ORGANIC CHEMISTRY

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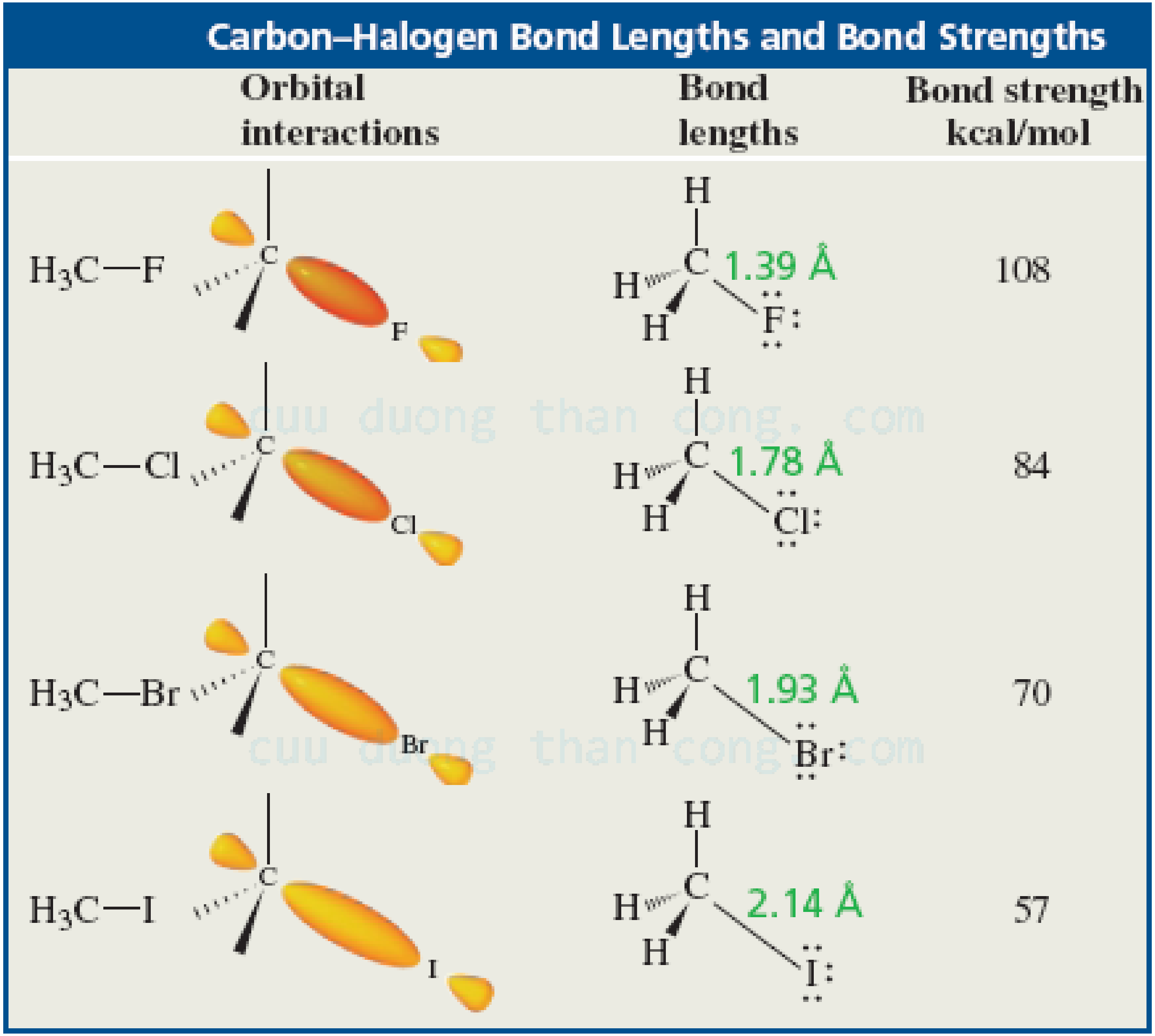
Chapter 9: ALKYL HALIDES

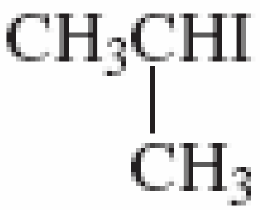


Carbon–Halogen Bond Lengths and Bond Strengths

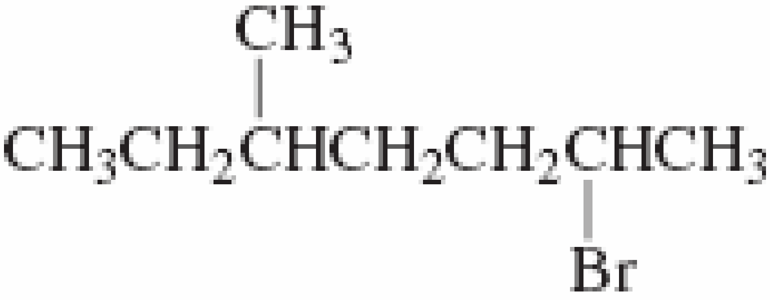
	Orbital interactions	Bond lengths	Bond strength kcal/mol
$H_3C—F$		1.39 Å	108
$H_3C—Cl$		1.78 Å	84
$H_3C—Br$		1.93 Å	70
$H_3C—I$		2.14 Å	57

NOMENCLATURE OF ALKYL HALIDES

Common names: ***alkylhalide (chloride, bromide…)***

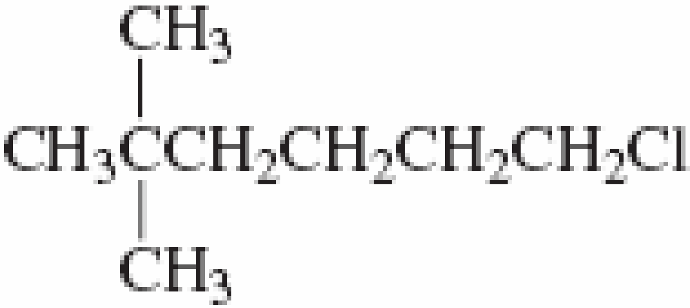
	CH_3Cl	CH_3CH_2F	 $CH_3\underset{\displaystyle CH_3}{\underset{|}{C}}HI$
common name:	methyl chloride	ethyl fluoride	isopropyl iodide
systematic name:	chloromethane	fluoroethane	2-iodopropane

IUPAC names: ***halogeno + alkane (chloro, bromo…)***



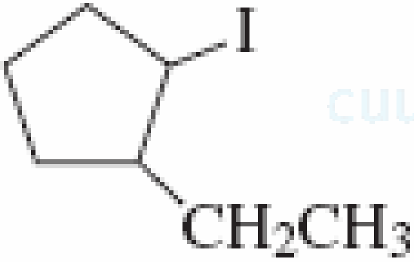
$$CH_3CH_2\overset{\displaystyle CH_3}{\overset{|}{C}}HCH_2CH_2\underset{\displaystyle Br}{\underset{|}{C}}HCH_3$$

2-bromo-5-methylheptane

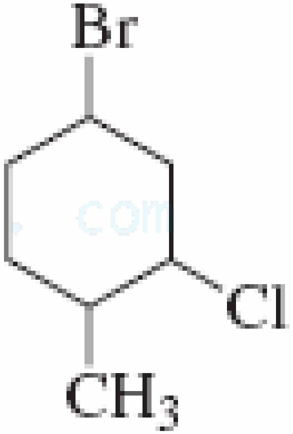


$$CH_3\underset{\displaystyle CH_3}{\underset{|}{\overset{\displaystyle CH_3}{\overset{|}{C}}}}CH_2CH_2CH_2CH_2Cl$$

1-chloro-5,5-dimethylhexane



1-ethyl-2-iodocyclopentane

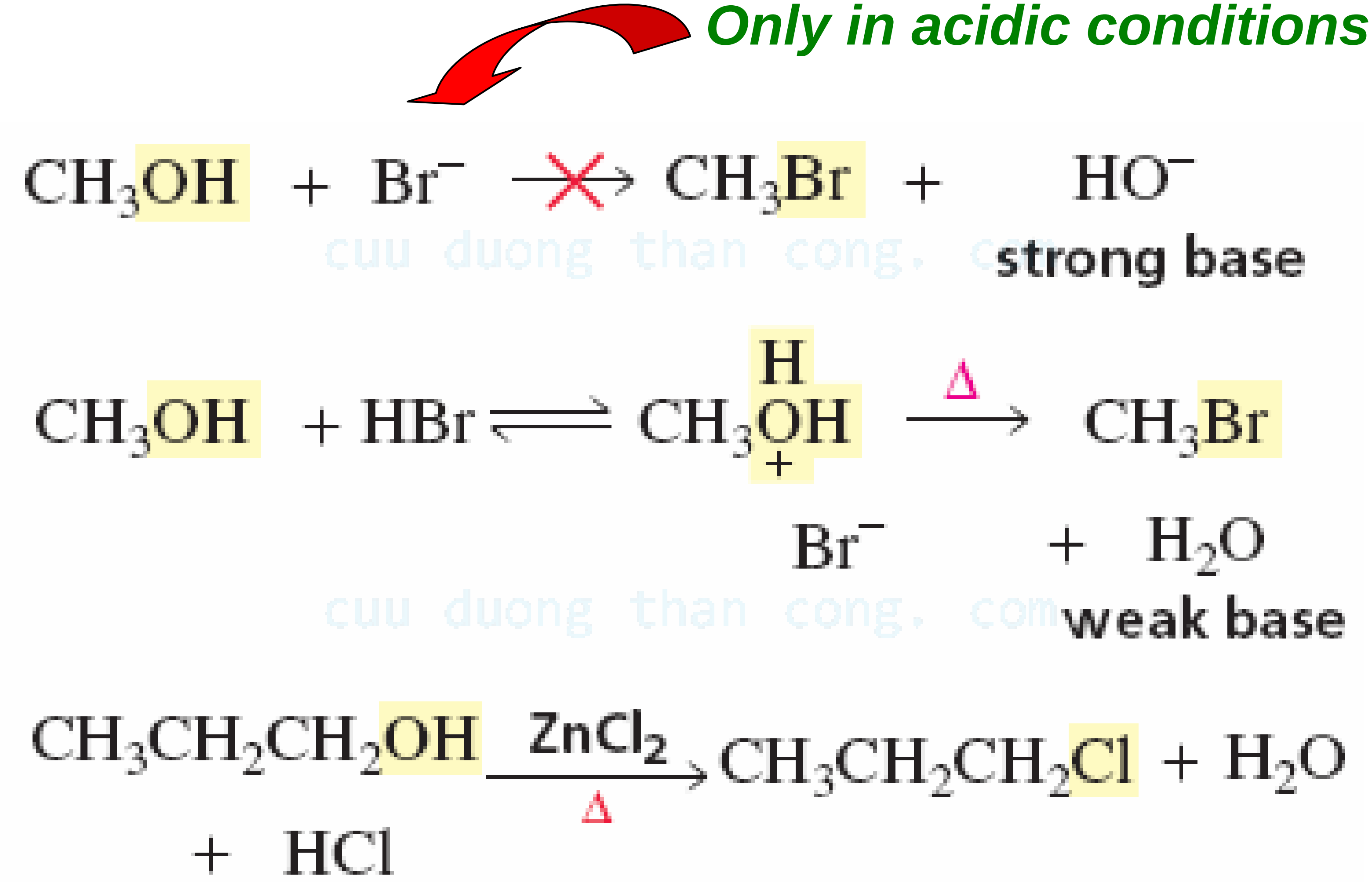


4-bromo-2-chloro-1-methylcyclohexane

Alkyl & halogen substituents are considered of <u>equal rank</u>

PREPARATION OF ALKYL HALIDES

Alkyl halides from alcohols



Only in acidic conditions

$CH_3OH + Br^- \not\longrightarrow CH_3Br + HO^-$

strong base

$CH_3OH + HBr \rightleftharpoons CH_3\overset{H}{\underset{+}{O}}H \xrightarrow{\Delta} CH_3Br$

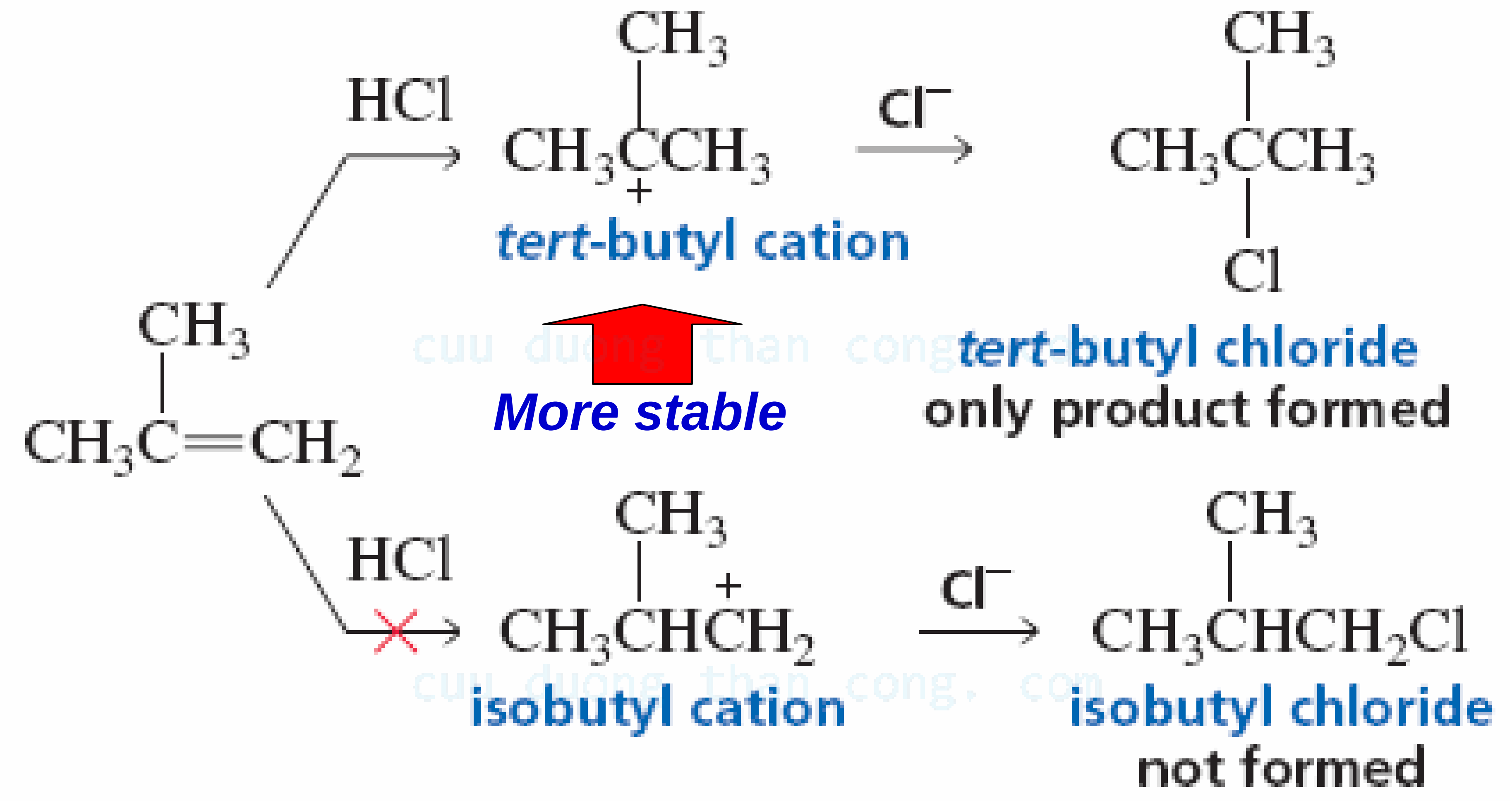
$Br^- \quad + \quad H_2O$

weak base

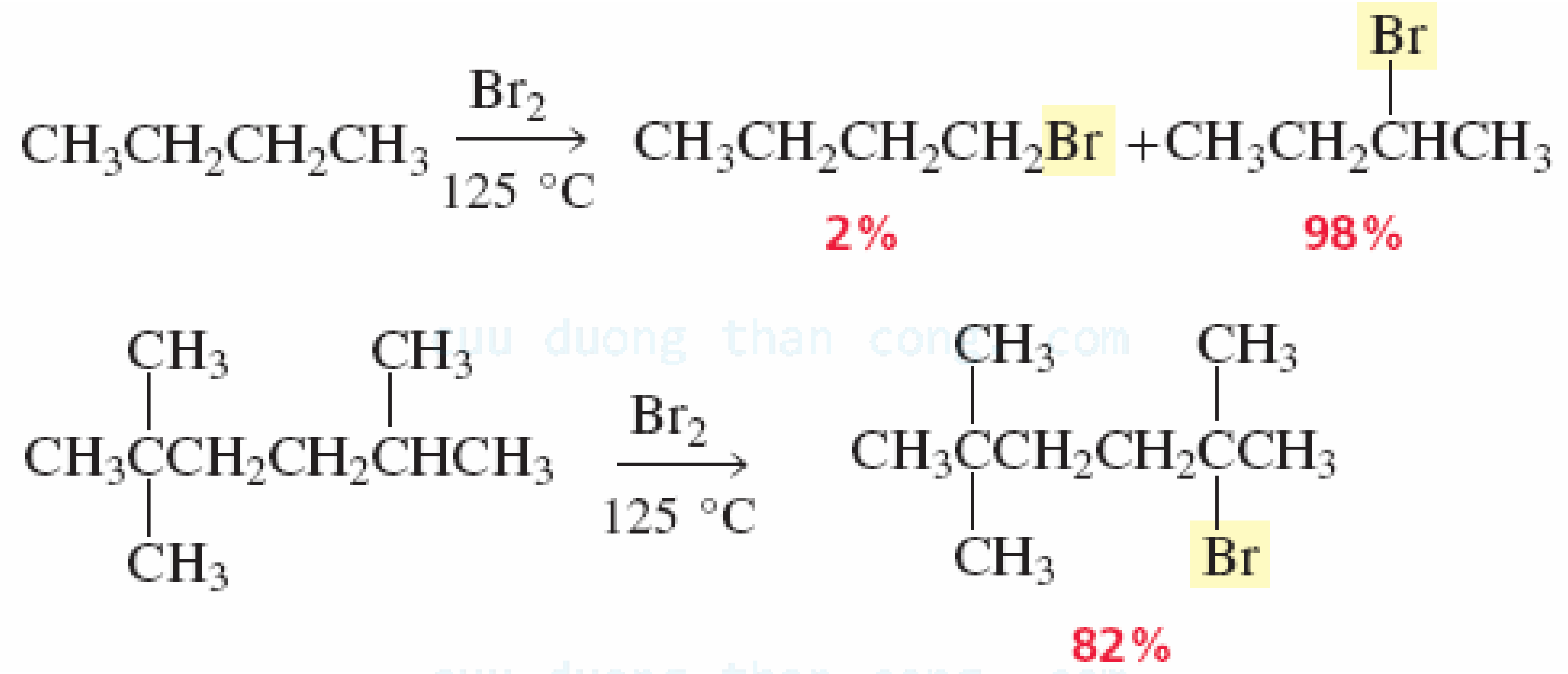
$CH_3CH_2CH_2OH \xrightarrow[\Delta]{ZnCl_2} CH_3CH_2CH_2Cl + H_2O$

$+ \quad HCl$

Alkyl halides from alkenes



Alkyl halides from alkanes



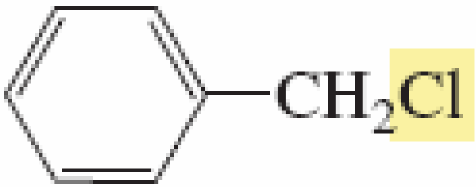
$$CH_3CH_2CH_2CH_3 \xrightarrow[125\ °C]{Br_2} CH_3CH_2CH_2CH_2Br + CH_3CH_2\overset{\overset{\displaystyle Br}{|}}{C}HCH_3$$

$$CH_3\underset{\underset{\displaystyle CH_3}{|}}{\overset{\overset{\displaystyle CH_3}{|}}{C}}CH_2CH_2\overset{\overset{\displaystyle CH_3}{|}}{C}HCH_3 \xrightarrow[125\ °C]{Br_2} CH_3\underset{\underset{\displaystyle CH_3}{|}}{\overset{\overset{\displaystyle CH_3}{|}}{C}}CH_2CH_2\underset{\underset{\displaystyle Br}{|}}{\overset{\overset{\displaystyle CH_3}{|}}{C}}CH_3$$

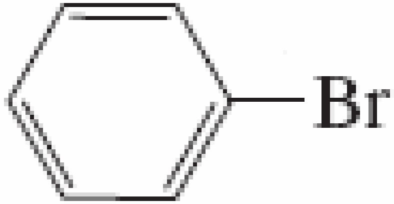
Chlorination is much less selective

REACTIONS OF ALKYL HALIDES

Very reactive



$CH_2=CHCH_2Br$



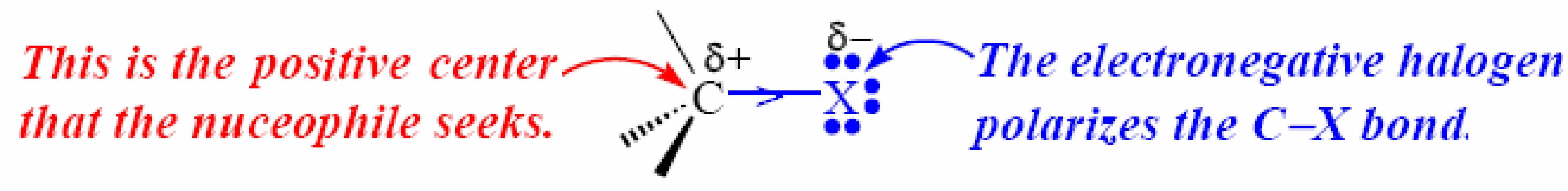
$RCH=CH-Cl$

Very unreactive

most reactive > RI > RBr > RCl > RF < least reactive

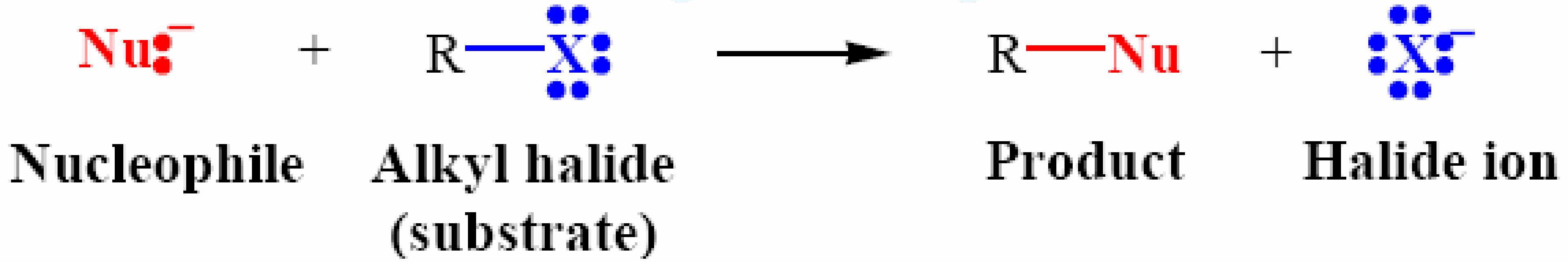
With the same R

NUCLEOPHILIC SUBSTITUTION REACTIONS



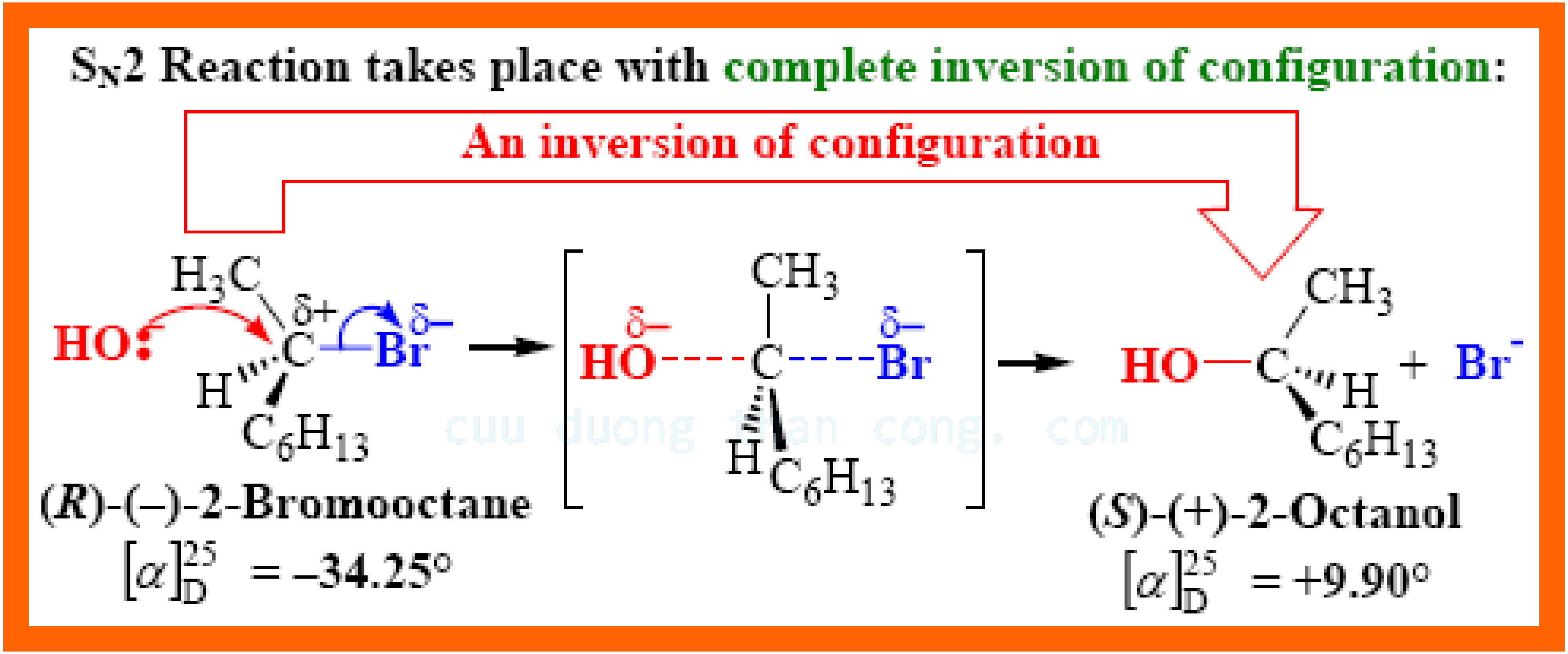
This is the positive center that the nuceophile seeks.

The electronegative halogen polarizes the C–X bond.



S_N1 vs S_N2 – depending on alkyl structure, nucleophile concentration & reactivity, and solvent

Stereochemistry of S_N2 reactions



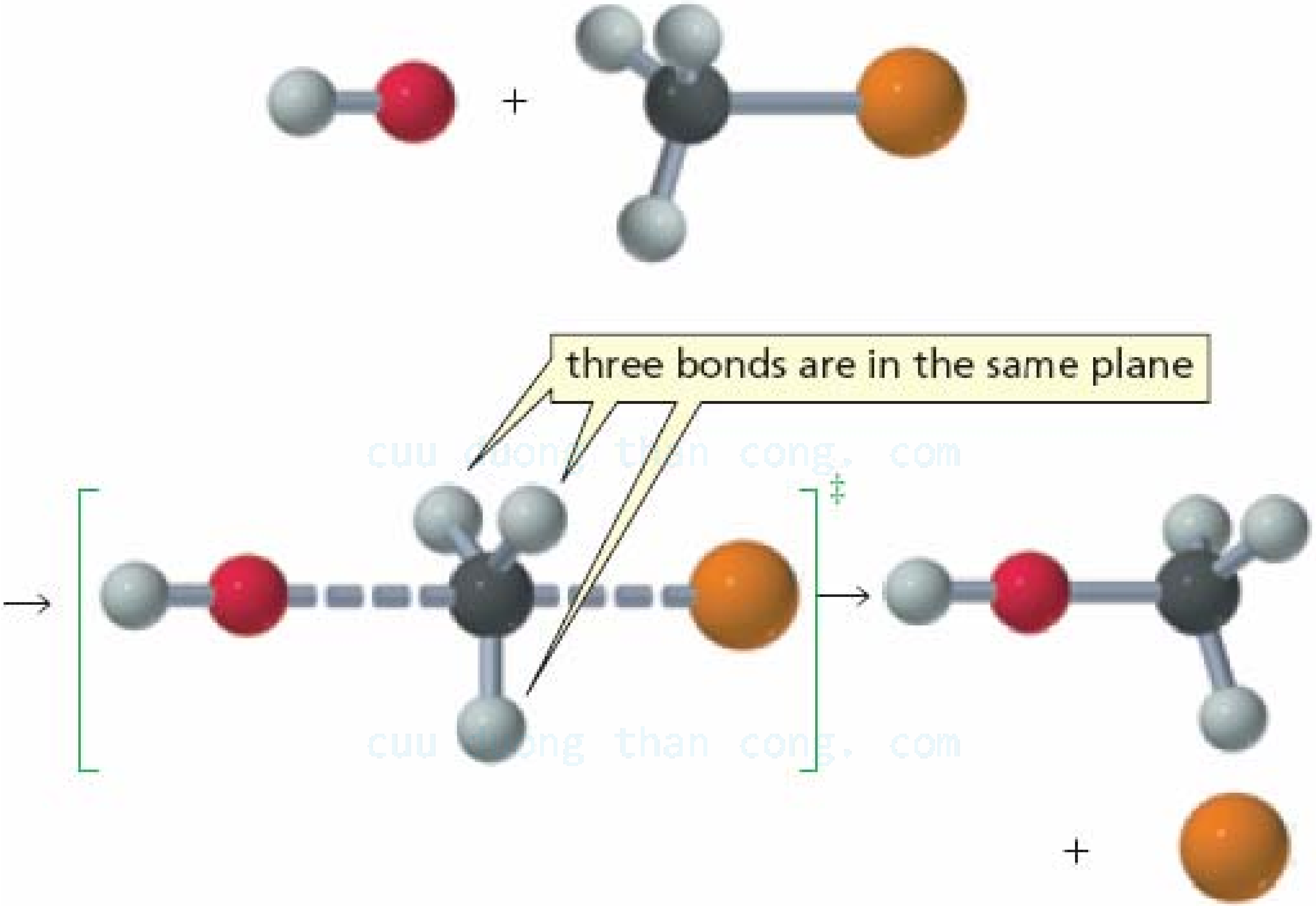
S_N2 Reaction takes place with complete inversion of configuration:

(*R*)-(–)-2-Bromooctane $[\alpha]_D^{25} = -34.25°$

(*S*)-(+)-2-Octanol $[\alpha]_D^{25} = +9.90°$

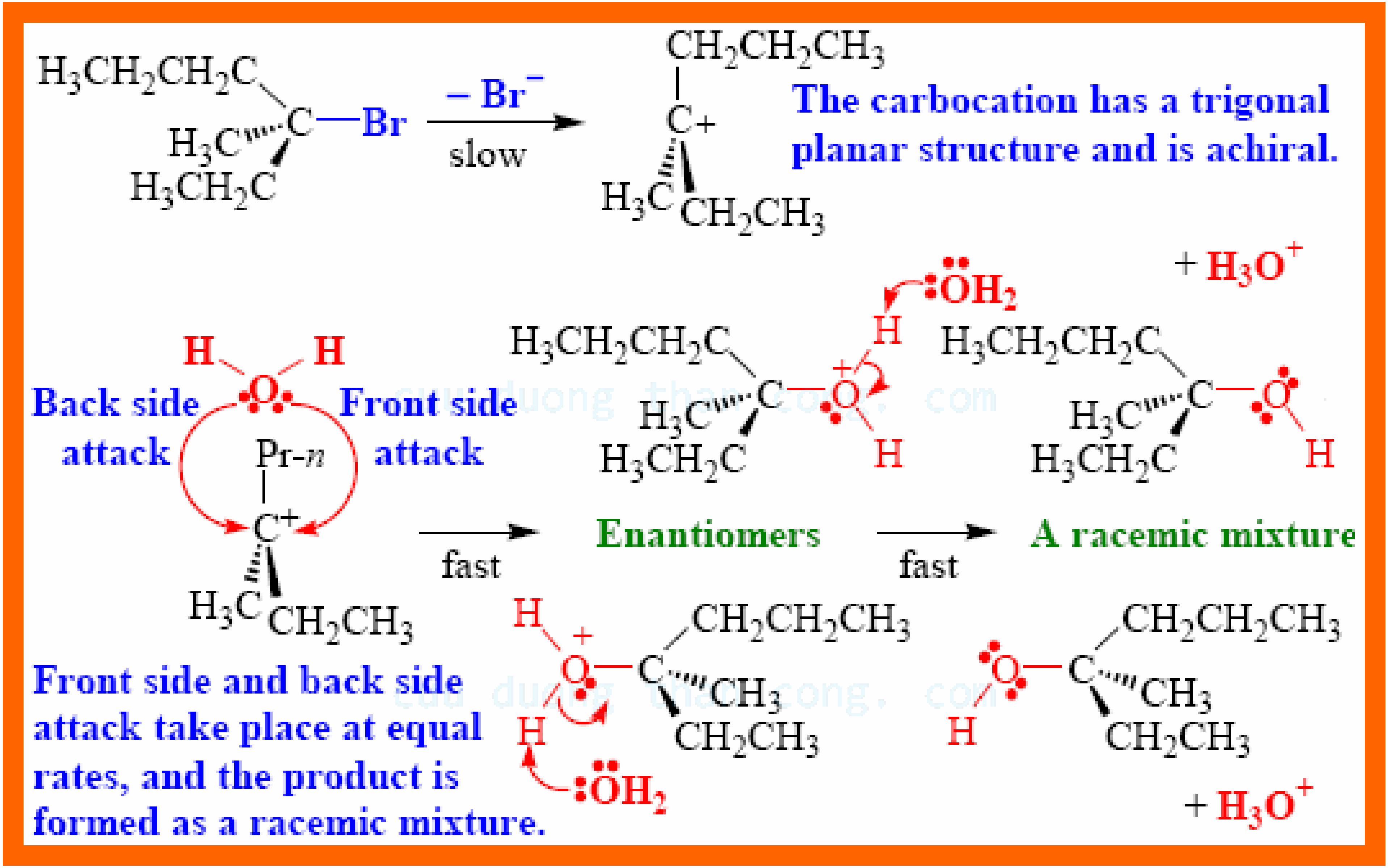
- The nucleophile attacks from the back side / the side directly opposite the leaving group

- This attacks causes an inversion of configuration



three bonds are in the same plane

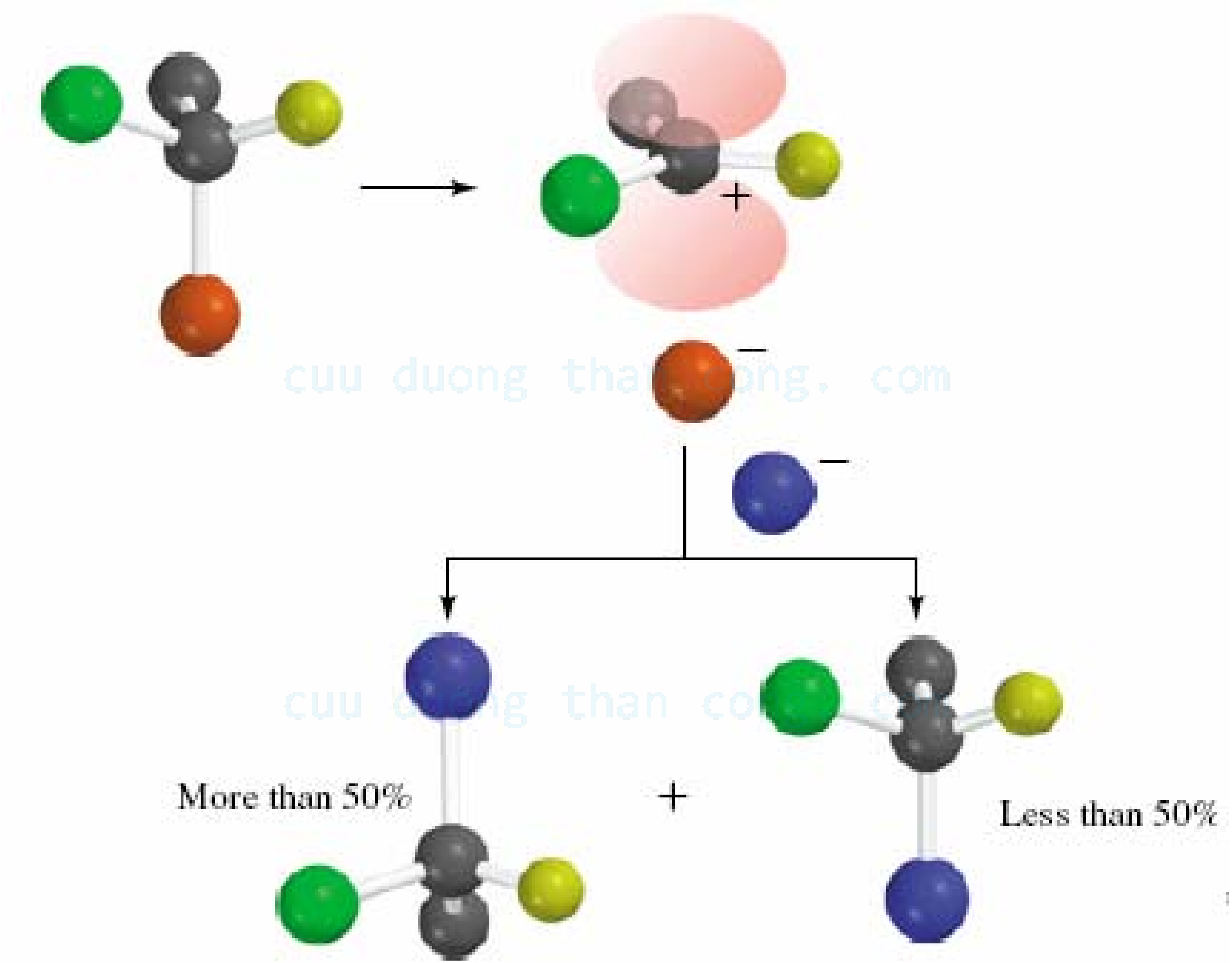
Stereochemistry of S_N1 reactions



The carbocation has a trigonal planar structure and is achiral.

Front side and back side attack take place at equal rates, and the product is formed as a racemic mixture.

However, __few__ S_N1 reactions occur with complete racemization



Factors affecting the rates of S_N1 & S_N2

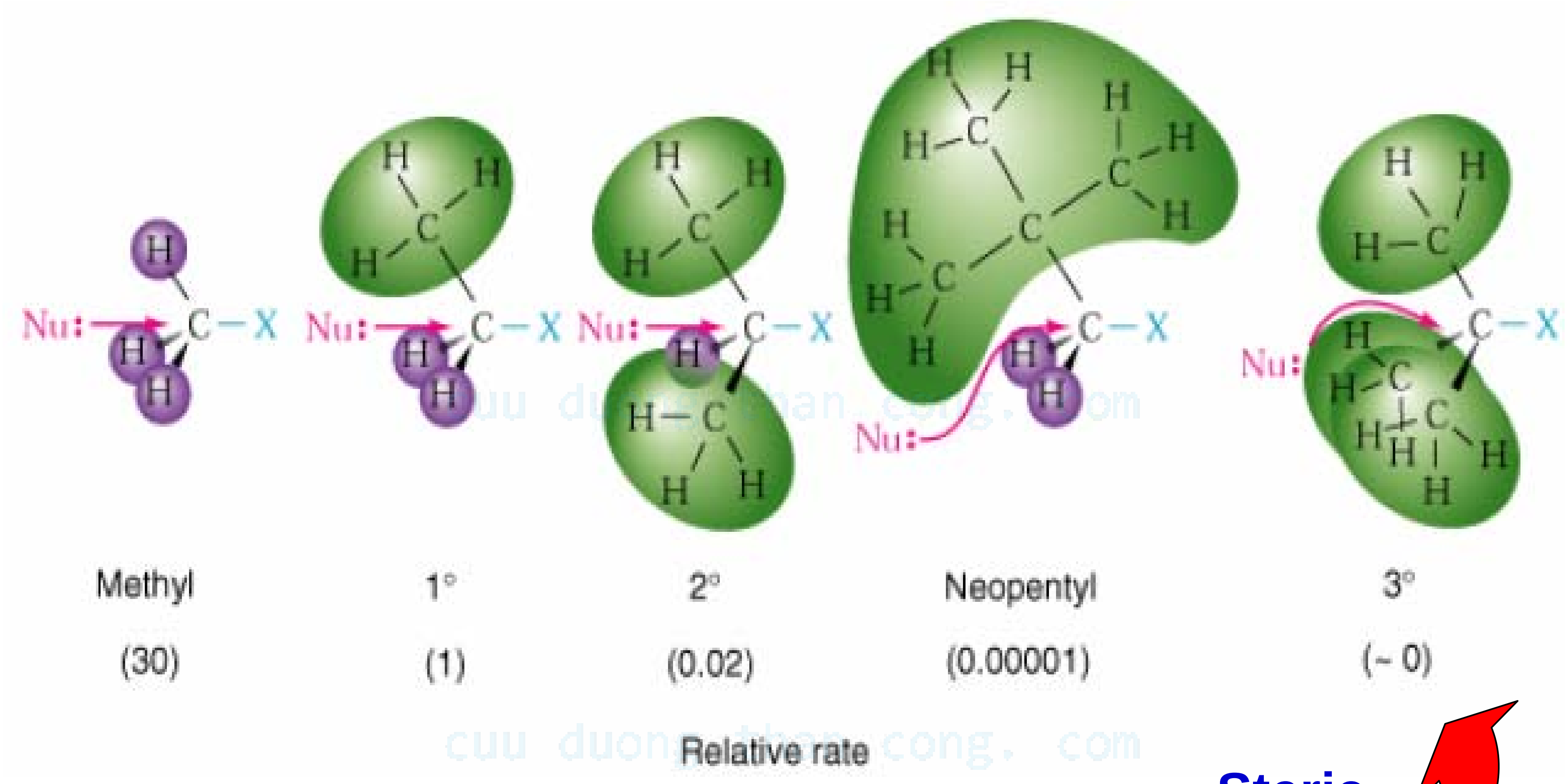
1. **The structure of the substrate**

2. **The concentration & reactivity of the nucleophile**

3. **The reaction solvent**

4. **The nature of the leaving group**

Affects of substrate structure

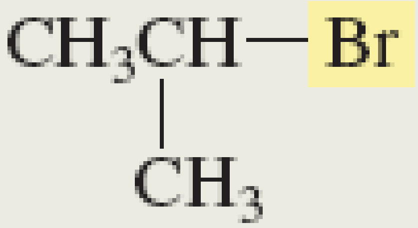
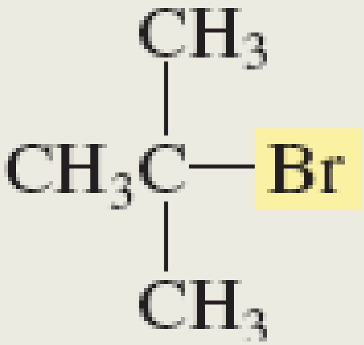


Steric hindrance

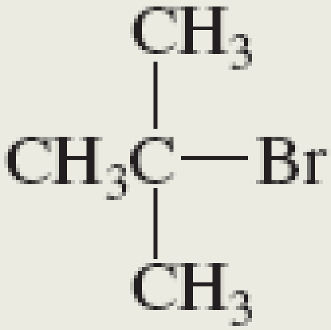
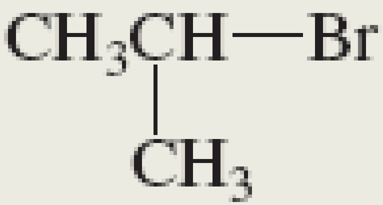
Steric effect in the S_N2 reaction

Relative Rates of S_N2 Reactions for Several Alkyl Halides

$$R{-}Br + Cl^- \xrightarrow{S_N2} R{-}Cl + Br^-$$

Alkyl halide	Class of alkyl halide	Relative rate
$CH_3{-}Br$	methyl	1200
$CH_3CH_2{-}Br$	primary	40
$CH_3CH_2CH_2{-}Br$	primary	16
 $CH_3\underset{\displaystyle CH_3}{\underset{\vert}{CH}}{-}Br$	secondary	1
 $CH_3\overset{\displaystyle CH_3}{\overset{\vert}{\underset{\displaystyle CH_3}{\underset{\vert}{C}}}}{-}Br$	tertiary	too slow to measure

Relative Rates of S_N1 Reactions for Several Alkyl Bromides (solvent is H_2O, nucleophile is H_2O)

Alkyl bromide	Class of alkyl bromide	Relative rate
 $(CH_3)_3C{-}Br$	tertiary	1,200,000
 $CH_3CH(CH_3){-}Br$	secondary	11.6
$CH_3CH_2{-}Br$	primary	1.00*
$CH_3{-}Br$	methyl	1.05*

*Although the rate of the S_N1 reaction of this compound with water is 0, a small rate is observed as a result of an S_N2 reaction relative reactivities of alkyl halides in an S_N2 reaction

most reactive

methyl halide > 1° alkyl halide >

2° alkyl halide > 3° alkyl halide

least reactive

The primary factor that determines the reactivity of organic substrates in an S_N1 reaction is the relative stability of the carbocation that is formed

relative reactivities of alkyl halides in an S_N1 reaction

most reactive

3° alkyl halide > 2° alkyl halide

> 1° alkyl halide

least reactive

Affects of nucleophile concentration & strength

1) Neither the concentration nor the structure of the nucleophile affects the rates of S_N1 reactions since the nucleophile does not participate in the rate-determining step

2) The rates of S_N2 reactions depend on both the concentration and the structure of the nucleophile

$$Nu^{-} + CH_3Br \xrightarrow{S_N2} NuCH_3 + Br^{-}$$

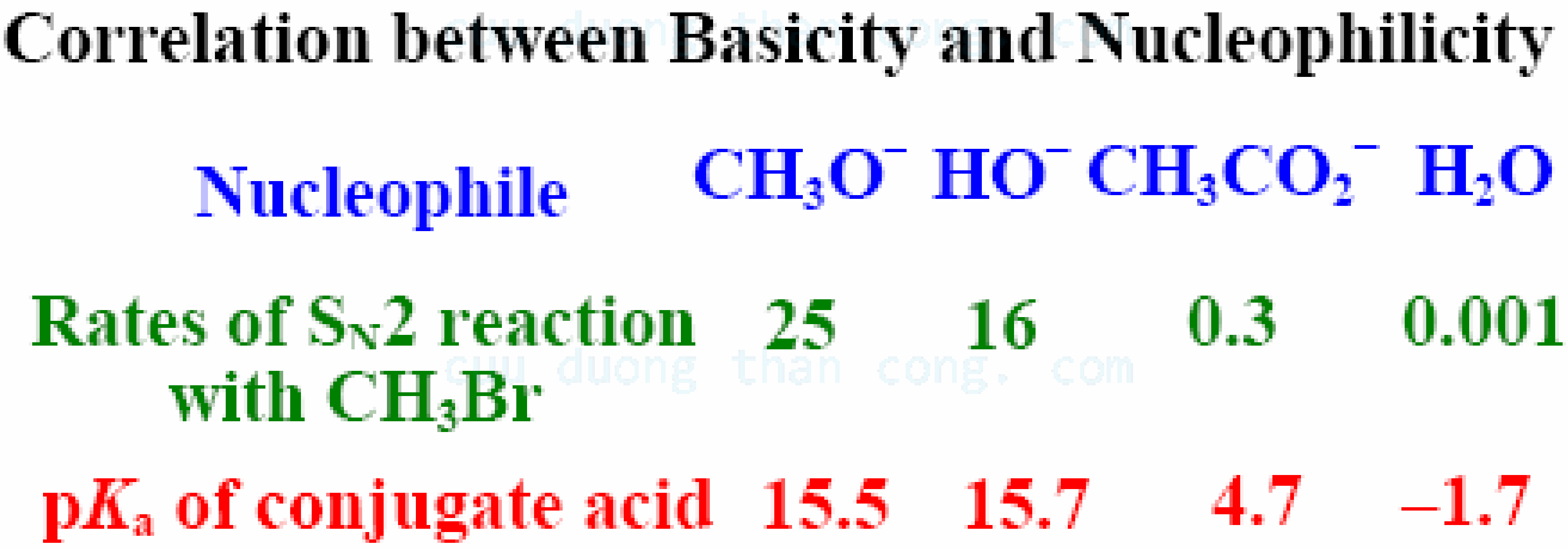
aqueous ethanol:

Nu =	HS^{-}	CN^{-}	I^{-}
Relative reactivity	125,000	125,000	100,000

CH_3O^{-}	HO^{-}	Cl^{-}	NH_3	H_2O
25,000	16,000	1,000	700	1

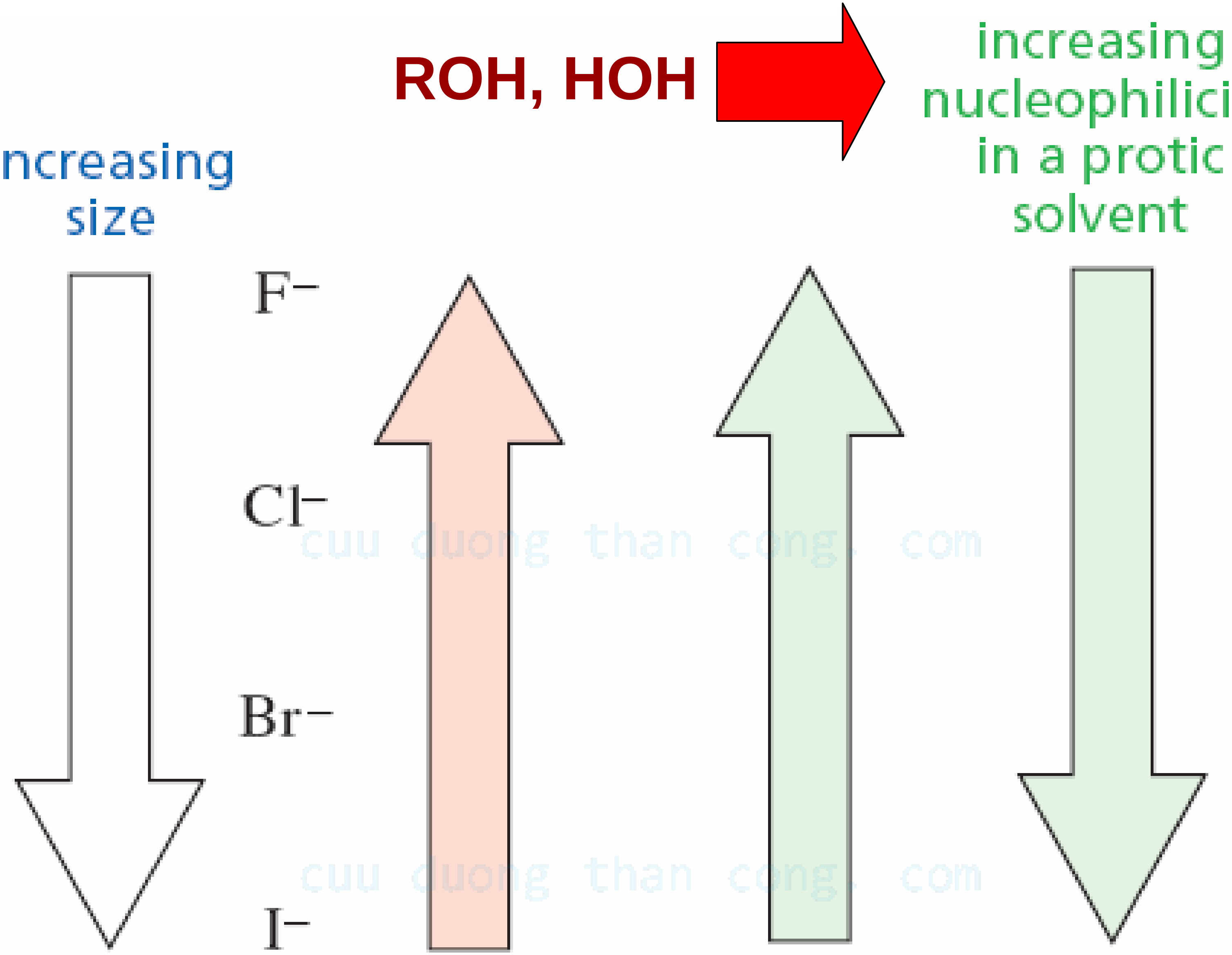
Nucleophiles that have the same attacking atom: nucleophilicity roughly parallels basicity:

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



Correlation between Basicity and Nucleophilicity

Nucleophile	CH_3O^-	HO^-	$CH_3CO_2^-$	H_2O
Rates of S_N2 reaction with CH_3Br	25	16	0.3	0.001
pK_a of conjugate acid	15.5	15.7	4.7	–1.7



ROH, HOH

increasing nucleophilicity in a protic solvent

increasing size

F⁻

Cl⁻

Br⁻

I⁻

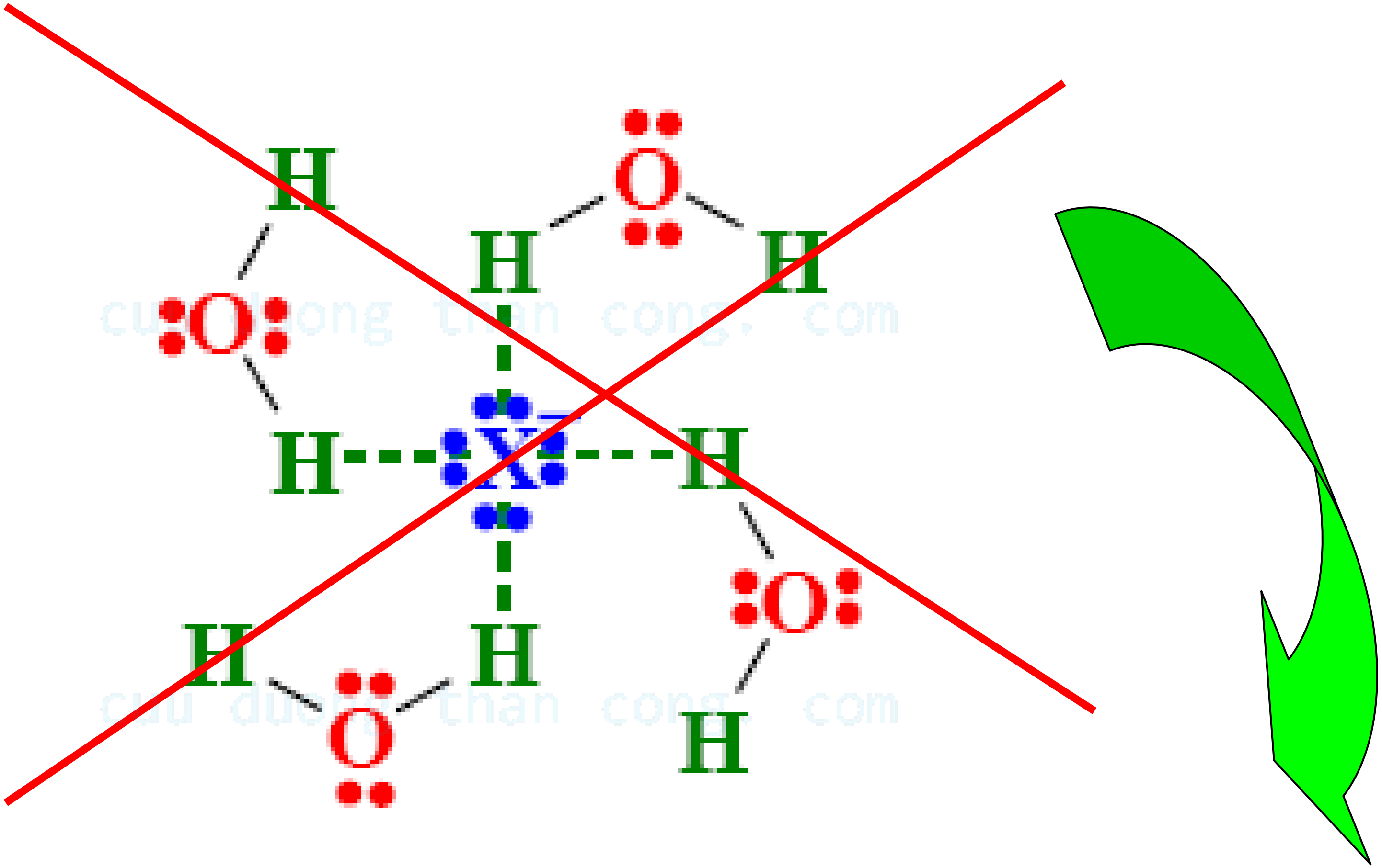
increasing basicity

increasing nucleophilicity in the gas phase

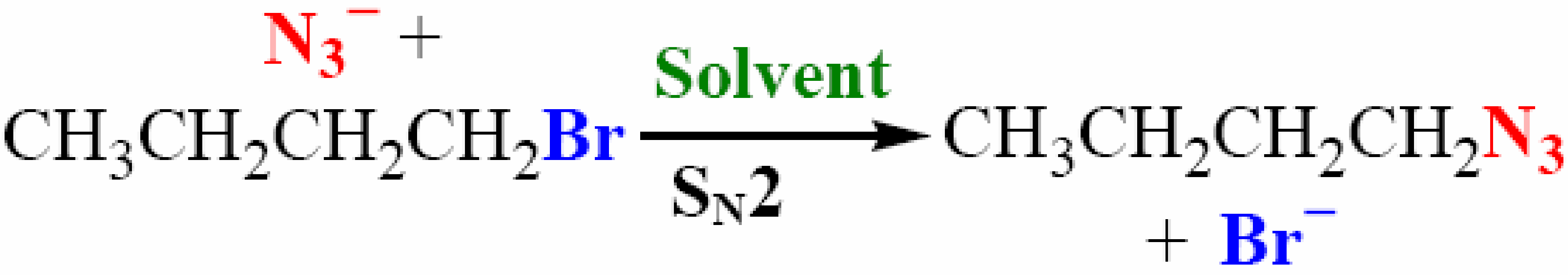
Affects of solvents on S_N2

- ***In <u>polar aprotic solvent</u>, nuceophilicity parallels basicity***

Polar aprotic solvents <u>solvate cation</u> but not anions



Rates of S_N2 reactions are generally increased in <u>polar aprotic solvent</u>

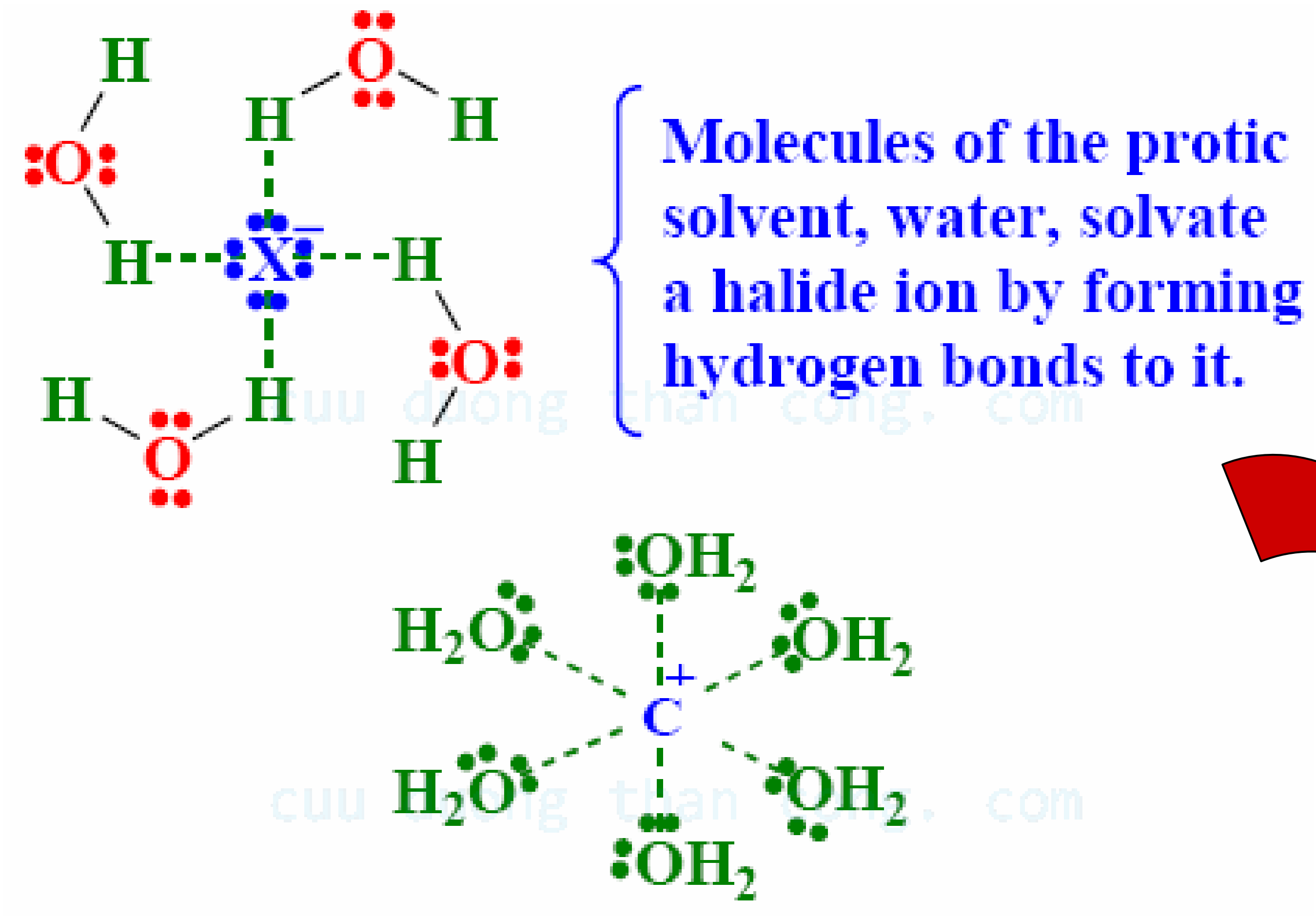


$$N_3^- + CH_3CH_2CH_2CH_2Br \xrightarrow[S_N2]{\text{Solvent}} CH_3CH_2CH_2CH_2N_3 + Br^-$$

Solvent	HMPA	CH_3CN	DMF	DMSO	H_2O	CH_3OH
Relative reactivity	200,000	5,000	2,800	1,300	6.6	1

Affects of solvents on S_N1

Polar protic solvents <u>solvate cation & anions</u> effectively



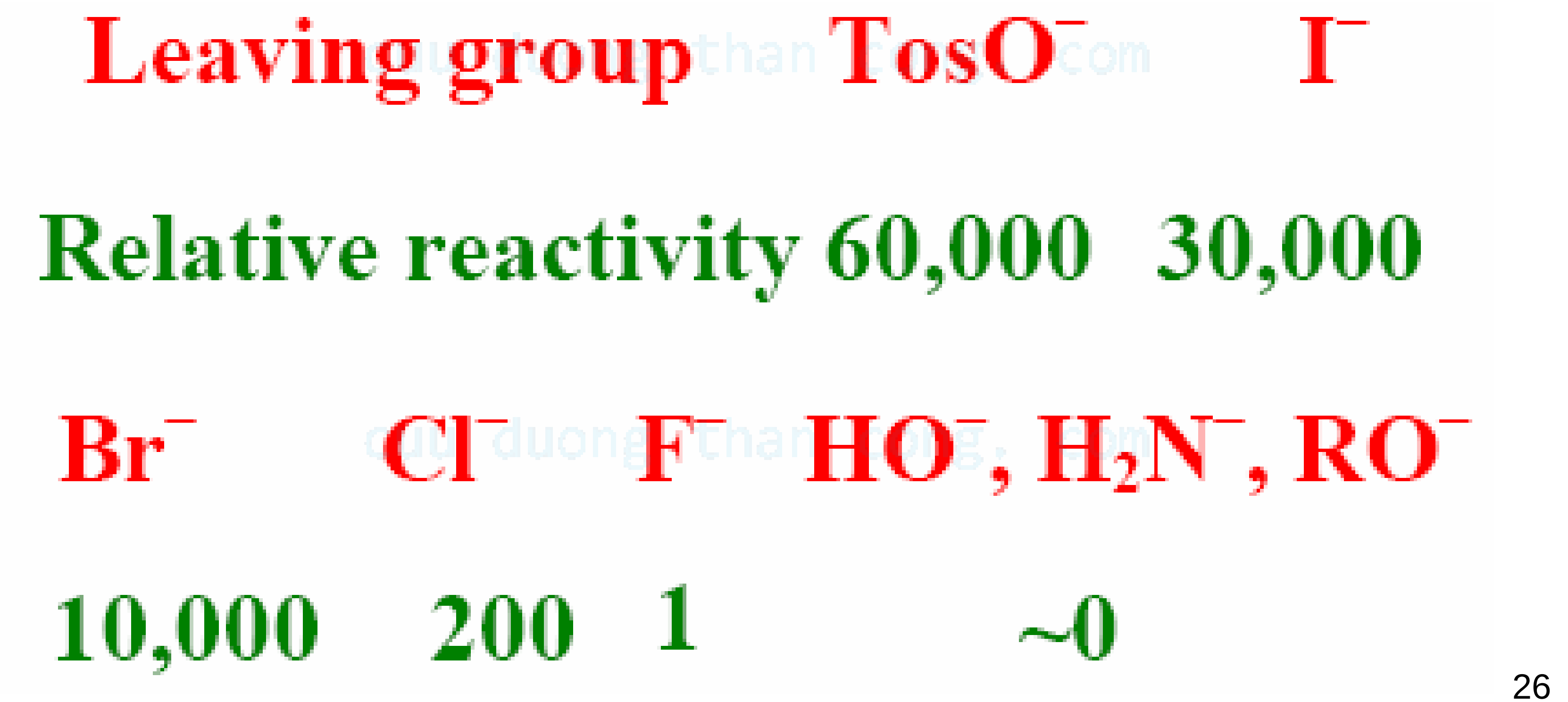
Molecules of the protic solvent, water, solvate a halide ion by forming hydrogen bonds to it.

Rates of S_N1 reactions are generally increased in <u>polar protic solvent</u>

Affects of leaving group

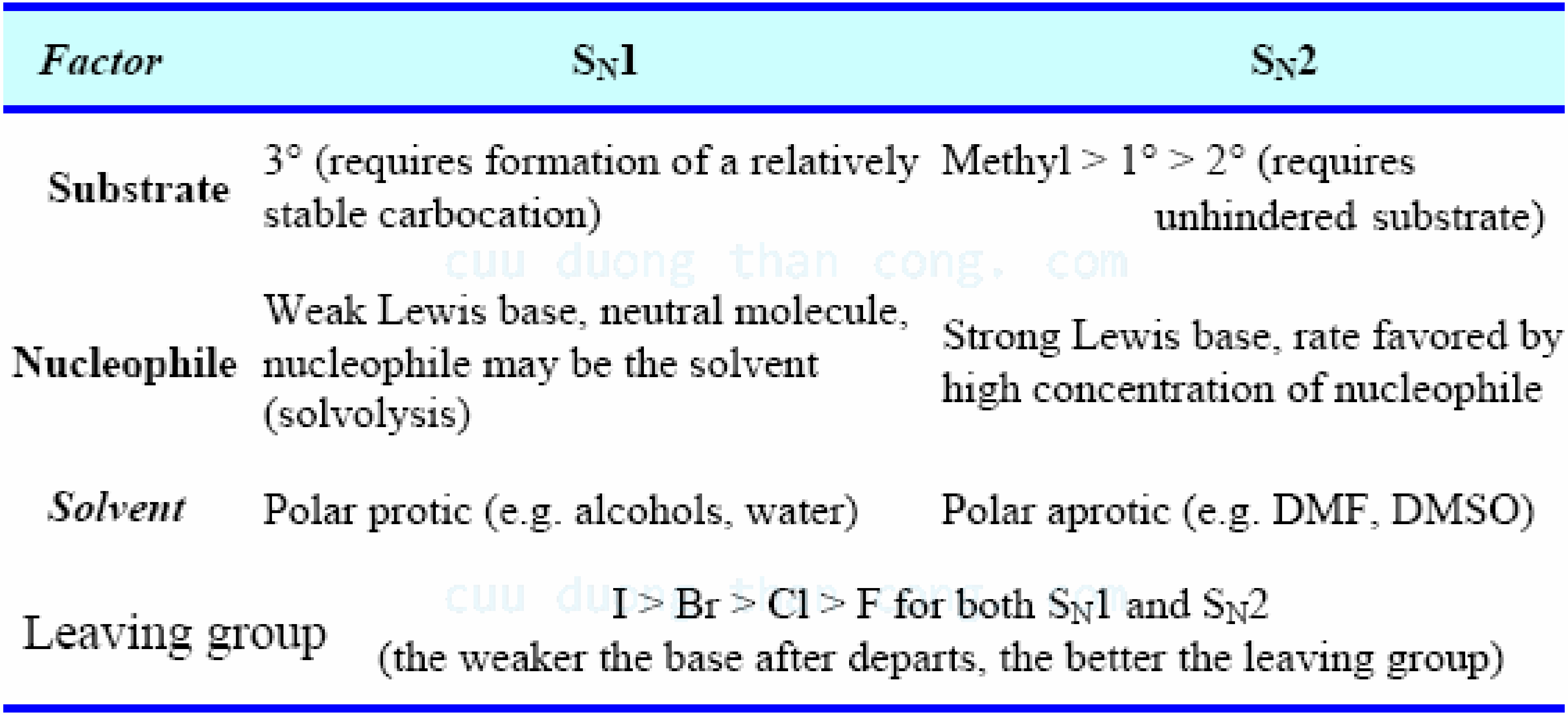
The best leaving groups are those that become the most stable ions after they depart

The best leaving groups are <u>weak bases</u>



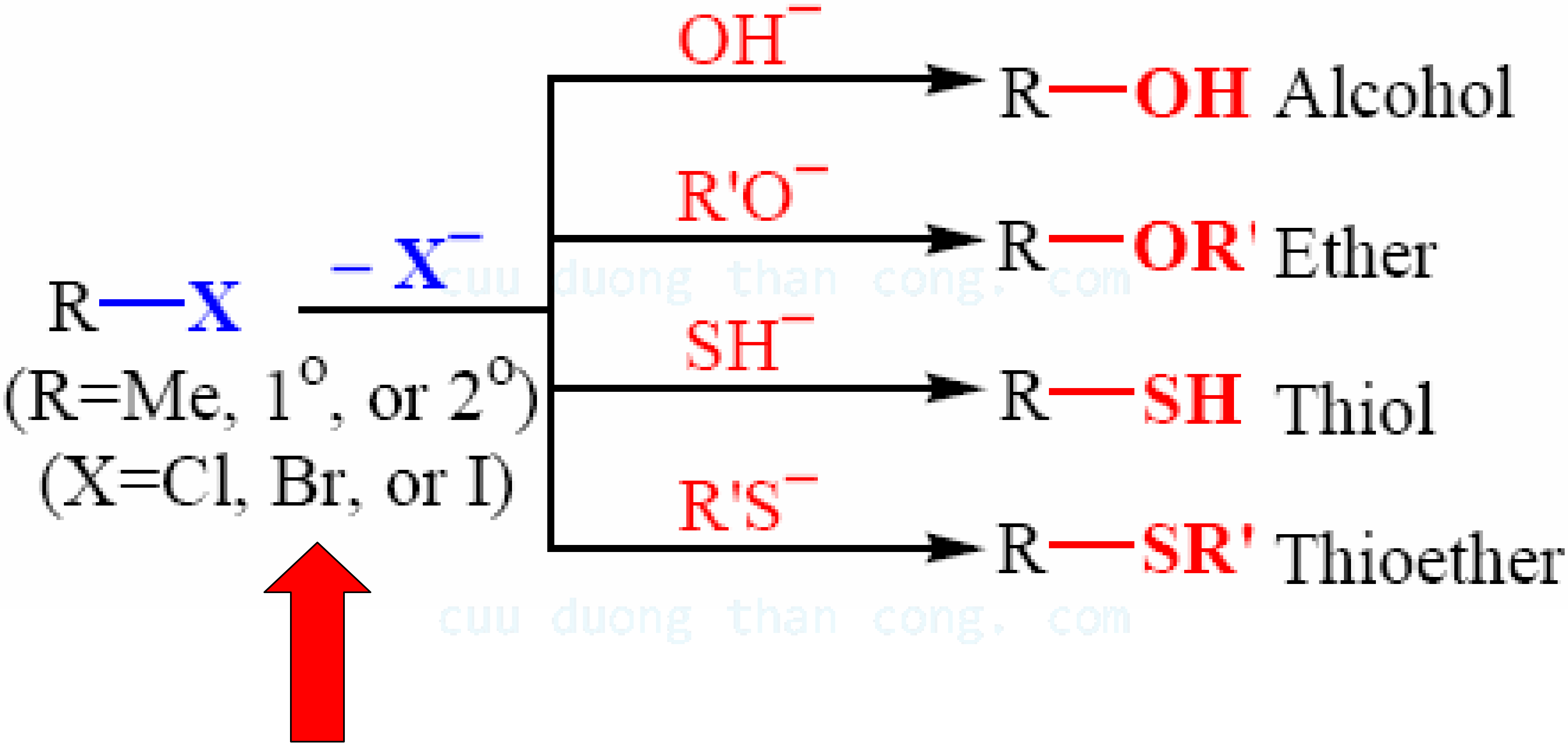
Leaving group	$TosO^-$	I^-	Br^-	Cl^-	F^-	HO^-, H_2N^-, RO^-
Relative reactivity	60,000	30,000	10,000	200	1	~0

S_N1 *vs* S_N2

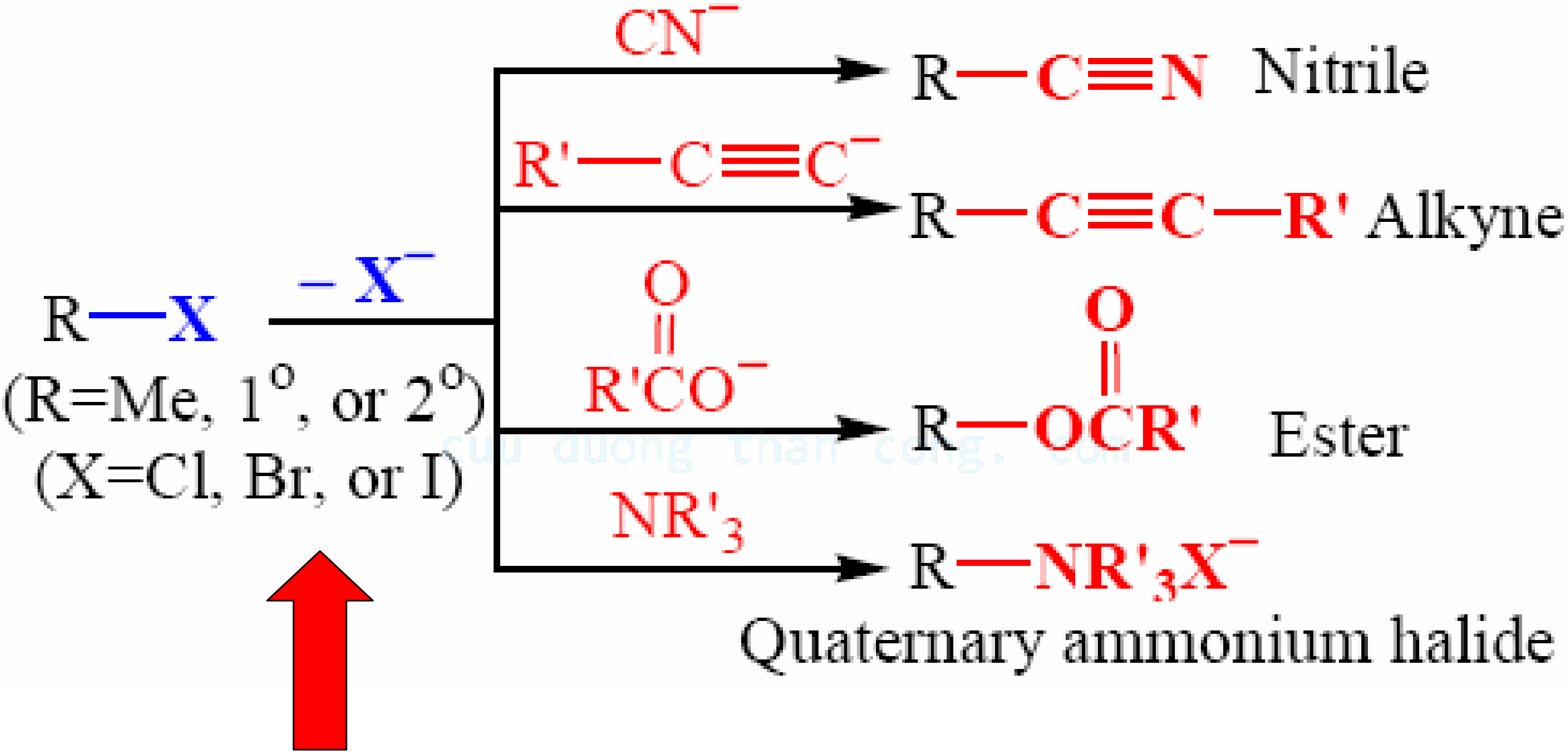


Factor	S_N1	S_N2
Substrate	3° (requires formation of a relatively stable carbocation)	Methyl > 1° > 2° (requires unhindered substrate)
Nucleophile	Weak Lewis base, neutral molecule, nucleophile may be the solvent (solvolysis)	Strong Lewis base, rate favored by high concentration of nucleophile
Solvent	Polar protic (e.g. alcohols, water)	Polar aprotic (e.g. DMF, DMSO)
Leaving group	I > Br > Cl > F for both S_N1 and S_N2 (the weaker the base after departs, the better the leaving group)	

Functional group interconversions of 1º & 2º alkyl halides



Elimination reactions will occur for 3º alkyl halides



Elimination reactions will occur for 3^o alkyl halides

Williamson ether synthesis

$$ROH + Na \longrightarrow RO^- + Na^+ + \tfrac{1}{2}H_2$$

$$ROH + NaH \longrightarrow RO^- + Na^+ + H_2$$

$CH_3CH_2CH_2Br$ +
propyl bromide

$CH_3CH_2CH_2CH_2O^-$
butoxide ion

$\longrightarrow CH_3CH_2CH_2OCH_2CH_2CH_2CH_3$
butyl propyl ether

$+ Br^-$

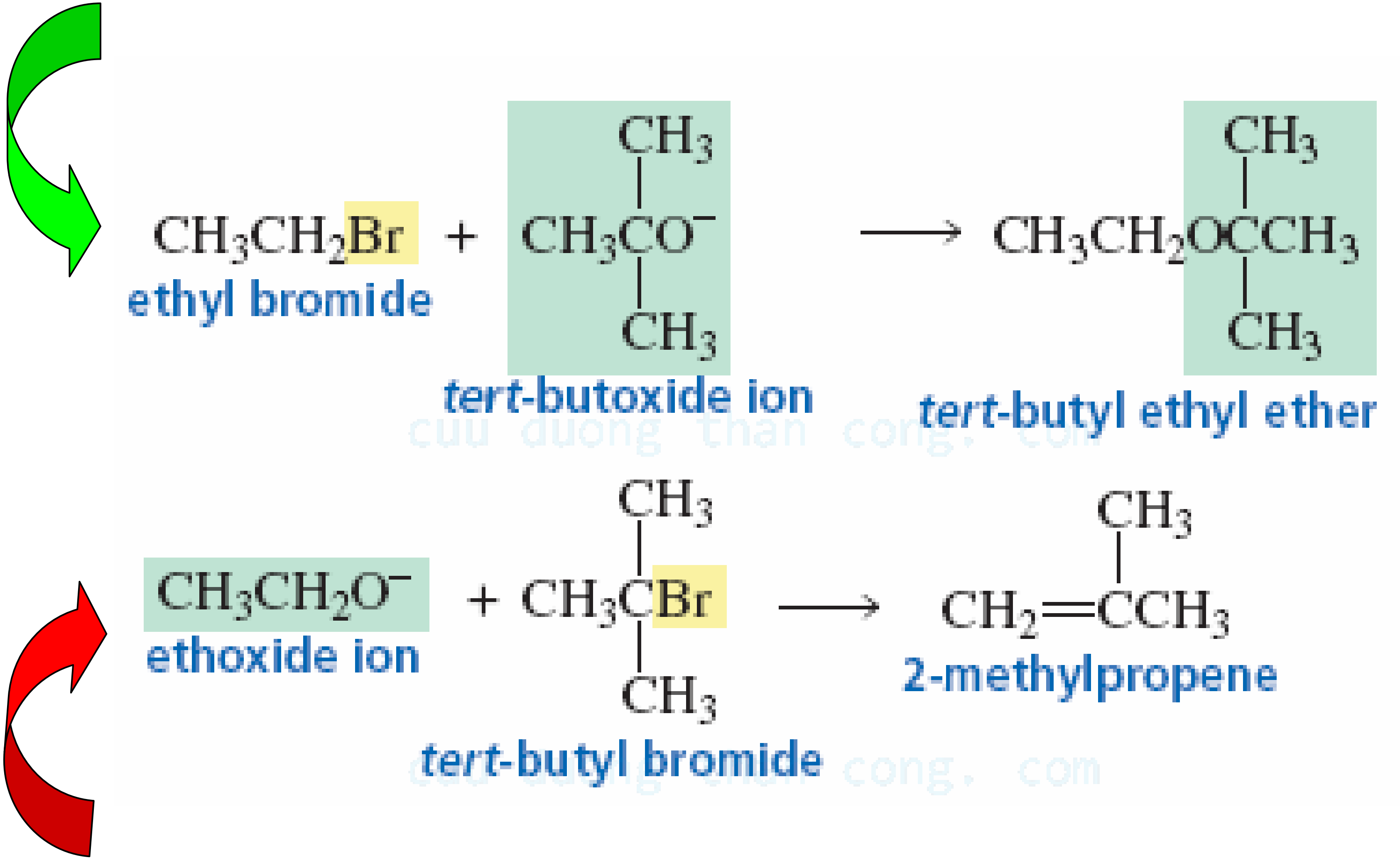
$CH_3CH_2CH_2CH_2Br$ +
butyl bromide

$CH_3CH_2CH_2O^-$
propoxide ion

$\longrightarrow CH_3CH_2CH_2OCH_2CH_2CH_2CH_3$
butyl propyl ether

$+ Br^-$

Nucleophilic substitutions

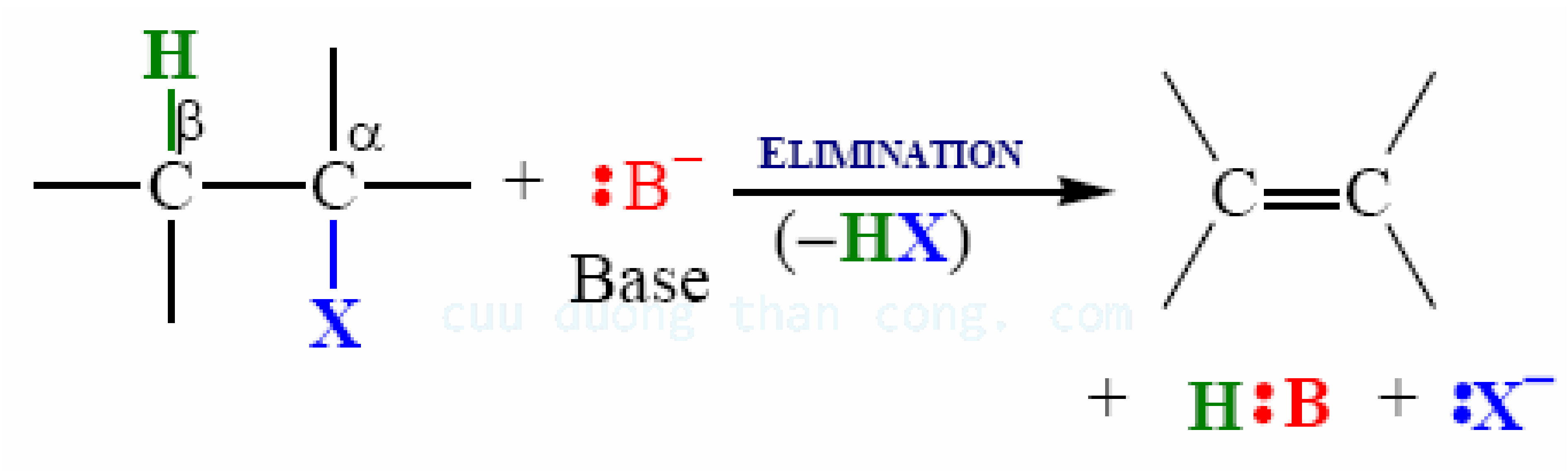


$$CH_3CH_2Br + CH_3\overset{CH_3}{\underset{CH_3}{C}}O^- \longrightarrow CH_3CH_2O\overset{CH_3}{\underset{CH_3}{C}}CH_3$$

$$CH_3CH_2O^- + CH_3\overset{CH_3}{\underset{CH_3}{C}}Br \longrightarrow CH_2{=}\overset{CH_3}{C}CH_3$$

Eliminations

ELIMINATION REACTIONS



In an elimination reaction:

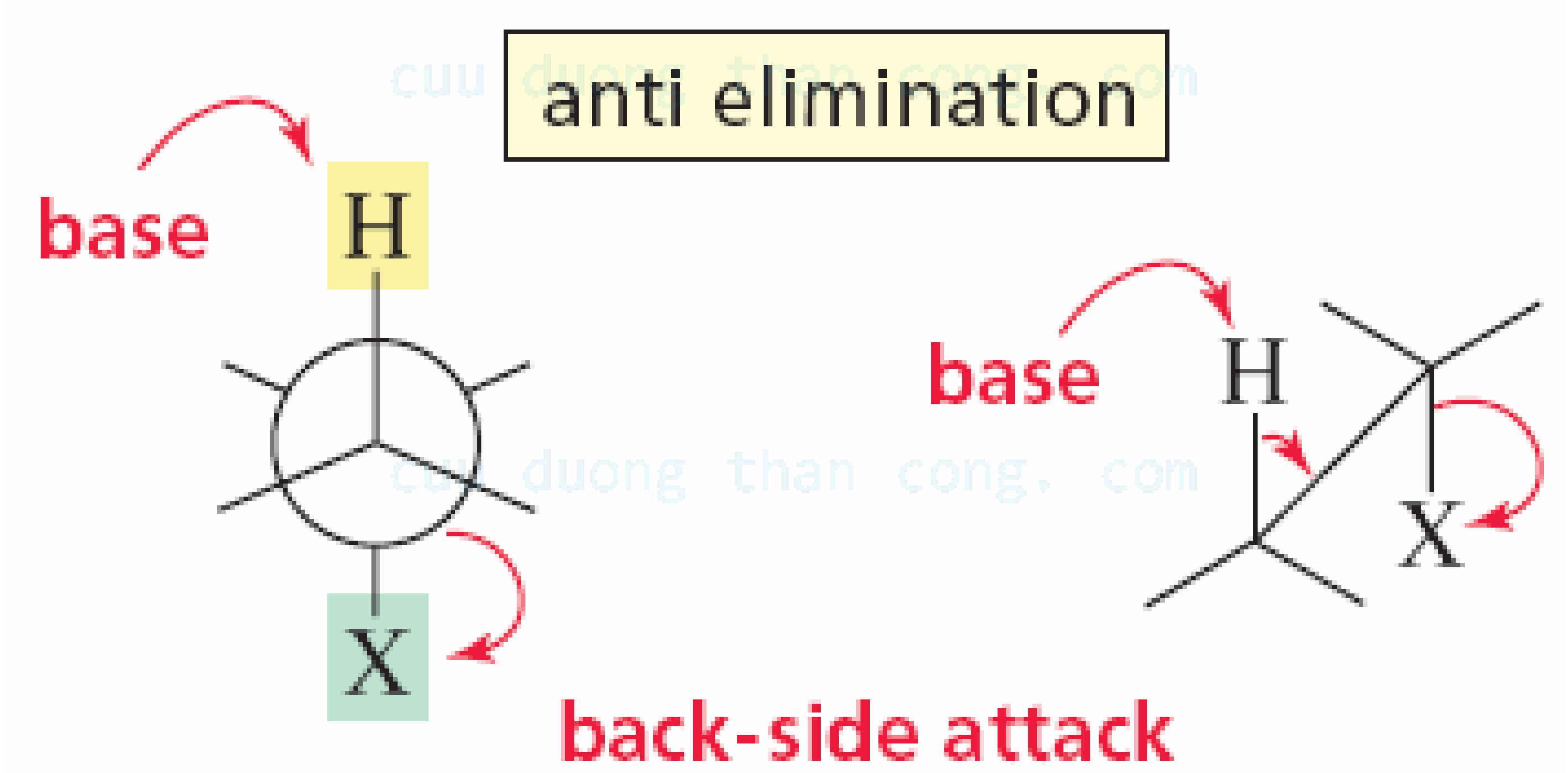
+ Groups / atoms are eliminated from a reactant

+ A double bond is formed between the 2 carbons from which atoms are eliminated

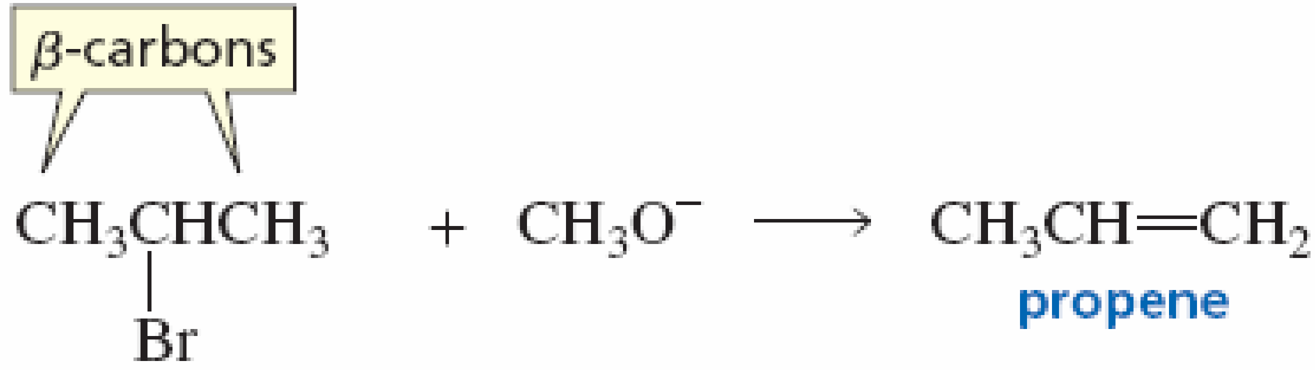
Stereochemistry of E2 reactions

- **<u>Anti-elimination</u> is highly favored in an E2 reaction**

2 groups / atoms are removed from opposite sides of C-C bond



Regioselectivity of E2 reactions



$$\underset{\displaystyle Br}{CH_3\underset{|}{C}HCH_3} + CH_3O^- \longrightarrow CH_3CH{=}CH_2$$

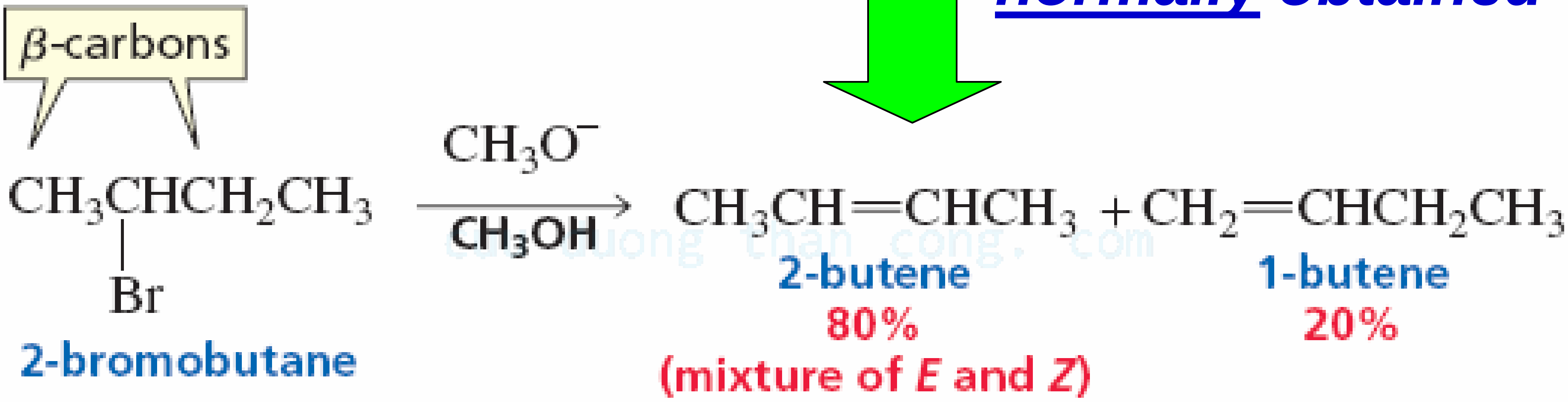
2-bromopropane

propene

Zaitsev's rule for an E2 reaction:

more substituted alkene is

<u>normally</u> obtained



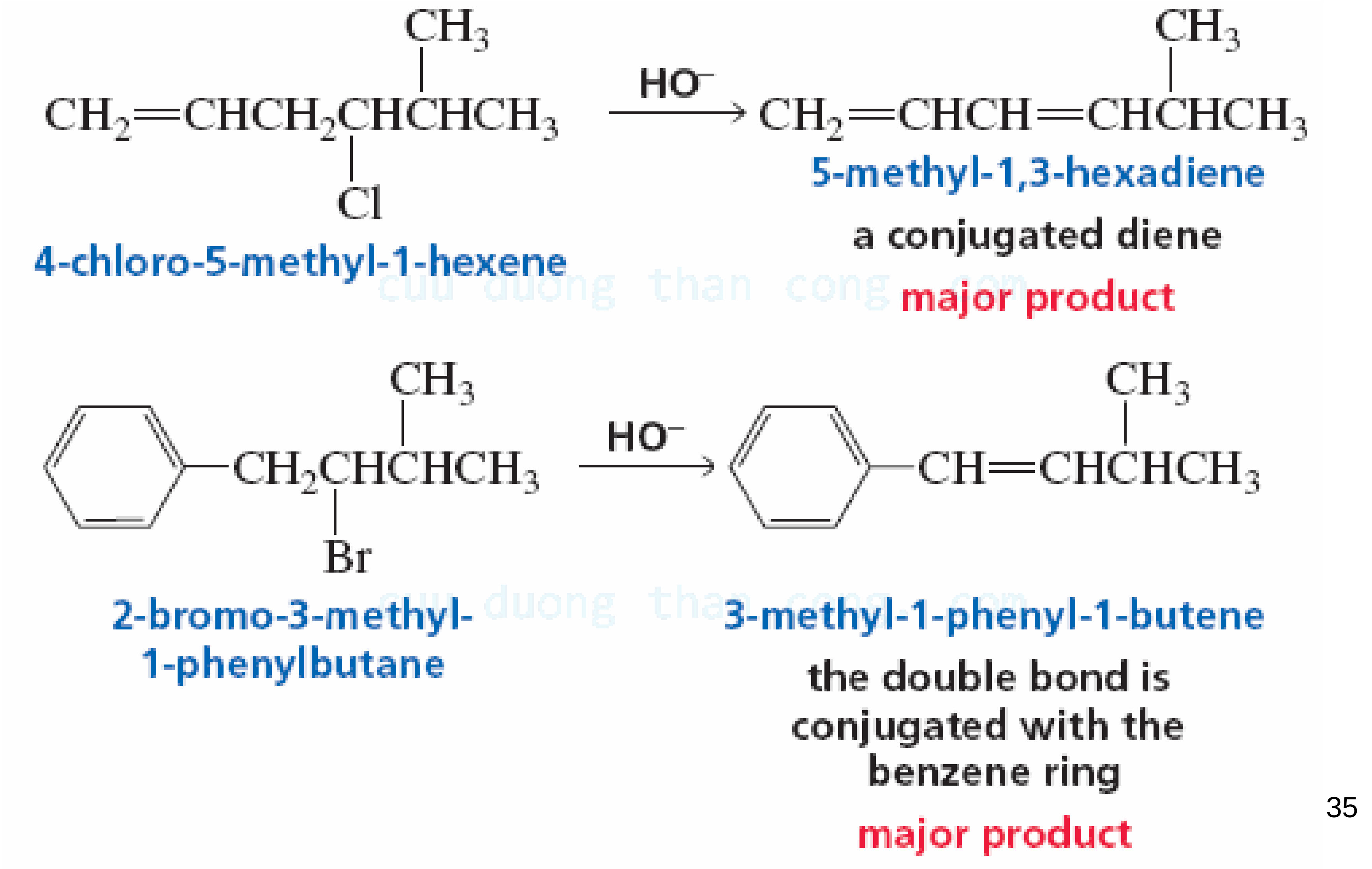
$$\underset{\displaystyle Br}{CH_3\underset{|}{C}HCH_2CH_3} \xrightarrow[CH_3OH]{CH_3O^-} CH_3CH{=}CHCH_3 + CH_2{=}CHCH_2CH_3$$

2-bromobutane

2-butene
80%
(mixture of *E* and *Z*)

1-butene
20%

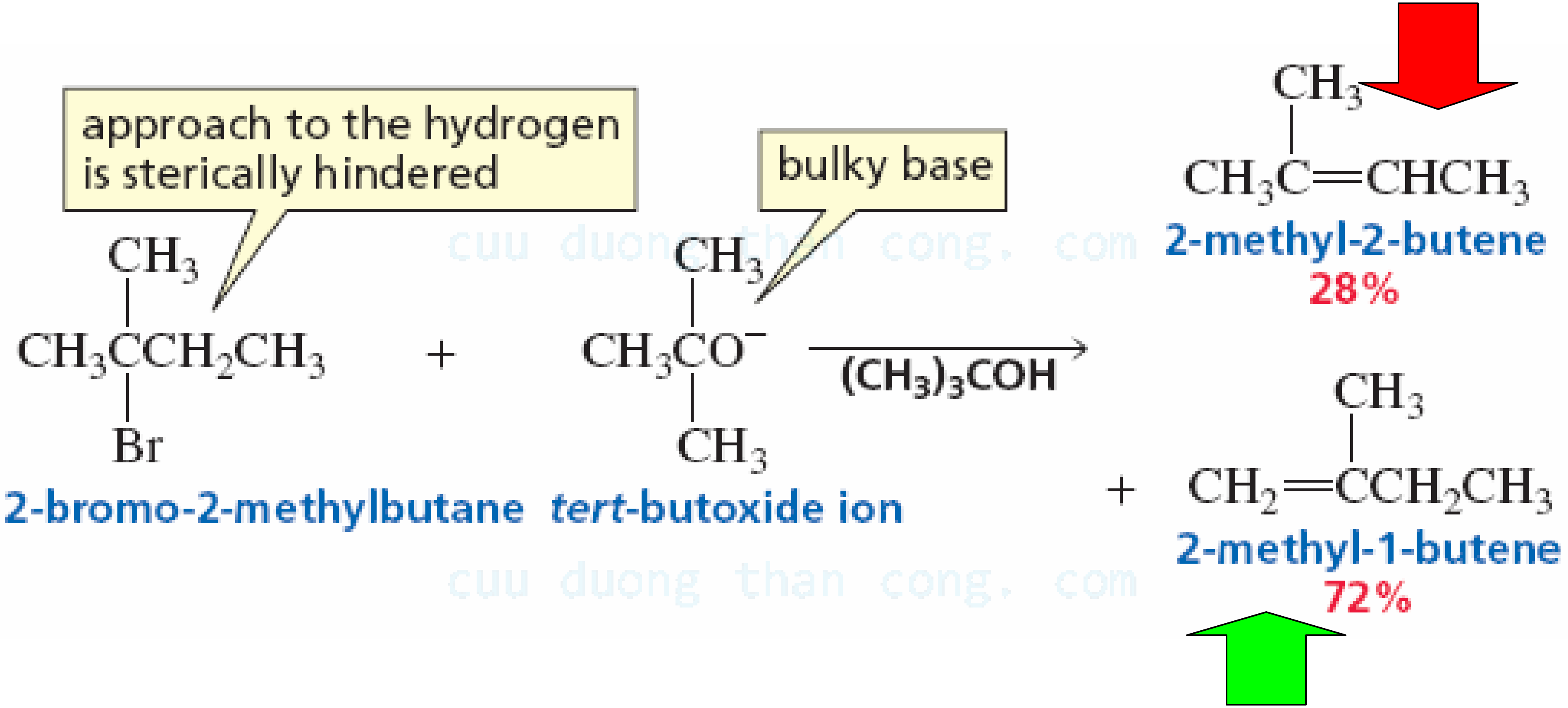
Keep in mind that the major product of an E2 reaction is <u>always</u> the more stable alkene (not always the more substituted alkene)



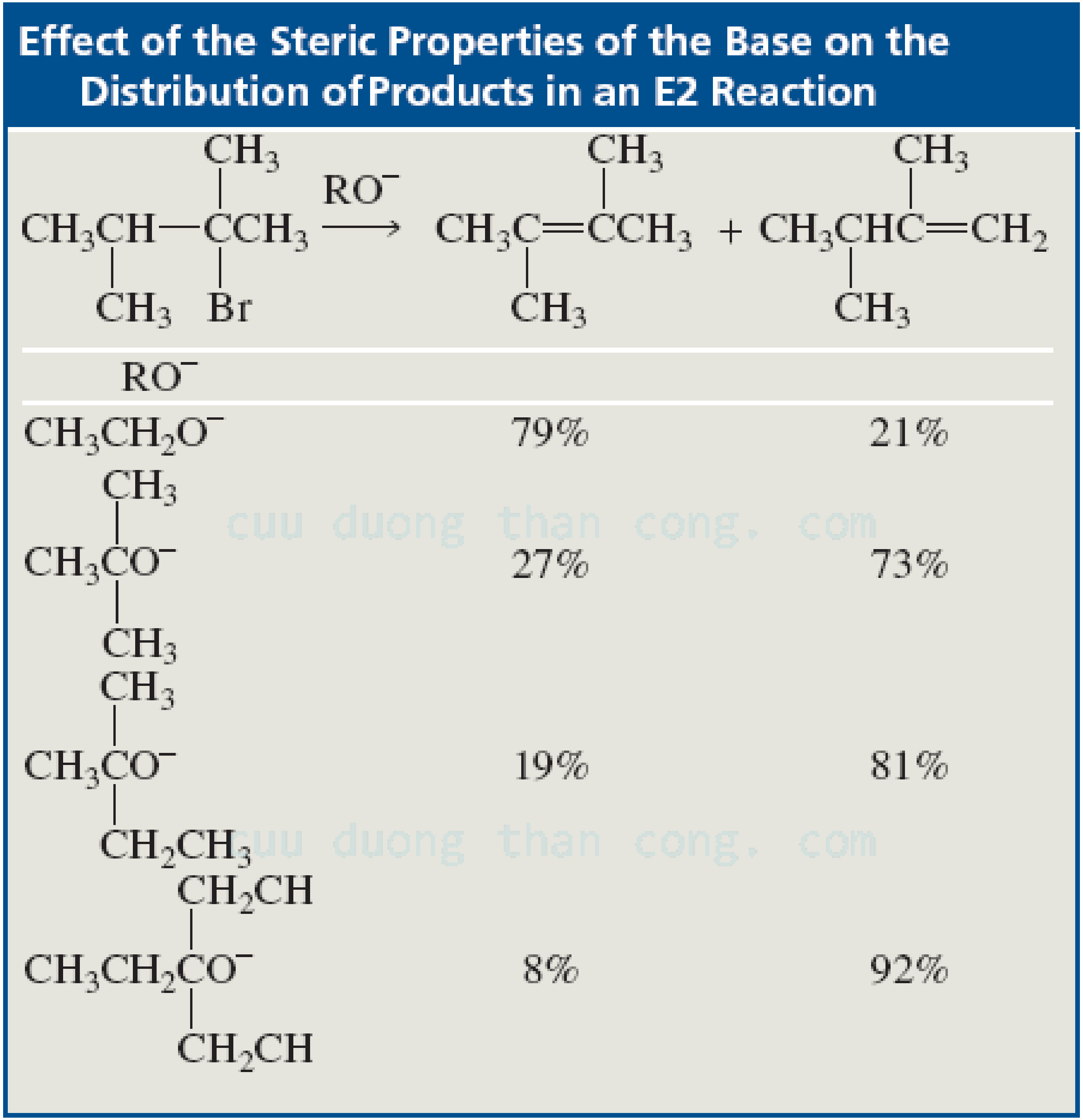
$$CH_2{=}CHCH_2\underset{\large Cl}{CH}\overset{\large CH_3}{CH}CH_3 \xrightarrow{HO^-} CH_2{=}CHCH{=}CH\overset{\large CH_3}{CH}CH_3$$

In some E2 reactions, the less stable alkene is the major product due to <u>steric effects</u>

Zaitsev's product



Hofmann's product

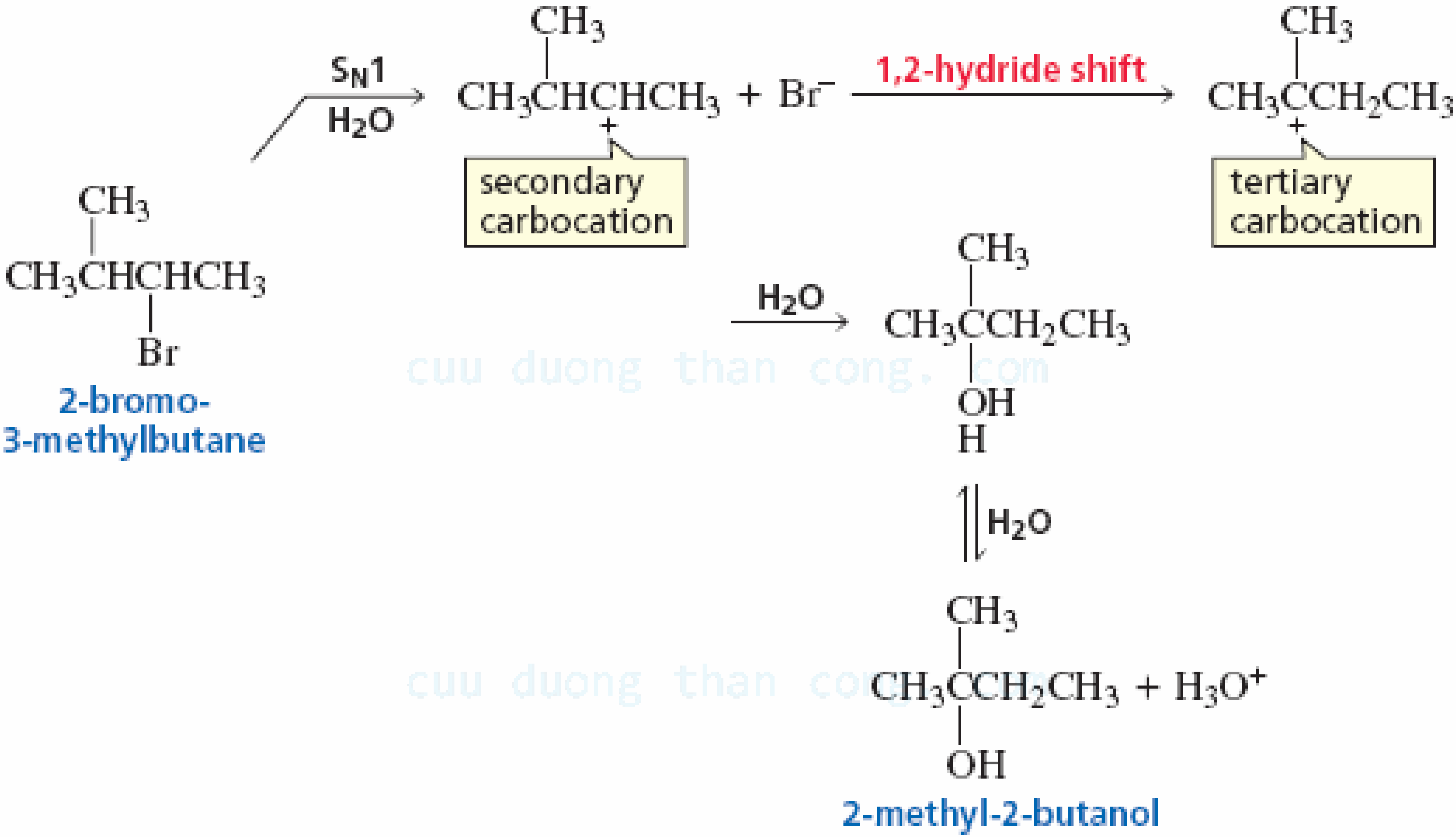


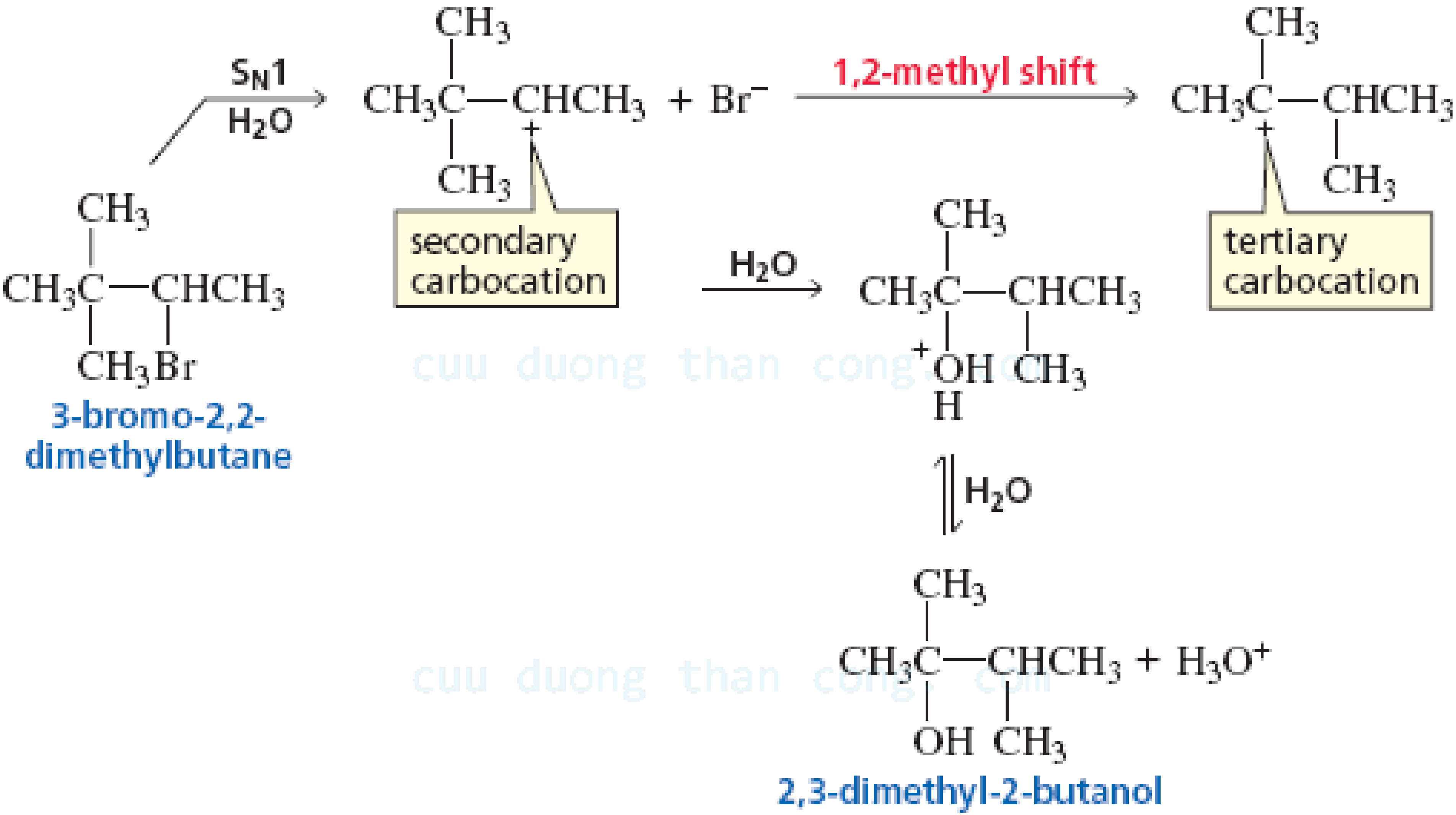
Effect of the Steric Properties of the Base on the Distribution of Products in an E2 Reaction

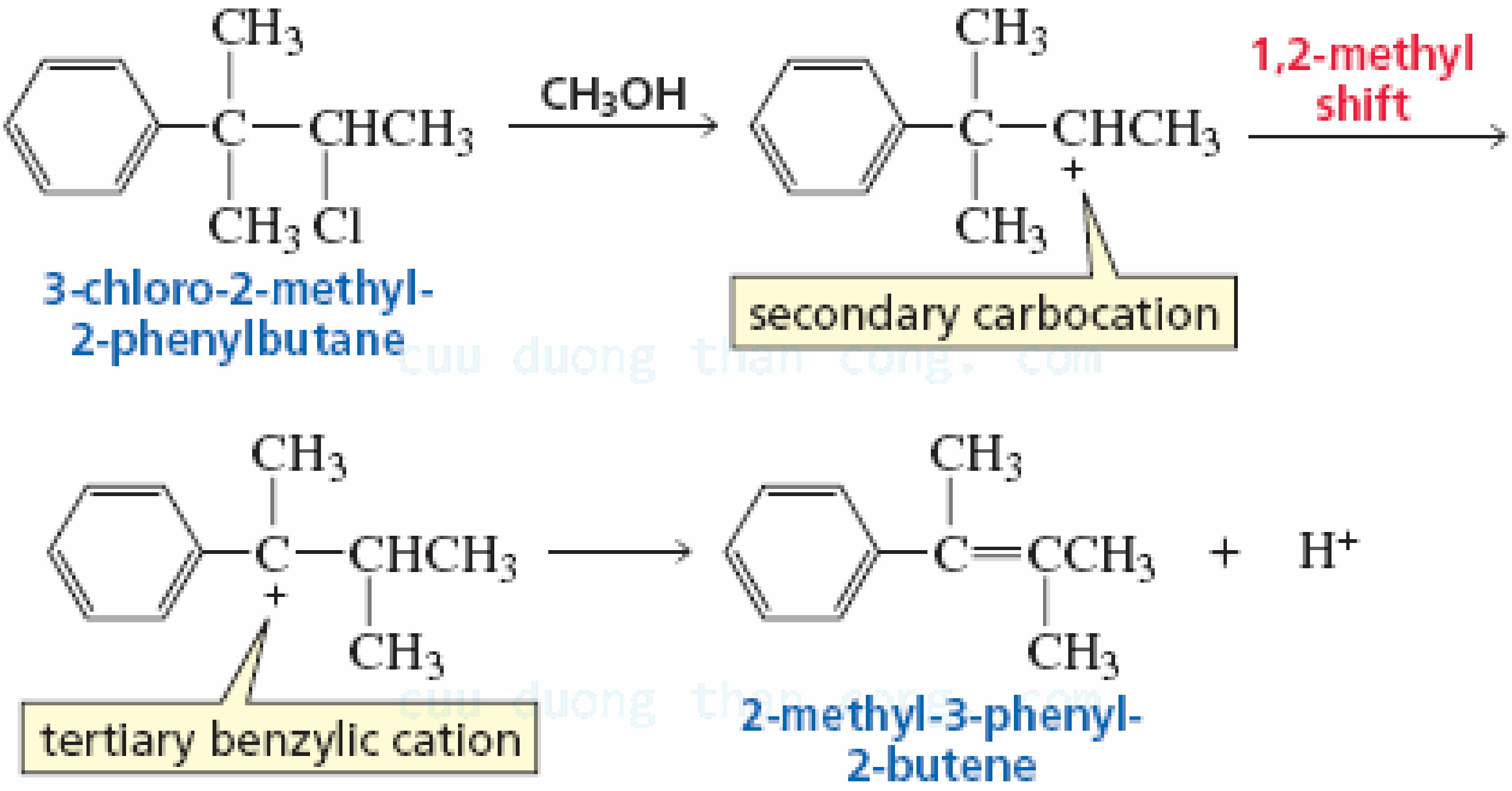
$$\underset{\displaystyle CH_3}{CH_3\underset{|}{C}H}-\overset{\displaystyle CH_3}{\overset{|}{\underset{\underset{\displaystyle Br}{|}}{C}}}CH_3 \xrightarrow{RO^-} CH_3\underset{\underset{\displaystyle CH_3}{|}}{C}=\overset{\overset{\displaystyle CH_3}{|}}{C}CH_3 + CH_3\underset{\underset{\displaystyle CH_3}{|}}{C}H\overset{\overset{\displaystyle CH_3}{|}}{C}=CH_2$$

RO^-		
$CH_3CH_2O^-$	79%	21%
$CH_3\overset{\overset{\displaystyle CH_3}{\vert}}{\underset{\underset{\displaystyle CH_3}{\vert}}{C}}O^-$	27%	73%
$CH_3\overset{\overset{\displaystyle CH_3}{\vert}}{\underset{\underset{\displaystyle CH_2CH_3}{\vert}}{C}}O^-$	19%	81%
$CH_3CH_2\overset{\overset{\displaystyle CH_2CH}{\vert}}{\underset{\underset{\displaystyle CH_2CH}{\vert}}{C}}O^-$	8%	92%

Rearrangements in E1 & S_N1




S_N1
H_2O
1,2-methyl shift
secondary carbocation
tertiary carbocation
H_2O
H_2O
3-bromo-2,2-dimethylbutane
2,3-dimethyl-2-butanol



3-chloro-2-methyl-2-phenylbutane

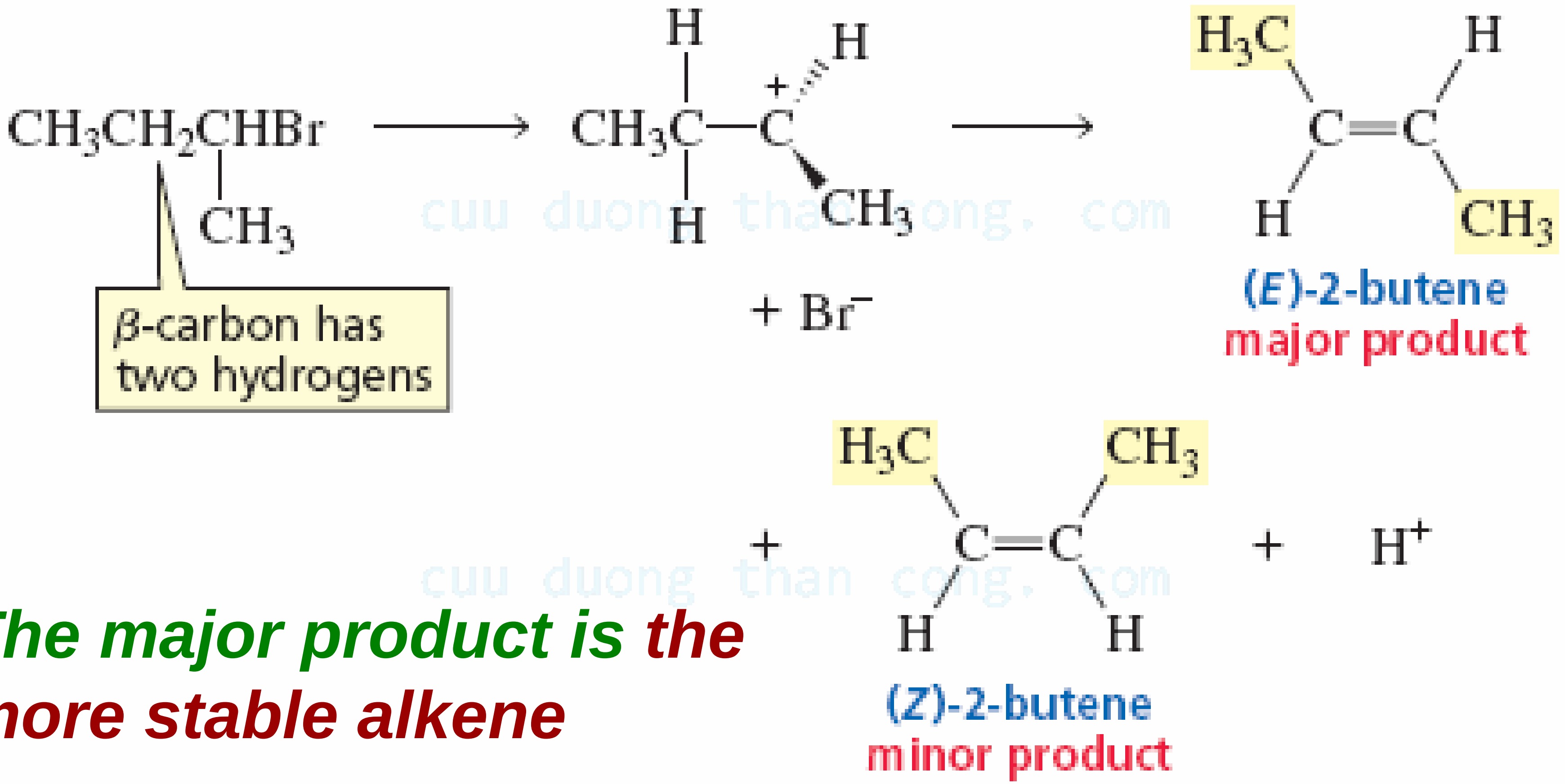
secondary carbocation

tertiary benzylic cation

2-methyl-3-phenyl-2-butene

Stereochemistry of E1 reactions

The carbocation formed in the 1st step is planar, so both syn & anti-elimination can occur

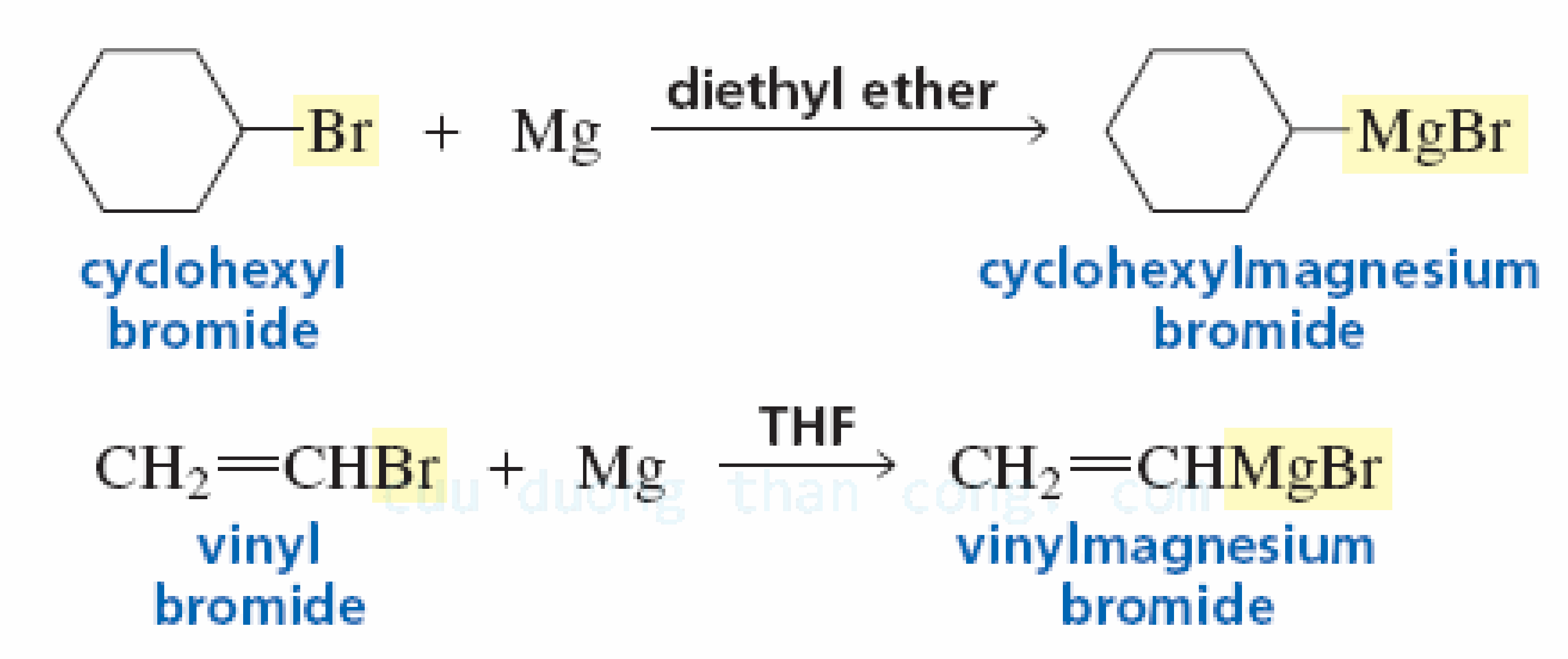


(*E*)-2-butene
major product

(*Z*)-2-butene
minor product

The major product is the more stable alkene

GRIGNARD REAGENTS



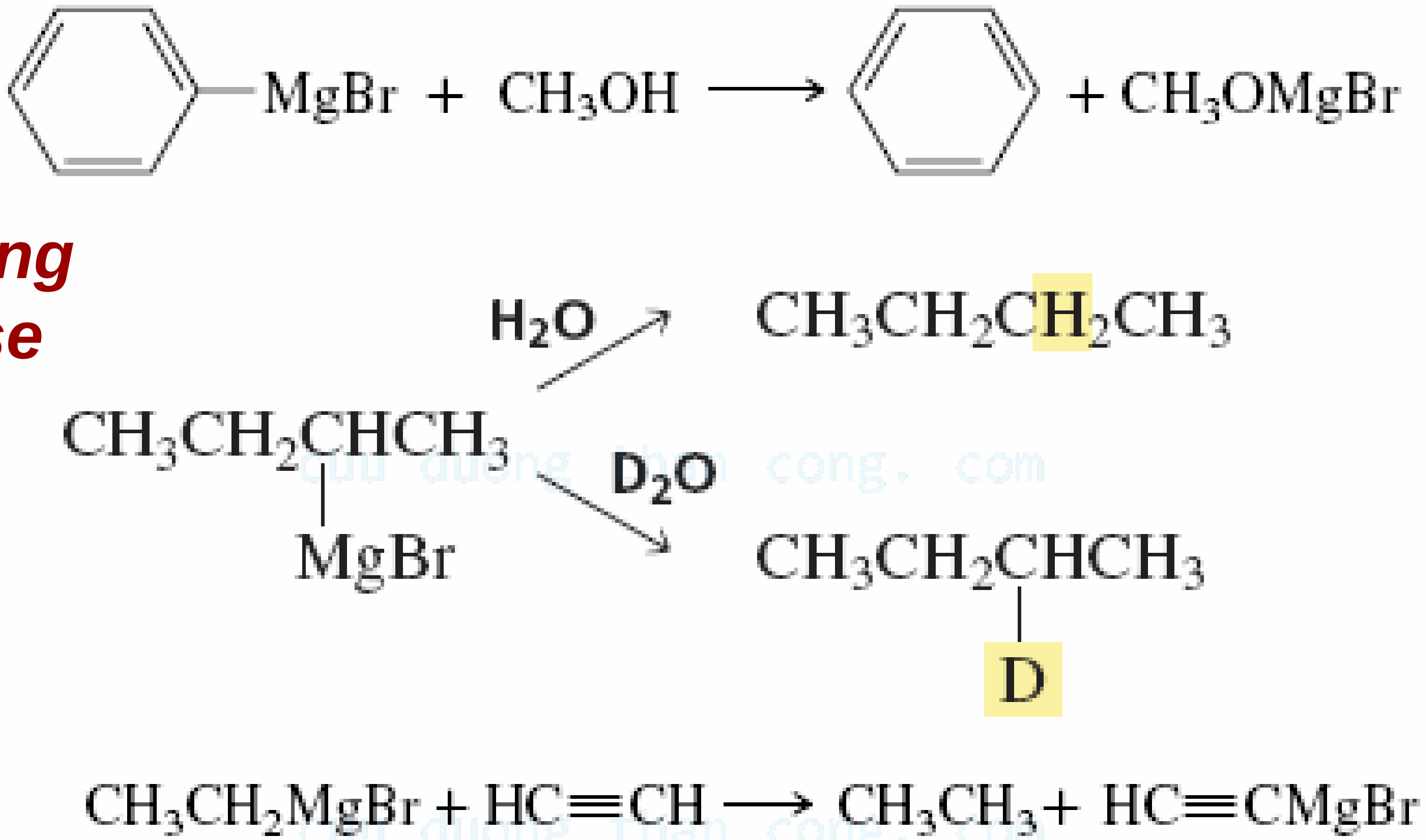
Strong base

CH_3CH_2MgBr reacts as if it were $CH_3\overset{-}{\ddot{C}}H_2$ $\overset{+}{Mg}Br$

Strong nucleophile

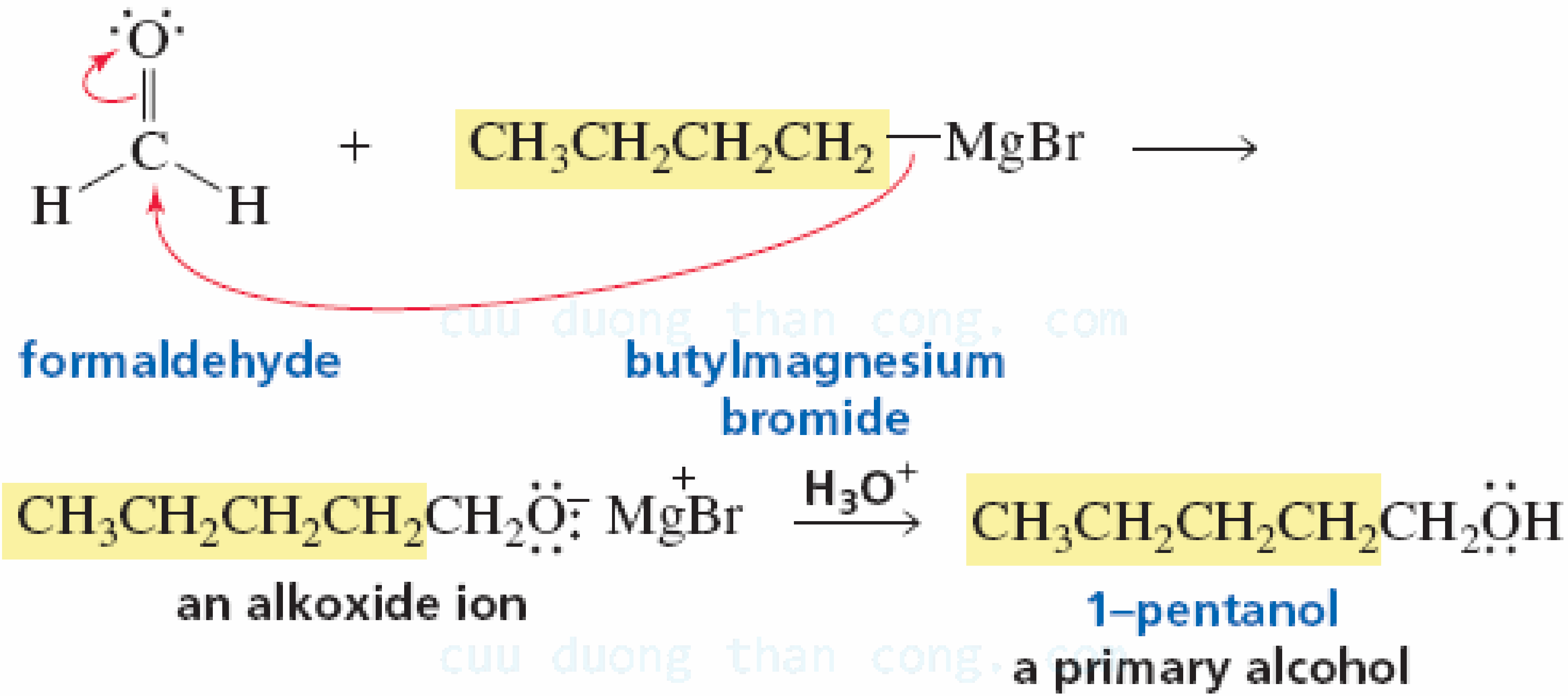
REACTIONS OF GRIGNARD REAGENTS

Strong base

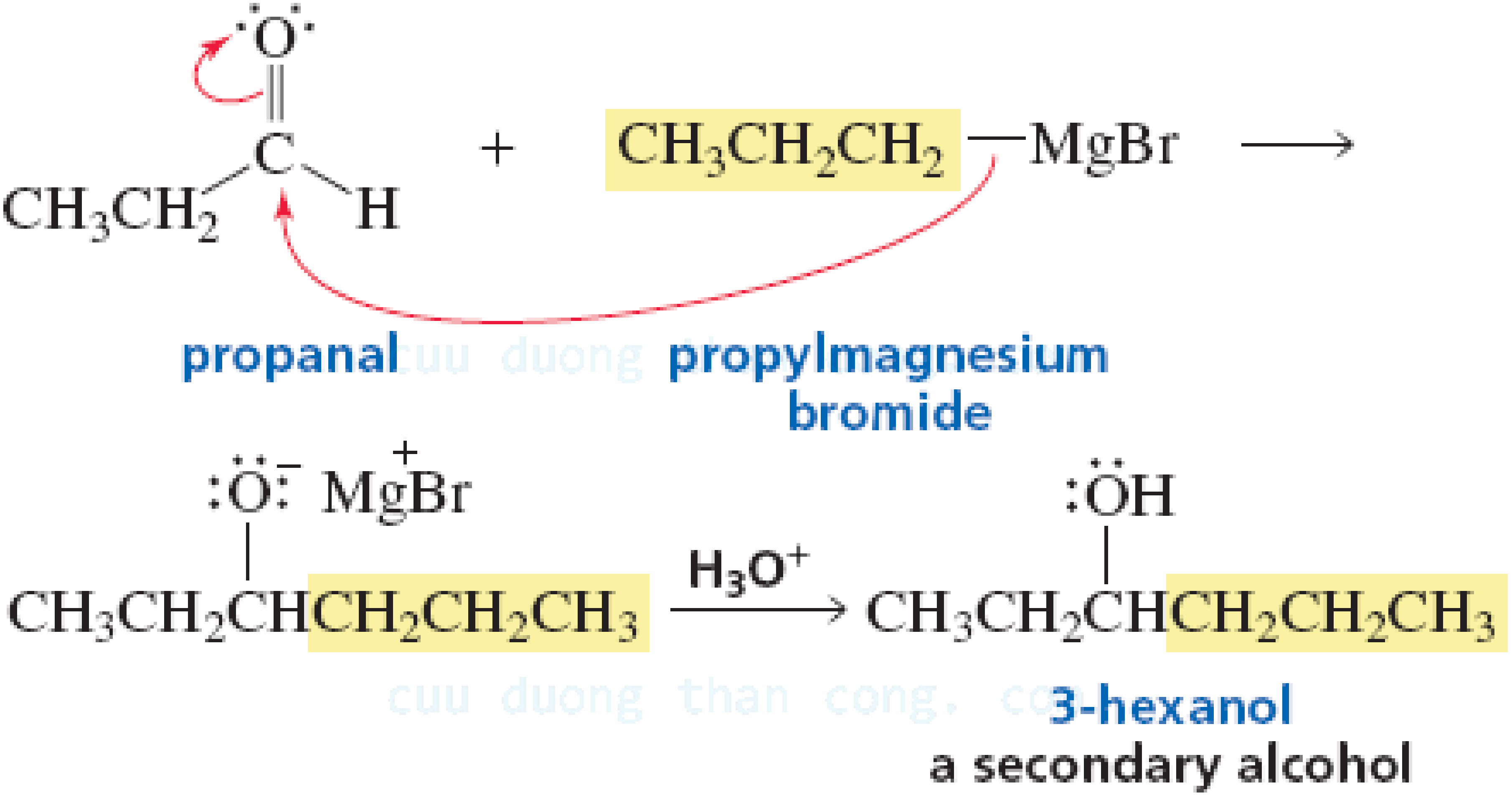


Grignard reagents readily react with *acidic groups*: -OH, -NH$_2$, -NHR, -SH, -C$\equiv$CH, -COOH

Reactions of Grignard reagents with aldehydes & ketones



Only for the reaction of HCHO



$CH_3CH_2CHO + CH_3CH_2CH_2{-}MgBr \longrightarrow$

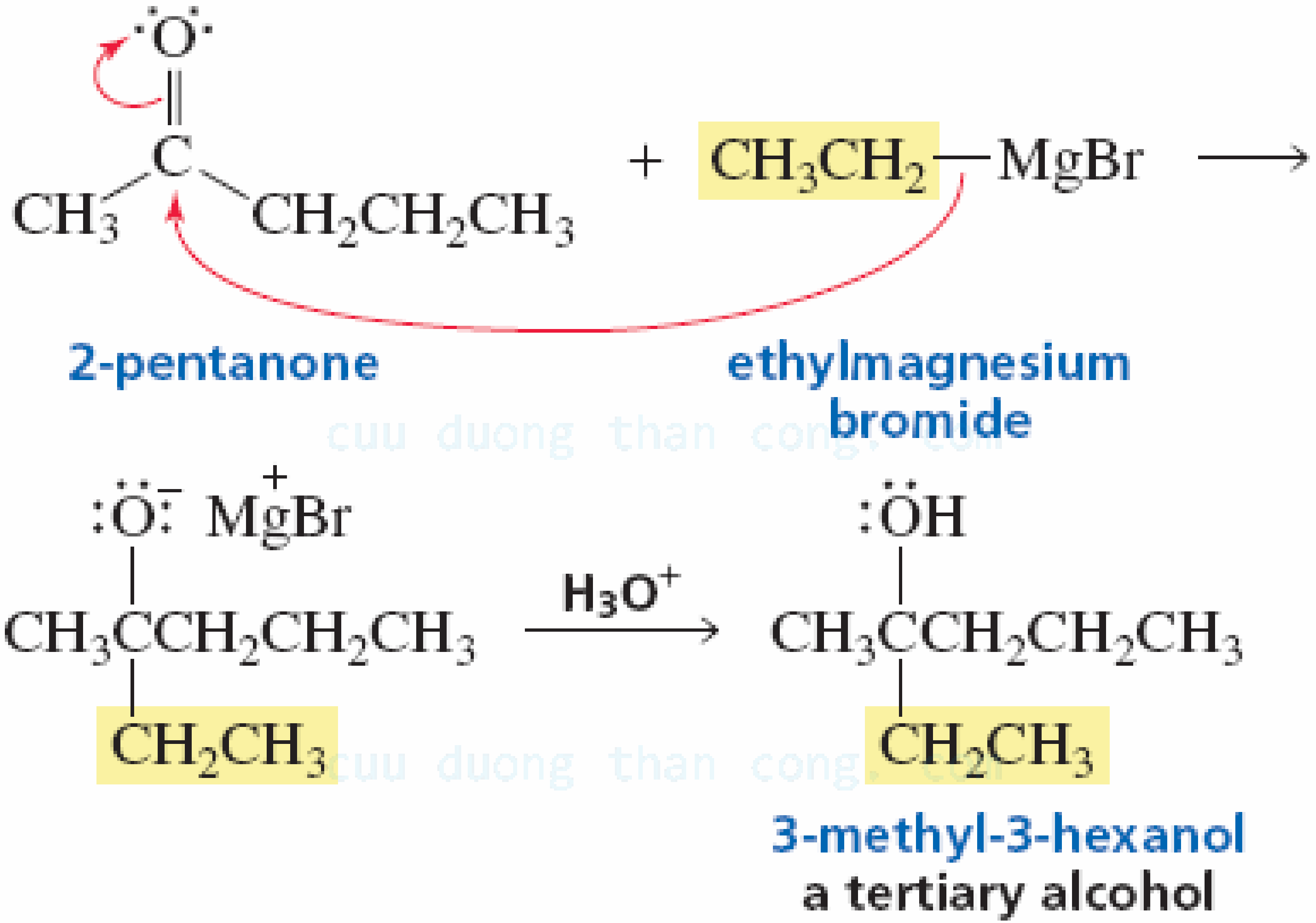
propanal

propylmagnesium bromide

$CH_3CH_2CH(O^-\,\overset{+}{M}gBr)CH_2CH_2CH_3 \xrightarrow{H_3O^+} CH_3CH_2CH(OH)CH_2CH_2CH_3$

3-hexanol

a secondary alcohol



$$CH_3COCH_2CH_2CH_3 + CH_3CH_2{-}MgBr \longrightarrow$$

2-pentanone

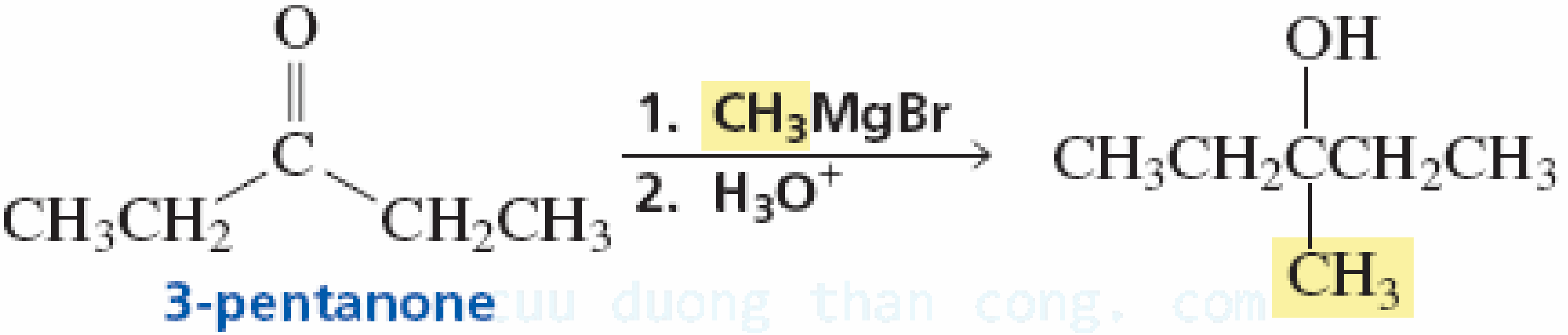
ethylmagnesium bromide

$$\overset{:\ddot{O}:^{-}\ \overset{+}{Mg}Br}{CH_3\underset{CH_2CH_3}{C}CH_2CH_2CH_3} \xrightarrow{H_3O^+} \overset{:\ddot{O}H}{CH_3\underset{CH_2CH_3}{C}CH_2CH_2CH_3}$$

3-methyl-3-hexanol

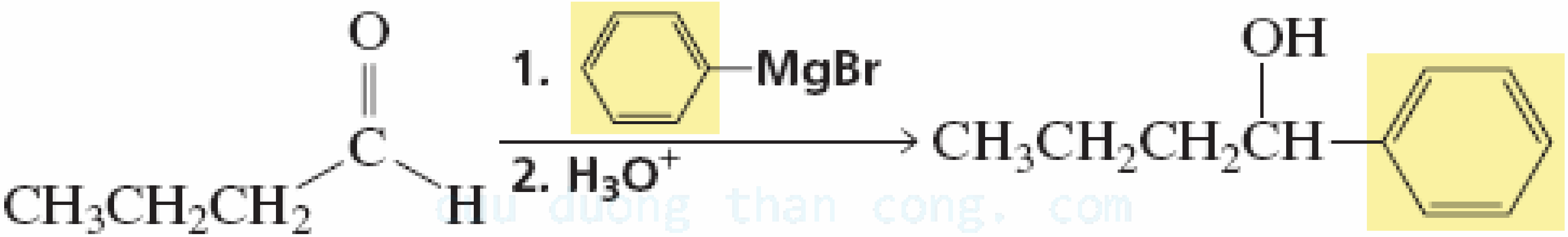
a tertiary alcohol

Numbers 1 & 2 are used to indicate that the acid is not added until the reaction with the Grignard reagent is complete



3-pentanone

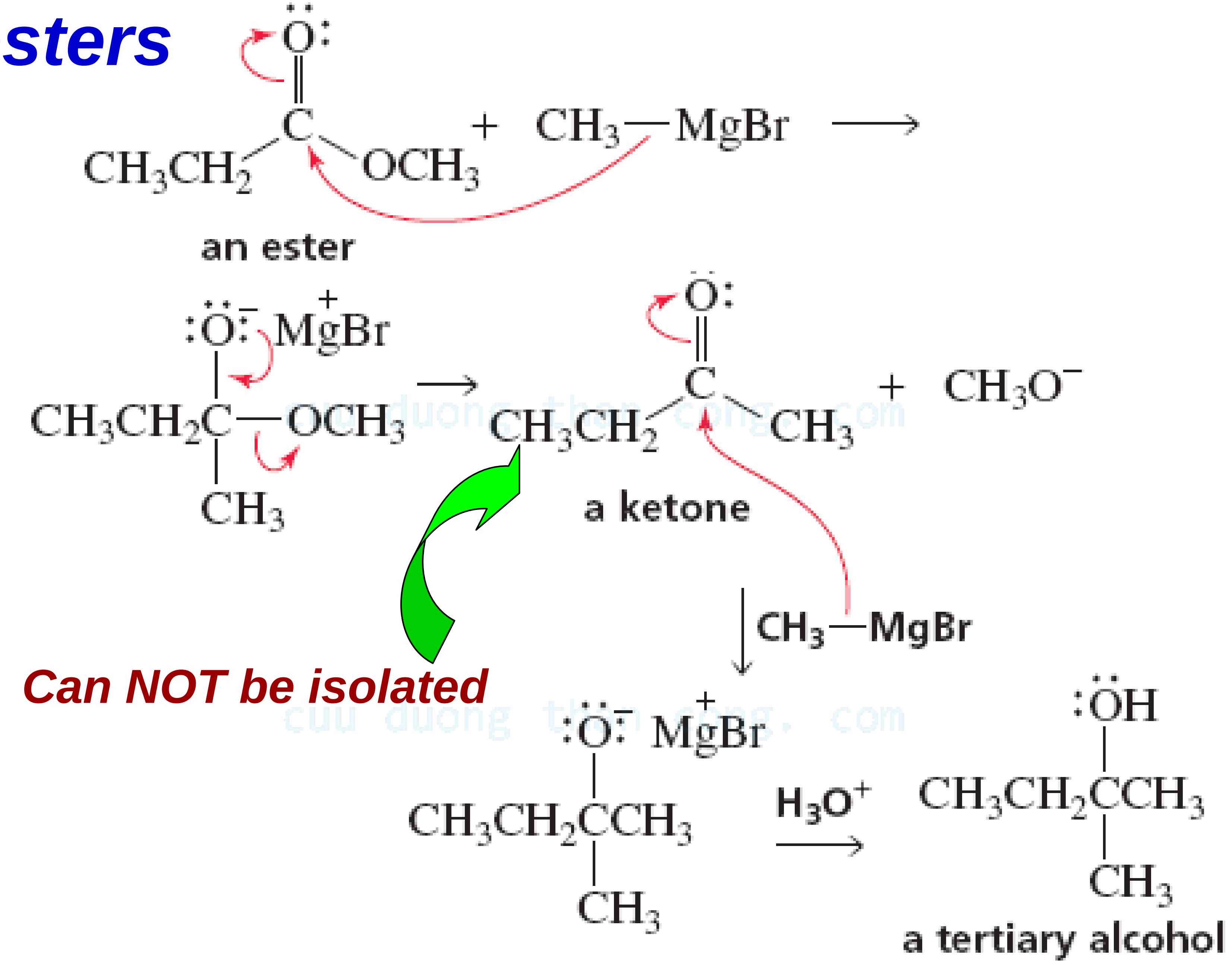
3-methyl-3-pentanol



butanal

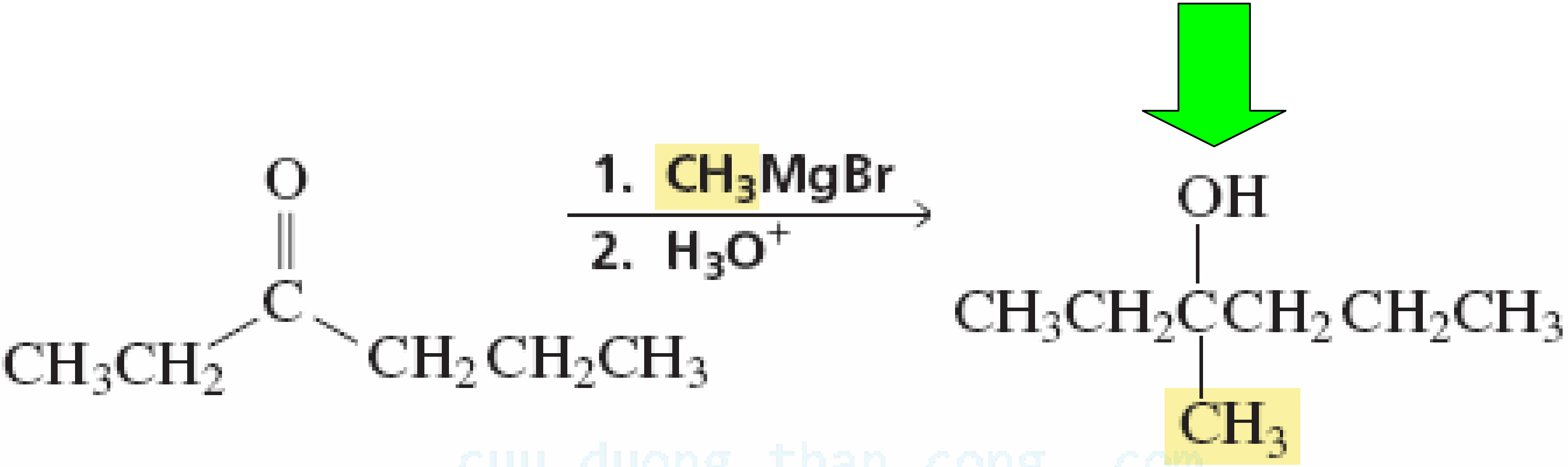
1-phenyl-1-butanol

Reactions of Grignard reagents with esters

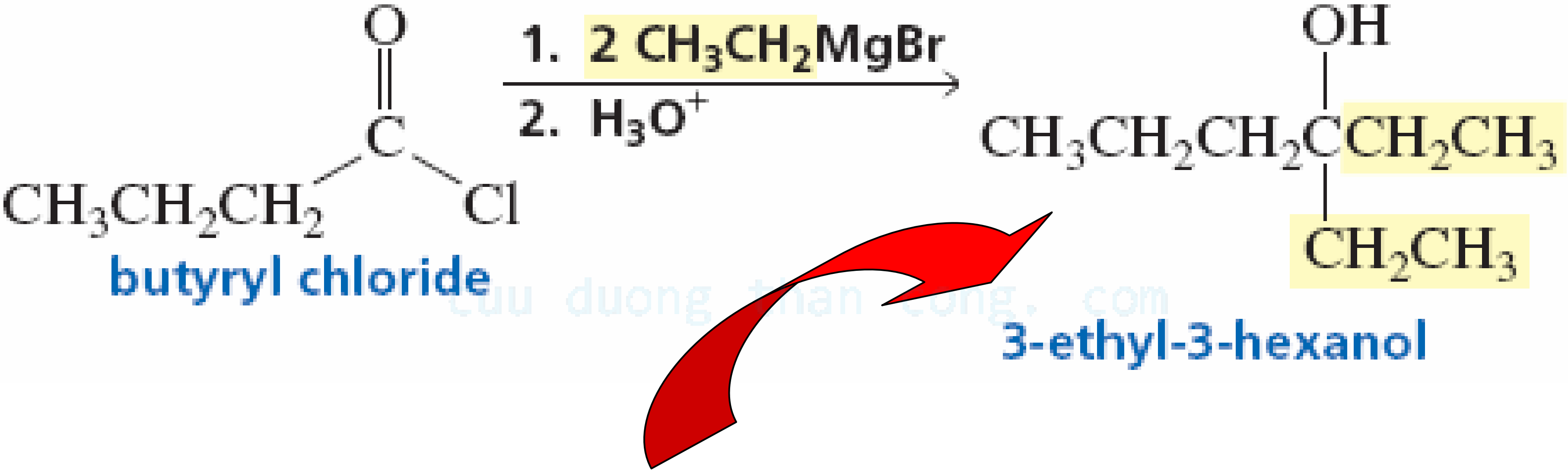


Can NOT be isolated

Can be chiral



$$CH_3CH_2COCH_2CH_2CH_3 \xrightarrow[2.\ H_3O^+]{1.\ CH_3MgBr} CH_3CH_2C(OH)(CH_3)CH_2CH_2CH_3$$



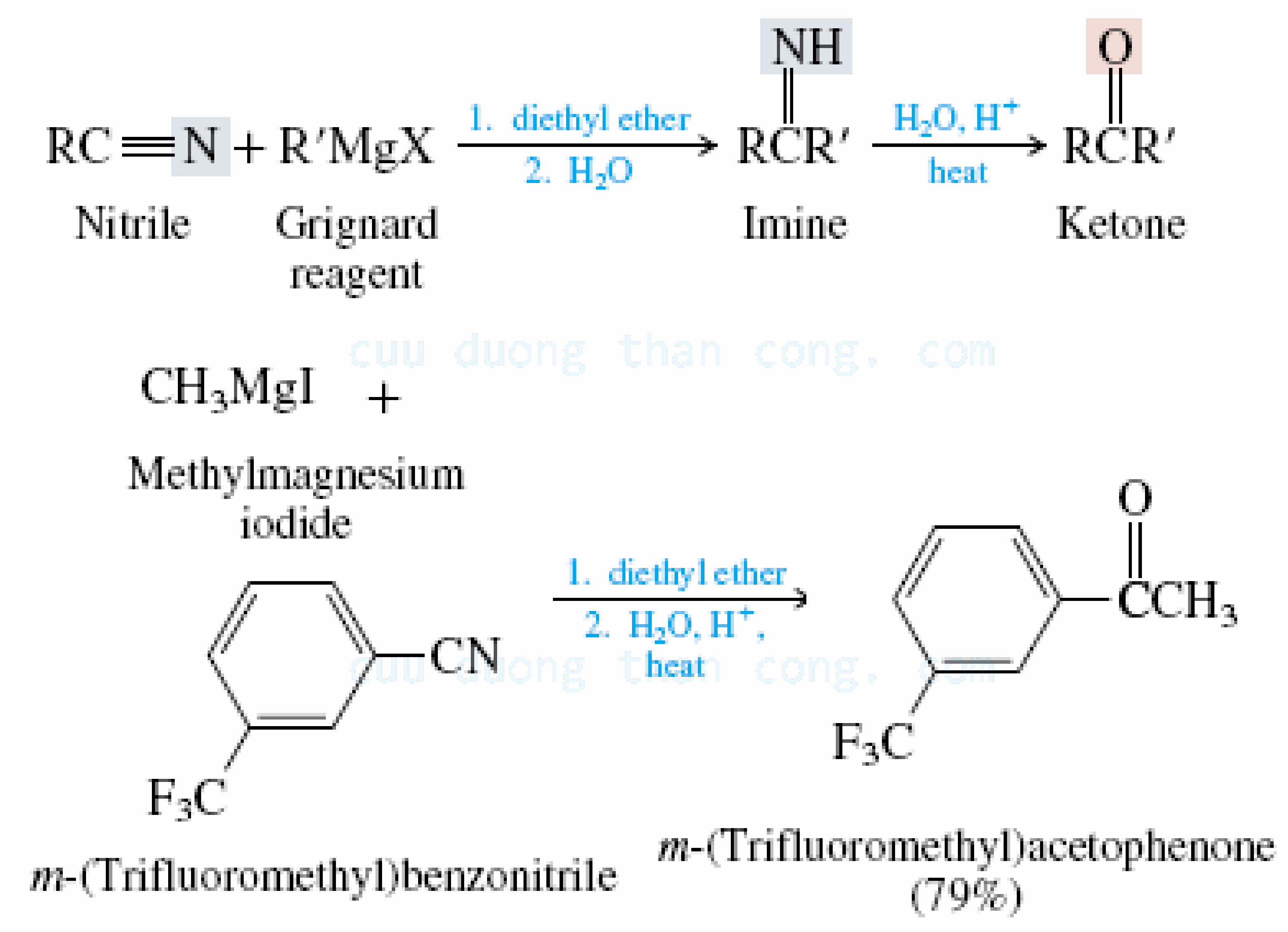
$$CH_3CH_2CH_2COCl \xrightarrow[2.\ H_3O^+]{1.\ 2\ CH_3CH_2MgBr} CH_3CH_2CH_2C(OH)(CH_2CH_3)CH_2CH_3$$

butyryl chloride

3-ethyl-3-hexanol

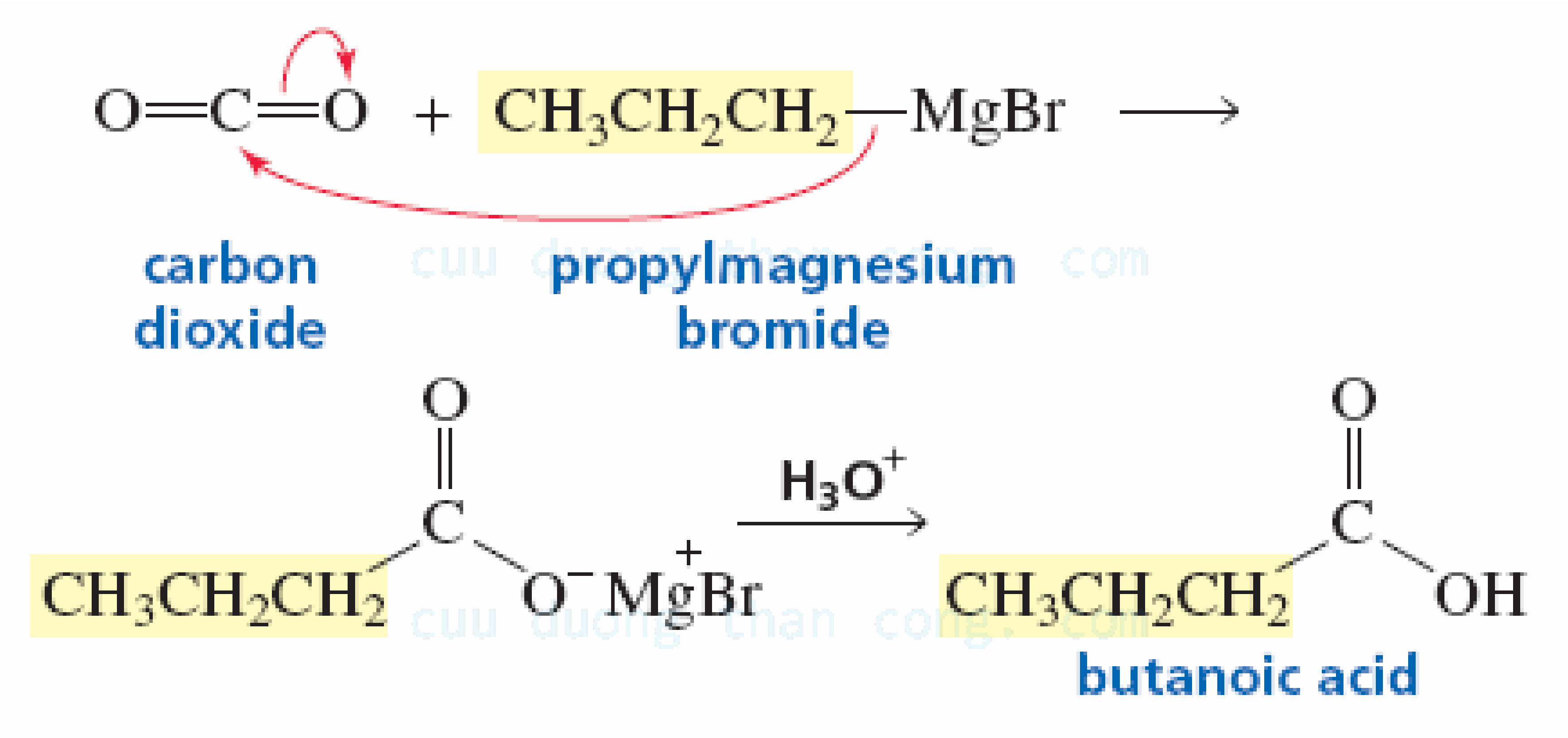
Alcohols from esters / acyl halides Can NOT be chiral

Reactions of Grignard reagents with nitriles



$$RC{\equiv}N + R'MgX \xrightarrow[\text{2. } H_2O]{\text{1. diethyl ether}} R\overset{NH}{\overset{\|}{C}}R' \xrightarrow[\text{heat}]{H_2O,\ H^+} R\overset{O}{\overset{\|}{C}}R'$$

Reactions of Grignard reagents with carbon dioxide



Reactions of Grignard reagents with epoxides