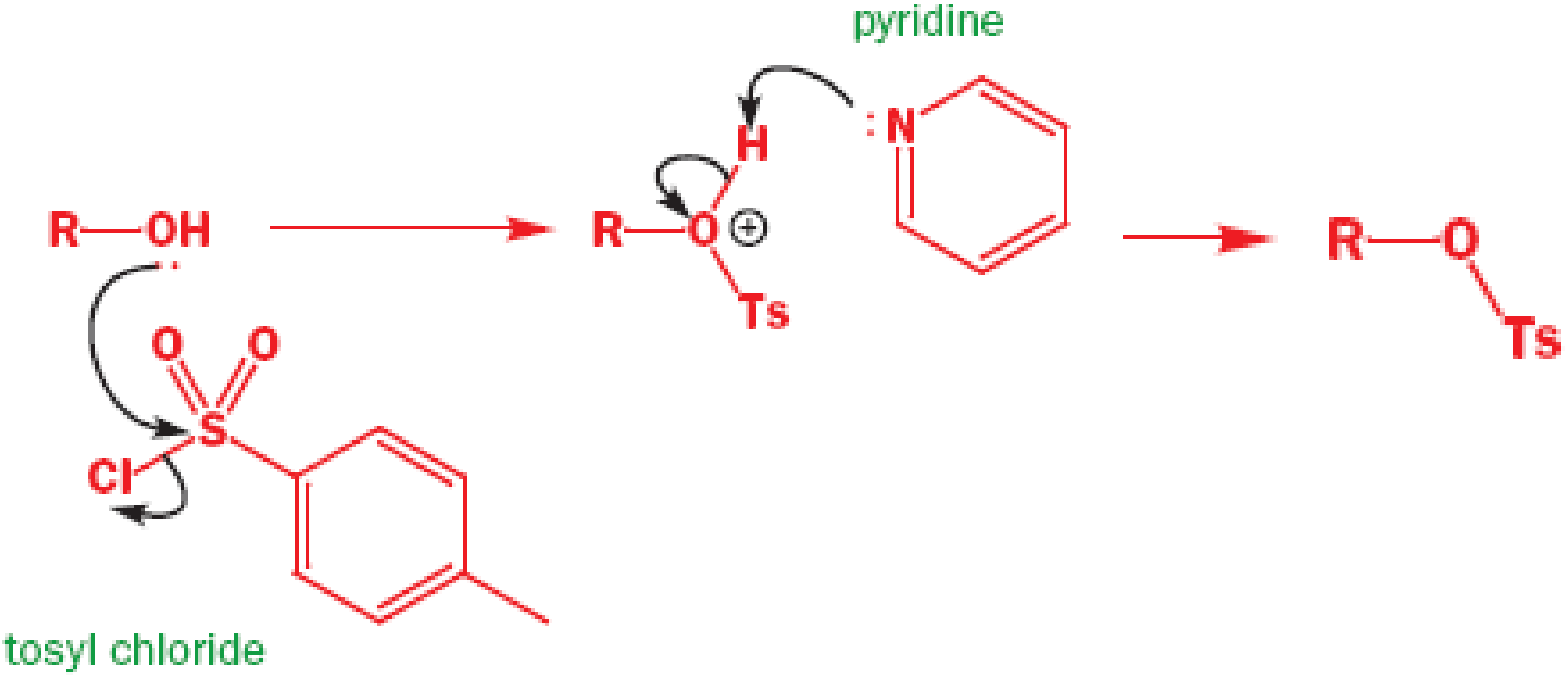
methanesulfonyl chloride
(mesyl chloride, MsCl)

E2 eliminations of tosylates



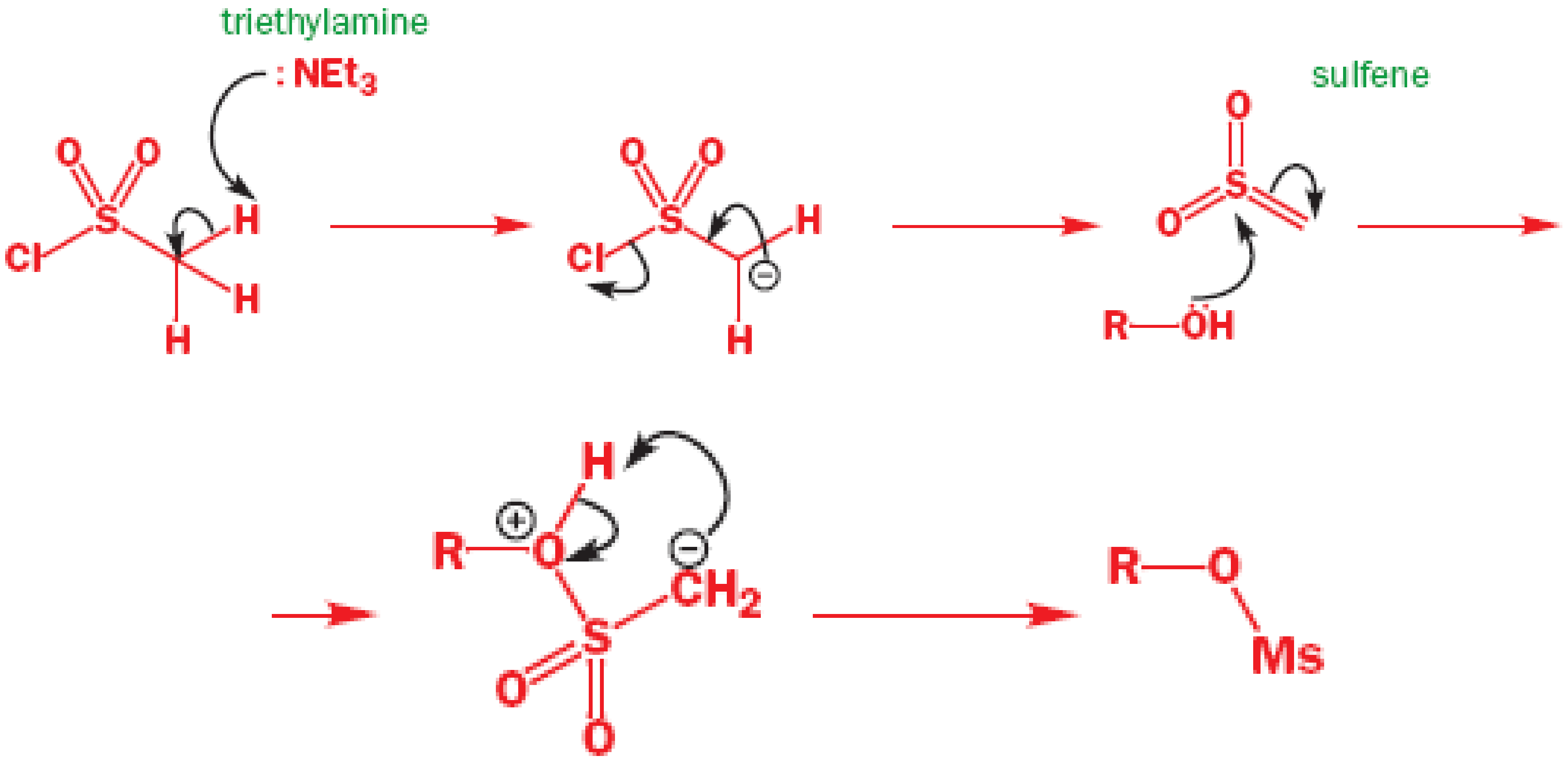
Sự tạo thành Tosylate

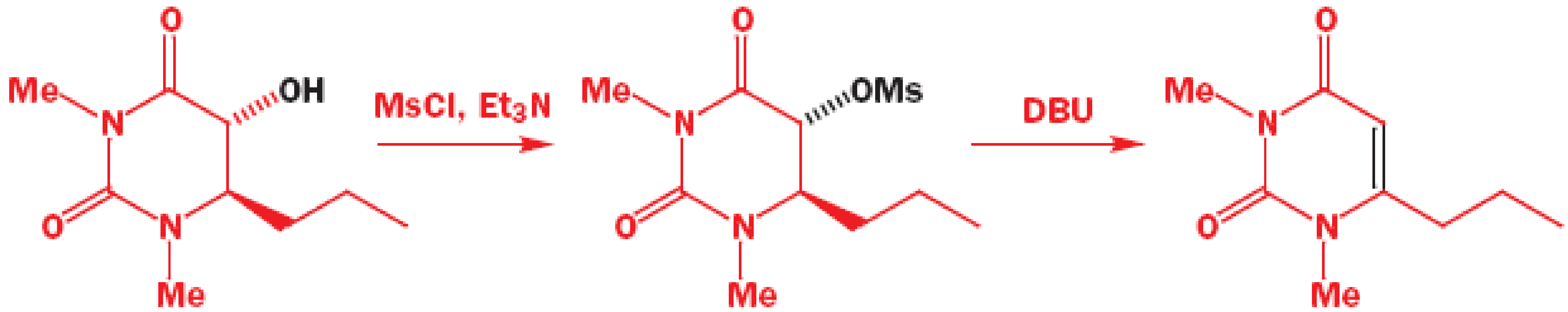
Reagents: **ROH + TsCl + Pyridine**

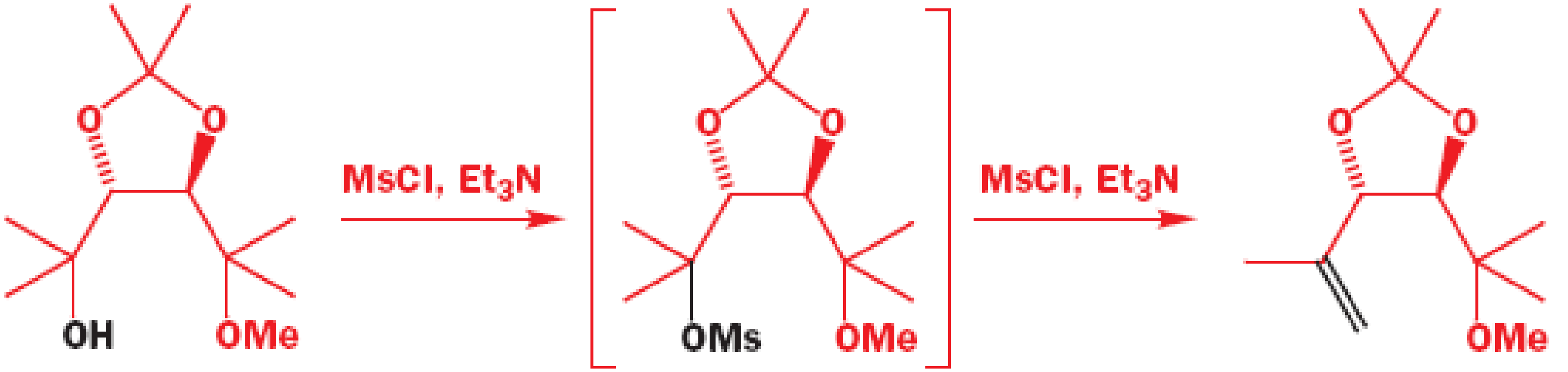


Sự tạo thành Mesylate

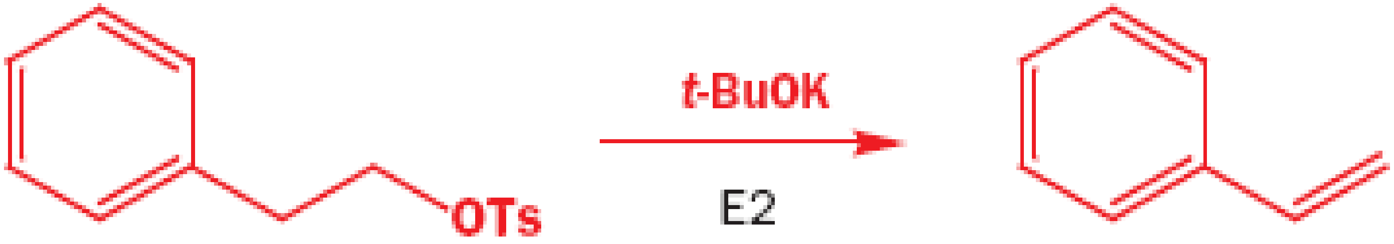
Reagents: **ROH + MsCl + Triethylamine**

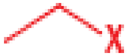
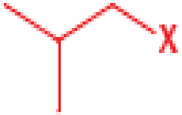
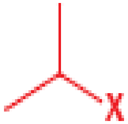
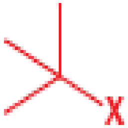






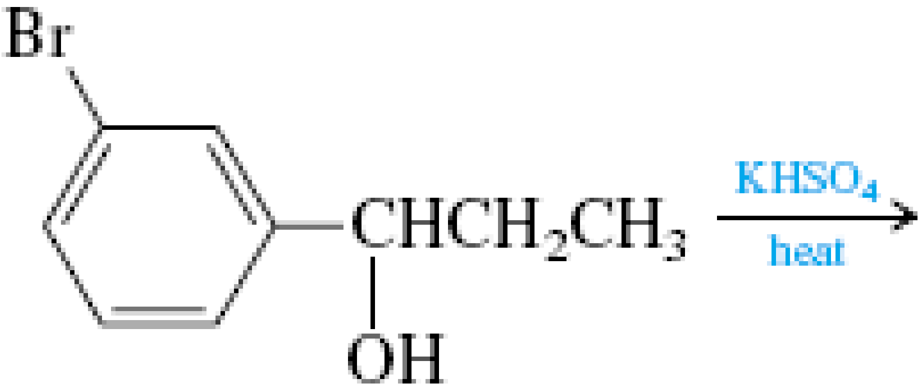
E2 eliminations of tosylates



	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 	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

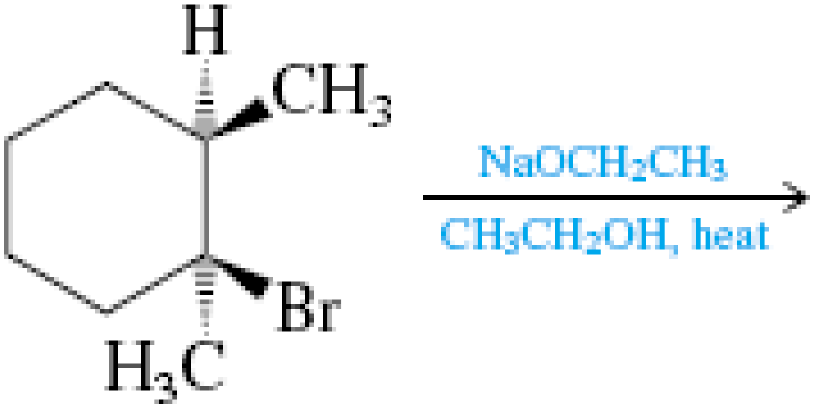
Sản Phẩm Chính?

(a)



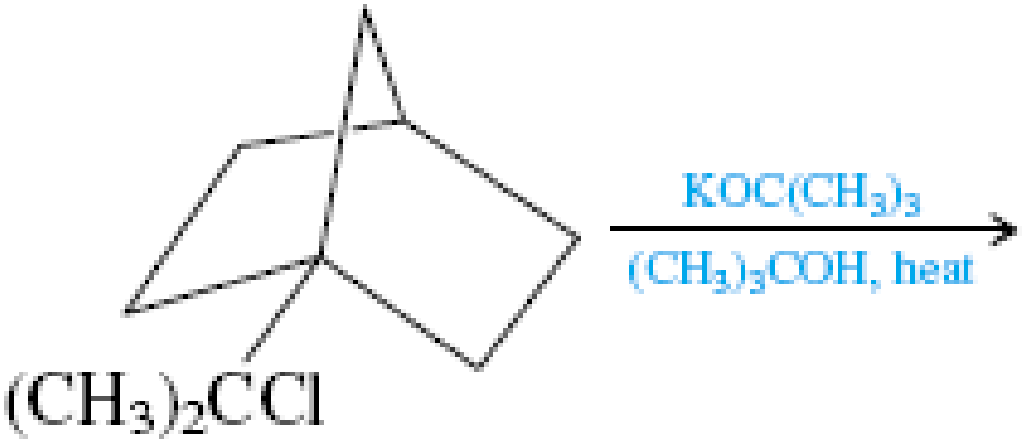
(b) $ICH_2CH(OCH_2CH_3)_2 \xrightarrow[(CH_3)_3COH,\ heat]{KOC(CH_3)_3}$

(c)

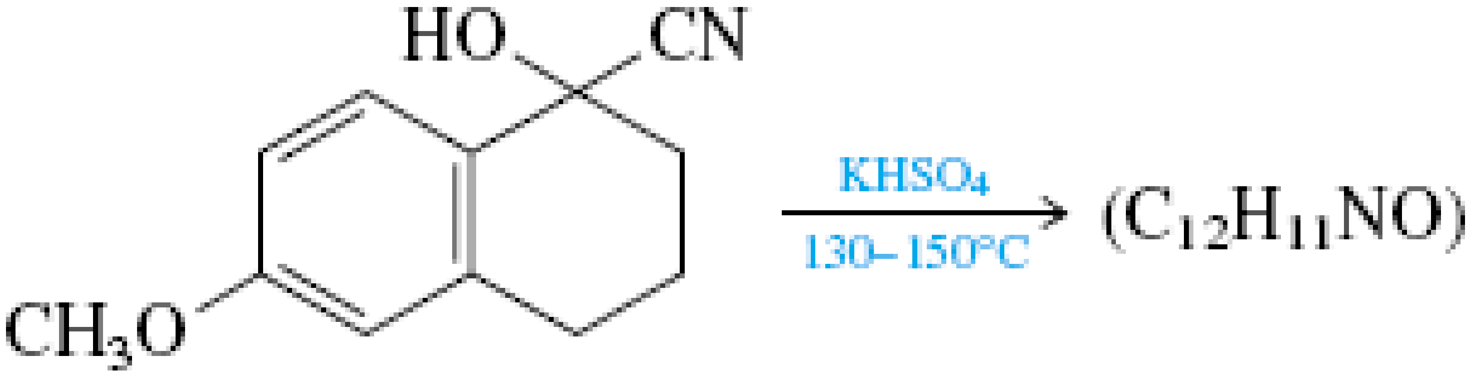


Sản Phẩm Chính?

(d)

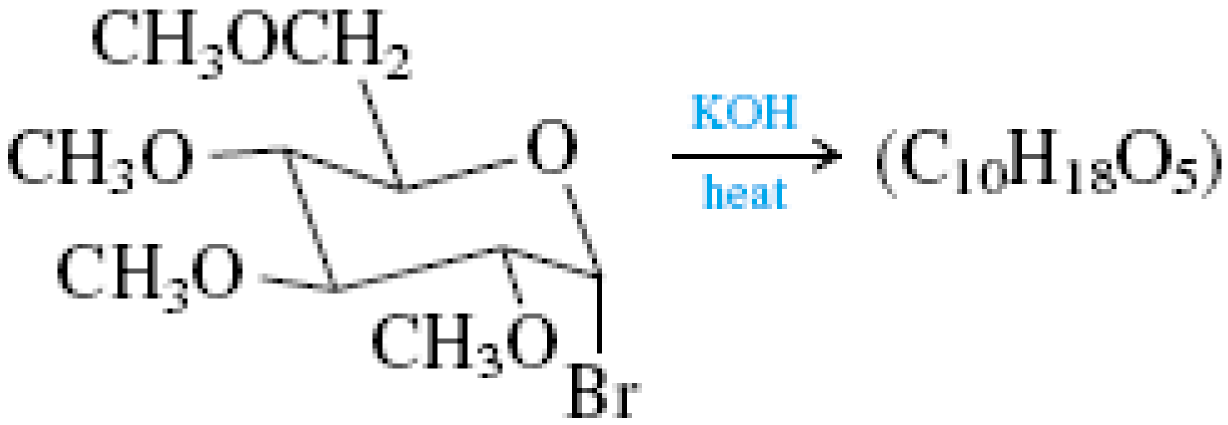


(e)

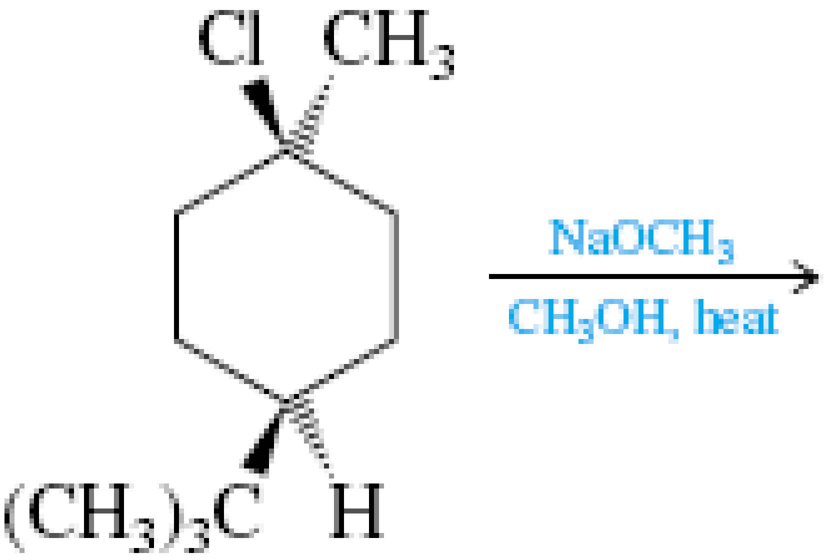


Sản Phẩm Chính?

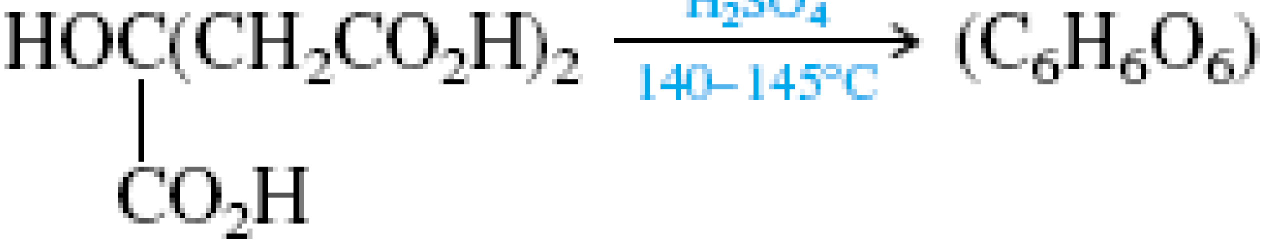
(i)



(j)

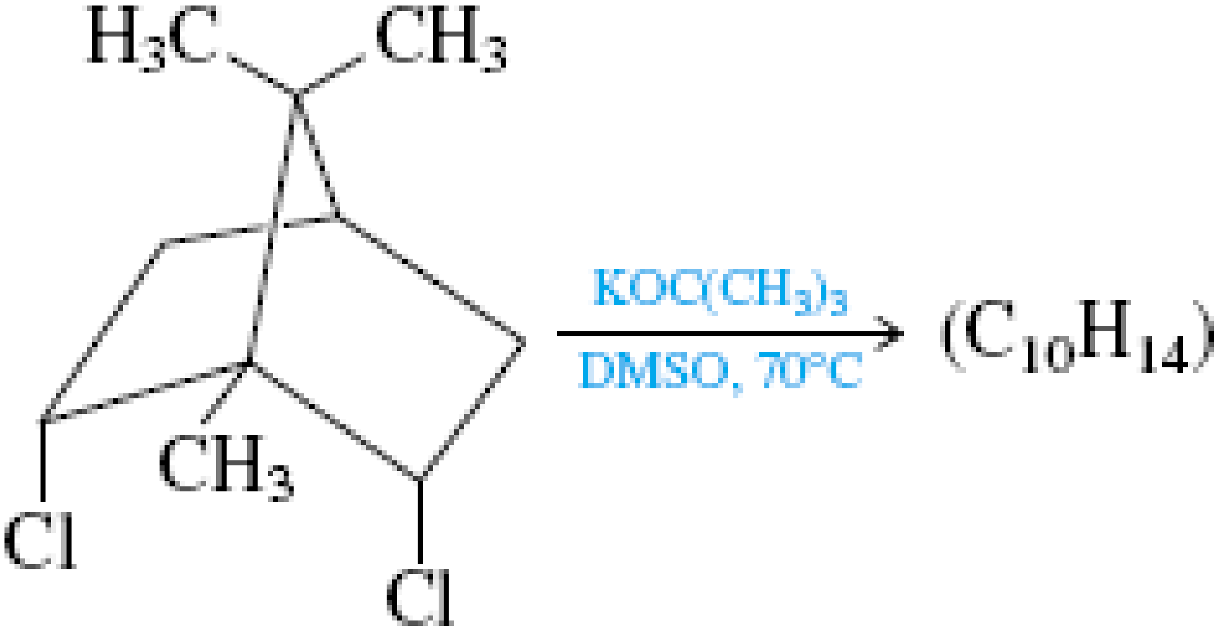


Sản Phẩm Chính?

(f)


$$HOC(CH_2CO_2H)_2 \text{ (with } CO_2H \text{ below C)} $$

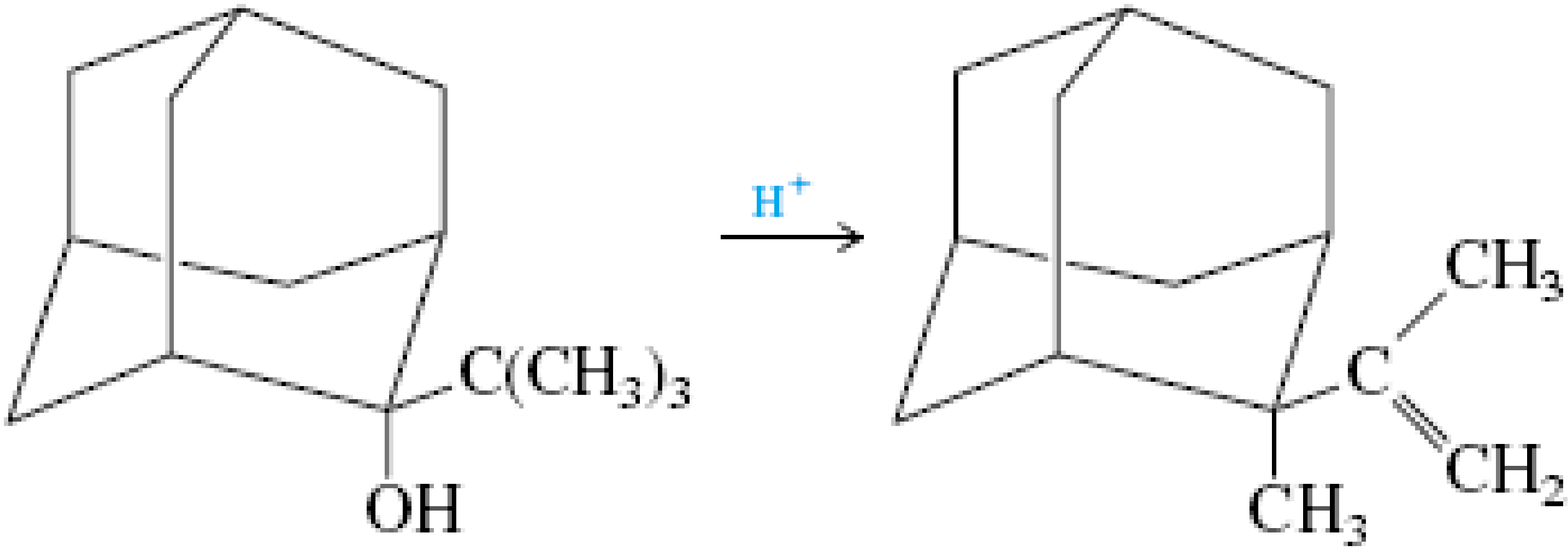
Citric acid

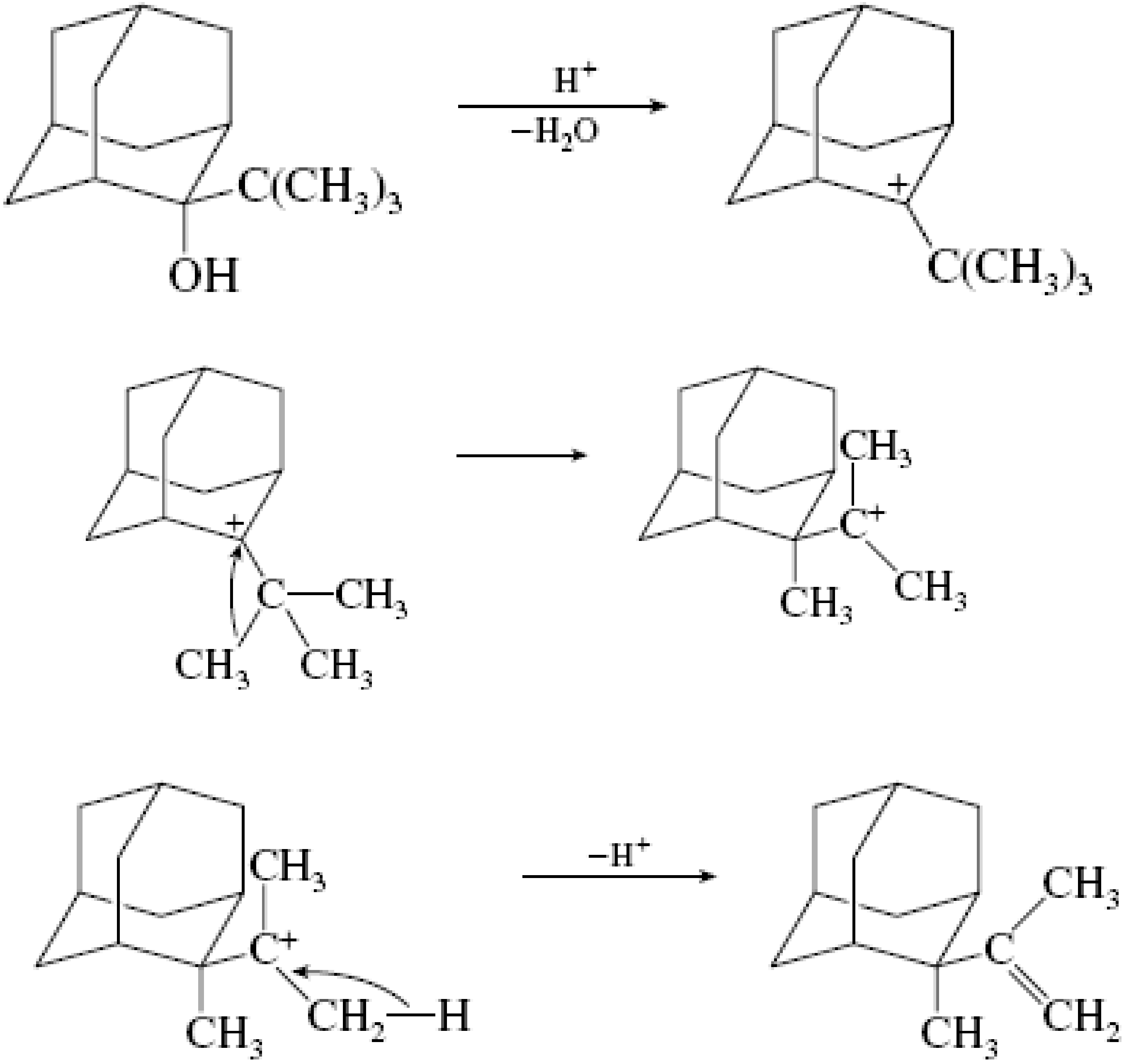
(g)


$$\xrightarrow[\text{DMSO, 70°C}]{KOC(CH_3)_3} (C_{10}H_{14})$$

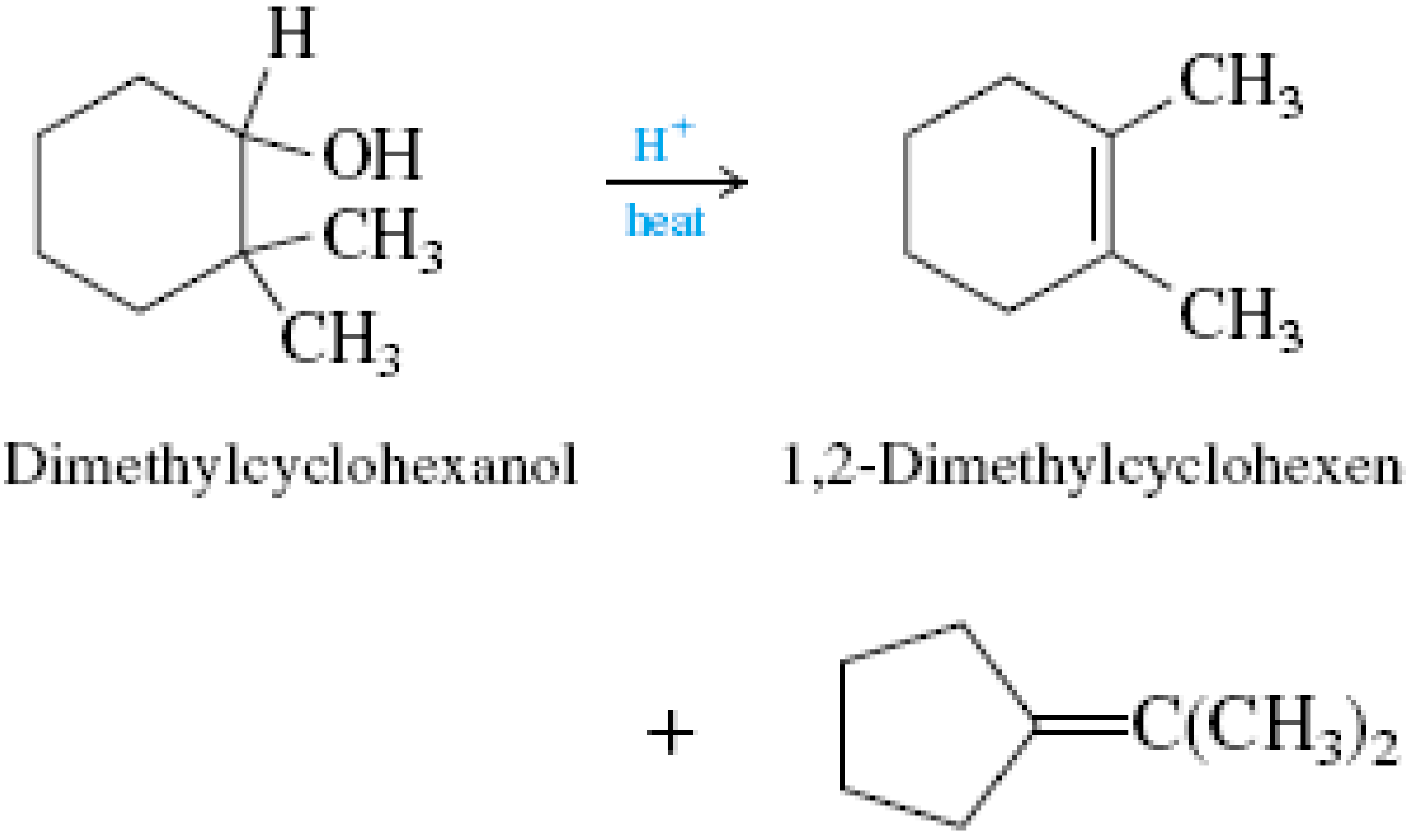
Cơ chế ?

(a)




C(CH3)3
OH
H+
−H2O
+
C(CH3)3
+
C—CH3
CH3
CH3
CH3
C+
CH3
CH3
CH3
C+
CH3
CH2—H
−H+
CH3
C
CH3
CH2

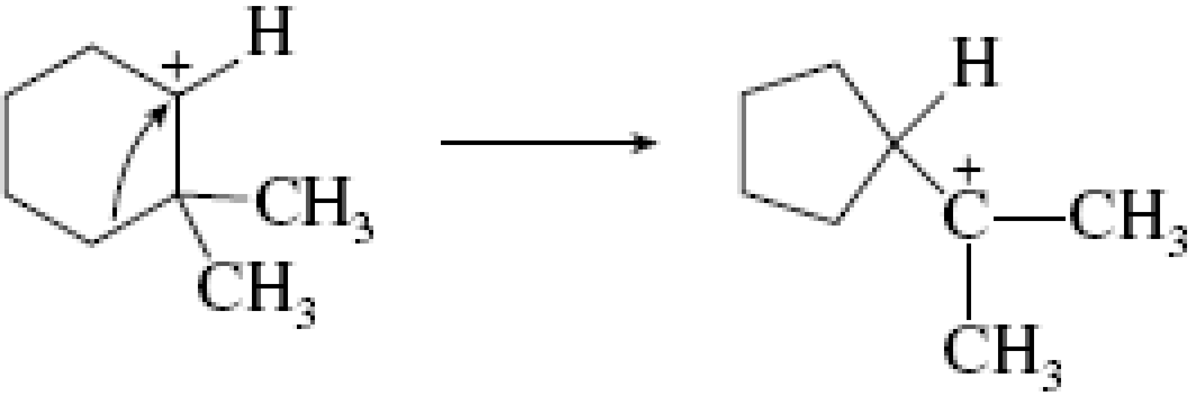
Cơ chế ?



2,2-Dimethylcyclohexanol

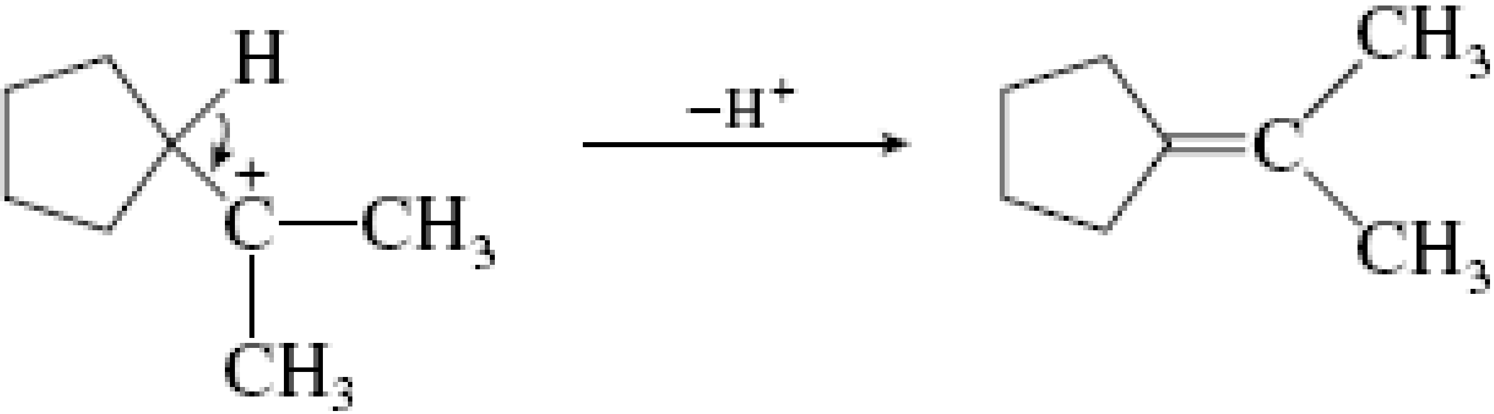
1,2-Dimethylcyclohexene

Isopropylidenecyclopentane



Secondary carbocation

Tertiary carbocation



Isopropylidenecyclopentane