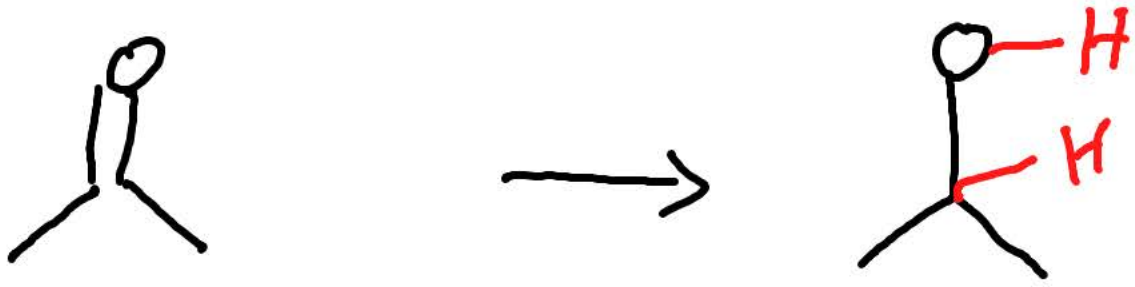


cétone

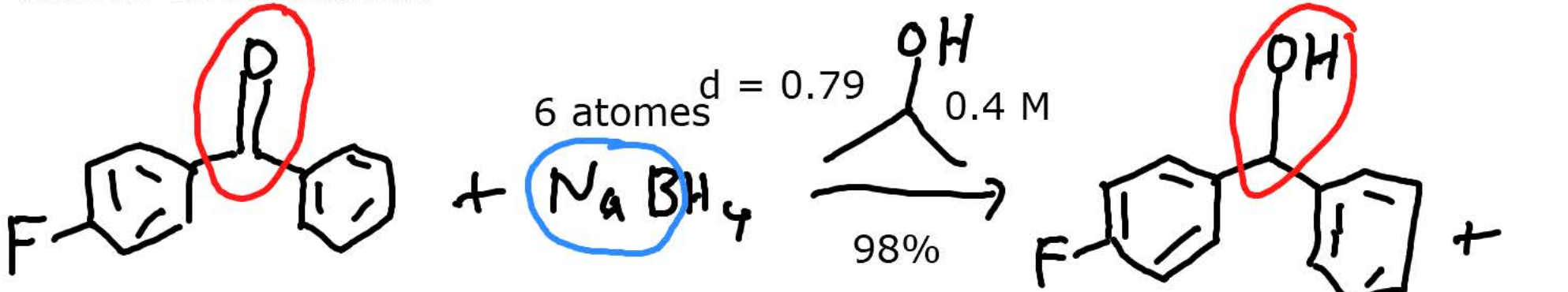
Alcool

① $Nu^{\oplus}$ $H-\overset{H}{\underset{H}{\overset{|}{\underset{|}{B}}}}-H^{\ominus}$

② H_2 , Ru cat.

procédé 1: Albany, Org. proc. res. dev. 2002, 621.

C13H9FO: 24 atomes



200 g/mol

1 equiv

37.8 g/mol

0.38 equiv

202 g/mol

$NaB(OH)_4$

0.20 Kg/Kg

purification: extraction

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

économie d'atome:
28/30, 93%

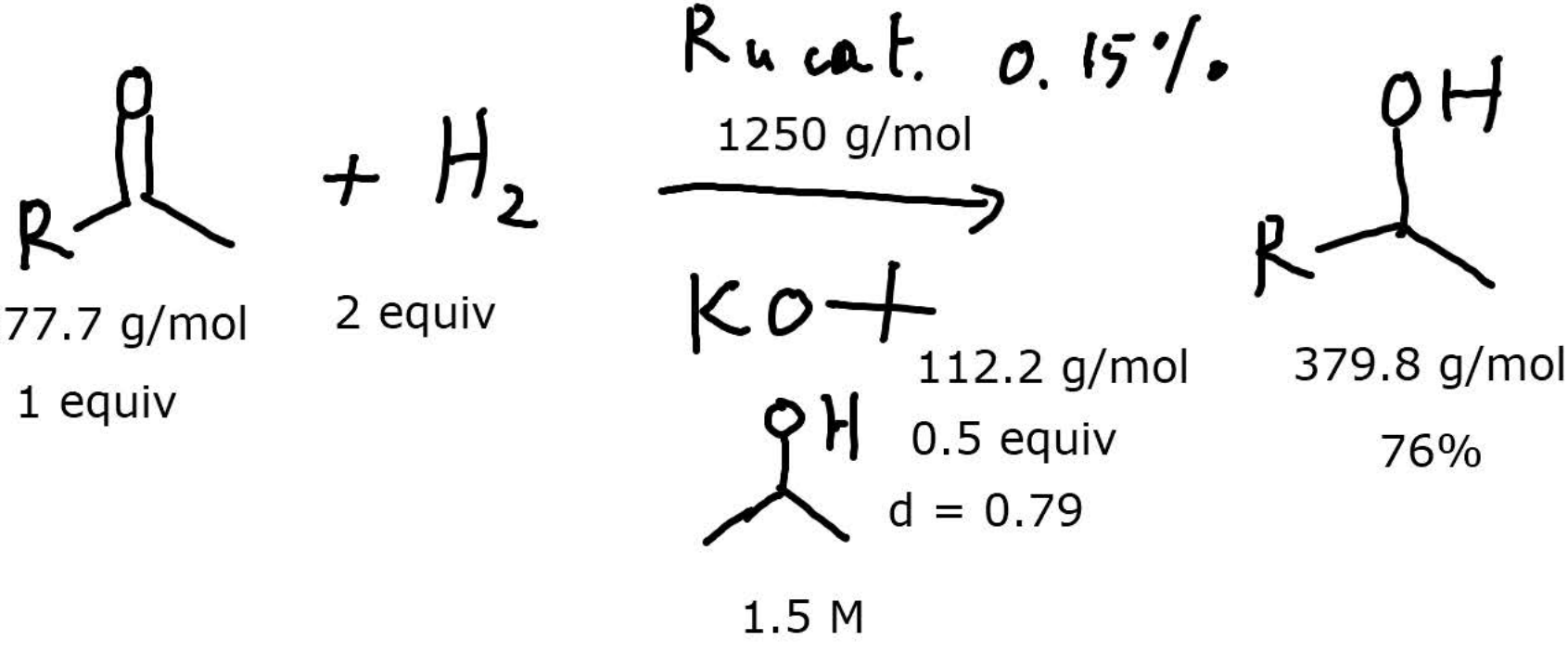
Bilan de masse, 1 kg de produit

1000/202 = 4.95 mol produit
98% rendement: 5.05 mol produit de départ, 1.01 Kg
NaBH4: 0.073 Kg, NaB(OH)4: 0.200 Kg
0. 4 M d'isopropanol, 12.6 L, 10 Kg
Extraction:
1 volume d'acétate d'éthyle: 12.6 L, 11.3 Kg
1.5 volume d'eau: 18.9 L, 18.9 Kg
0.200 Kg Na2SO4

PMI: (1.01+0.073+ 10 + 11.3 + 18.9 + 0.200)/1 = 41.5

E: (10+11.3 + 18.9 + 0.200 + 0.200)/1 = 40.6

procédé 2: Merck, Org proc. res. dev. 2007, 616 (simplifié)



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

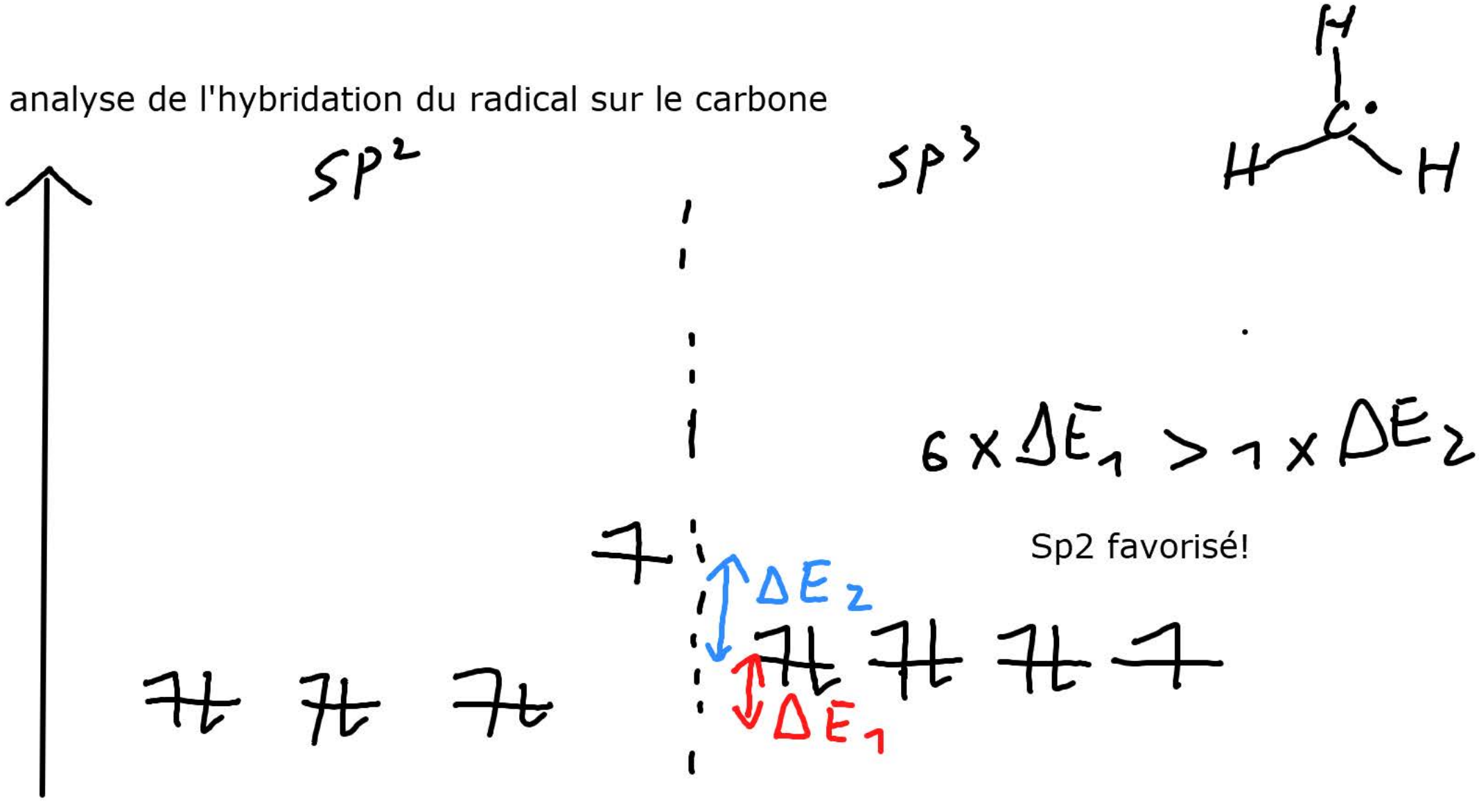
Economie d'atome: 100%!

Bilan de masse:
1 kg produit: 2.63 mol
produit départ: 76% rendement: 3.46 mol: 1.30 Kg
H2: 0.015 Kg
Ru cat: 0.0065 Kg
KOtBu: 0.12 Kg
isopropanol: 2.3 L, 1.8 Kg
Toluene: 6.5 volume: 13 Kg
Eau: 6.5 volume: 15 Kg

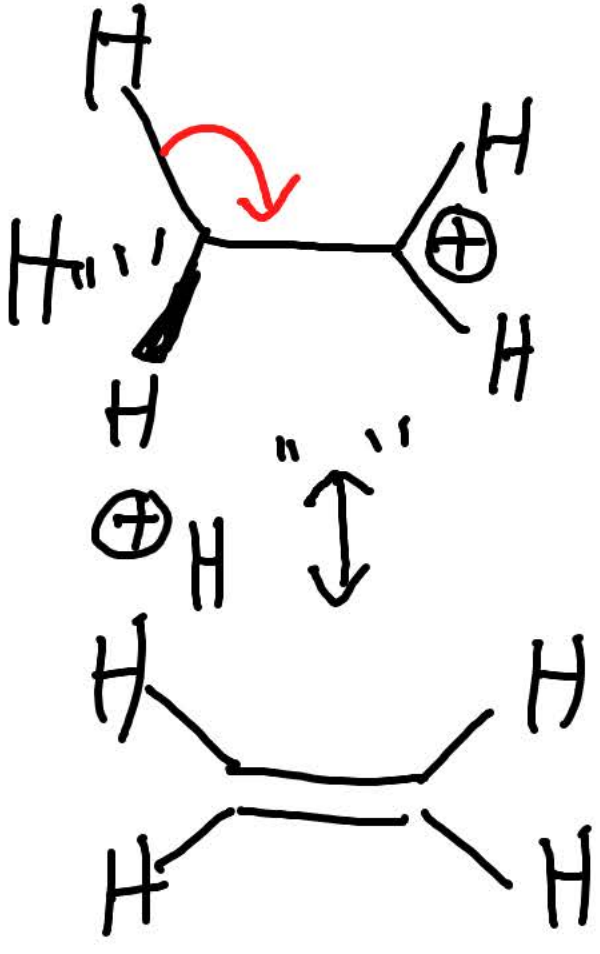
PMI: (1.30 + 0.015 + 0.0065 +0.12+1.8+13+15)/1 = 31.2

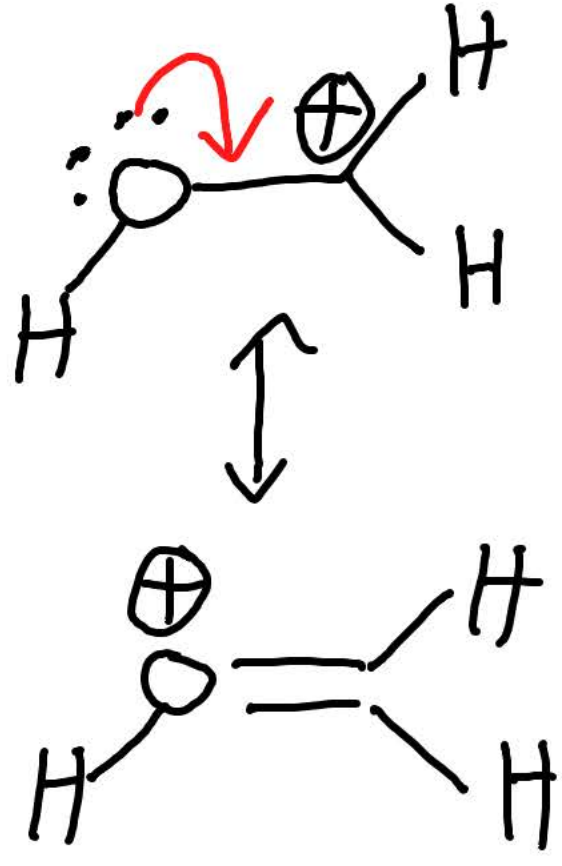
E: (0.0075 (1/2 de H2) + 0.0065 + 0.12 +1.8+13+15) = 29.9

analyse de l'hybridation du radical sur le carbone



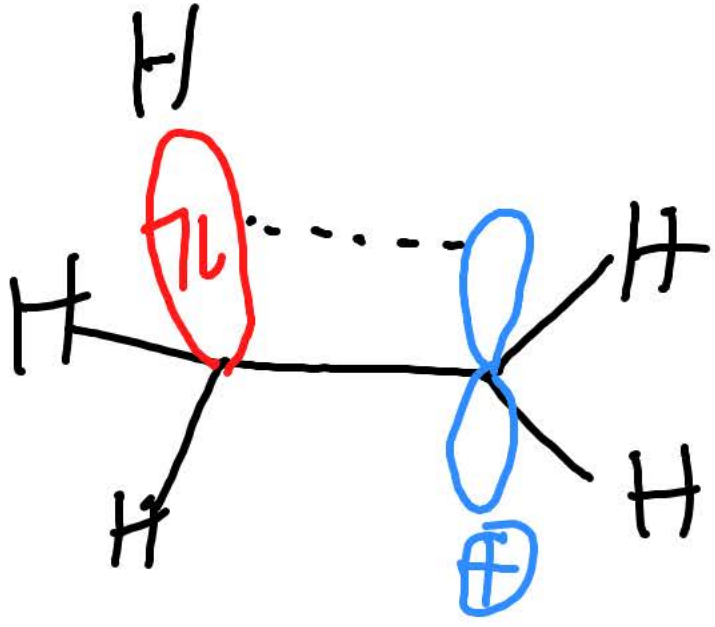
résonance vs orbitales





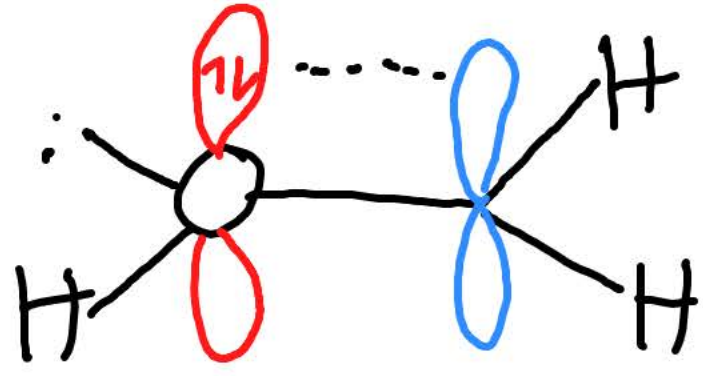
bonne résonance,
mieux stabilisé

interactions orbitalaires secondaires



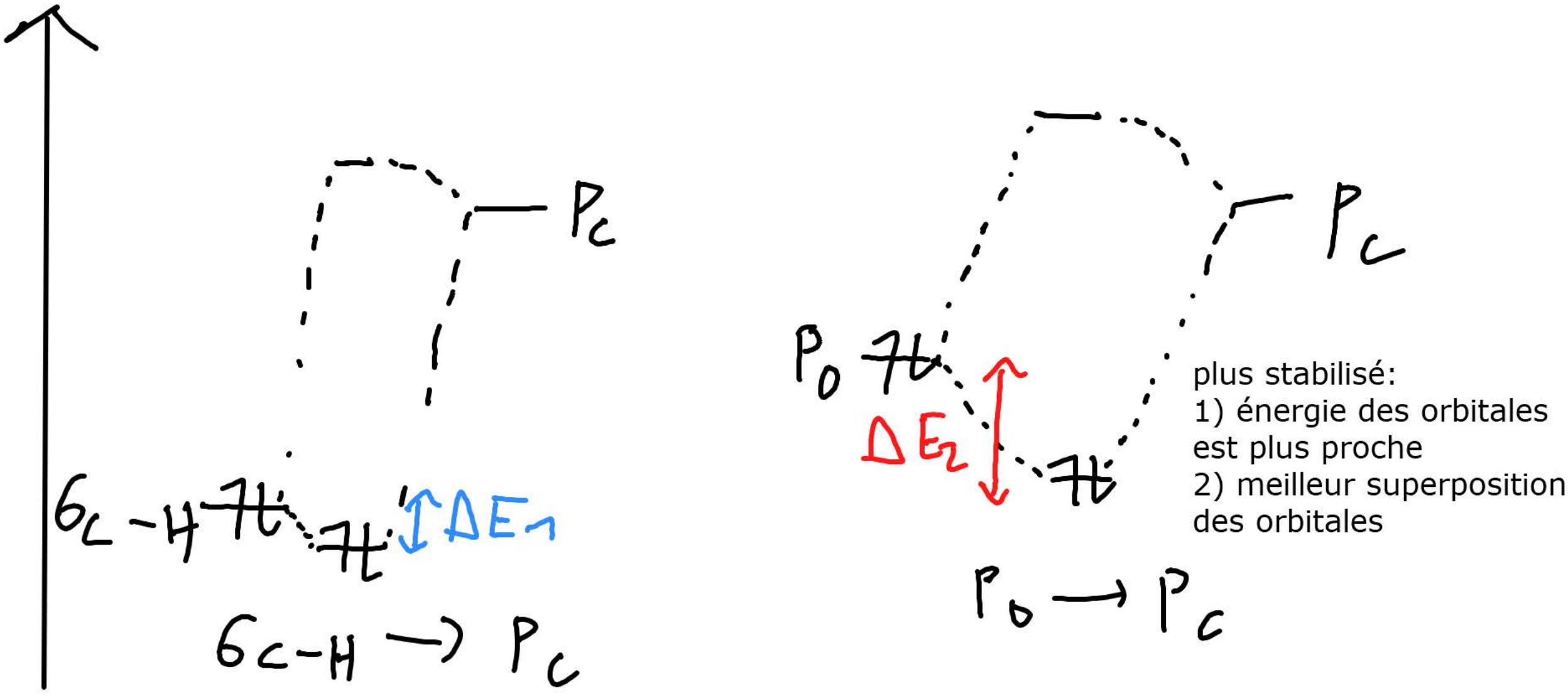
σ_{C-H}
HOMO

p_C
LUMO



p_O
HOMO

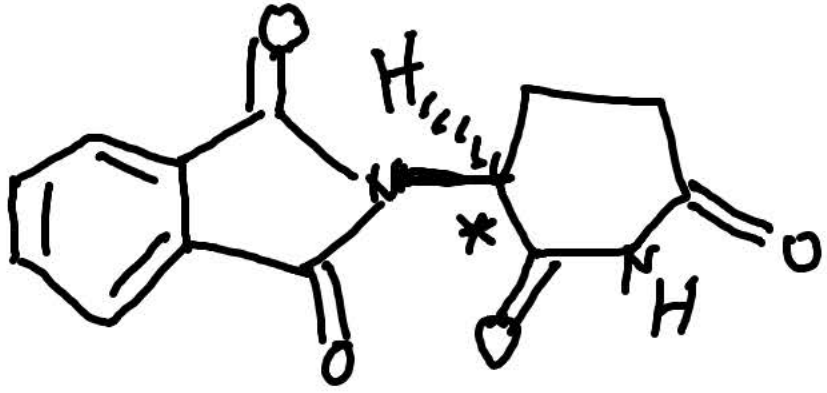
p_C
LUMO


π_C
σ_{C-H} π π
ΔE_1
$\sigma_{C-H} \rightarrow \pi_C$
π_C
π_0 π
ΔE_2
π
plus stabilisé:
1) énergie des orbitales est plus proche
2) meilleur superposition des orbitales
$\pi_0 \rightarrow \pi_C$

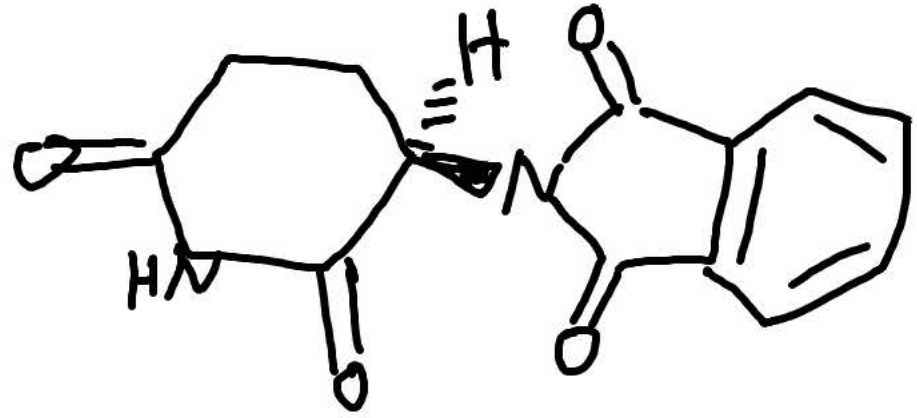
importance de la chiralité

bioactivité différente

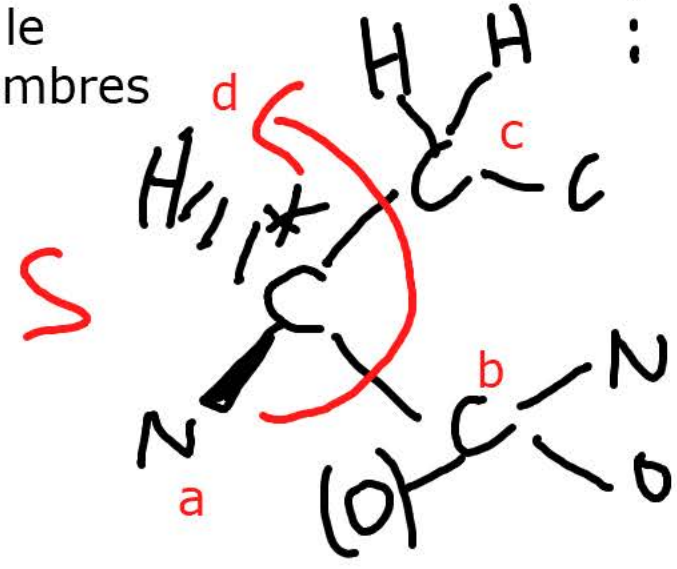
thalidomide



tératogène (empêche le dévelopement des membres du foetus)

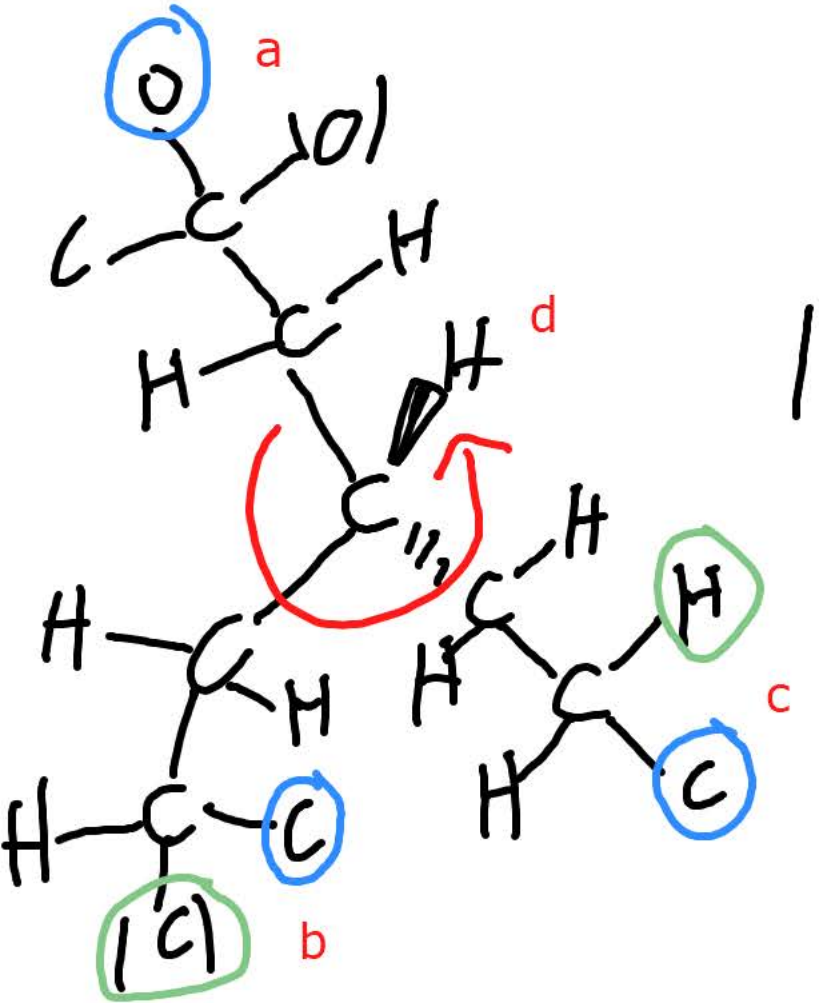


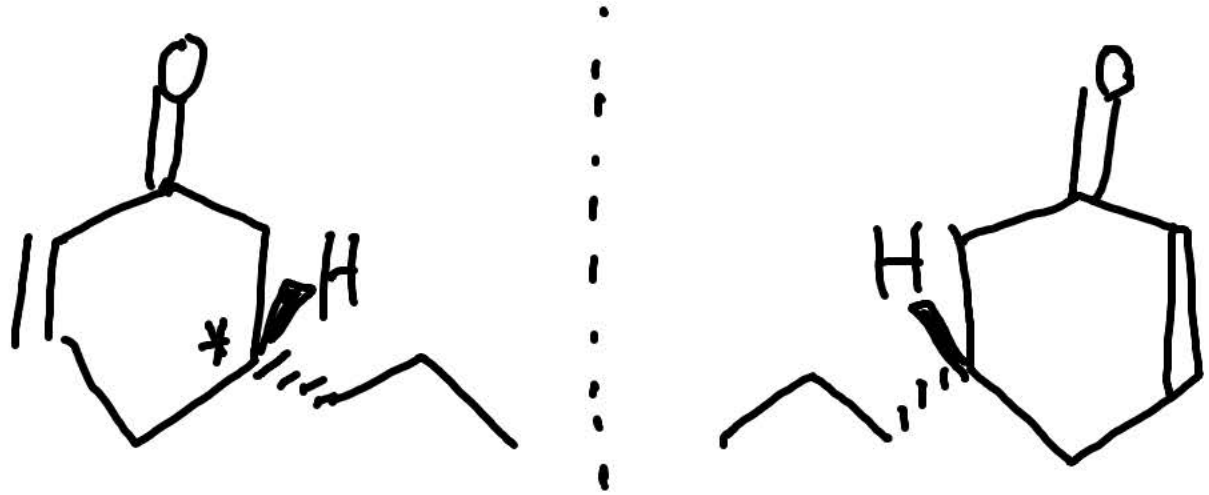
sédatif



d derrière!

odeur/gouts



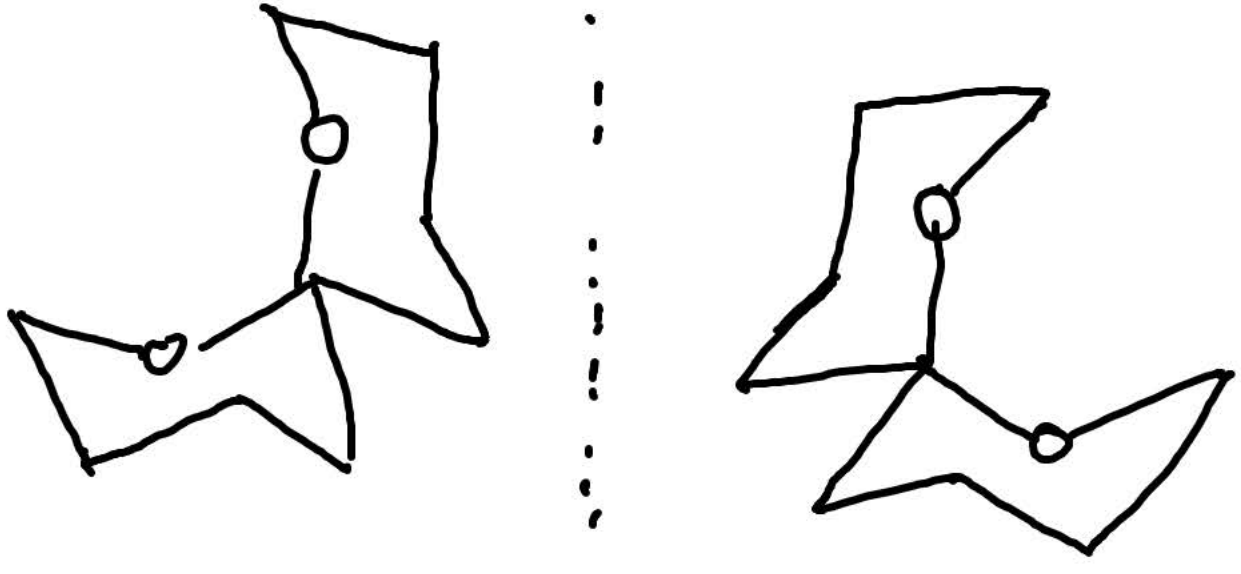


céleri

anis

"S" mais d est devant, donc la configuration est R

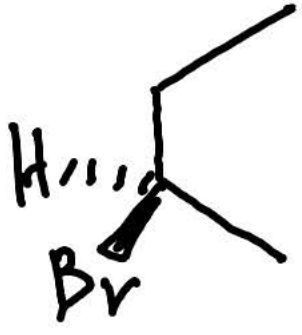
phéromone



attire les insectes mâles

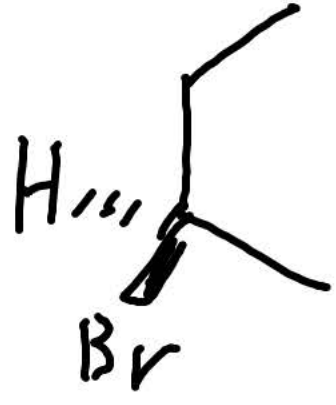
attire les insectes femelles

exemple de mesure de la rotation optique



mesure labo: [alpha]: 20°
Substance pure: 23.1°
pureté optique: 20/23.1 = 87%
ee = 87%

93.5-6.5 = 87
er = 93.5: 6.5

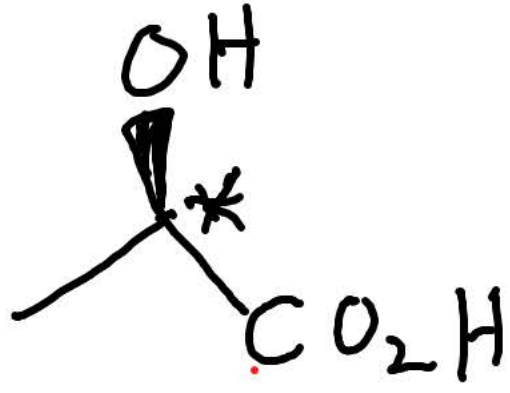


93.5%

6.5%

Techniques de dessin en chimie organique

acide lactique



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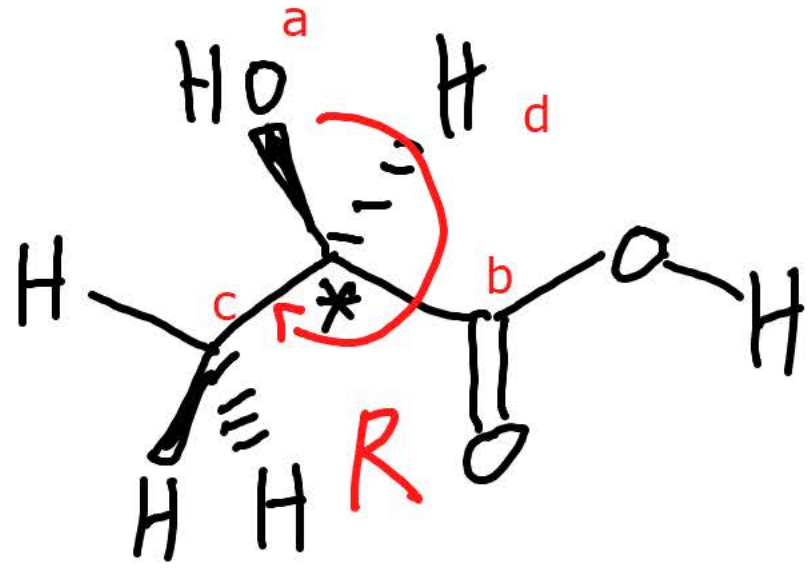
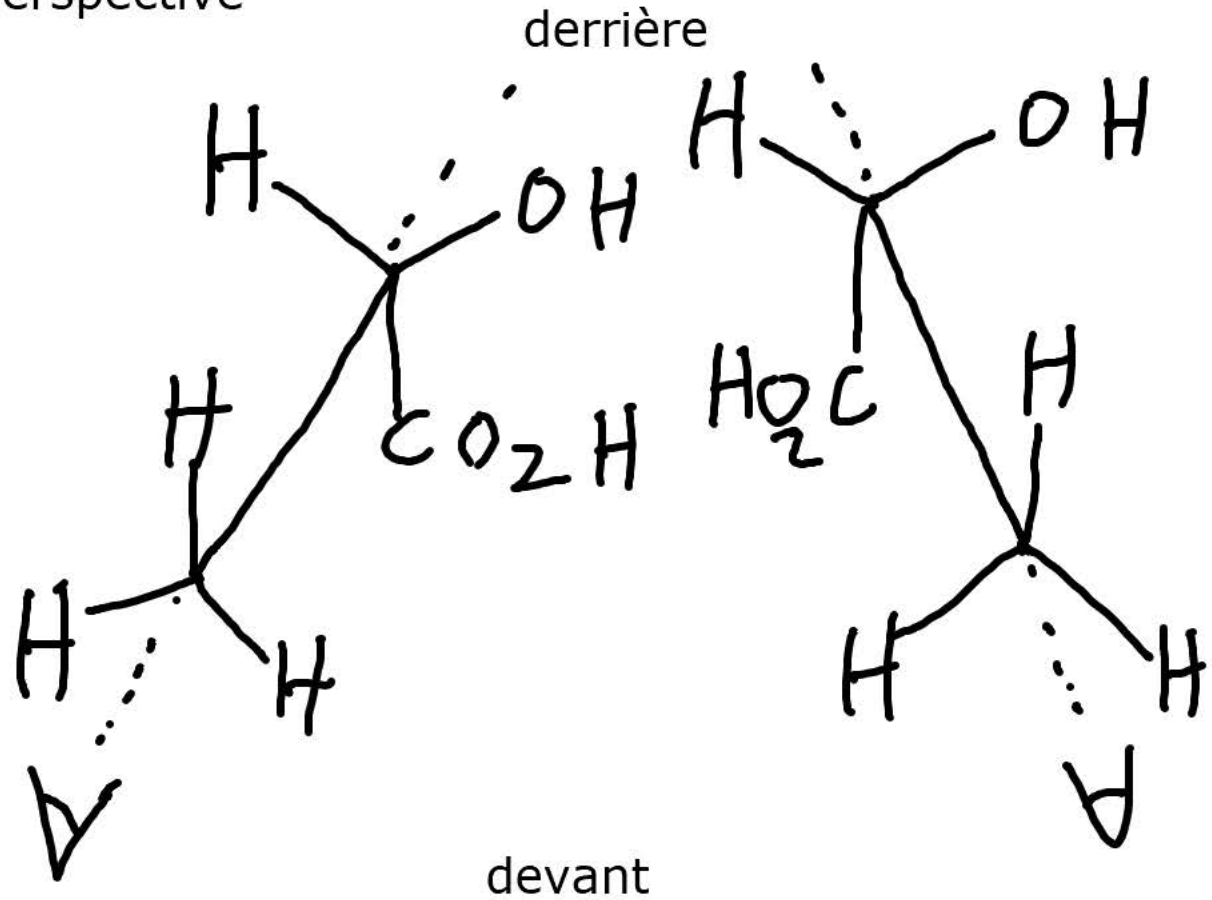
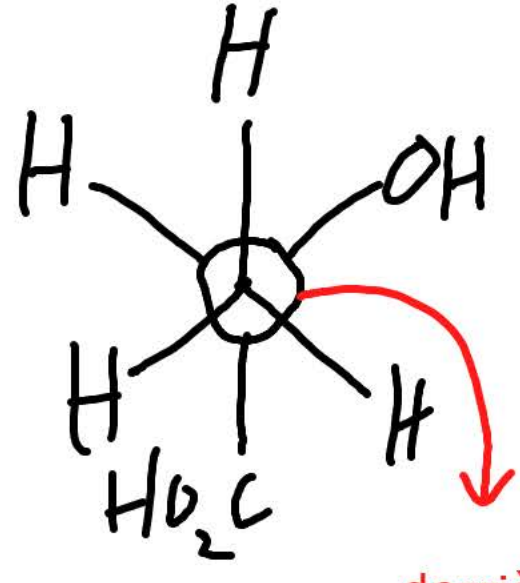


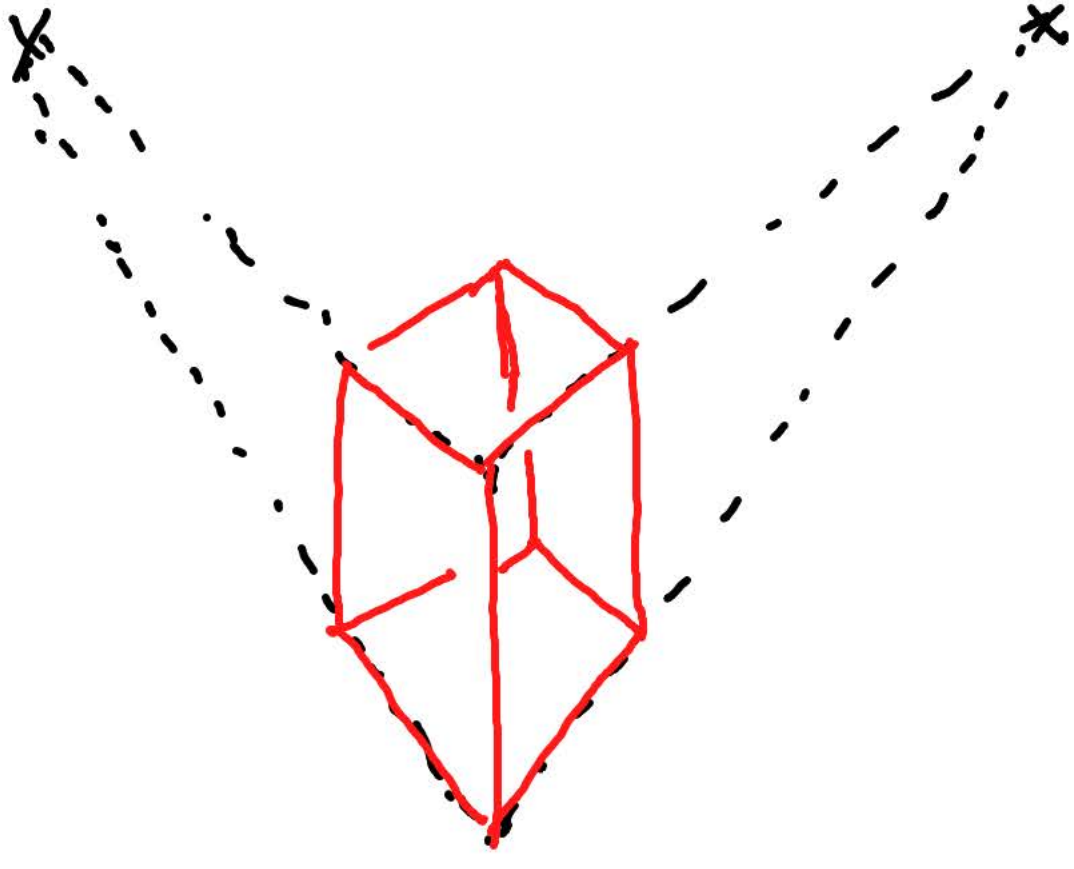
dessin en perspective



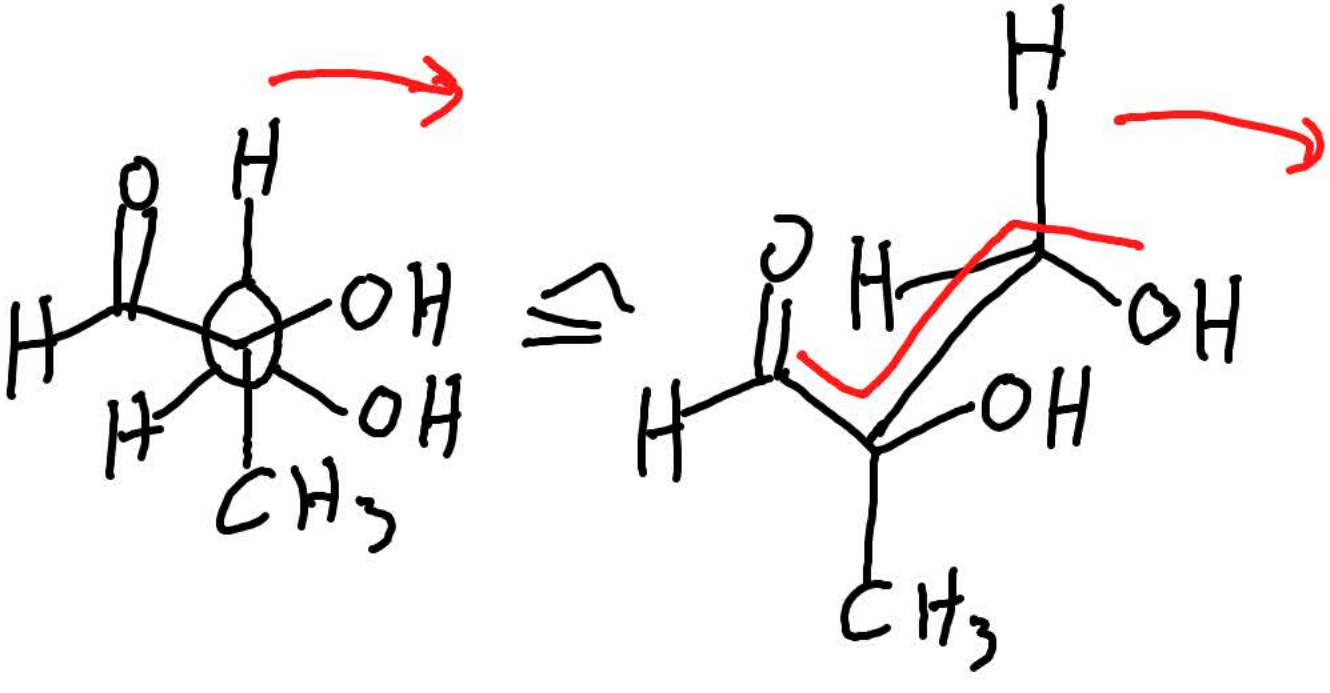
projection de Newman sur un axe



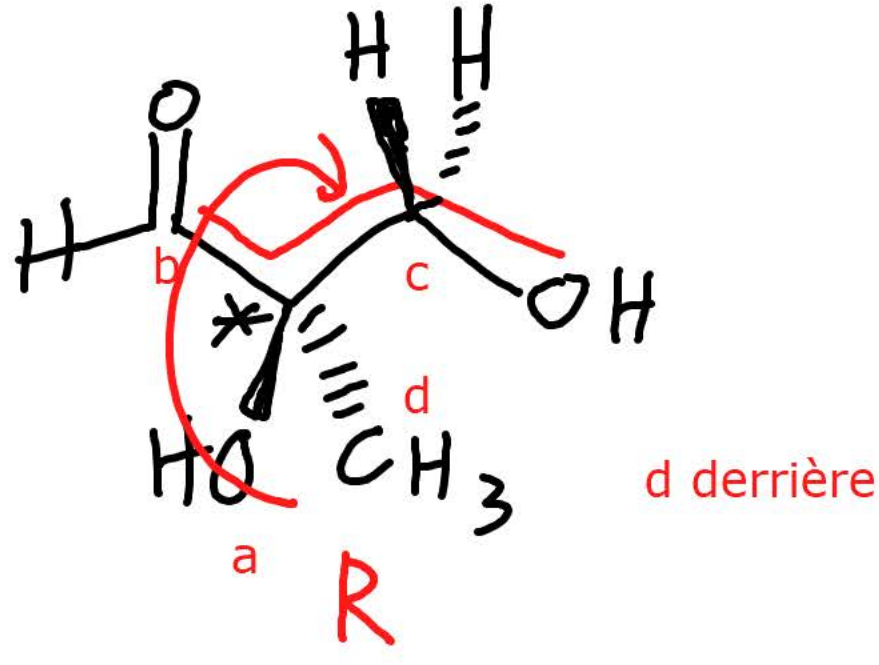
système des points de fuites



De Newman à "zigzag"

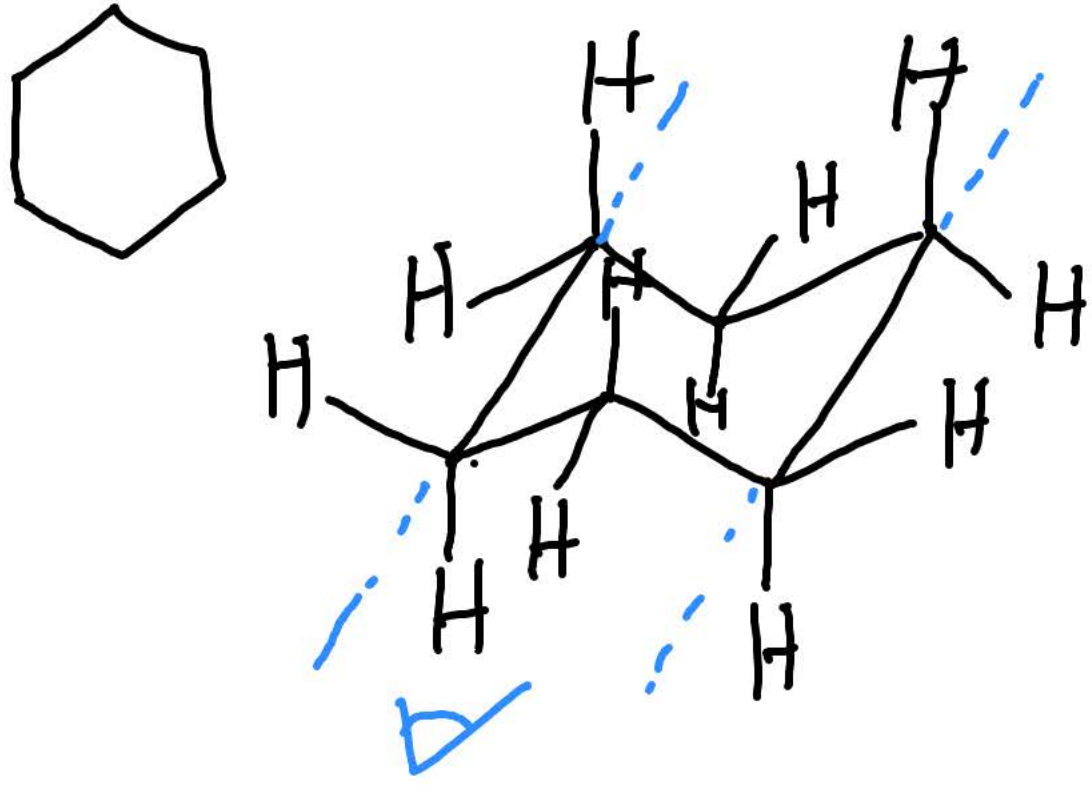


Newman perspective

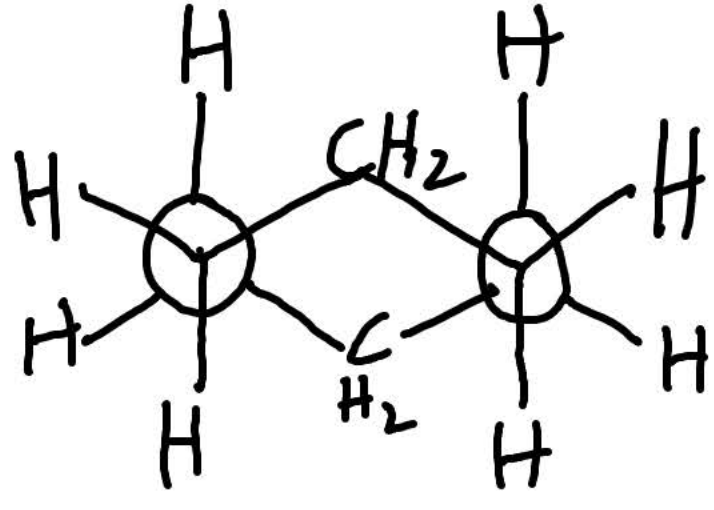


d derrière

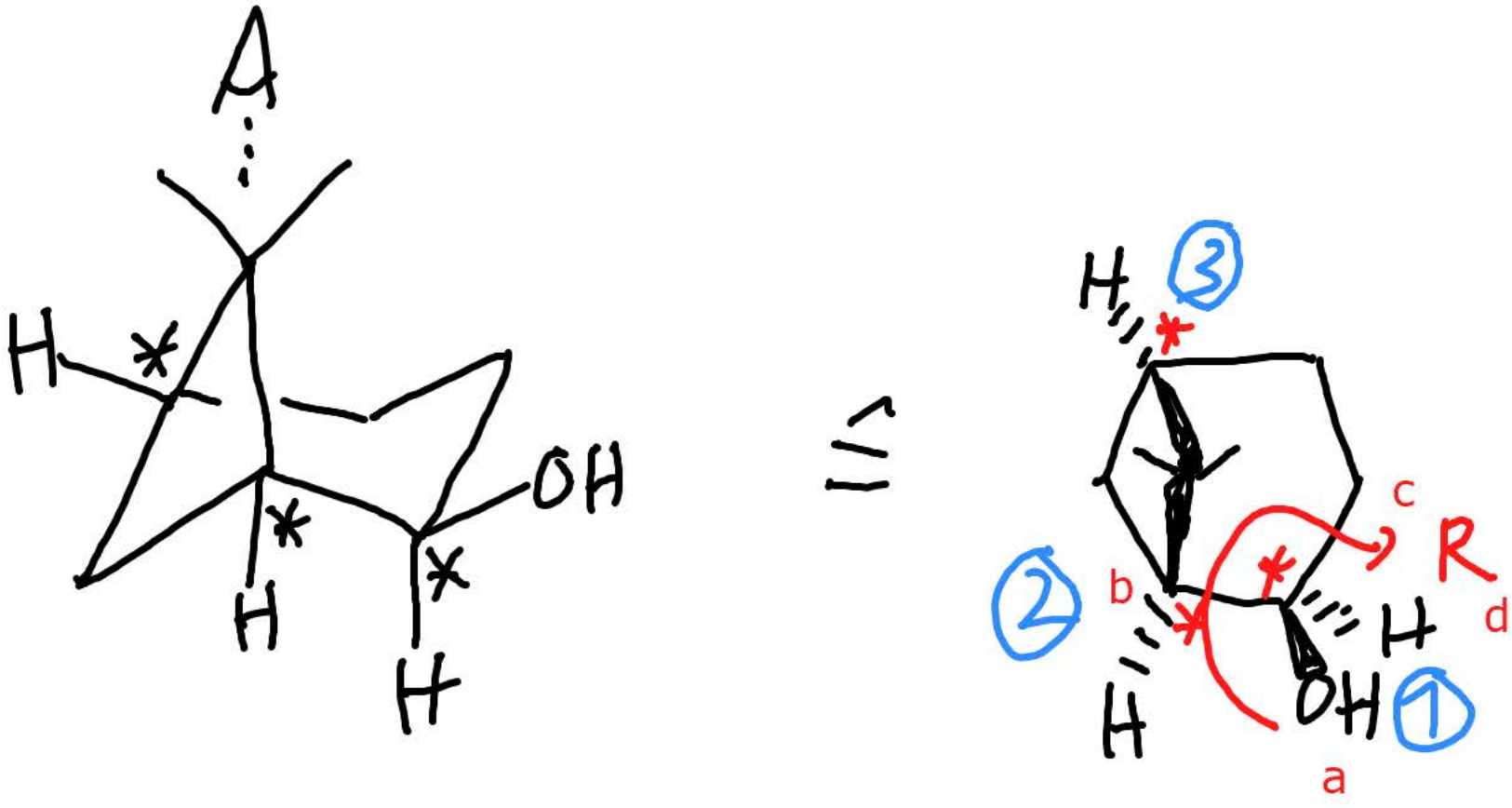
Molécules cycliques



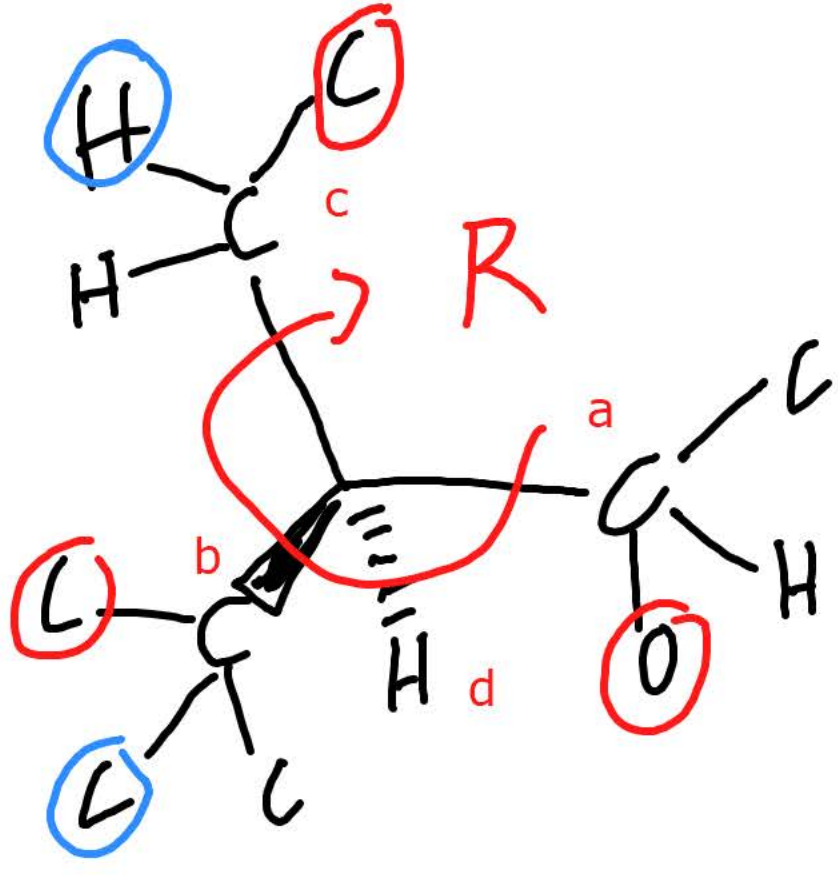
devant



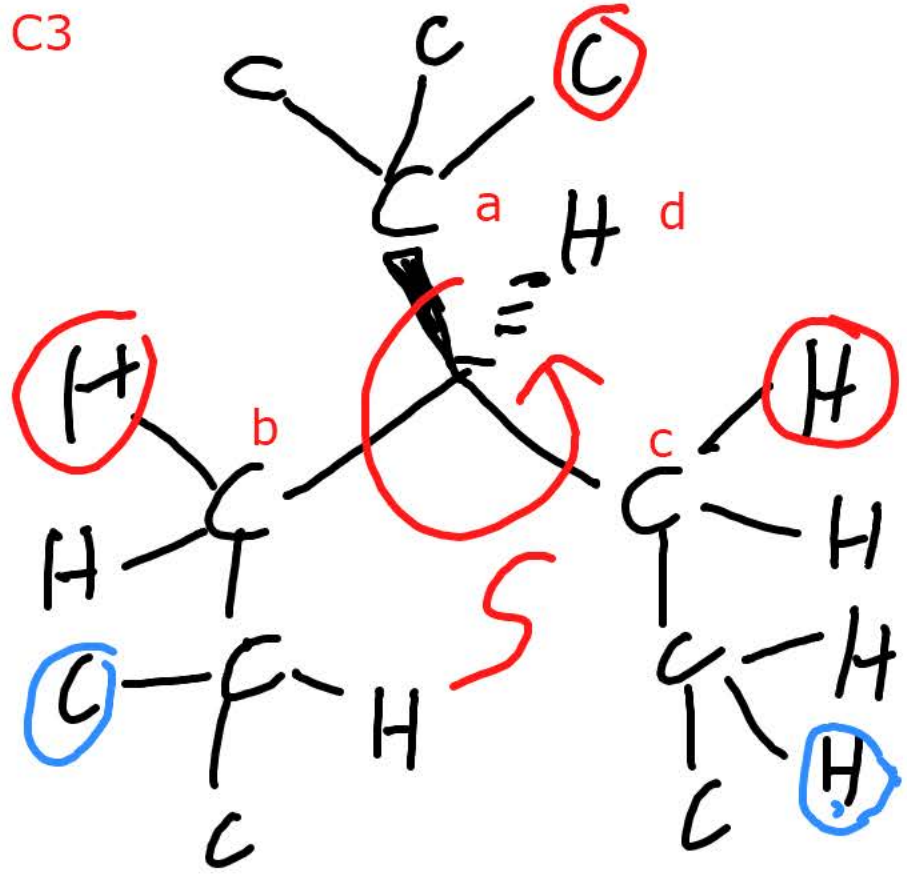
Newman


A
H
OH
H
H
≅
H
3
2
b
c
R
d
H
OH
1
a

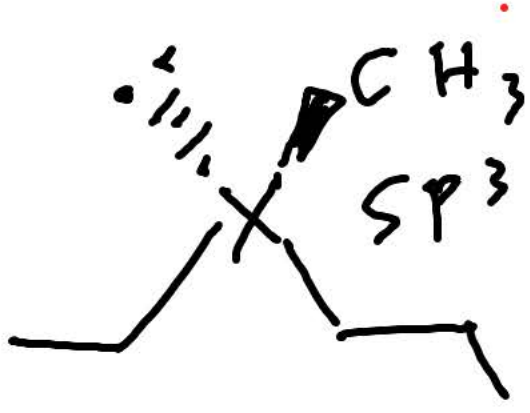
C2

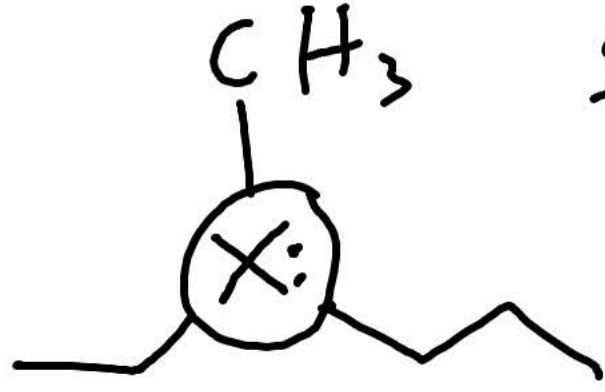


C3



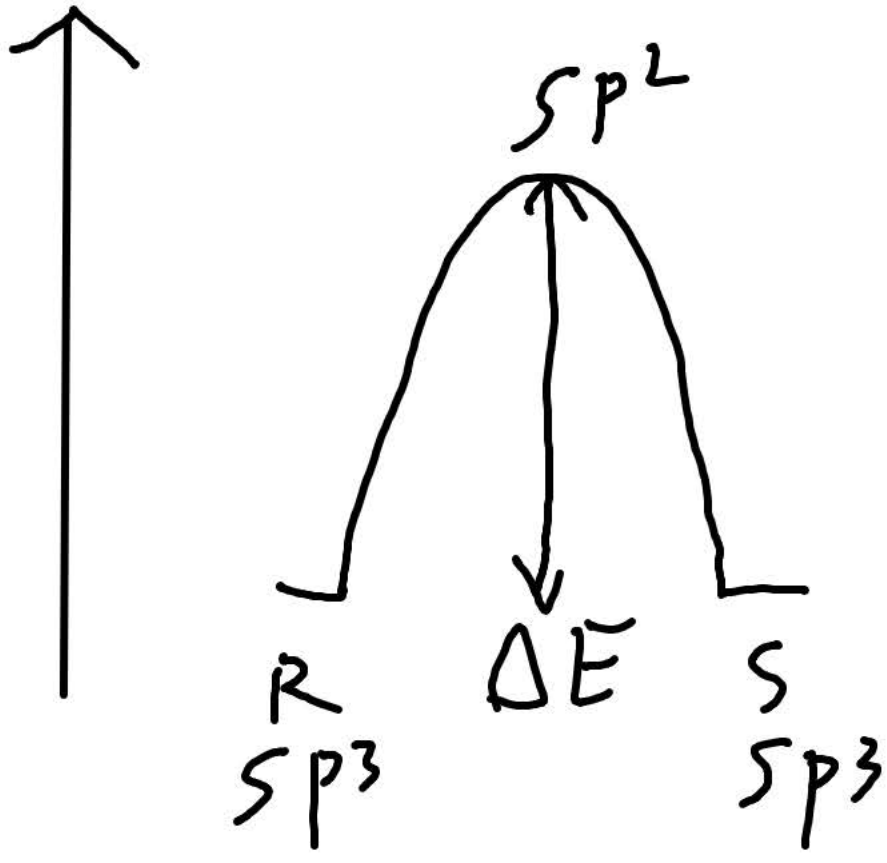
centres sur hétéroatomes





en principe centre de chiralité
X = N [alpha] = 0
X = P [alpha] n'est pas égal à 0

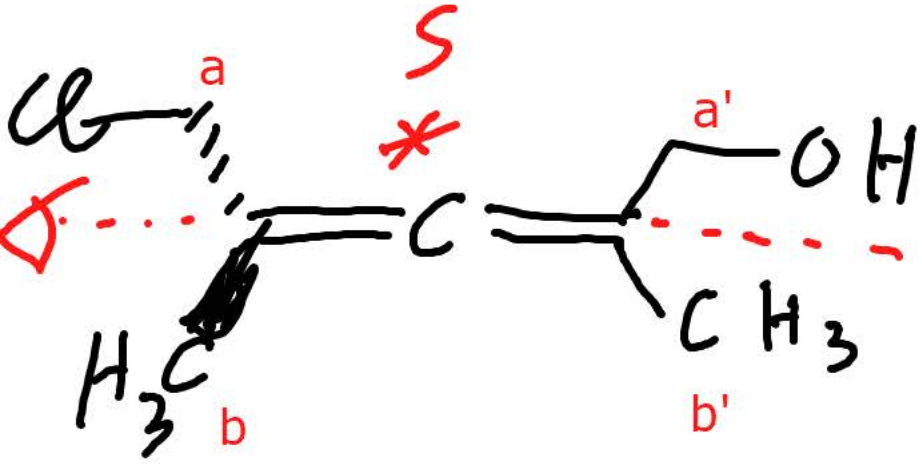
plan de symmétrie, donc non chiral

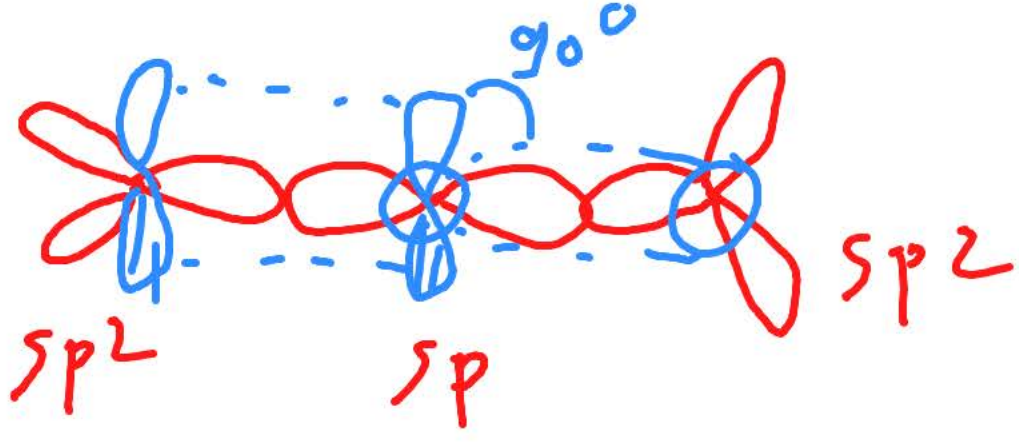


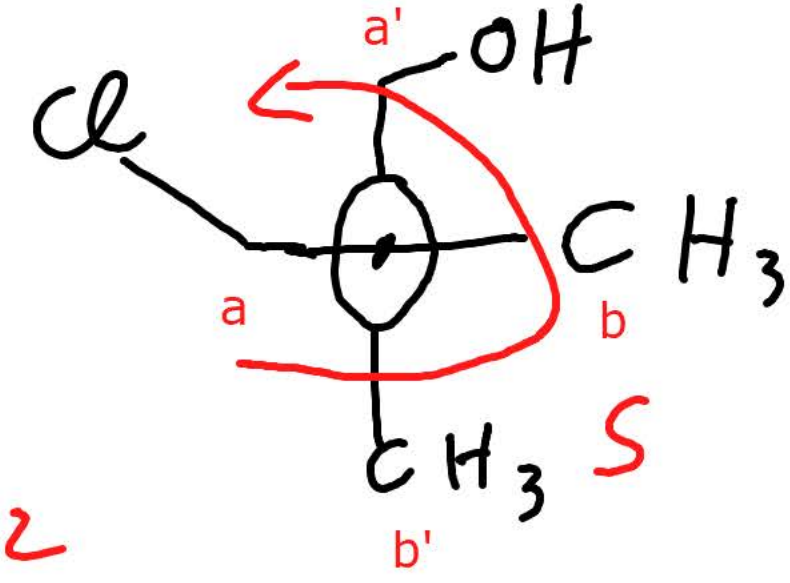
pour P : deltaE = 25 kcal/mol
pour N: delaE = 10kcal/mol

T = 25 °C: 21 kcal/mol

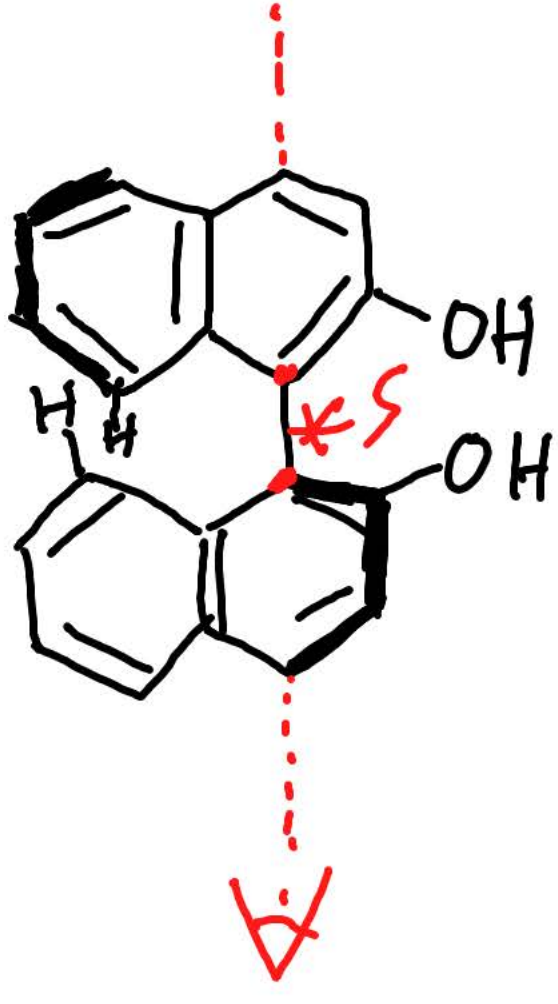
axe de chiralité

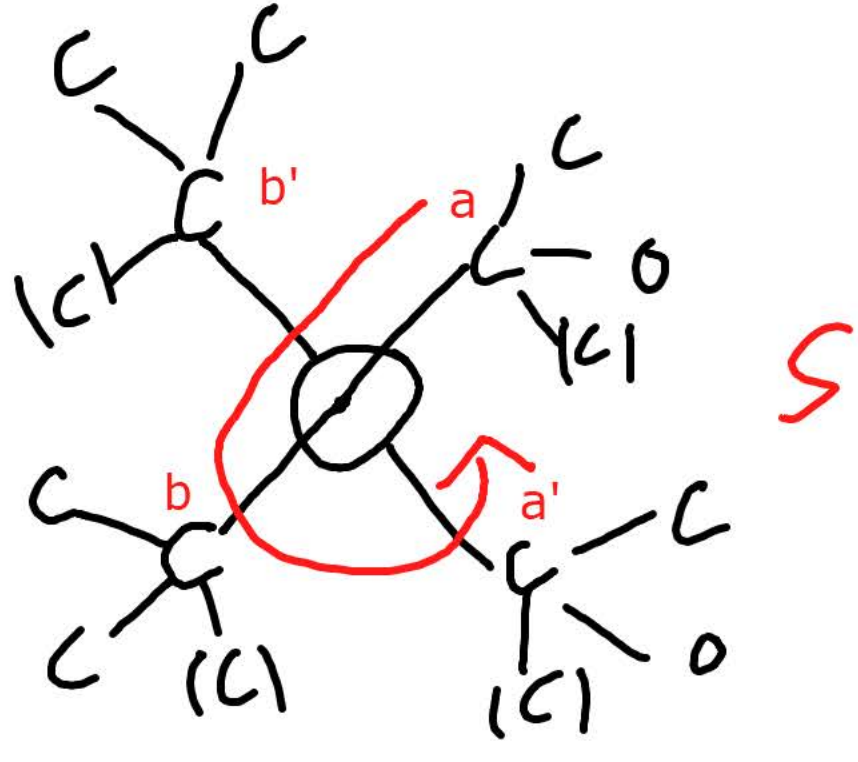


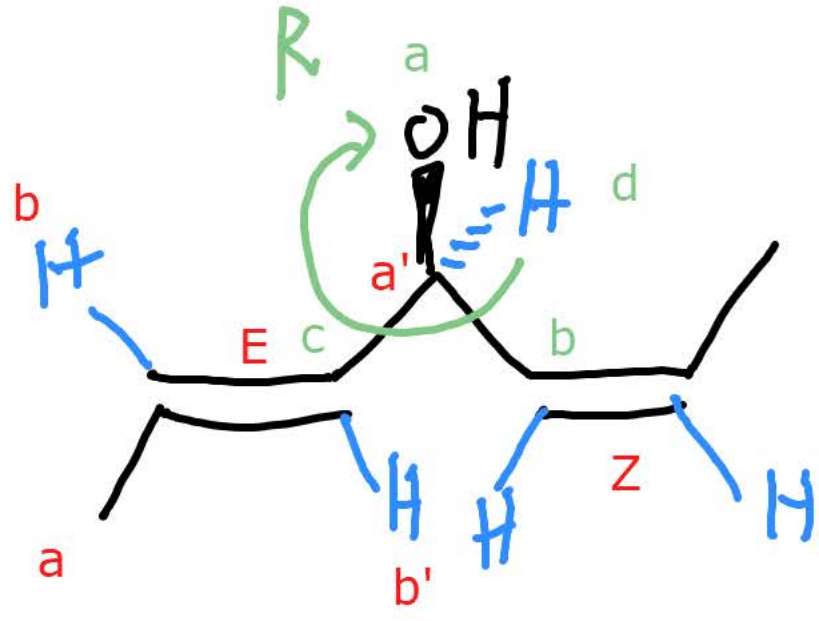




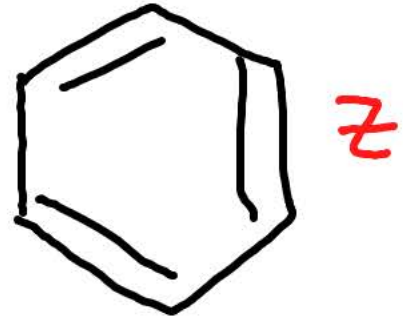
Binol





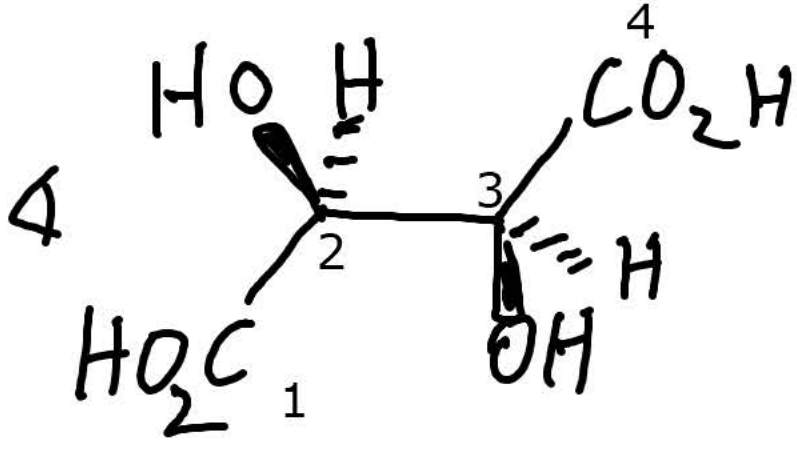


règle: Z à la priorité sur E



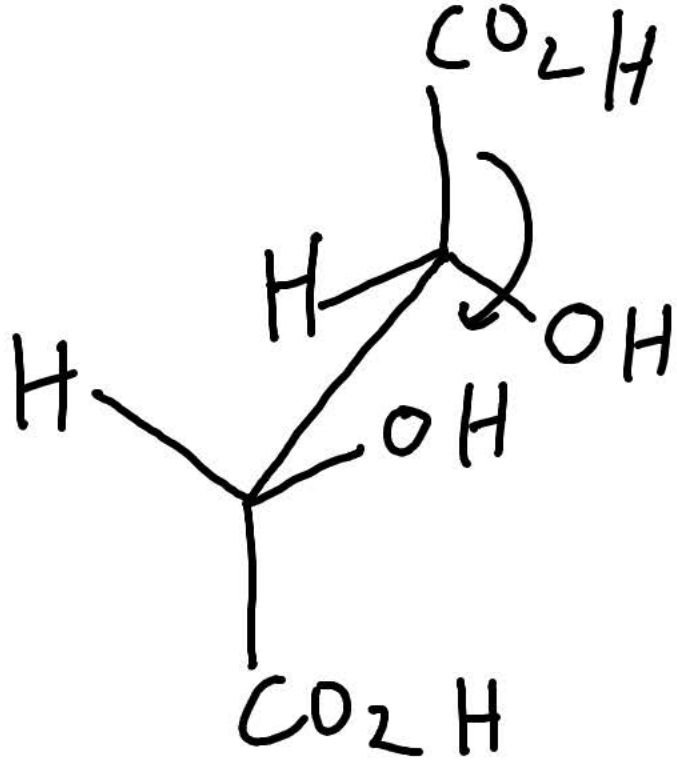
toujours Z, pas nécessaire d'indiquer

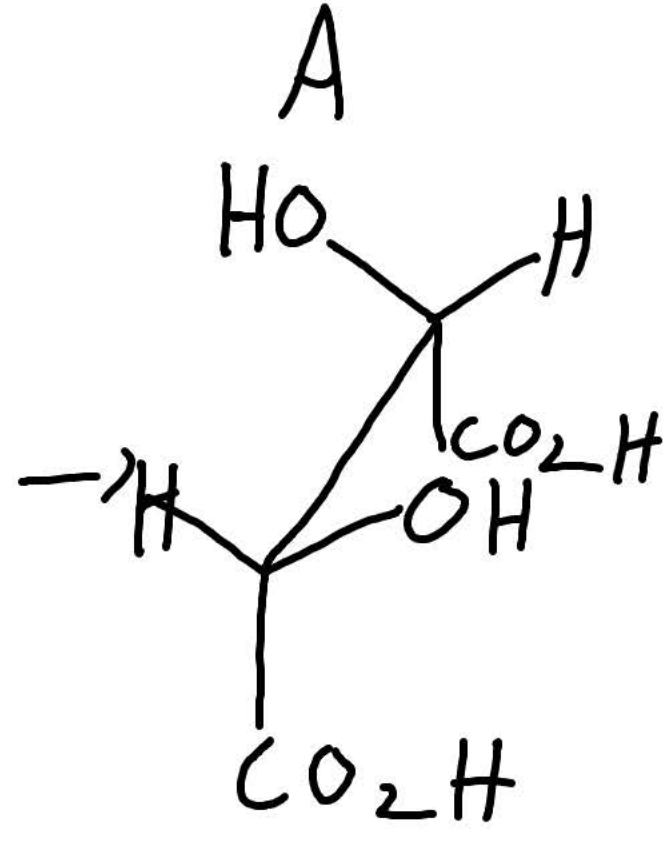
acide tartrique

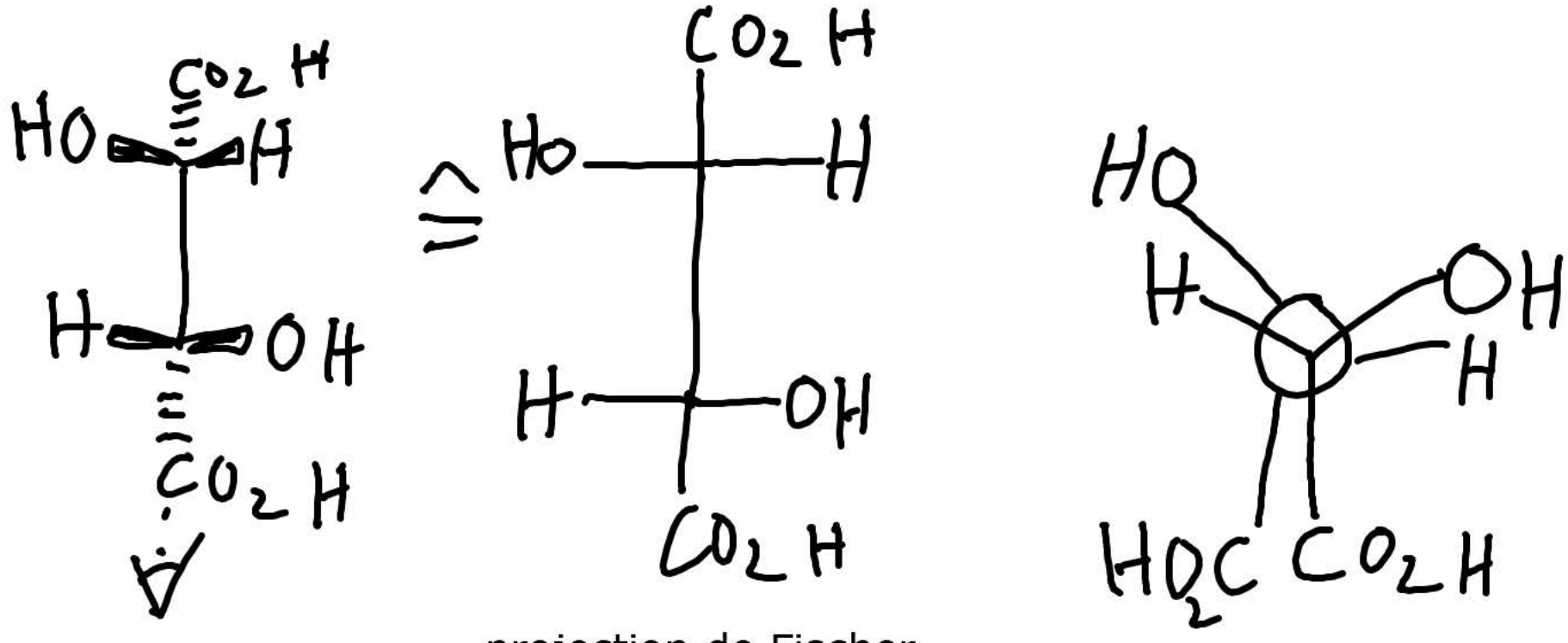


alphaD = -12°

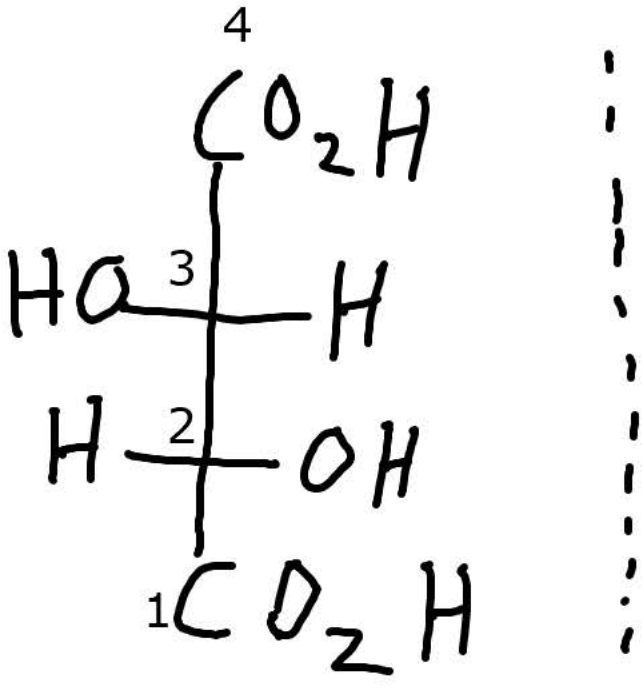
(-)-(2S,3S)



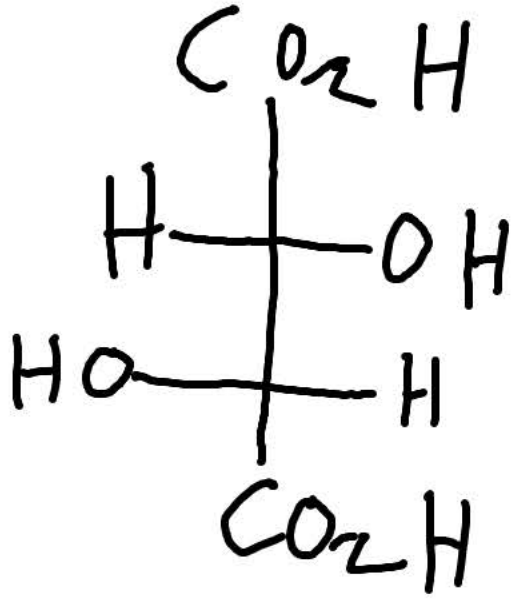




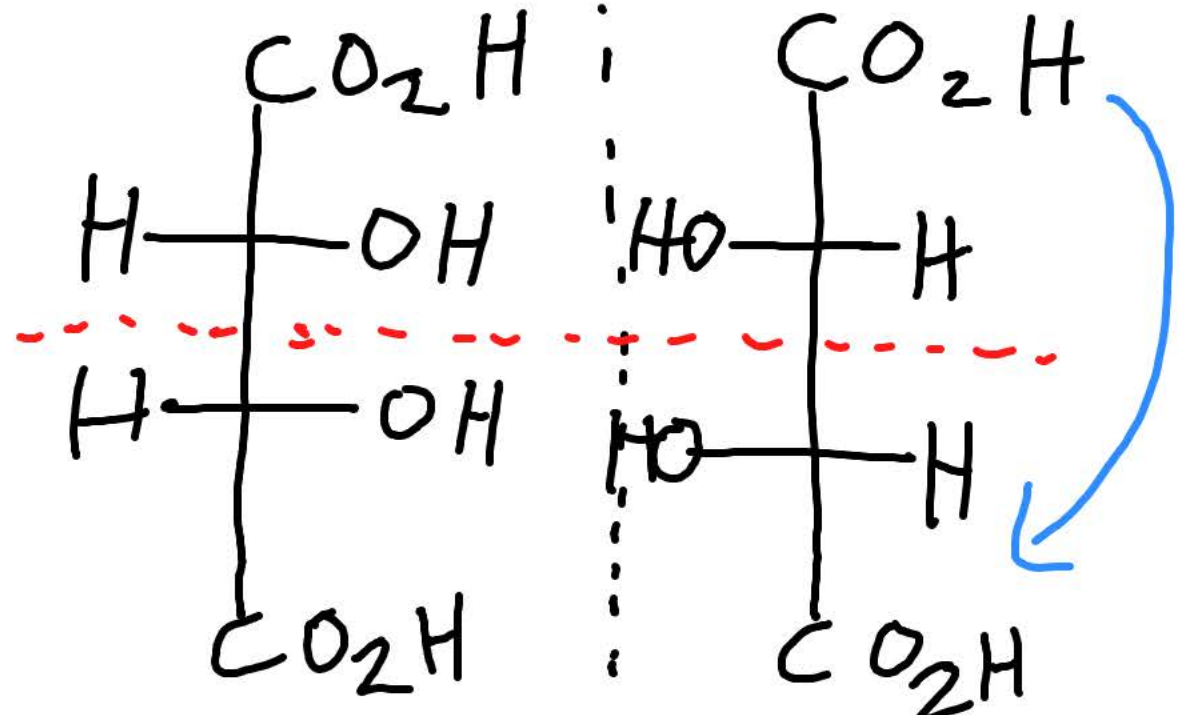
projection de Fischer



(-)-(2S,3S)- acide tartrique
-12°



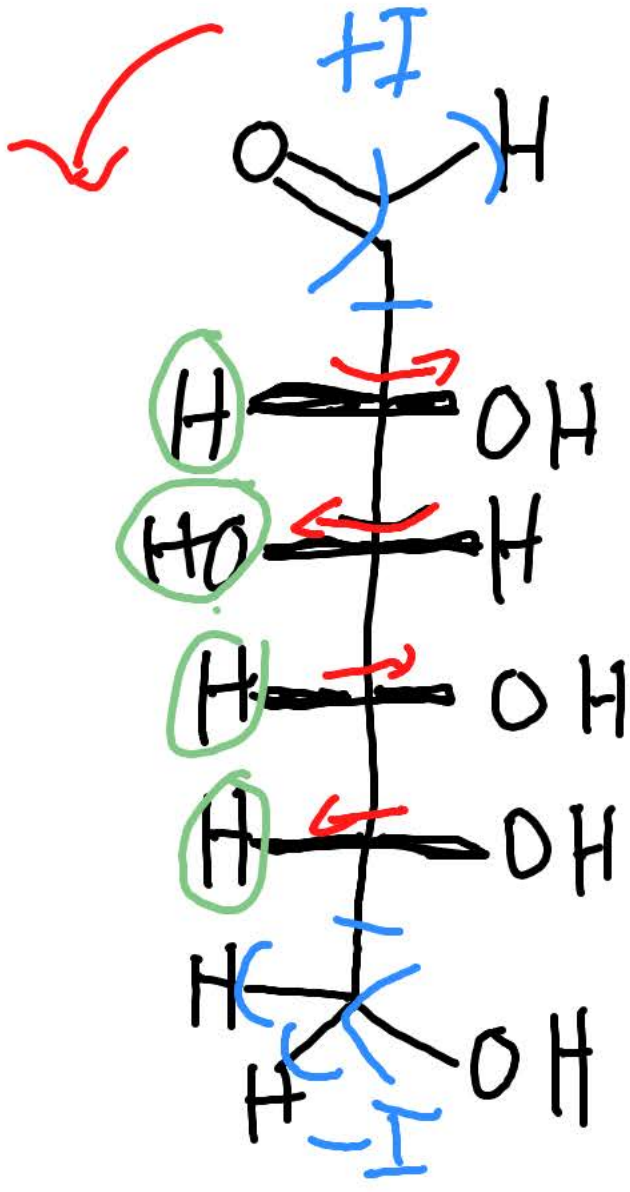
(+)-(2R,3R)
+12°

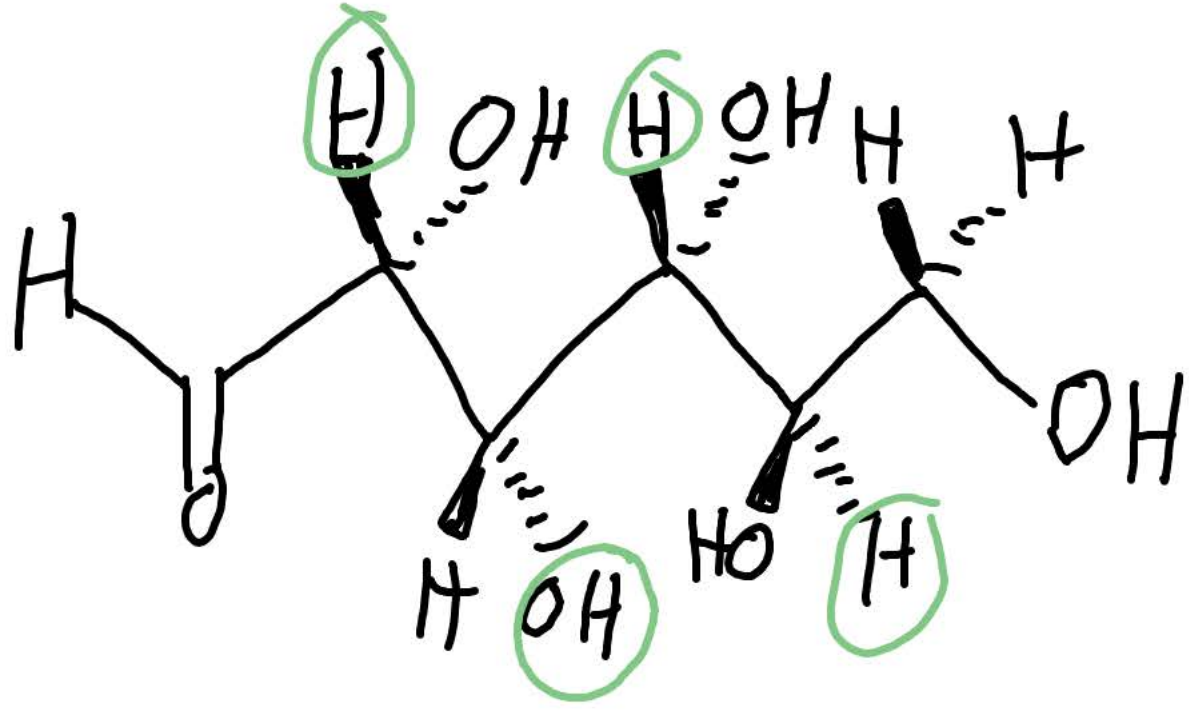


(2S,3R)
0°

(2R,3S)
0°

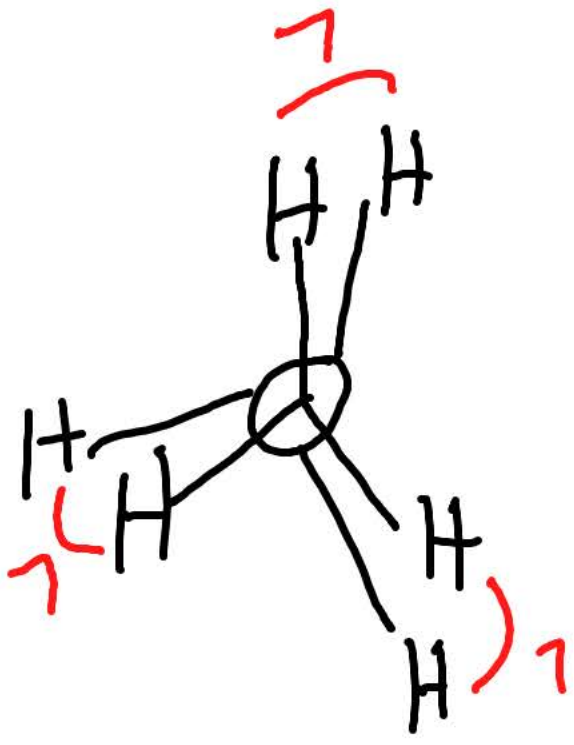
molécules identiques
plan de symétrie, molécule méso non chirale



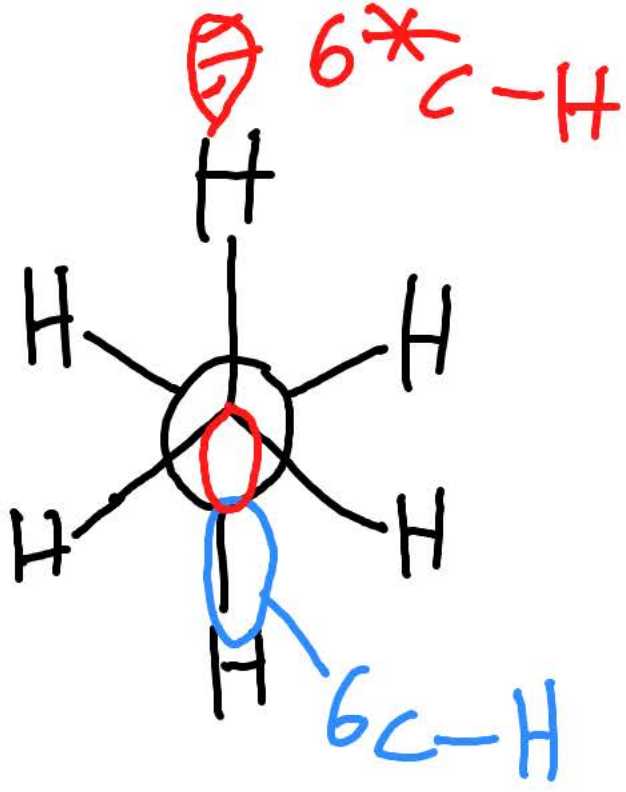


même côté sur Fischer = côté opposé sur "zigzag"

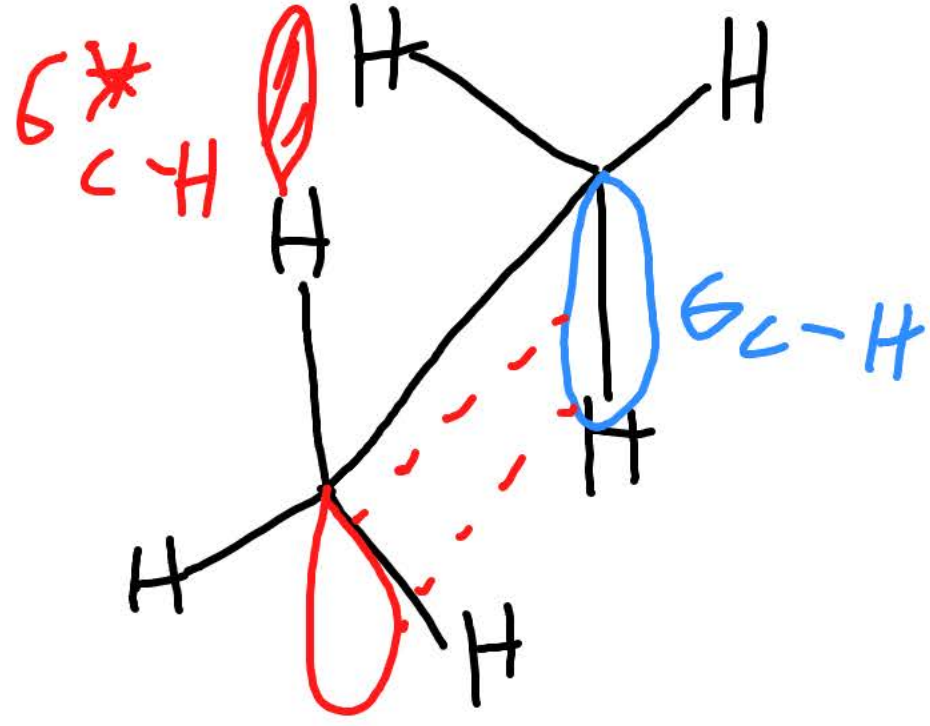
origine de la barrière pour l'éthane



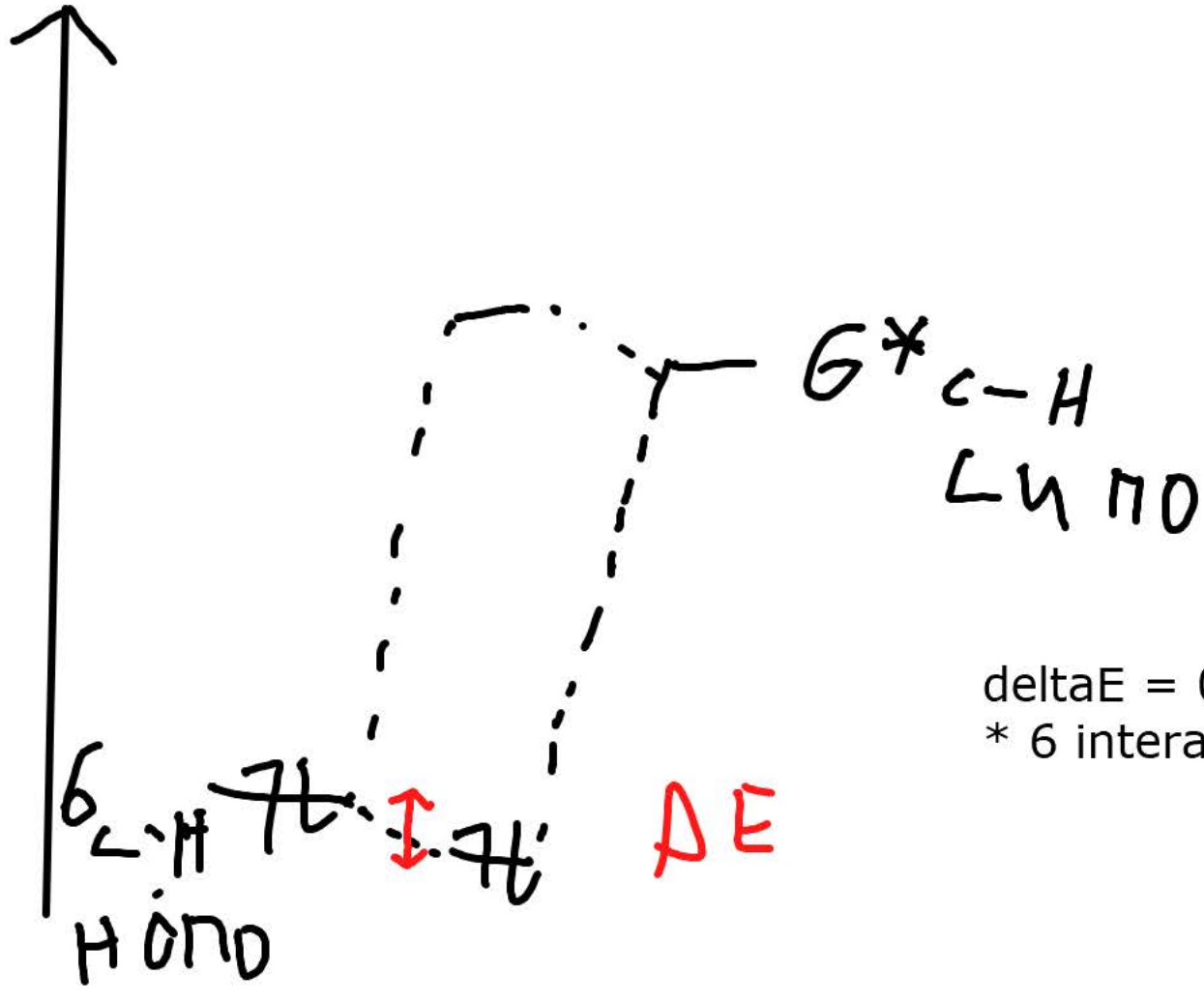
environ 3 kcal/mol



orbitales superposées!

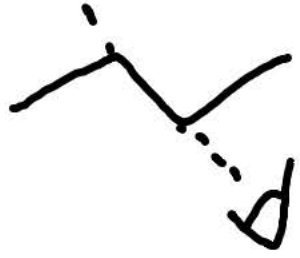


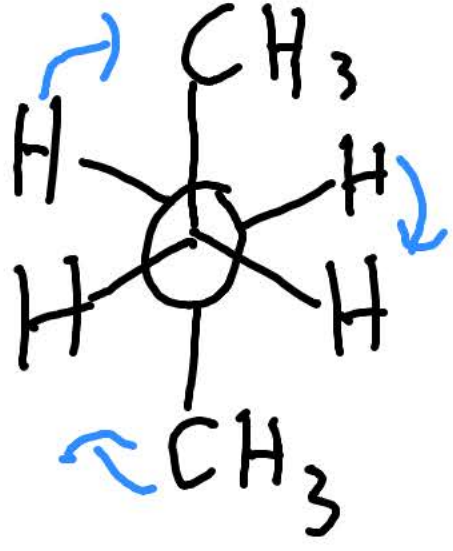
interactions orbitalaires seulement pour conformation décalée



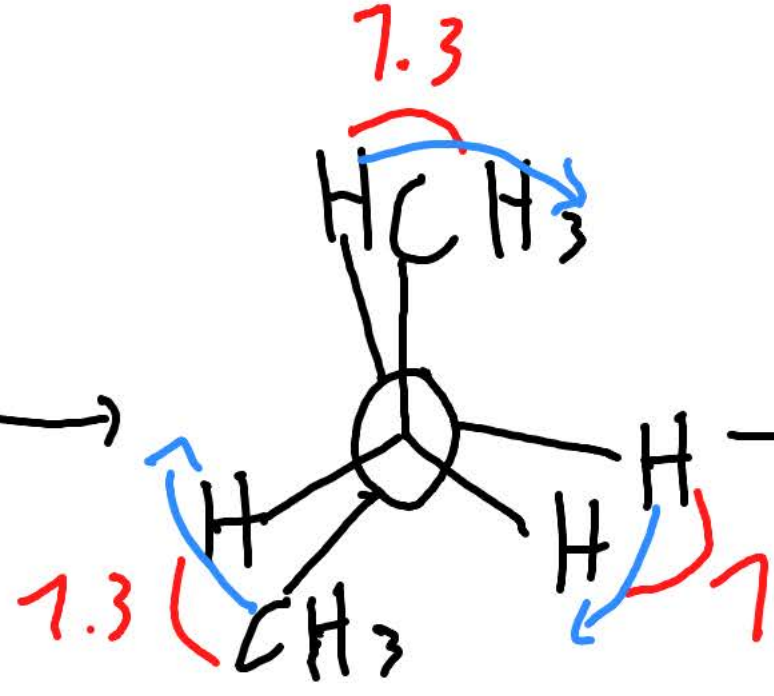
deltaE = 0.25 kcal/mol * 2 électrons
* 6 interactions = 3 kcal/mol

butane



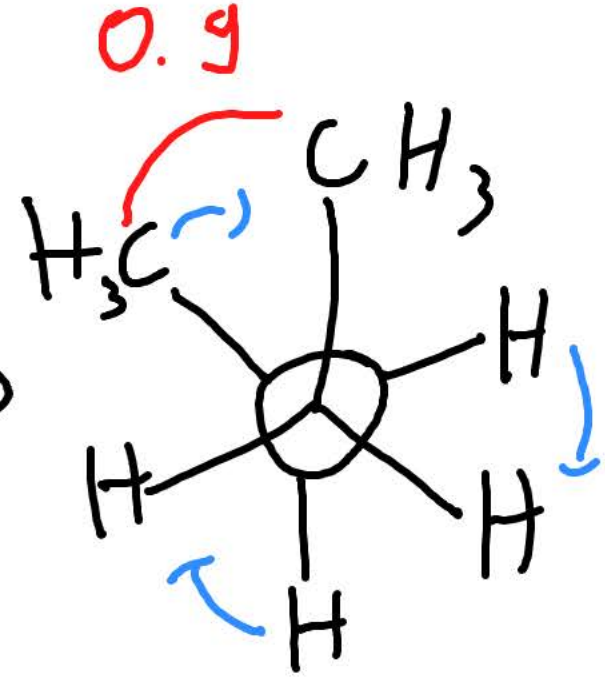


décalée, antipériplanaire
E = 0



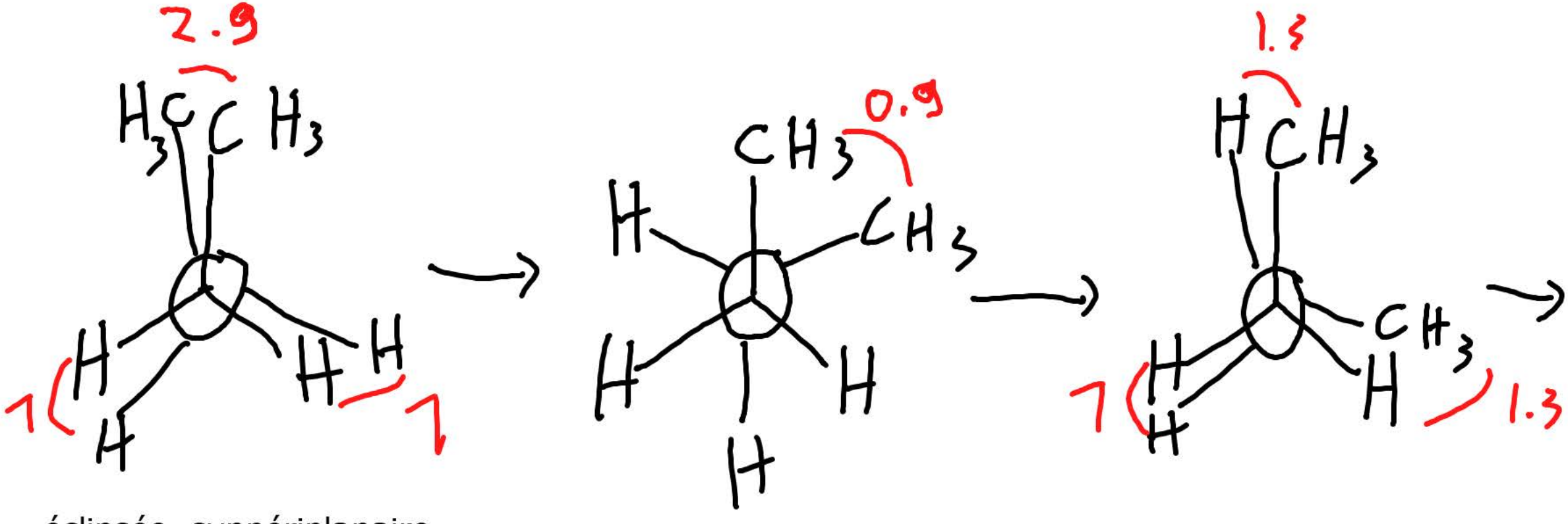
éclipsée, anticlinale

E = 3.6



décalée, synclinale ou gauche

E = 0.9

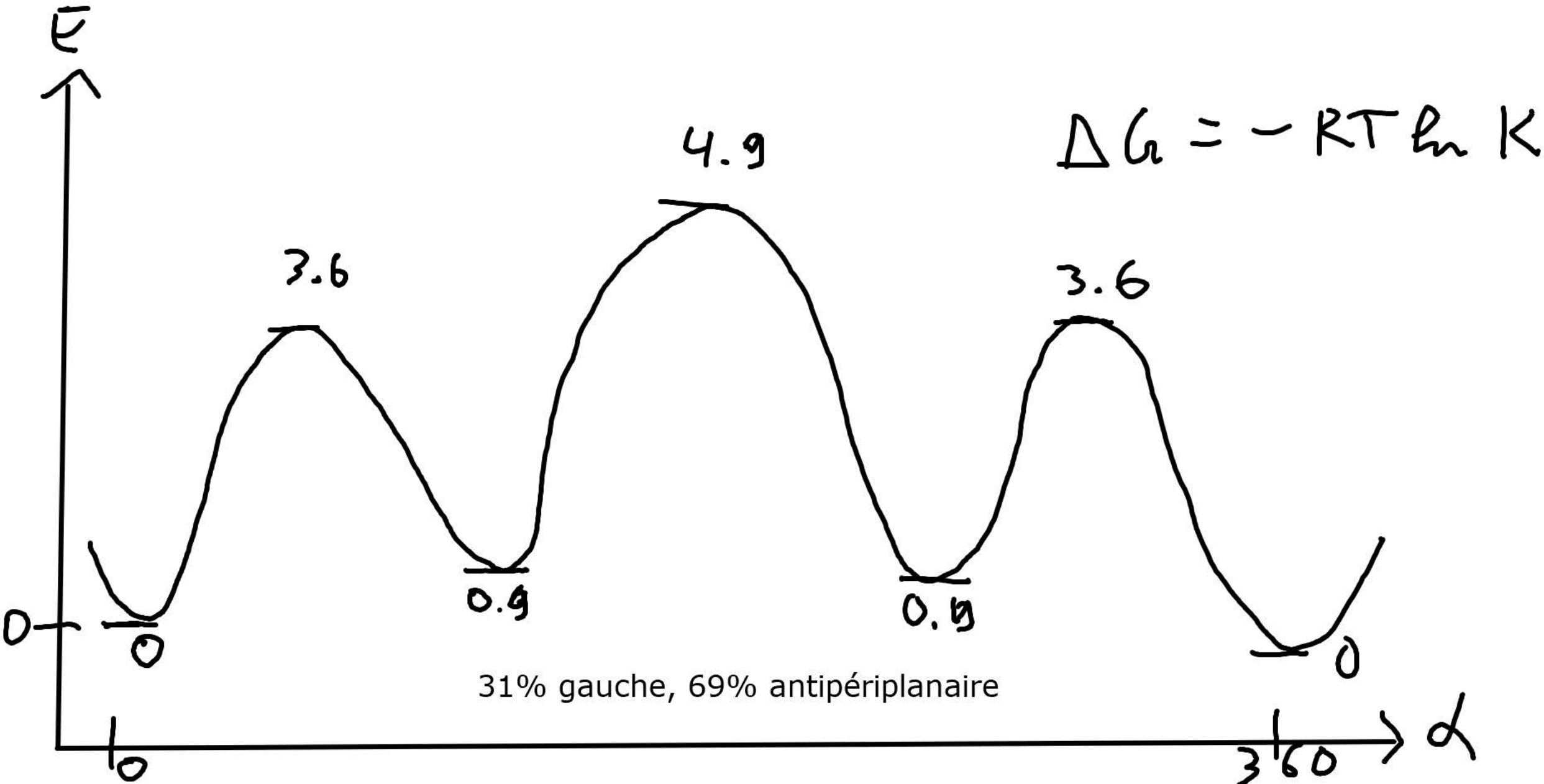


éclipsée, synpériplanaire

E = 4.9

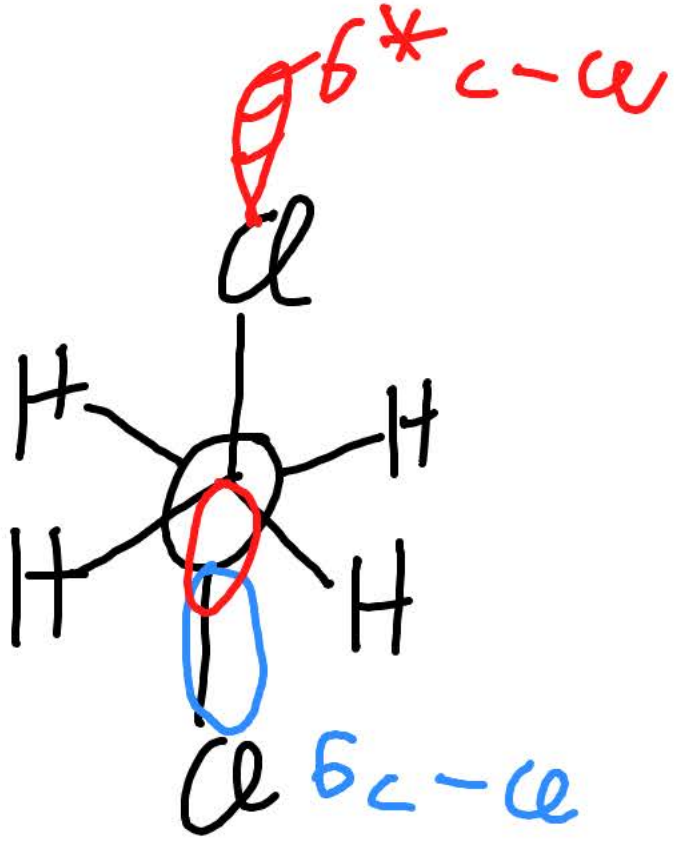
décalée, synclinale ou gauche
E = 0.9

éclipsée, anticlinale
E = 3.6

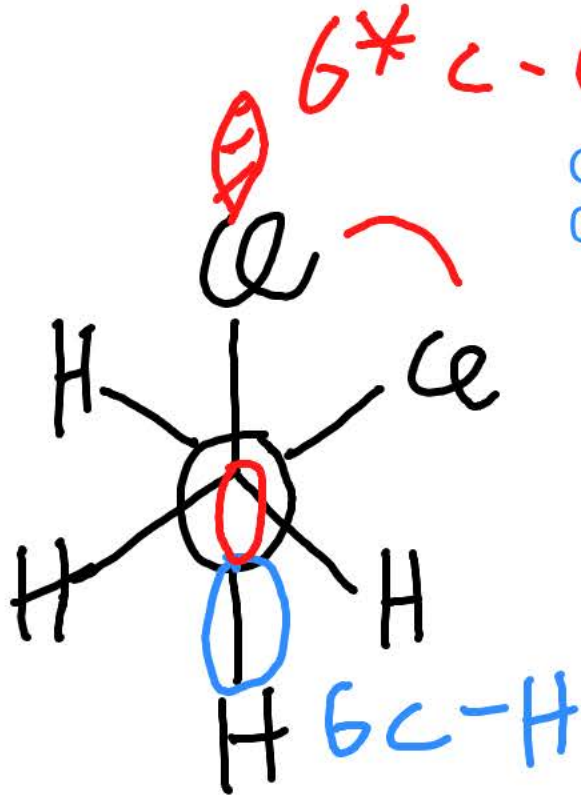


31% gauche, 69% antipériplanaire

butane: antipériplanaire est plus stable que gauche
Dichloroéthane: gauche est plus stable qu'antipériplanaire!

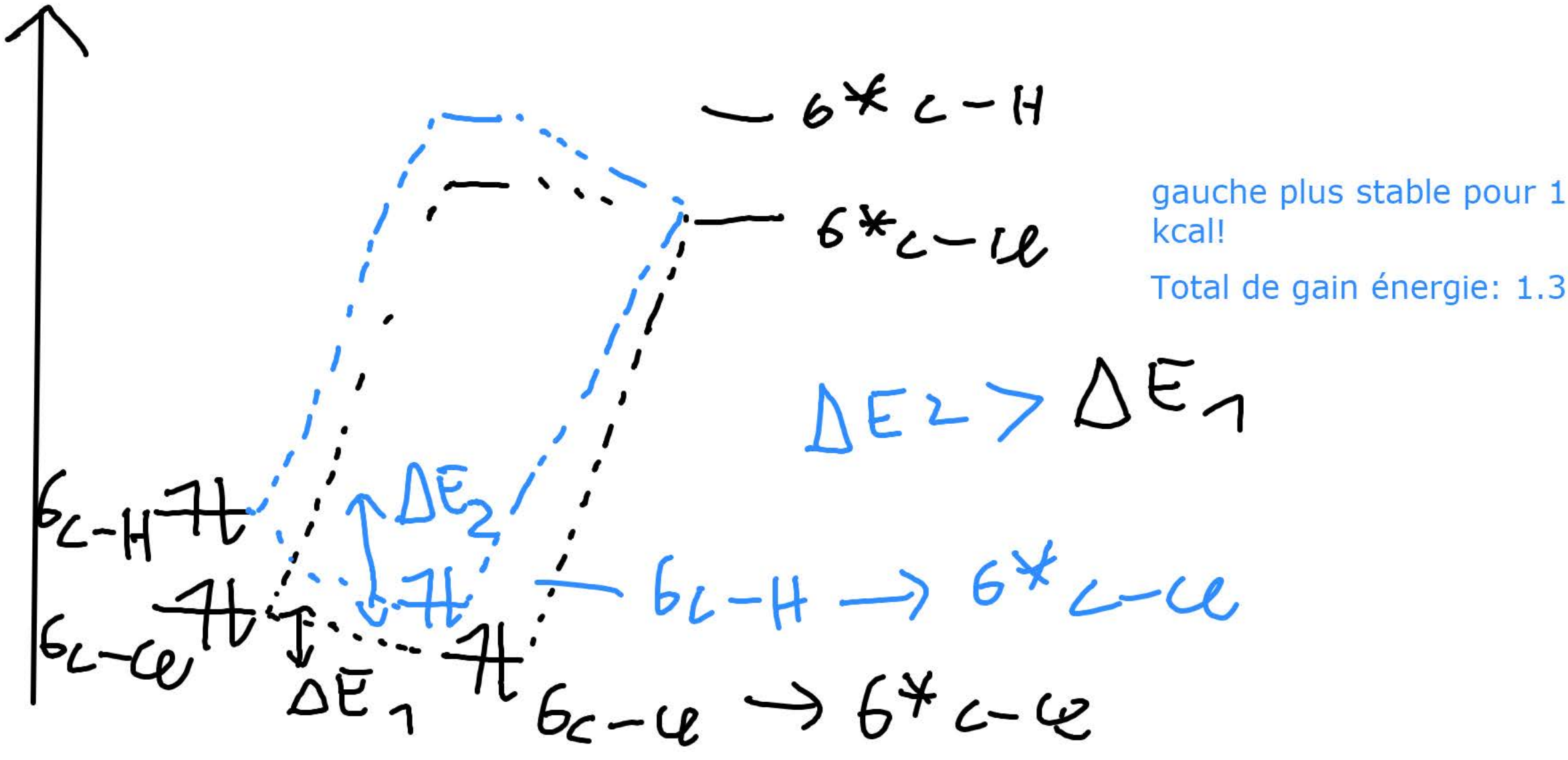


antipériplanaire



gauche

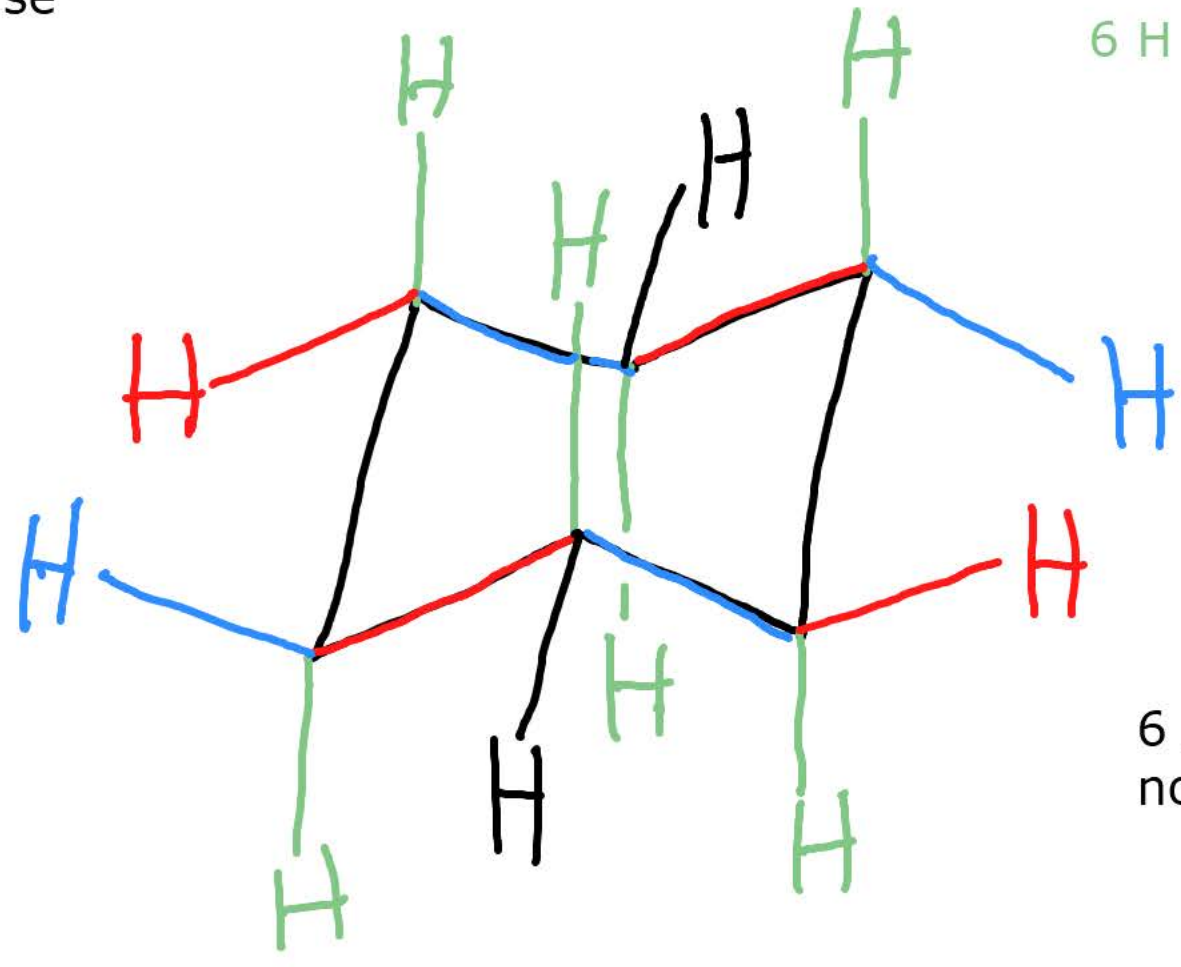
Cl plus petit que CH3, environ 0.3 plutôt que 0.9



gauche plus stable pour 1 kcal!

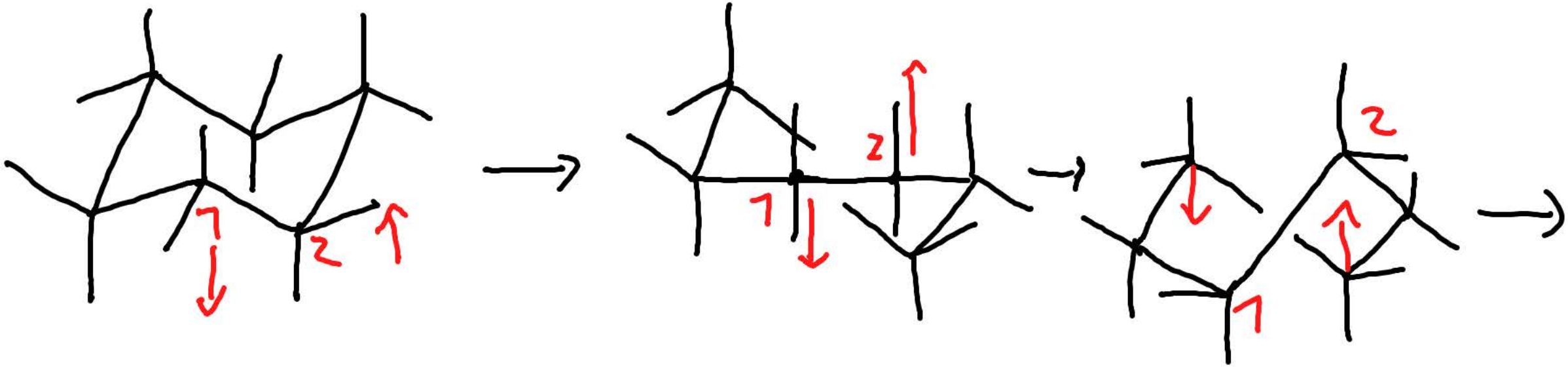
Total de gain énergie: 1.3

cyclohexane: chaise



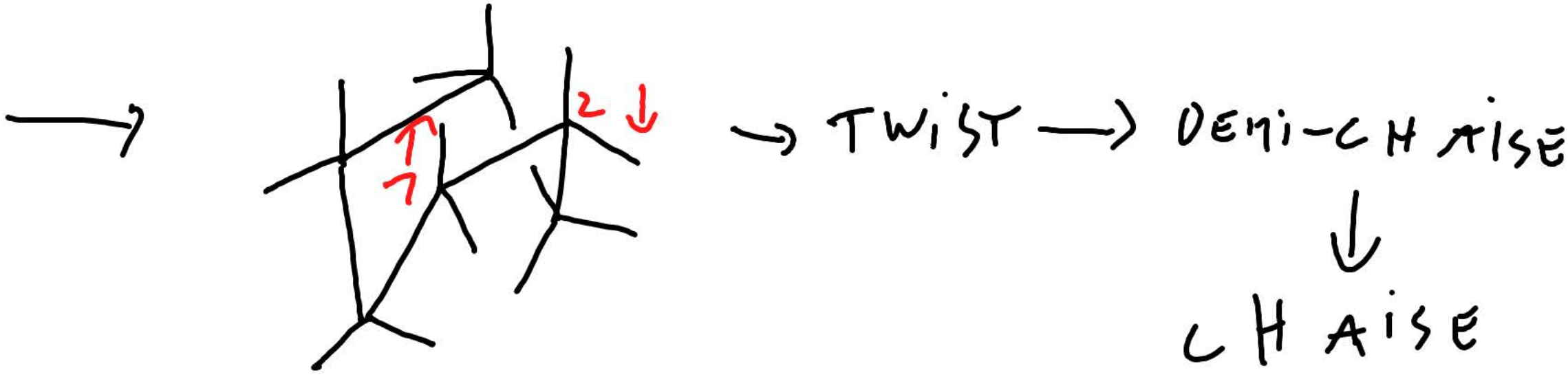
6 H axial

6 H équatorial (rouge, bleu, noir)



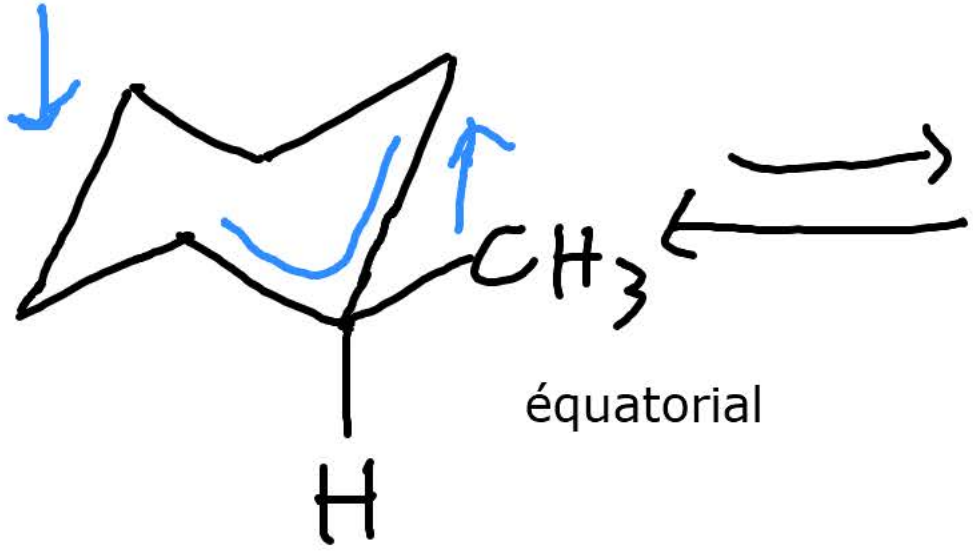
demi-chaise
E = 10.8

bateau croisé ou twist
E = 5.5

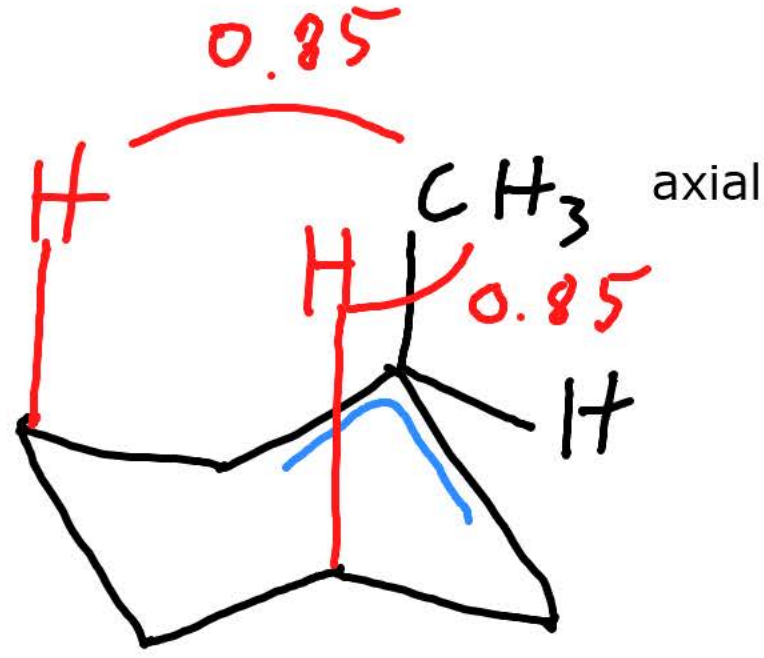


bateau, E = 6.9

méthylcyclohexane

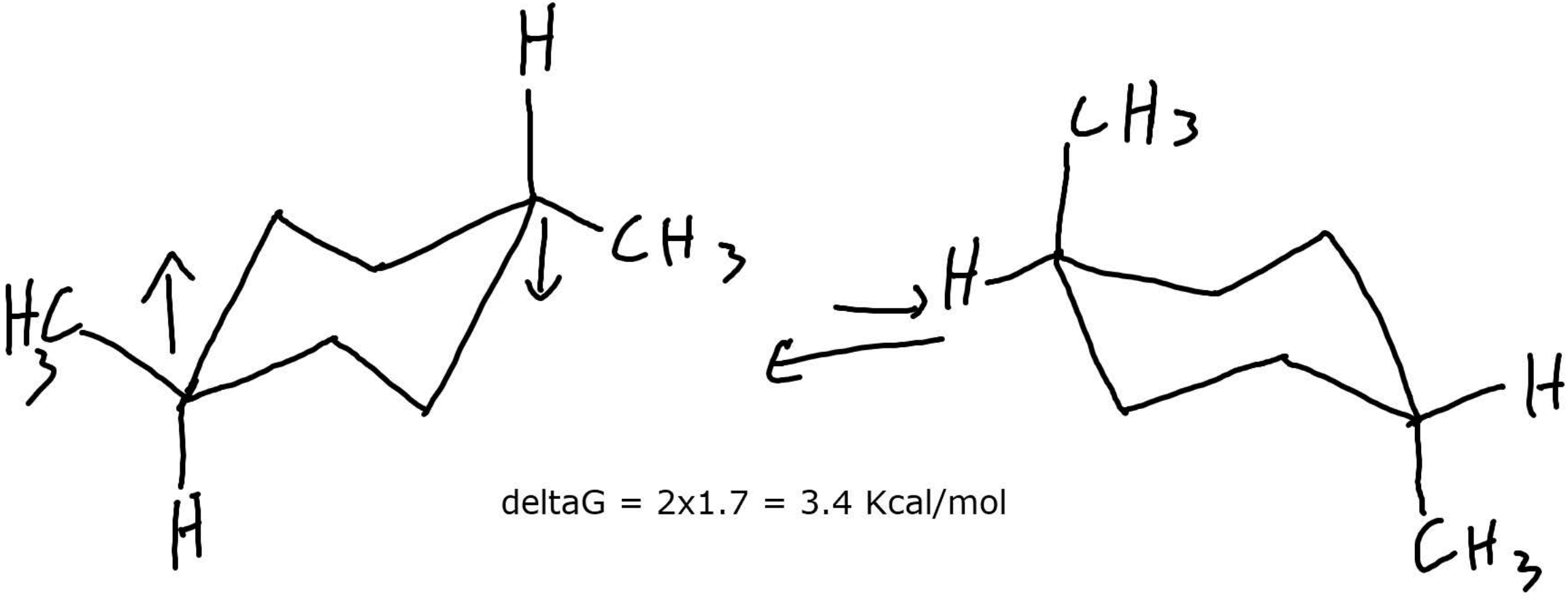


équatorial



axial

deltaG = 1.7 Kcal/mol
= Valeur A du méthyle
mélange de 95:5

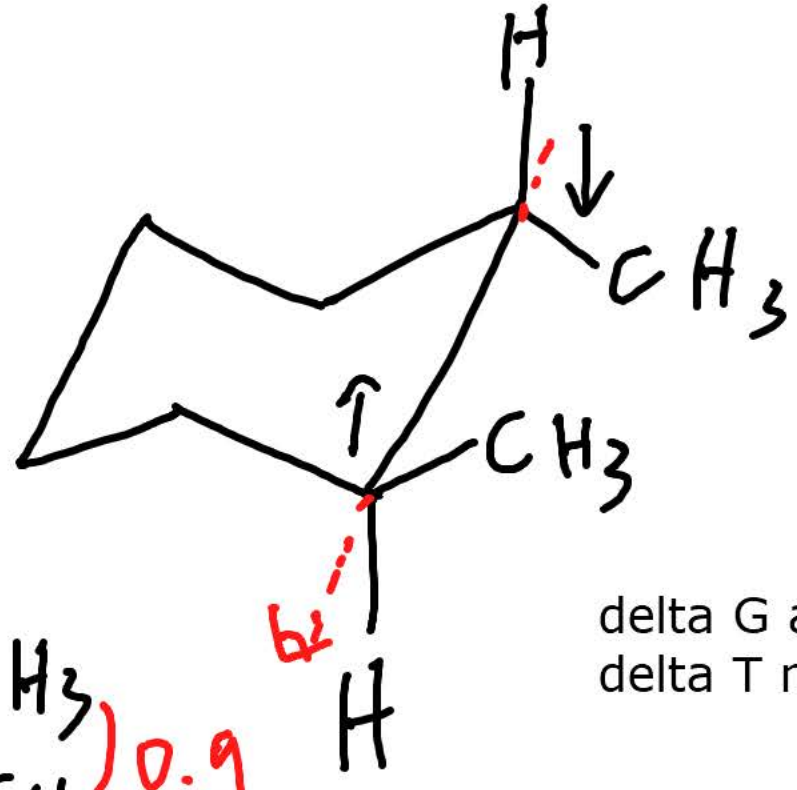


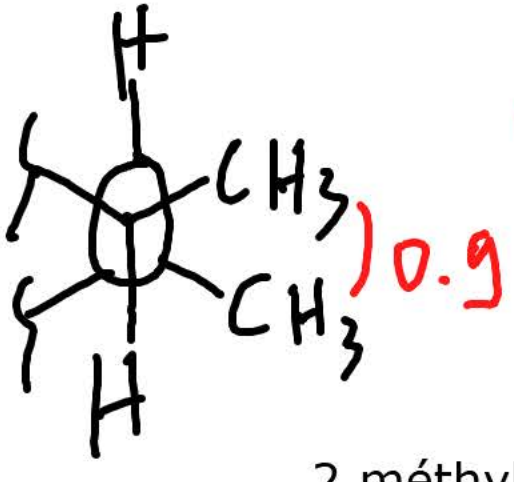
deltaG = 2x1.7 = 3.4 Kcal/mol

2 méthyles équatorials

2 méthyles axiales

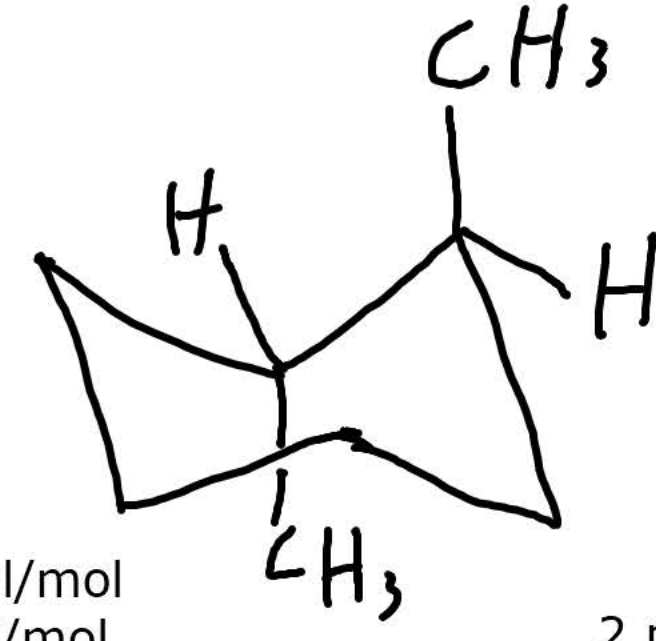
1,2-trans-diméthylcyclohéxane





2 méthyles équatorials

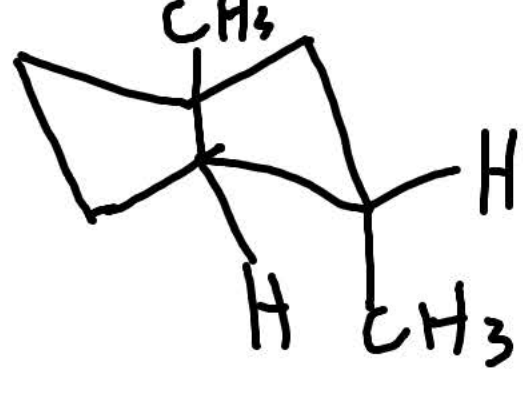
+ 1 conformation gauche de 0.9 kcal/mol



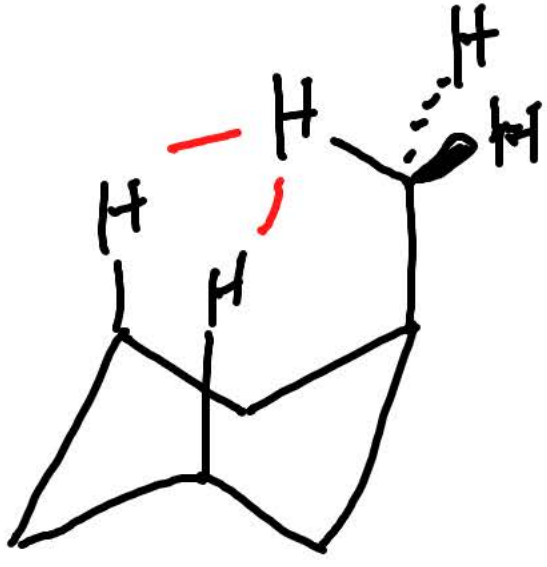
delta G attendu: 3.4 kcal/mol
delta T mesuré: 2.5 kcal/mol

2 méthyles axiales

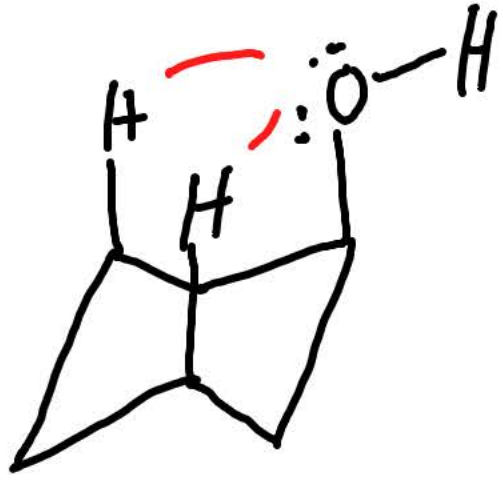
ou



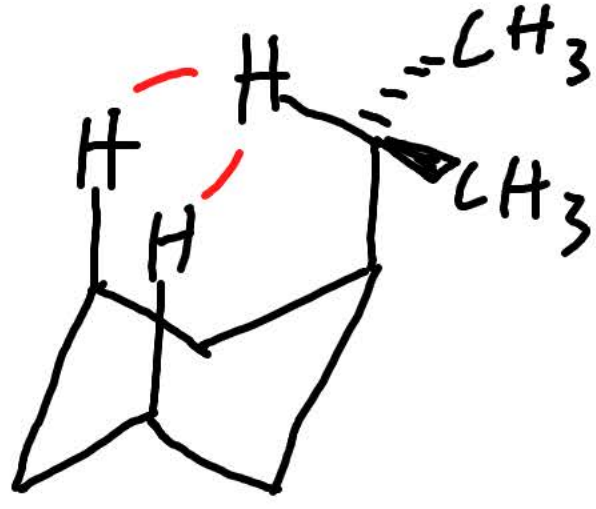
exemples de valeurs A



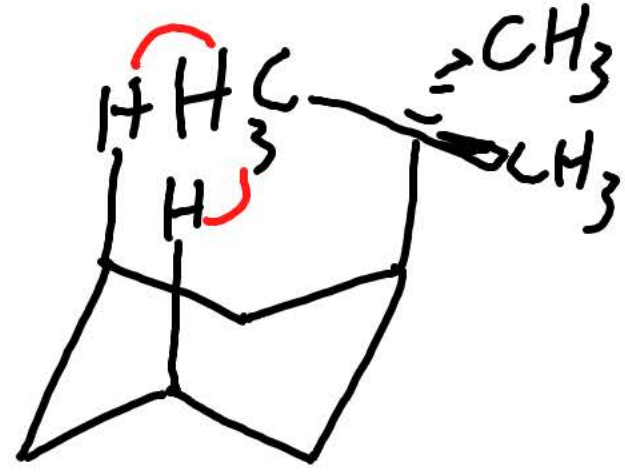
A = 1.7



A = 0.9

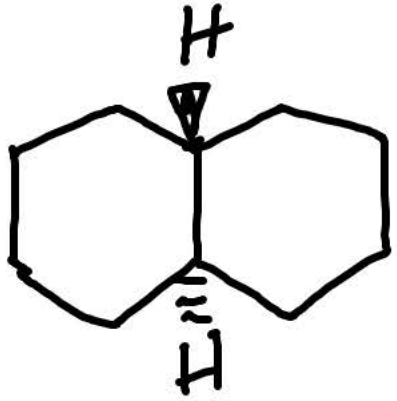


A = 2.2

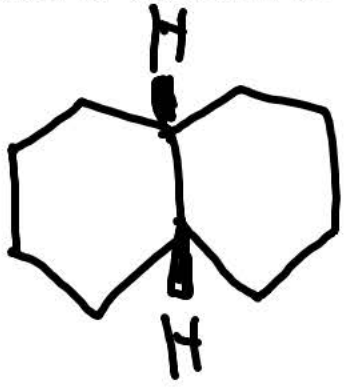


A = 5

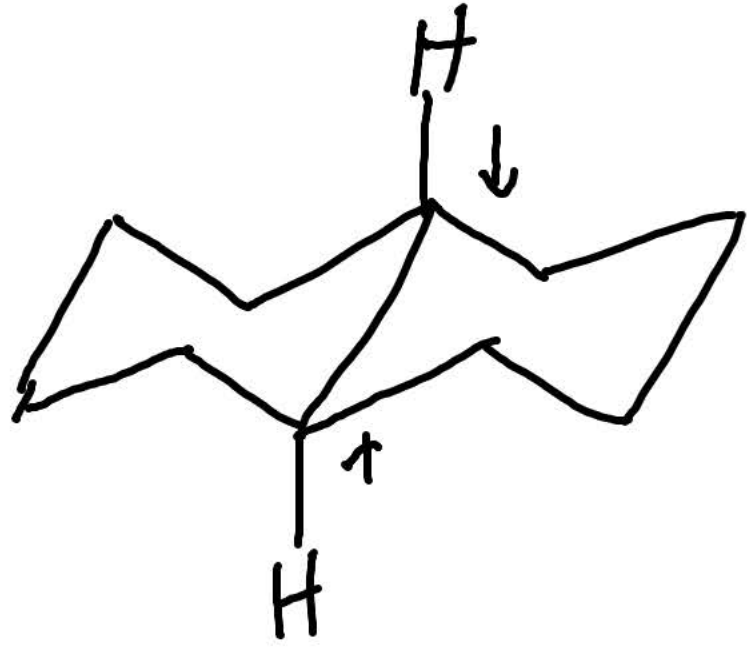
les décalines



trans-décaline

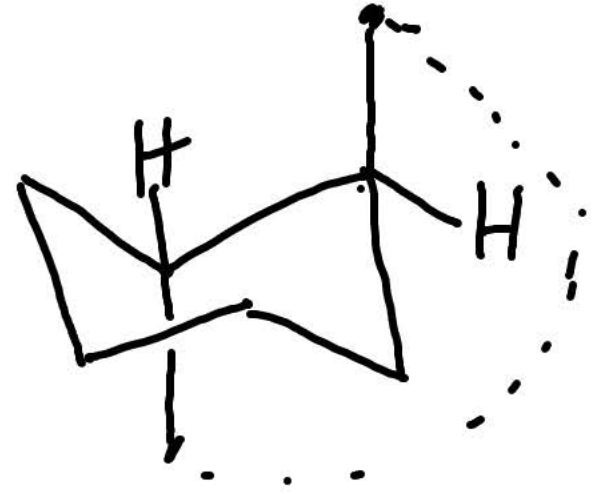


cis-décaline

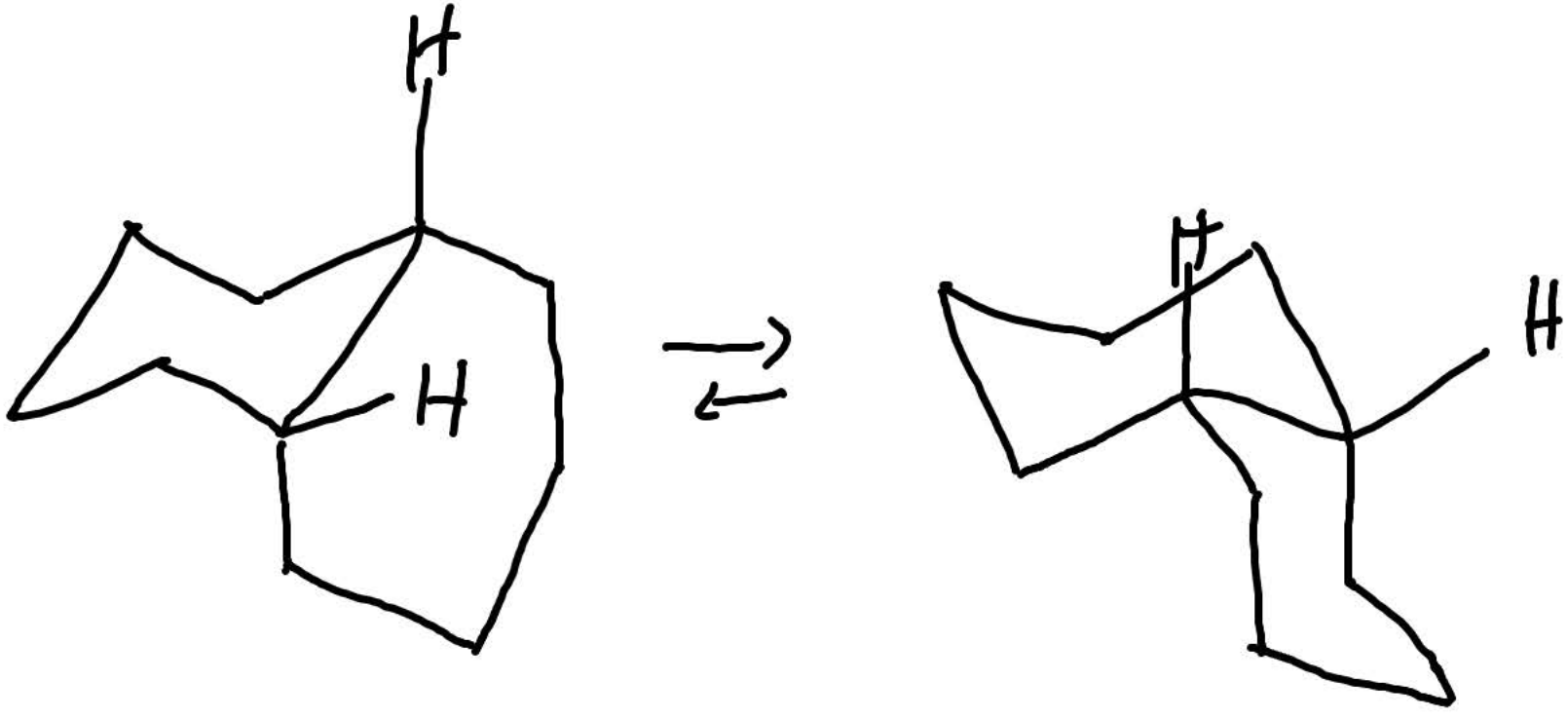


structure planaire

seulement un conformère pour la trans-décaline!



trop éloigné pour fermer le cycle à 6

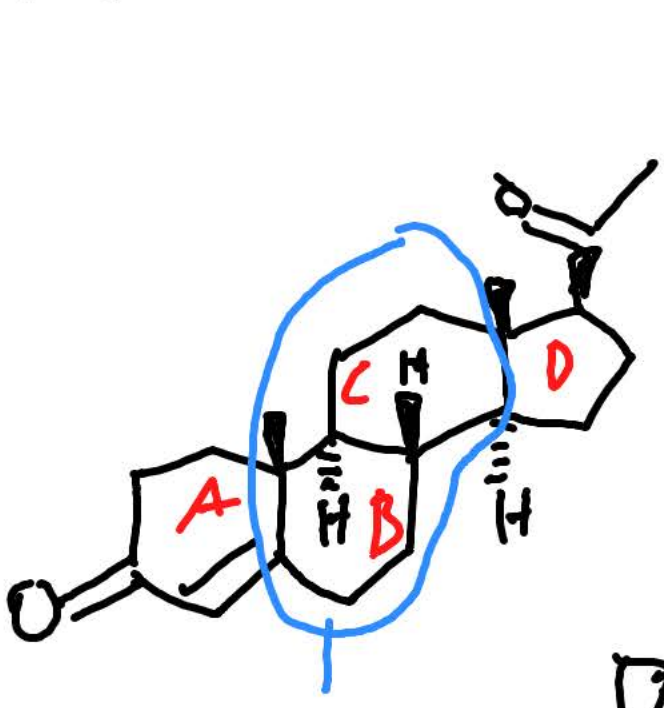


1 CH2R et 1 H axial

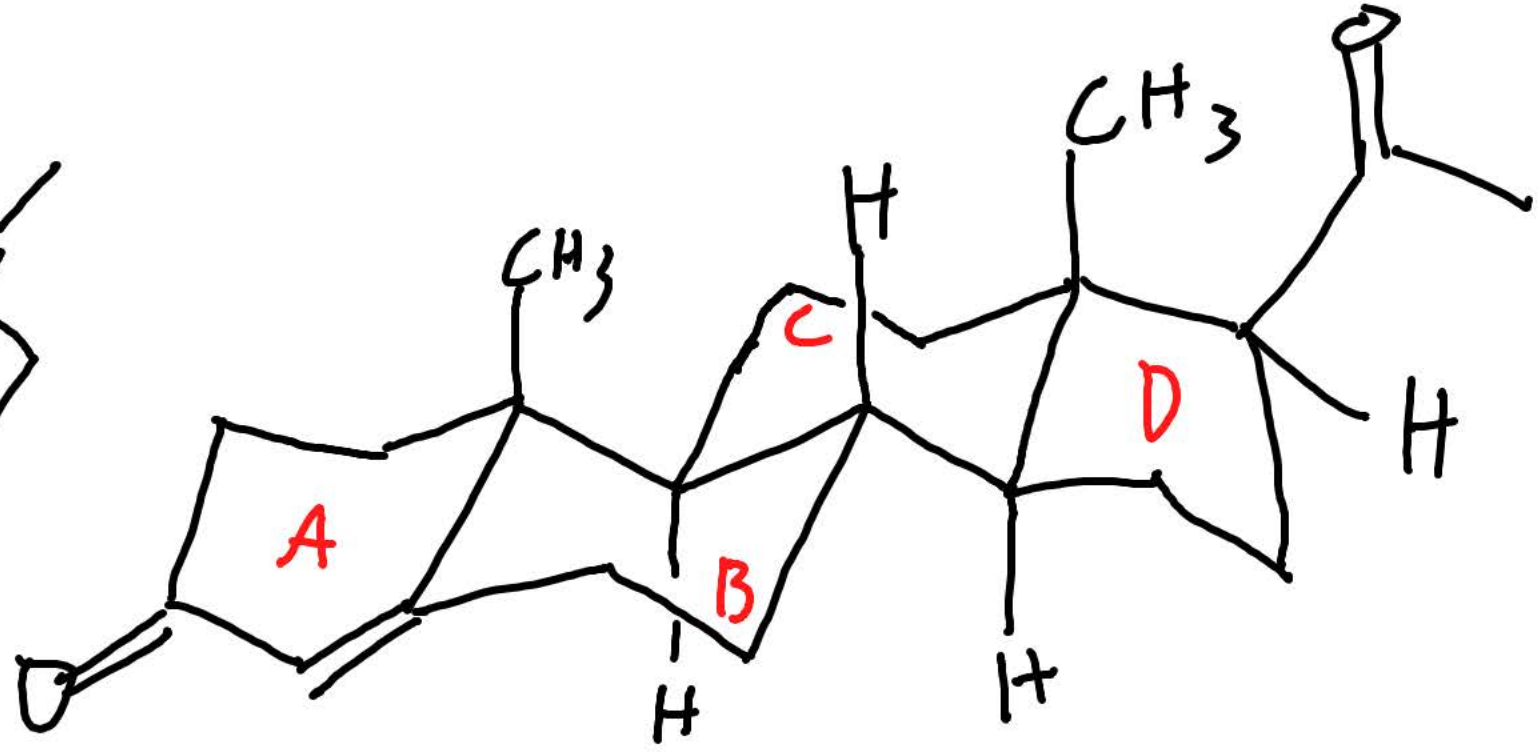
1 CH2R et 1 H axial

2 conformations égales

progesterone

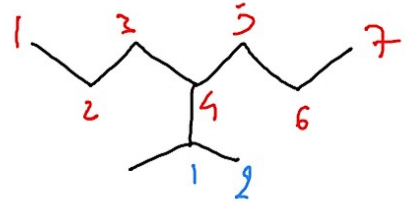


trans-décaline

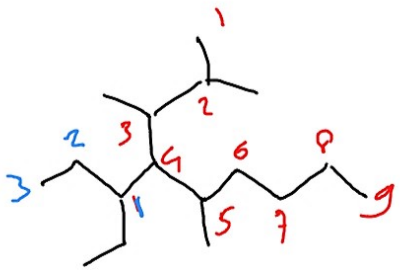


structure très plate!

Nomenclature des alcanes



4-(1-méthyléthyl)heptane

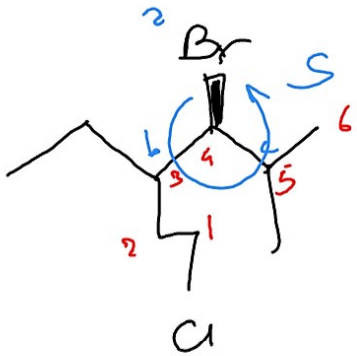


nonane

2,3,5-triméthyl

4-(1-éthylpropyl)

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

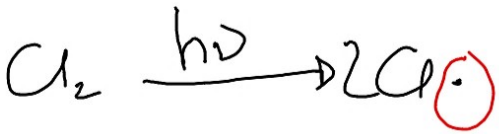


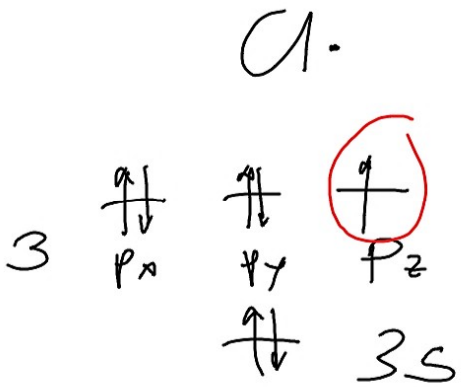
Halogènes: nom de l'halogène, avec suffix "O"
fluoro, chloro, bromo, iodo

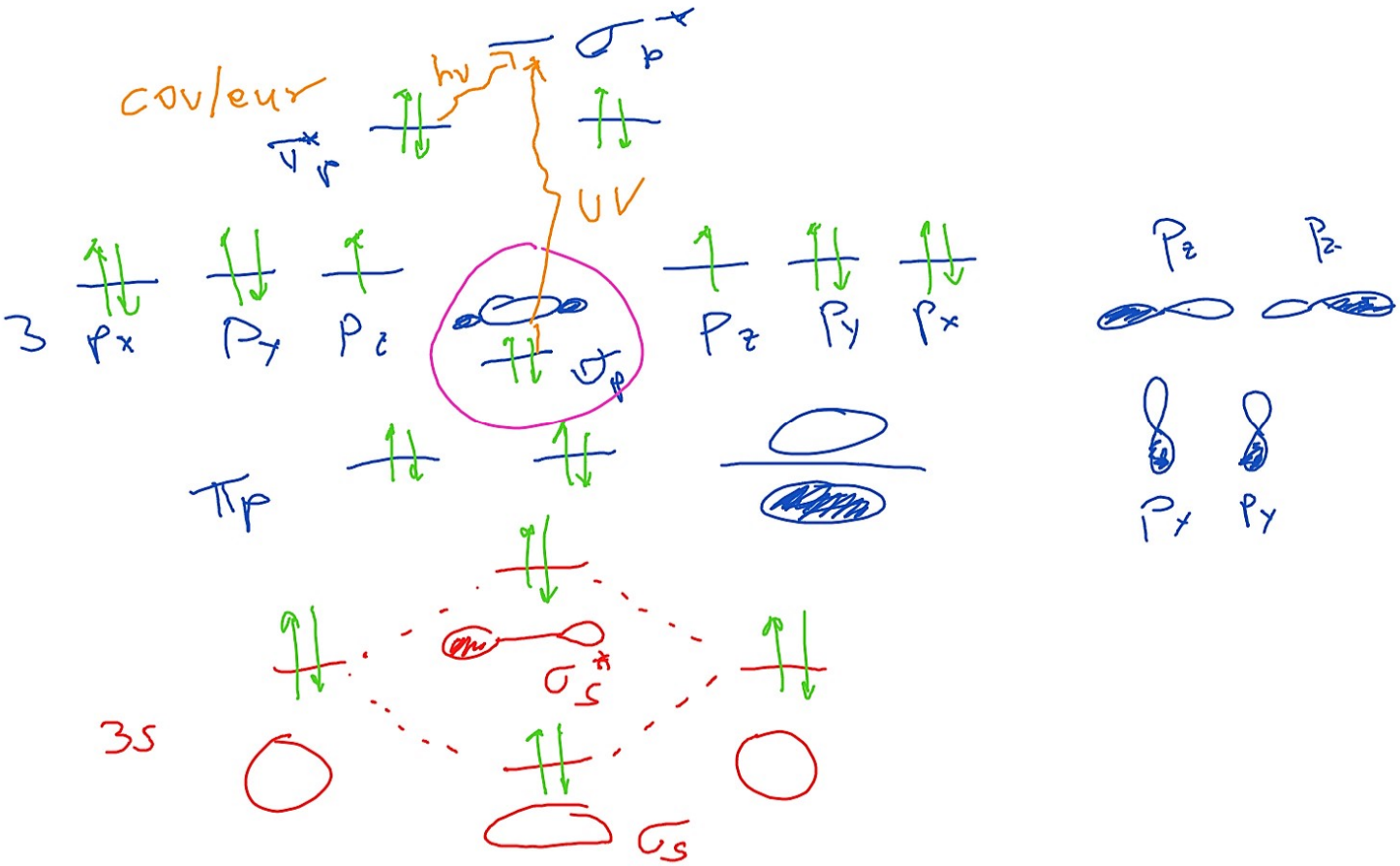
(4S)-4-bromo-1-chloro-3-éthyl-5-méthylhexane

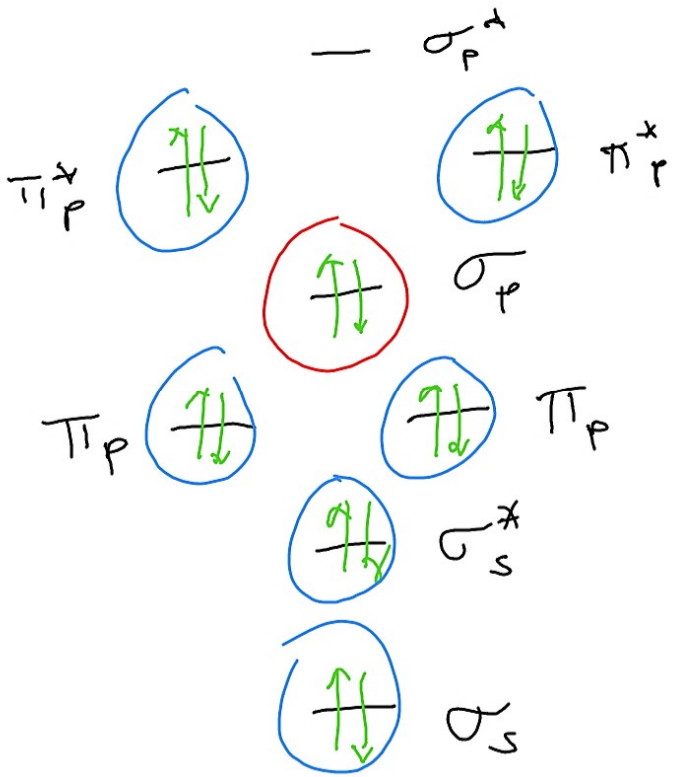
Chloration du méthane

a) Initiation





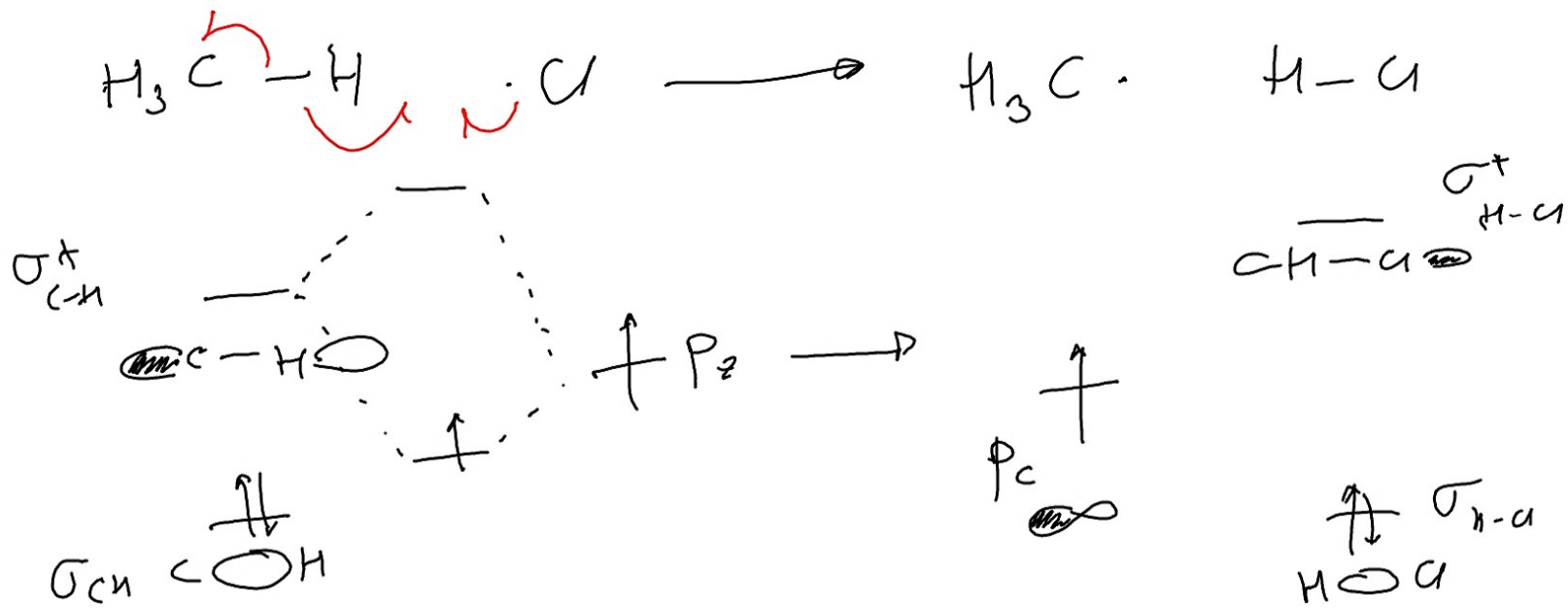

couleur
hν
UV
3 px
py
pz
pz
py
px
πp
3s
pz
pz
px
py



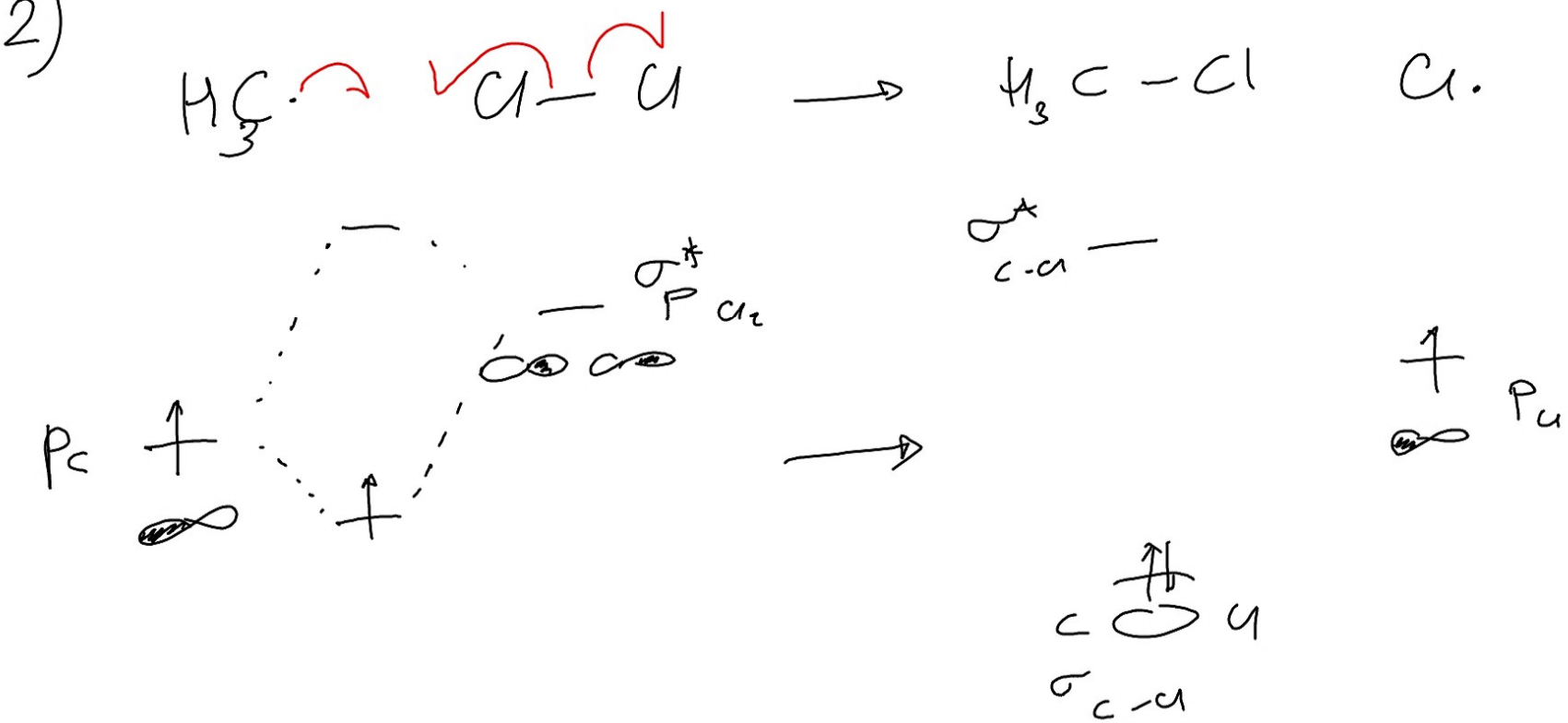
14 e^-

b) propagation

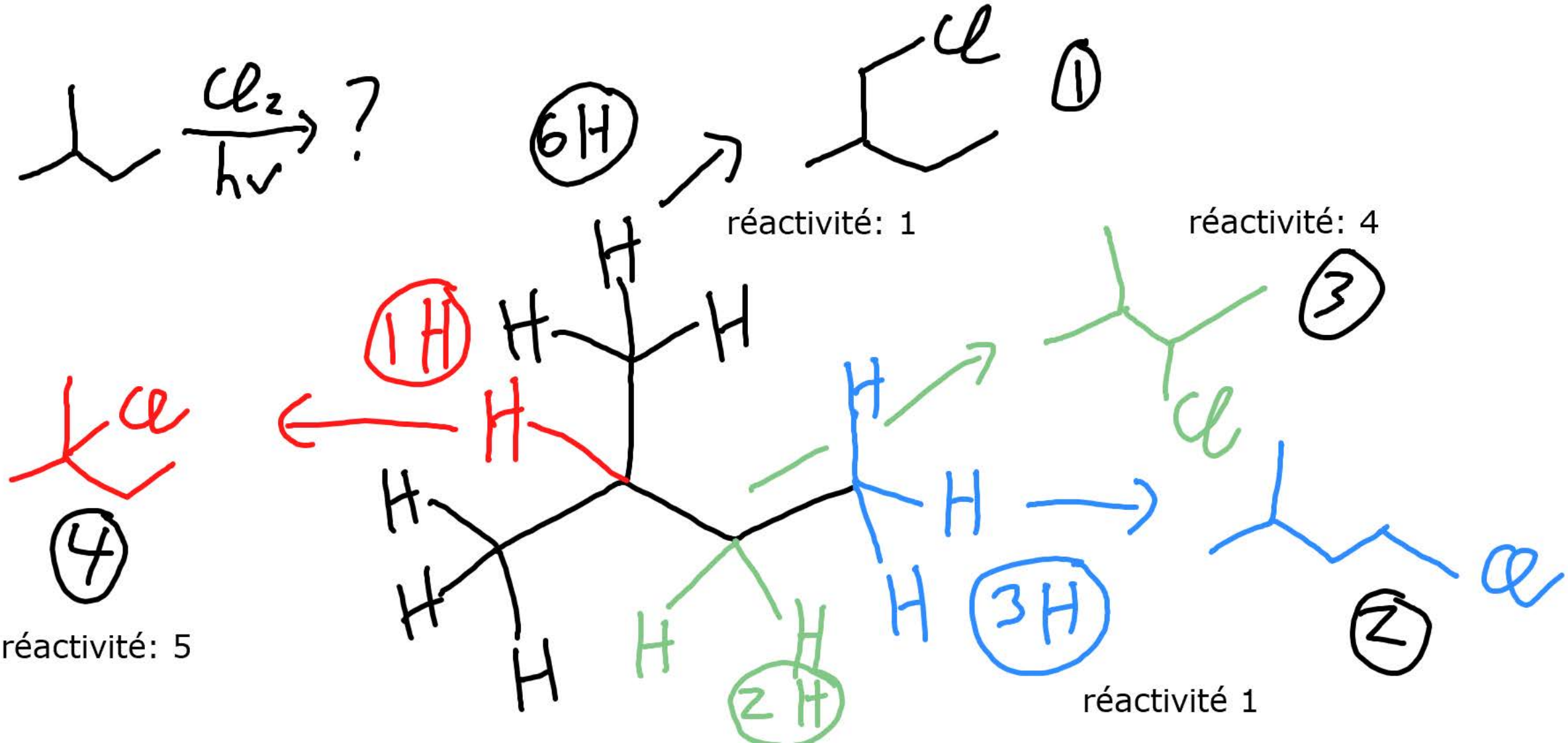
1)



2)



prédire le résultat d'une chlorination



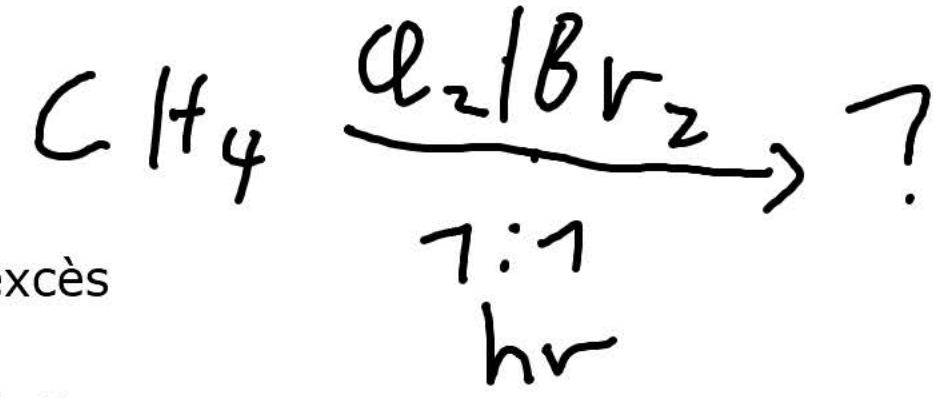
composé	nombre de H	réactivité corrigée	proportion
①	6	$6 \times 1 = 6$	$6/22 = 27\%$
②	3	$3 \times 1 = 3$	$3/22 = 14\%$
③	2	$2 \times 4 = 8$	$8/22 = 36\%$
④	1	$1 \times 5 = 5$	$5/22 = 23\%$

22

Que se passe-t-il avec F2?
Très réactif, seul le nombre de H va compter
1:2:3:4 = 6:3:2:1

Que se passe-t-il avec Br2?
Beaucoup moins réactif, la stabilisation du radical est essentielle
Le produit obtenue par le radical le plus stable est formé
1:2:3:4 = <5%, <5%, <5%, >95%

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



excès

Initation:

$$Cl_2 \xrightarrow{h\nu} Cl\cdot + Cl\cdot$$

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

Propagation:

1)

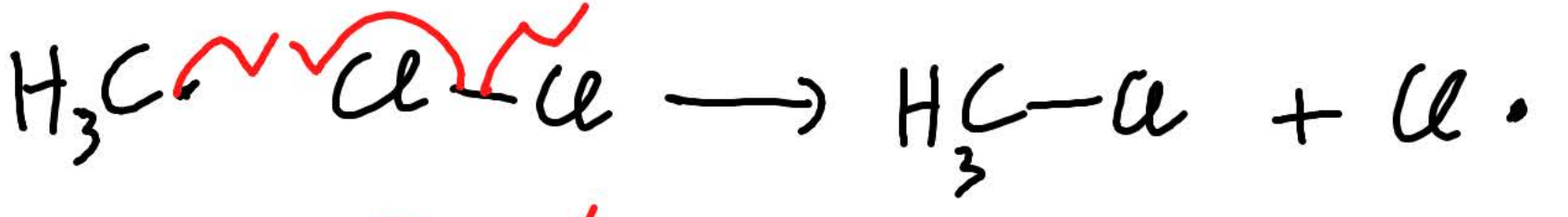
favorable!

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

défavorable.

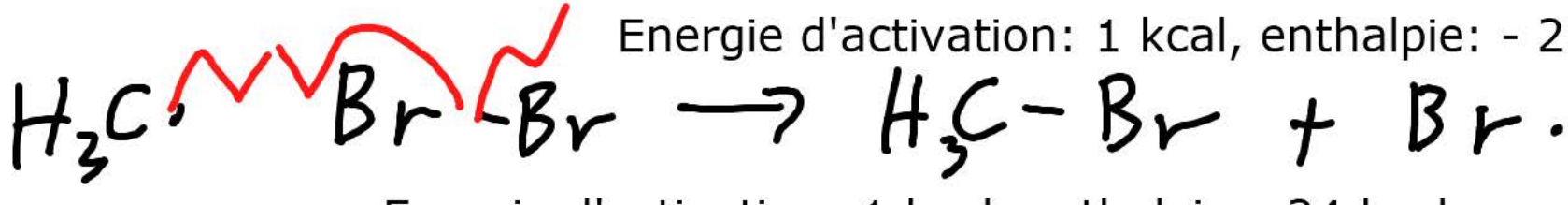
Energie d'activation: 20 kcal, Enthalpie: 18 kcal

2)



favorable

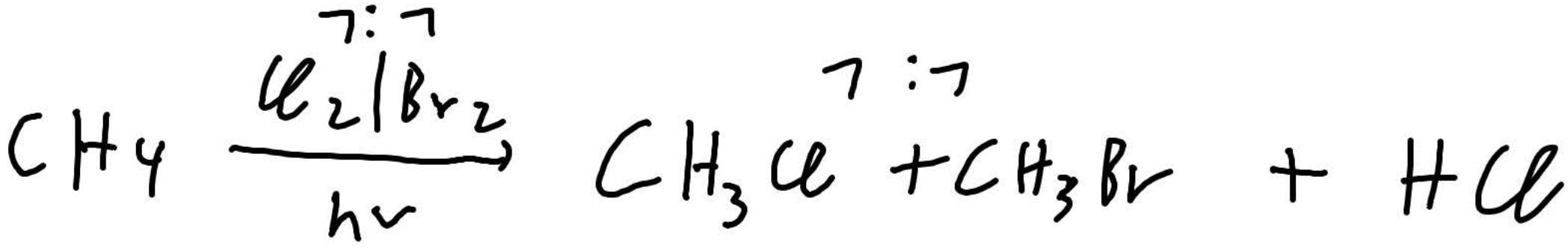
Energie d'activation: 1 kcal, enthalpie: - 27 kcal



favorable

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

Au début de la réaction, on a donc:



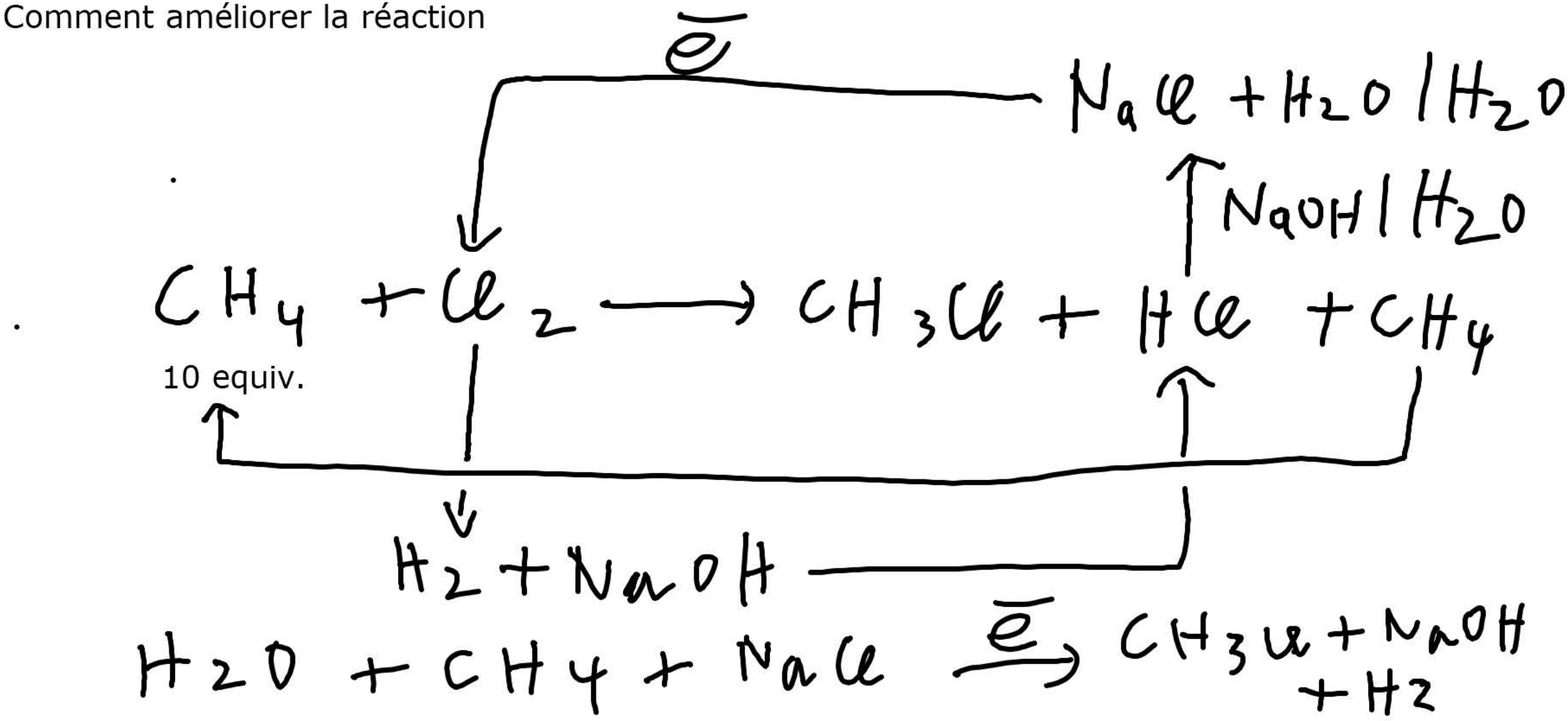
Analyse semi-quantitative de la chlorination

économie d'atomes: 5/7 = 71%

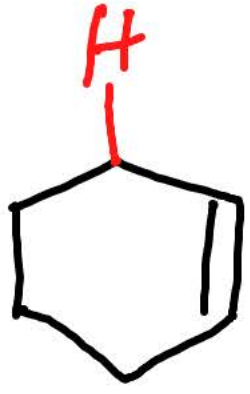
PMI (process mass intensity) (produits de départs+solvents+...)/produits
(16+71)/50.5 = 1.7

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

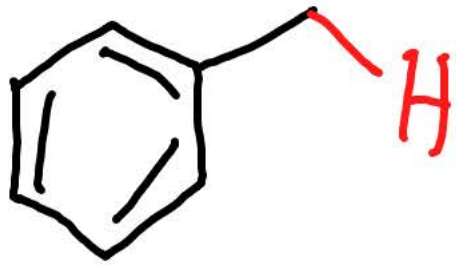
Comment améliorer la réaction



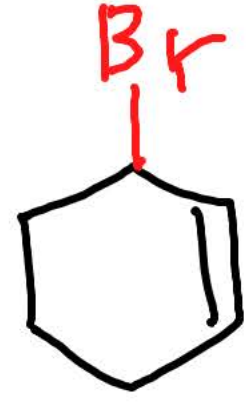
Bromination des positions allyliques et benzyliques

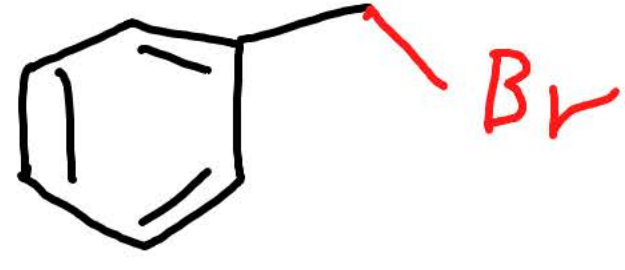


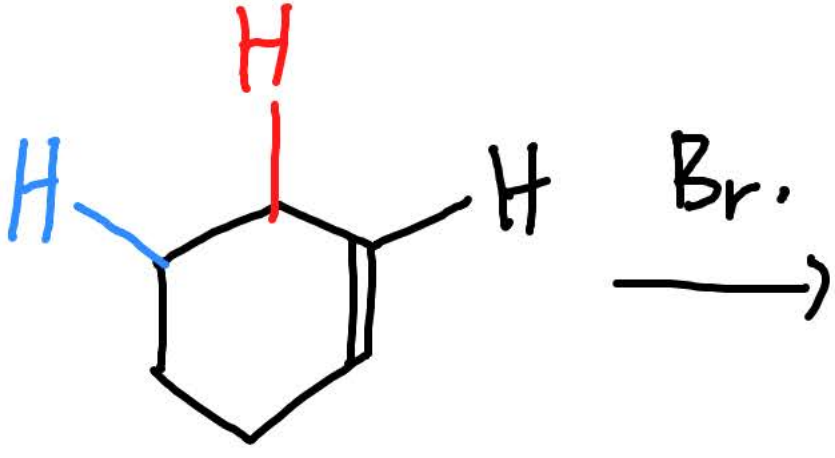
position allylique

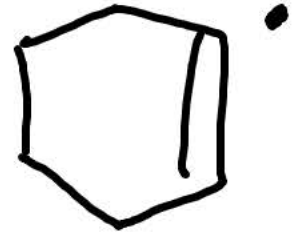


position benzylique





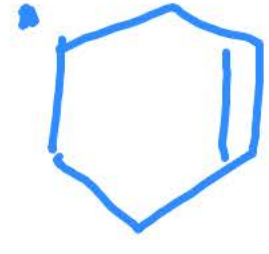




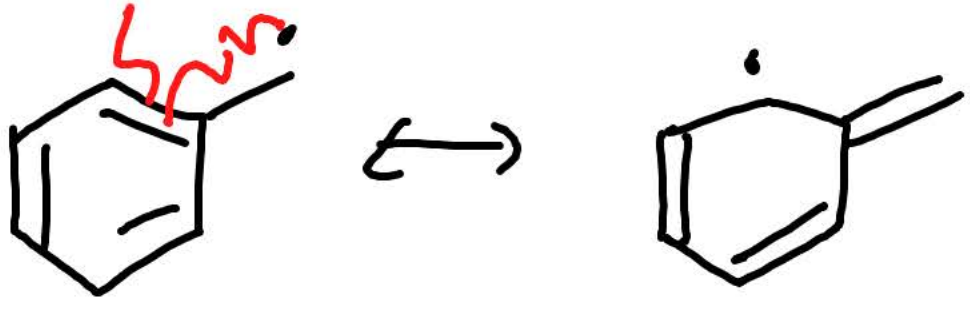
radical sp2, moins stables, pas observé

structure de résonance identique! Très stabilisé

Très bonne sélectivité!



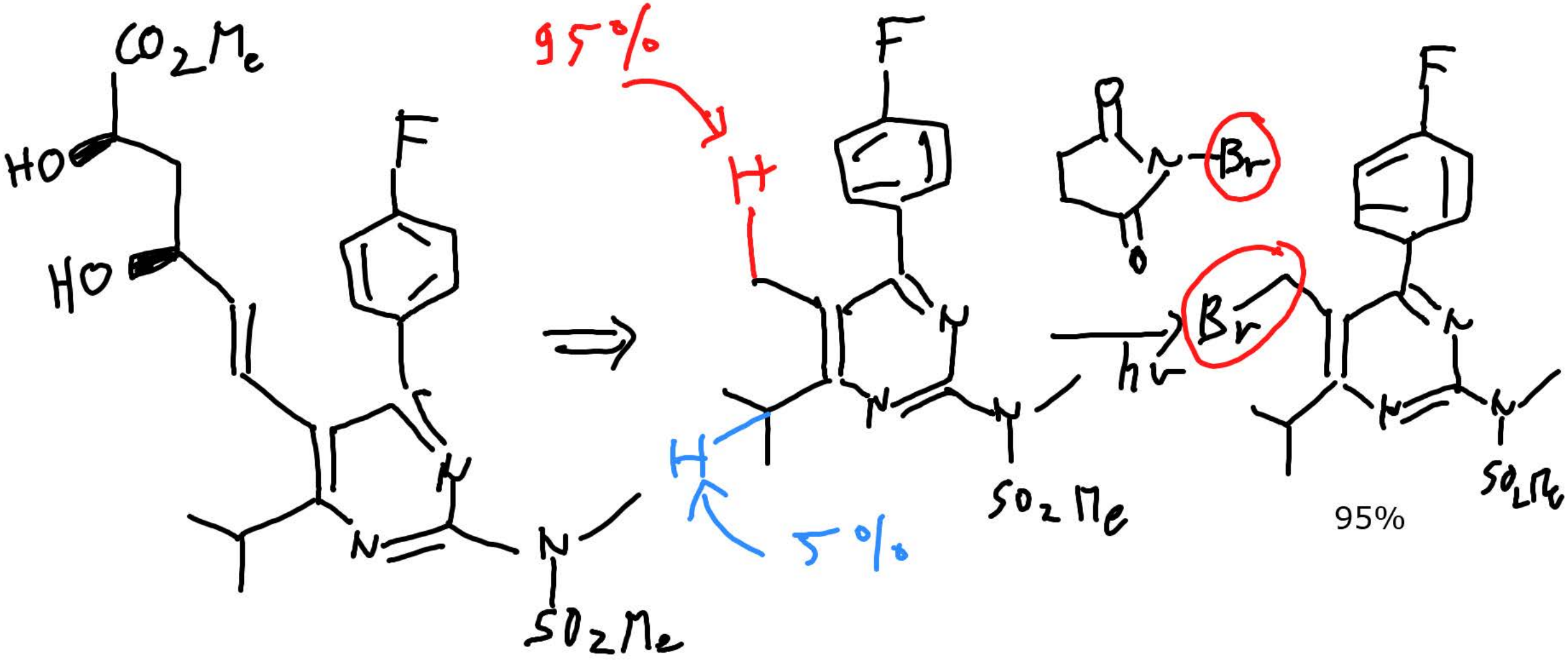
radical sp3 secondaire, moins stabilisé

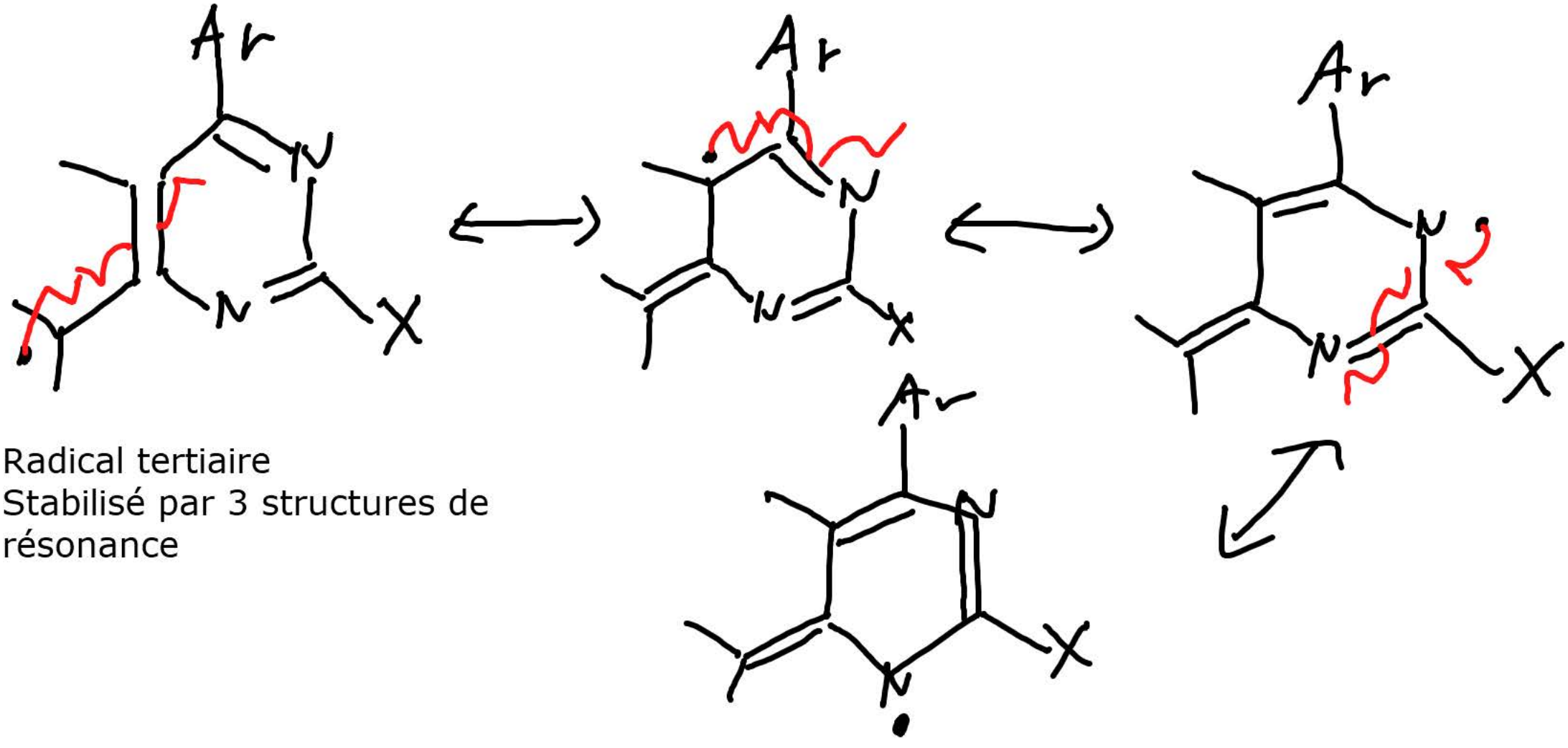


+ 2 autres dans le cycle

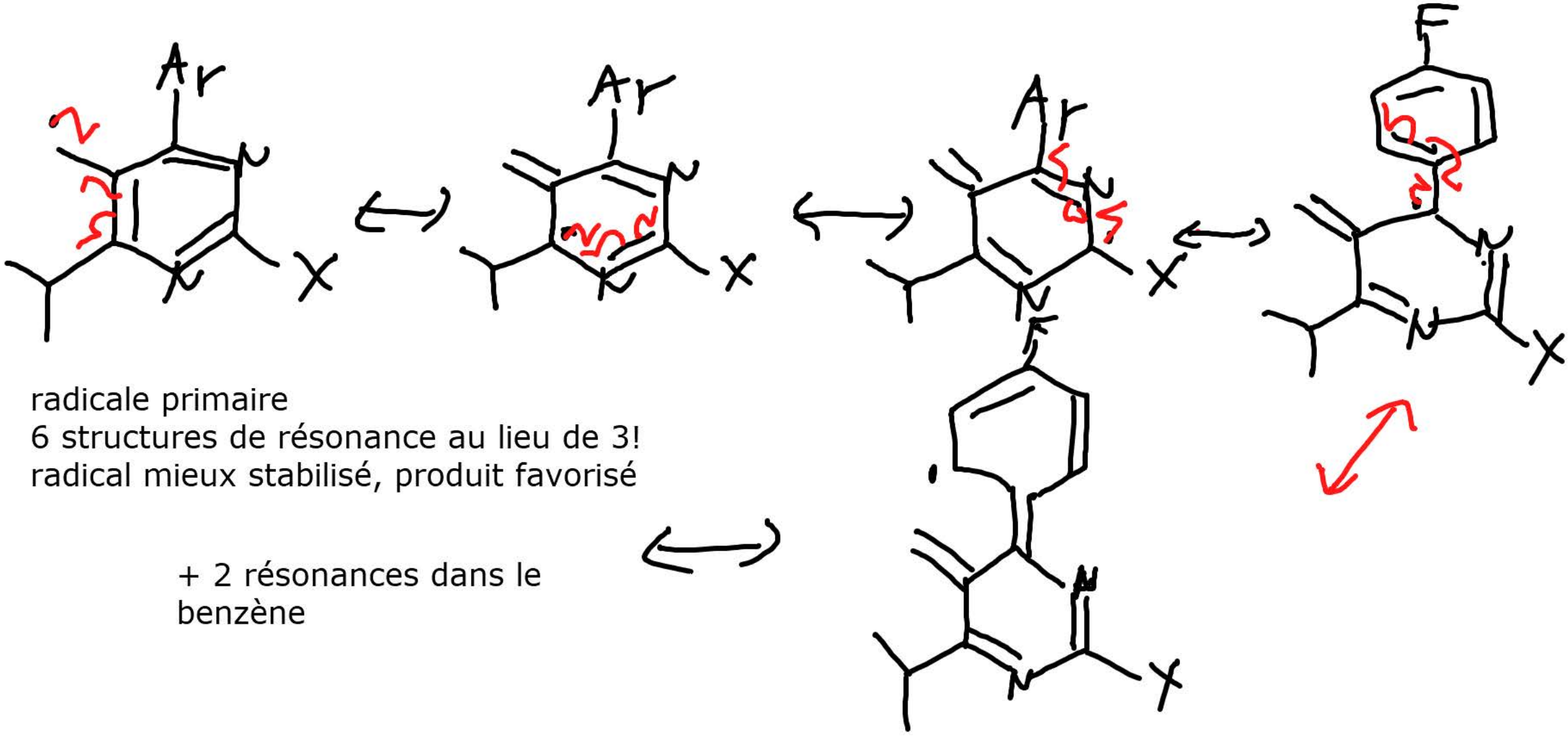
position stabilisée, réaction facile

Rosuvastatine





Radical tertiaire
Stabilisé par 3 structures de résonance



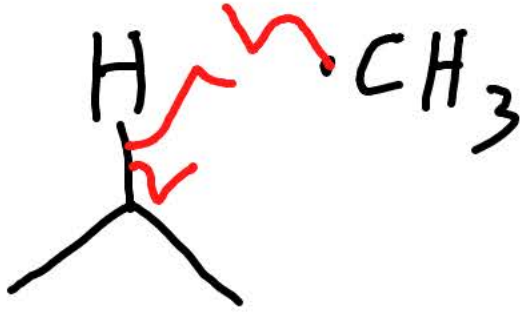
radicale primaire
6 structures de résonance au lieu de 3!
radical mieux stabilisé, produit favorisé

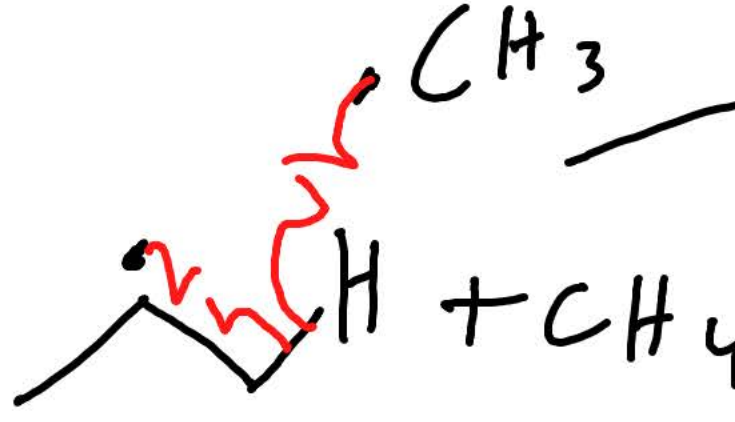
+ 2 résonances dans le benzène

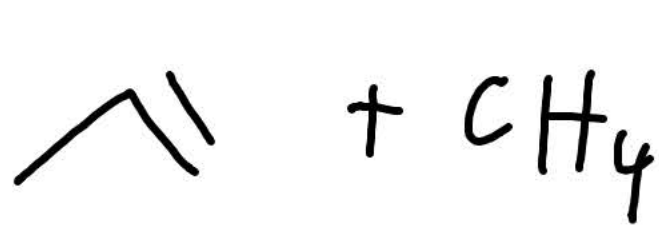
chimie "bulk": cracking = racourcir les alcanes + former des alcènes

500 °C

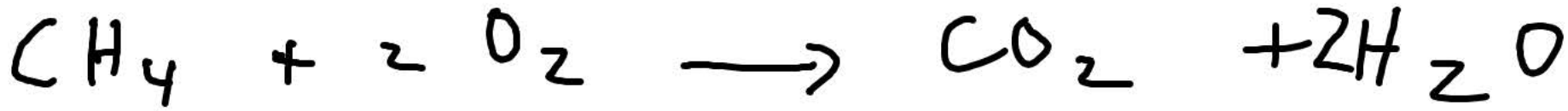
C-C: 85 kcal/mol
C-H: 104 kcal/mol







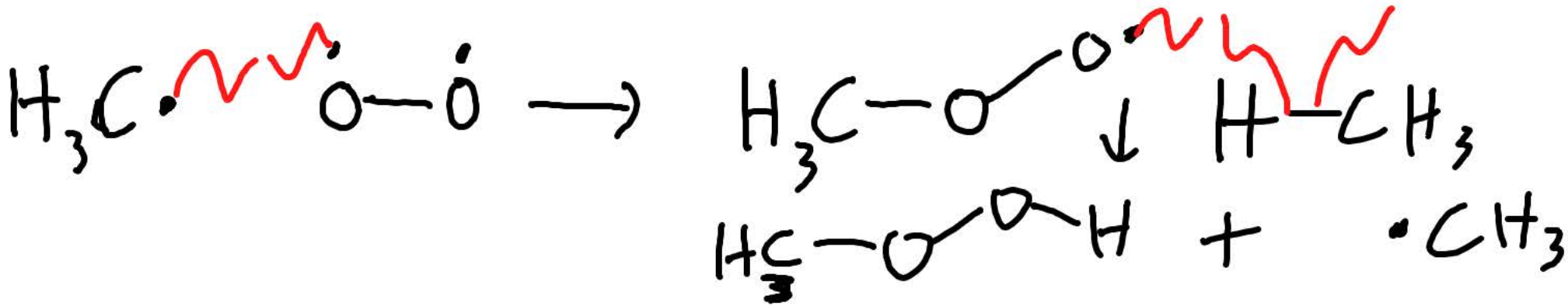
combustion du méthane



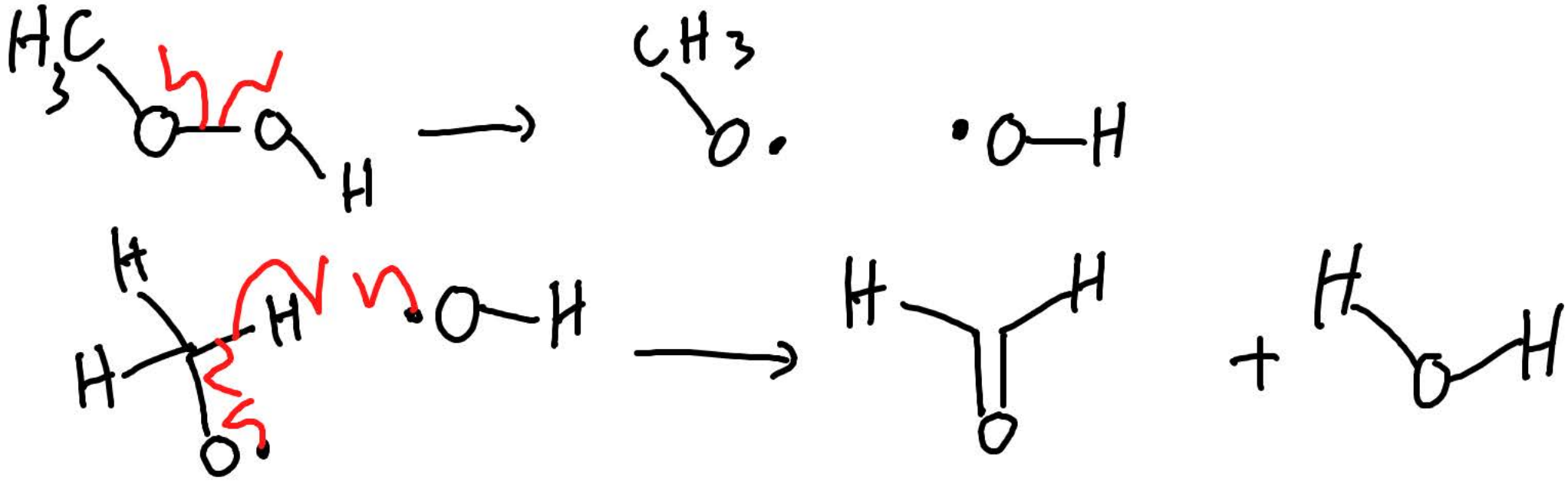
Initiation

très lente

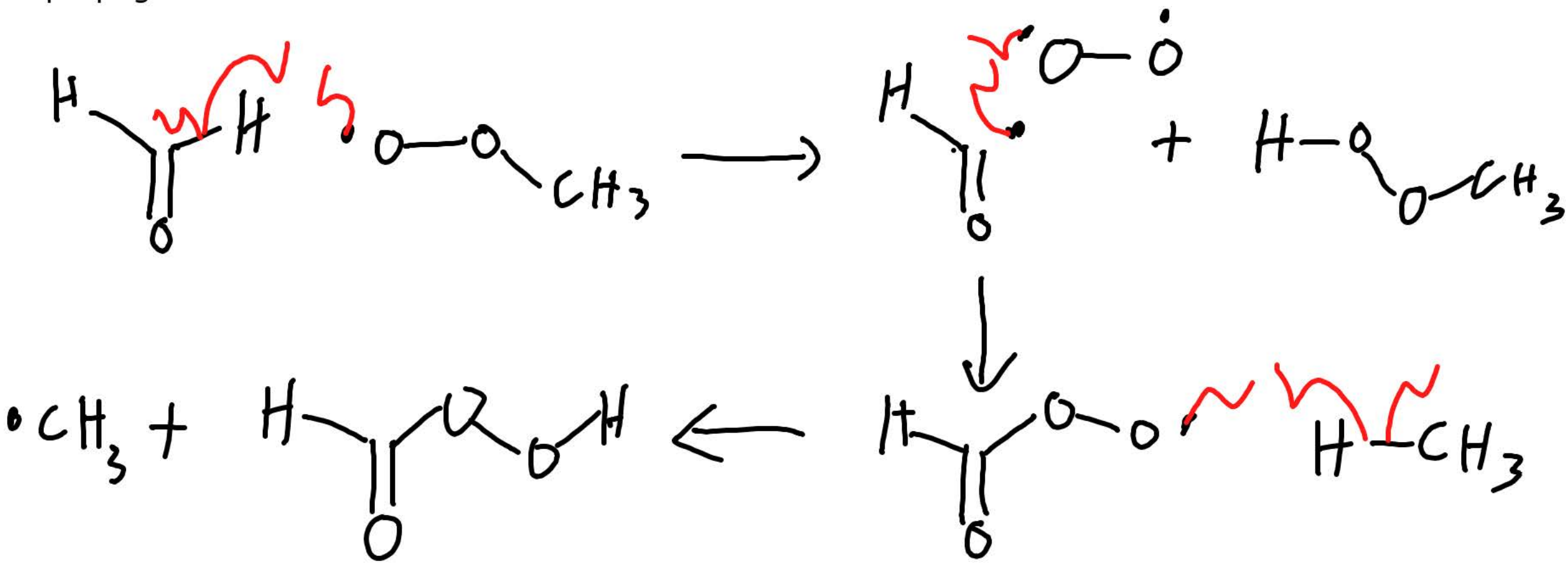
propagation 1

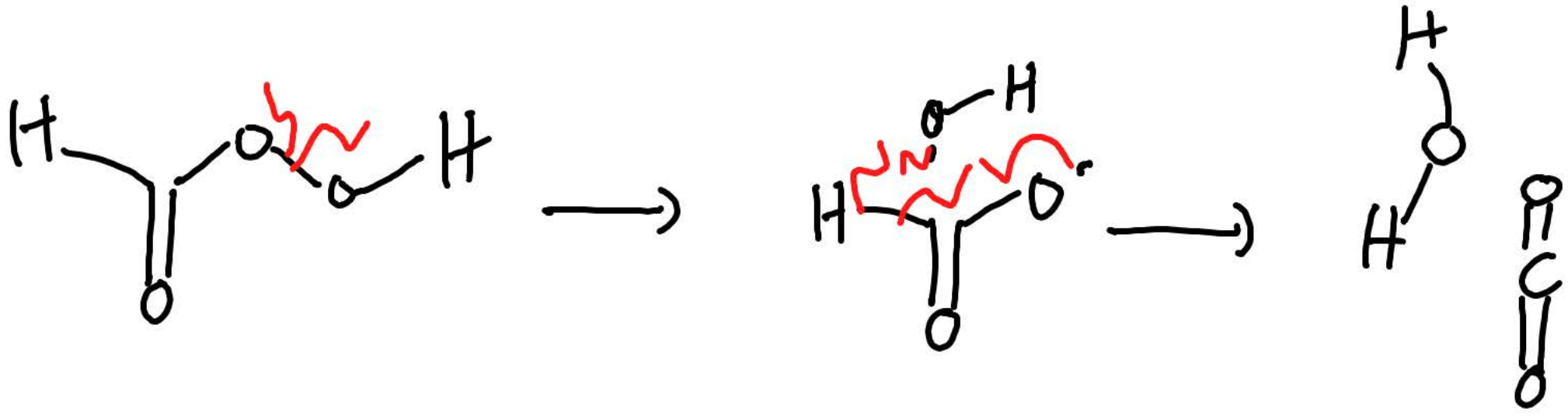


Initiation 2:

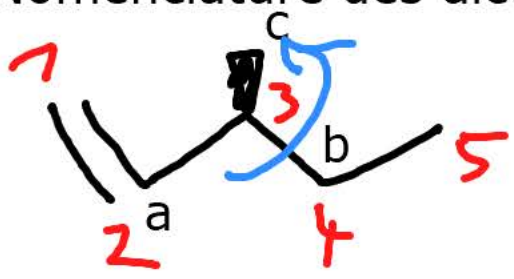


propagation

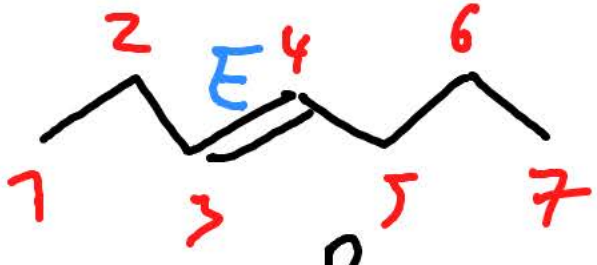




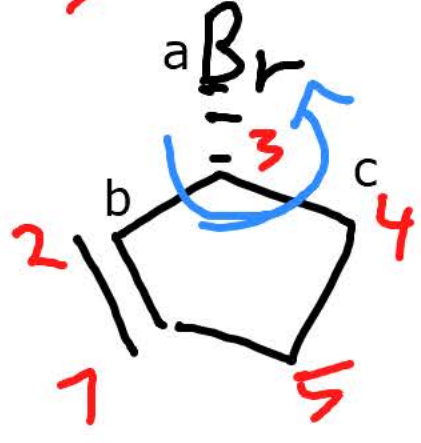
Nomenclature des alcènes



(S)-3-methylpent-1-ene

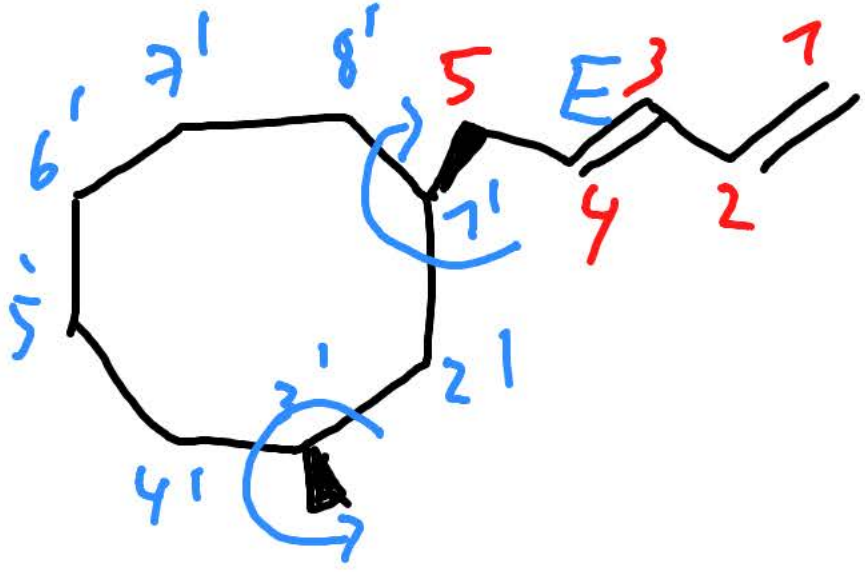


(E)-hept-3-ene



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

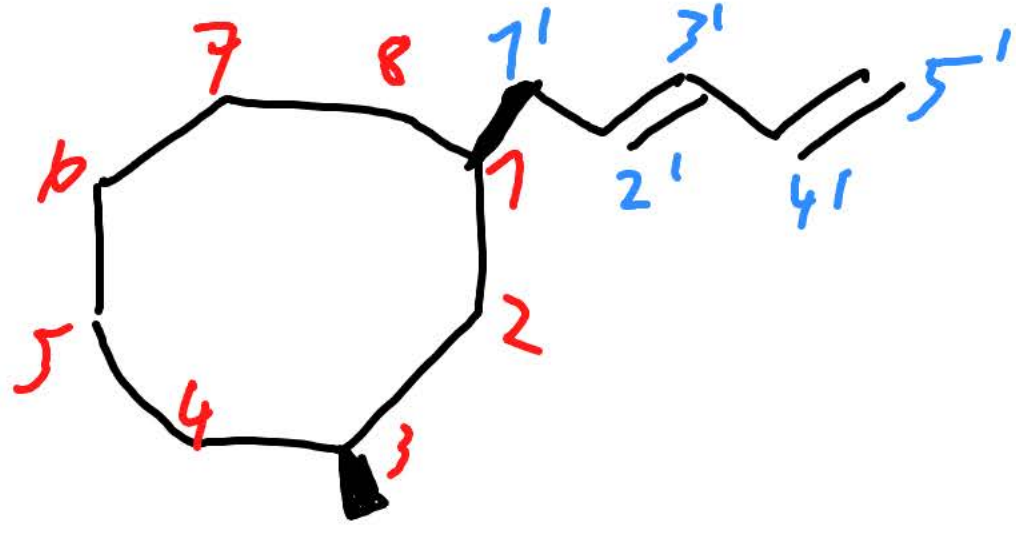
ancienne règles: insaturation domine



penta-1,3-diene

3-methylcyclooctyl

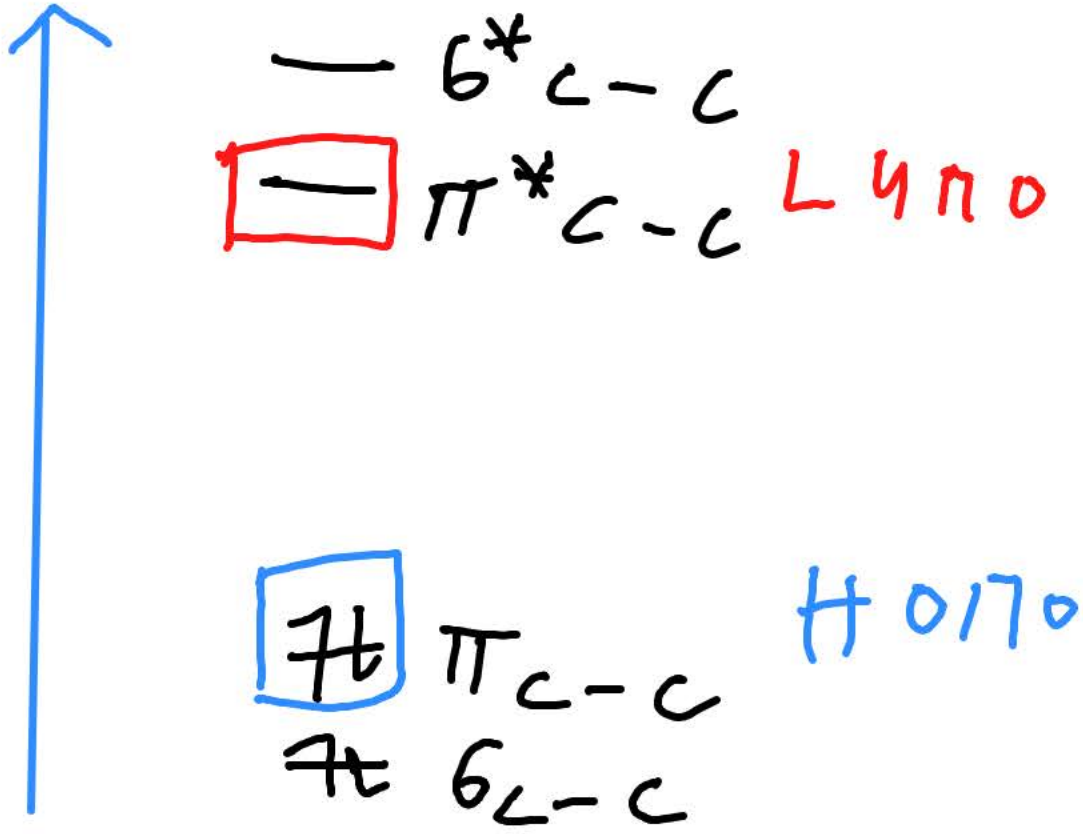
nouvelle règle: 1) cycle, 2) atomes, 3) insaturations

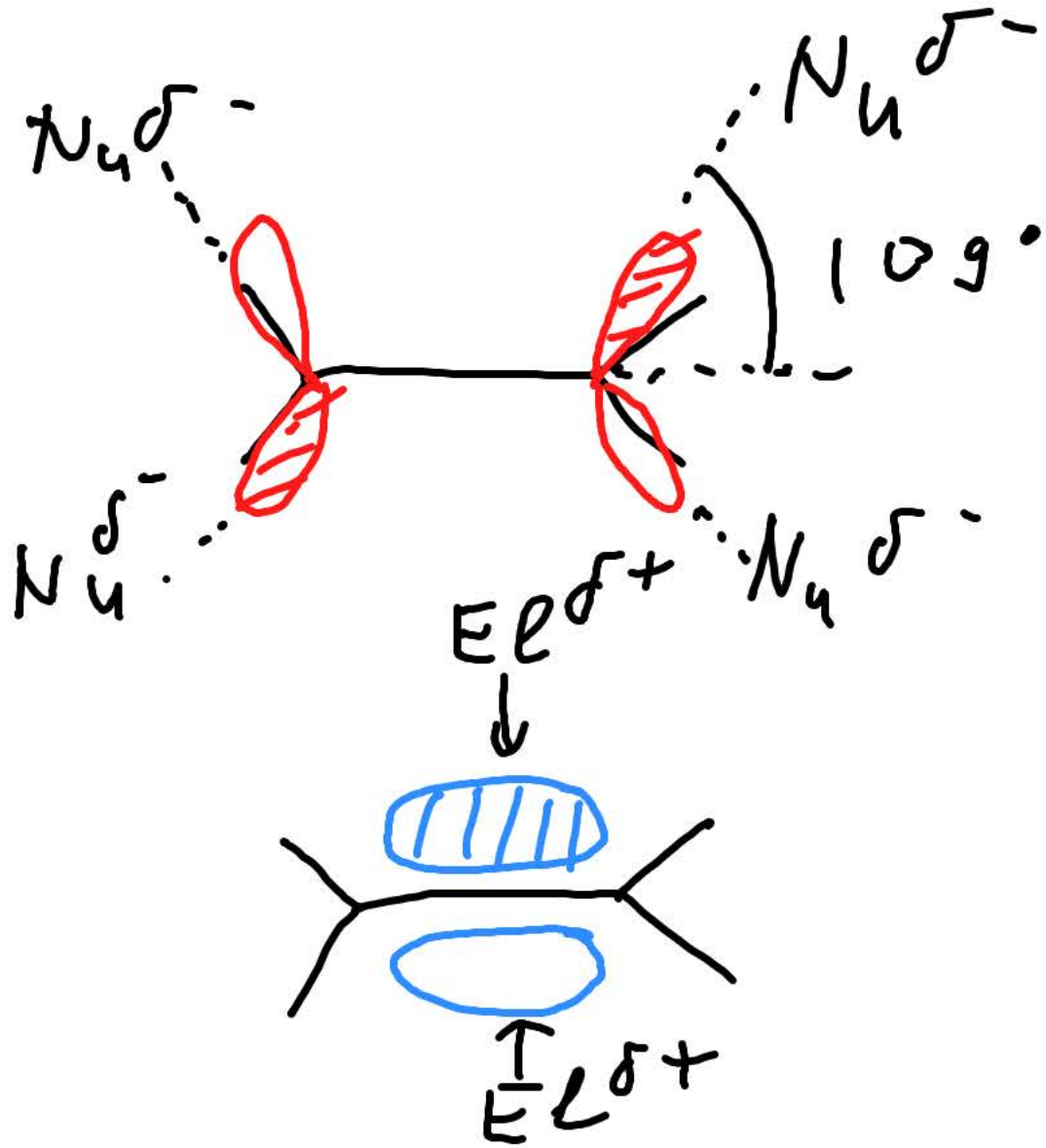


3-(S)-methyl-1-(R)-((E)-penta-2,4-dienyl)-cyclooctane

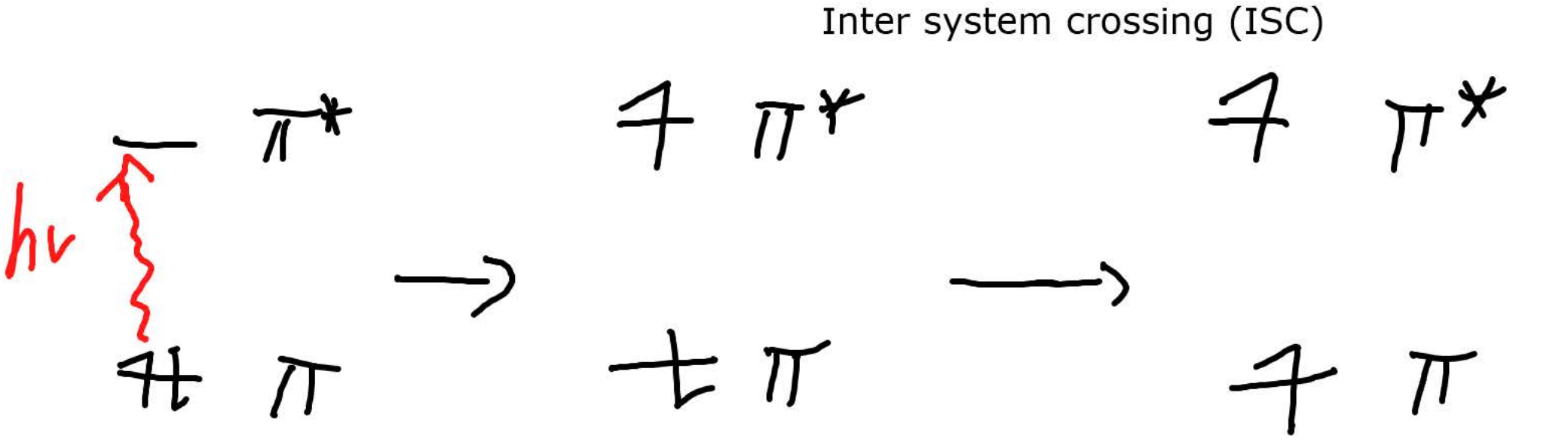
(E)-5-(R)-(3-(S)-methylcyclooctyl)penta-1,3-diene

Analyse de la liaison pi





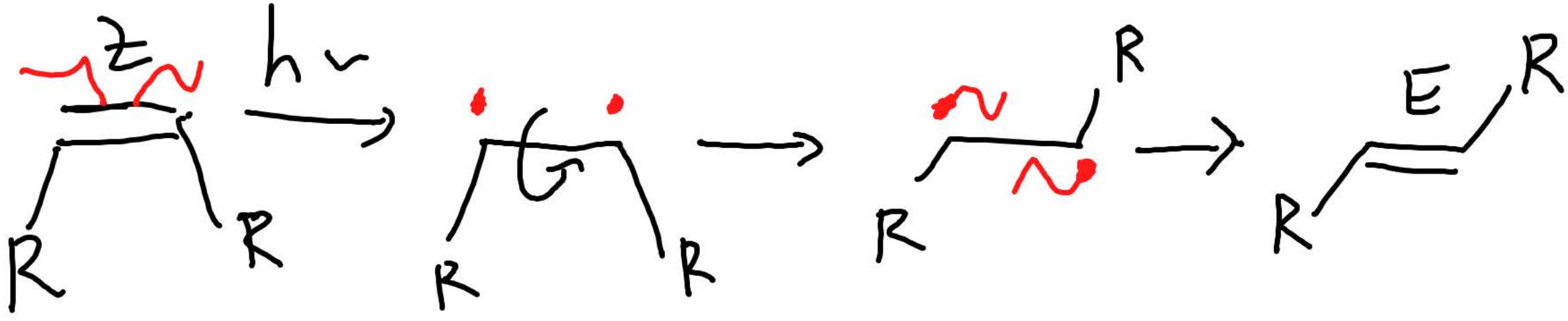
irradiation des doubles liaisons



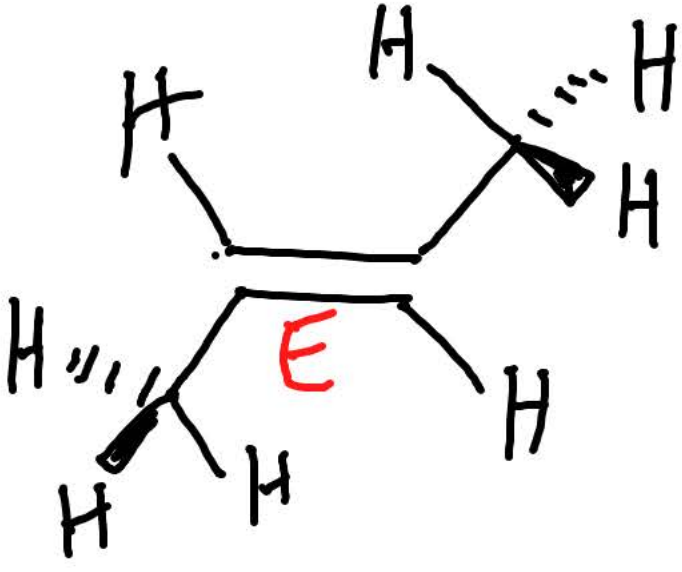
lumière UV pour alcène seul
lumière visible pour alcènes conjugués

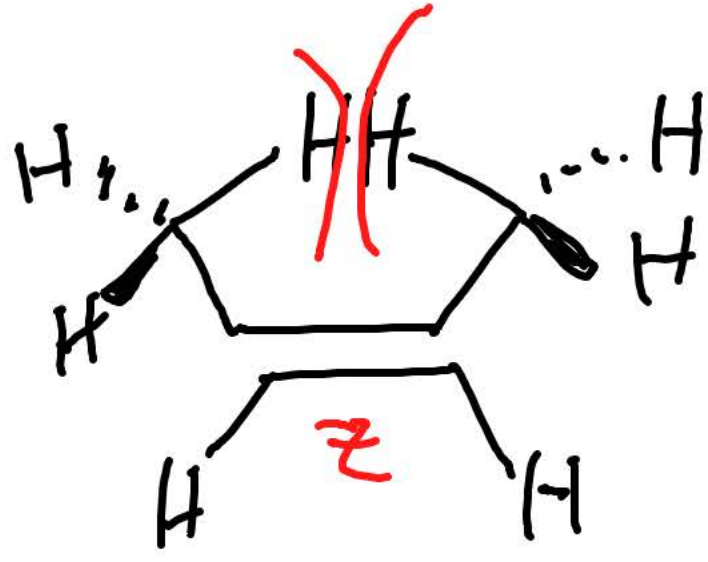
singlet (spin opposé)

triplet (spins parallèles)


Z
hν
R
R
R
R
R
R
E
R
R

Stabilité: E vs Z

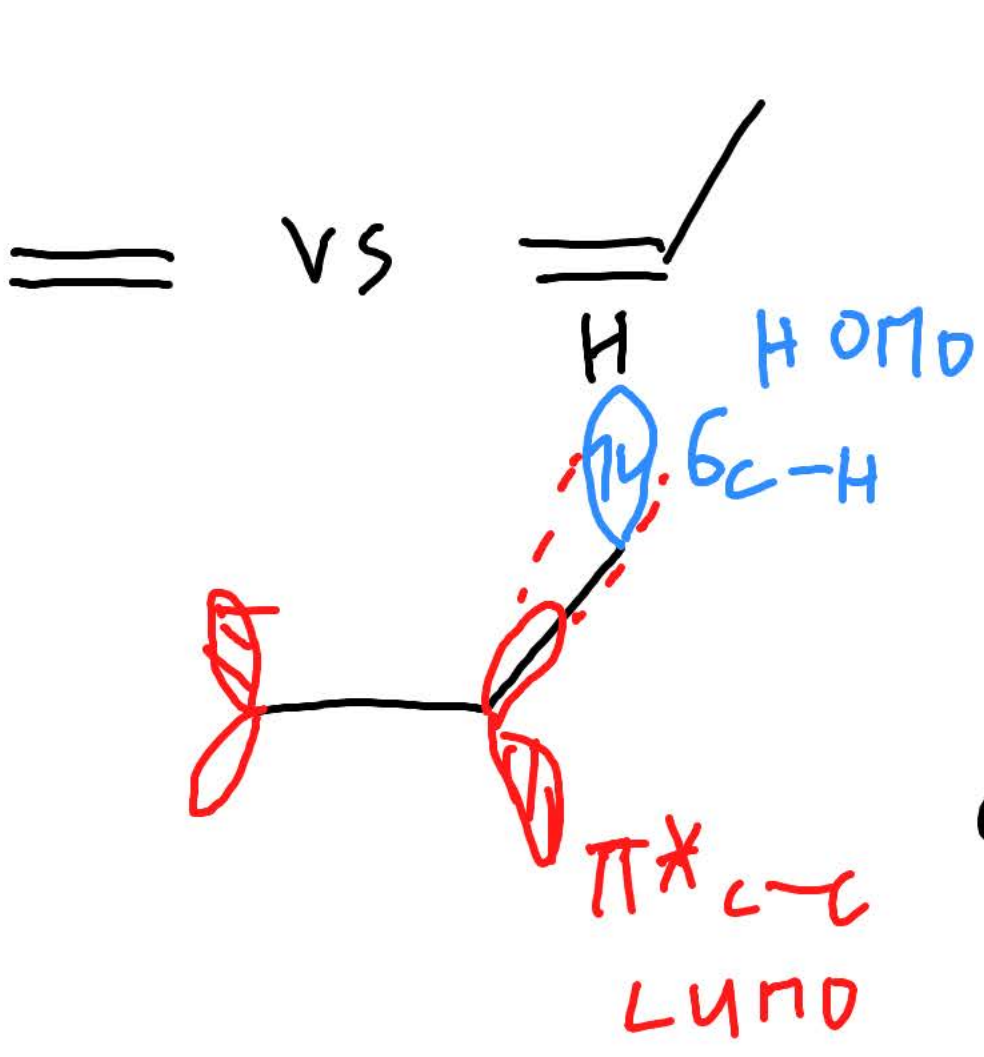


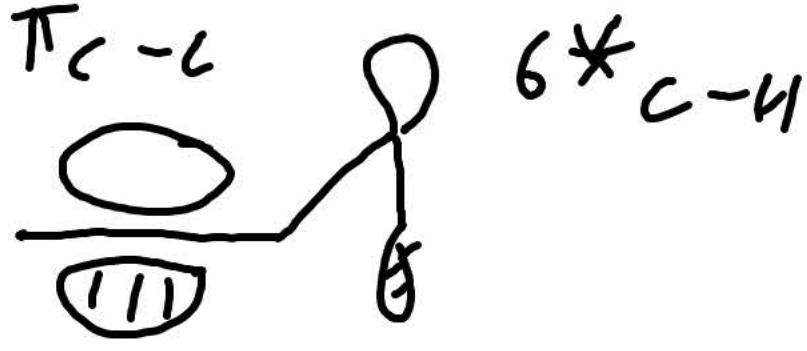


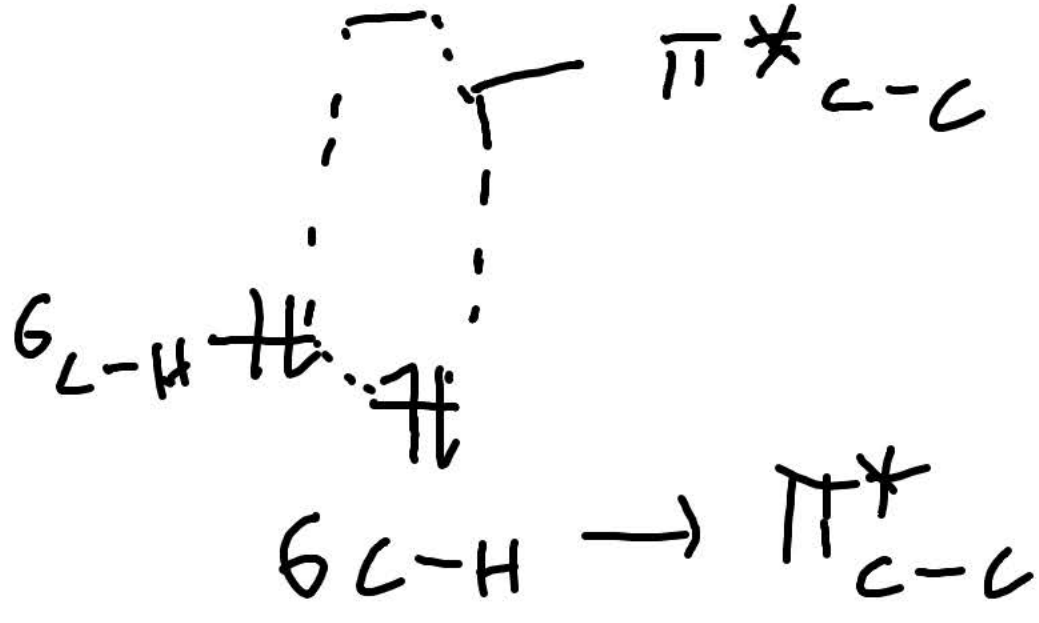
stérique défavorable

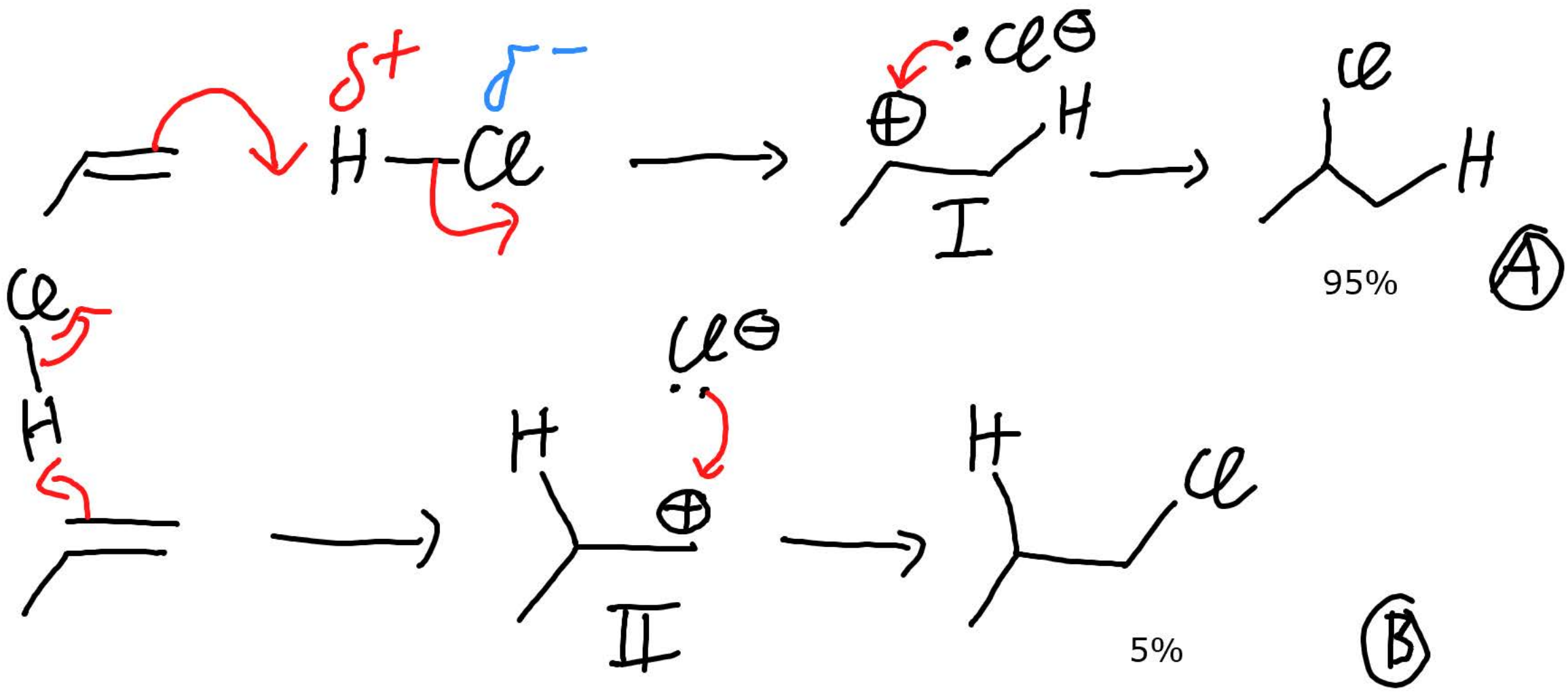
E est plus stable

stabilisation par susbtituants



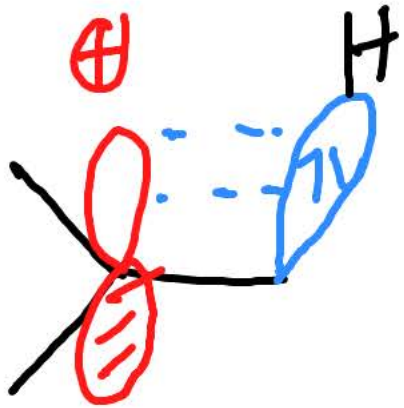






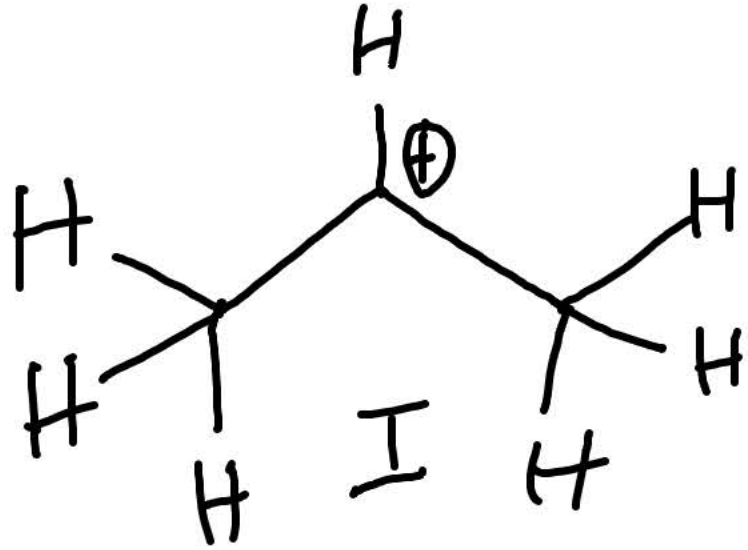
Thermodynamique: analyse les liaisons: les 2 produits ont la même énergie

Hyperconjugaison



p_c

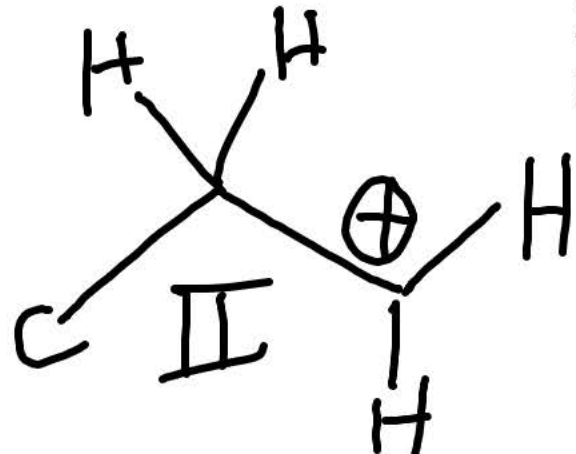
$\sigma_{C-H} \rightarrow p_c$



I

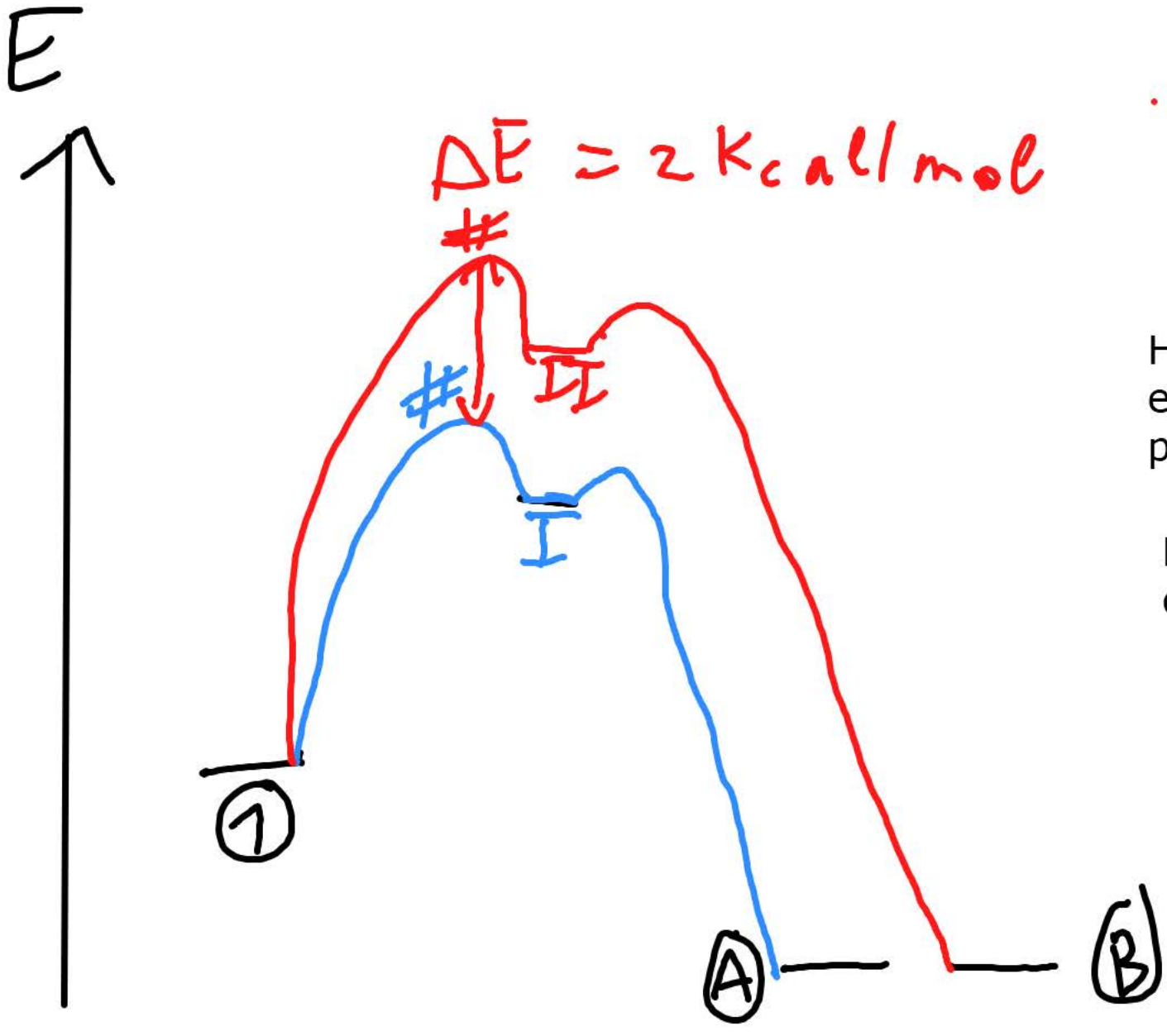
6 liaisons C-H peuvent faire hyperconjugaison

Plus favorable!



II

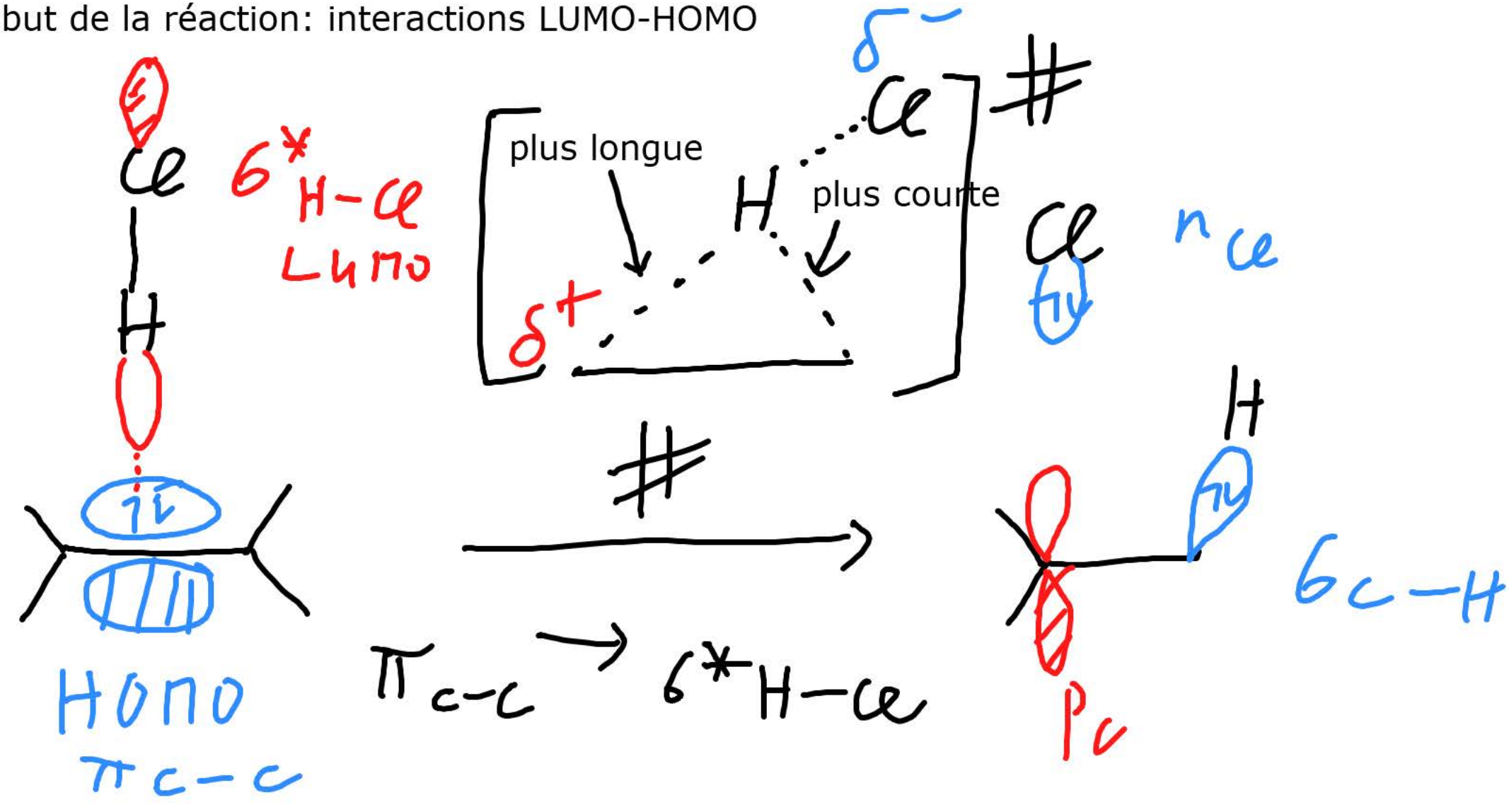
2 liaisons C-H + une liaison C-C peuvent faire hyperconjugaison



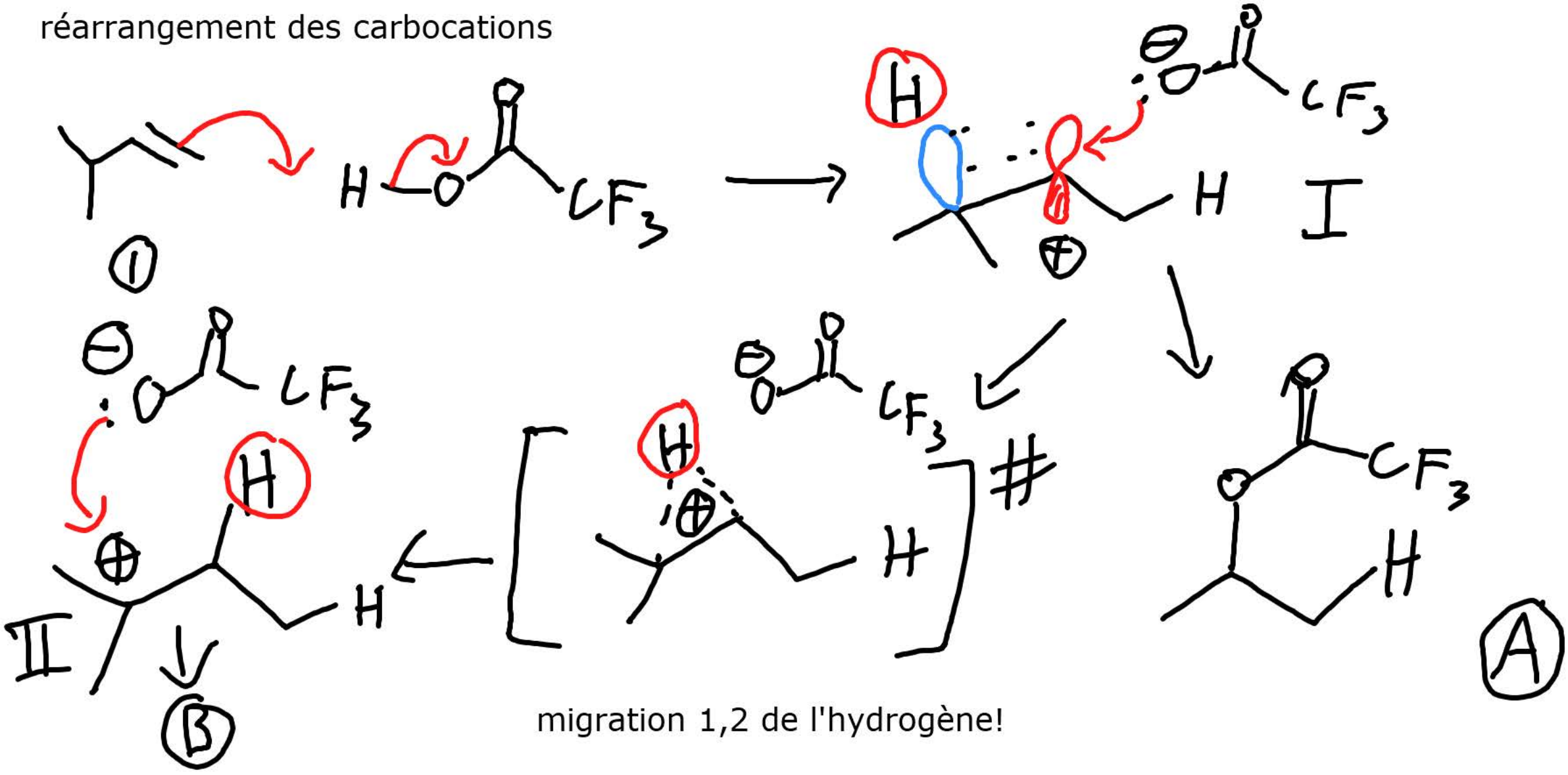
Hammond: l'état de transition est similaire à l'intermédiaire le plus proche en énergie

Dans ce cas, similaires aux carbocations I et II

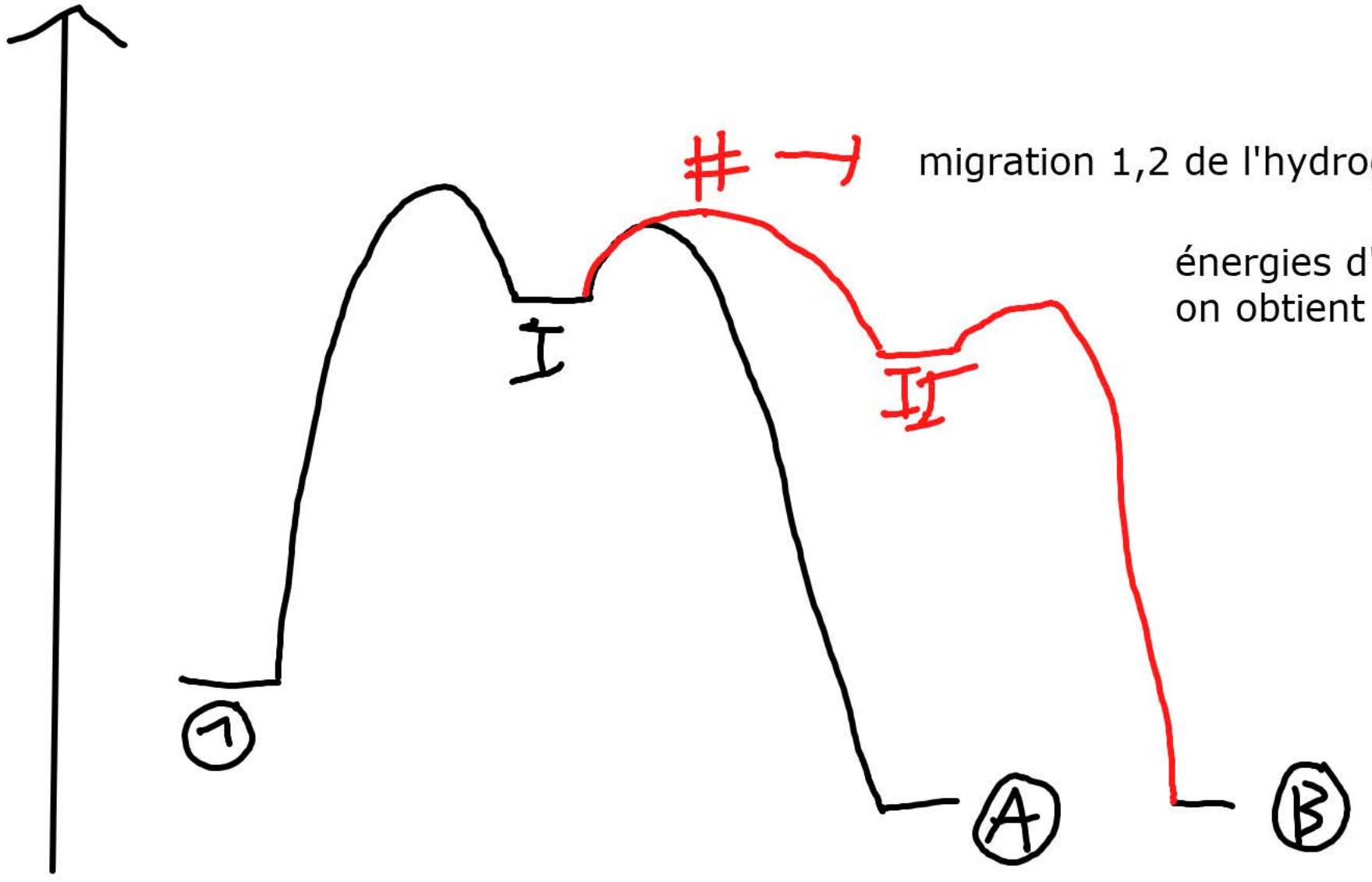
Début de la réaction: interactions LUMO-HOMO

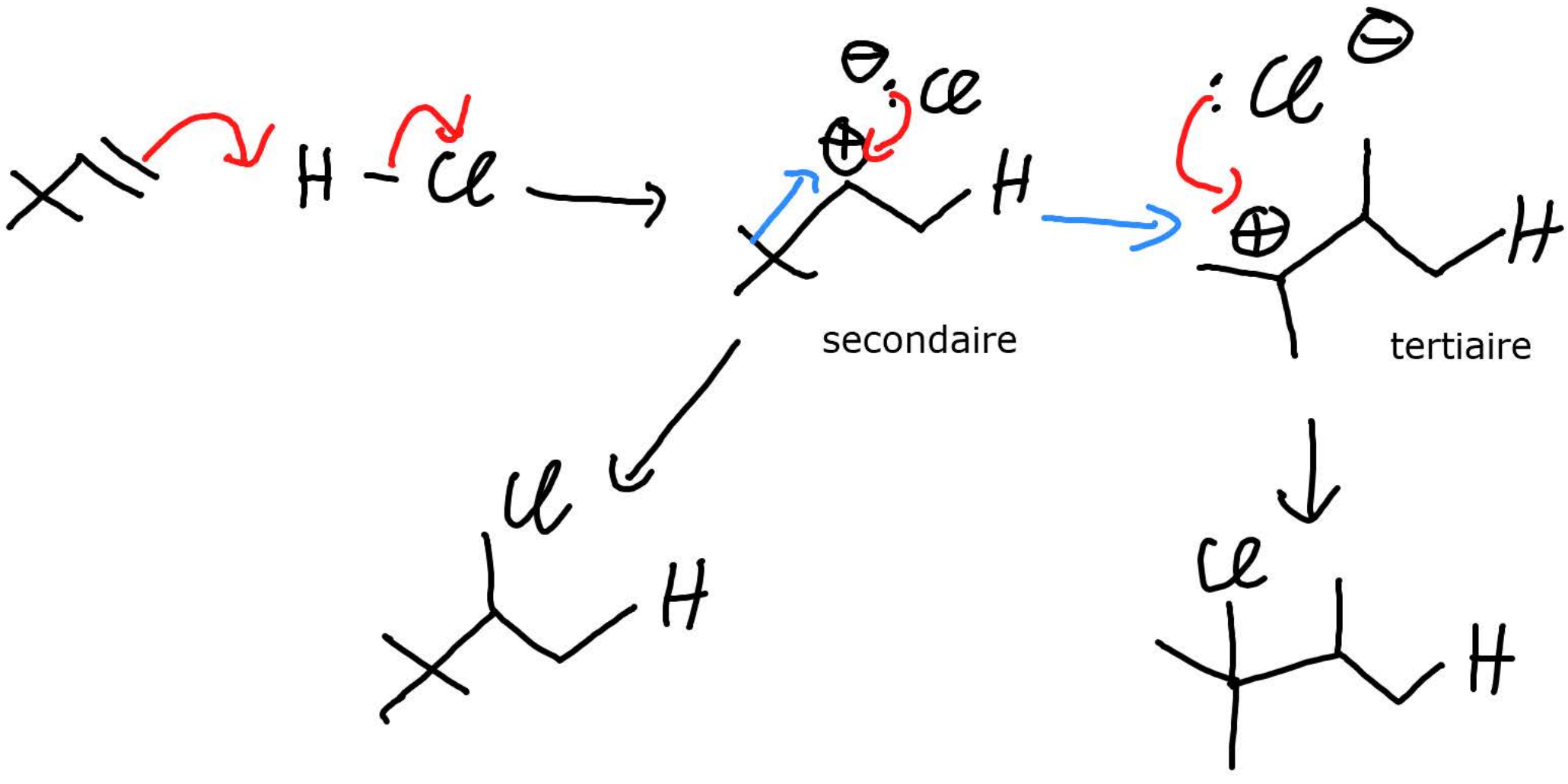


réarrangement des carbocations

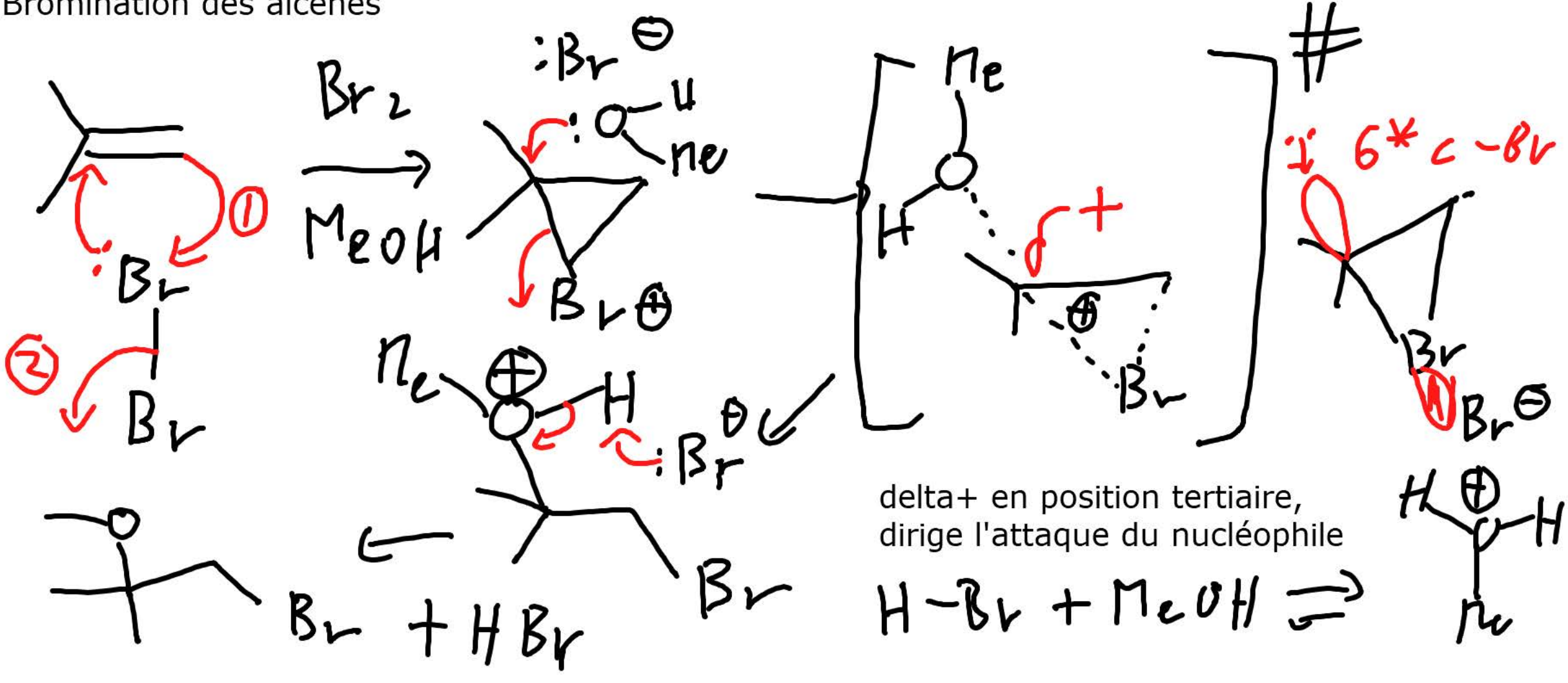


migration 1,2 de l'hydrogène!

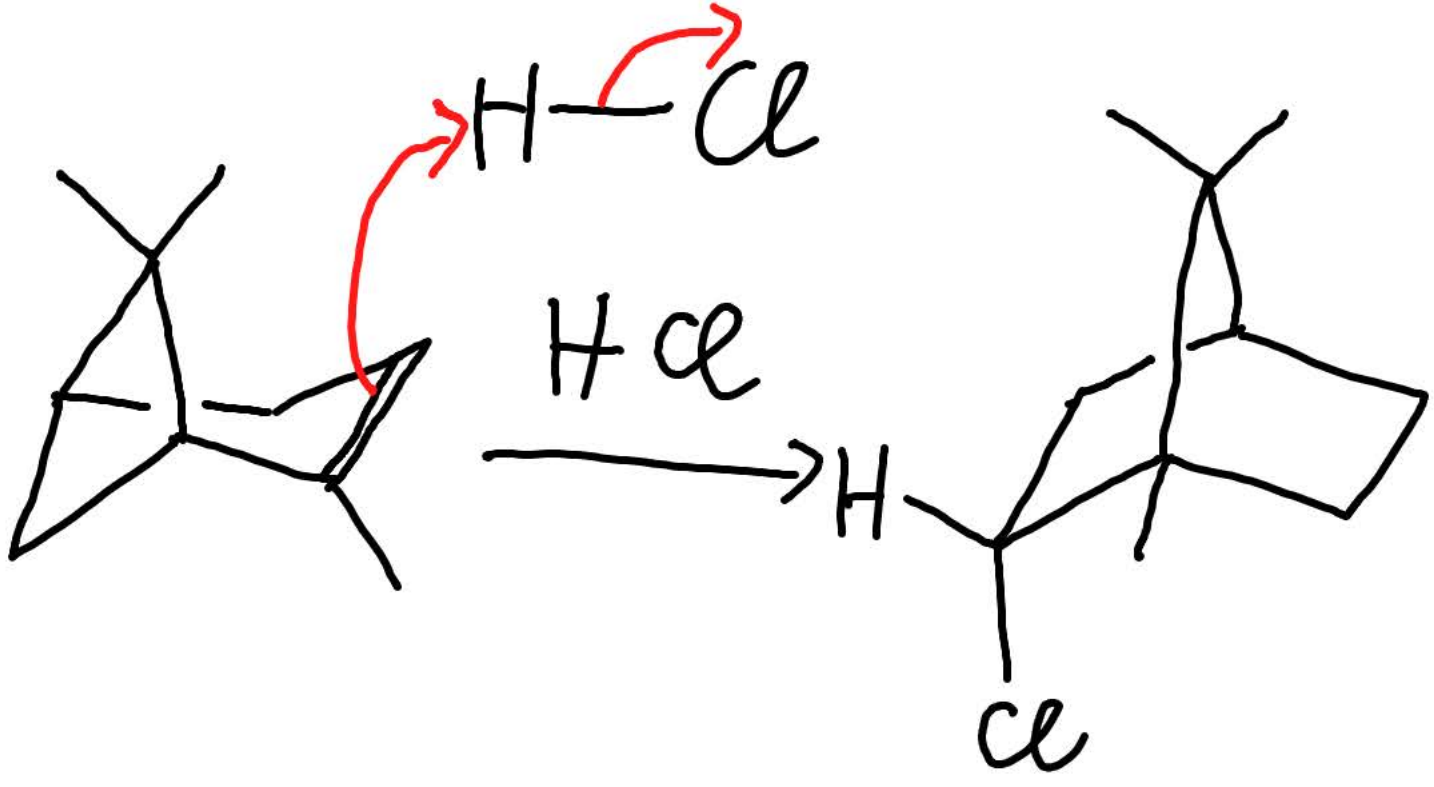

migration 1,2 de l'hydrogène
énergies d'activation similaires
on obtient un mélange
I
II
A
B

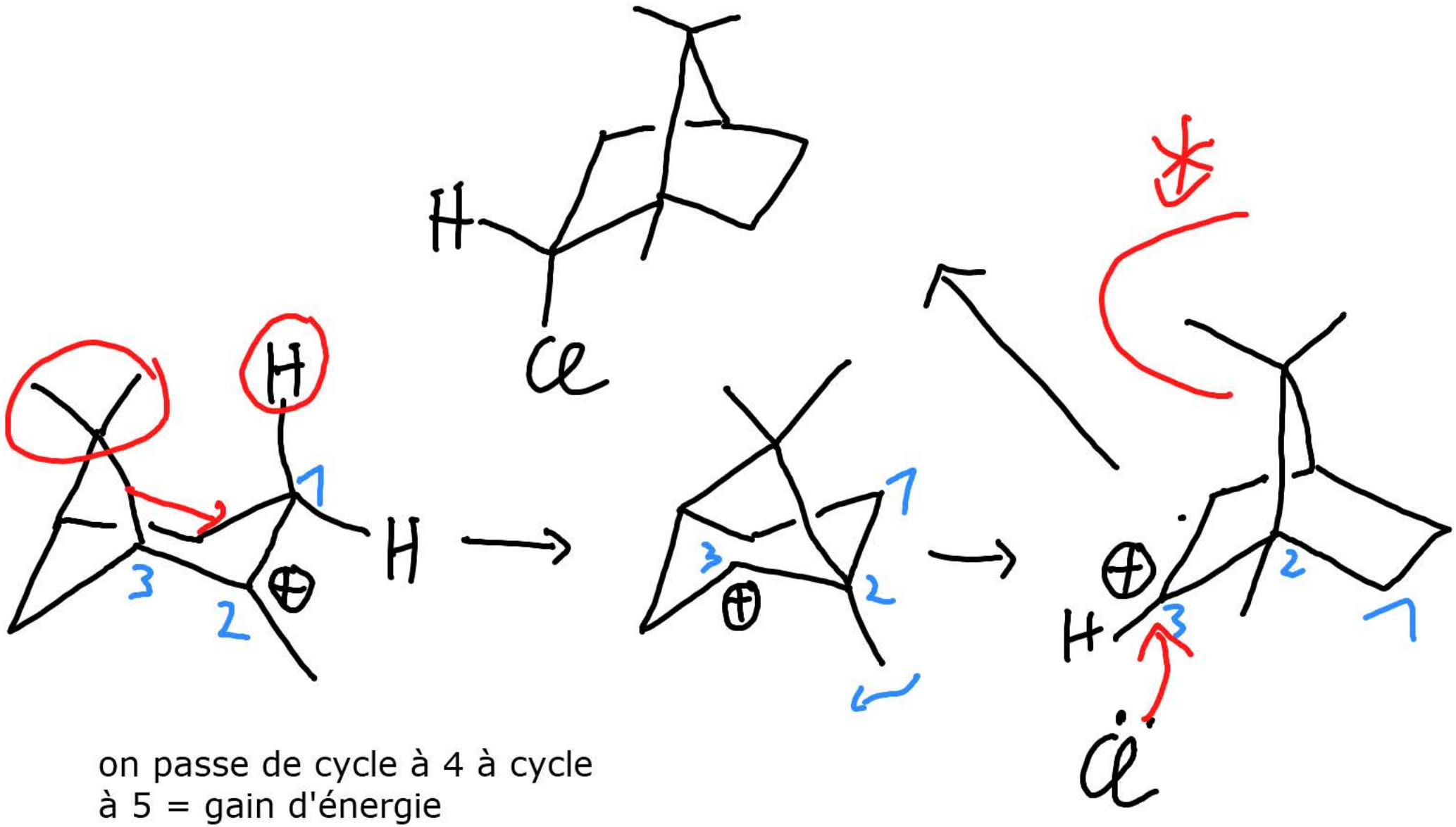

secondaire
tertiaire

Bromination des alcènes



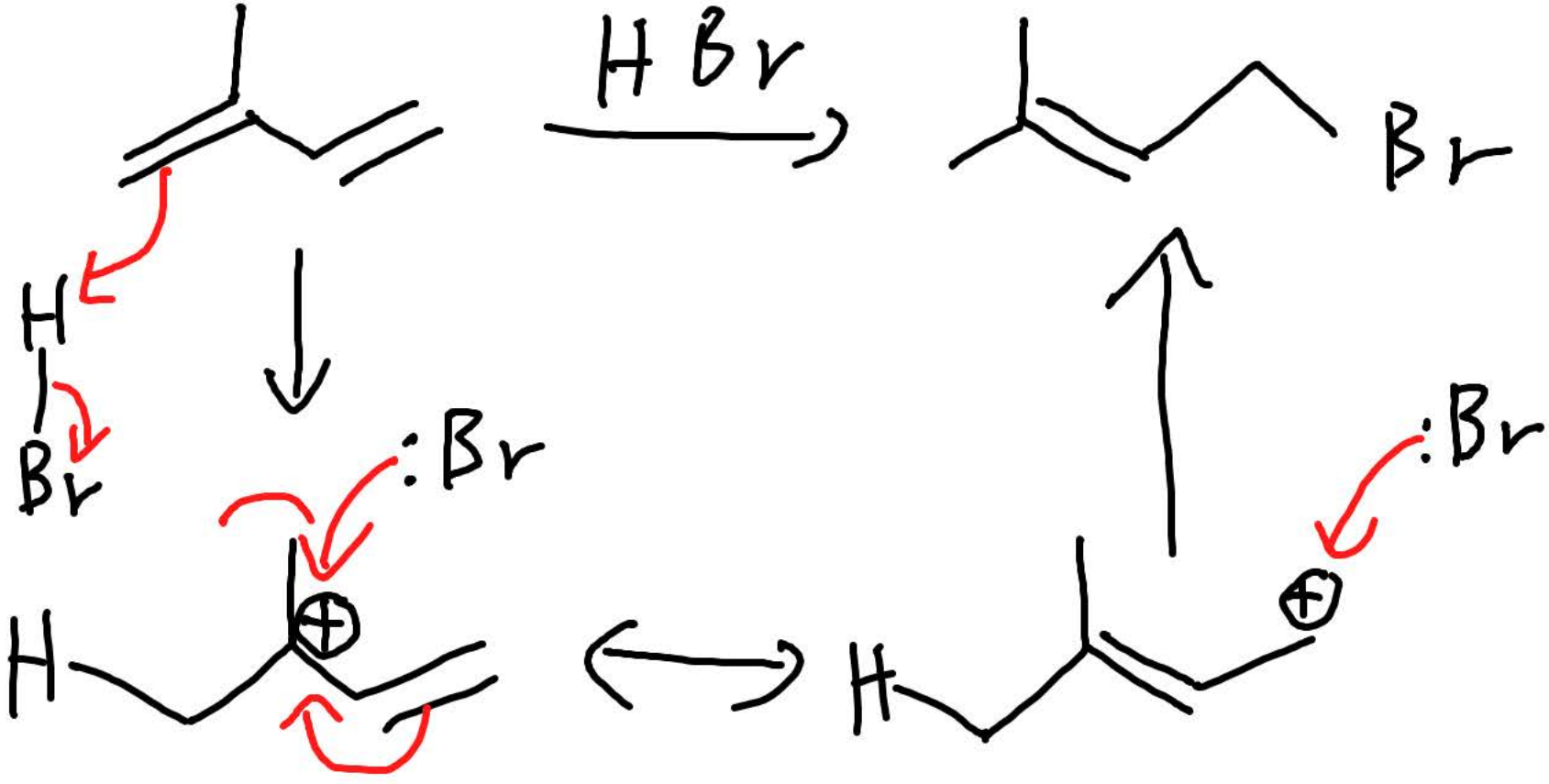
Découverte du réarrangement des carbocations: Wagner-Meerwein (1899)





on passe de cycle à 4 à cycle
à 5 = gain d'énergie

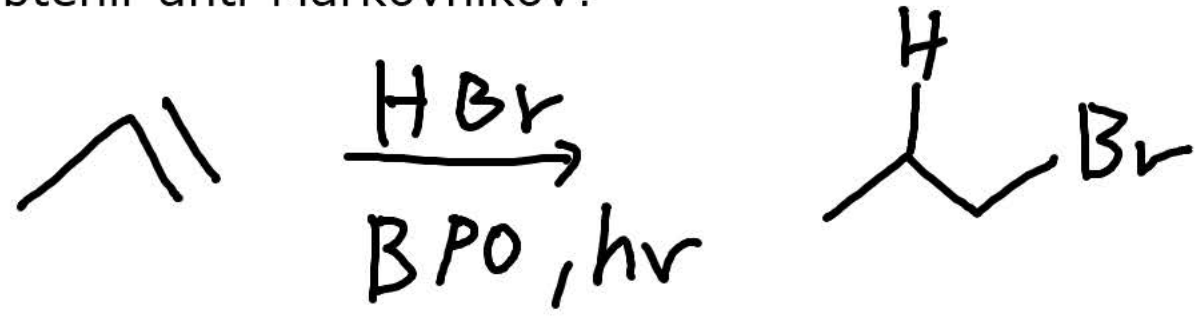
exception à la règle de Markovnikov



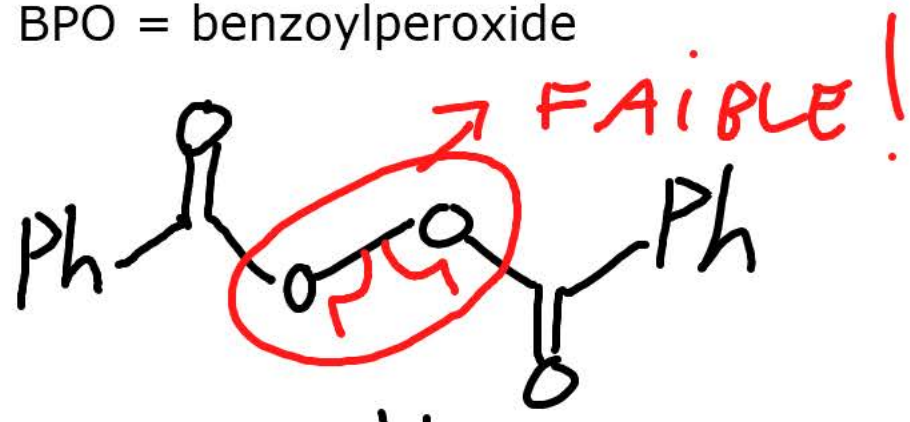
attaque ralentie par Me

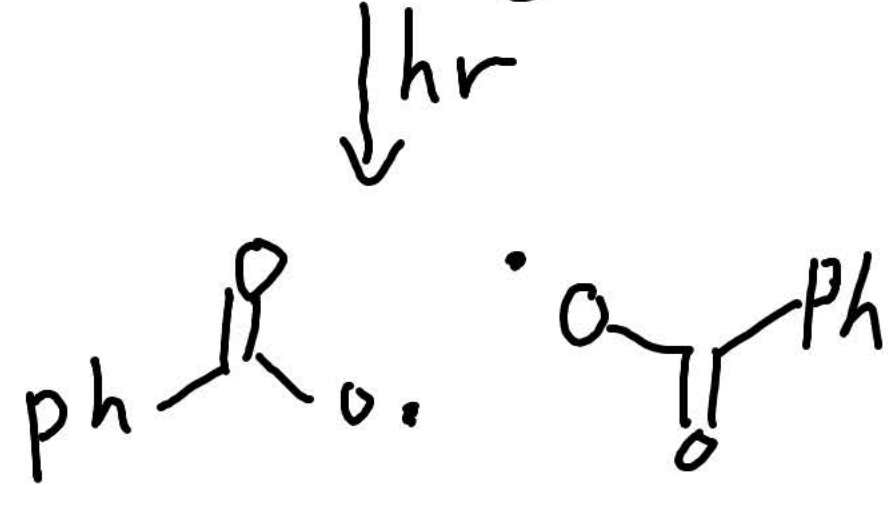
attaque rapide et facile:
favorisé!

obtenir anti-Markovnikov?



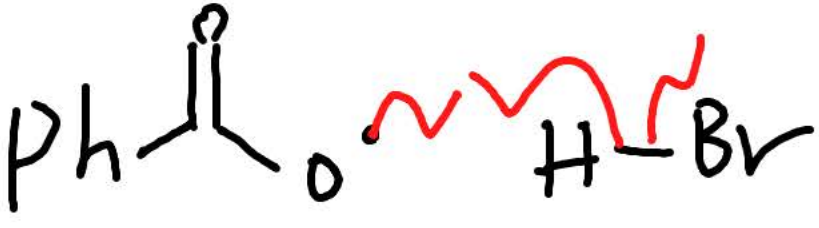
BPO = benzoylperoxide

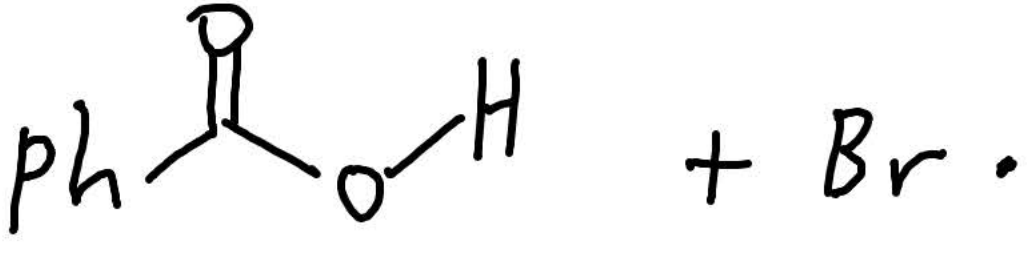




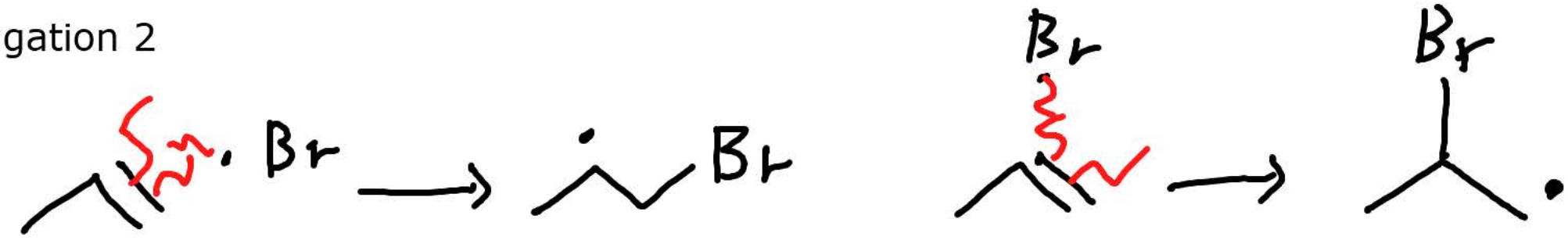
initiation

Propagation 1

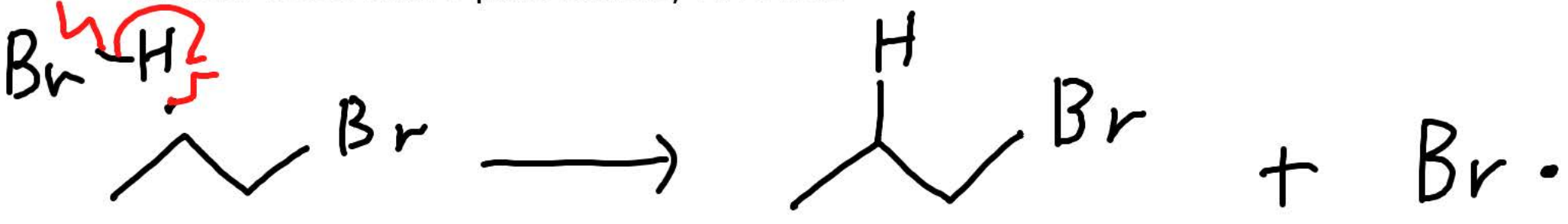




propagation 2



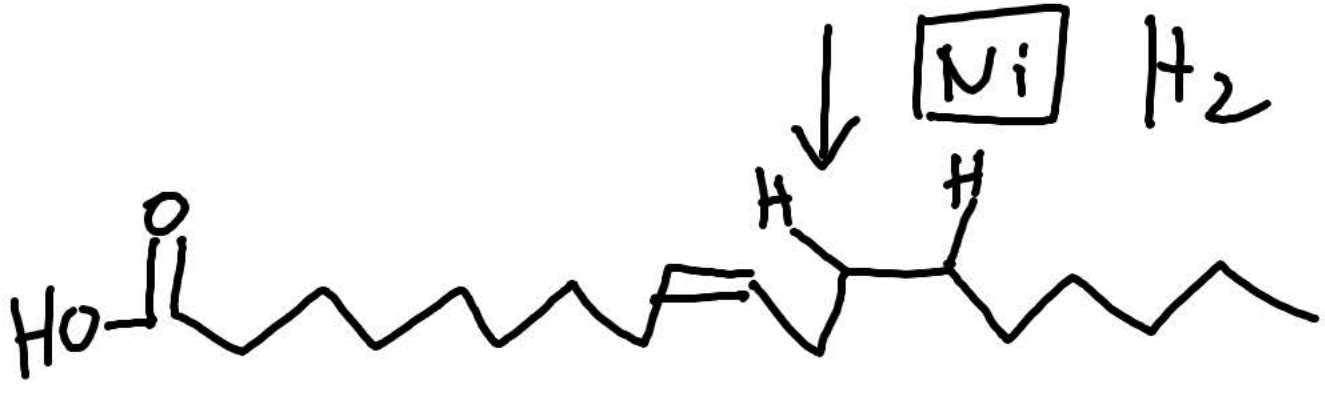
radical secondaire plus stable, favorisé



propagation 3

Example d'hydrogenation: les acides gras

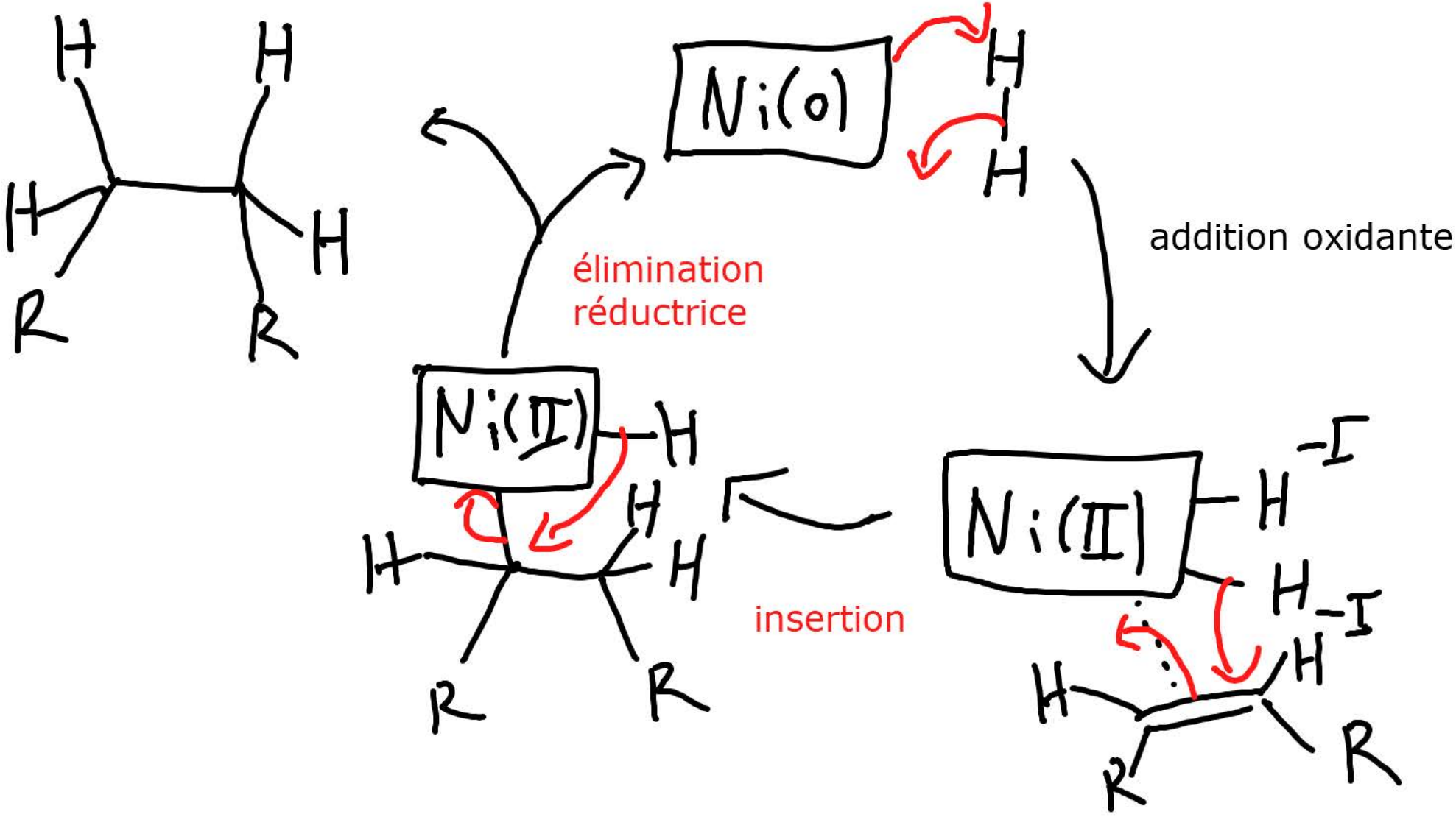
acide linoléique: abondant
dans les huiles végétales



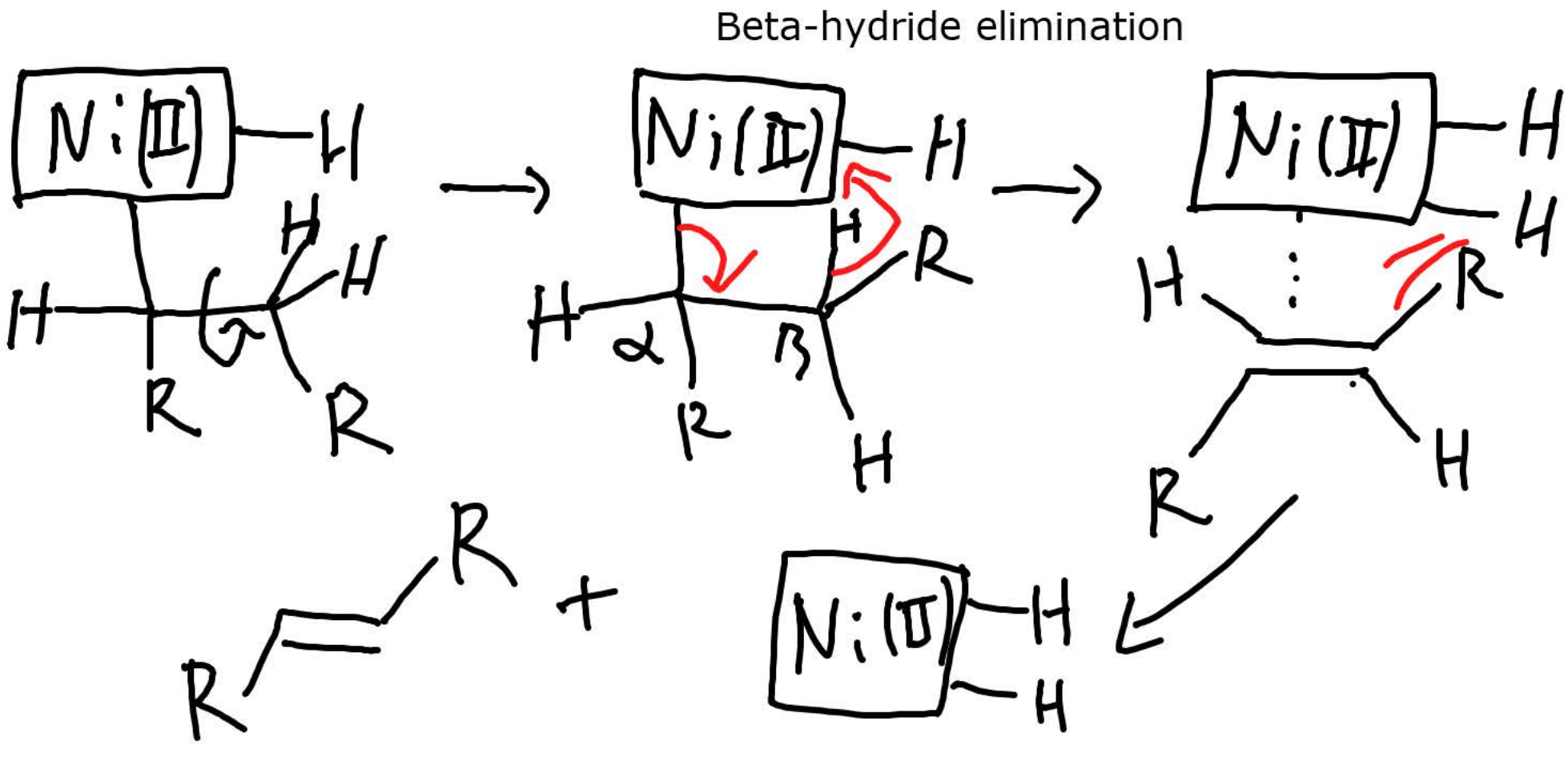
parafine/solide

\+

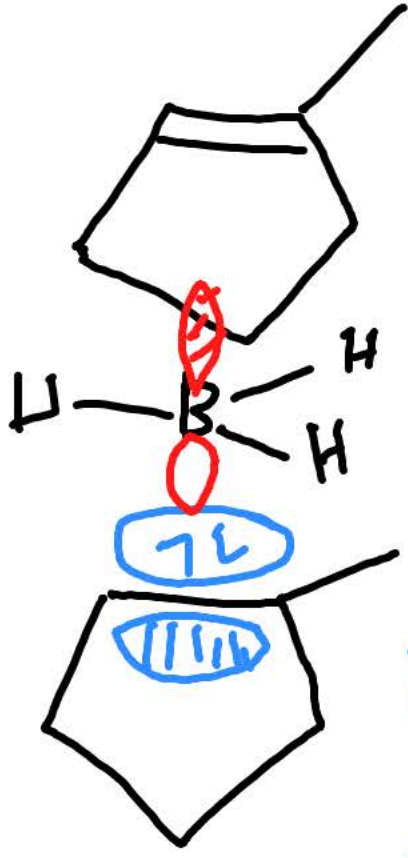
produit secondaire
artériosclérose
trans-fat

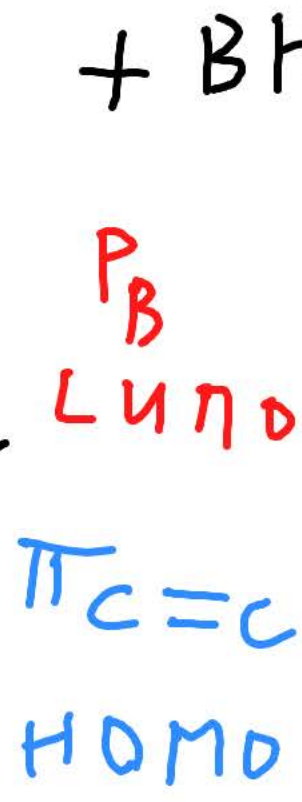

Ni(0)
addition oxidante
élimination
réductrice
Ni(II)
insertion
Ni(II)
-I
-I

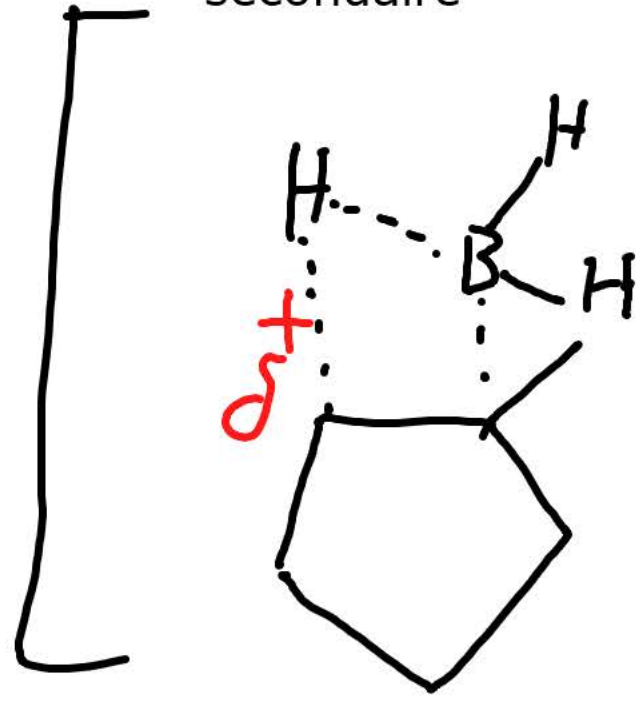
réaction secondaire



Réaction d'hydroboration





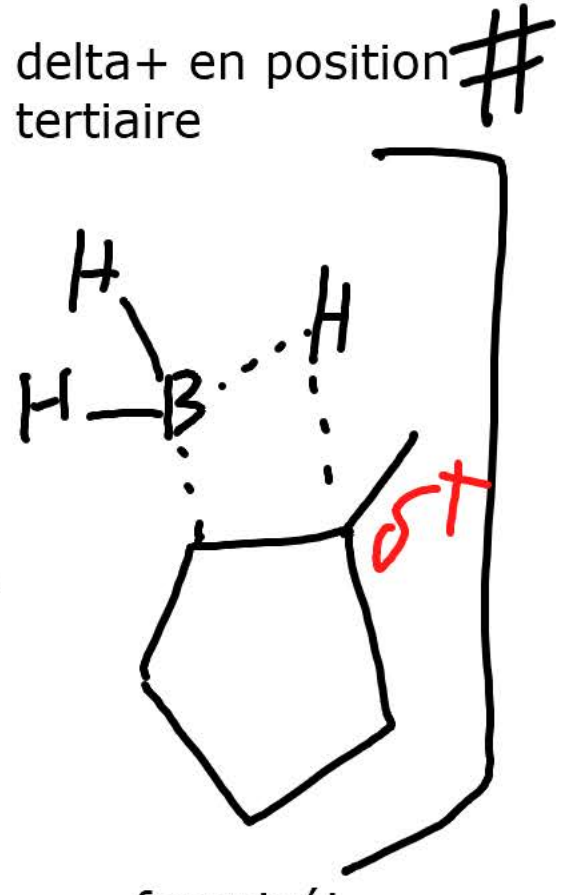


delta+ en position secondaire

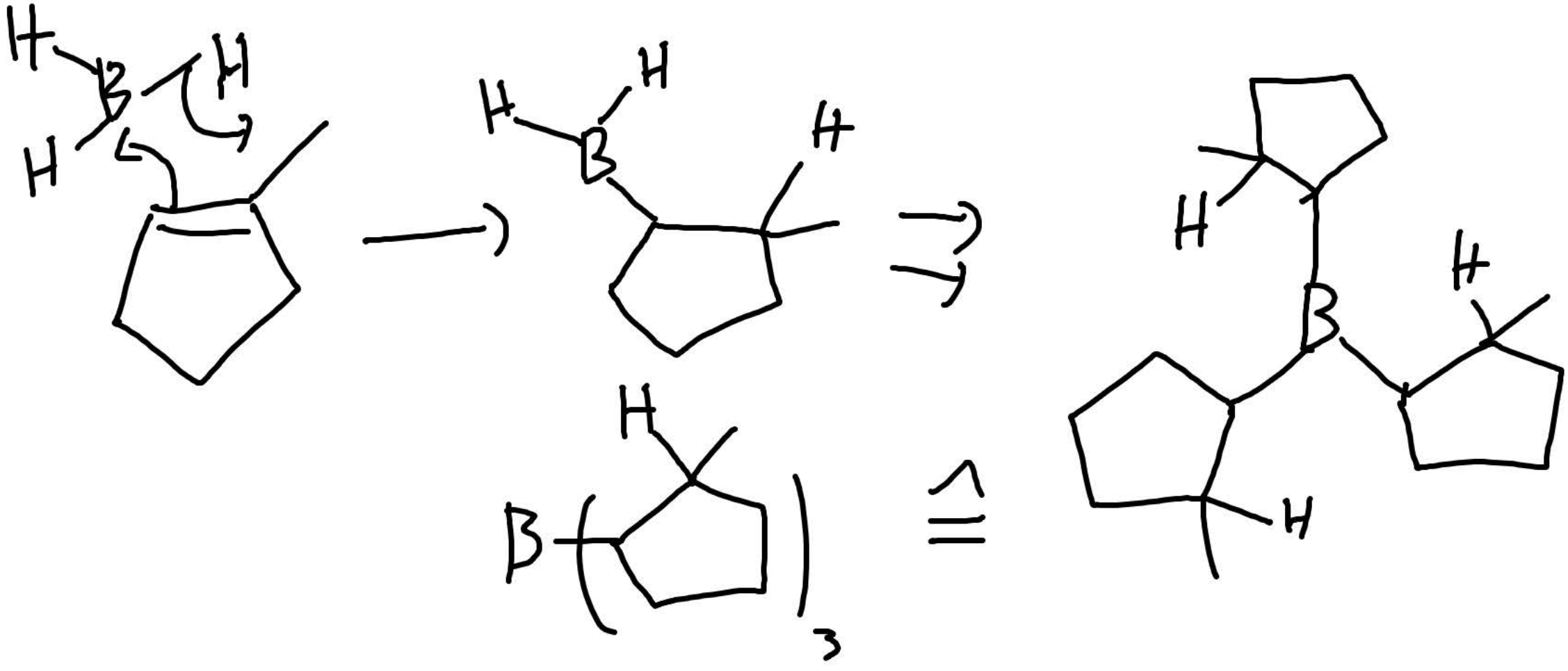
Liaison C-B plus courte que C-H dans l'état de transition

ou

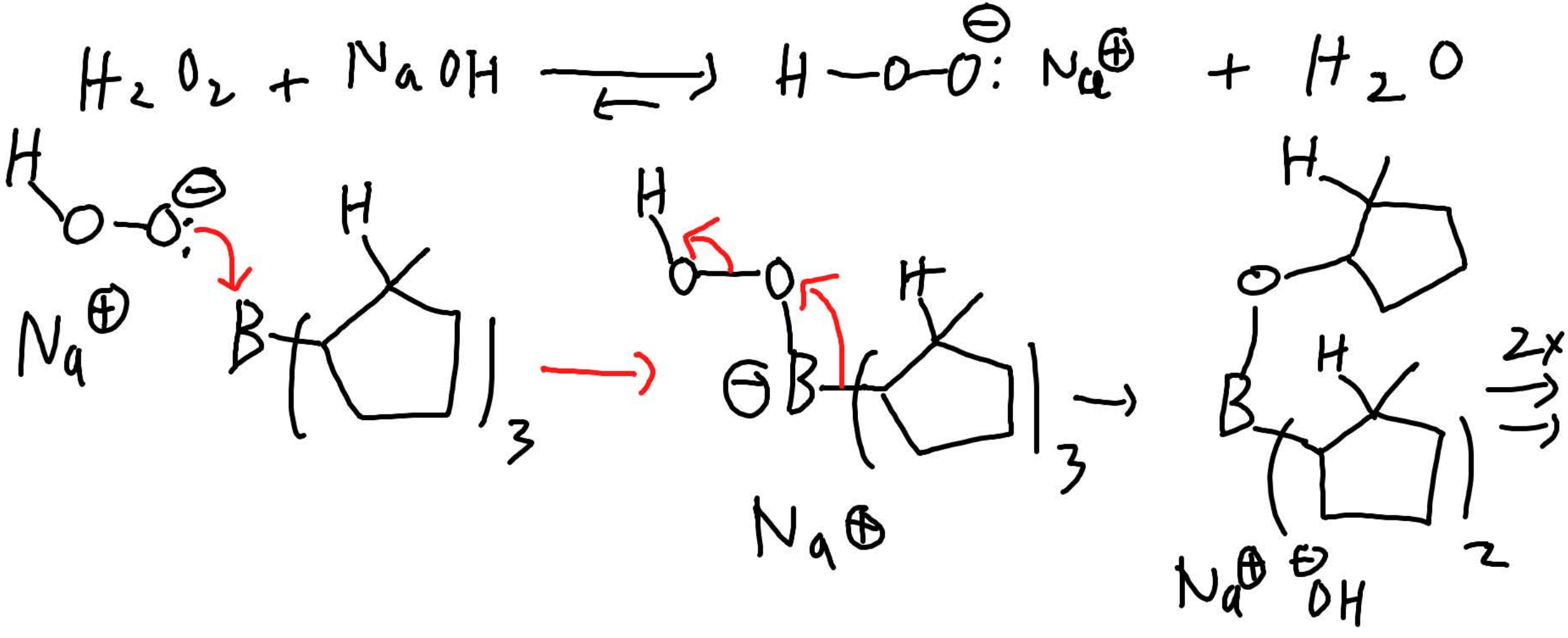
delta+ en position tertiaire

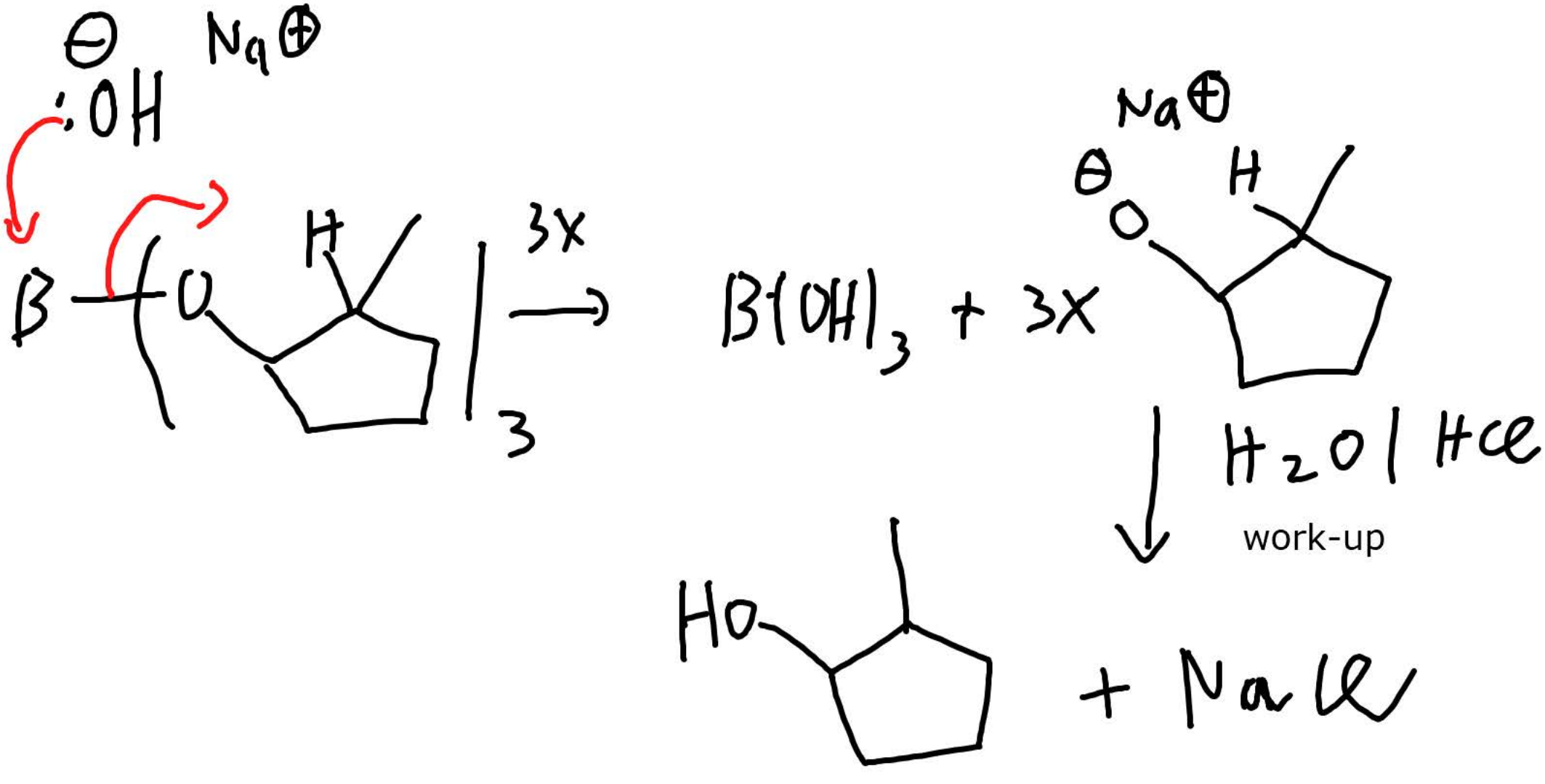


favorisé!

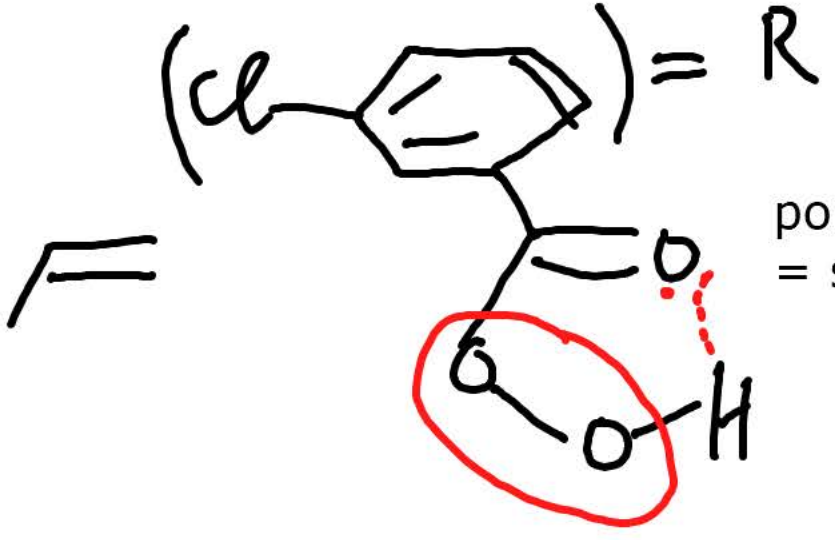

H
B
H
H
H
B
H
H
B
H
3

étape d'oxidation



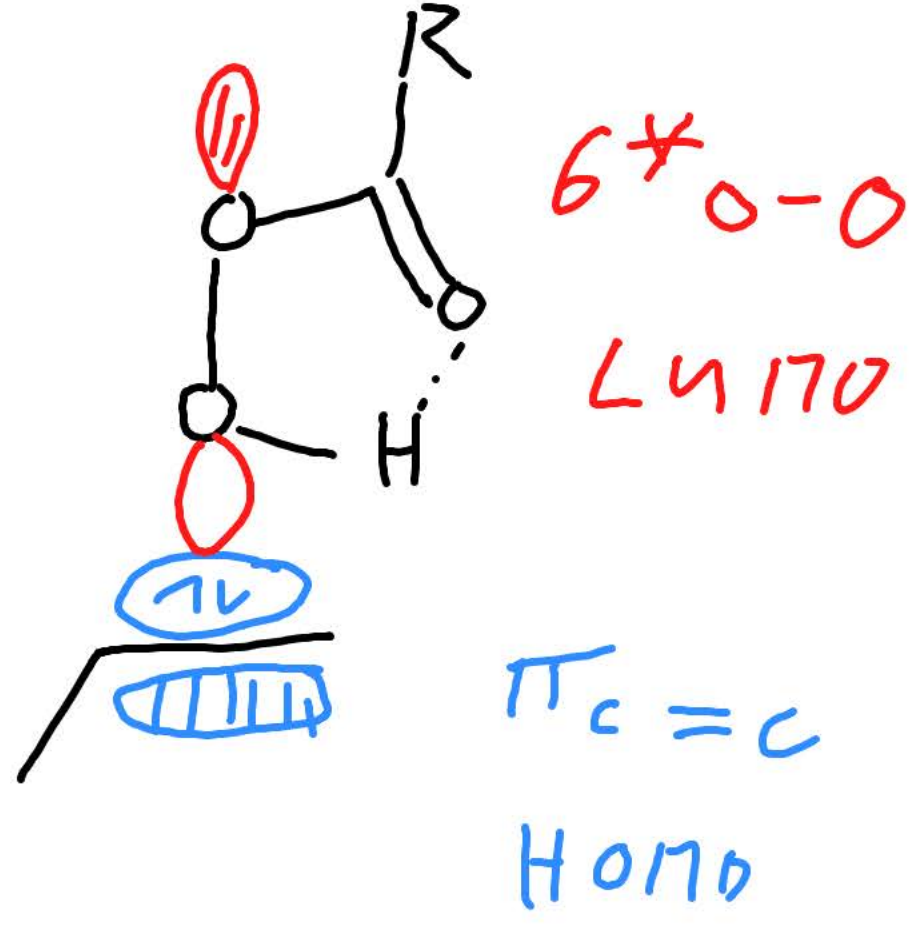

Θ
Na⊕
:OH
B
O
H
3
3X
B(OH)3 + 3X
Na⊕
Θ
O
H
H2O / HCl
work-up
HO
+ NaCl

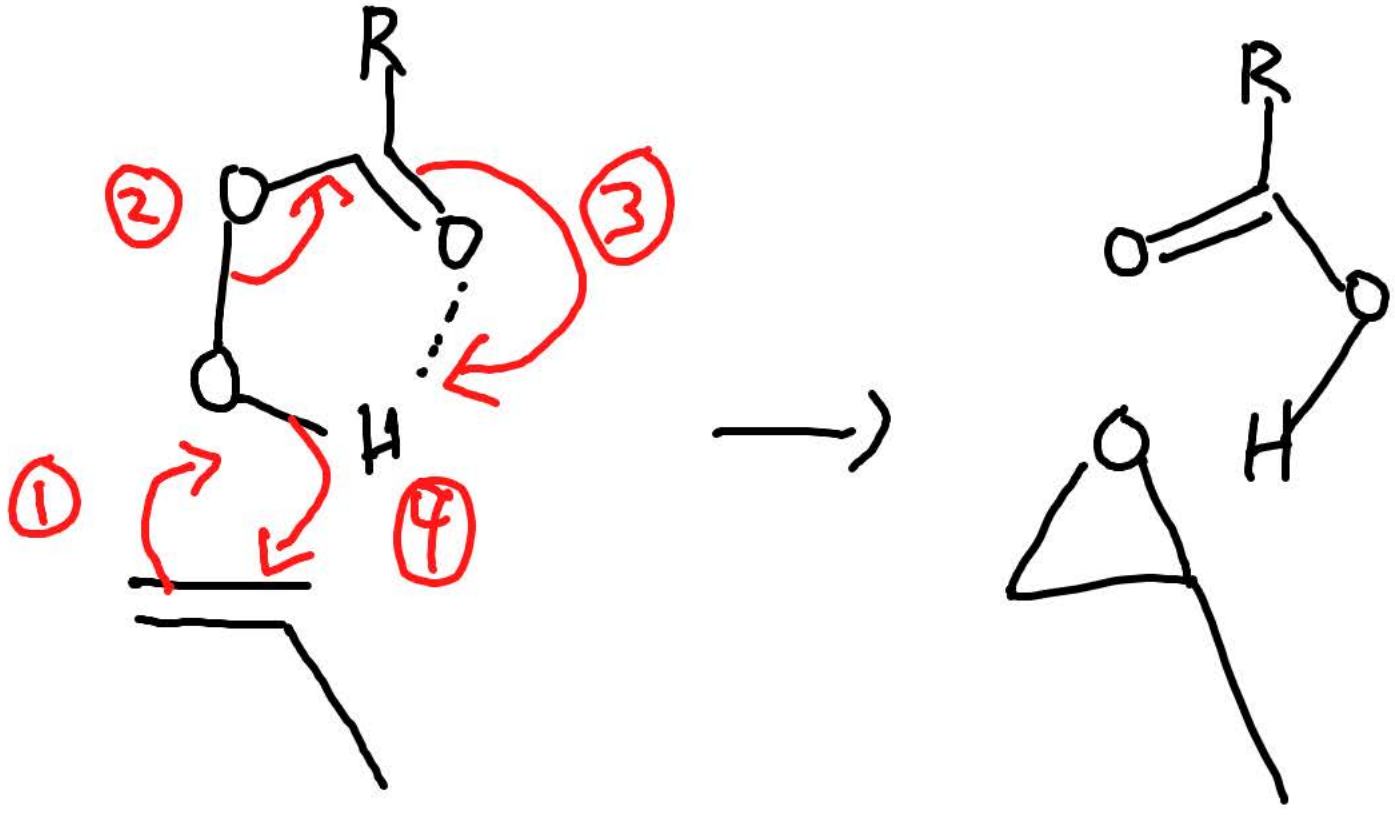
époxidation des alcènes



pont hydrogène
= soluble

meta-chloroperbenzoic acid
m-CPBA

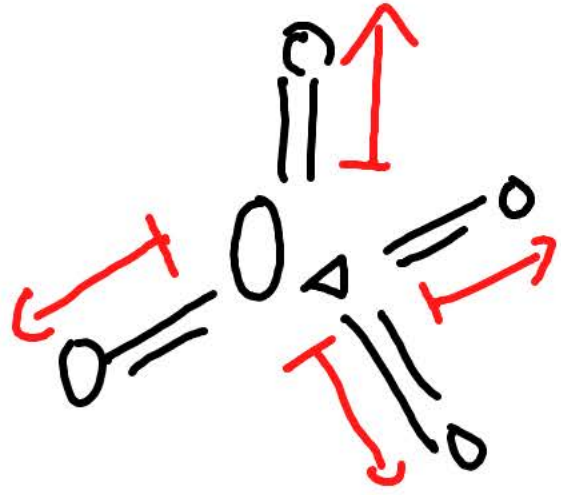




pas de pont hydrogène
moins soluble, précipite

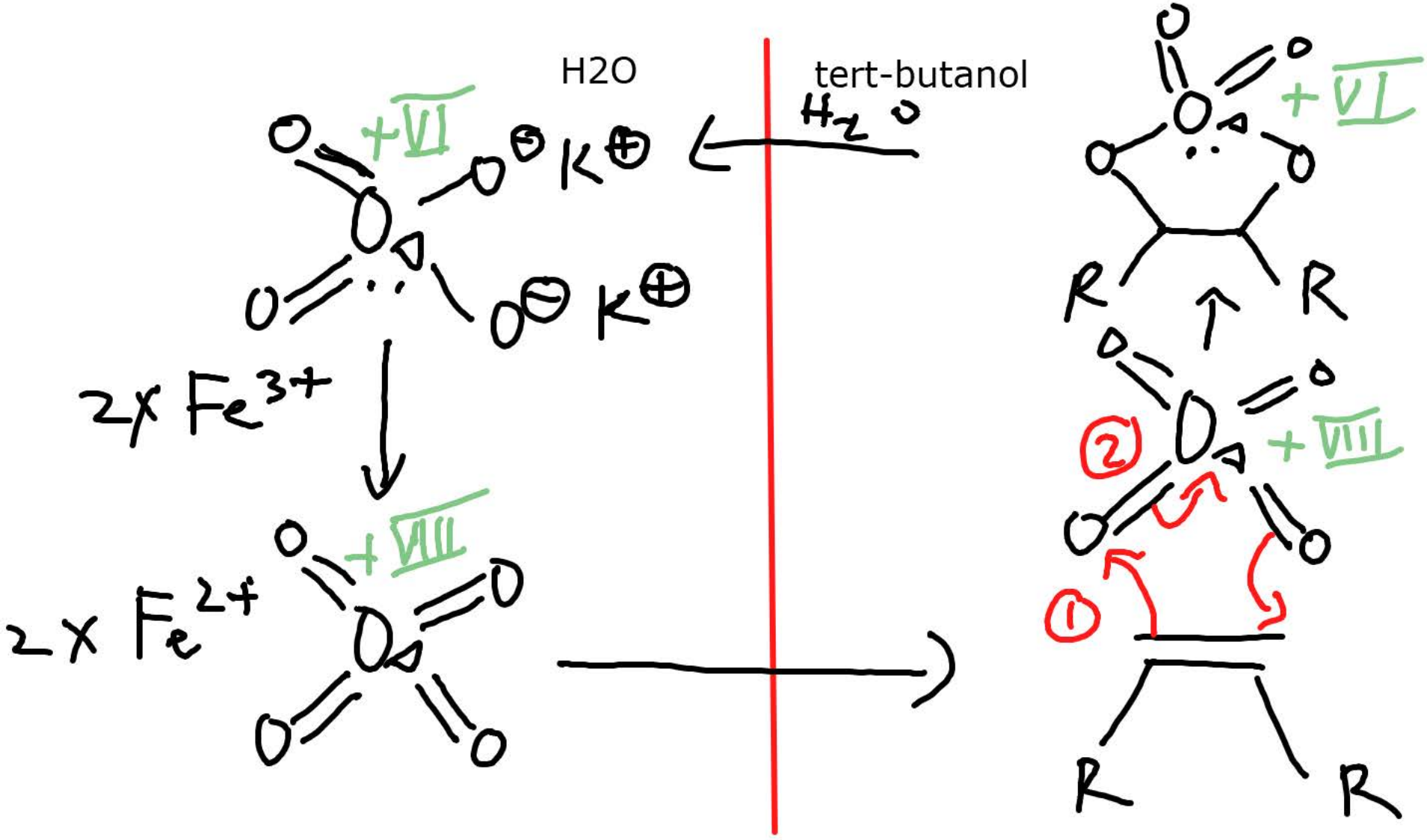
réaction de dihydroxylation

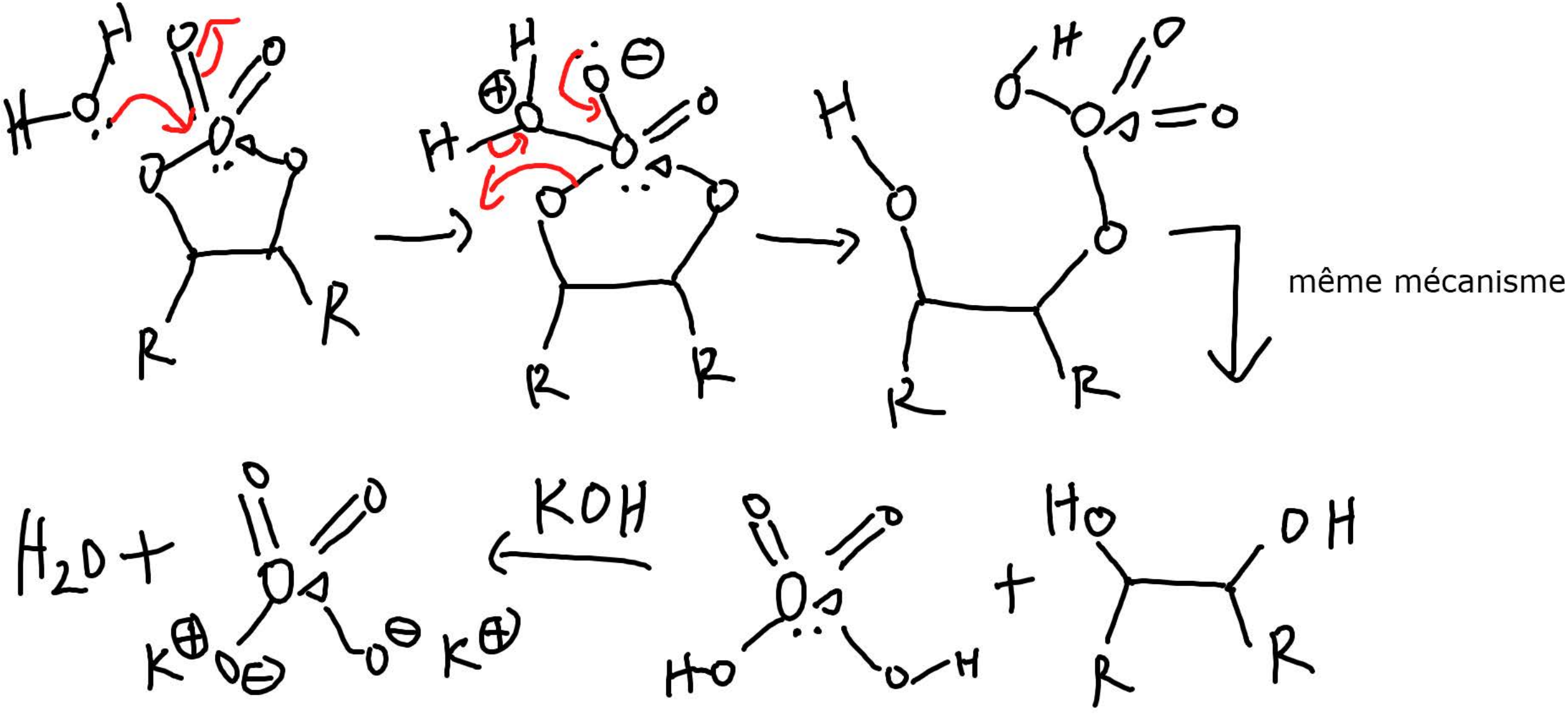
OsO_4



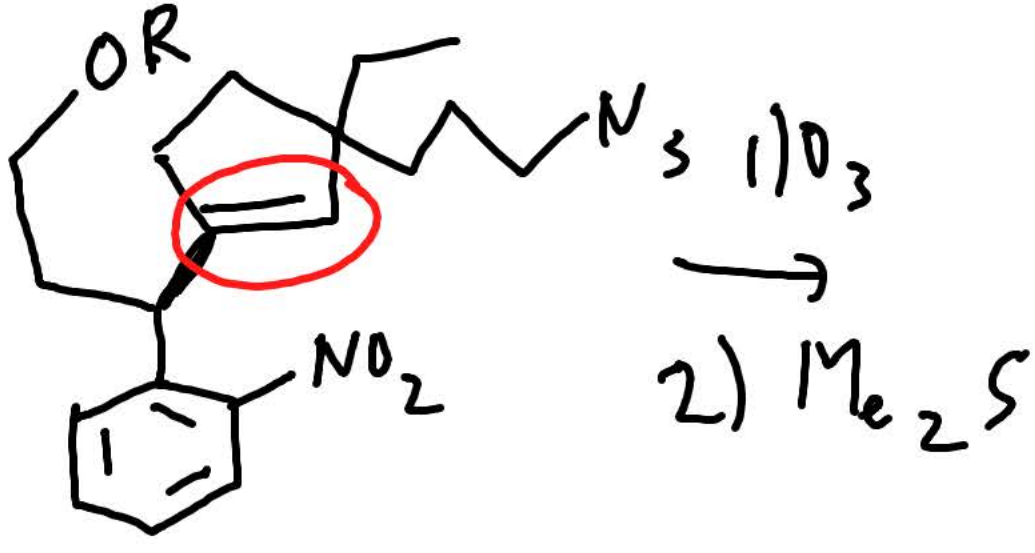
4 substituants = tétrahédrique
dipole total = 0
lipophilique, passe la barrière sang-cerveau
sublime facilement

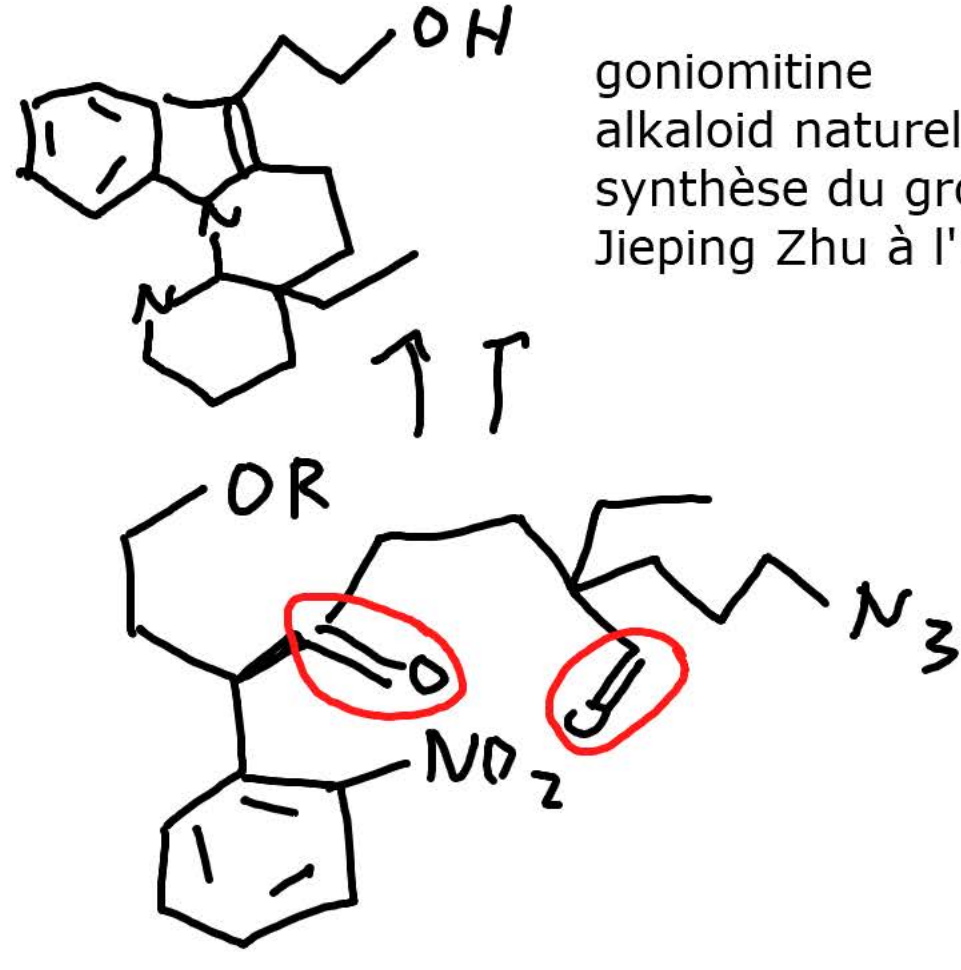
méthode de Sharpless: K_2OsO_4 catalytique, Fe^{3+} (stoichiométrique), H_2O/tert-butanol


H2O
tert-butanol
H2O
+VI
K⊕
K⊕
2x Fe3+
+VIII
2x Fe2+
+VI
R
R
2
+VIII
1
R
R

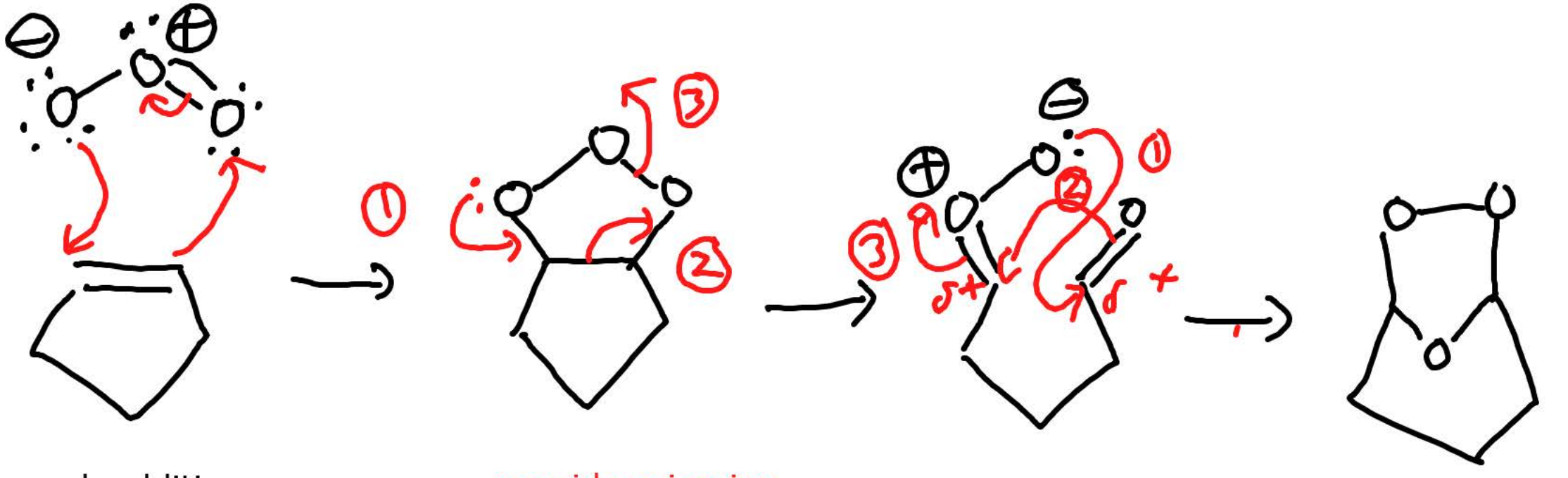

même mécanisme
KOH

réaction d'ozonolyse





goniomitine
alkaloid naturel
synthèse du group de
Jieping Zhu à l'EPFL

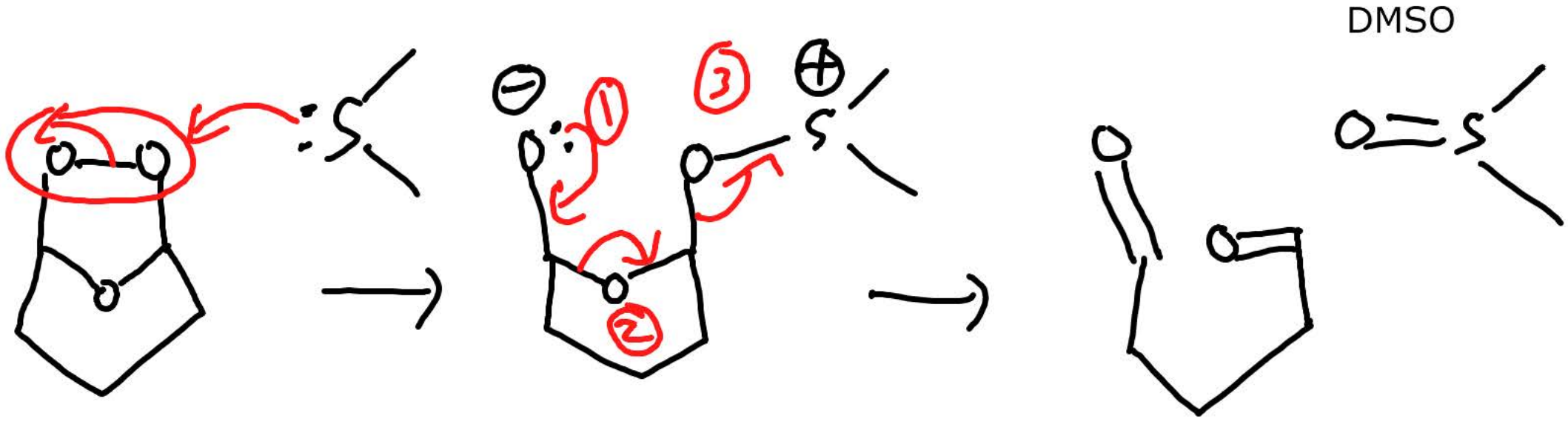


cycloaddition

ozonide primaire,
instable

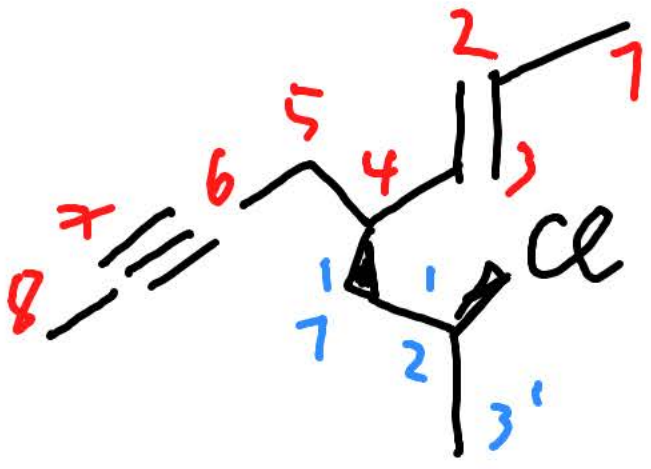
ozonide secondaire
plus stable

2) étape de réduction



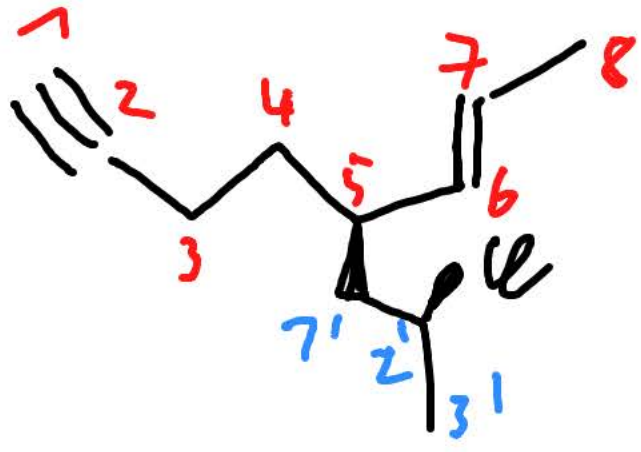
dicarbonyl, produit final

nomenclature des alcynes



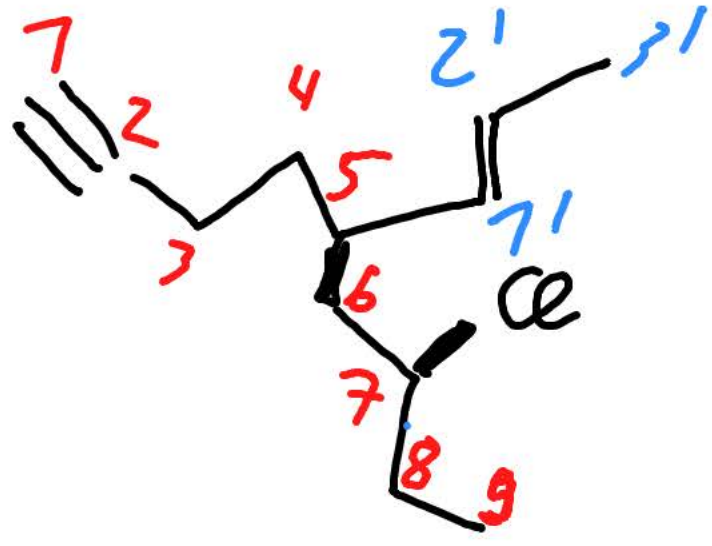
1) le plus long (identique)
2) le plus d'insaturation
3) le chiffre le plus bas pour l'alcène

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



chiffr le plus bas pour insaturation

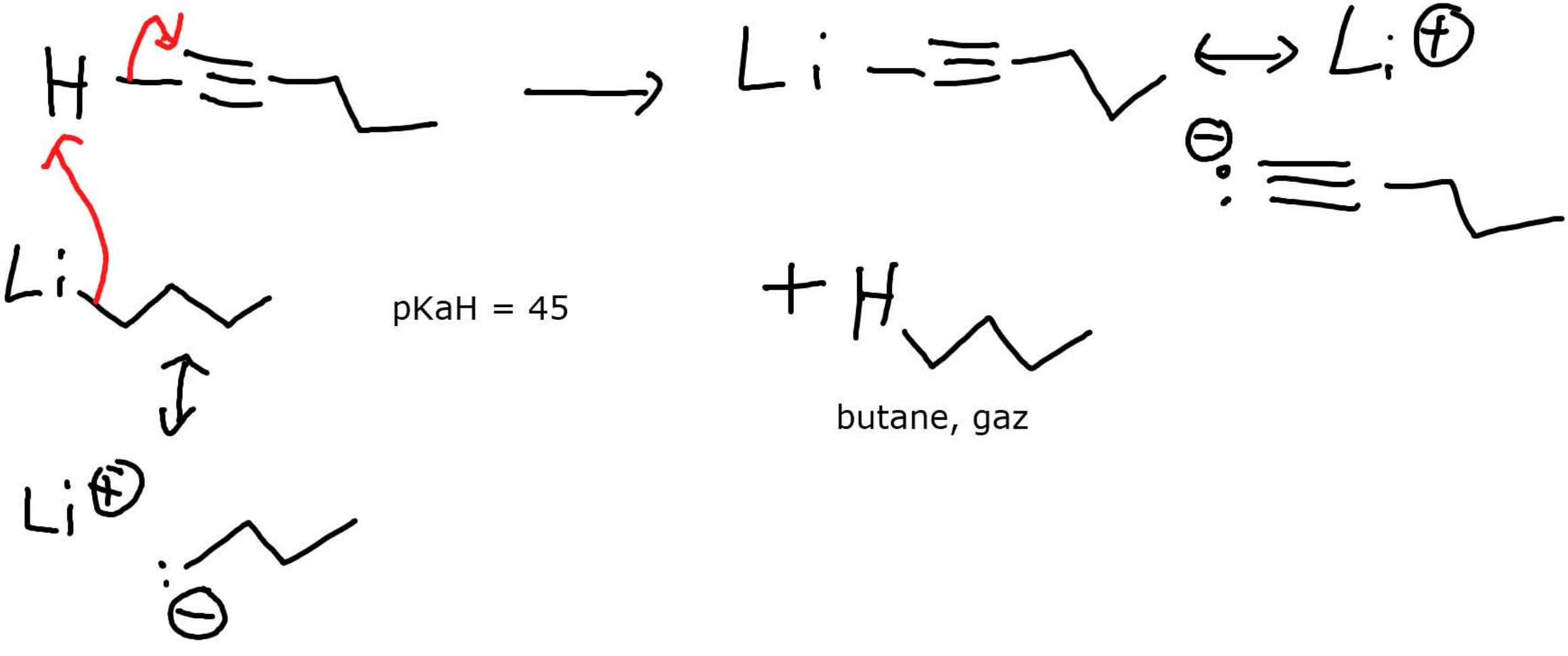
(E,5R)-5-((S)-2-chloropropyl)-oct-6-ene-1-yne

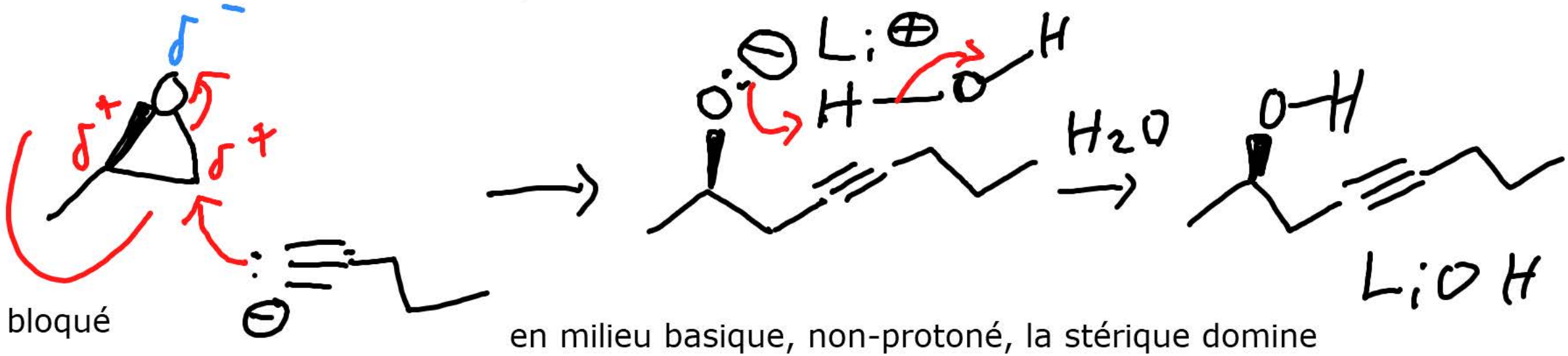


(5R,7S)-5-((E)-prop-1-enyl)-non-1-yne

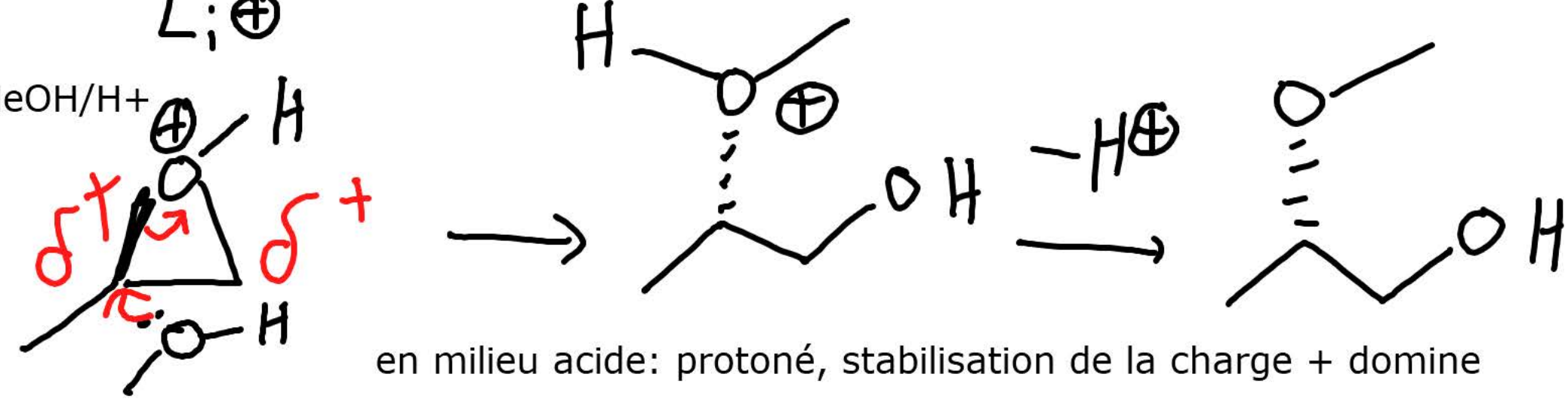
déprotonation des alcynes

pkA = 25

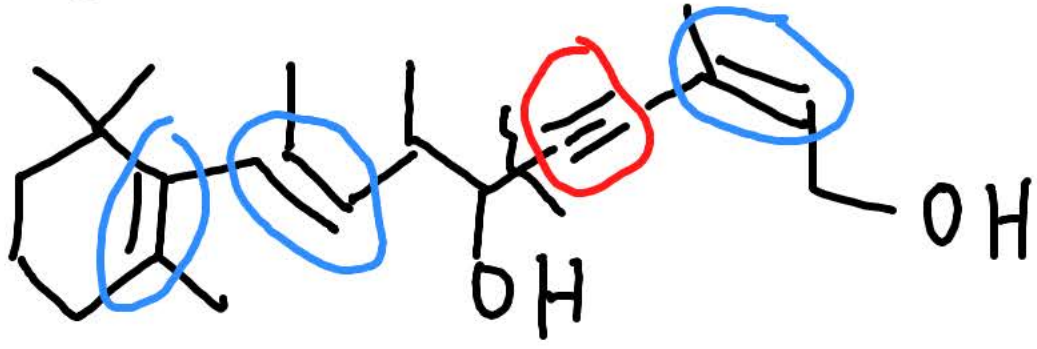


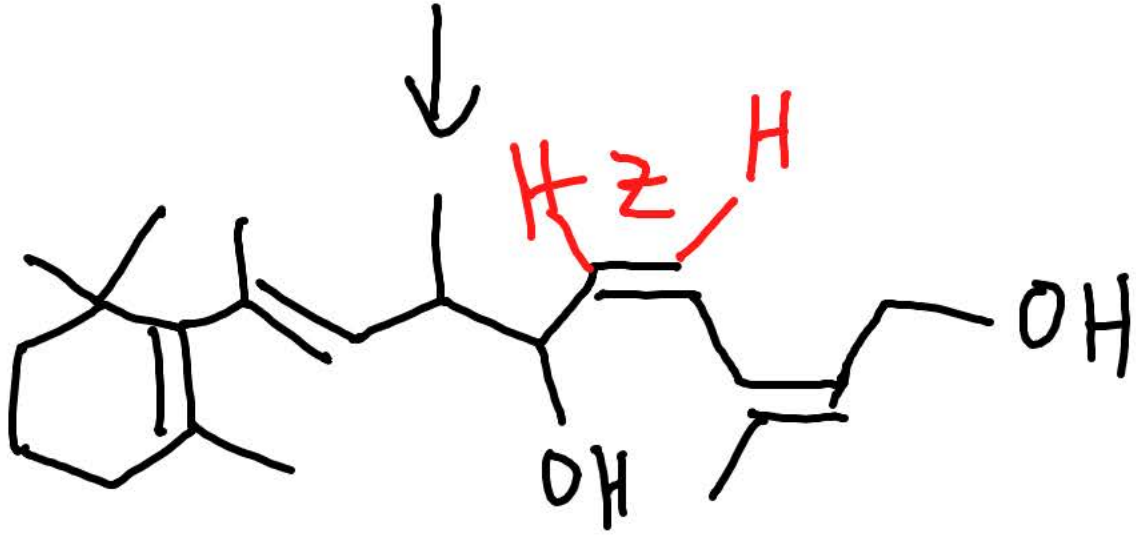

bloqué
en milieu basique, non-protoné, la stérique domine

avec MeOH/H+

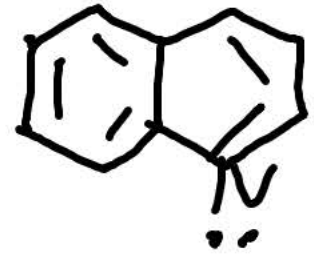

en milieu acide: protoné, stabilisation de la charge + domine

Hydrogénation de Lindlar: Hoffmann-LaRoche





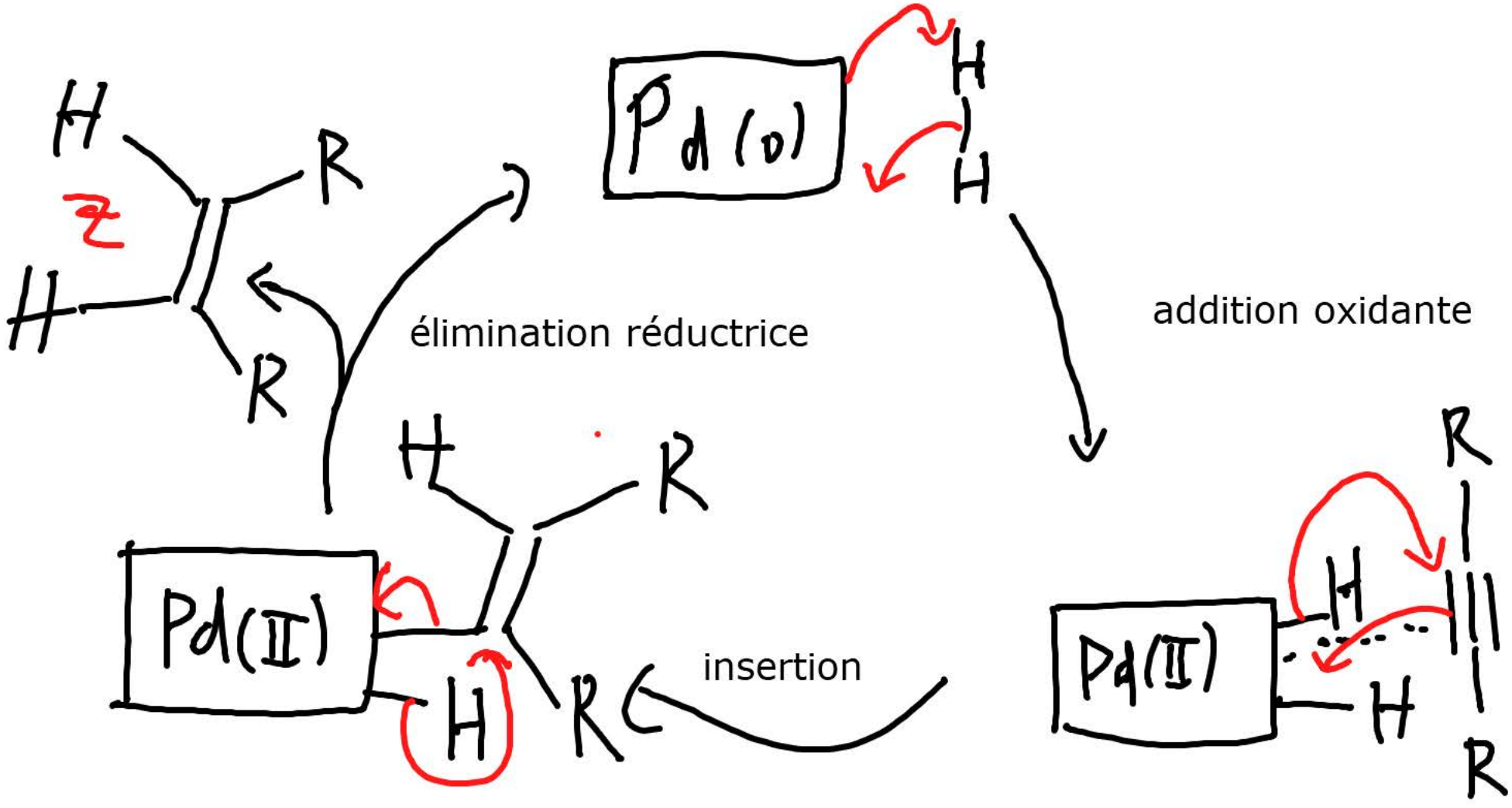
Pd I (PbSO4) BaSO4



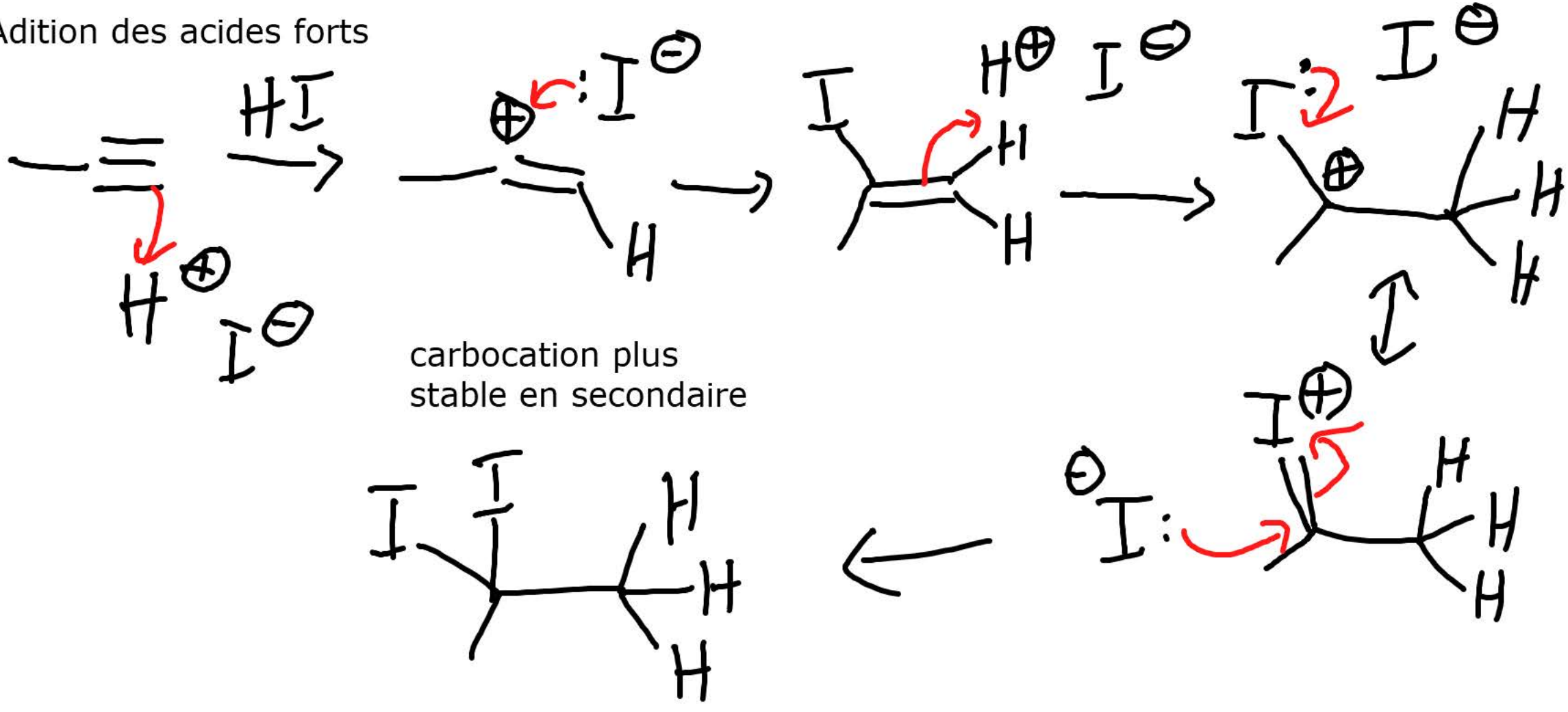
quinoline

se lie à la surface de Pd et diminue la réactivité
seulement les liaisons triples sont hydrogénées!

rétinol, vitamine A

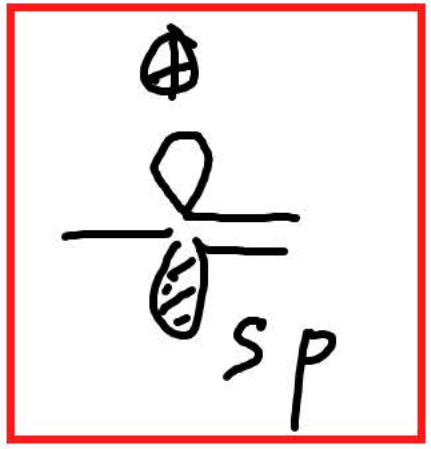

Pd(0)
H
H
addition oxidante
R
Pd(II)
H
H
R
insertion
H
R
Pd(II)
élimination réductrice
H
R
R

Adition des acides forts

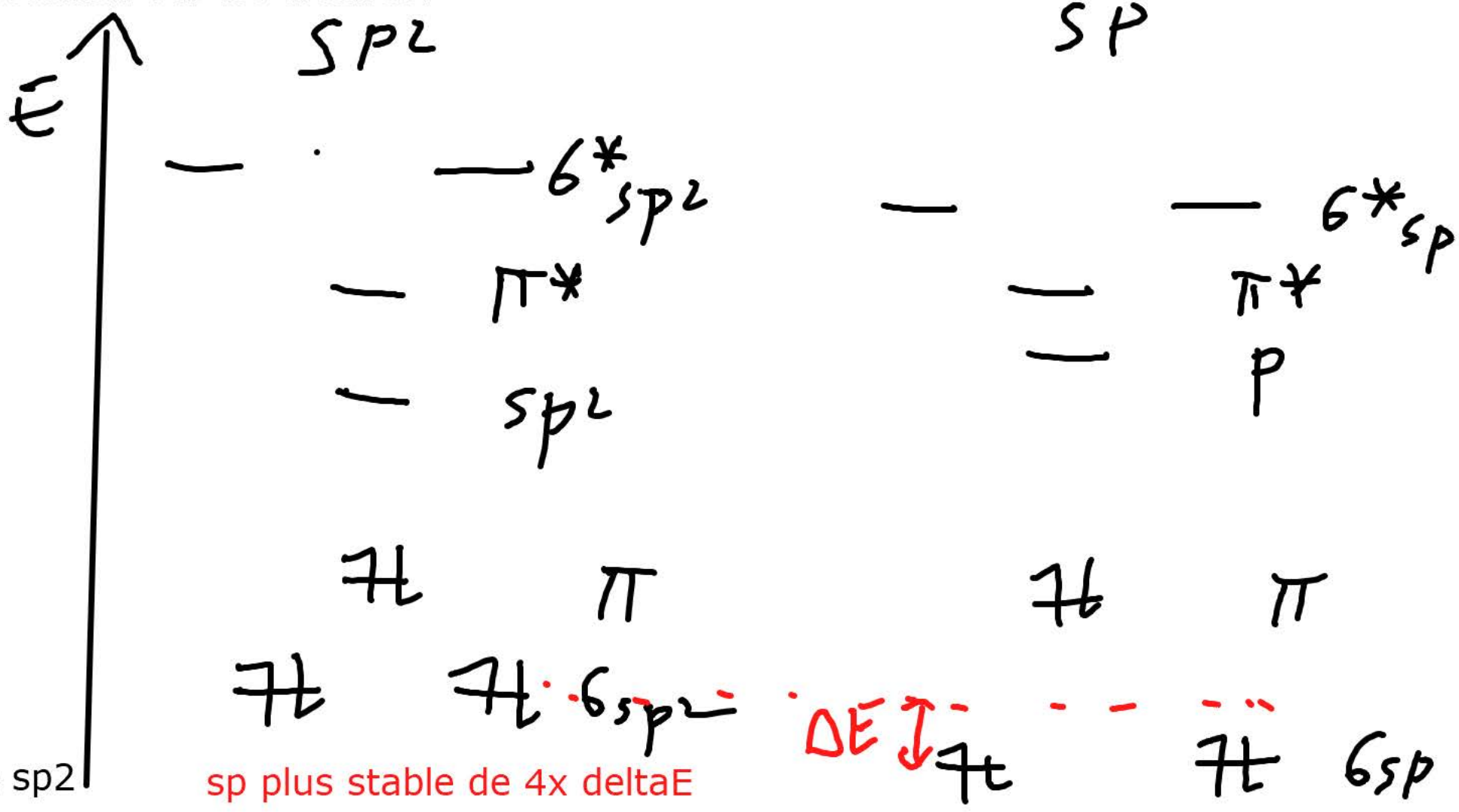


carbocation plus
stable en secondaire

Structure du carbocation sur les alcènes?



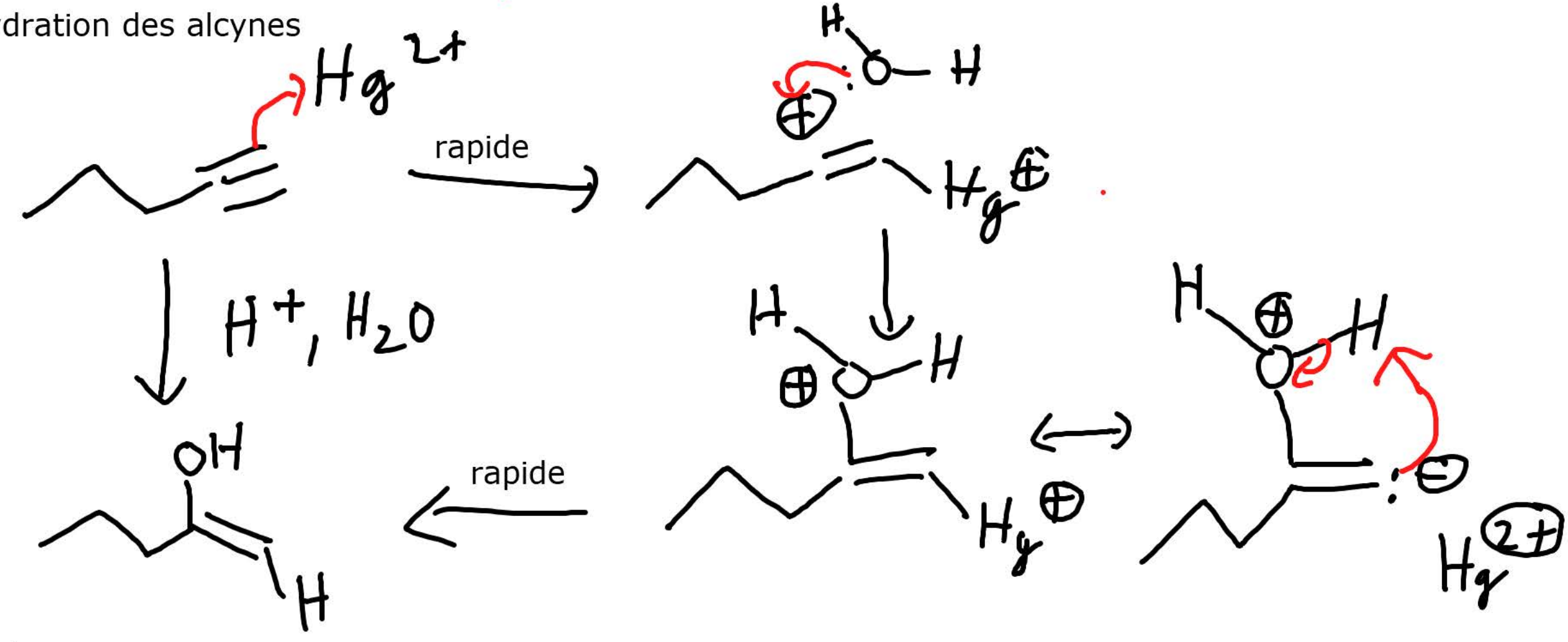
ou



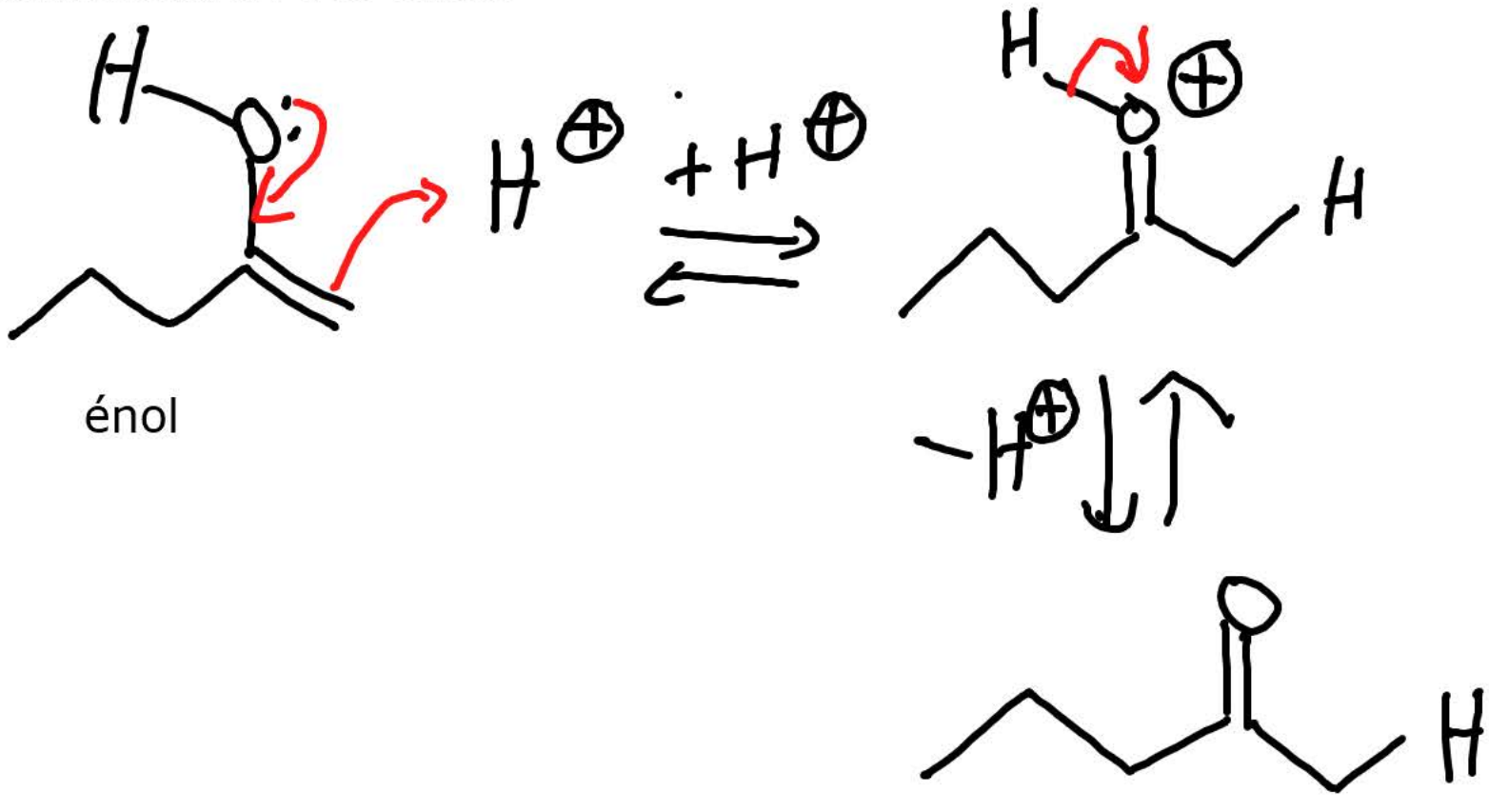
sp plus stable que sp2

sp plus stable de 4x deltaE

hydration des alcynes



tautomérisation des énols



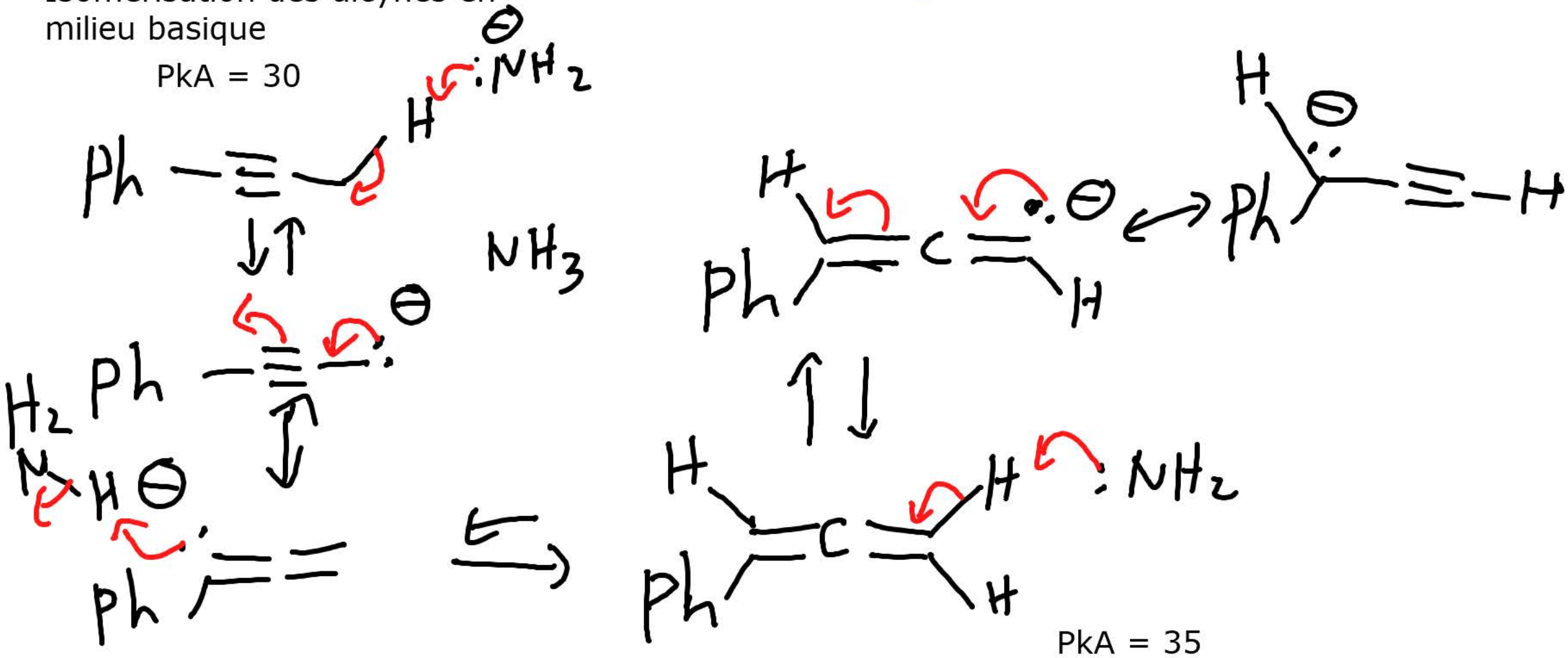
énol

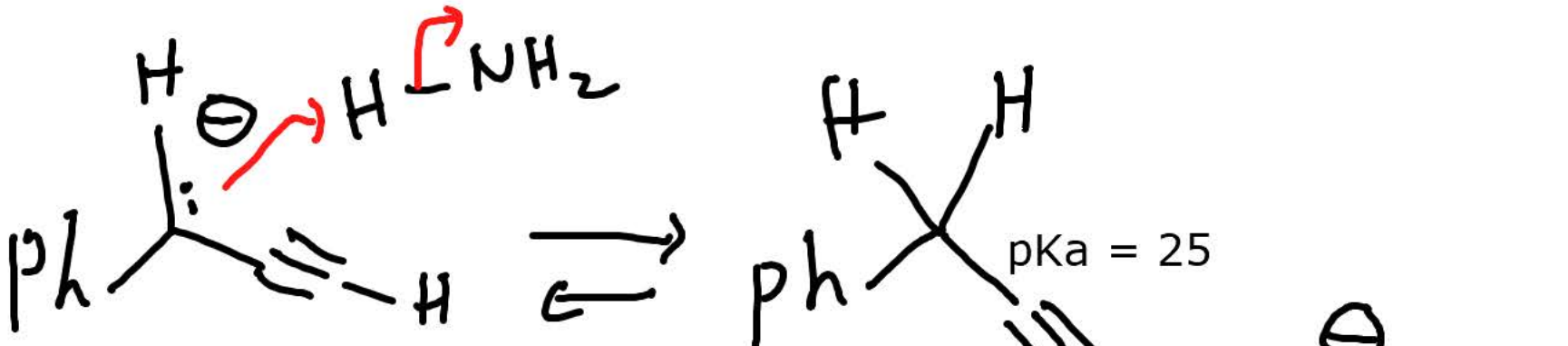
cétone

double liaison C=O plus forte que double liaison C=C, équilibre en faveur de la cétone

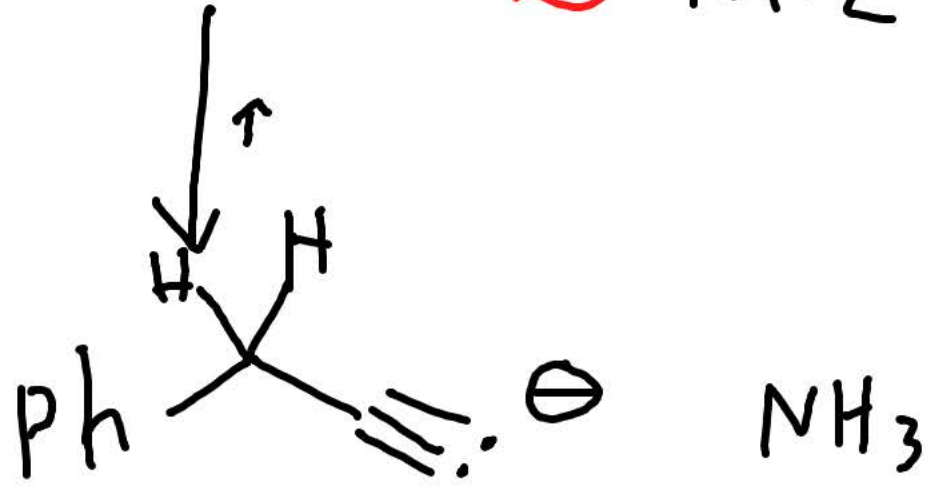
Isomérisation des alcynes en milieu basique

PkA = 30

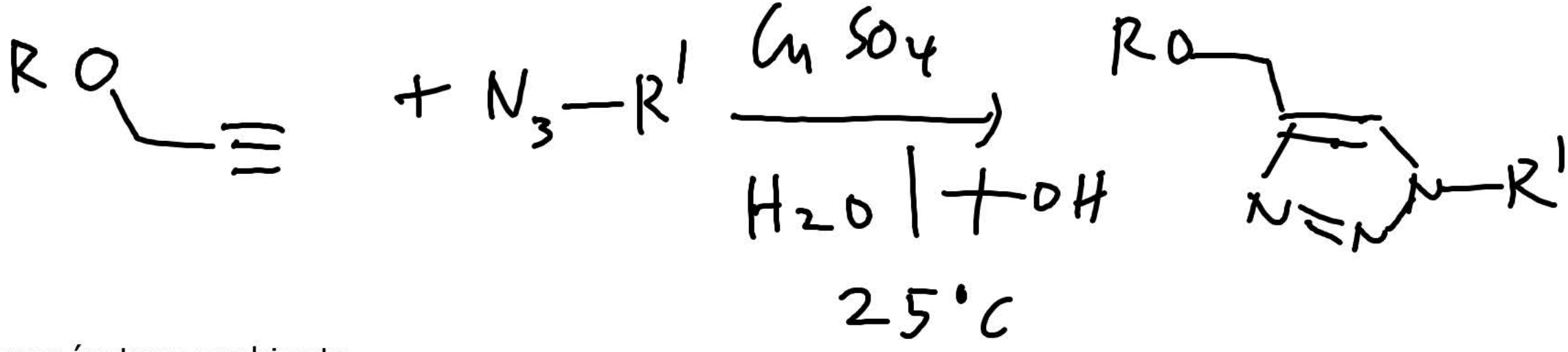




anion le plus stable,
la réaction stoppe

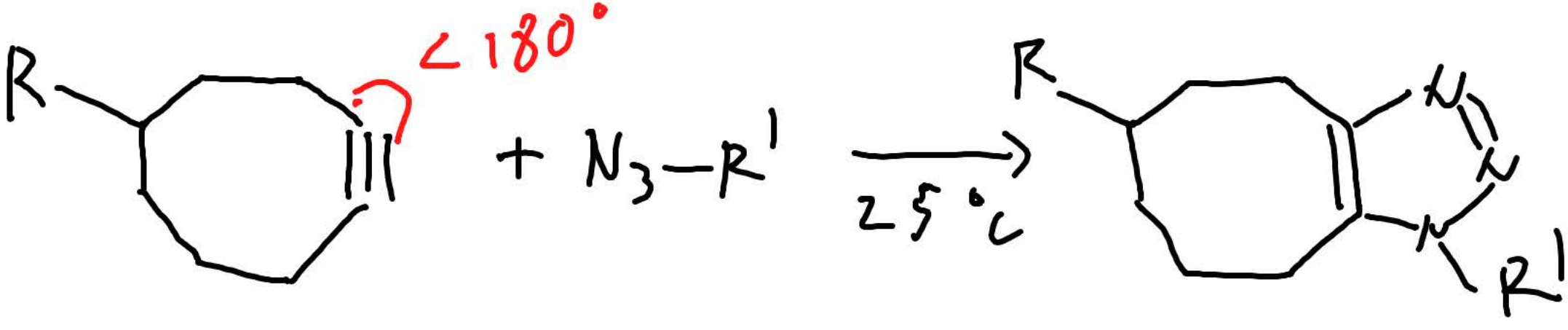


cycloaddition avec les azoture: Sharpless/Medal: catalyse au cuivre



A température ambiante
Un seul produit
Marche pour "n'importe quels R et R'"
Mais... Le cuivre peut être toxique pour les cellules

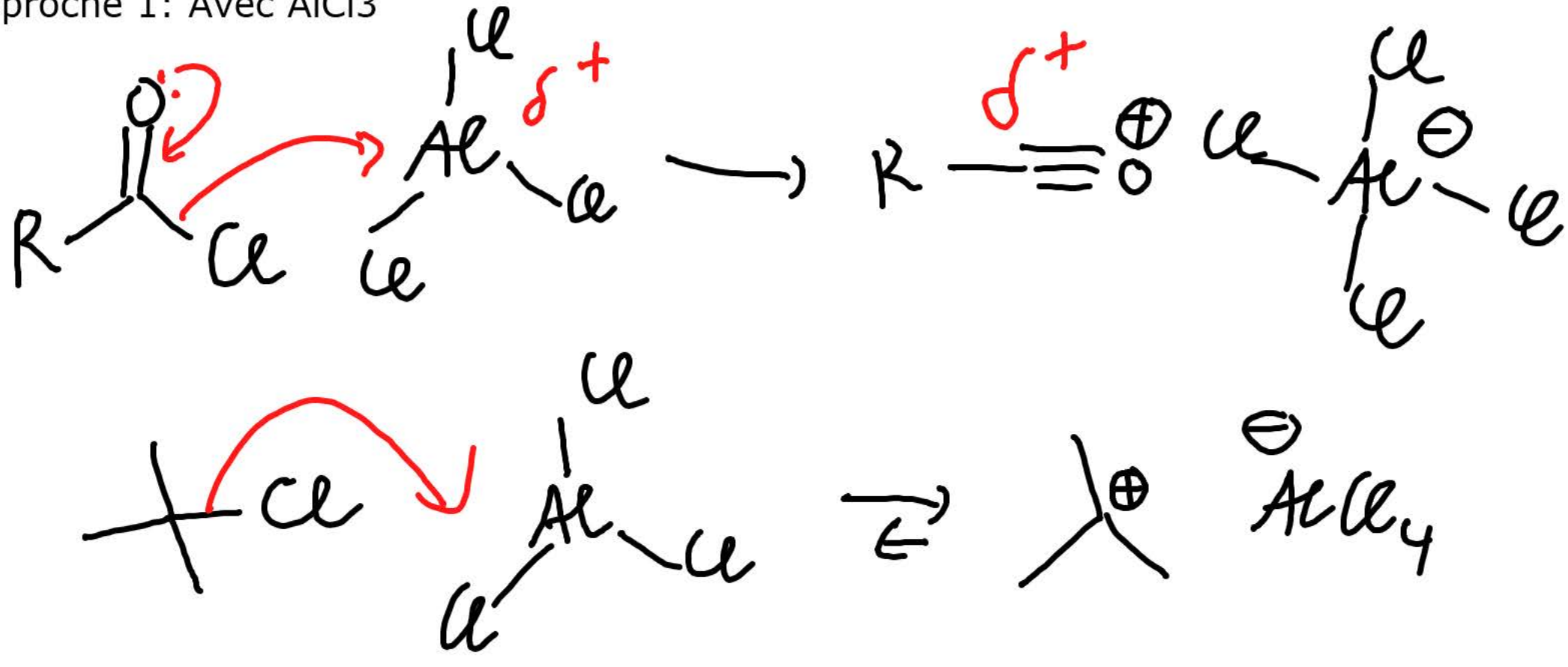
procédé de Carolyn Bertozzi (sans cuivre)



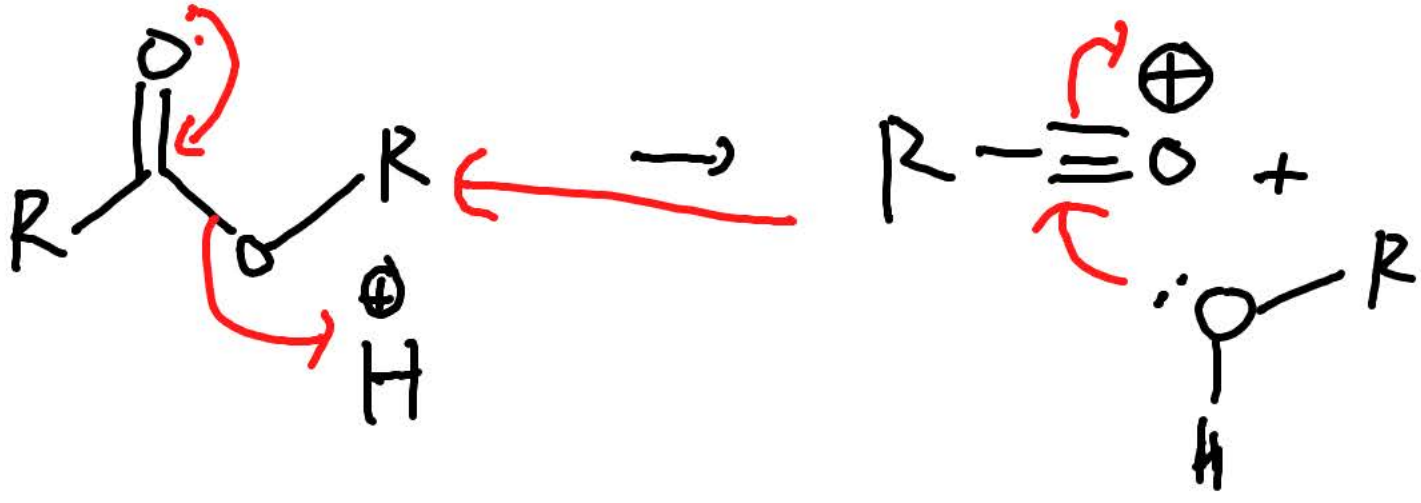
A cause du cycle: angle < 180°
Alcyne plus réactif, réaction est à 25 °C au lieu de 150 °C
Cycle idéal: 8 atomes.

Réaction de Friedel-Craft
1) activation de l'électrophile

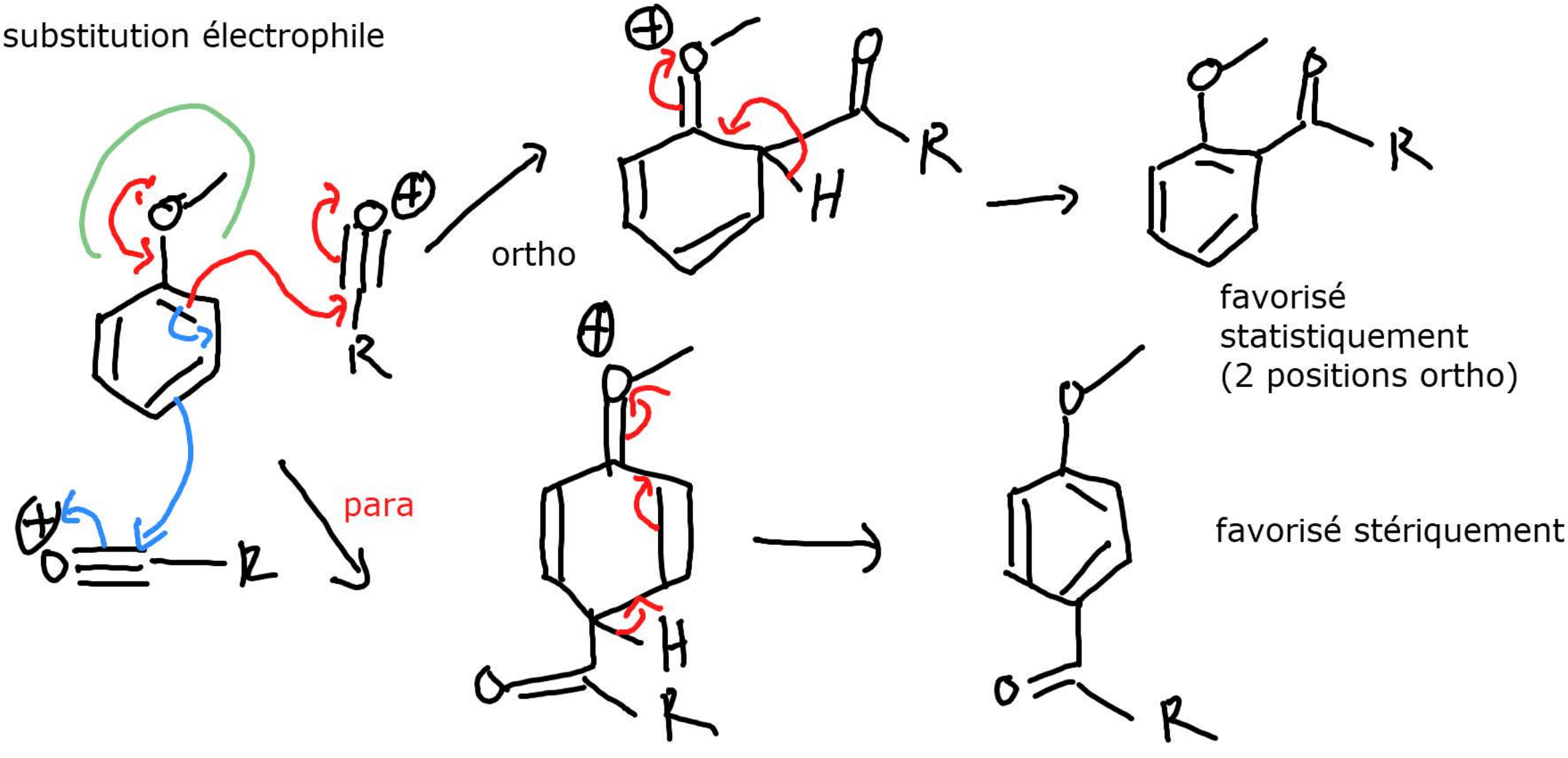
Approche 1: Avec AlCl3

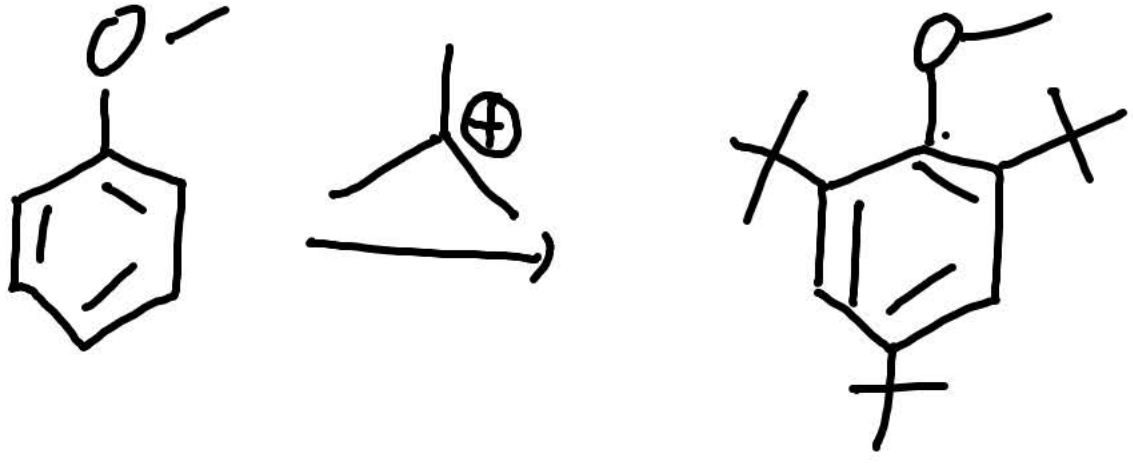


approche 2:

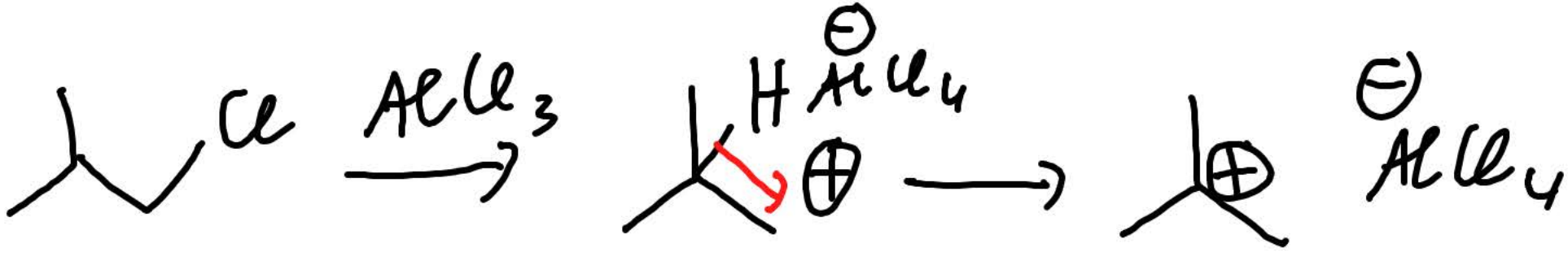


2) substitution électrophile



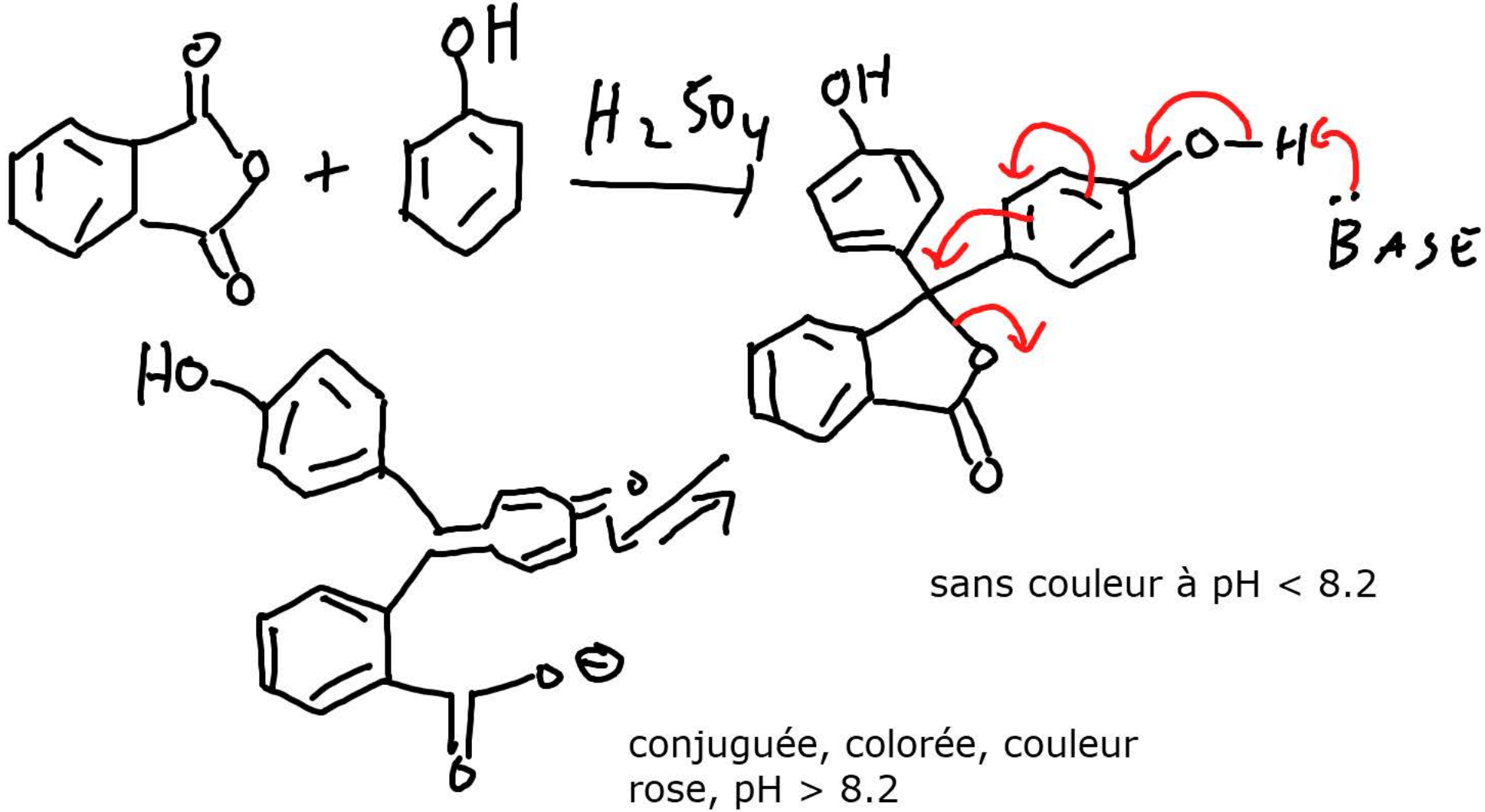


group tBu riche en électrons, donc la réaction accélère à chaque étape (jusqu'à 3 groupe max)



(seul les groupes alkyle tertiaires/substitués peuvent être introduits!)

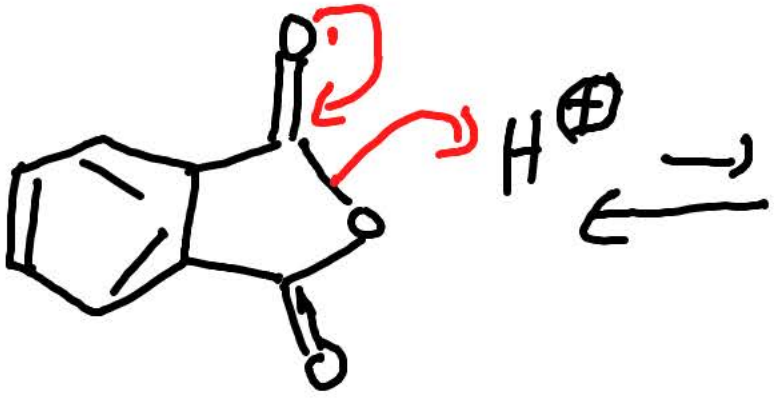
synthèse de la phénolphtalein

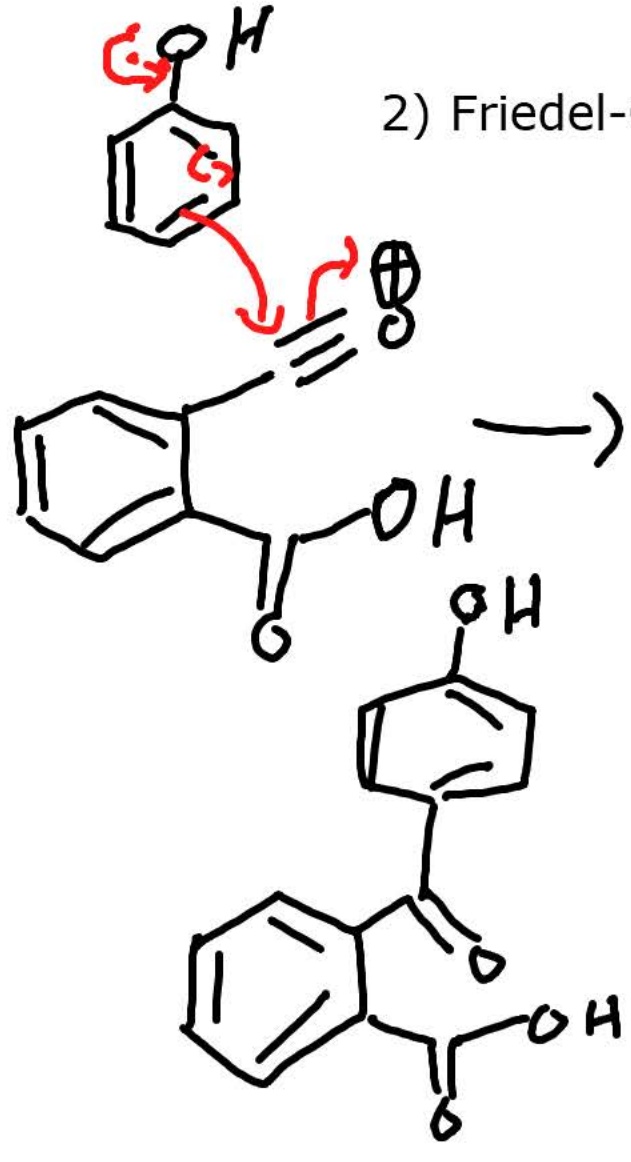


sans couleur à pH < 8.2

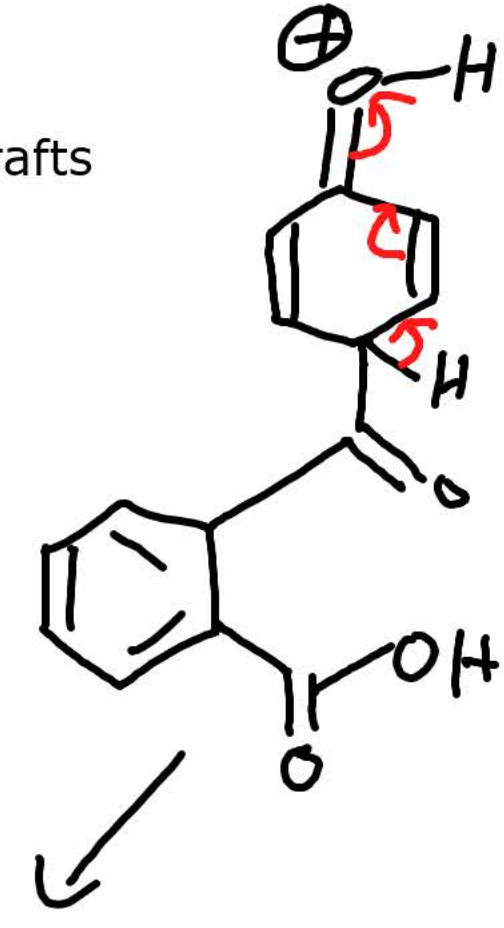
conjuguée, colorée, couleur rose, pH > 8.2

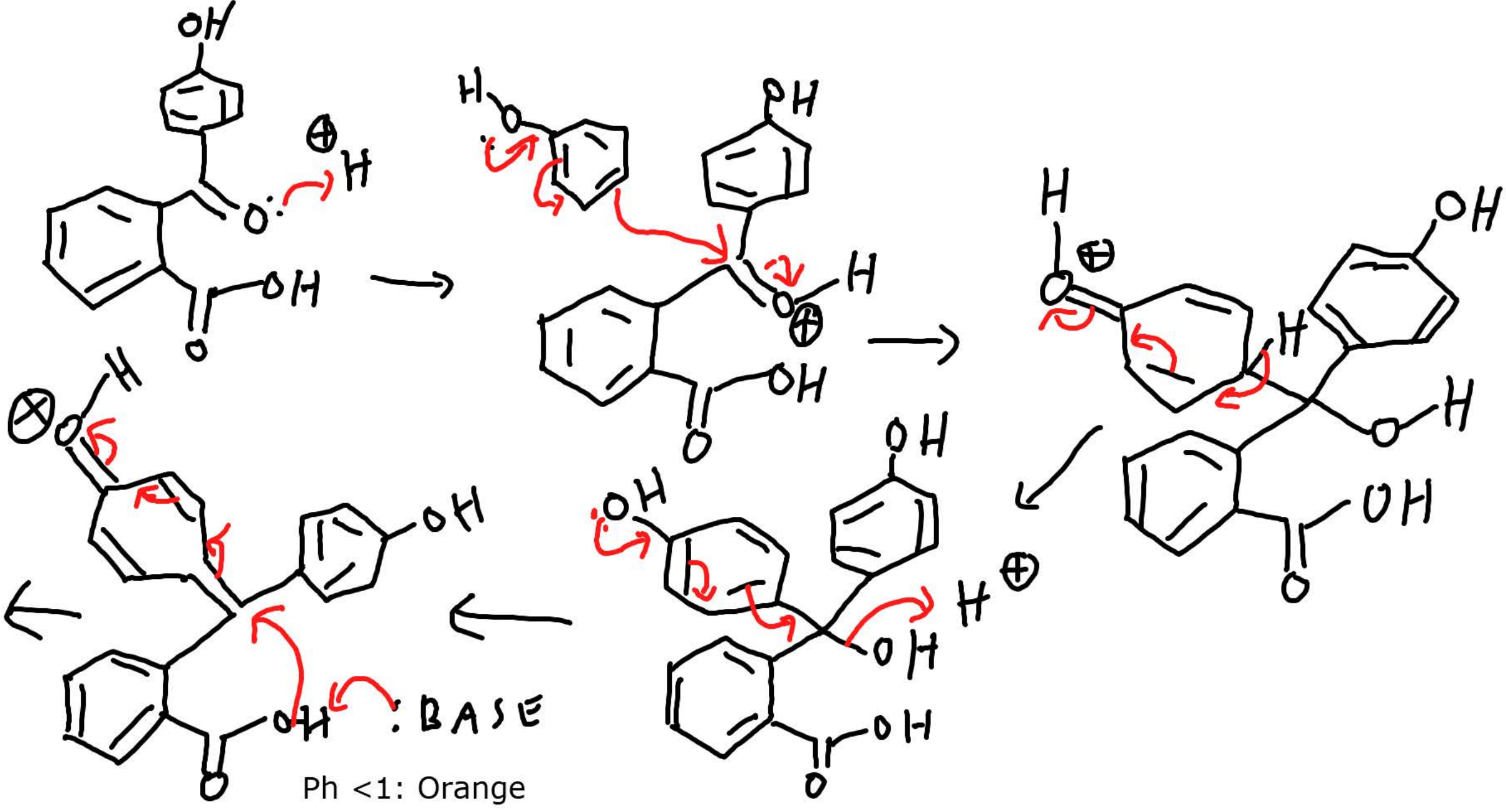
1) activation de l'électrophile



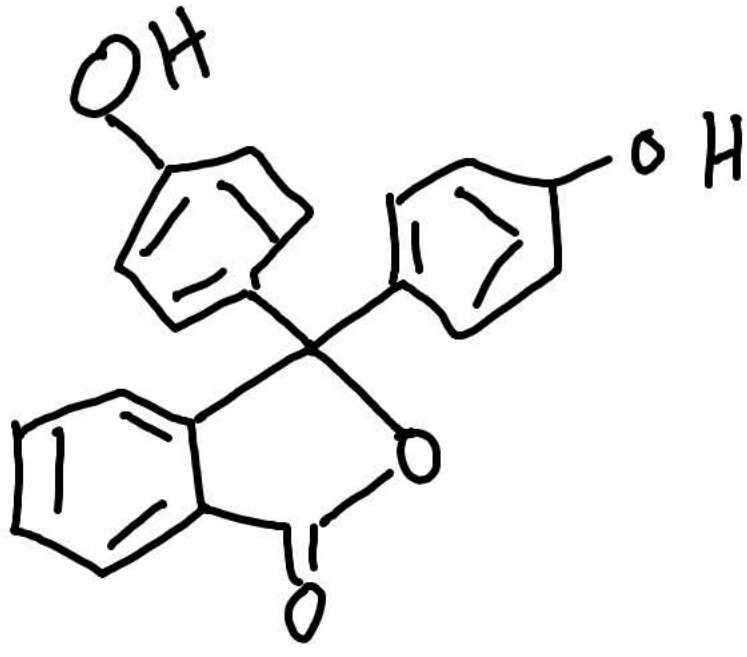


2) Friedel-Crafts



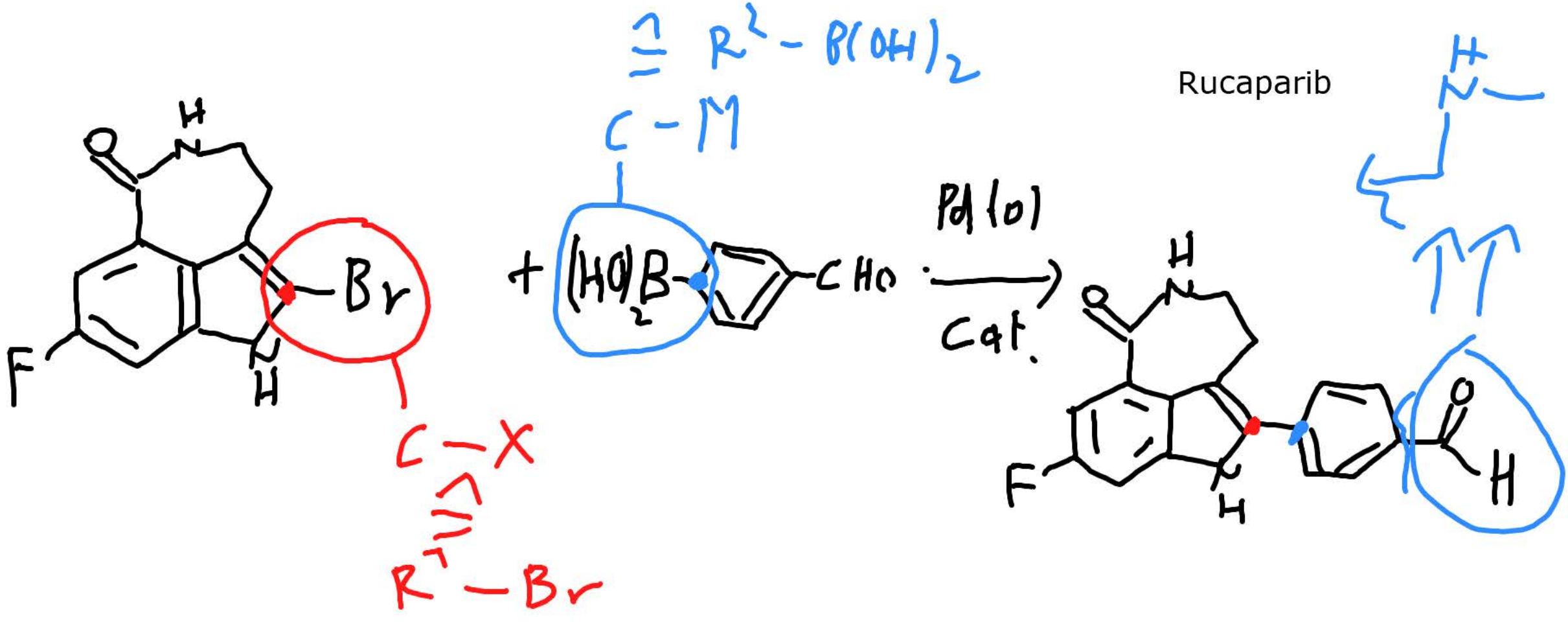


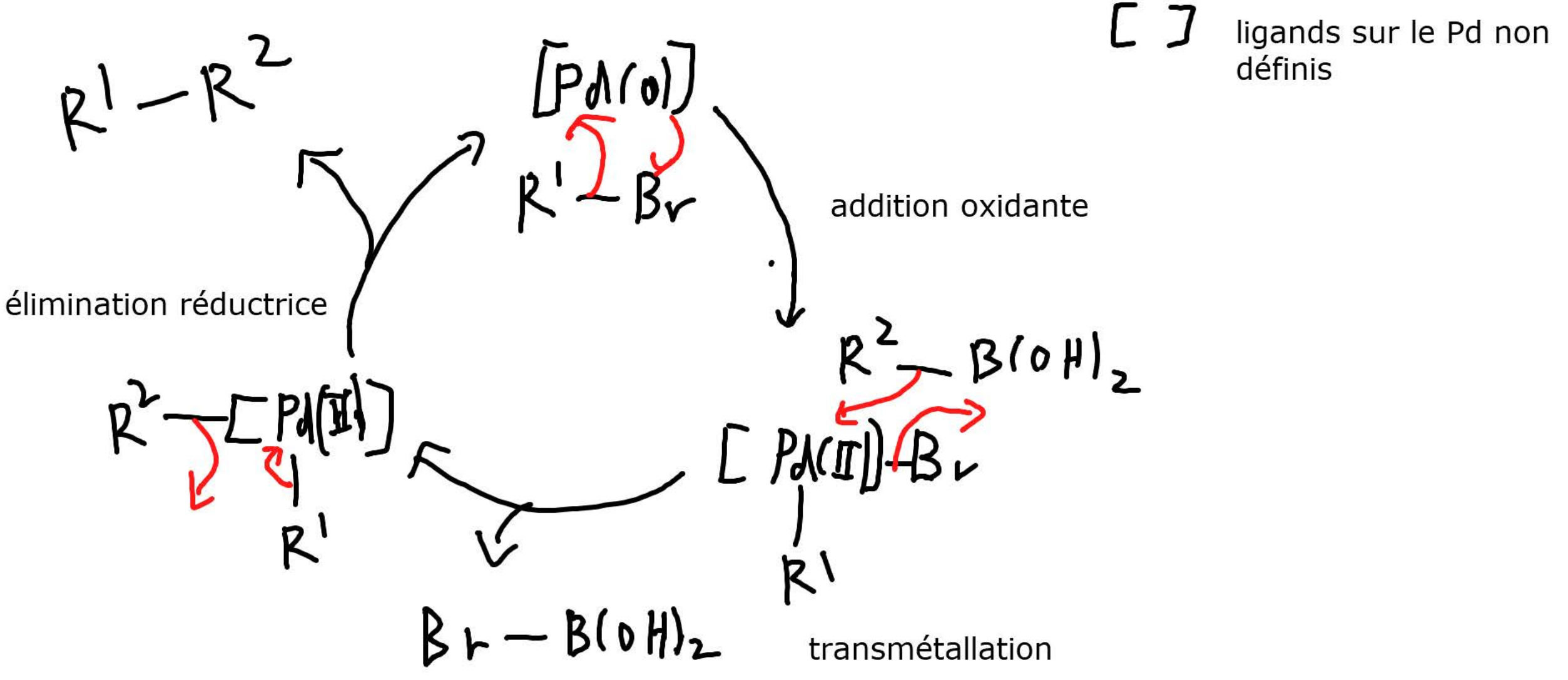
Ph <1: Orange



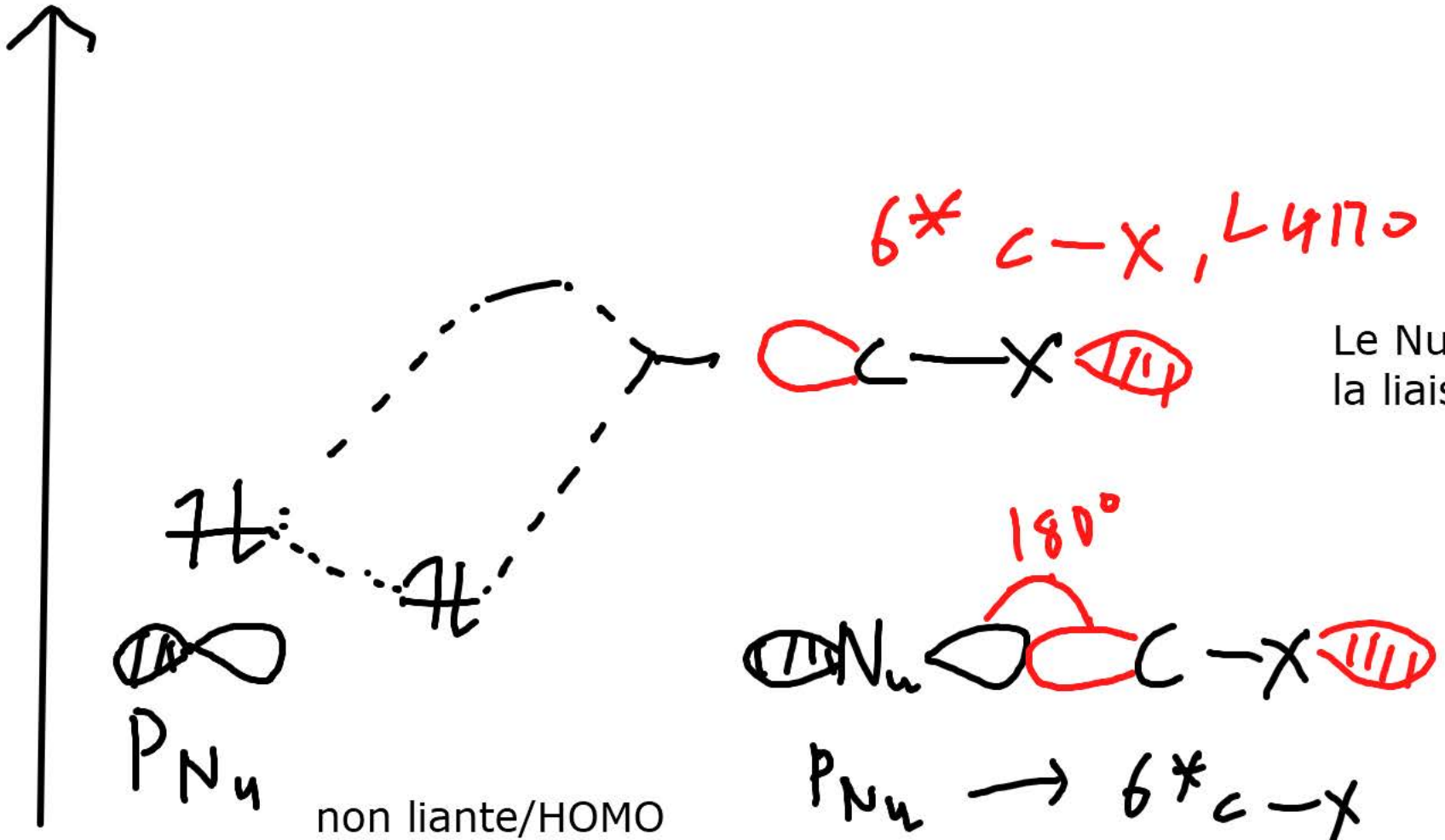
phenolphthaleine, form neutre
pH entre 1 et 7

Couplage croisé au Pd: Synthèse du Rucaparib: Pfizer, traitement du cancer des ovaires

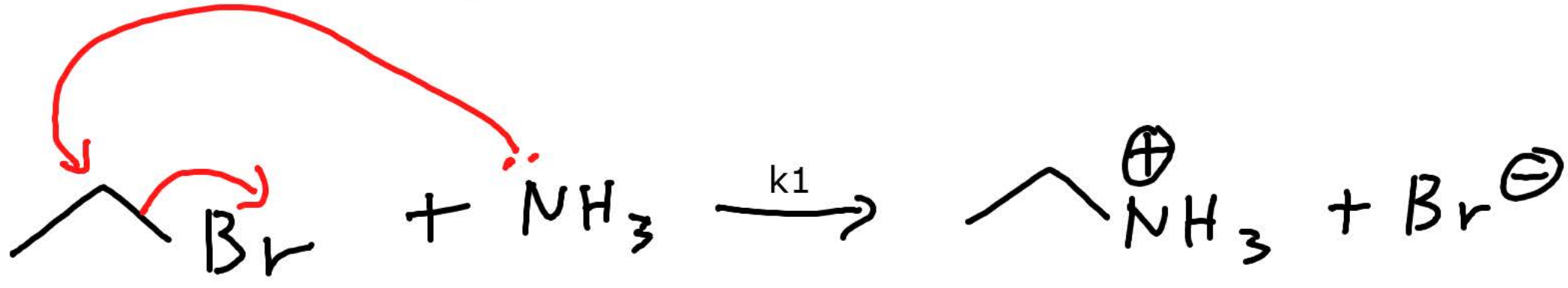



[ ] ligands sur le Pd non définis
addition oxidante
transmétallation
élimination réductrice

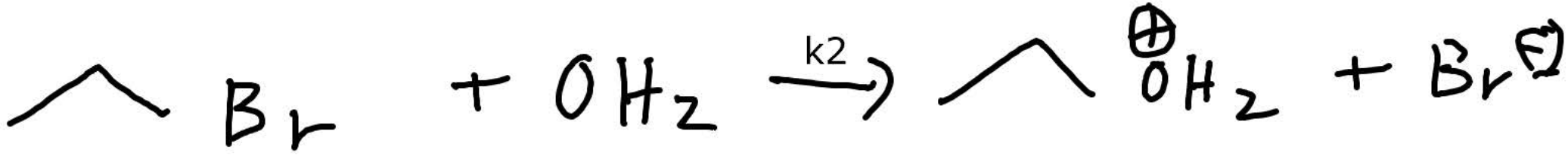
SN2 mécanisme avec orbitales moléculaires



comparaison basicité et nucléophilie



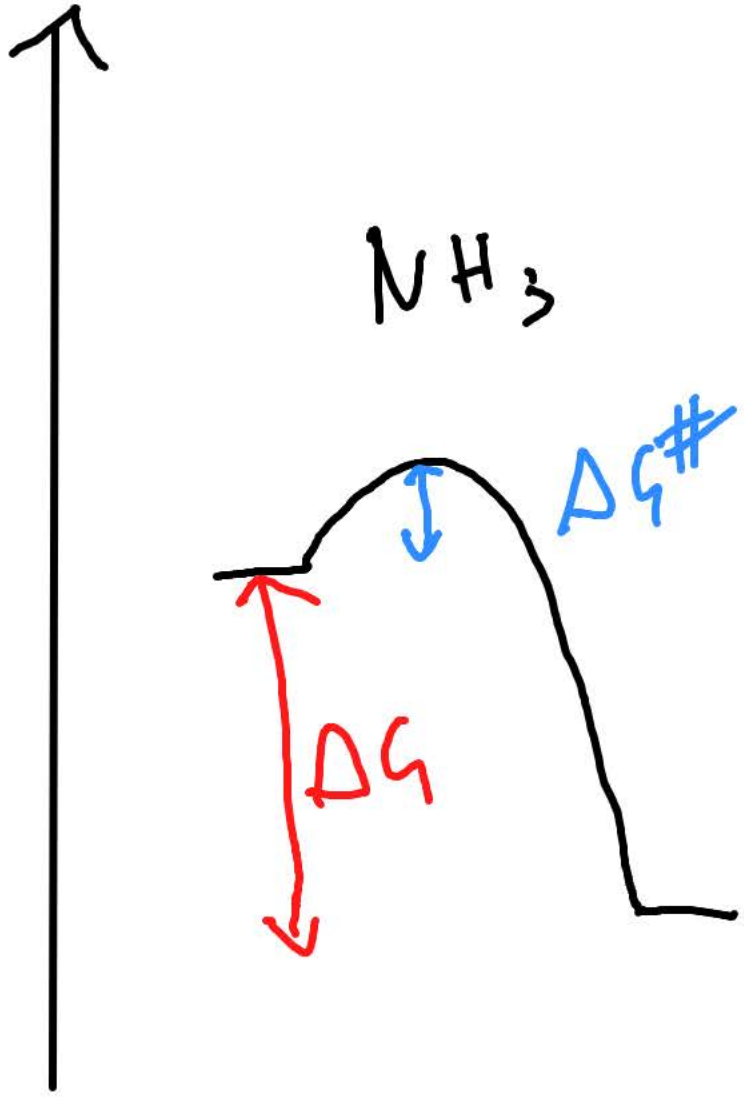
pKaH = 9

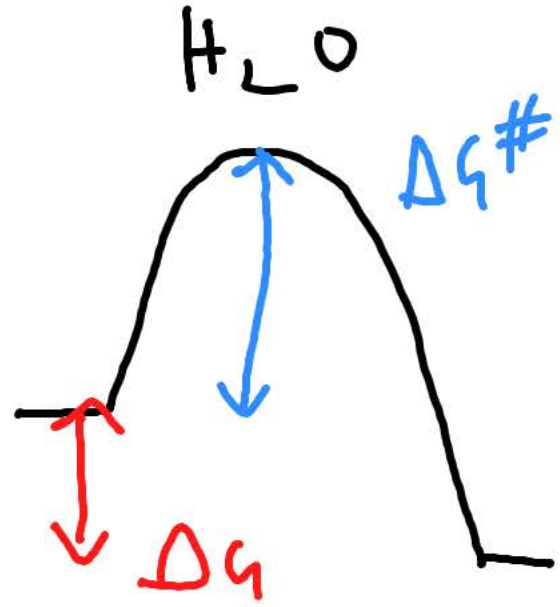


pKaH = -1.7

ammoniaque plus basique que l'eau (effet d'électronégativité)

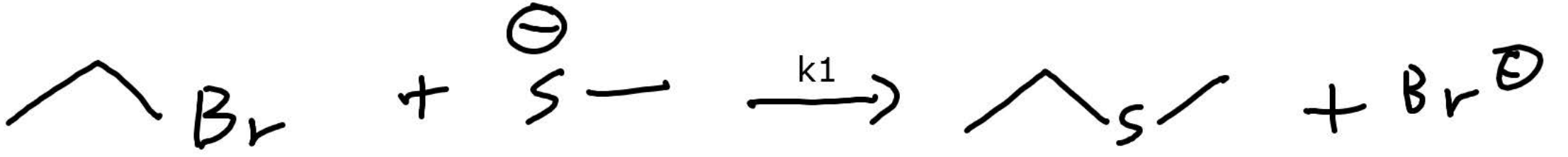
k1 >> k2, nucléophile: l'ammoniaque est plus nucléophile, car moins électronégatif





basicité est corrélée à deltaG
nucléophilicité est corrélée à l'énergie d'activation

Ici: la réaction la plus favorable à une énergie d'activation plus basse, il y a corélation

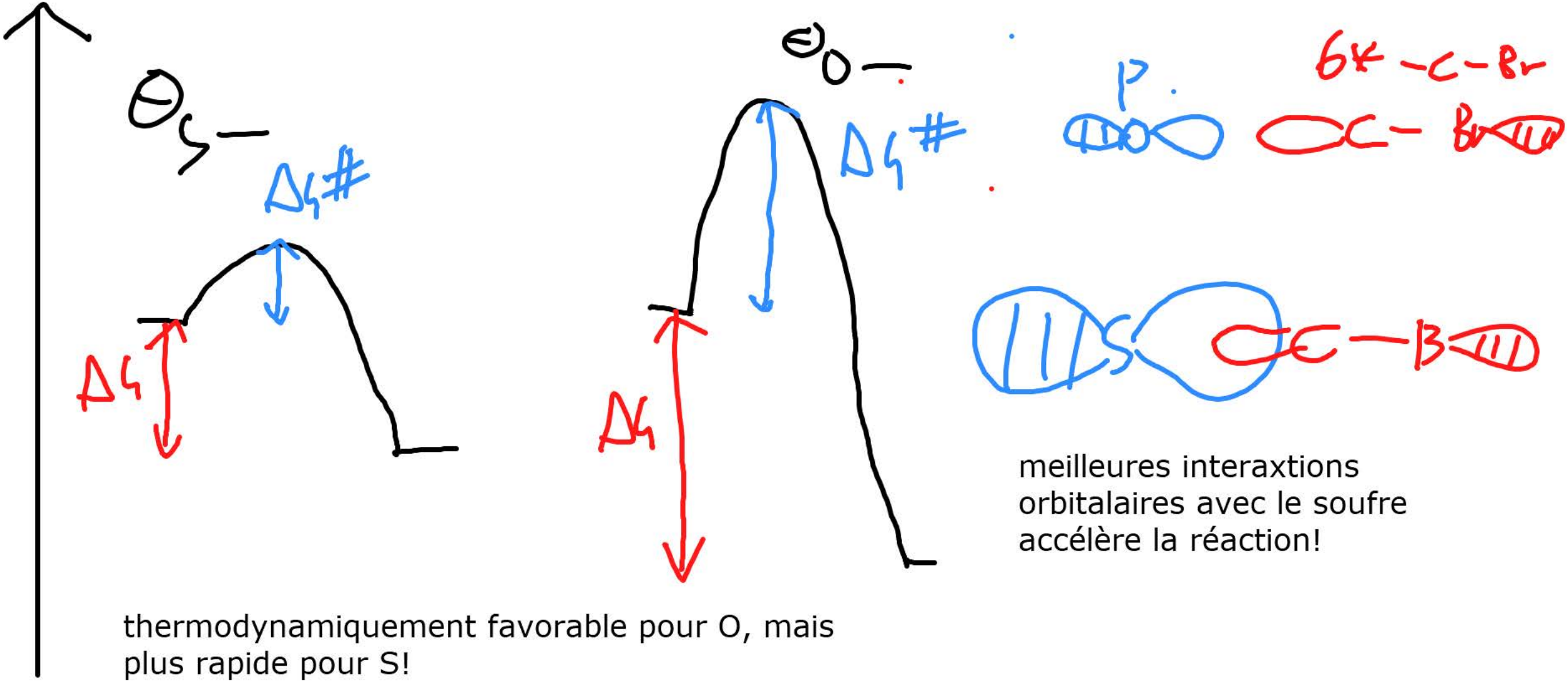


pkAH = 8

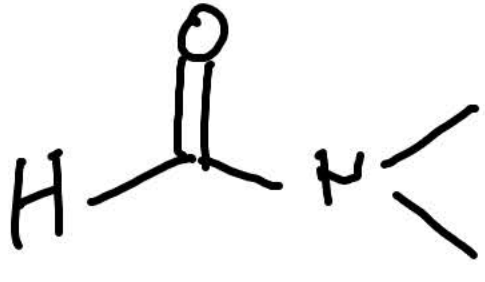
PkA H = 16

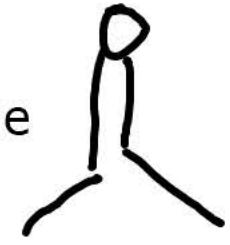
methoxide est plus basique que le sulfide

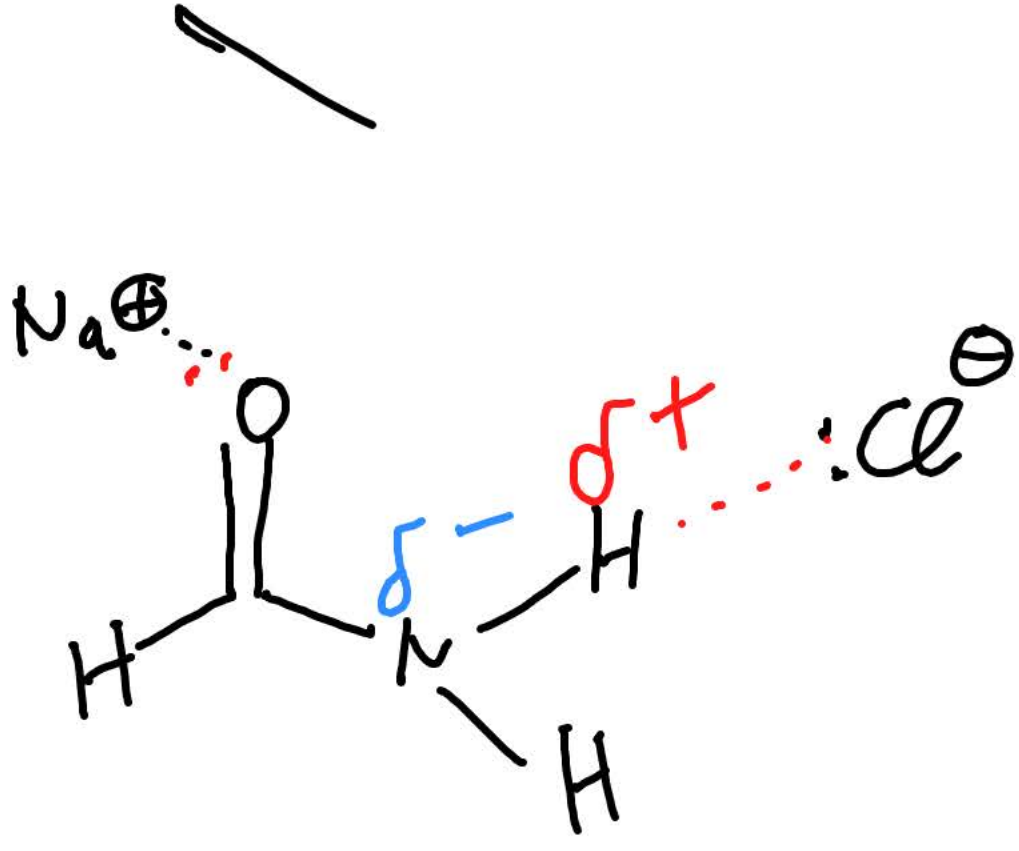
k1 > k2, le sulfide est plus nucléophile!


ΔG#
ΔG
ΔG#
ΔG
meilleures interaxtions
orbitalaires avec le soufre
accélère la réaction!
thermodynamiquement favorable pour O, mais
plus rapide pour S!

Effet du solvant sur SN2

Solvant	k
CH_3OH	1
formamide 	12.5
dimethylformamide DMF 	1'200'600

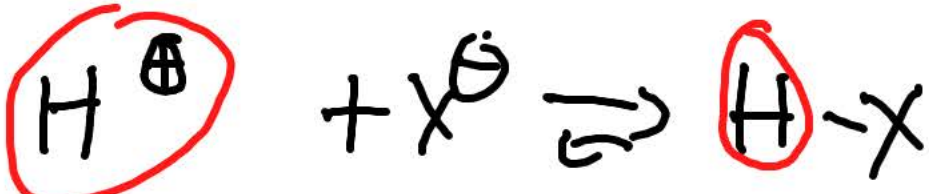
acétone  7'500'000



nucléophile déactivé par un pont hydrogène, réaction plus lente

conclusion: les solvants polaires, mais non protiques sont les meilleures pour la SN2

comparaison base/nucléophile vs base/ groupe partant

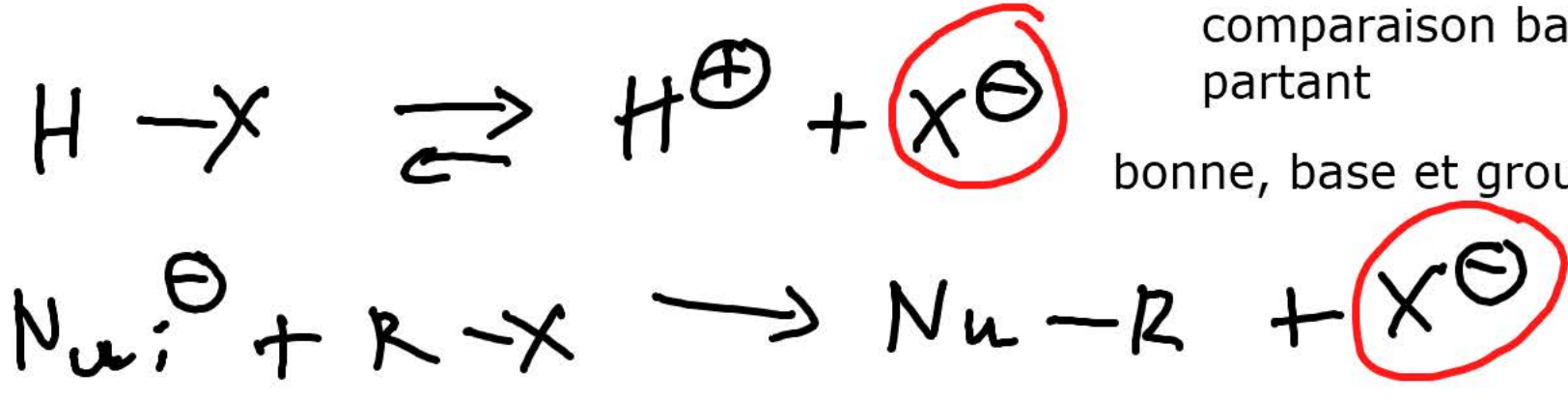


comparaison base/nucléophile

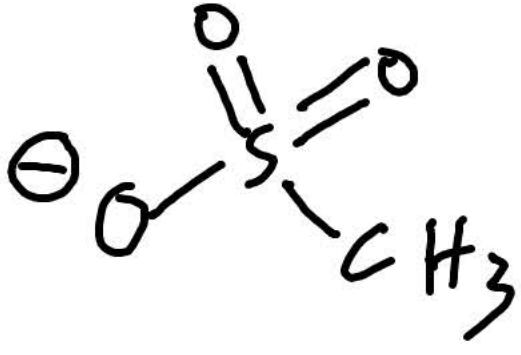
mauvaise, R très différent de H!

comparaison base/groupe partant

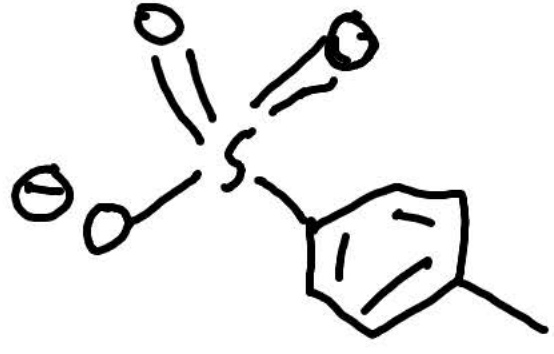
bonne, base et groupe partant identique



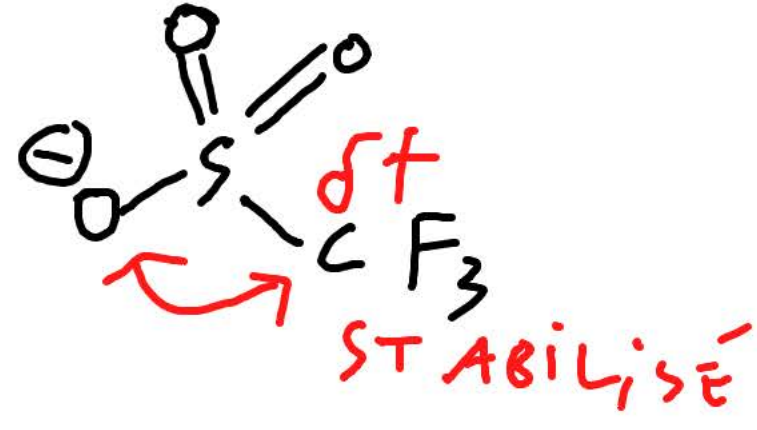
important en chimie organique: groupe partant dérivé de l'acide sulfurique



mésylate, OMs



tosylate, OTs



triflate, OTf,
Meilleur groupe partant

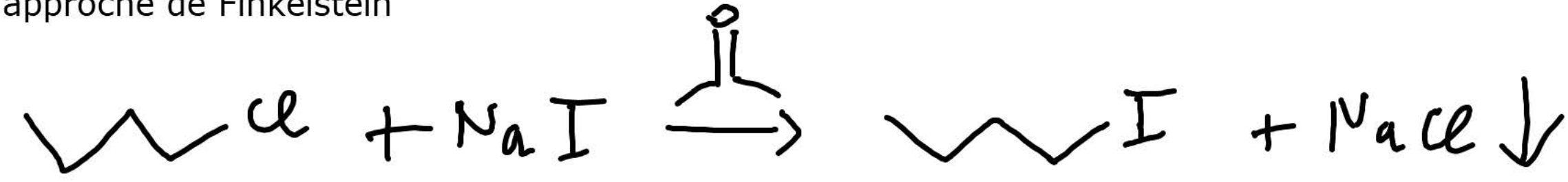
Synthése des iodures.

synthèse des iodures

soluble

soluble

approche de Finkelstein

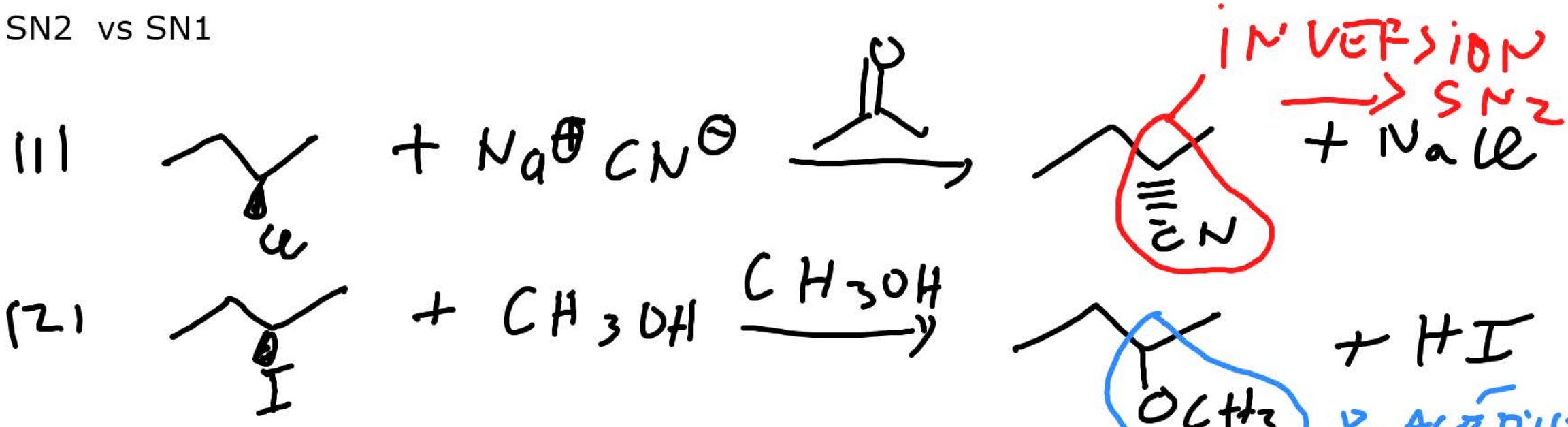


soluble

non soluble

principe de Le Chatelier: le NaCl est "enlevé" est peut "pousser" l'équilibre défavorable

SN2 vs SN1



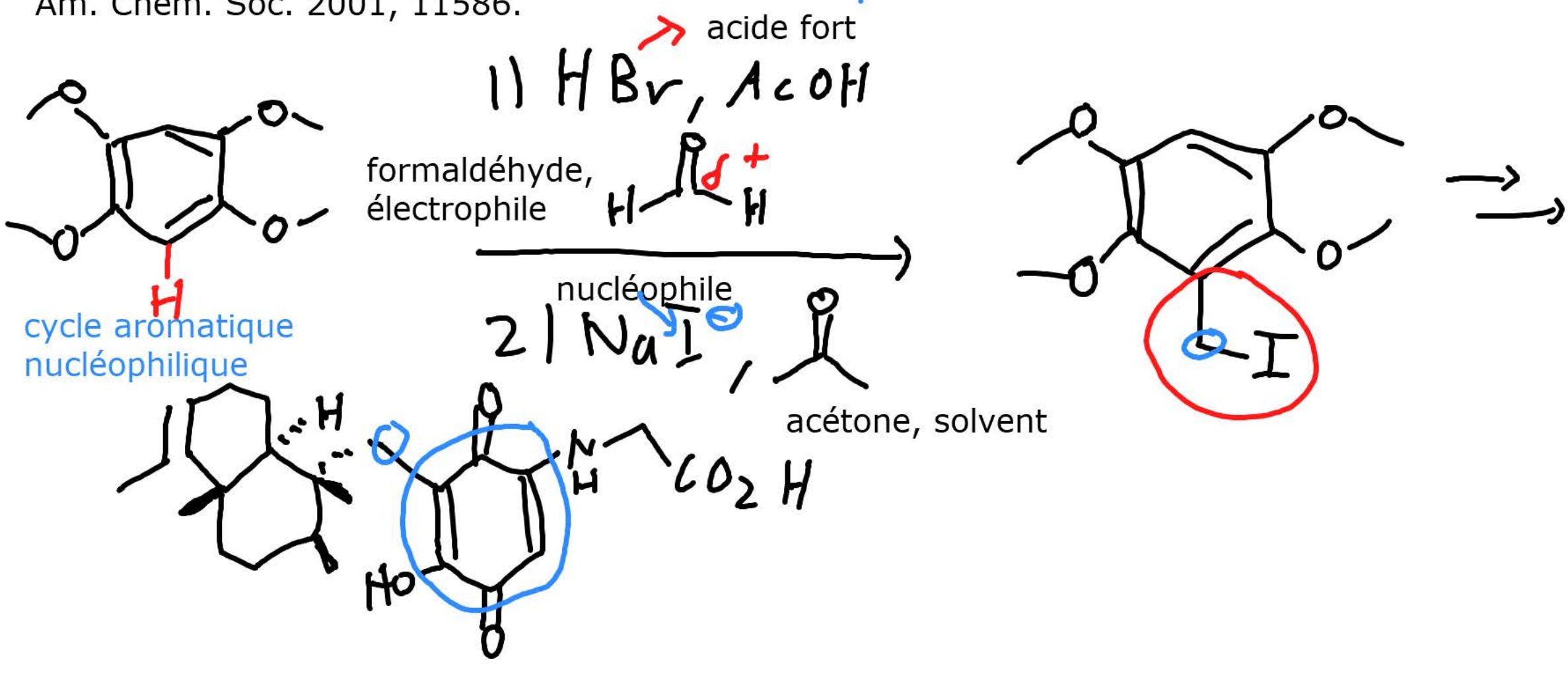
Substrat: secondarie: SN1 ou SN2

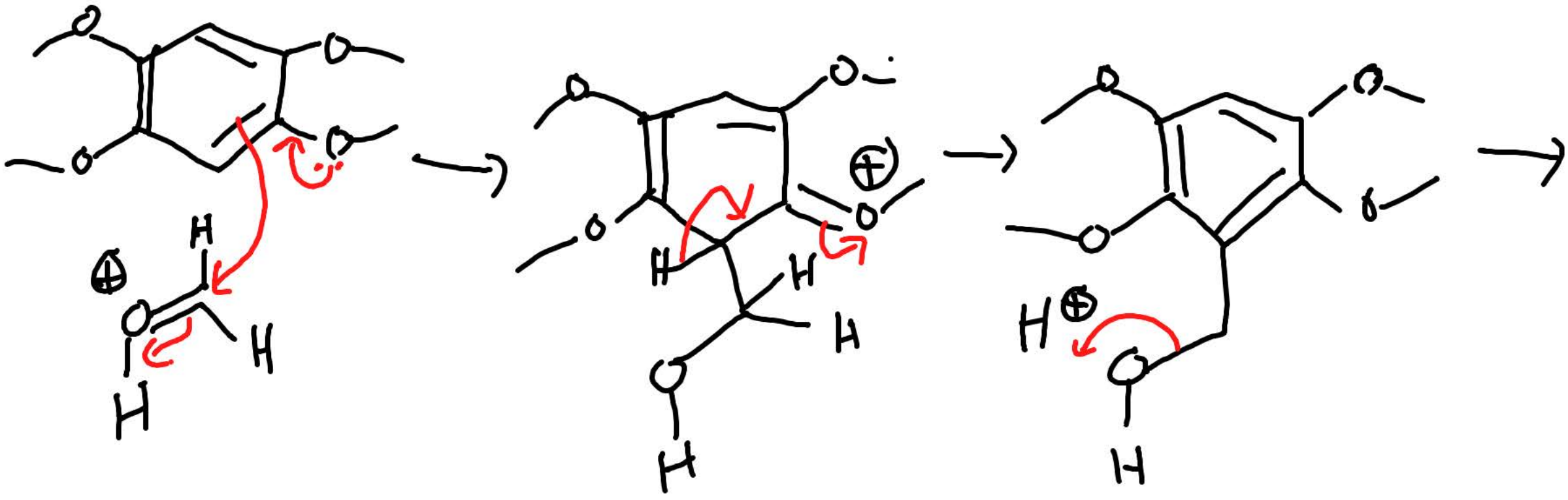
Groupe partant: Cl = moyen, I = très bon (pas de décision)

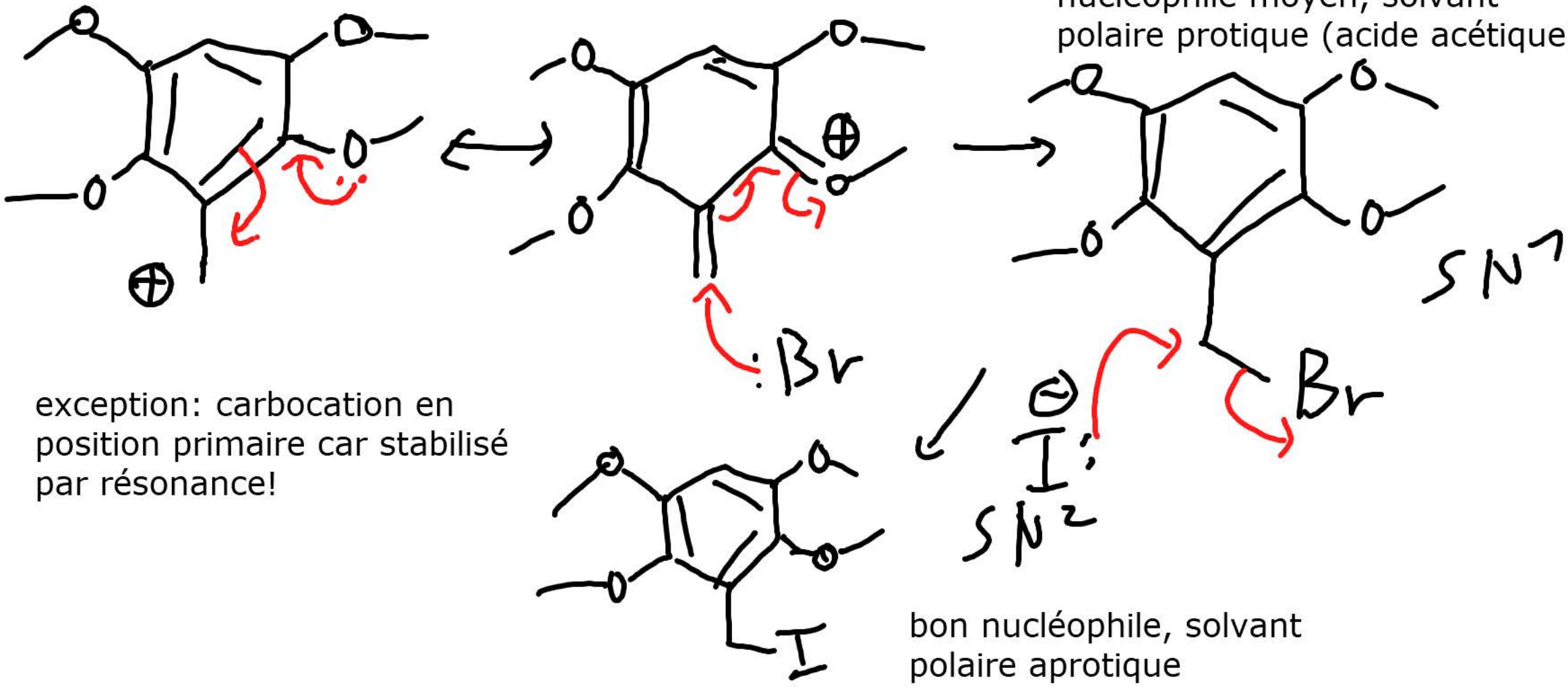
Nucléophile: CN- bon nucléophile, favoirse SN2, MeOH = faible nucléophile, favorise SN1

Solvant: acétone: polaire aprotique: favorise SN2, MeOH: polaire protique: favorise SN1

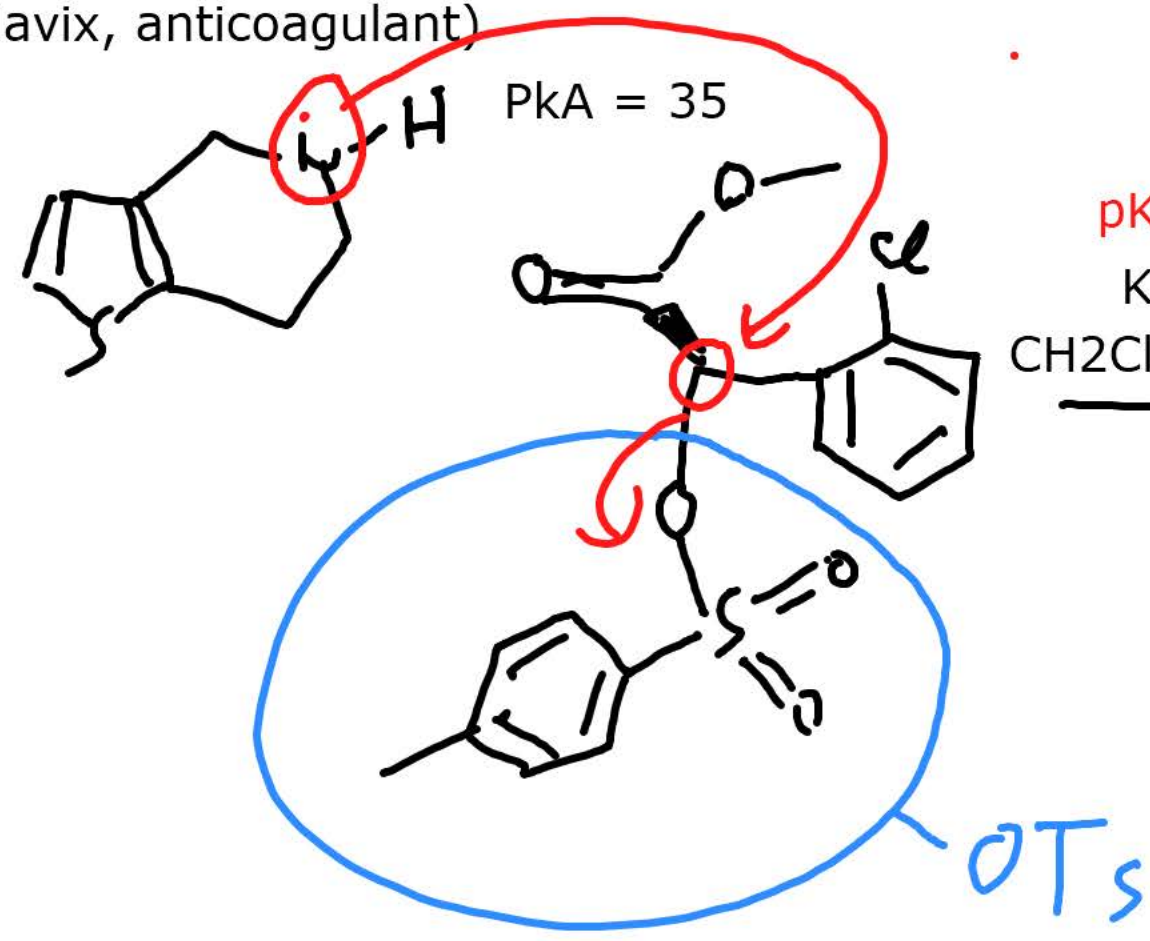
exemples de SN: 1) Synthèse du produit naturel Nakijiquinone (anticancer), Waldmann, J. Am. Chem. Soc. 2001, 11586.






nucléophile moyen, solvant
polaire protique (acide acétique)
exception: carbocation en
position primaire car stabilisé
par résonance!
SN1
SN2
bon nucléophile, solvant
polaire aprotique

Synthèse du Clopidogrel
(Plavix, anticoagulant)



bon groupe partant

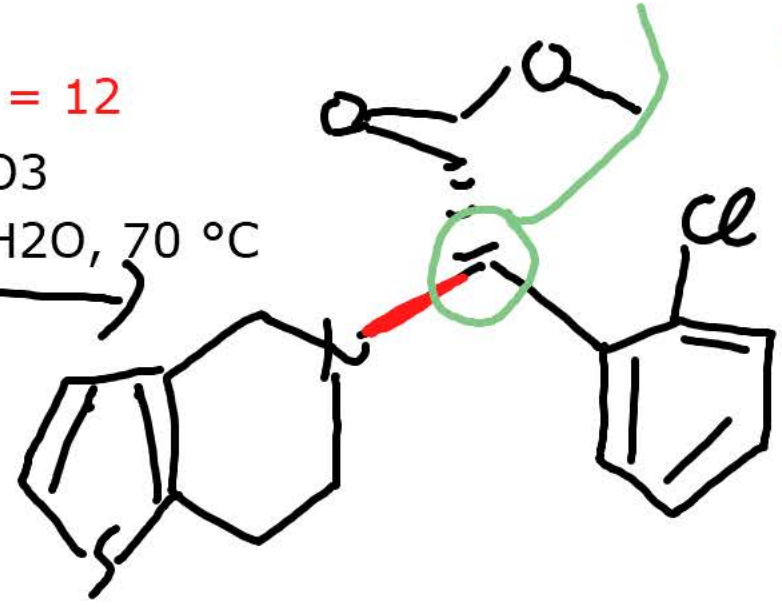
pKaH = 12

K2CO3

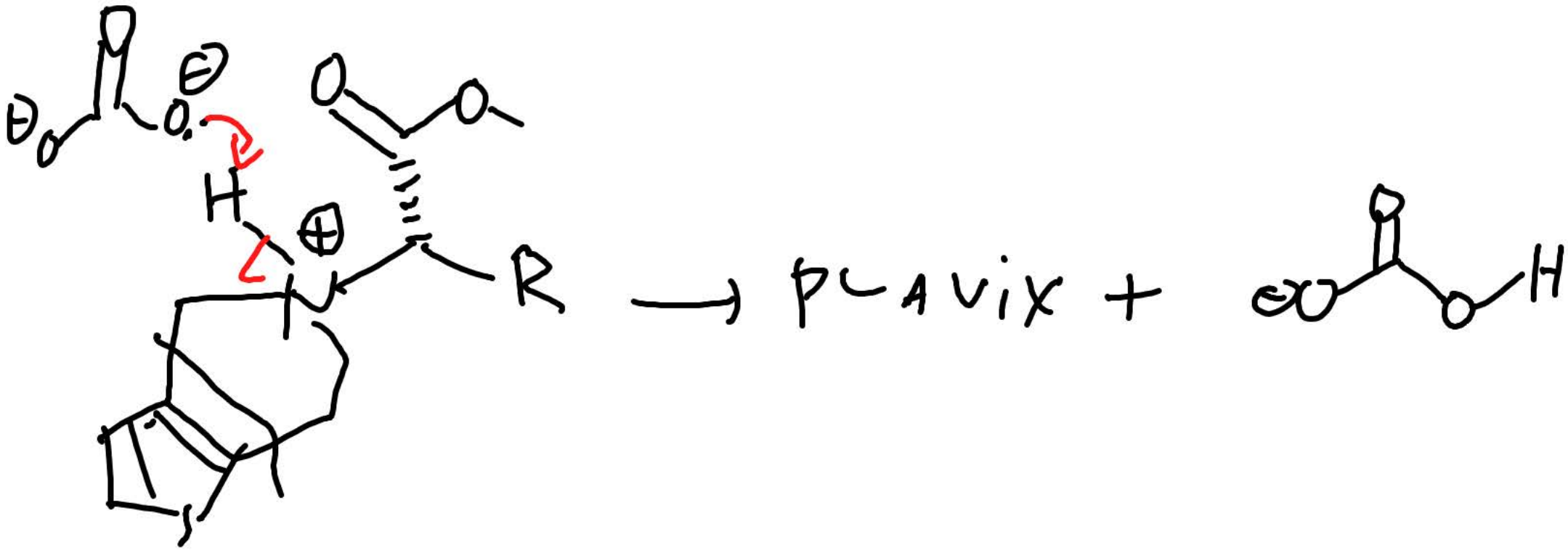
CH2Cl2, H2O, 70 °C

inversion de la stéréochimie

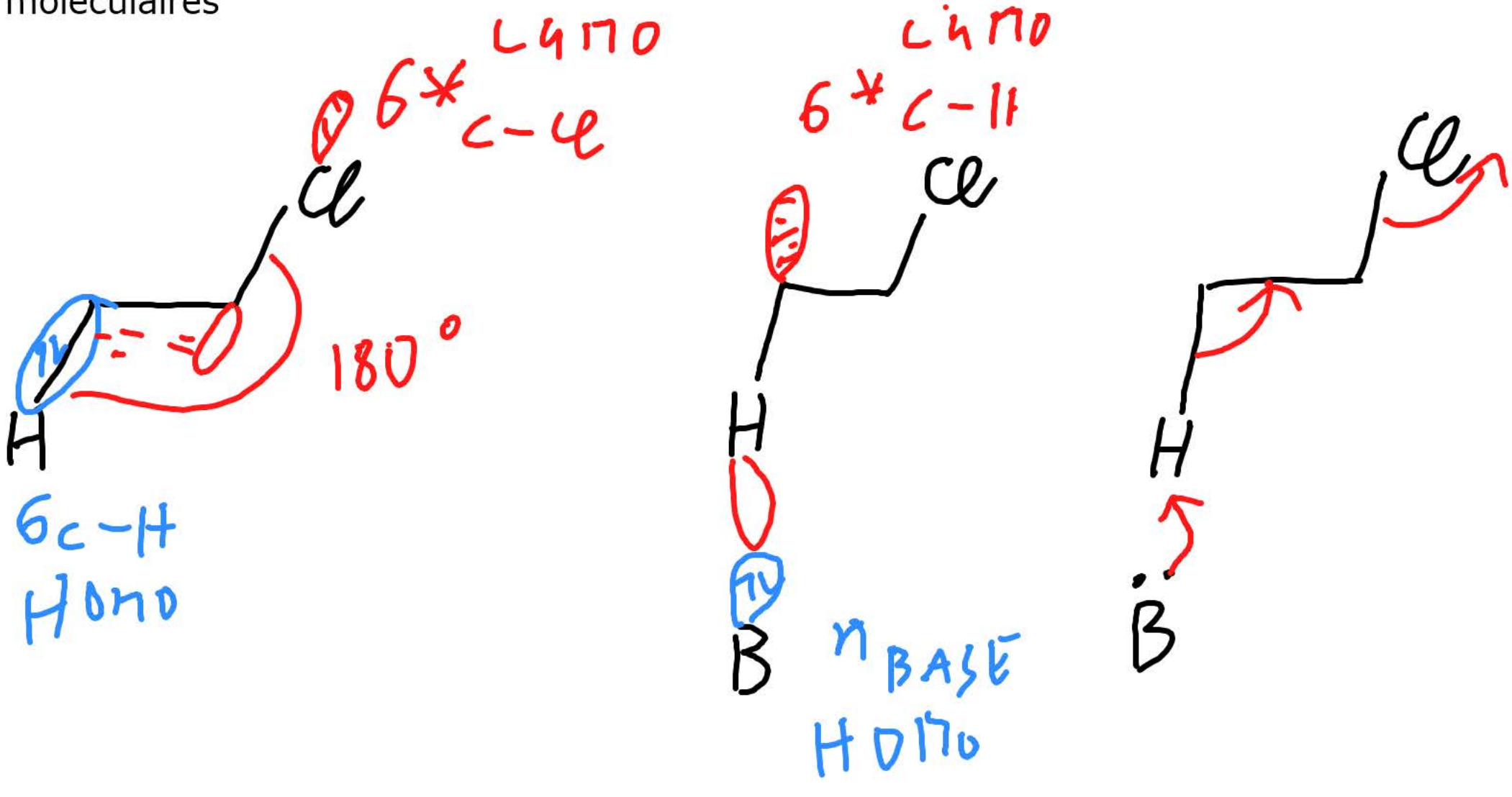
SN2!

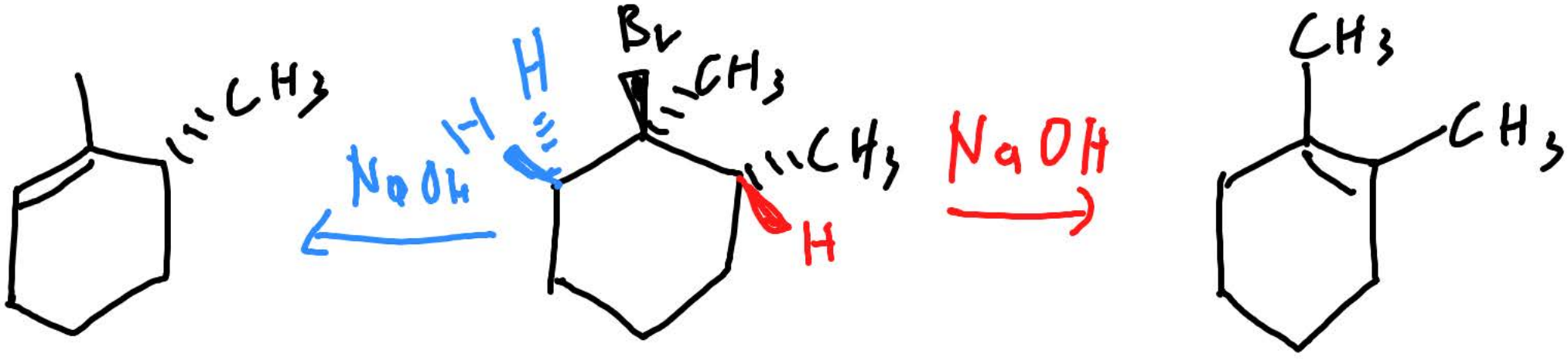


Plavix/clopidogrel


R
PLAVIX +

élimination E2, orbitales moléculaires

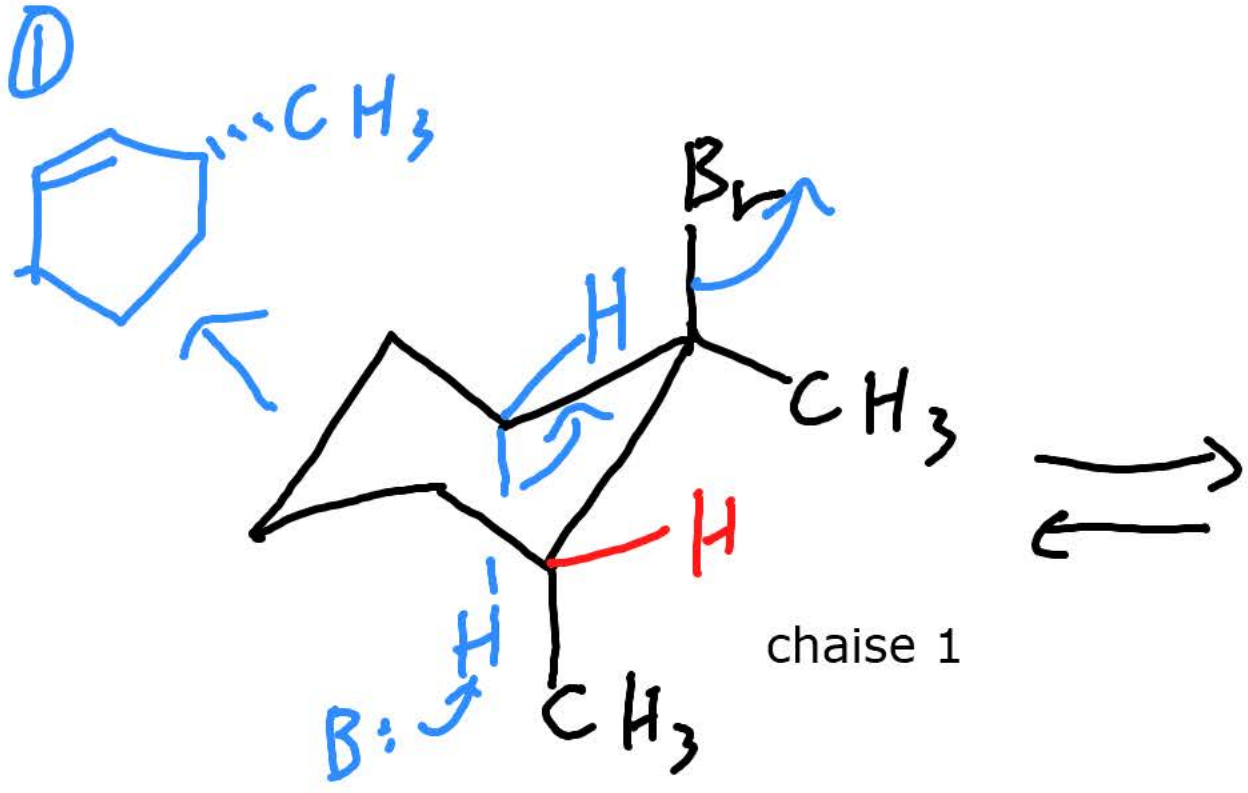




alcène trisubstitué

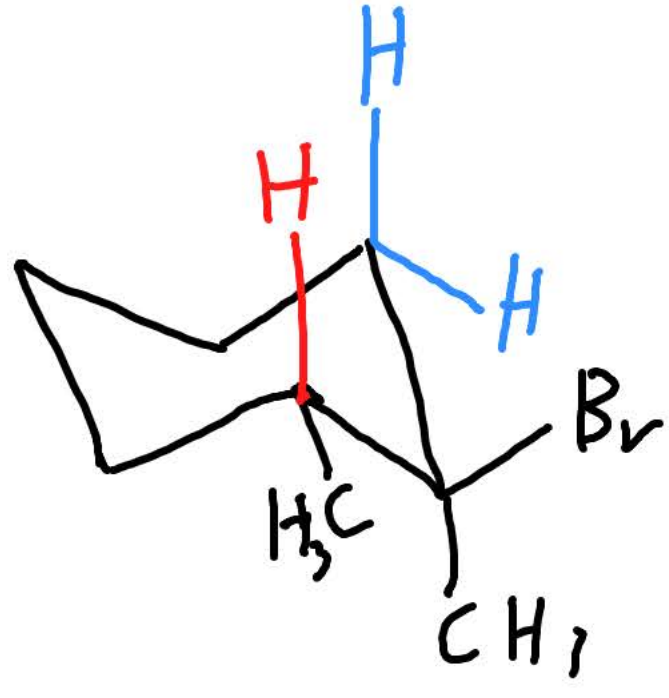
produit observé
produit cinétique

alcène tétrasubstituée
plus stable
produit thermodynamique



chaise 1

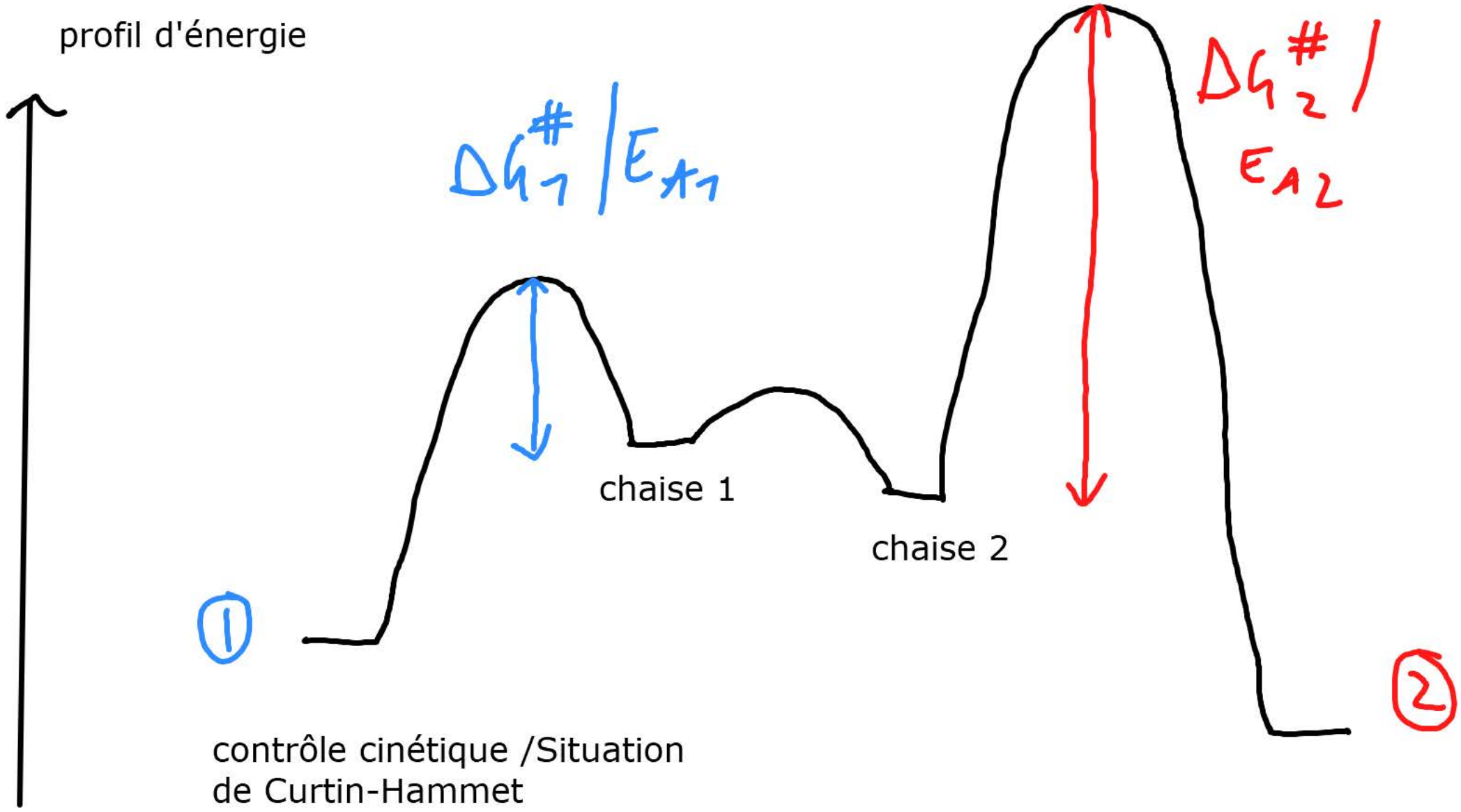
1 Me, 1 Br axial
1 Me équatorial



chaise 2

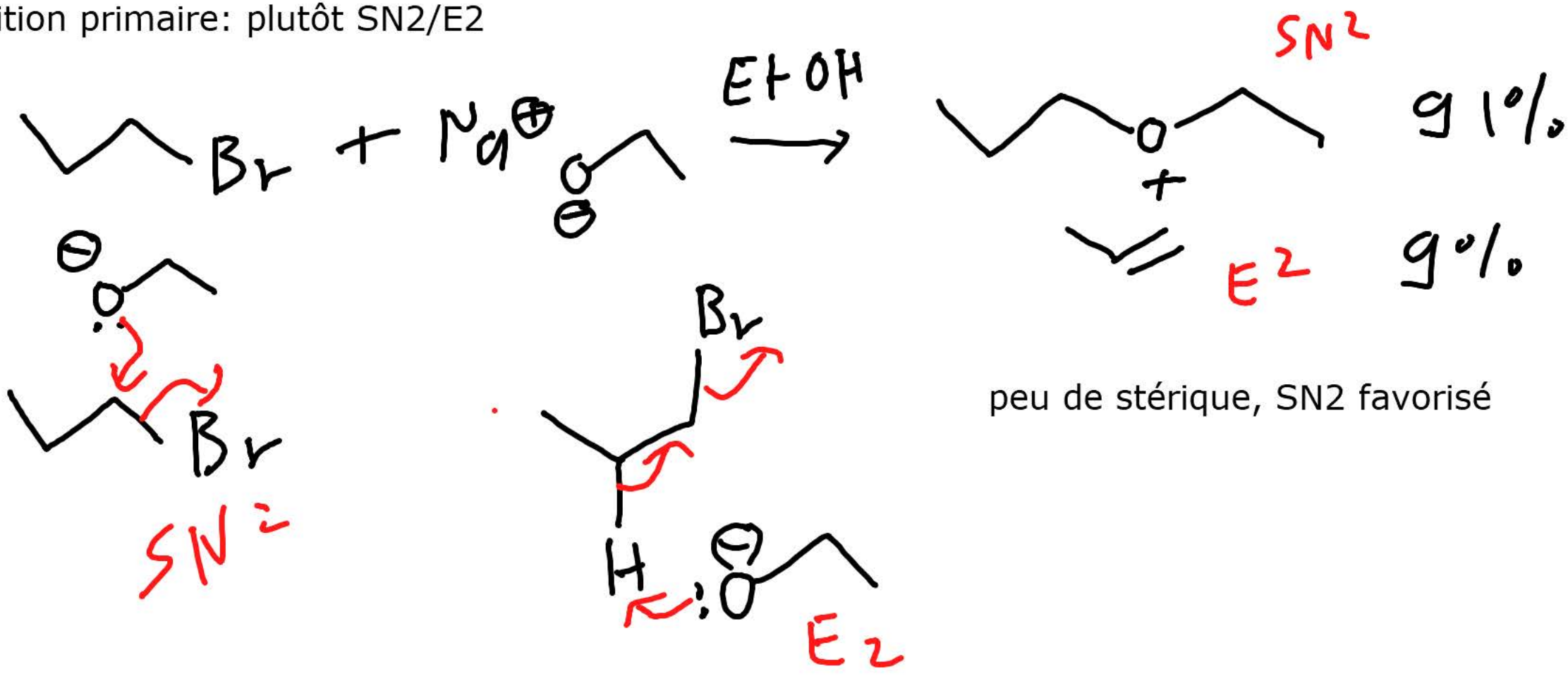
1 Me axial
1 Me, 1Br équatorial
plus stable

pour E2: proton et groupe partant doivent être à 180°

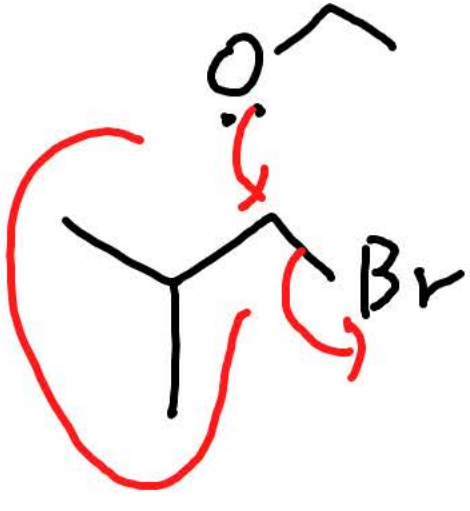

profil d'énergie
$\Delta G_1^{\#}$ / E_{A1}
$\Delta G_2^{\#}$ / E_{A2}
chaise 1
chaise 2
1
2
contrôle cinétique /Situation
de Curtin-Hammet

Sn vs E: 1) influence du substrat

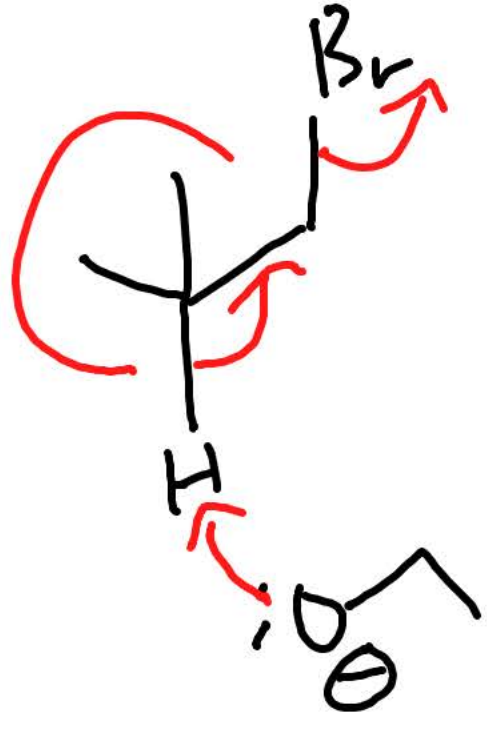
position primaire: plutôt SN2/E2



peu de stérique, SN2 favorisé



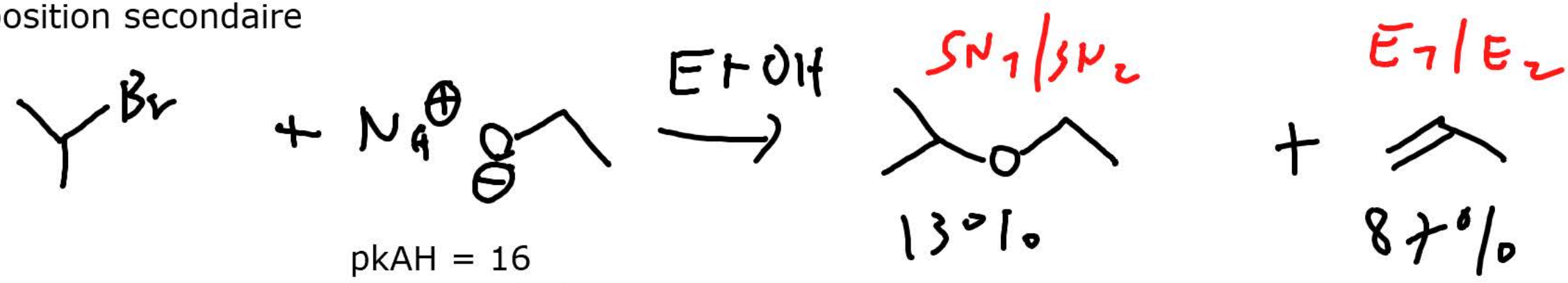
Sn2 ralentie par stérique



E2 plus favorisée

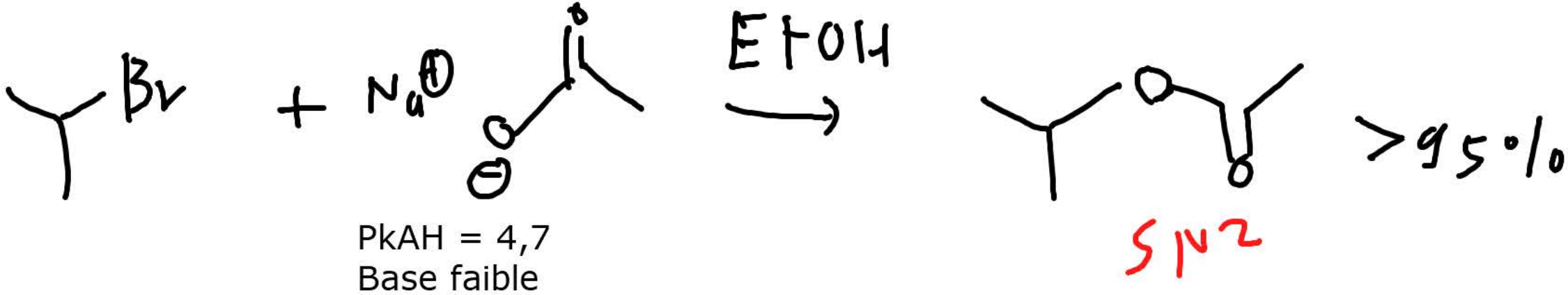
E2
peu d'influence de la stérique

position secondaire



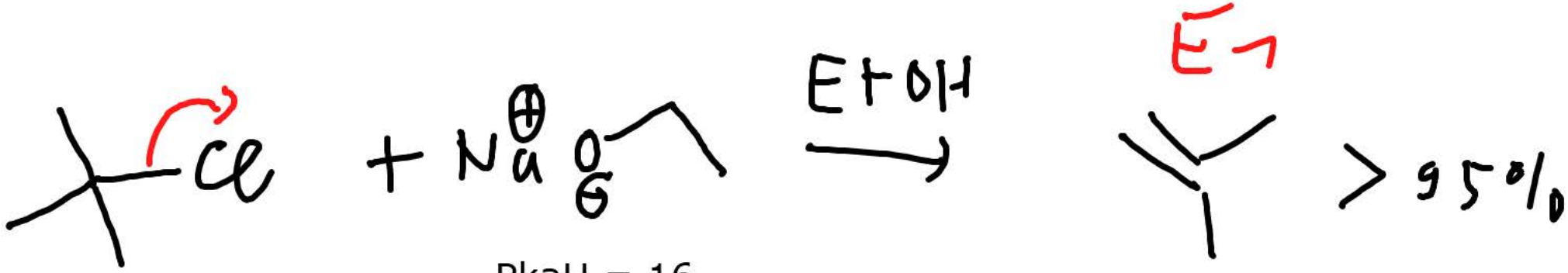
pkAH = 16
moyenne forte

Pour favoriser la substitution, il faut diminuer la basicité!



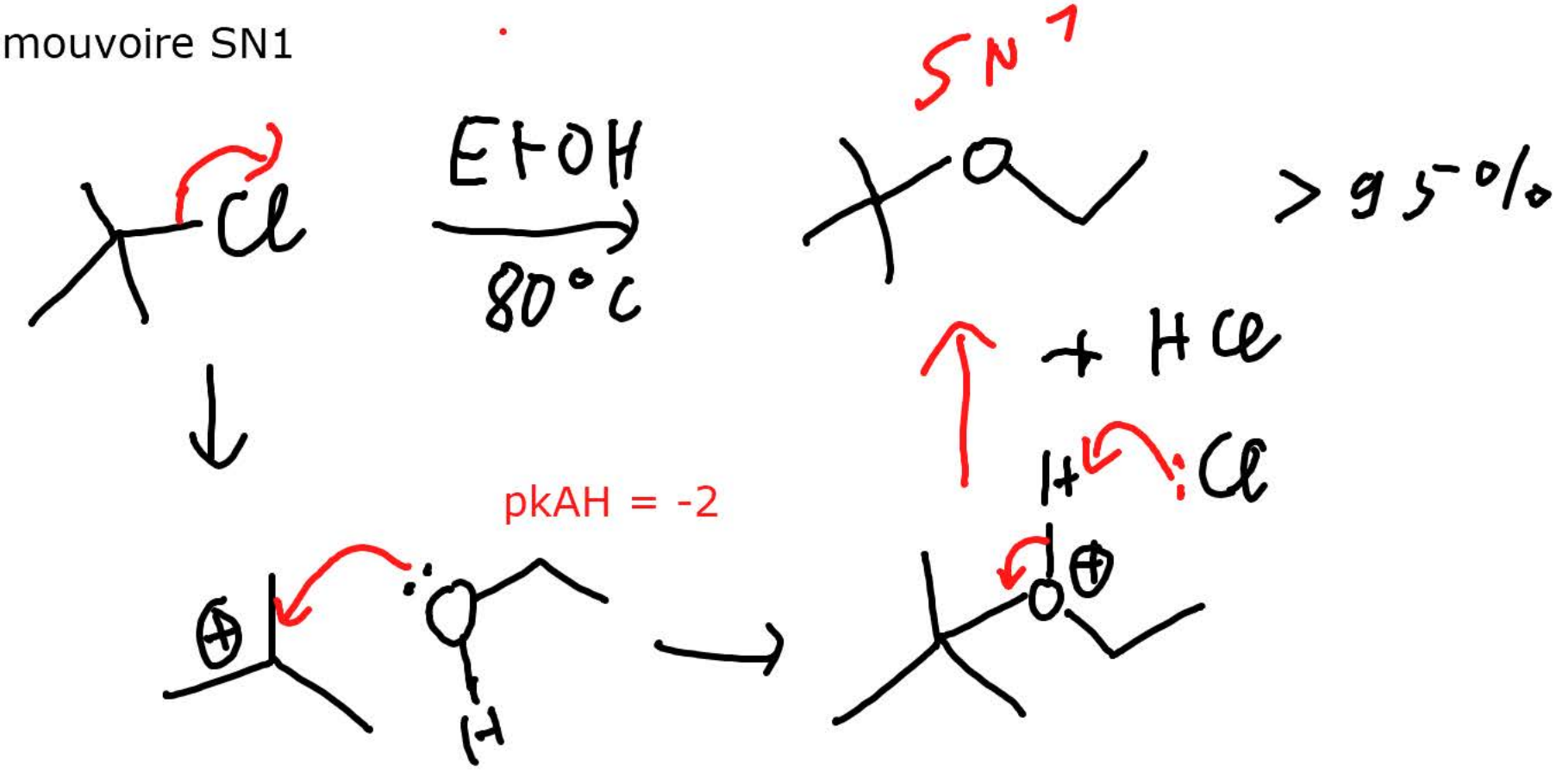
PkAH = 4,7
Base faible

position tertiaire: E1 ou SN1

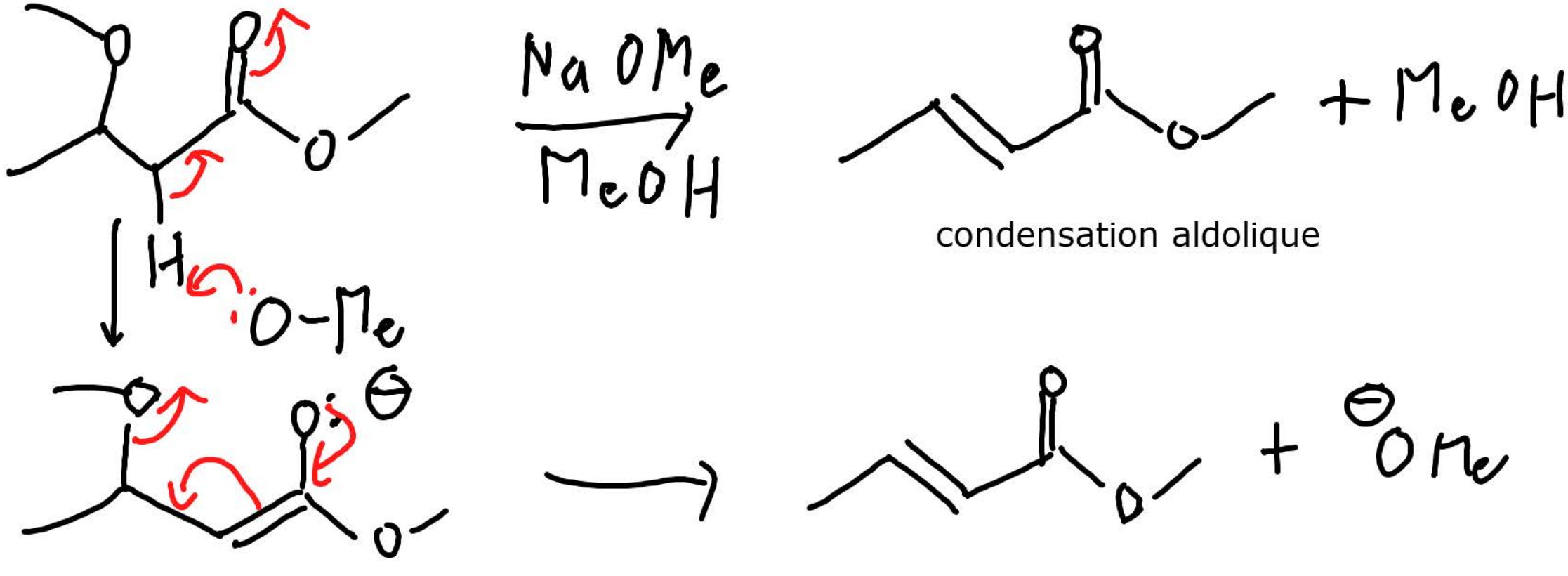


PkaH = 16

promouvoire SN1



Cas particulier E1cb, proton très acide

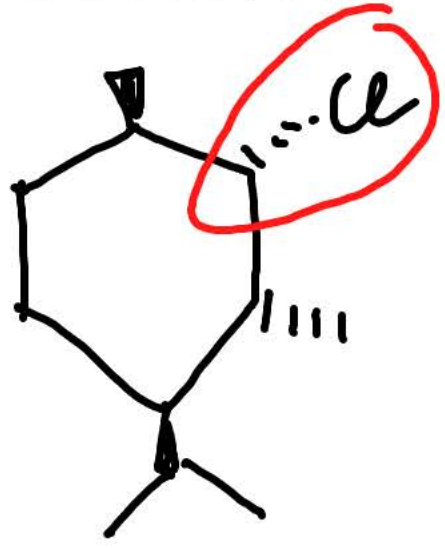


condensation aldolique

anion comme intermédiaire!

possible seulement pour proton très acide

stérique: très encombré



groupe partant

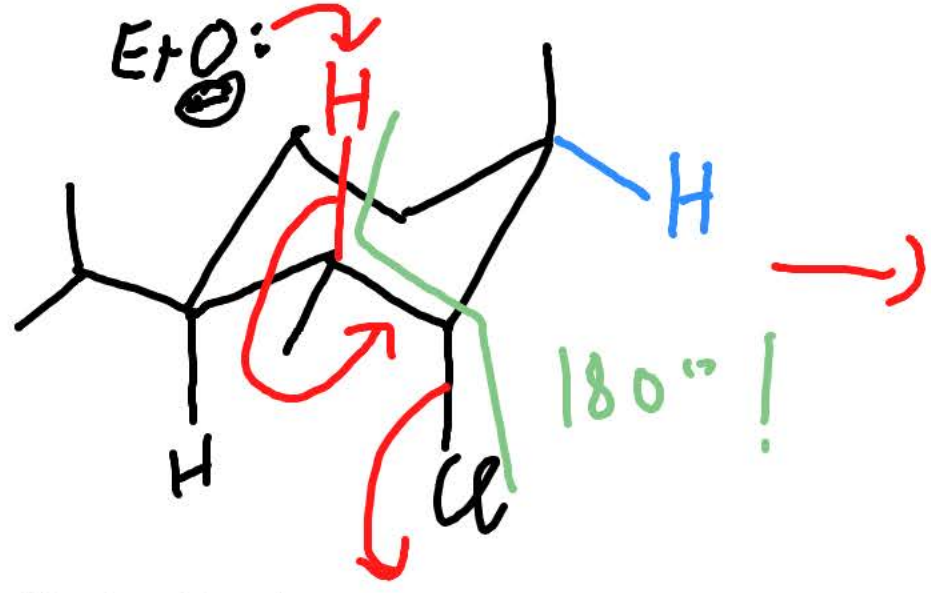
base forte

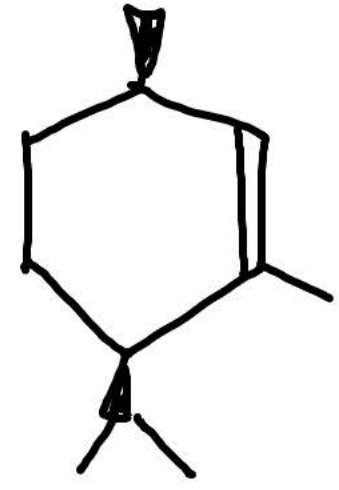
$NaOEt$

$EtOH$

?

grand groupe en équatorial





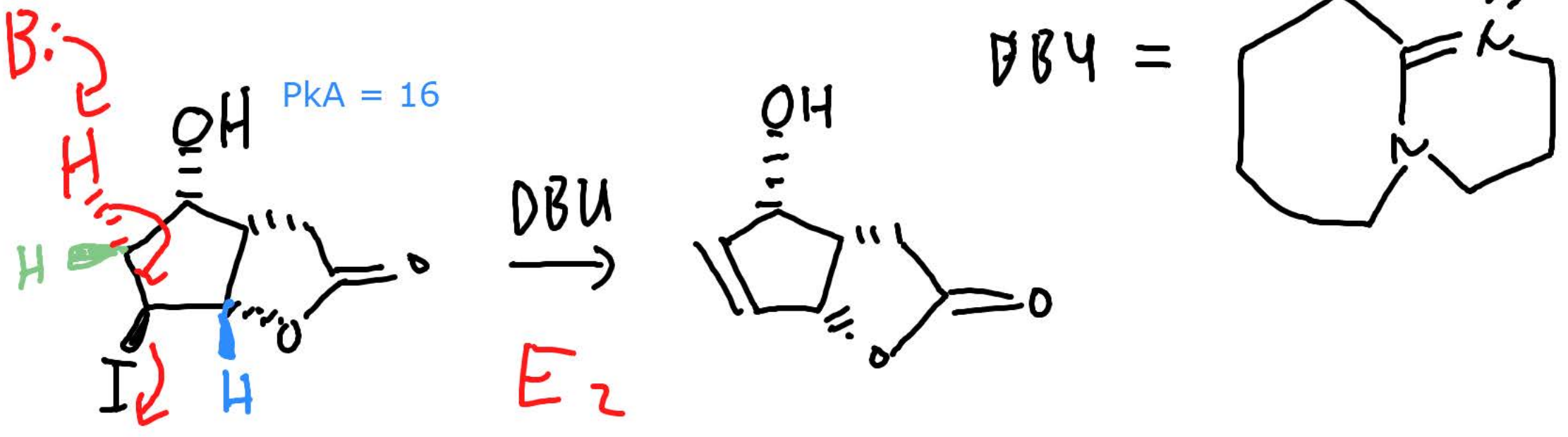
on pourrait avoir une substitution ou une élimination!

base forte, substrat encombré: élimination

Si hydrogène à 180°: E2,
sinon on aura E1

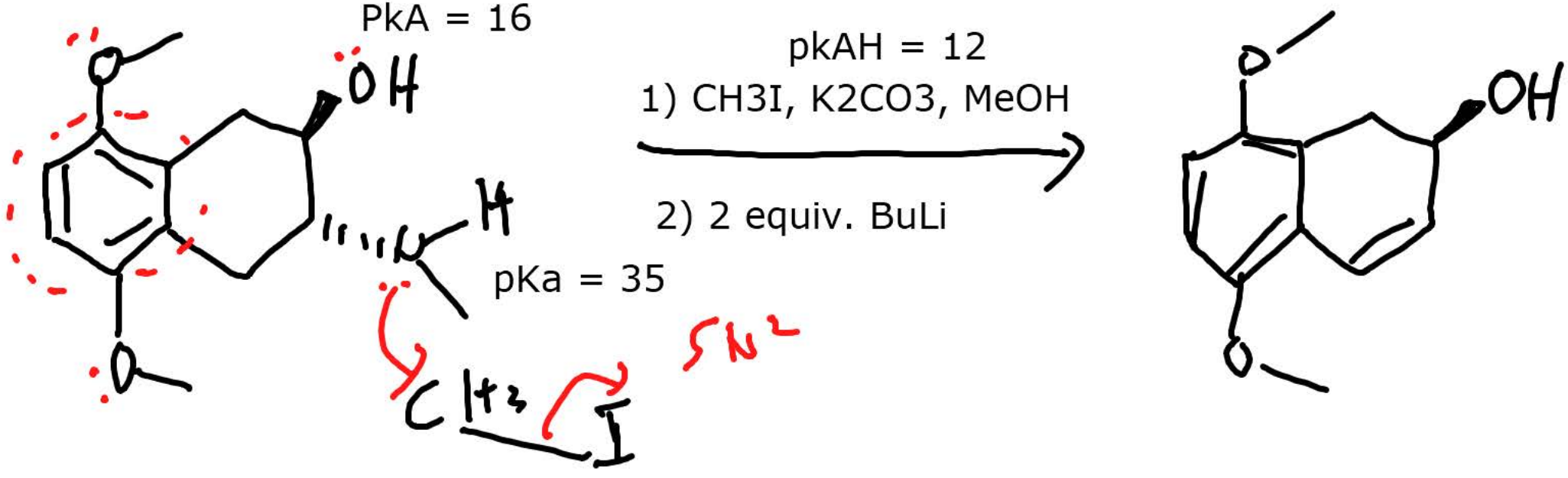
Synthèse des prostaglandines

Bonne base: pkAH= 14



Elimination selon Hofmann

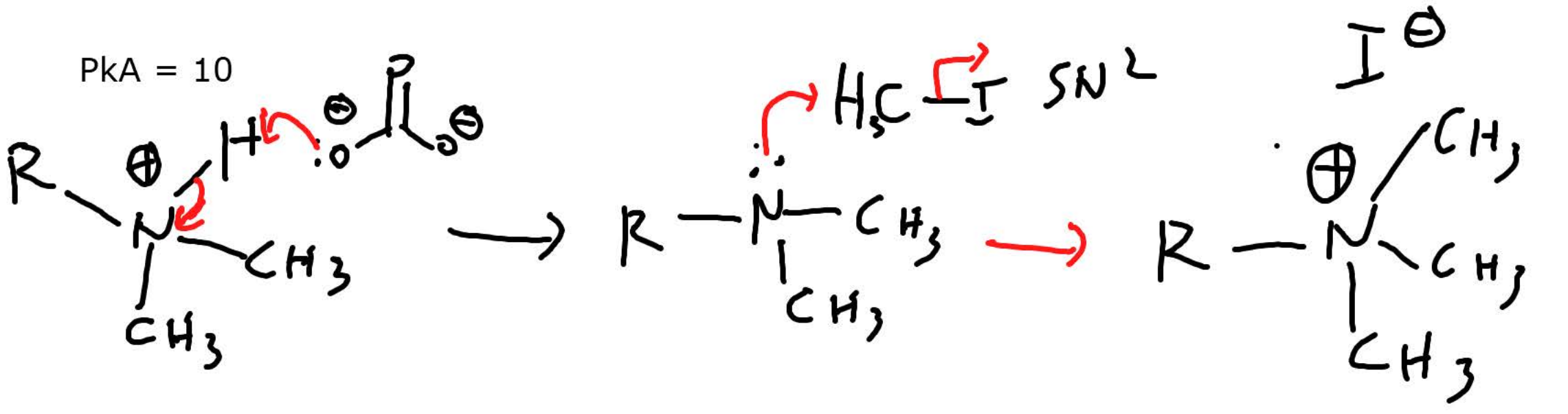
élimination à partir des amines

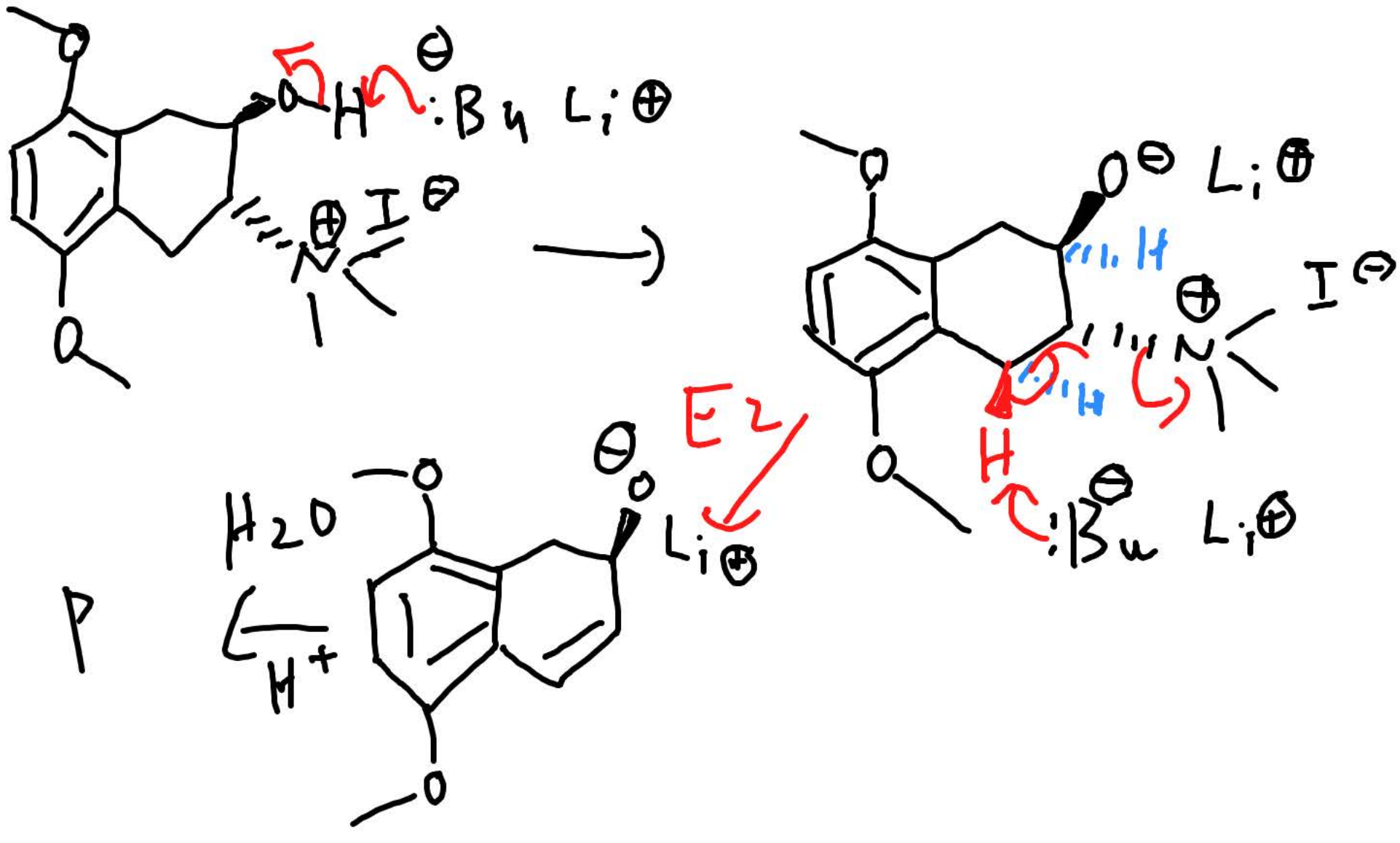


CH3I: excellent électrophile pour substitution

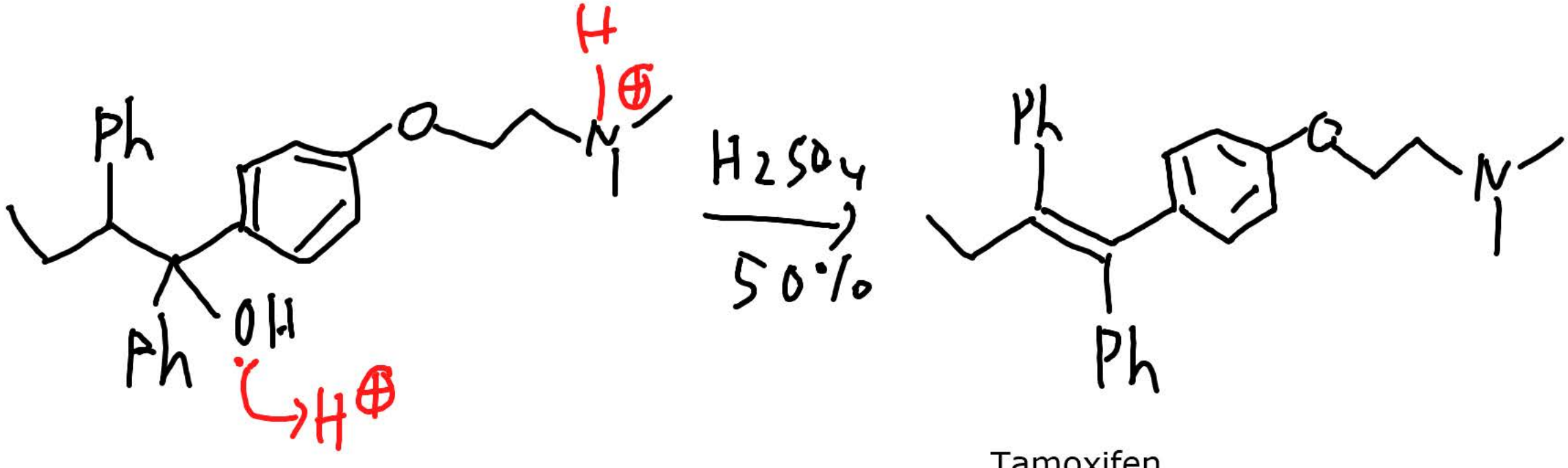
basé sur l'électronégativité: le meilleur nucléophile est sur l'azote (moins électronégatif)

PkA = 10

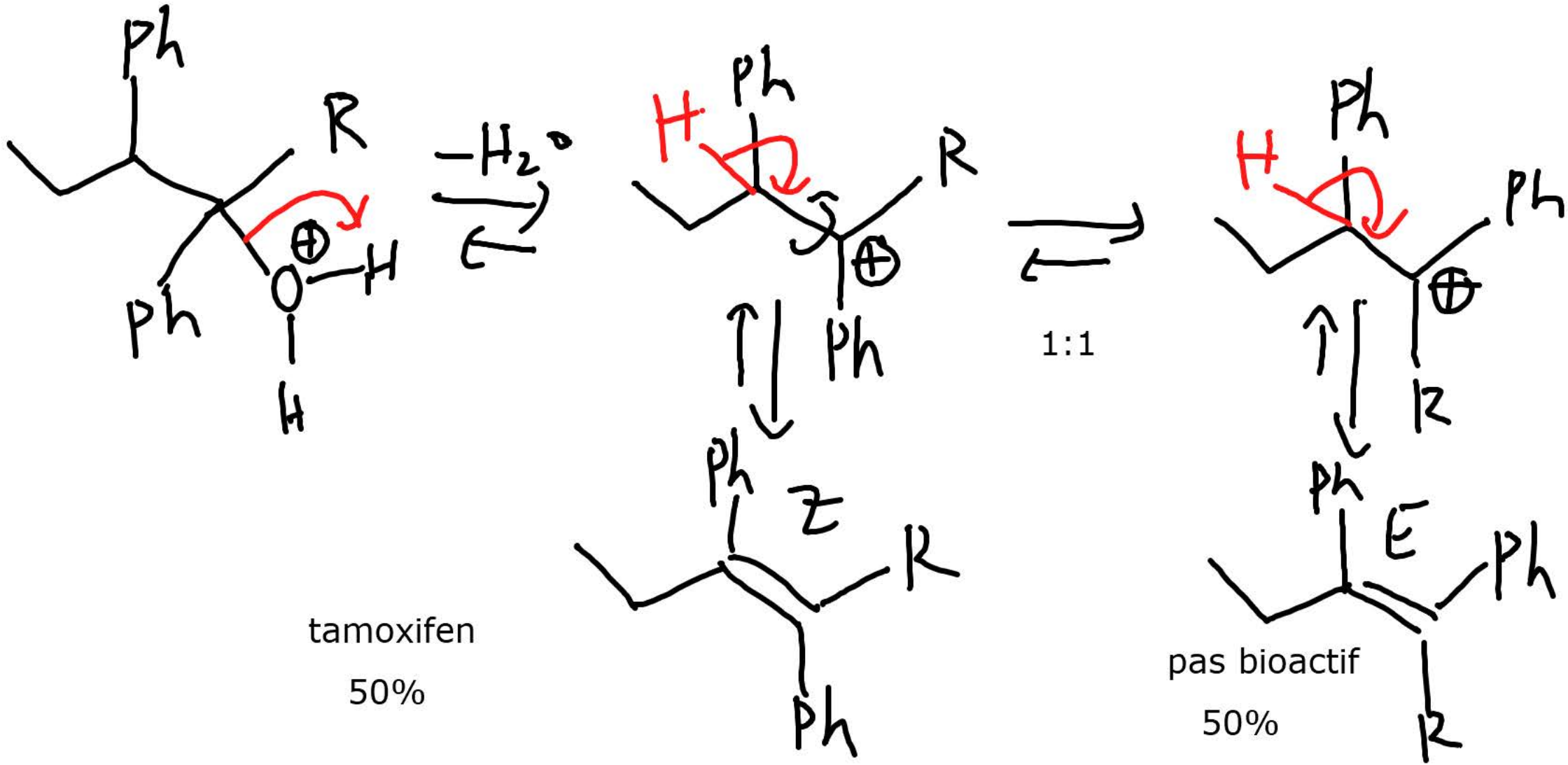



E2
H2O
H+
P

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



Tamoxifen



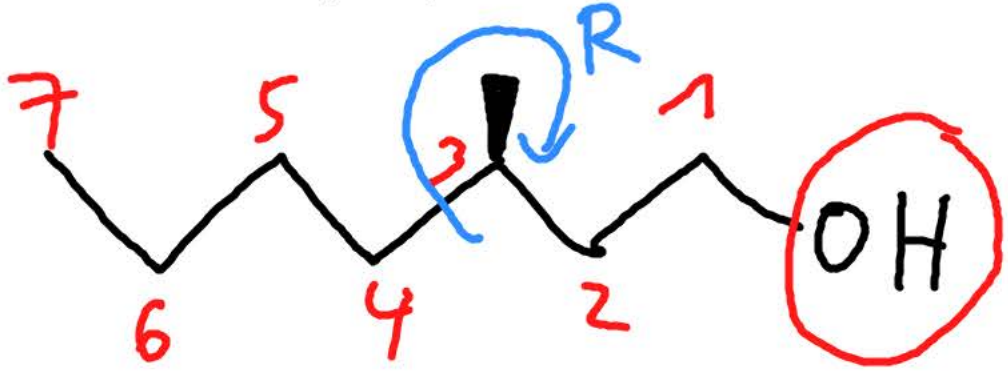
tamoxifen

50%

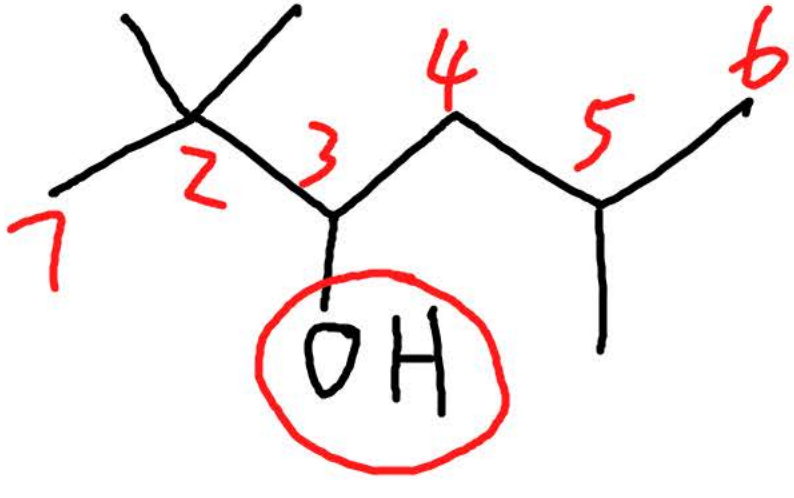
pas bioactif

50%

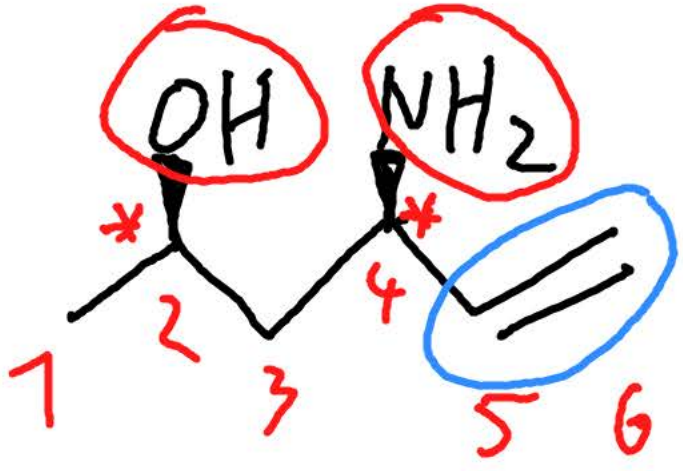
nomenclature des groupes fonctionnels



(R)-3methylheptan-1-ol

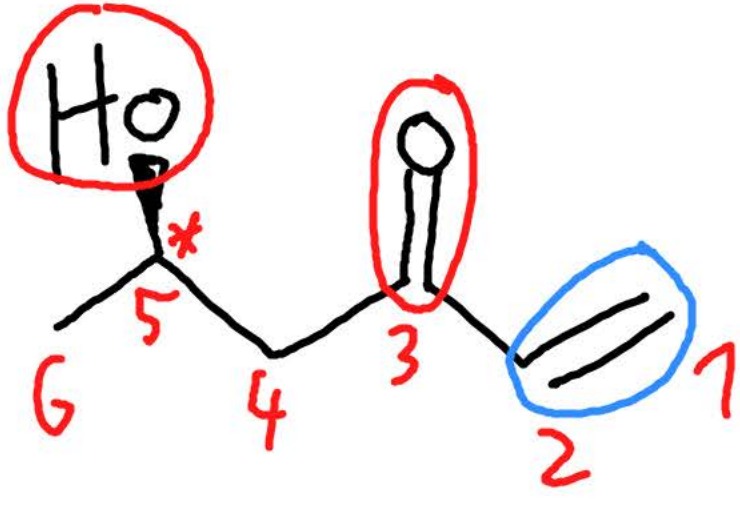


2,2,5-trimethylhexan-3-ol



Alcool > amine >alcènes

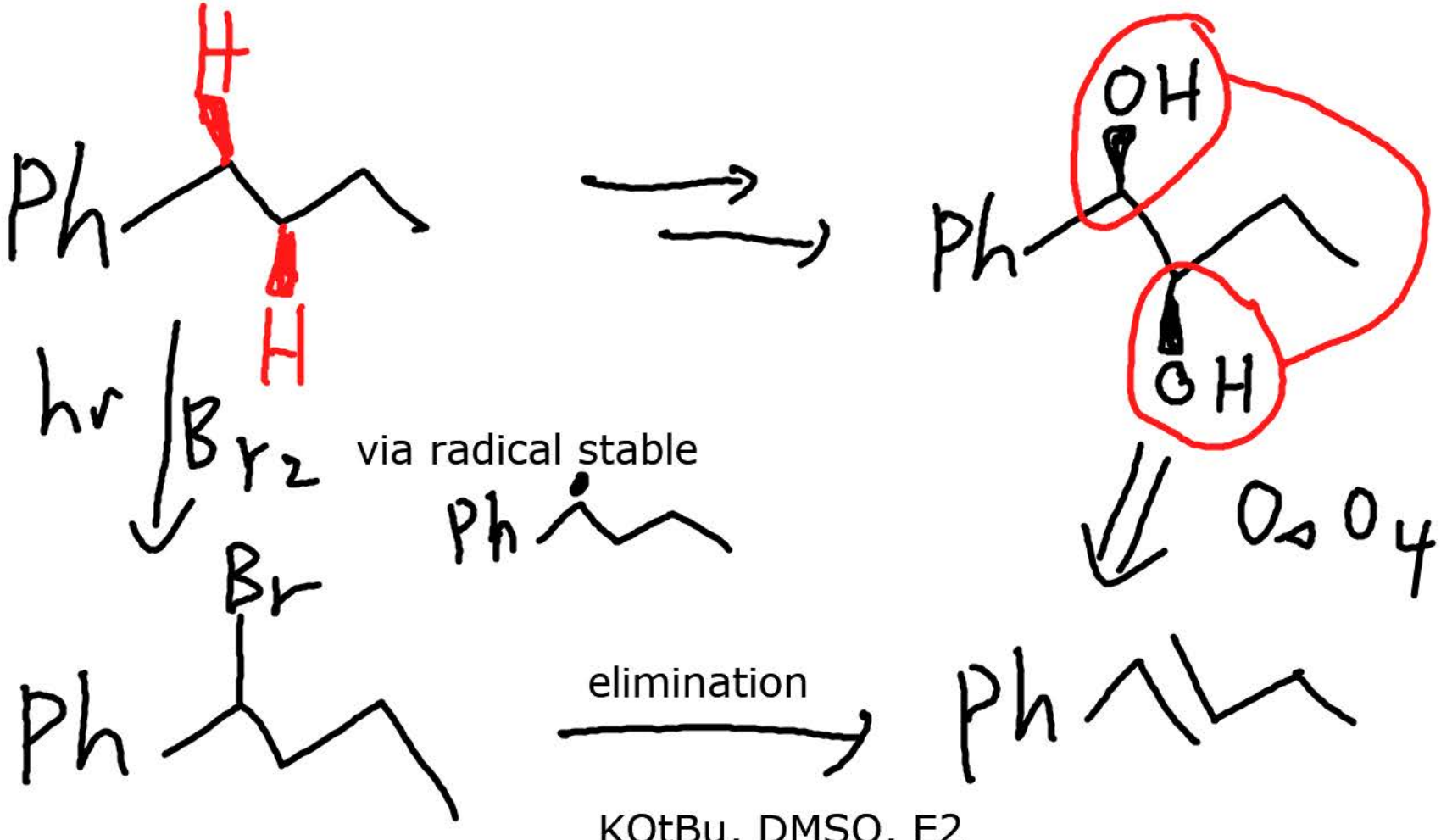
(2R, 4R)-4-amino-hex-5-en-2-ol



cétone > alcool > alcènes

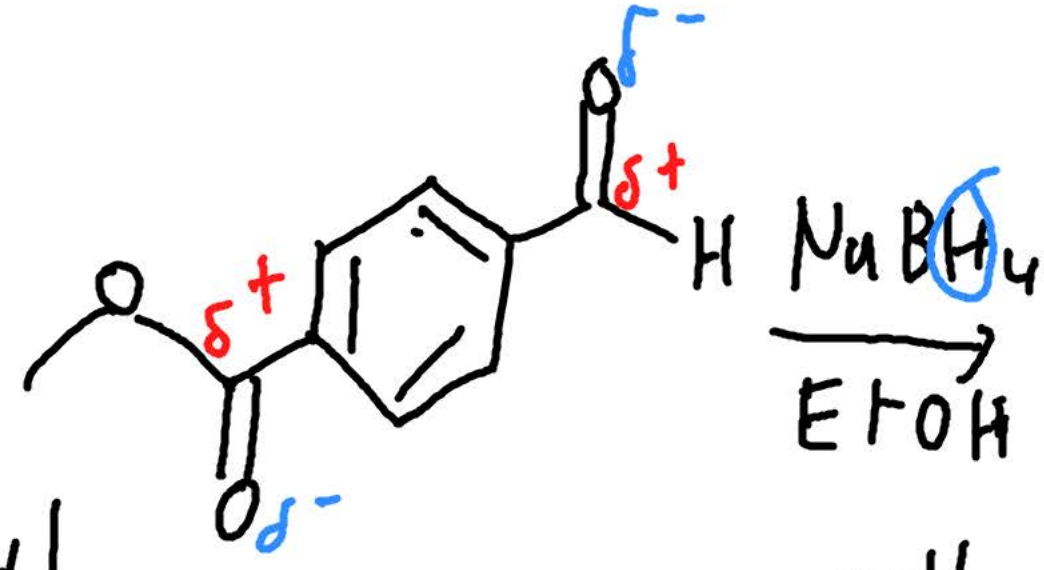
(R)-5-hydroxy-hex-1-en-3-one

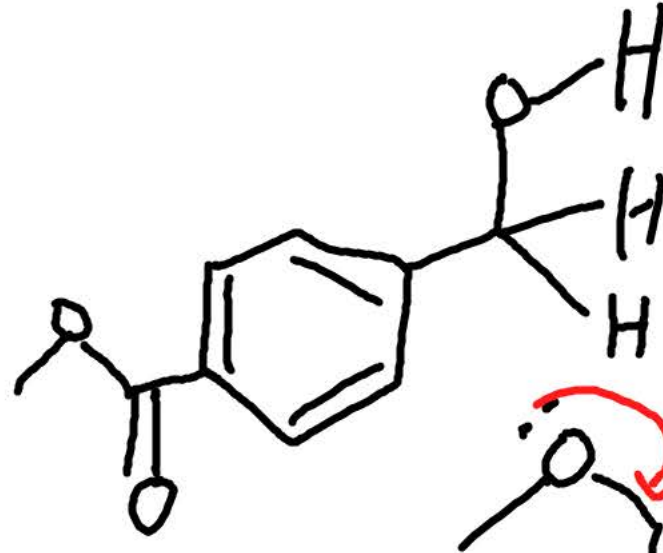
synthèse d'alcool multi-étape

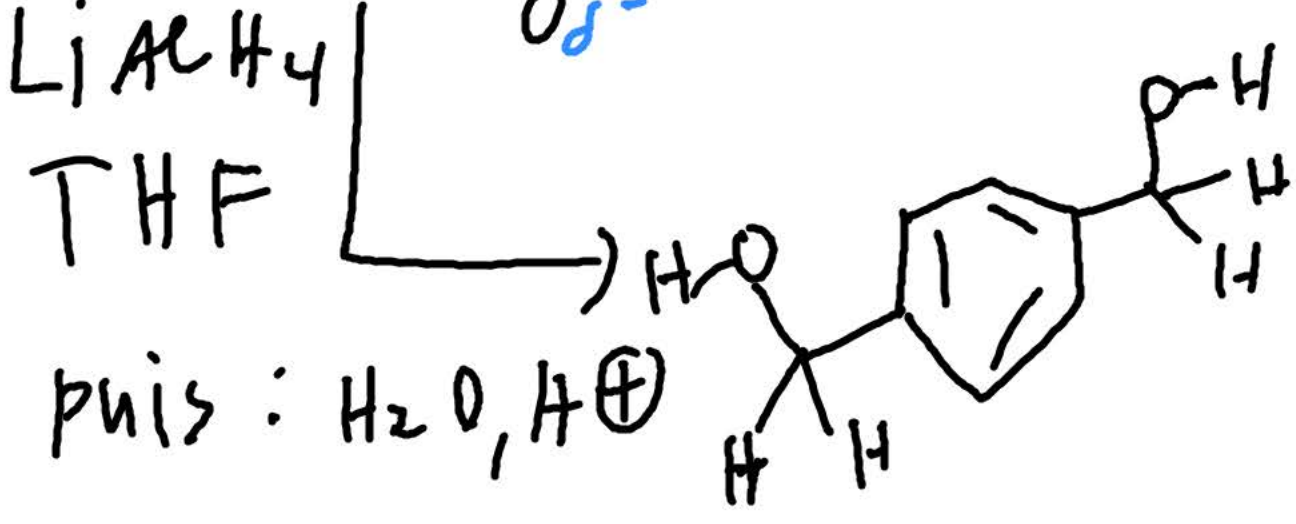


2 alcools cis (du même côté), dihydroxylation d'un alcène!

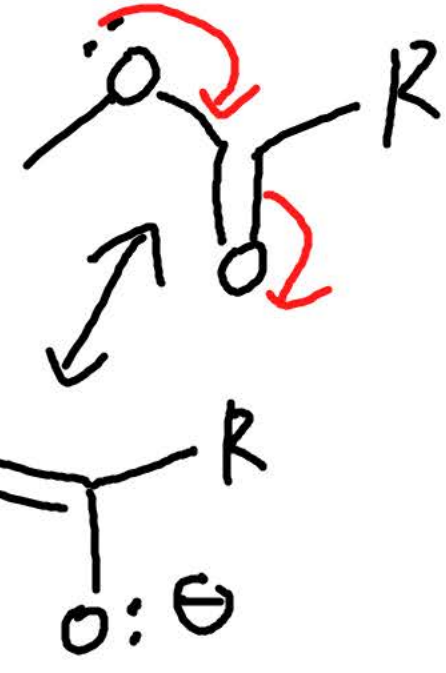
réduction des cétones avec les hydrures

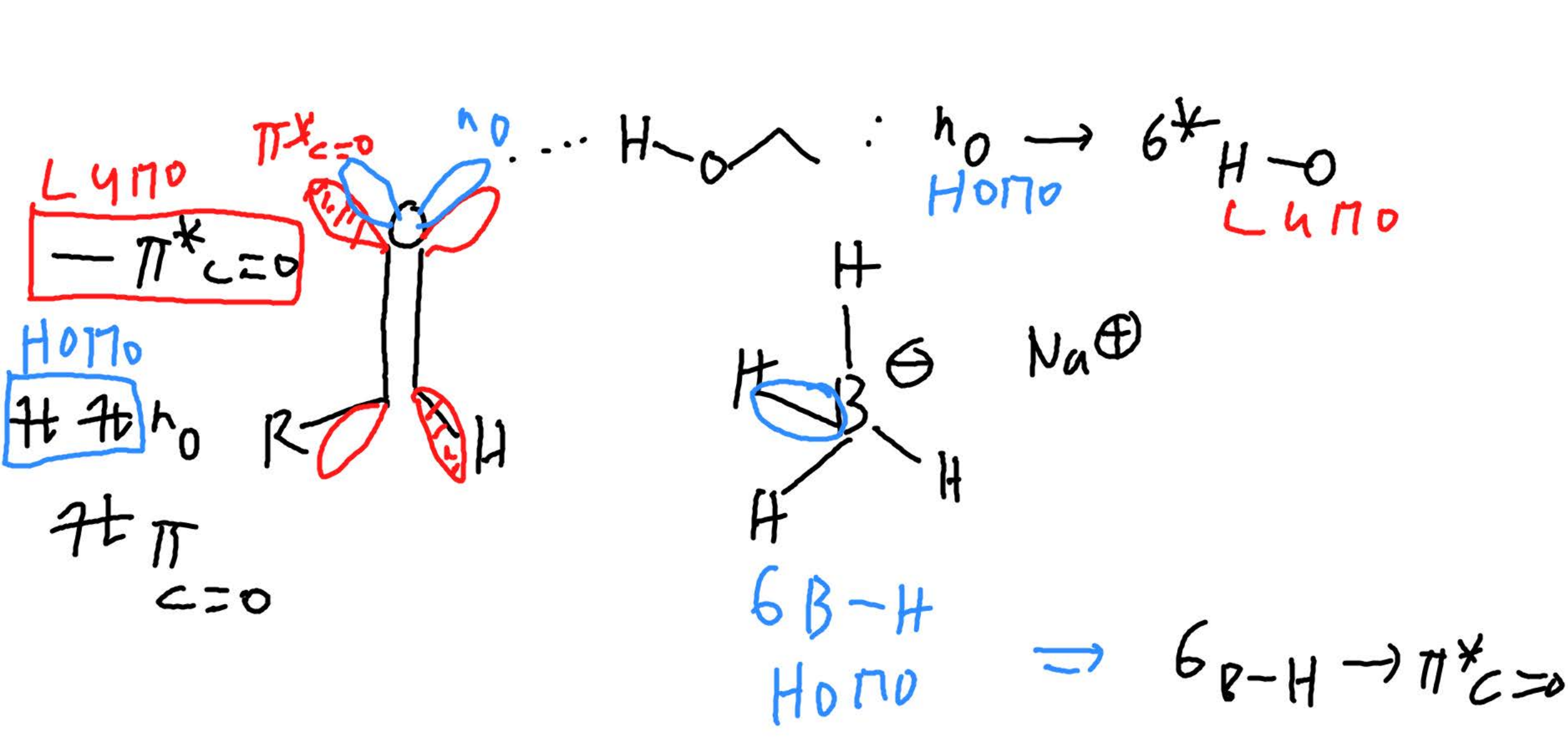


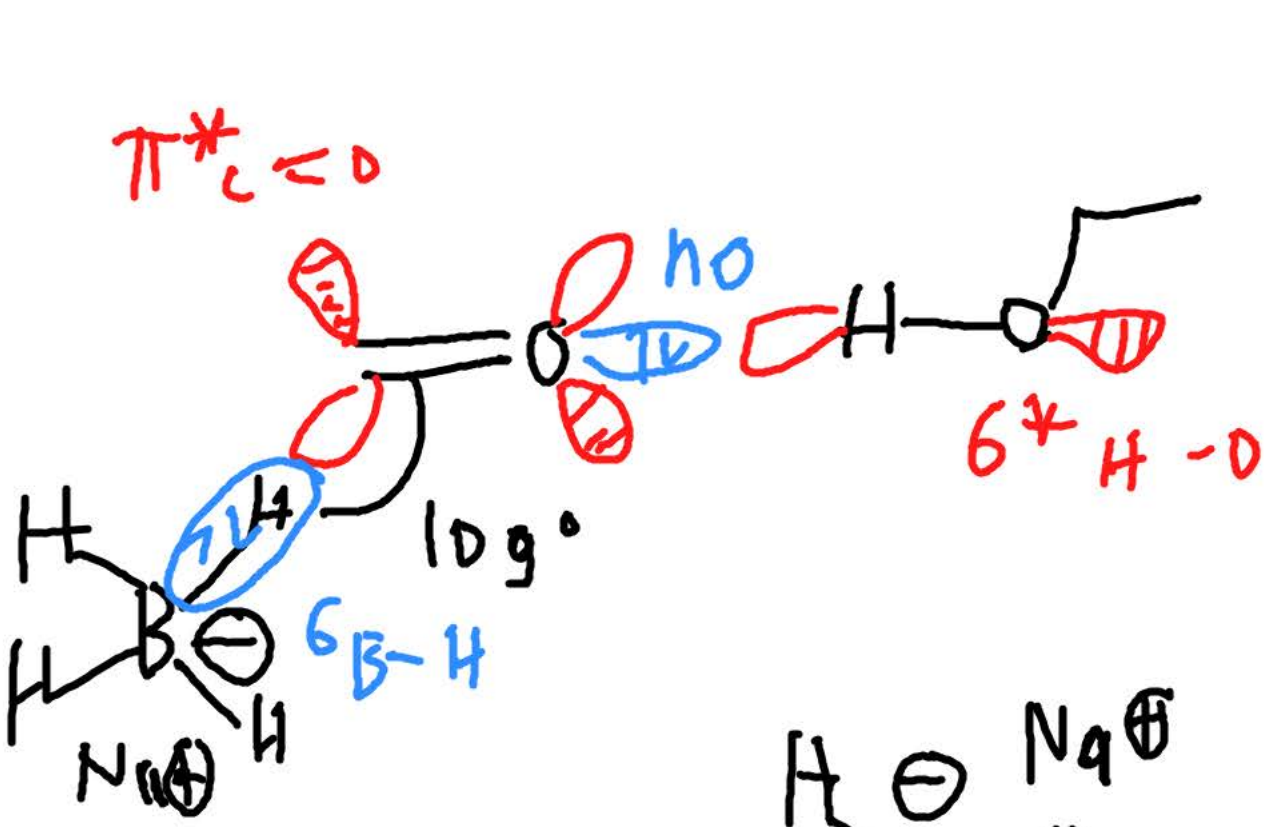




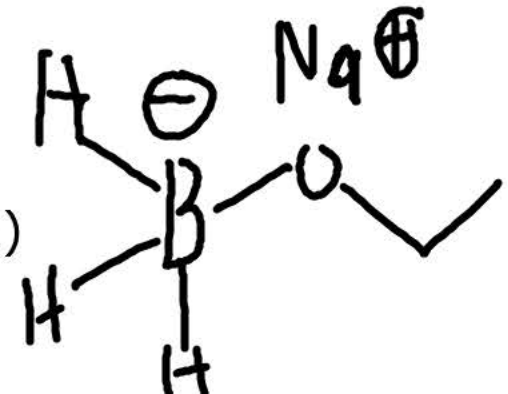
ester stabilisé,
moins réactif

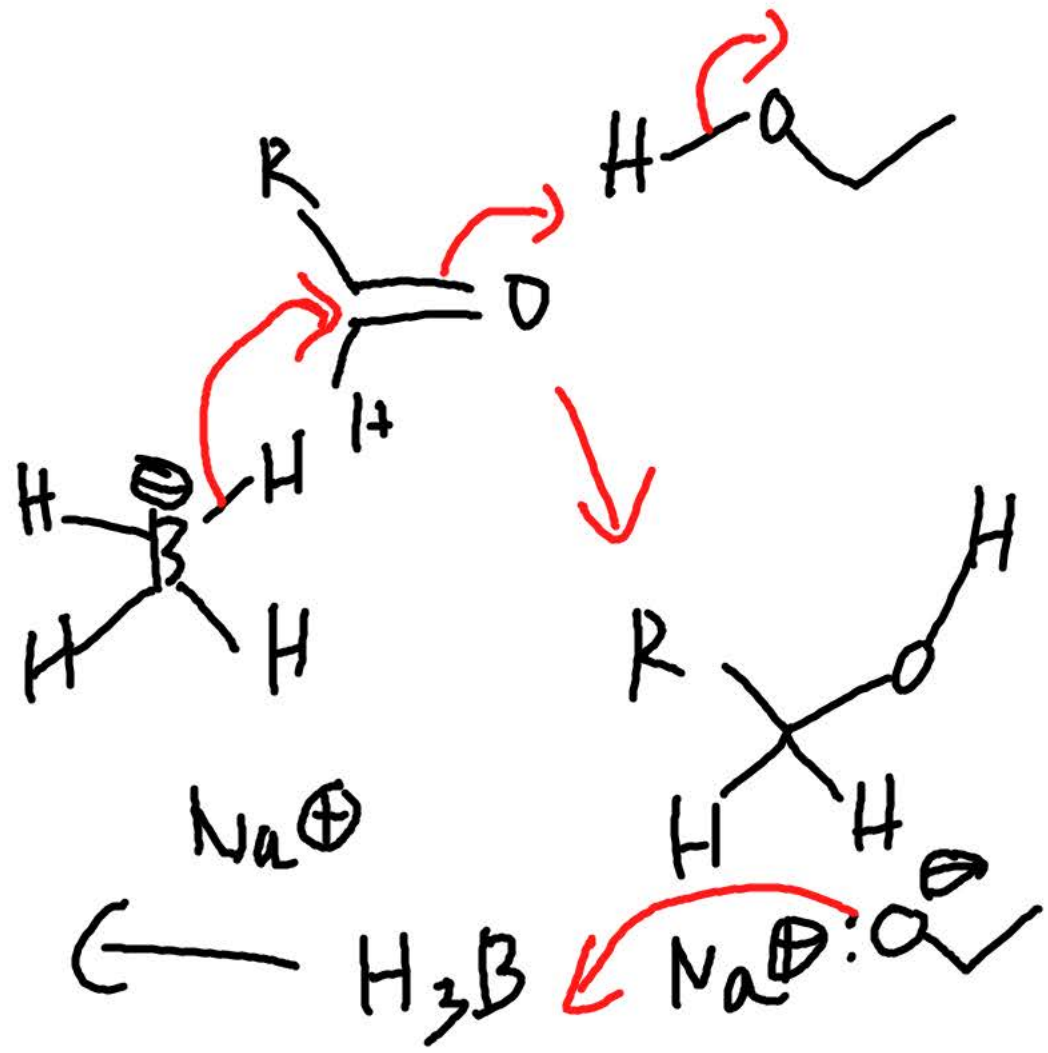



LUMO
$-\pi^*_{C=O}$
HOMO
$\pi\pi n_O$
$\pi^*_{C=O}$
n_O
R
H
$\pi\pi$
π
$C=O$
n_O
HOMO
σ^*
LUMO
Na⊕
σ_{B-H}
HOMO
$\Rightarrow$
$\sigma_{B-H} \rightarrow \pi^*_{C=O}$

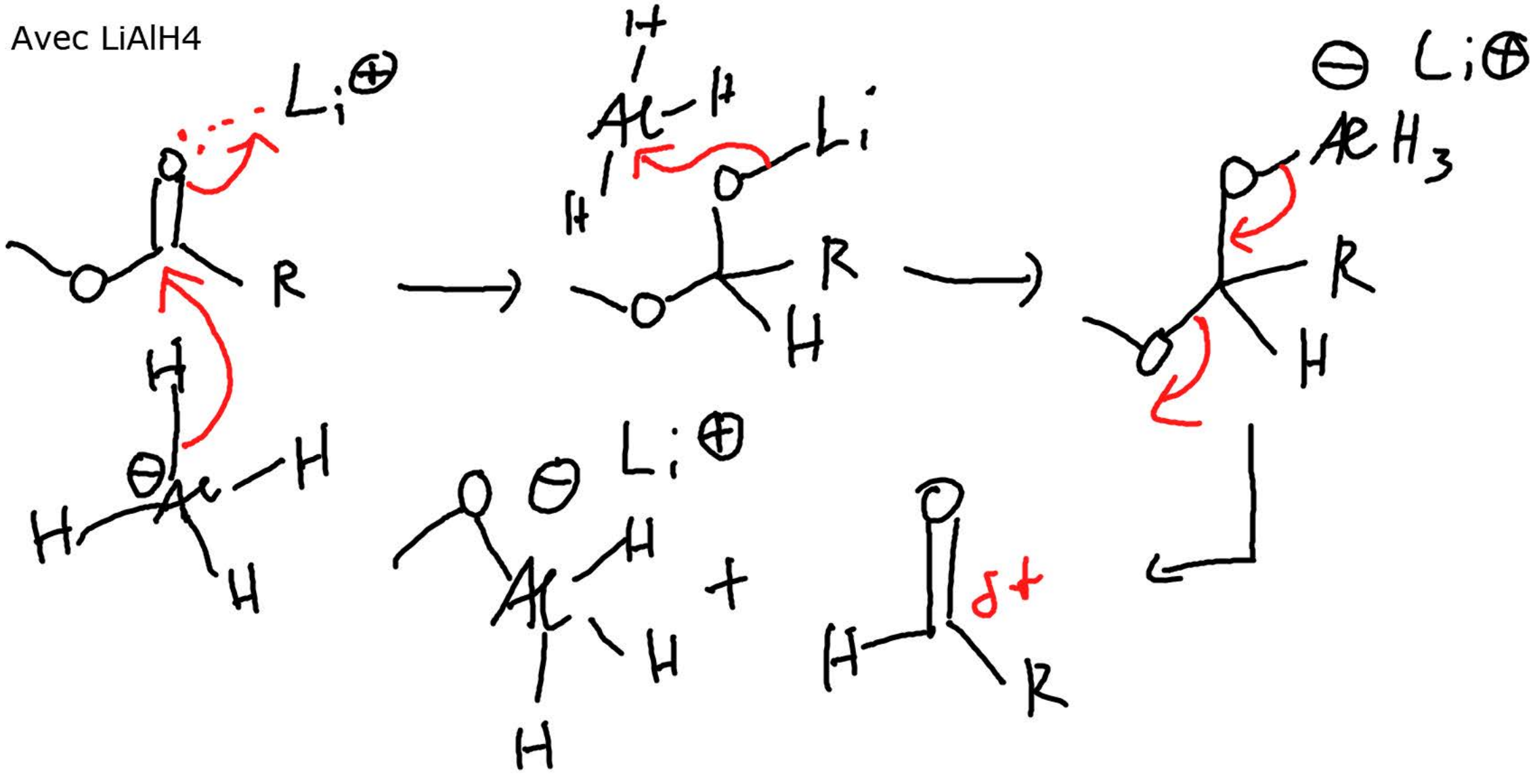


Angle de Bürgi-Dunitz (ETHZ)

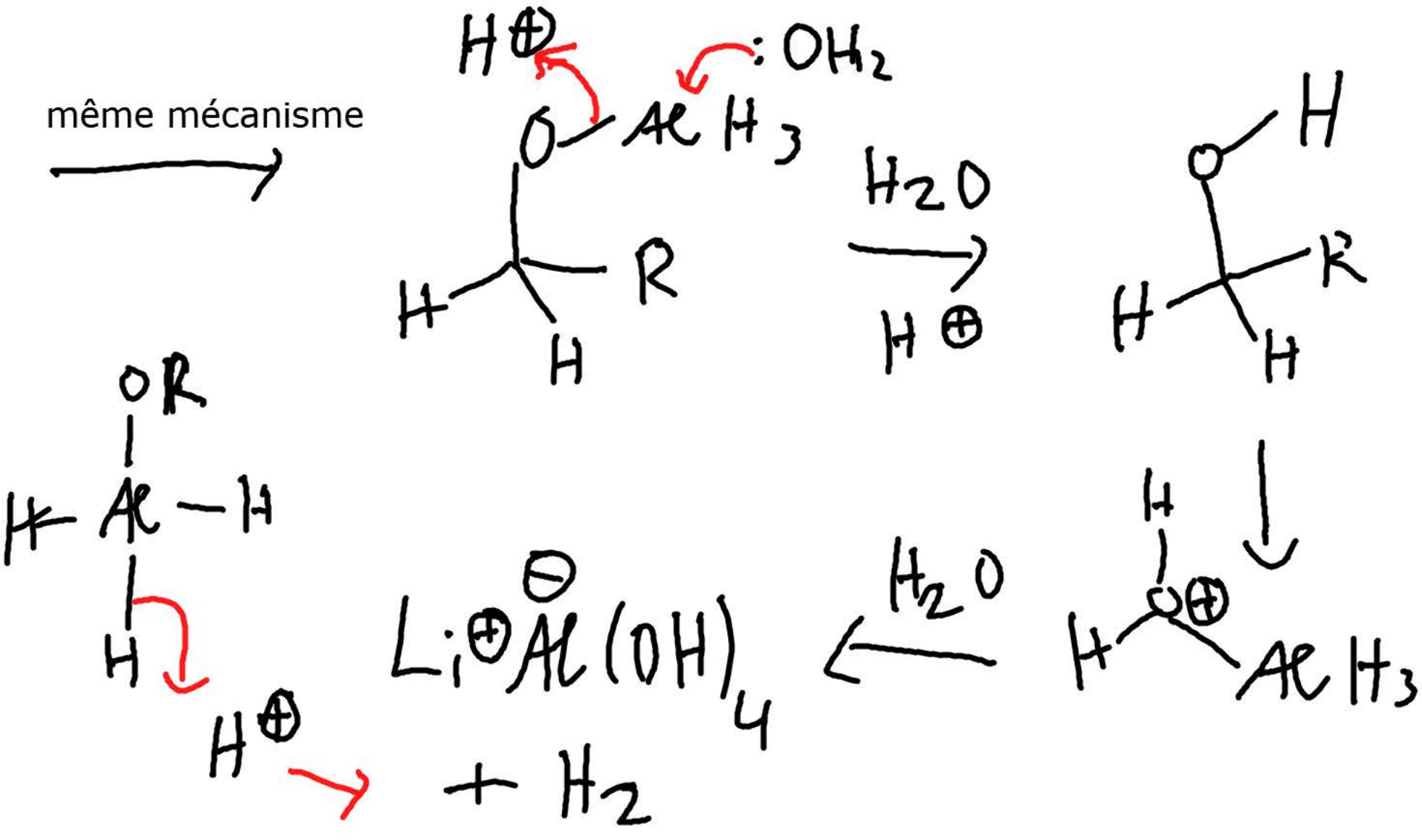




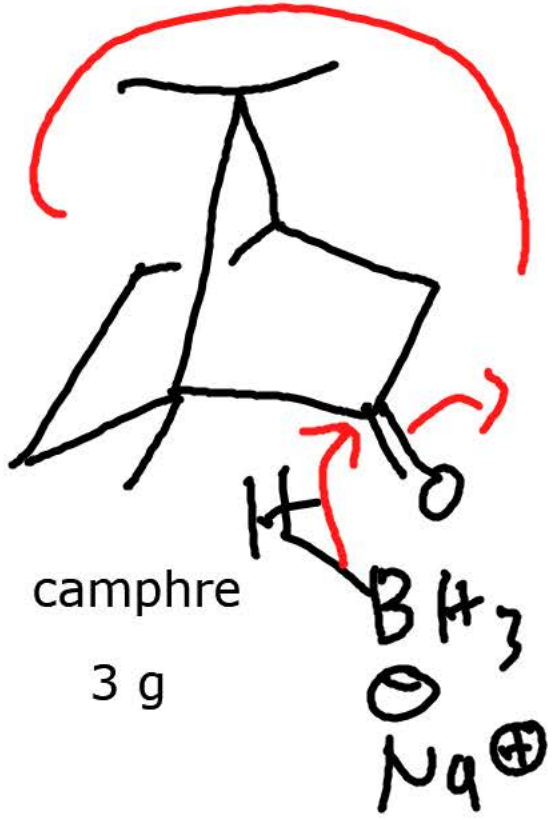
Avec LiAlH4



même mécanisme



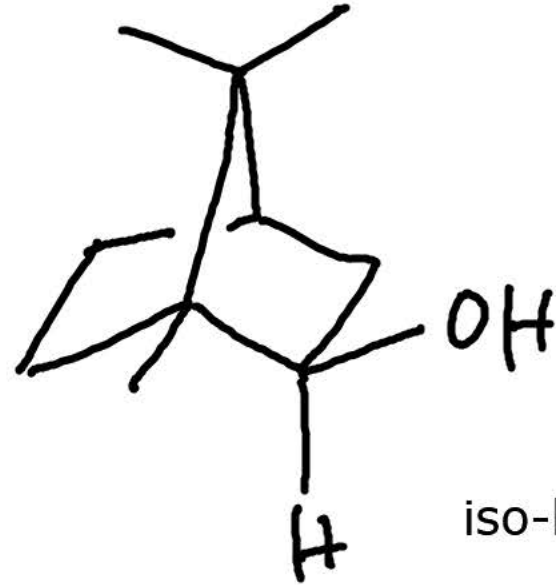
exemples des TP de chimie organique



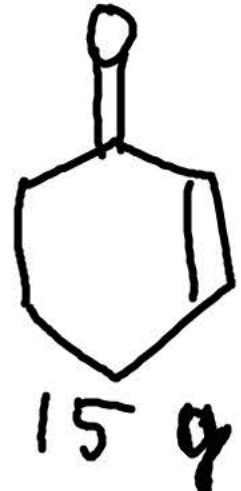
face bloquée

camphre

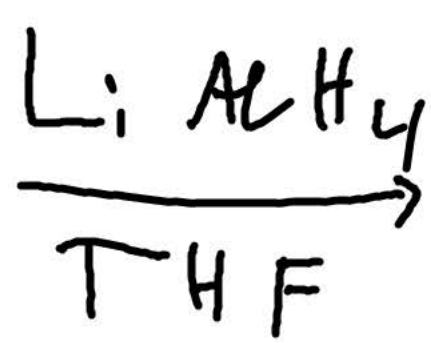
3 g



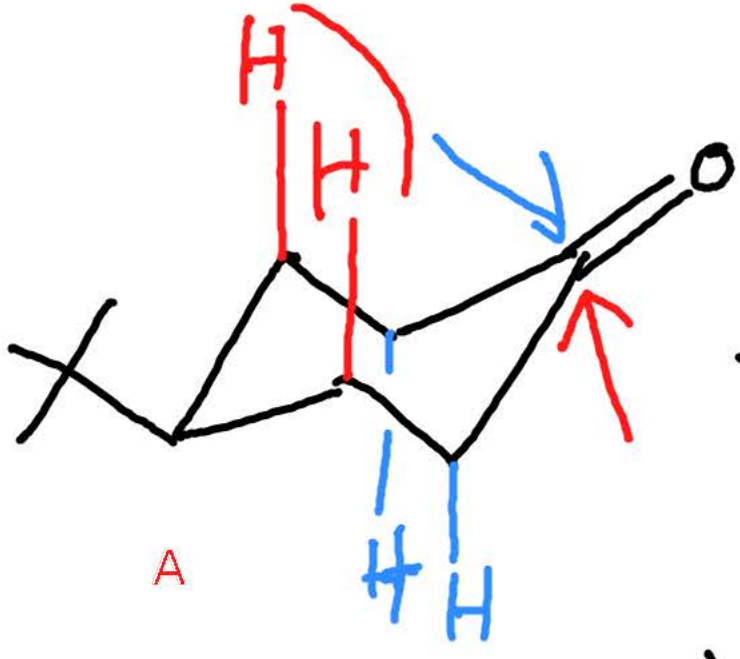
iso-borneol



15 g

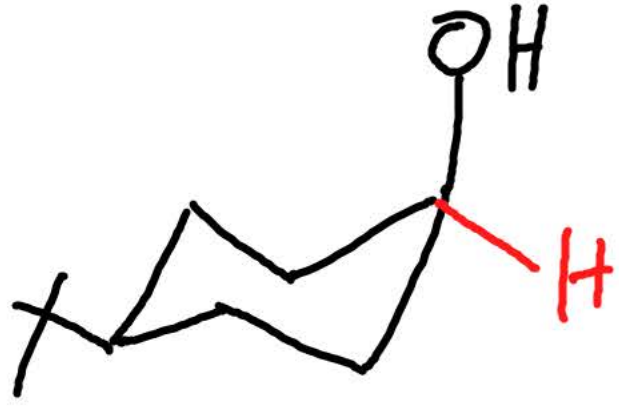


réduction de cyclohéxanone



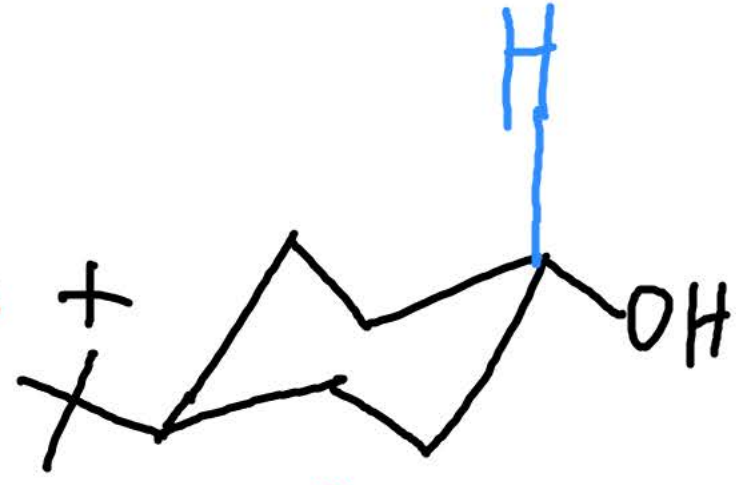
A

[H]



1

+

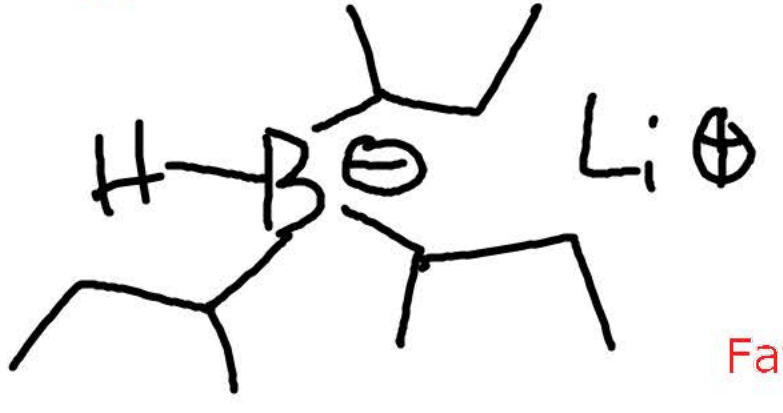


2

plus stable: OH est équatorial

L-Selectride

"très gros"



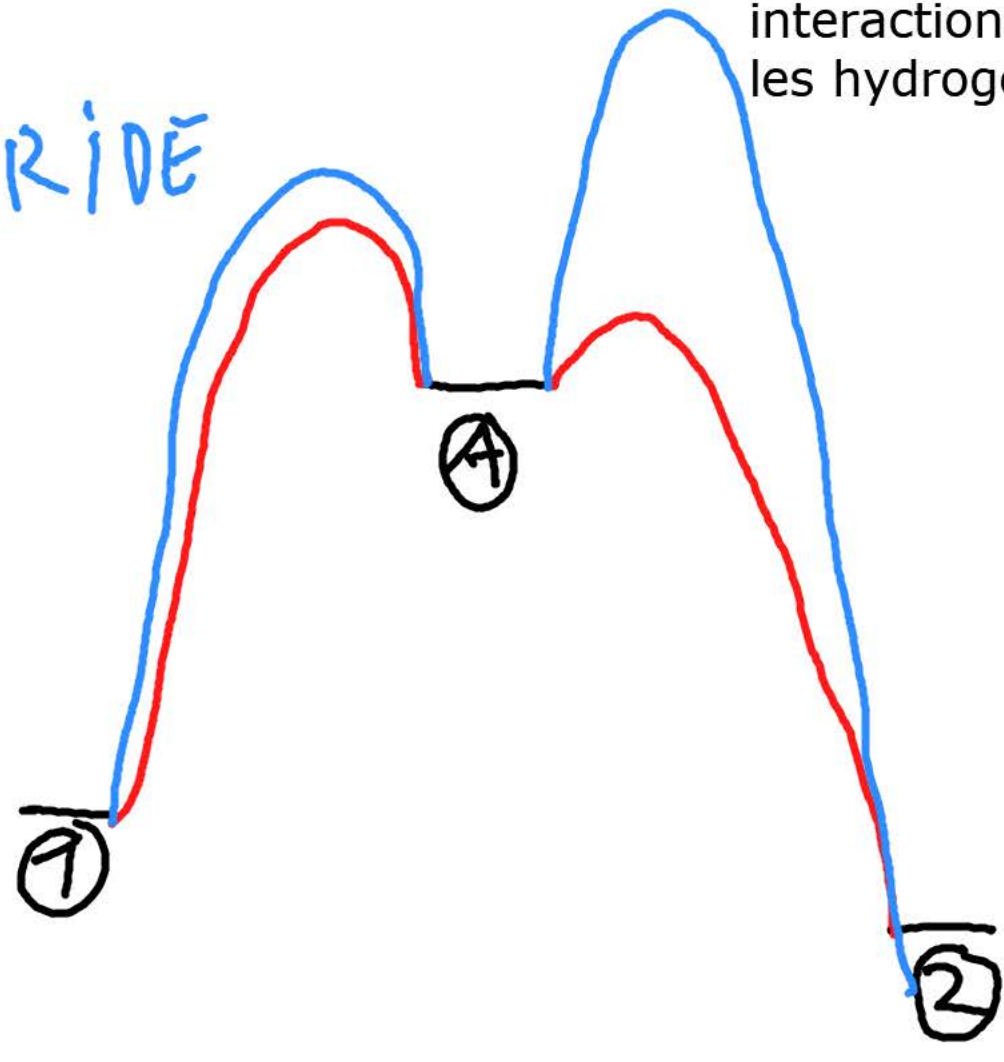
[H] = LiBH4, 9:91
[H] = L-selectride: 86:14

Favorise de venir en équatorial!

L-SELECTRIDE

produit cinétique (1)

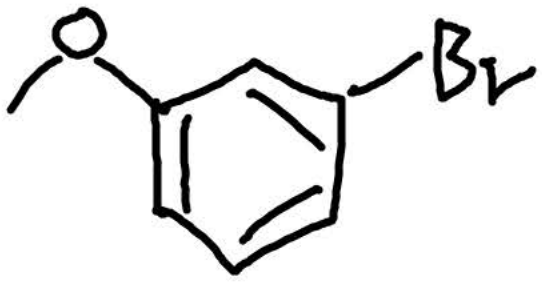
interaction défavorable avec
les hydrogènes axiaux

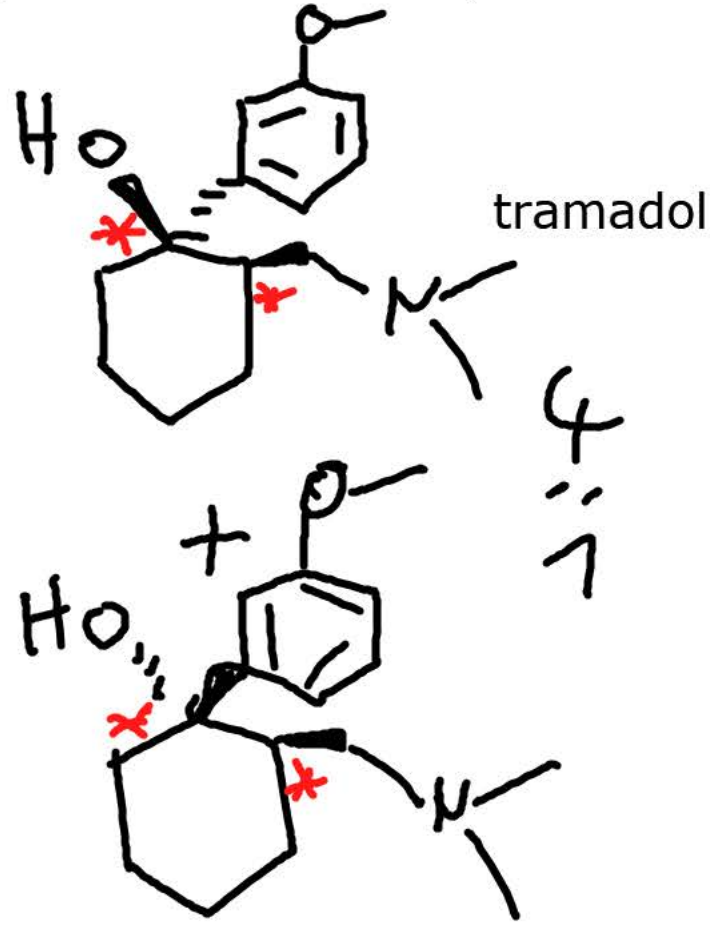


$LiBH_4$

produit thermodynamie
(2)

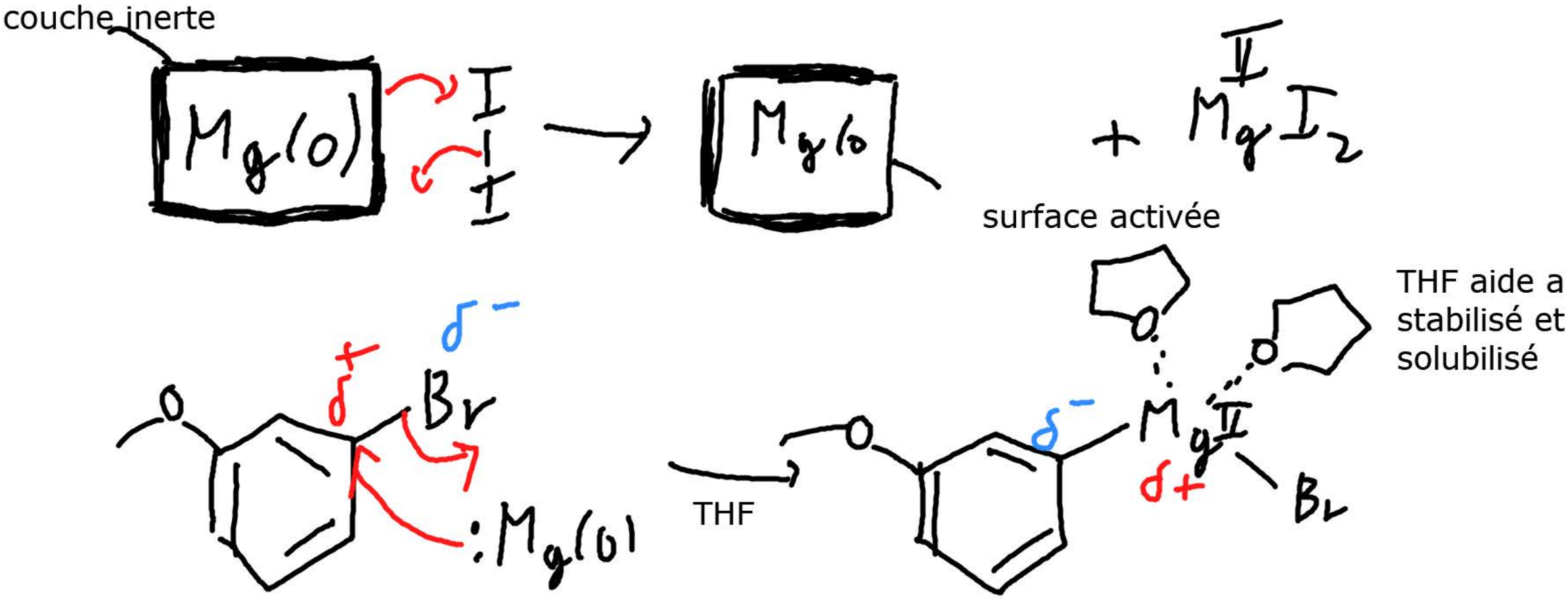
réaction de Grignard: synthèse du Tramadol (analgésique, drogue de Boko Haram)



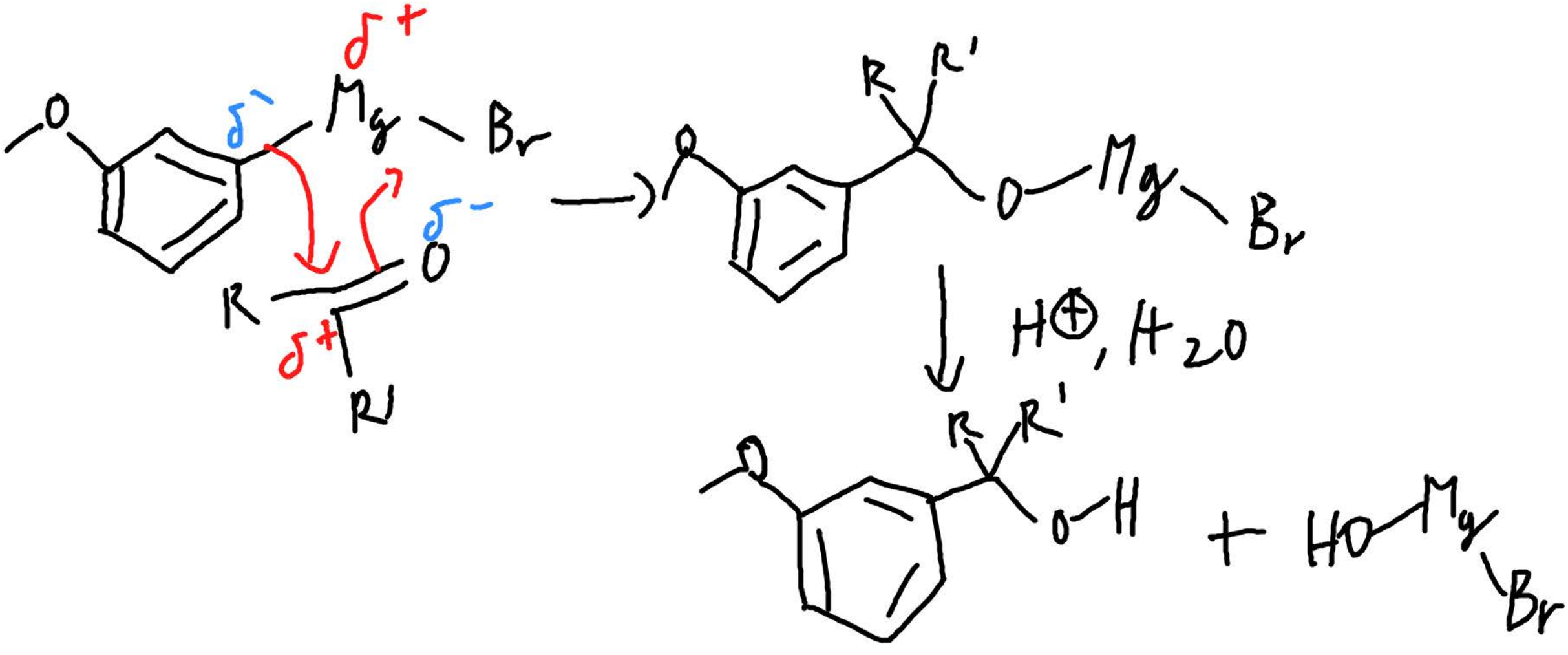


tramadol

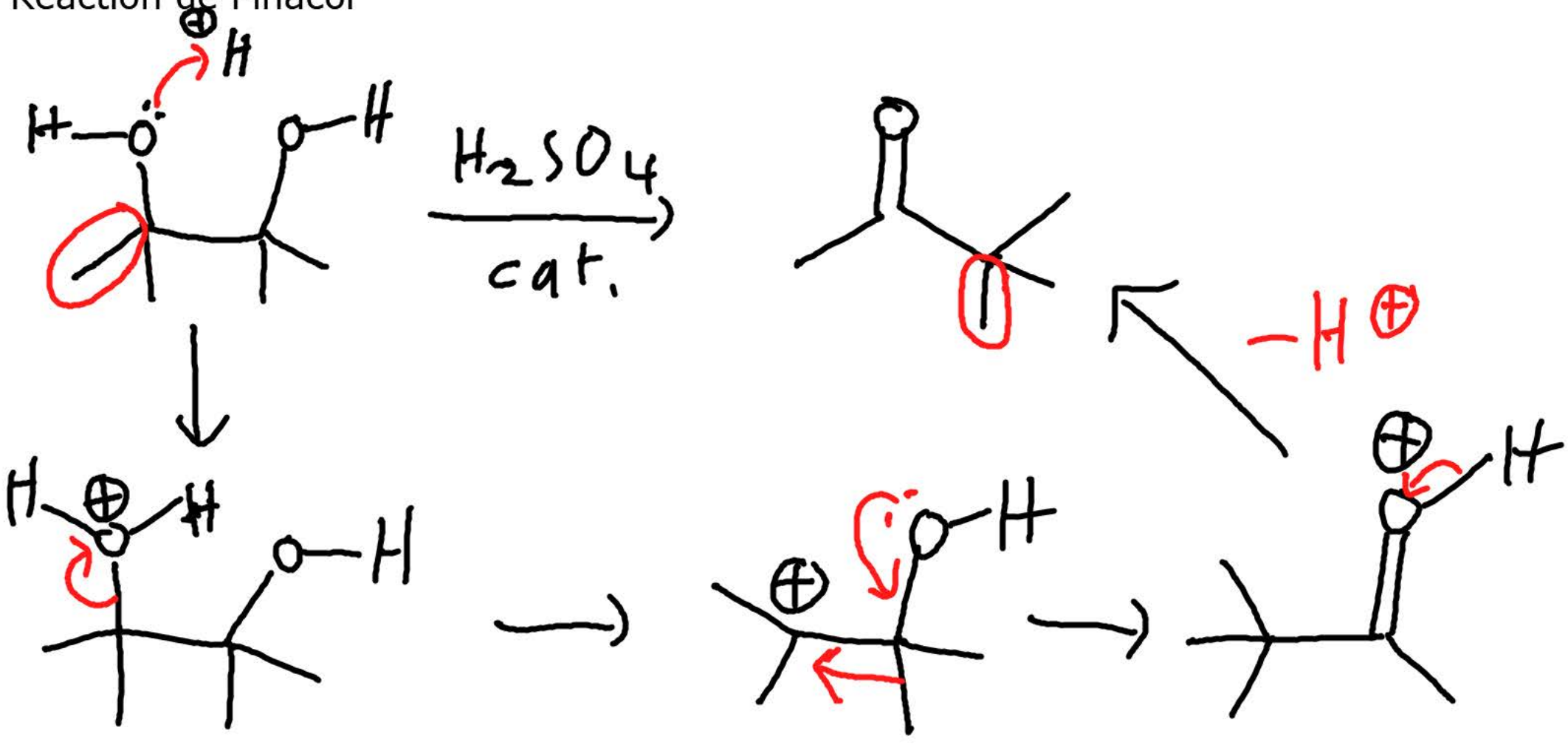
diastéréoisomères



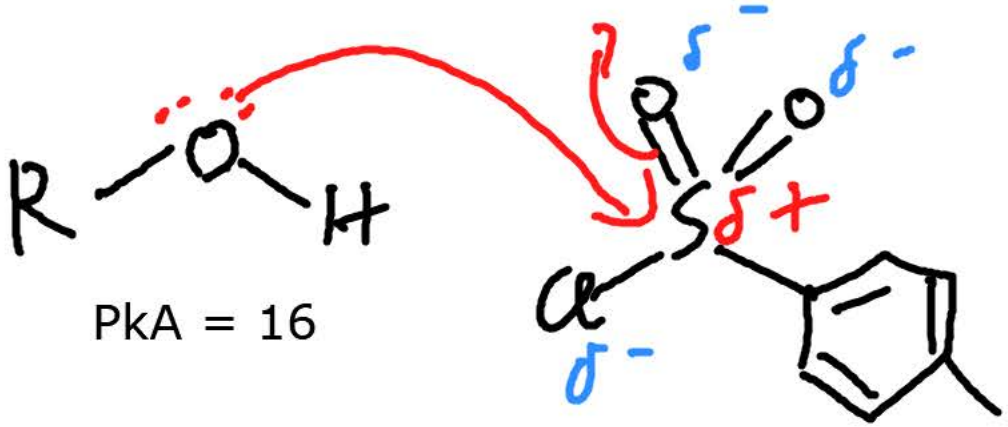
on a inversé la réactivité (Umpolung)


δ+
δ−
Mg
Br
O
R
R'
δ−
O
R
δ+
R'
O
Mg
Br
H⊕, H2O
R
R'
O
H
+
HO
Mg
Br

Réaction de Pinacol



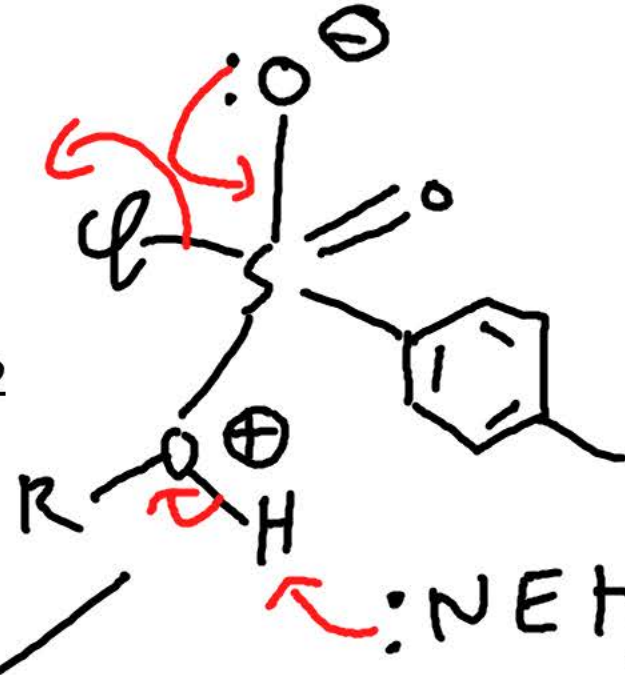
1) activation avec les composés du soufre



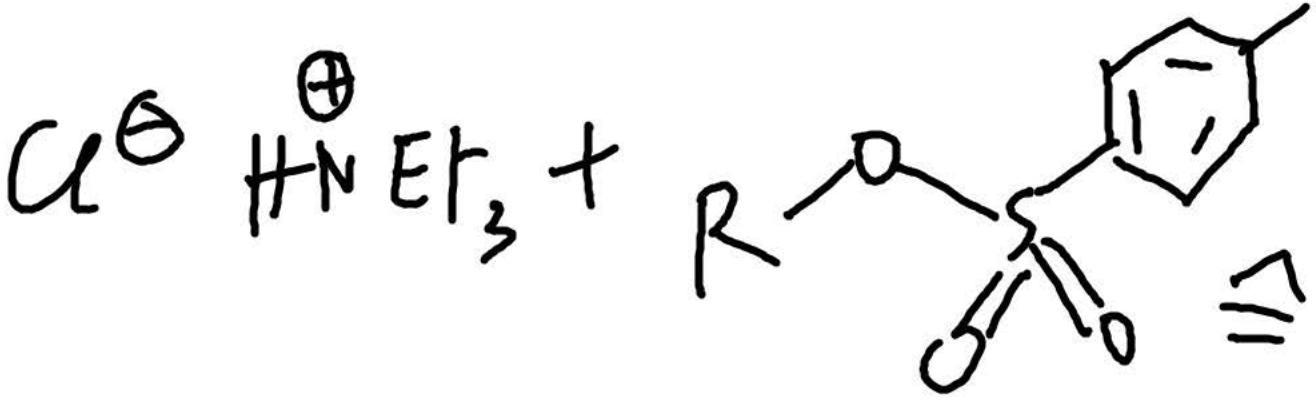
PkA = 16

TsCl

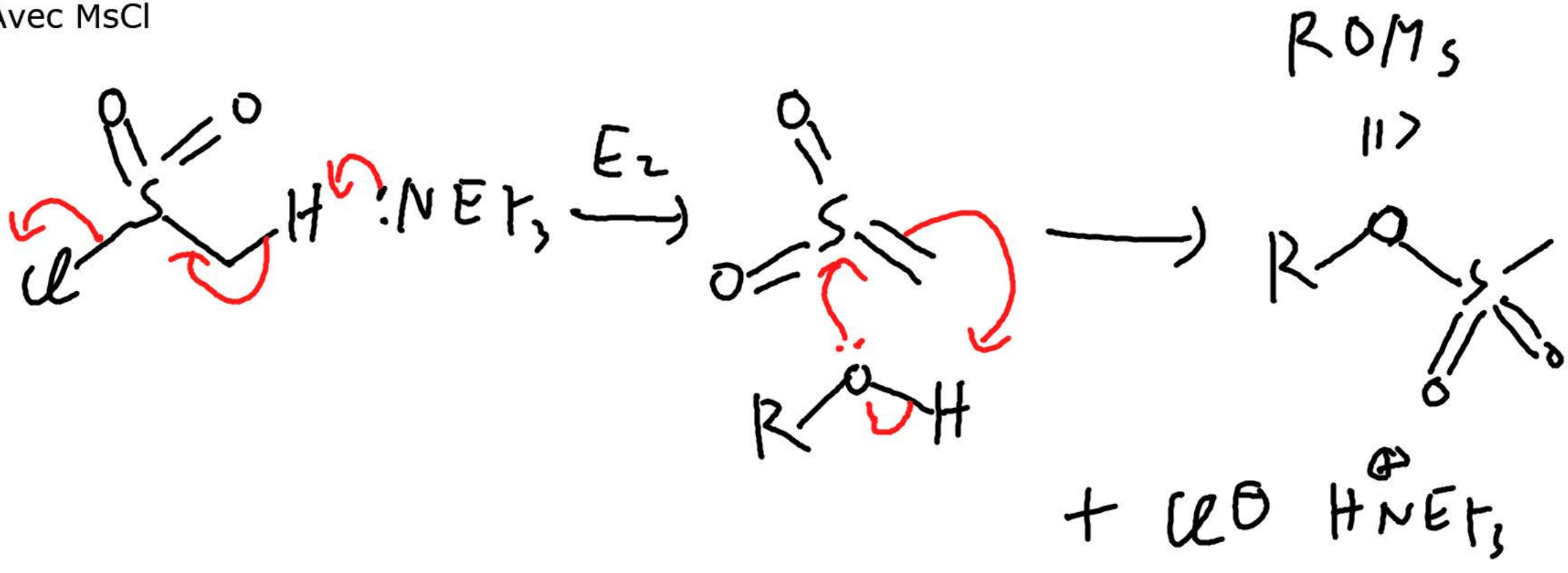
pkaH = -2



PkAH = 10

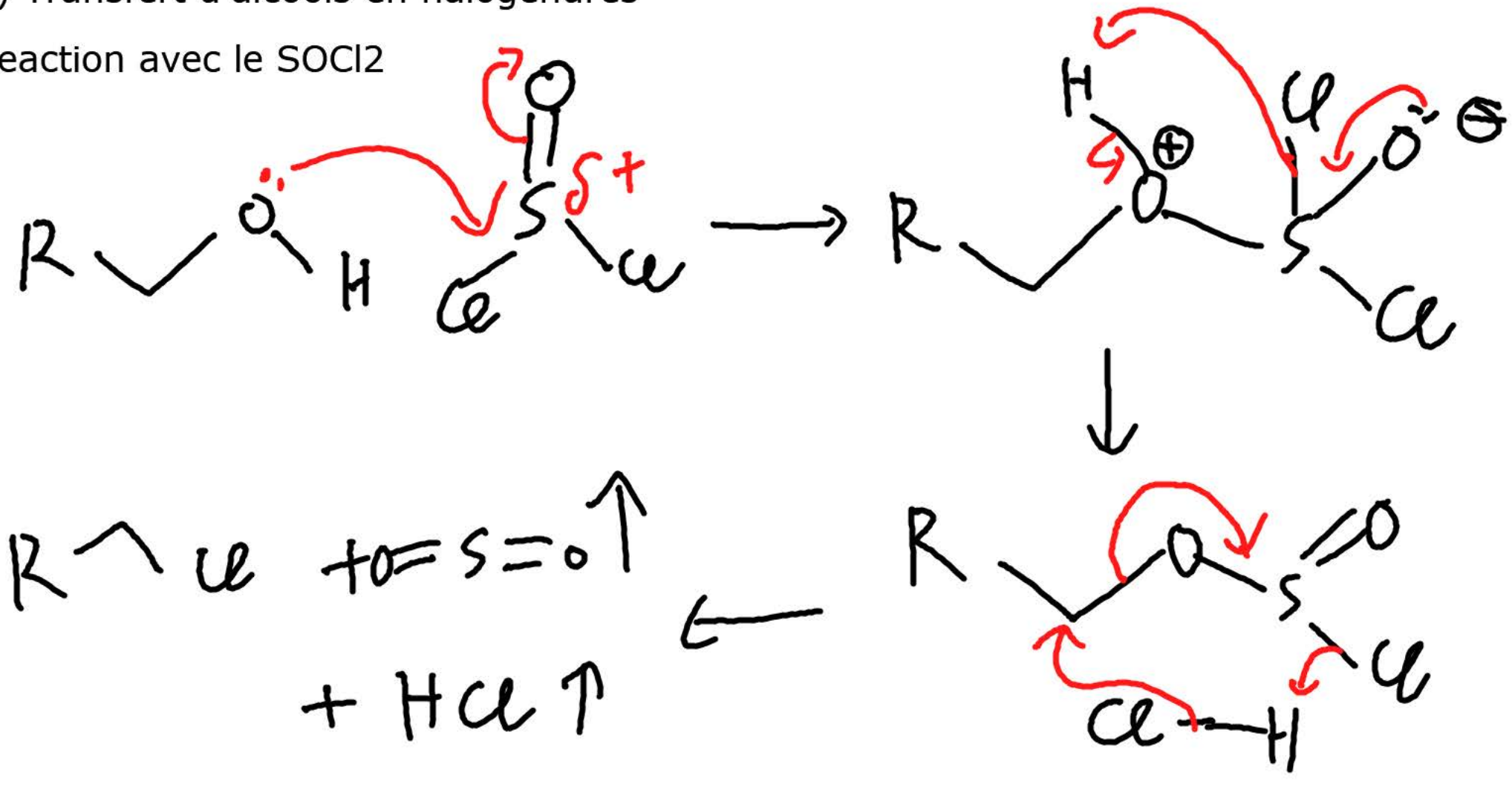


Avec MsCl

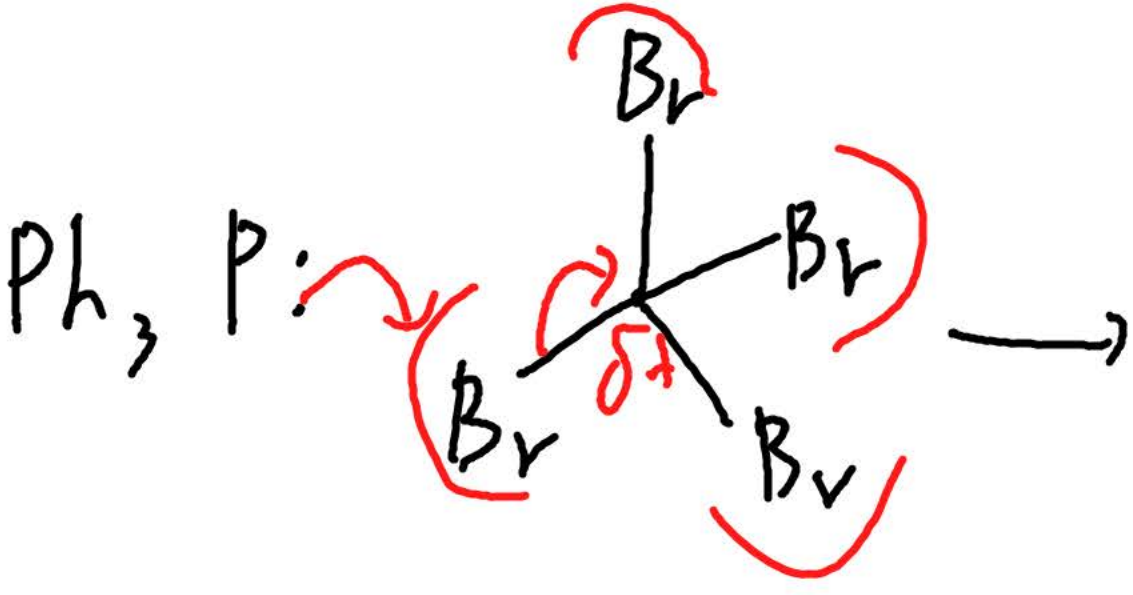


2) Transfert d'alcools en halogénures

reaction avec le SOCl2

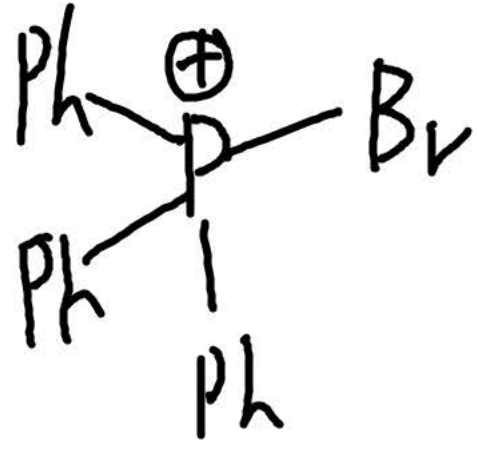


réaction d'Appel

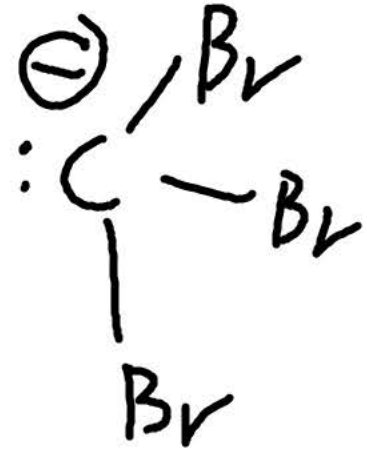


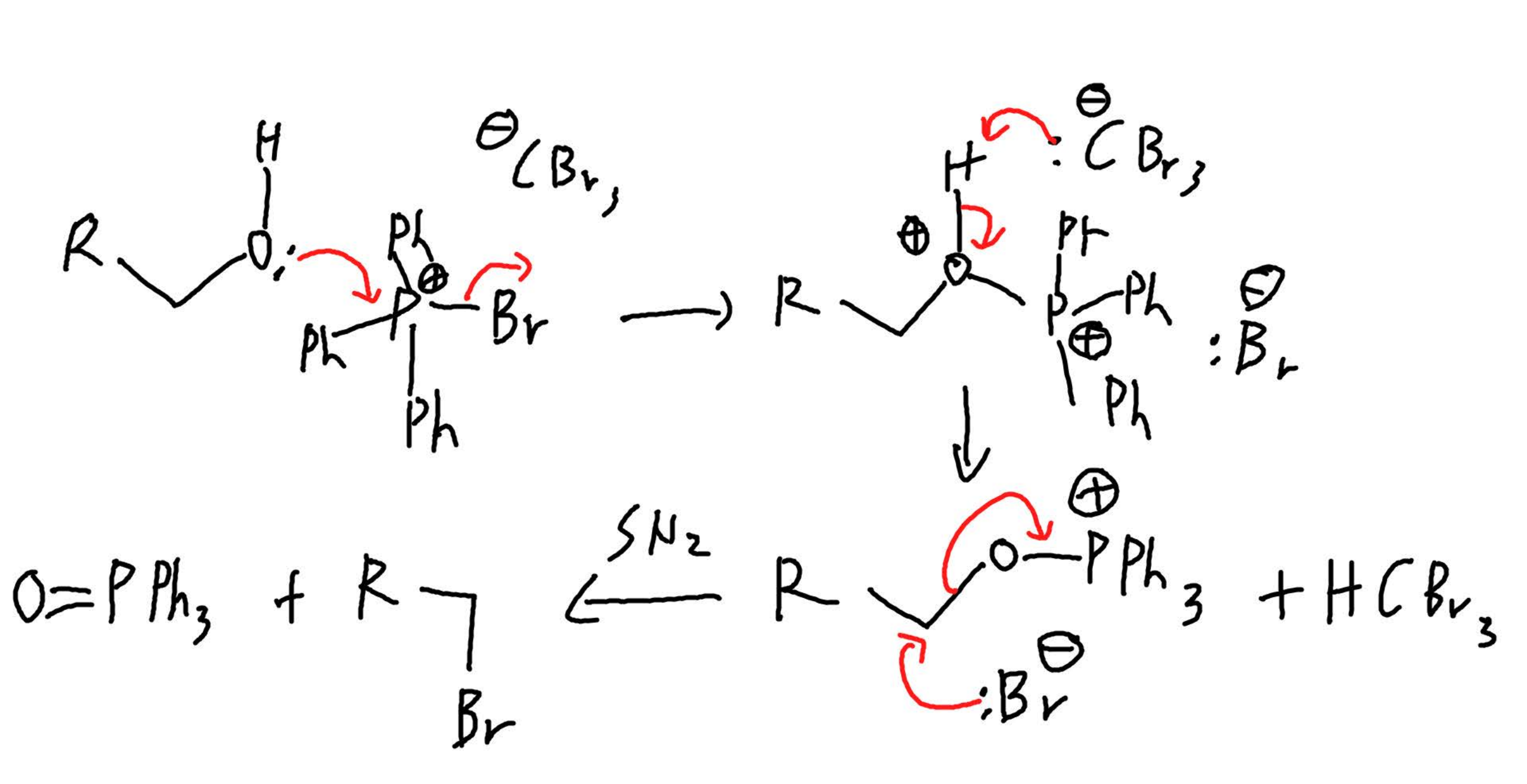
delta+ pas accessible!

bon électrophile

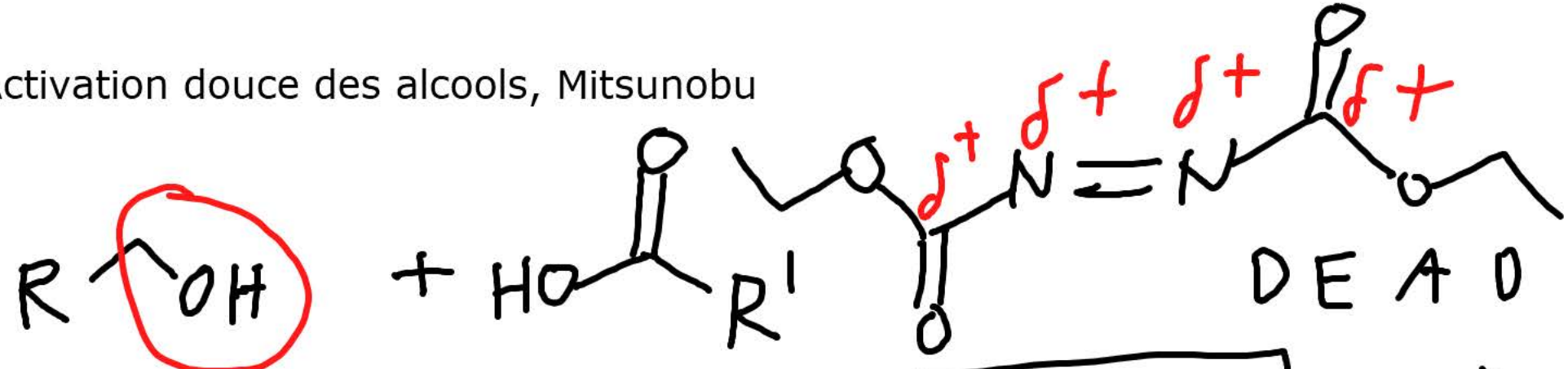


bonne base

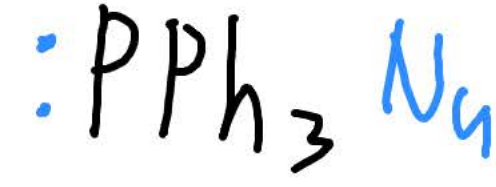


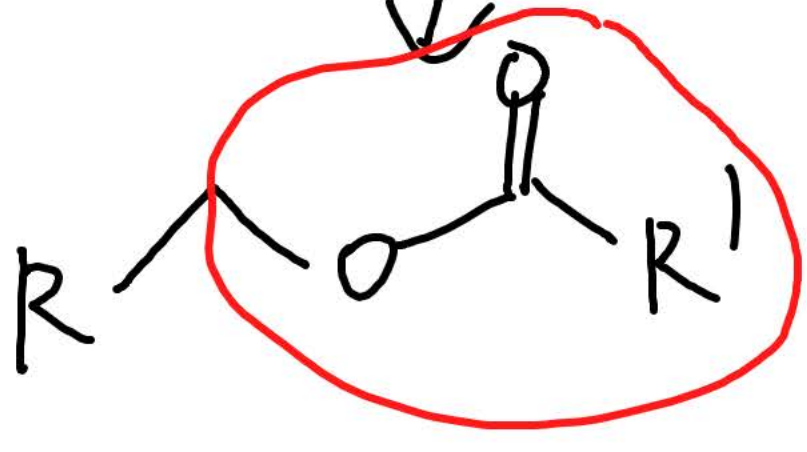

H
R
O
Ph
Ph
Ph
Br
⊖
CBr3
H
⊕
⊖
:CBr3
R
O
P
Ph
Ph
Ph
⊖
:Br
⊕
O
PPh3
R
⊕
:Br
⊖
SN2
O=PPh3
+
R
Br
+
HCBr3

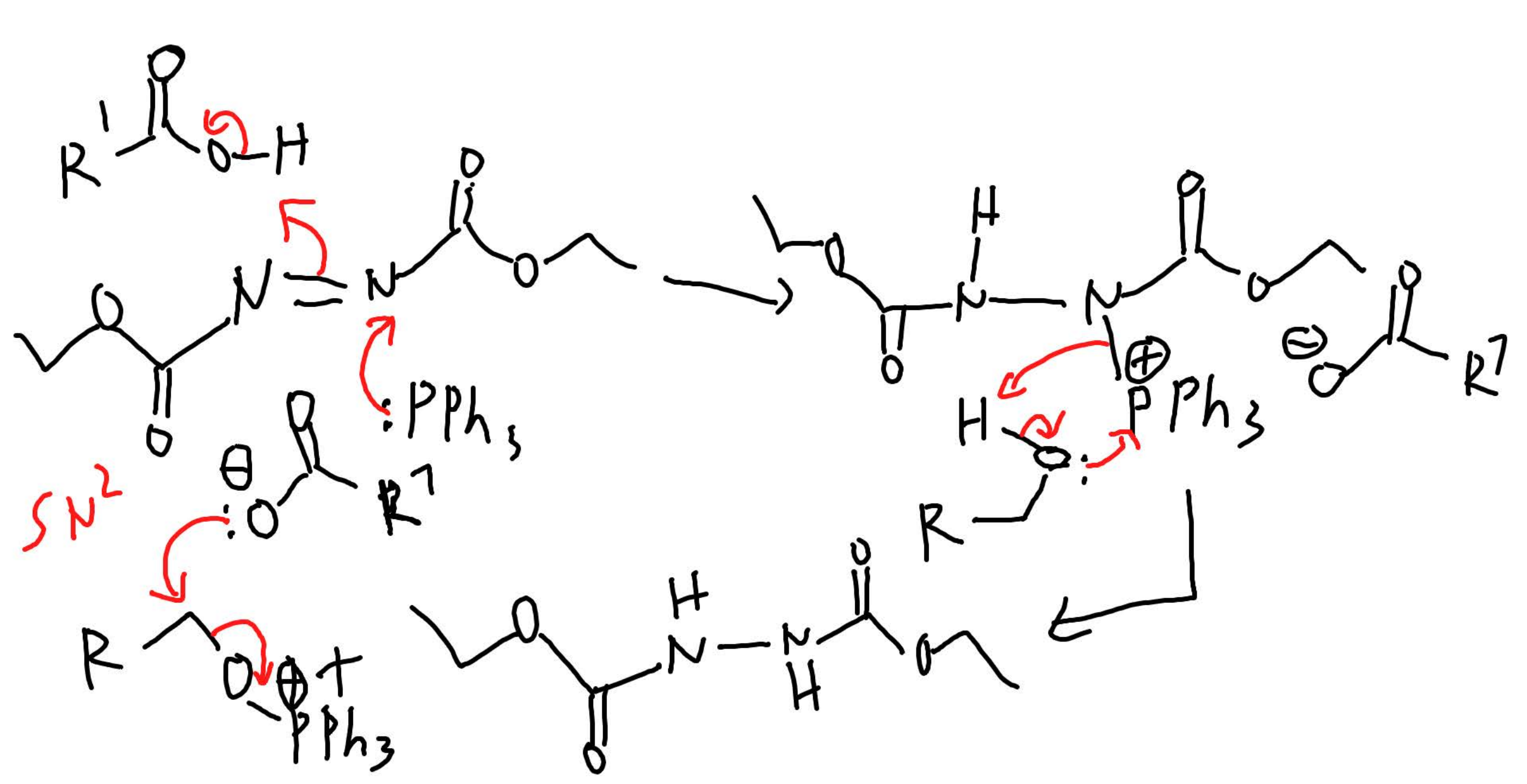
Activation douce des alcools, Mitsunobu

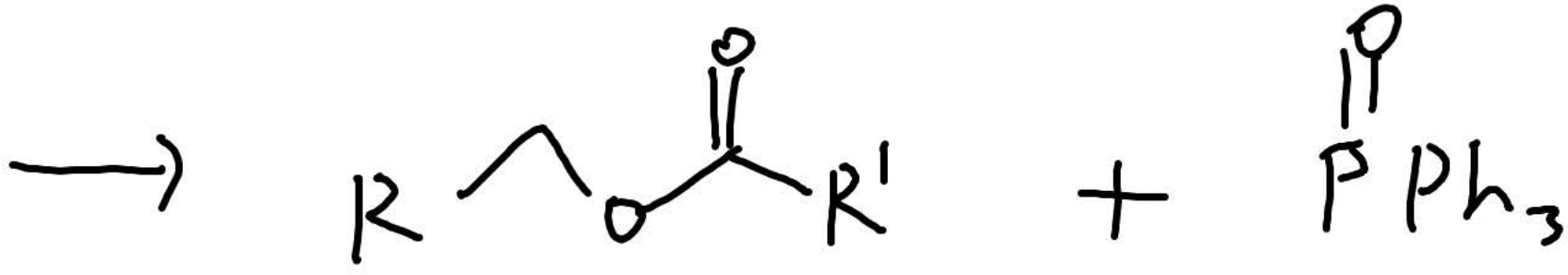


doit contenir un proton
avec PKa < 10



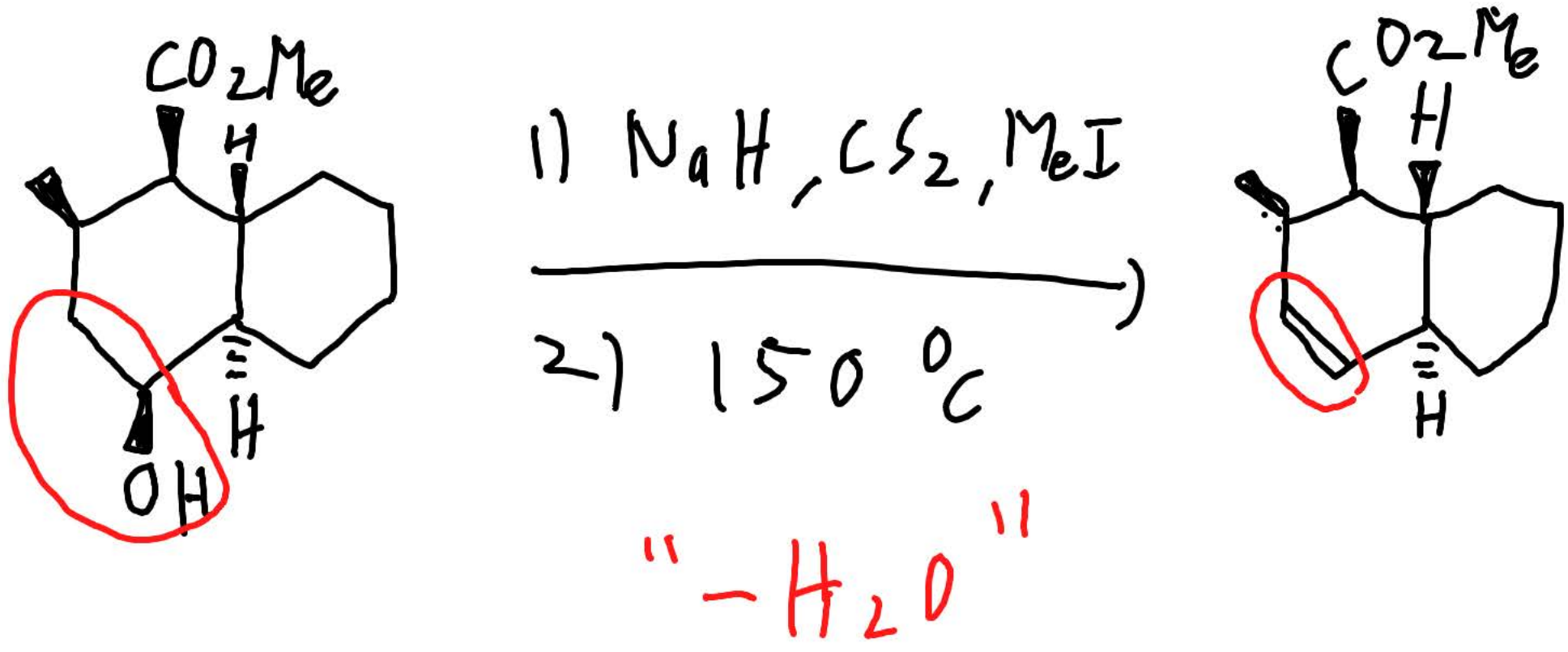



R1
H
N
O
:PPh3
R7
SN2
H
R
PPh3
R7

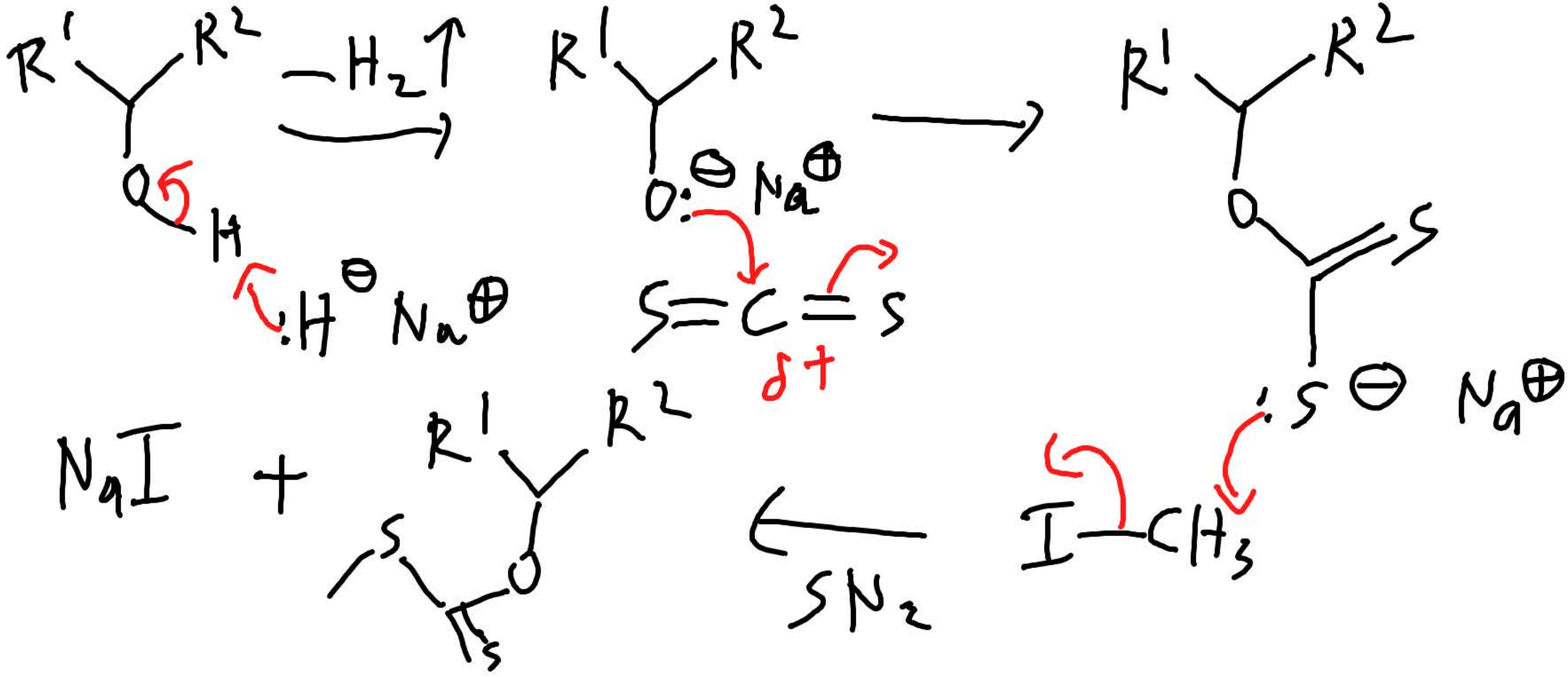


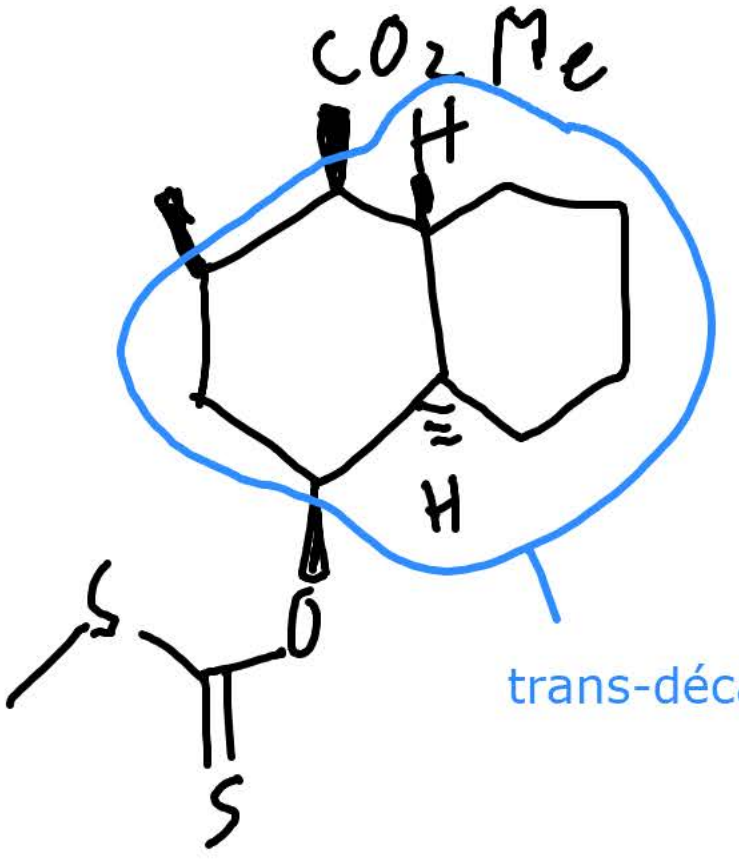
+ réactions très douces, très sélectives pour les alcools
- Beaucoup de déchets sont générés (hydrazine, phosphine oxide)
Réaction utilisée sur les molécules complexes et précieuses uniquement

Réaction d'élimination: Chugaev: application à la synthèse de Solanapyrone E

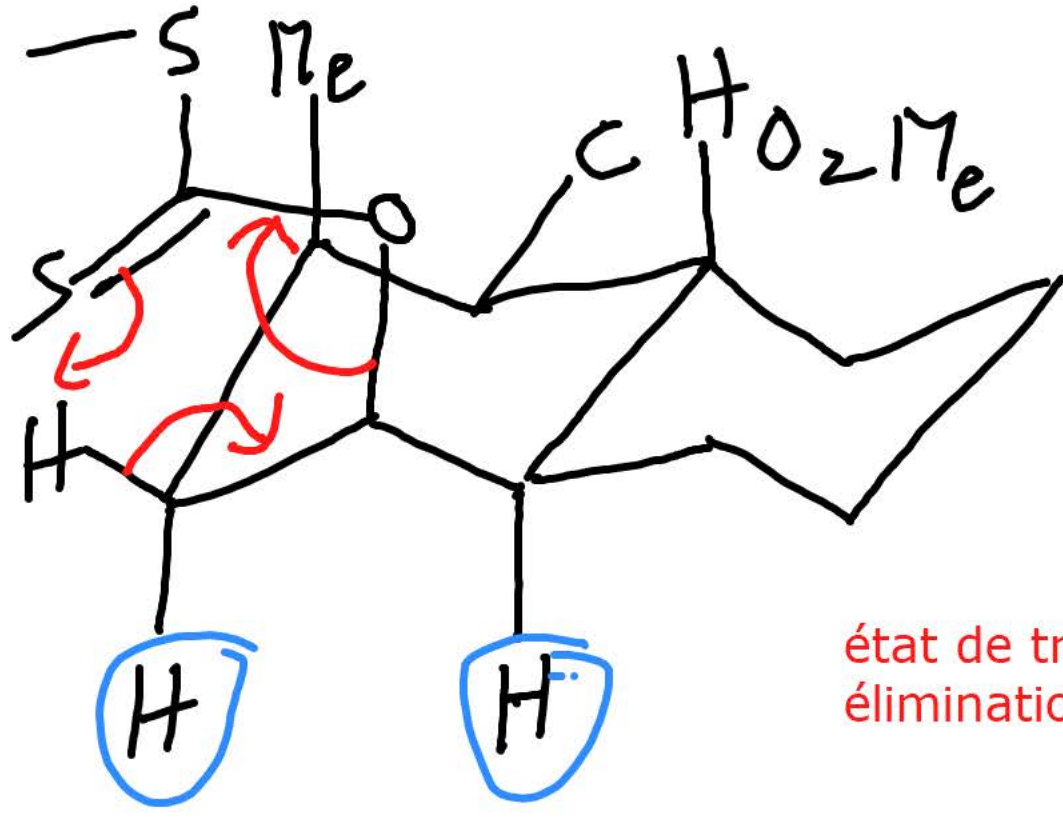


Etape 1: activation



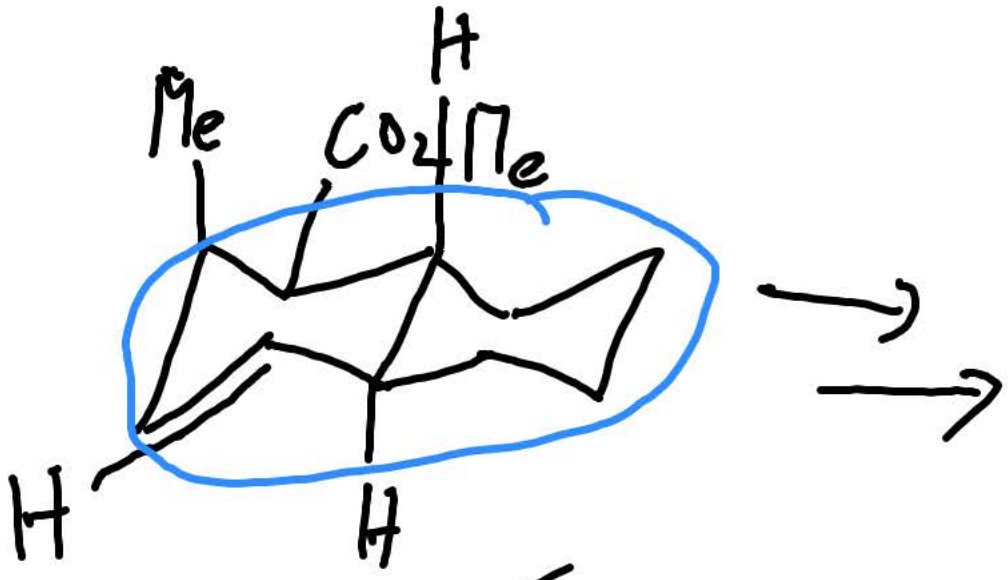


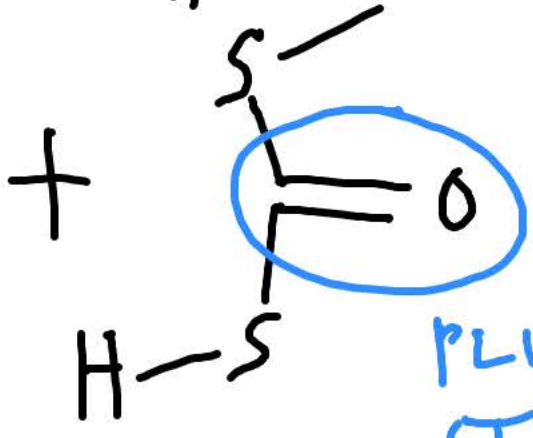
trans-décaline



trop éloignés

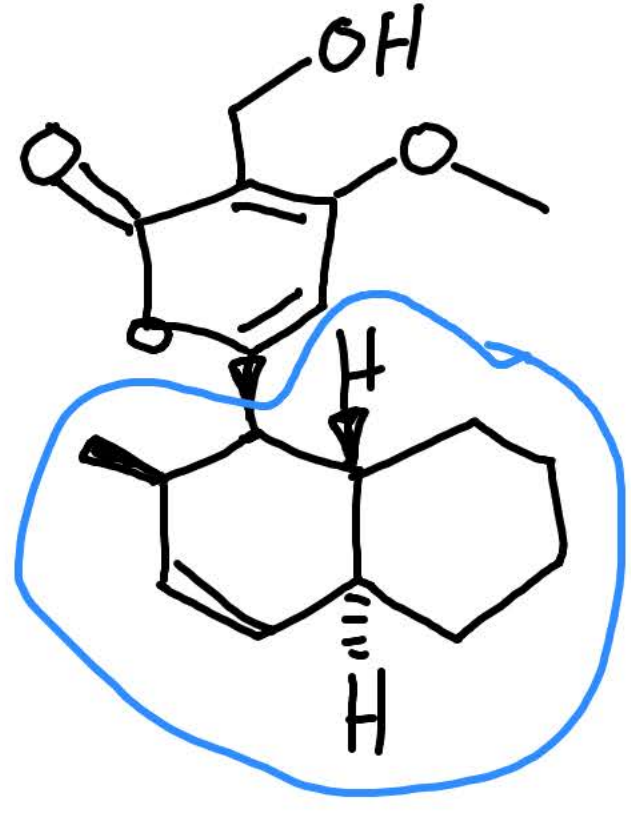
état de transition cyclique
élimination syn.





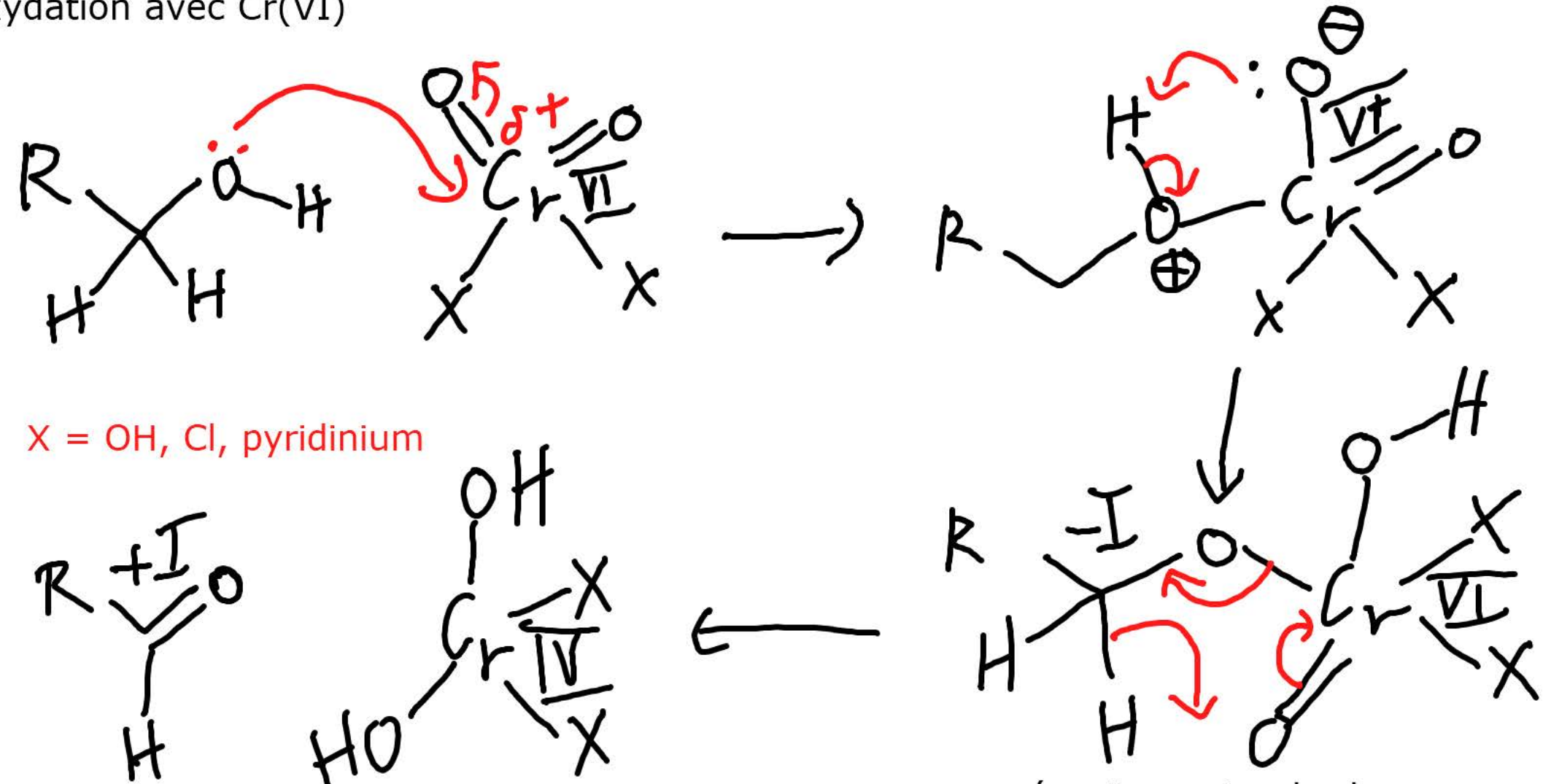
PLUS

STABLE

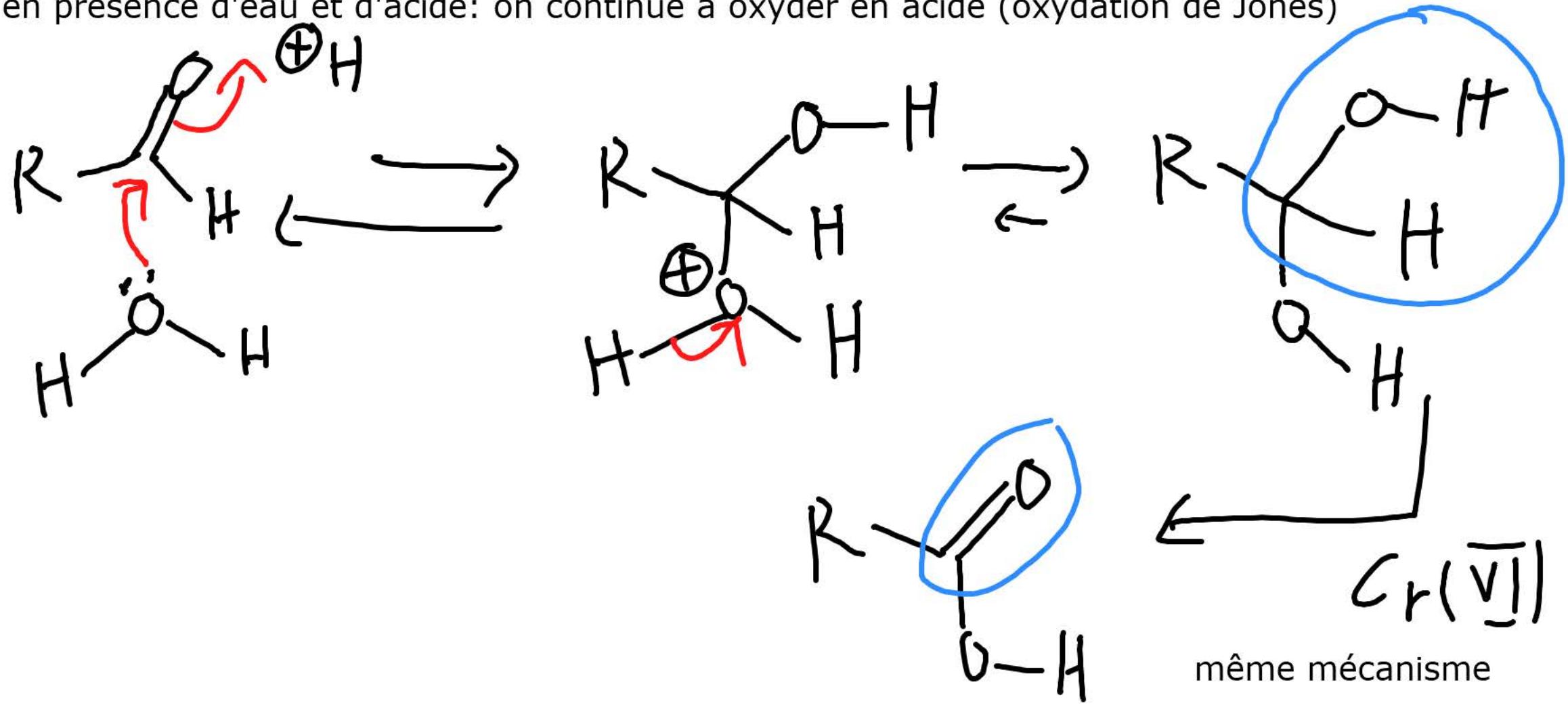


Solanapyrone E

oxydation avec Cr(VI)



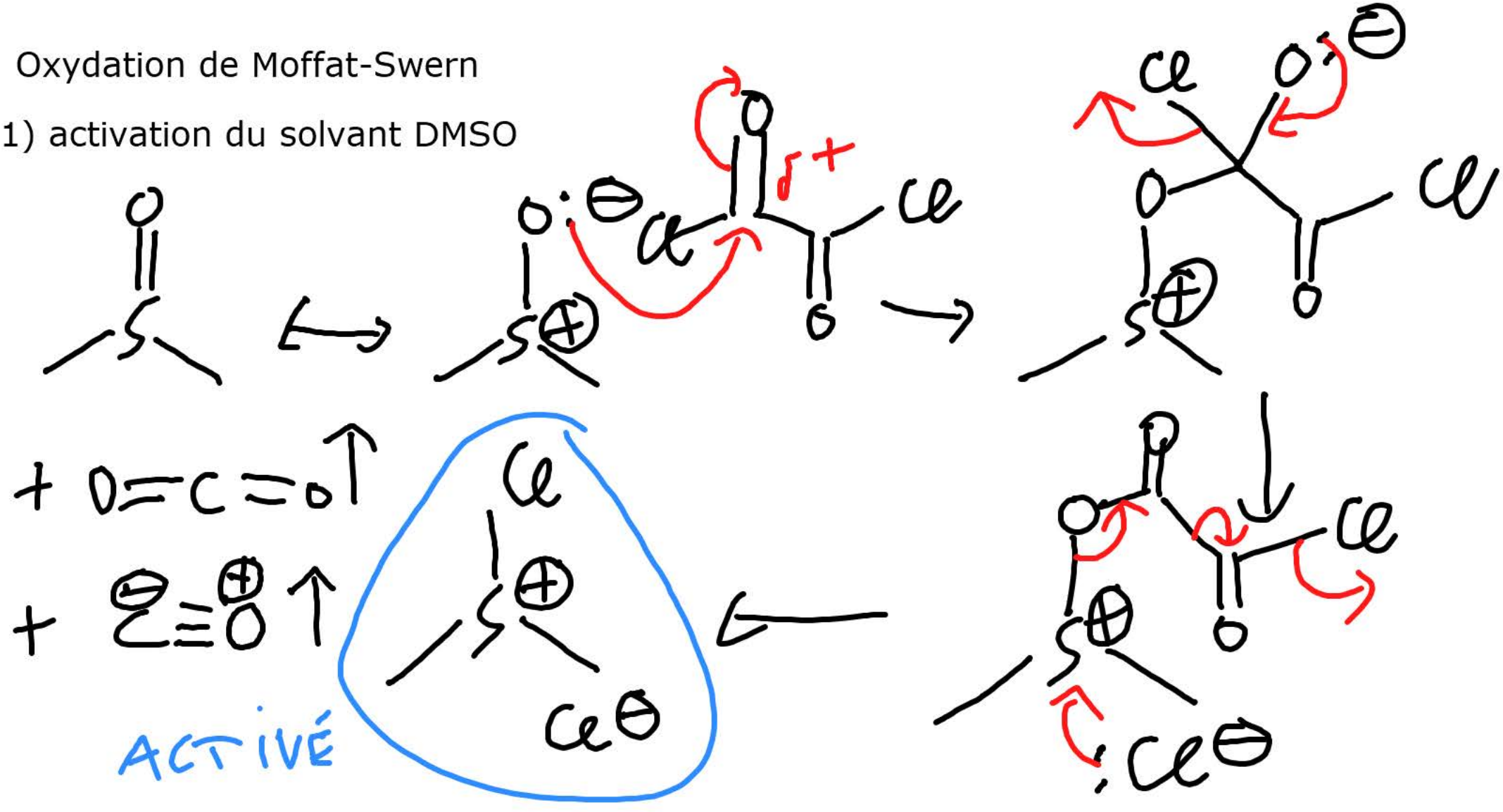
en présence d'eau et d'acide: on continue à oxyder en acide (oxydation de Jones)



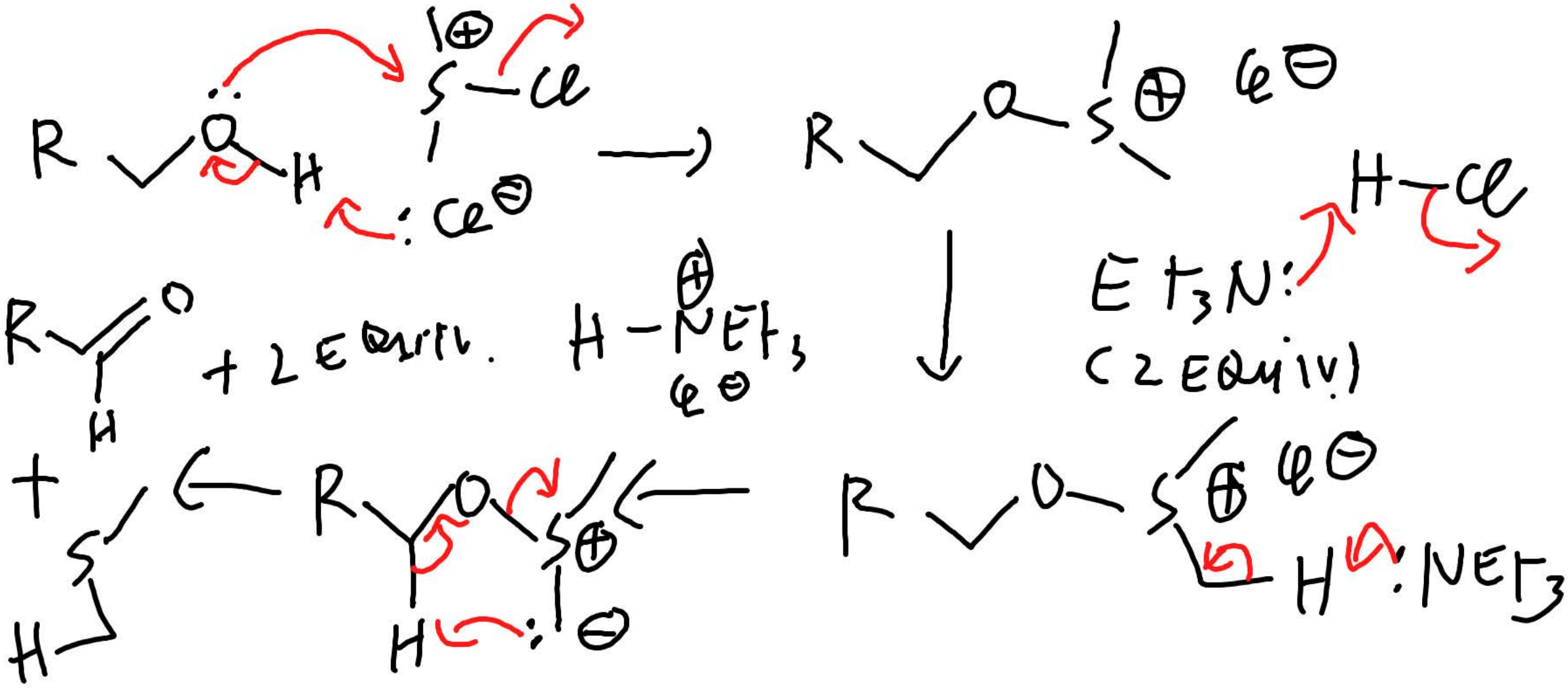
même mécanisme

Oxydation de Moffat-Swern

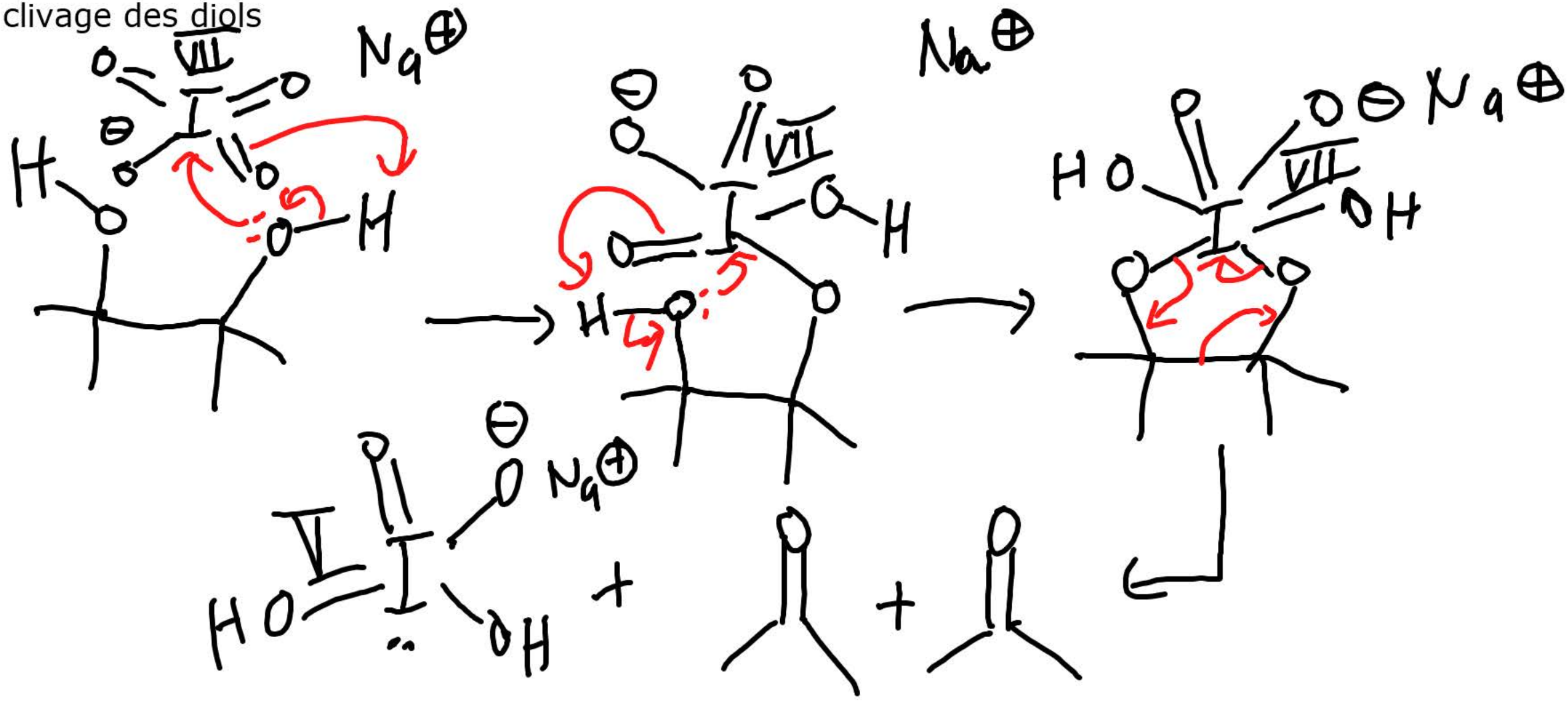
1) activation du solvant DMSO



2) oxydation de l'alcool

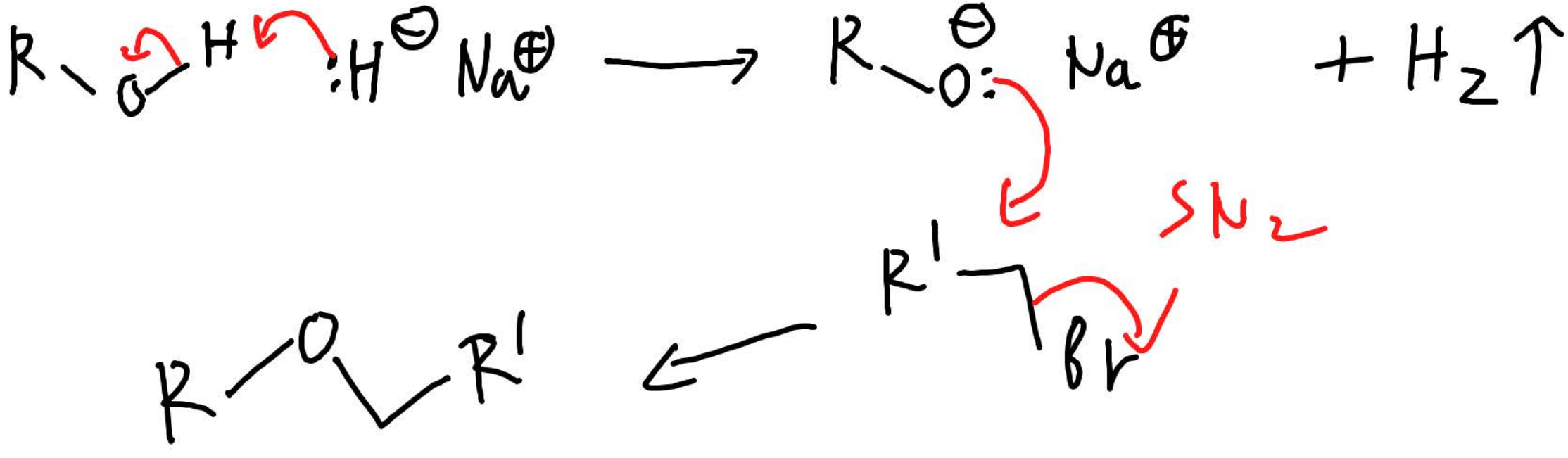


clivage des diols



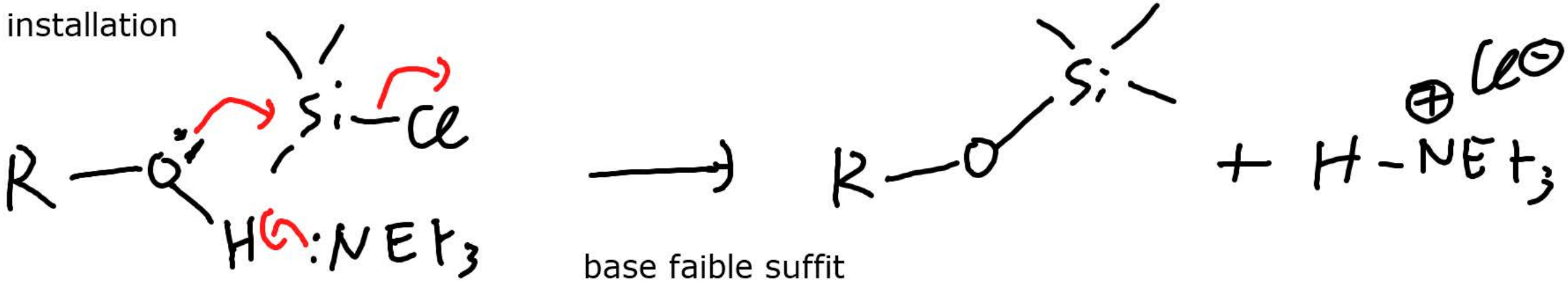
synthèse de Williamson des éthers

Nu et base forte: compétition entre SN et E

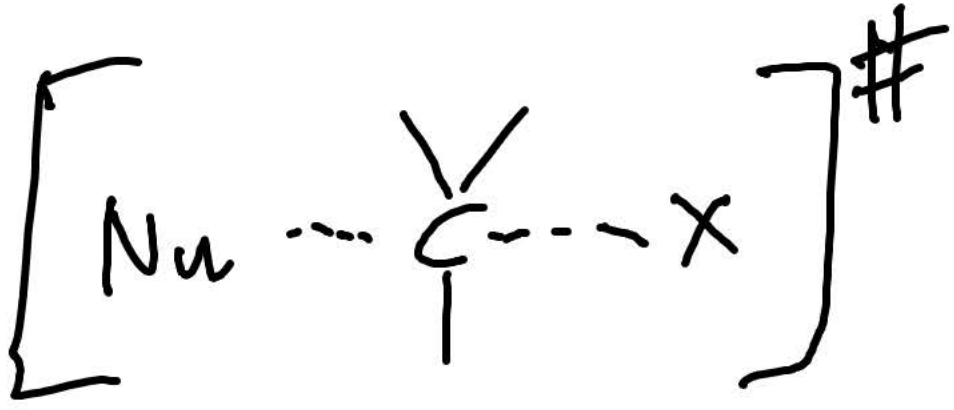


éther de silyl

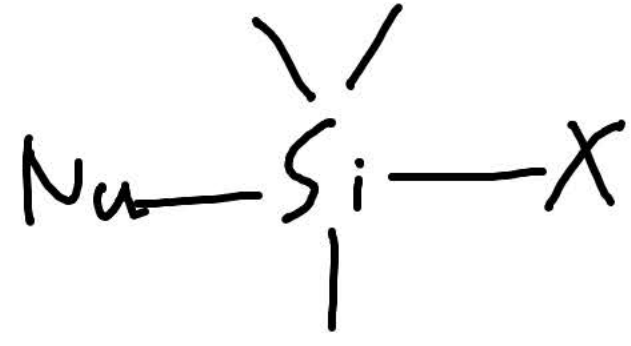
1) installation



base faible suffit

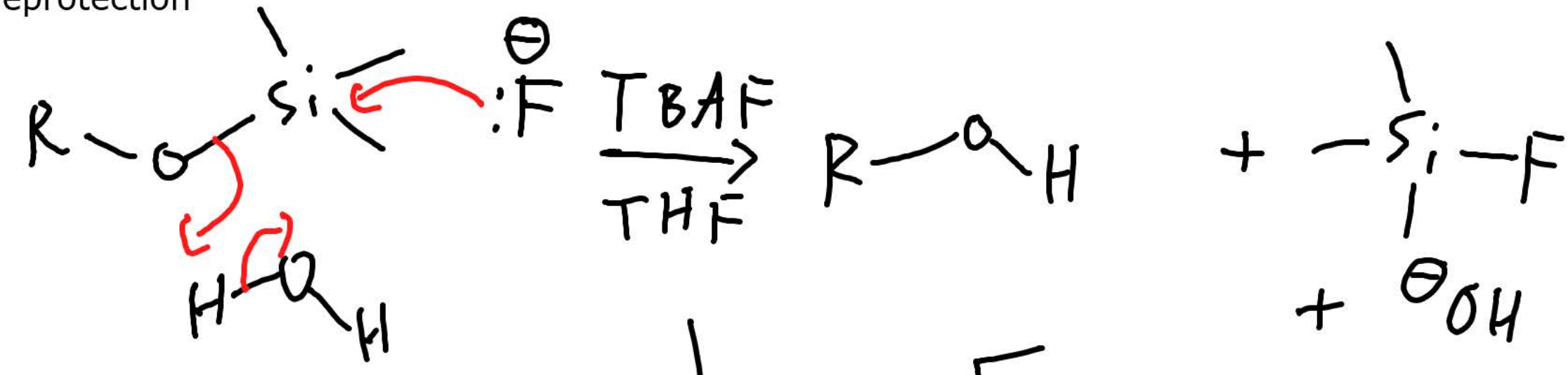


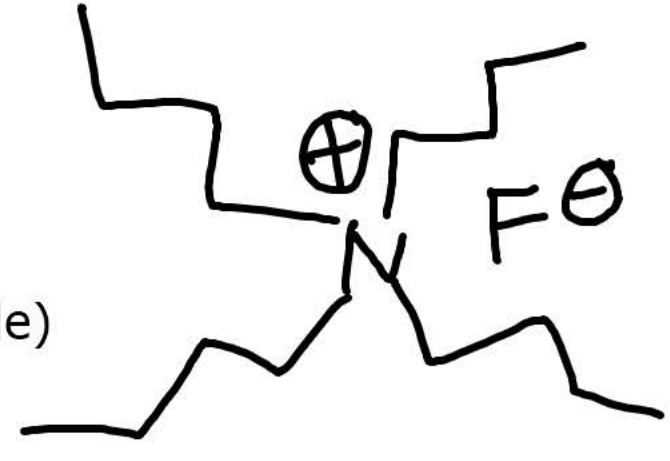
Avec C: état de transition



Avec Si: intermédiaire, Si n'a pas besoin de respecter l'octet

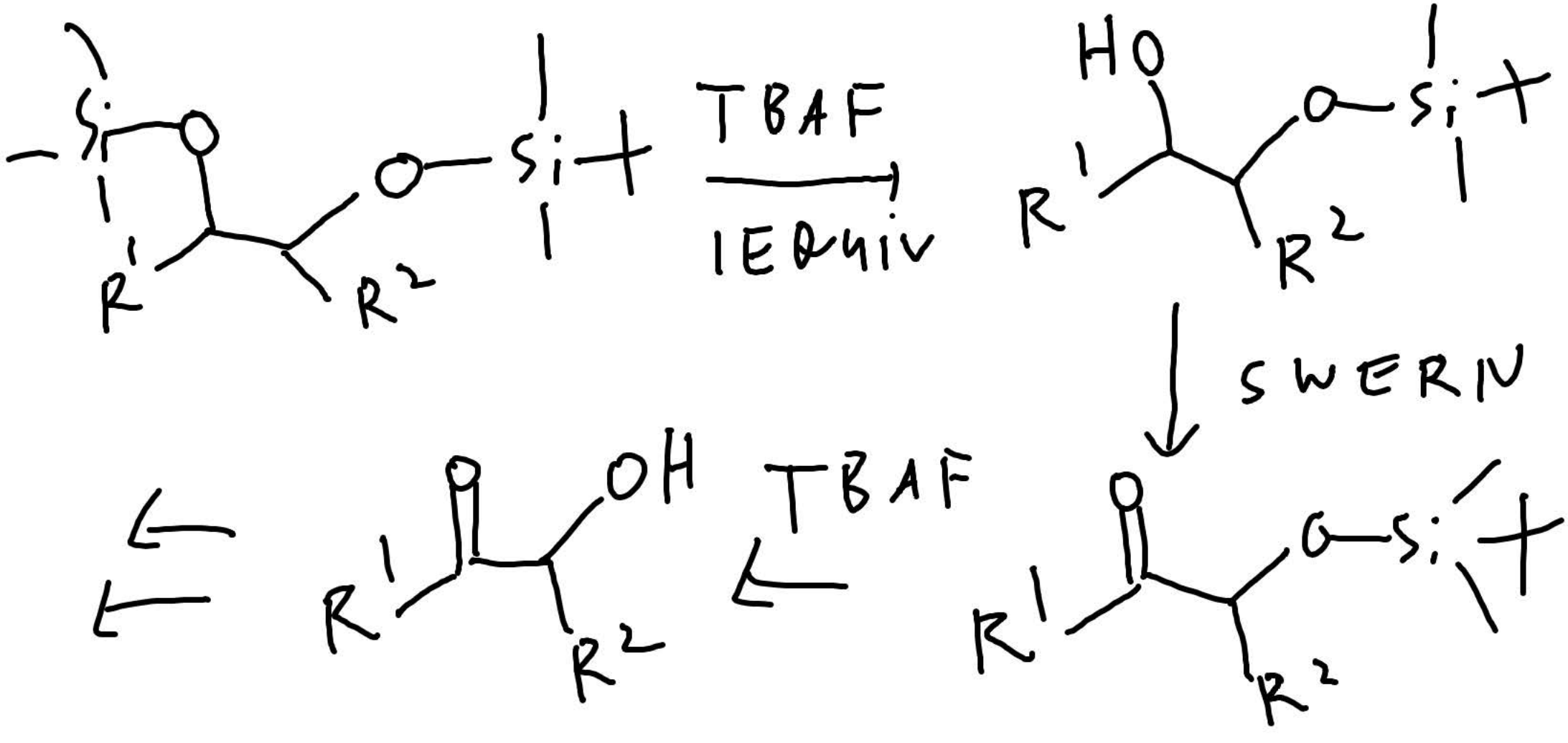
déprotection



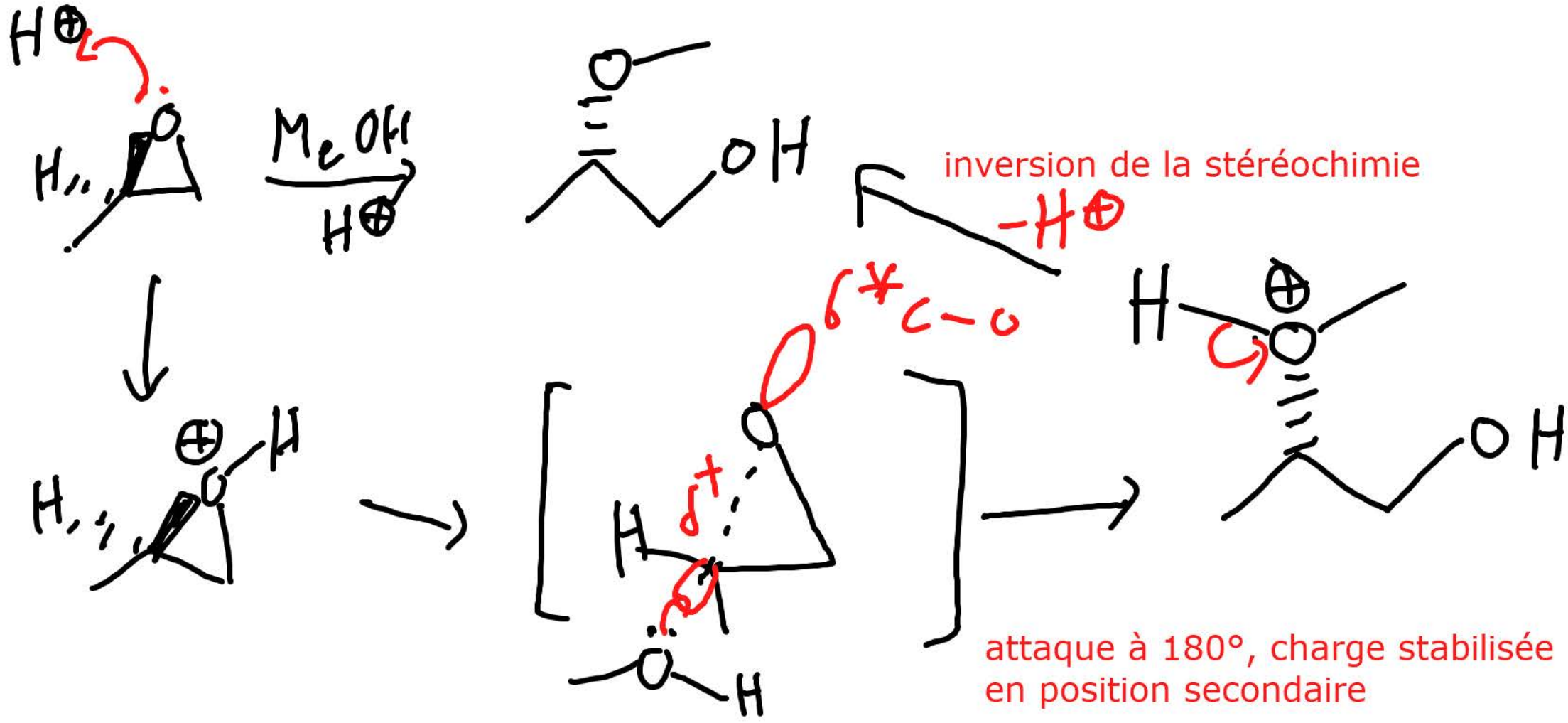


TBAF (tétrabutylammonium fluoride)

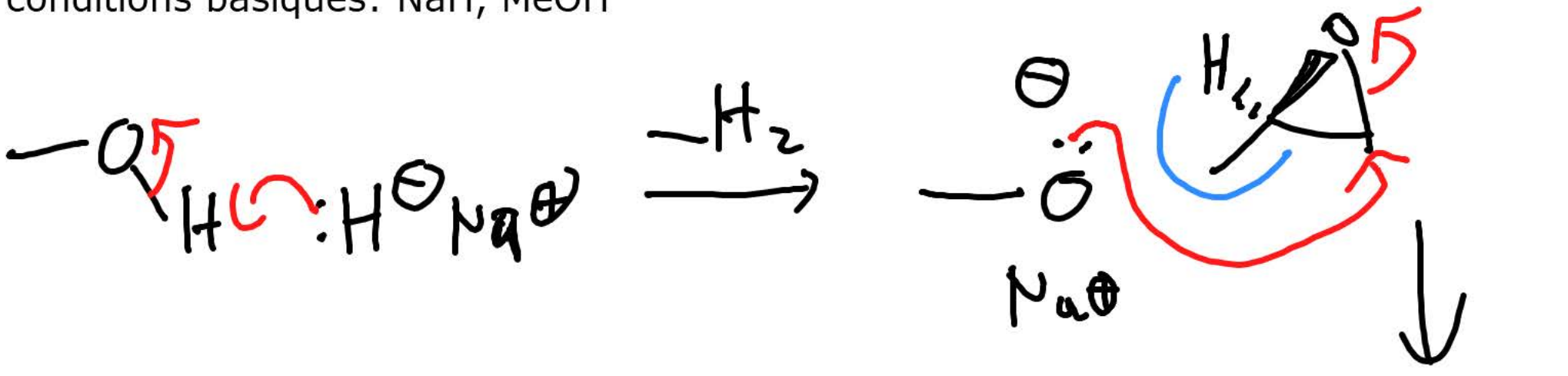
soluble dans les solvants organiques


TBAF
1EQUIV
SWERN
TBAF

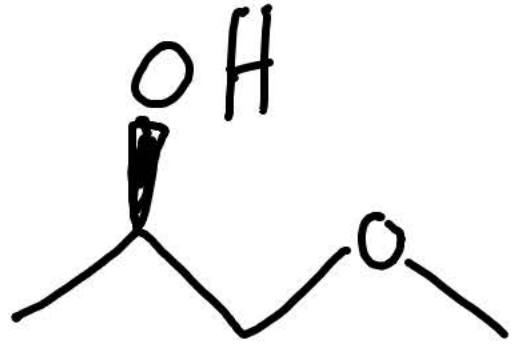
Ouvertures des époxides: 1) conditions acides

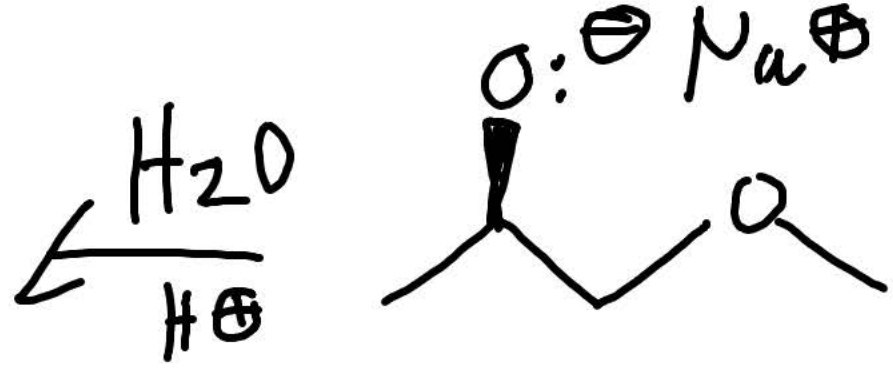


2) conditions basiques: NaH, MeOH



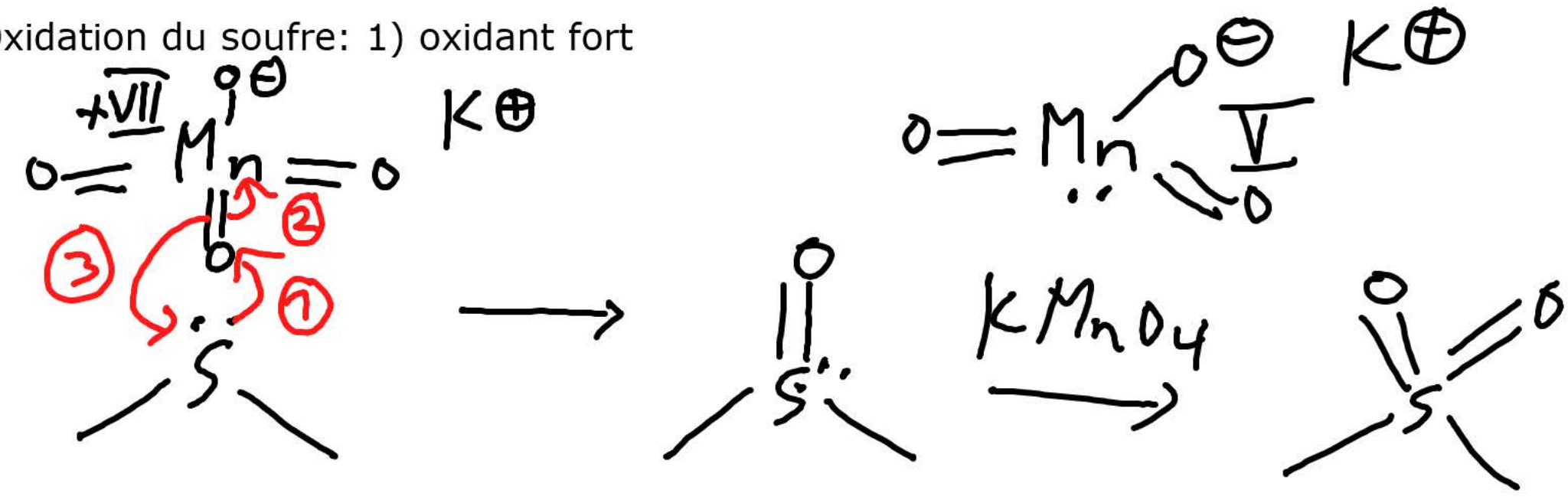
rétention de la stéréochimie





work-up

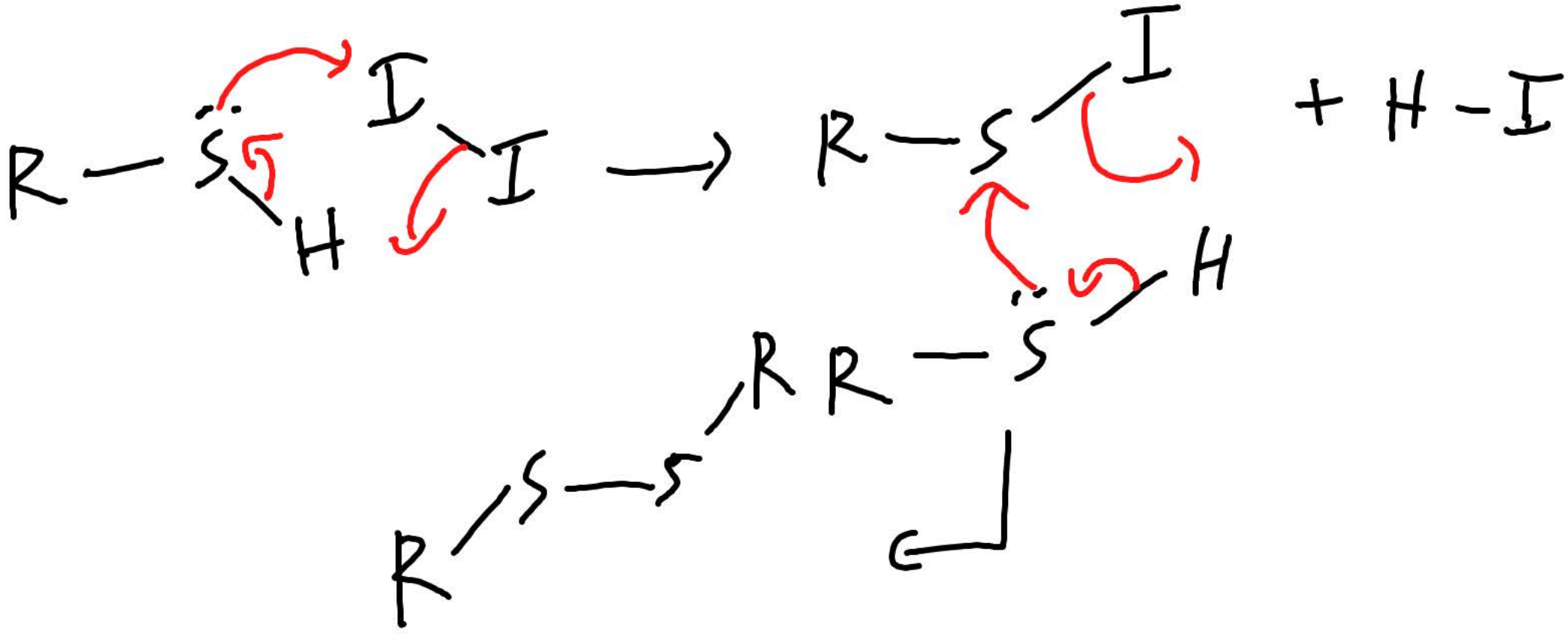
Oxidation du soufre: 1) oxidant fort



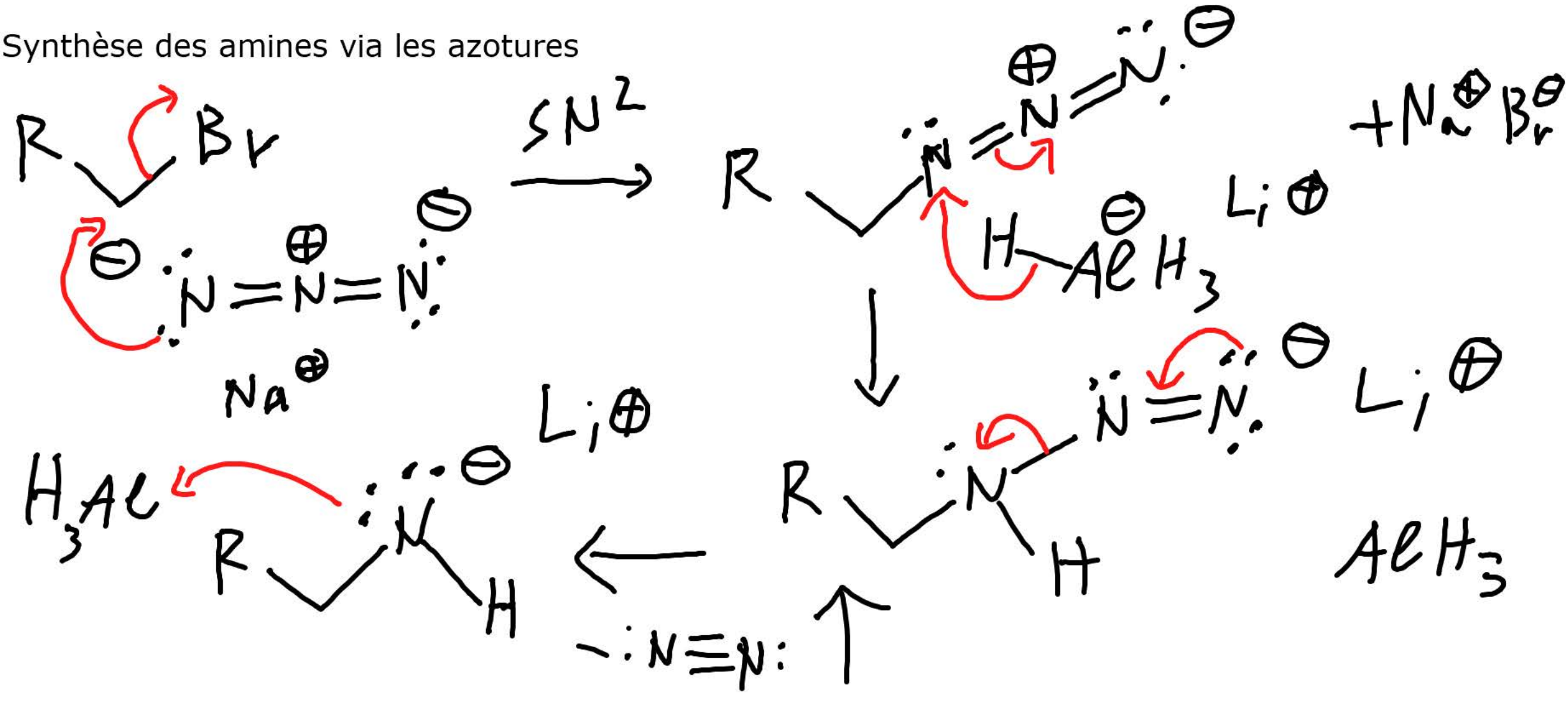
même mécanisme

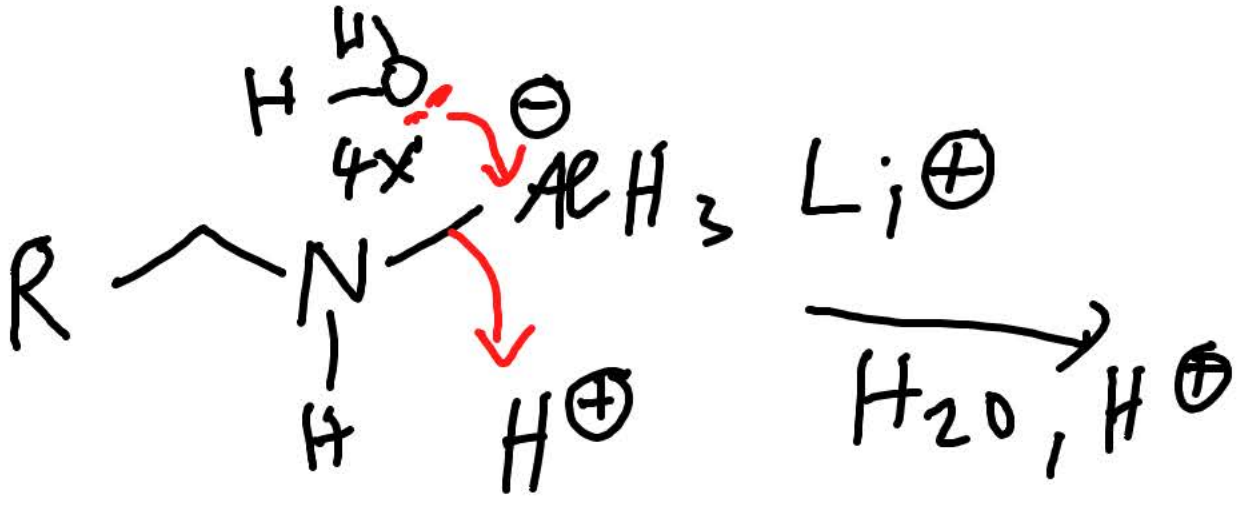
permanganate: KMnO4

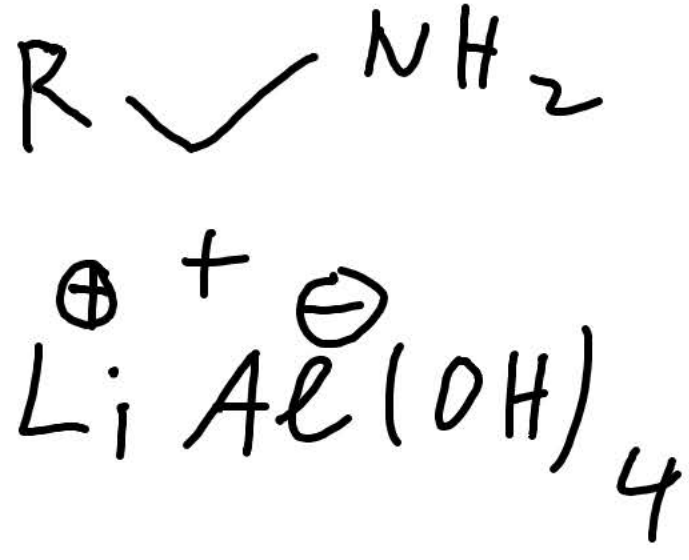
oxydation des thiols avec l'iode



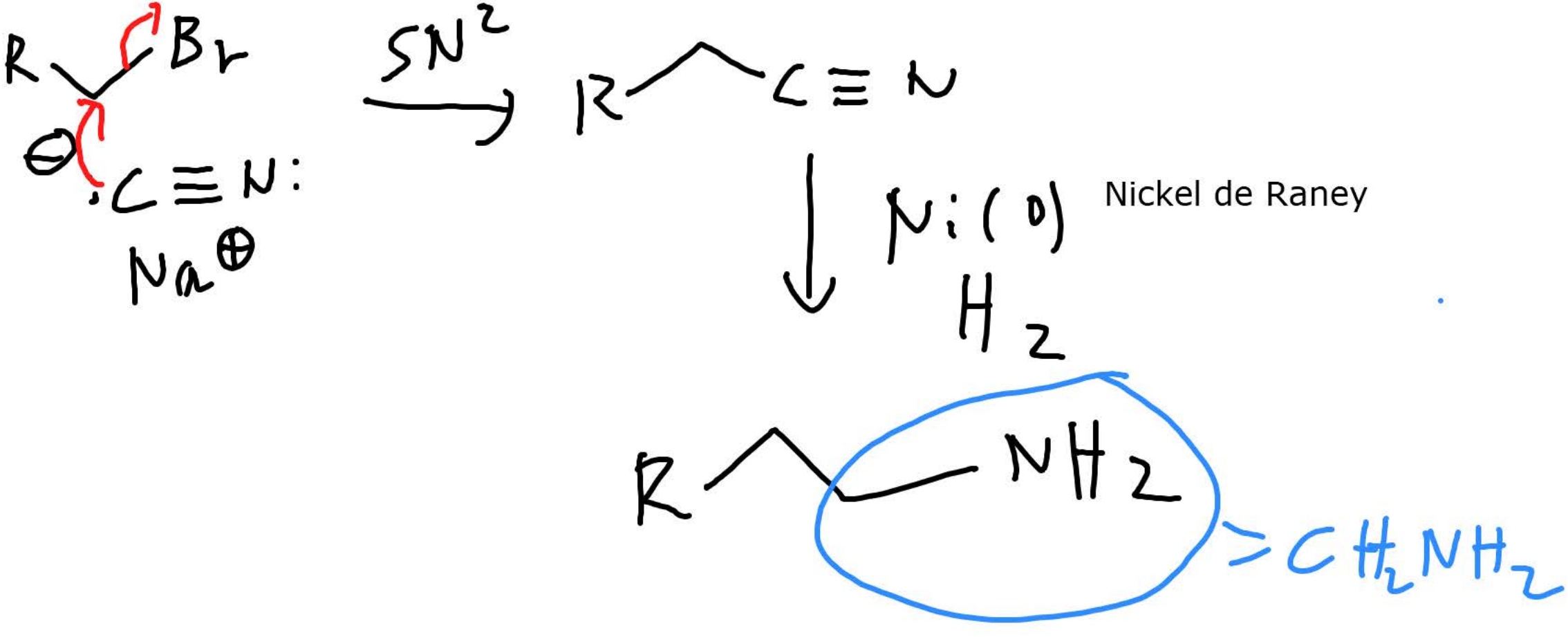
Synthèse des amines via les azotures



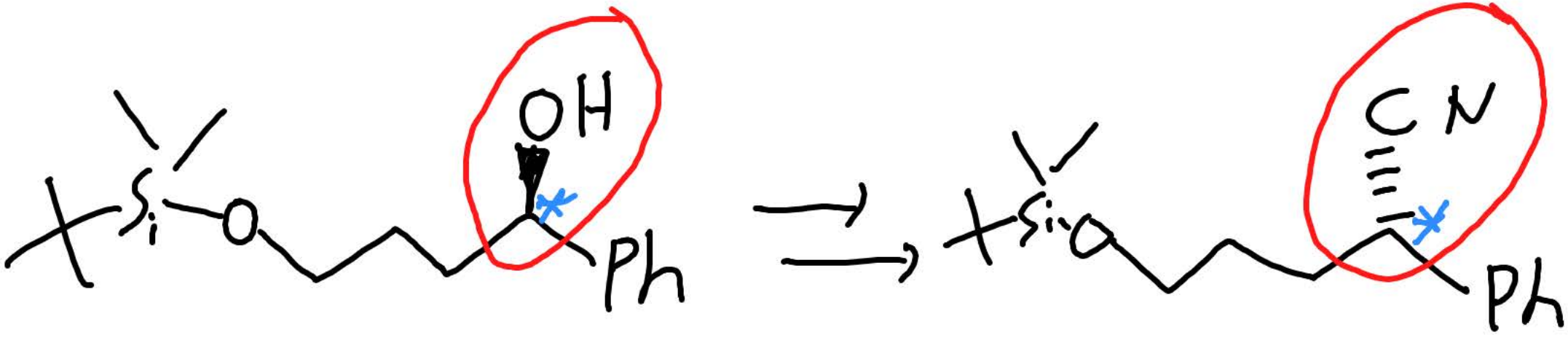

H
4x
AlH3
Li⊕
R
N
H
H⊕
H20, H⊕


R
NH2
⊕ + ⊖
LiAl(OH)4

en utilisant les cyanures



examen 2022, 4.A



OH est "remplacé" par CN

stéréochimie est inversée!

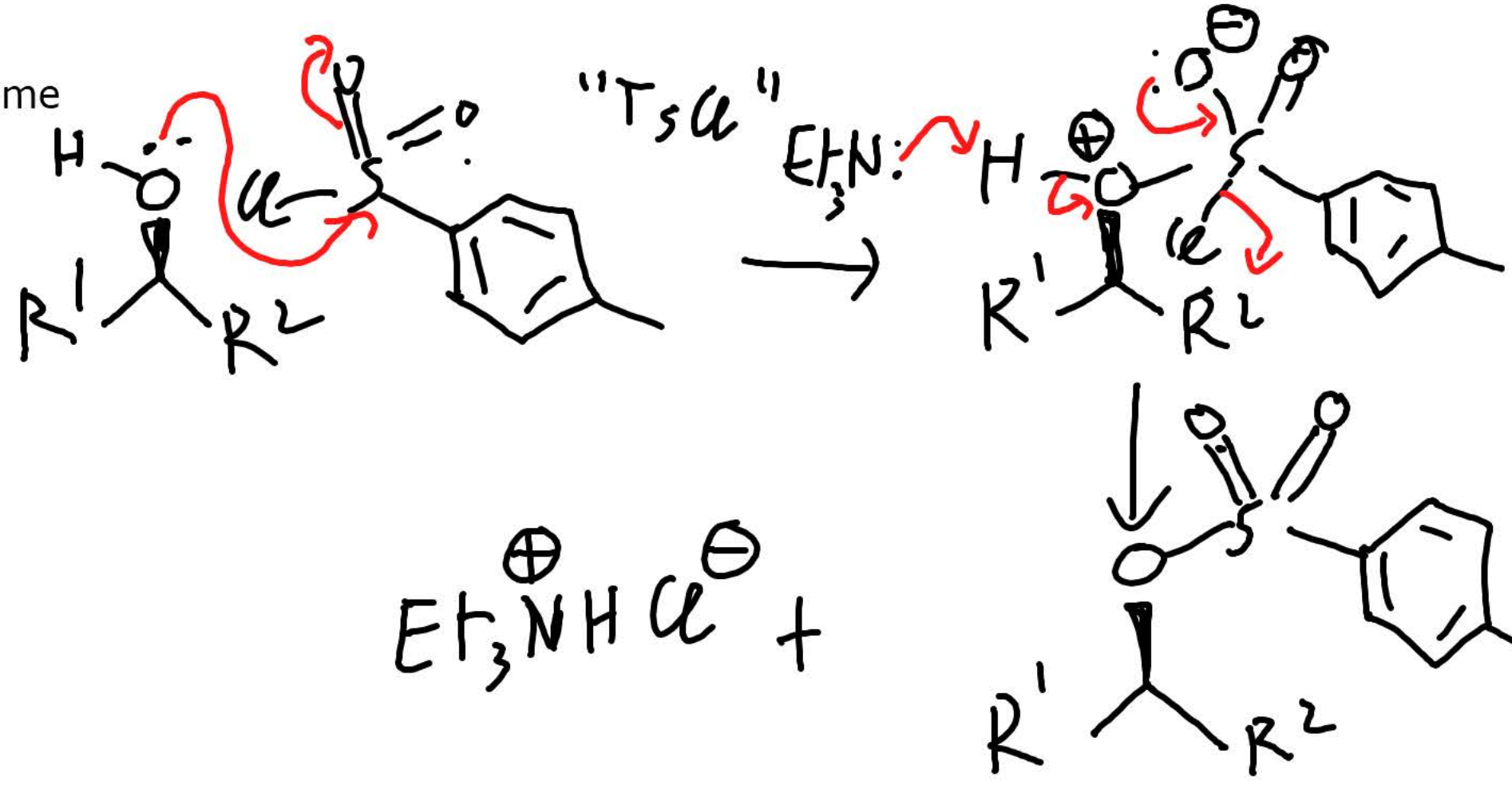
On doit faire une réaction SN2

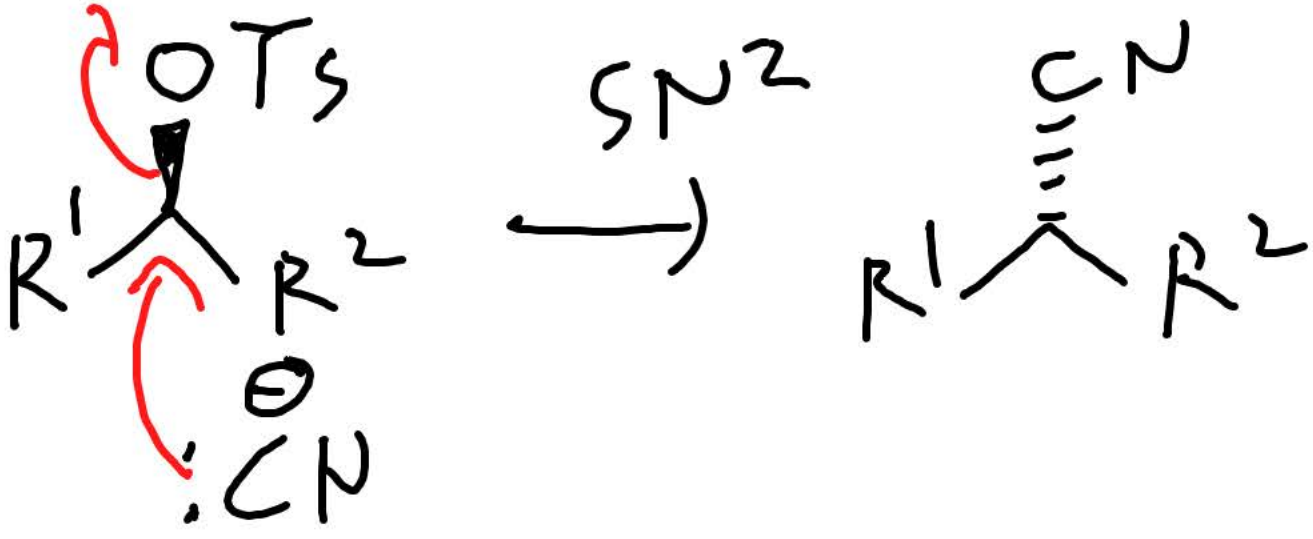
On devra utiliser une activation douce` !

1) $TsCl$, NEt_3

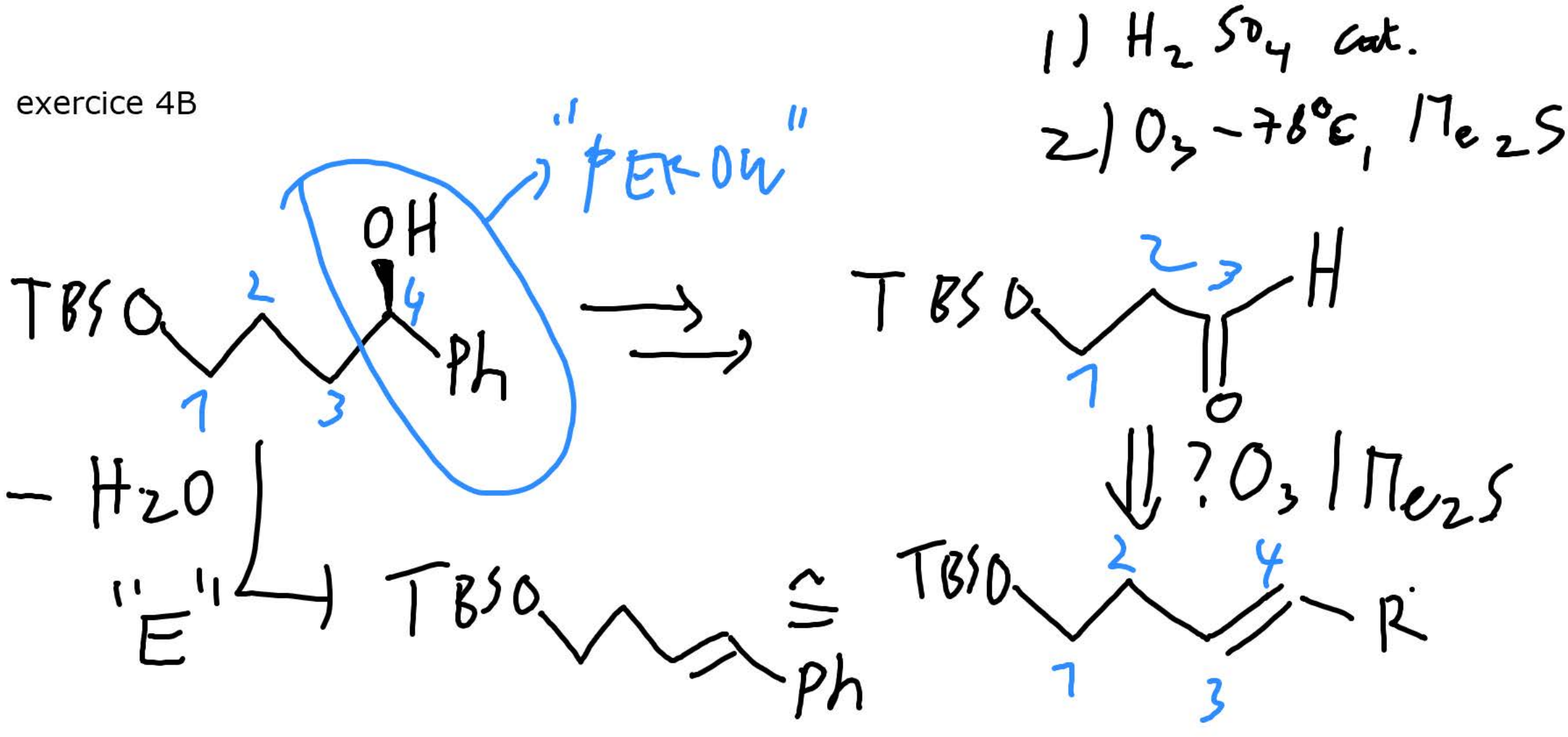
2) $NaCN$, DMSO S_N2

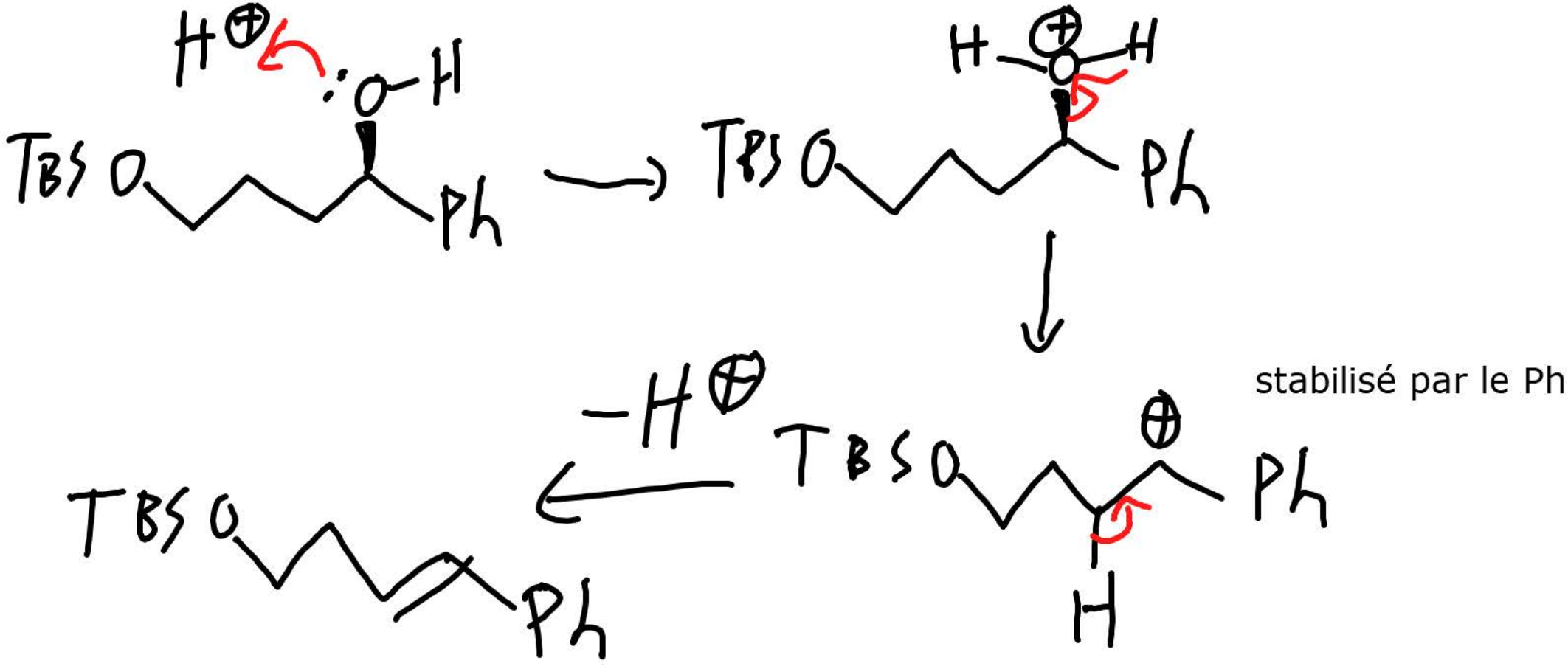
mécanisme

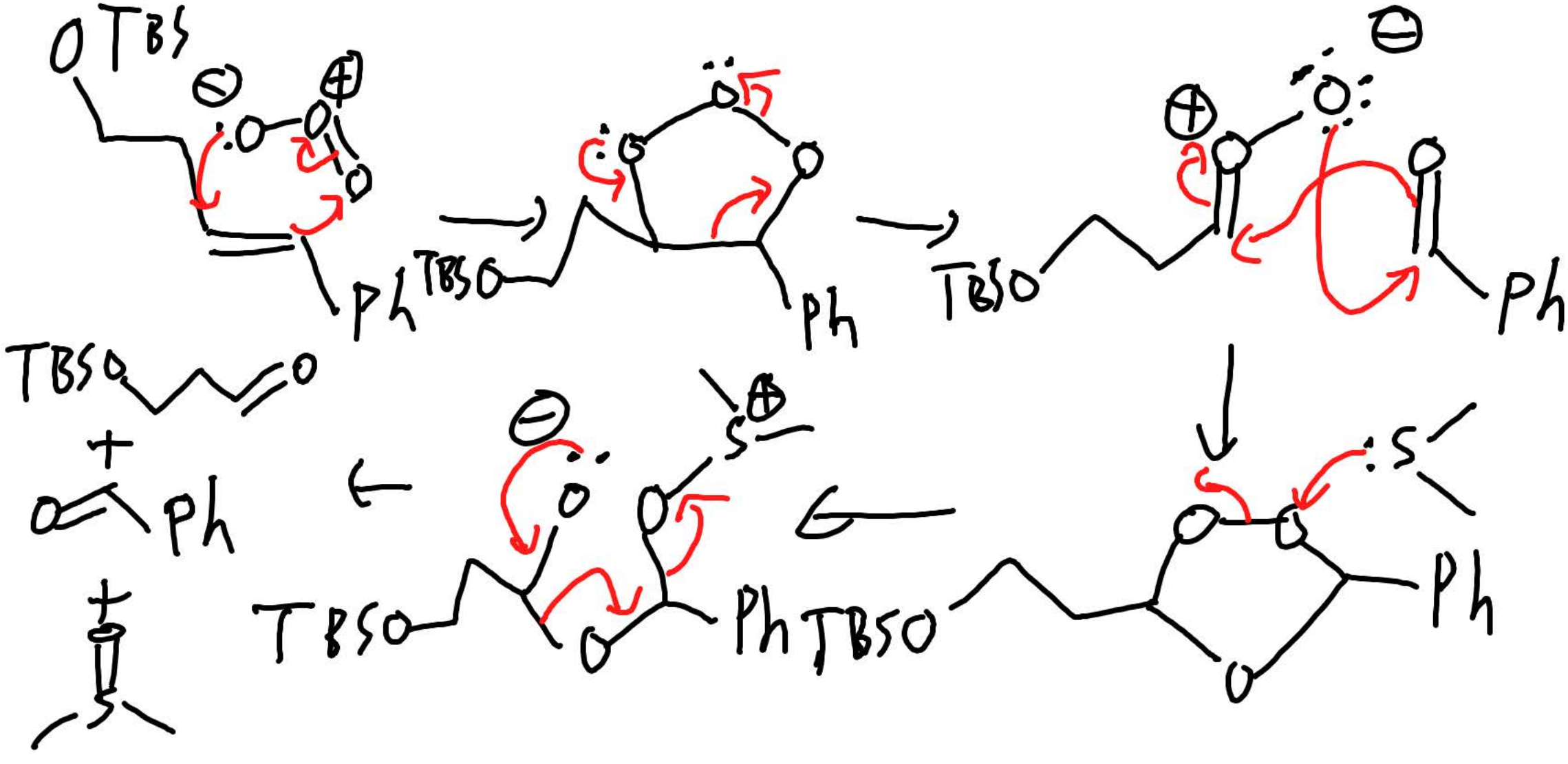



OTs
R1
R2
⊖
:CN
SN2
CN
R1
R2

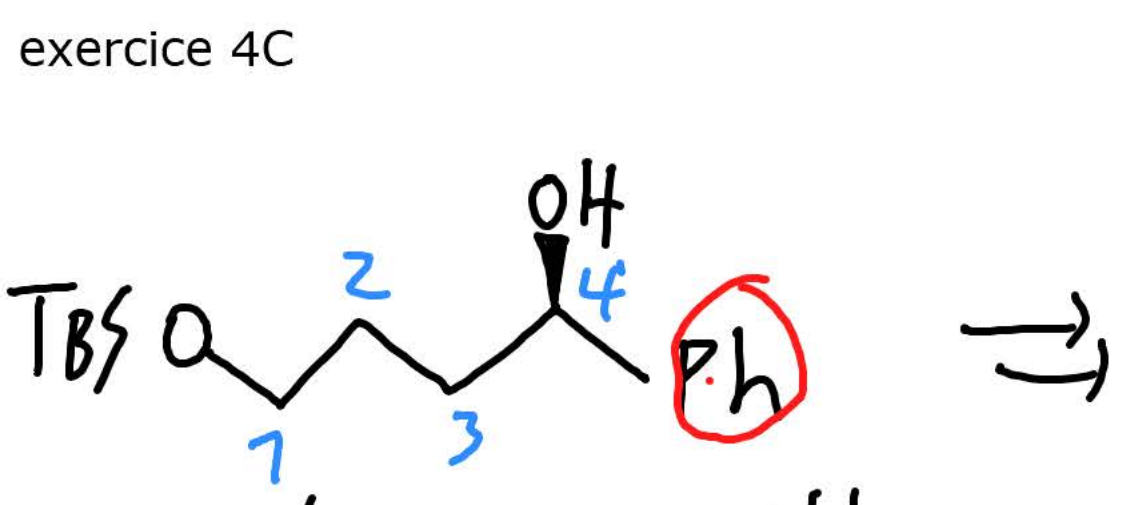
exercice 4B


1) H_2SO_4 cat.
2) O_3 -78°C, Me_2S
"PEROX"
OH
TBSO
Ph
- H_2O
"E"
TBSO
Ph
TBSO
H
?O_3 | Me_2S
TBSO
R

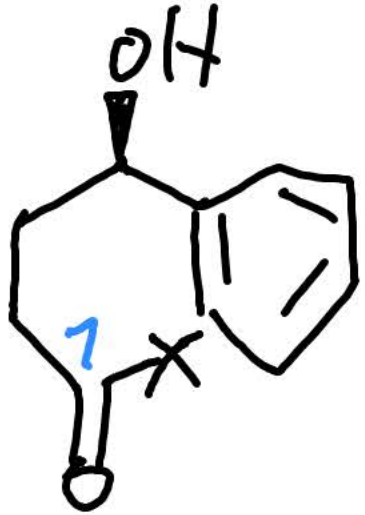

TBS O
Ph
TBS O
Ph
TBS O
Ph
TBS O
Ph
stabilisé par le Ph


TBSO
Ph
TBSO
Ph
TBSO
Ph
TBSO
Ph
TBSO
Ph
TBSO
Ph
S
S

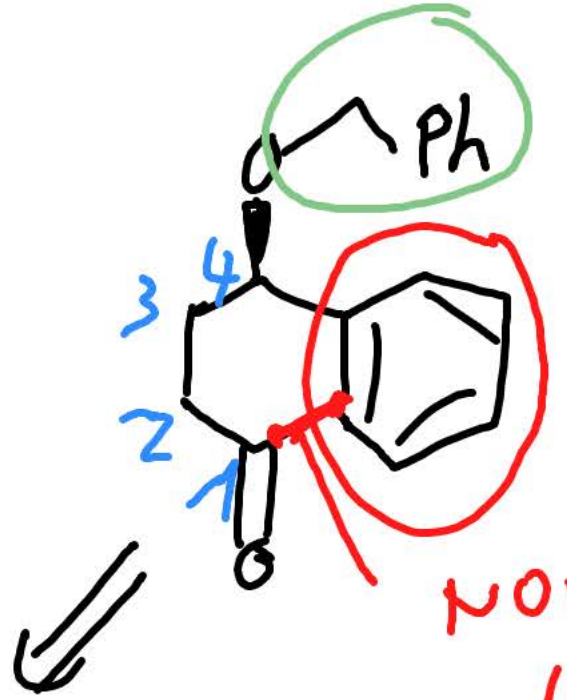
exercice 4C



1) déprotéger



2) oxider alcool en acide



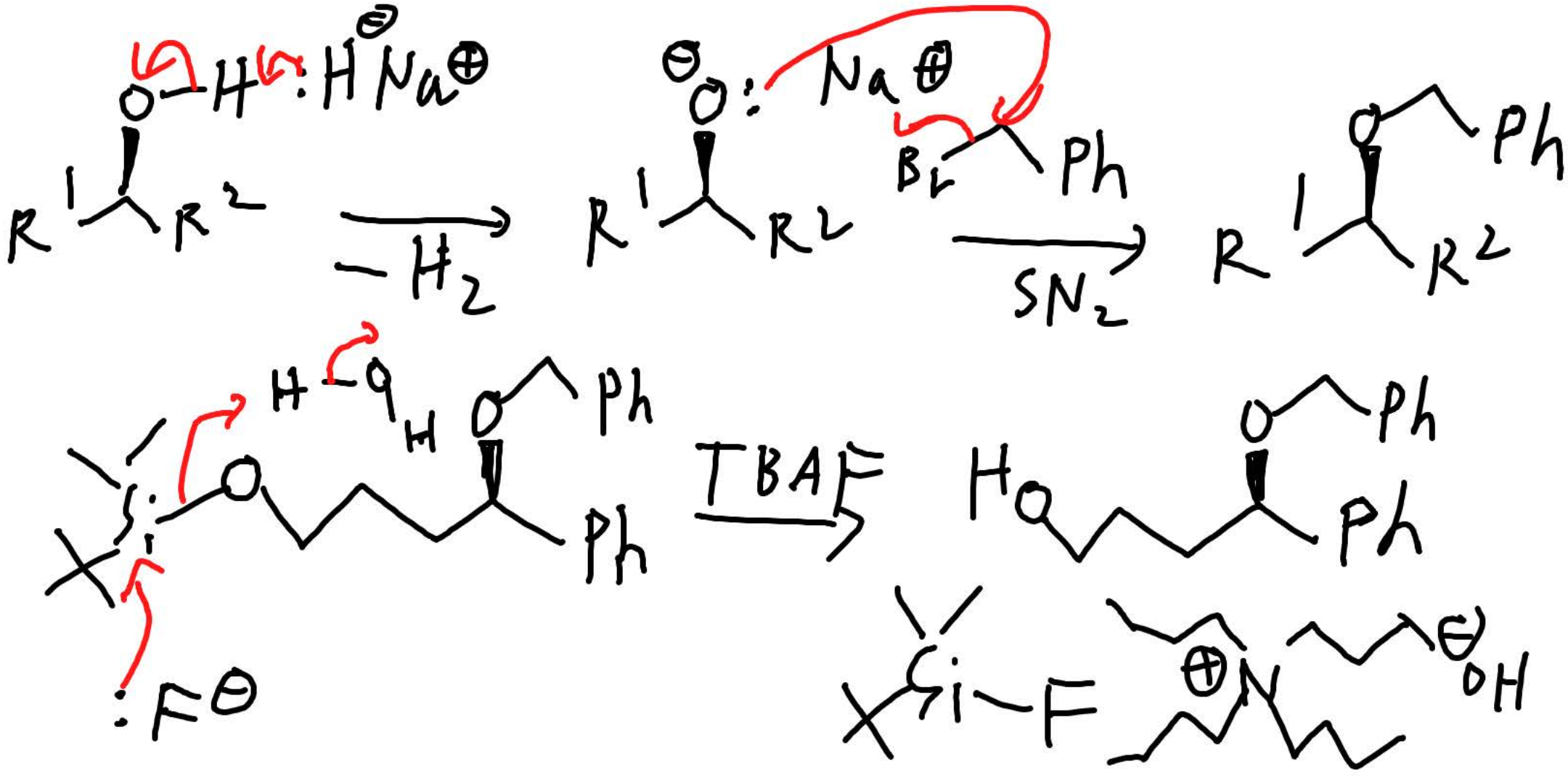
AJOUTER

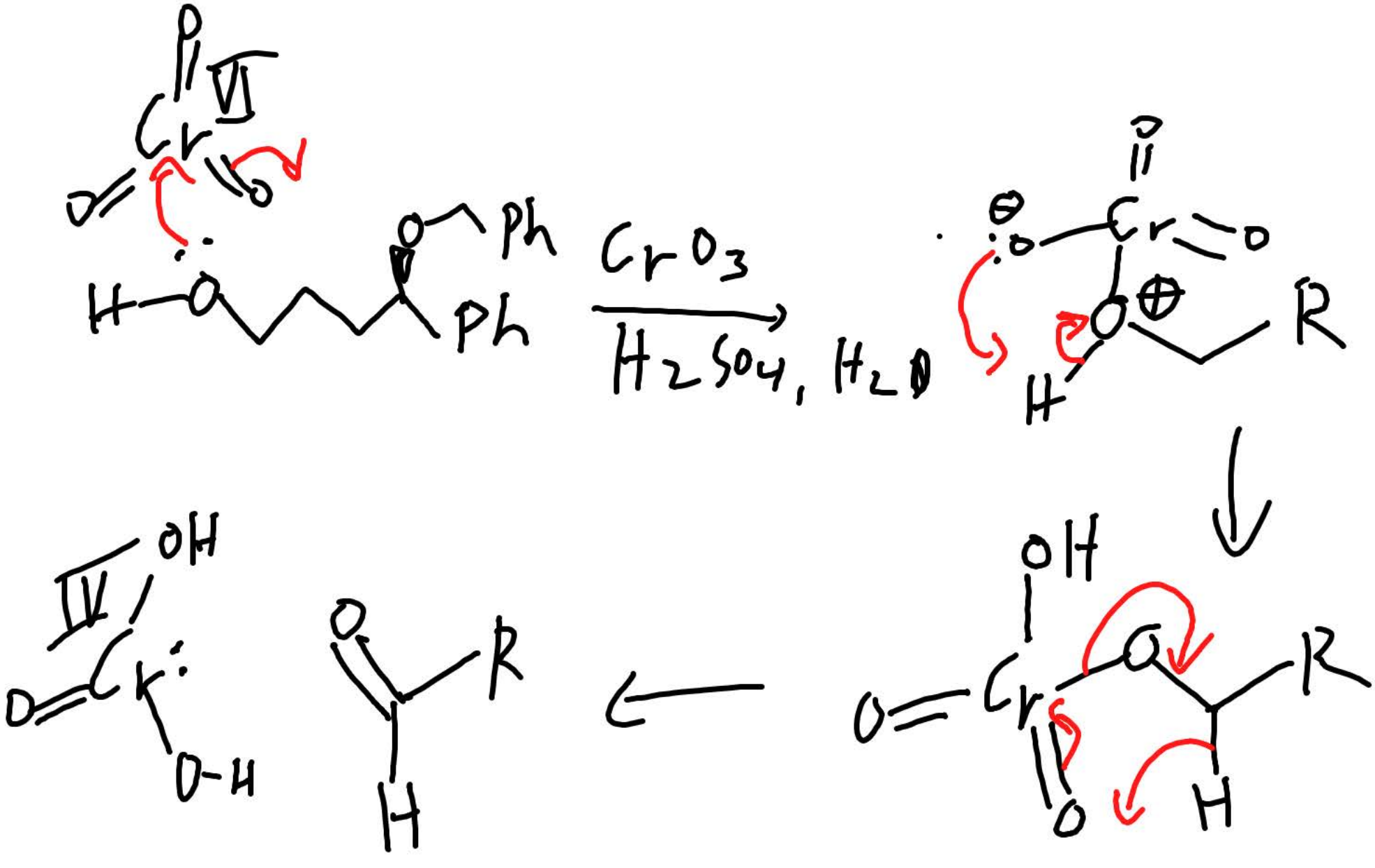
formation d'un éther
substitution/Williamson?

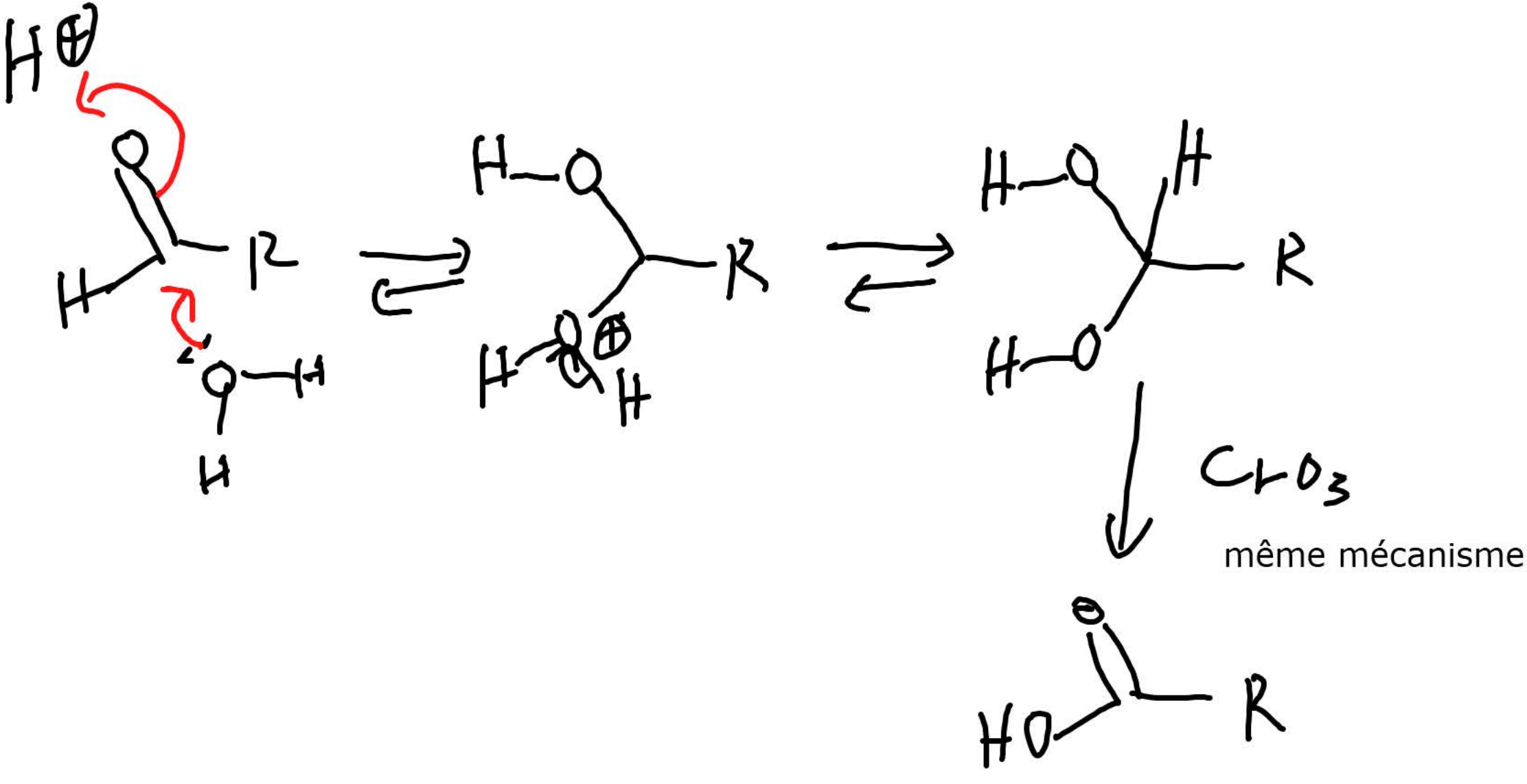
NOUVELLE LIAISON

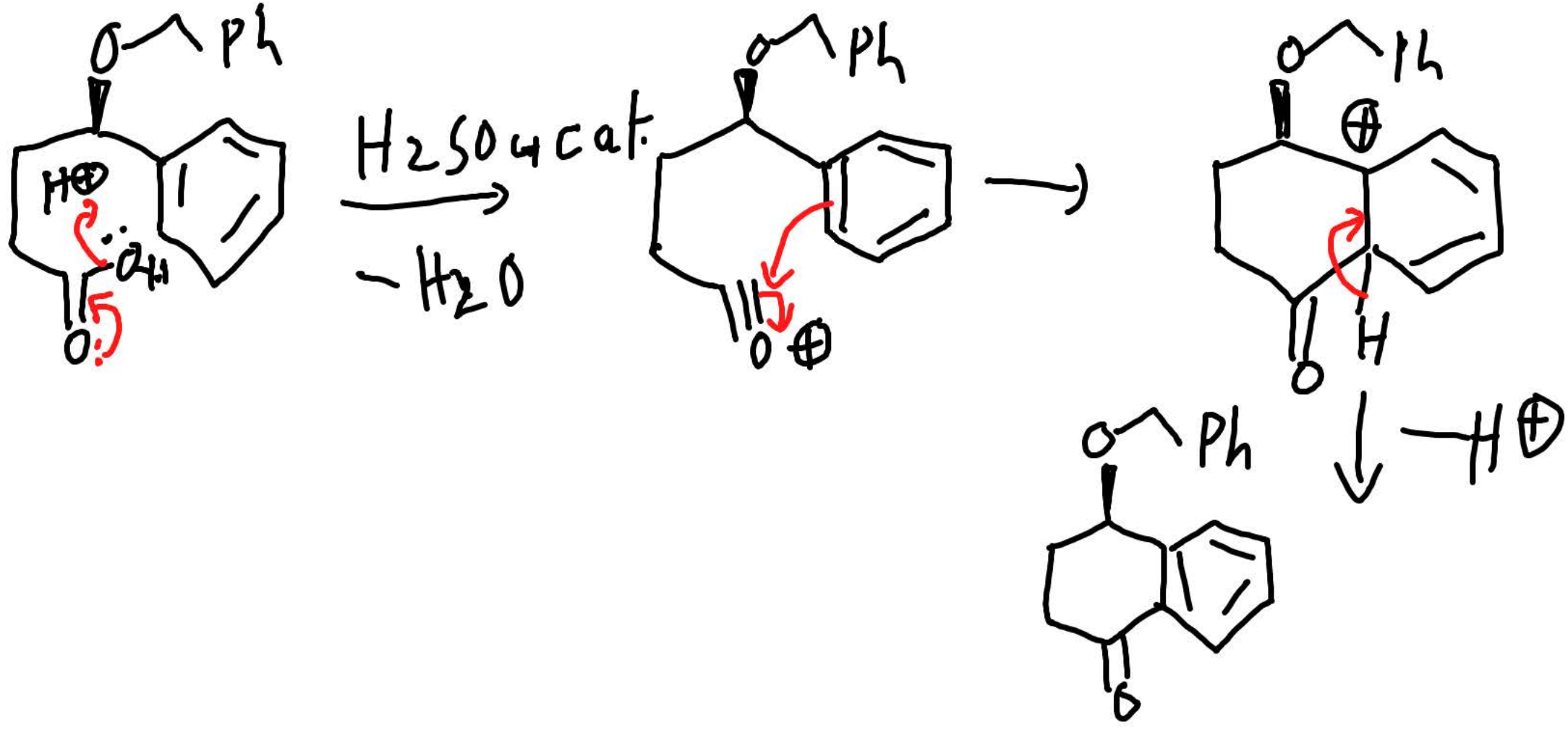
Acylation de Friedel-Crafts?

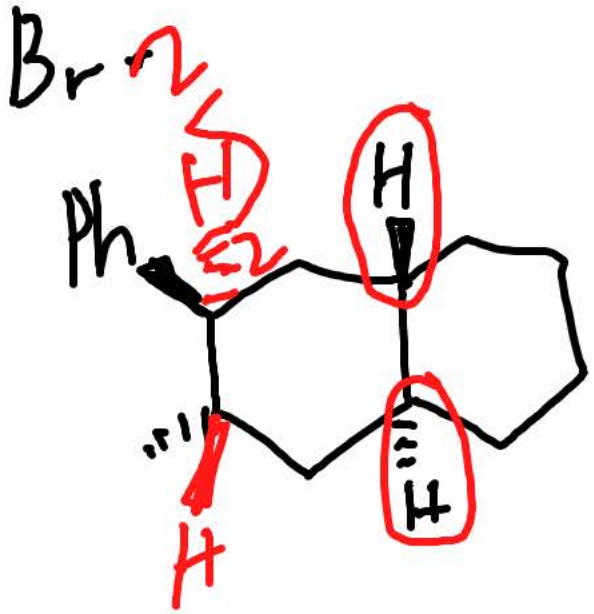
pour éviter des problèmes de sélectivité: d'abord former l'éther, ensuite déprotéger, oxyder

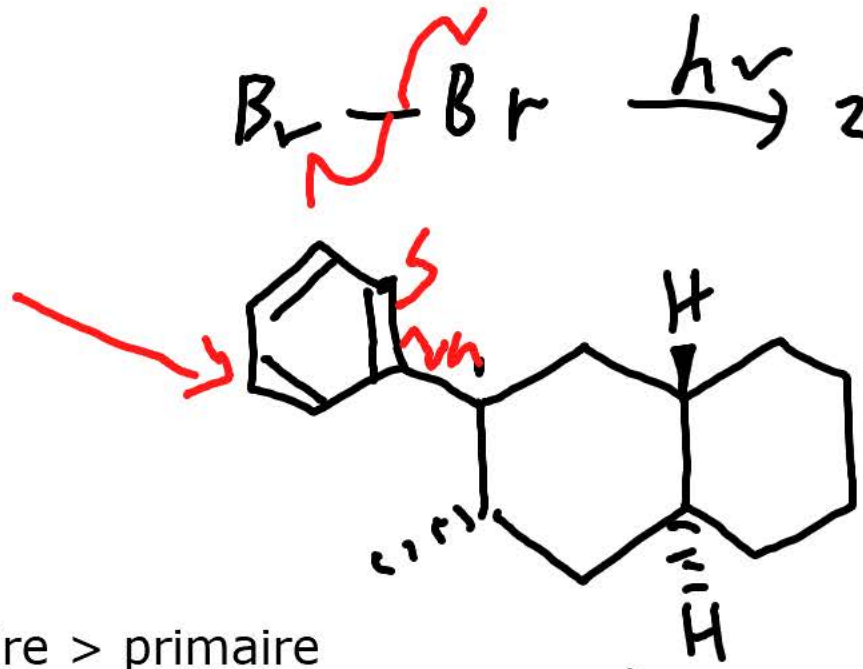

R1
R2
−H2
SN2
Ph
TBAF
OH


VI
Ph
Ph
CrO_3
H_2SO_4, H_2O
R
OH
IV
O-H
R
H
OH
R
H
O


même mécanisme


O
Ph
H⊕
O
O
Ph
H
O⊕
H2SO4 cat.
– H2O
O
Ph
⊕
O
H
– H⊕
O
Ph
O



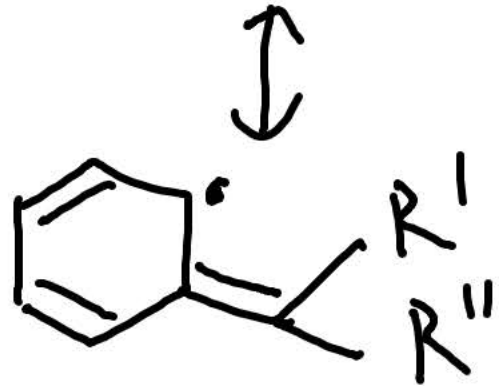


initiation

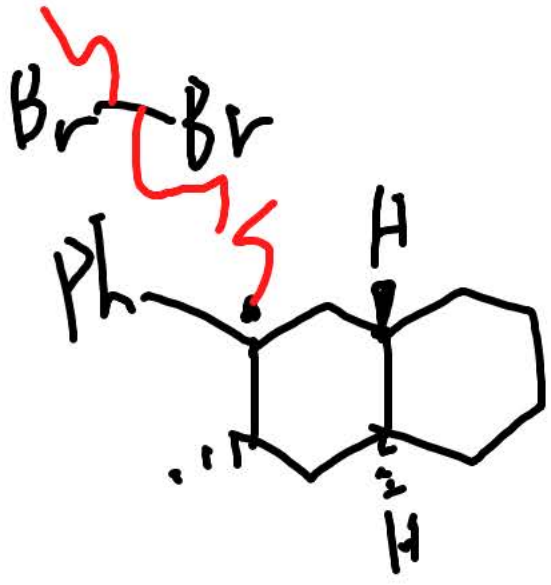
+ H – Br

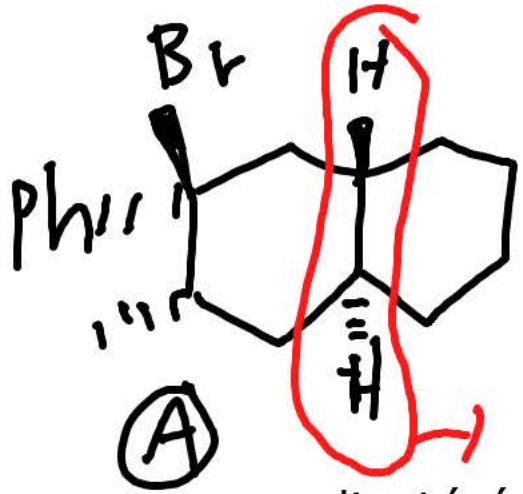
abstraction d'hydrogène:
radicaux tertiaire > secondaire > primaire

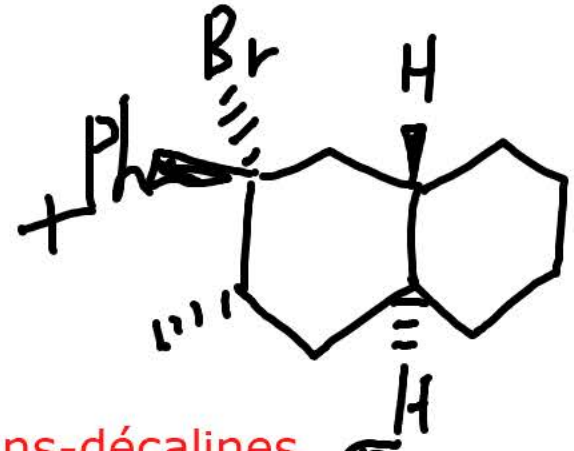
radical stabilisé par résonance



+2 résonance dans le cycle







propagation

A

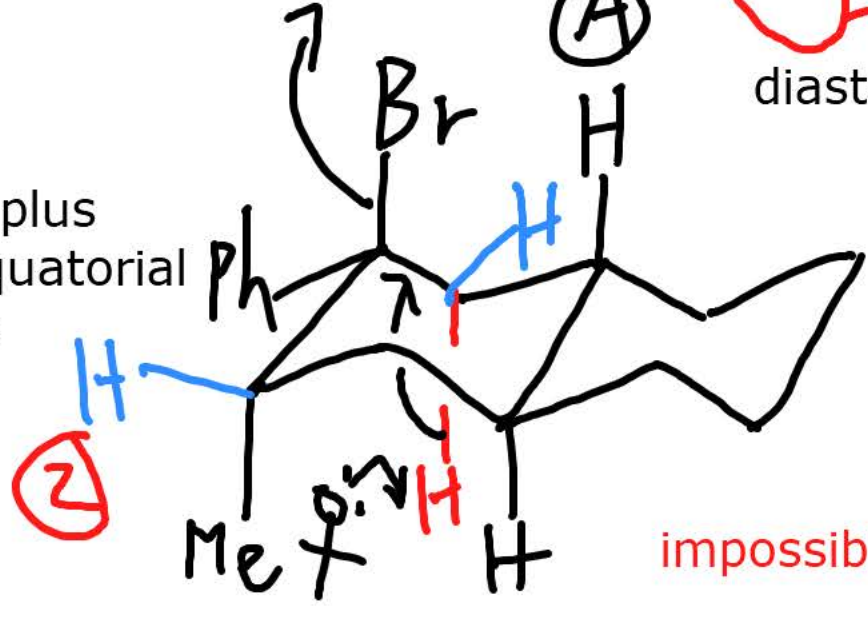
diastéréoisomères

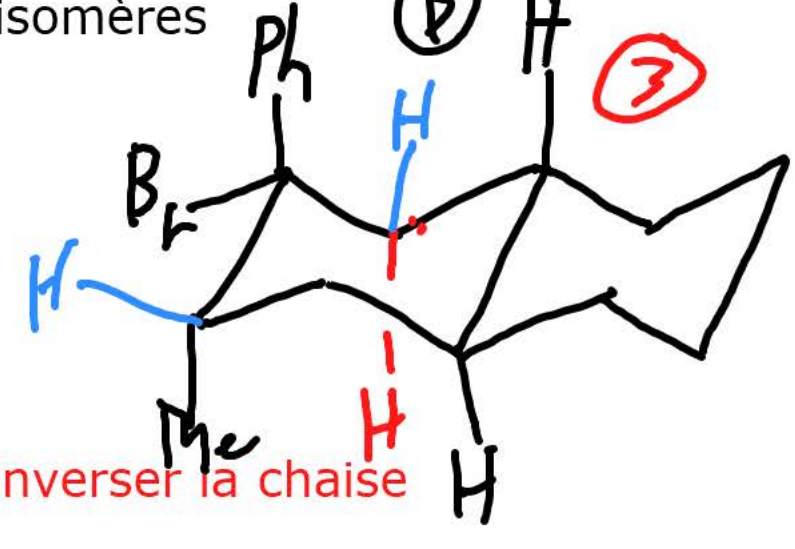
B

trans-décalines

2) Conformation

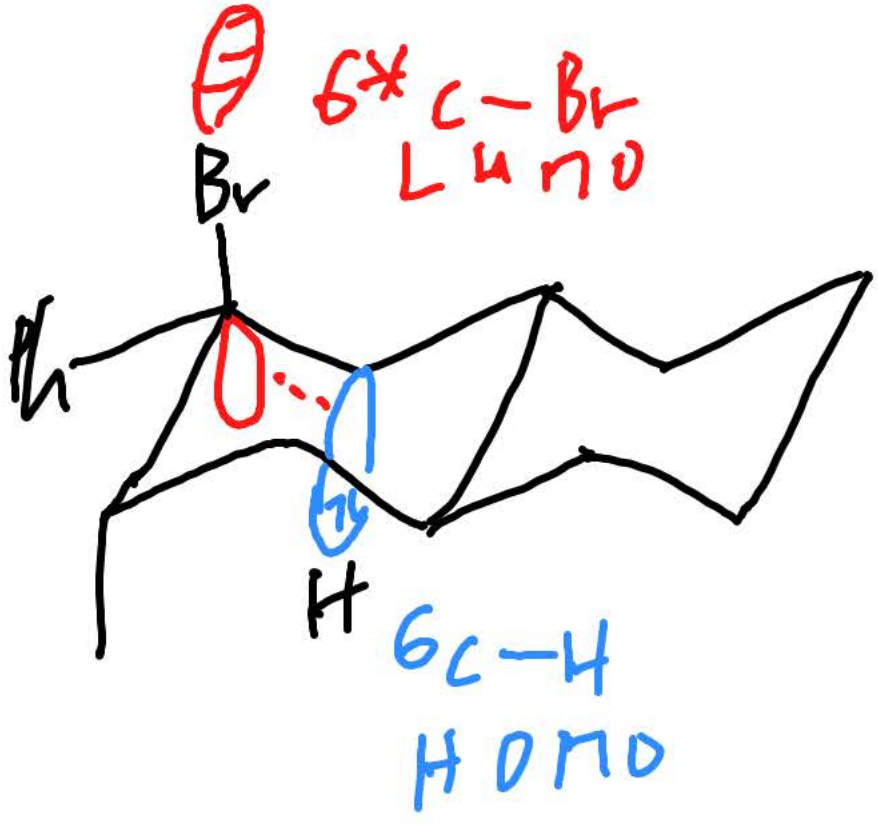
Grand group Ph plus
favourable en équatorial
A est plus stable



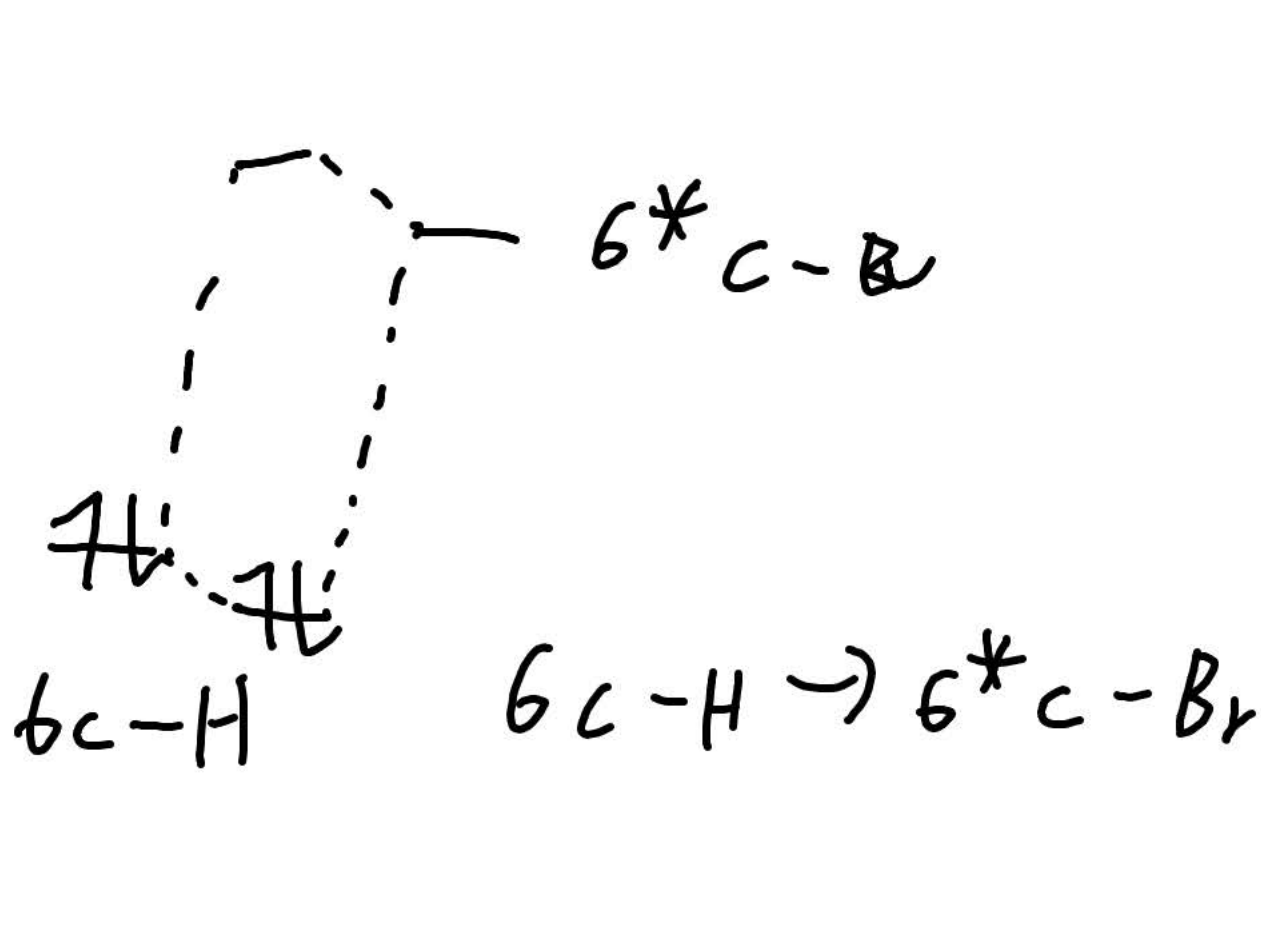


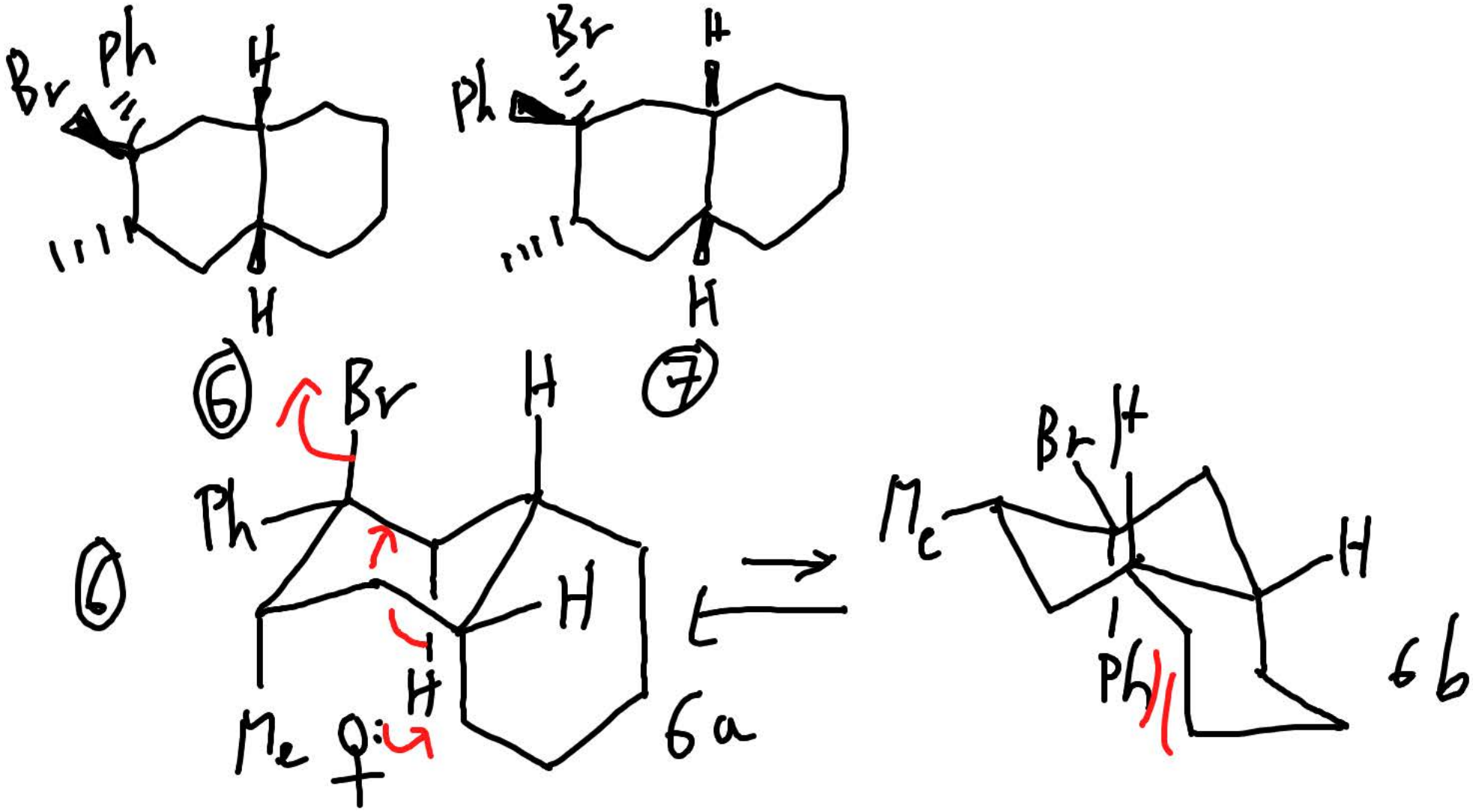
impossible d'inverser la chaise

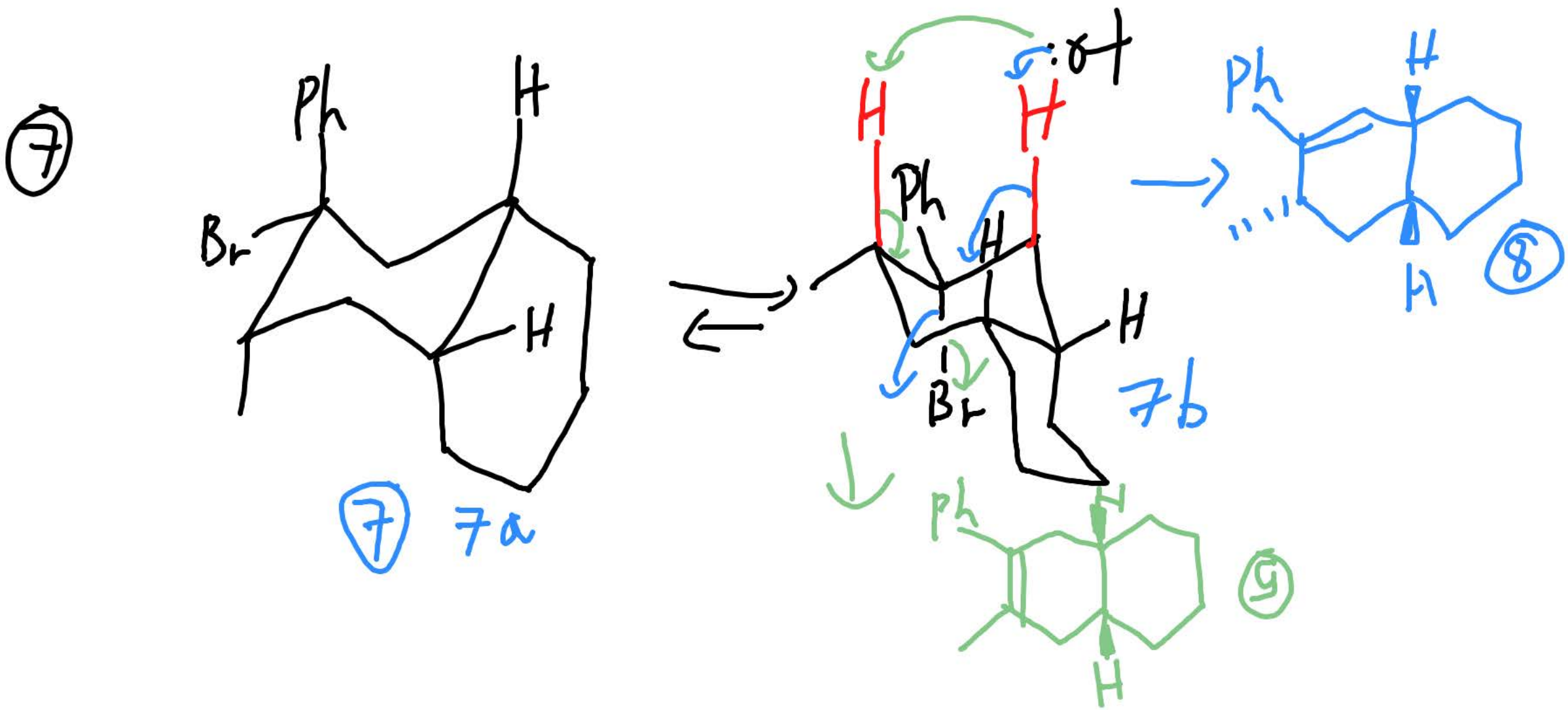
orbitales pour E2?

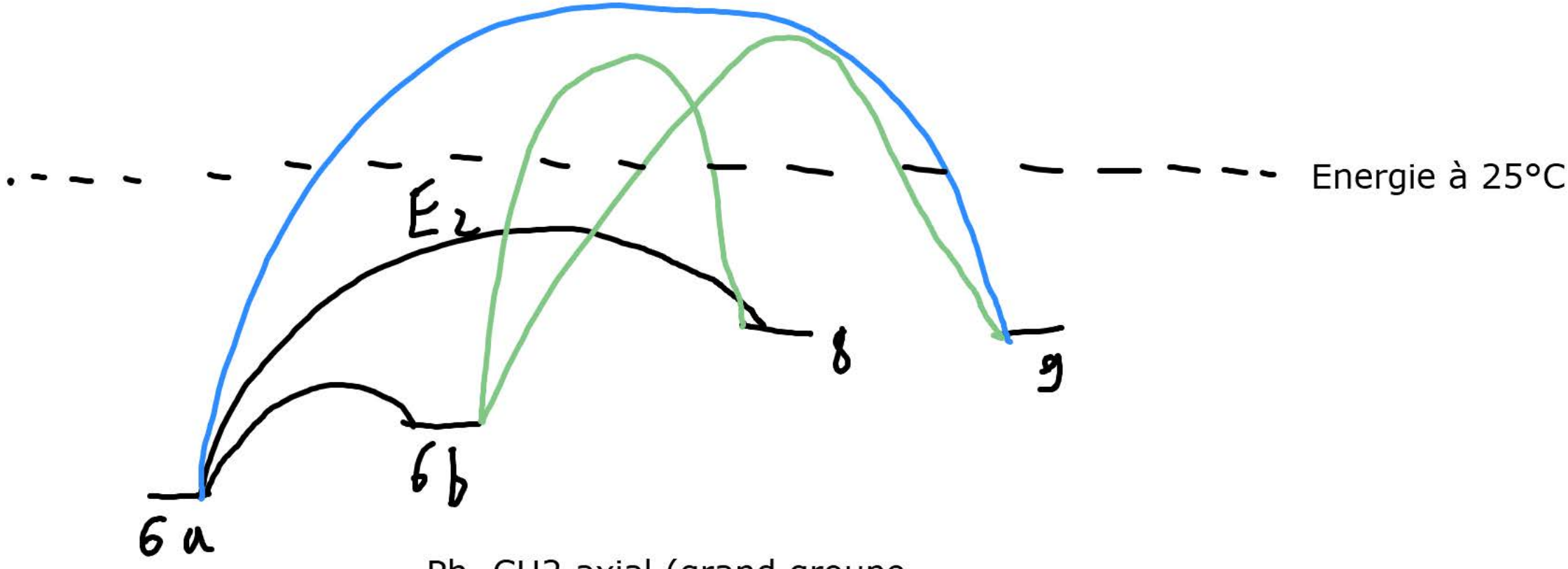


angle de 180°, antipériplanaire



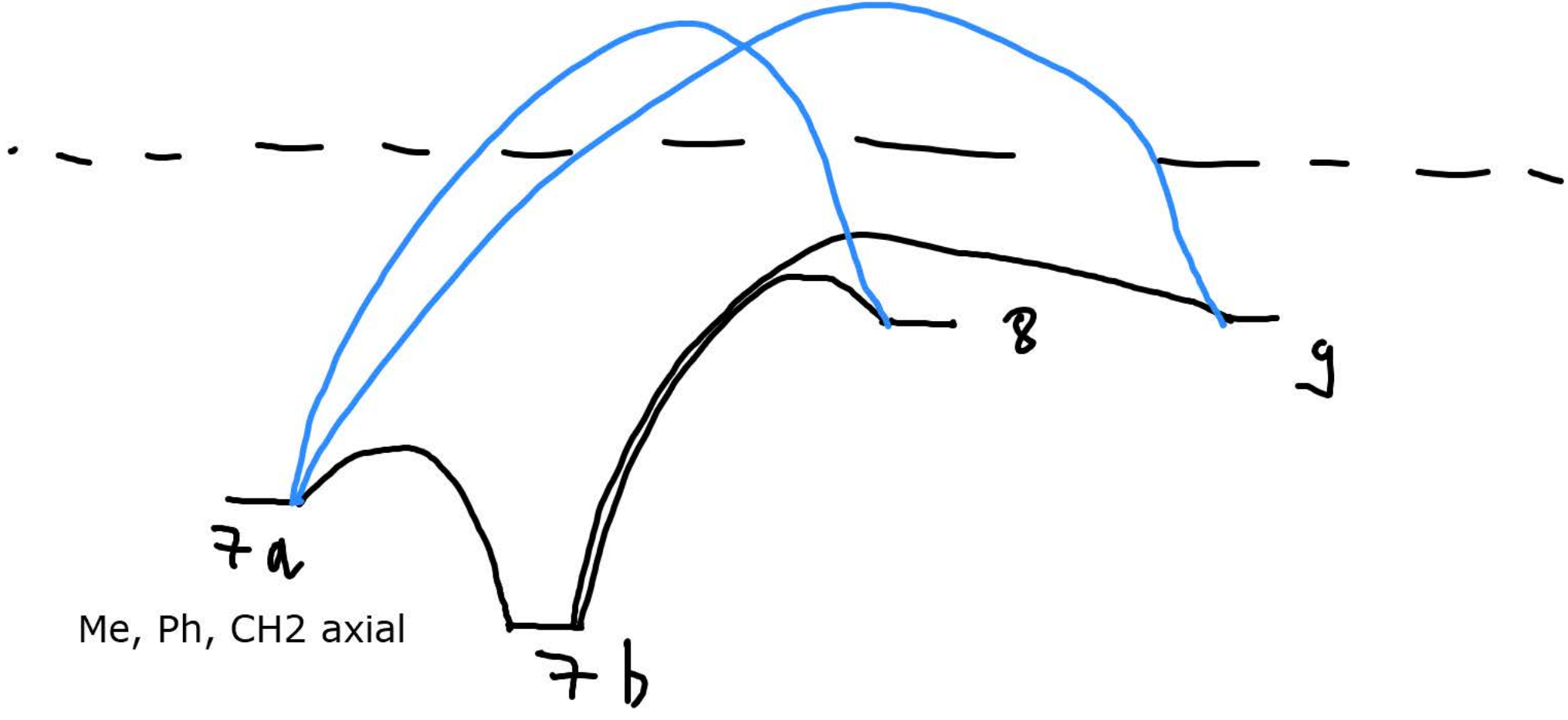

Br
Ph
H
H
⑥
Br
Ph
H
H
⑦
Br
H
Ph
H
H
Me
⑤
6a
Br
H
Me
H
Ph
6b


7
Ph
H
Br
H
7
7a
H
H
Ph
H
H
Br
7b
Ph
H
H
8
Ph
H
9



Me, Br, CH2 axial

Ph, CH2 axial (grand groupe axial)


7a
8
9
7b
Me, Ph, CH2 axial
Br, CH2 axial