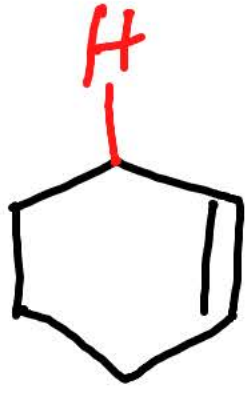
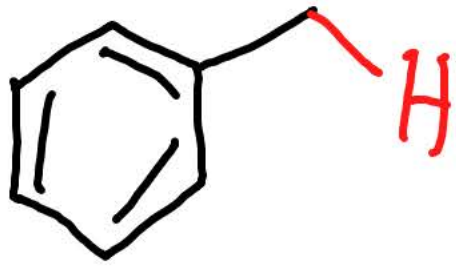
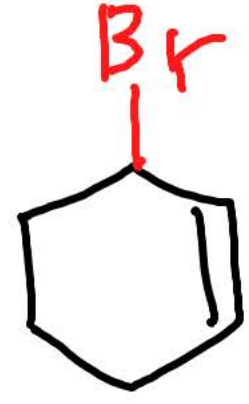
Bromination des positions allyliques et benzyliques

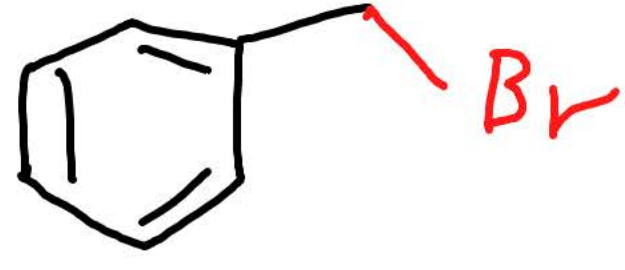


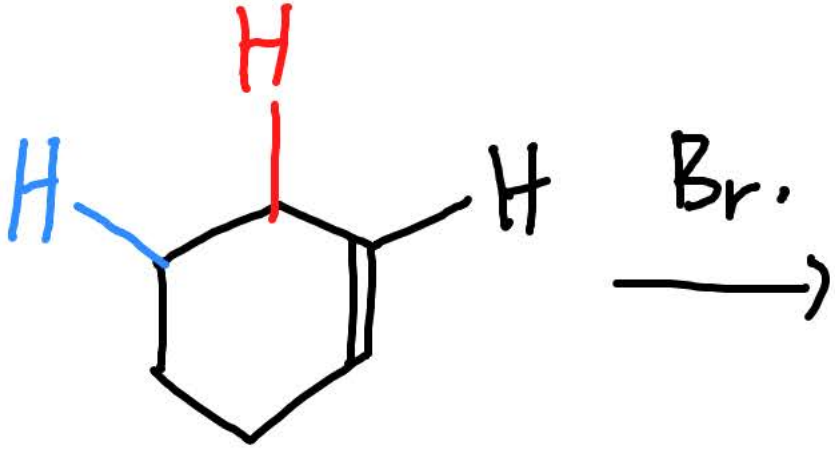
position allylique

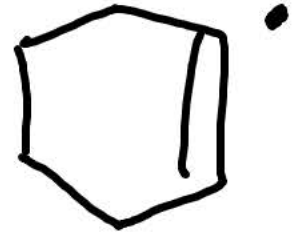


position benzylique





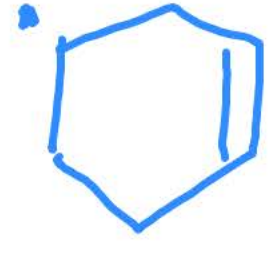




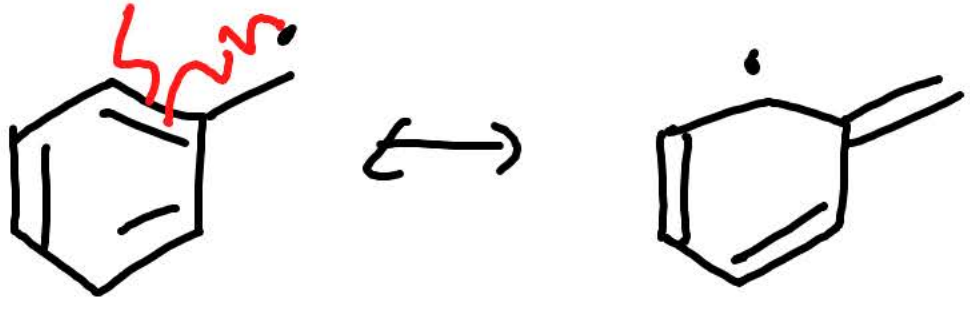
radical sp2, moins stables, pas observé

structure de résonance identique! Très stabilisé

Très bonne sélectivité!



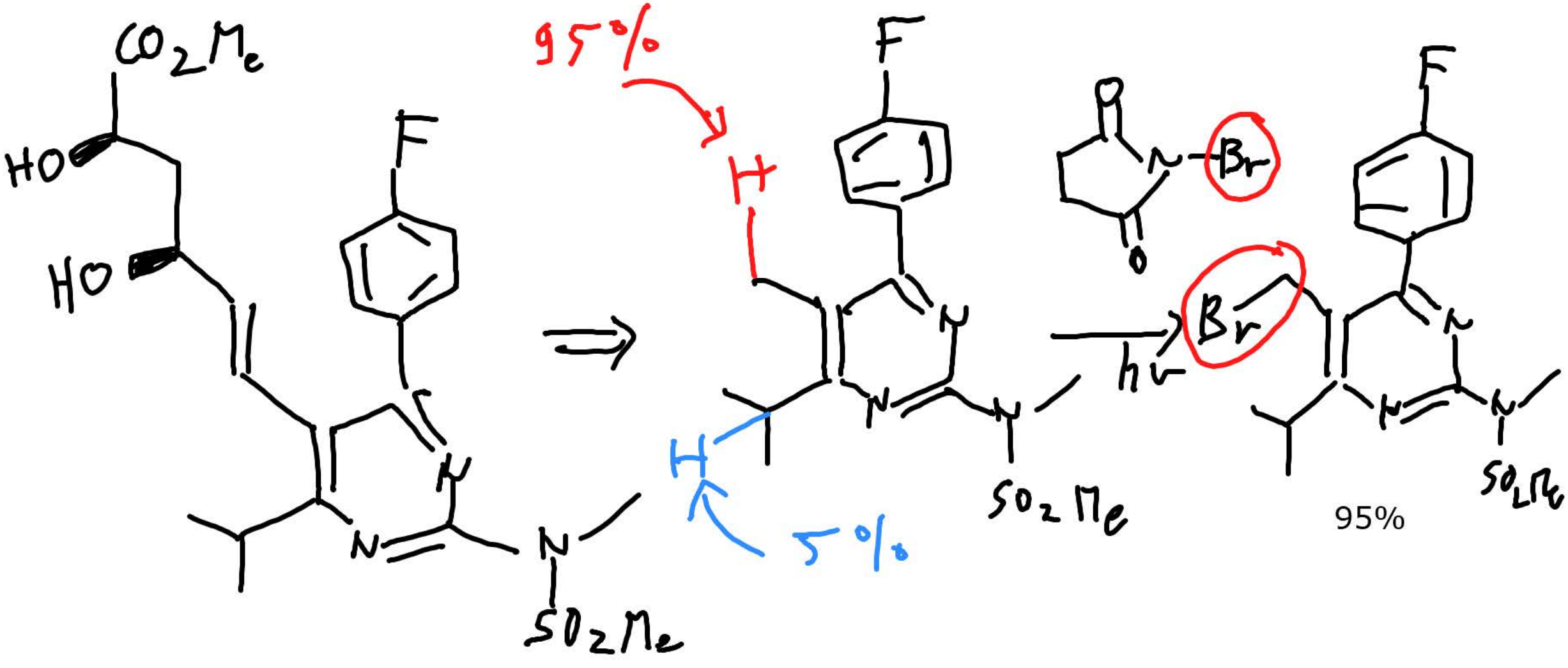
radical sp3 secondaire, moins stabilisé

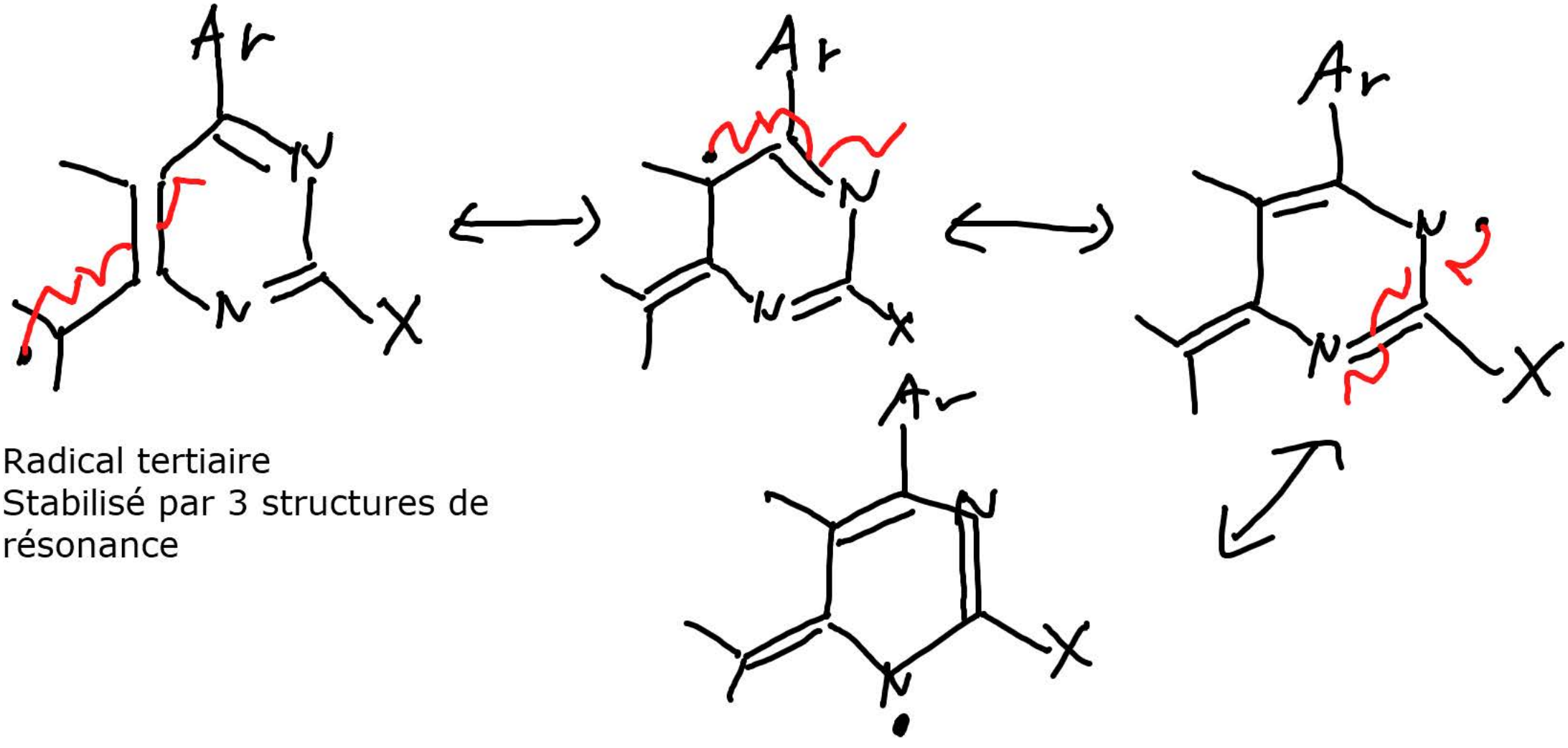


+ 2 autres dans le cycle

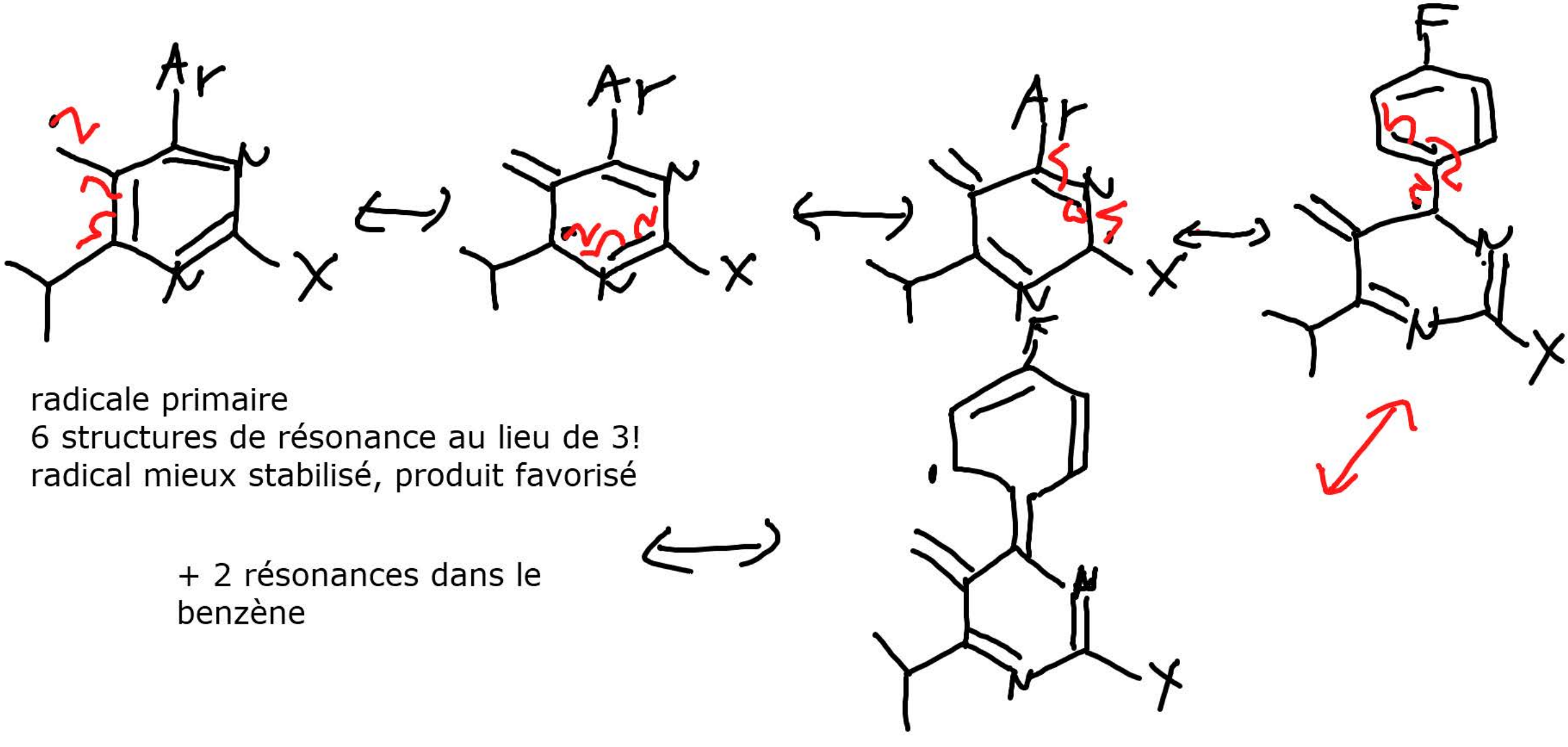
position stabilisée, réaction facile

Rosuvastatine





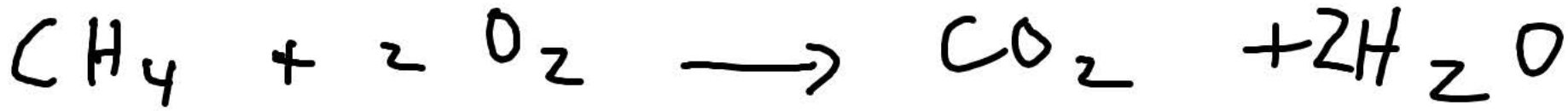
Radical tertiaire
Stabilisé par 3 structures de résonance



radicale primaire
6 structures de résonance au lieu de 3!
radical mieux stabilisé, produit favorisé

+ 2 résonances dans le benzène

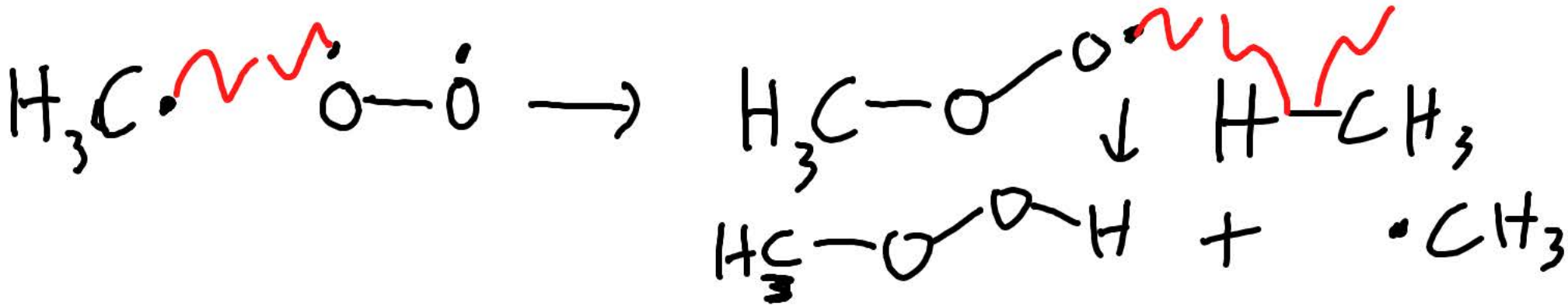
combustion du méthane



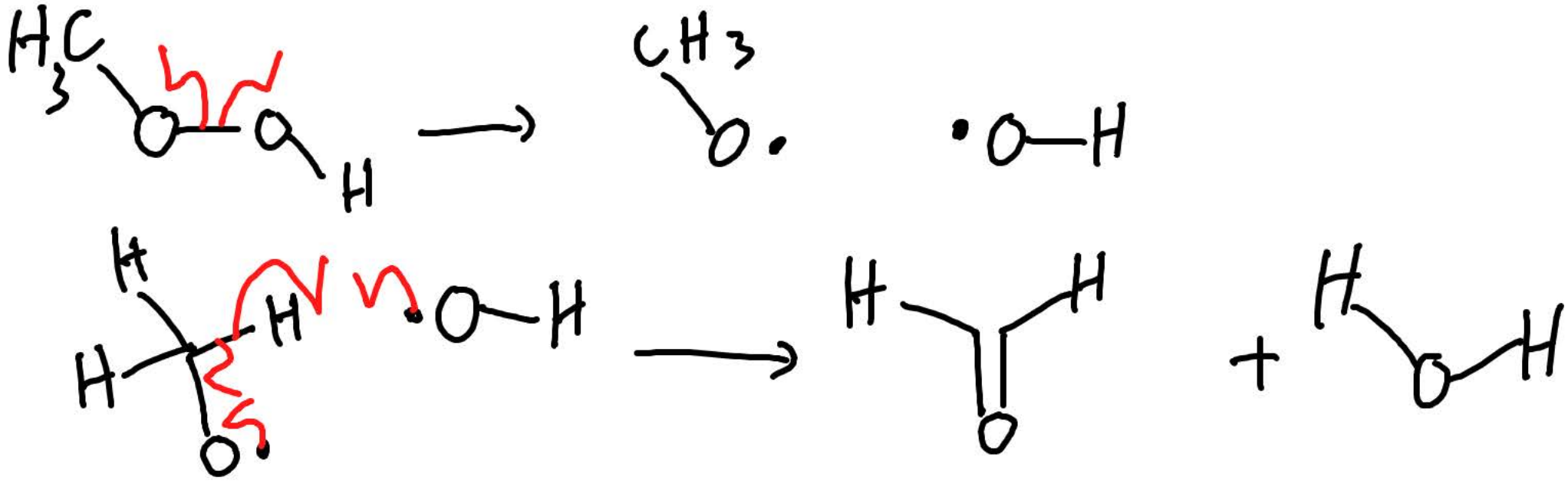
Initiation

très lente

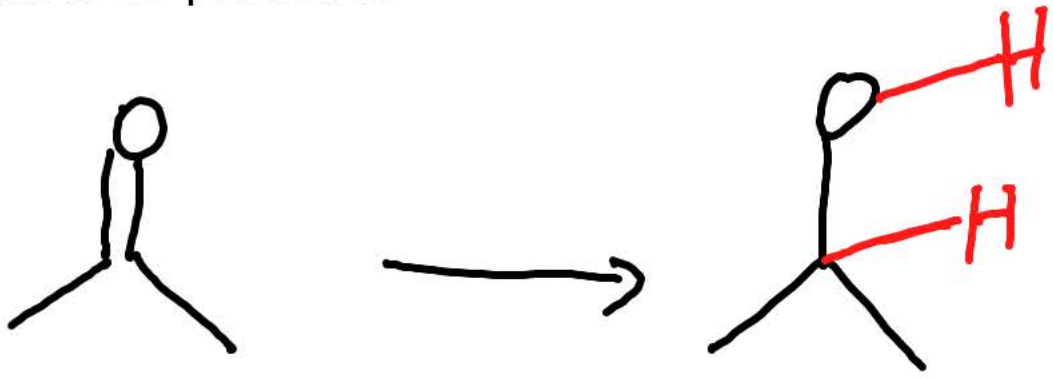
propagation 1



Initiation 2:



comparaison de procédés



réduction des cétones

cétone

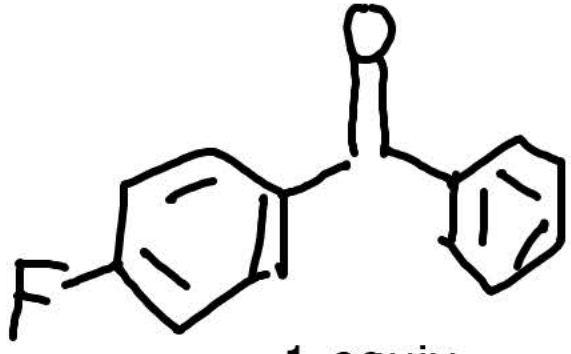
Alcool

① $Na^{\oplus}$ $H_3B^{\ominus}$

② H_2 , Ru cat.

procédé 1: Albany, Org. Proc. Res. Dev. 2002, 621.

C13H9FO: 24 atomes



1 equiv

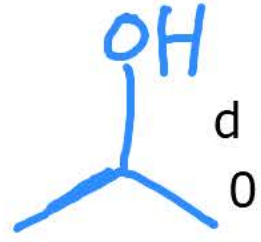
200 g/mol

6 atomes

+ $NaBH_4$

0.38 equiv

37.8 g/mol

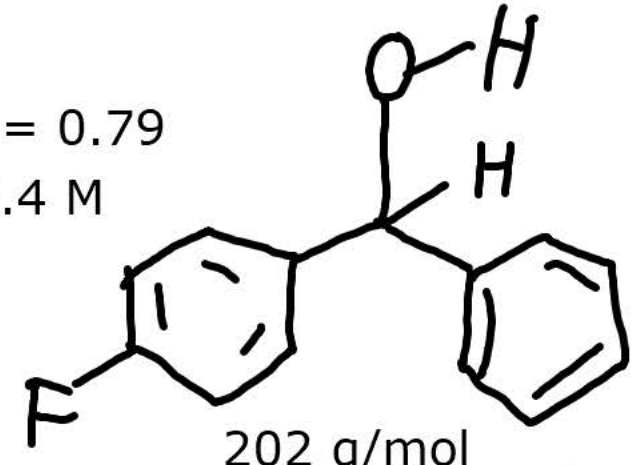


d = 0.79

0.4 M

98%

C13H11FO: 26



202 g/mol

+ $NaB(OH)_4$

économie d'atome? 26/(24+6)= 87%

purification: extraction

acétate d'éthyle: 1 volume, d = 0.90
Eau: 1.5 volume , d = 1.0
0.200Kg/Kg Na2SO4

0.20 Kg/Kg

(Kg par Kg de produit)

Bilan de masse pour produire 1 kg de produit

1000/202 = 4.95 mol de produit

98% de rendement: 4.95/0.98 = 5.05 mol produit de départ = 1.01 Kg

NaBH4: 0.38*37.* 5.05 = 73 g, 0.073 Kg

NaB(OH)4 = 0.200 Kg

solvant: 0.4 M d'isopropanol, 12.6 L, 10 Kg

Extraction:

acétate d'éthyle: 1 volume, 12.6 L, 11.3 Kg

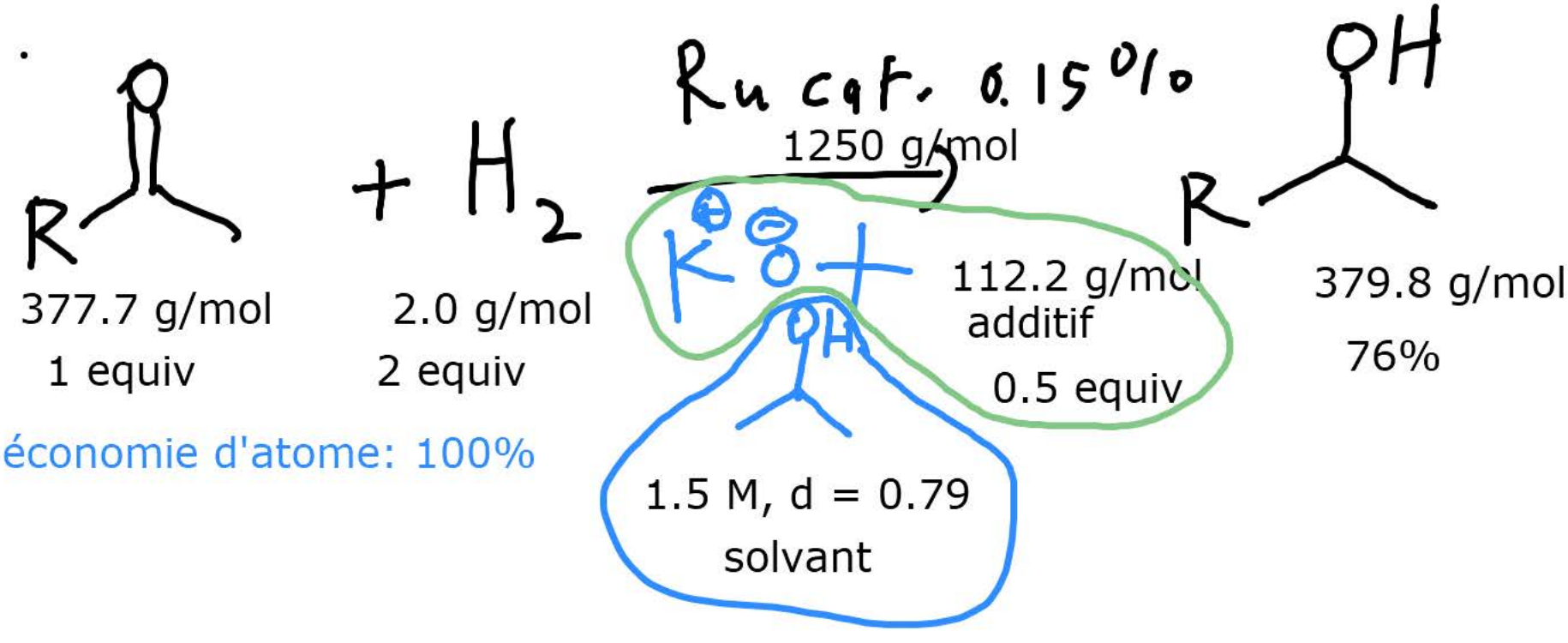
Eau: 1.5 volume, 18.9 L, 18.9 Kg

0.200 Kg Na2SO4

PMI:(1.01 + 0.073+10+ 11.3+ 18.9+ 0.2)/1 = 41.5

E:(10+11.3+18.9+0.20+0.20)/1 = 40.6

procédé 2: Merck, Org. Proc. Res. Dev. 2007, 616 (simplifié).



économie d'atome: 100%

Extraction: Toluene: 6.5 volume, d = 0.87
H2O: 6.5 volume, d = 1

Bilan de masses:

1 Kg produit: 2.63 mol

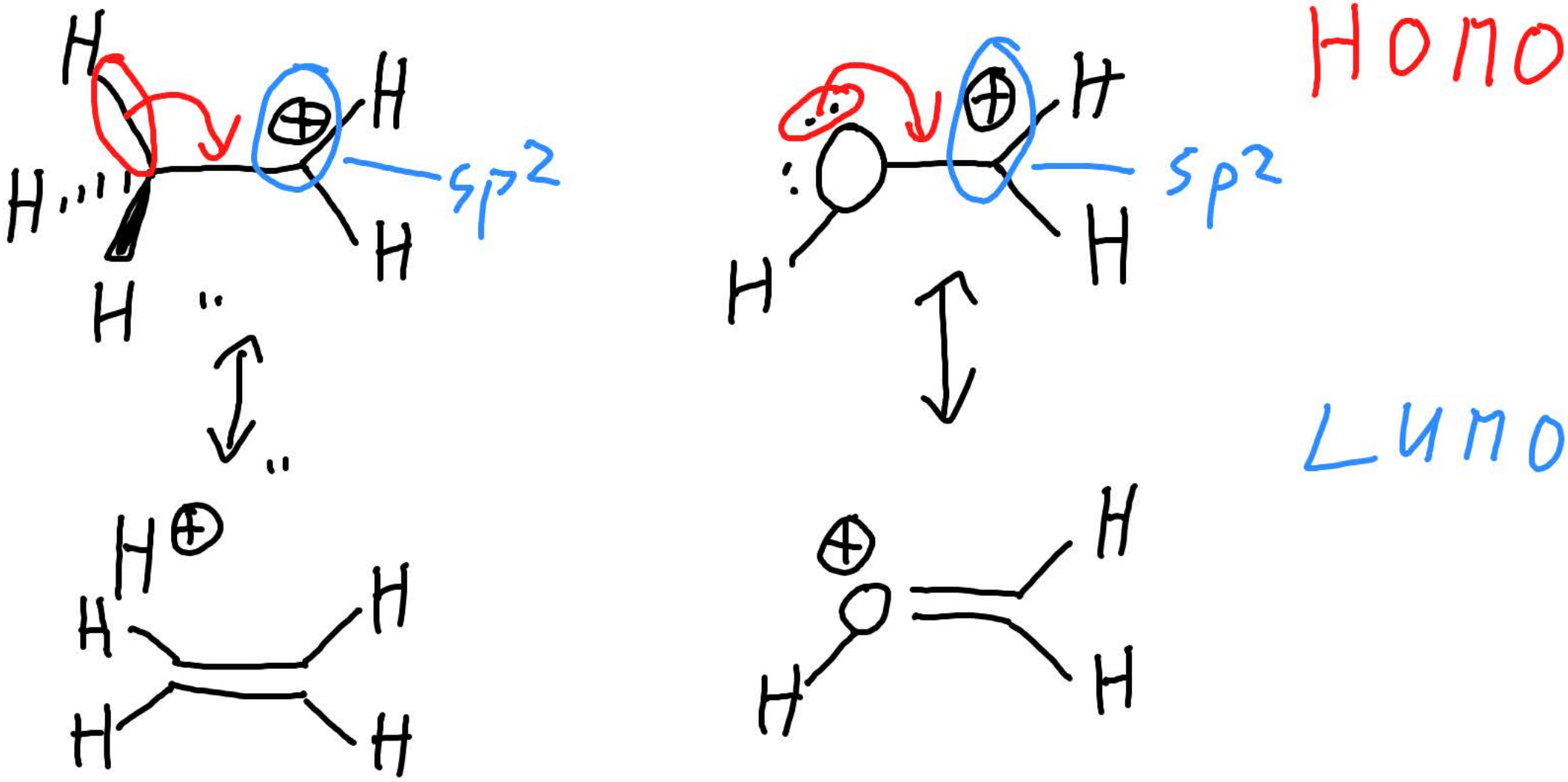
Produit de départ: 76% rendement, 3.46 mol, 1.30 K

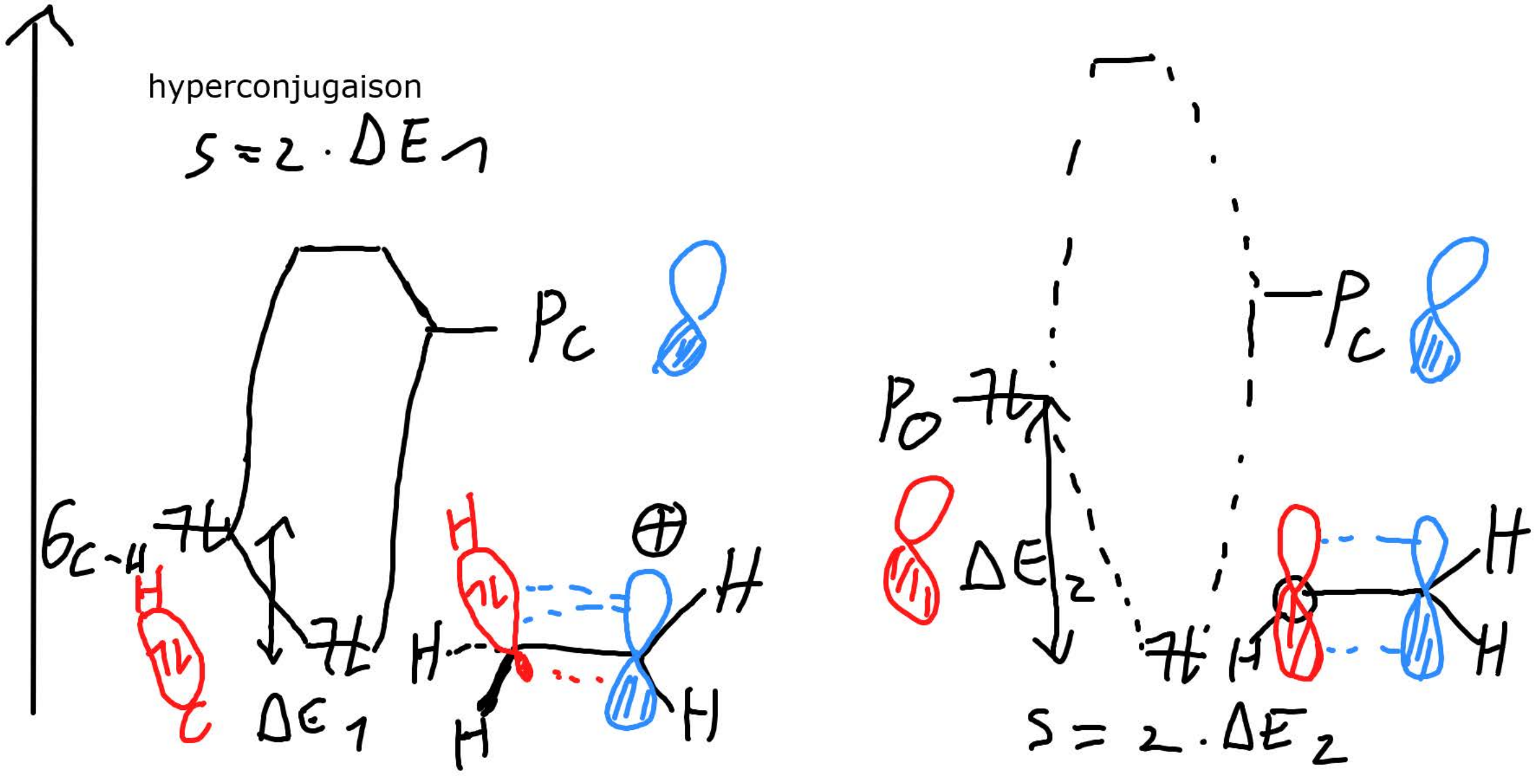
H2: 0.015 Kg
Ru cat: 0.0065 Kg
KOtBu: 0.12 Kg
Isopropanol: 2.3 L, 1.8 Kg
Toluene: 6.5 volumes: 13 Kg
Eau: 6.5 volumes, 15 Kg

PMI: (1.30 + 0.015 + 0.0065 + 0.12 + 1.8 + 13 + 15)/1 = 31.2

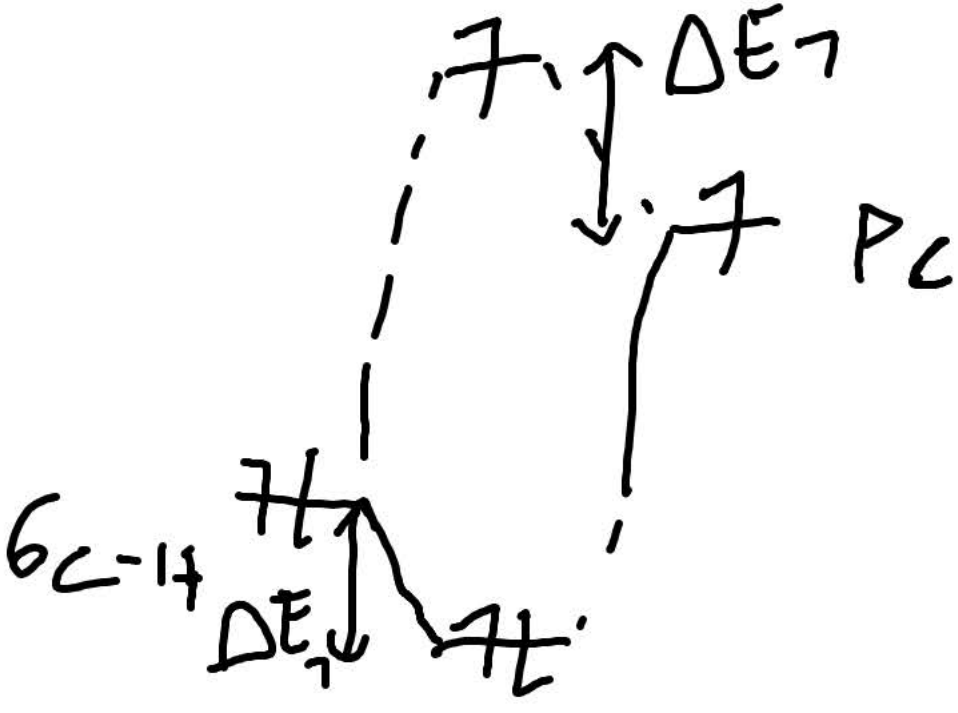
E: ((0.5*0.015)+0.0065 + 0.12 + 1.8 + 13 + 15)/1 = 29.9

résonance et orbitales pour les carbocations



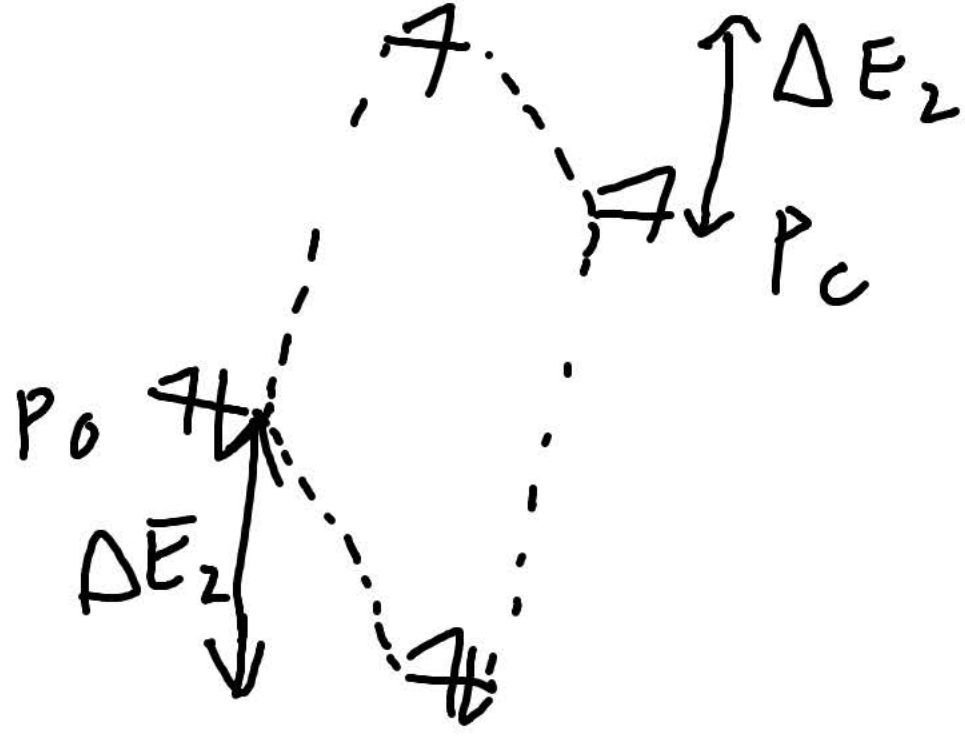

hyperconjugaison
S = 2 · ΔE1
Pc
σC-H
ΔE1
H
H
H
H
H
H
C
Po
Pc
ΔE2
H
H
H
S = 2 · ΔE2

radicaux



$S = \Delta E_1$

$2 \cdot \Delta E_1 - \Delta E_1$

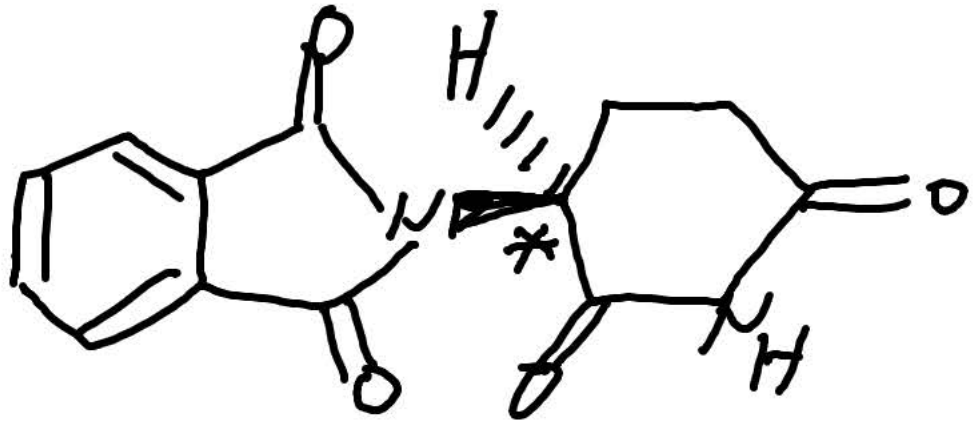


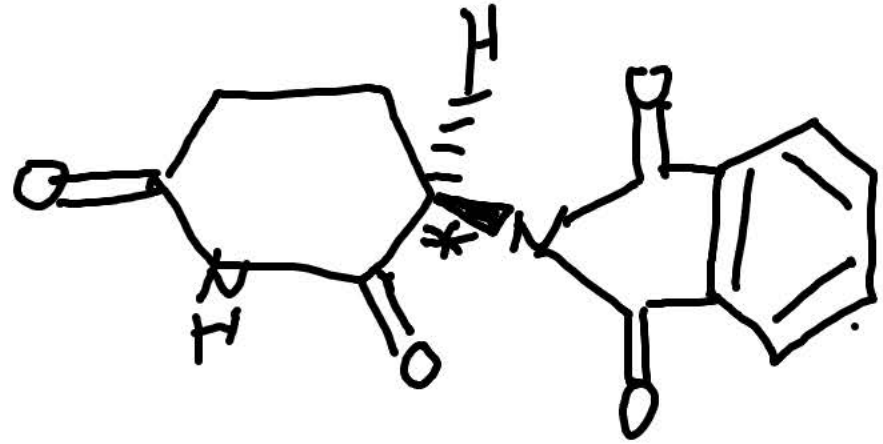
$S = \Delta E_2$

Importance de la chiralité

bioactivité différente

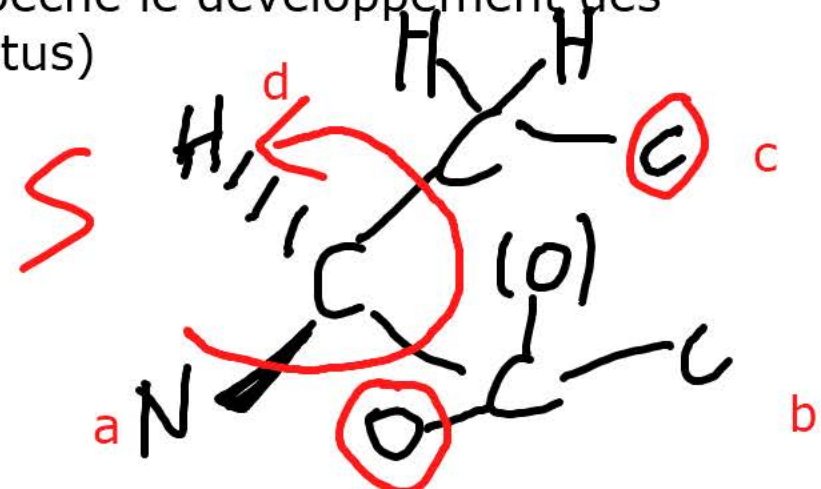
thalidomide





tératogène (empêche le développement des membres du foetus)

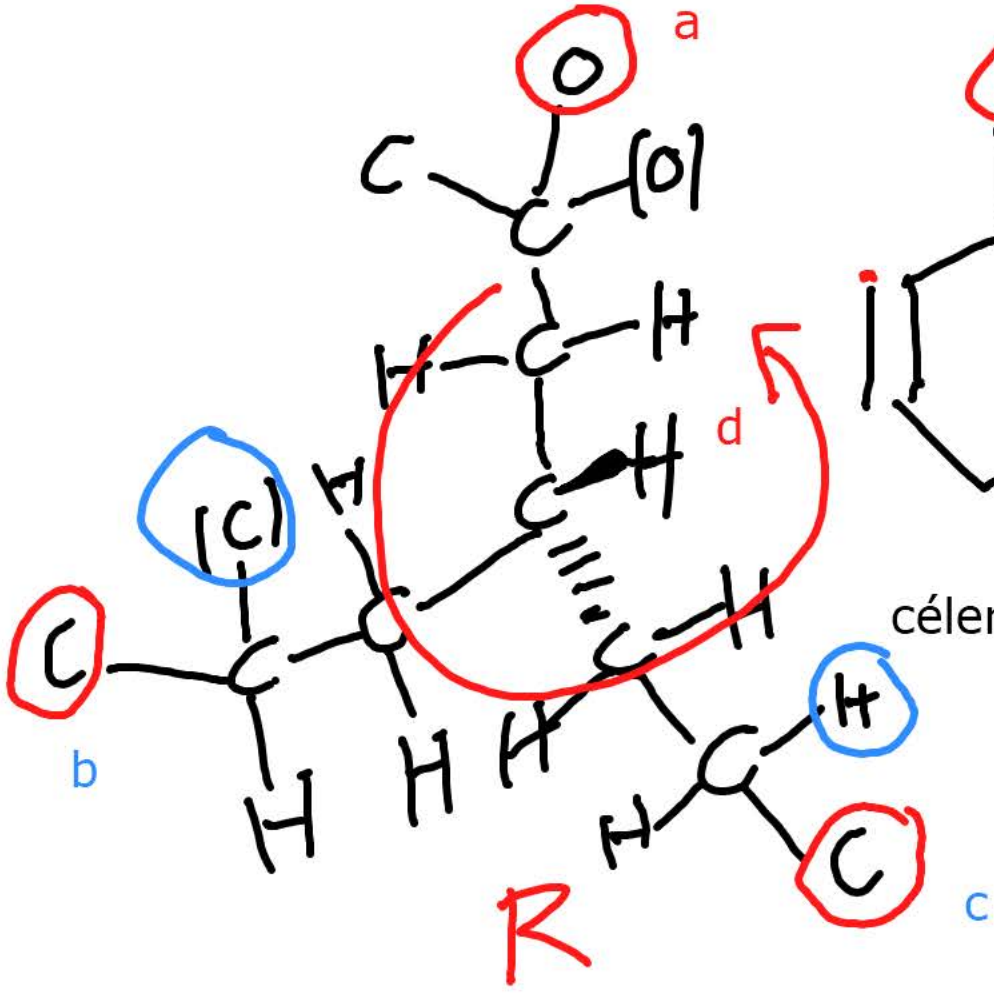
sédatif



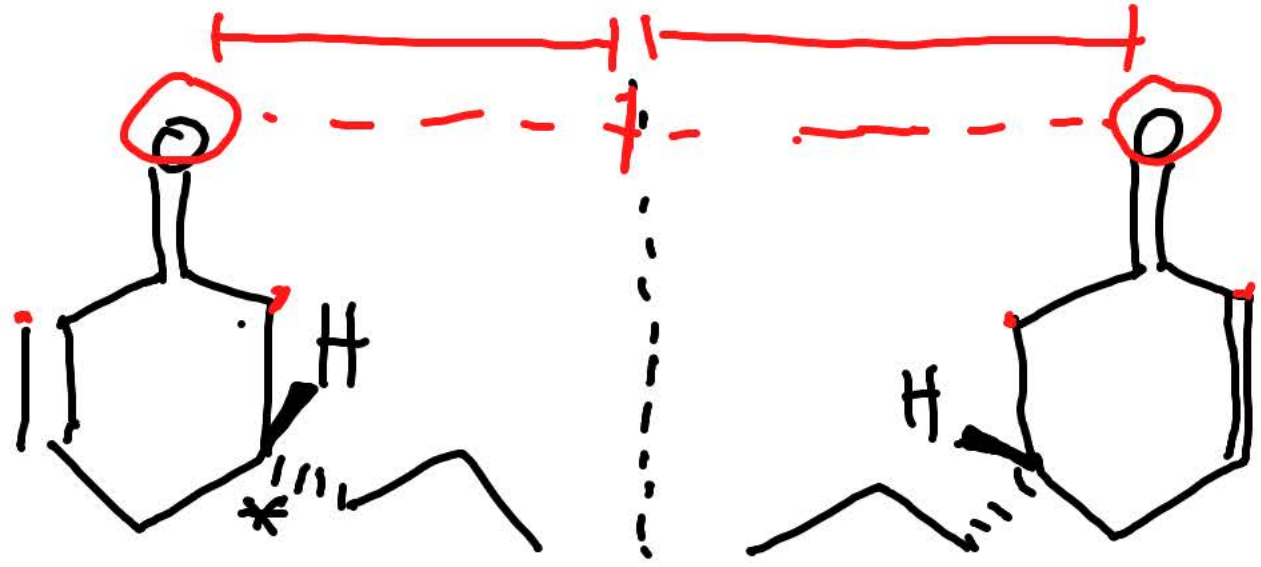
d doit être derrière!

a-b-c: sense inverse des aiguilles d'une montre: S

odeurs/gouts



céleri

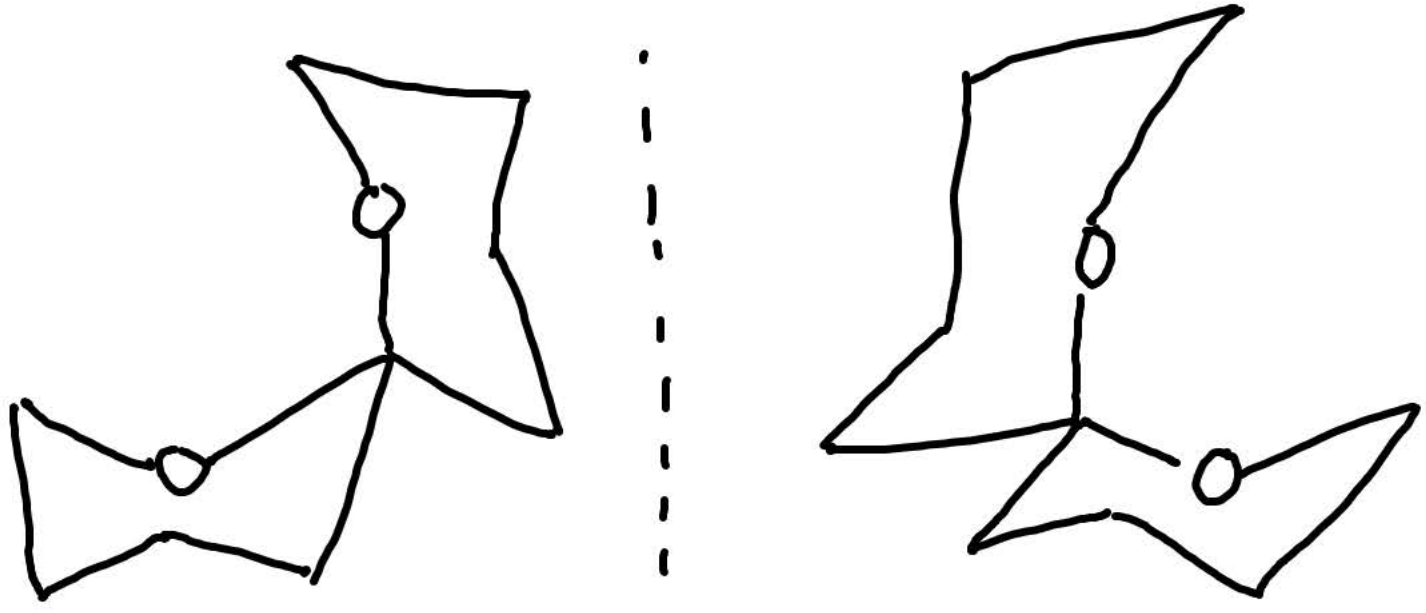


anis

d doit être derrière

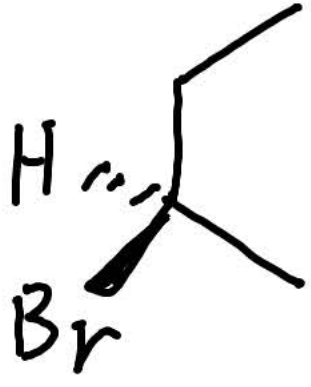
a-b-c vas dans le sens inverse
des aiguilles d'une montre
"S", mais d devant, donc R

phéromone



attire les insectes mâles

attire les insectes femelles



mesure: alpha + 20°

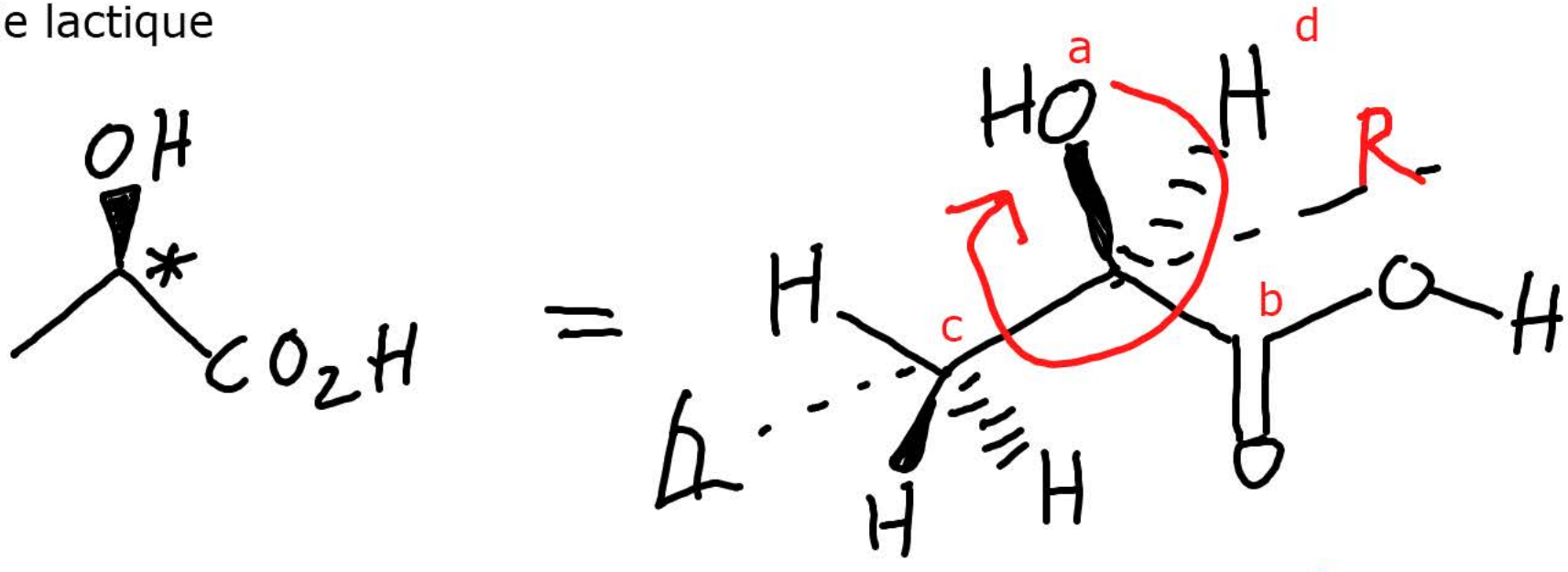
Substance pure: +23.1°

pureté optique: 20/23.1 = 87%
excès énantiomérique (ee): 87%

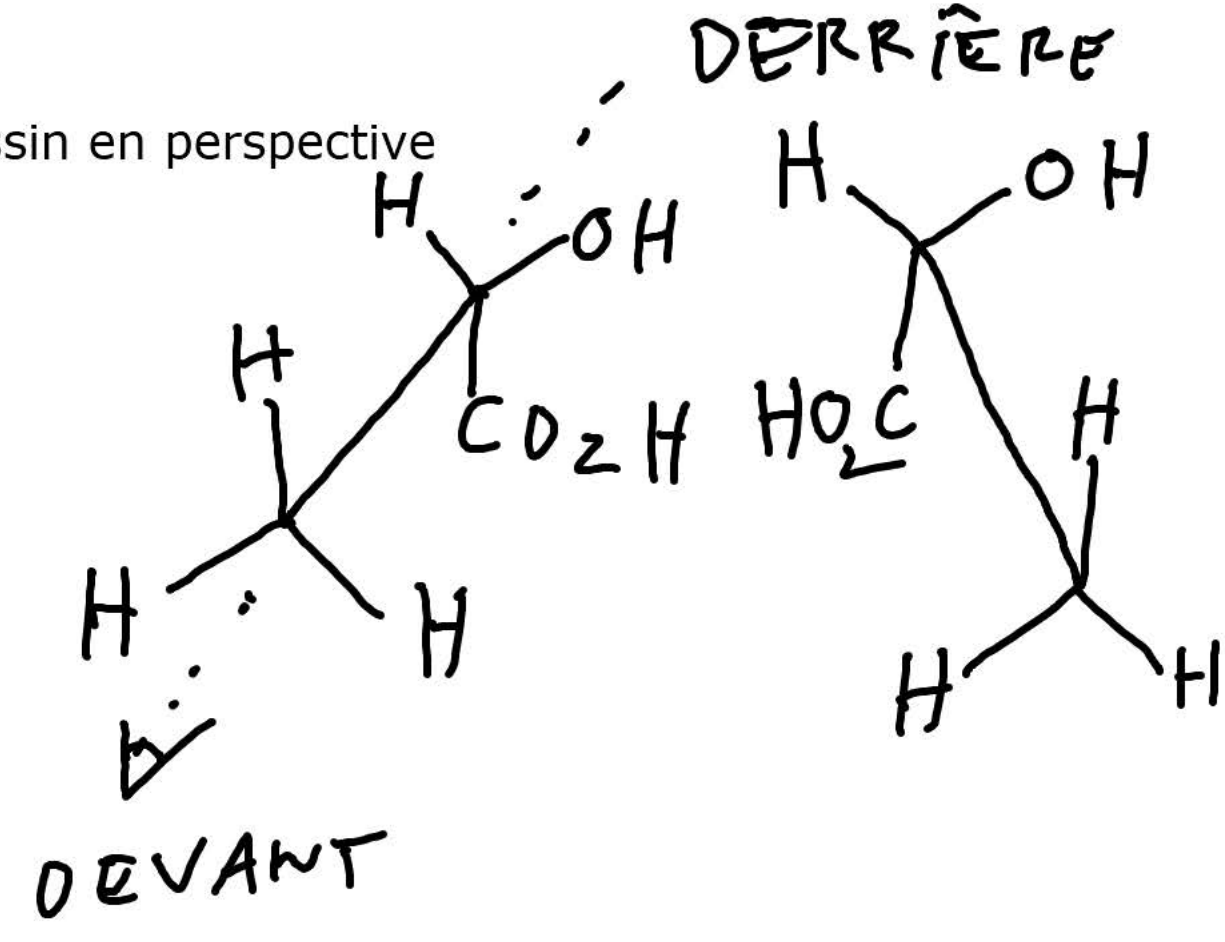
93.5-6.5 = 87
ratio énantiomérique (er): 93.5:6.5

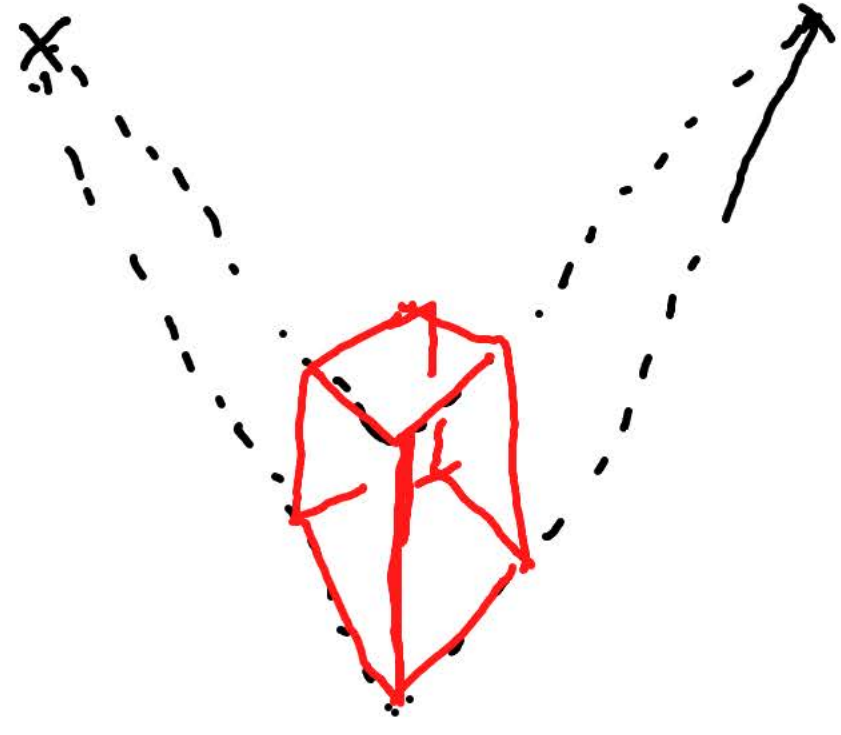
techniques de dessin en chimie organique

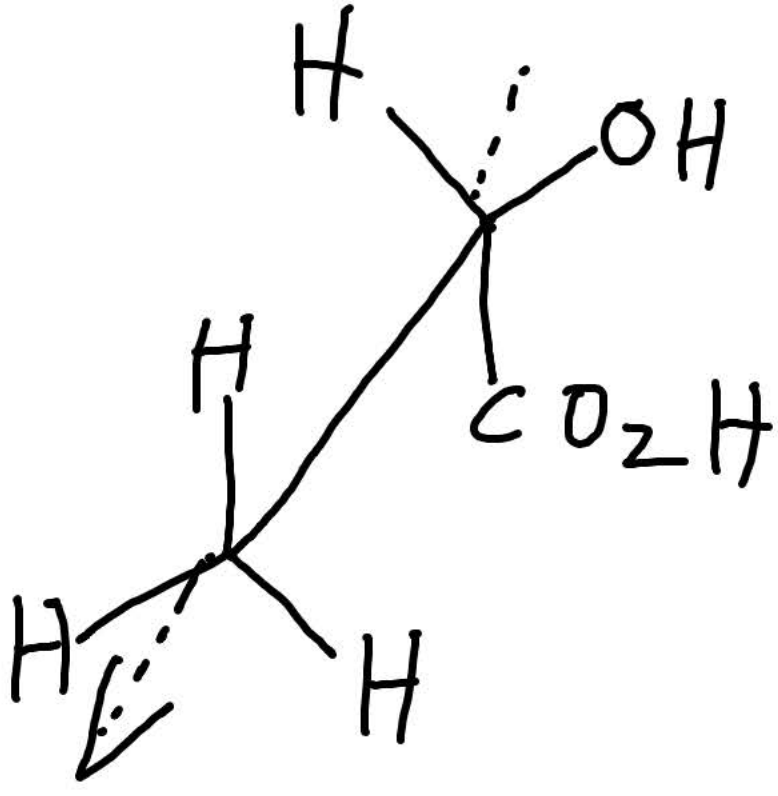
acide lactique

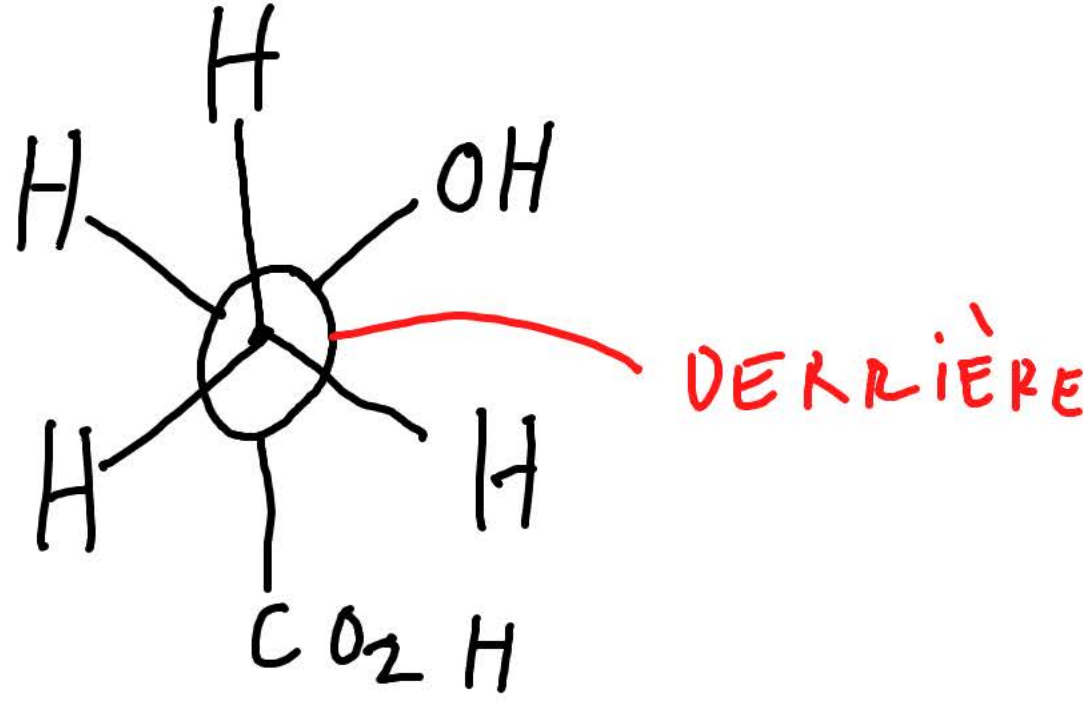


dessin en perspective



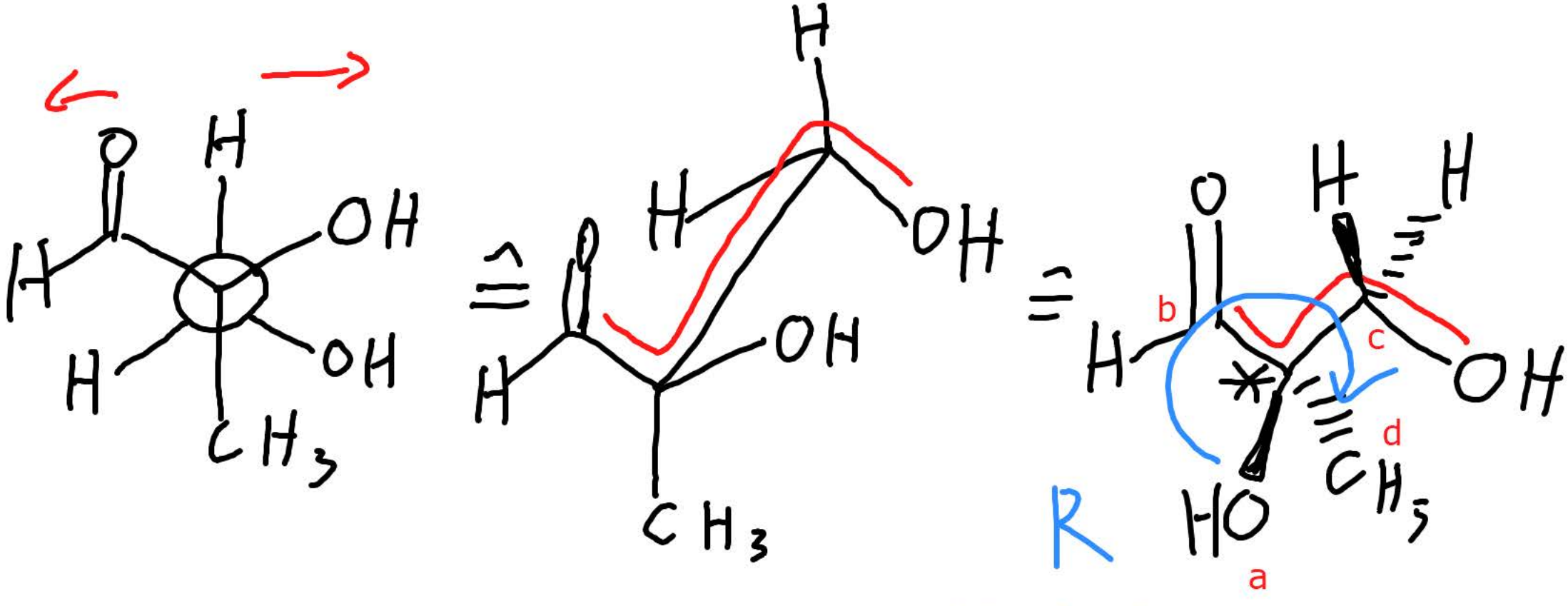






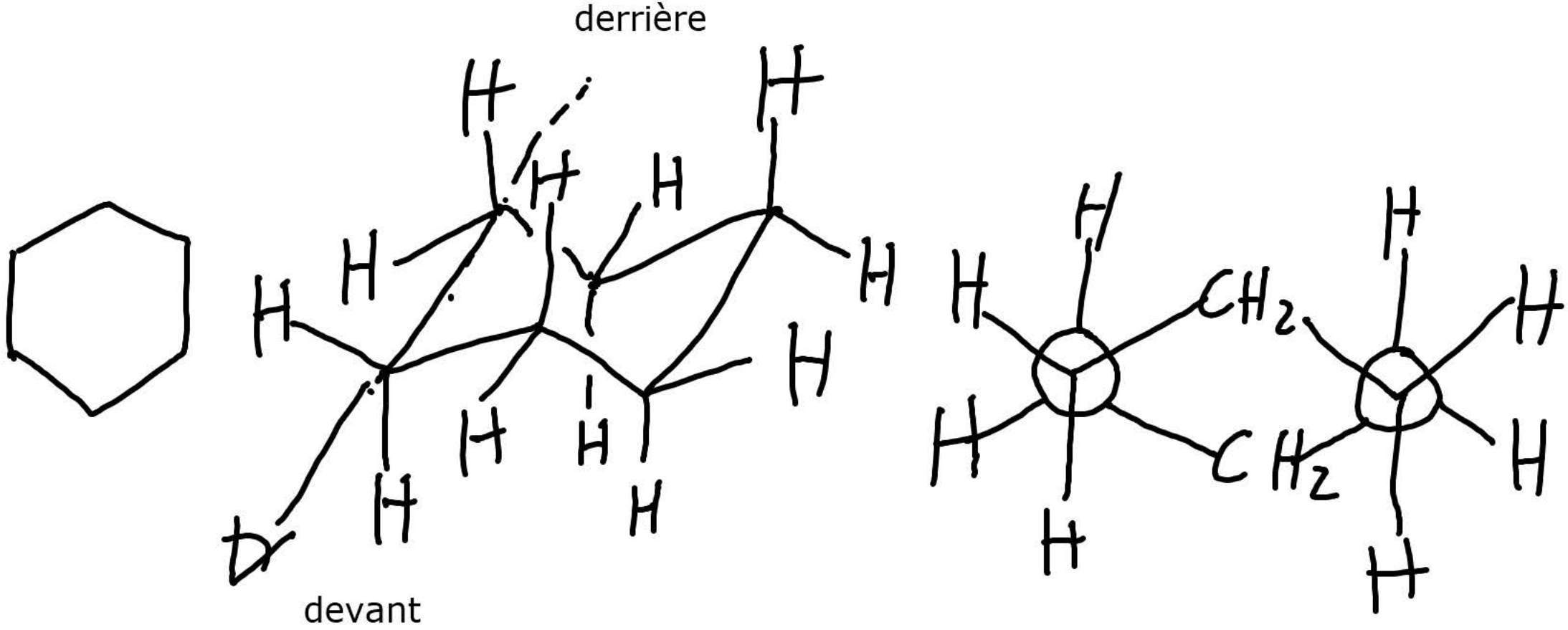
projection de Newman

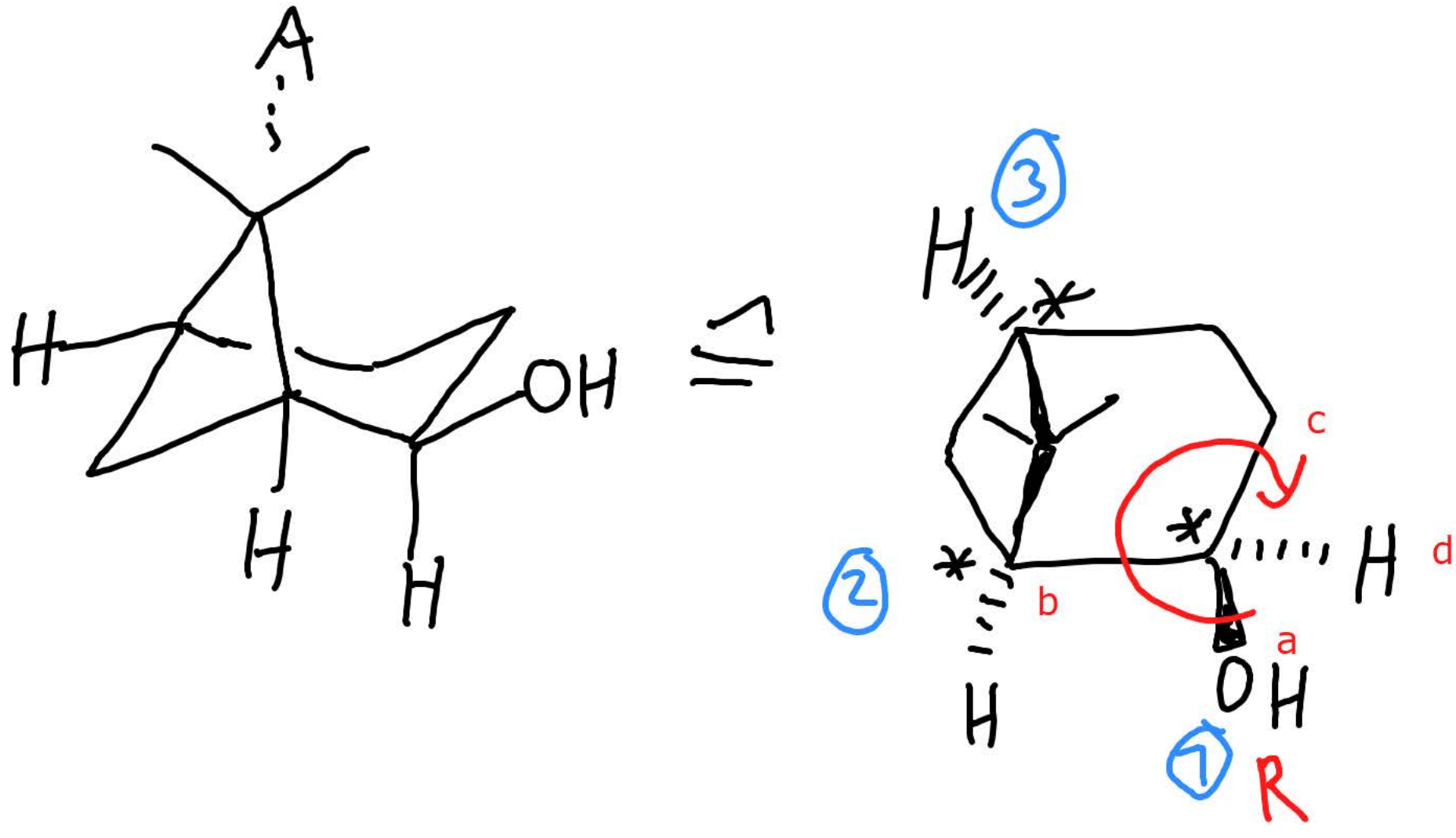
passer de Newman au "zigzag"

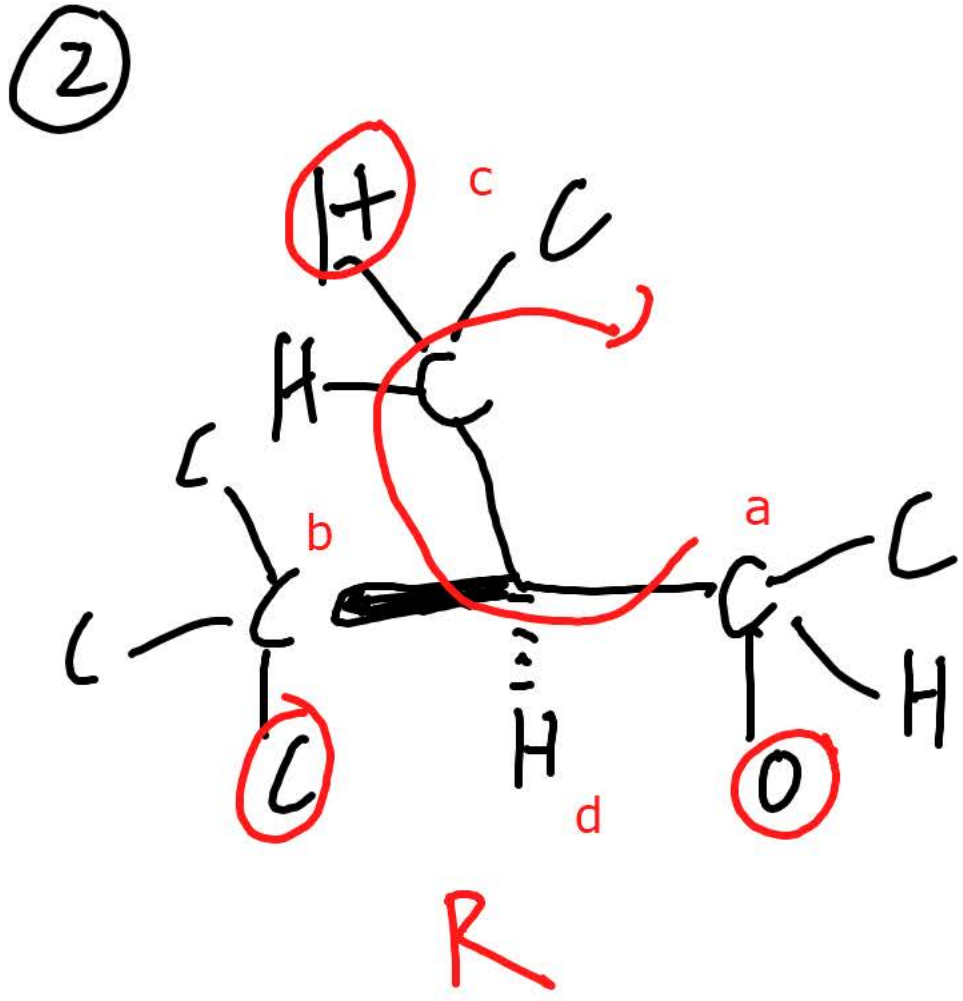


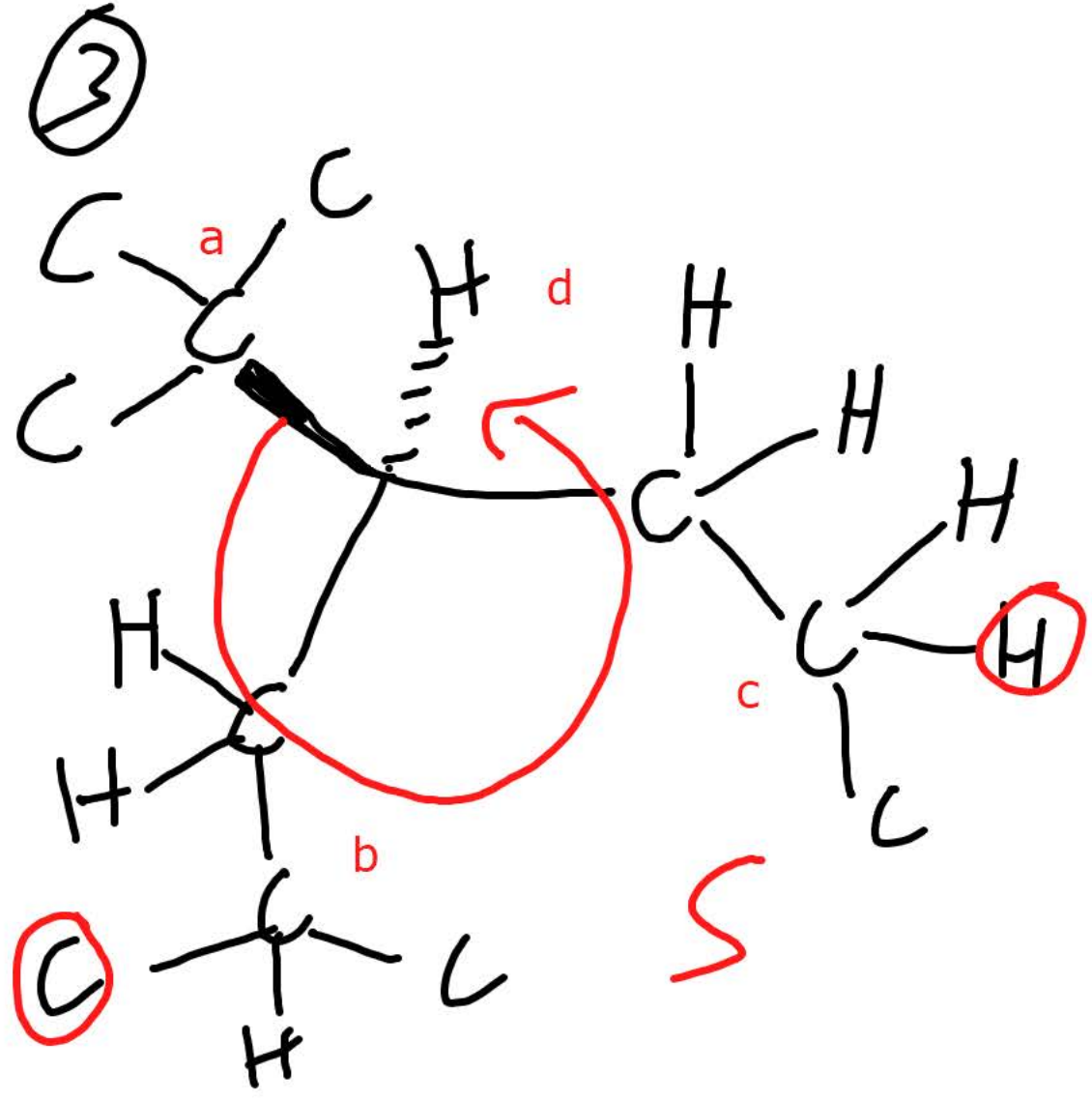
d derrière, directement OK

molécules cycliques

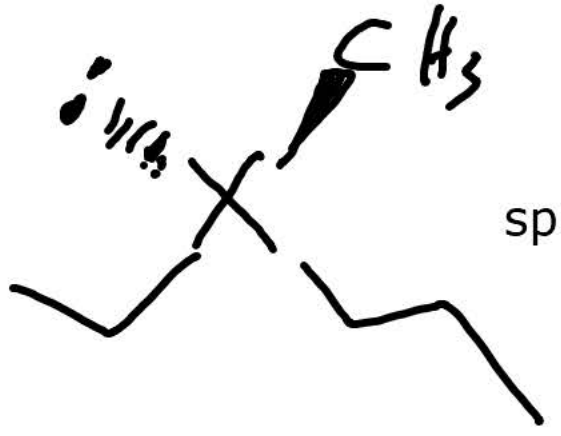



A
H
OH
H
H
≅
3
H
*
c
*
H
d
2
*
b
a
H
OH
1
R

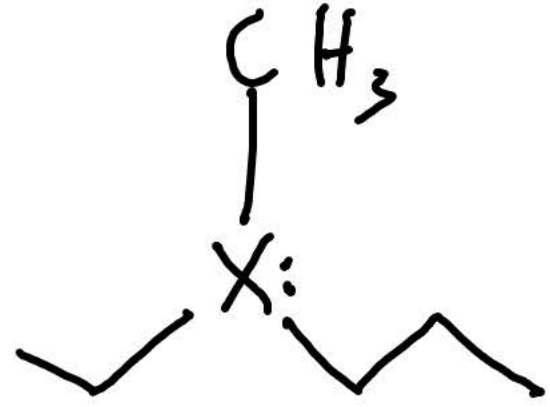

2
c
b
a
d
R

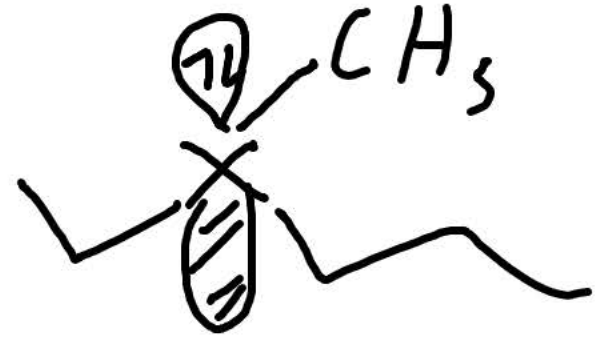

3
a
d
c
b
S

stéréocentres sur les hétéroatomes



sp3: est chiral

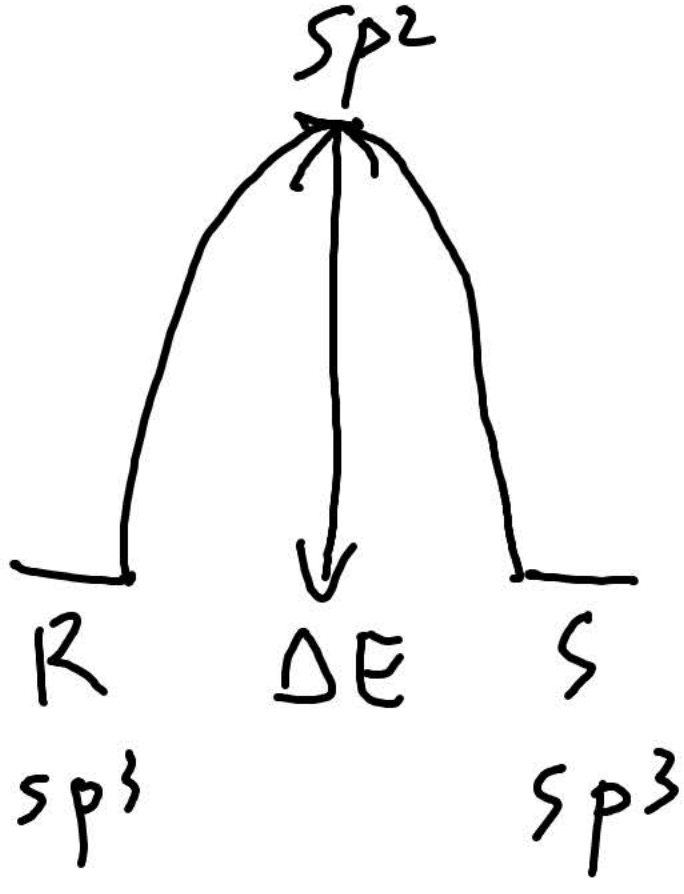




X = N, alpha = 0
X = P, apha non égal à 0

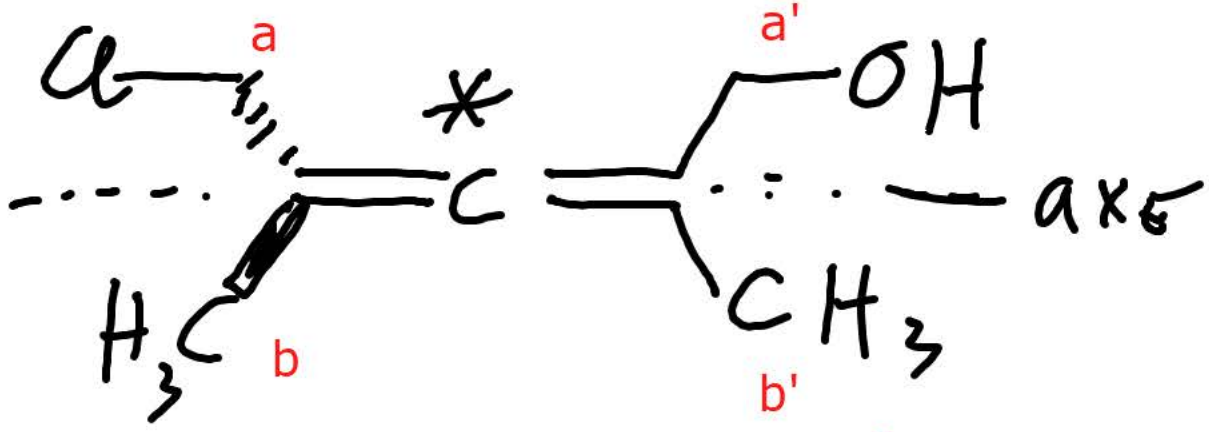
sp 2 est non chiral

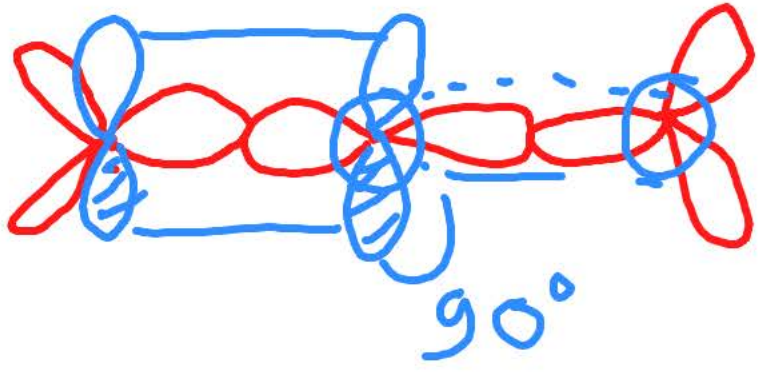
on a un stéréocentre, uniquement si sp2 ne peut pas être atteint à température ambiante



pour P : deltaE = 25 kcal/mol
Pour N: deltaE = 10 kcal/mol
T = 25 °C, 21 kcal/mol

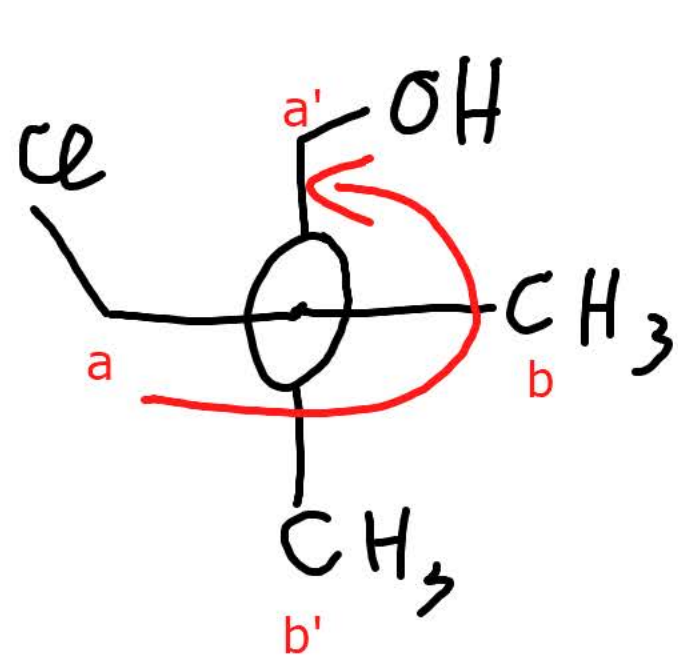
axe de chiralité 1: allènes





1) déterminer le groupe prioritaire, on le placera devant
2) priorité devant et derrière

3) dessiner Newman

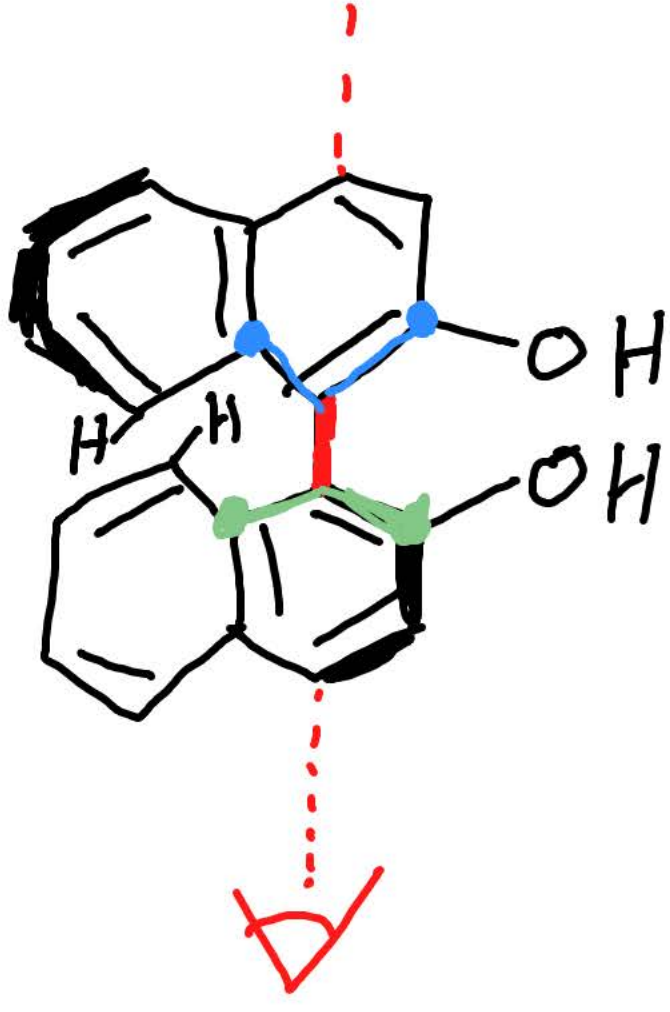


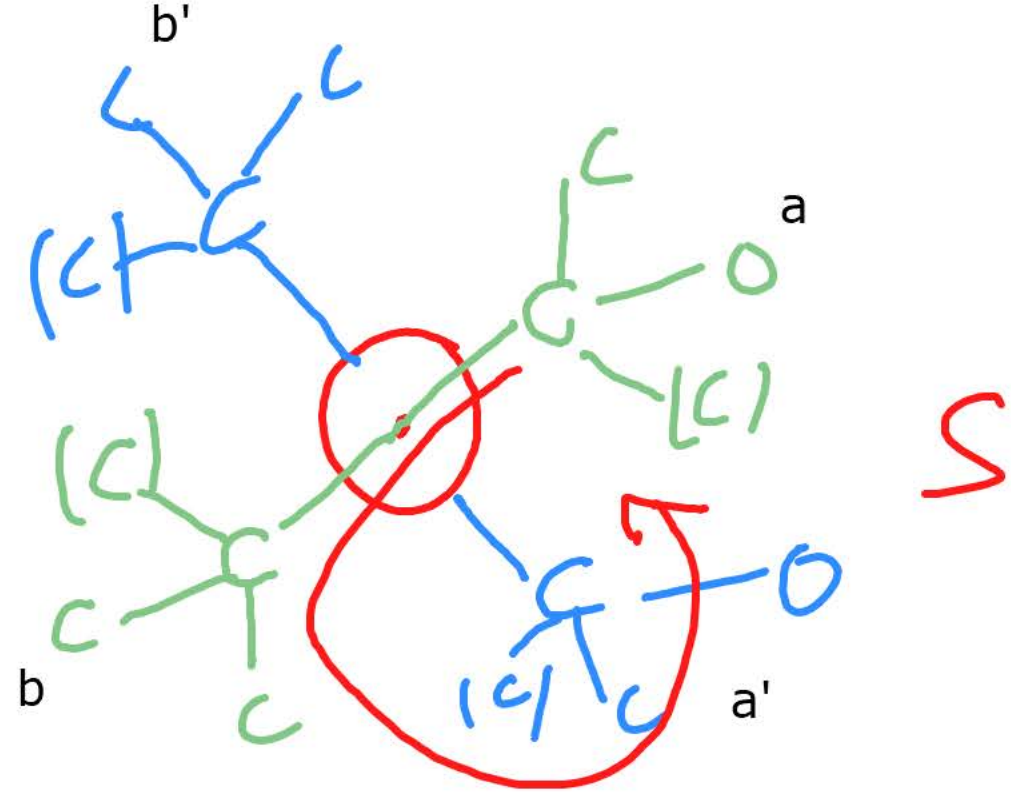
axe

S

4) on tourne a-b-a'

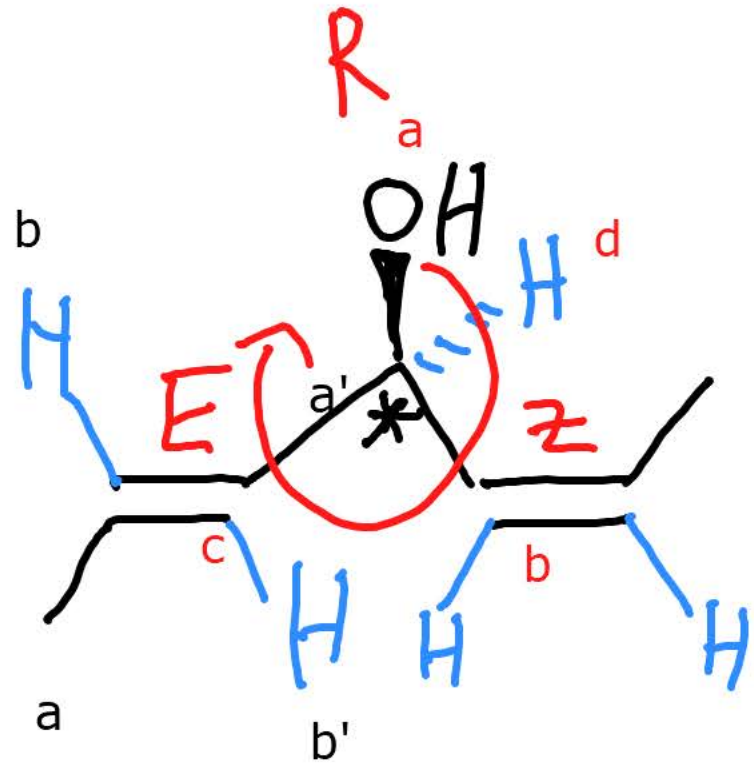
axe de chiralité: BINOL





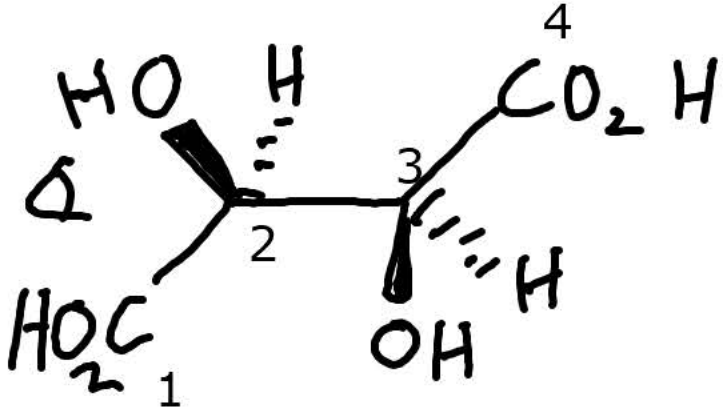
sens: grand devant, petit devant, grand derrière

alcènes



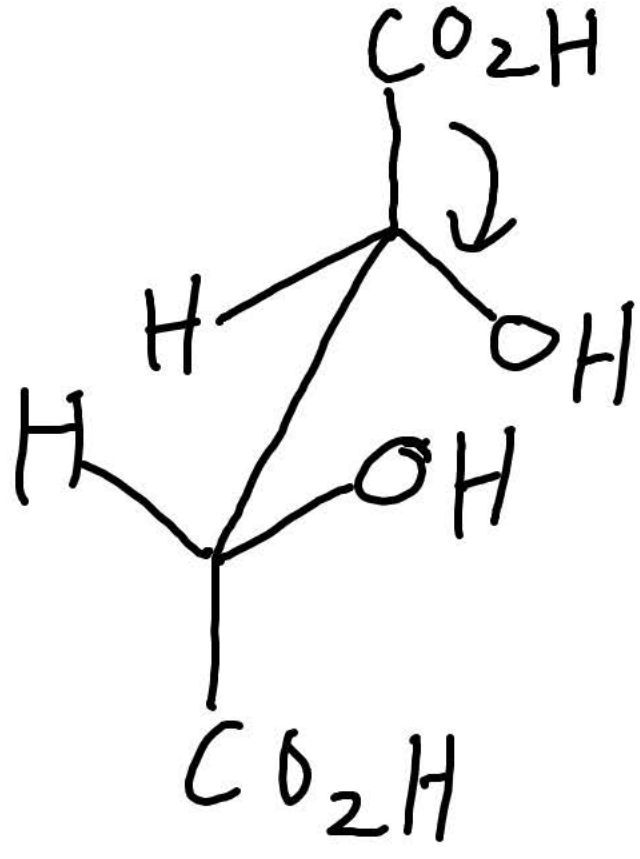
règle: Z à la priorité sur E

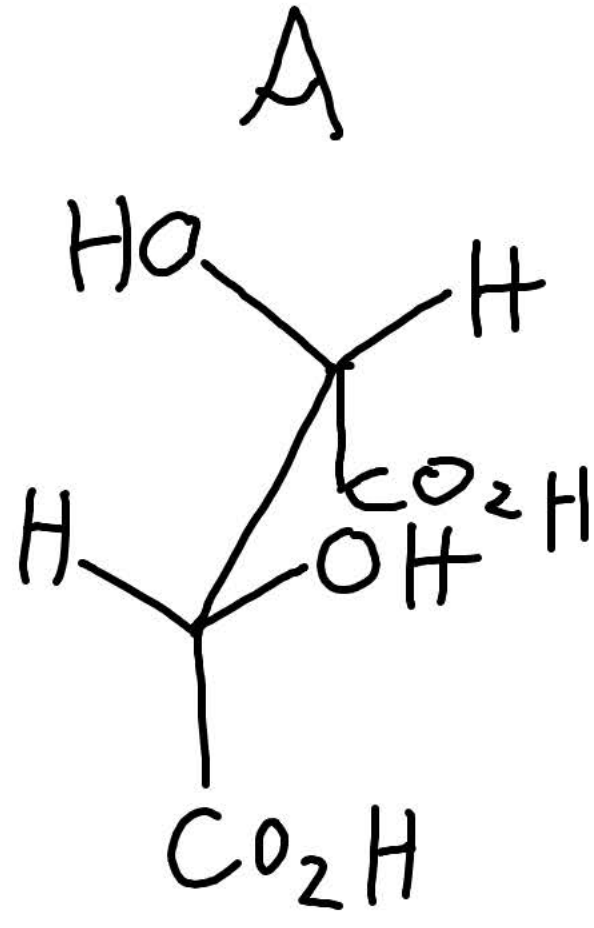
acide tartrique

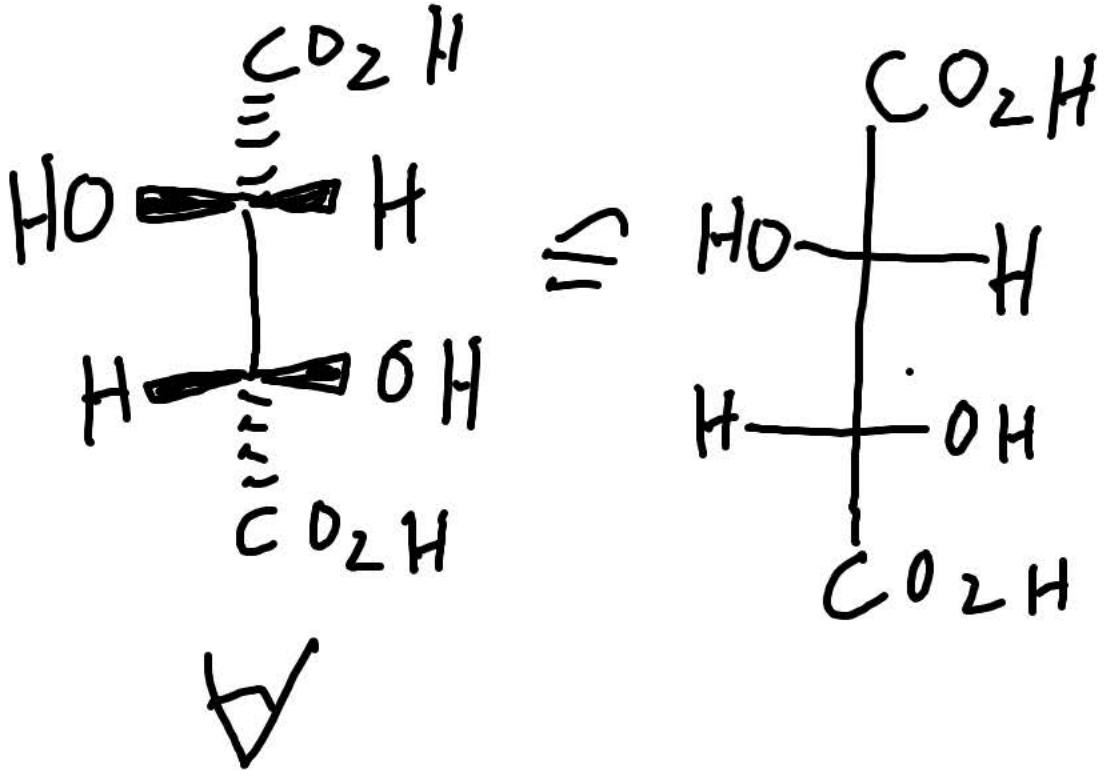


(-)-(2S,3S)

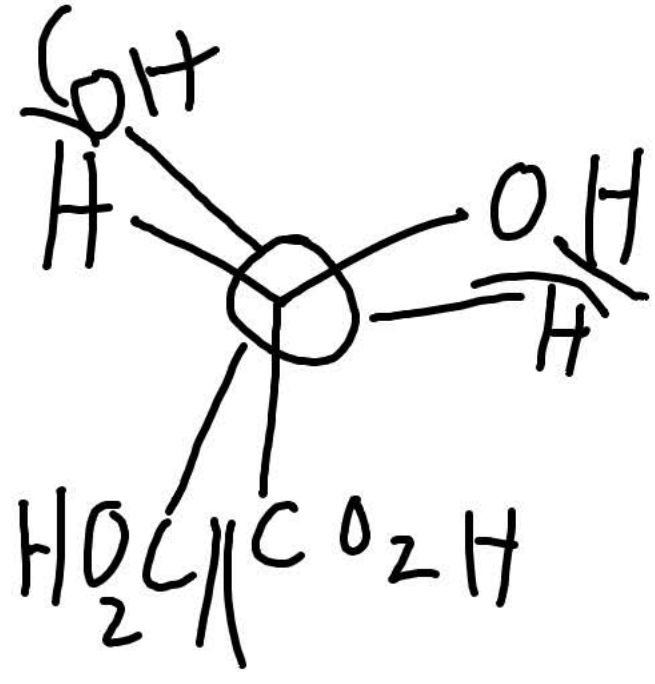
alphaD = -12°





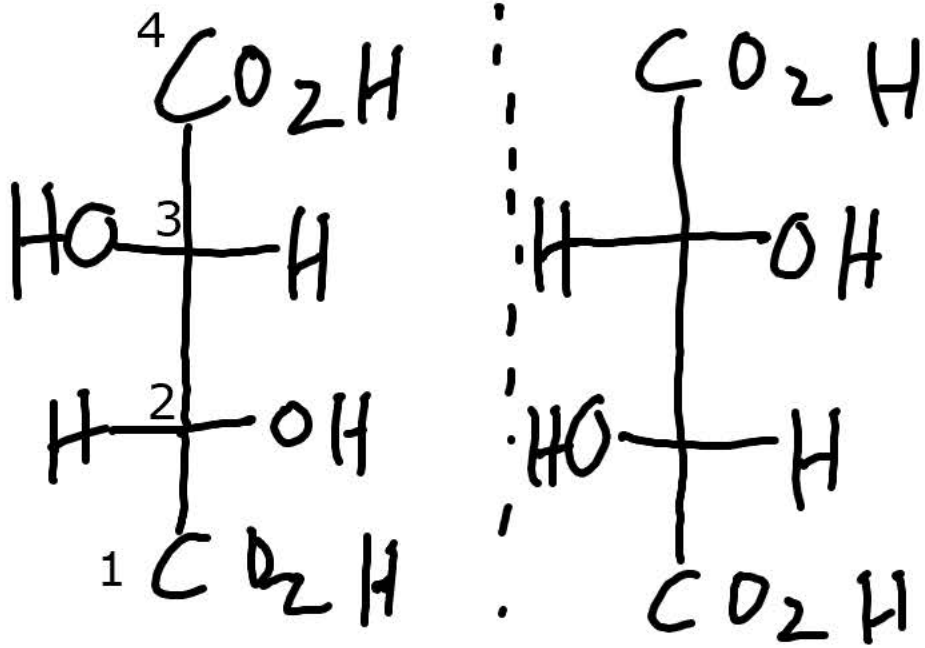


projection de Fischer



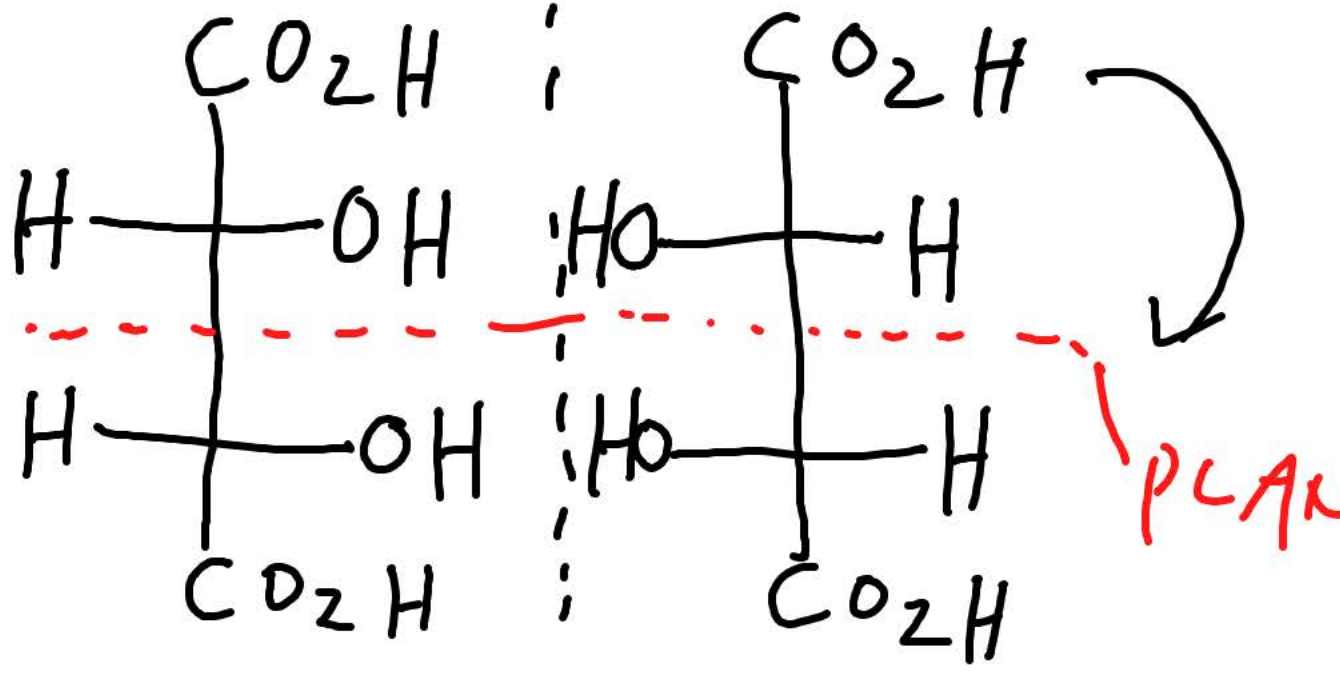
situation pas favorable

plan de symmétrie. meso, non chiral



(-)-(2S,3S)

(+)-(2R,3R)



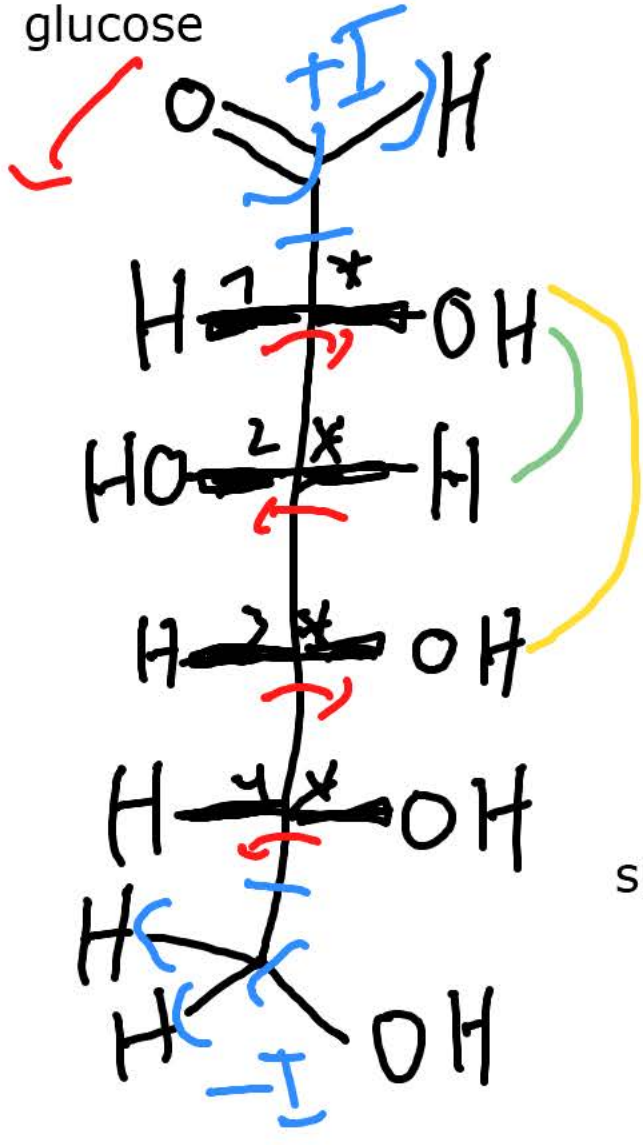
(2S,3R)

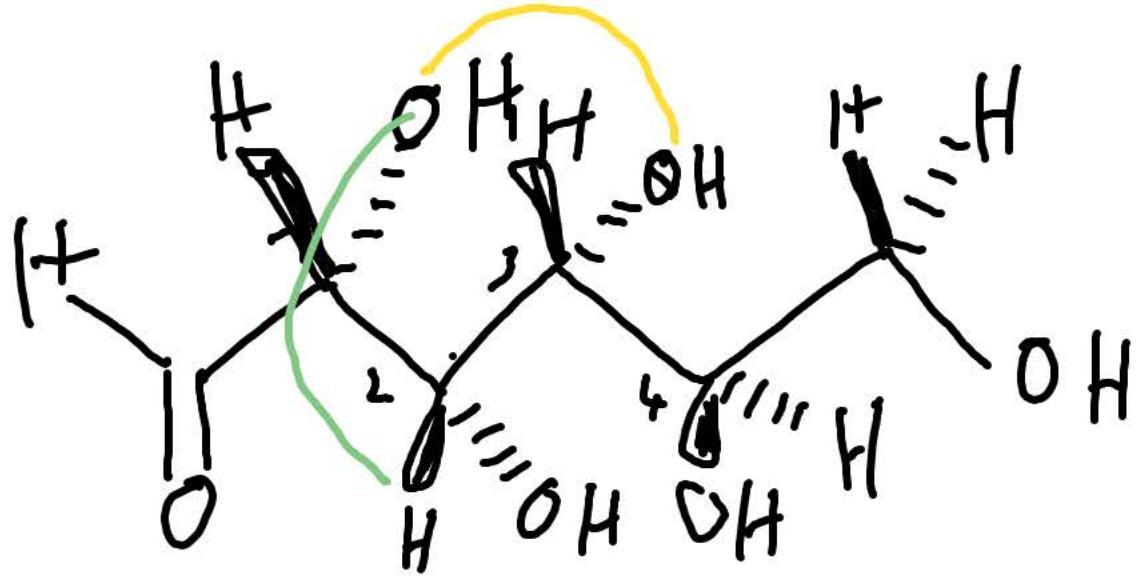
(2R,3S)

molécules identiques

alphaD = 0

glucose





substituant 1,2 du même côté sur Fischer: côté opposé en zigzag

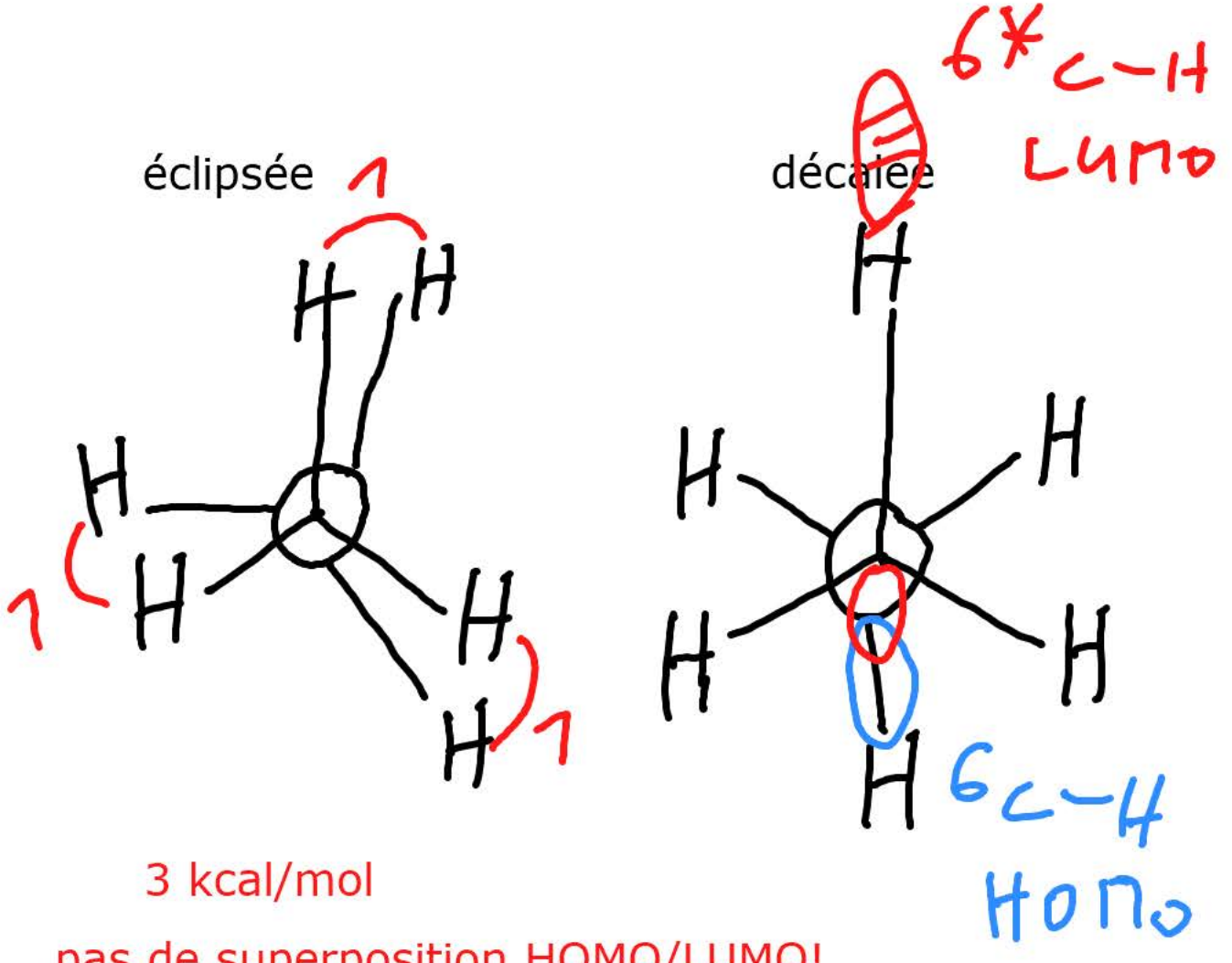
substituant 1,3 du même côté sur Fischer: du même côté en zigzag

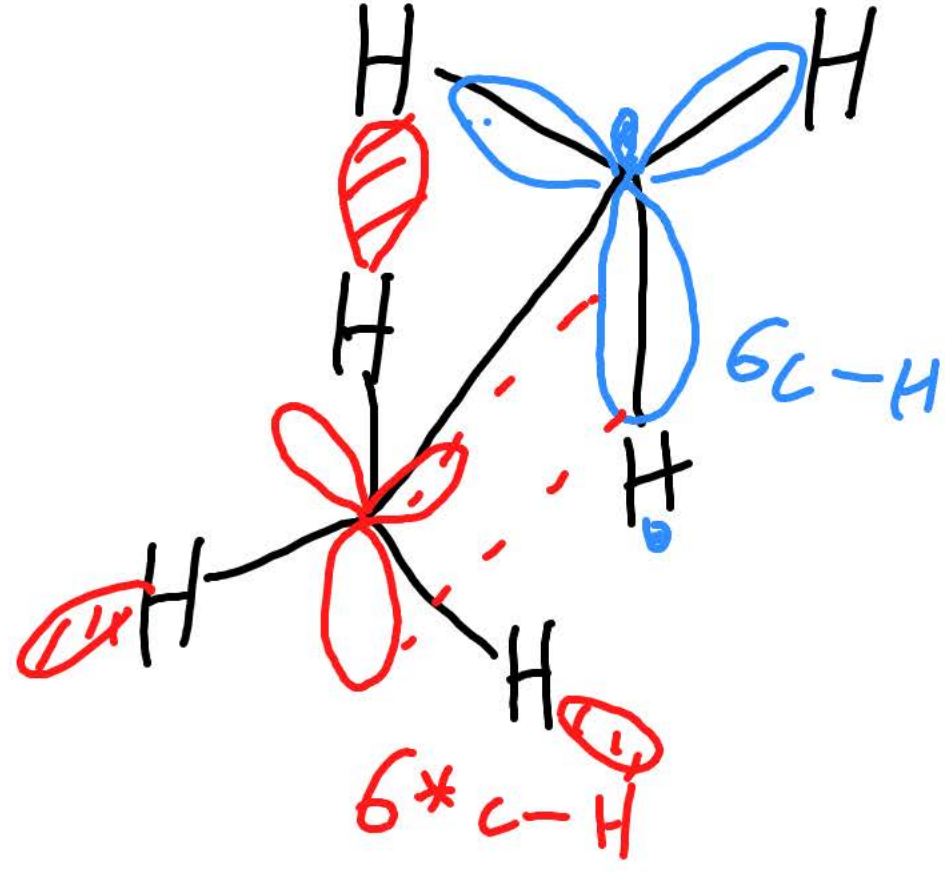
convention pour dessin: le centre le plus oxidé en haut

origine de la barrière pour l'éthane

éclipsée

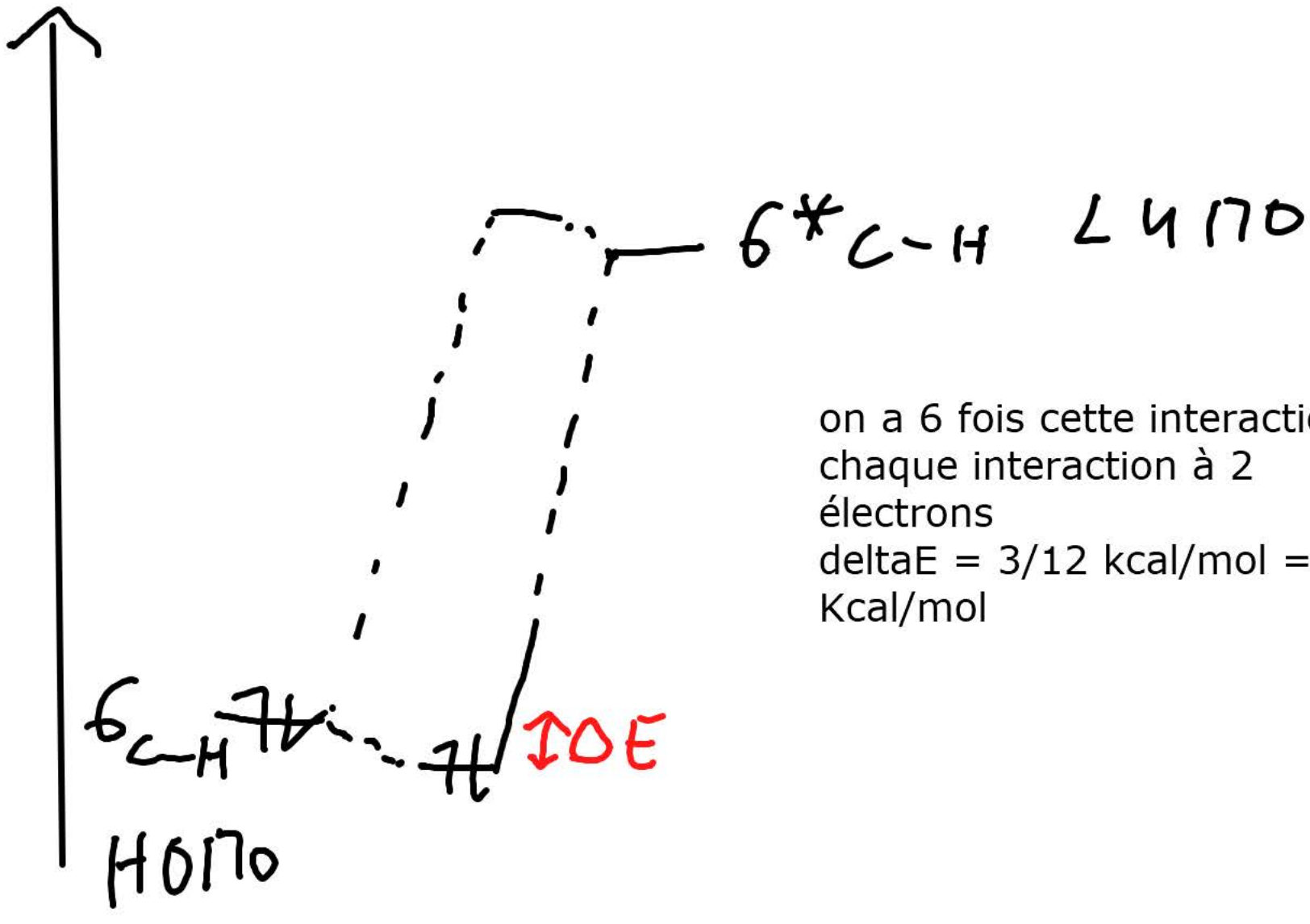
décalée





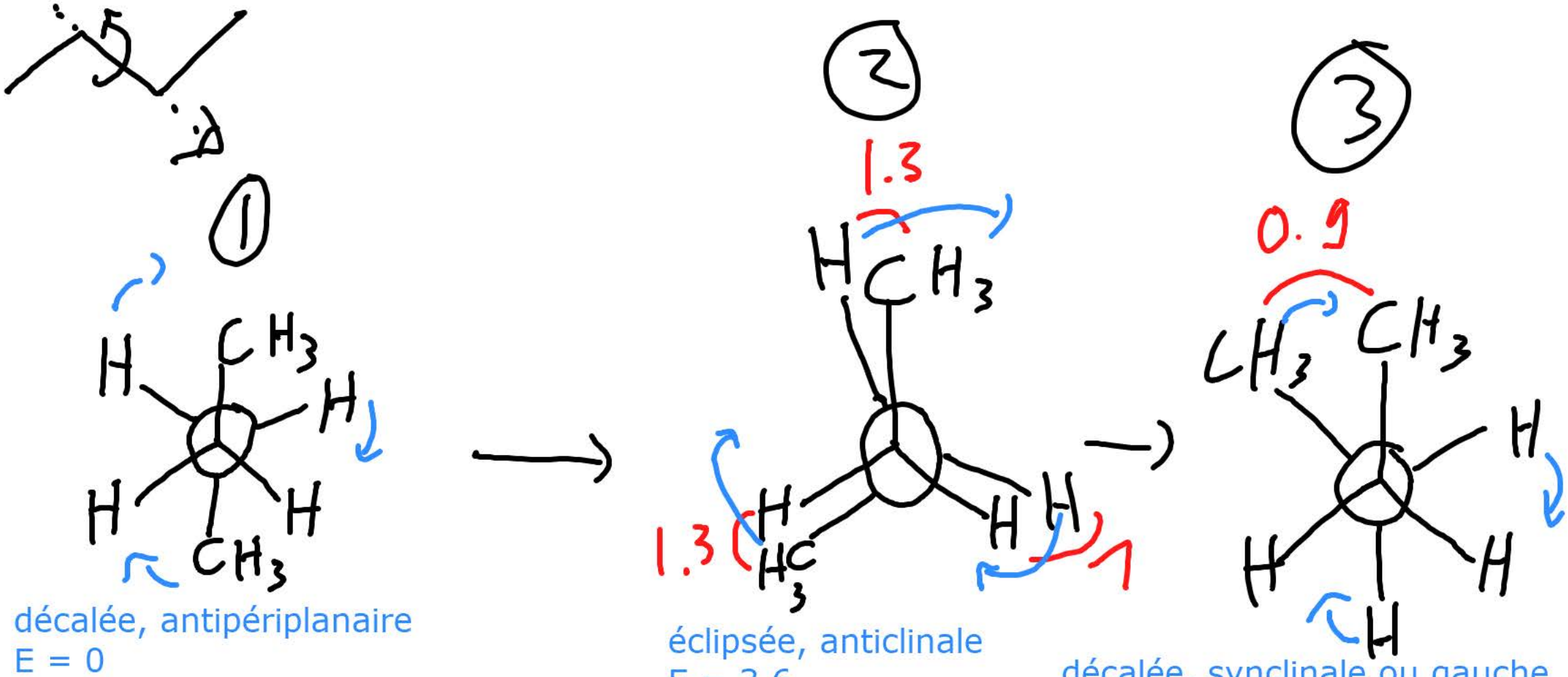
3 kcal/mol

pas de superposition HOMO/LUMO!



on a 6 fois cette interaction, chaque interaction à 2 électrons
deltaE = 3/12 kcal/mol = 0.25 Kcal/mol

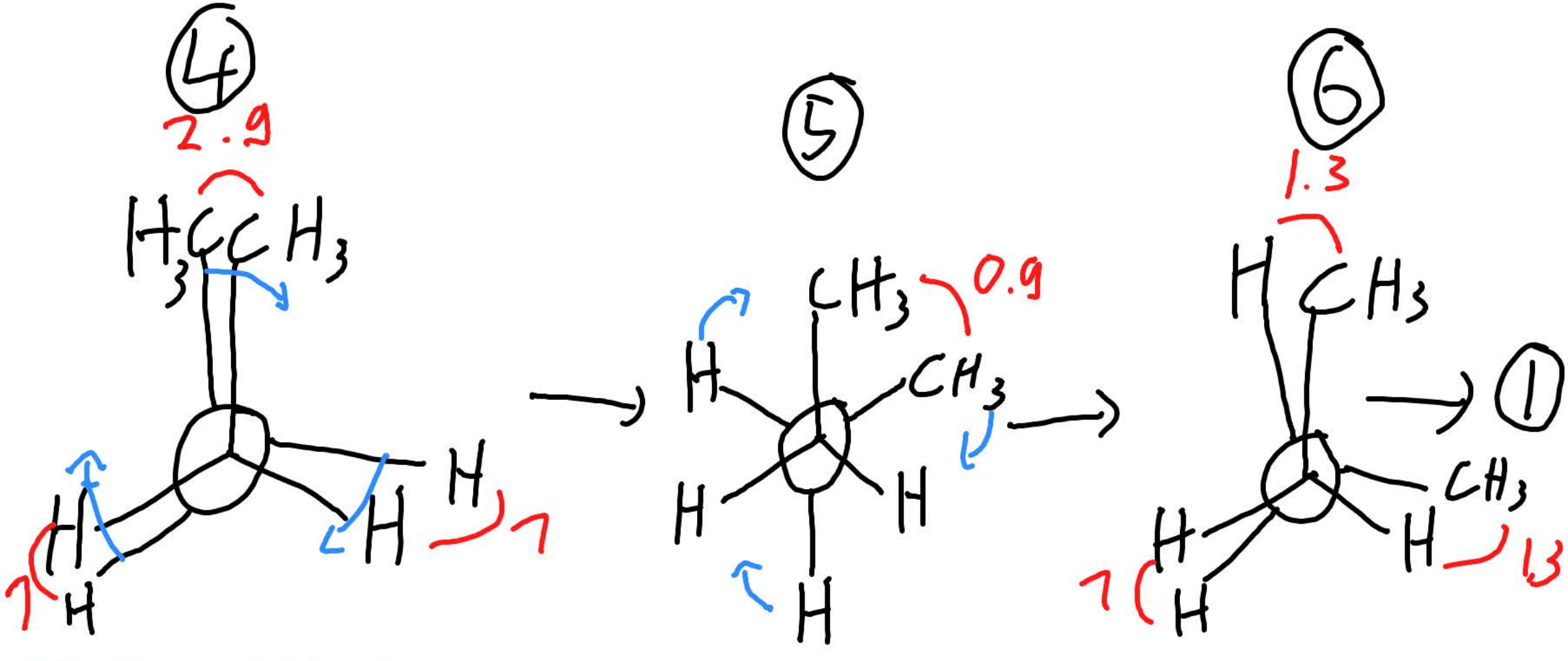
butane



décalée, antipériplanaire
E = 0

éclipsée, anticlinale
E = 3.6

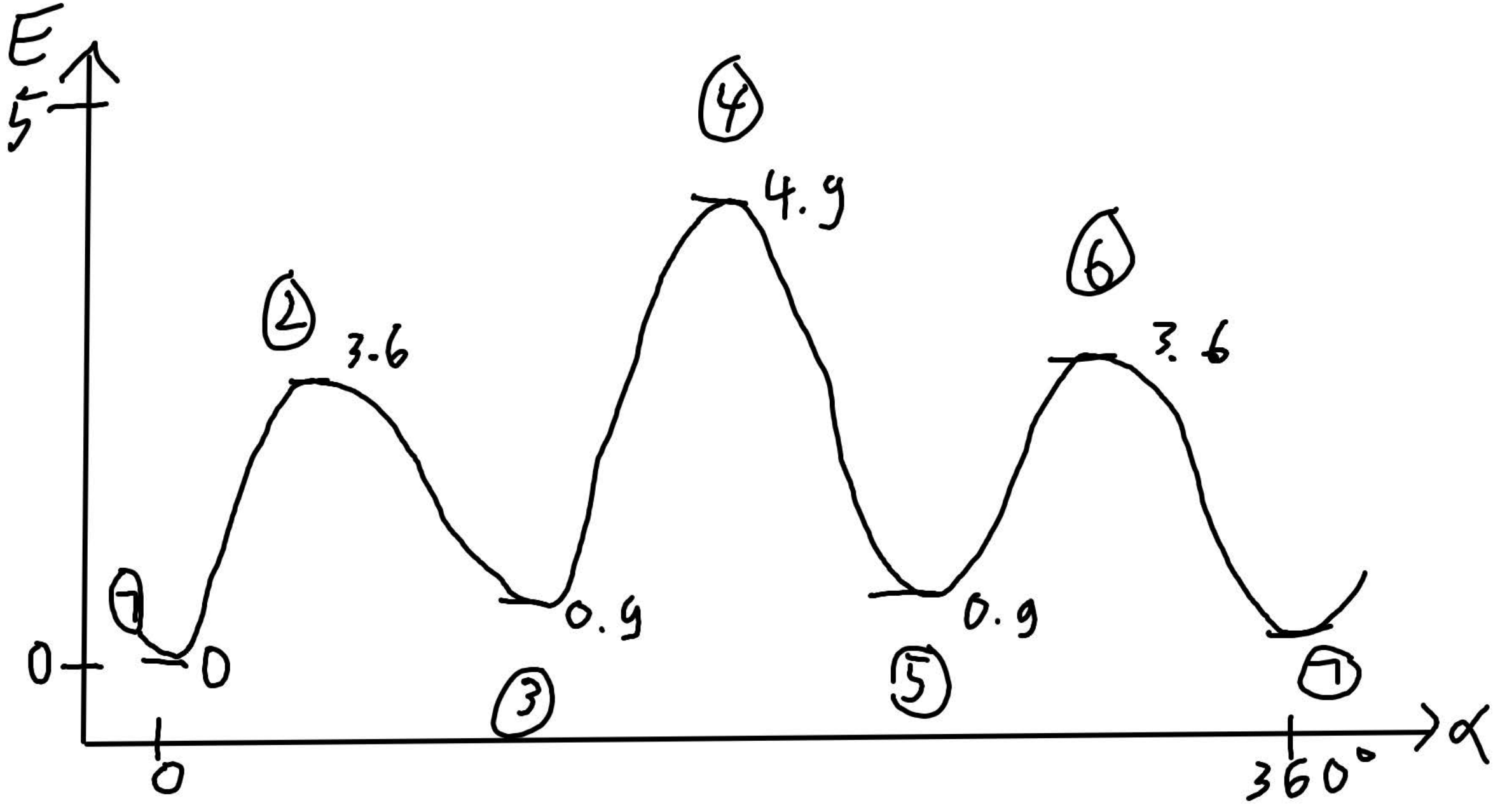
décalée, synclinale ou gauche
E = 0.9



éclipsée, synpériplanaire
E = 4.9

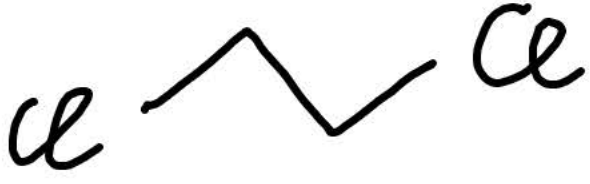
décalée, synclinale/gauche
E = 0.9

éclipsée, anticlinale
E = 3.6

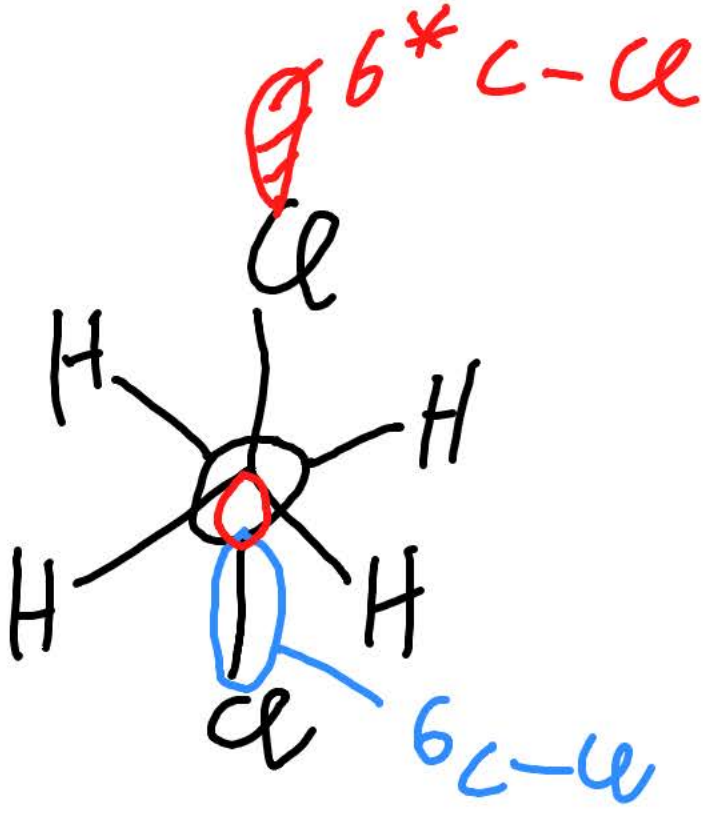

E
5
0
0
0
3.6
0.9
4.9
0.9
3.6
1
2
3
4
5
6
7
0
360°
α

comparaison butane dichloroéthane

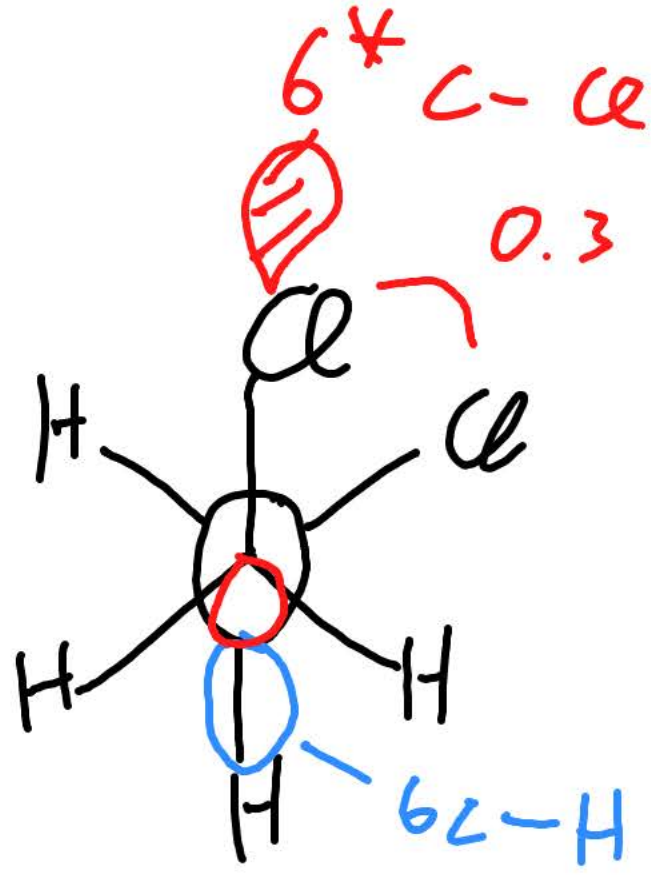
conformation antipériplanaire est la plus stable



conformation gauche (synclinale) est plus stable que antipériplanaire!

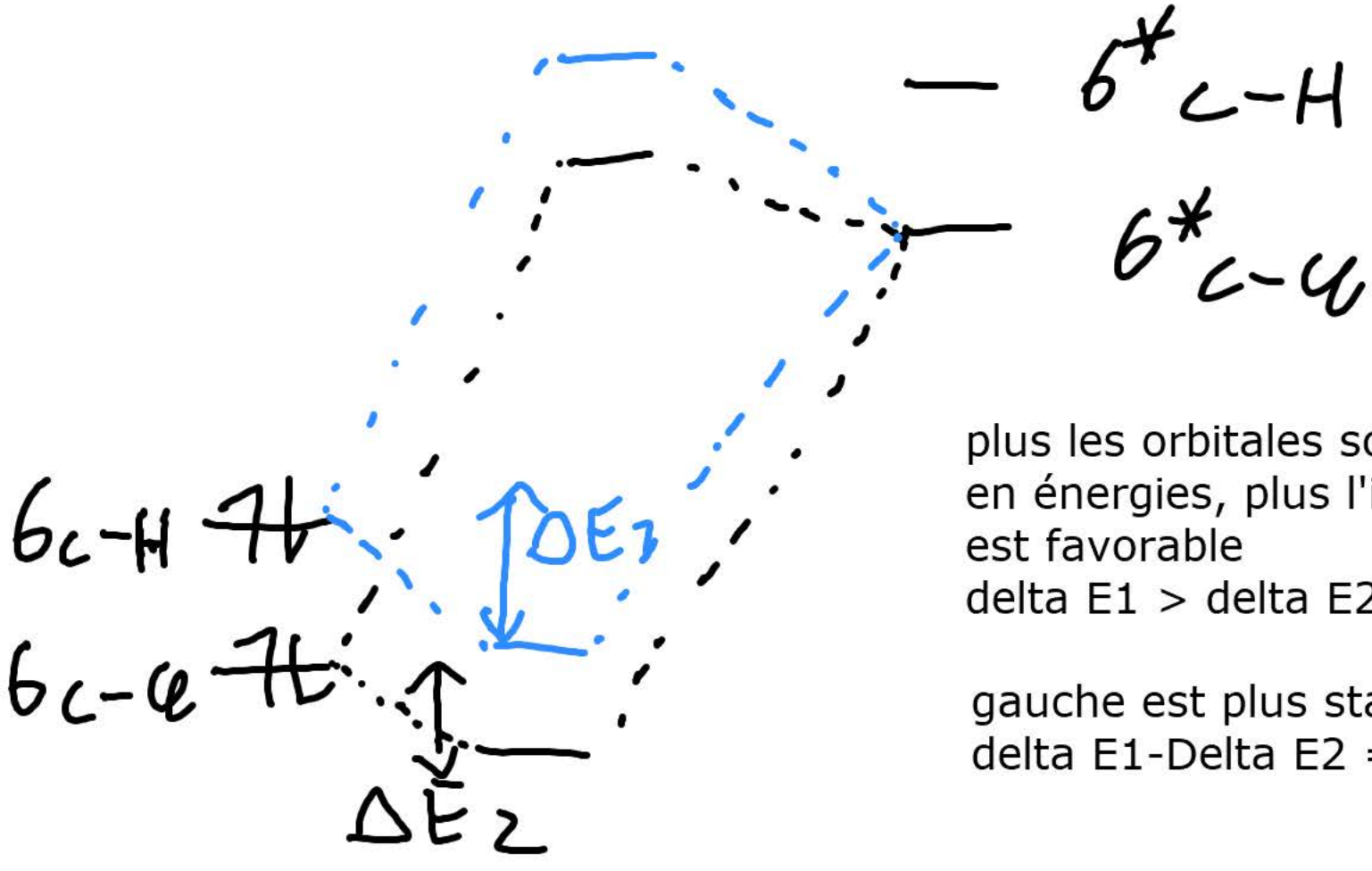


antipériplanaire



0.3 au lieu de 0.9, car Cl plus petit que CH3

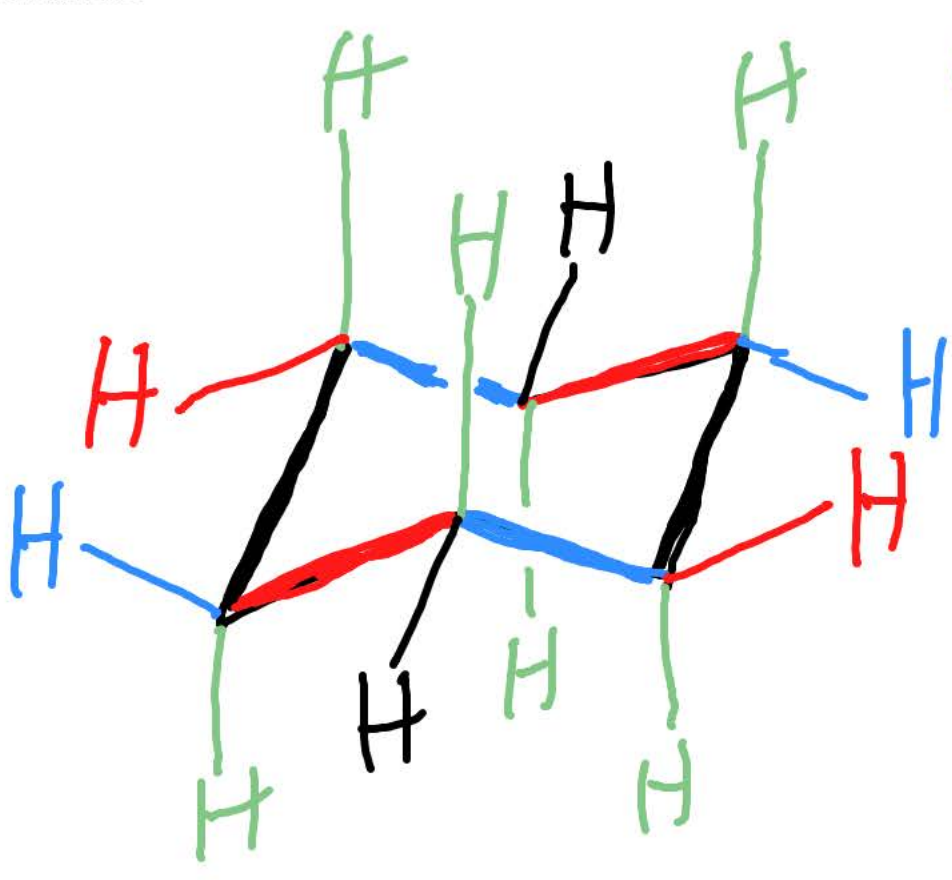
gauche



plus les orbitales sont proches en énergies, plus l'interaction est favorable
delta E1 > delta E2

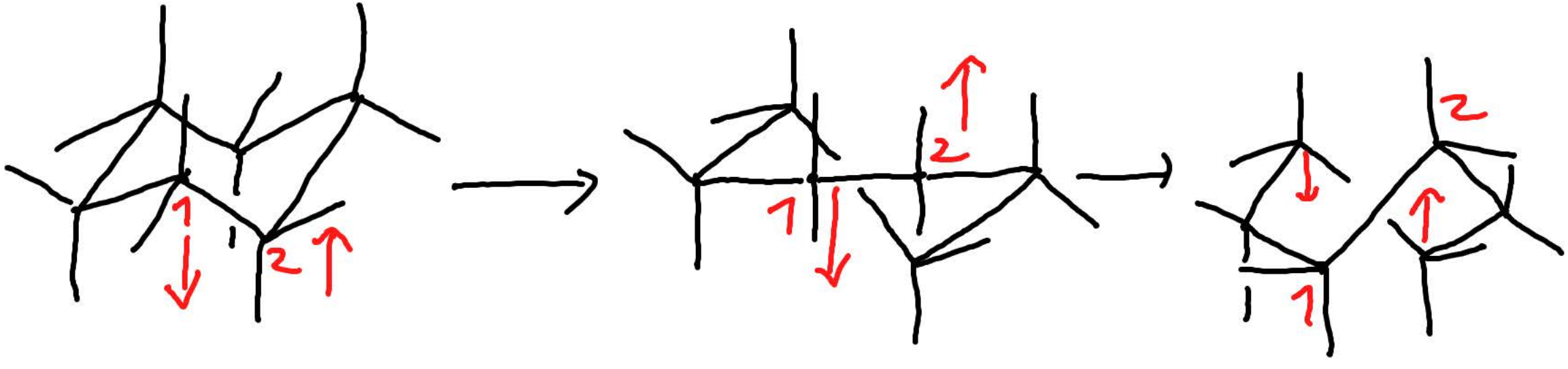
gauche est plus stable de 1 kcal/mol
delta E1-Delta E2 = 1.3 kcal/mol

cyclohéxane: chaise



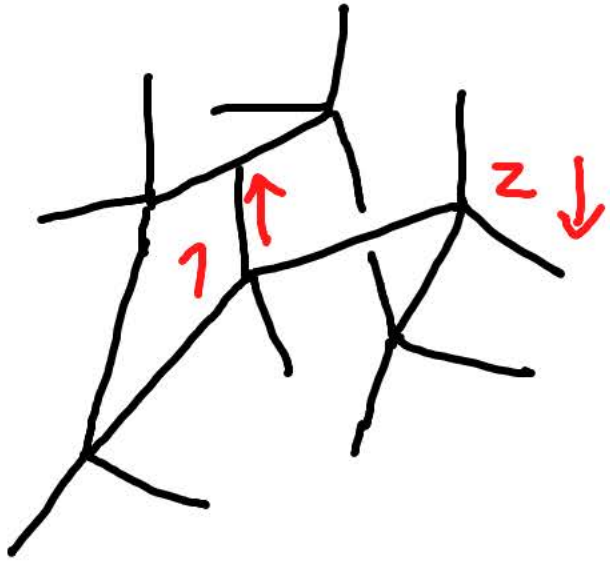
6 H équatorial (rouge, bleu, noir)

inversion de la chaise



demi-chaise
E = 10.8

bateau croisé, ou twist
E = 5.5



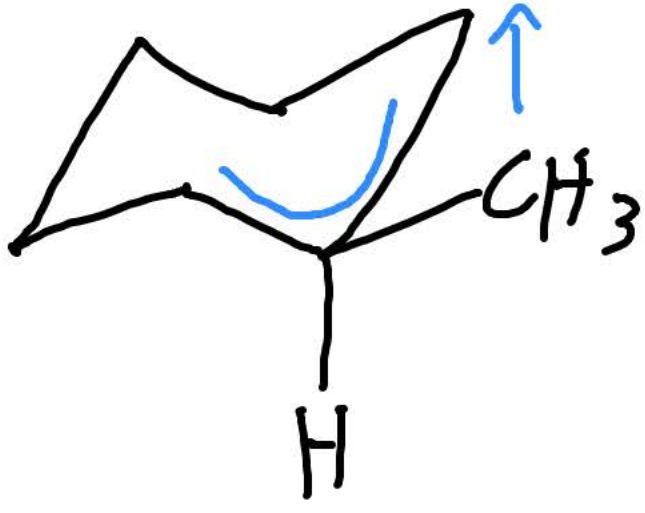
bateau, E = 6.9

→ TWIST → DEMI-CHAISE

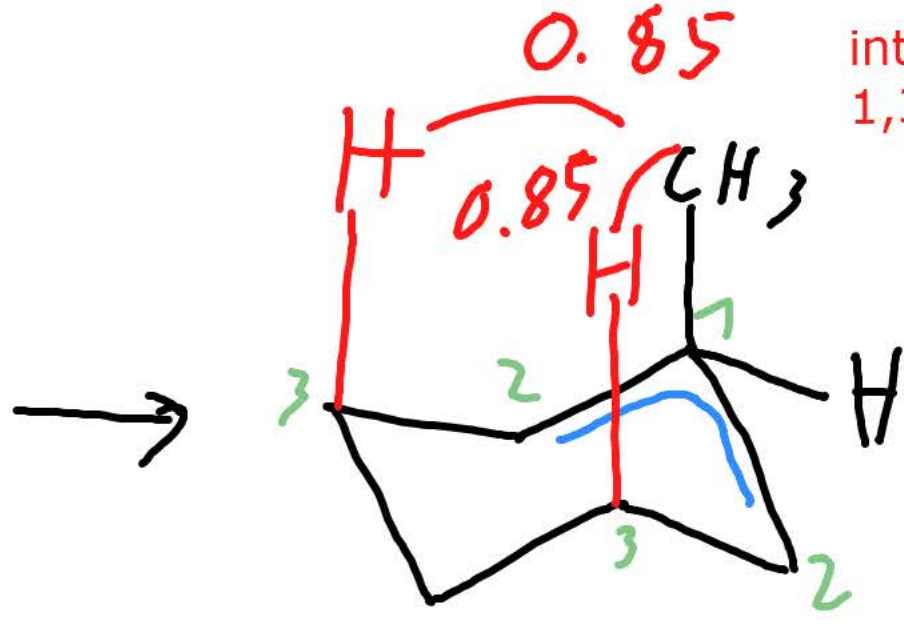
↓

CHAISE

methylcyclohexane



méthyl en équatorial

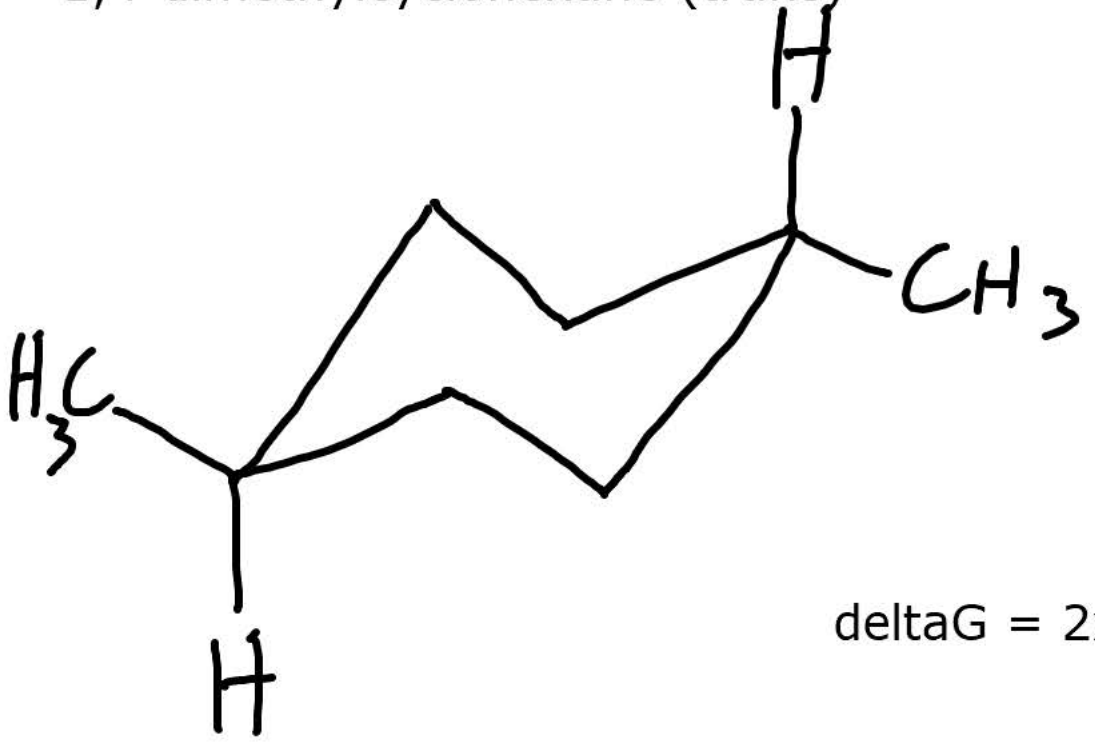


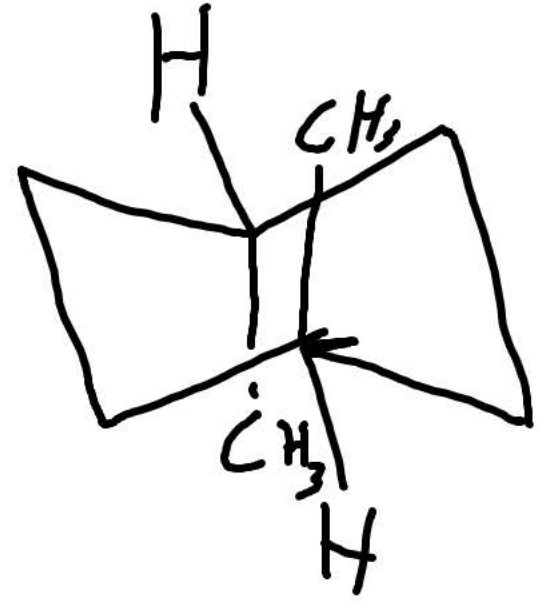
interactions
1,3-diaxiales

méthyl en axial

deltaG = 1.7 Kcal/mol,
valeur A du méthyle
deltaG = RT LnK
mélange: 95:5

1,4-dimethylcyclohexane (trans)



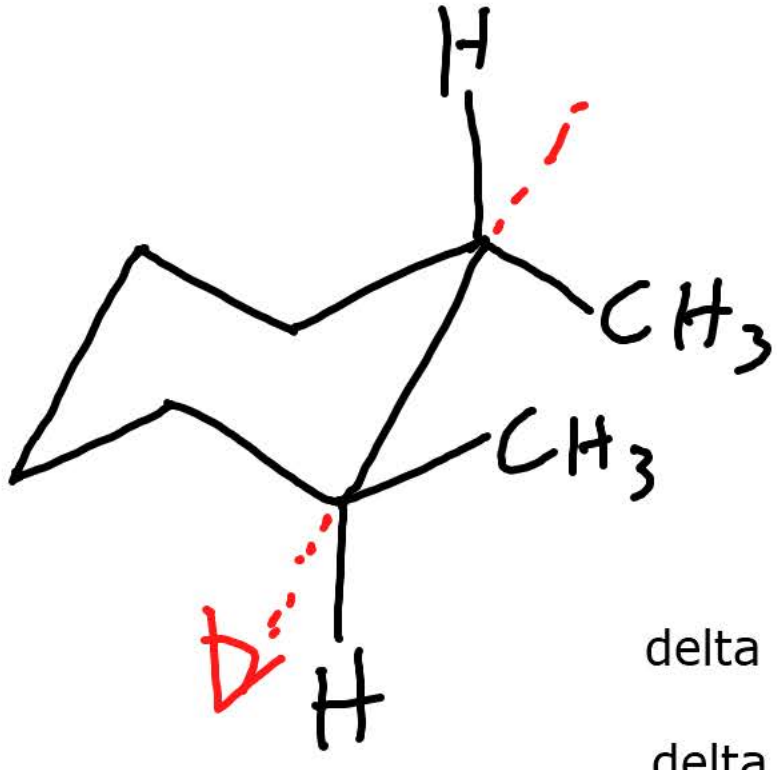


deltaG = 2x1.7 = 3.4

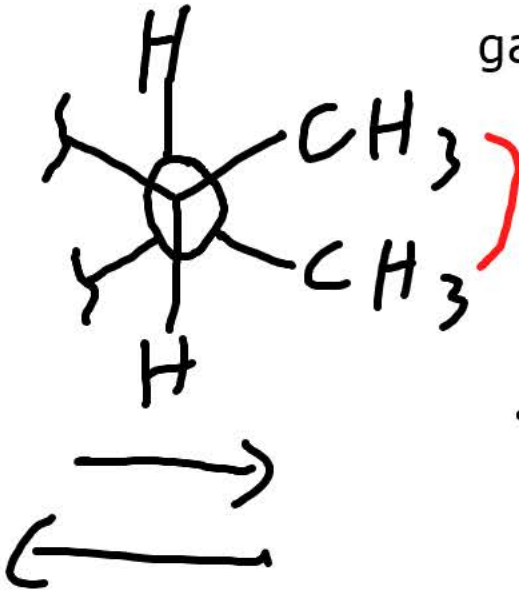
2 méthyl équatorial

2 méthyl axiales

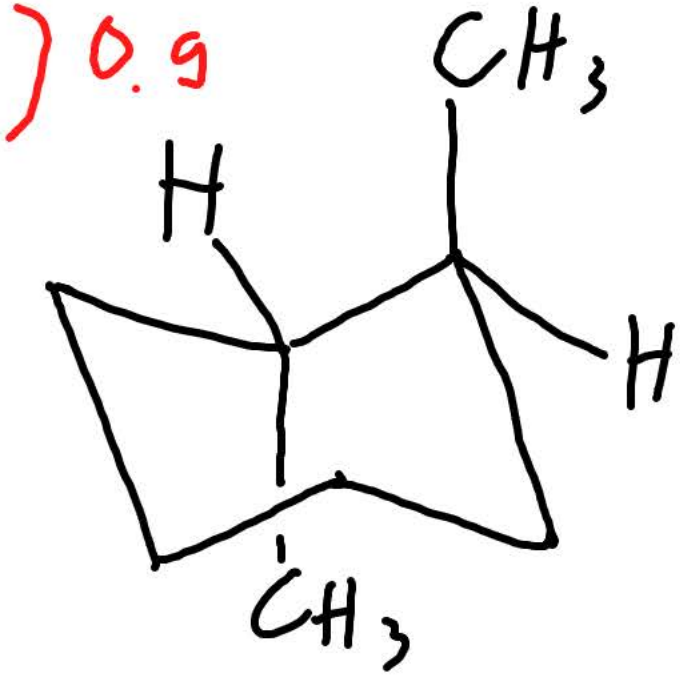
1,2-dimethylcyclohexane (trans)



2 méthyls équatoriales



gauche



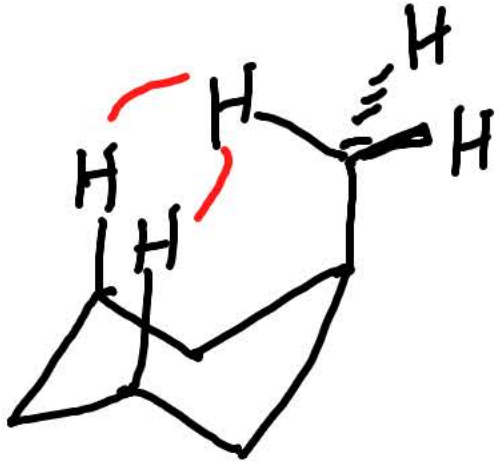
2 méthyl axiales

delta G attendu: 3.4

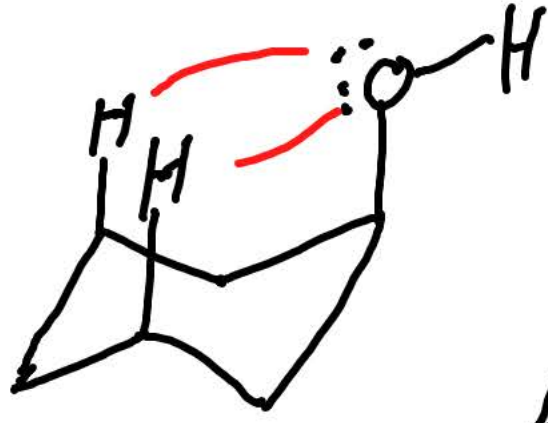
delta G mesuré: 2.5!

delta G corrigé: 3.4-0.9 = 2.5

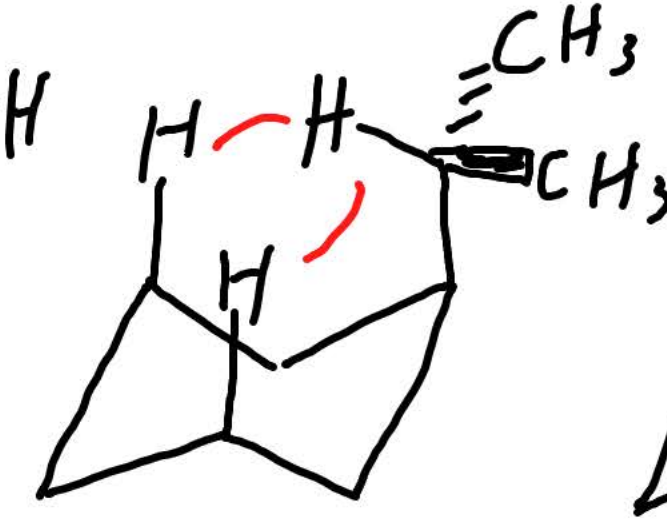
exemples de valeur A



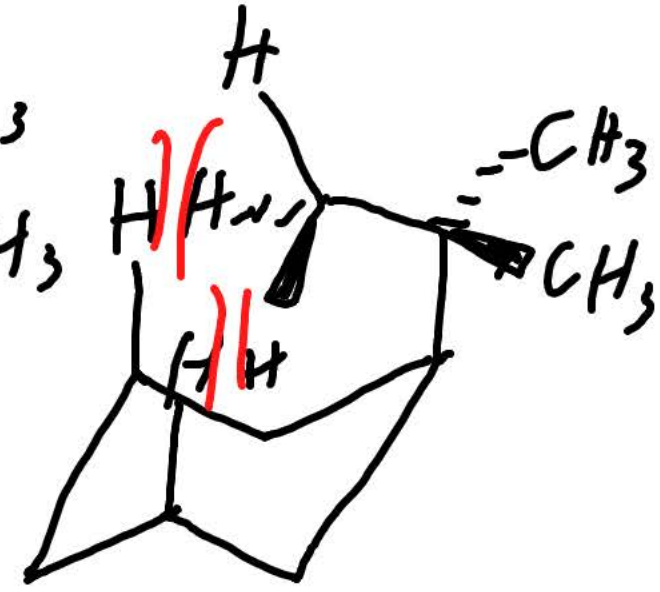
A = 1.7



A = 0.9



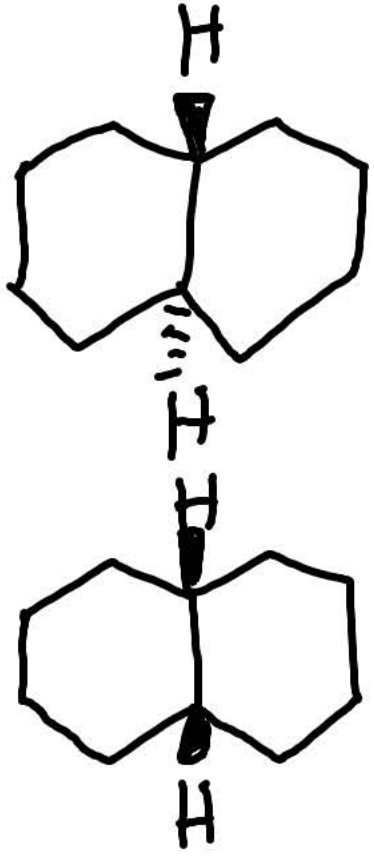
A = 2.2



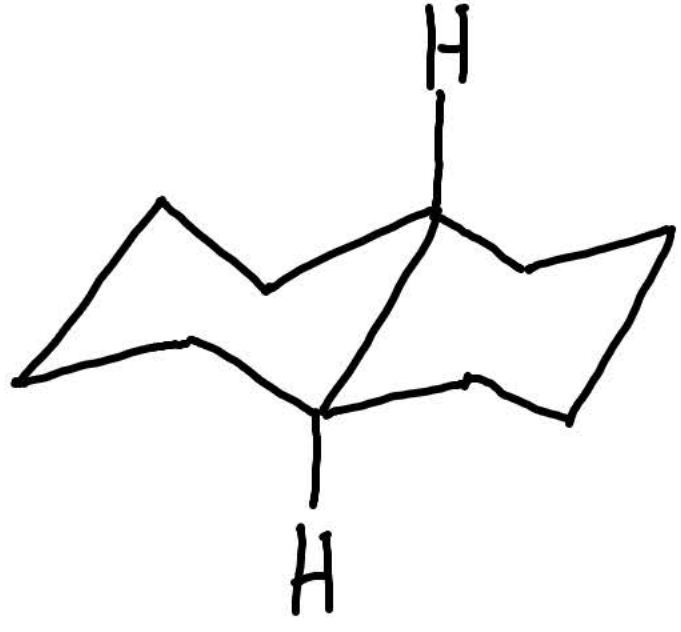
A = 5

les décalines

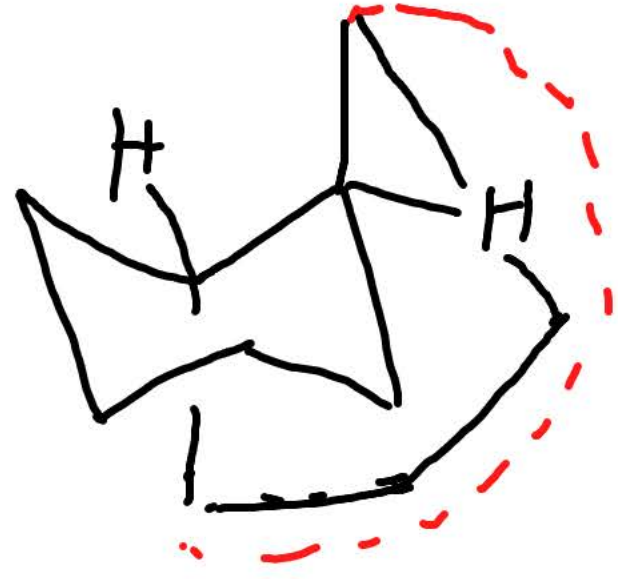
trans-décaline



cis-décaline

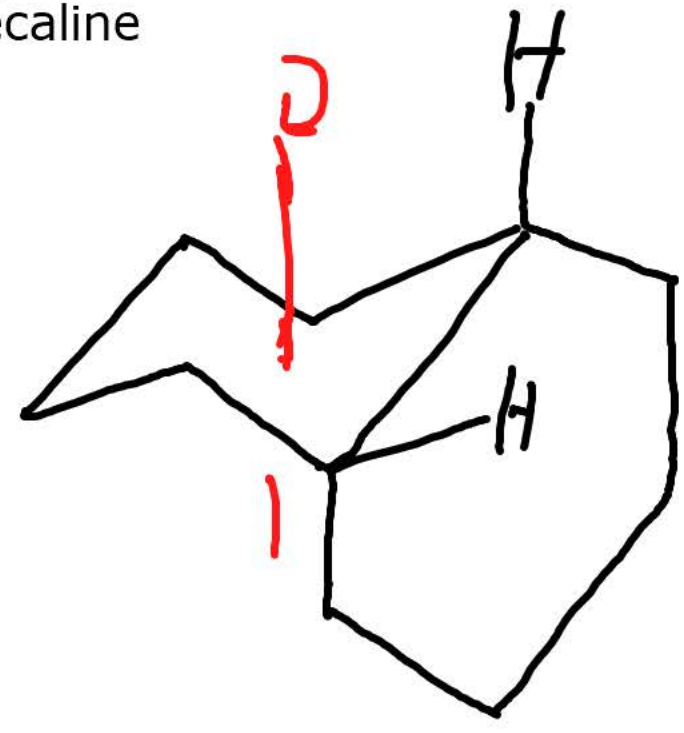


une seule conformation, presque "plate"

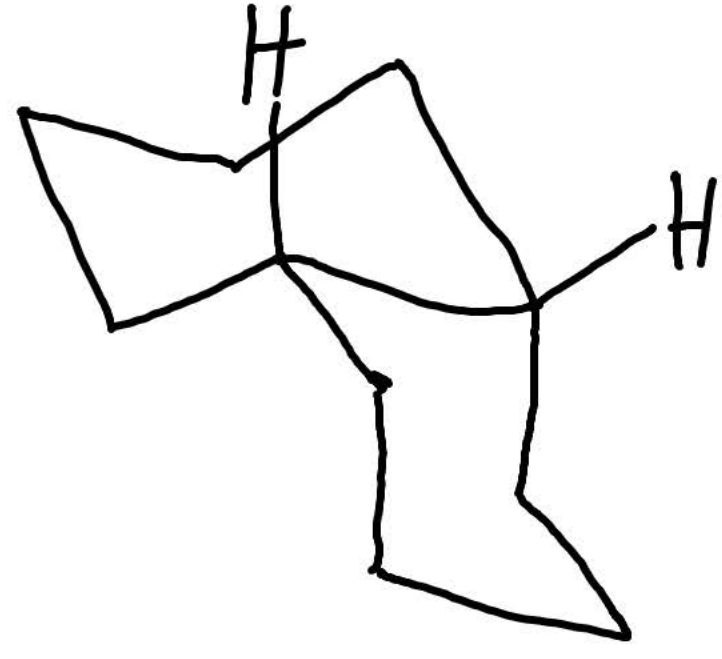


impossible de joindre les deux atomes avec 2 de plus

cis-décaline



deltaG = 0



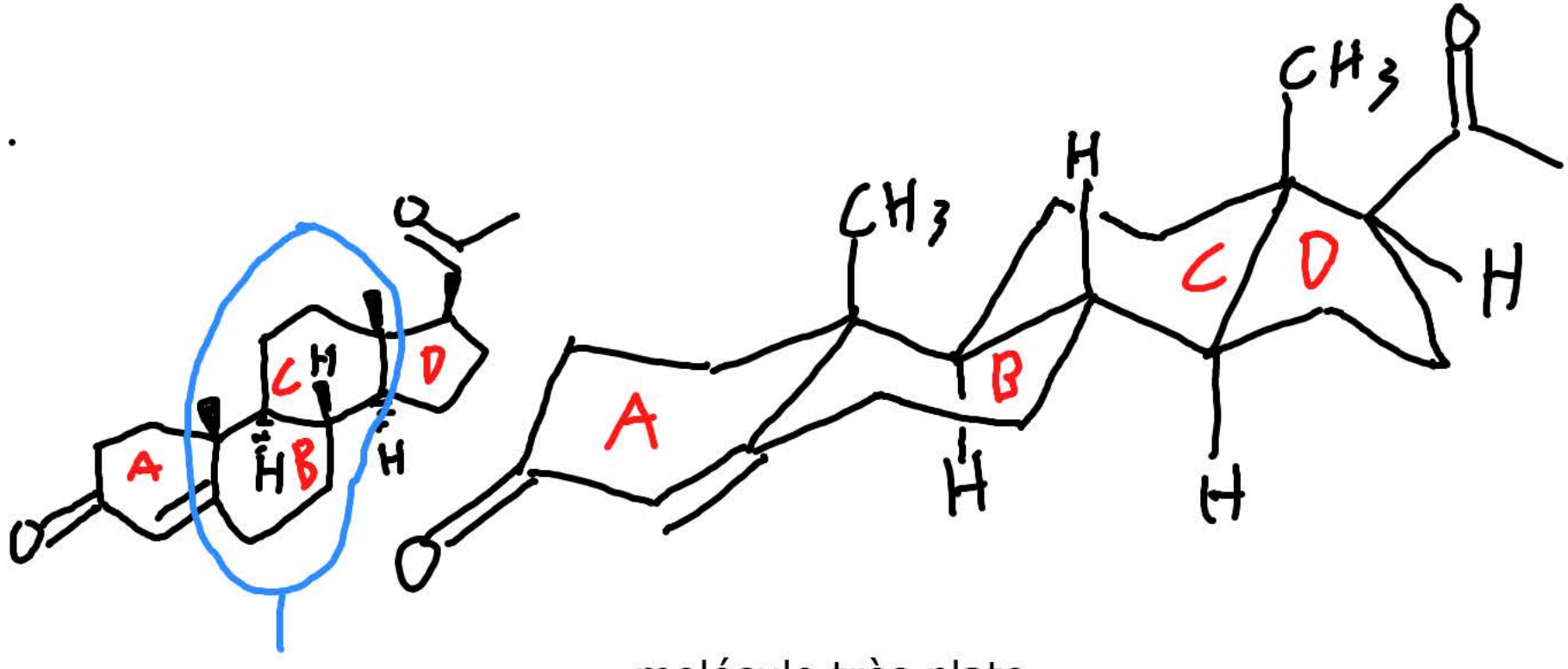
1 CH2R en axial, et 1 H en axial

1 CH2R axial, 1 H axial

cis-décaline est flexible!

progesterone

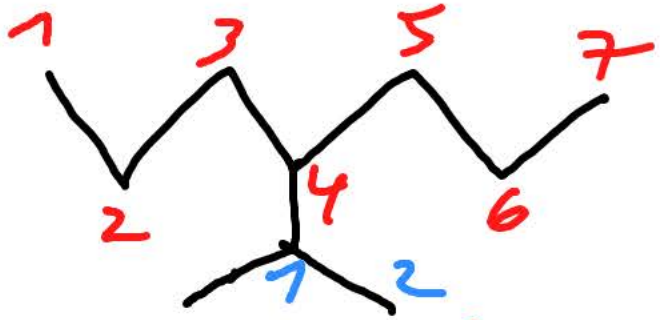
Commencer par le cyclohéxane parfait: C



trans-décaline

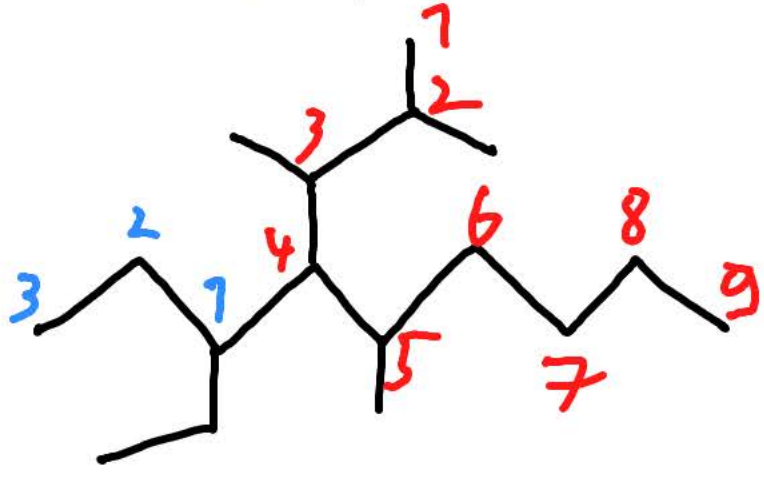
molécule très plate

nomenclature des alcanes



4-(1-méthyl-éthyl)heptane

4-isopropylheptane



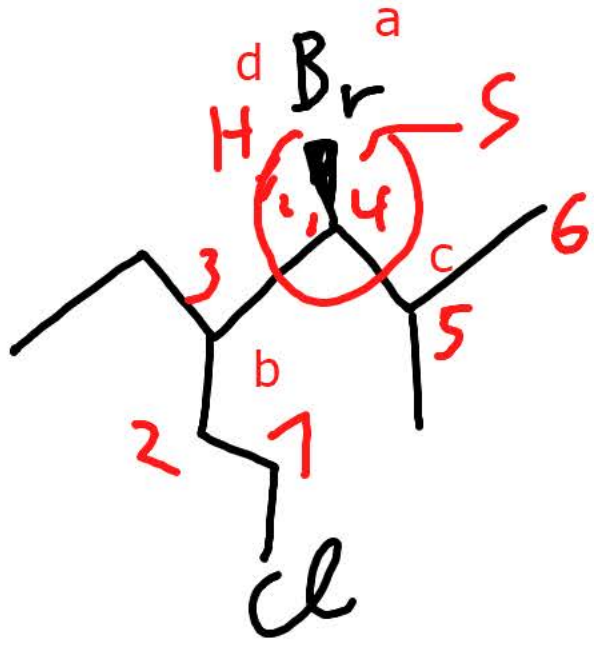
nonane

2,3,5-triméthyl

4-(1-éthylpropyl)-

4-(1-éthylpropyl)-2,3,5-triméthylnonane

halogènes? nom de l'halogène avec suffixe "O", toujours considéré comme substituant fluoro, chloro, bromo, iodo

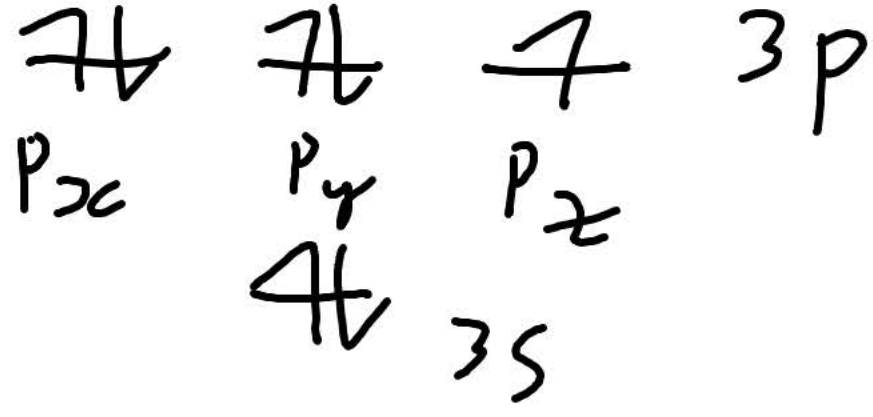


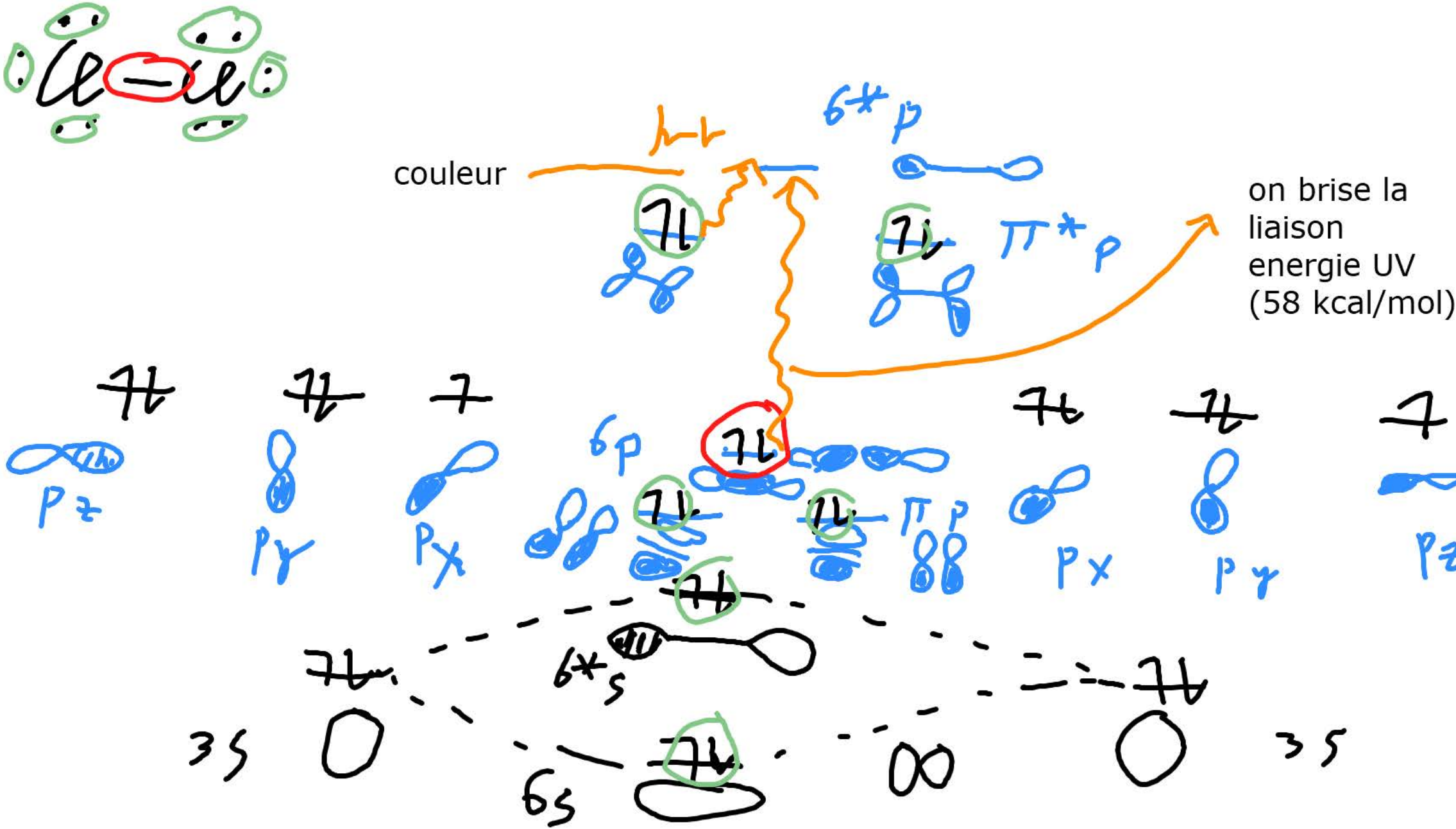
(4S)-4-bromo-1-chloro-3-éthyl-5-méthylhexane

chlorination du méthane

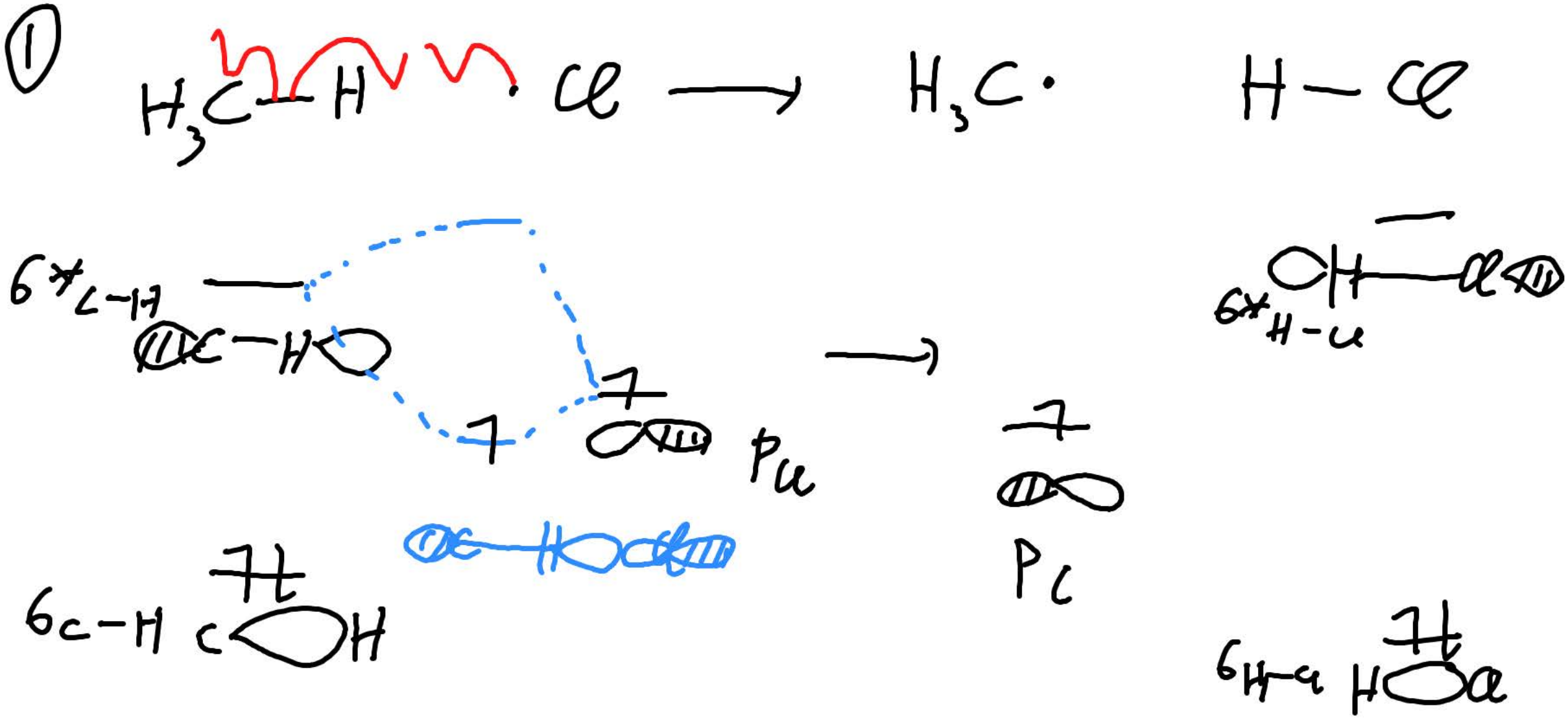
1) initiation

pour Cl2: pas de carbone, on fait une liaison sans hybridation

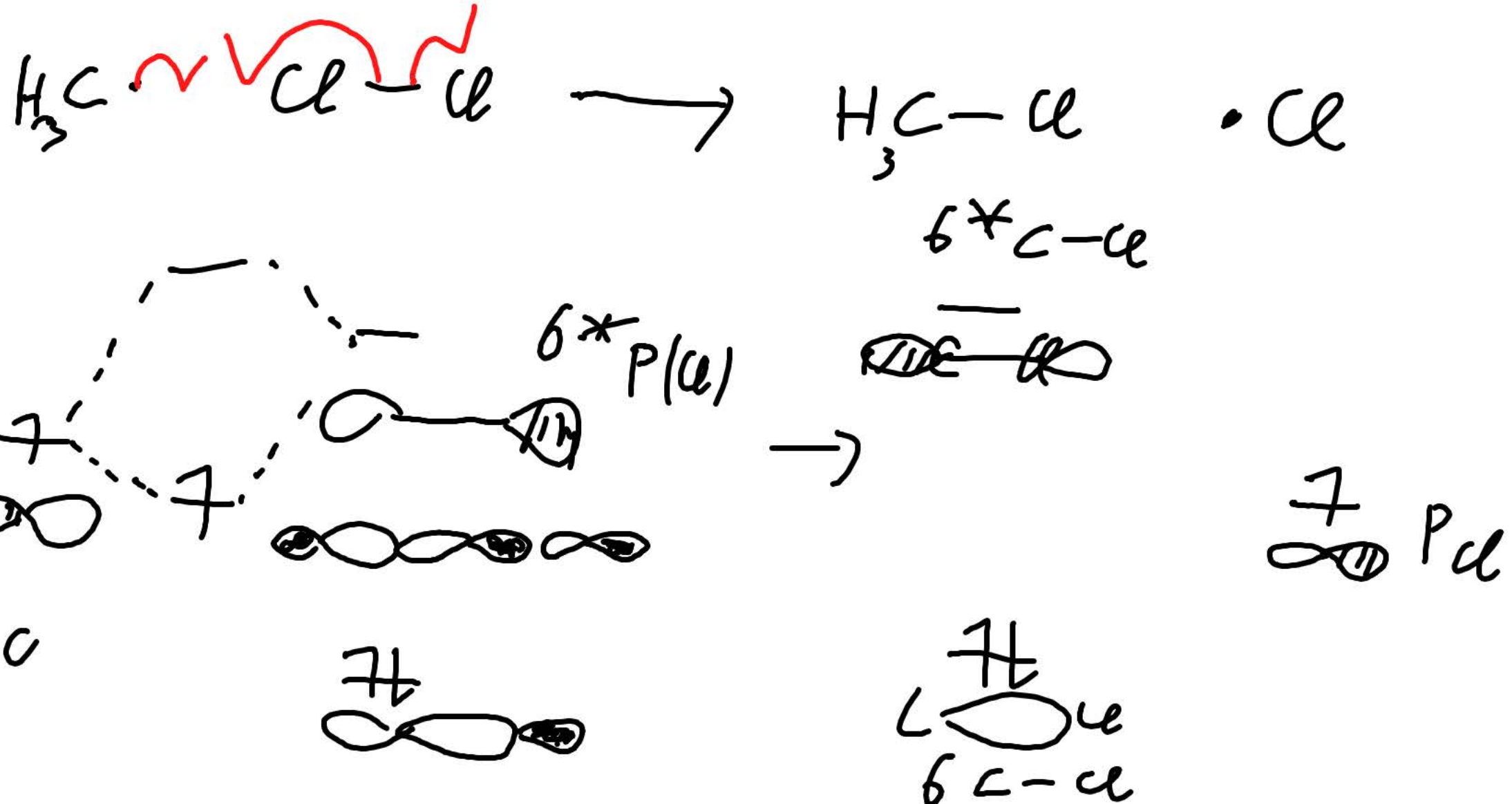



couleur
on brise la
liaison
energie UV
(58 kcal/mol)

propagation (1 et 2)

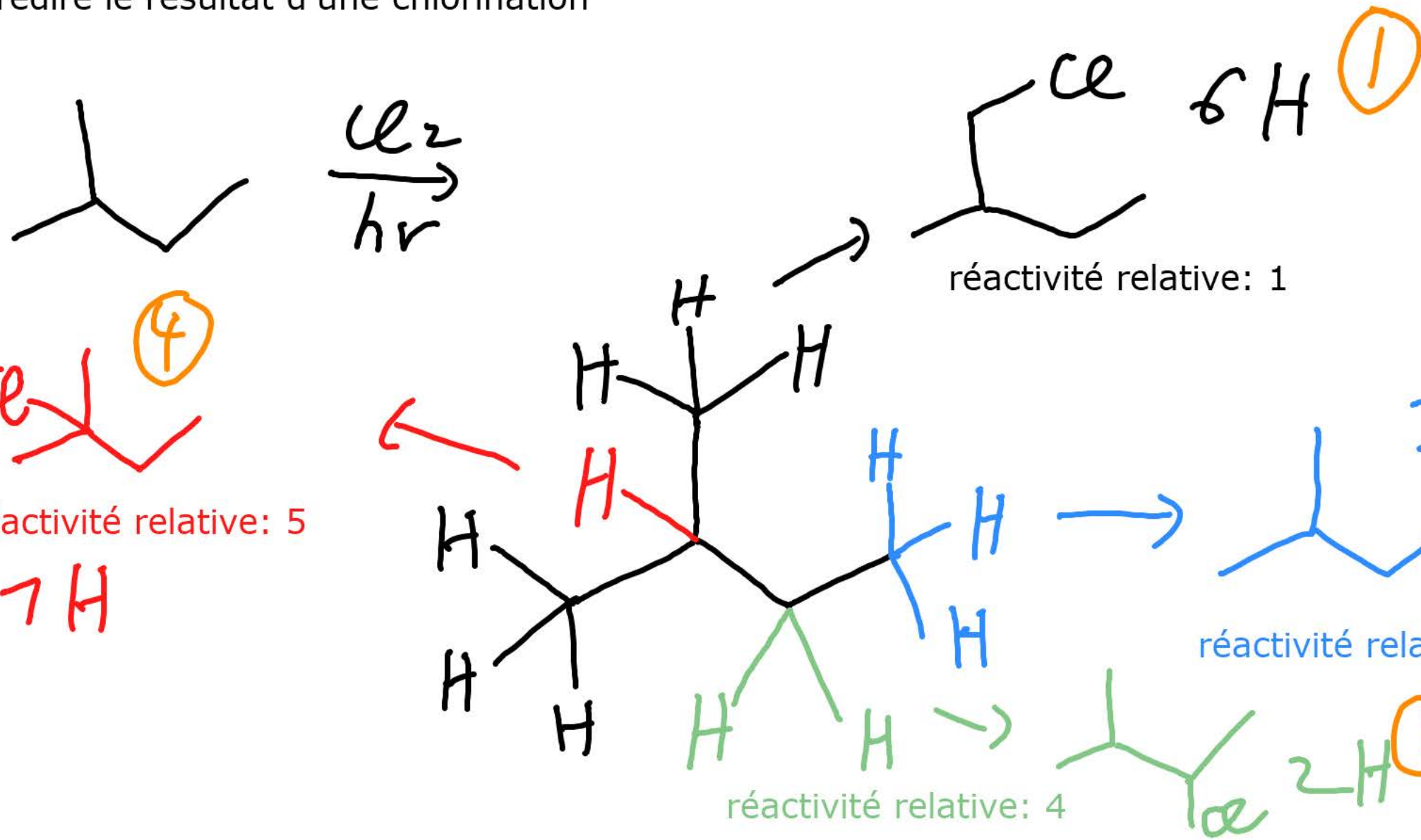


②



prédire le résultat d'une chlorination

.



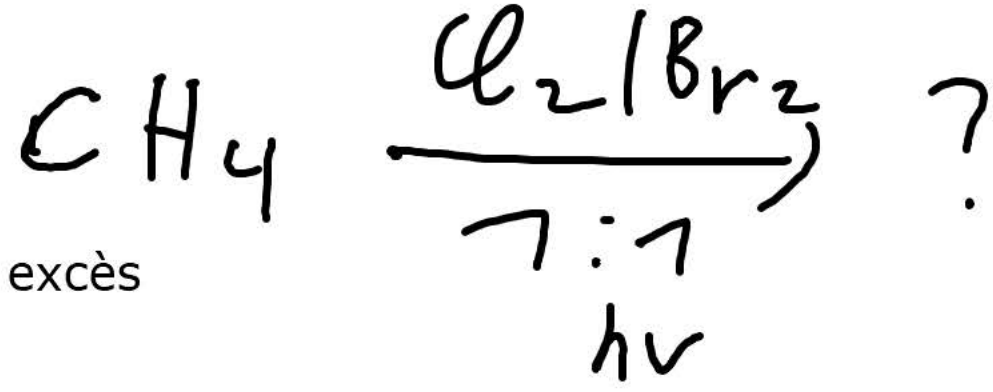
composé	nombre de H	réactivité corrigée	proportion
①	6	$6 \times 1 = 6$	$6/22 = 27\%$
②	3	$3 \times 1 = 3$	$3/22 = 14\%$
③	2	$2 \times 4 = 8$	$8/22 = 36\%$
④	1	$1 \times 5 = 5$	$5/22 = 23\%$
		$= 22$	

que se passe-t-il avec F2?

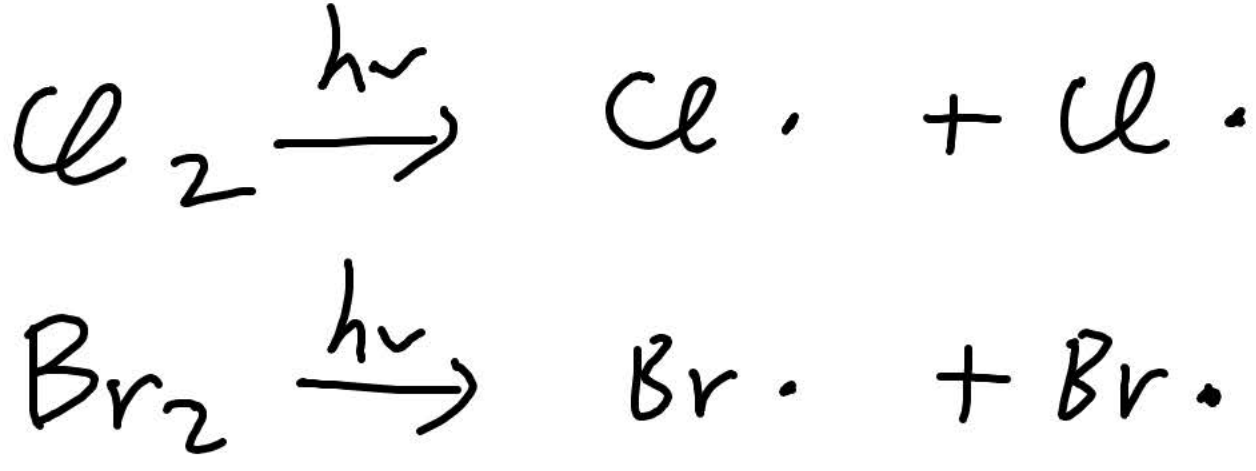
Très réactif, seul le nombre de H compte
1:2:3:4 = 6:3:2:1

Que se passe-t-il avec Br2?
Moins réactif, la stabilité du radical joue un rôle essentiel (proche du rapport thermodynamique de 2.4 kcal/mol)
Le produit le plus stable est formé
1:2:3:4 = <1%, <1%, <5%, >95%

Que se passe-t-il avec I2?
rien, pas de réaction.


CH_4
excès
Cl_2/Br_2
1:1
hν
?

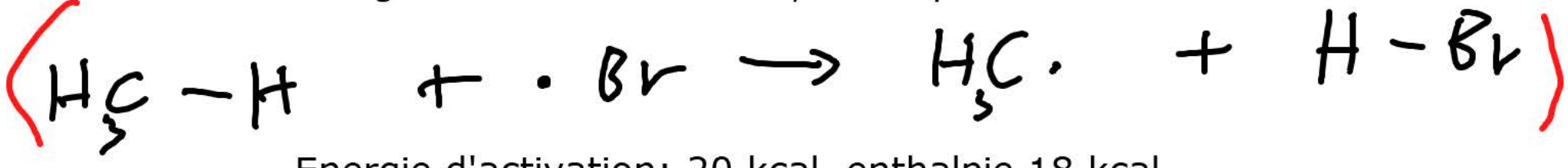
initiation


$Cl_2 \xrightarrow{h\nu} Cl\cdot + Cl\cdot$
$Br_2 \xrightarrow{h\nu} Br\cdot + Br\cdot$
plus rapide

propagation

1)

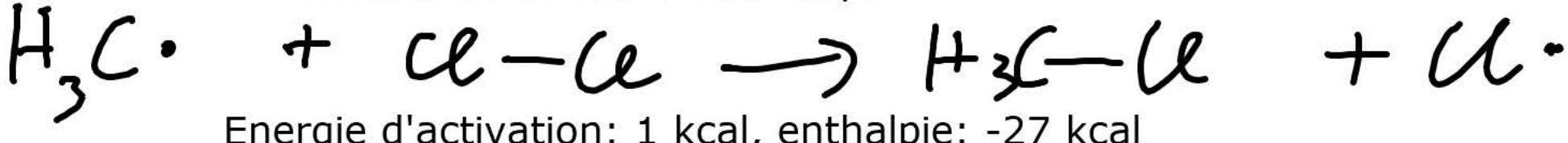
Energie d'activation: 1 kcal, enthalpie: 2 kcal



Energie d'activation: 20 kcal, enthalpie 18 kcal

2)

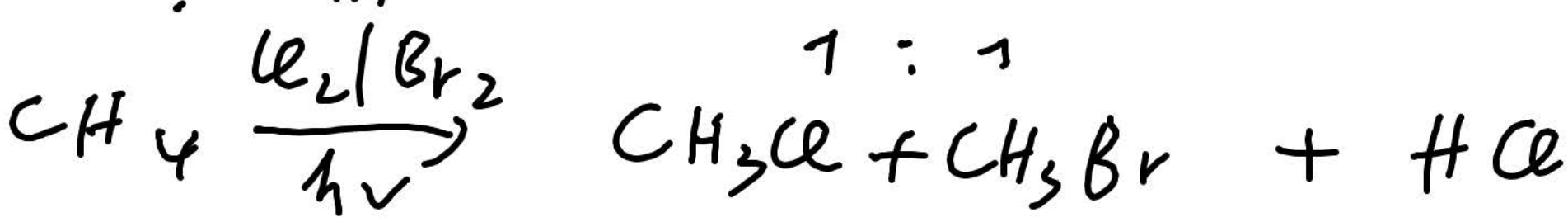
2 réactions de vitesse identique



Energie d'activation: 1 kcal, enthalpie: -27 kcal

Energie d'activation: 1 kcal, enthalpie -24 kcal

Au temps zéro:



poids	16	71	50.5	36.5

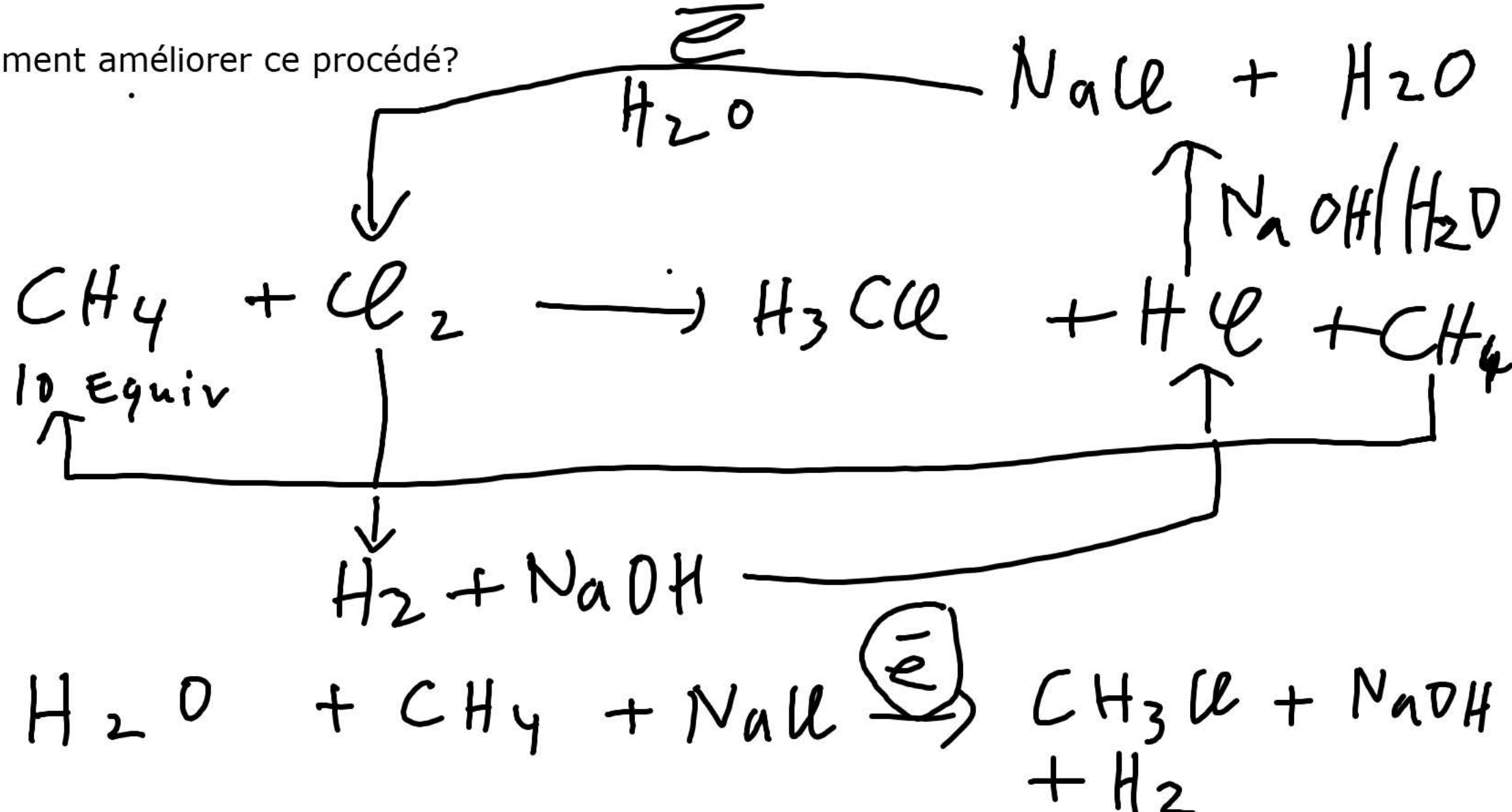
économie d'atomes: 5/7 = 71%

PMI (produit de départs+solvents/masse des produits):
(16+71)/50.5 = 1.7

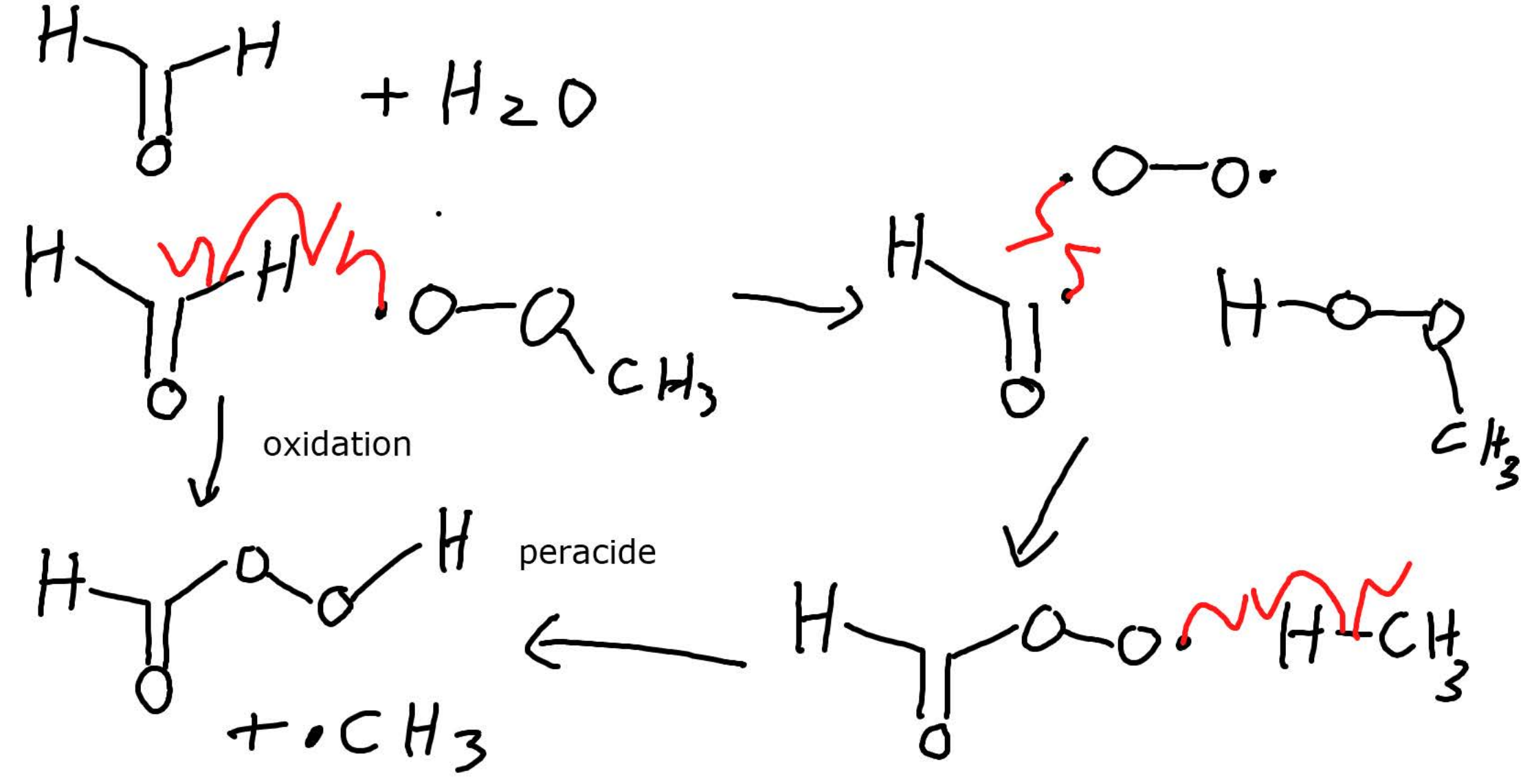
E: (masse des déchets/masse des produits):
36.5/50.5 = 0.73

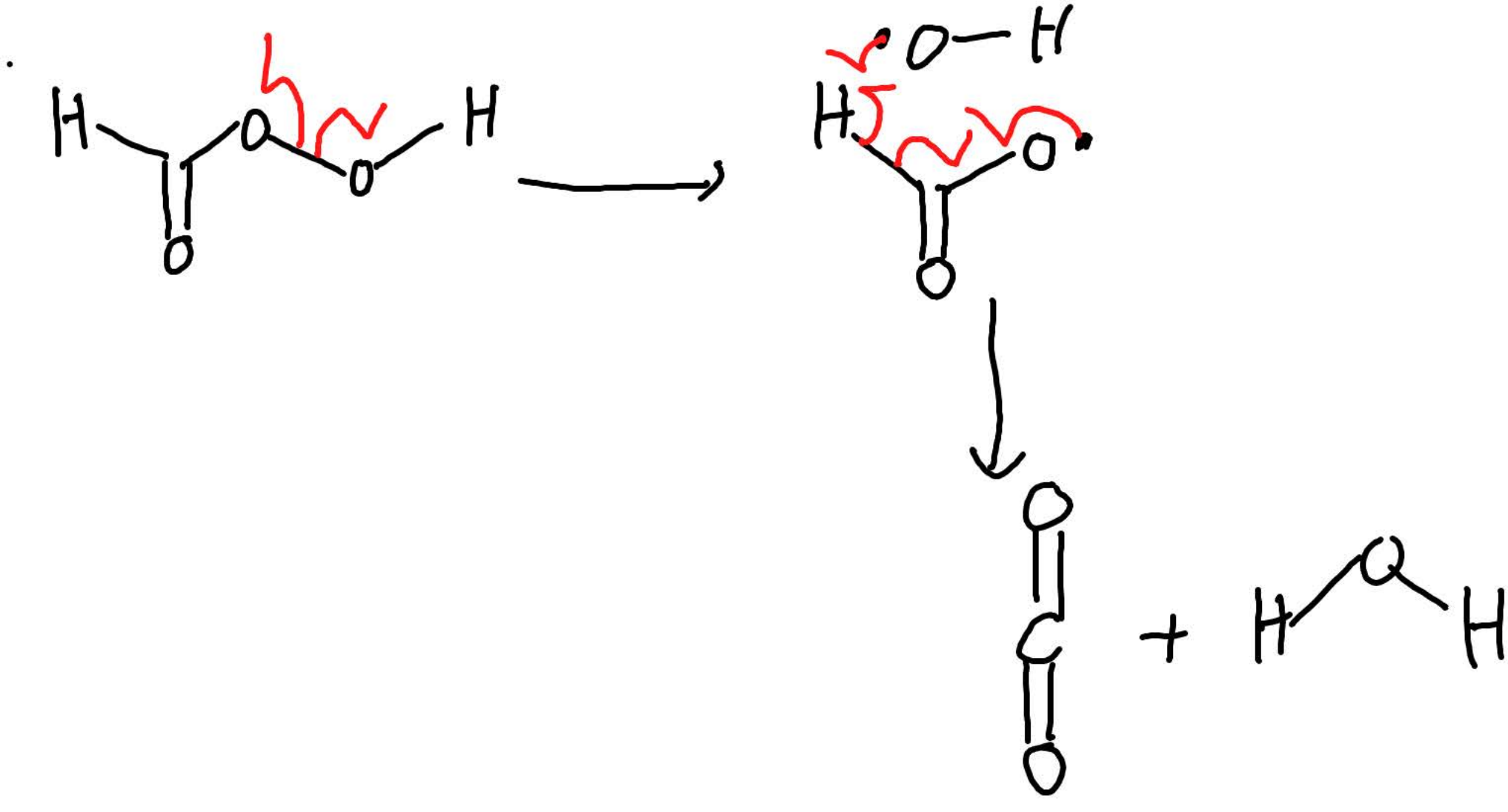
en pratique: un excès de méthane est nécessaire!

Comment améliorer ce procédé?

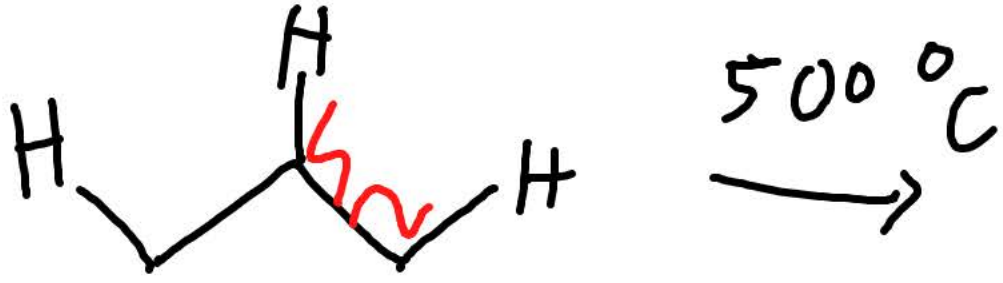


combustion du méthane, partie 2

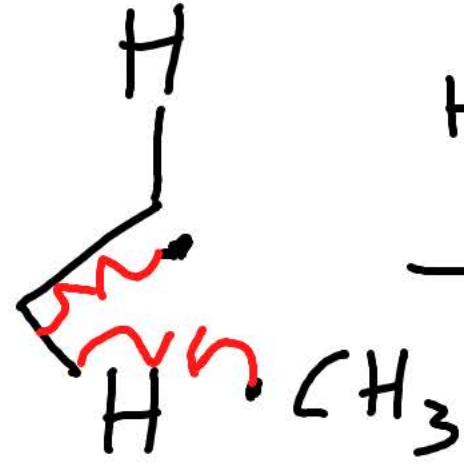


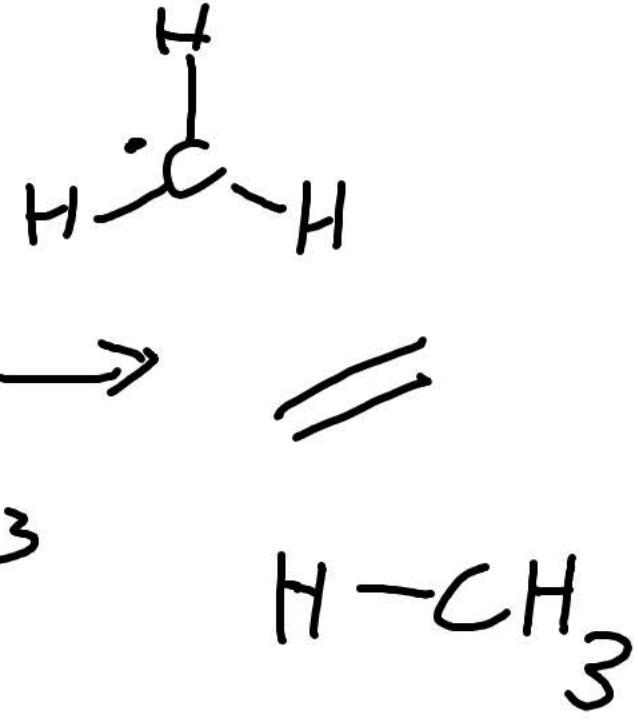


- cracking du pétrole

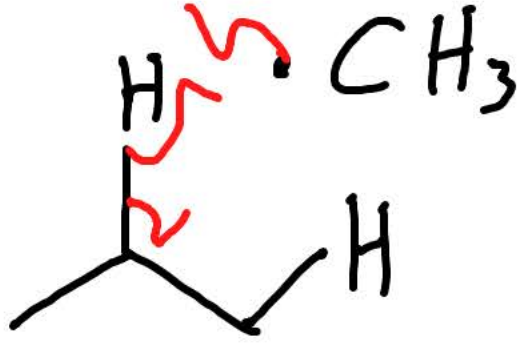


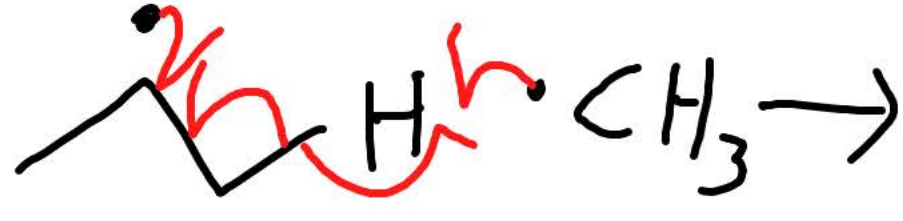
500 °C





C-C 85 kcal/mol
C-H 104 kcal/mol

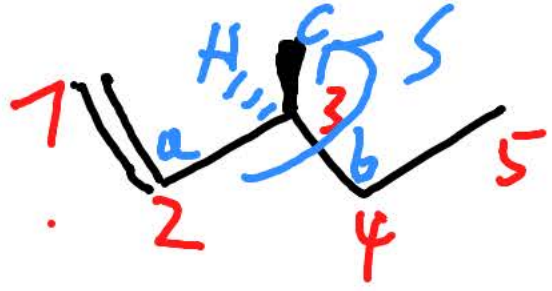




radical plus stable en secondaire

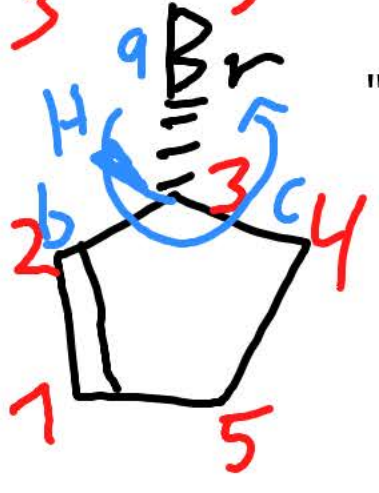
résultat: les chaines sont raccourcies, et on produits des alcènes

nomenclature des alcènes



(3S)-3-methylpent-1-ene

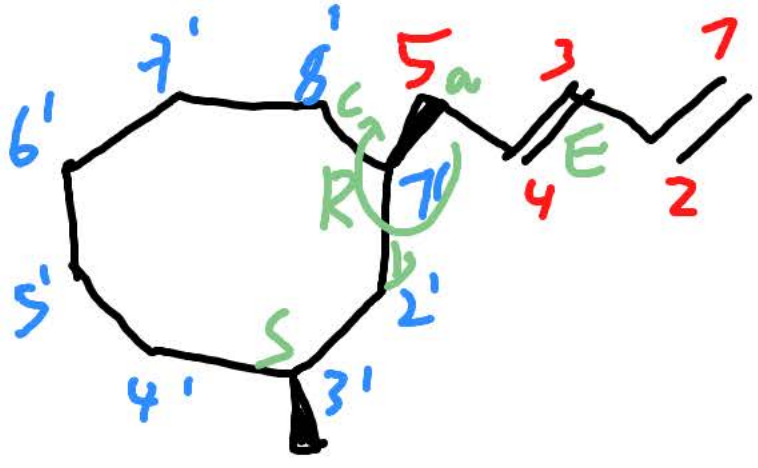
(E)-hept-3-ene



"S" mais H devant, donc R

(R)-3-bromo-cyclopent-1-ene

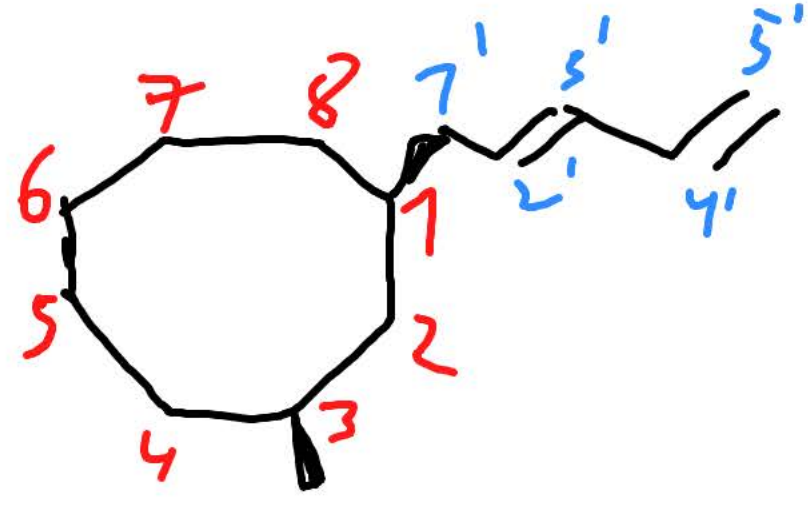
anciennes règles: les insaturations dominent!



penta-1,3-diene

3-methyl-cyclooctyl

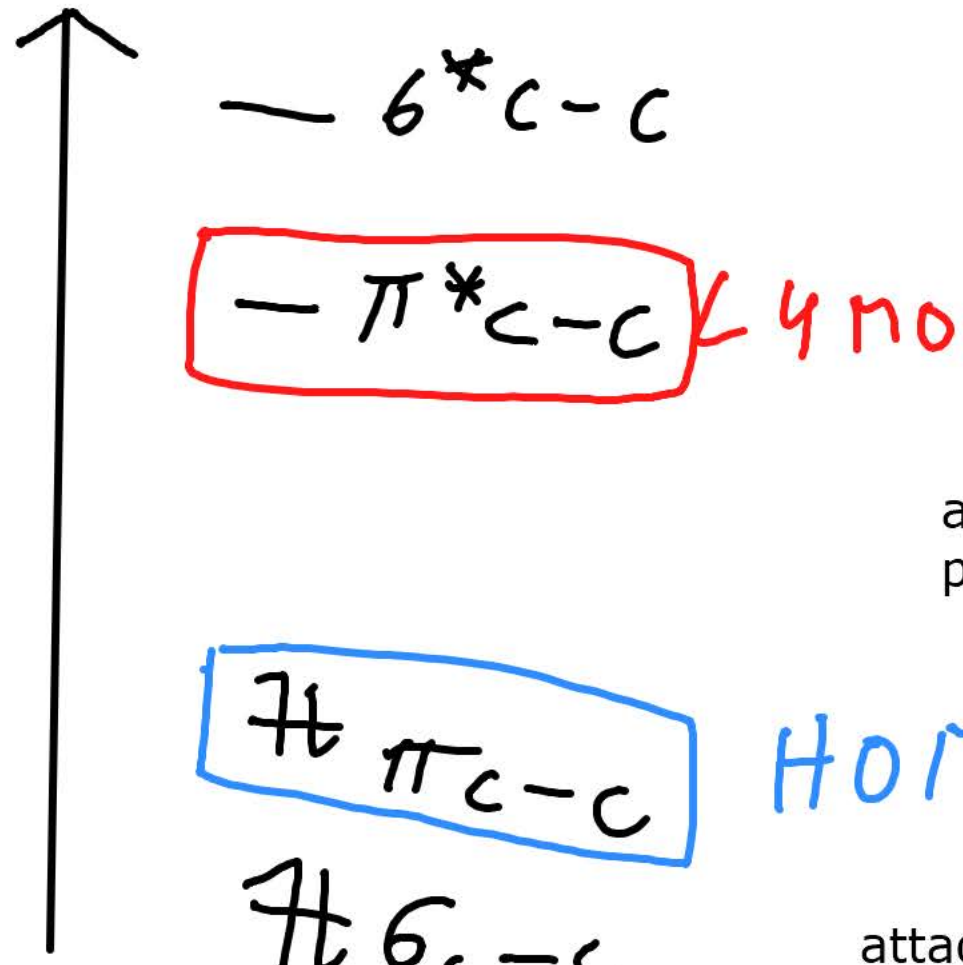
nouvelles règles: 1) cycle, 2) nombre d'atomes 3) insaturations

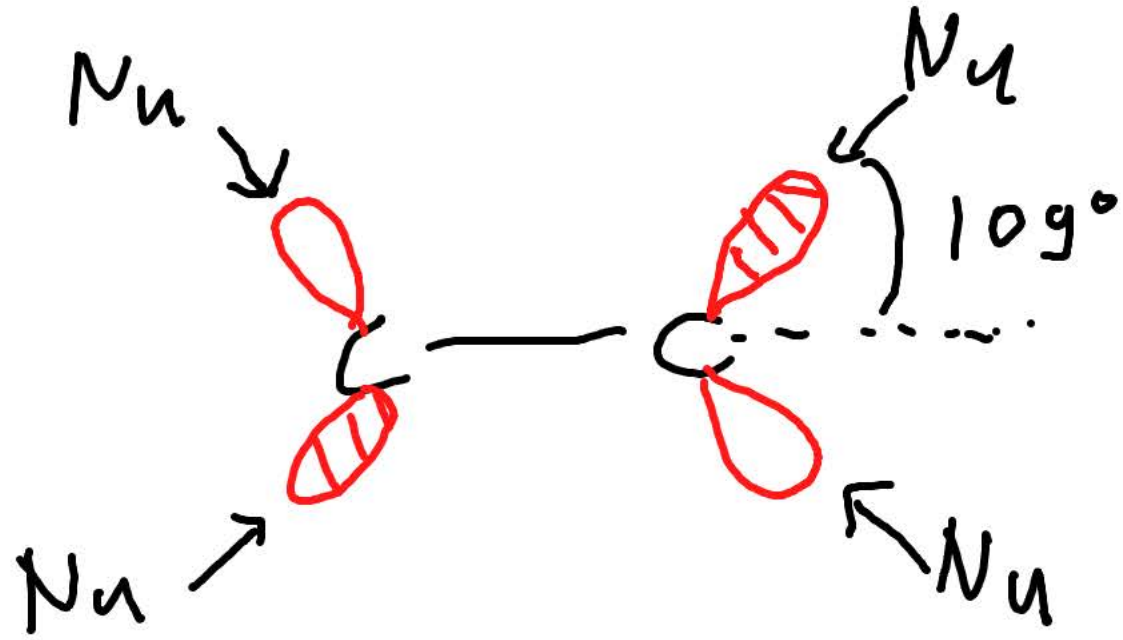


(1R,3S)-3-methyl-1-((E)-penta-2,4-dienyl)-cyclooctane

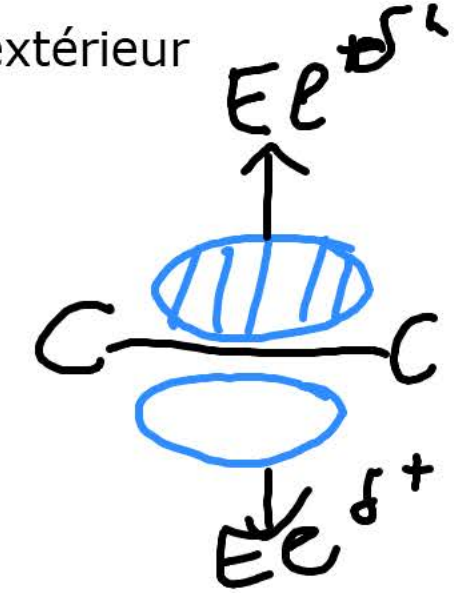
(E)-5-((1R, 3S)-(3-methyl-cyclooctyl))-penta-1,3-diene

HOMO/LUMO des alcènes



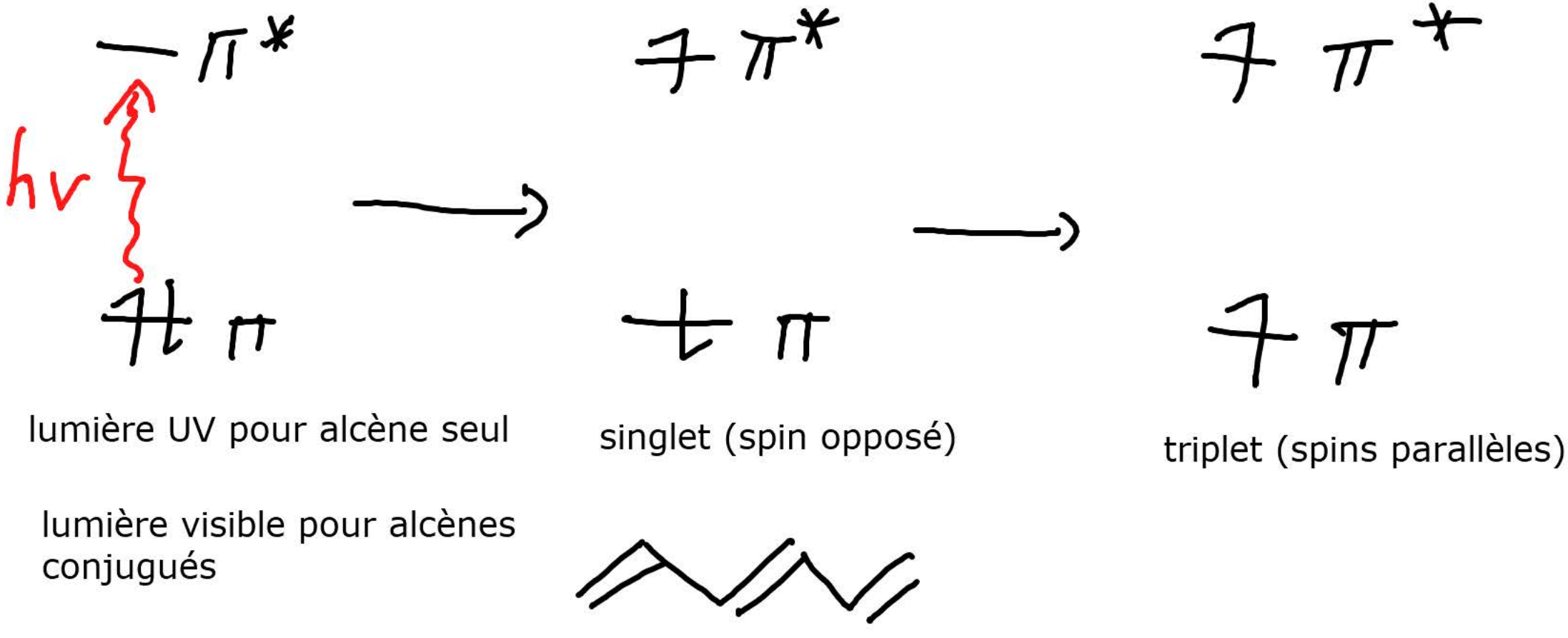


attaque à 109° de l'extérieur
pour les nucléopiles



attaque à 90° pour les
électrophiles

irradiation des doubles liaisons

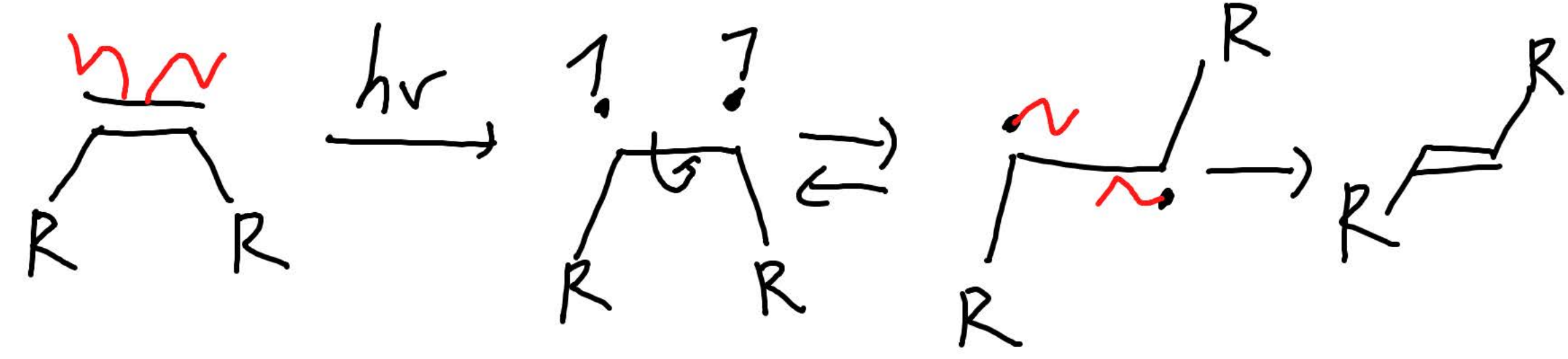


lumière UV pour alcène seul

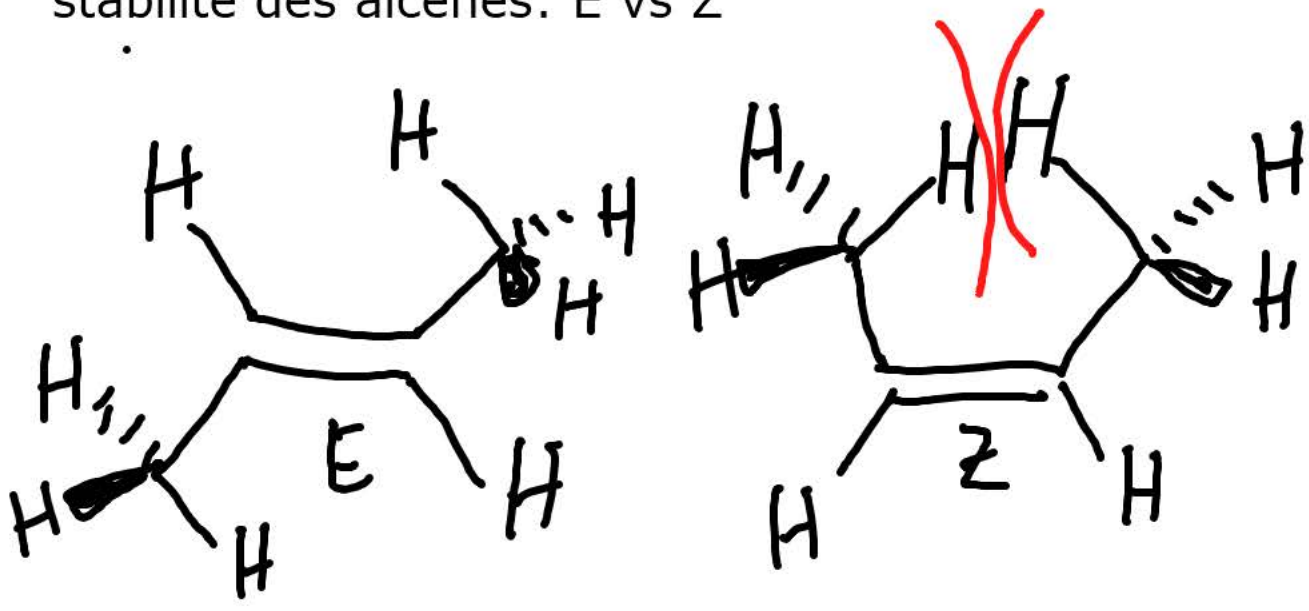
singlet (spin opposé)

triplet (spins parallèles)

lumière visible pour alcènes conjugués

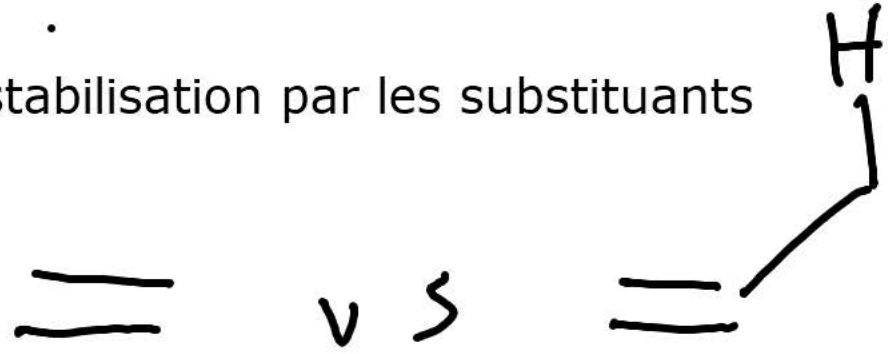

hν
R
R
R
R
R
R

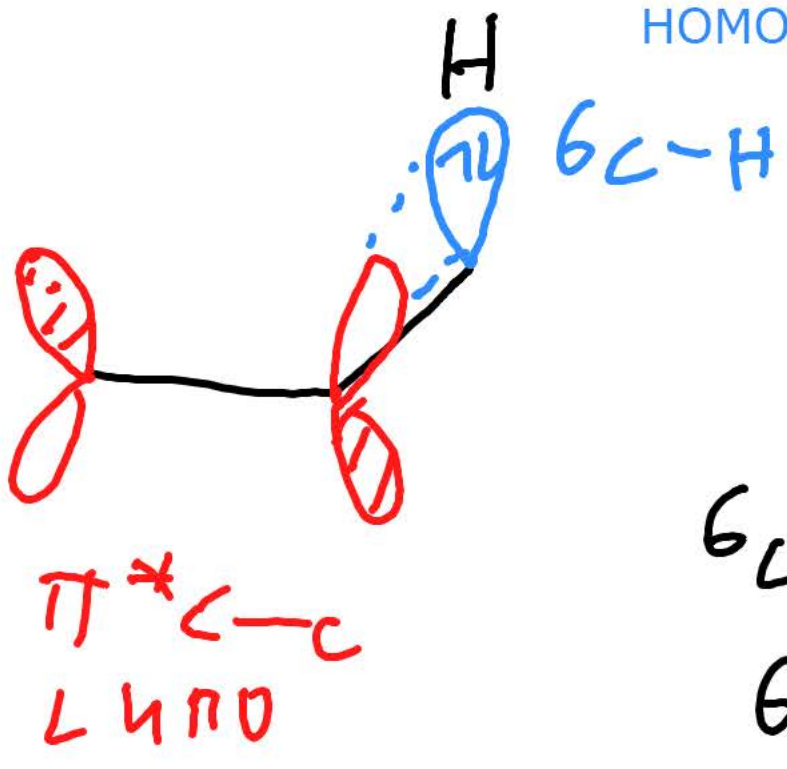
stabilité des alcènes: E vs Z

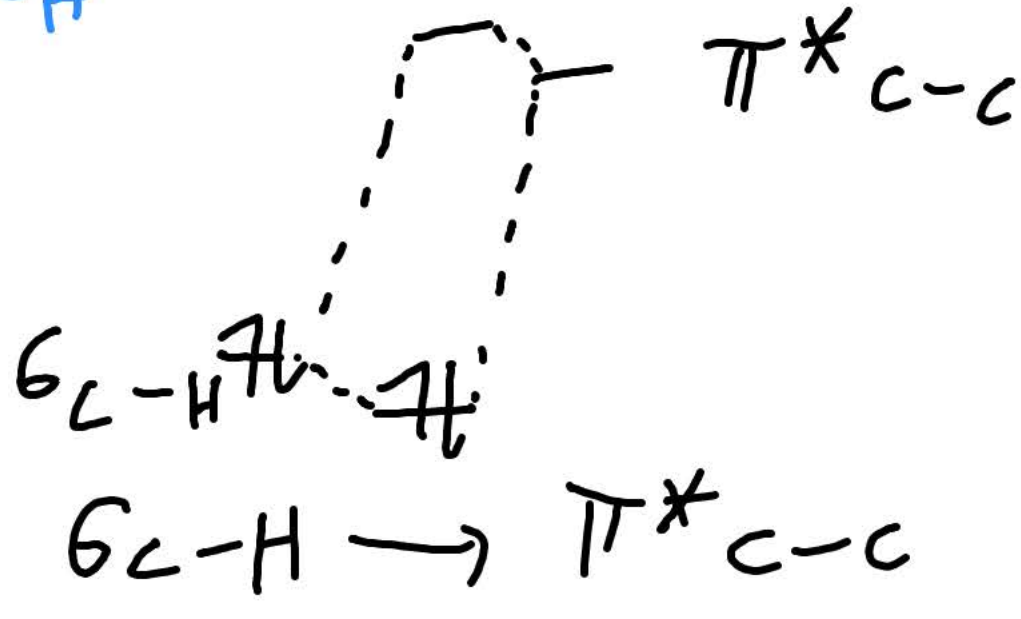


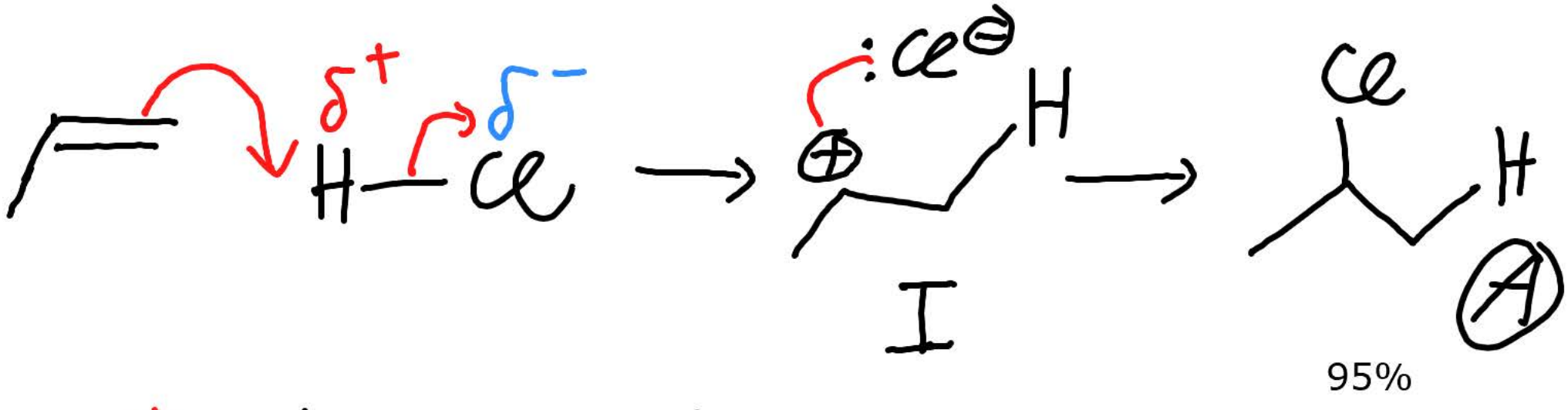
stérique est défavorable
E est plus stable
plus les substituants sont grands, plus la différence de stabilité est grande

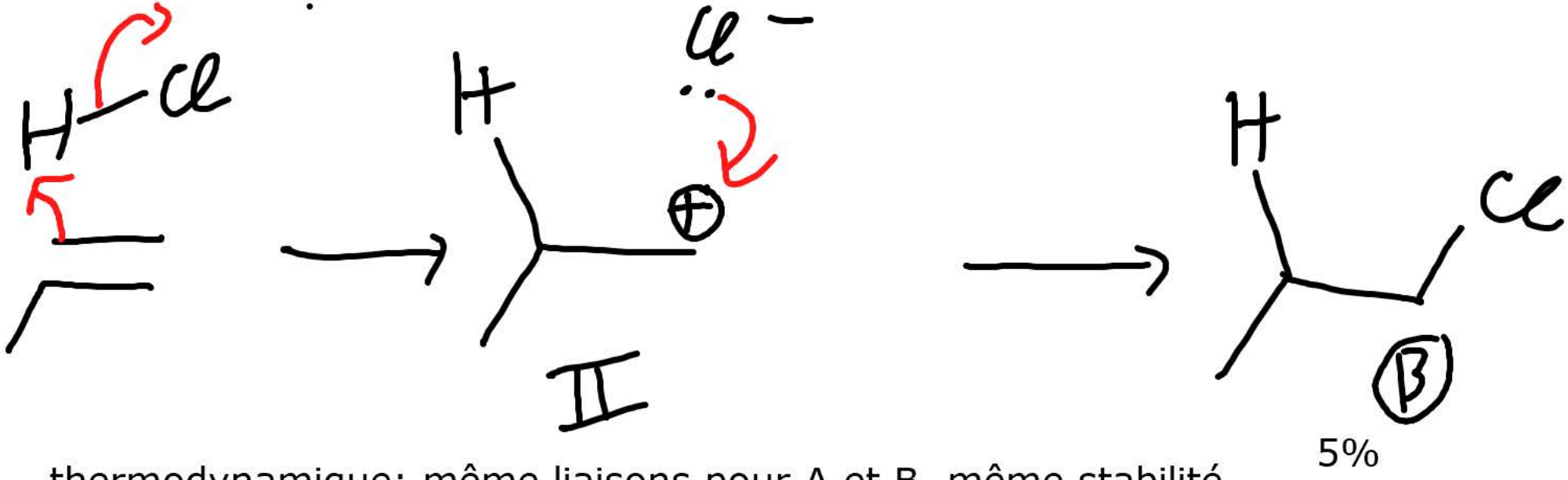
stabilisation par les substituants





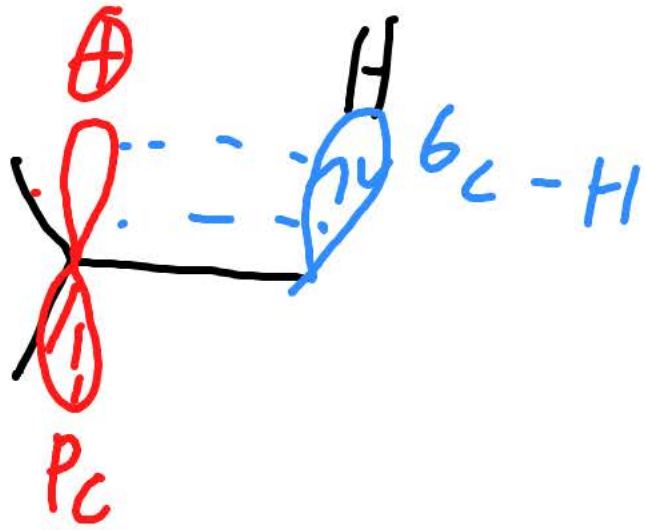






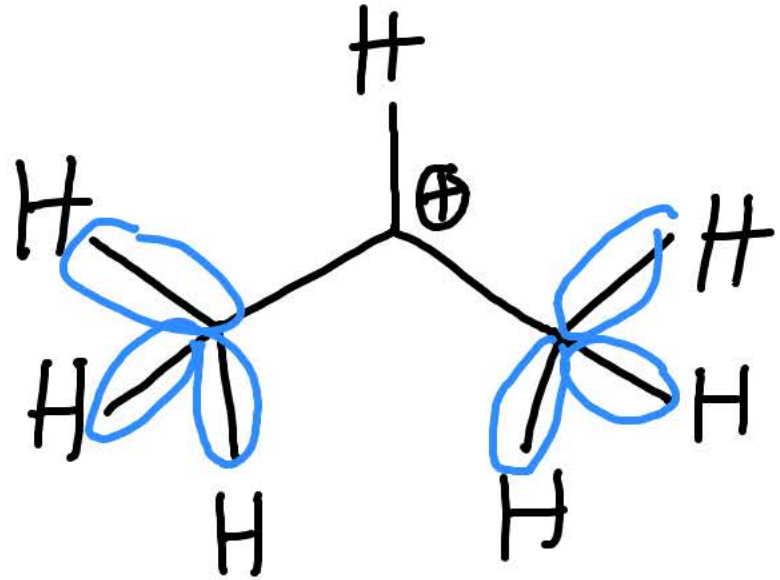
thermodynamique: même liaisons pour A et B, même stabilité

Hyperconjugaison



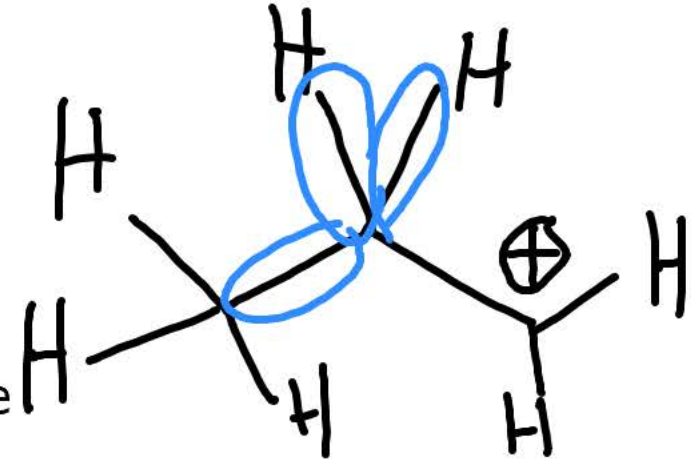
$\sigma_{C-H} \rightarrow p_C$

I



6 liaisons C-H pour hyperconjugaison

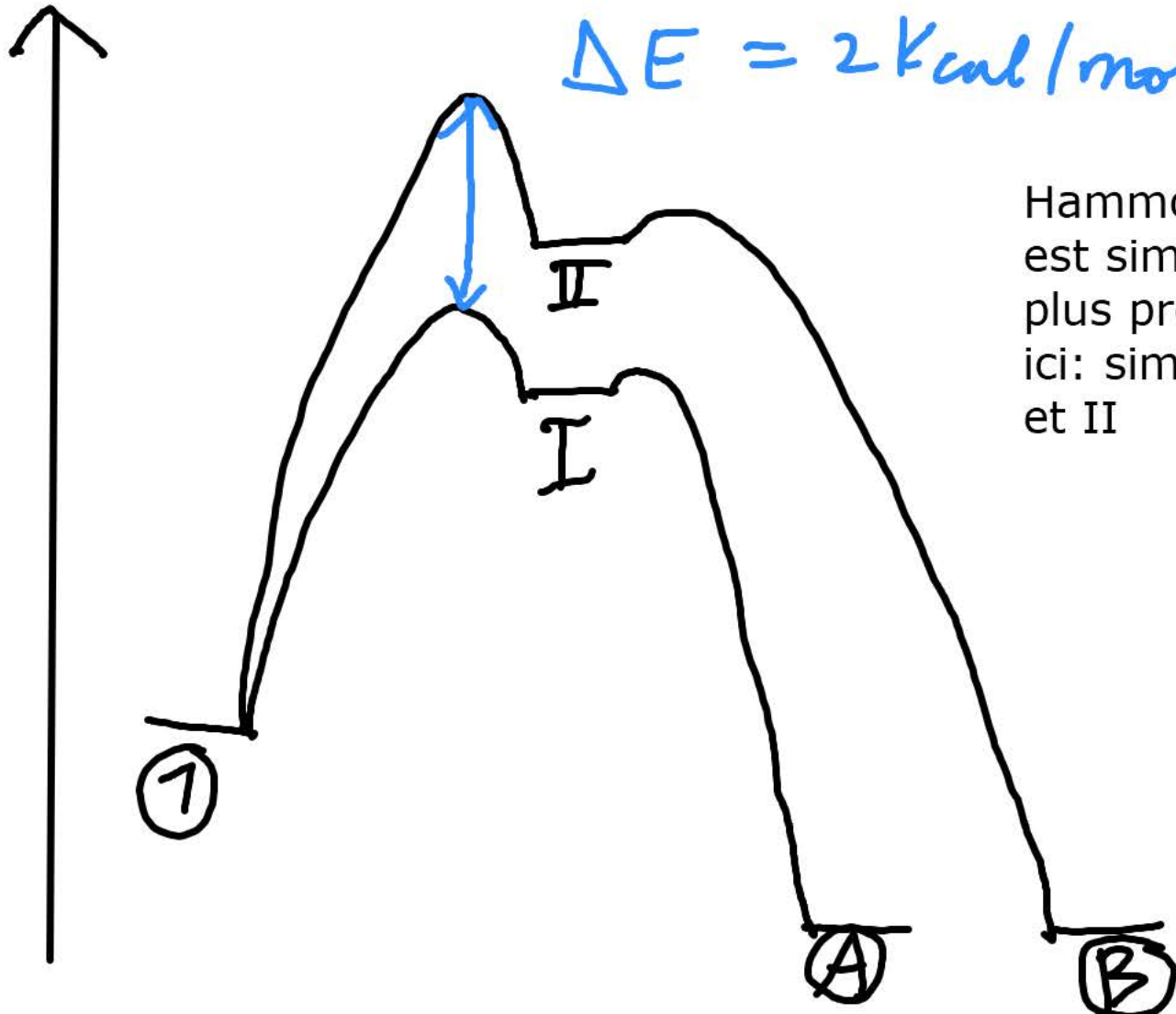
II



2 liaisons C-H et 1 liaison C-C pour hyperconjugaison

I (secondaire) plus stable que primaire

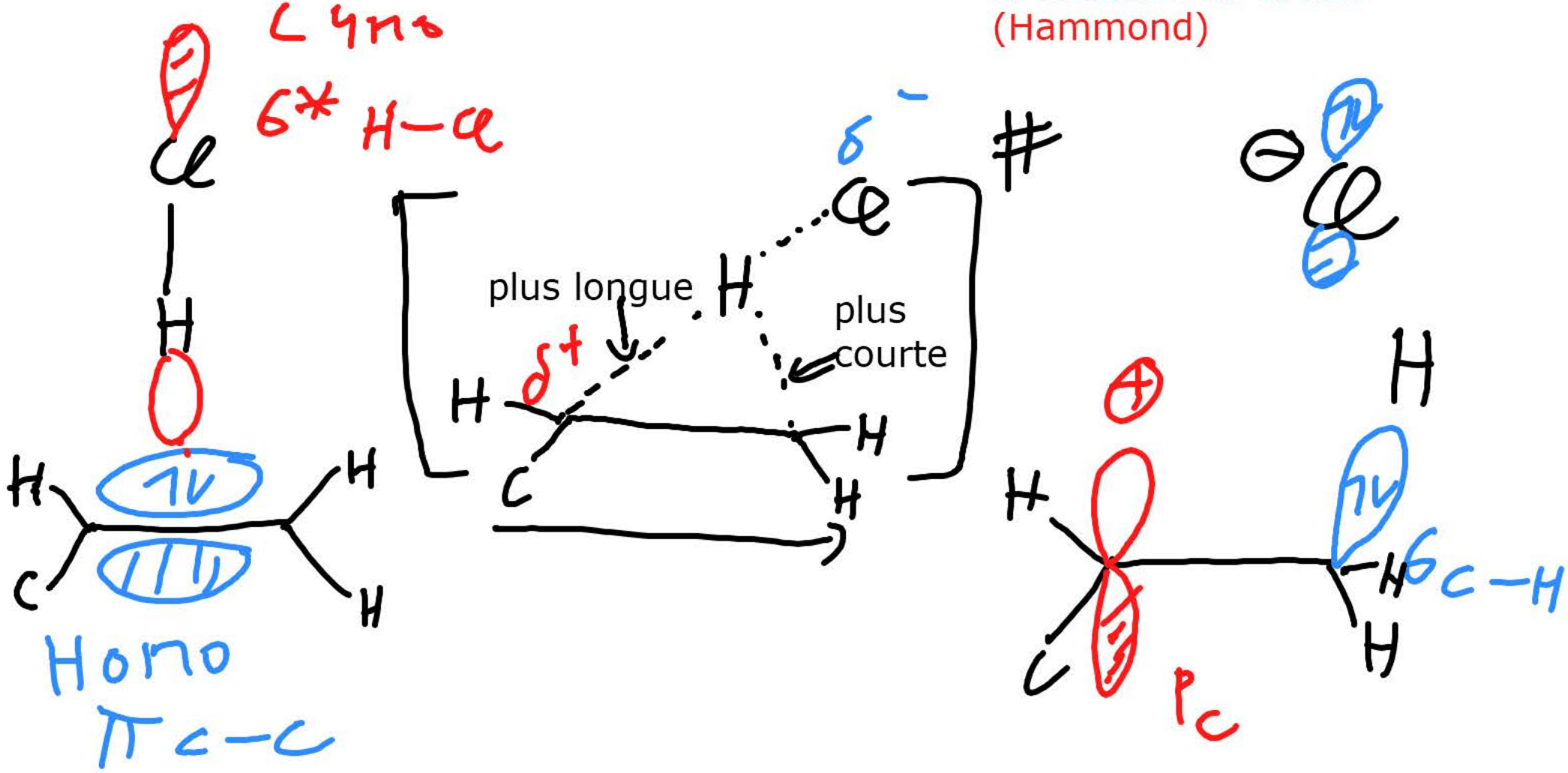
profil d'énergie de la réaction



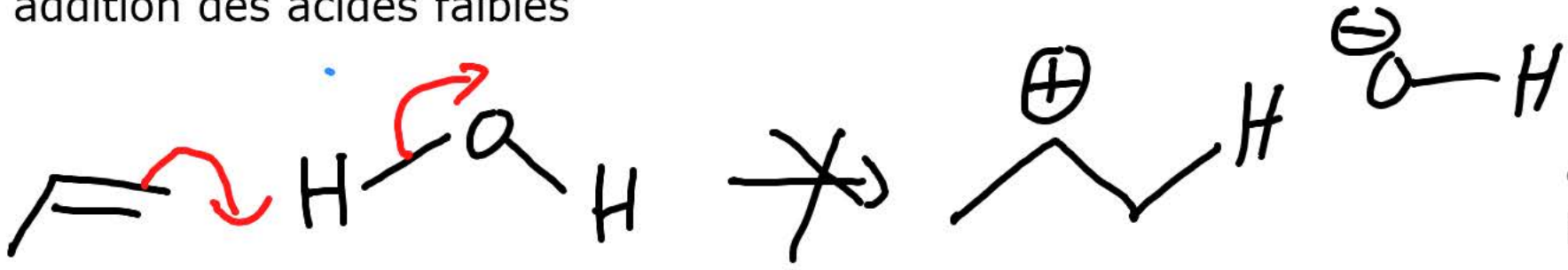
Hammond: l'état de transitio
est similaire à l'intermédiaire le
plus proche en énergie
ici: similaire au carbocations I
et II

Début de la réaction: Interactions LUMO-HOMO

état de transition ressemble à la situation de droite (Hammond)

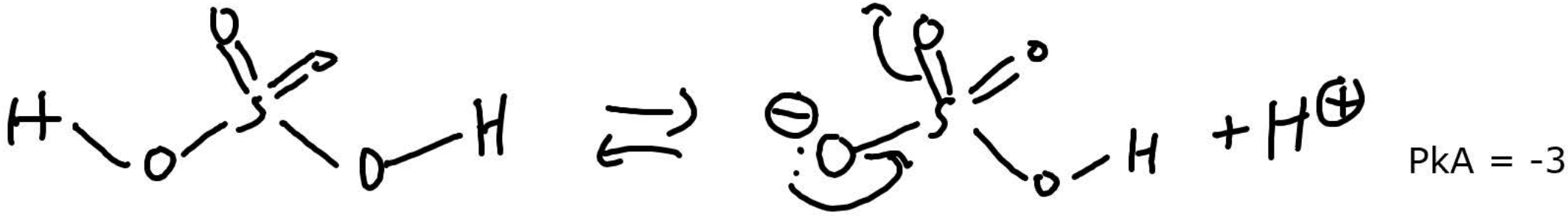


addition des acides faibles



acide trop faible
pas de réaction

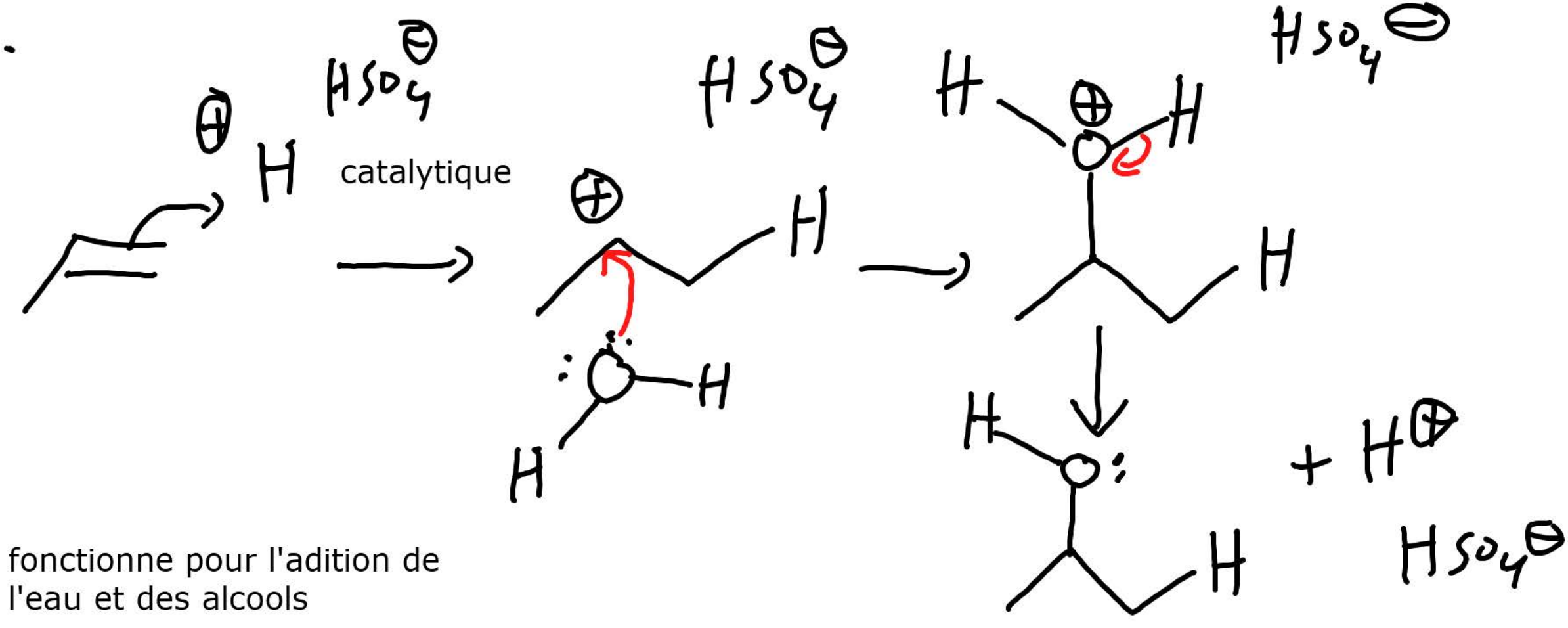
PkA = 16



PkA = -3

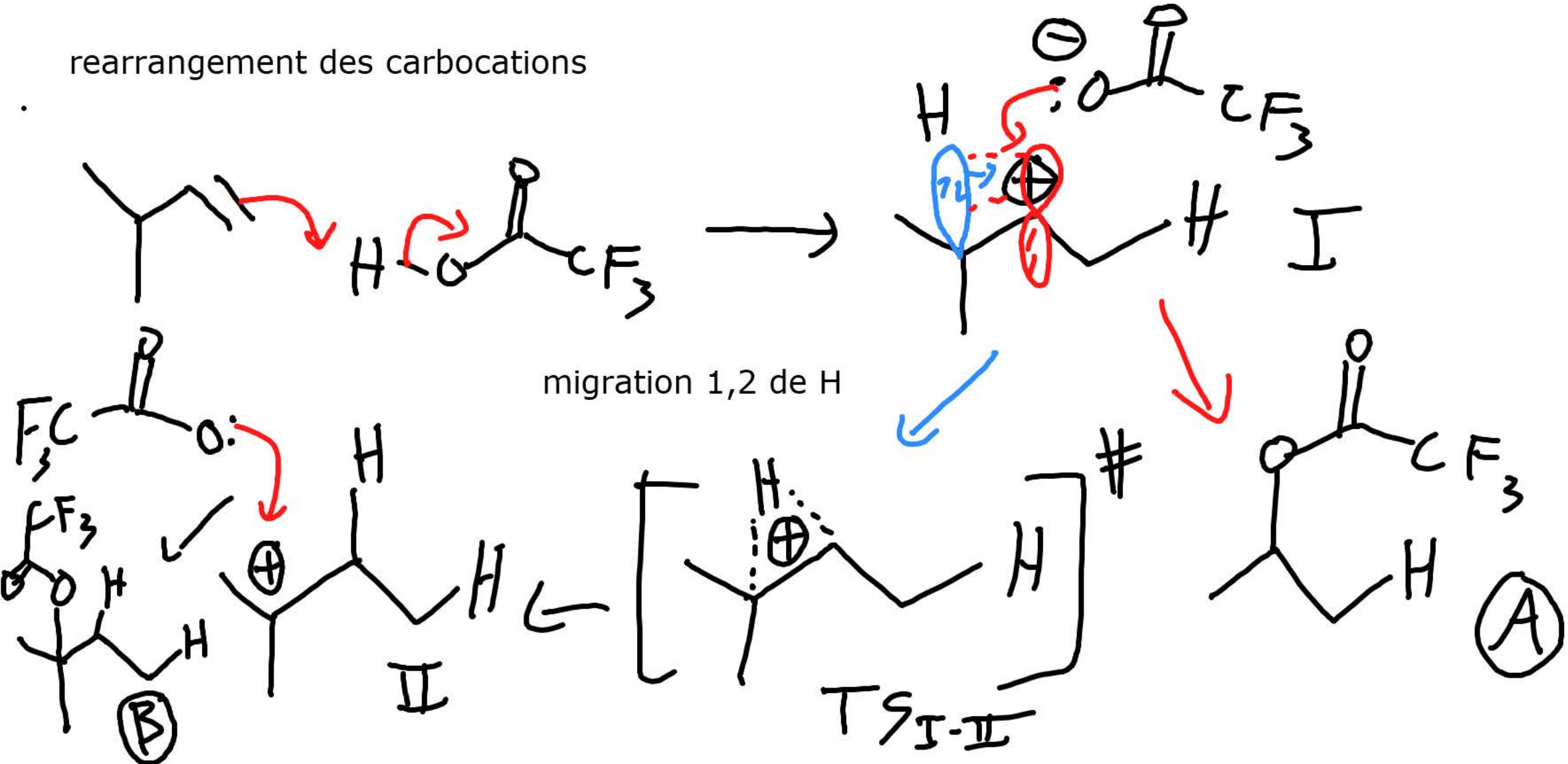
acide suffisament fort

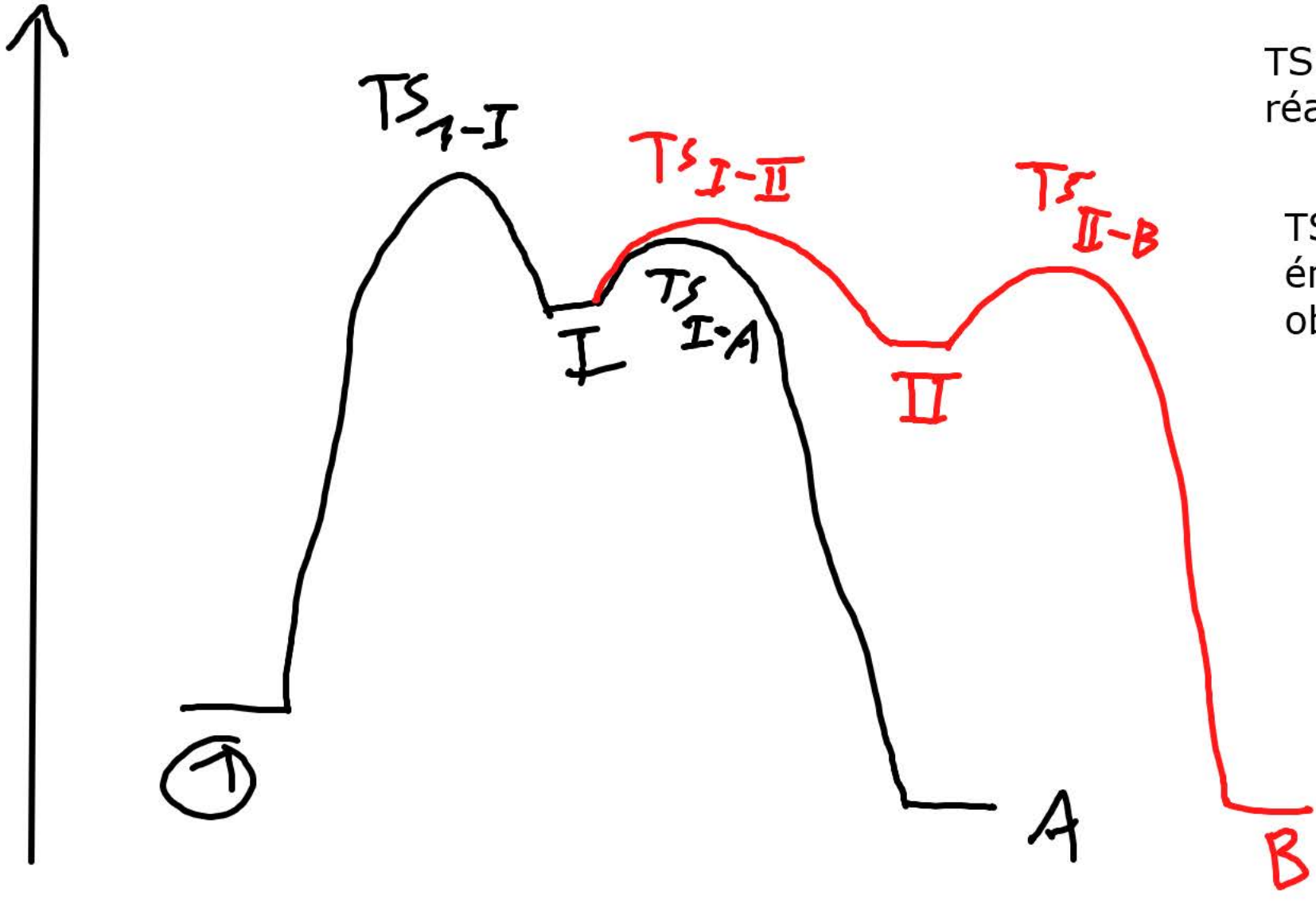
très mauvais nucléophile



fonctionne pour l'adition de
l'eau et des alcools

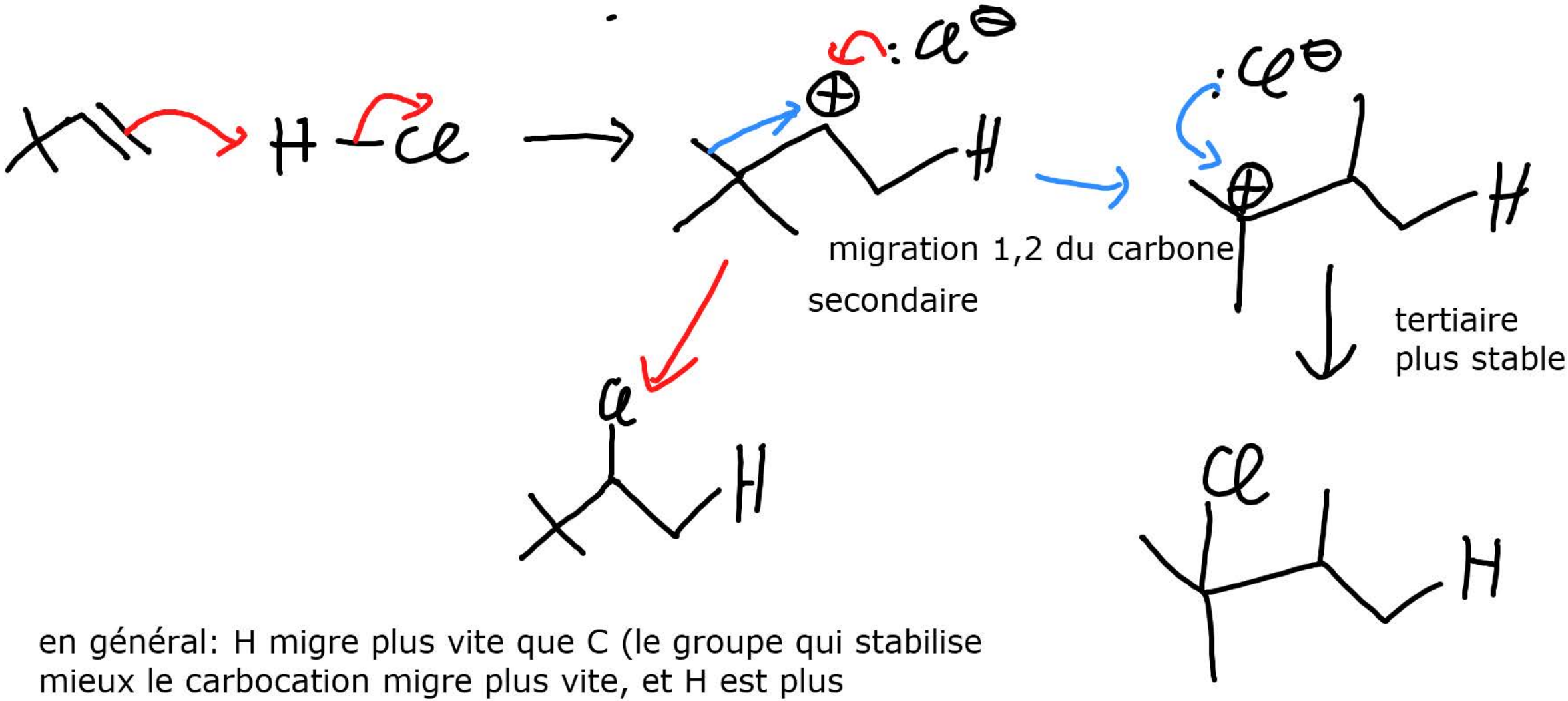
rearrangement des carbocations





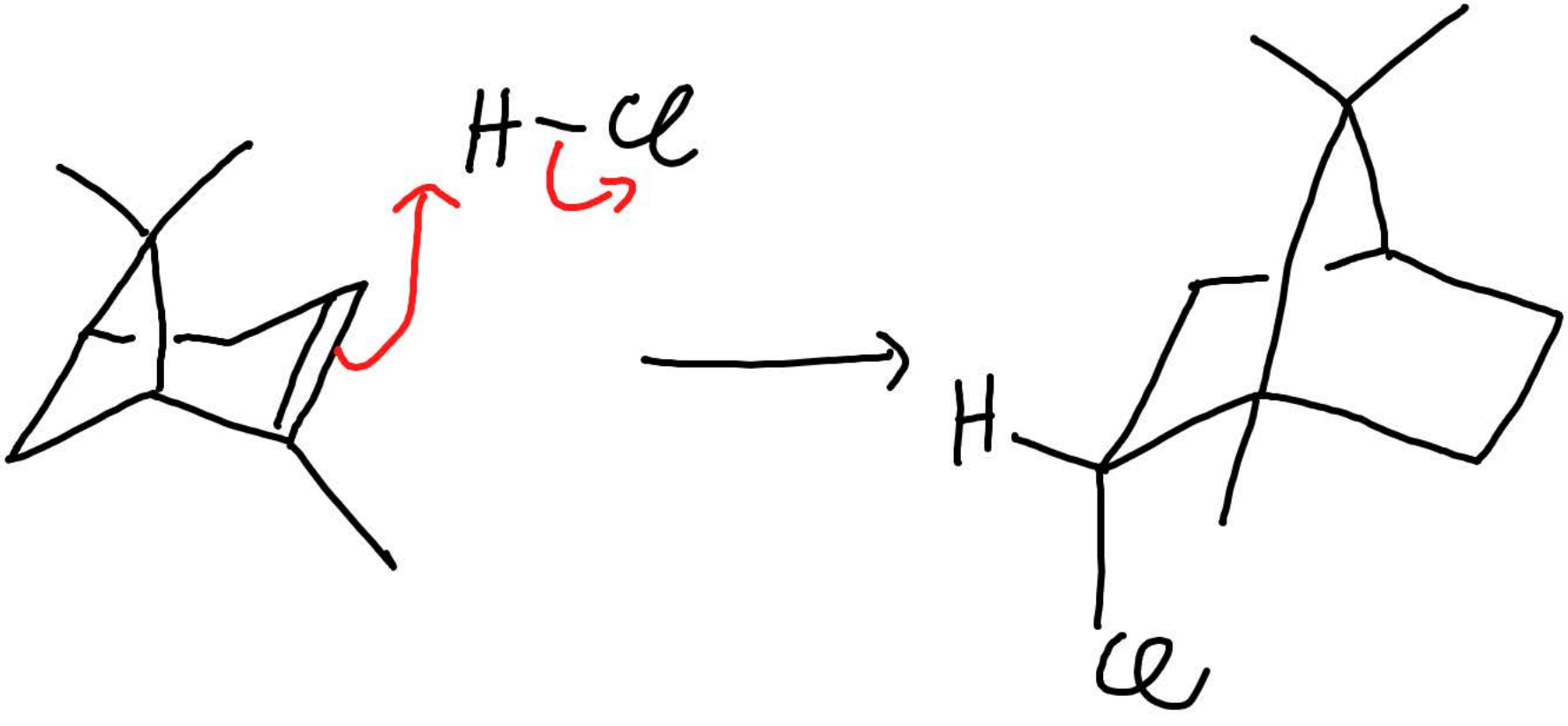
TS1-I détermine la vitesse de la réactio (le plus haut en énergie)

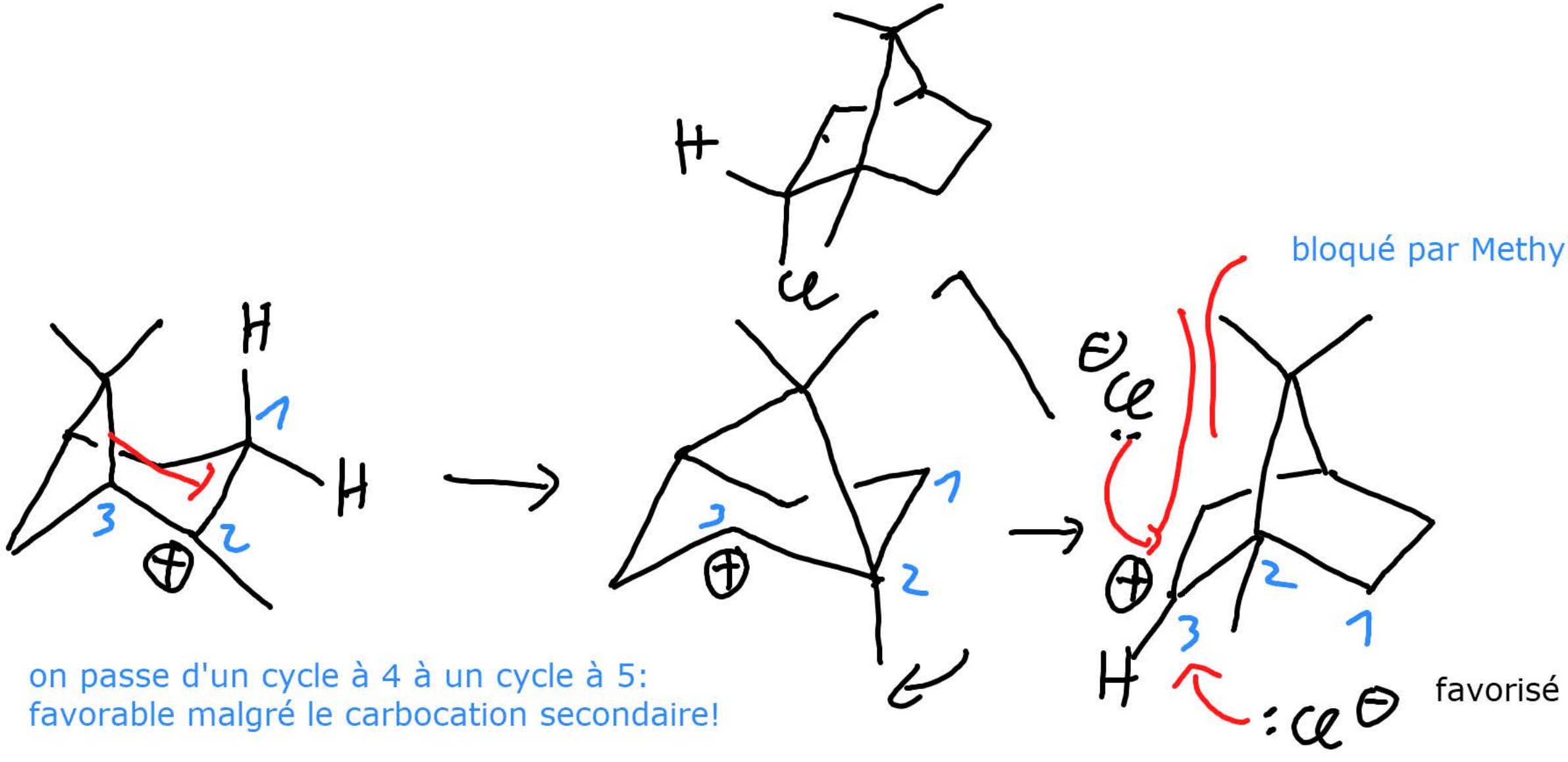
TSI-II et TSI-A très proche en énergie, les deux produits sont observés!



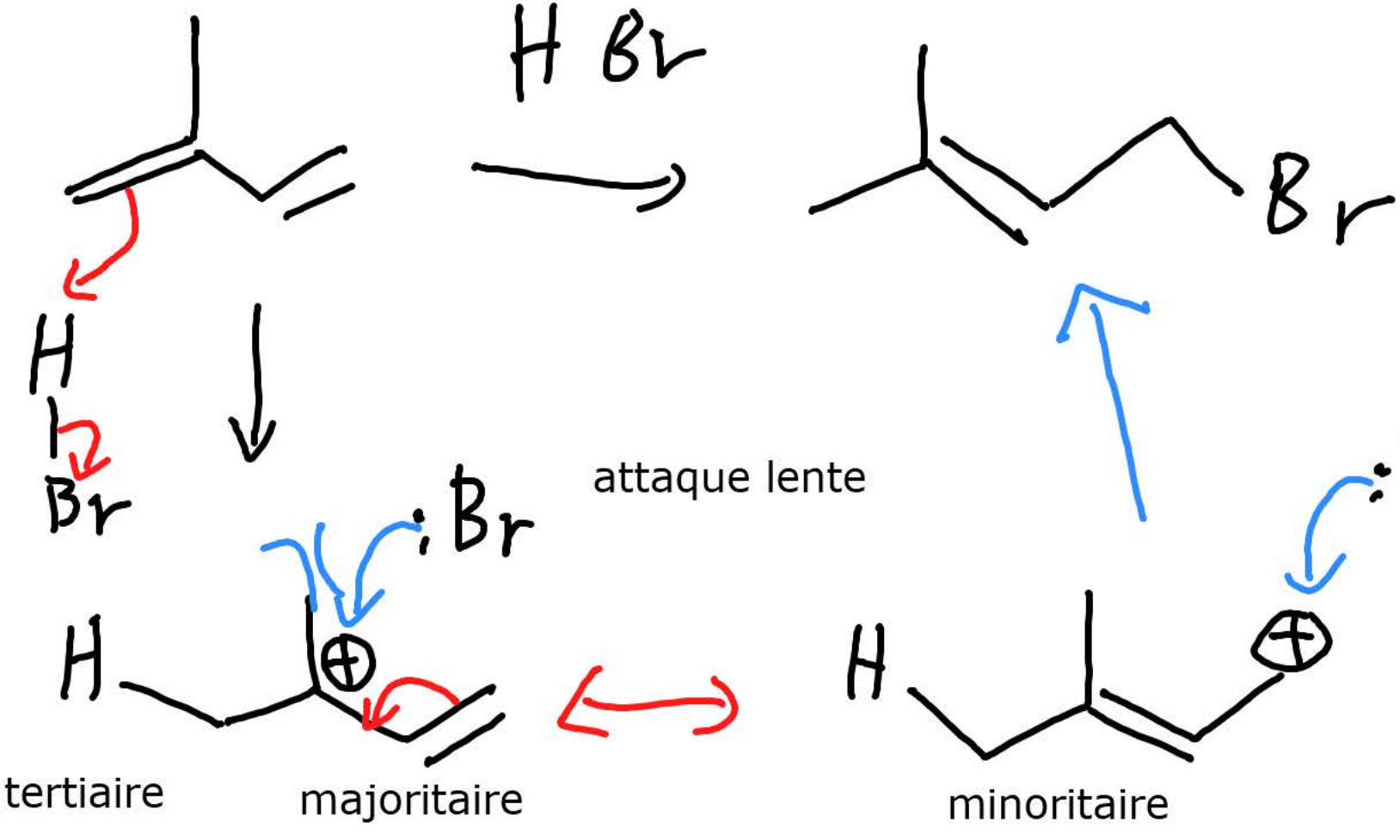
en général: H migre plus vite que C (le groupe qui stabilise mieux le carbocation migre plus vite, et H est plus électropositif)

découverte pas Wagner-Meerwein (1899)




bloqué par Methyl
on passe d'un cycle à 4 à un cycle à 5:
favorable malgré le carbocation secondaire!
favorisé

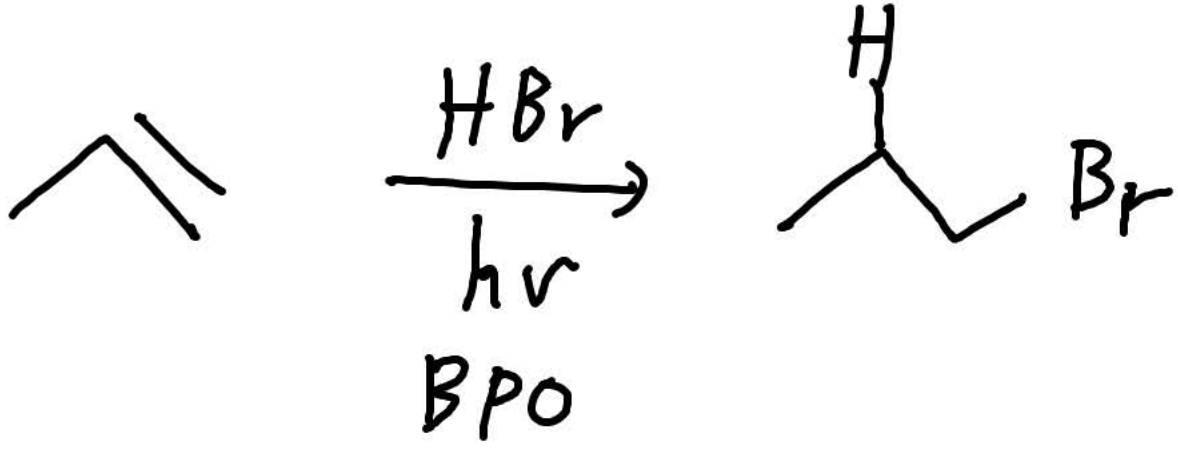
exception à Markovnikov



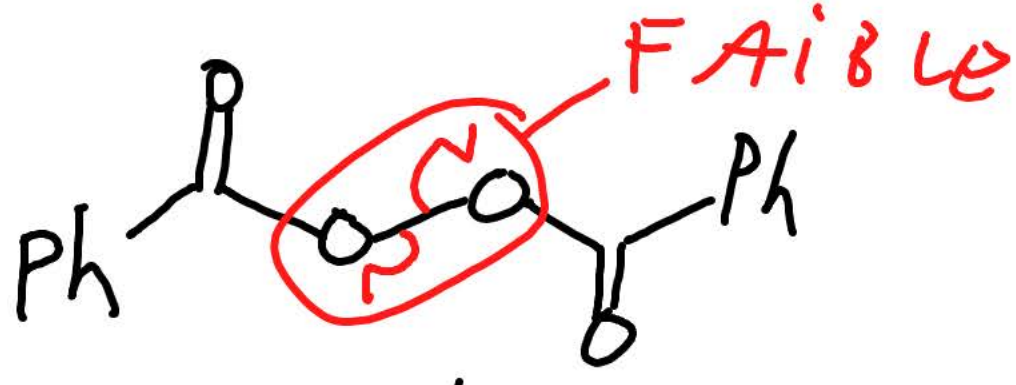
ici: l'attaque plus rapide de Br en position primaire est décisif!

structures de résonance

Comment synthétiser le produti anti-Markovnikov

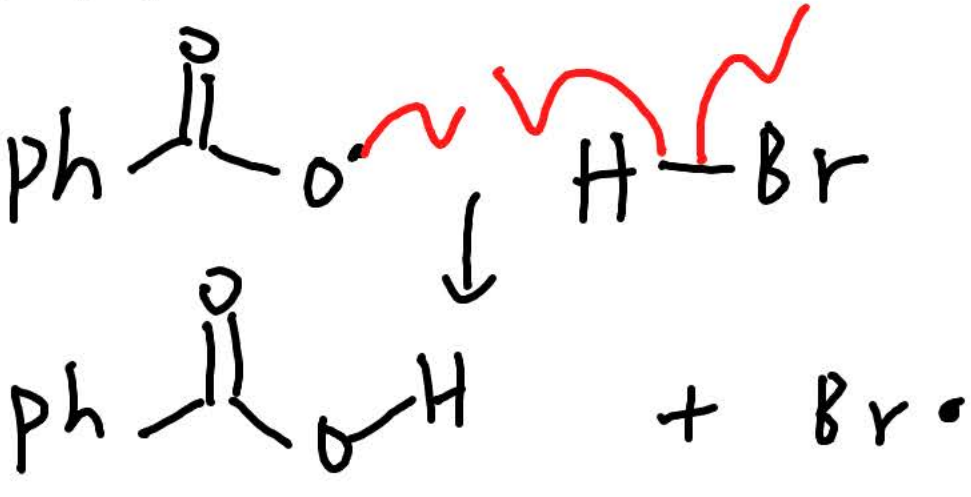


BPO: benzoylperoxide



initiation

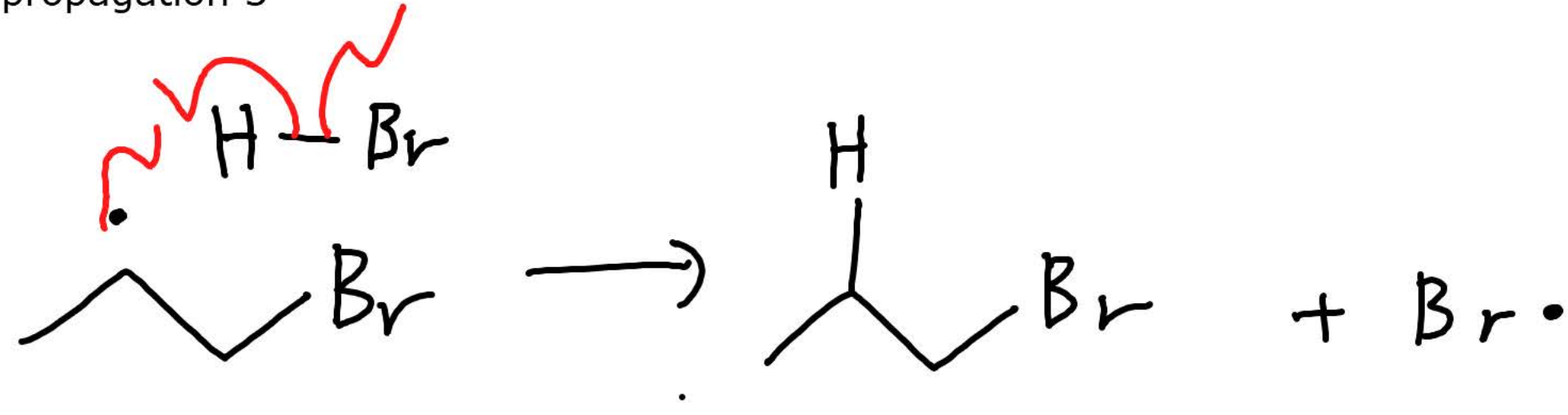
propagation 1



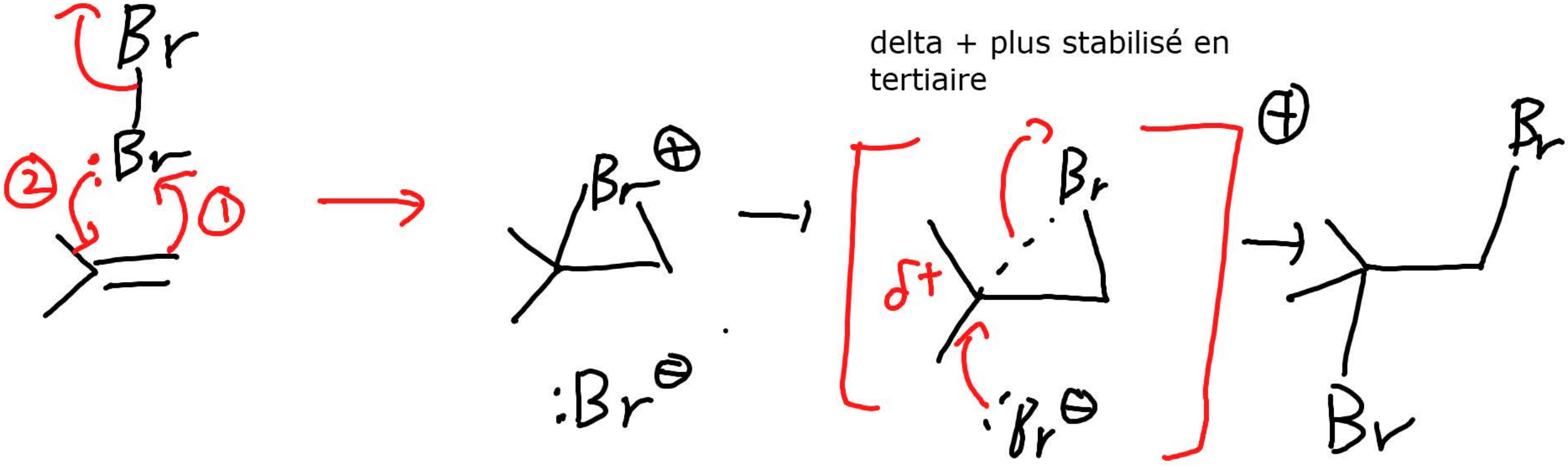
propagation 2

radical secondaire plus stable

propagation 3



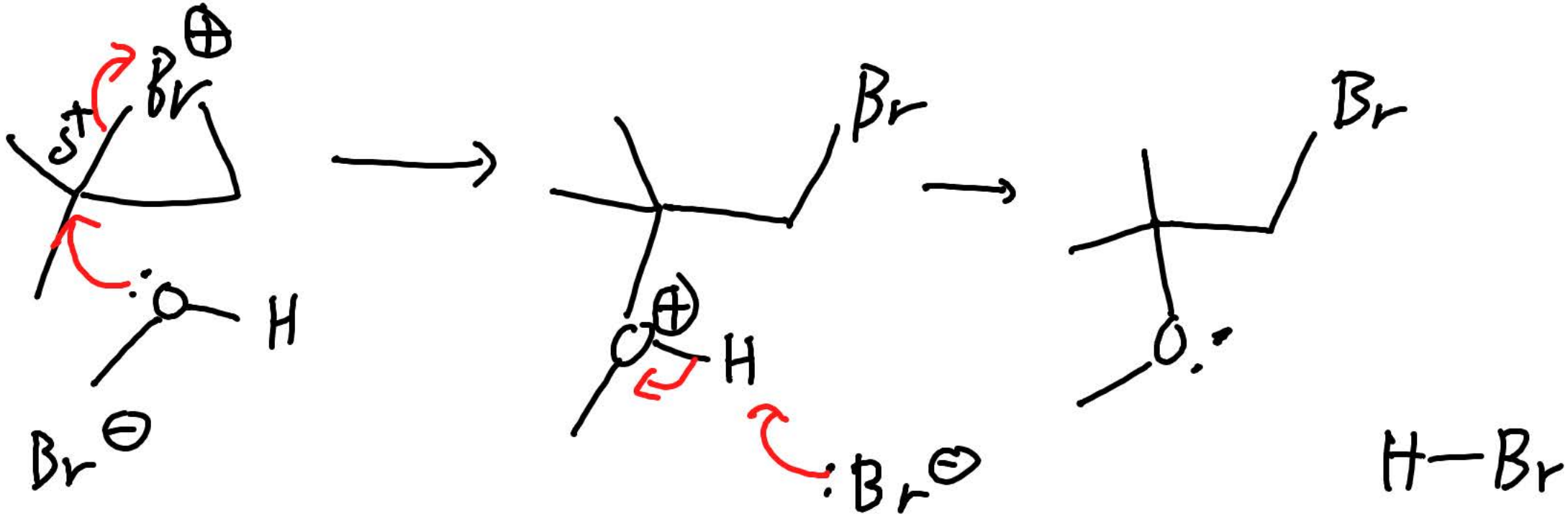
réaction des alcènes avec les "gros" électrophiles (Cl+, Br+, I+, S+, etc...)



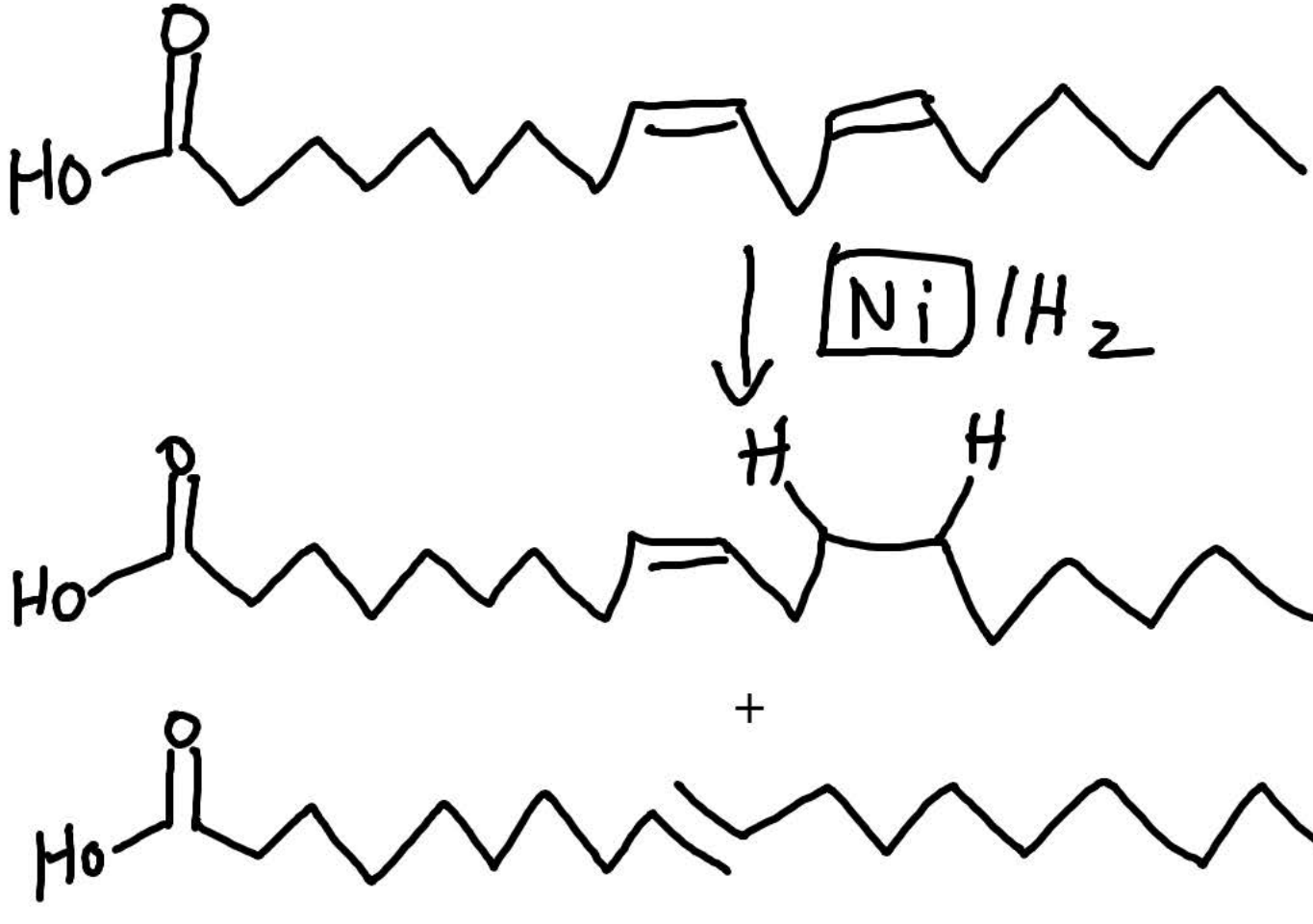
stable avec les gros atomes

les Br sont en trans

Avec Br2 et MeOH?



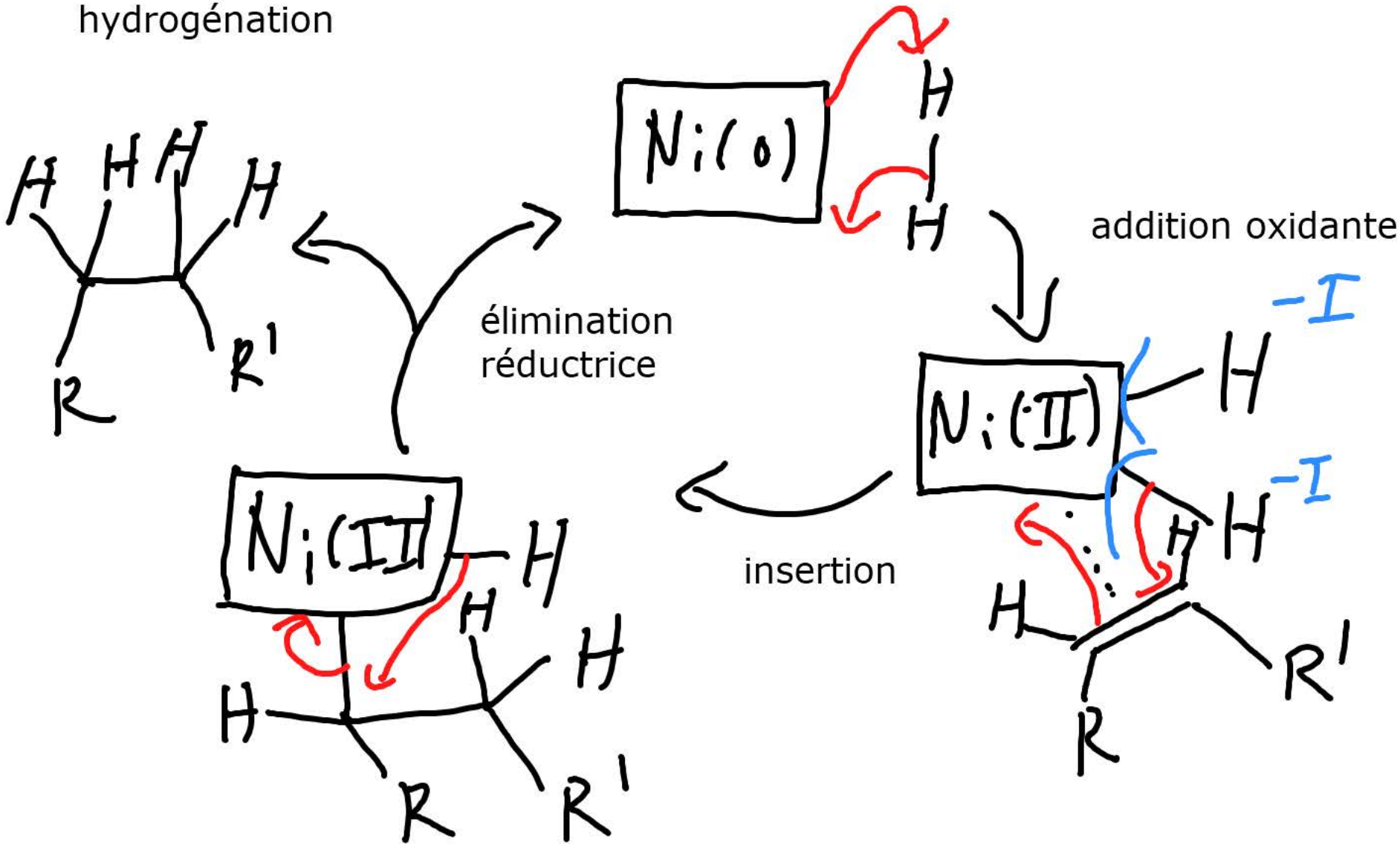
- example d'hydrogénation: les acides gras



acide linoléique: abondant dans les huiles végétales (liquide visqueux)

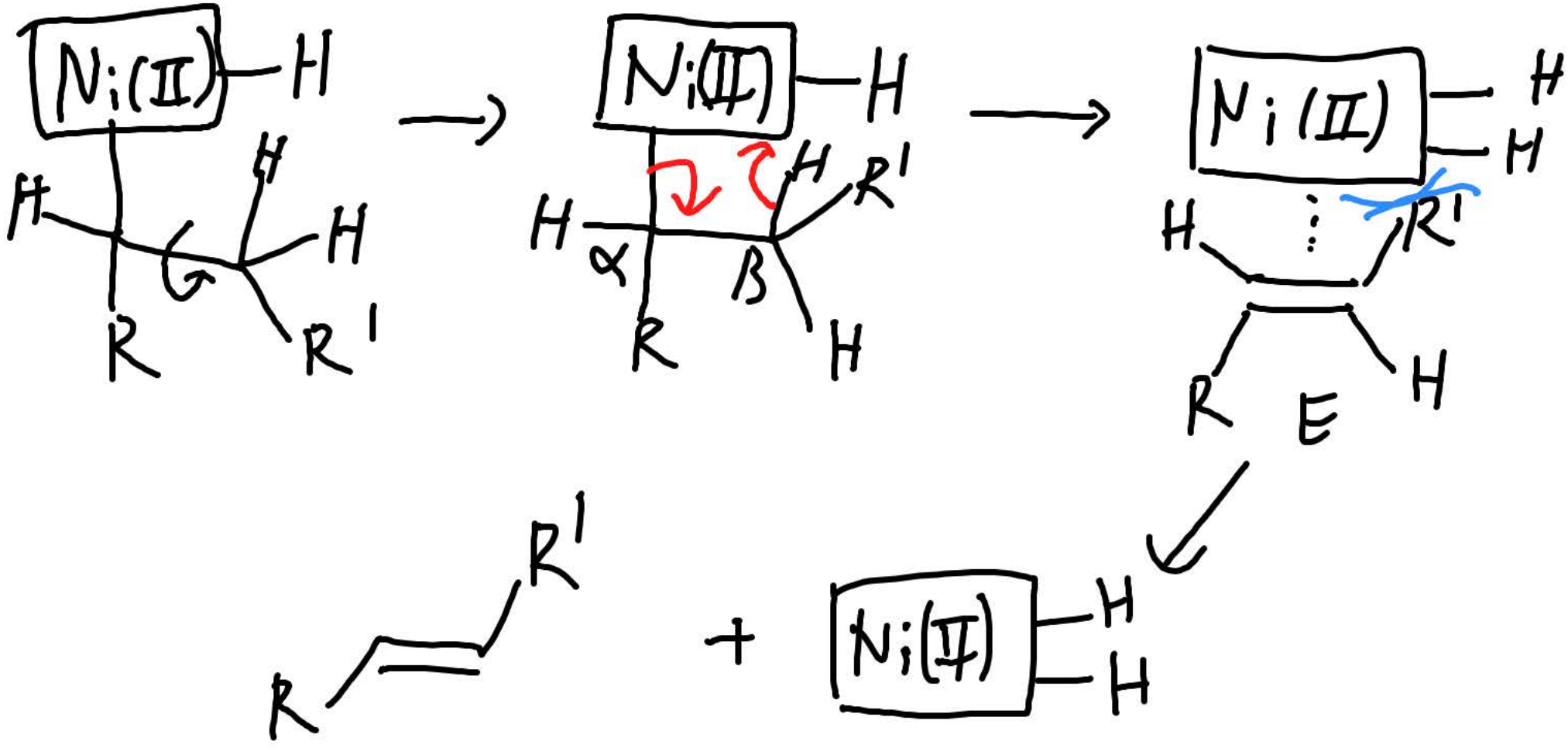
parafine/solide

E/trans, trans-fat, artériosclérose!

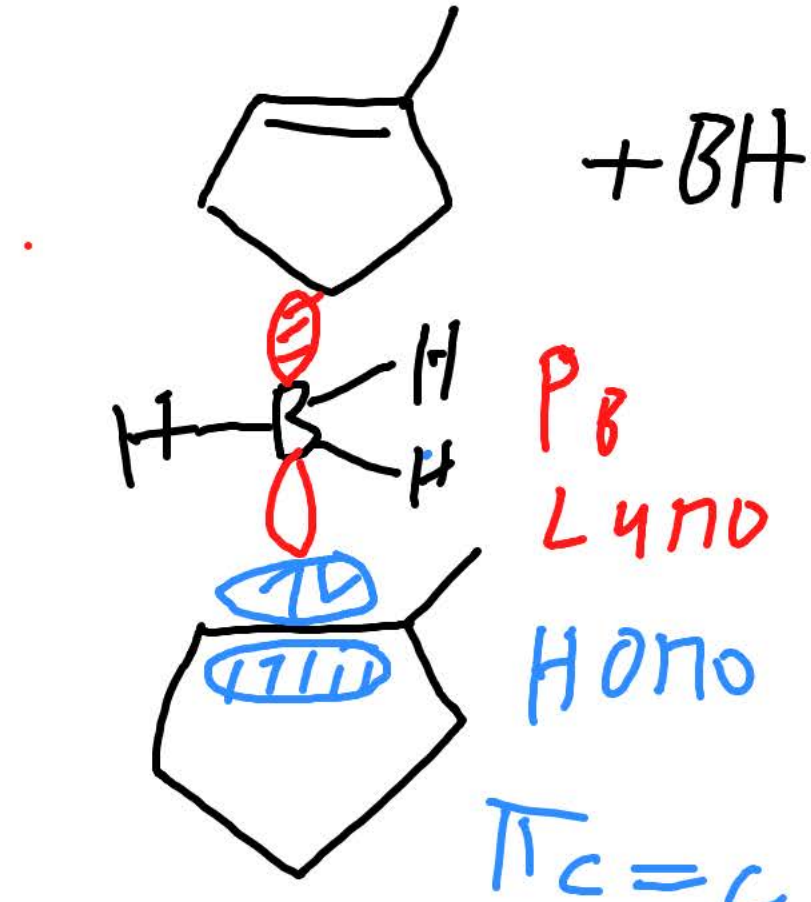

hydrogénation
Ni(0)
addition oxidante
élimination
réductrice
insertion
Ni(II)
Ni(II)
-I
-I
H
R
R'

réaction secondaire: isomérisation

Beta-hydride elimination



hydroboration



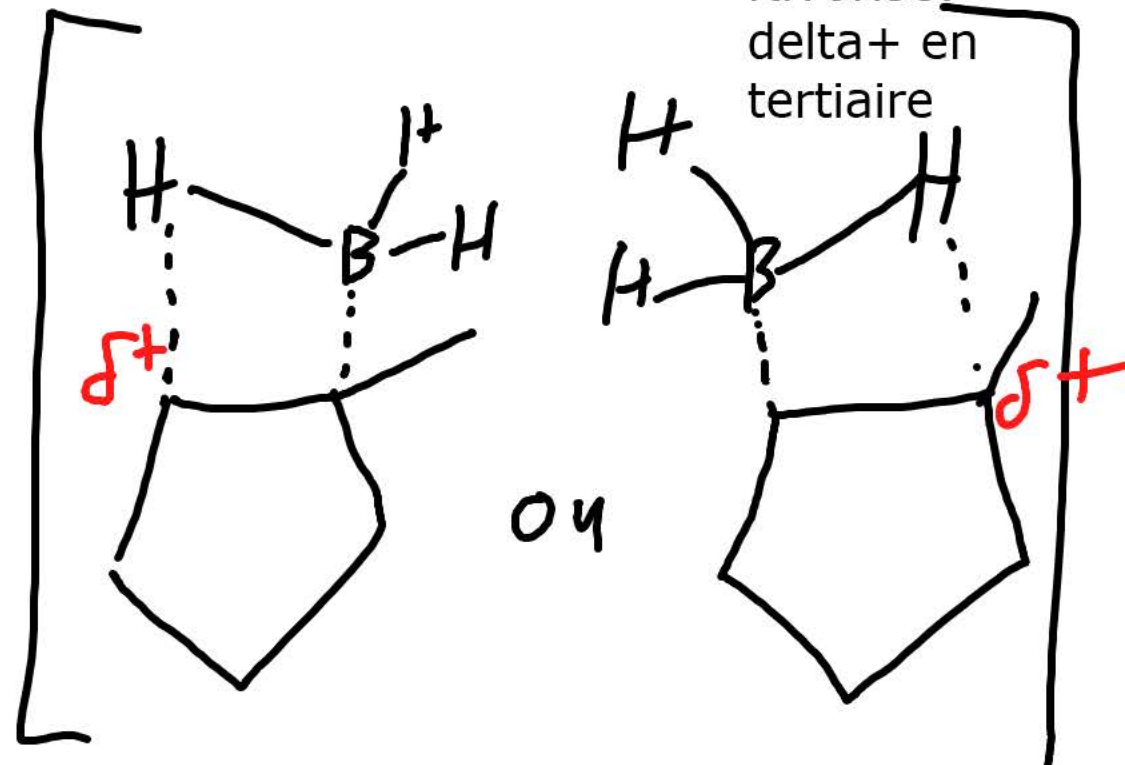
$+BH_3$

P_B

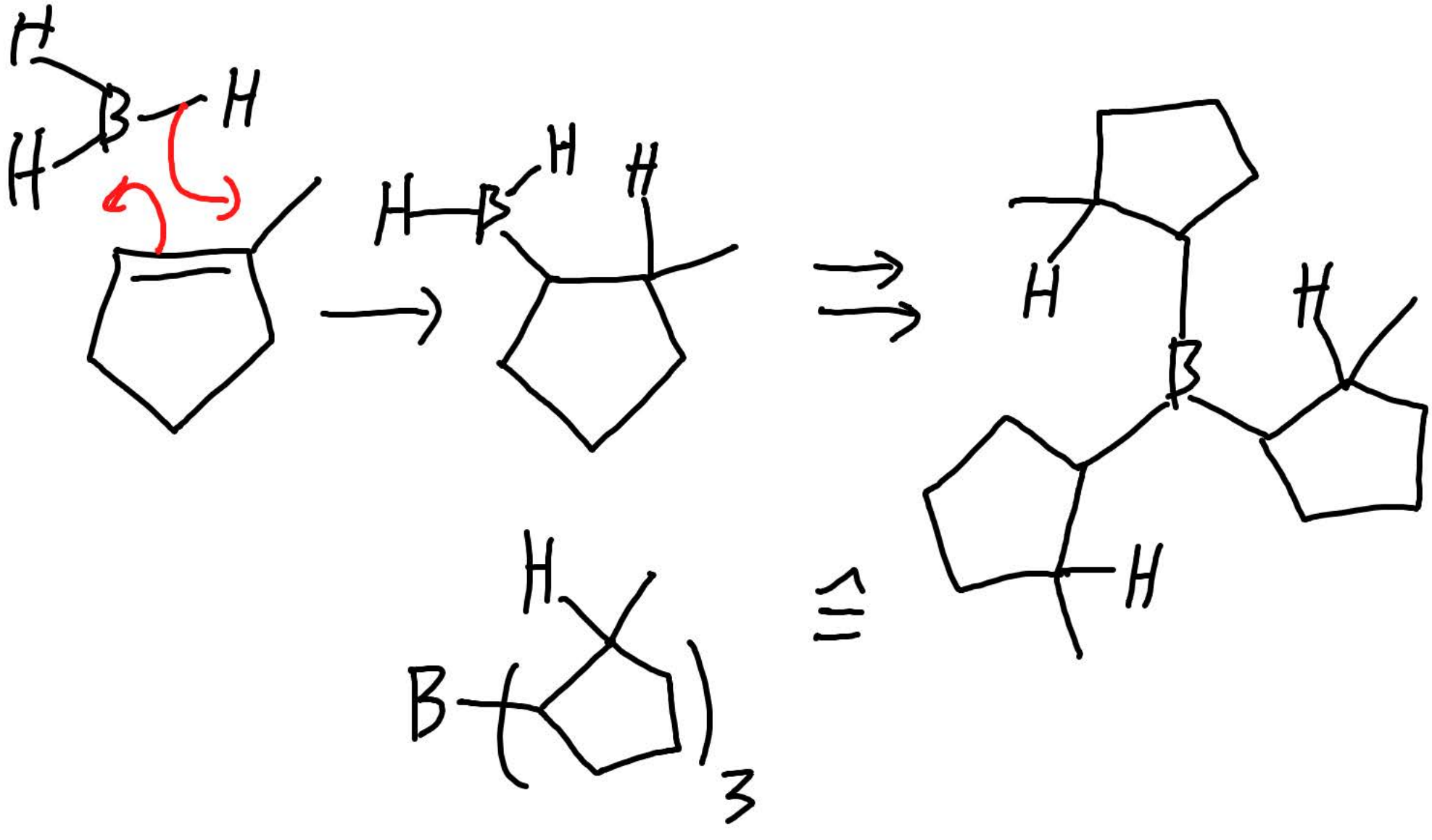
Lumo

Homo

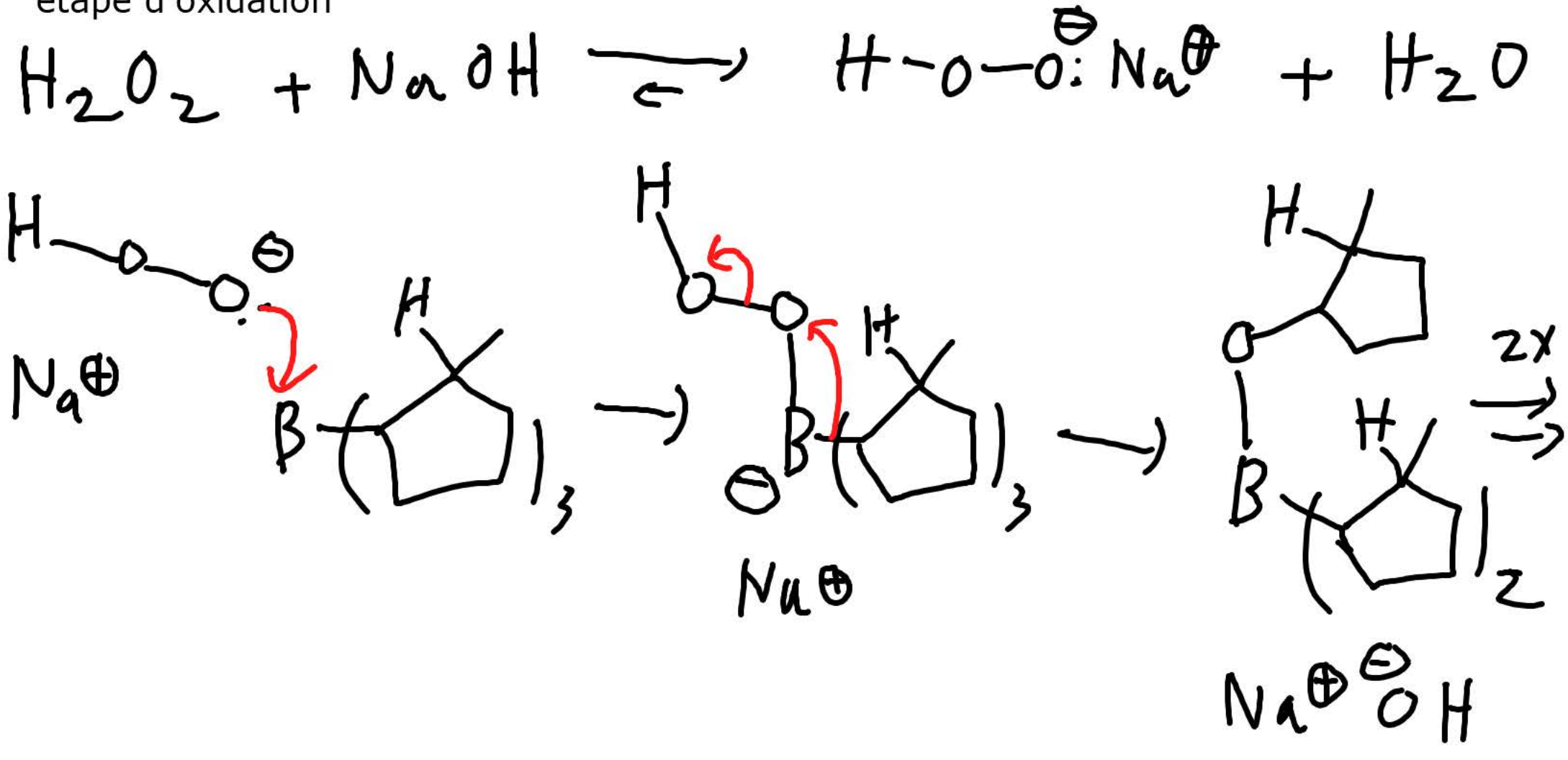
$\pi_{C=C}$

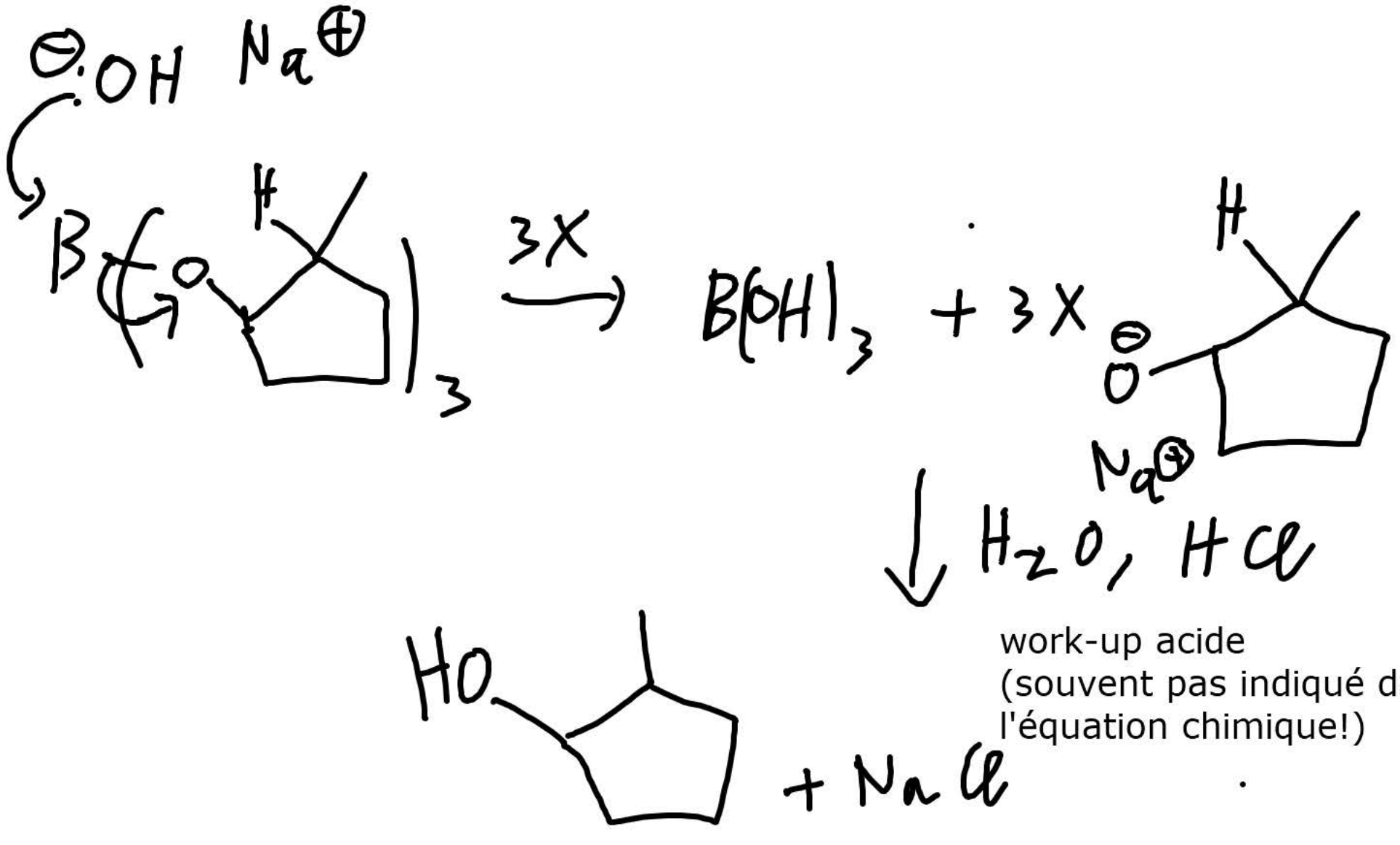


liaison C-B est plus courte que
C-H dans l'état de transition


H
H
B
H
H
B
H
H
H
B
H
H
B
H
H
H
B
3

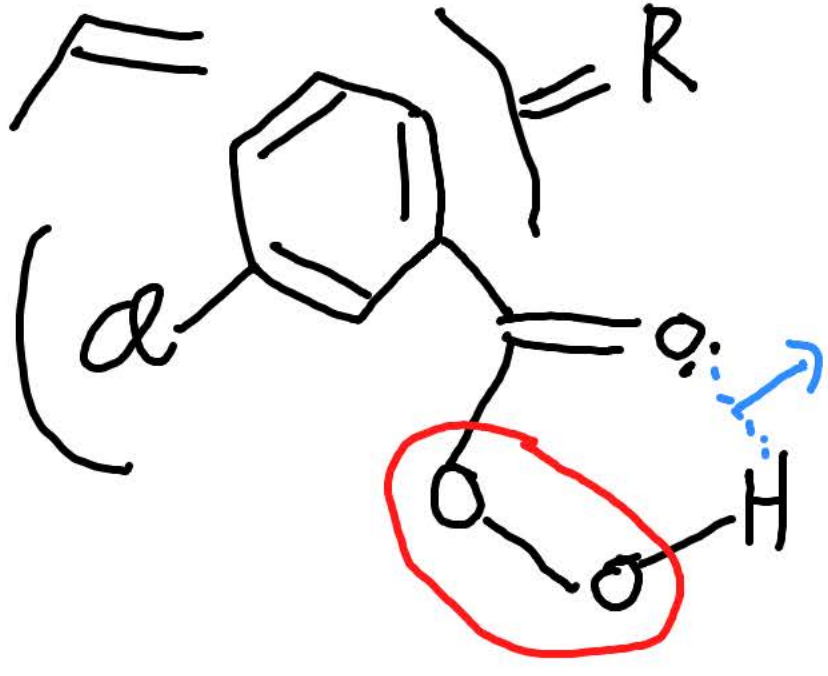
étape d'oxidation





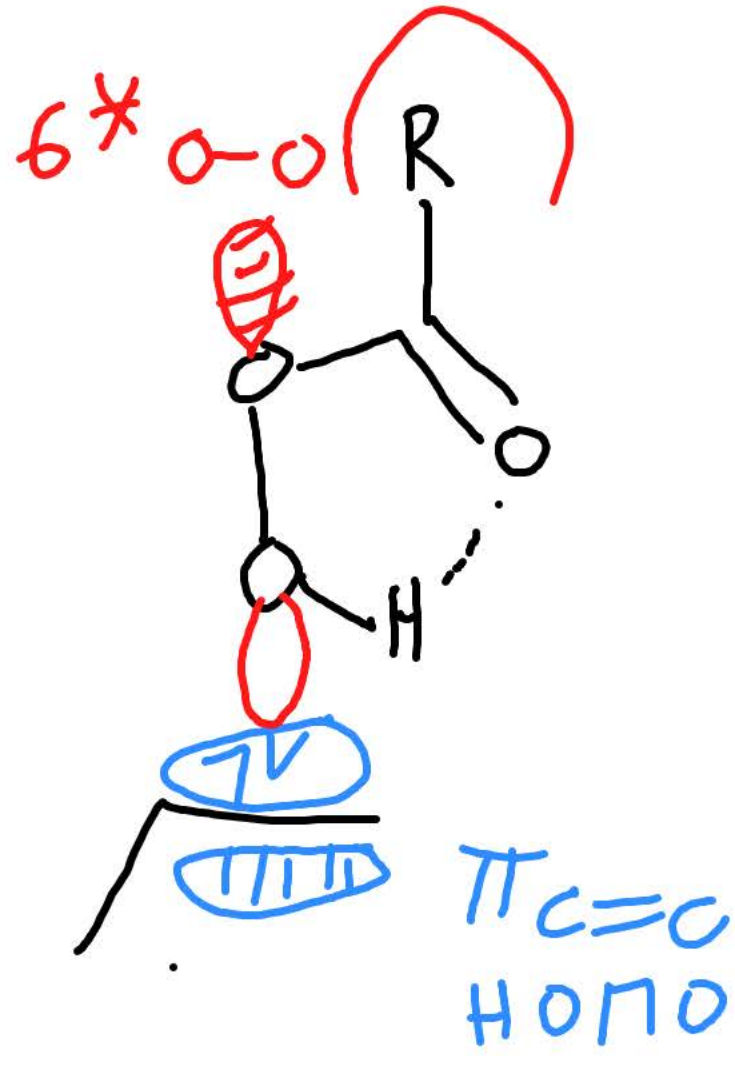
work-up acide
(souvent pas indiqué dans l'équation chimique!)

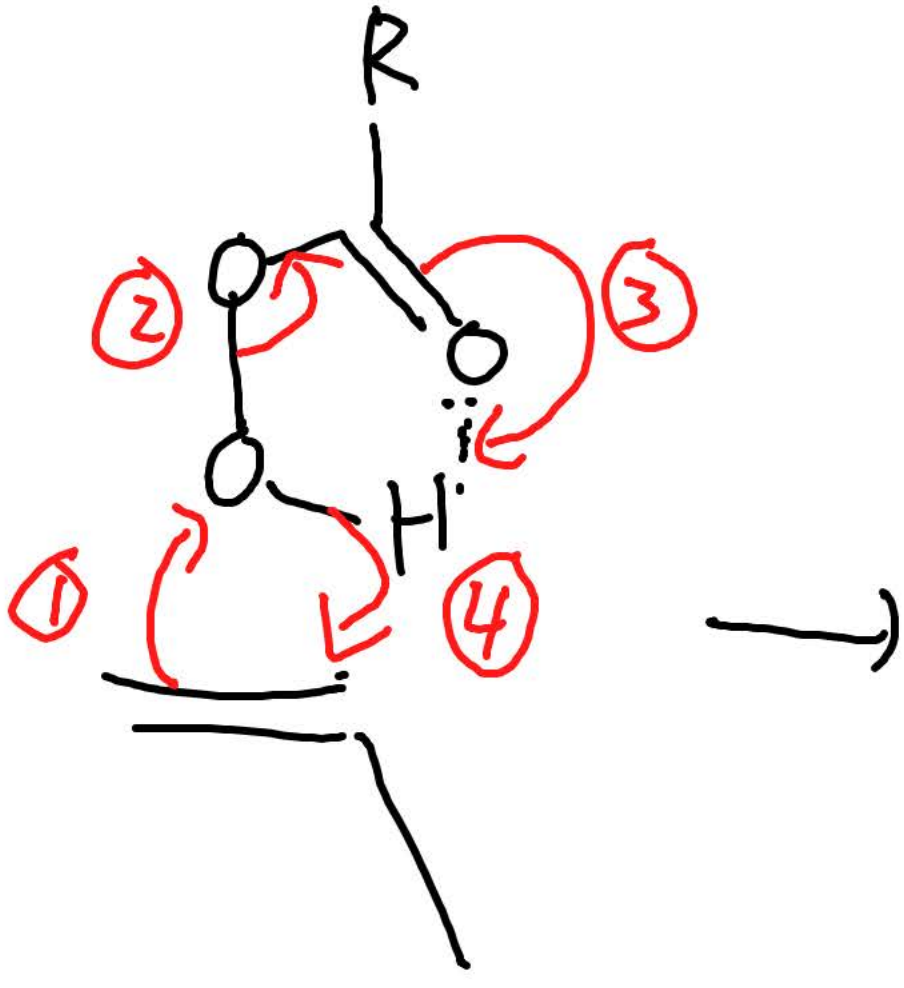
réaction 1: époxidation avec les peroxides

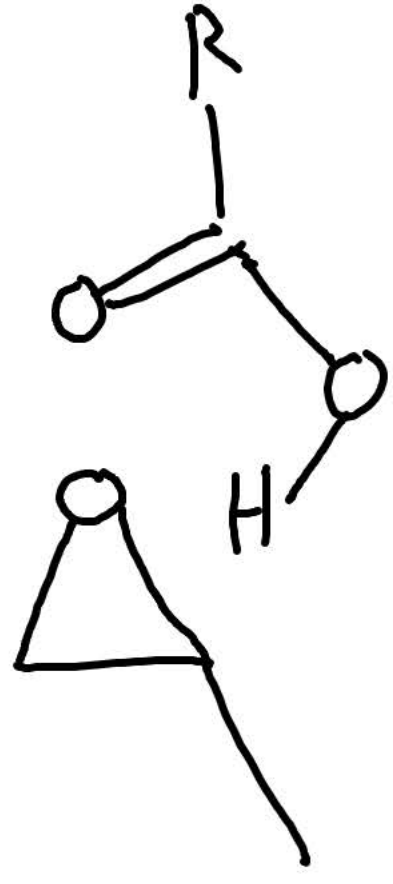


meta-chloroperbenzoic acid
m-CPBA

pont hydrogène
bien soluble dans
les solvants organique



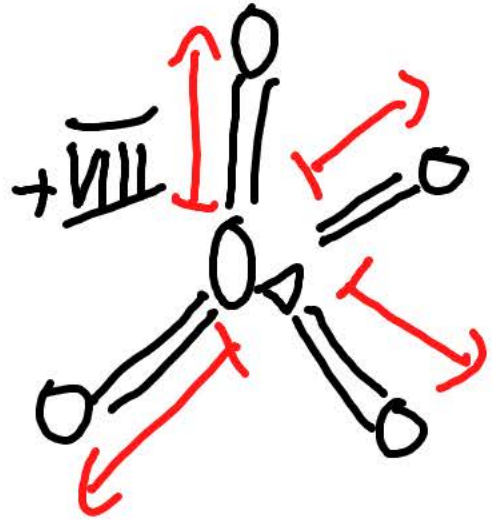




pas de pont hydrogène
moins soluble
précipite

réaction de dihydroxylation

réactif: OsO4

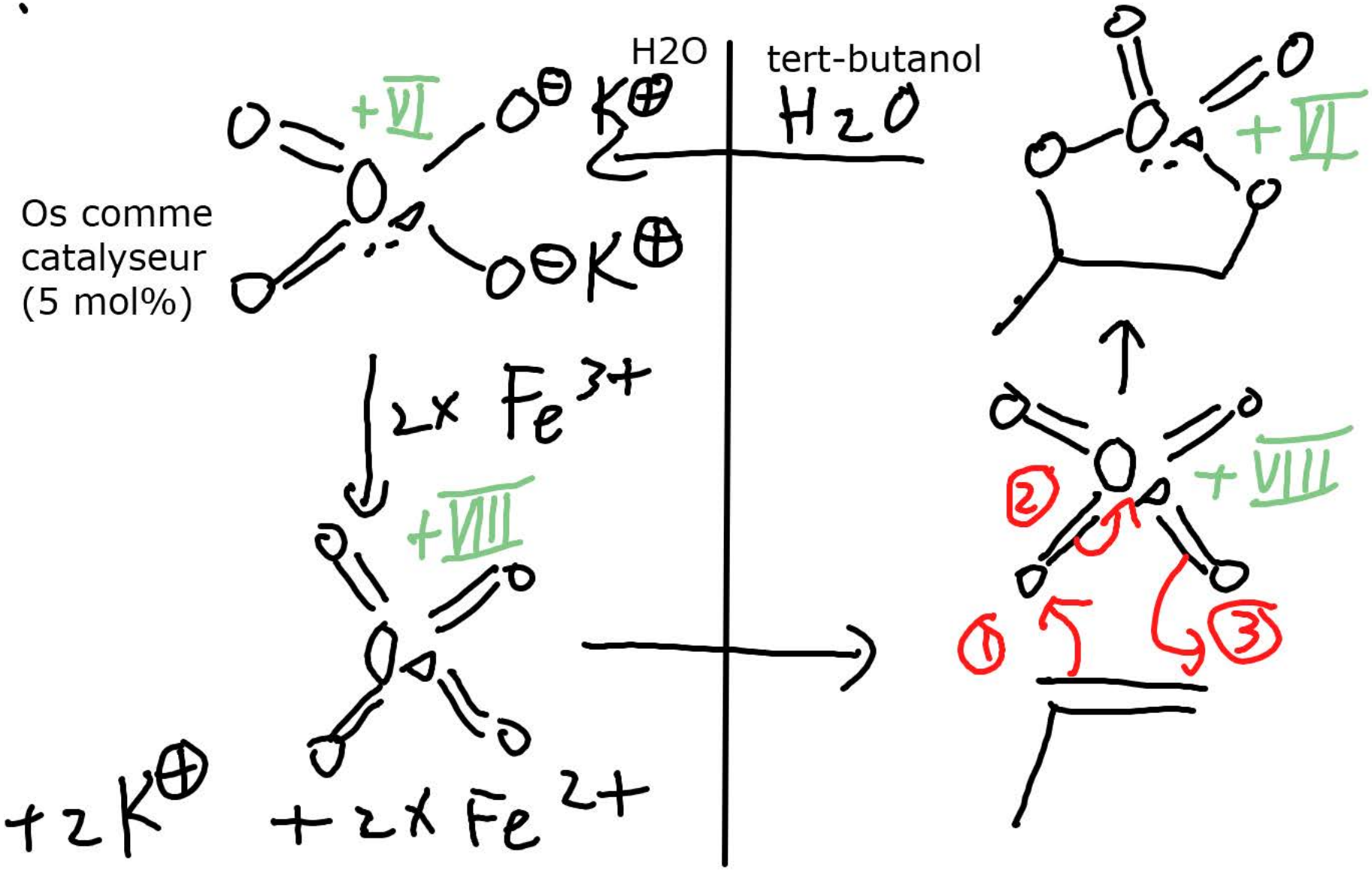


lipophilique, passe la barrière sang-cerveau
sublime facilement

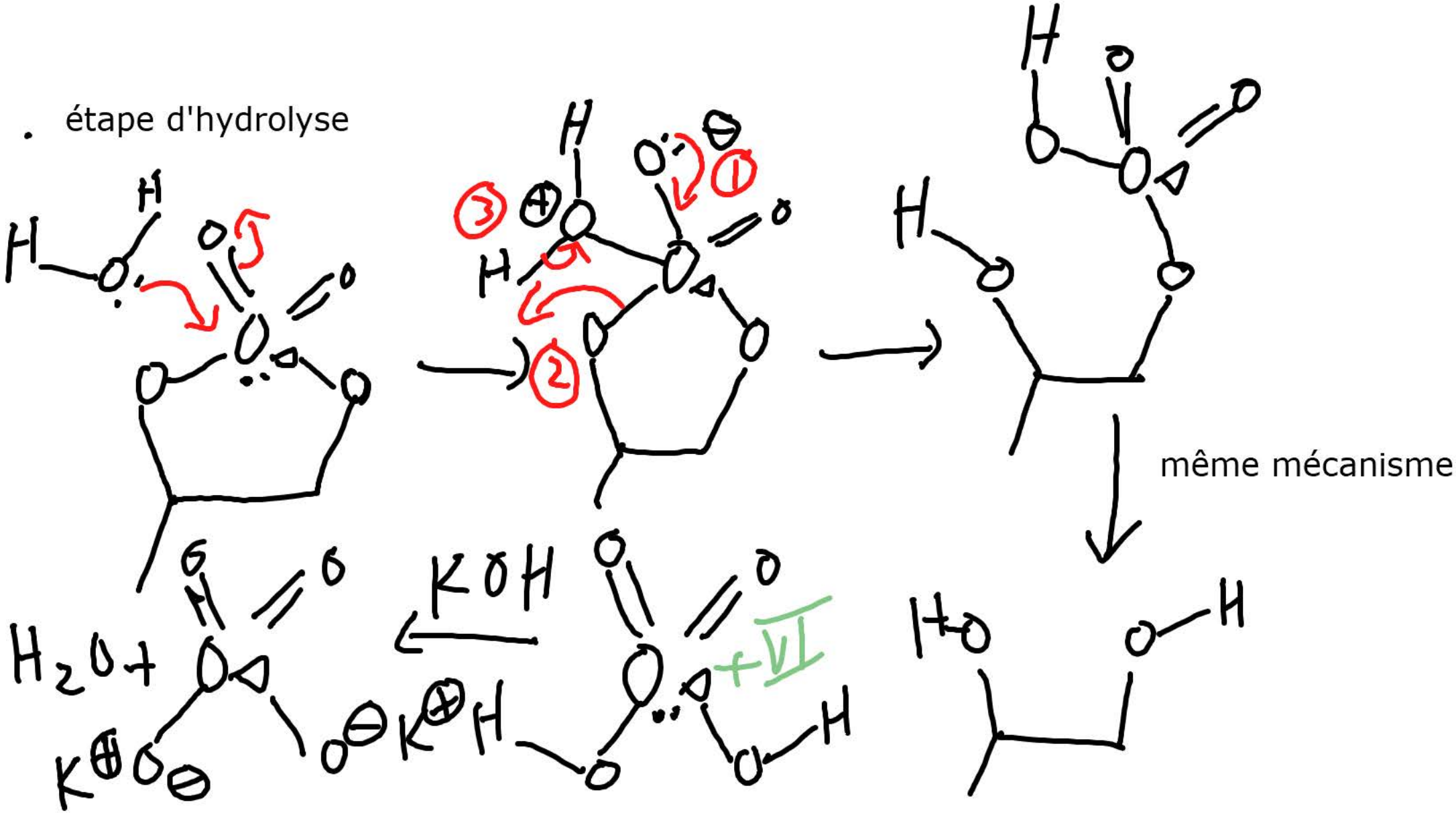
dipole total = 0 (tétrahèdre)

méthode de Sharpless: K2OSO4, Fe3+, H2O/tert-butanol

réaction "biphasique"

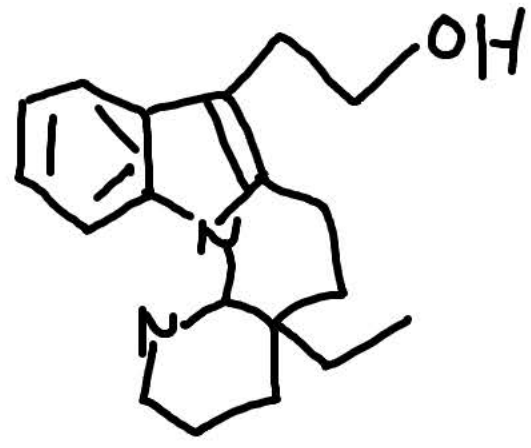


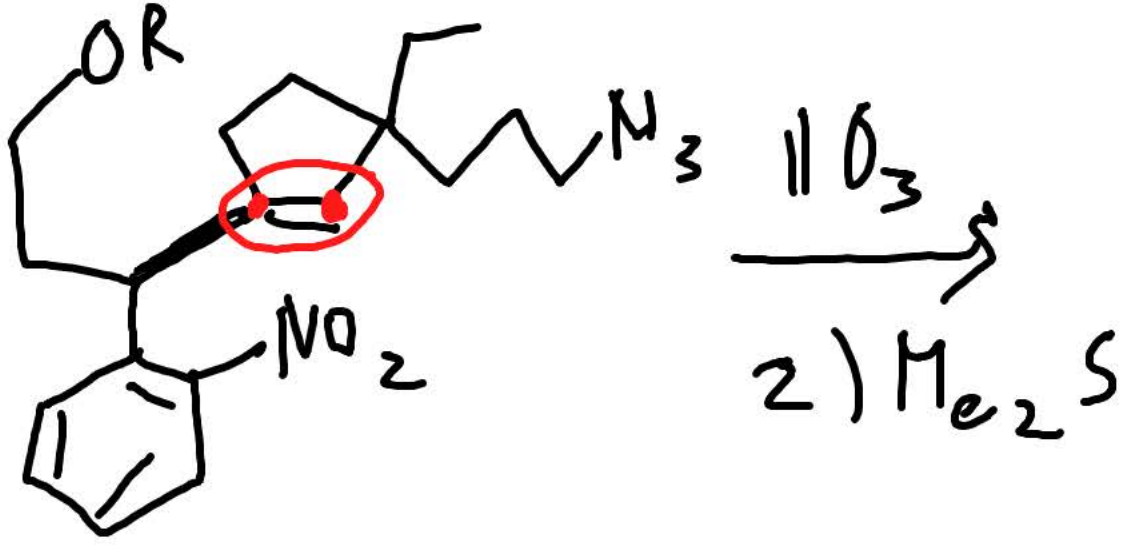
étape d'hydrolyse

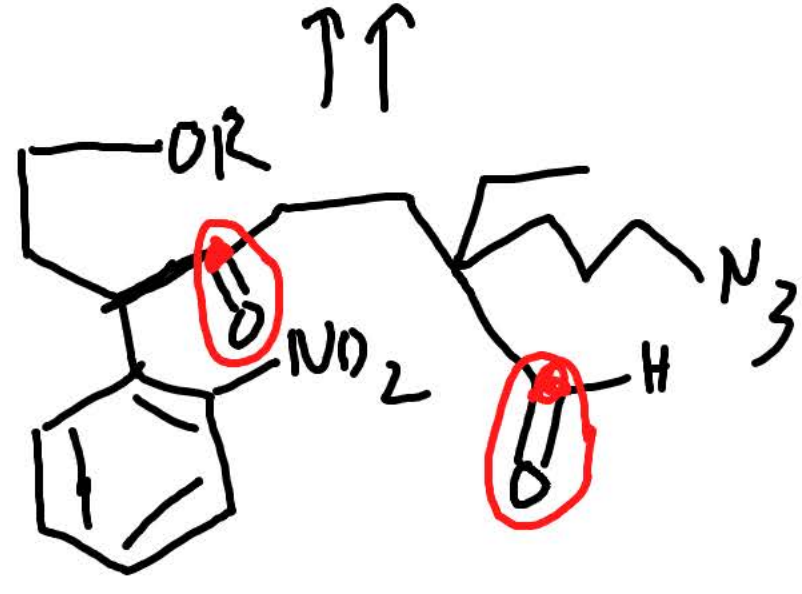


réaction d'ozonolyse

goniomitine
produit naturel
synthèse du groupe
de Jieping Zhu à l'EPFL

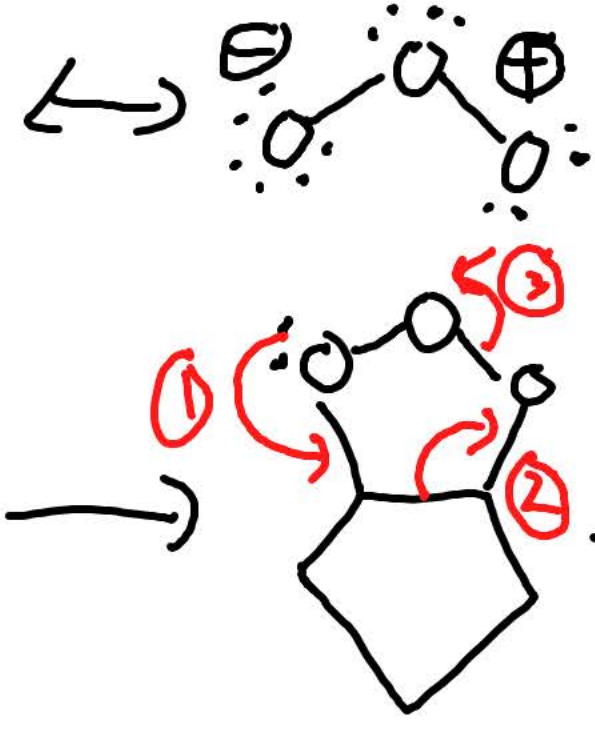






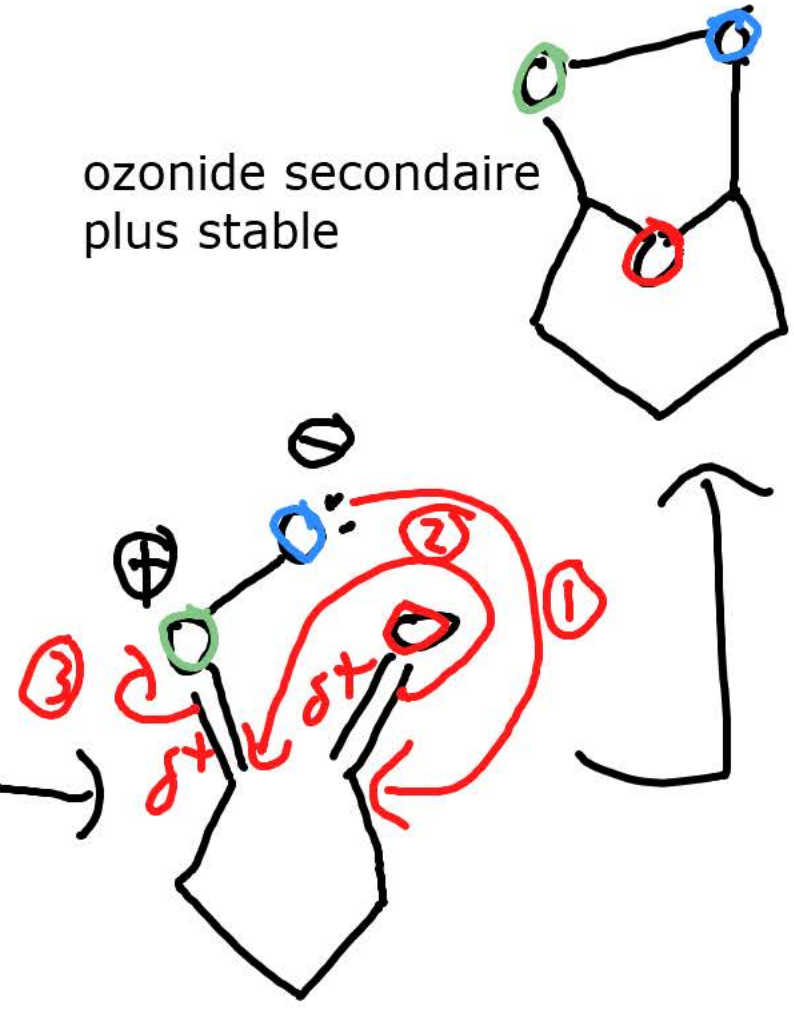
mécanisme

moins favorable
dipole 1,3

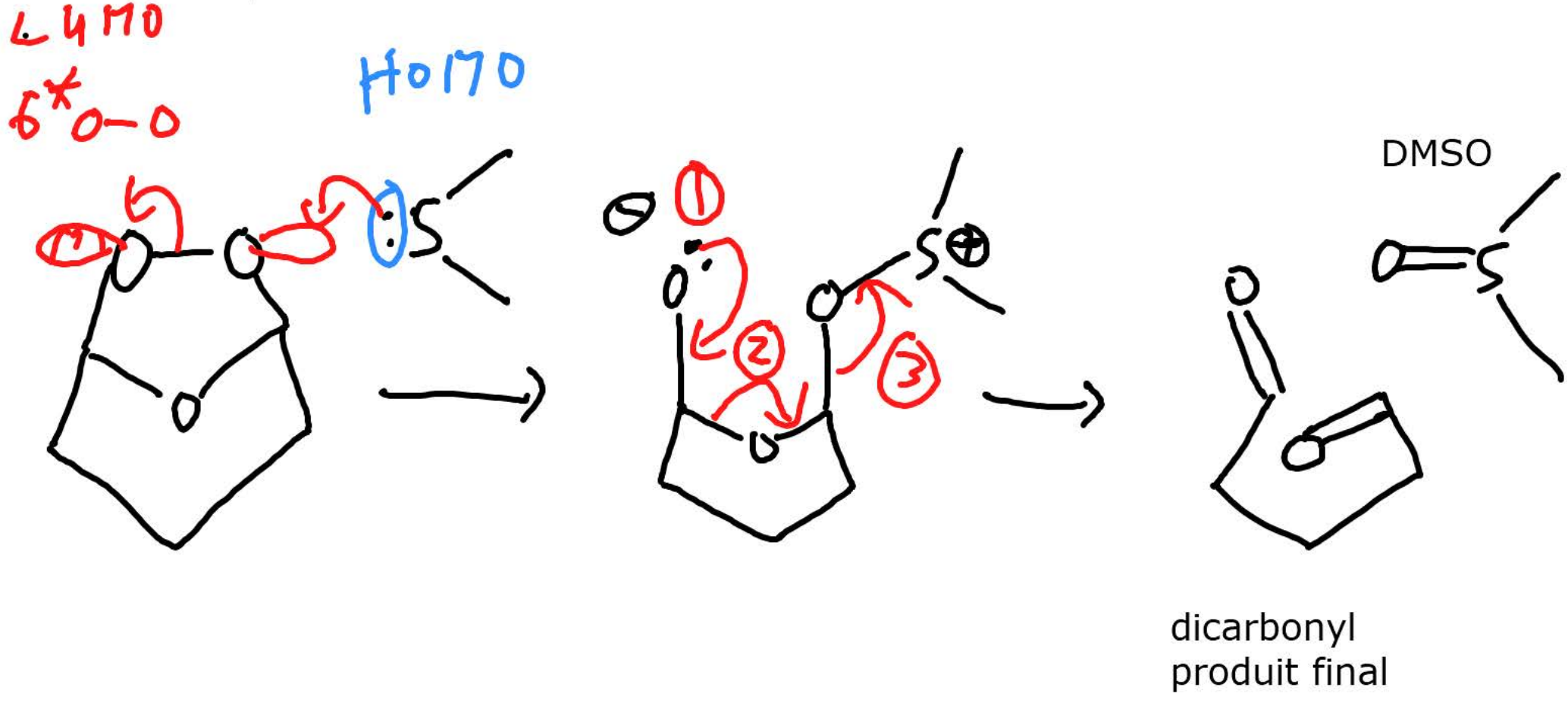


ozonide primaire
instable

ozonide secondaire
plus stable

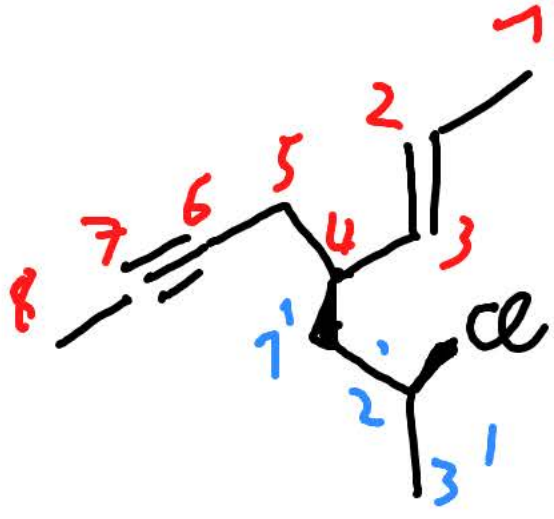


seconde étape: réduction



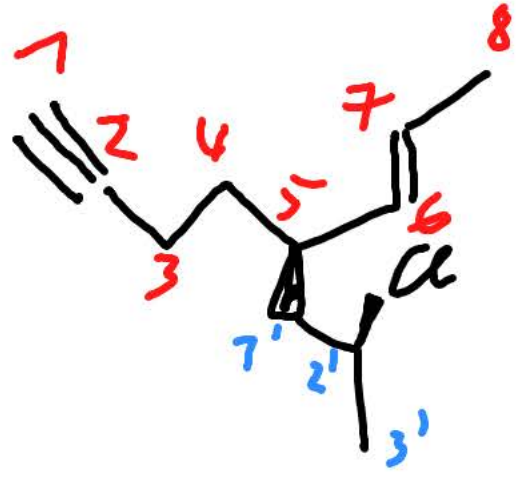
dicarbonyl
produit final

nomenclature des alcynes



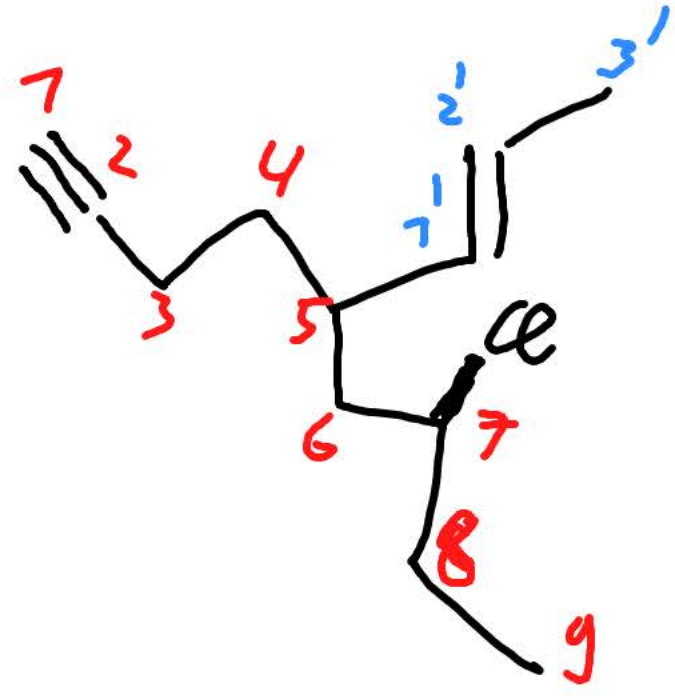
1) la plus longue(identique)
2) le plus d'insaturation
3) chiffre le plus bas pour alcène

(E,4R)-4-((S)-2-chloropropyl)-oct-2-ene-6-yne



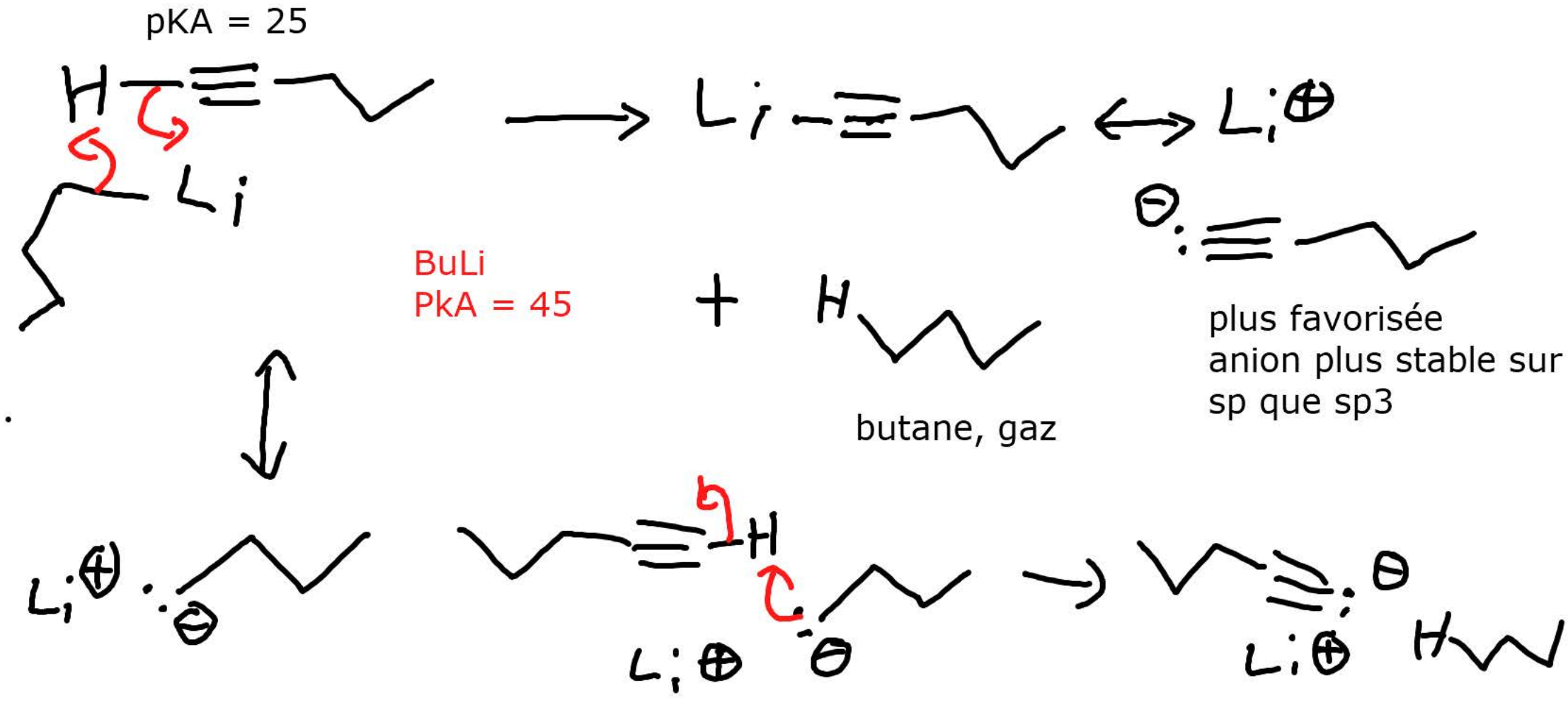
chiffre le plus bas
pour première insaturation

(E,5R)-5-((S)-2-chloropropyl)-oct-6-ene-1-yne

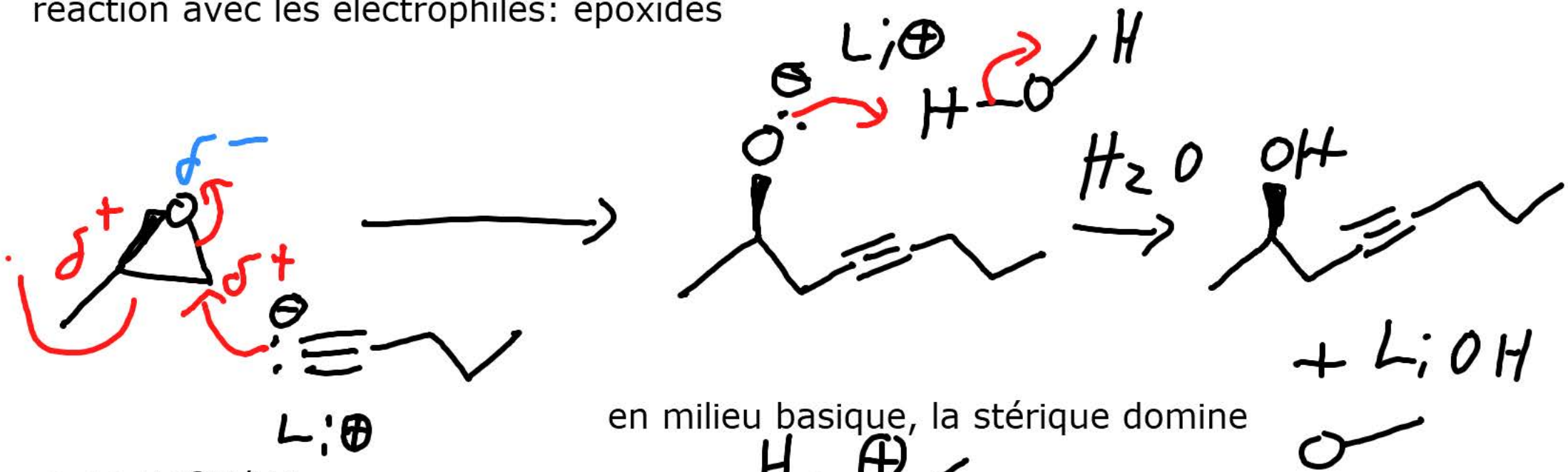


(5R,7S)-7-chloro-5-((E)-prop-1-enyl)-non-1-yne

déprotonation et réaction des alcynes

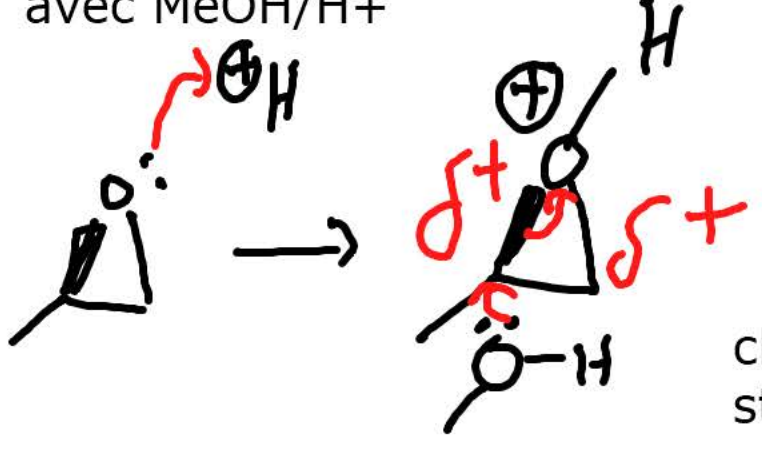


réaction avec les électrophiles: époxides



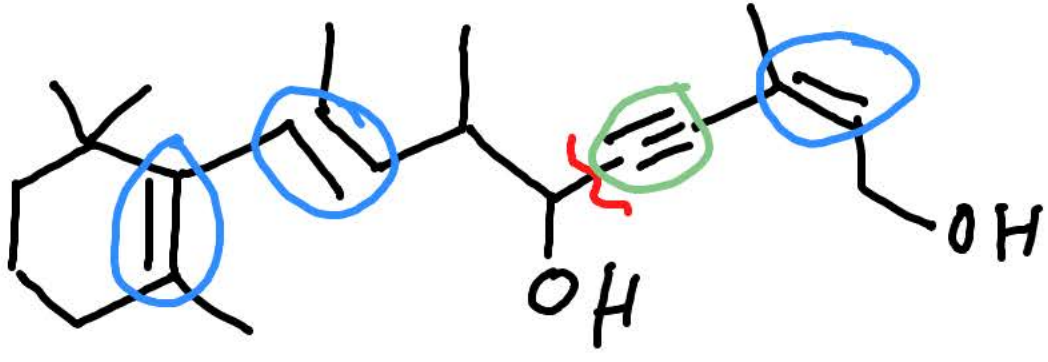
en milieu basique, la stérique domine

avec MeOH/H+

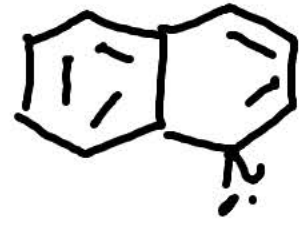


charge partielle augmentée: le plus important devient de stabiliser la charge, donc attaque en tertiaire

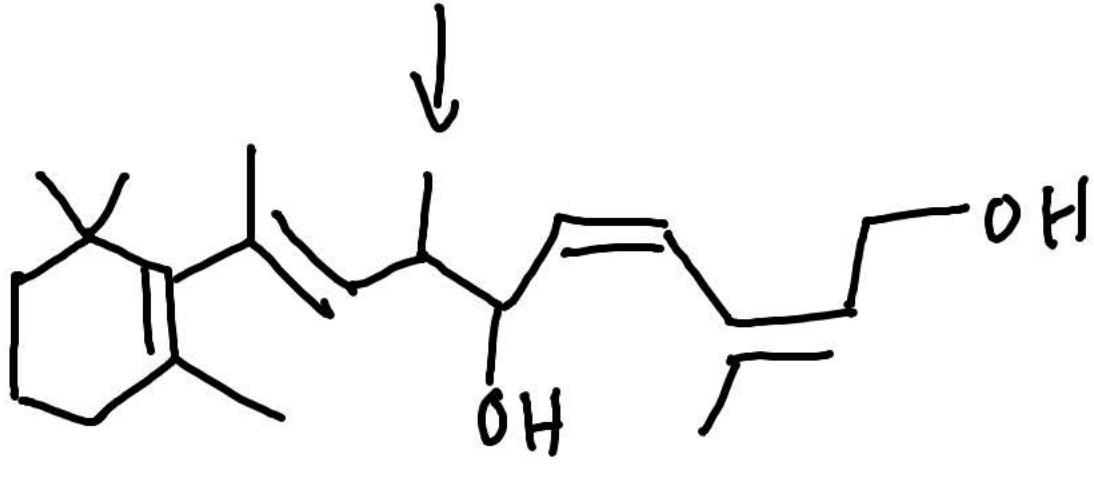
Hydrogénation de Lindlar: Hofmann-LaRoche



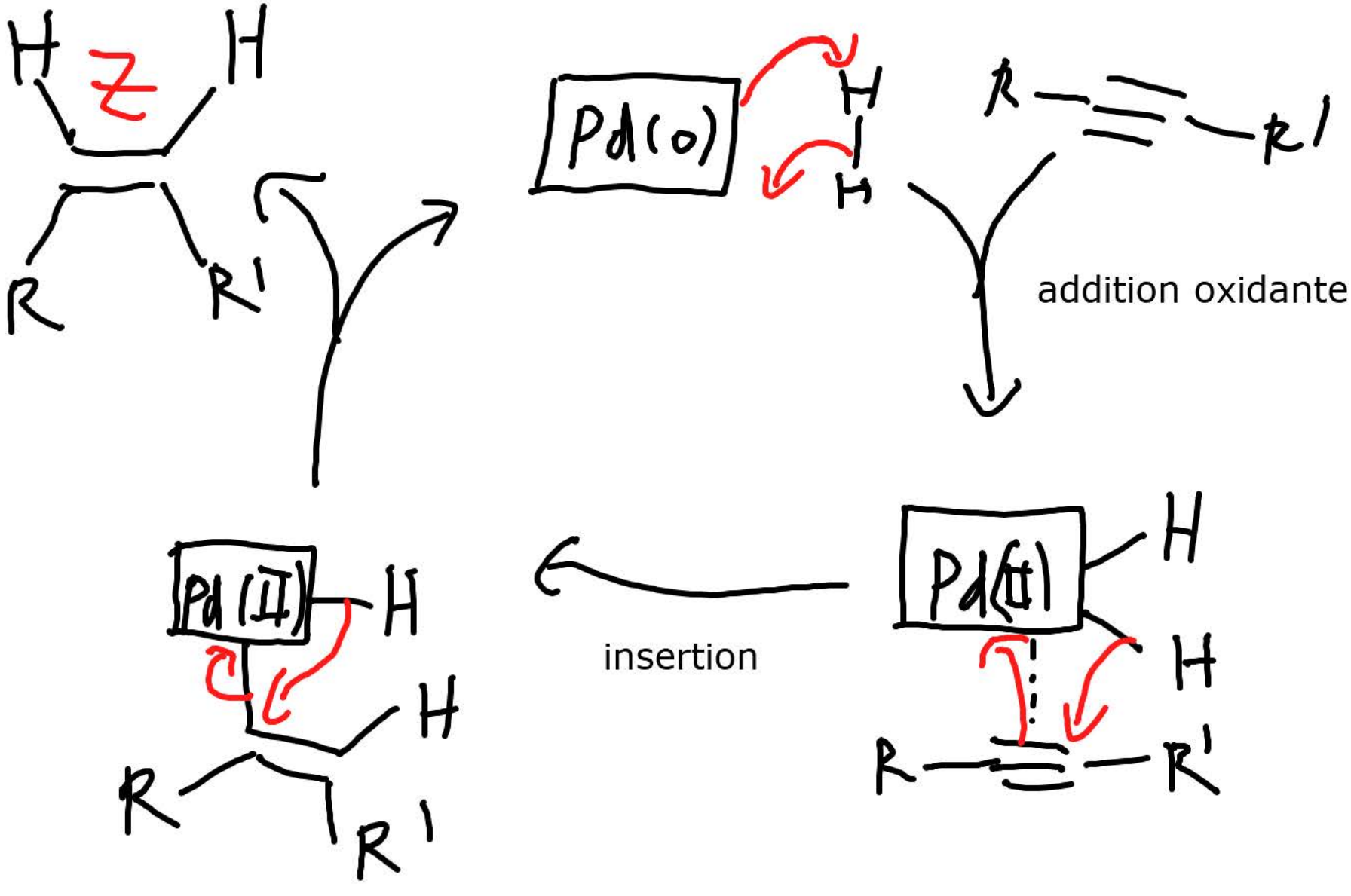
Pd/C ($PbSO_4$) $BaSO_4$



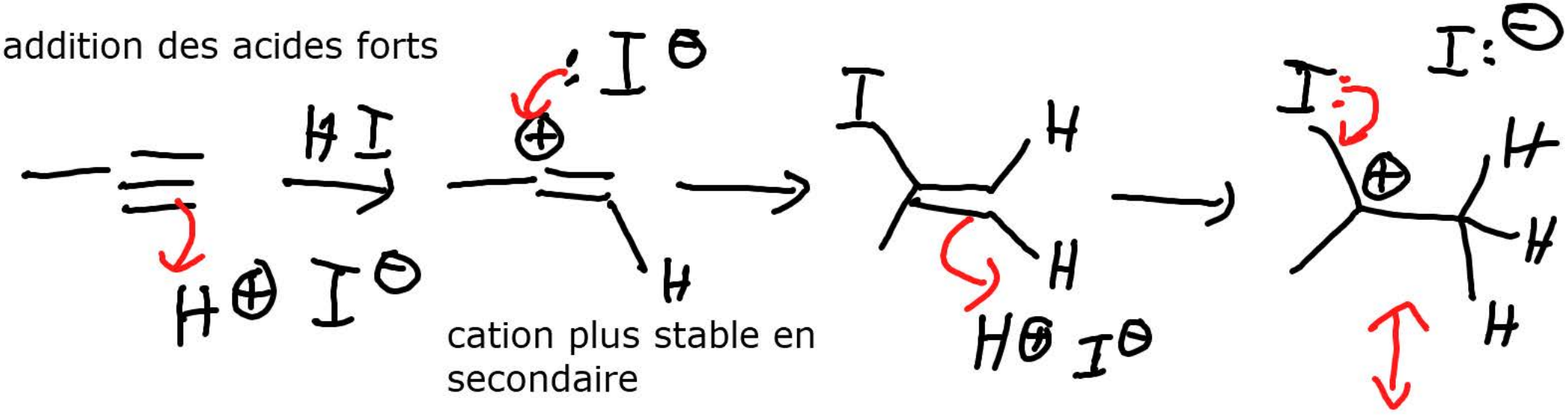
quinoline
se lie sur la surface
du palladium et
diminue la réactivité



rétinol, vitamine A

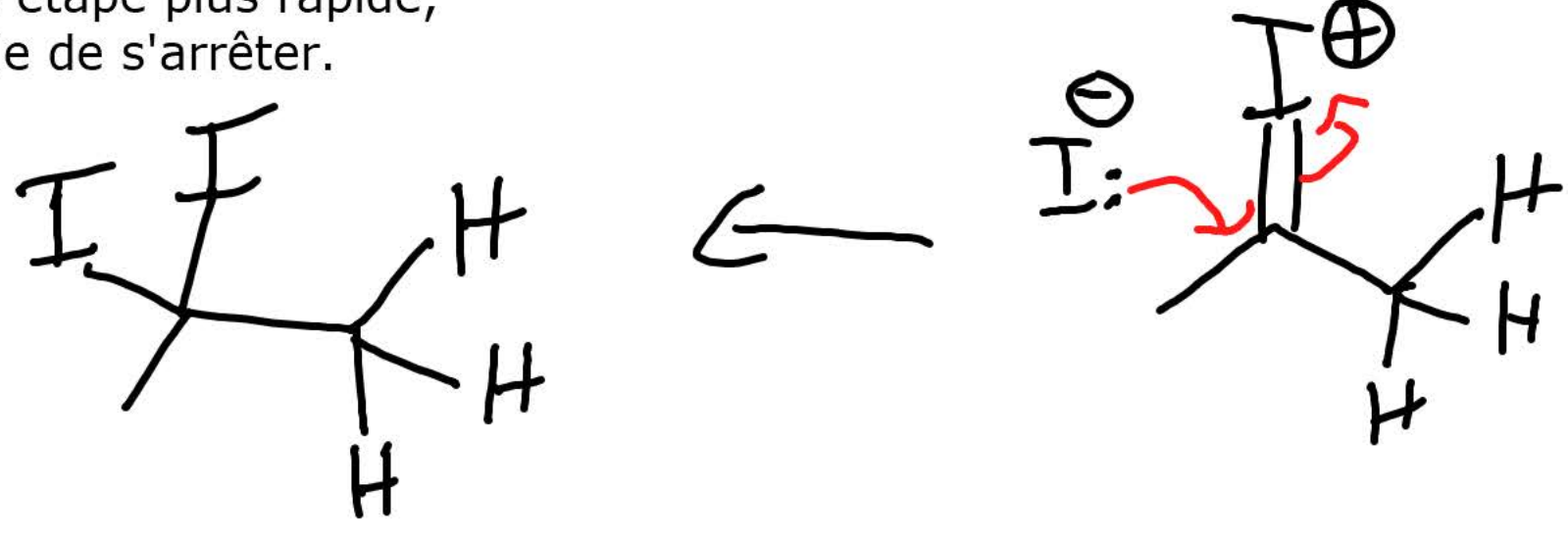

Pd(0)
addition oxidante
insertion
Pd(II)

addition des acides forts

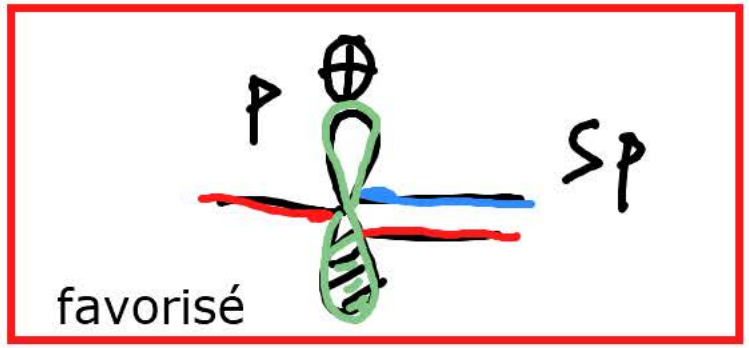


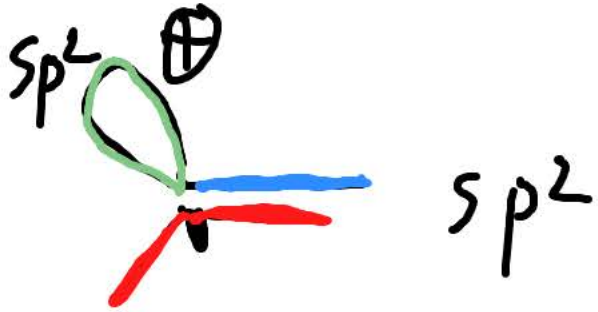
cation plus stable en secondaire

2ème étape plus rapide, difficile de s'arrêter.

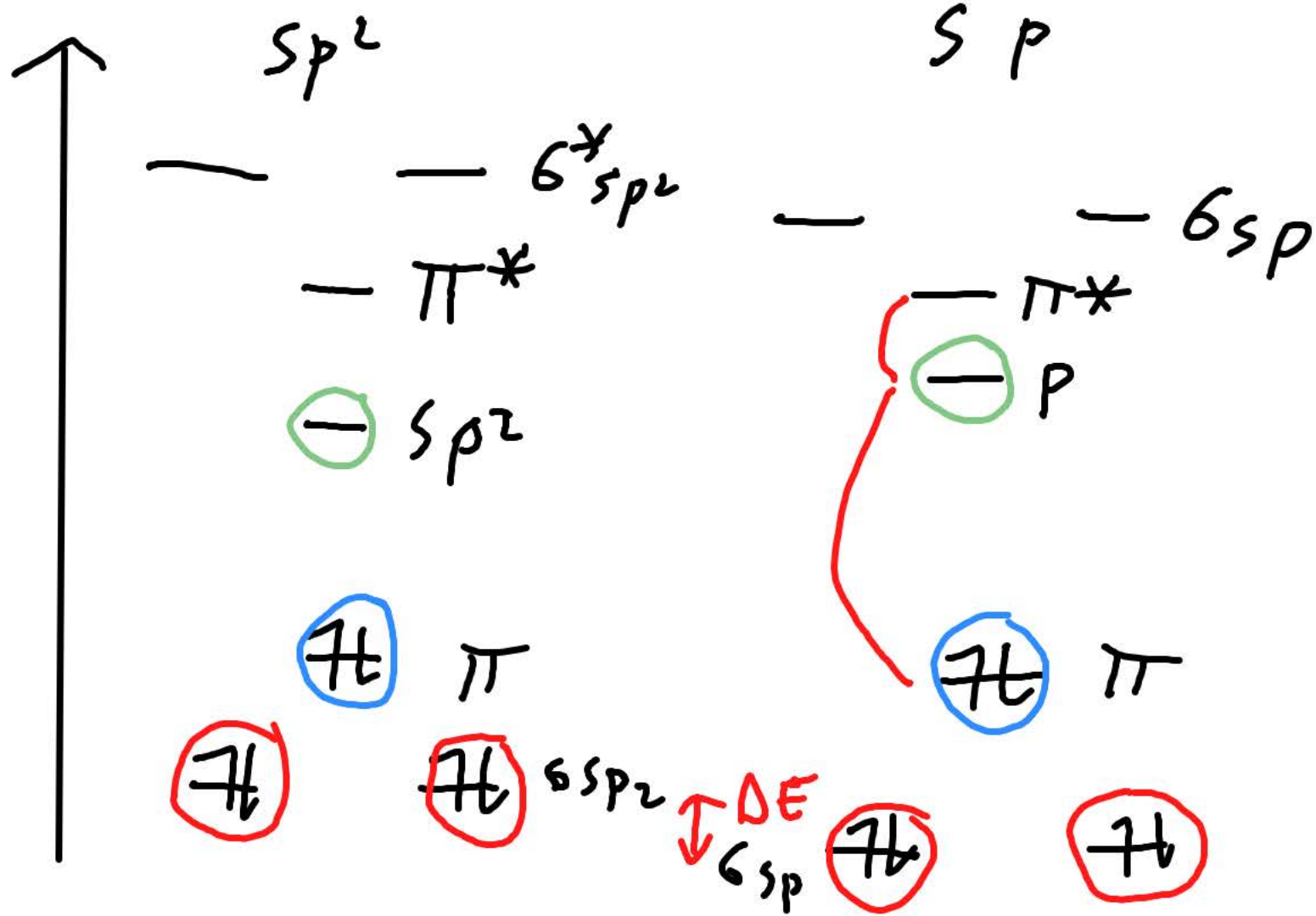


structure du carbocation sur les alcènes

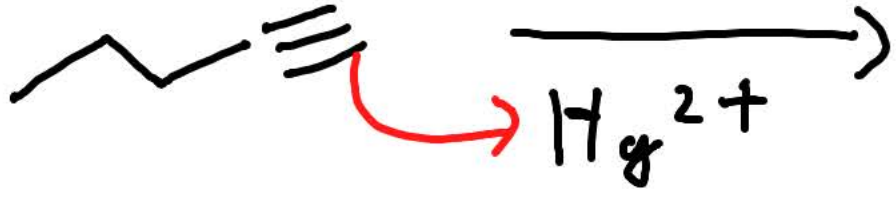


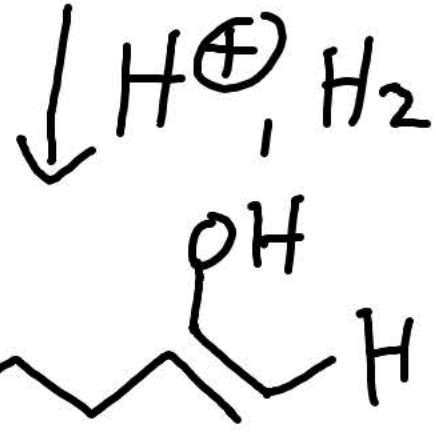


sp est plus stable pour
4x deltaE



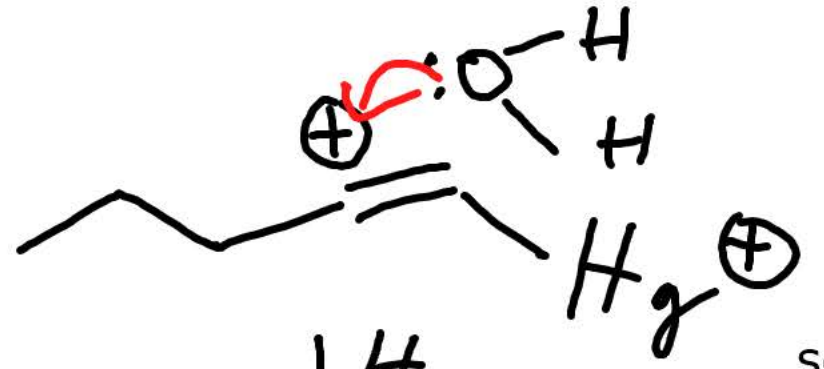
Hydration des alcynes



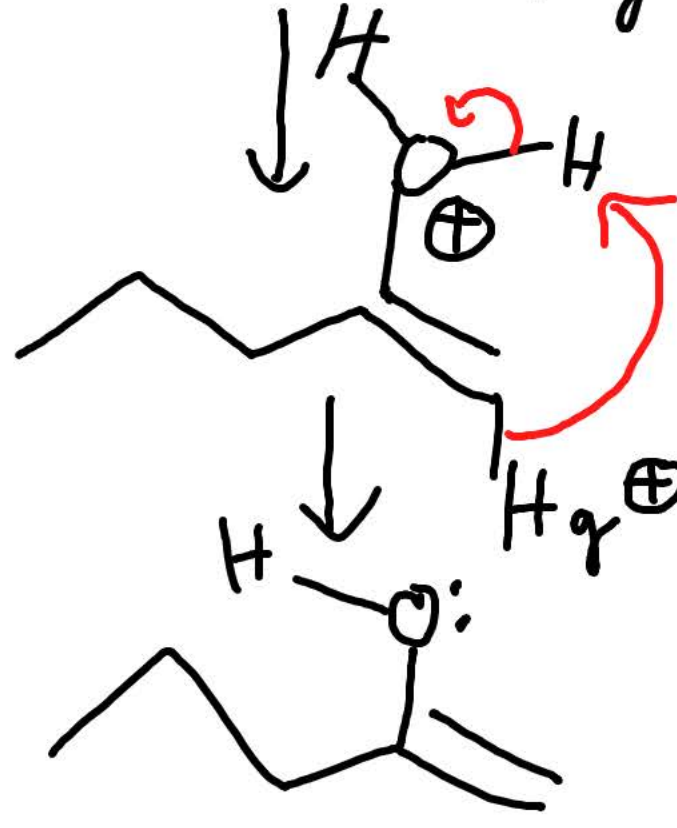


rapide pour les alcènes
très lente pour les alcynes

Hg2+ réagit beaucoup plus vite avec l'alcyne que H+

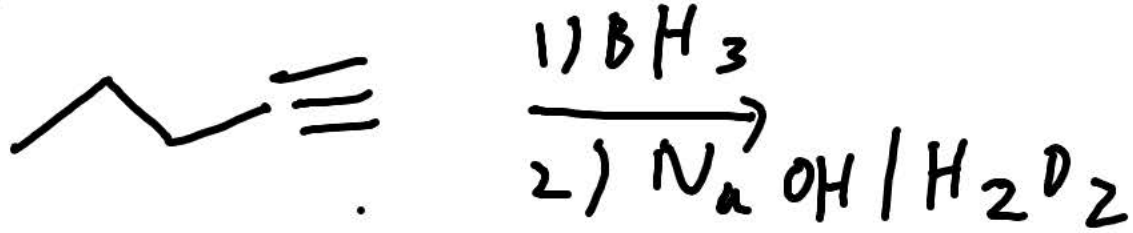


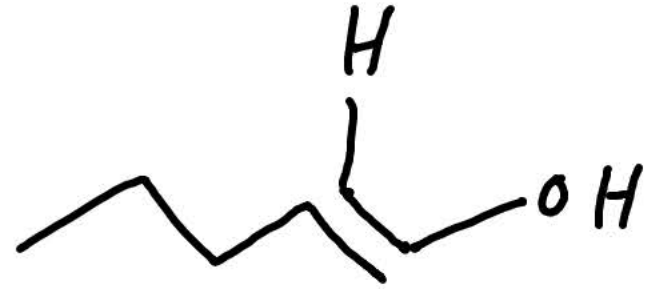
rapide



secondaire
plus stable

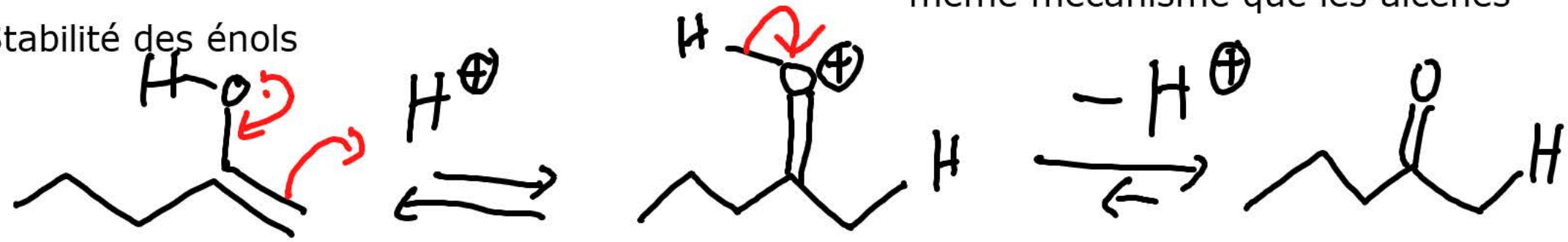
produit anti-Markovnikov?





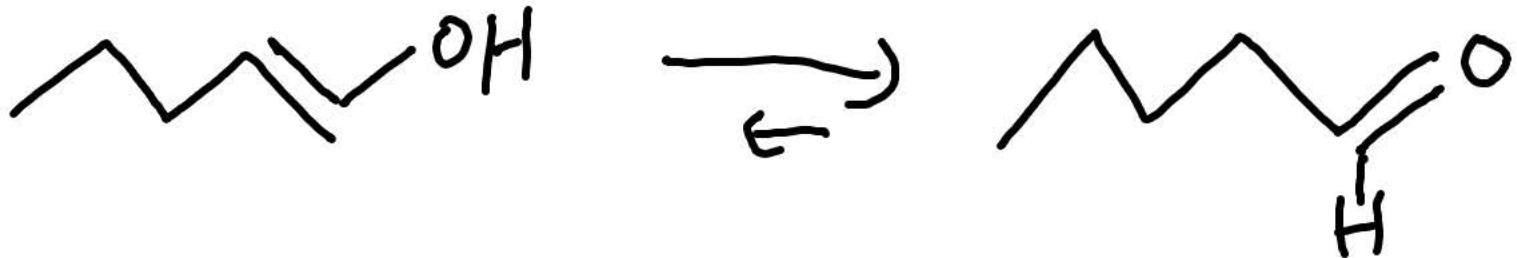
même mécanisme que les alcènes

Stabilité des énols



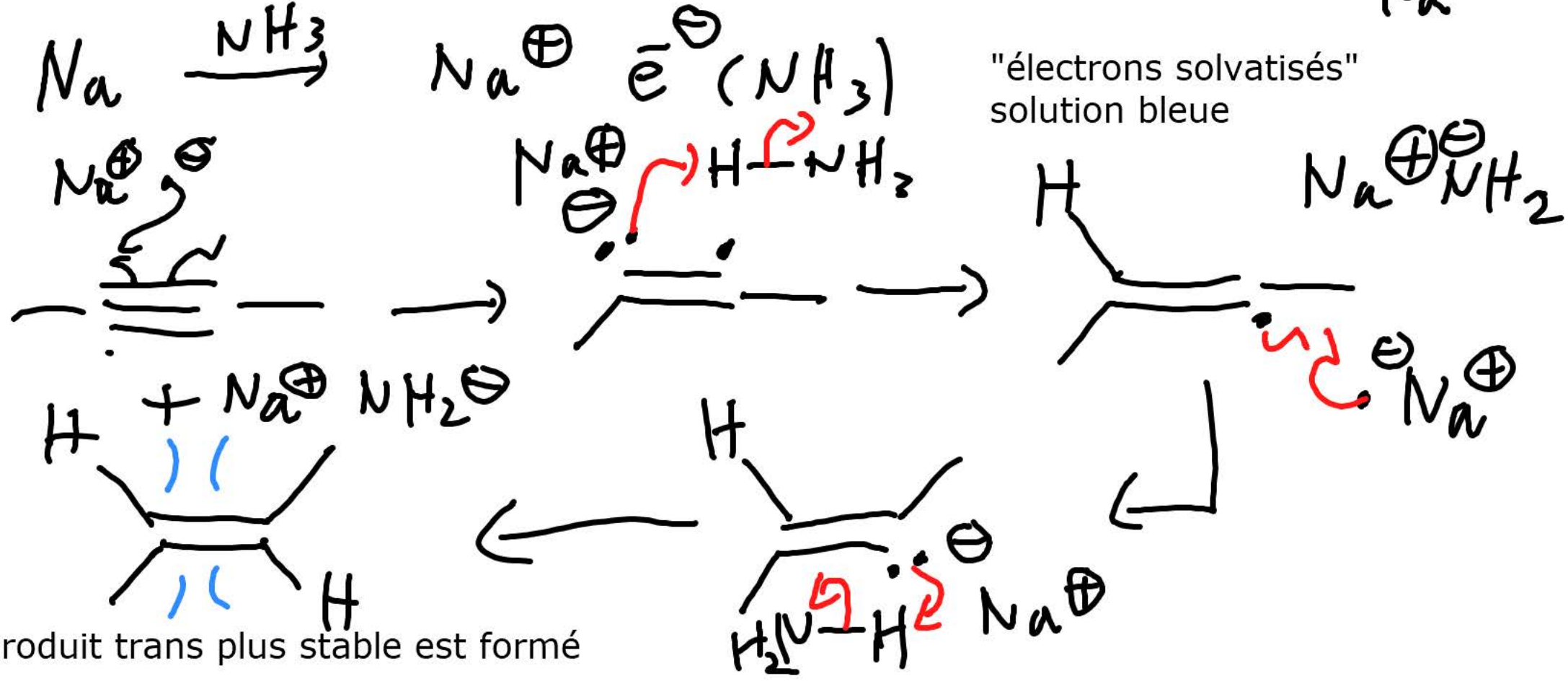
enol

carbonyl plus stable,
équilibre très rapide durant le work-up



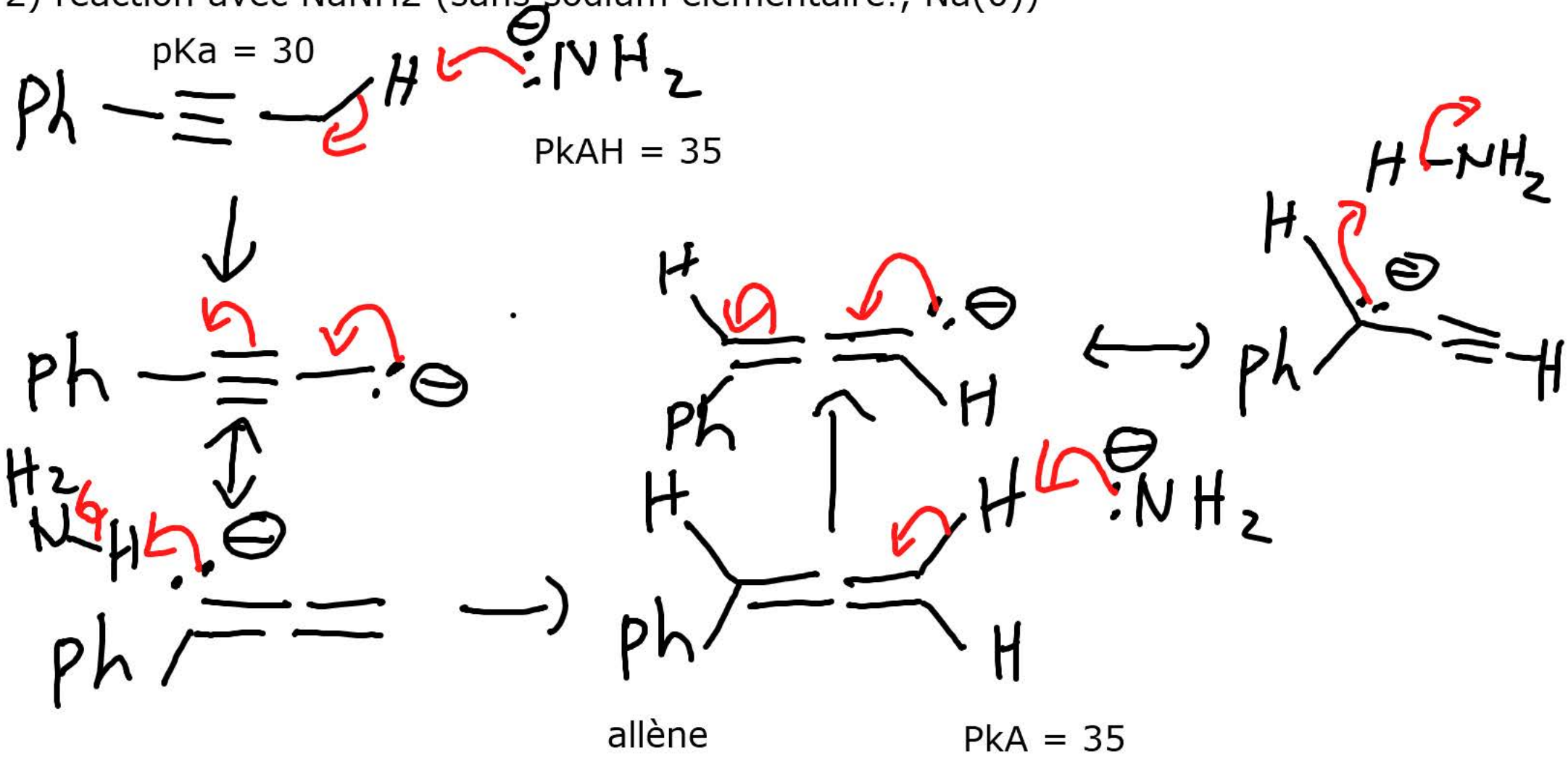
réaction entre le sodium et les alcynes

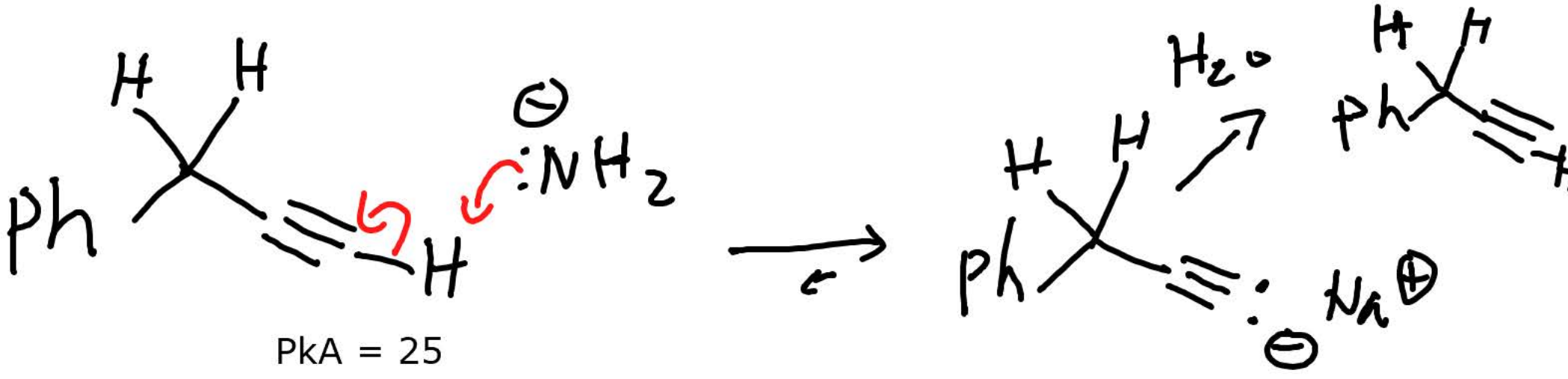
1) sodium dans l'ammoniaque (Birch)



produit trans plus stable est formé

2) réaction avec NaNH2 (sans sodium élémentaire!, Na(0))





PkA = 25

la réaction stope!
situation la plus stable

BASE

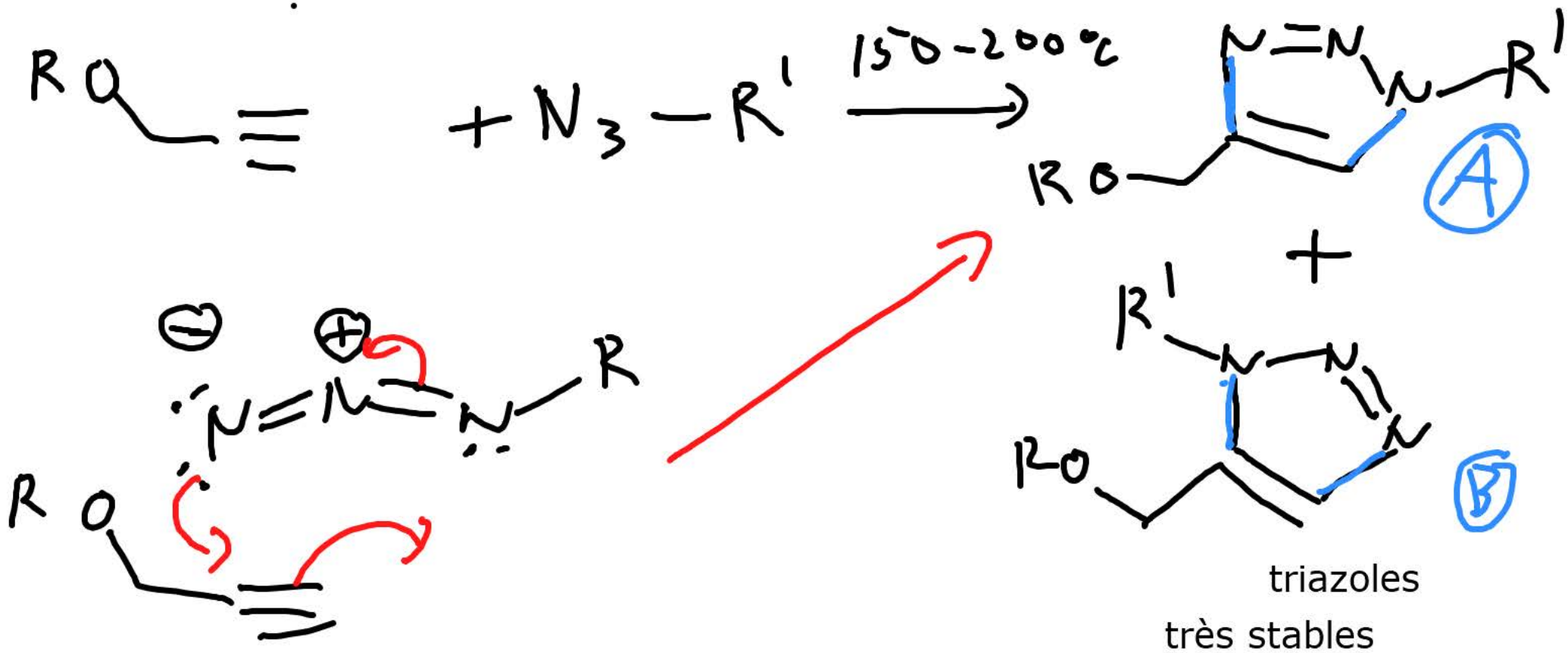
PkAH < 30

réactions d'isomérisation

PkAH > 30-35

cycloaddition avec les azotures: Sharpless,Medal, Bertozzi

Huisgen:



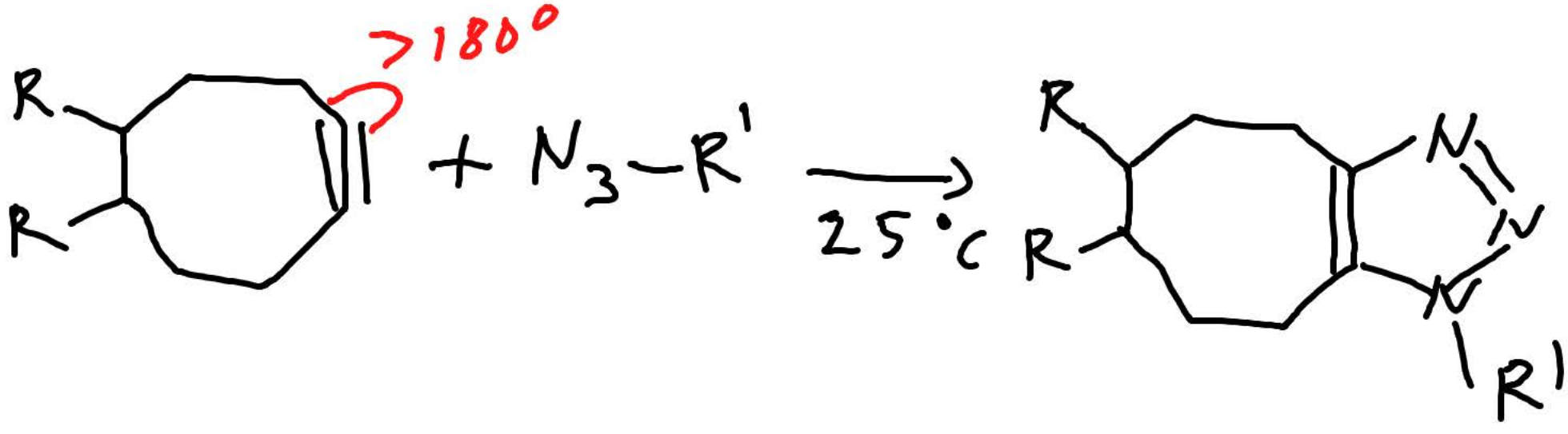
triazoles

très stables

aromatiques

Sharpless/Medal: Avec 5 mol% CuSO4: seulement A à 25 °C

Carolyn Bertozzi: Comment faire la réaction à 25 °C sans cuivre?

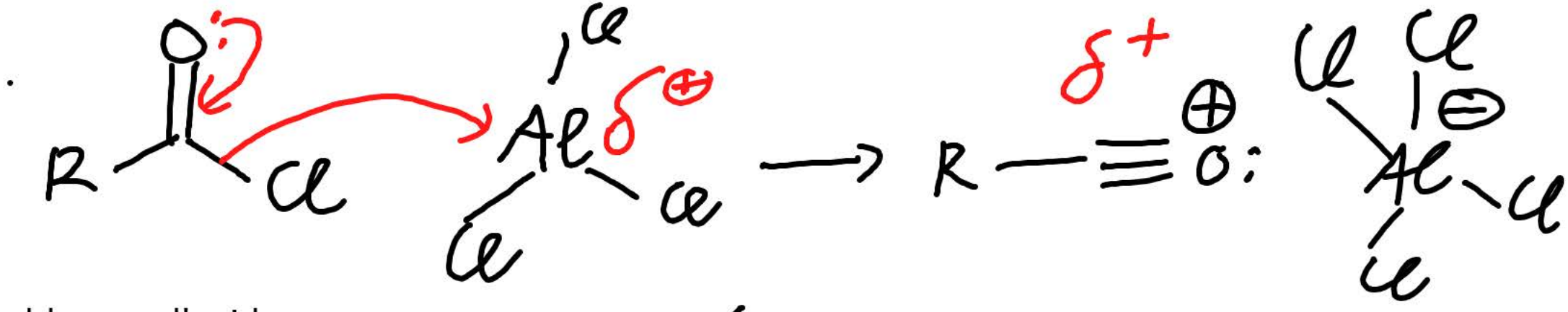


A cause de l'angle pas idéal, le cyclooctyne est plus réactif qu'un alcyne ordinaire!
Cycle idéal: 8 atomes: 7 atomes est instable, 9 atomes n'est pas assez réactif

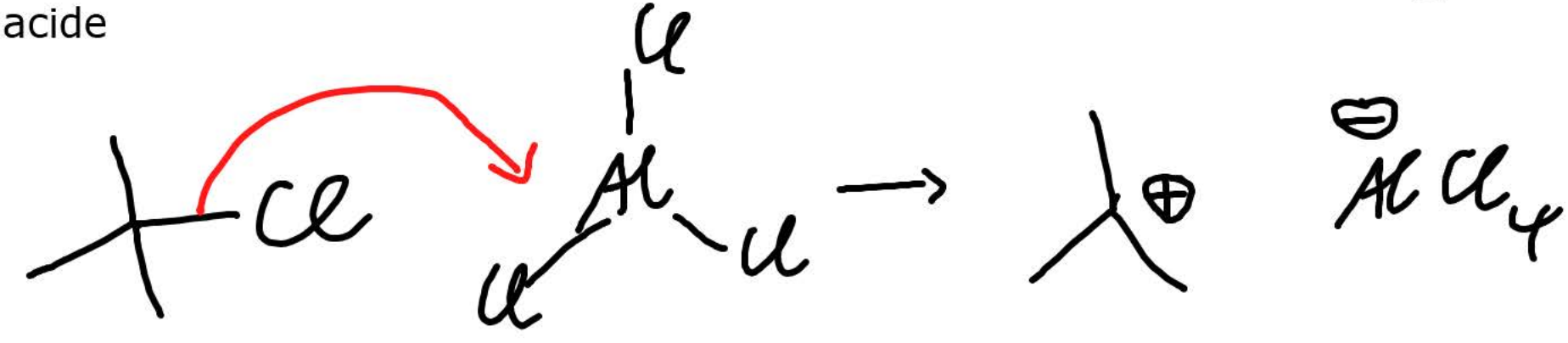
réaction de Friedel-Craft

1) activation de l'électrophile

2) Approche 1: chlorure d'acide avec AlCl3

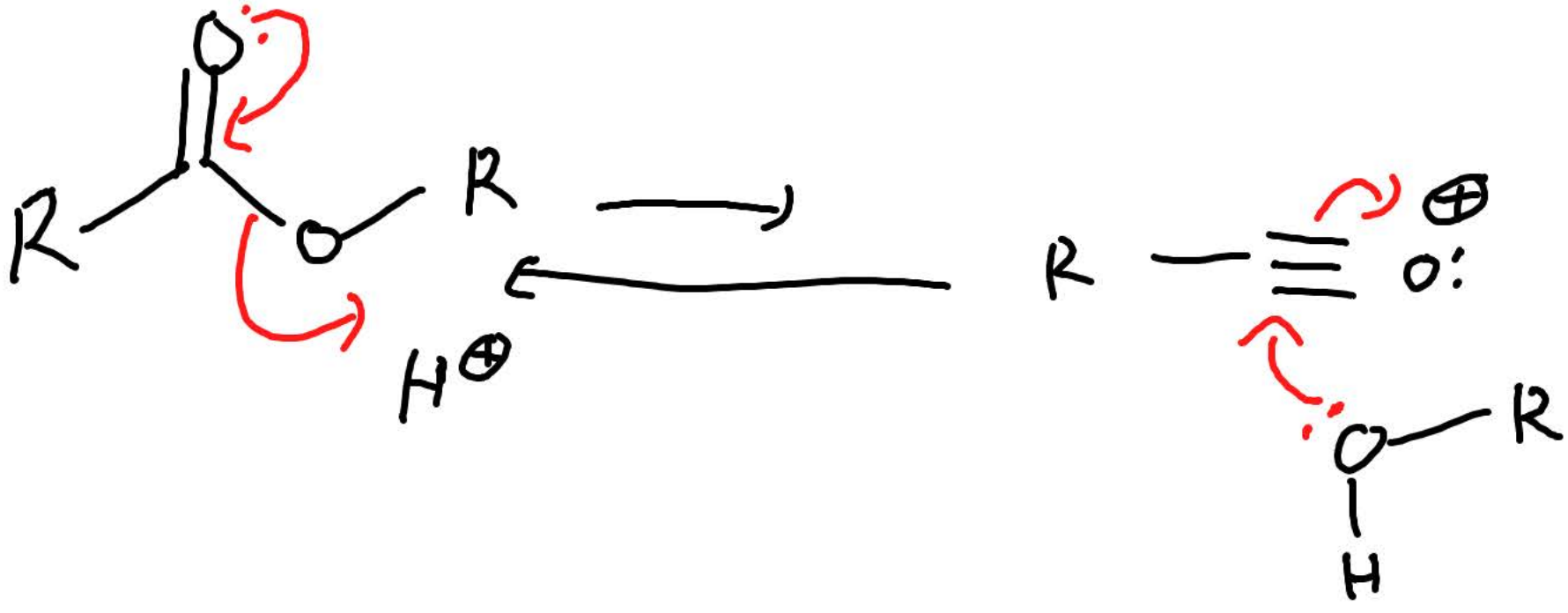


chlorure d'acide



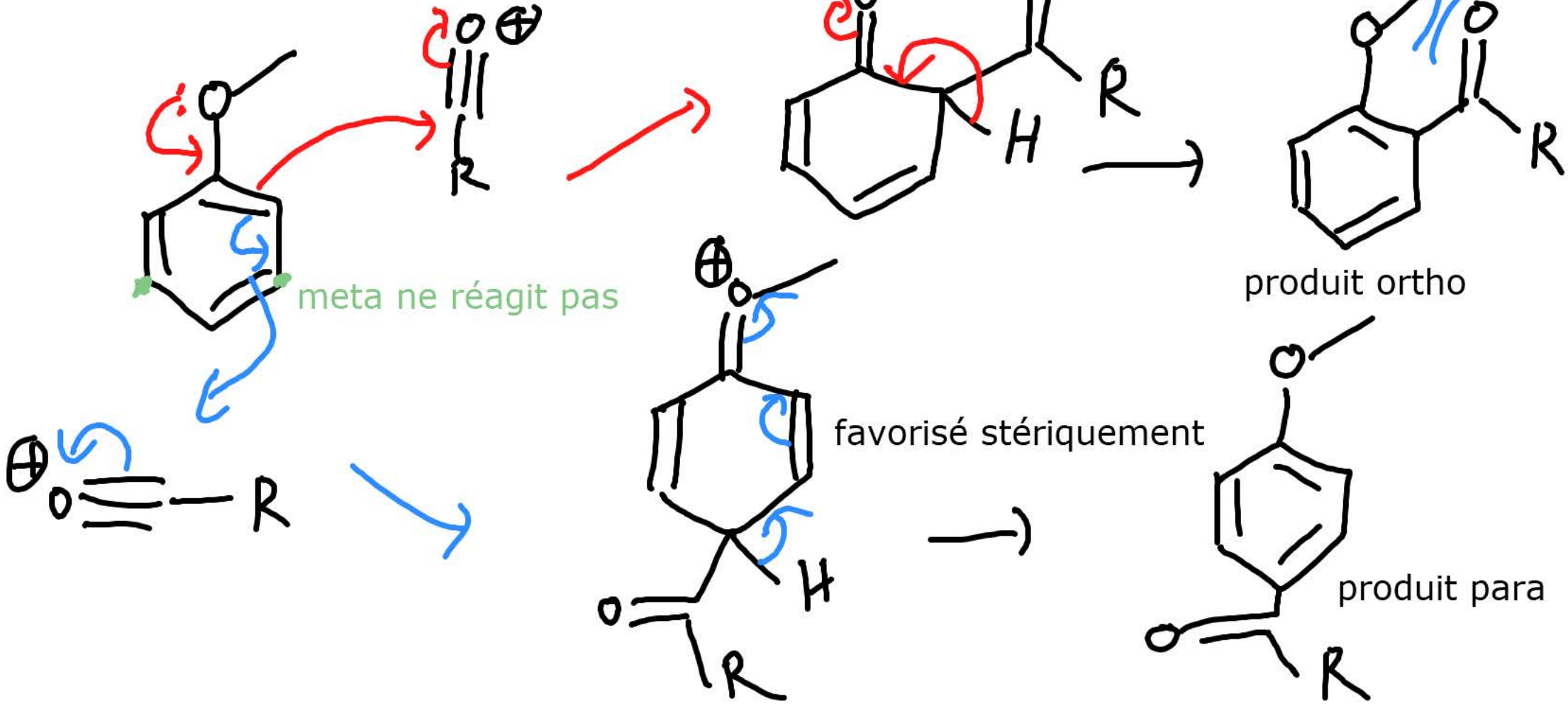
.

approche 2: plus douce

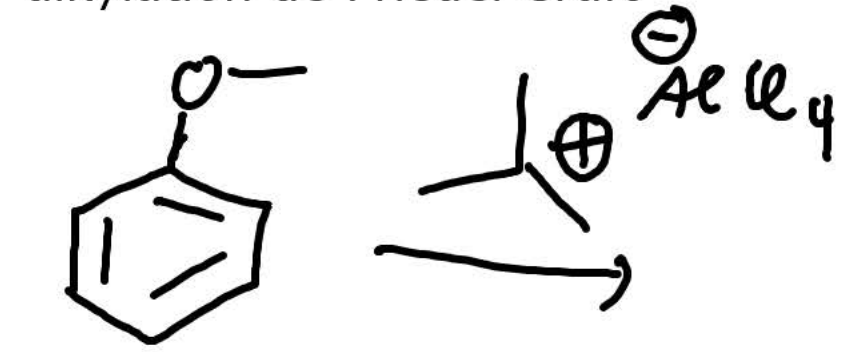


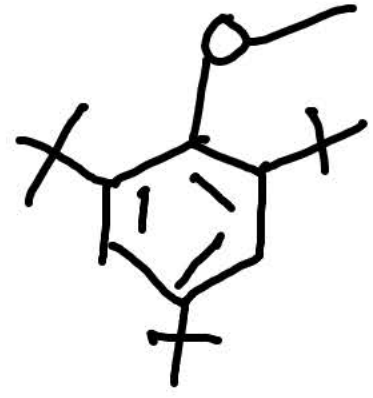
en milieu acide: de très petites quantité d'intermédiaire réactif sont formées

réaction avec l'anisole

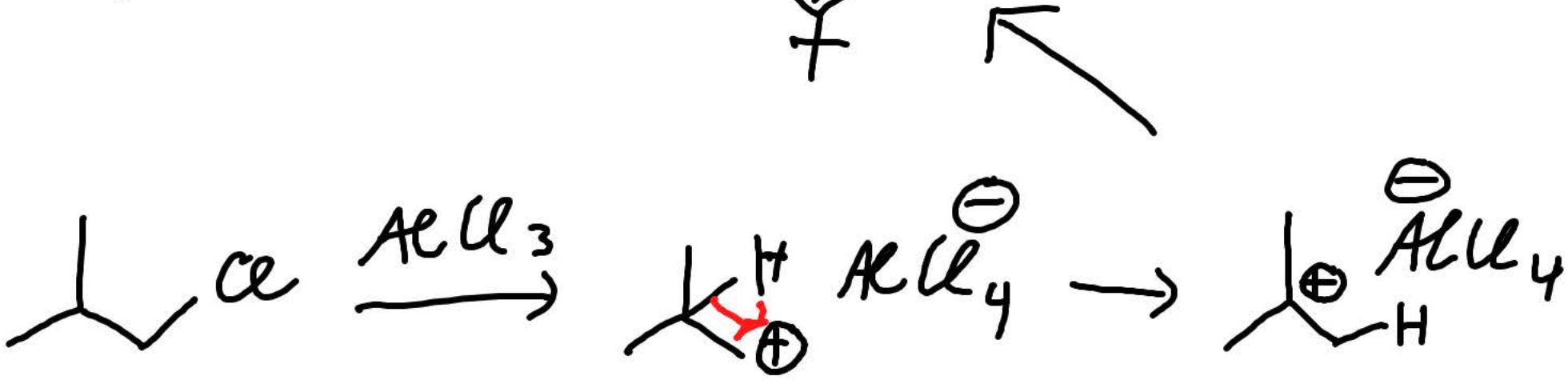


alkylation de Friedel Craft





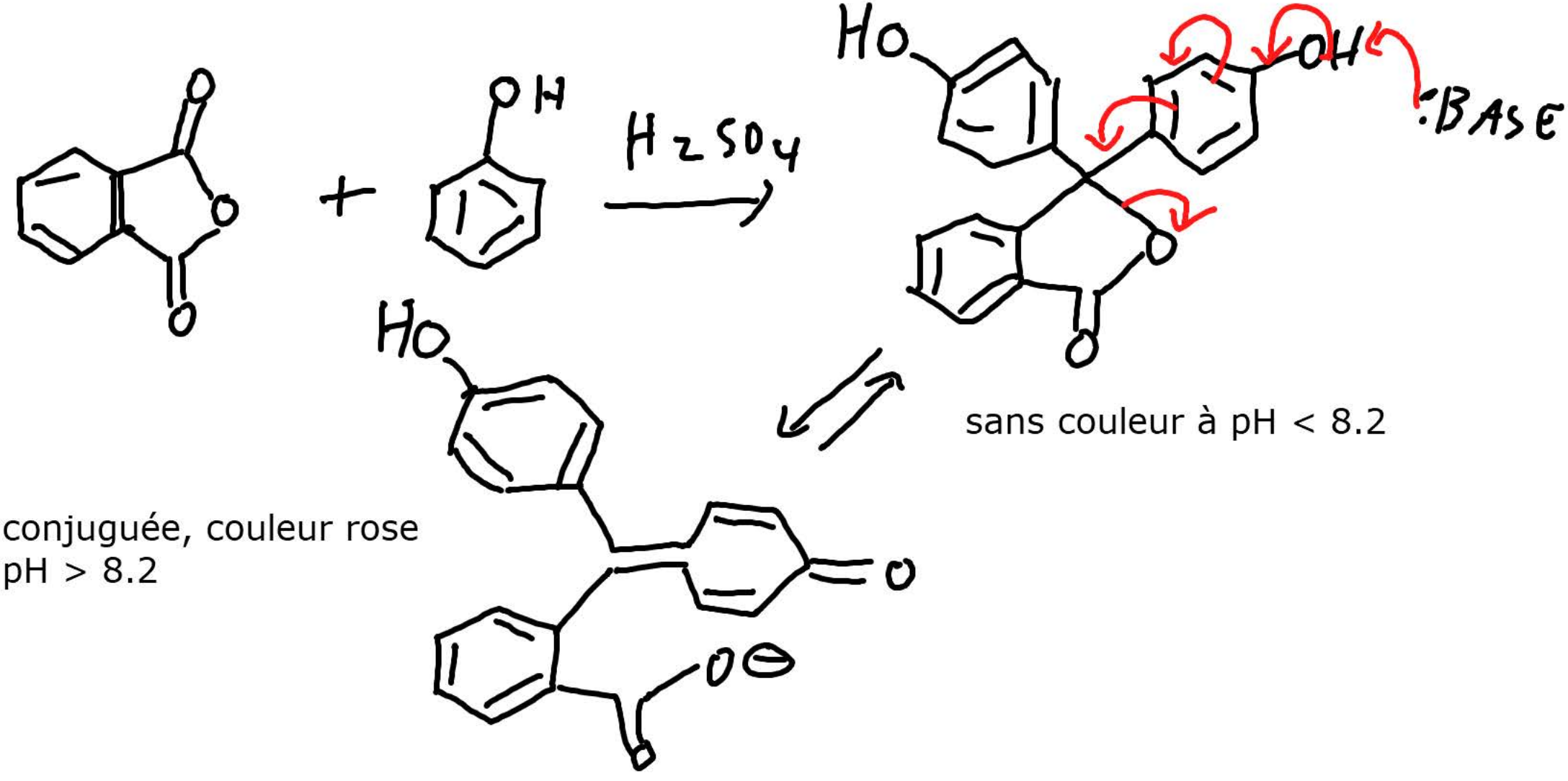
groupe tBu est riche en électron,
le cycle est activé et réagit 3x



La réaction ne fonctionne pas pour les carbocations primaires, car la migration est plus rapide

.

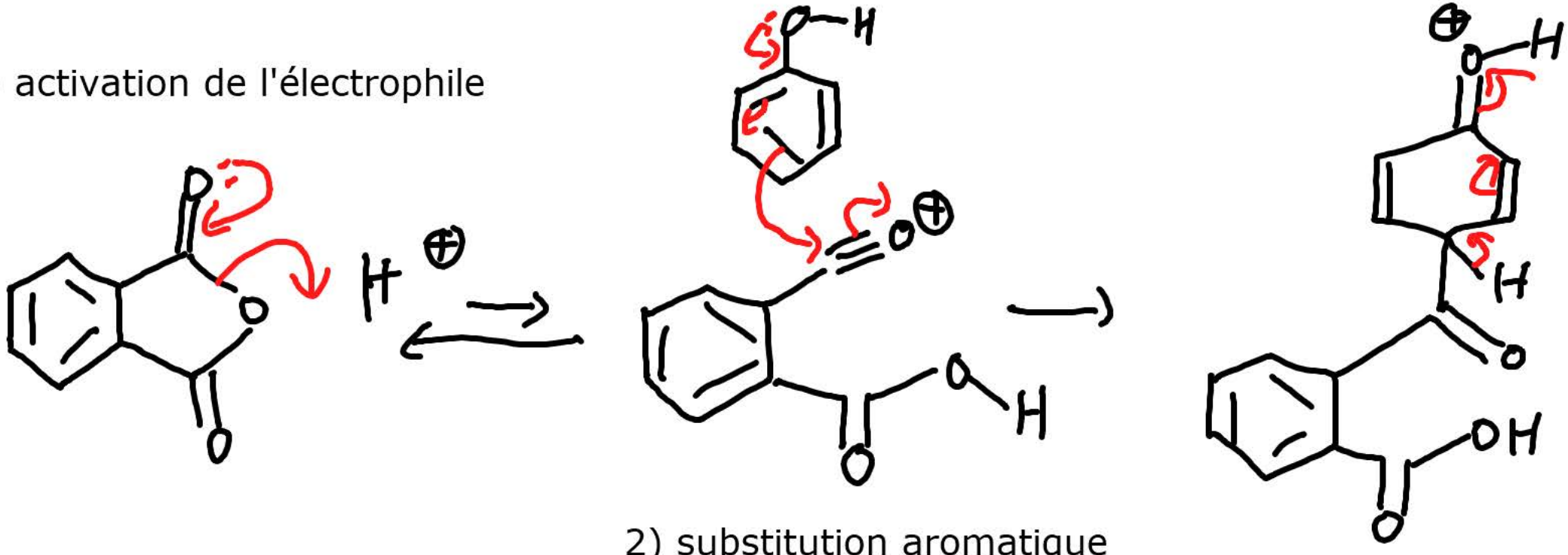
synthèse de la phénolphtalein



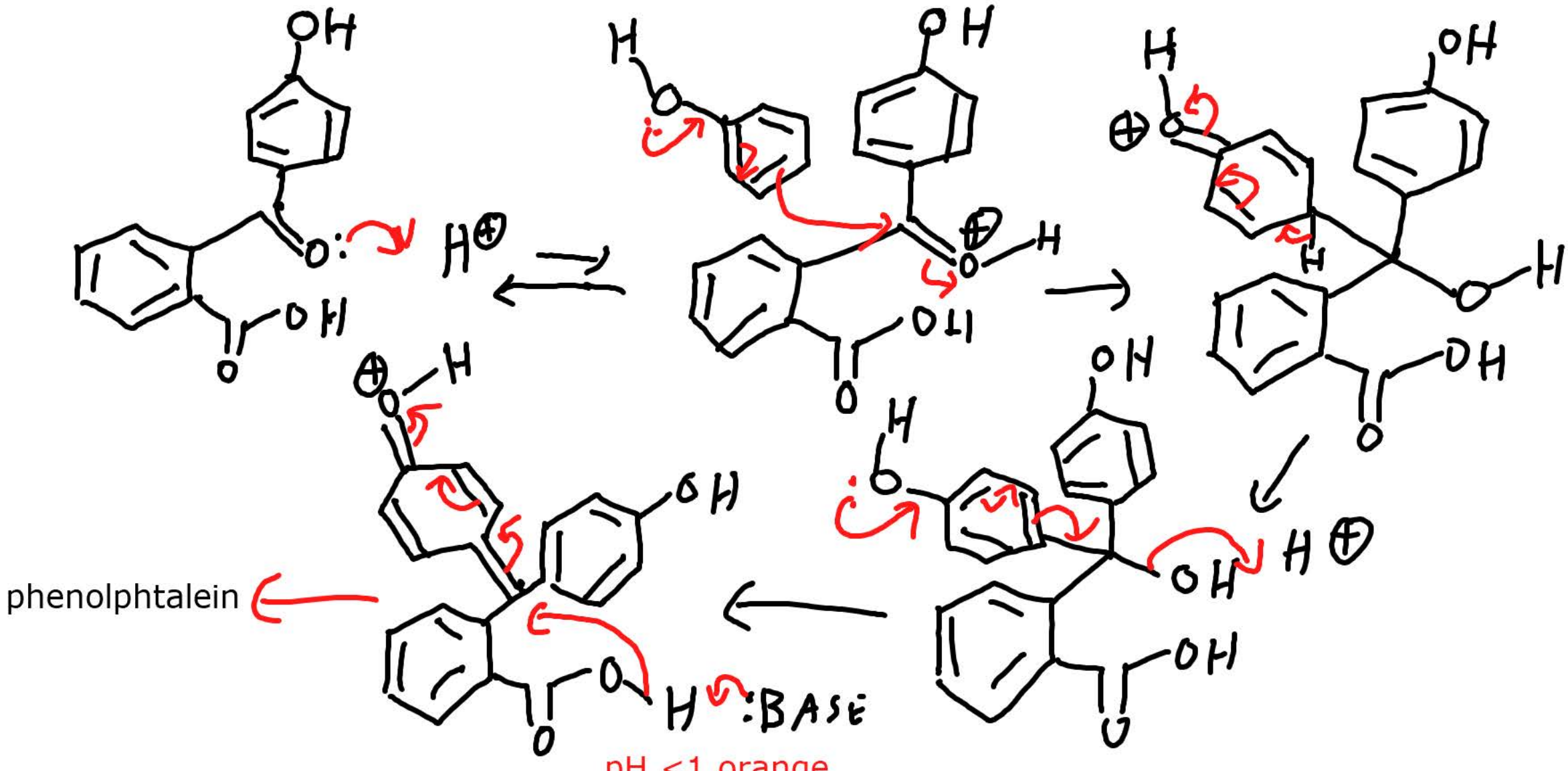
sans couleur à pH < 8.2

conjuguée, couleur rose
pH > 8.2

1) activation de l'électrophile

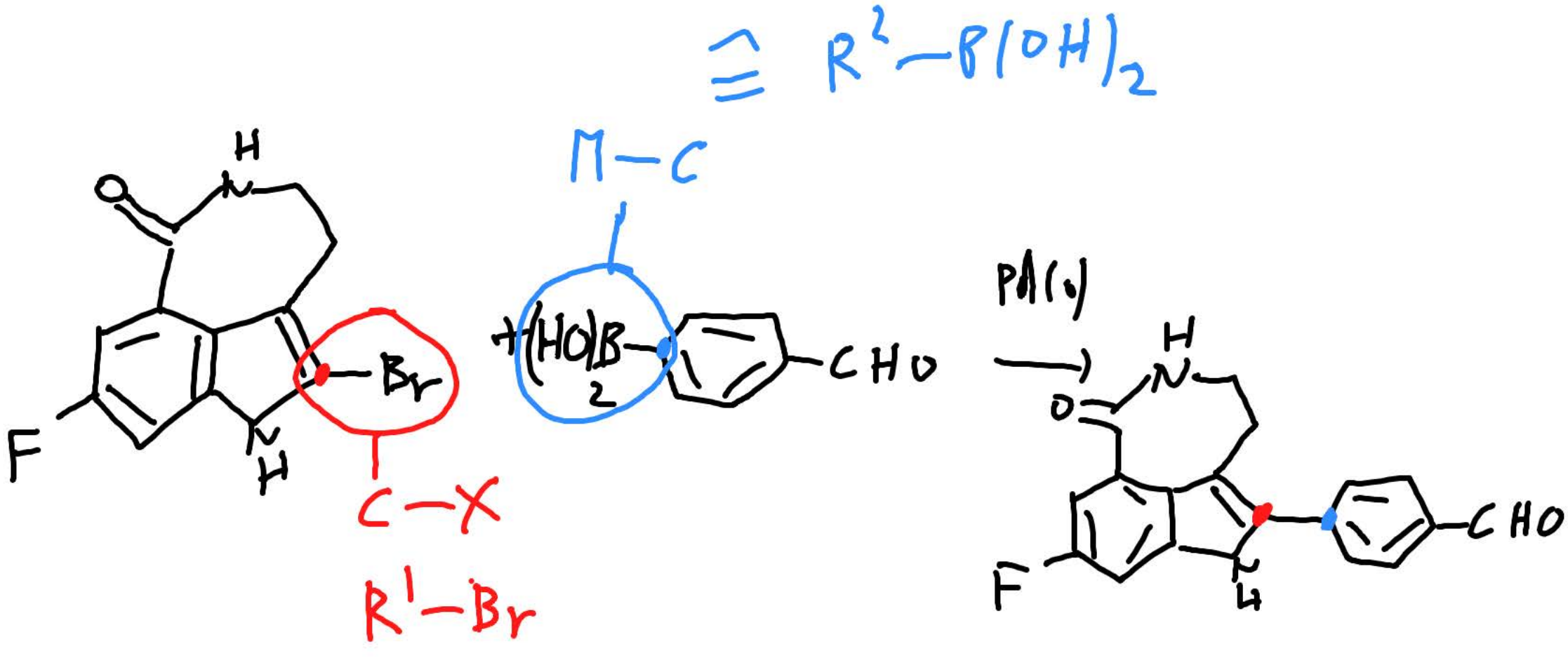


2) substitution aromatique électrophile

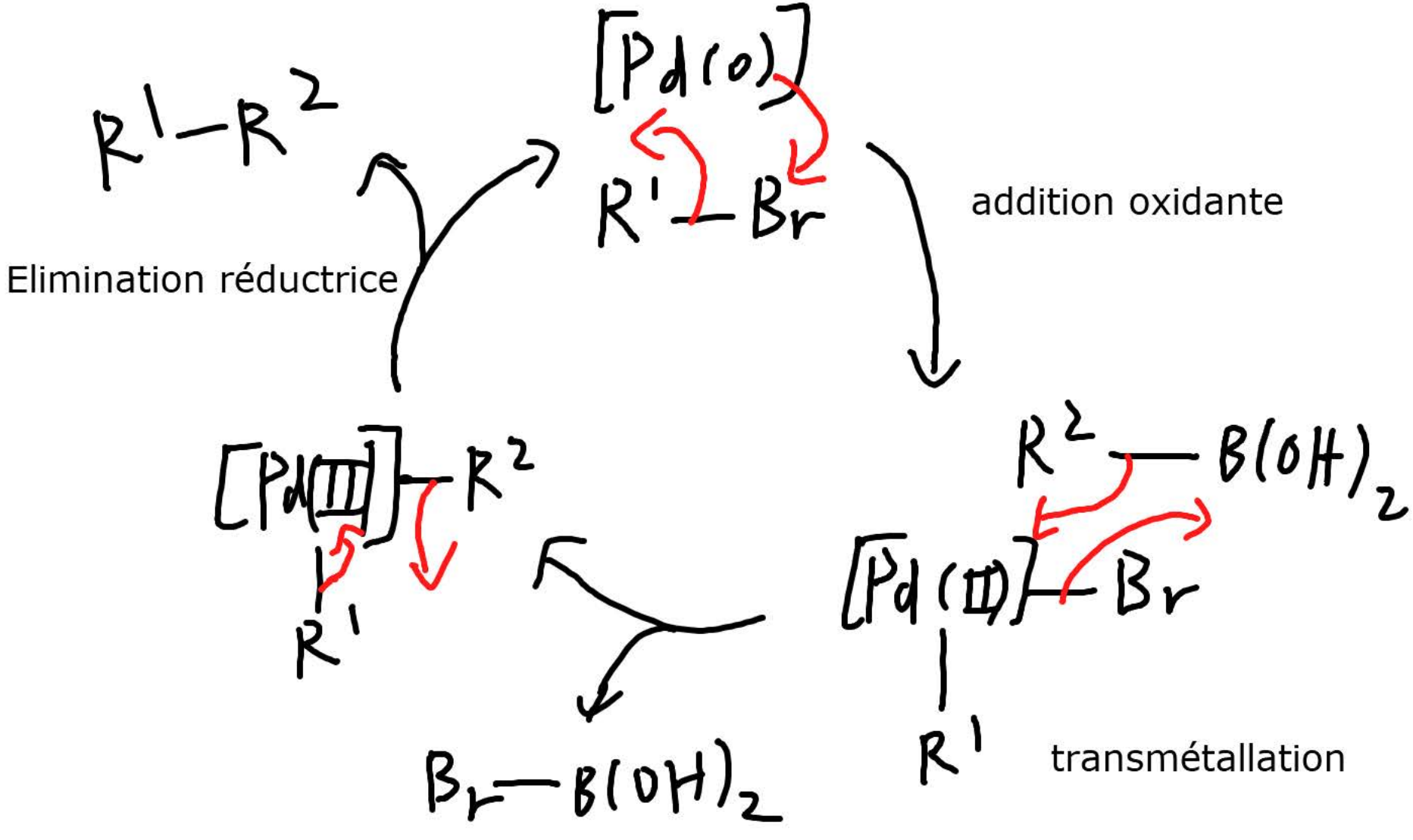

phenolphtalein
:BASE
pH <1 orange

couplage croisé au Pd: synthèse de Rucaparib: Pfizer, traitement du cancer des ovaires

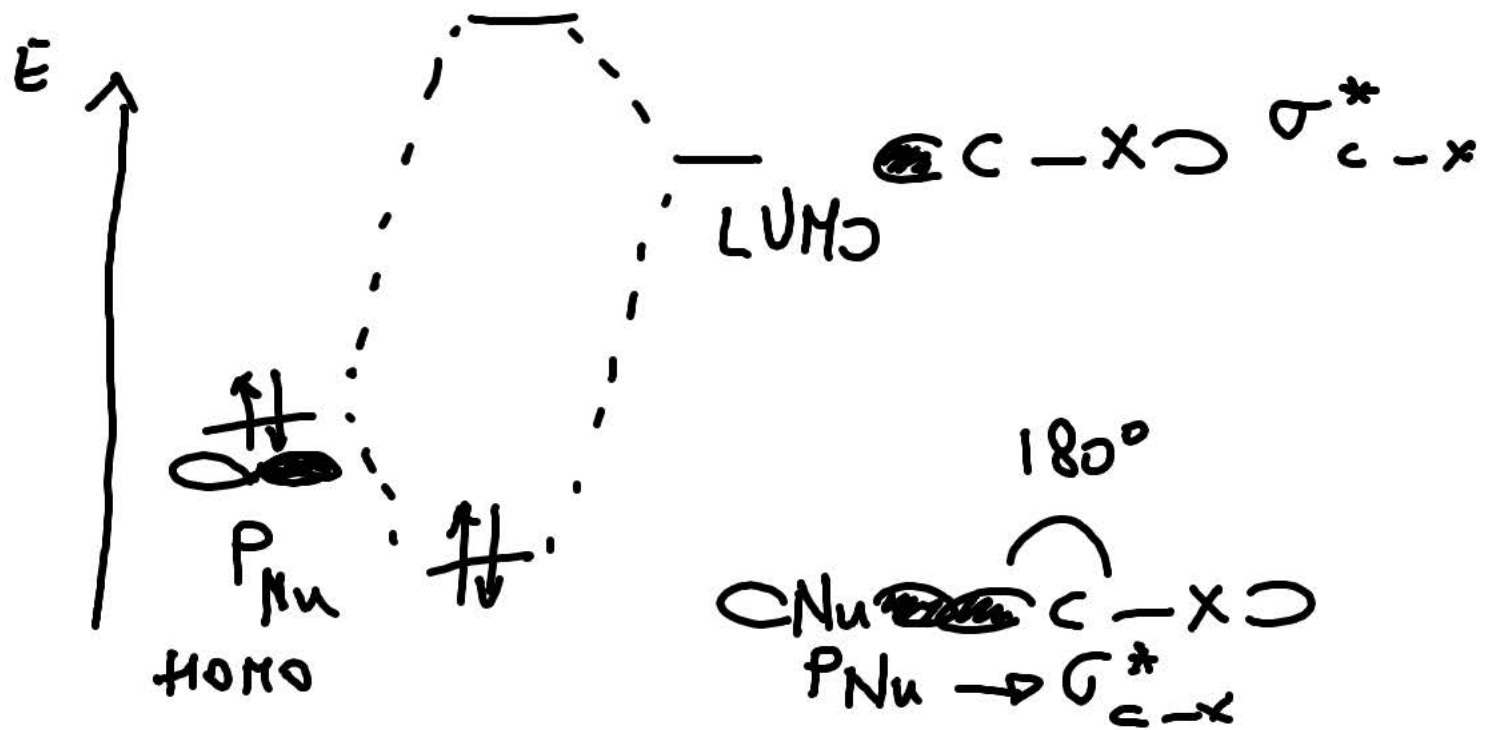
.



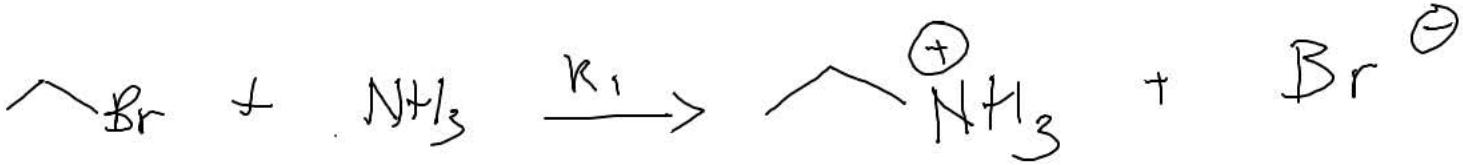
mécanisme


[Pd(0)]
R1—Br
addition oxidante
R2—B(OH)2
[Pd(II)]—Br
R1
transmétallation
Br—B(OH)2
[Pd(III)]—R2
R1
Elimination réductrice
R1—R2

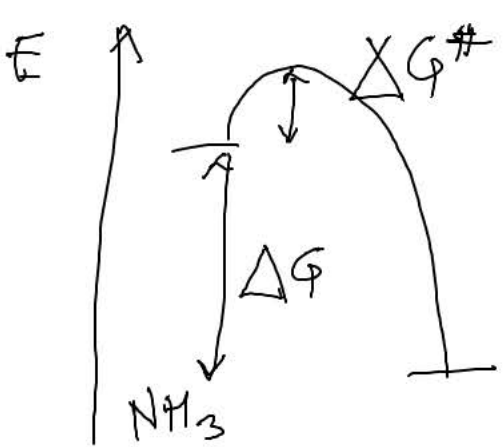
Mechanisme SN2 avec
orbitales moléculaires

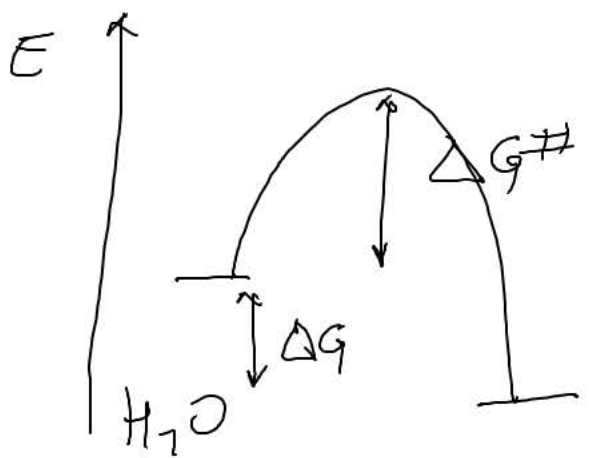


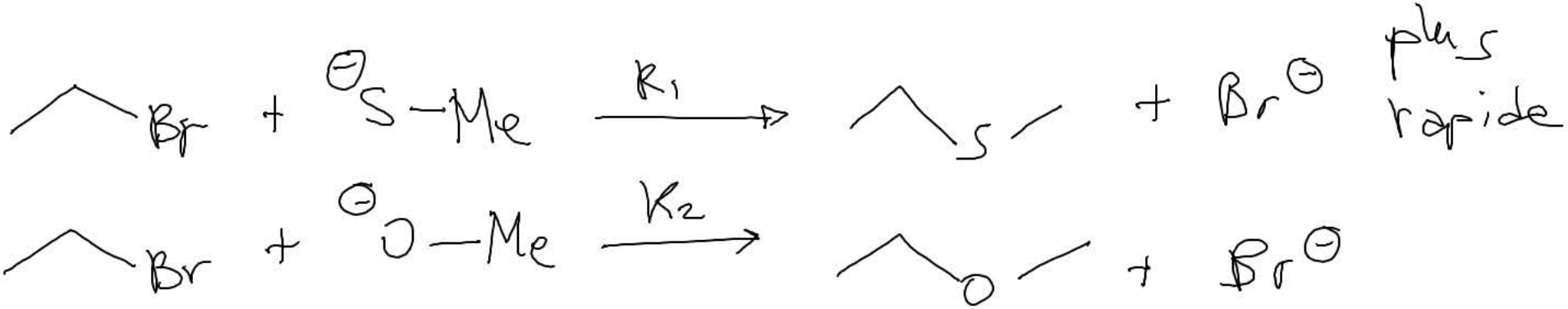
basicité vs nucléophilie



NH_3 $pK_{aH} = 9$ H_2O $pK_{aH} = -1,7$



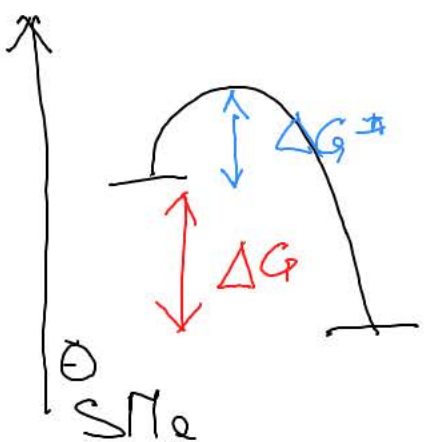


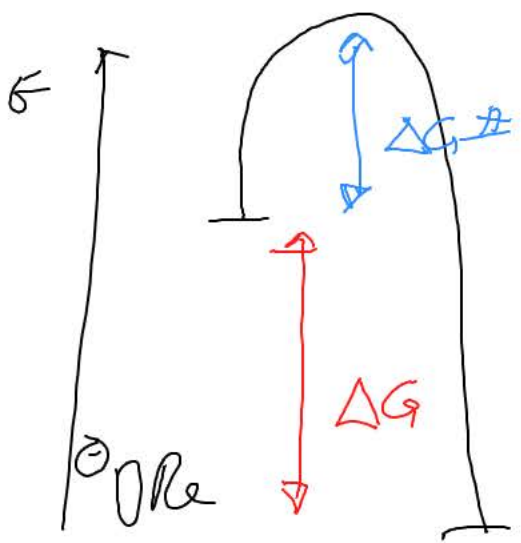


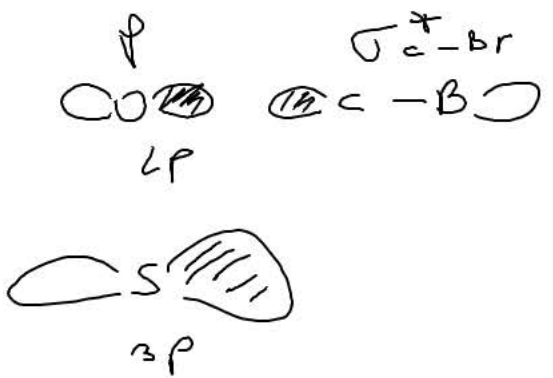
$^{\ominus}$S–Me $pk_{AH} = 8$

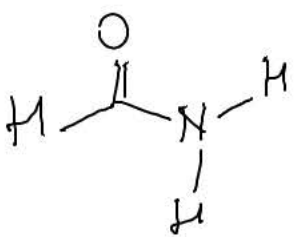
$^{\ominus}$O–Me $pk_{AH} = 16$

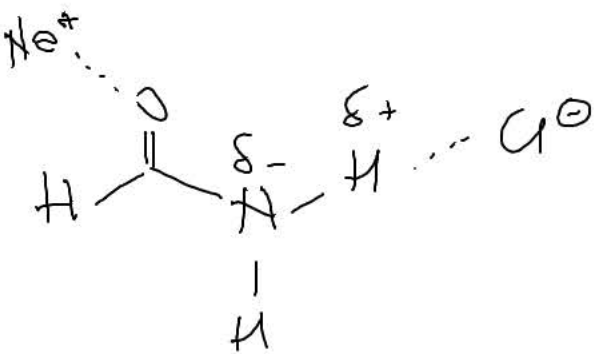
$k_1 > k_2$



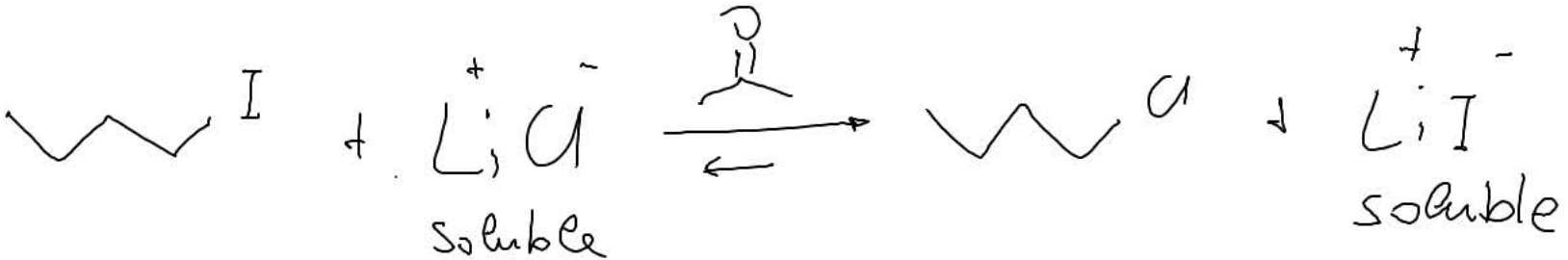




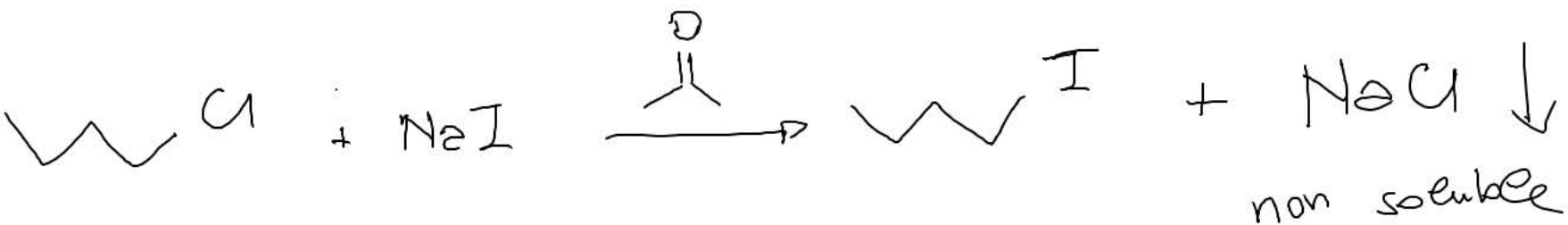
Solvant	k
CH_3OH	1
	1'500'000
Formamide 	12,5
Dimethylformamide DMF 	1'200'000



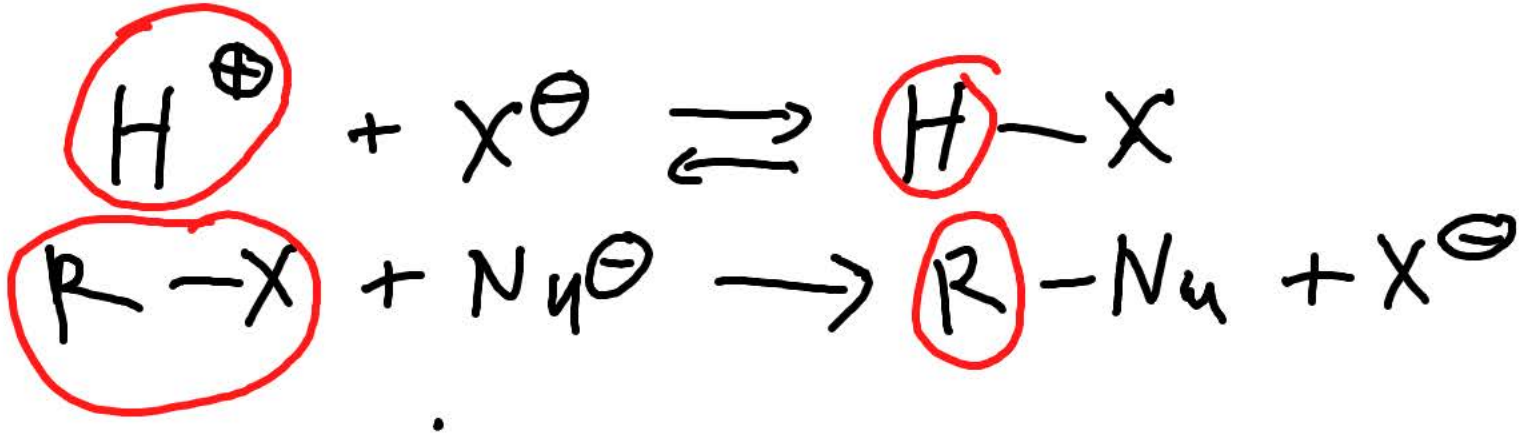
Synthèse des Iodures



Approche de Finkelstein

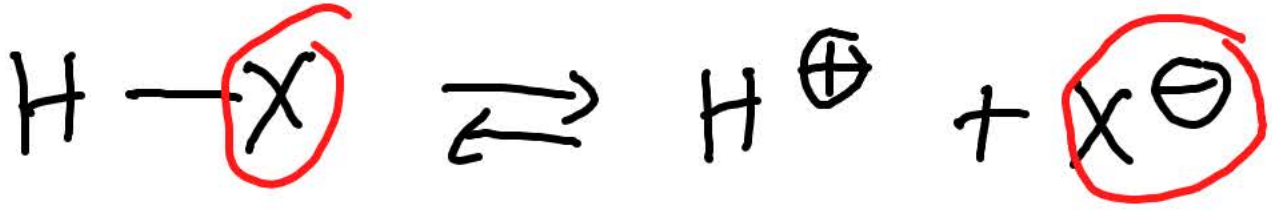


comparaison base/nucléophile vs base/groupe partant

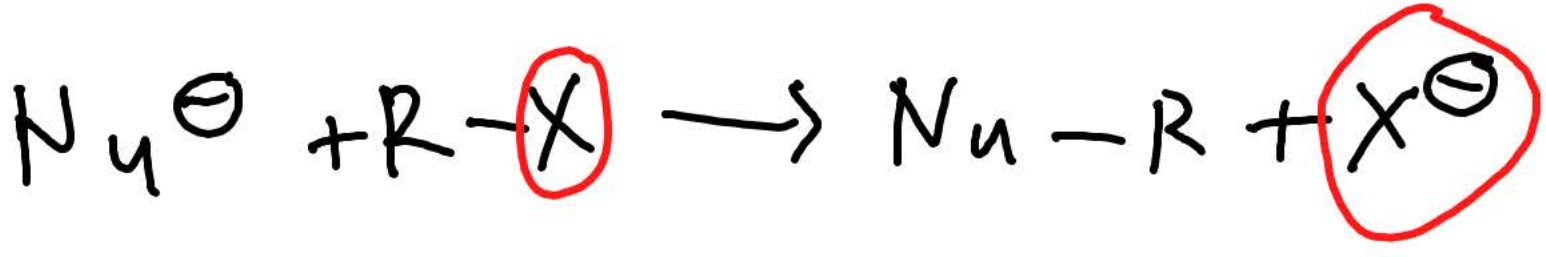


comparaison
base-nucléophile

mauvaise comparaison
R différent de H+



comparaison
base/groupe partant

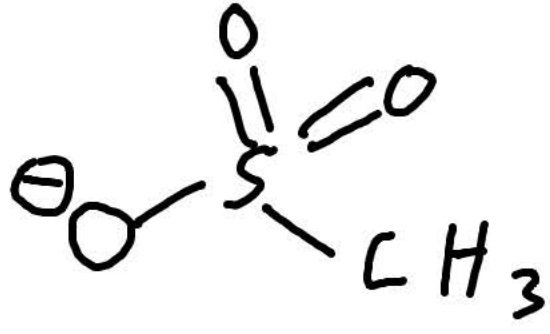


bonne, structure
de la base et
groupe partant
identique

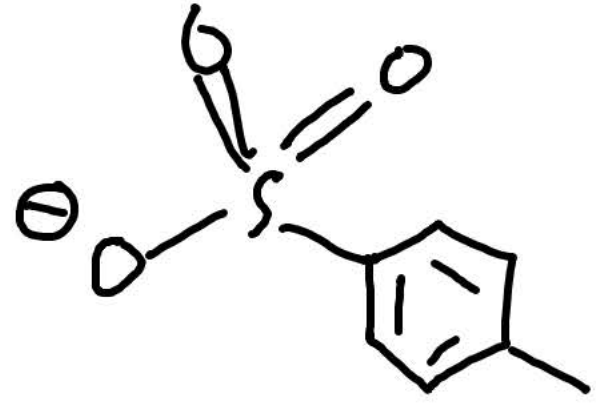
.

important en chimie organique: group partant dérivé de l'acide sulfurique

.

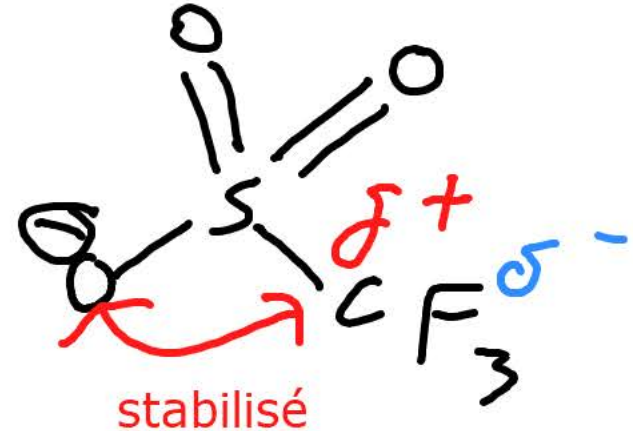


mésylate, OMs



tosylate, OTs

même réactivité



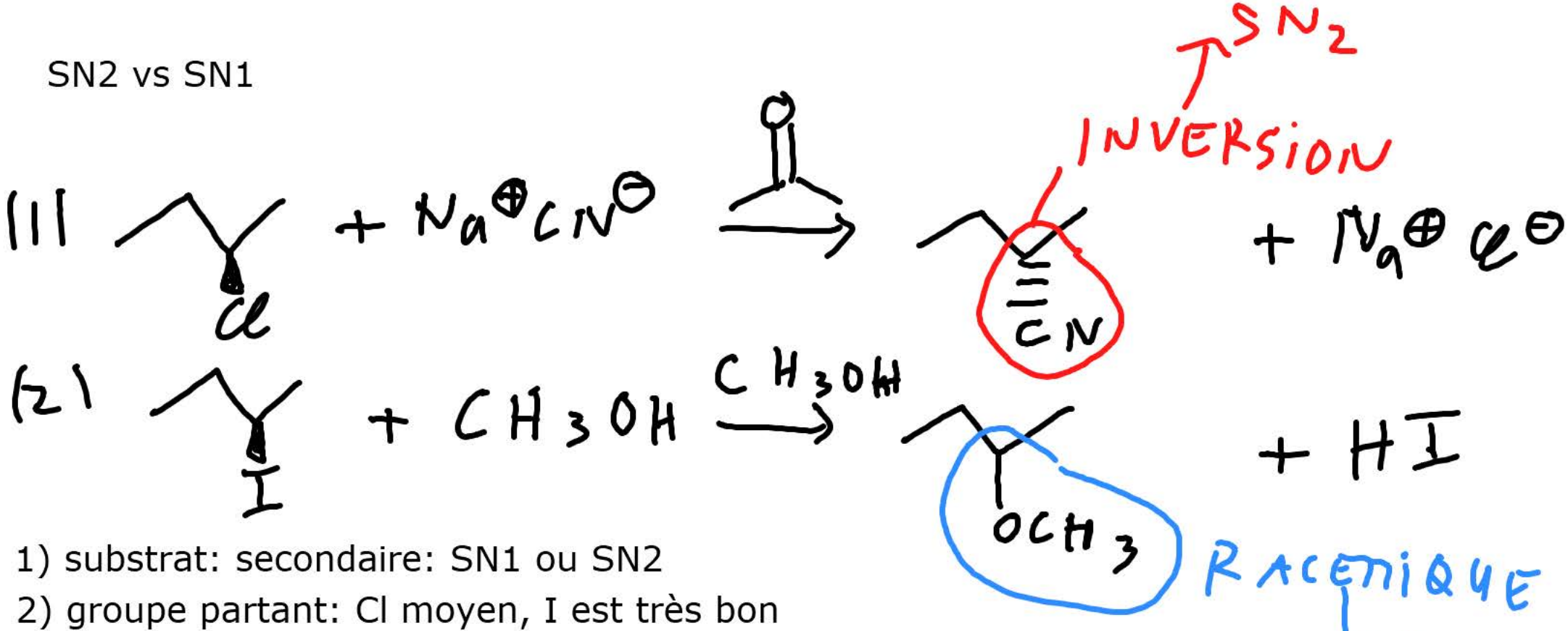
stabilisé

triflate, OTf
Meilleur groupe parant

plus économique
en atome

plus crystallin
(facile à purifier)

SN2 vs SN1



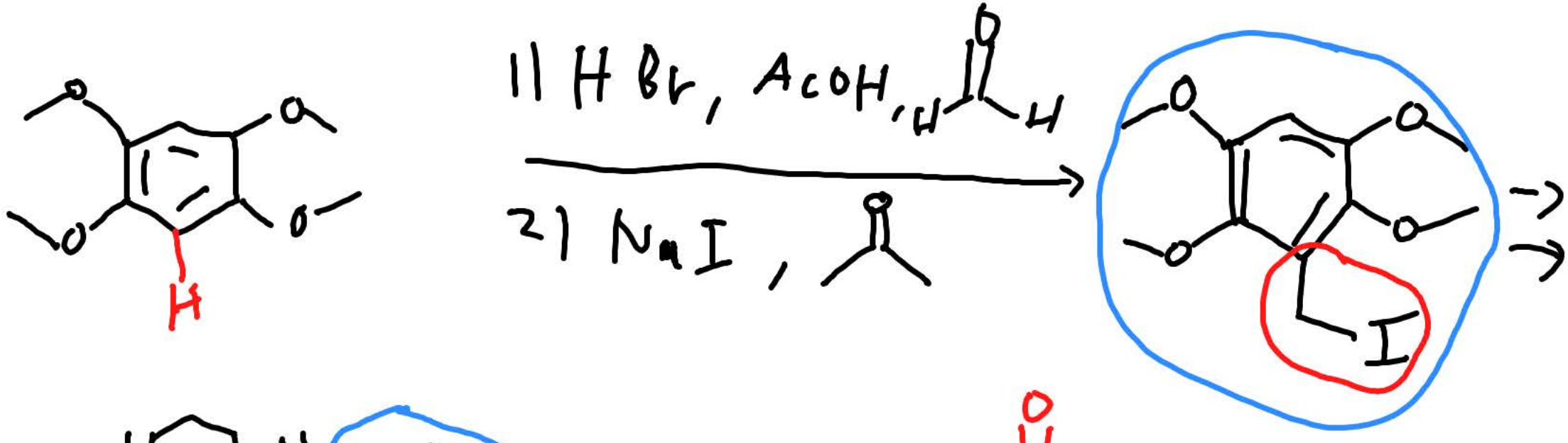
1) substrat: secondaire: SN1 ou SN2

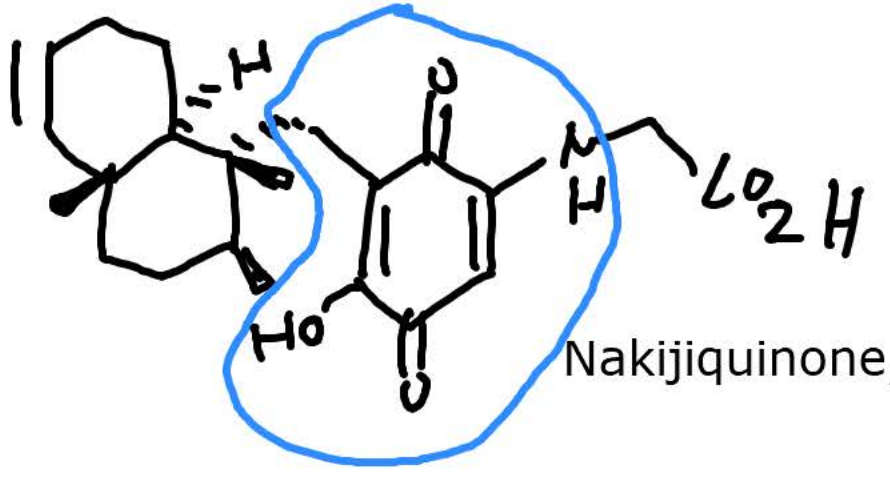
2) groupe partant: Cl moyen, I est très bon

3) Nucléophile: CN- est un bon nucléophile: plutôt SN2
MeOH = faible nucléophile, favorise plutôt une SN1

4) Solvant: acétone: polaire aprotique, favorise une SN2
MeOH: polaire protique, favorise une SN1

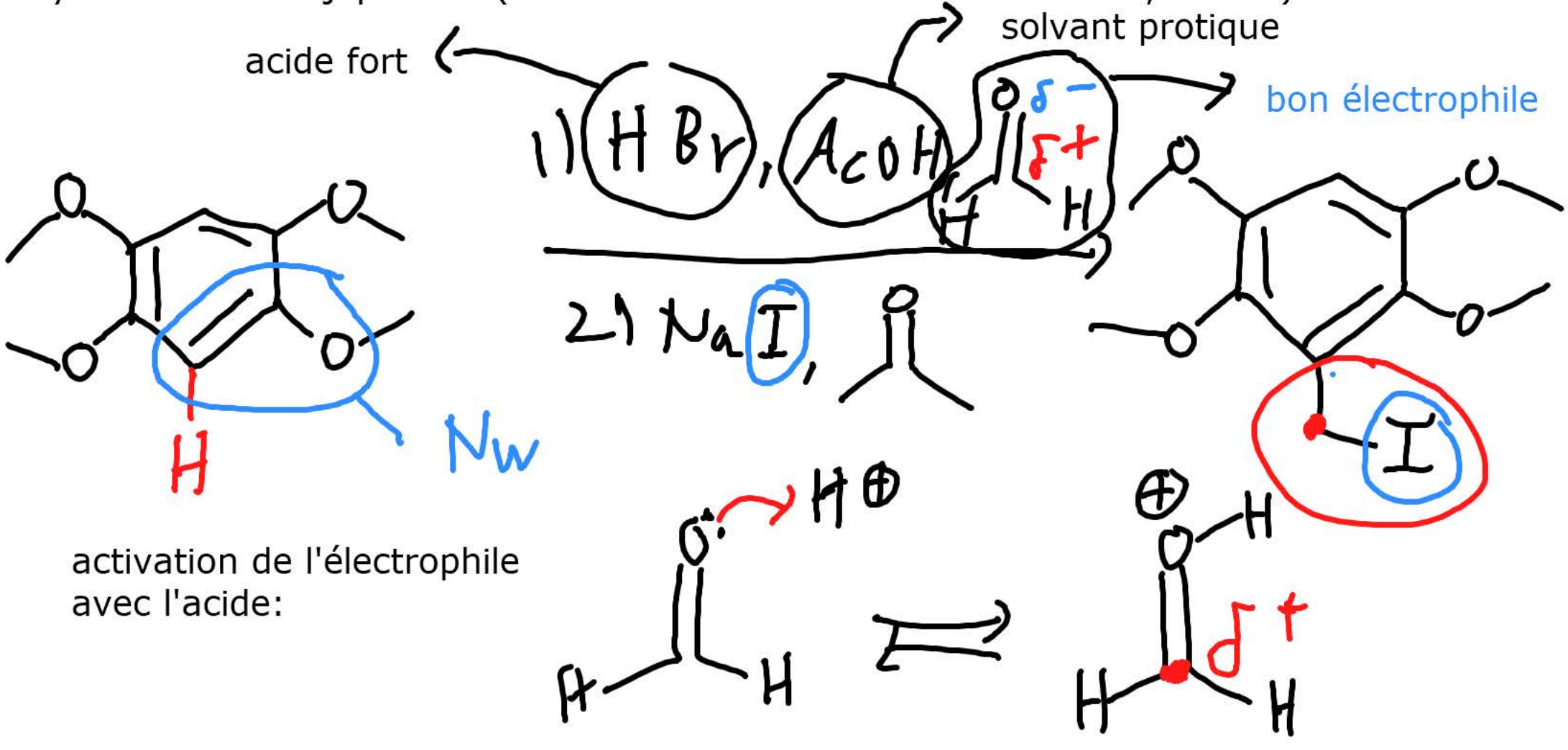
exemple de SN: synthèse de produit naturel

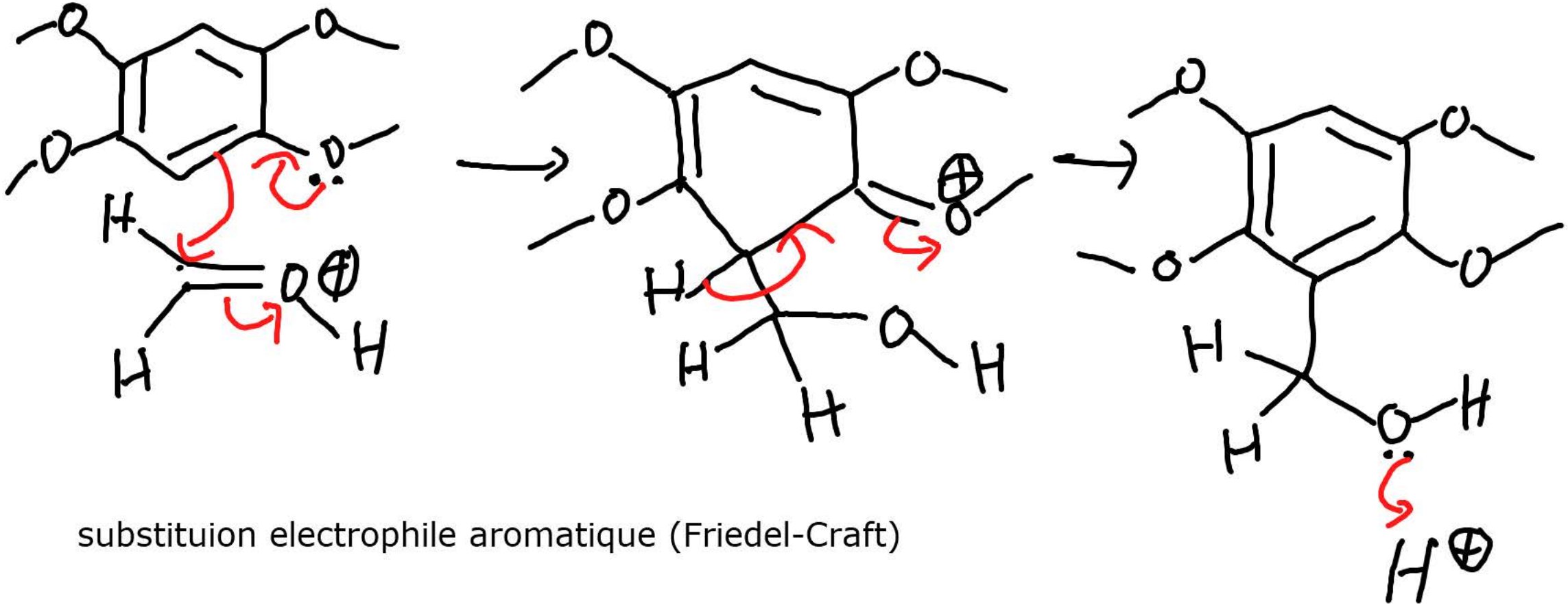




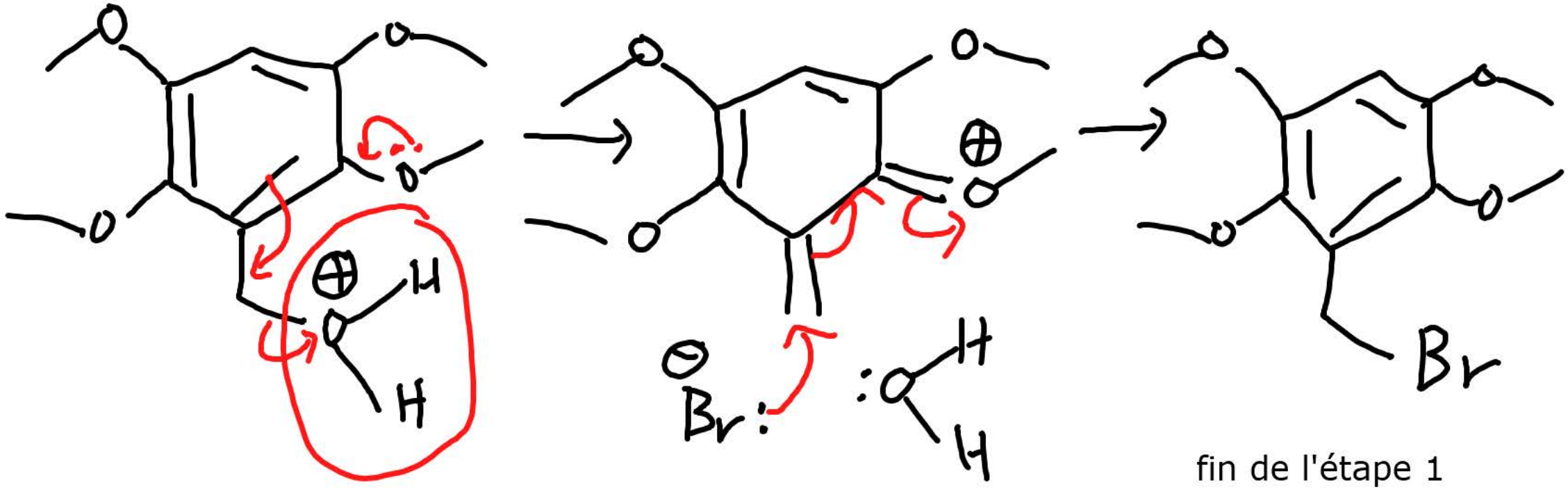
Nakijiquinone, anticancer

synthèse de nakijiquinone (Waldmann: J. Am. Chem. Soc. 2001, 11586)





substituion electrophile aromatique (Friedel-Craft)



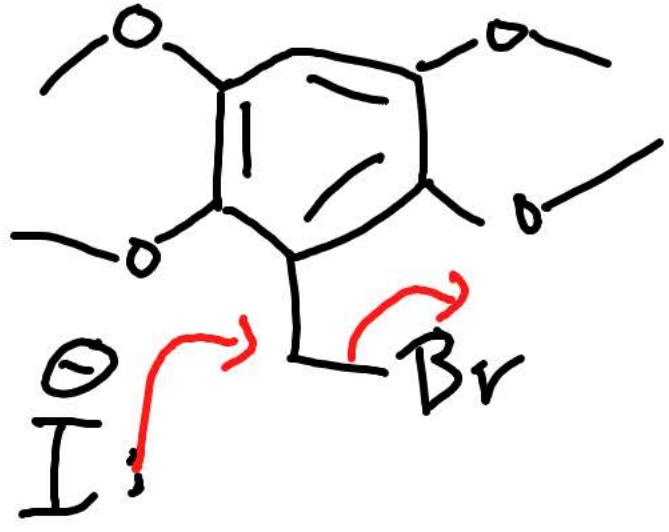
bon group partant

fin de l'étape 1

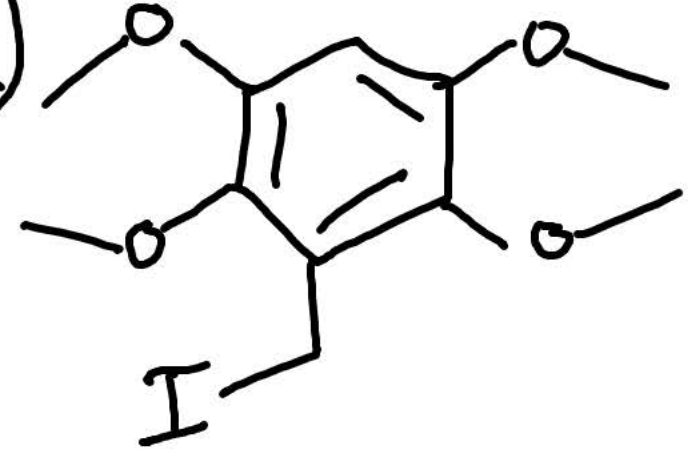
protique: plutôt SN1
carbocation stabilisé: SN1!

position benzylique

bon nucléophile



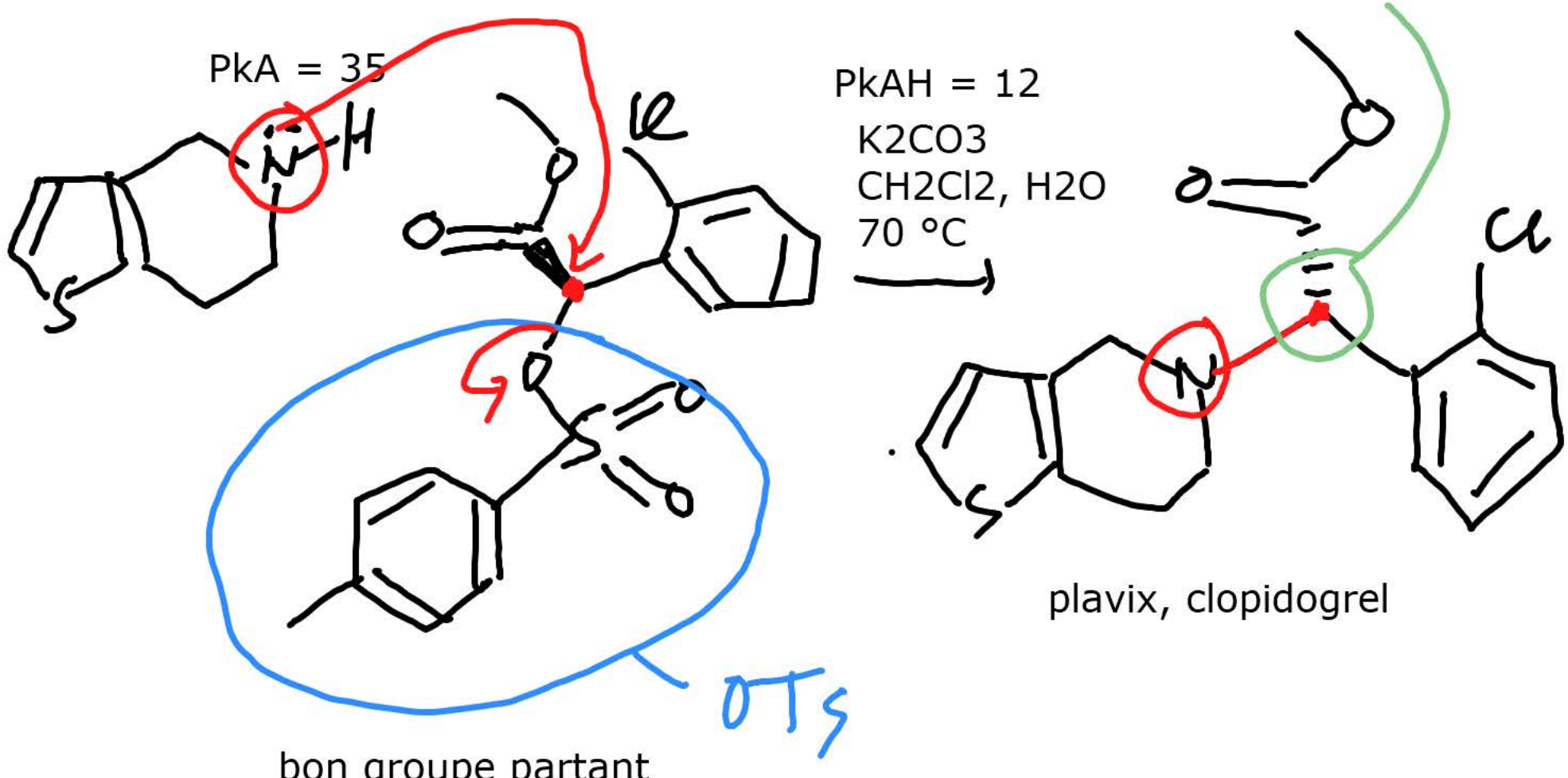
solvant polaire non-protique



conditions favorisant la SN2!

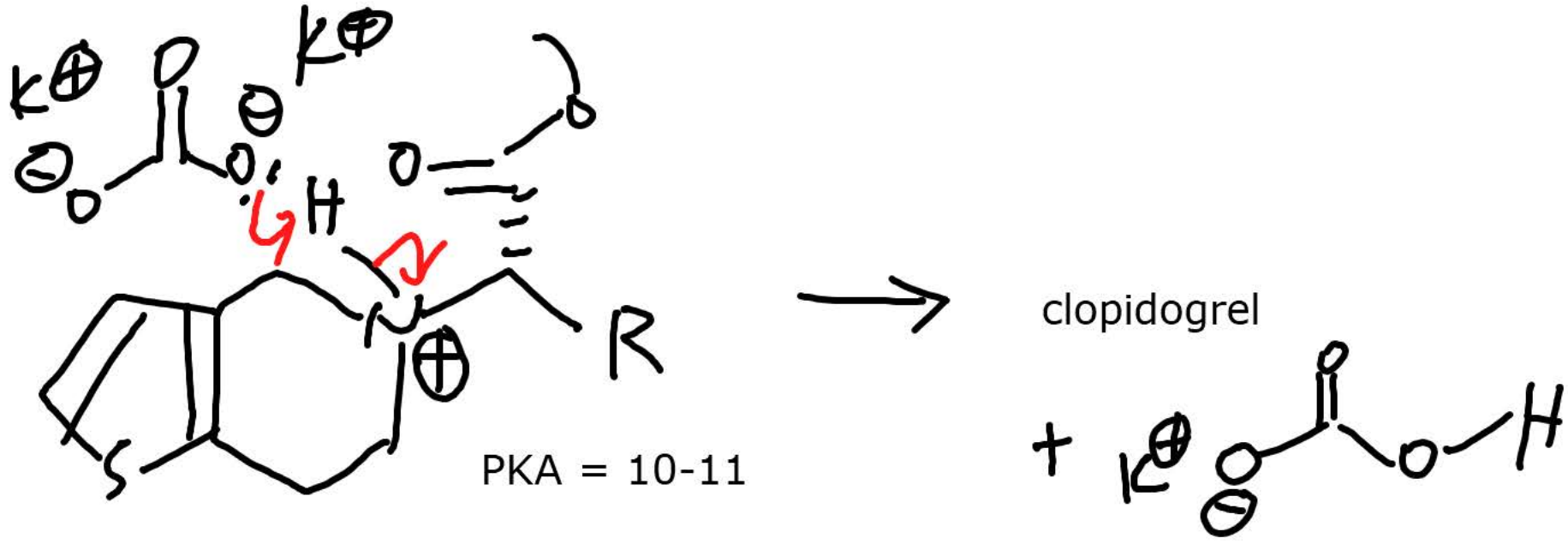
synthèse du Clopidogrel (Plavix, anticoagulant)

stéréochimie inversée: SN2

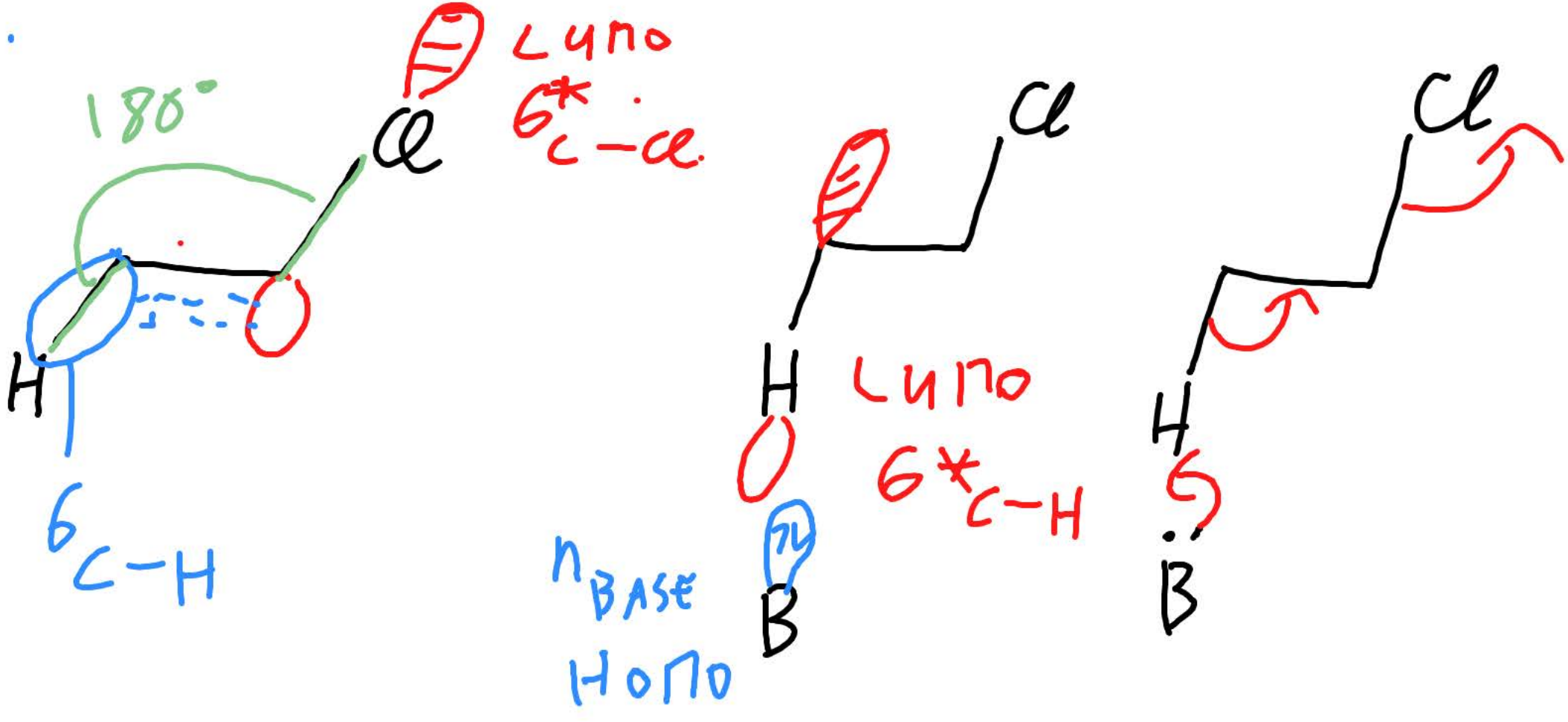


bon groupe partant

plavix, clopidogrel

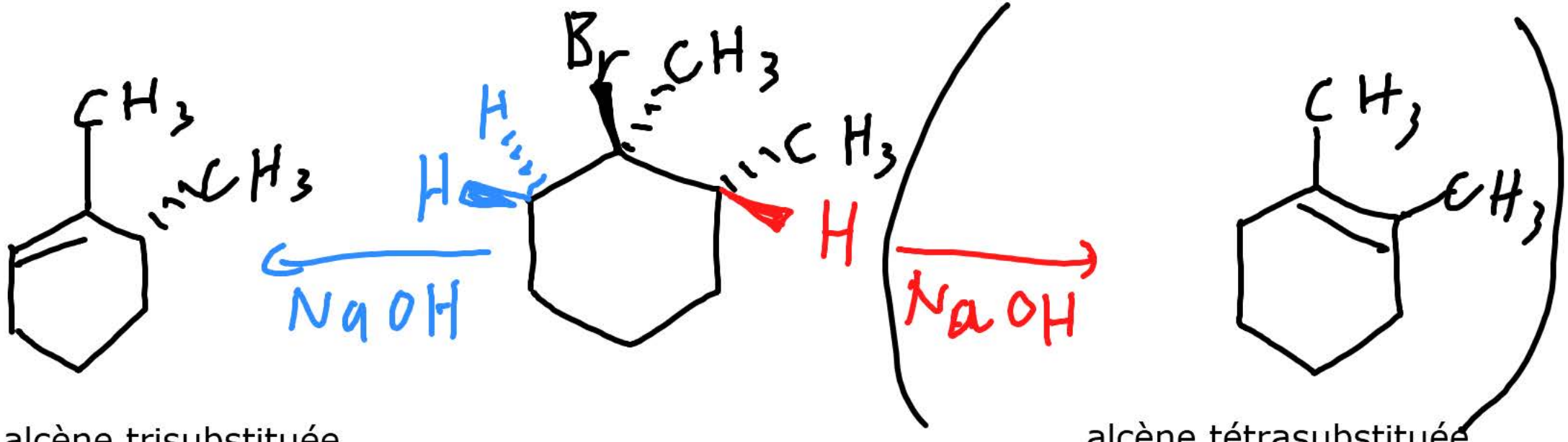

R
PKA = 10-11
clopidogrel

Elimination E2, orbitales moléculaires



.

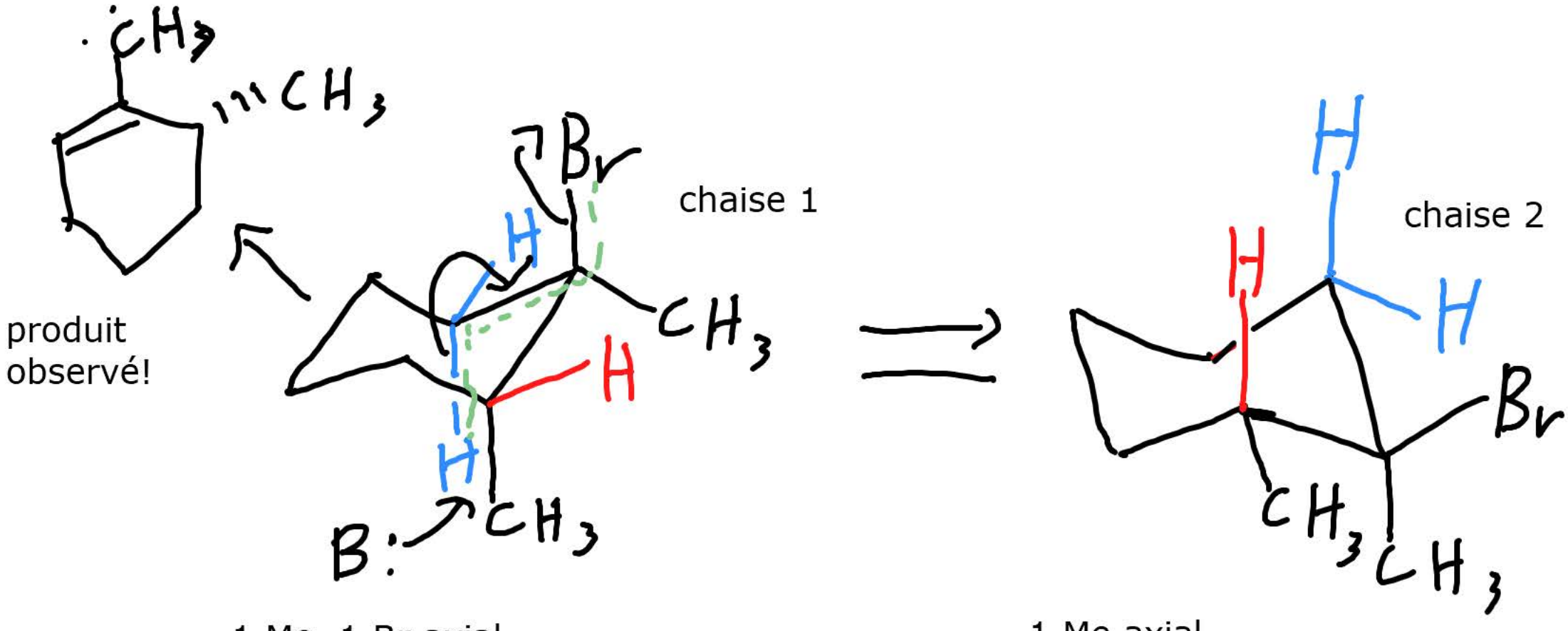
pas observé



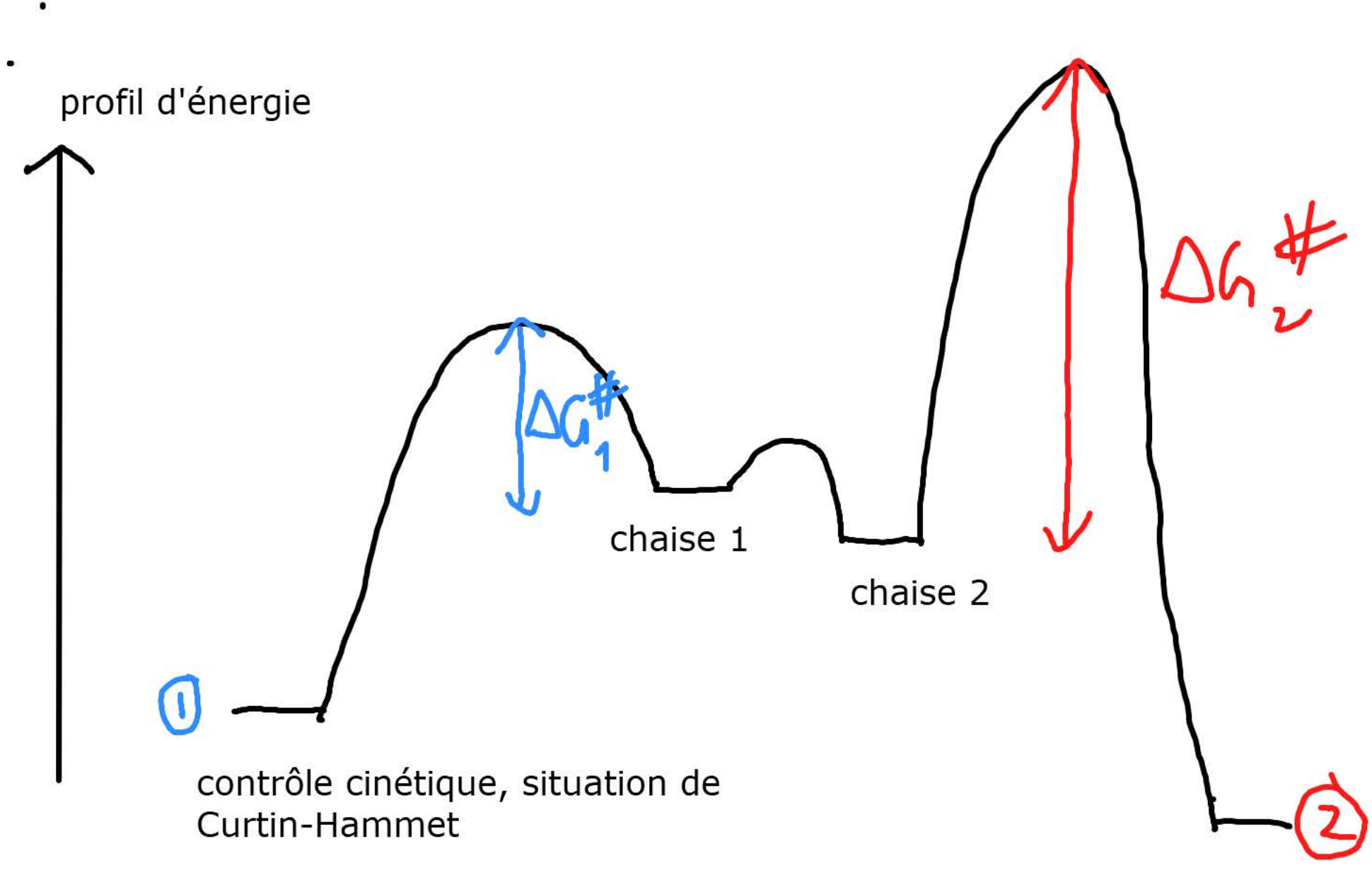
alcène trisubstituée

moins stable, mais c'est le produit observé!
produit cinétique

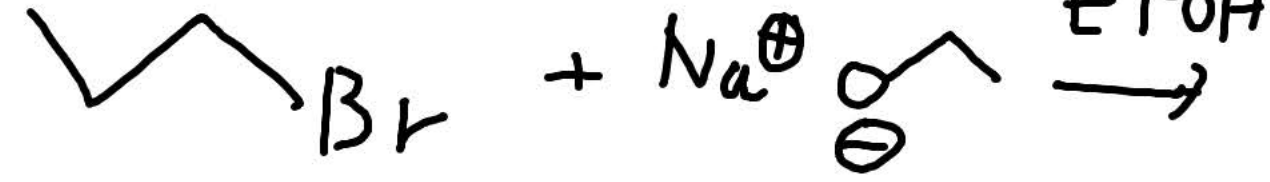
alcène tétrasubstituée
plus stable
produit thermodynamique

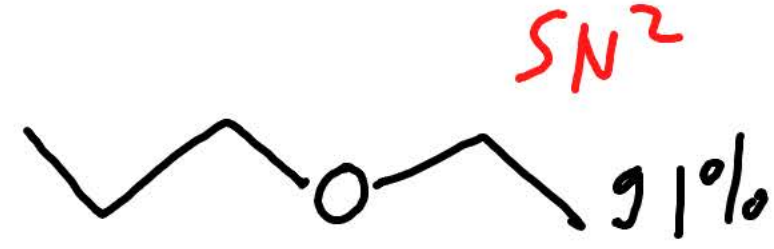


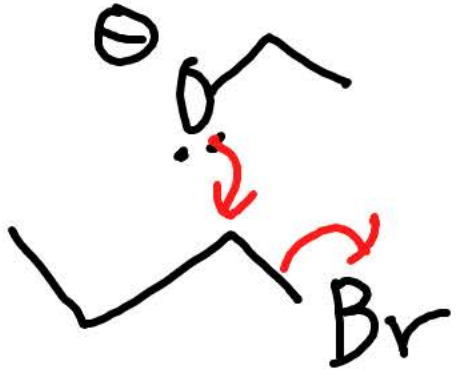
E2 seulement pour un angle de 180°

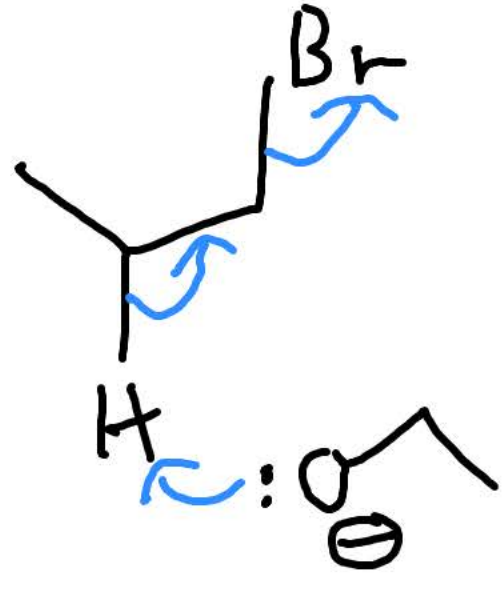

profil d'énergie
ΔG#1
chaise 1
chaise 2
ΔG#2
1
2
contrôle cinétique, situation de
Curtin-Hammet

Sn vs E: Influence du substrat: position primaire: plutôt SN2/E2

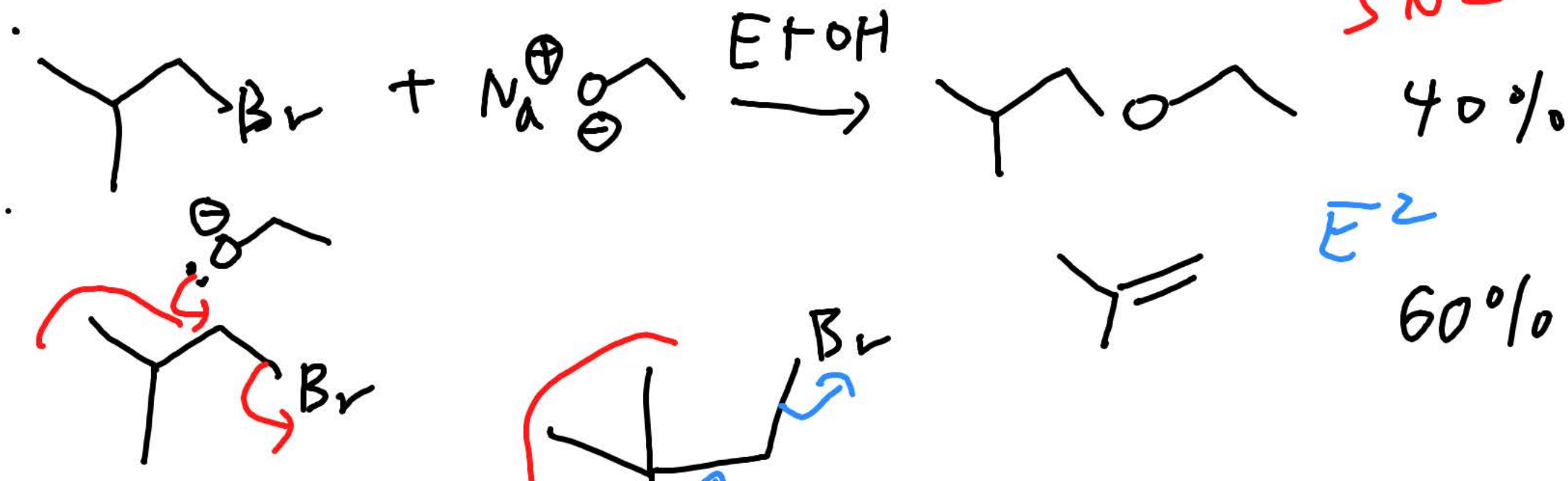




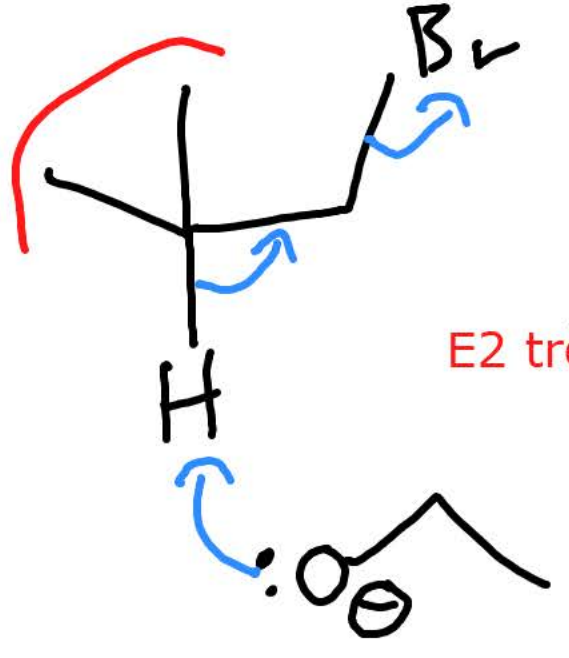




NaOEt: bon nucléophile et bonne base



SN2 ralentie



E2 très peu ralentie

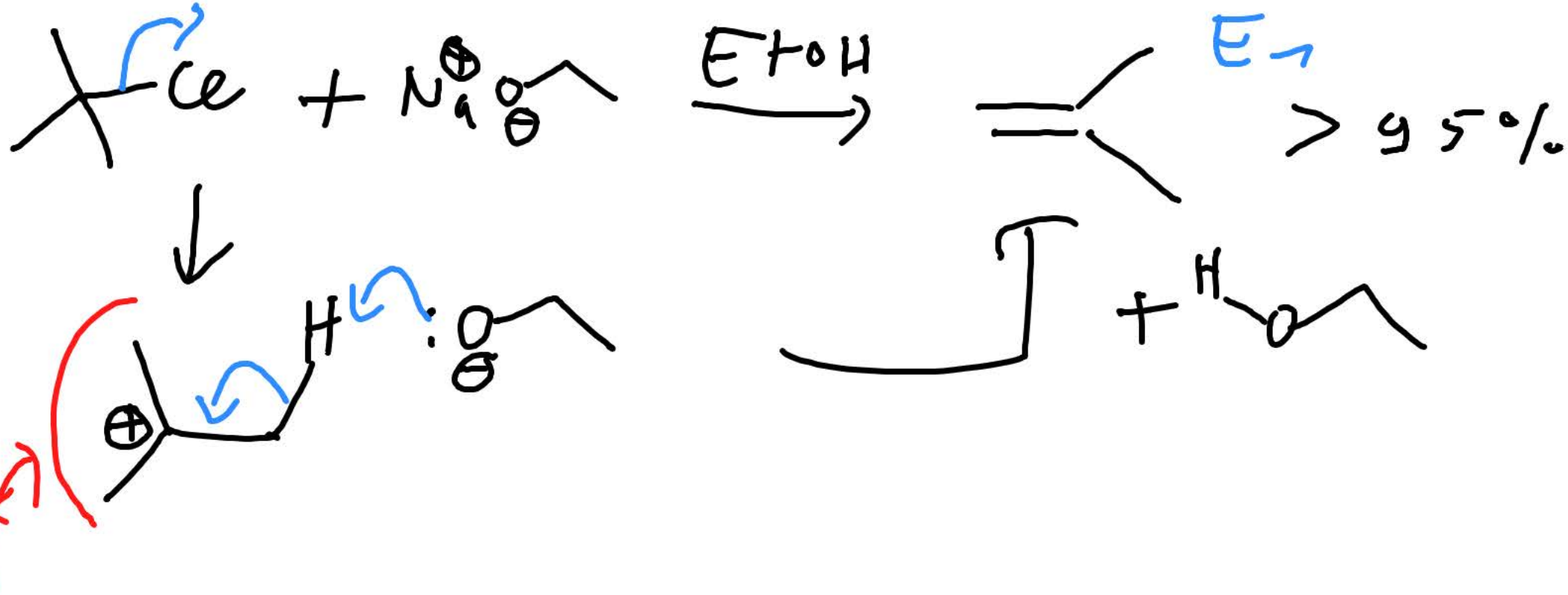
position secondaire

pkAH = 16

pour favoriser la substitution?
il faut diminuer la basicité!

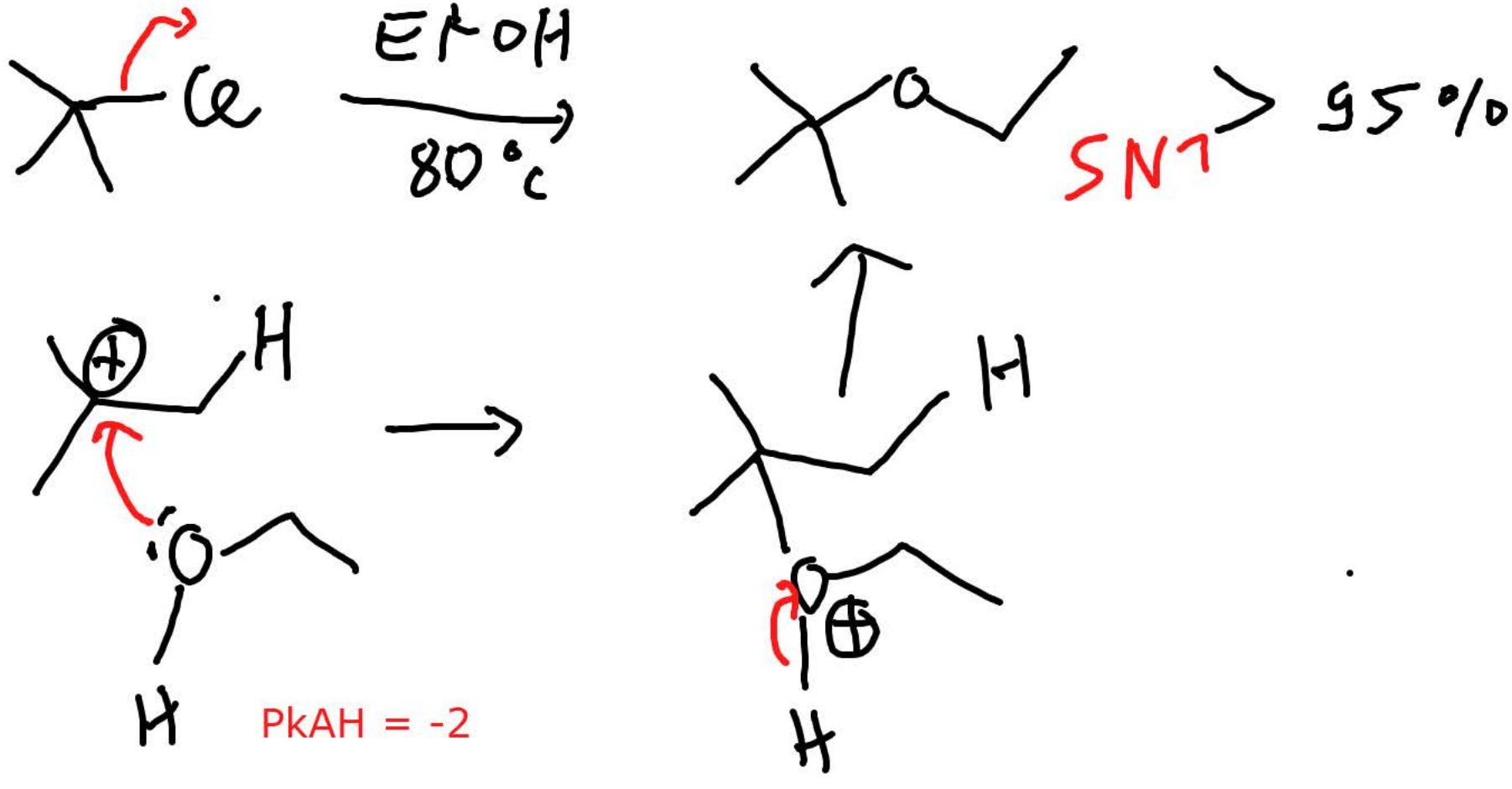
PkAH = 4.7

position tertiaire: E1 ou SN1

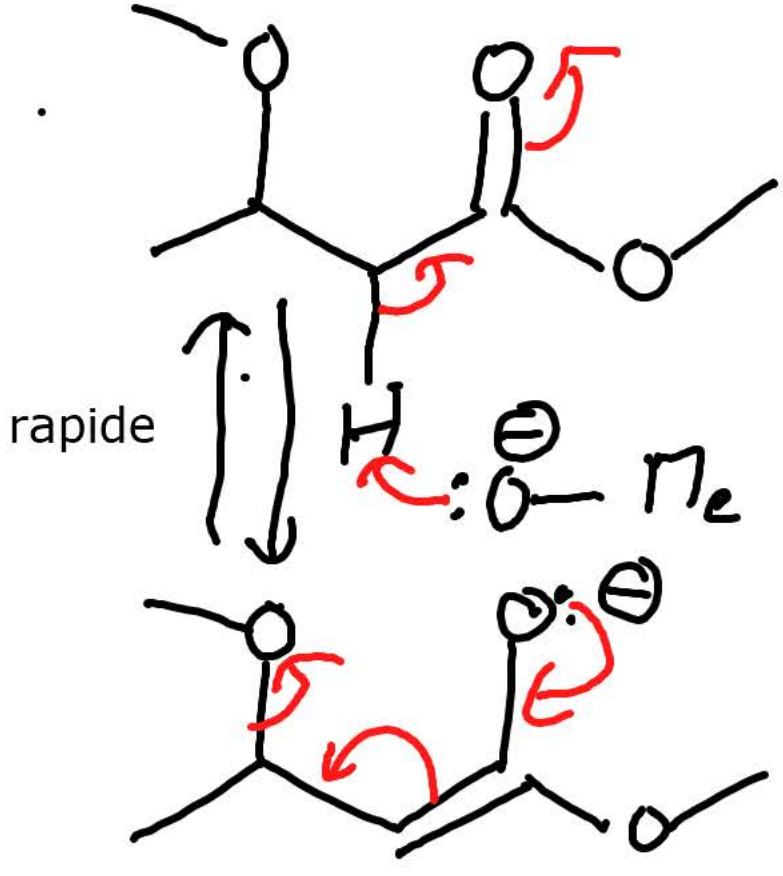


SN1 difficile

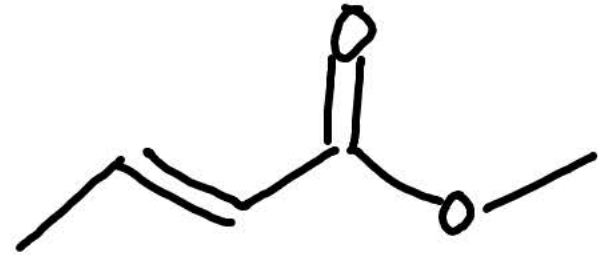
pour obtenir SN1: éviter les bases!



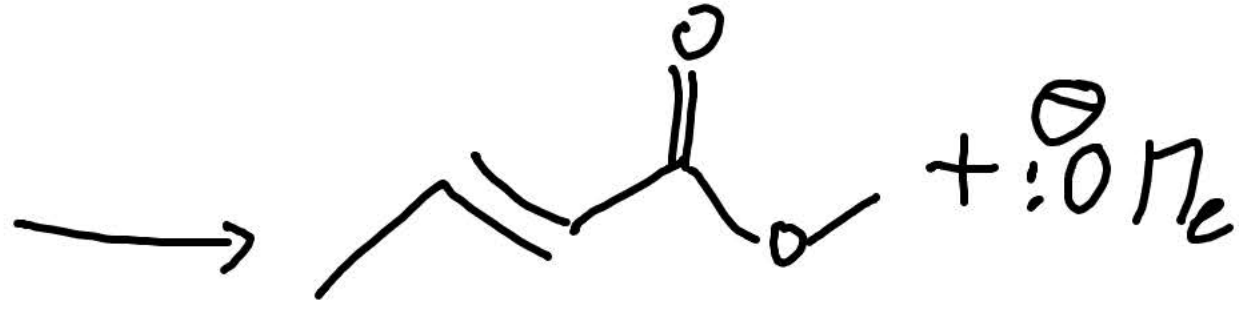
"5ème" mécanisme: cas particulier E1cb des protons acides



anion comme intermédiaire

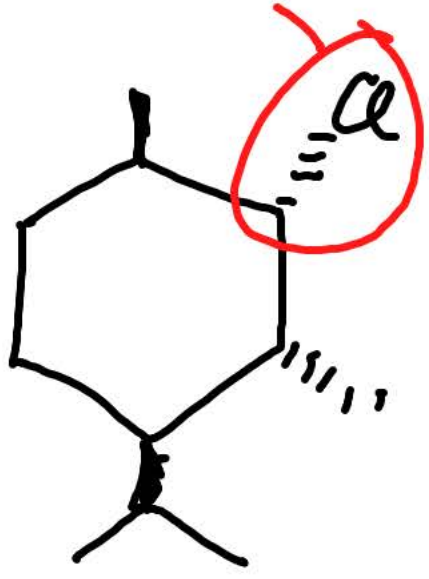


condensation aldolique



possible pour les protons très acides

groupe partant

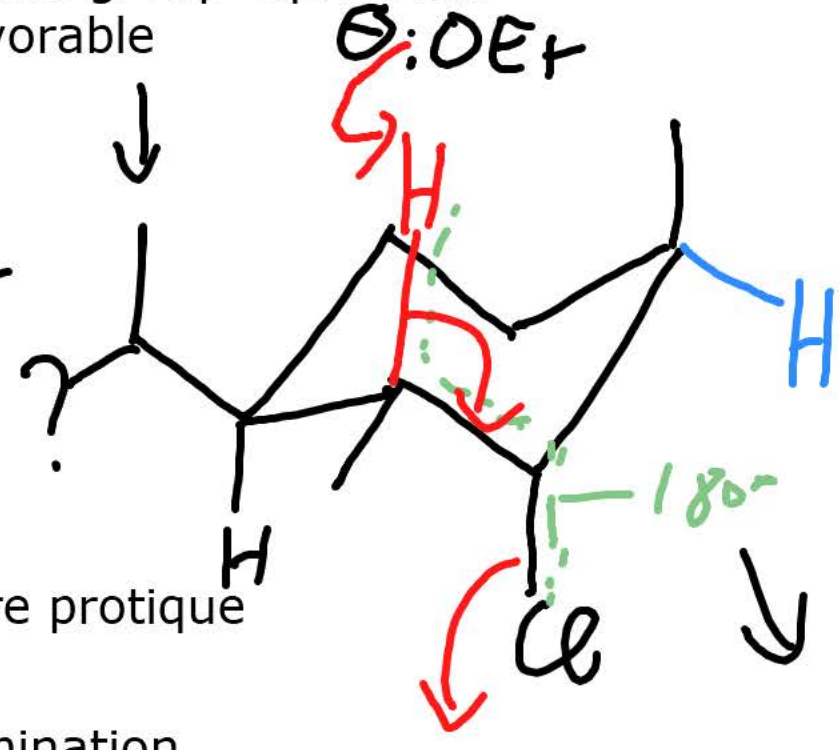


grand group équatorial favorable

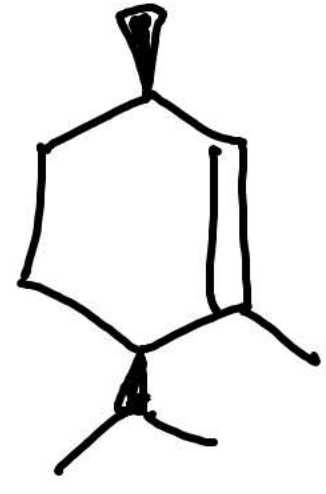
base forte

$NaOEt$

$EtOH$



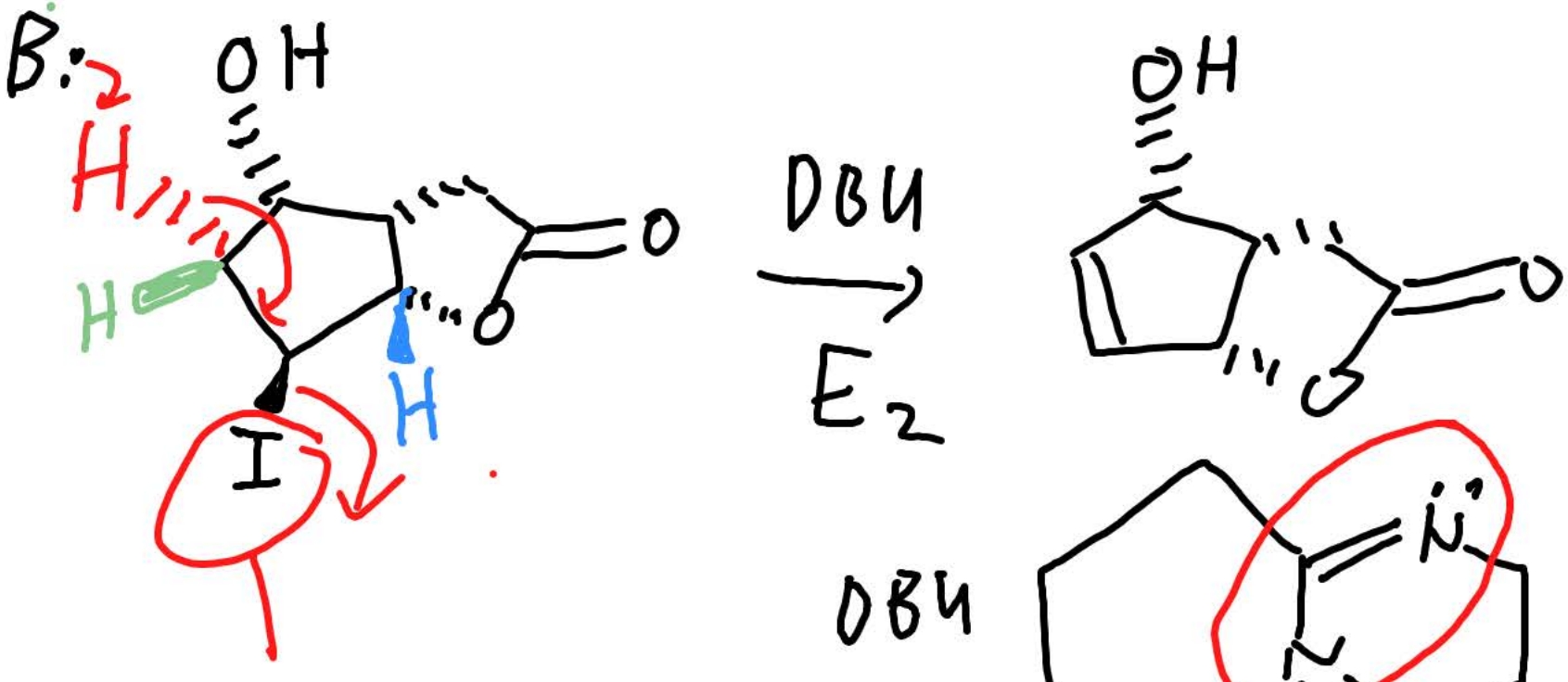
solvant polaire protique



groupe partant: substitution ou élimination
base forte, solvant protique: plutôt élimination
Si on a l'angle idéal de 180+: E2, sinon E1 possible
Il faut dessiner en 3D

.

synthèse des prostaglandines (hormones naturelles)

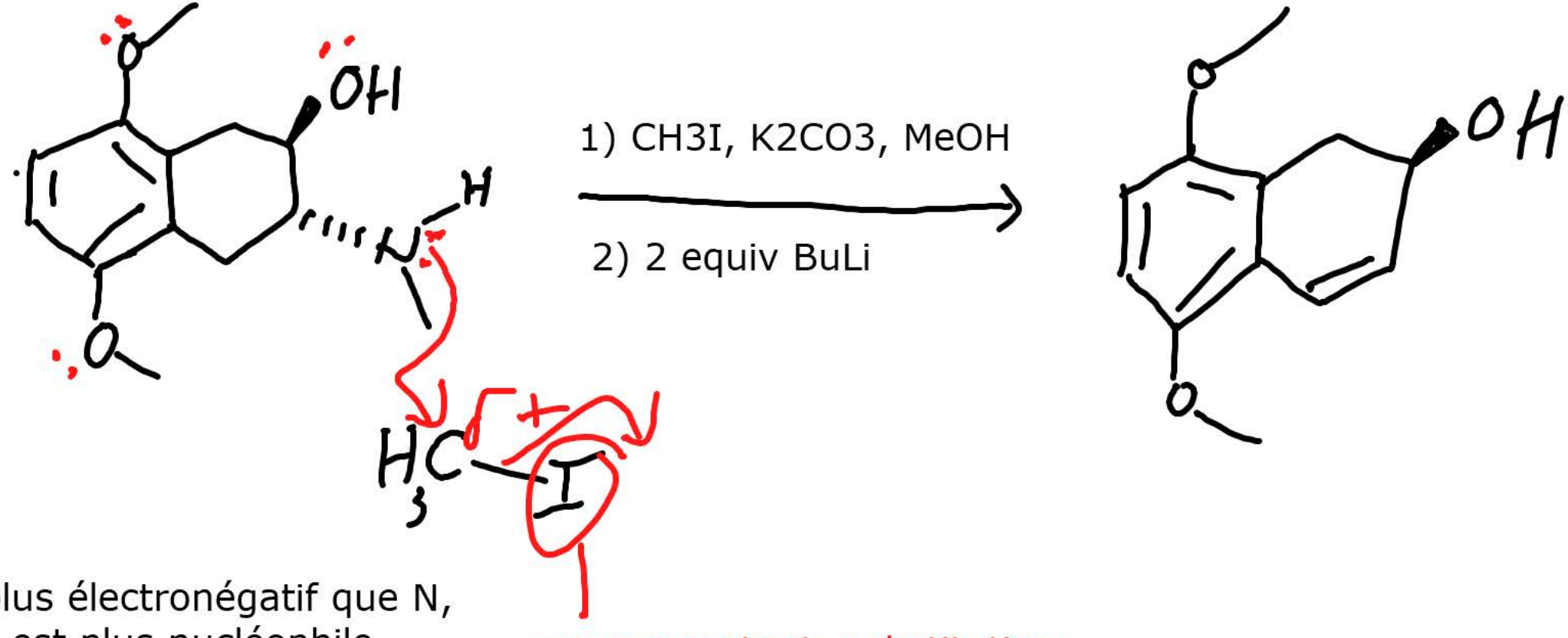


groupe partant

cyle à 5 plus "plat", seul le H en trans/anti peuvent réagir (rouge)

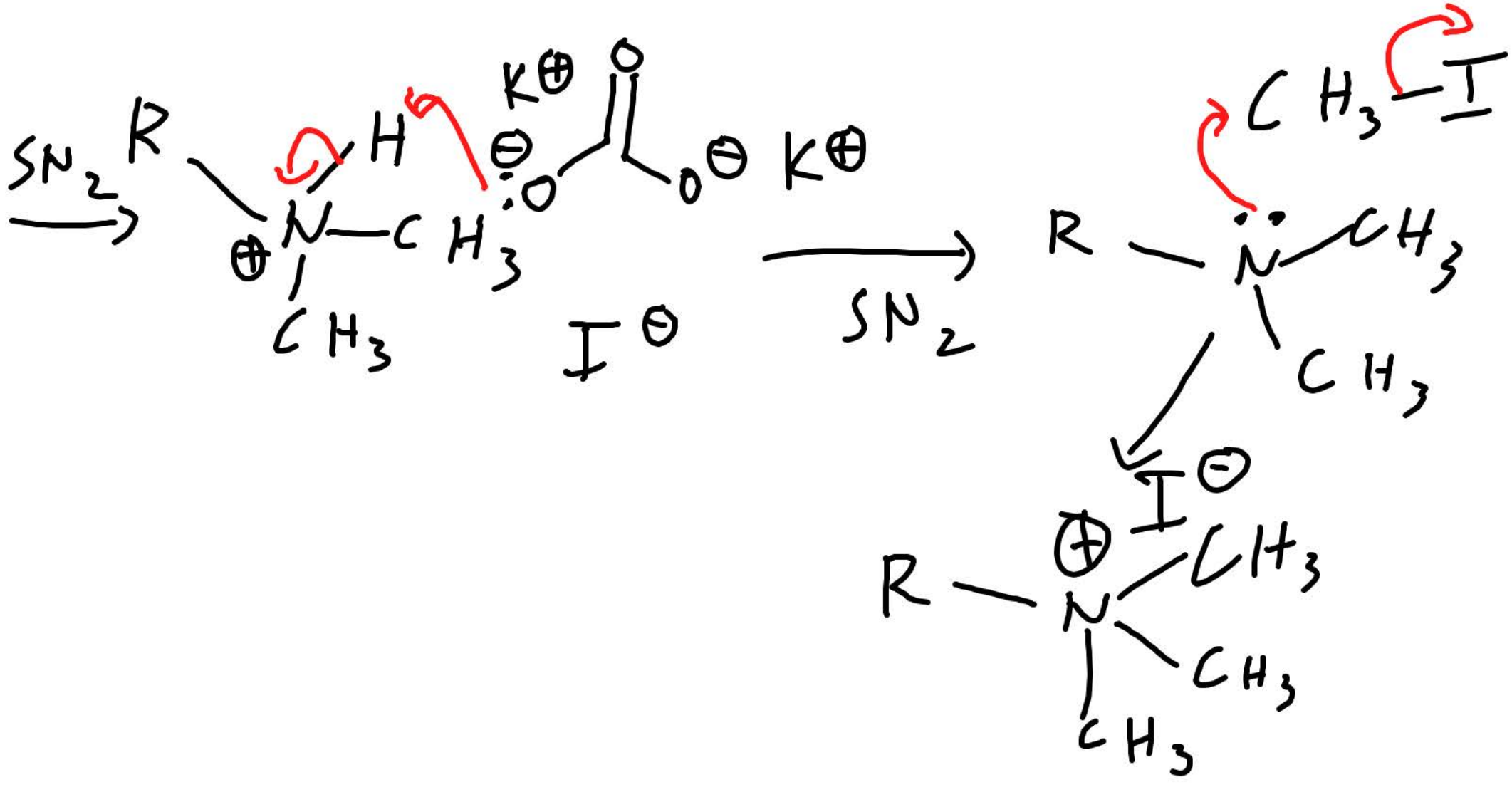
bonne base, pkAH = 14

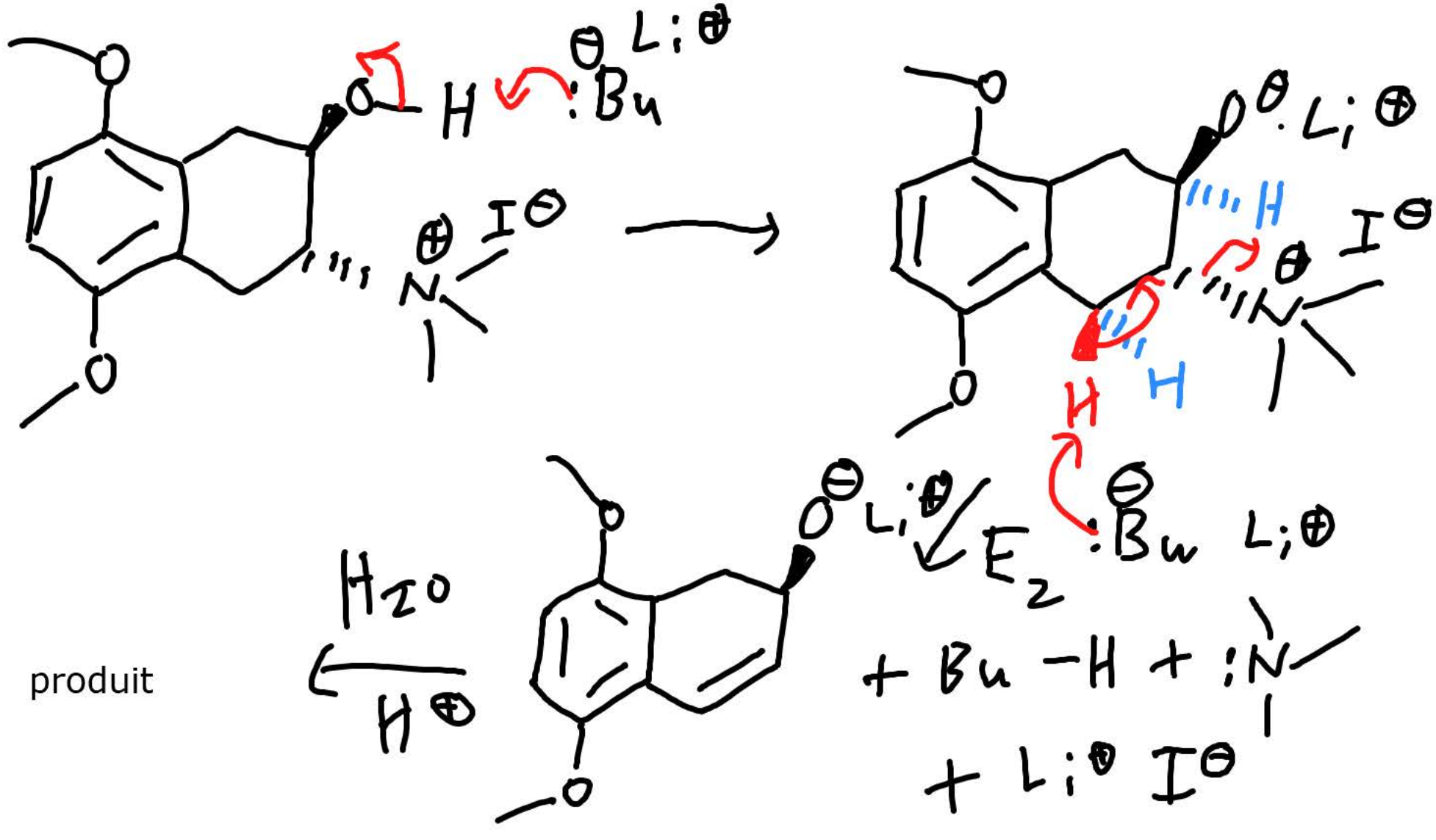
Elimination selon Hofmann (à partir des amines)



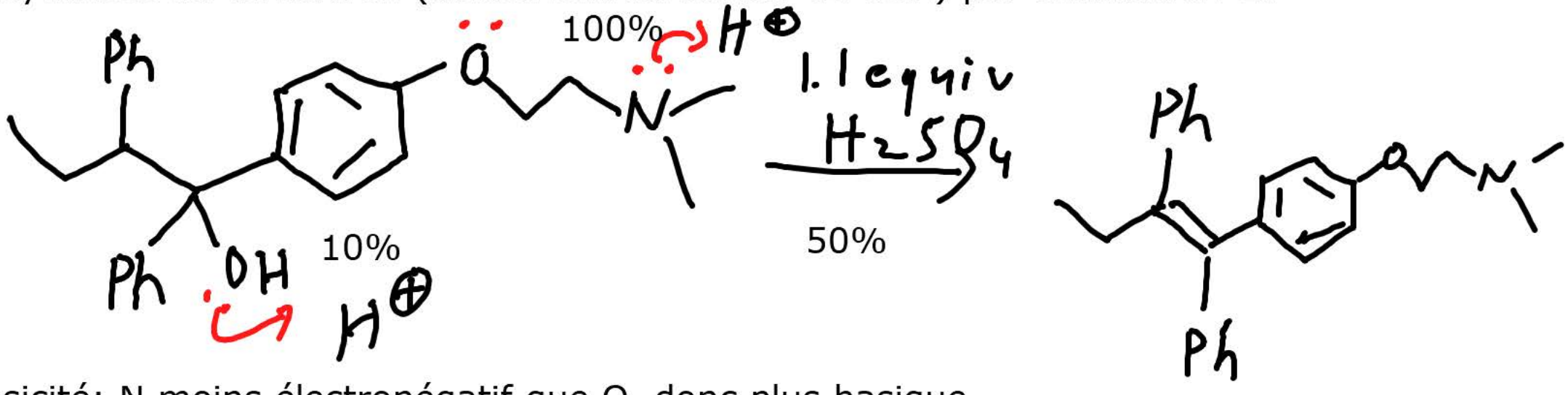
O est plus électronégatif que N,
donc N est plus nucléophile

groupe partant, substitution


SN2
R
H
K⊕
O⊖
K⊕
N
CH3
CH3
I⊖
SN2
CH3
I
R
N
CH3
CH3
I⊖
R
N
CH3
CH3
CH3

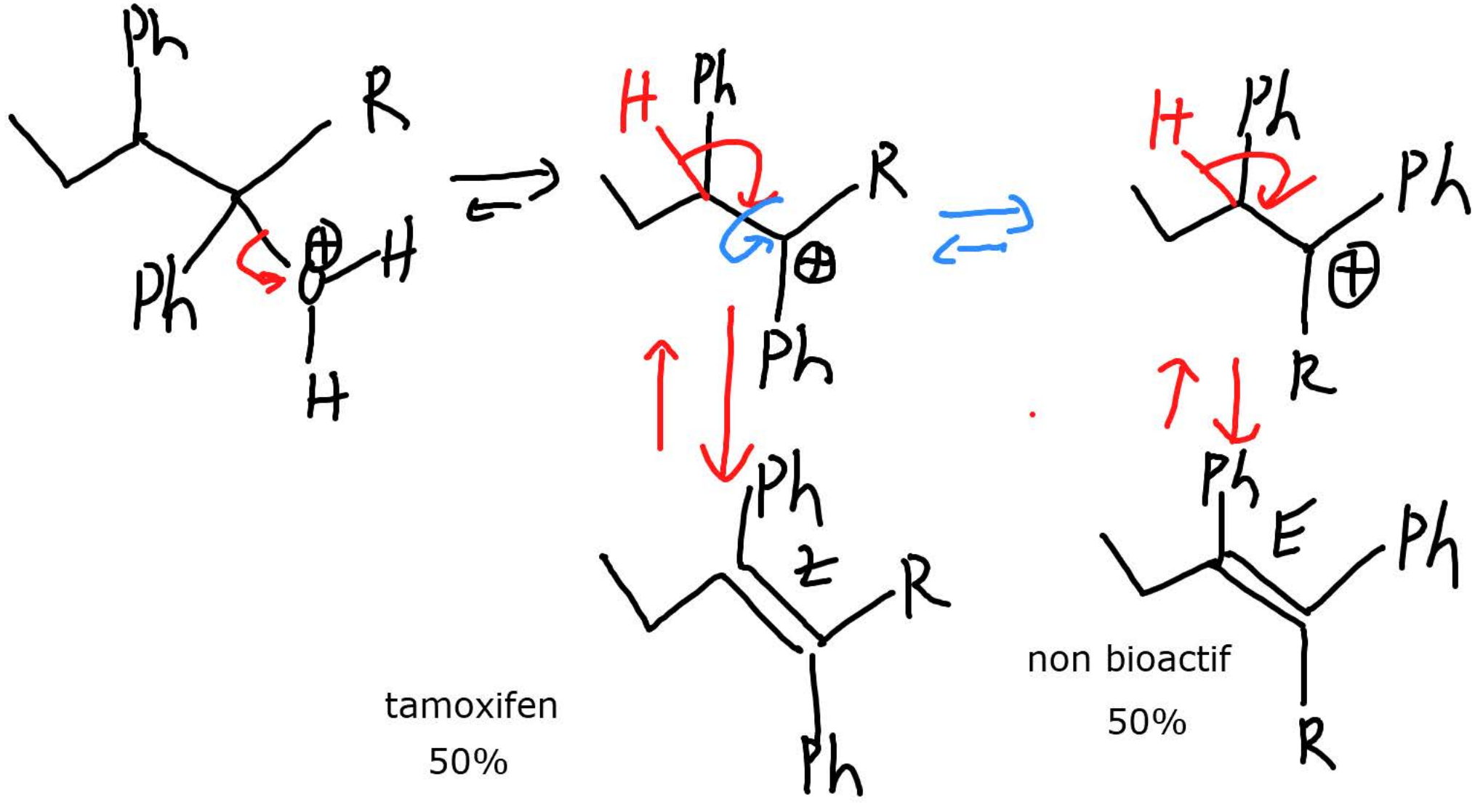

produit
H_2O
$HO^\ominus$
E_2
+ Bu−H +
+ $Li^\oplus$ $I^\ominus$

synthèse du tamoxifen (traitement du cancer du sein) par élimination E1



basicité: N moins électronégatif que O, donc plus basique

tamoxifen



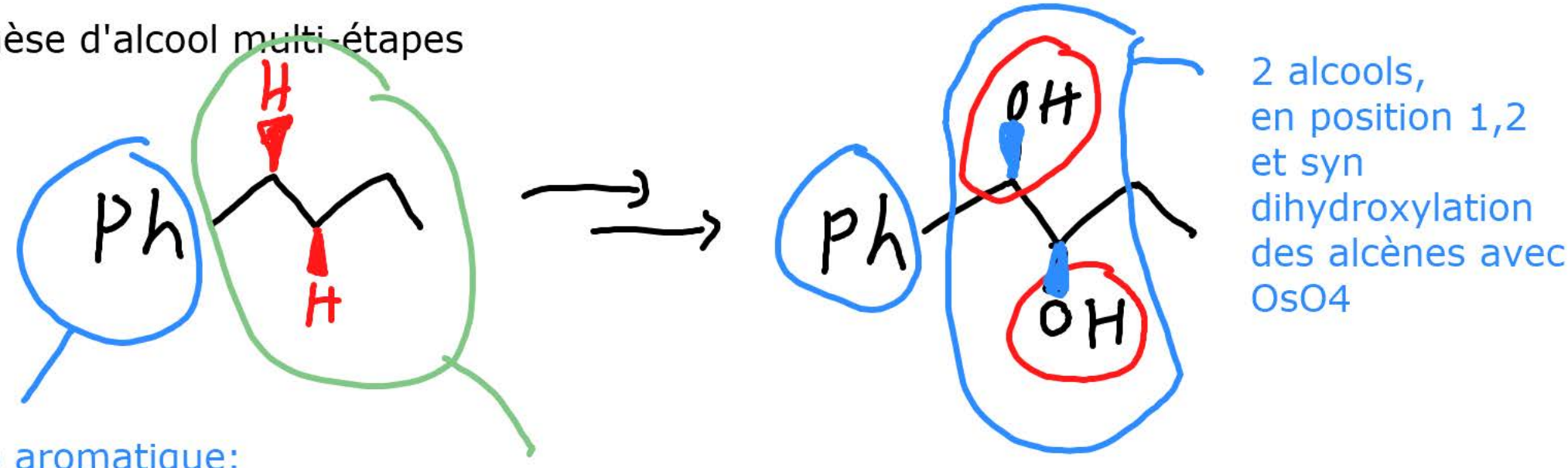
tamoxifen

50%

non bioactif

50%

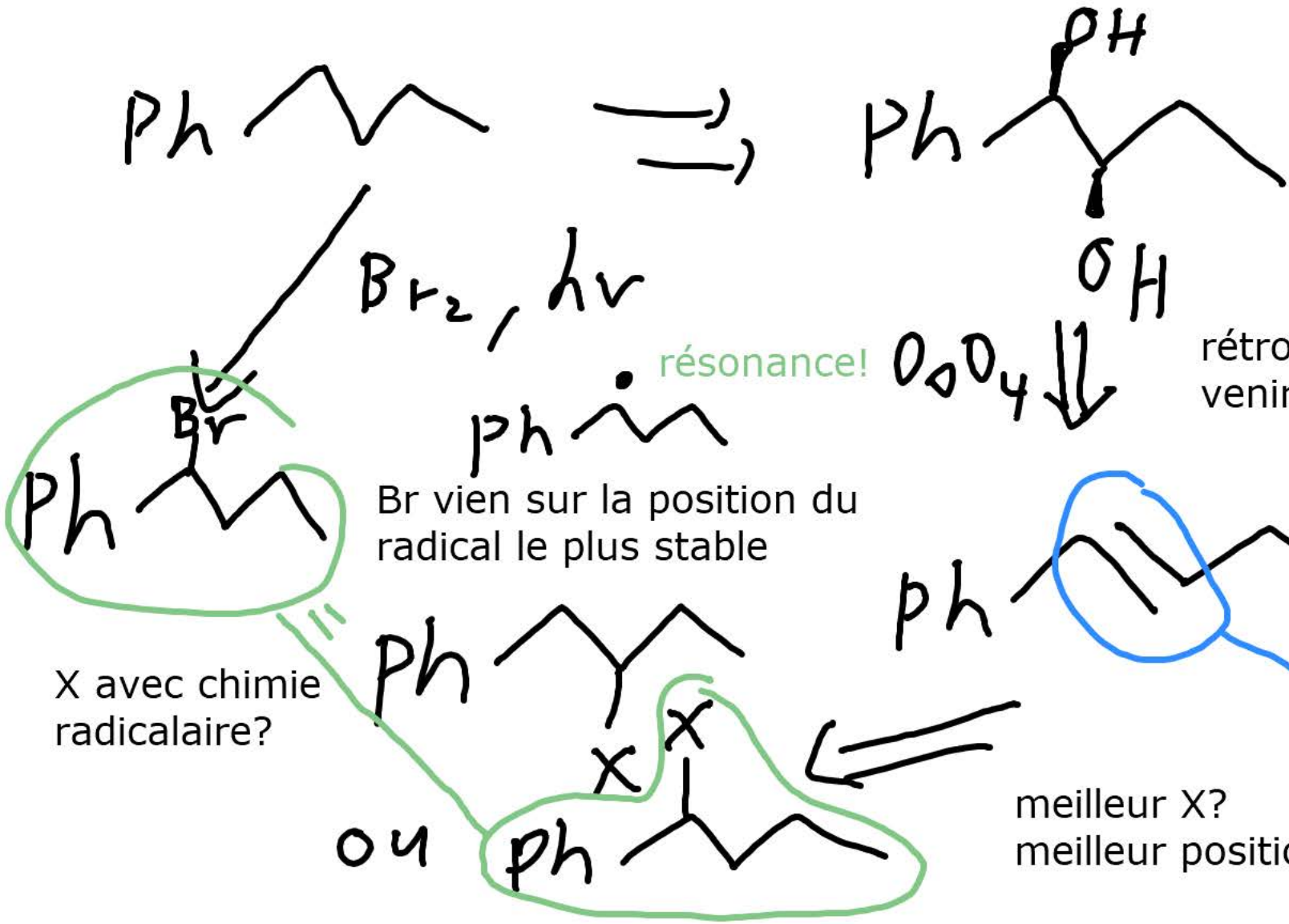
synthèse d'alcool multi-étapes



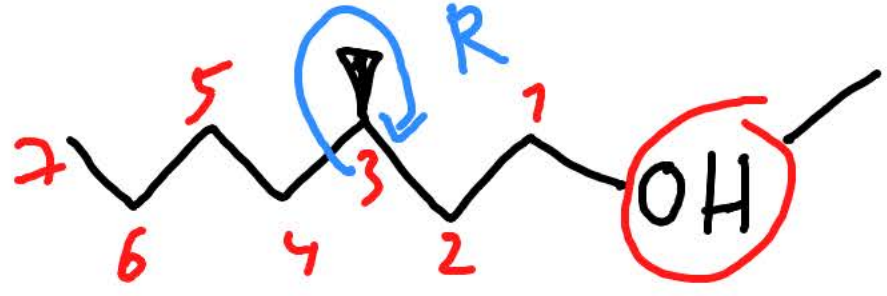
2 alcools,
en position 1,2
et syn
dihydroxylation
des alcènes avec
OsO4

cycle aromatique:
1)substitution aromatique électrophile: inchangé, donc pas rélévant
2) Attention résonance!

liaisons C-H uniquement
Chimie radicalaire?

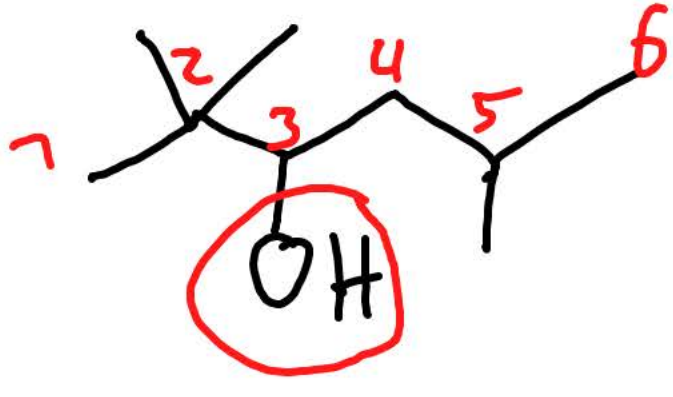

Ph
OH
Ph
Br_2, hv
OH
OsO_4
rétrosynthèse = "pourrait venir de"
résonance!
Ph
Br
Ph
Br vien sur la position du radical le plus stable
Ph
X avec chimie radicalaire?
Ph
double liaison? élimination
X
X
ou
Ph
meilleur X?
meilleur position de X?

nomenclature des groupes fonctionnels

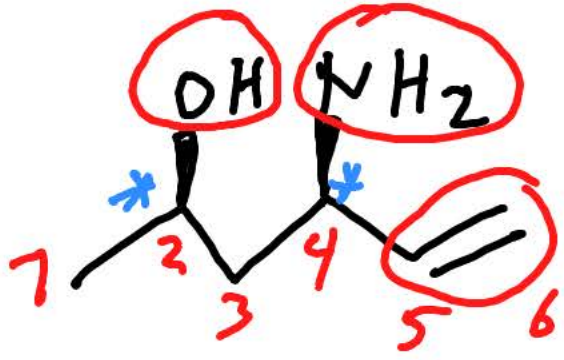


alcool

(R)-3-methyl-heptan-1-ol

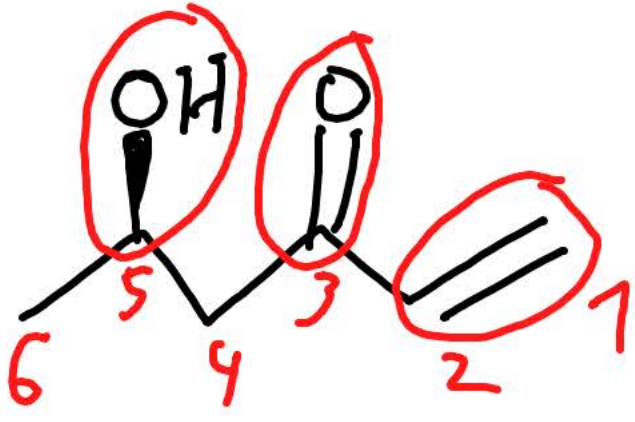


2,2,5-trimethyl-hexan-3-ol



Alcool > amines > alcènes

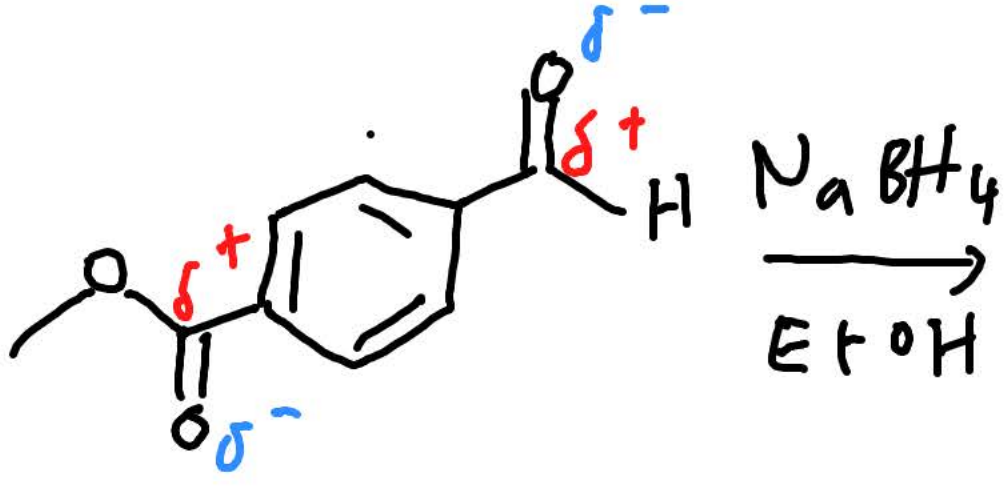
(2R, 4R)-4-amino-hex-5-en-2-ol



cétone > alcool > alcène

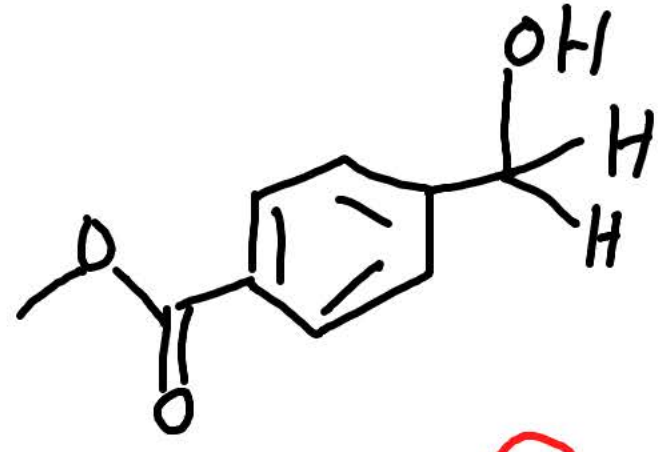
(R)-5-hydroxy-hex-1-en-3-one

réduction des carbonyls avec des hydrures



$NaBH_4$

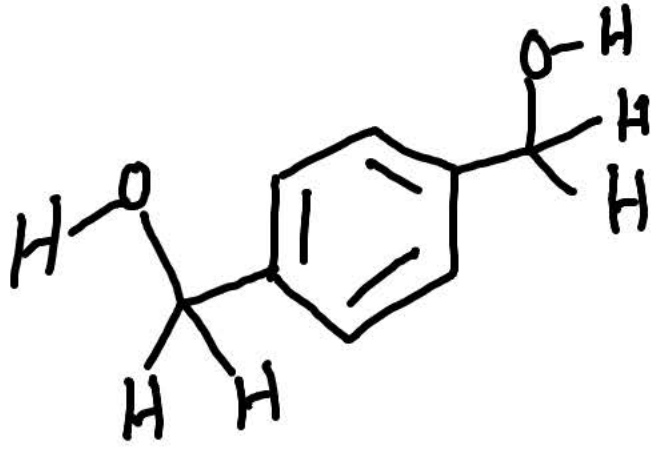
EtOH

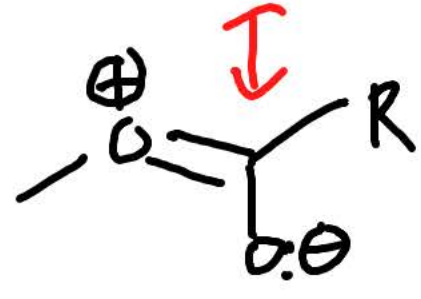


1) $LiAlH_4$

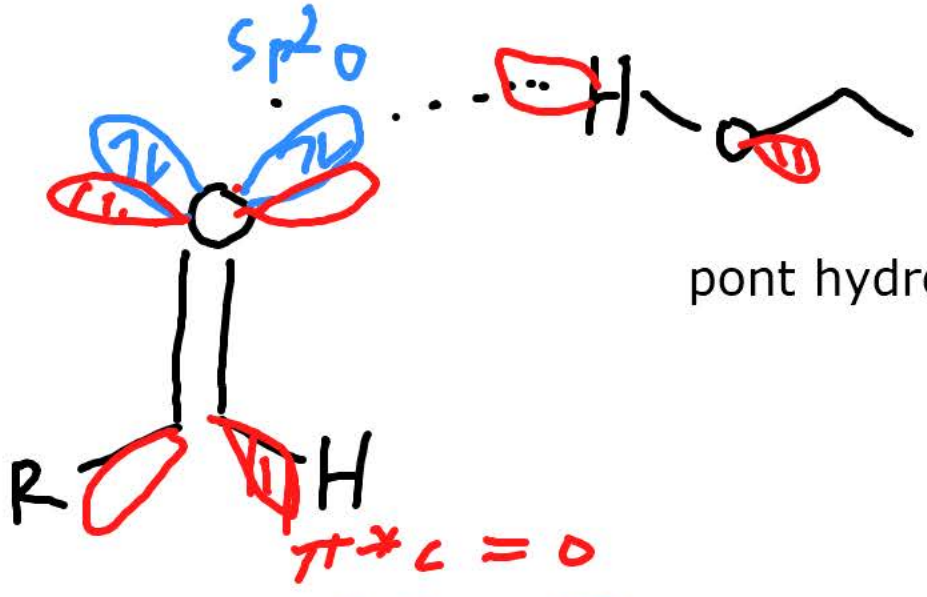
THF

2) $H^{\oplus}$, H_2O





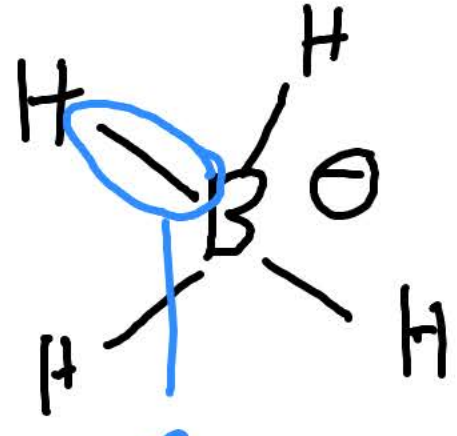
ester stabilisé
par résonance
moins réactif



$sp^2 O \longrightarrow 6^* \; H-O$

LUMO

pont hydrogène avec la paire d'électron



Na^+

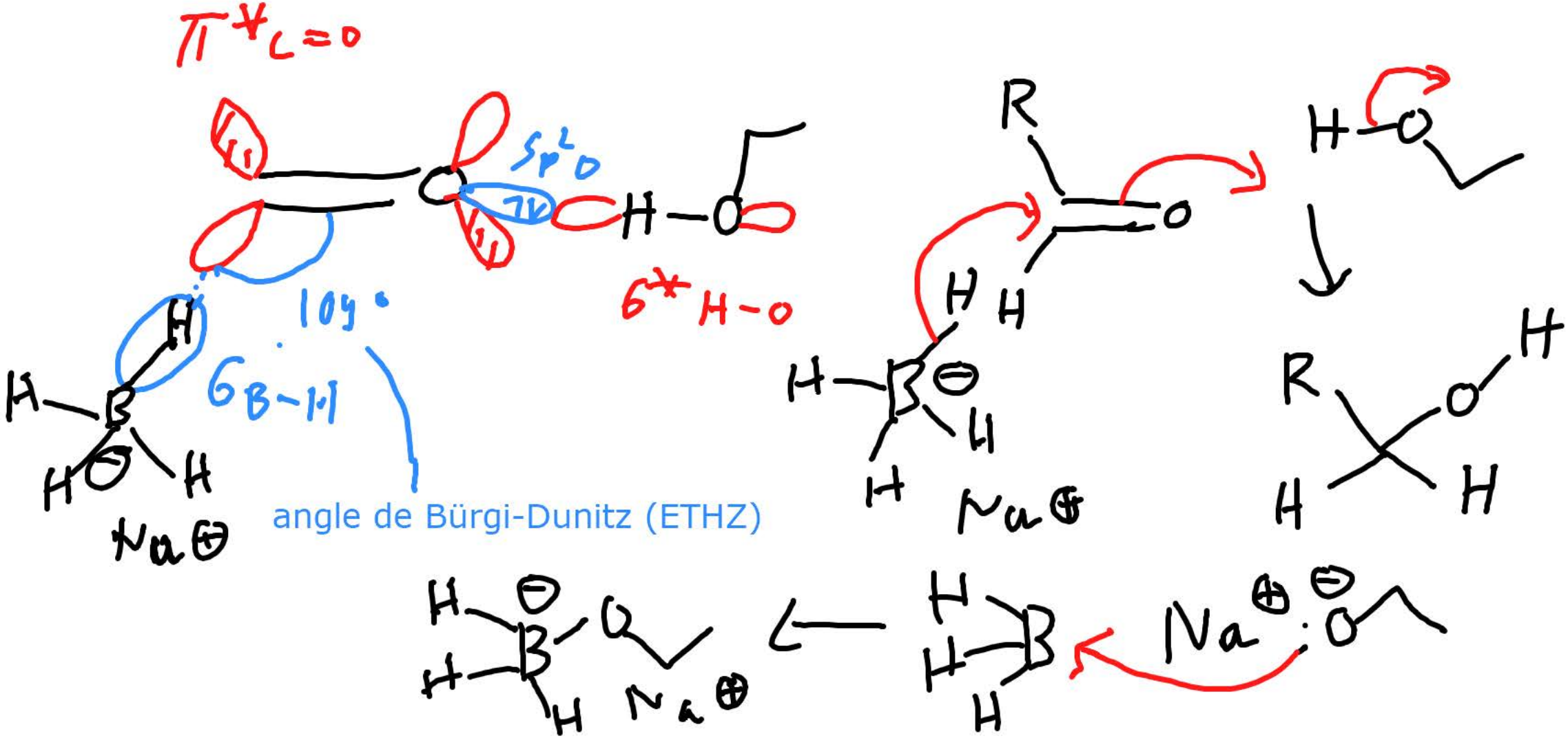
$\pi^* C=O$ LUMO

$\pi \; \pi \; sp^2 O$ HOMO

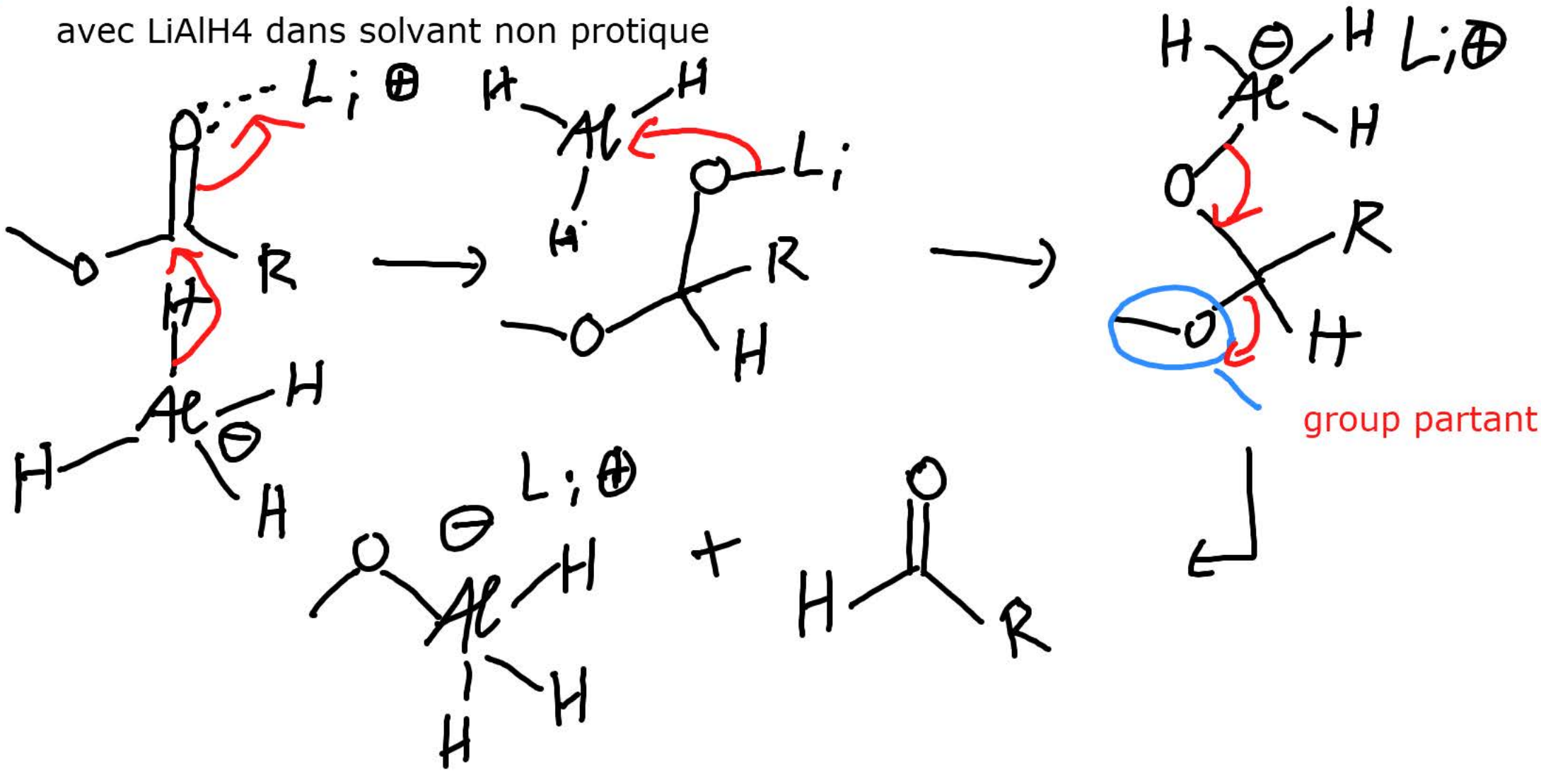
$\pi \; \pi C=O$

6_{B-H}

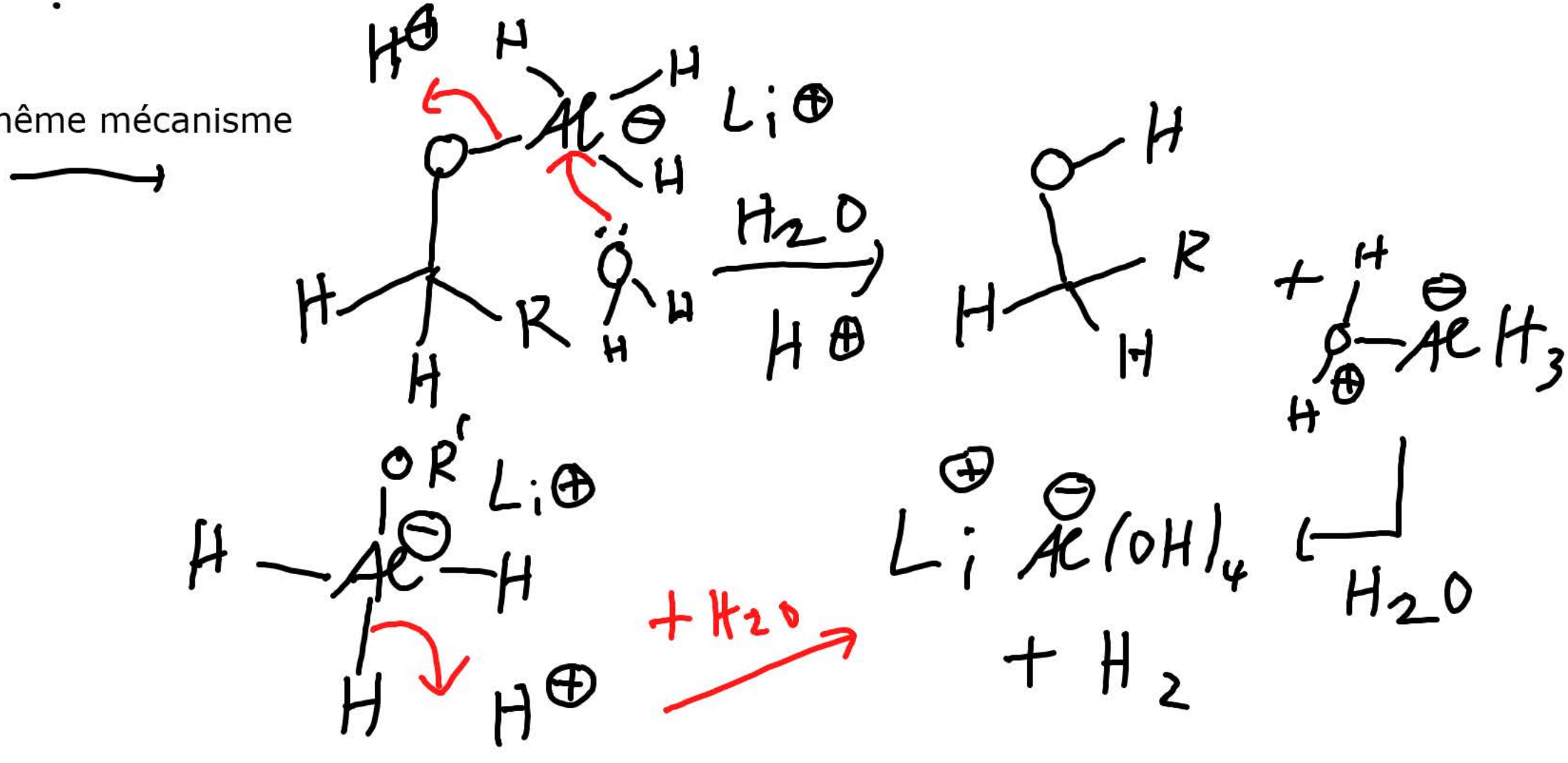
HOMO


π*C=O
sp2 O
π
104°
σB-H
σ*H-O
angle de Bürgi-Dunitz (ETHZ)

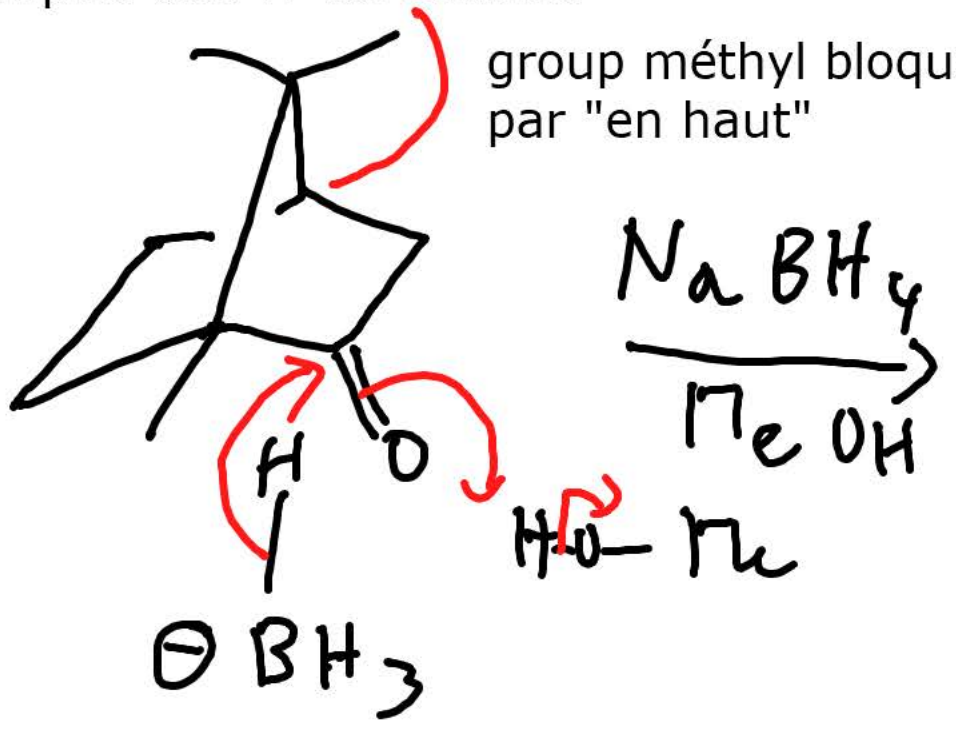
avec LiAlH4 dans solvant non protique



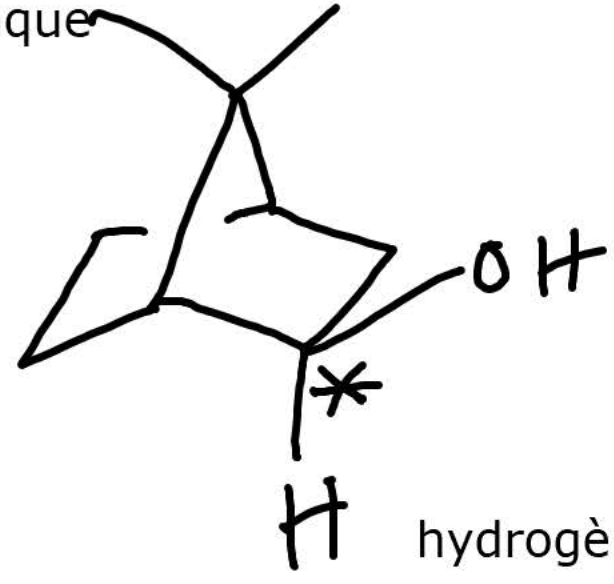
même mécanisme



exemples des TP de chimies



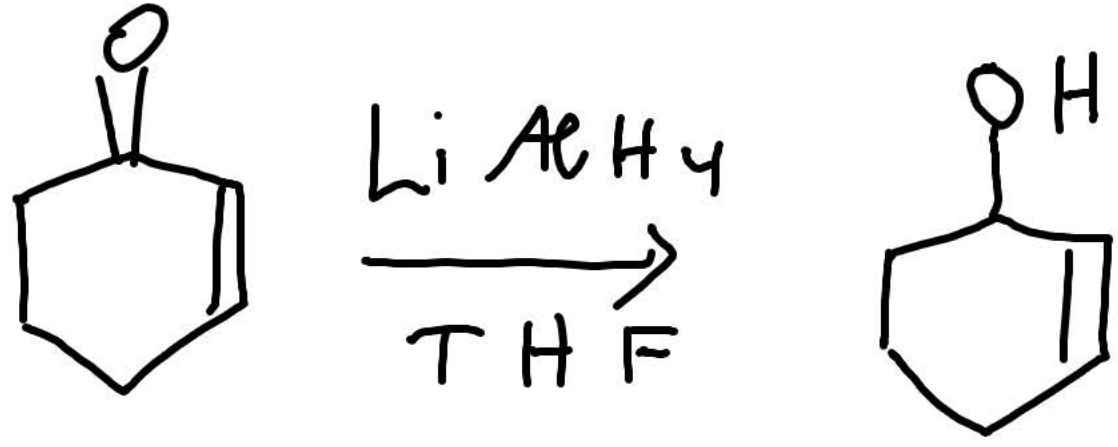
group méthyl bloque l'attaque par "en haut"



hydrogène "en bas"

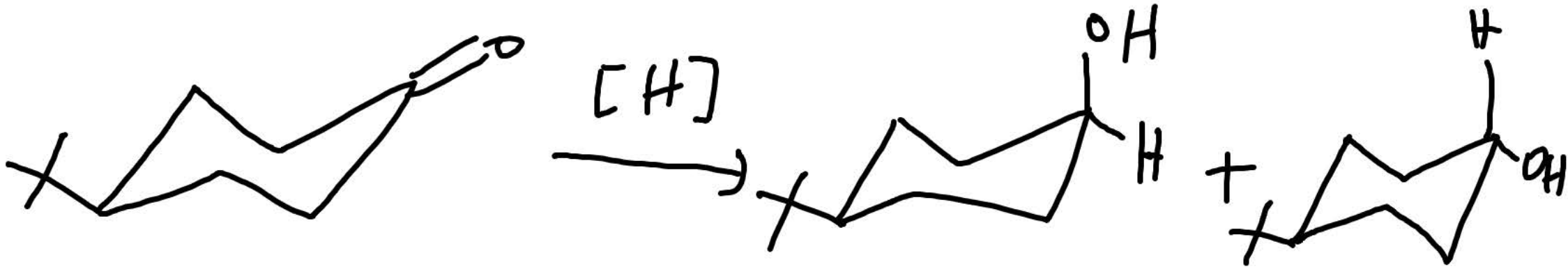
camphre, 3 g

iso-borneol

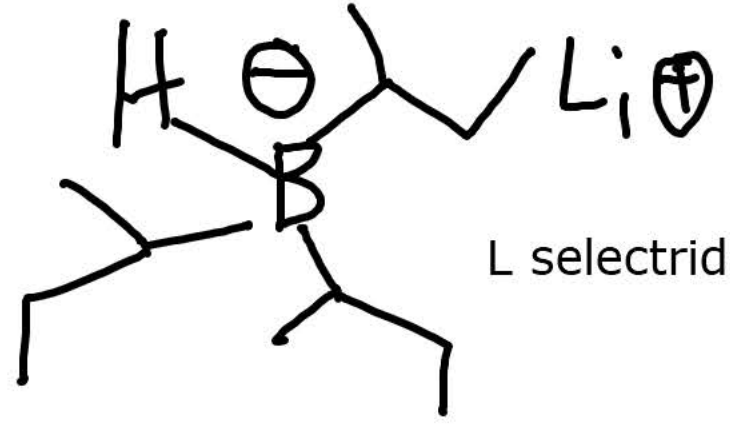


cyclohexenone

15 g

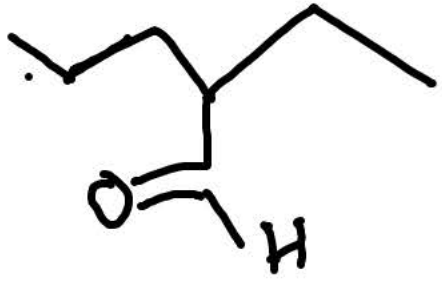


[H] = LiBH4: 9: 91
L-selectride: 86:14



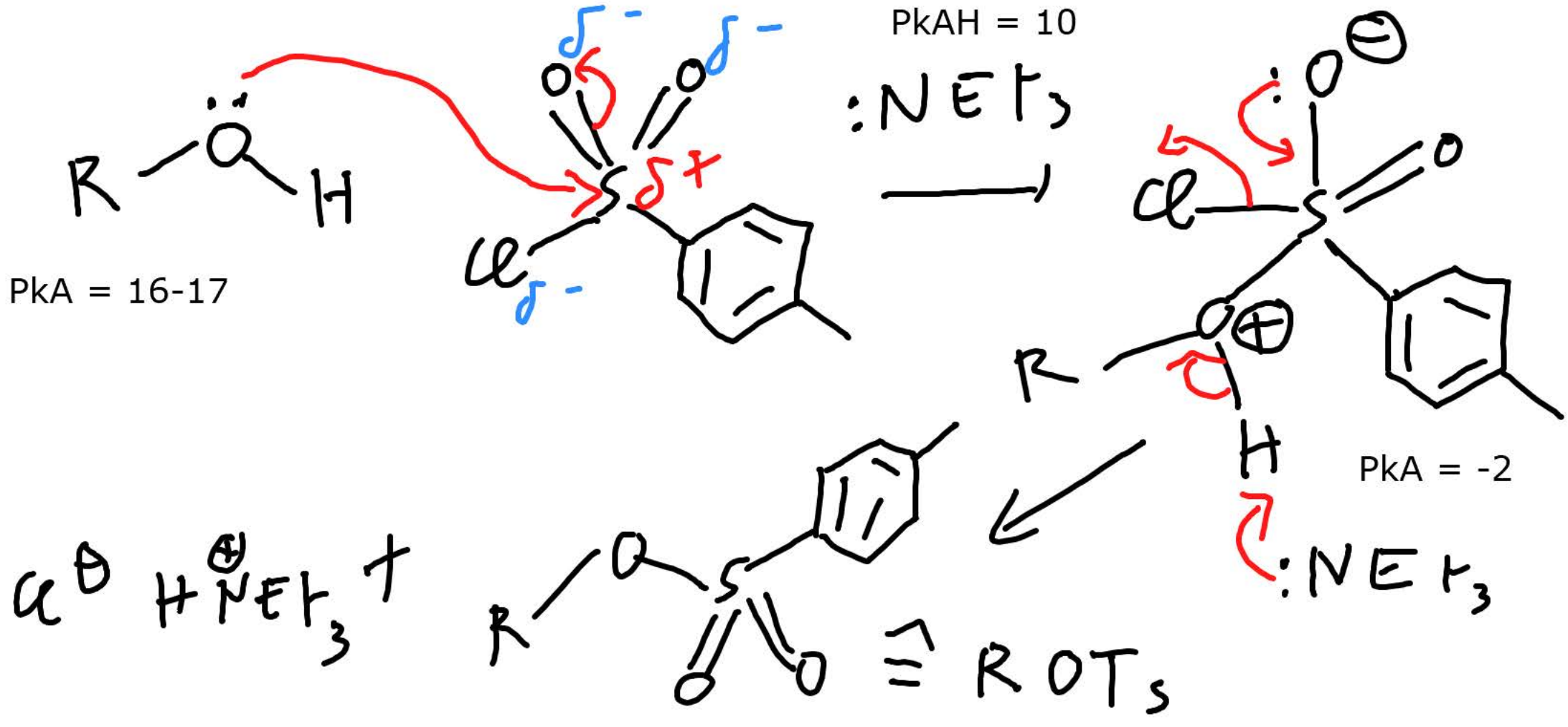
L selectride

précision de nomenclature: aldéhyde
préfixe: oxo

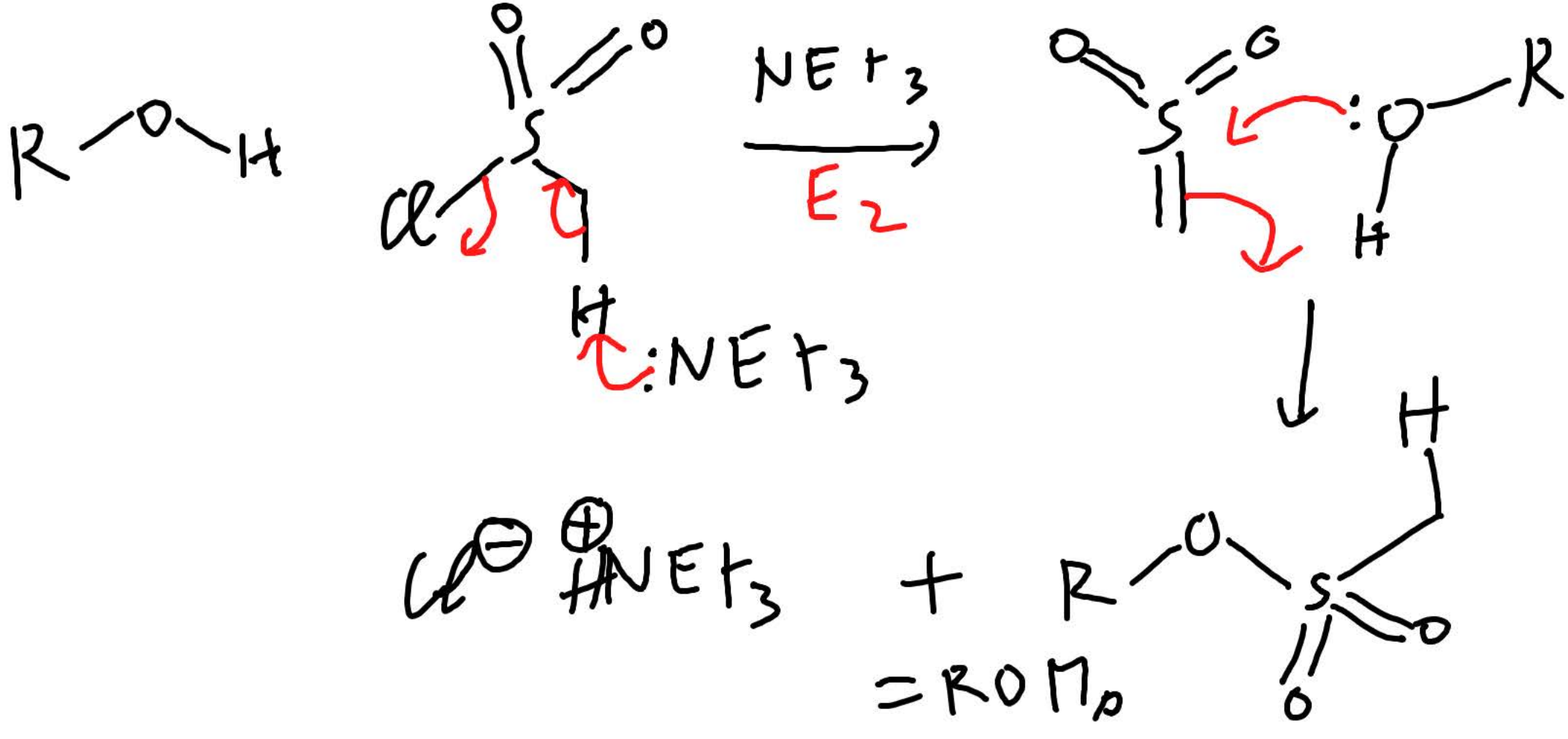


chaine secondaire:
systématique: oxométhyl
non trivial plus fréquemment
utilisé: formyl

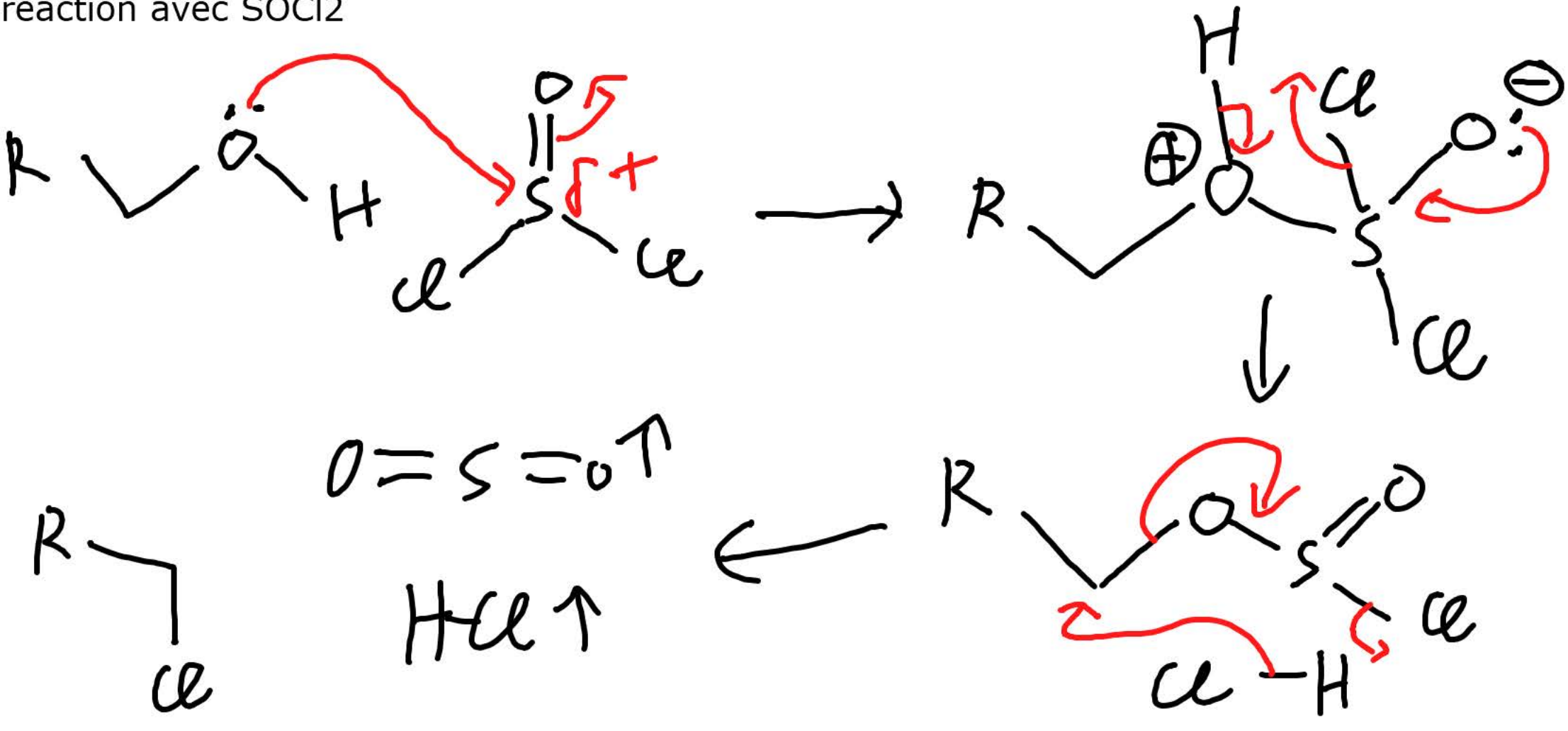
Activation des alcools avec les composés du soufre



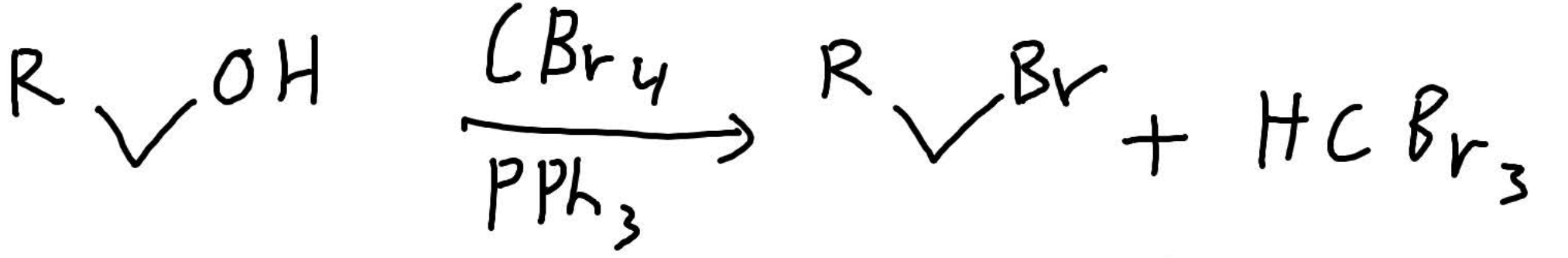
Avec Mscl

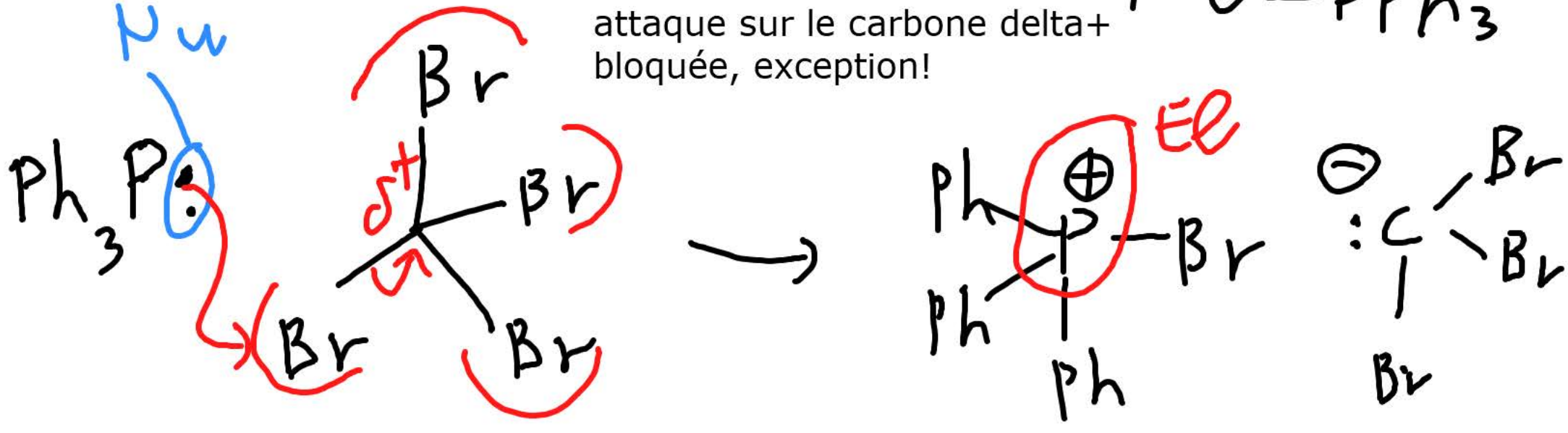


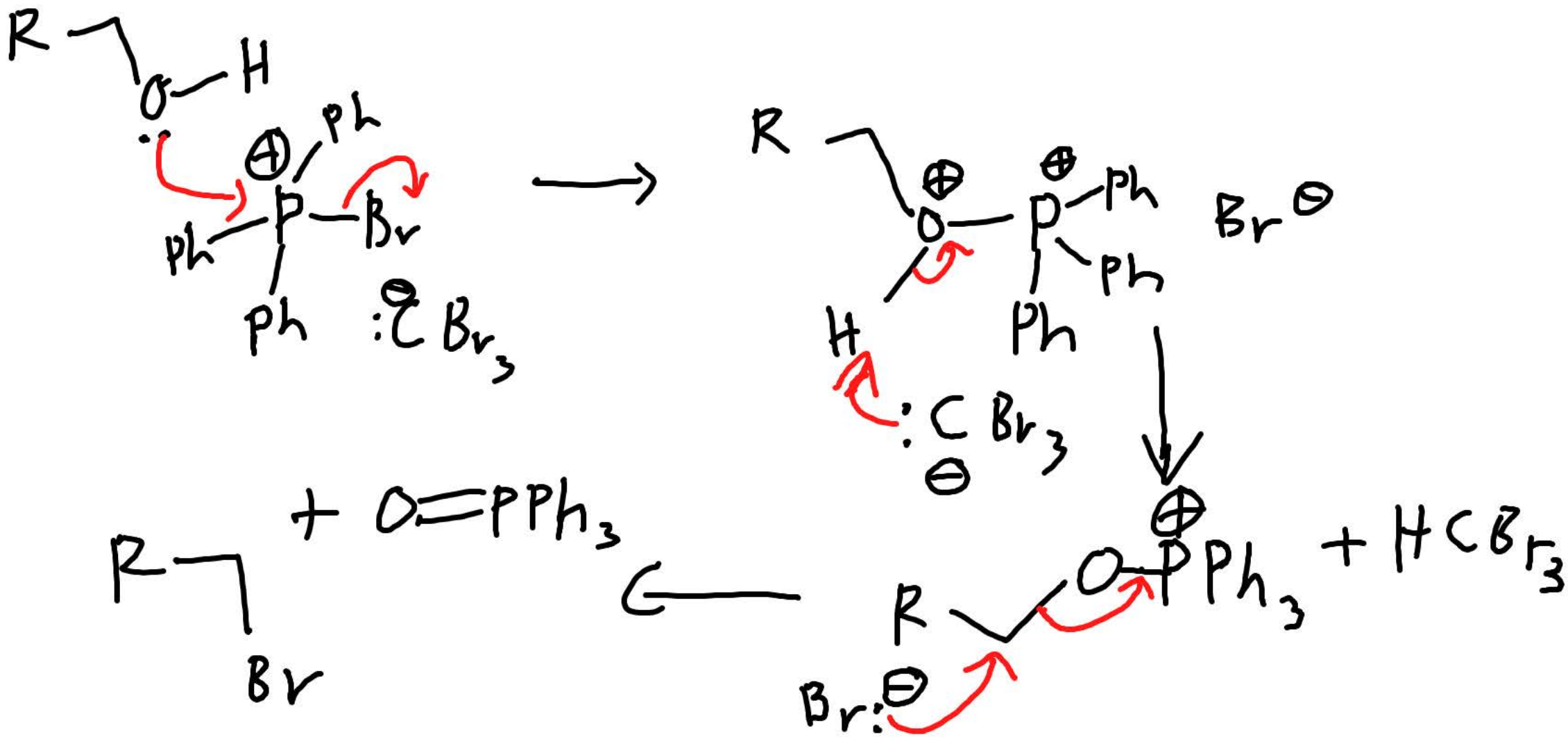
réaction avec SOCl2



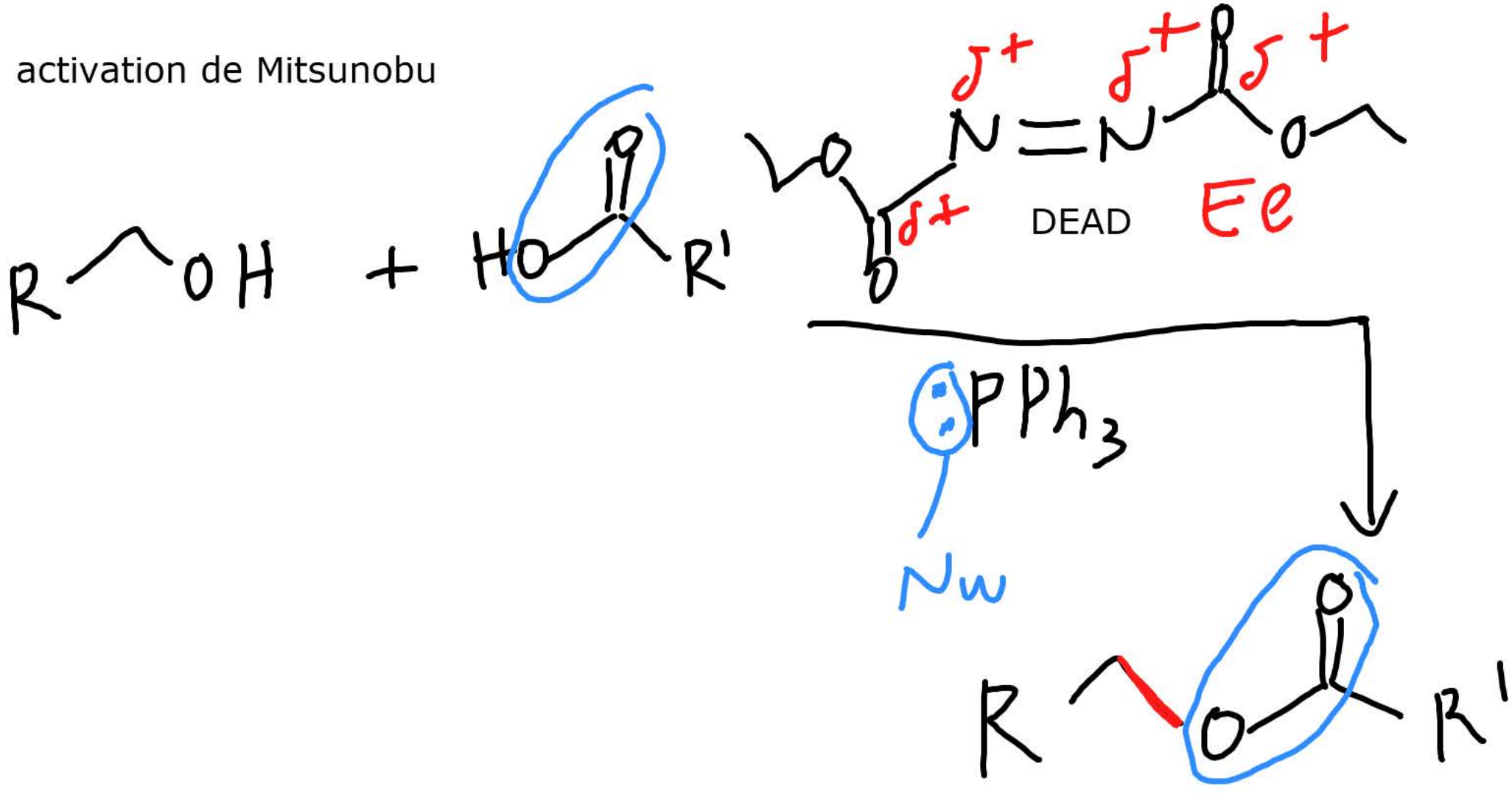
réaction d'Appel

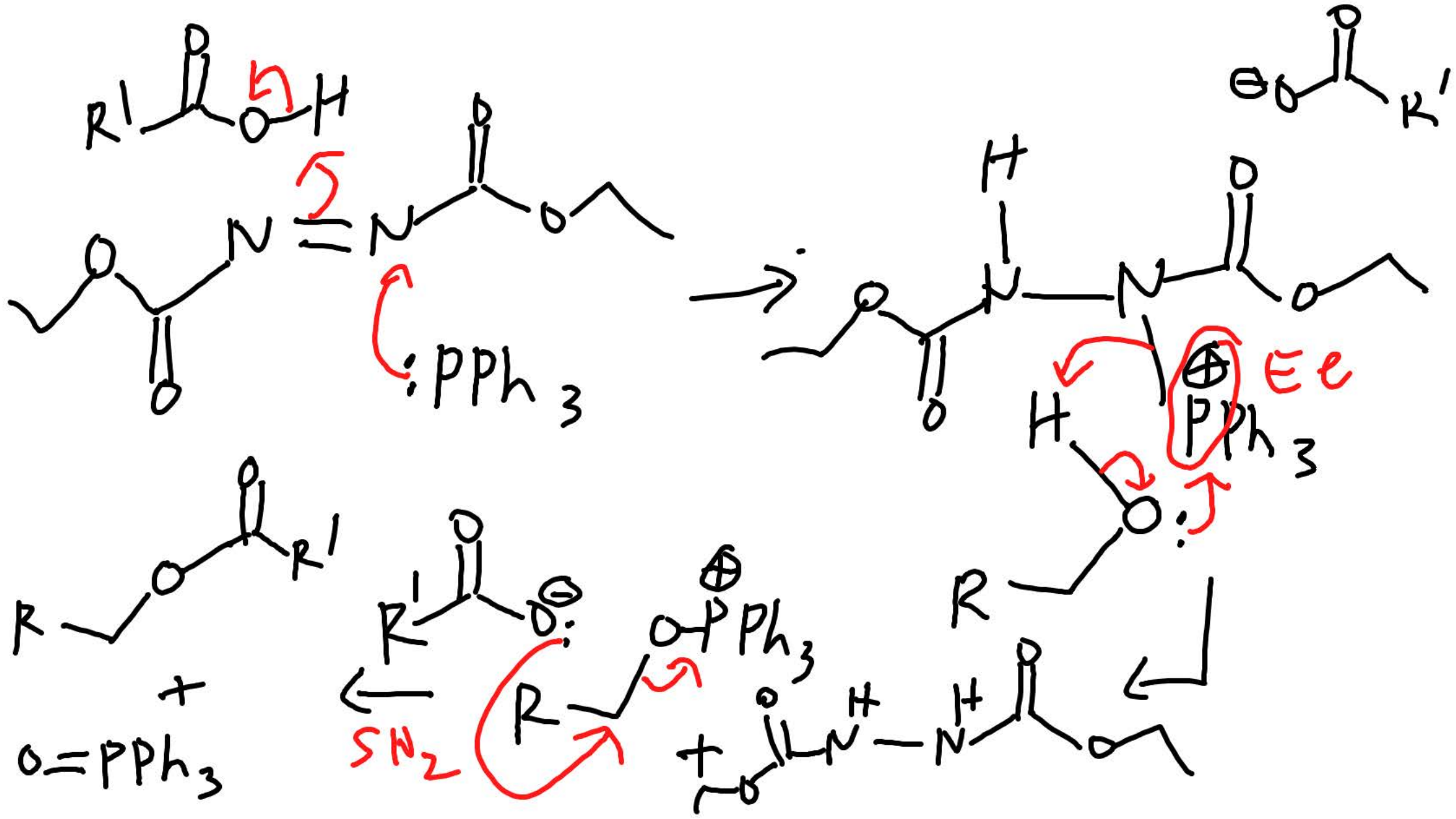




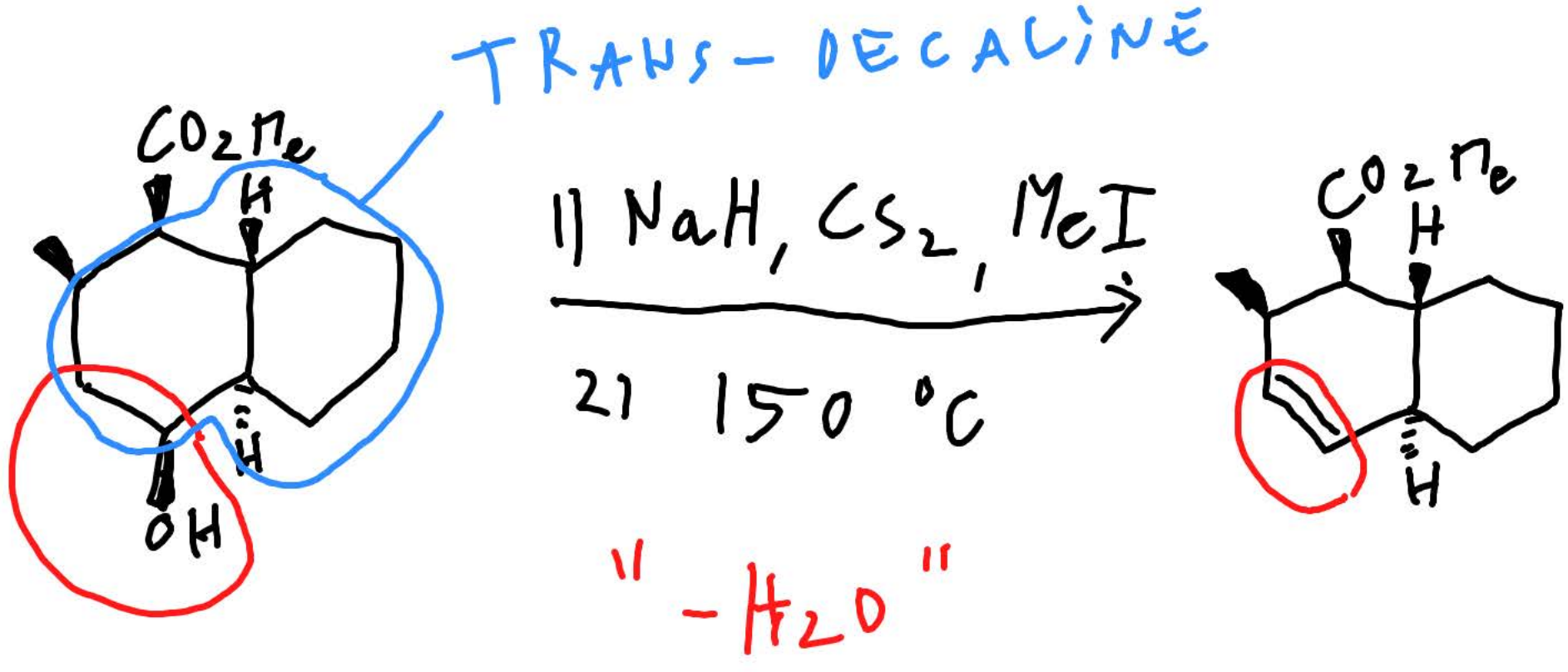

R
O
H
Ph
P
Ph
Ph
Br
Ph
:C Br3
R
O
P
Ph
Ph
Br⊖
H
:C Br3
+ O=PPh3
R
Br
R
O
PPh3
+ HCBr3
Br:⊖

activation de Mitsunobu



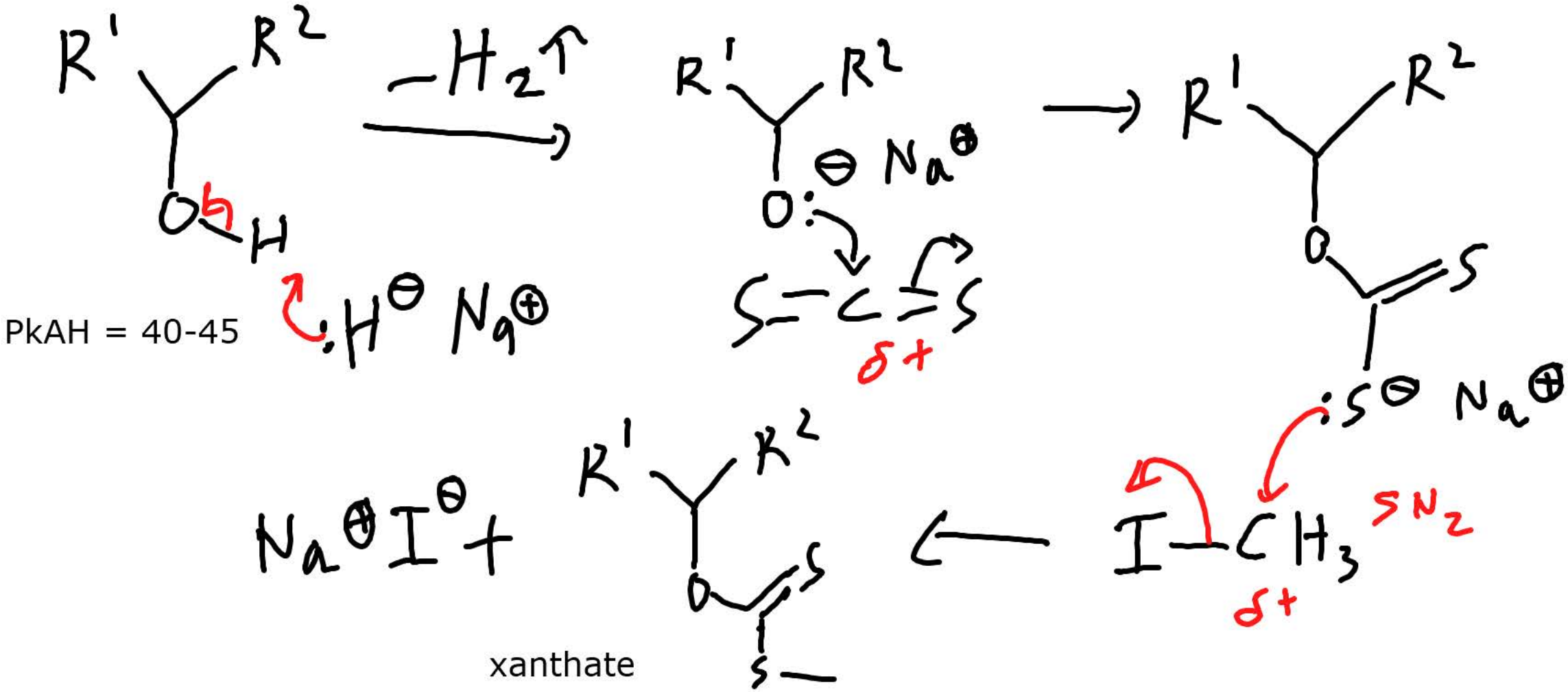

R1
H
:PPh3
K'
H
PPh3
R
R1
+
O=PPh3
SN2
PPh3
+

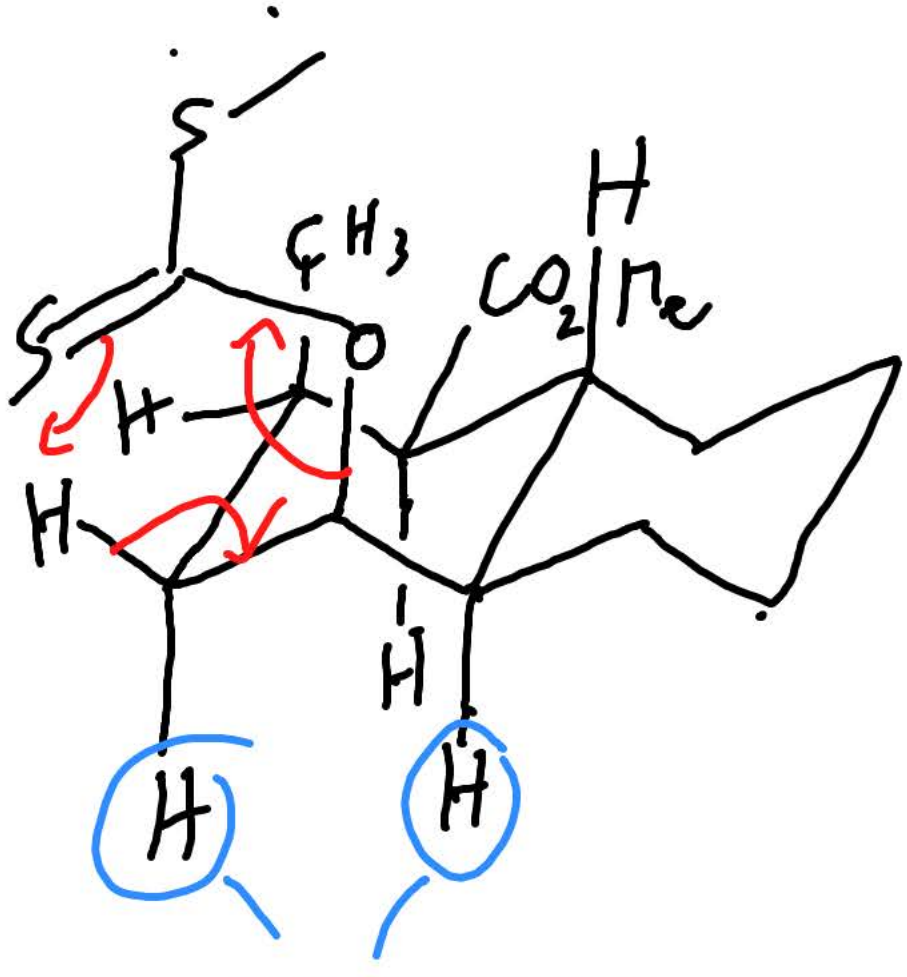
Elimination selon Chugaev, application à la synthèse de Solanapyrone E



élimination d'eau

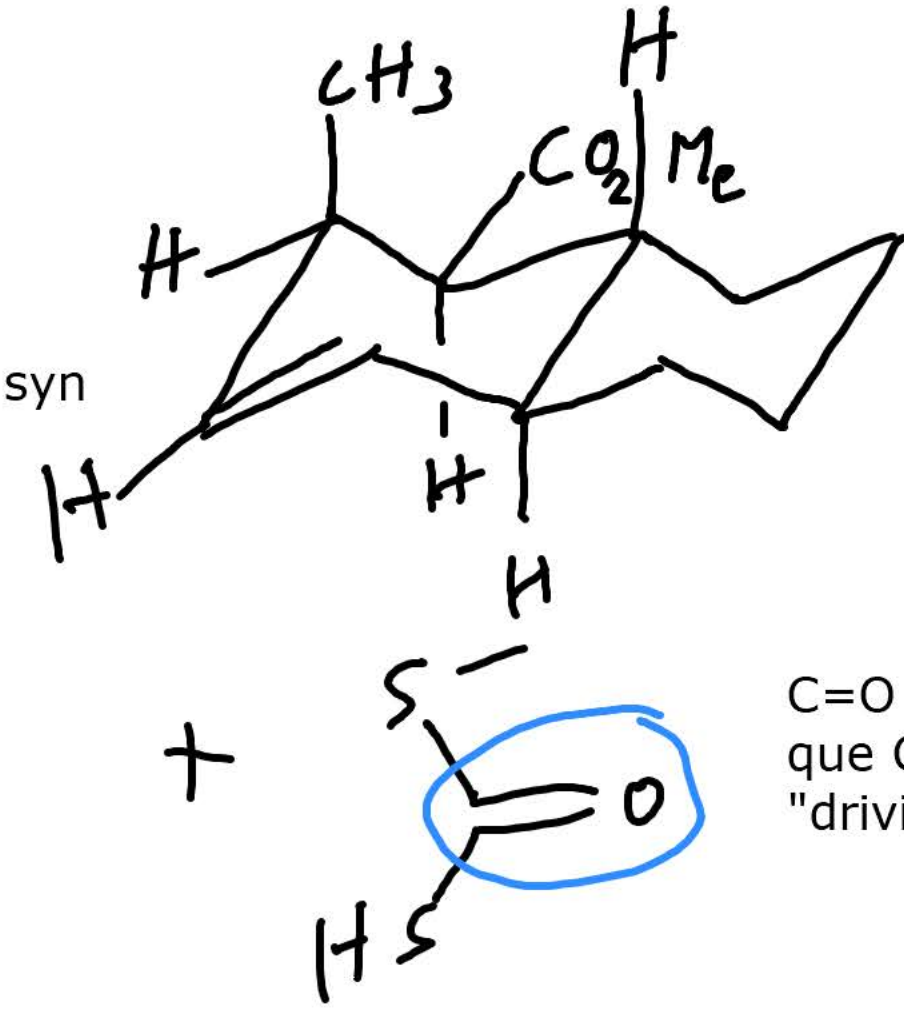
1) étape d'activation





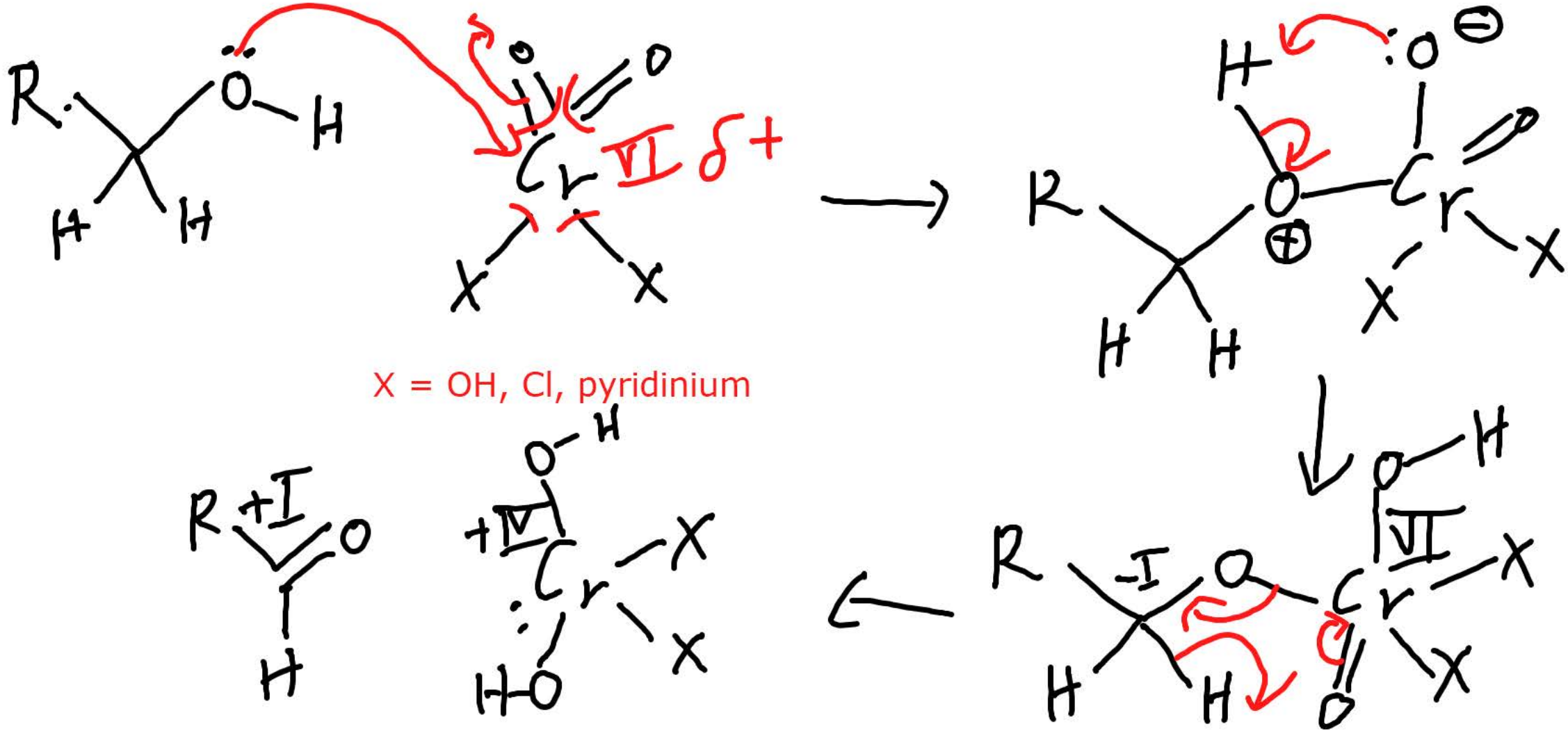
trop éloigné du S

élimination syn

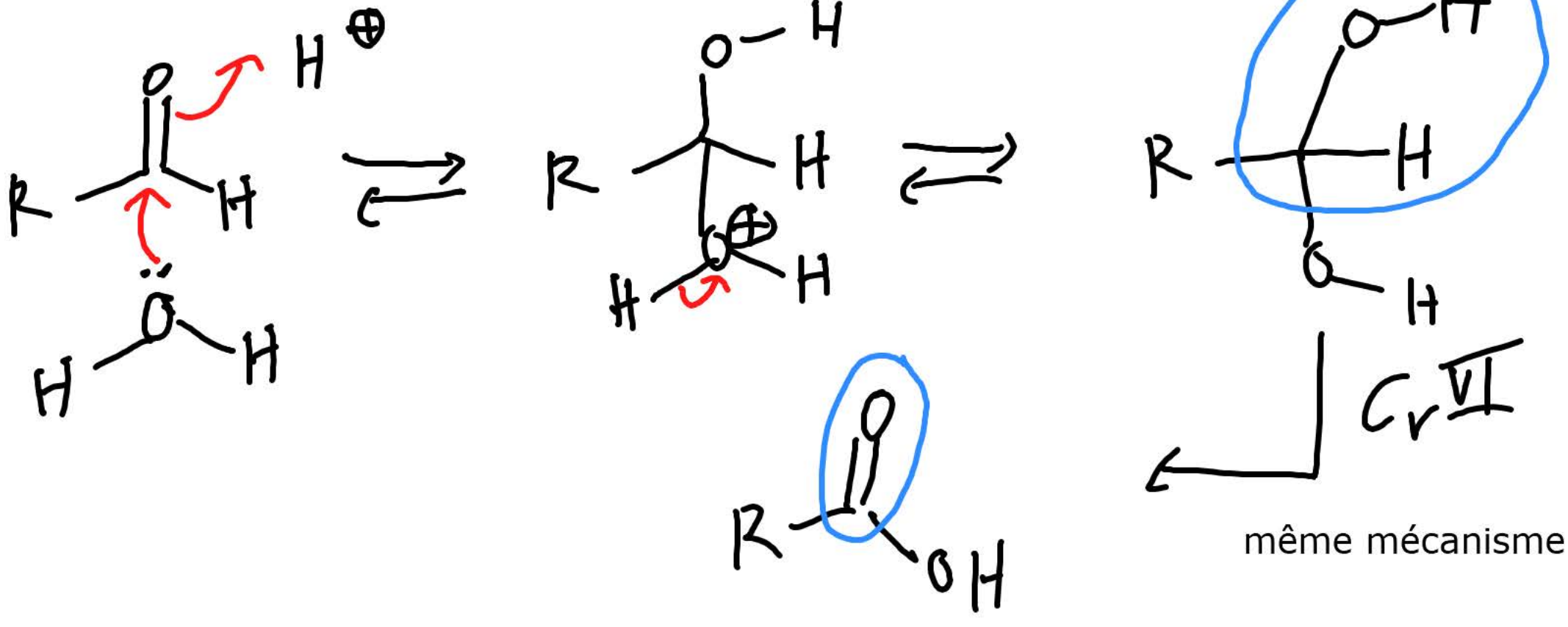


C=O plus forte que C=S "driving force"

oxidation avec Cr(VI)



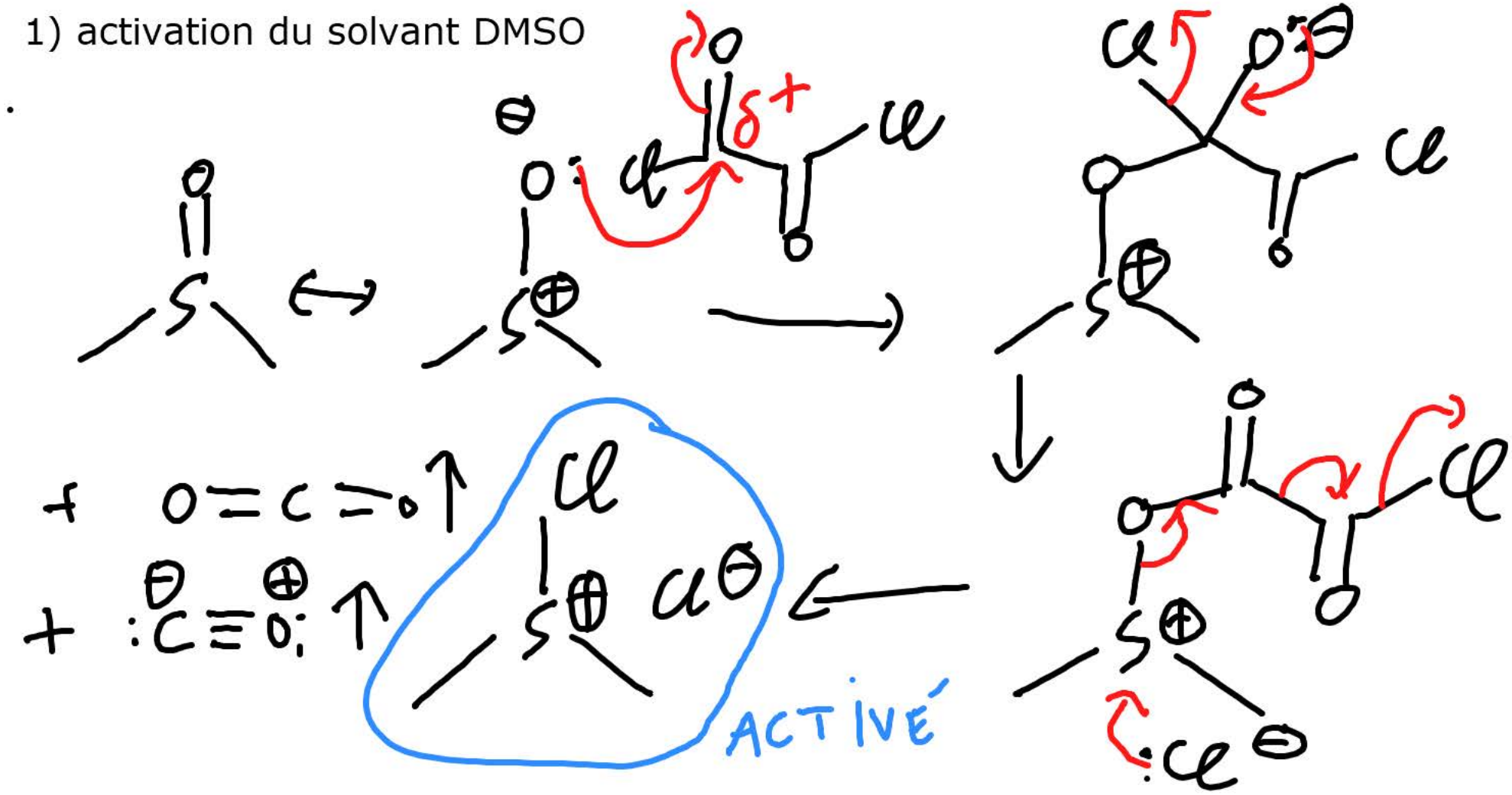
en présence d'eau et d'acide: la réaction continue



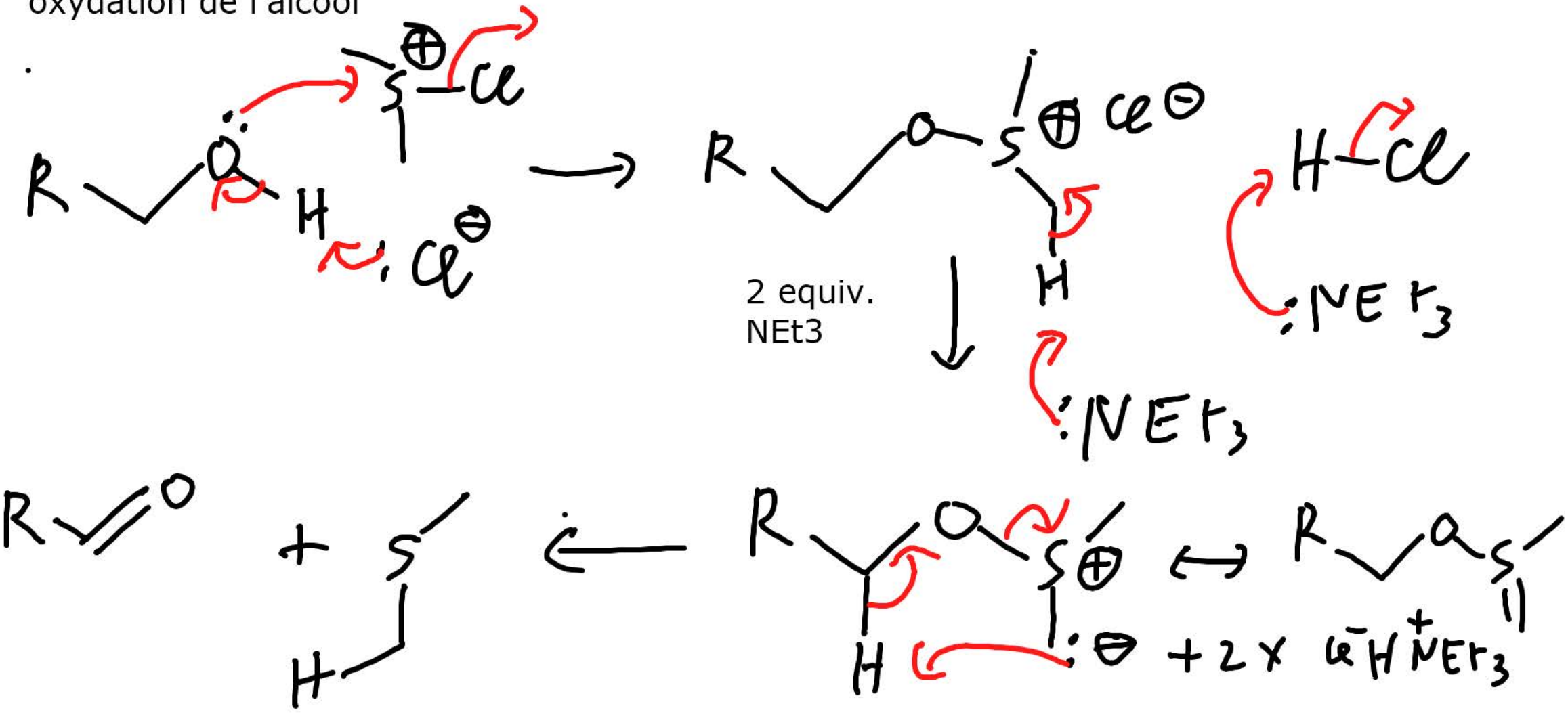
même mécanisme

réaction de Moffat-Swern

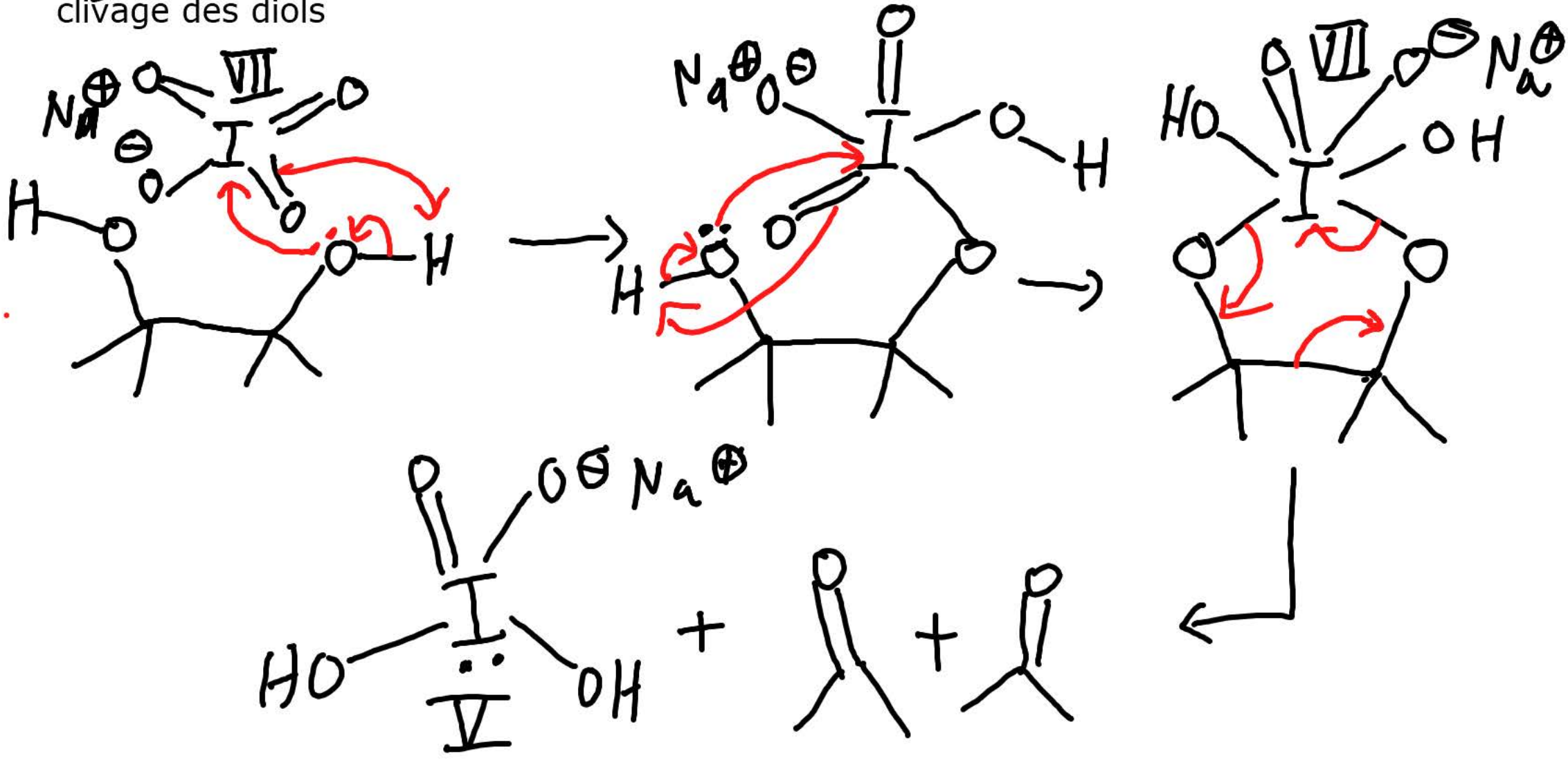
1) activation du solvant DMSO



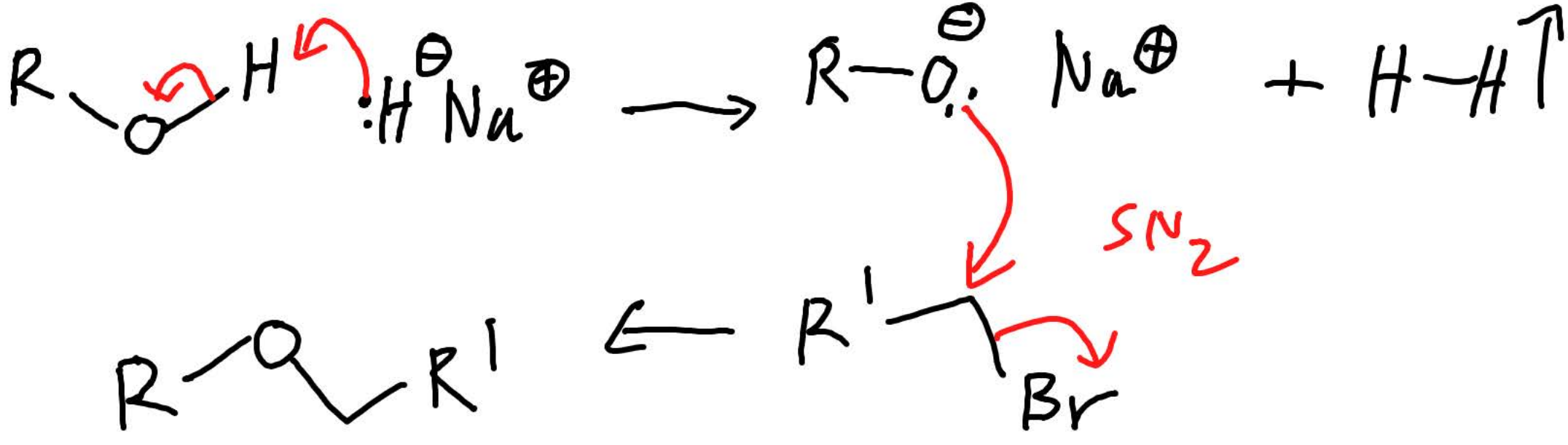
oxydation de l'alcool



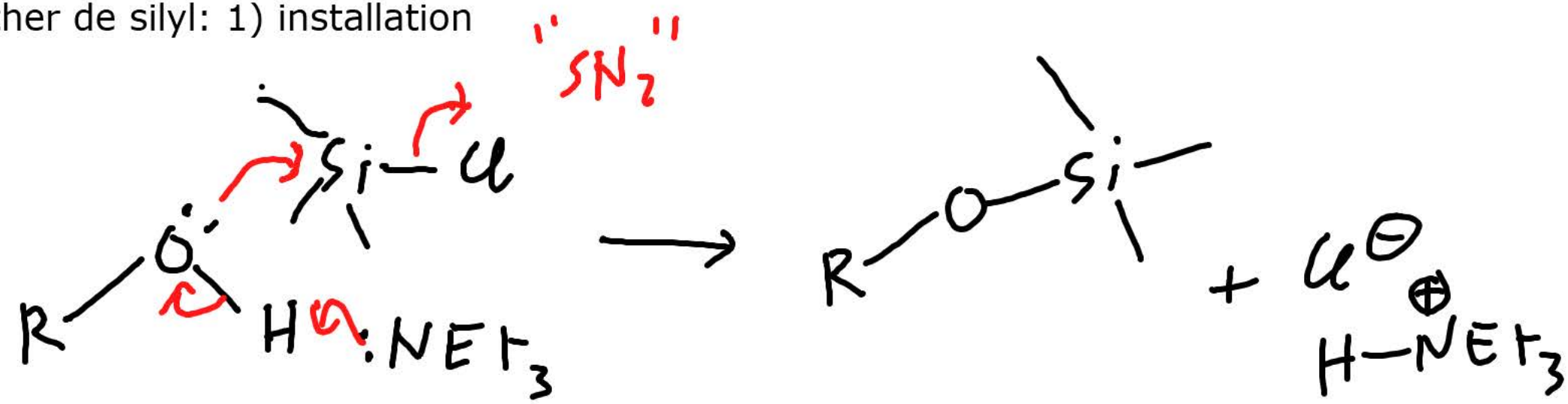
clivage des diols

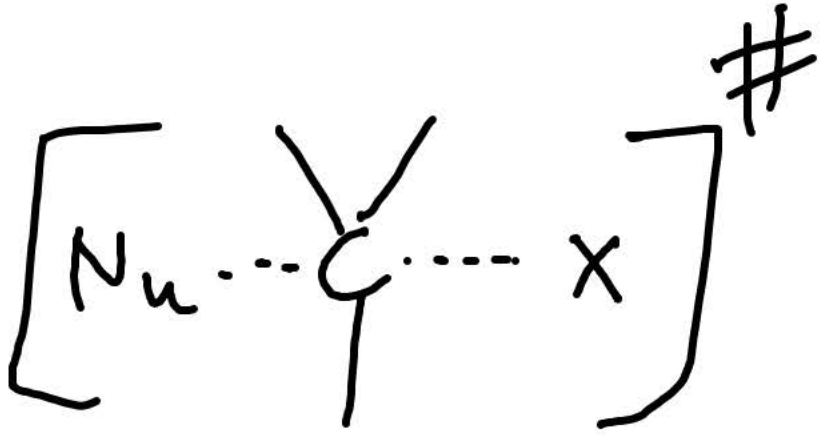


synthèse de Williamson des éthers

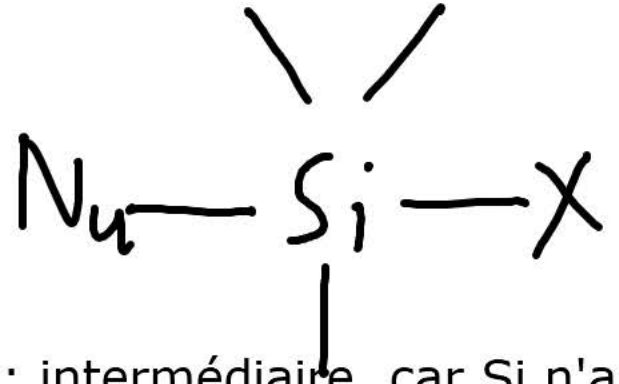


éther de silyl: 1) installation



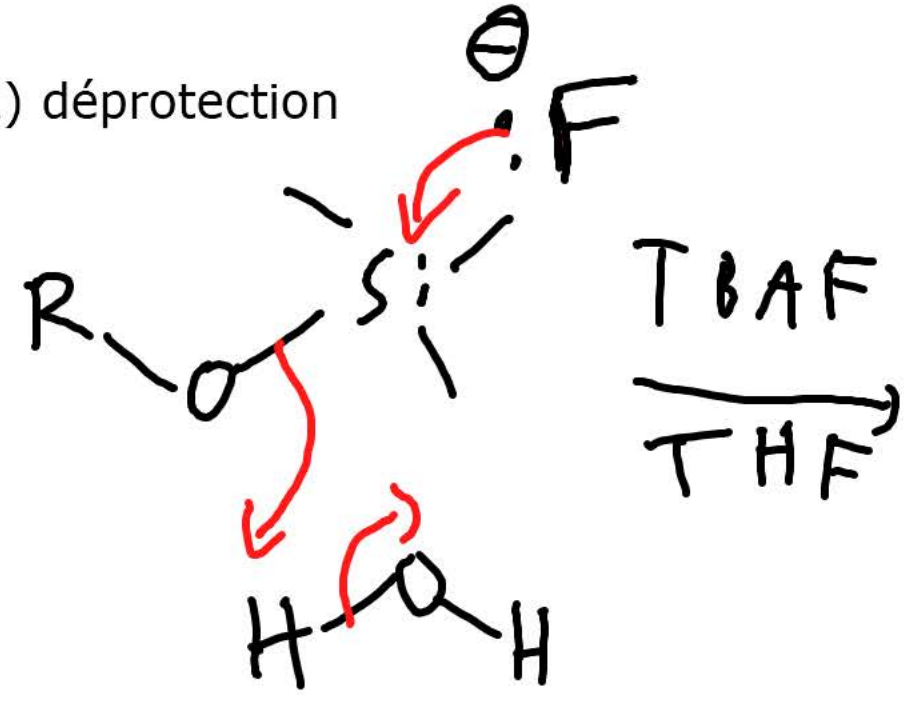


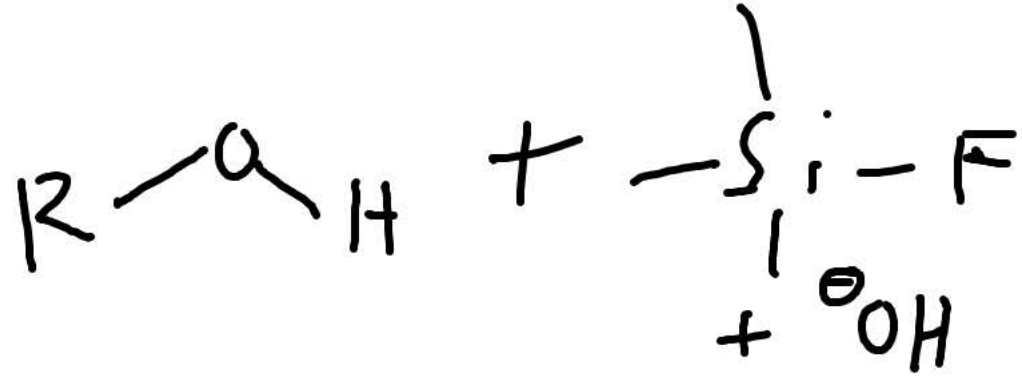
avec C: état de transition

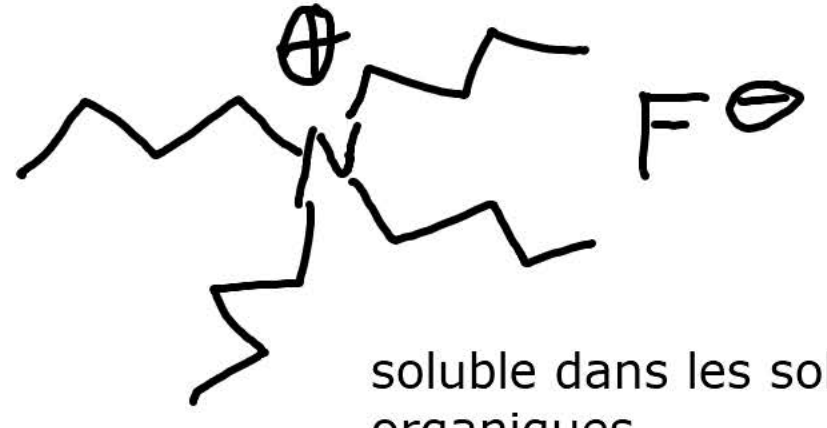


Avec Si: intermédiaire, car Si n'a pas besoint de suivre l'octet

2) déprotection

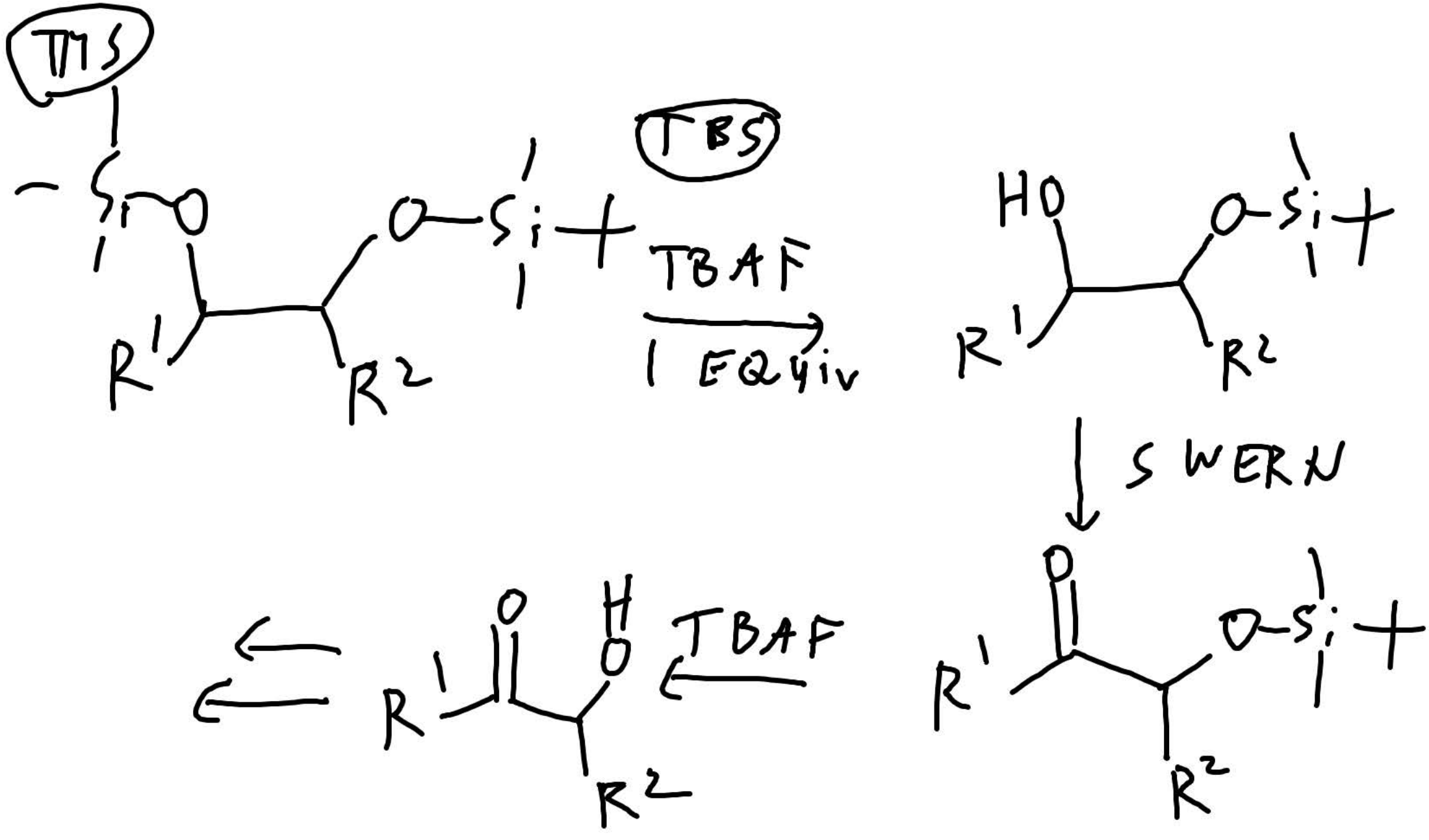




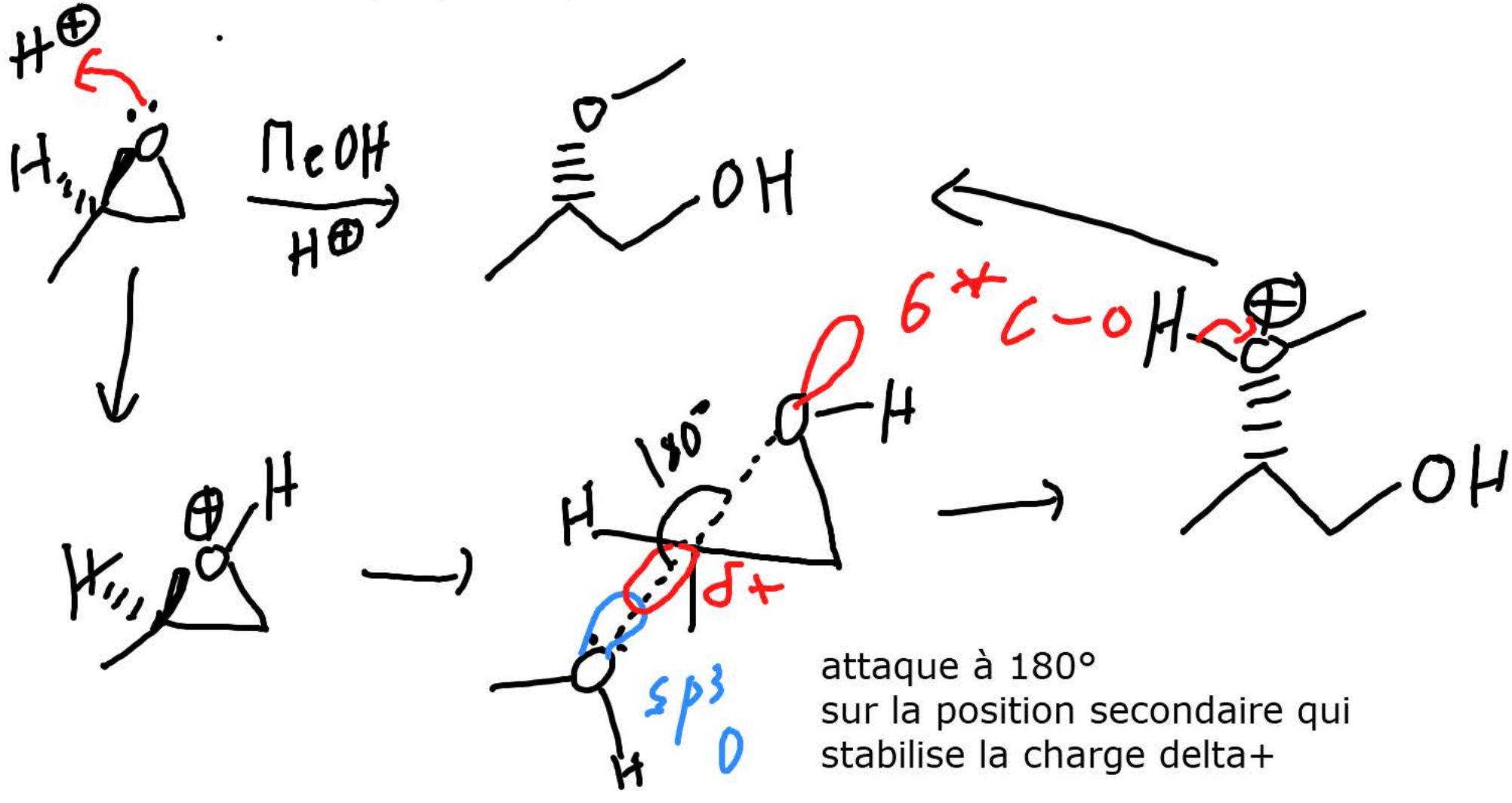


TBAF tétrabutylammonium fluoride

soluble dans les solvants organiques

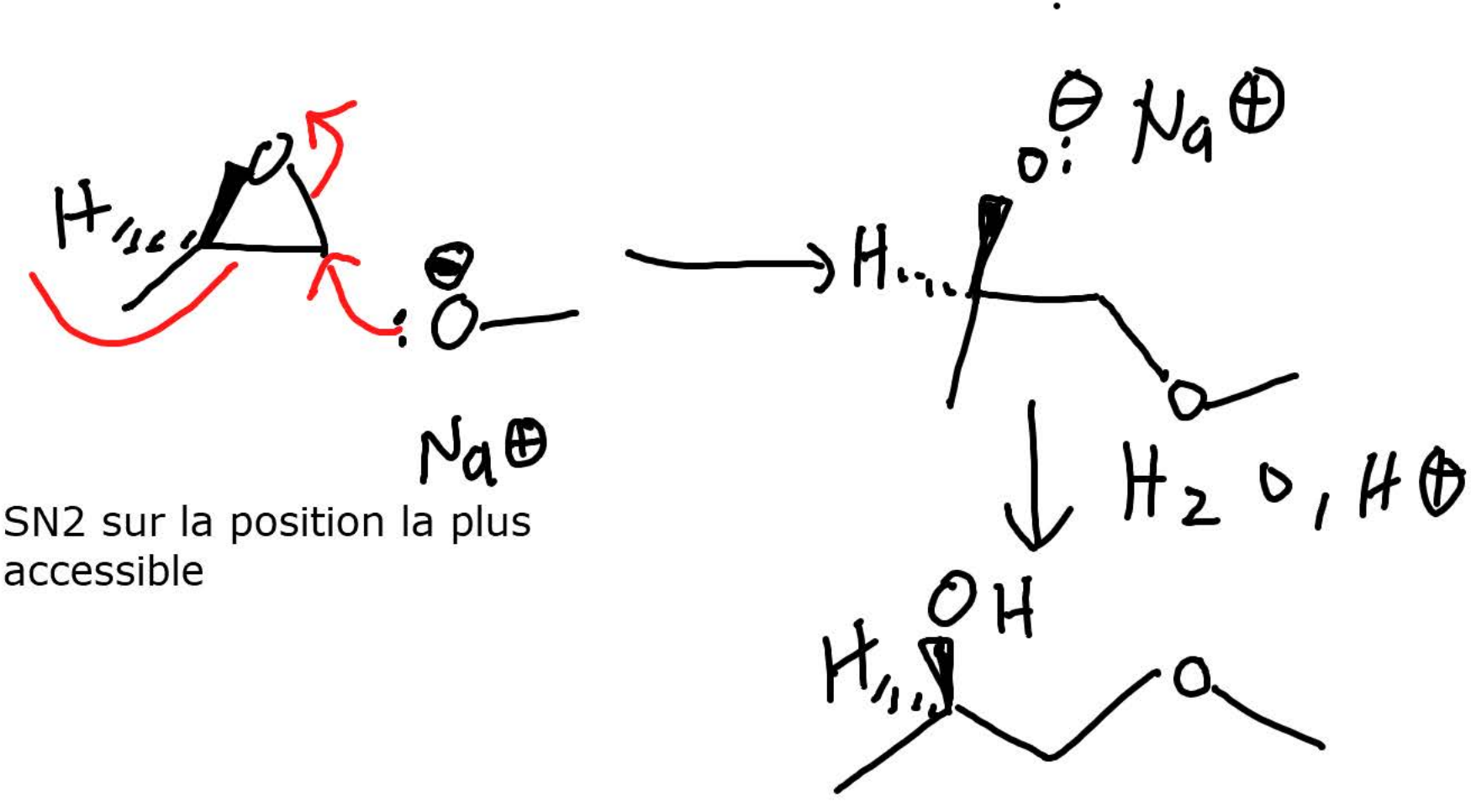

TMS
TBS
TBAF
1 EQuiv
HO
SWERN
TBAF

réactivité des éthers cycliques: 1) conditions acides



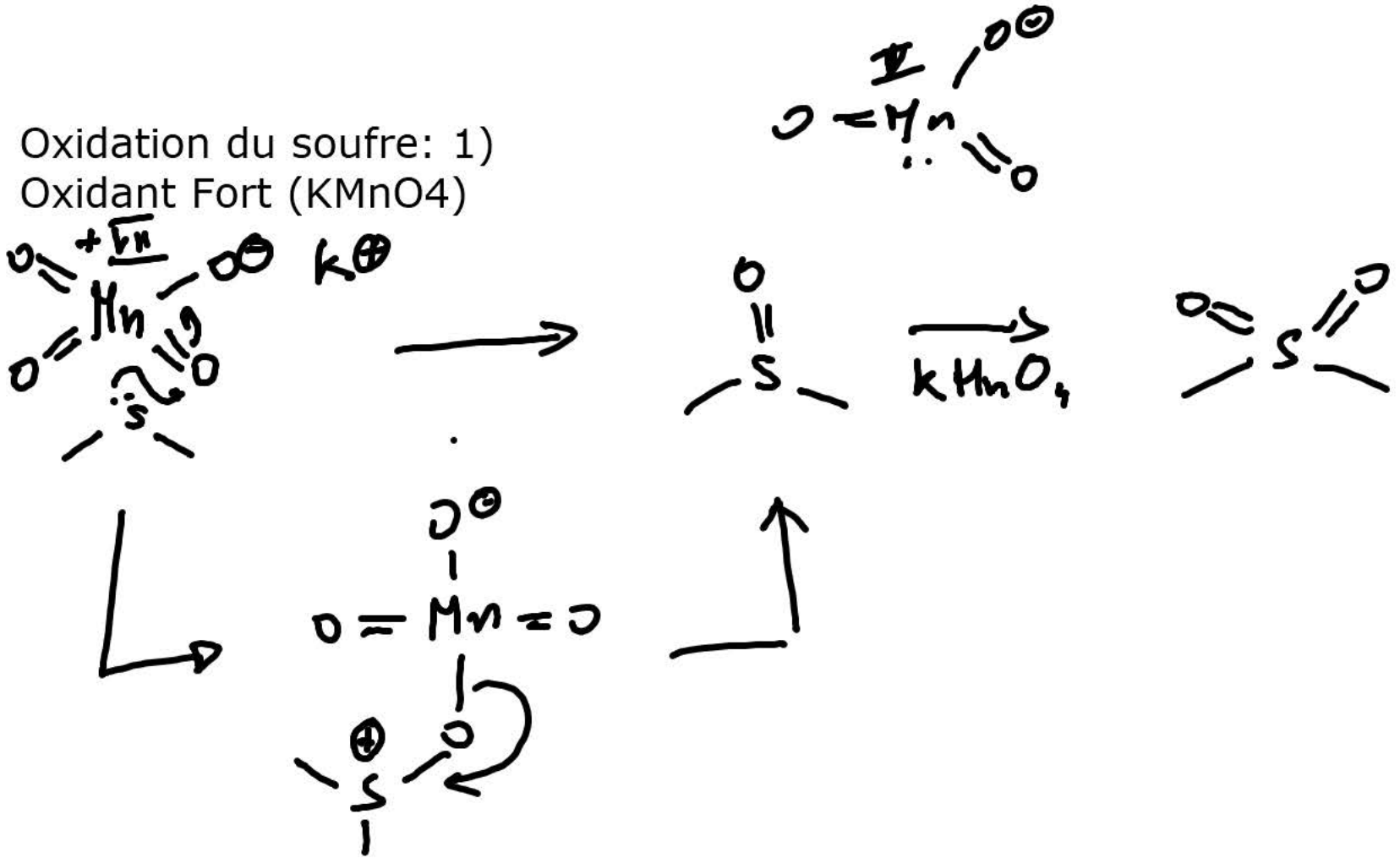
attaque à 180°
sur la position secondaire qui
stabilise la charge delta+

Conditions basiques: NaOMe

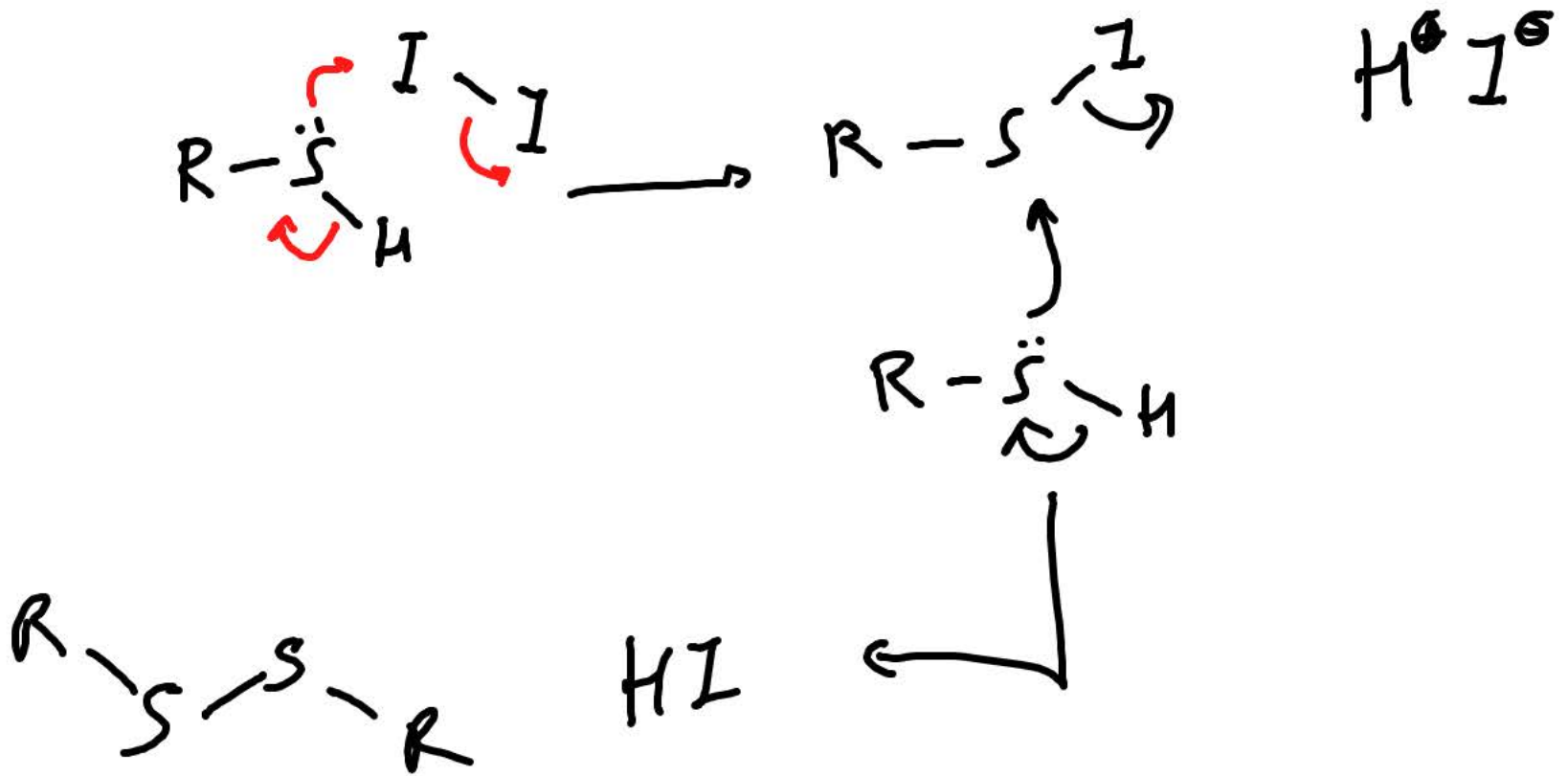


SN2 sur la position la plus accessible

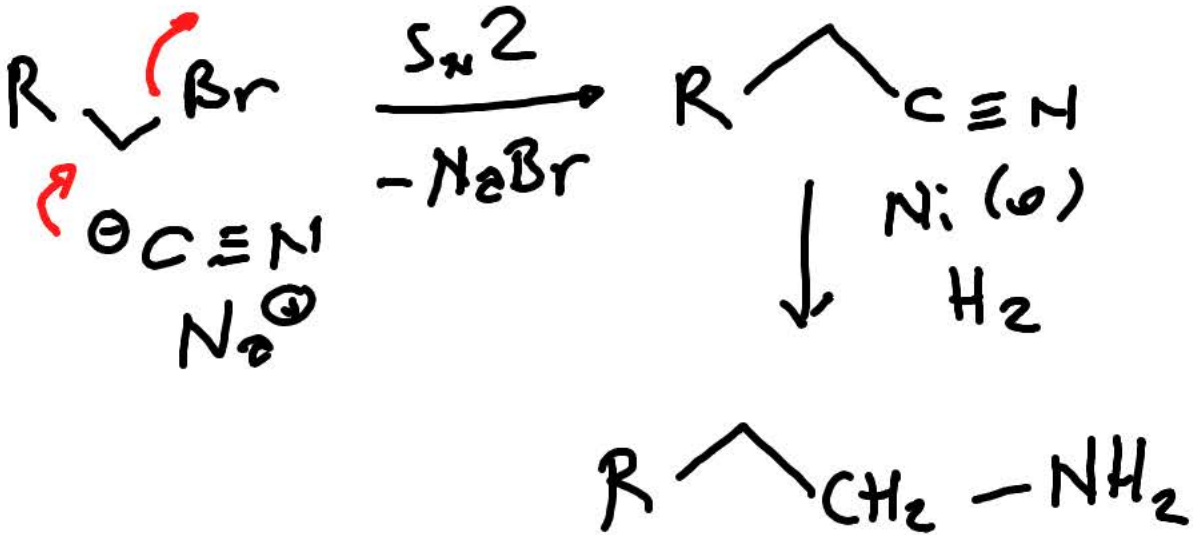
Oxidation du soufre: 1)
Oxidant Fort (KMnO4)



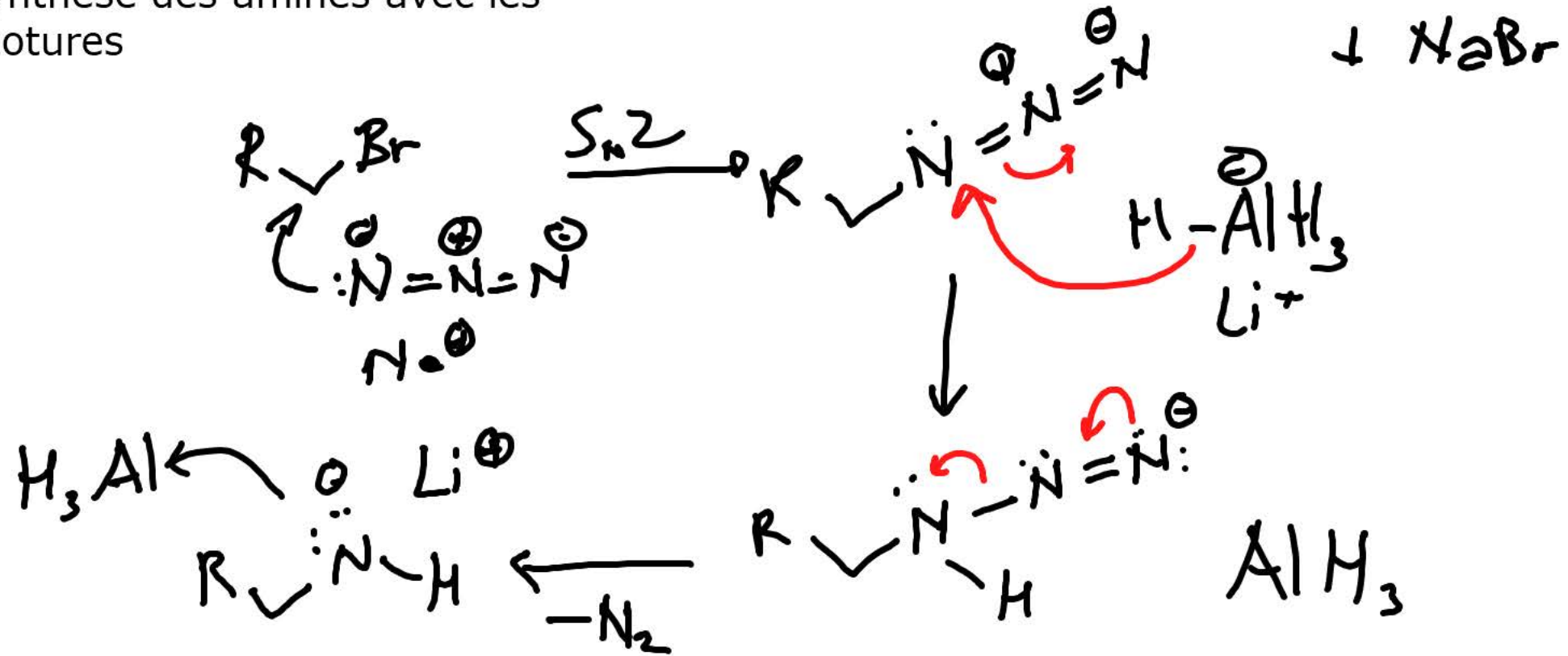
Oxydation des thiols avec l'Iode

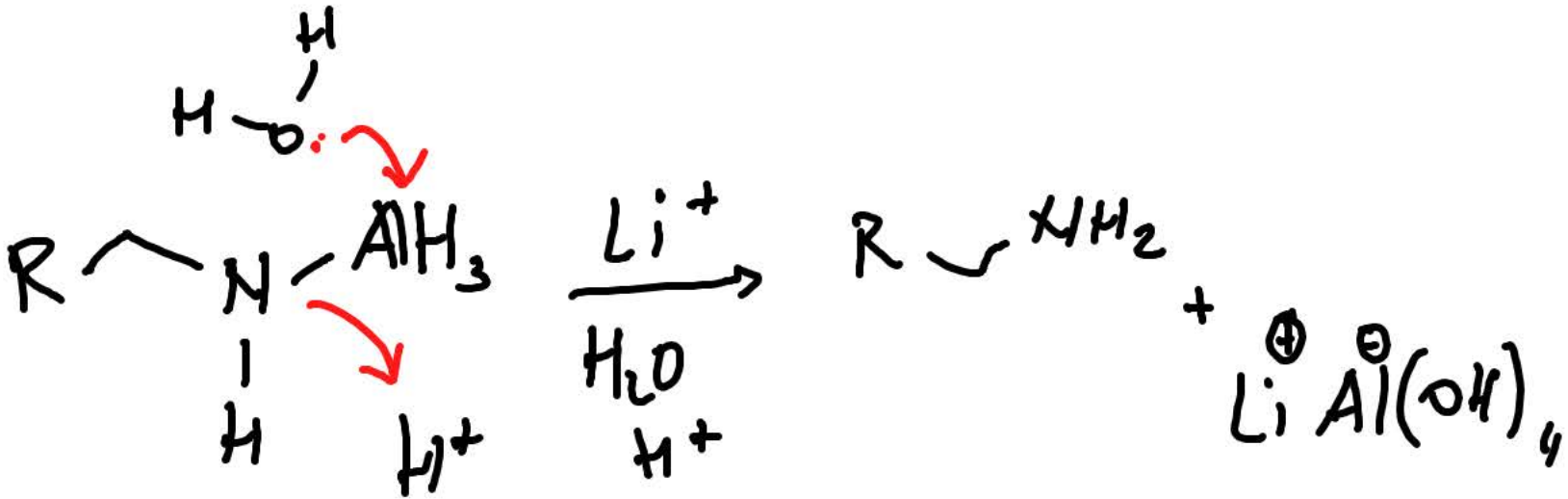


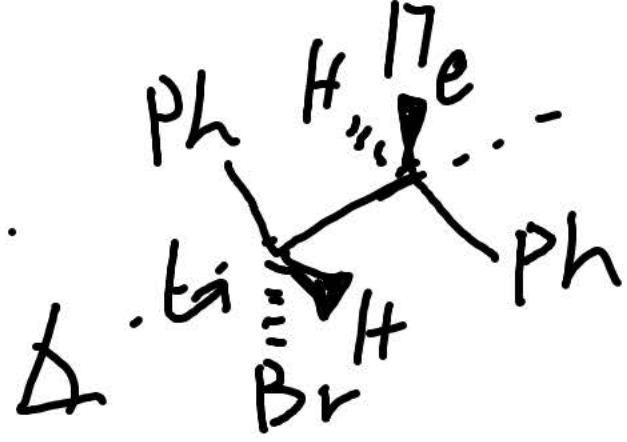
Synthèse d'amines primaire en utilisant les cyanures



Synthèse des amines avec les azotures

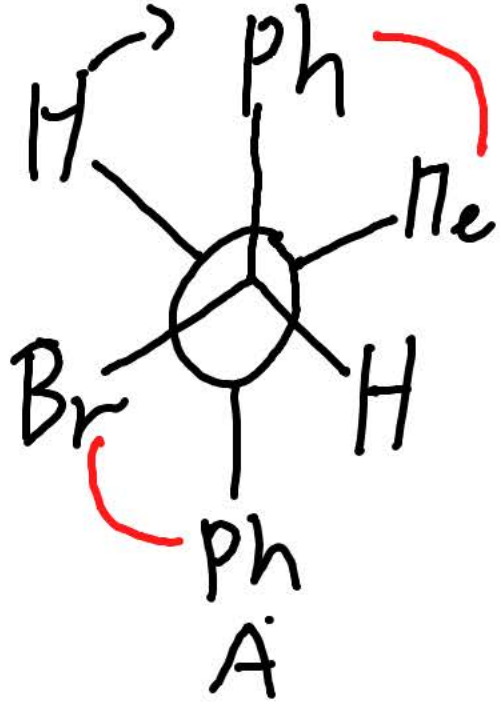



H
H
O
R
N
AlH3
H
Li+
Li+
H2O
H+
R
NH2
+
Li
Al(OH)4



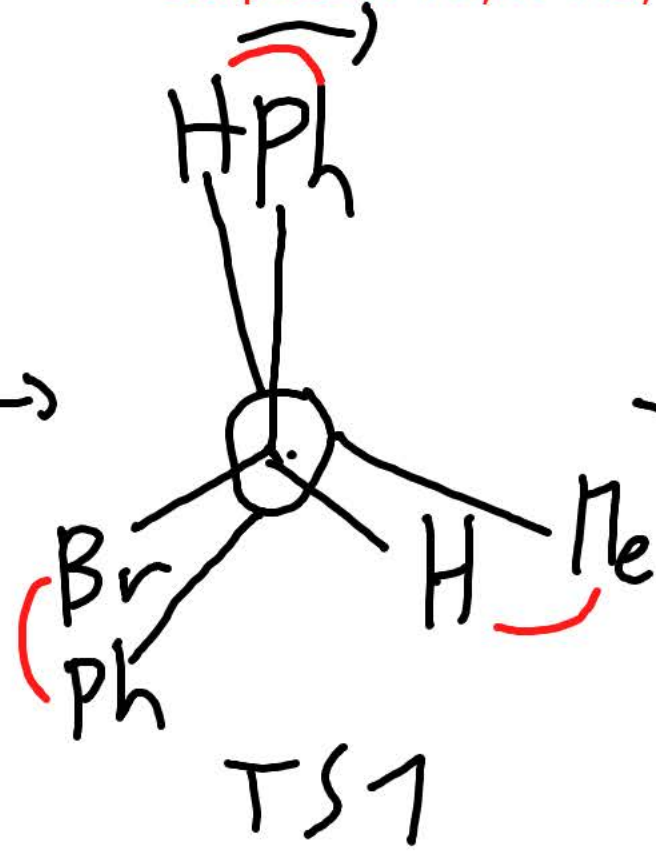
conformation: structures obtenues par rotation le long des liaisons simples pour les produits non cycliques
Analyse avec des projections de Newmann

gauche Me-Ph, Ph-Br



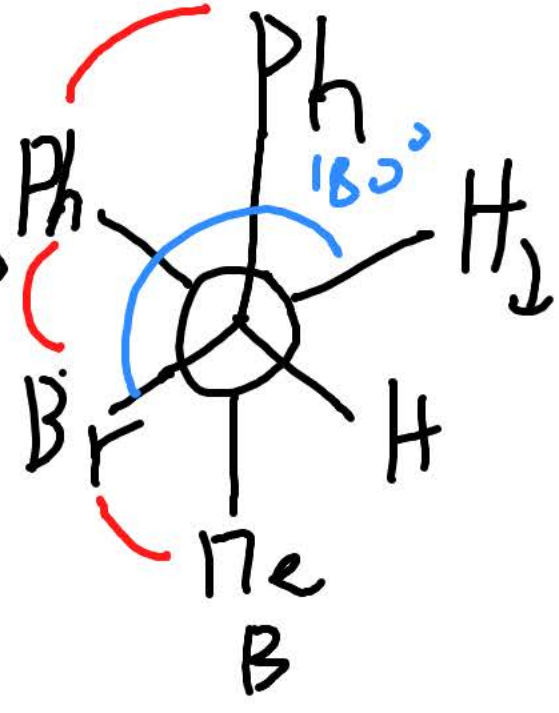
A

éclipsé: H-Ph, H-Me, Br-Ph



TS1

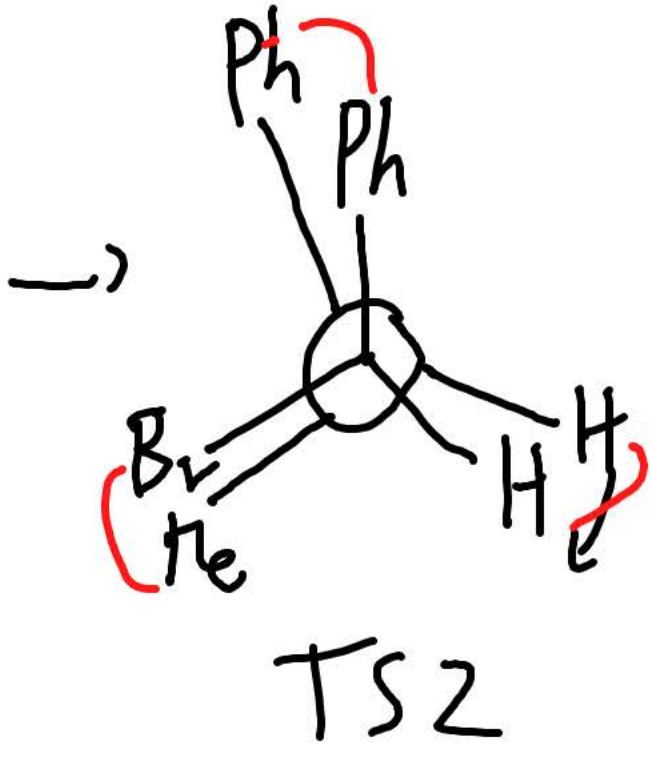
gauche: Ph-Ph, Ph-Br, Br-Me



B

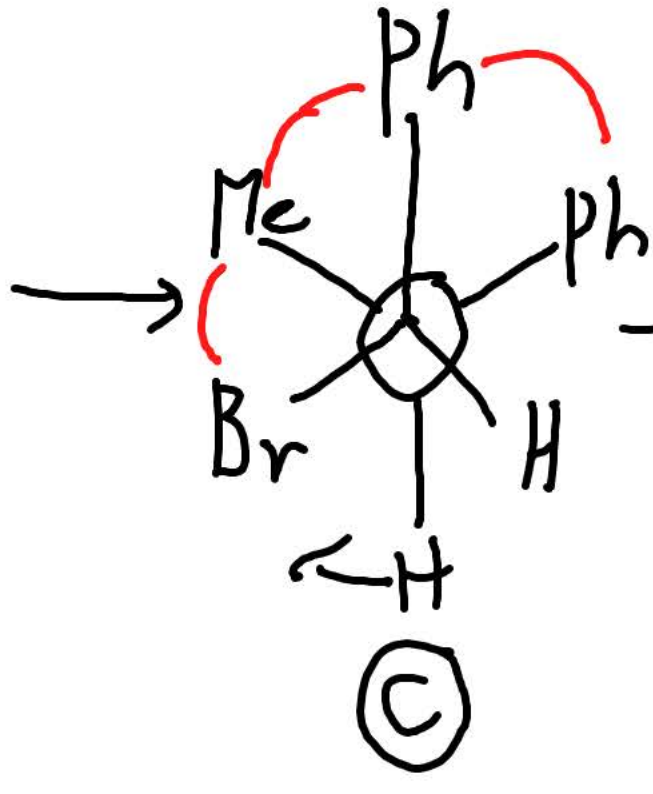
Taille des substituents: Ph > Me > Br > H

éclipsé: Ph-Ph, Br-Me, H-H



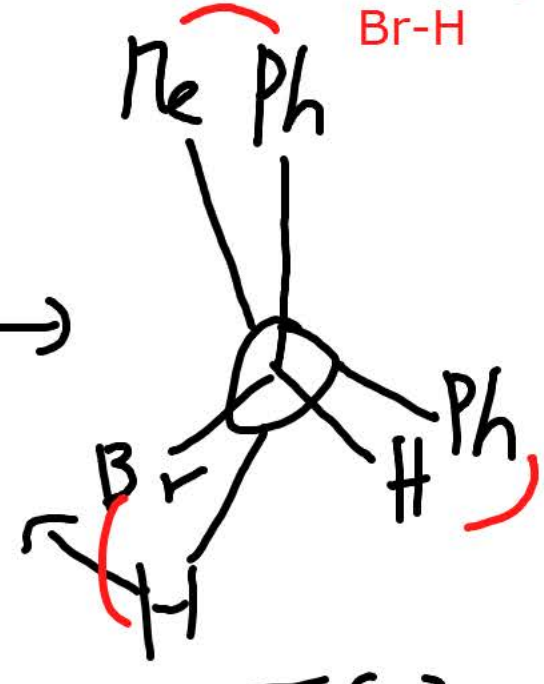
TS2

gauche: Br-Me, Me-Ph, Ph-Ph

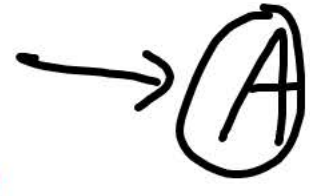


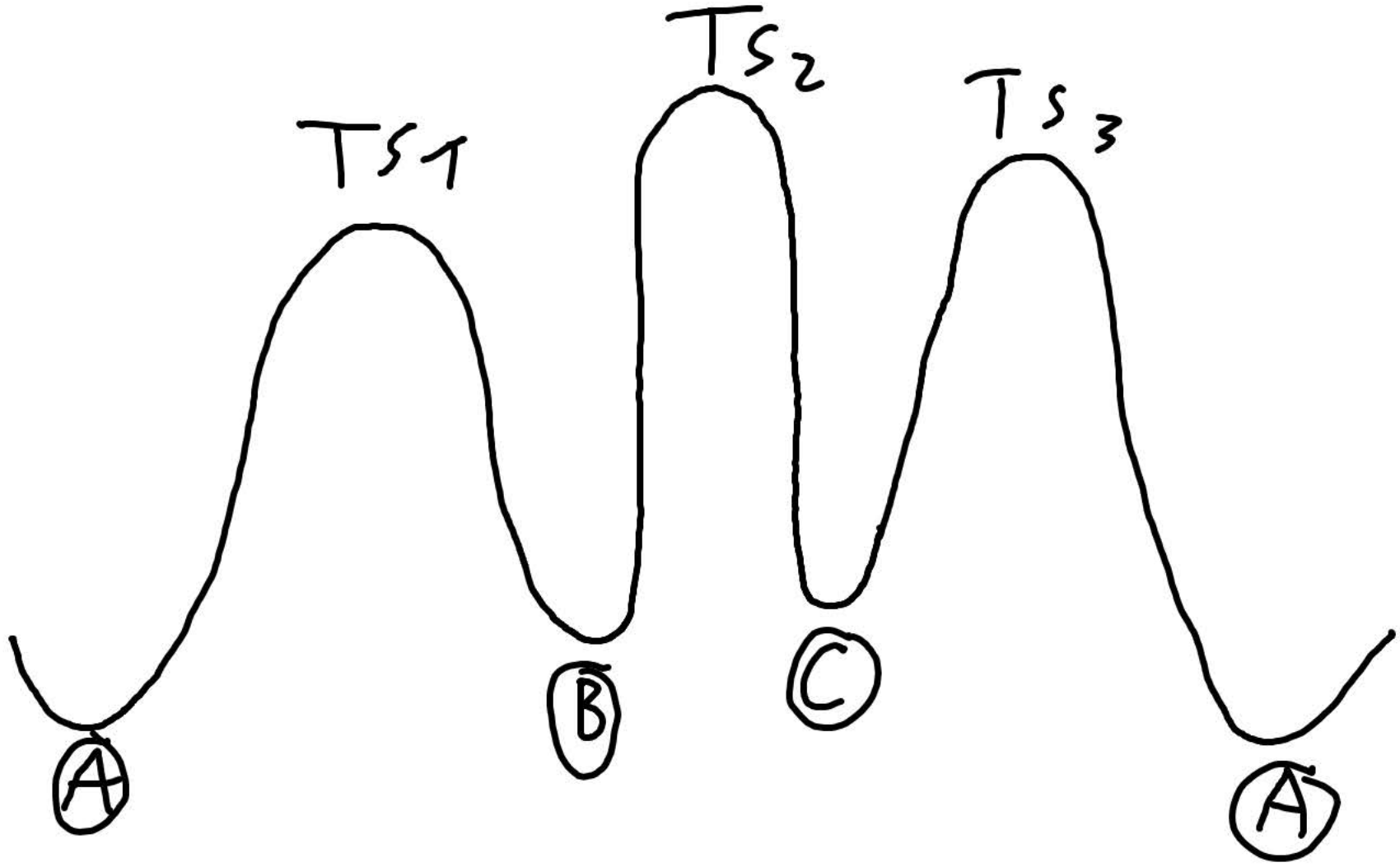
©

éclipsé, Me-Ph, Ph-H, Br-H

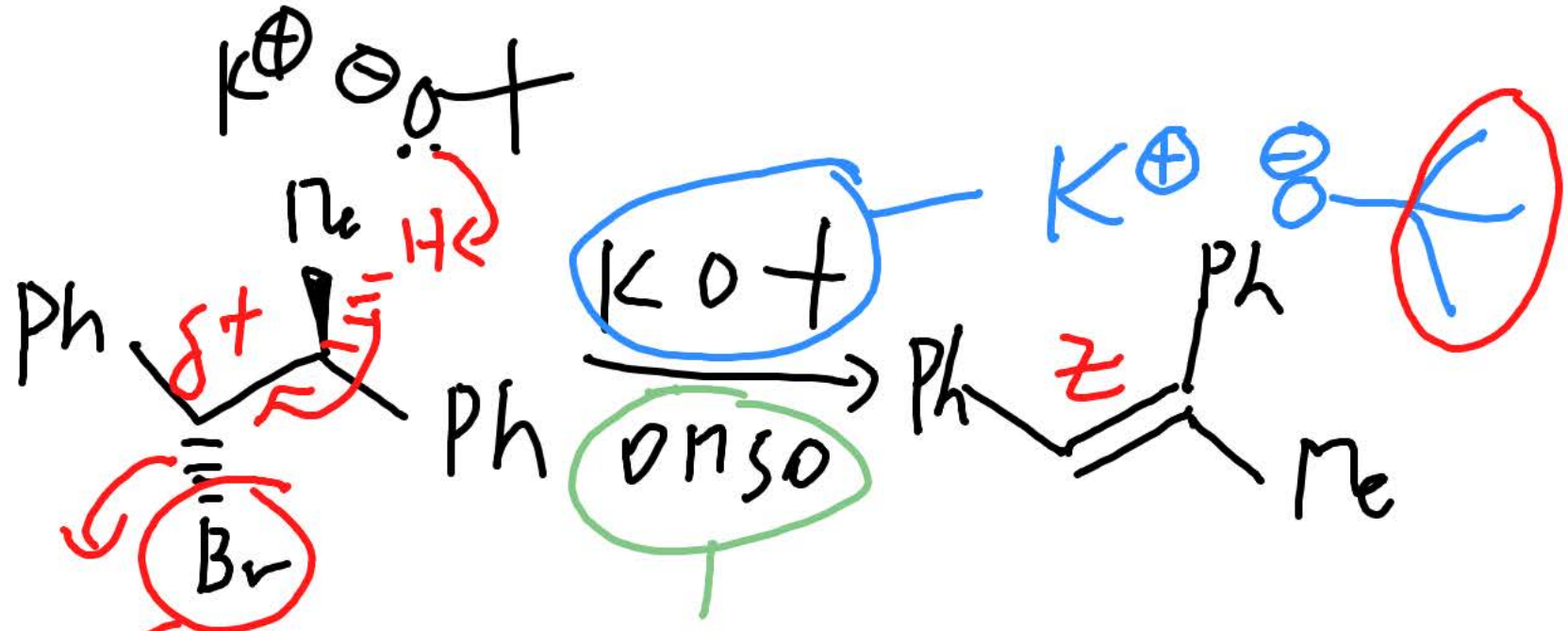


TS3





Intermédiaires: A << B<C, état de transition: TS1 <TS3 <TS2 (différences faibles), dominé pas interactions du Ph

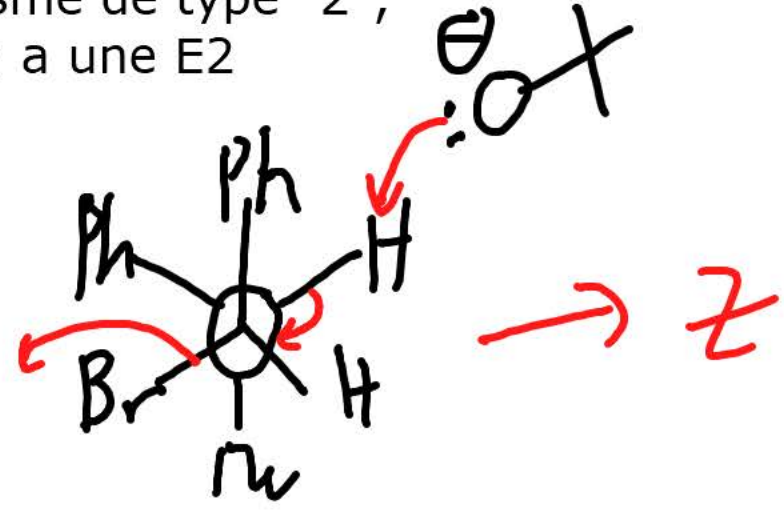


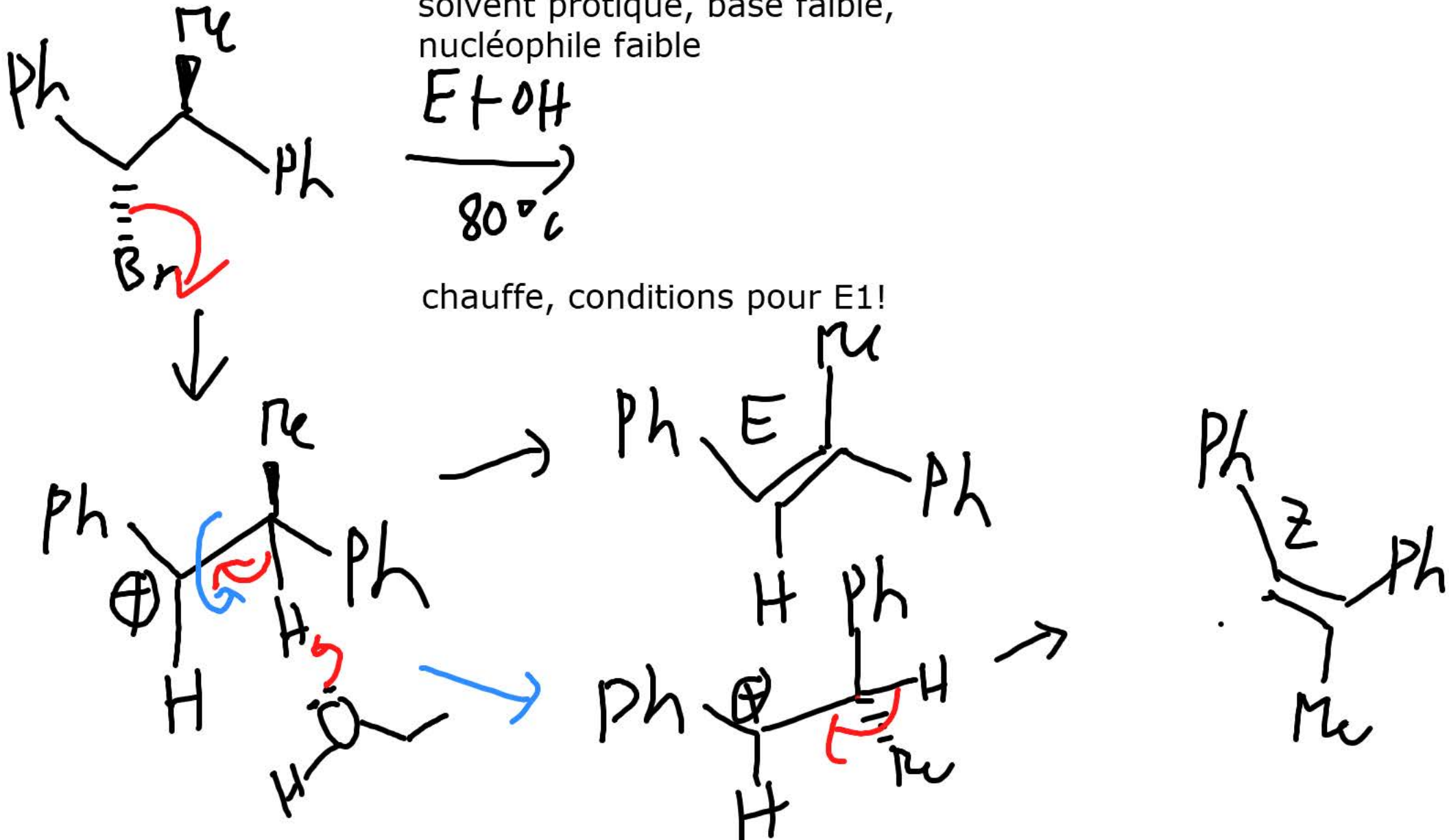
base forte, mauvais nucléophile (encombré) élimination!

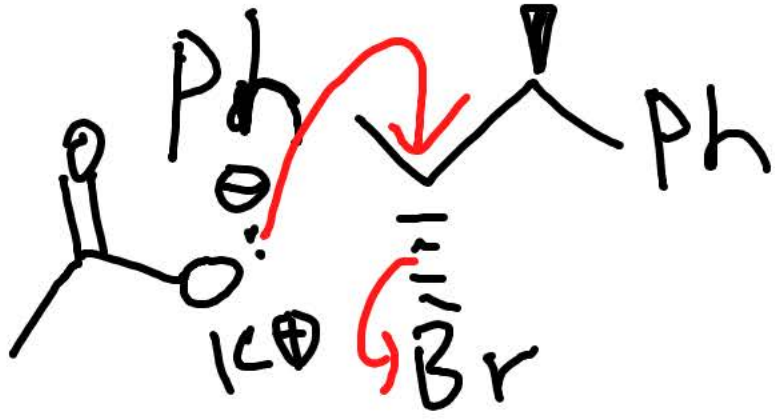
bon groupe partant: substitution, élimination

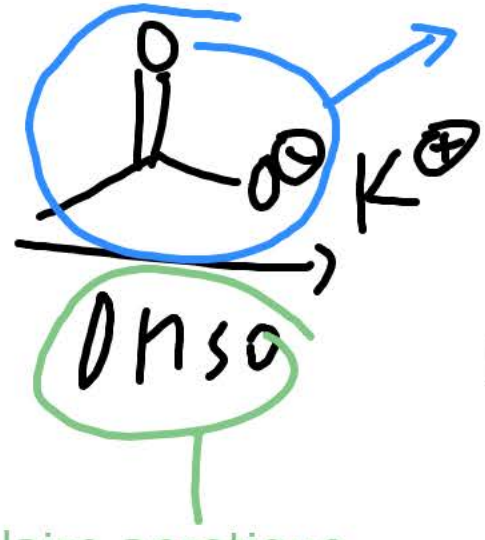
solvent polaire, aprotique
mécanisme de type "2",
donc on a une E2

Attention: angle de 180°!



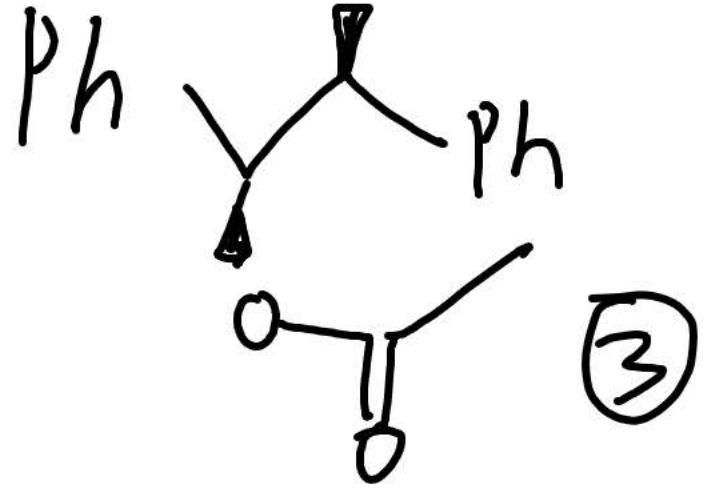

solvent protique, base faible,
nucléophile faible
EtOH
80°C
chauffe, conditions pour E1!



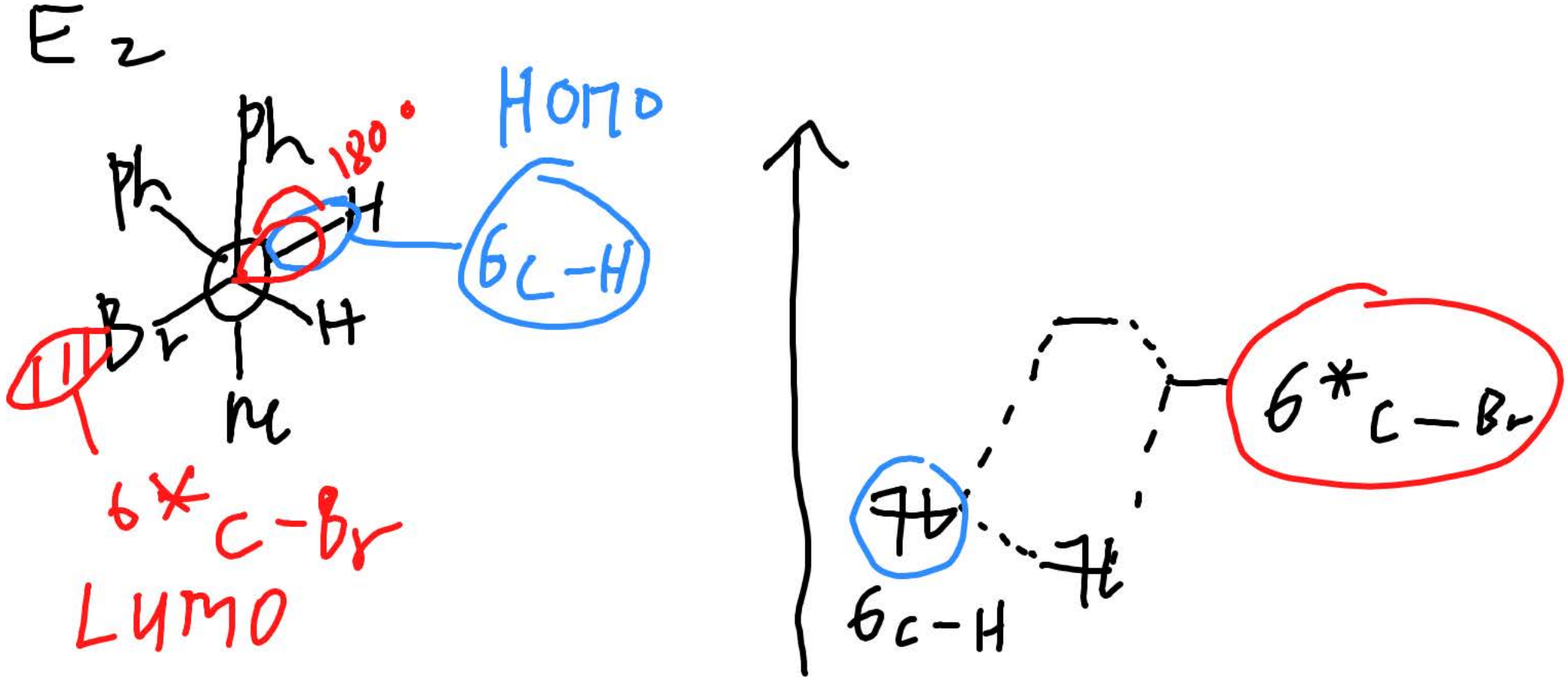


base faible, bon nucléophile, SN2!

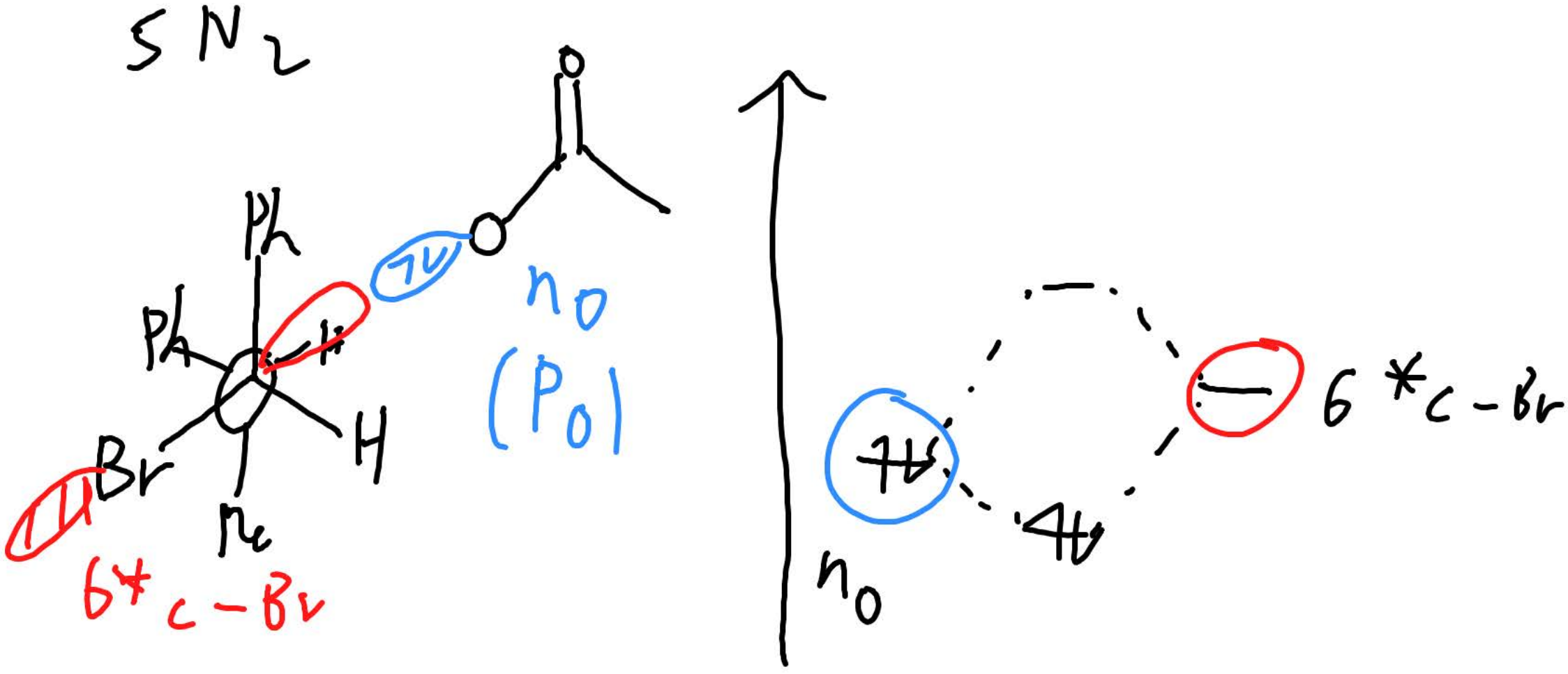
polaire aprotique, bon pour E2, SN2



justification théorique avec le orbitales

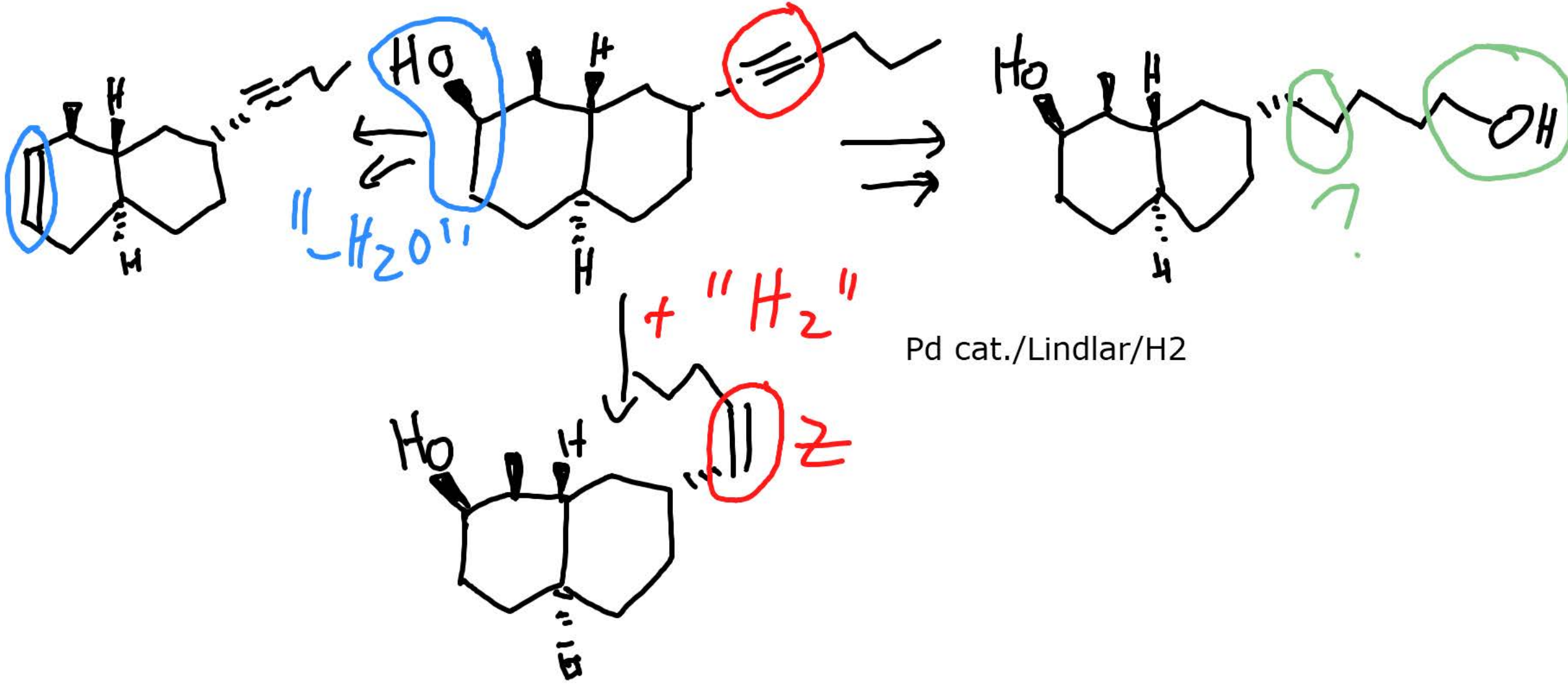


on doit avoir 180° pour superposer les orbitales de l'HOMO et de la LUMO

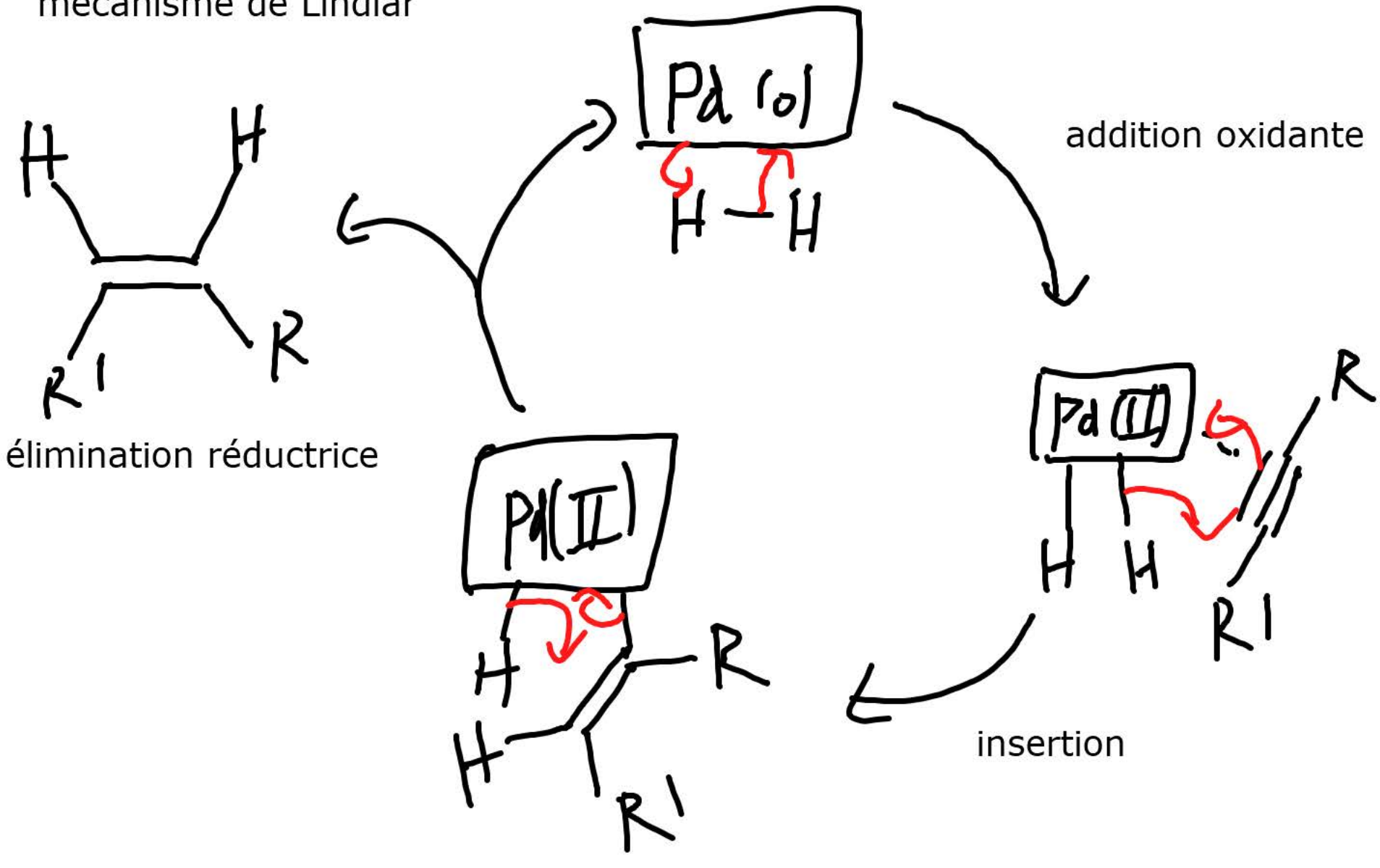


pour avoir la superposition, il faut attaquer à 180°, donc inversion

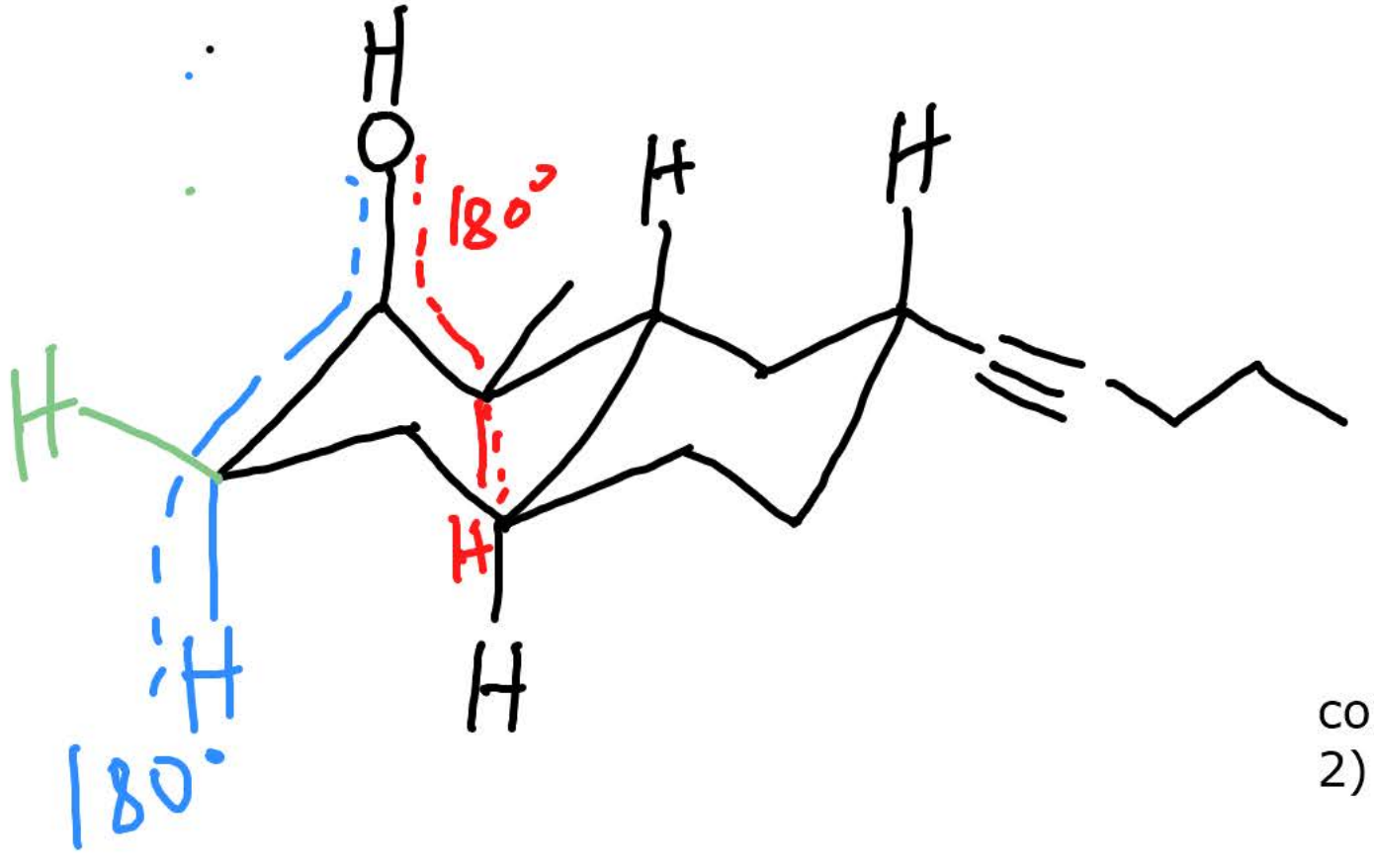
exercice 4



mécanisme de Lindlar



élimination sur structure cyclique: Attention dessiner en 3D!



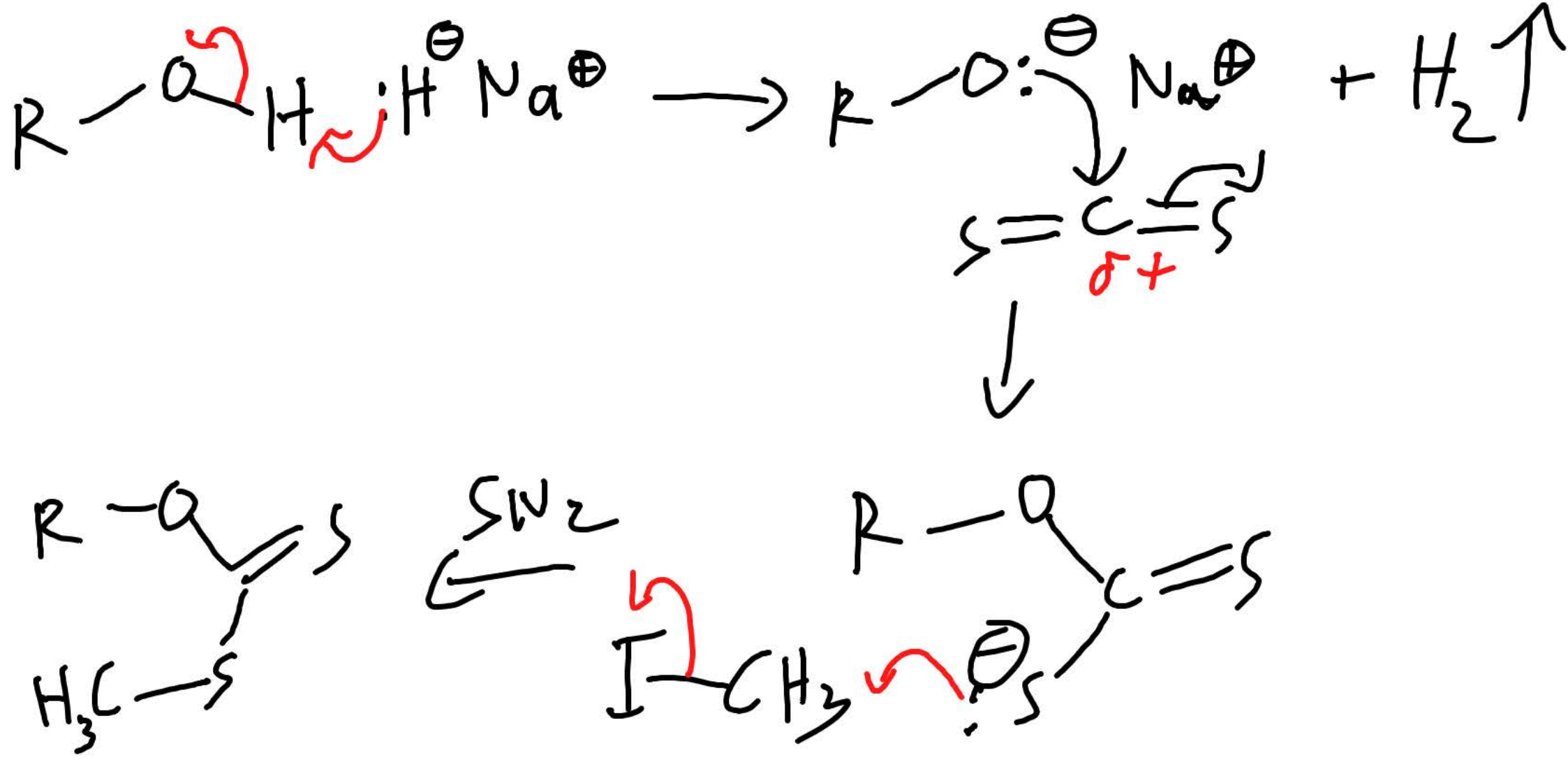
E1? mauvaise idée: mélange....

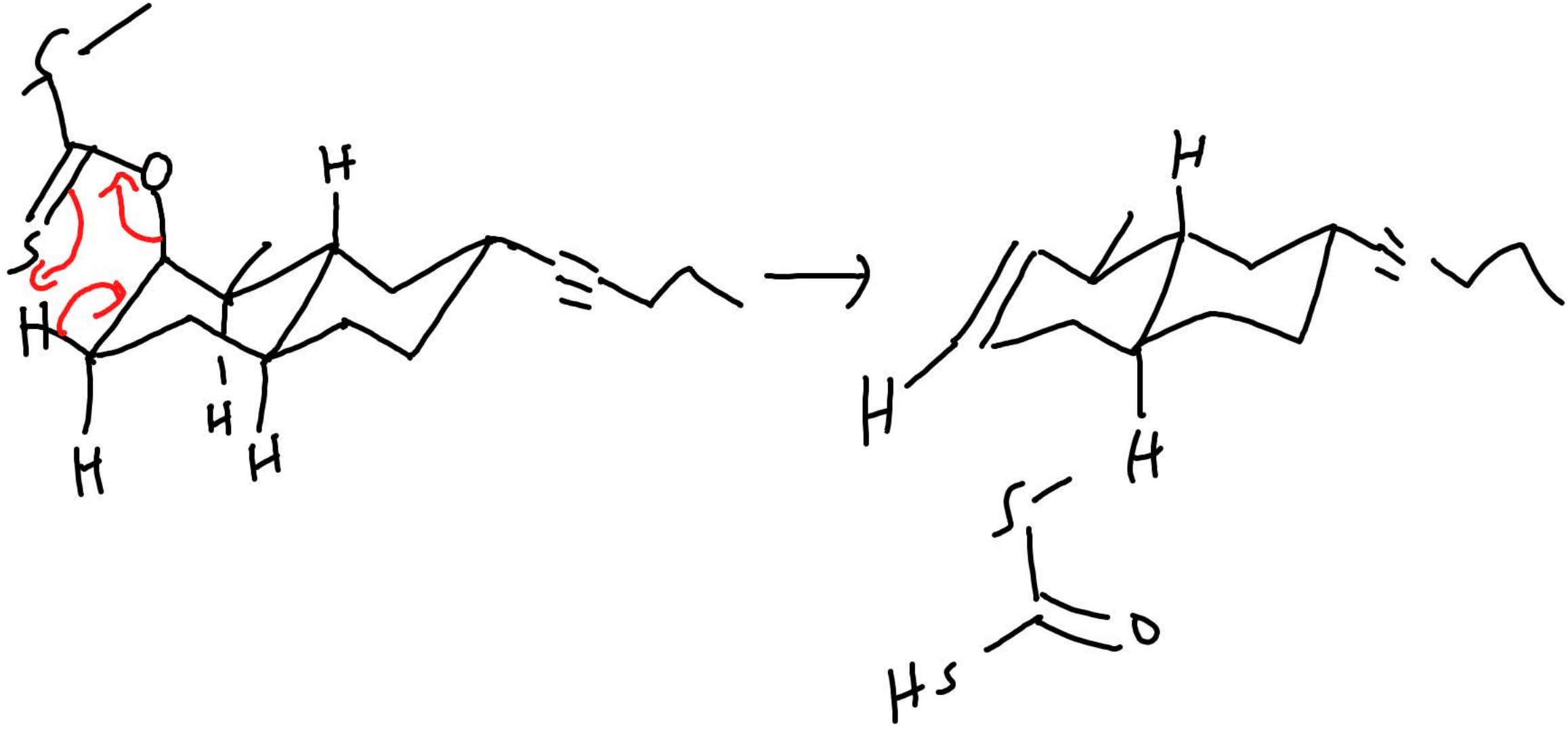
E2: mélange!

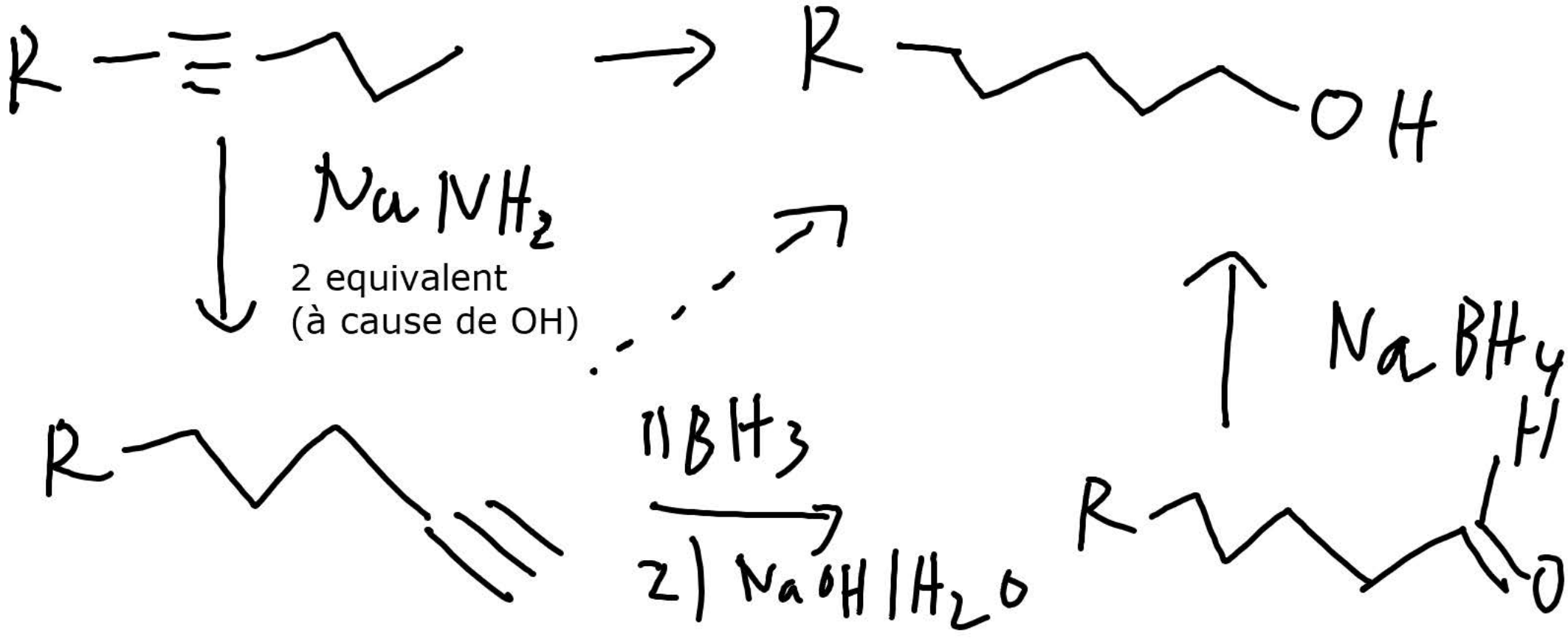
Il faut arracher le proton vert, du même côté: élimination en syn/cis, réaction de Chugaev!

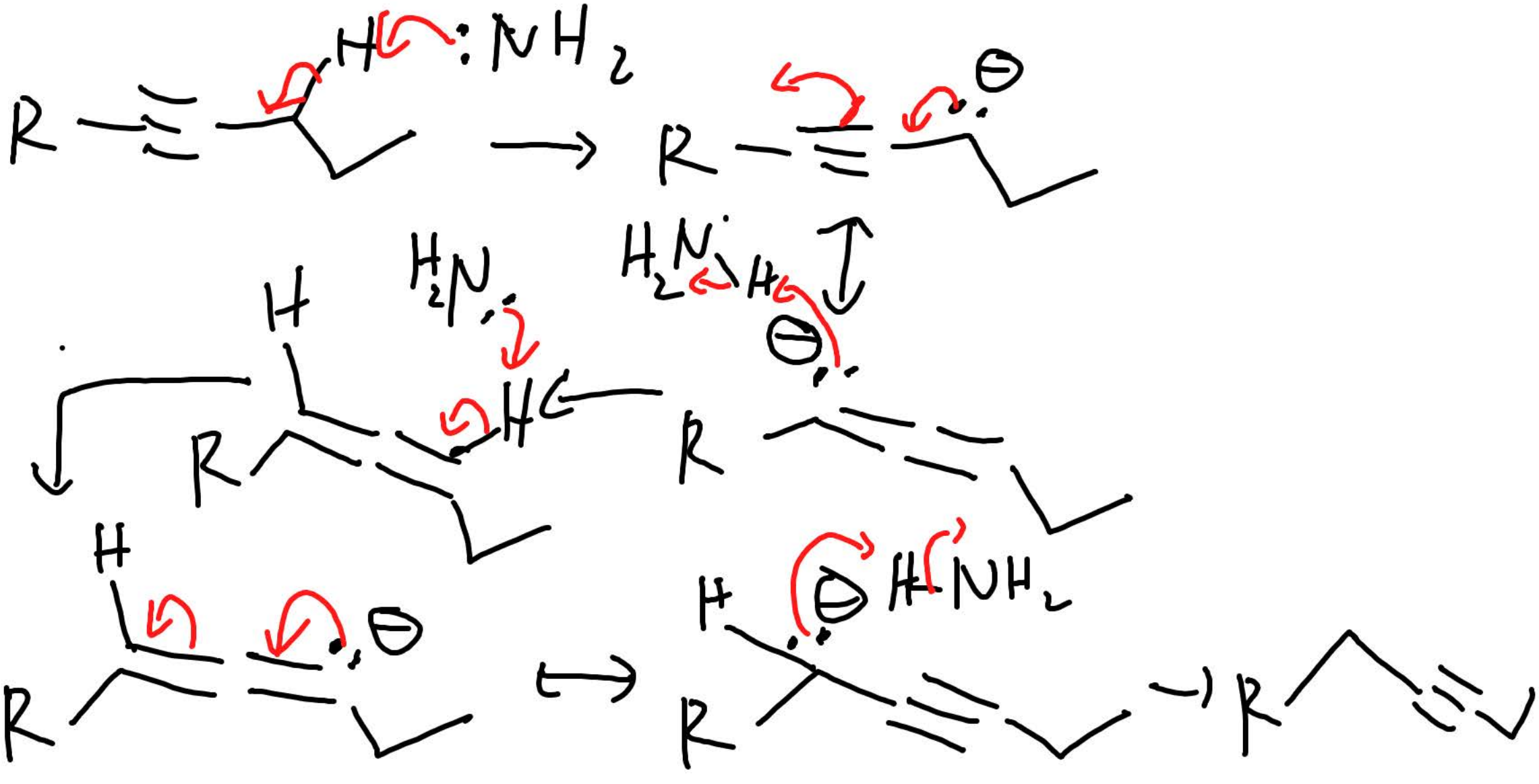
conditions: 1) NaH, CS2, MeI
2) 150 °C

étape 1

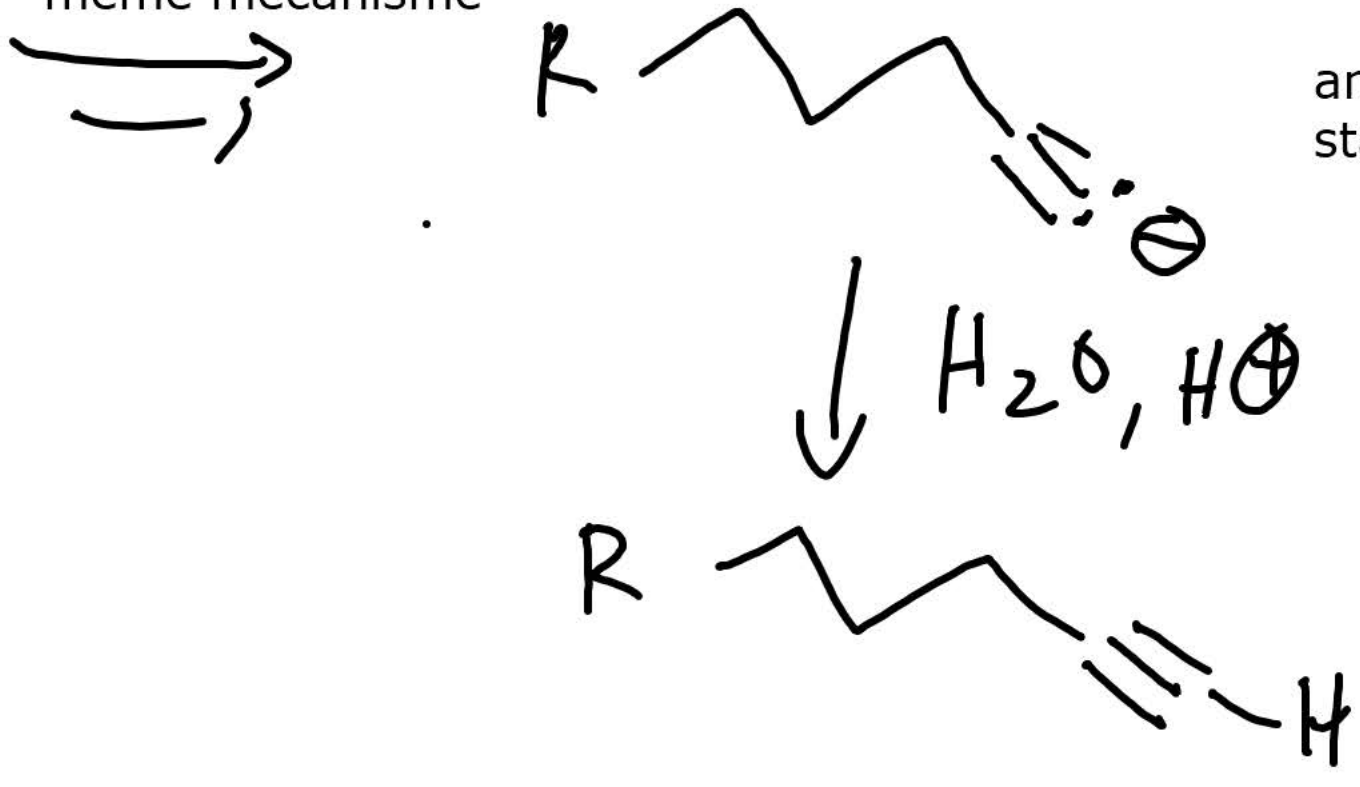





R
R
OH
NaNH2
2 equivalent
(à cause de OH)
R
1) BH3
2) NaOH/H2O
NaBH4
H
R
O



même mécanisme



anion en position sp, position stable, la réaction stope