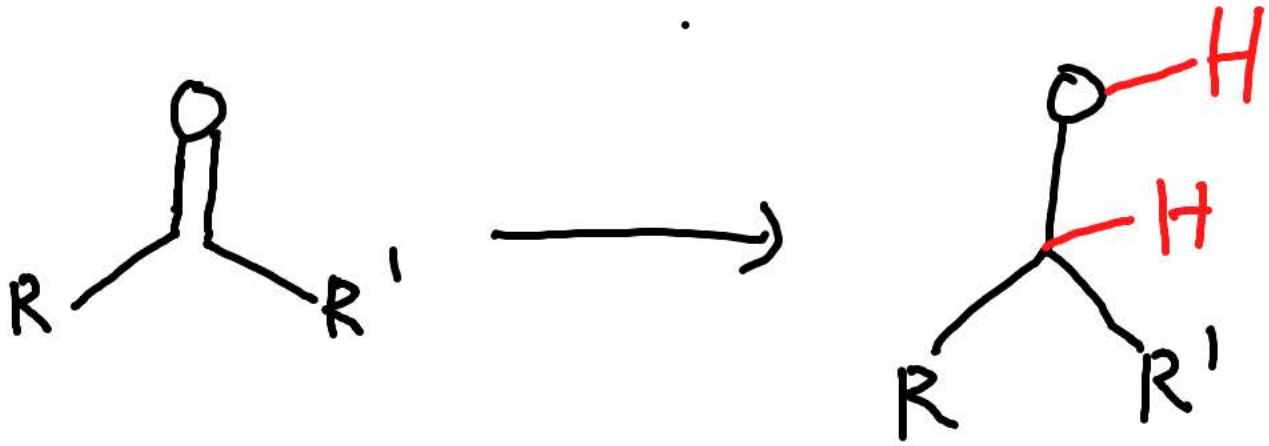
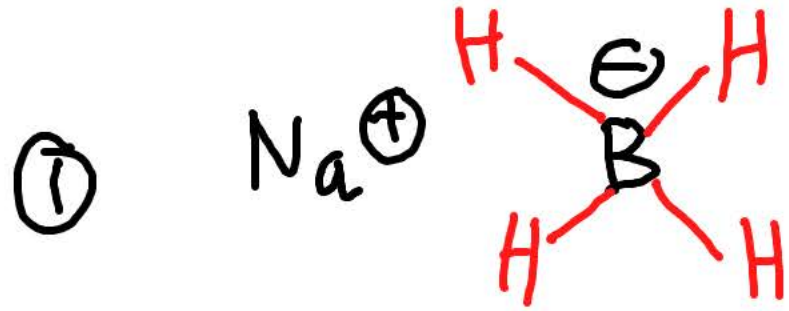
comparaison de procédés



cétone

alcool

réduction des cétones



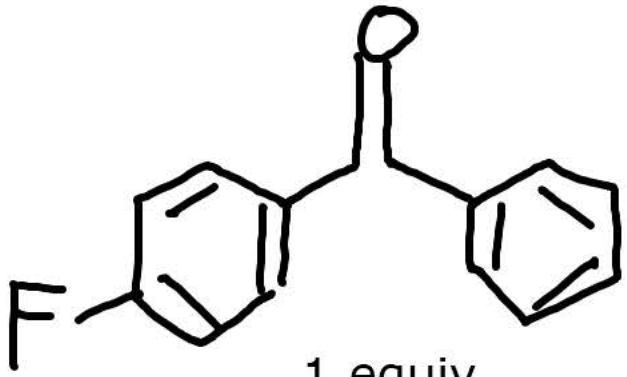
hydrure de bore

①

② H_2 , Ru cat.

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

C13H9FO: 24 atomes



1 equiv.

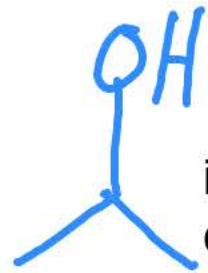
200 g/mol

6 atomes

+ $NaBH_4$

0.38 equiv

37.8 g/mol



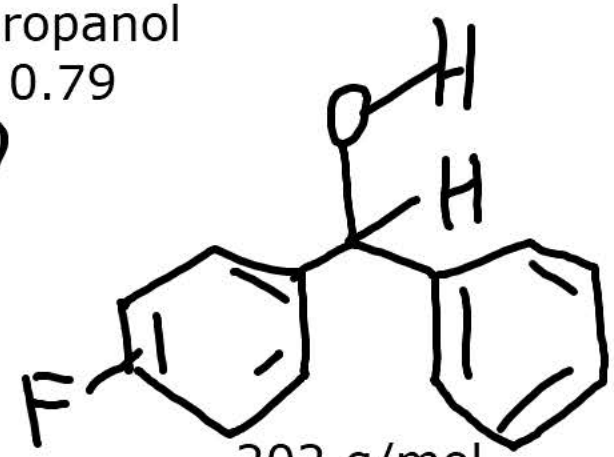
isopropanol

d = 0.79

0.4 M

98%

C13H11FO: 26 atomes



202 g/mol

économie d'atomes: 26/(24+6) = 87%

purification: extraction

acétate d'éthyle: 1 volume (égal à isopropanol), d = 0.90

Eau: 1.5 volume, d = 1

0.200 Kg/Kf Na2SO4 (pour sécher le produit)

+ $NaB(OH)_4$

0.20 Kg/Kg

(Kg déchet par Kg produit)

Bilan de masse pour produire 1 Kg de produit

1000/202 = 4.95 mol de produit
98% de rendement, 4.95/0.98 = 5.05 mol de produit de départ = 1.01 Kg

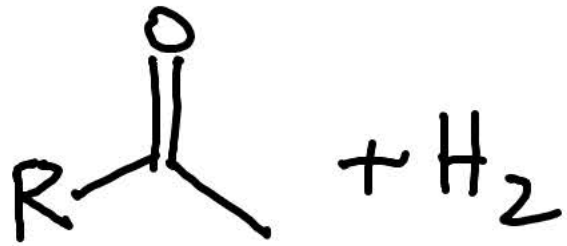
NaBH4: 0.38*37.8*5.05 = 73 g, 0.073 Kg
Solvant: 0.4 M d'isopropanol, 5.05/0.4 = 12.6 L* 0.79 = 10 Kg

Extraction:
acétate d'éthyle: 1 volume: 12.6 L, 11.3 Kg
Eau: 1.5 volume, 18.9 L, 18.9 Kg
Na2SO4: 0.200 Kg
déchet: NaB(OH)4 = 0.200 Kg

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

E: (10 + 11.3 + 18.9 +0.2 +0.2)/1 = 40.6

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



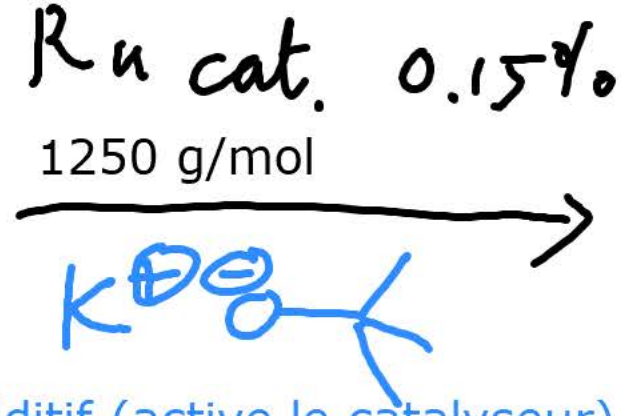
377.7 g/mol

1 equiv

+ H_2

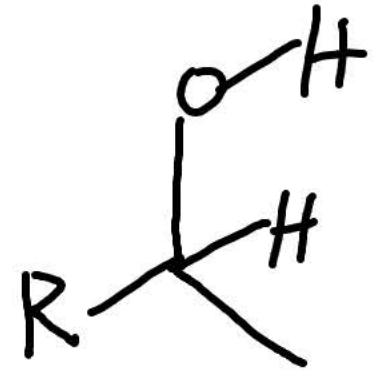
2.0 g/mol

2 equiv.



additif (active le catalyseur)

112 g/mol, 0.5 equiv



379.8 g/mol

76%

économie d'atome: 100%

purification:
extraction: toluene, 6.5 volume, d = 0.87
eau, 6.5 volume, d = 1

solvant, d = 0.79
1.5 M

calculer PMI et E pour 1 kg de produit

1 kg produit: 2.63 mol
produit de départ: 76% rendement, dong 3.46 mol, 1.30 Kg

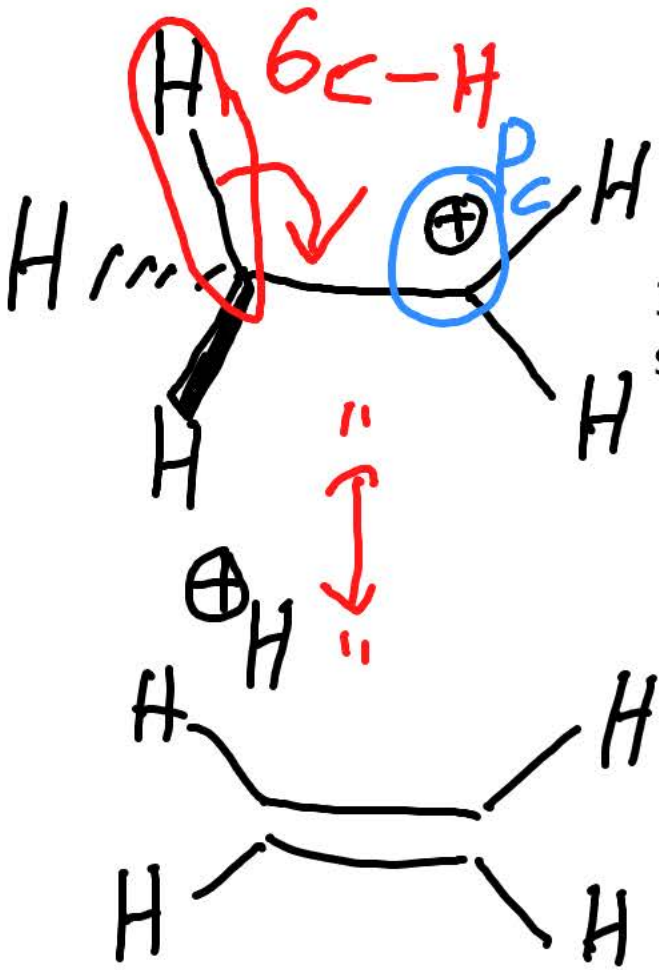
H2: 0.015 Kg
Ru cat: 0.0065 Kg
KOtBu: 0.12 Kg
Isopropanol: 2.3 L, 1.8 Kg
Toluene: 6.5 volume, 13 Kg
Eau: 6.5 volume, 15 Kg.

PMI: (1.3 + 0.015 + 0.0065+0.12+1.8+13+15)/1 = 31.2

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

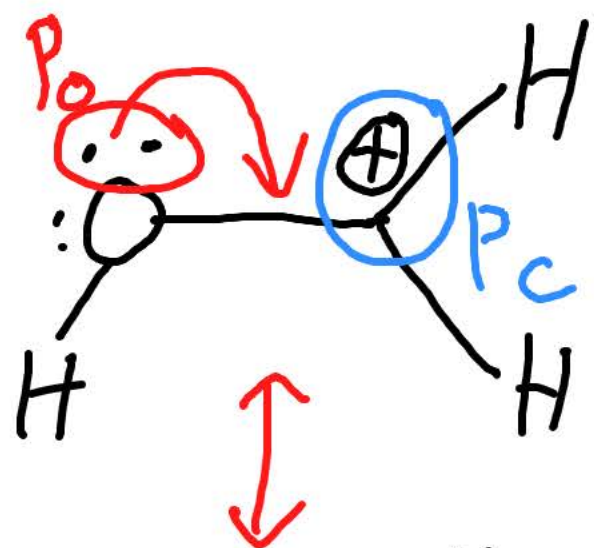
stabilisation des carbocations

hyperconjugaison



3 substituants
sp2

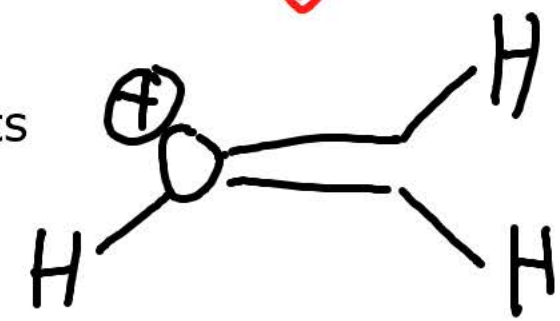
résonance

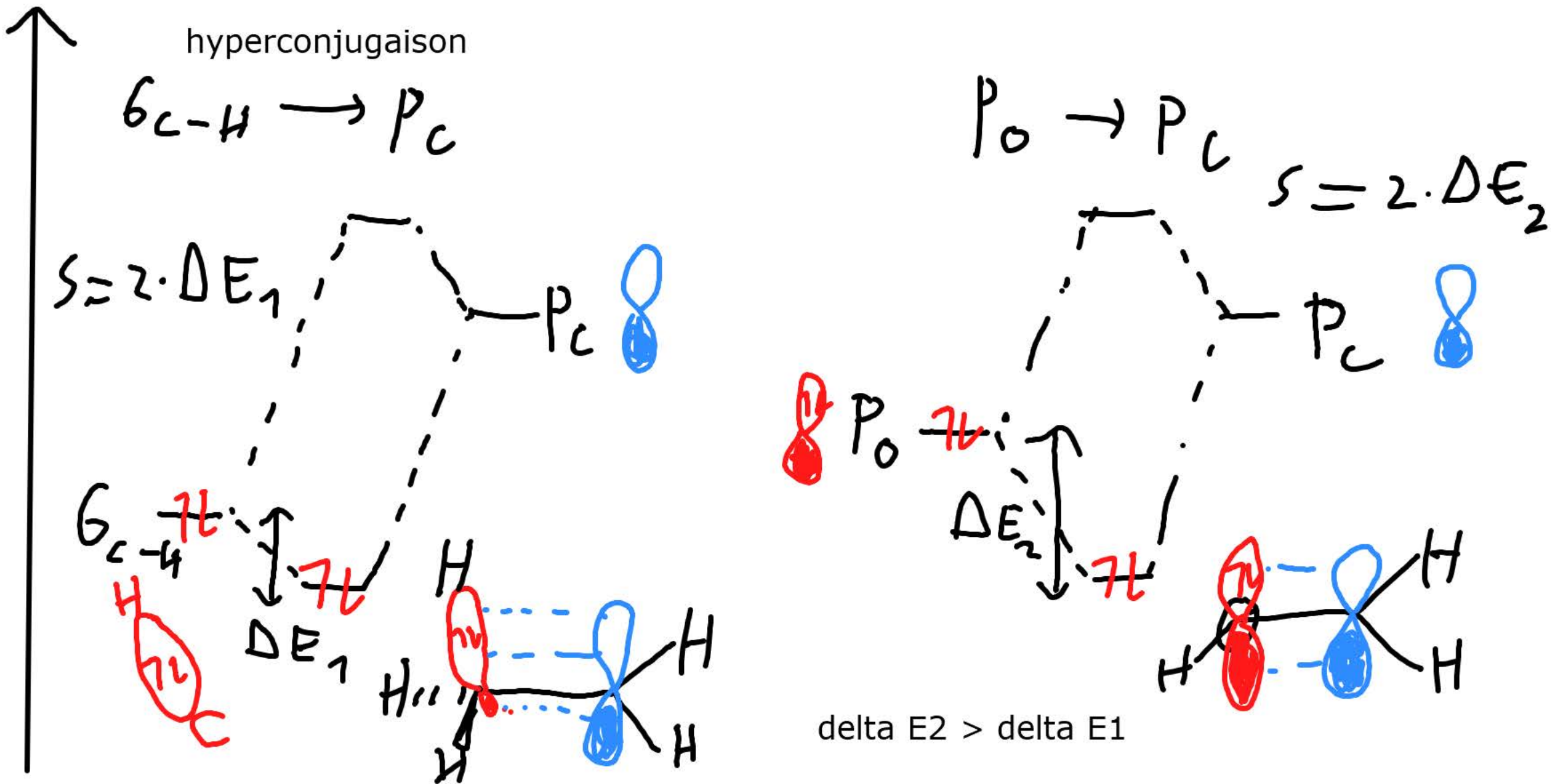


HOMO

LUMO

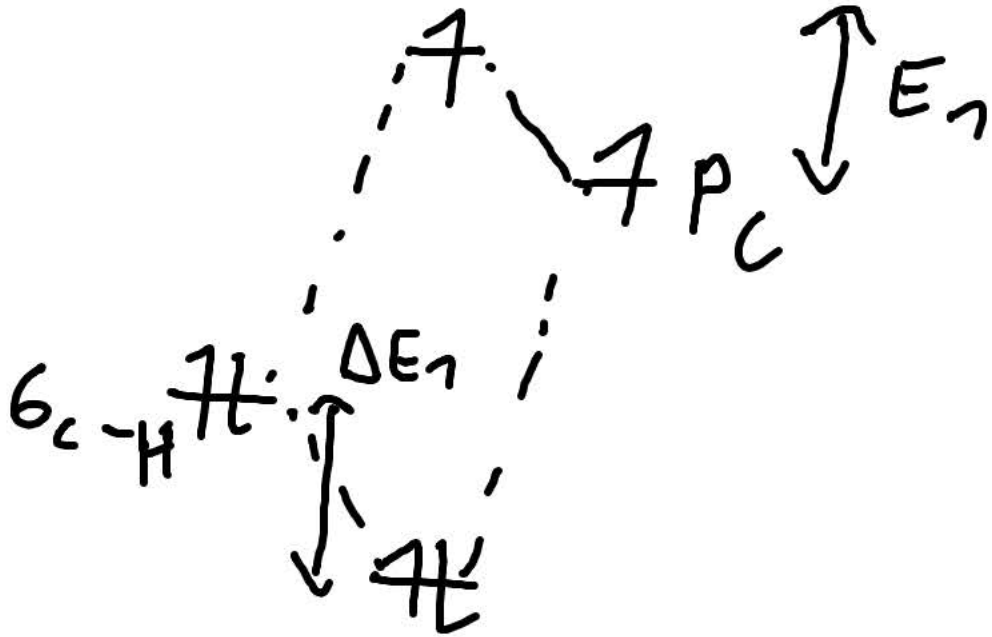
3 substituants
sp2



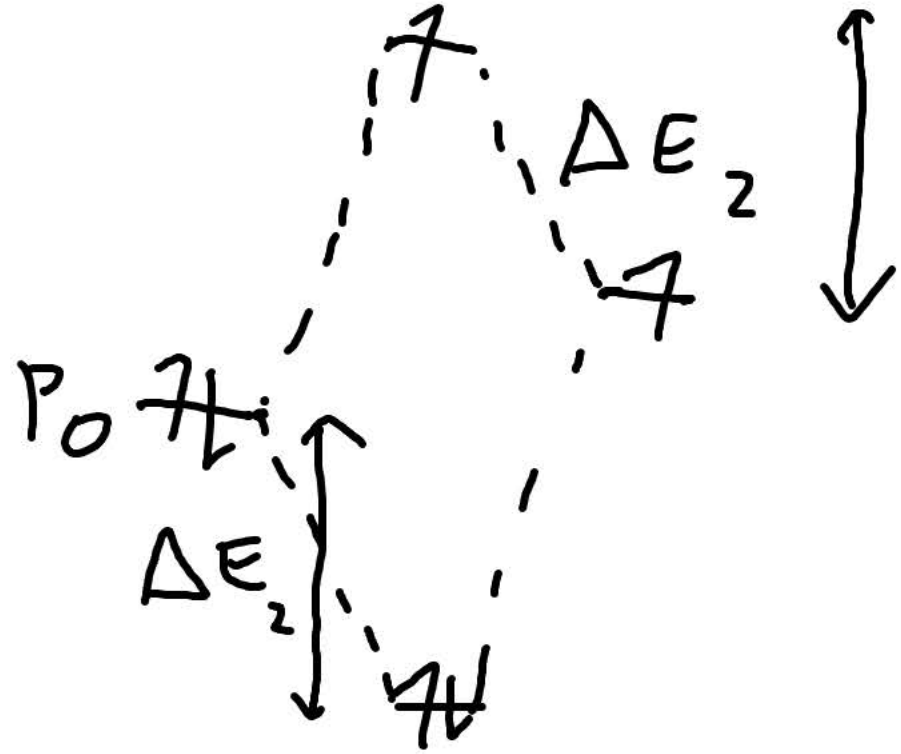


delta E2 > delta E1

radicaux



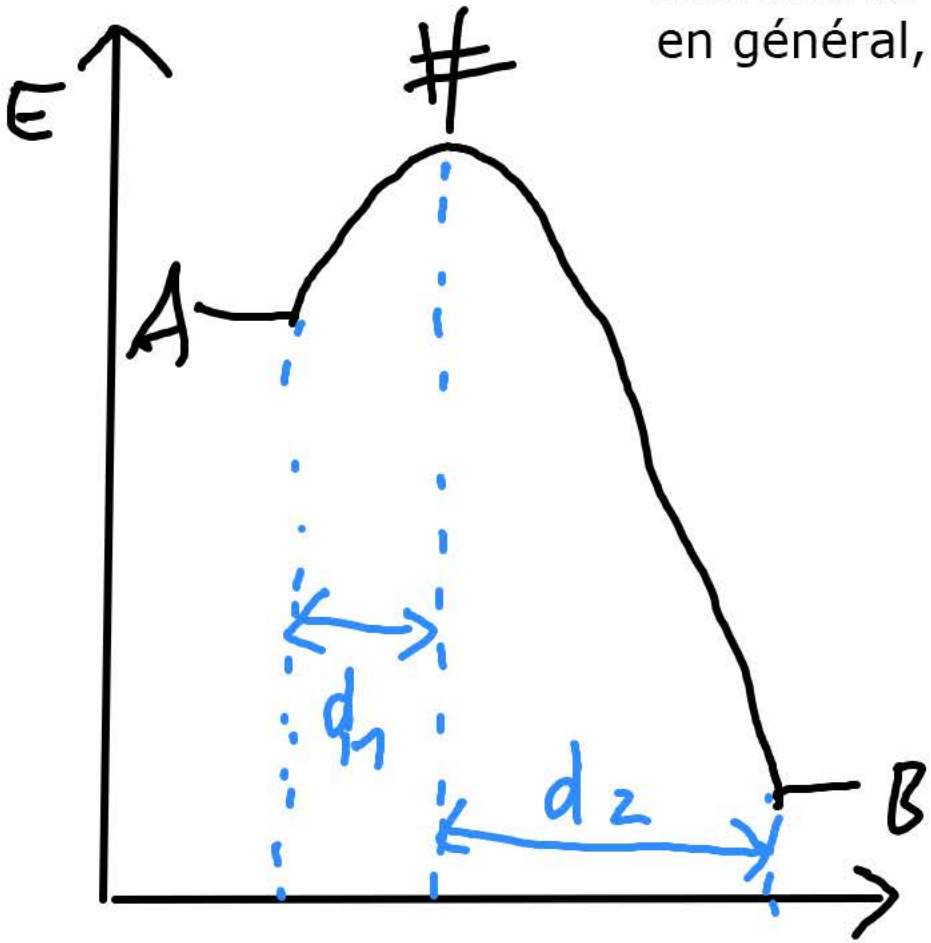
$$S = 2\Delta E_1 - \Delta E_1 = \Delta E_1$$



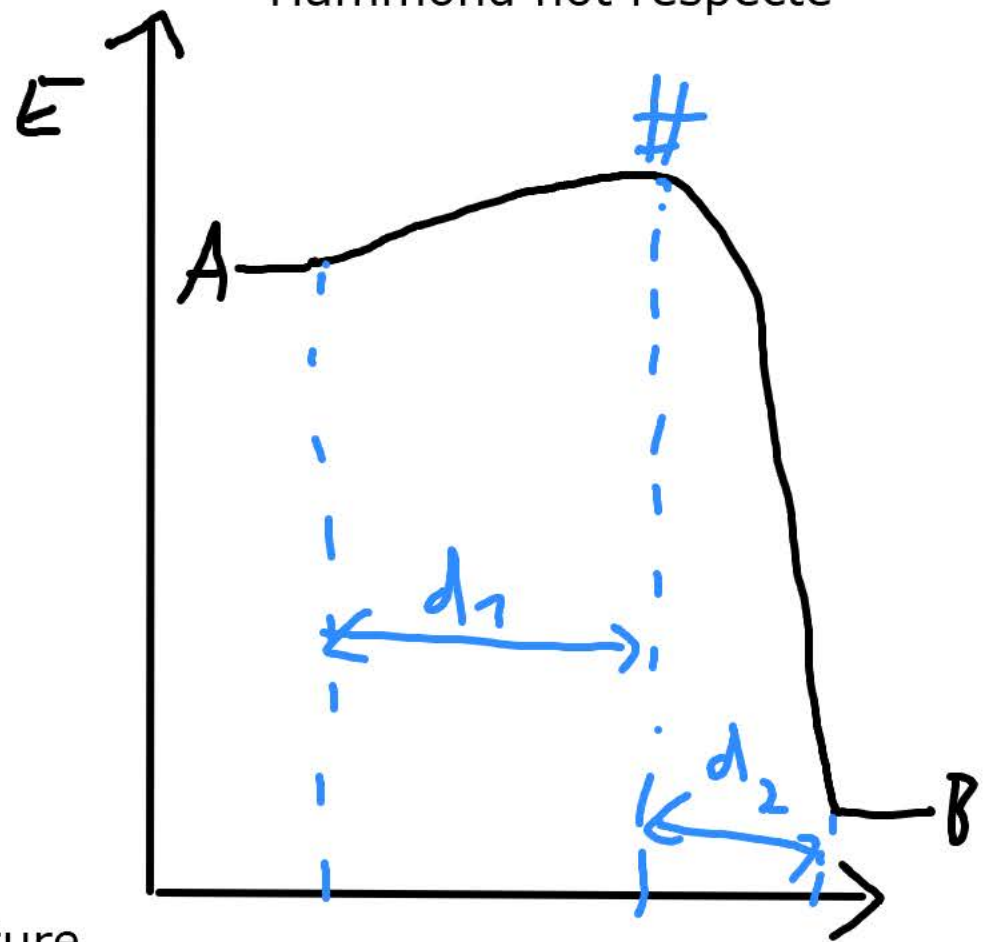
$$S = \Delta E_2$$

postulat de Hammond

Hammond:
en général, d1 < d2



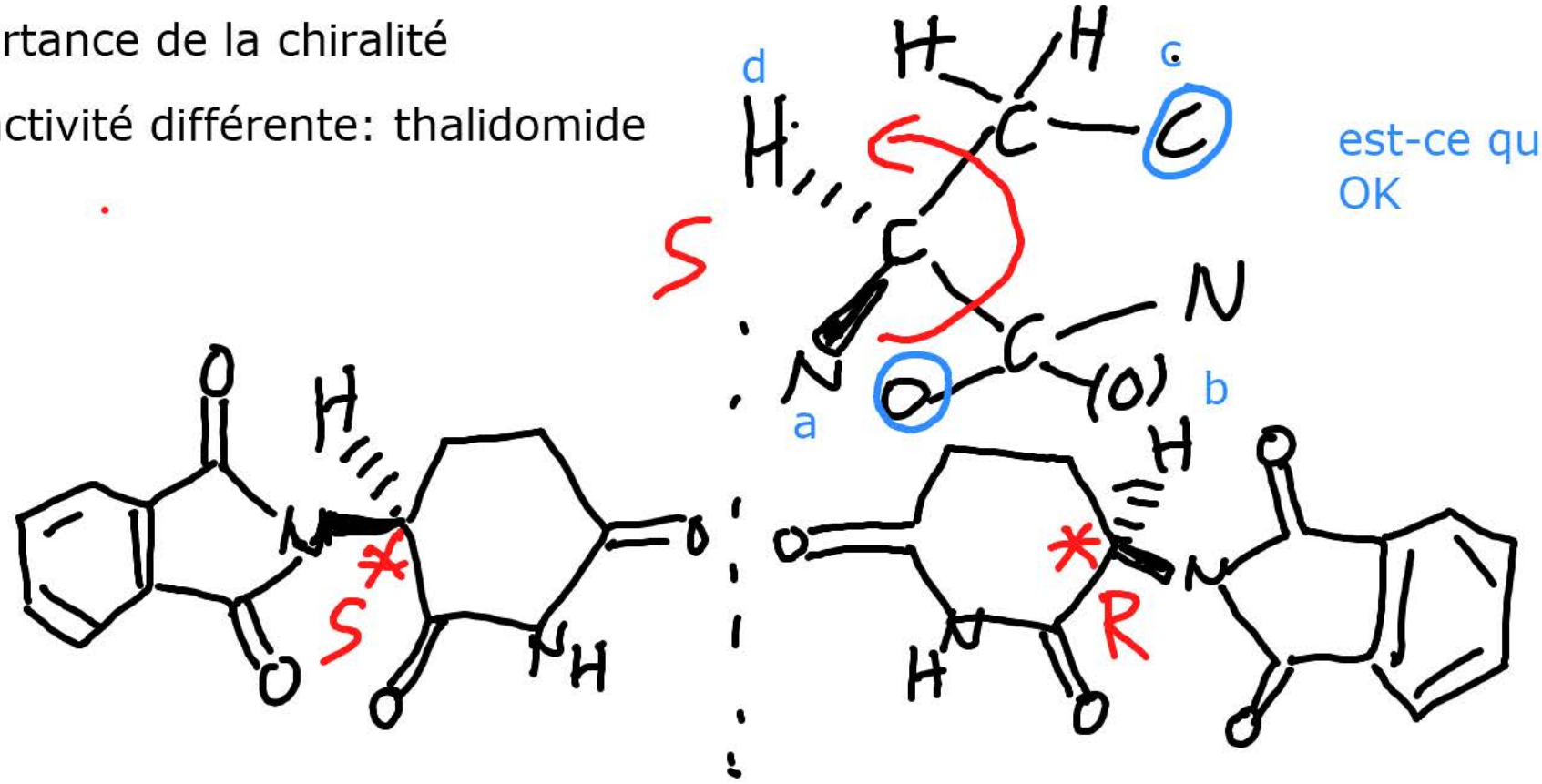
Hammond not respecté



coordonées réactionnelles = changement de structure

Importance de la chiralité

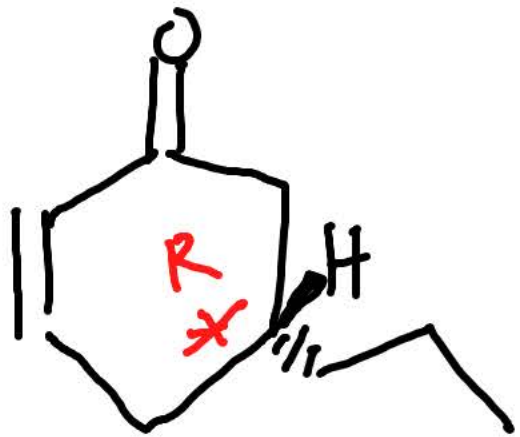
bioactivité différente: thalidomide



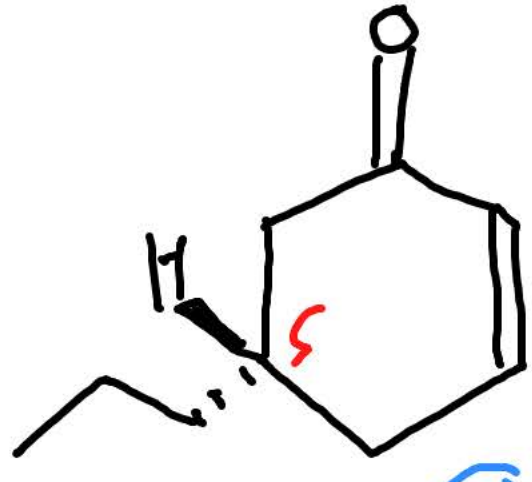
Tératogène (empêche le développement du foetus)

sédatif (donné aux femmes enceintes)

odeurs/gouts



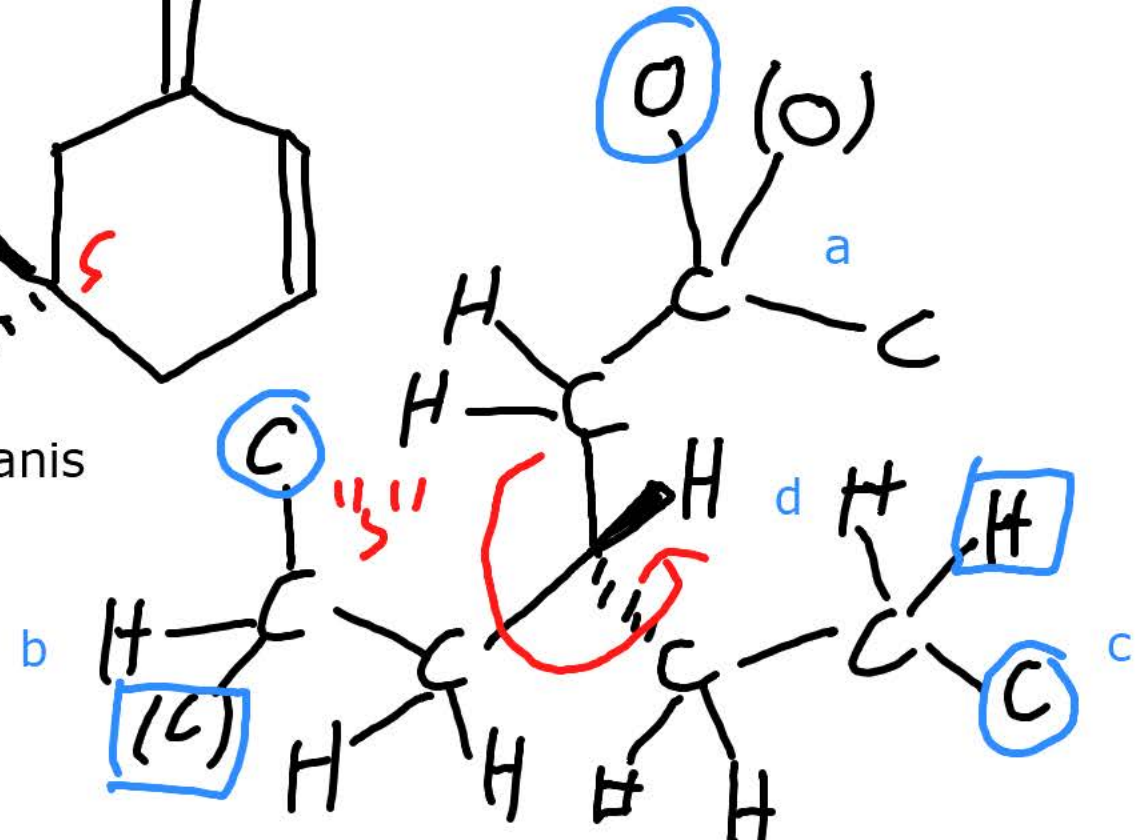
céleri



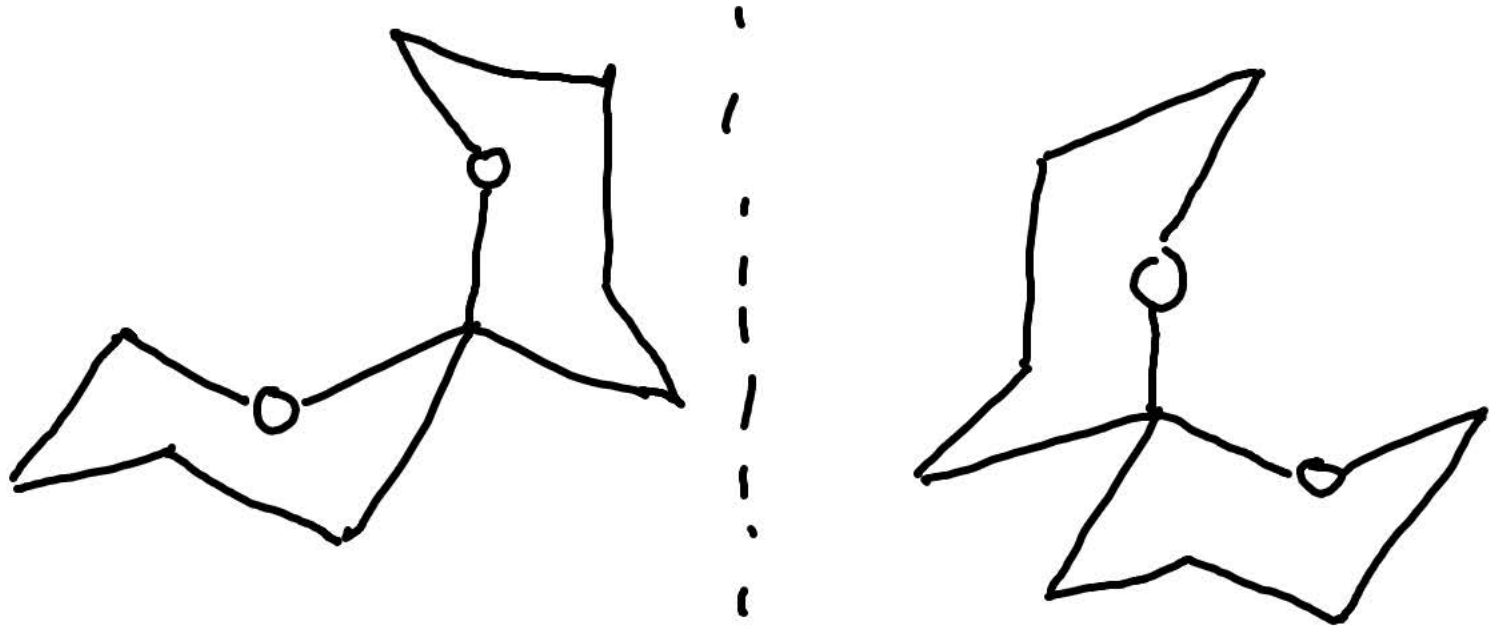
anis

d derrière? non devant

"S" → R



phéromone



attire les insectes mâles

attire les insectes femelles

mesure au polarimètre: + 20°

pour la substance pure: +23.1

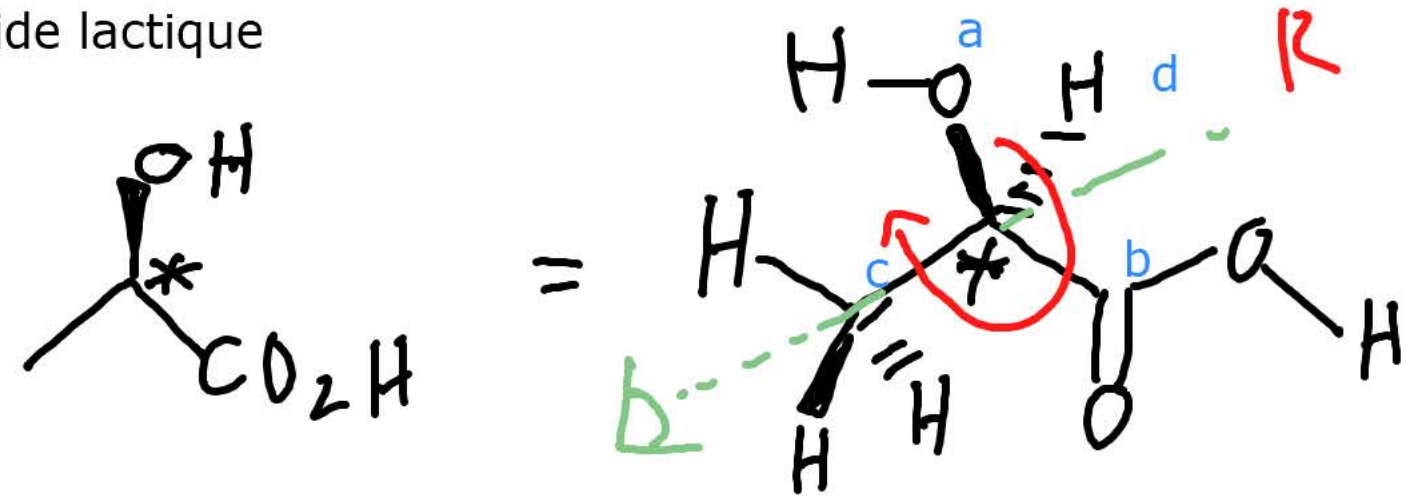
pureté optique: 20/23.1 = 87%

excès énantiomérique =
pureté optique: 87% ee

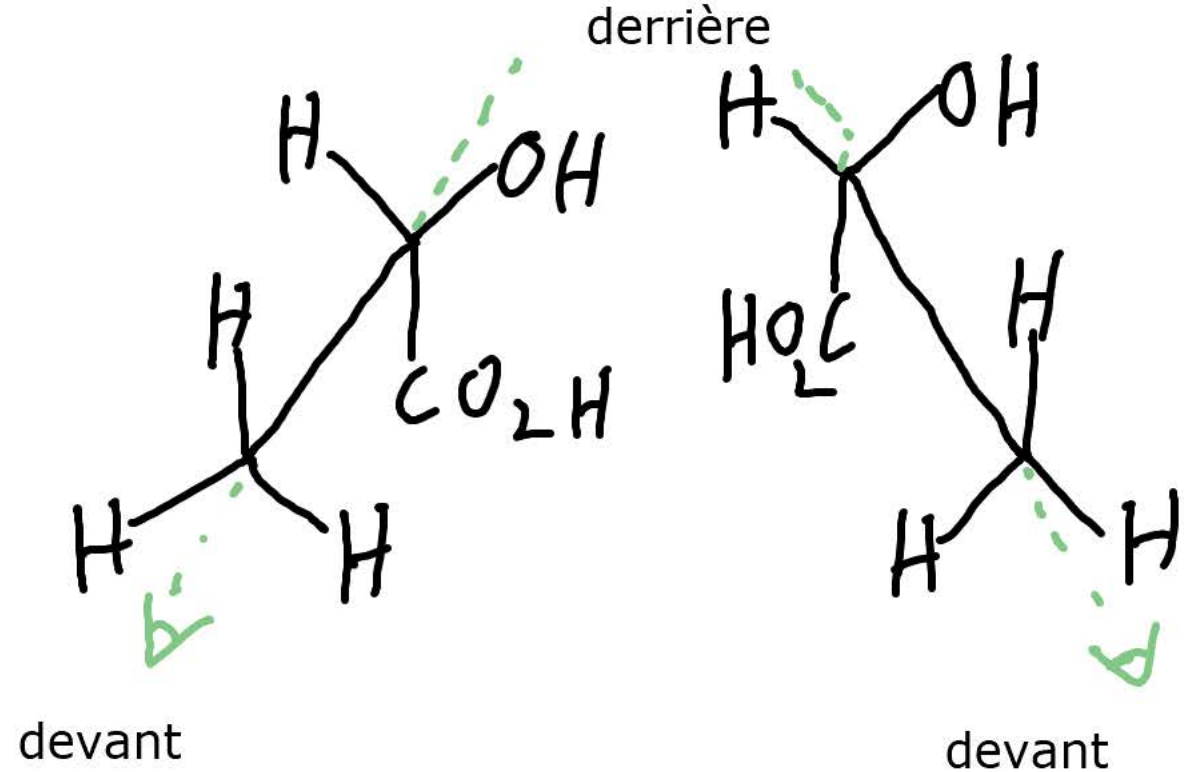
93.5-6.5 = 87
ratio énantiomérique: 93.5:6.5 er

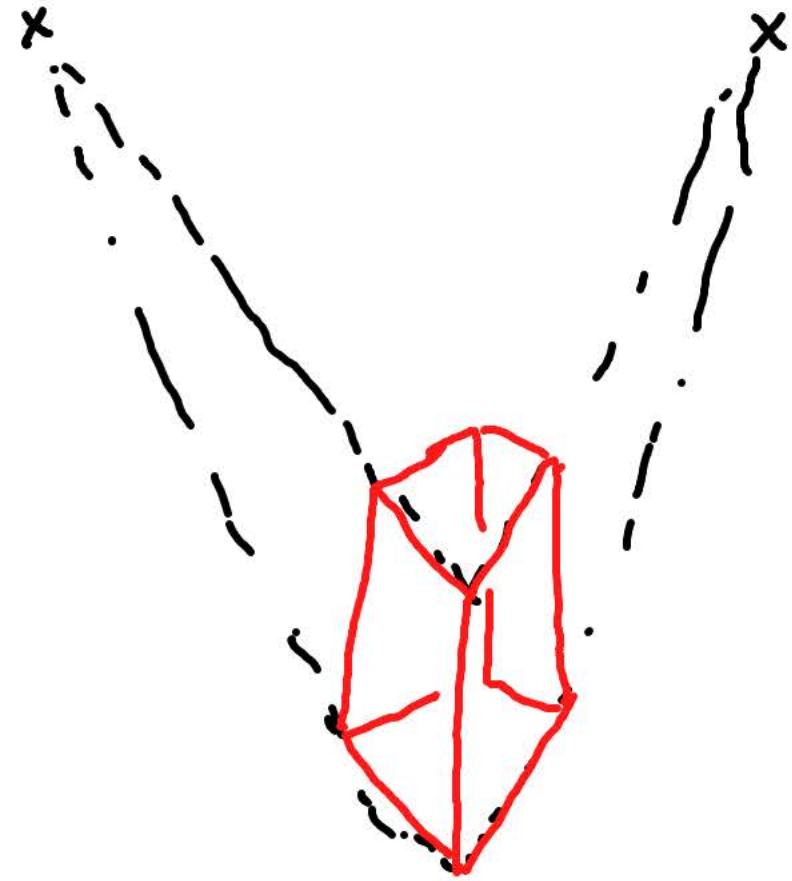
techniques de dessin en chimie organique

acide lactique

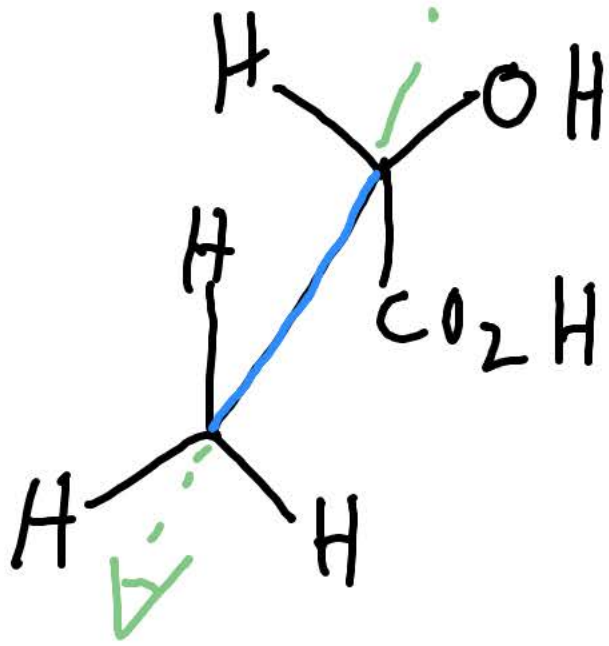


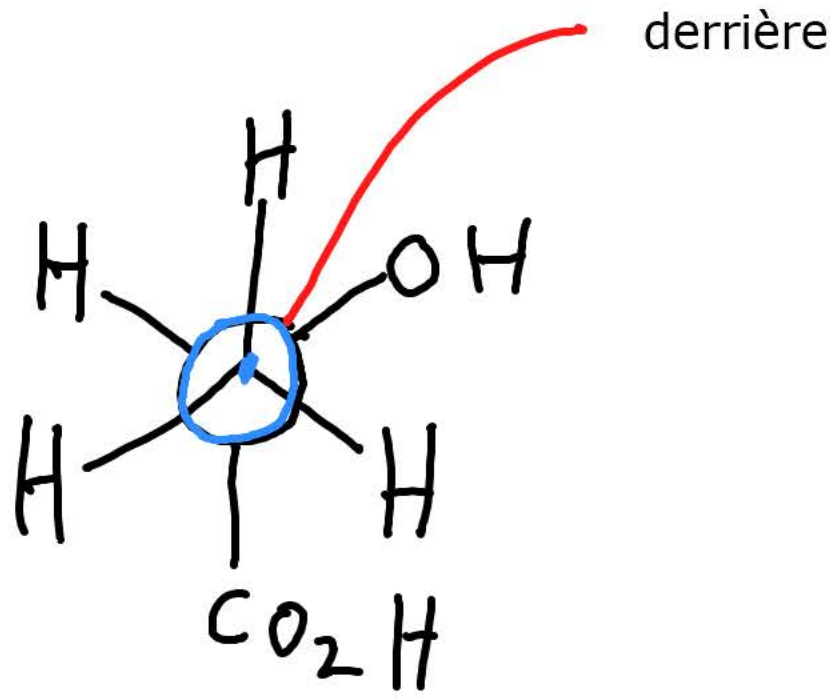
dessin en perspective

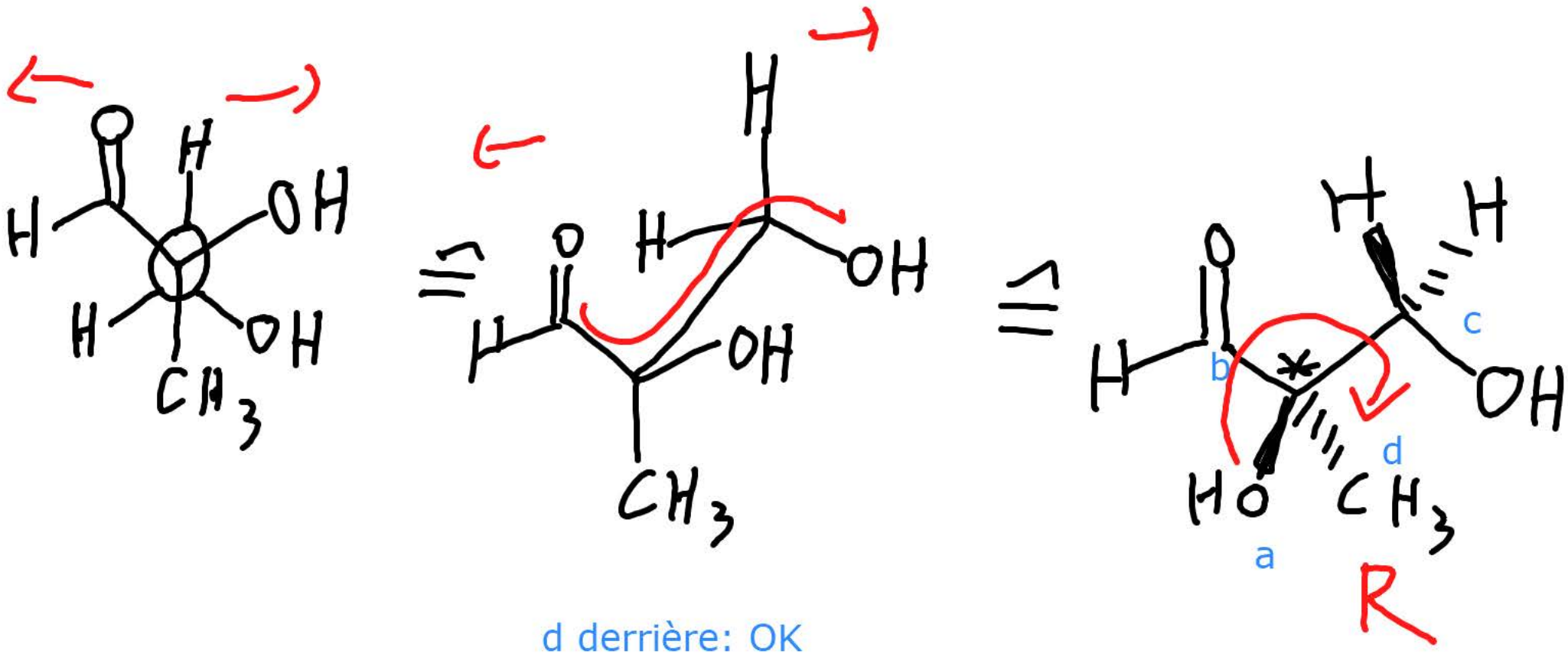




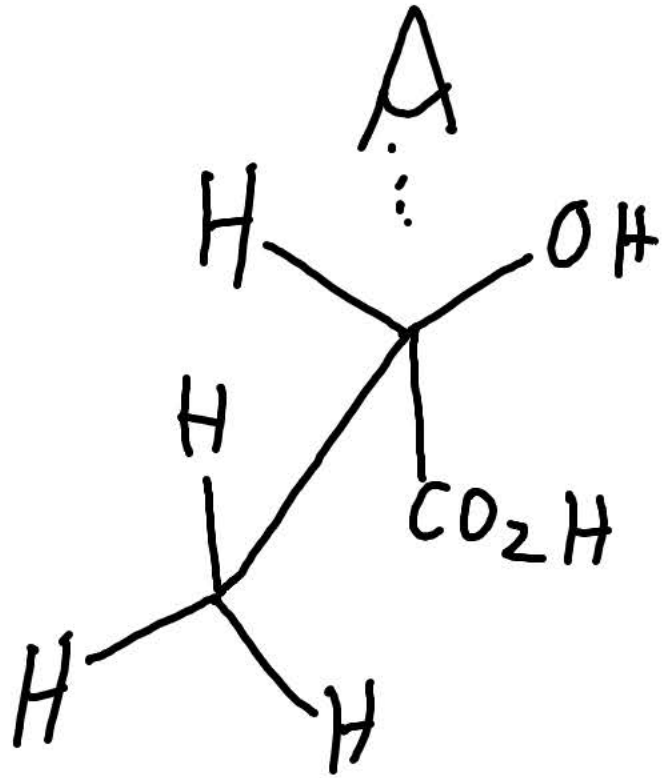
projection de Newman



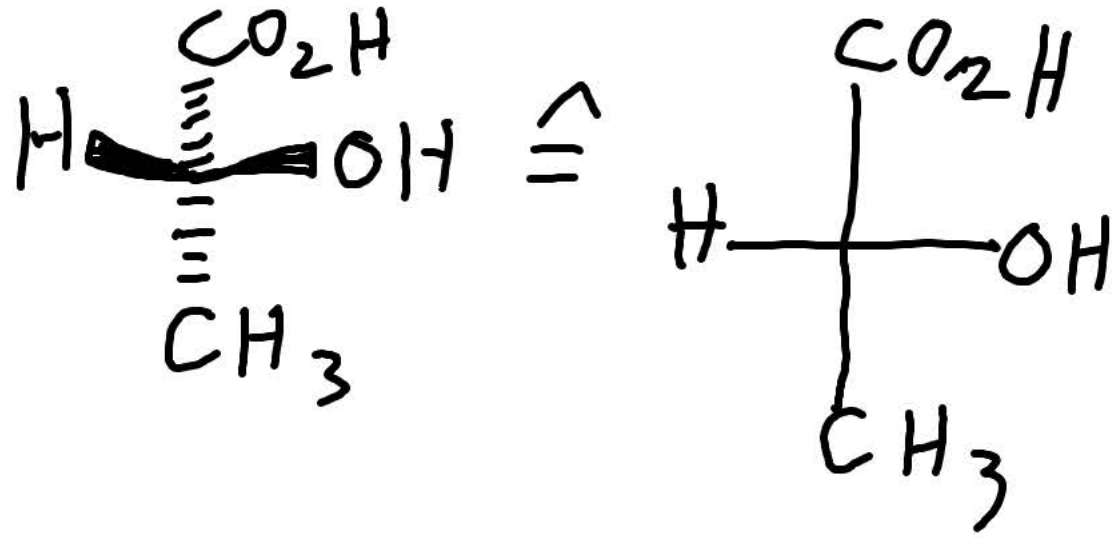




d derrière: OK

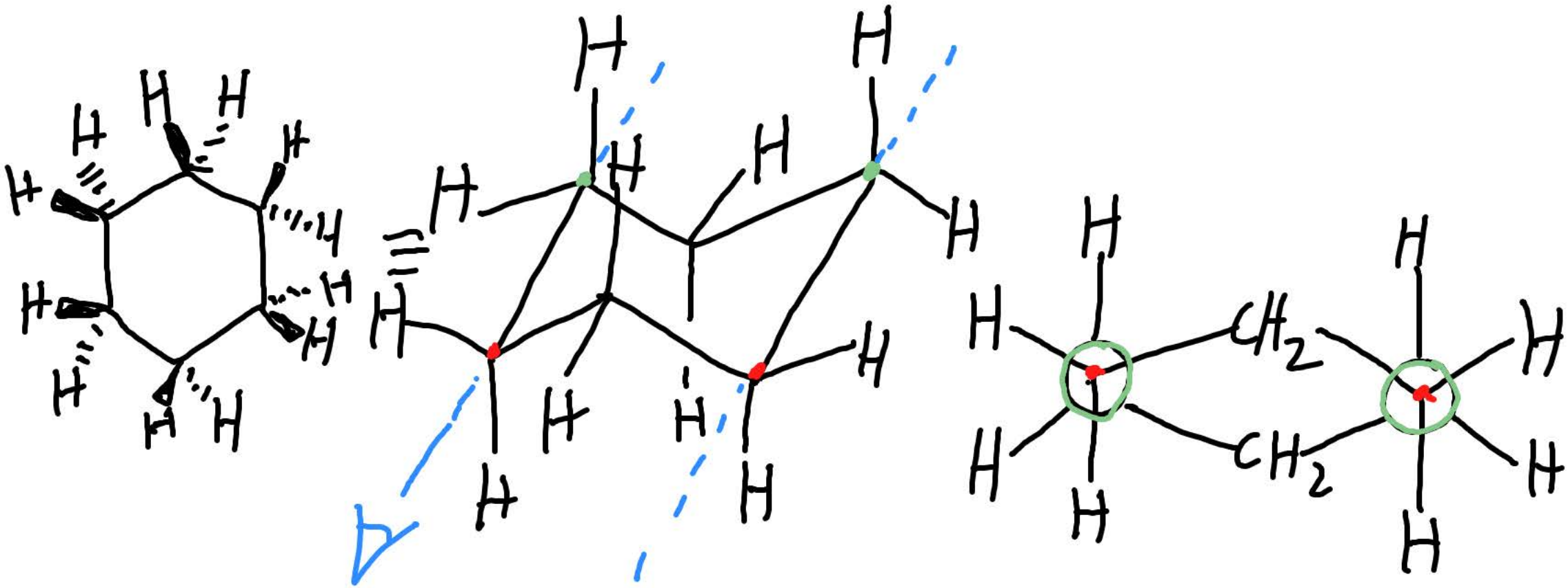


acide lactique, en perspective



projection de Fischer

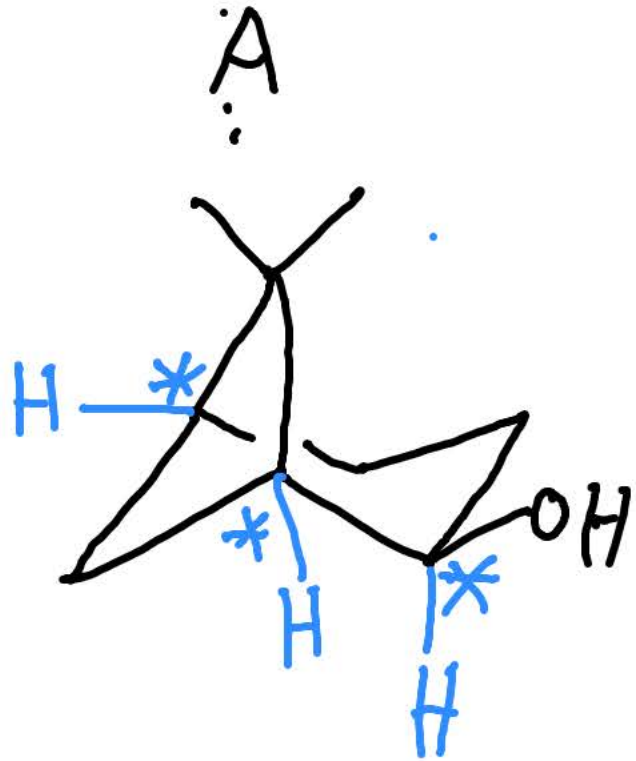
molécules cycliques



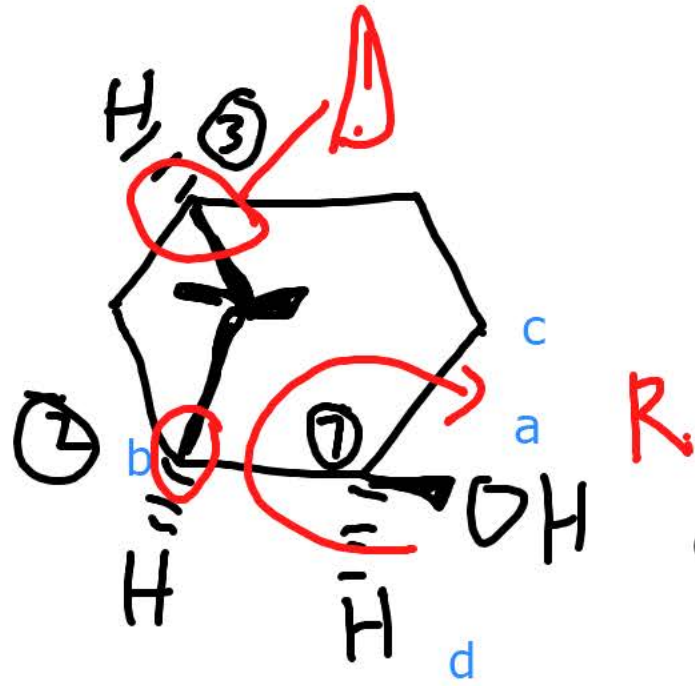
perspective

projection de Newman

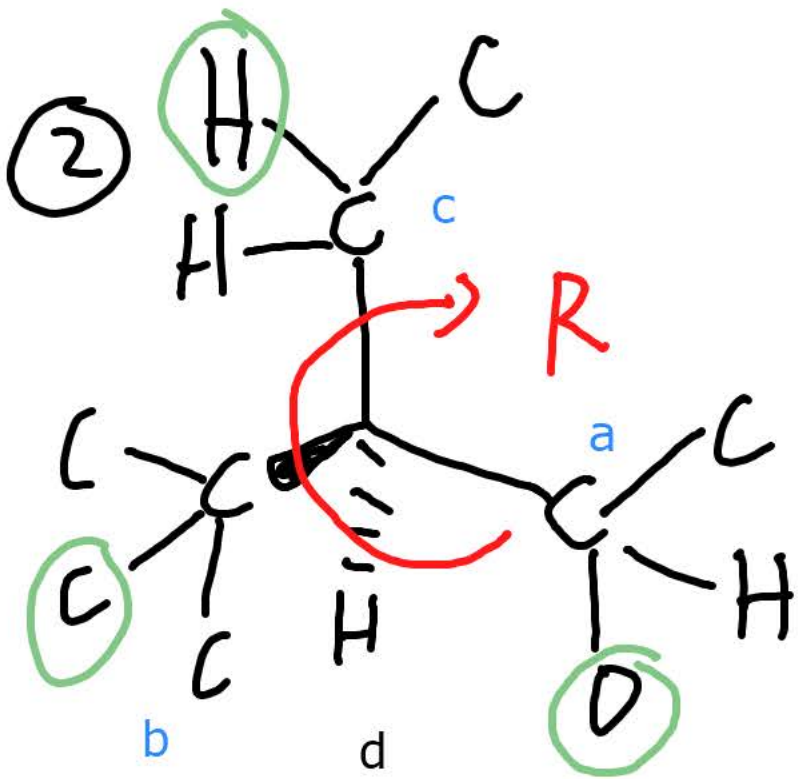
déterminer la configuration absolue (R ou S)

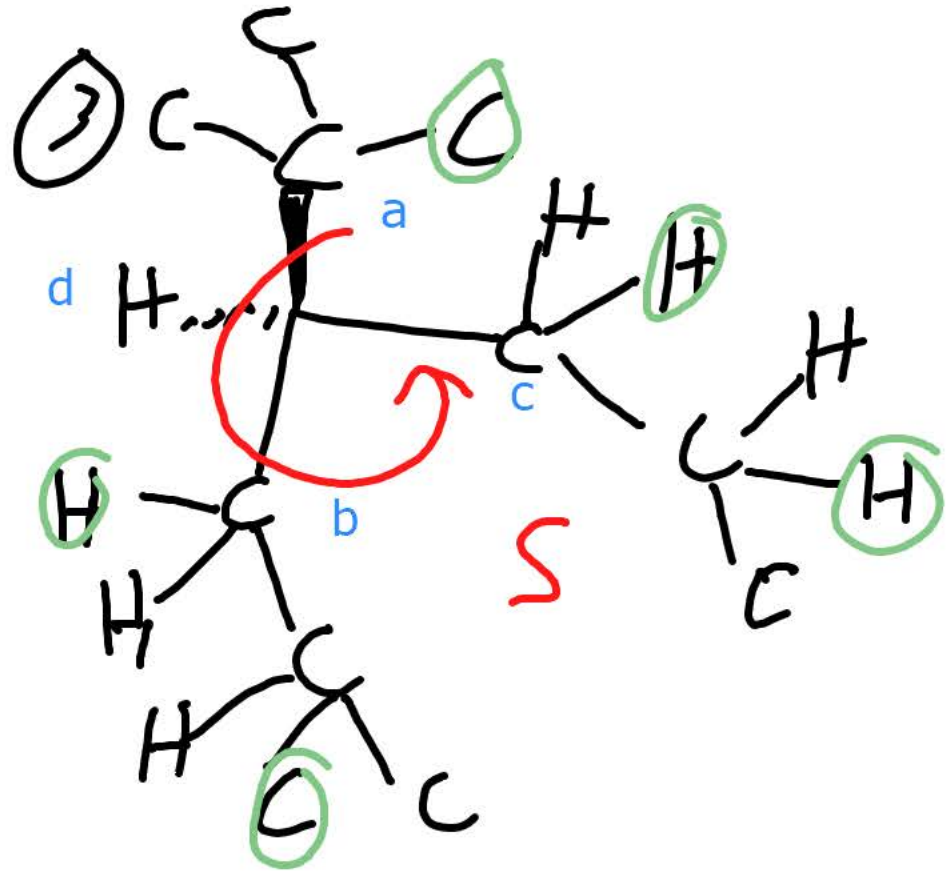


≡

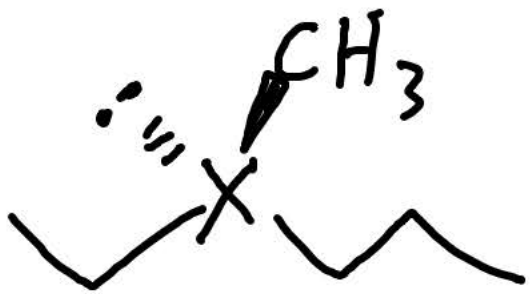


d derrière, OK


2
H
C
c
H
R
C
C
a
C
C
H
H
C
O
b
d

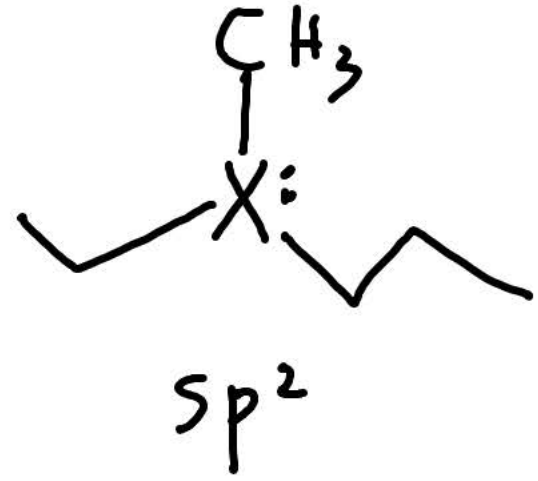

3
C
C
a
d
H
H
H
c
H
H
b
S
H
H
C
C
C

cas particulier des hétéroatomes avec paires d'électrons

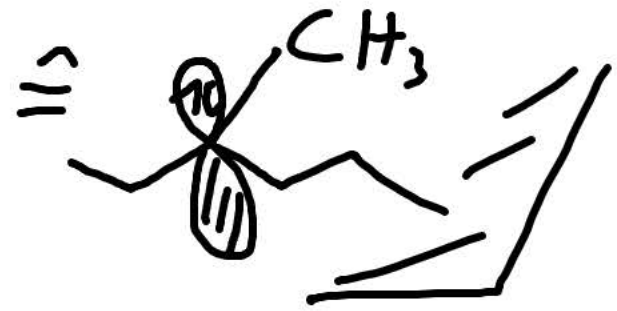


sp3, favorisé selon VSEPR
chiral

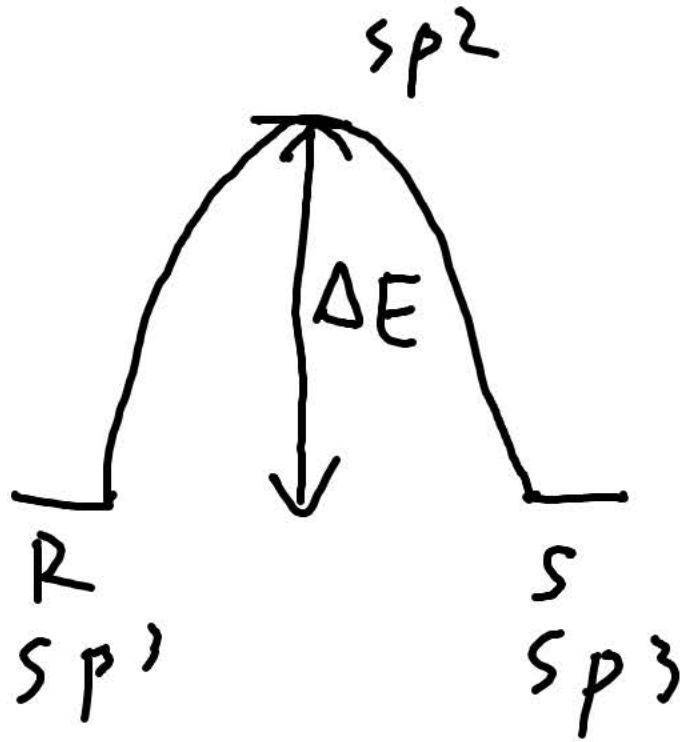
X= P, alpha non égal à 0, OK
X = N, alpha=0 (pas de chiralité à 25 °C!)



non chirale



plan de symétrie

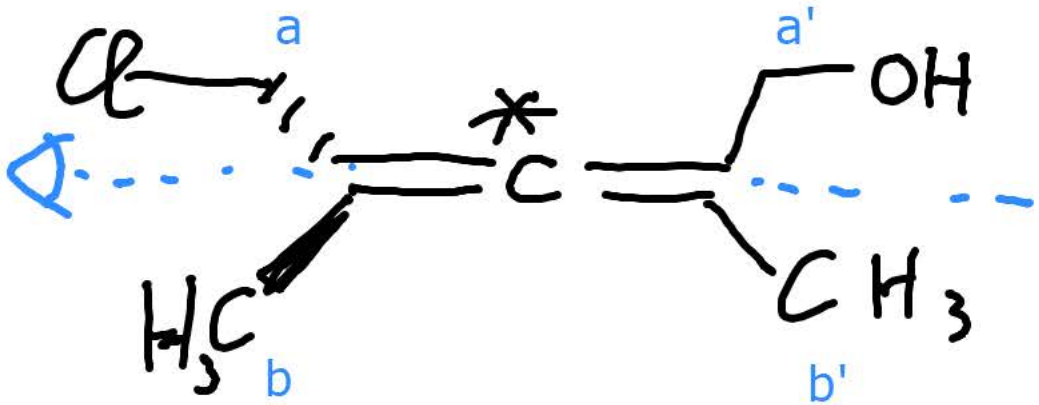


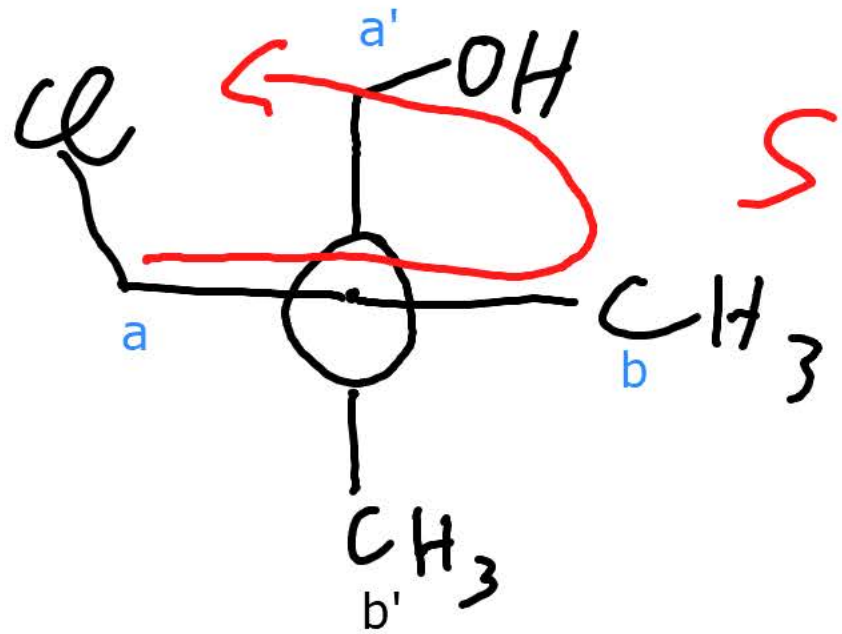
pour P: deltaE = 25 kcal/mol
pour N: delatE = 10 kcal/mol

temperature de 25 °C: = 21 kcal/mol

avec l'azote toujours racémique, pas de chiralité apparente!

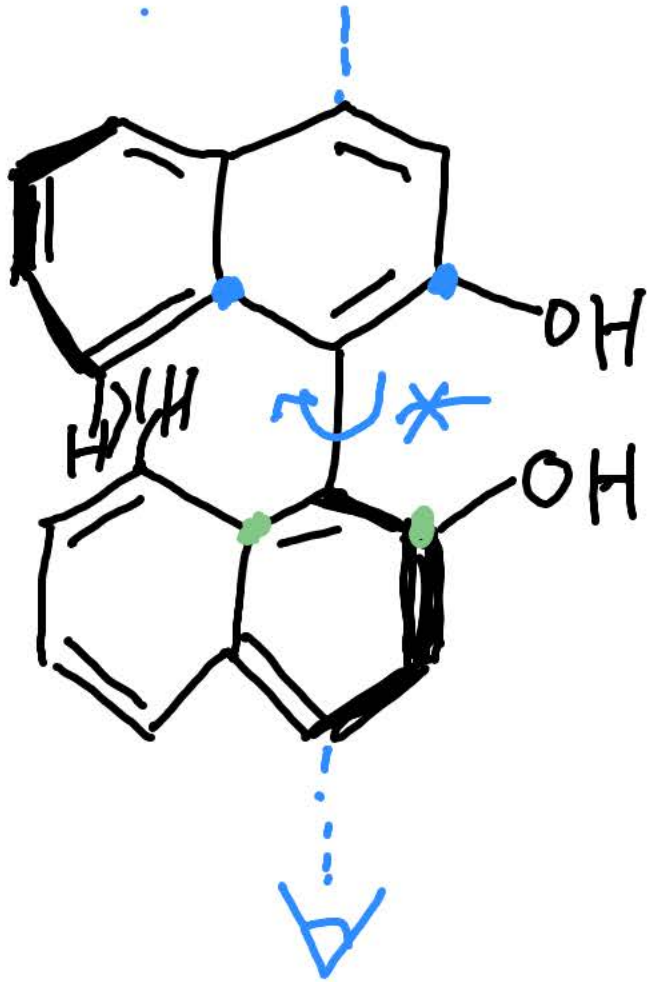
axes chiraux

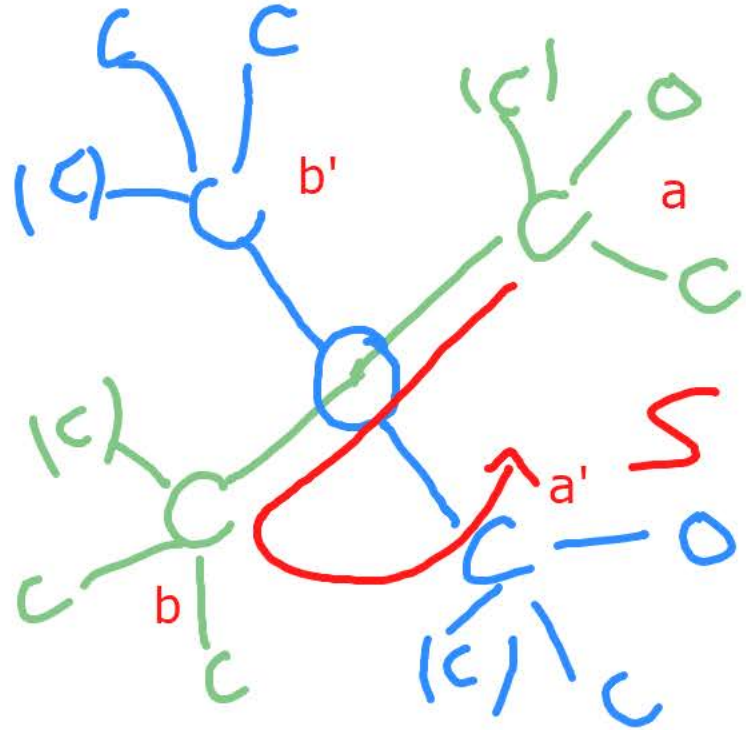


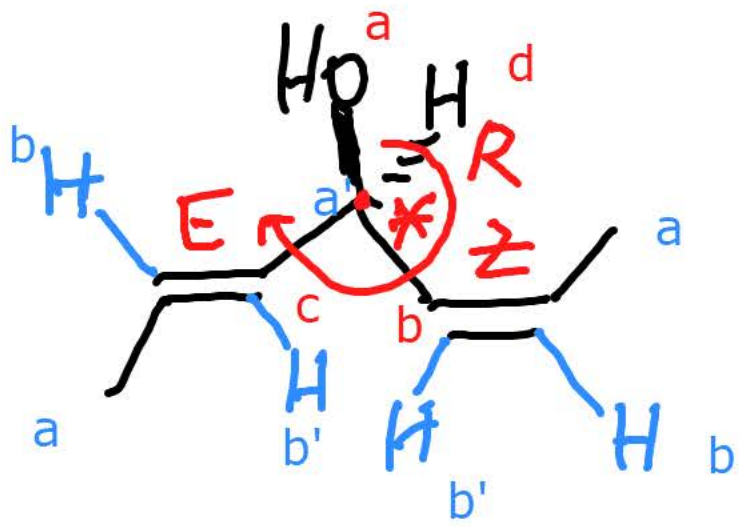


on tourne dans le sens:
grand devant, petit devant,
grand derrière

axe de chiralité le long d'une liaison avec rotation bloquée

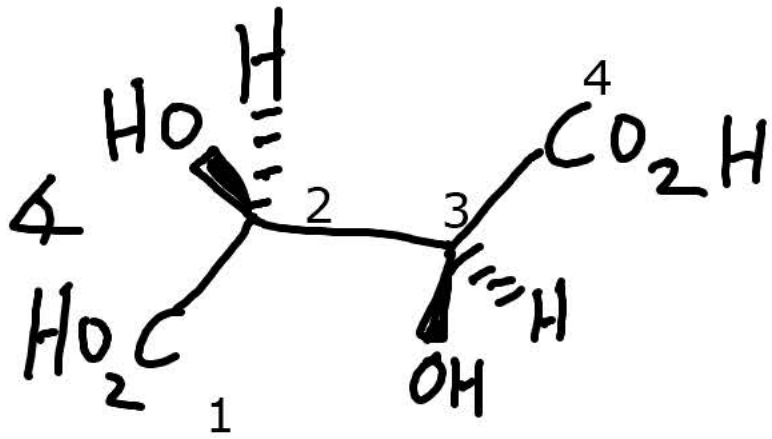






les substiuants sur C ne diffère que par la géométrie des alcènes
règle: Z à la priorité sur E

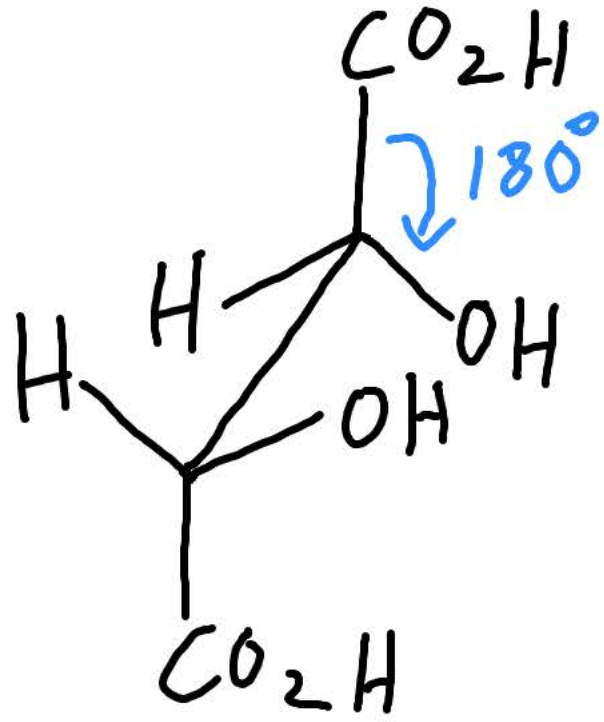
acide tartrique



(-)-(2S,3S)

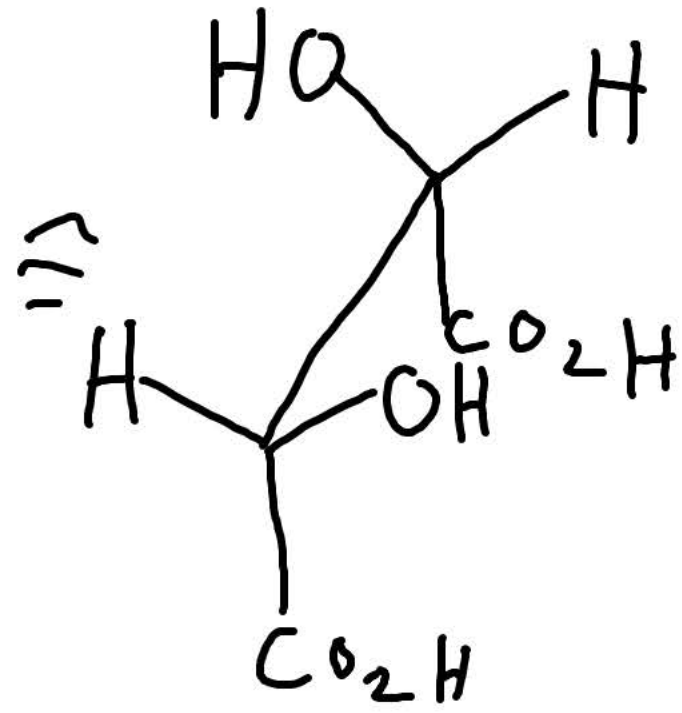
alphaD = -12°

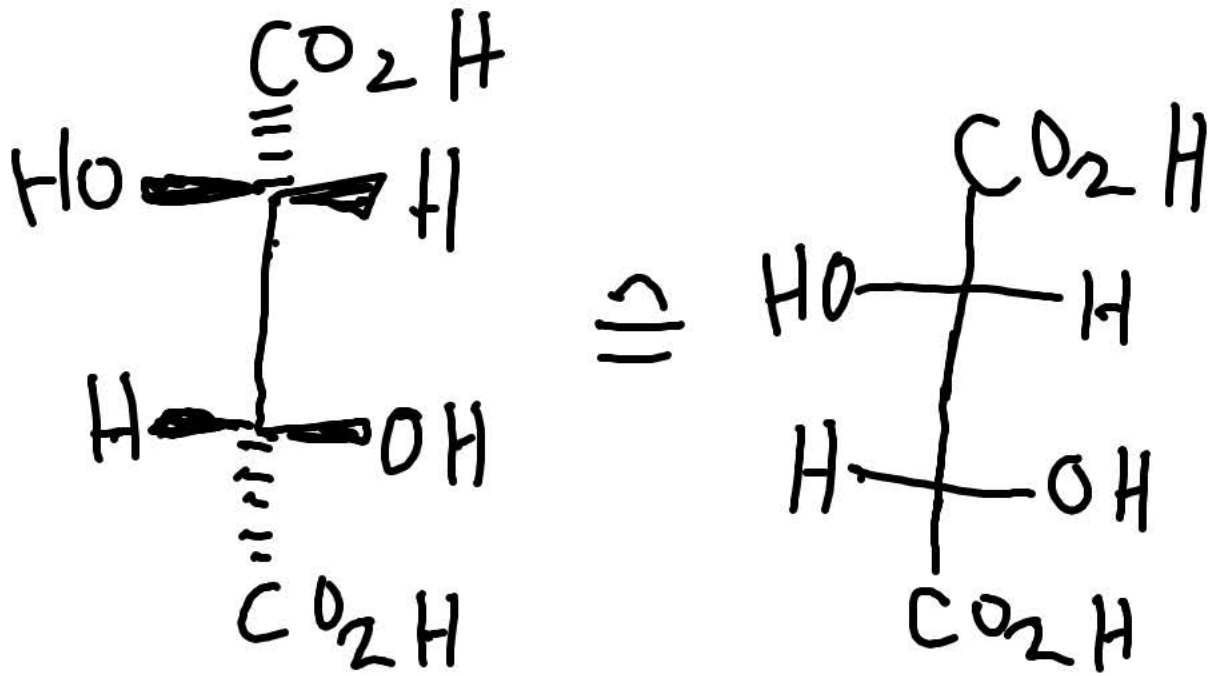
derrière

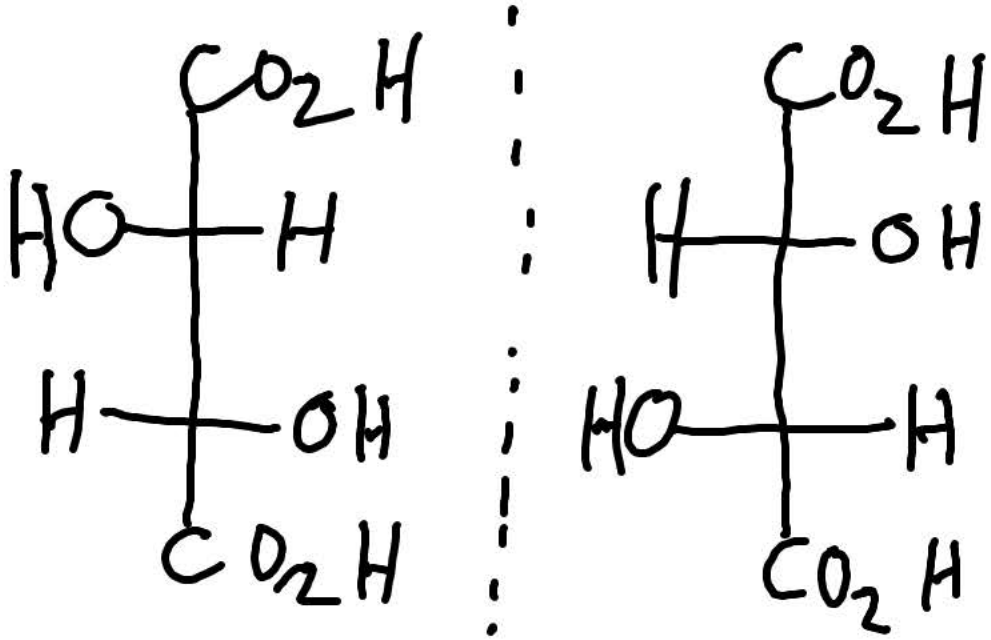


devant

A

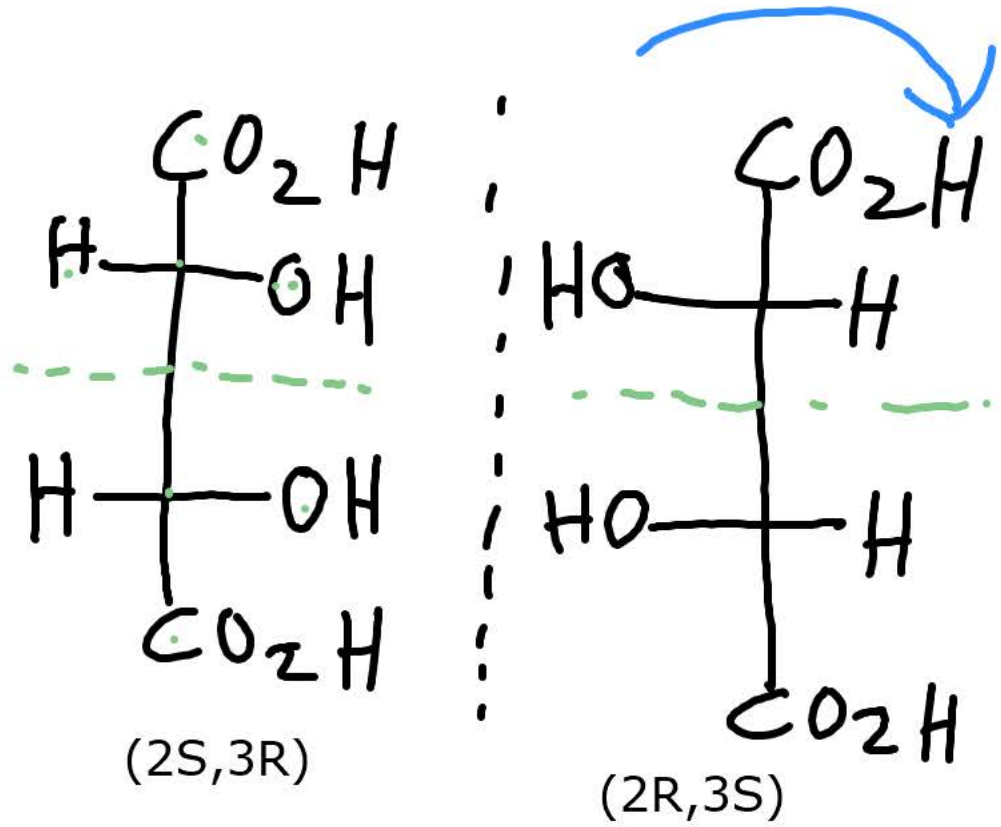



CO2H
HO
H
H
OH
CO2H
≙
CO2H
HO
H
H
OH
CO2H



(-)-(2S,3S)

(+)-(2R,3R)

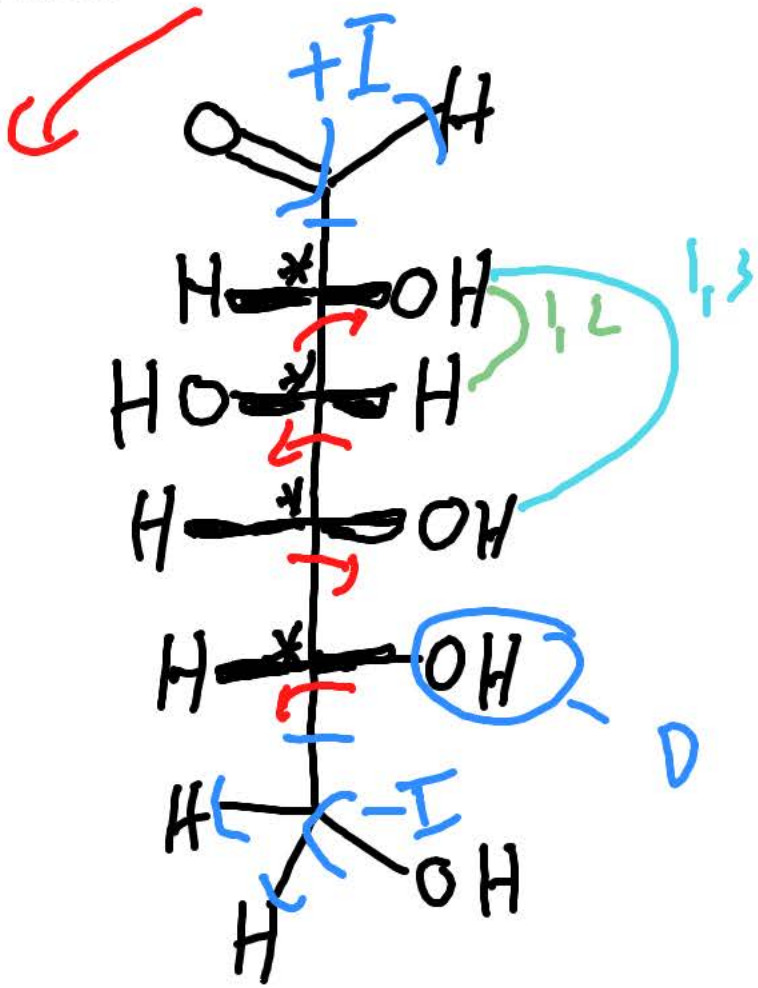


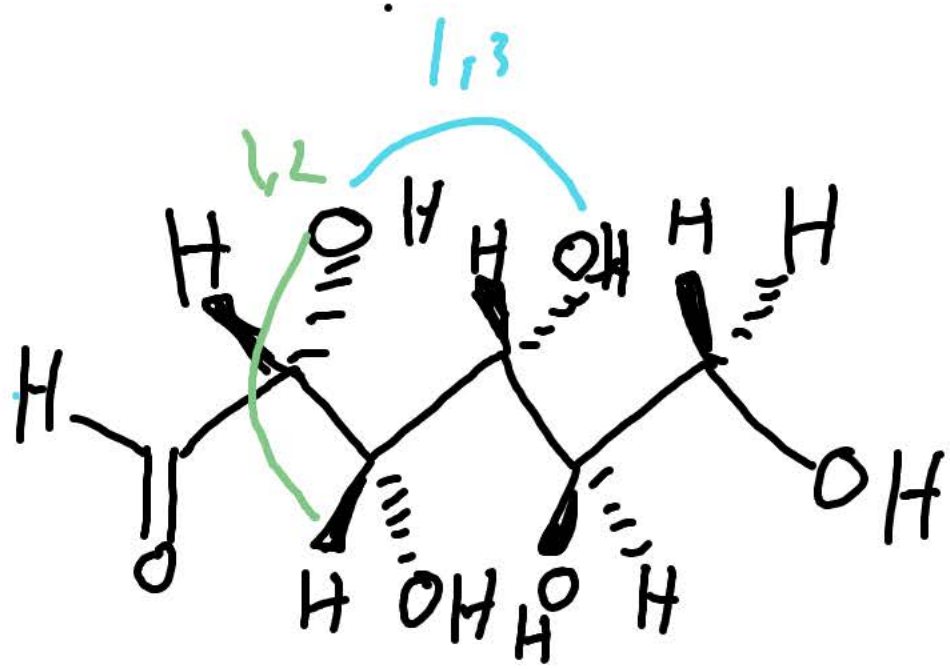
(2S,3R)

(2R,3S)

alphaD = 0
molécule identique!

Glucose

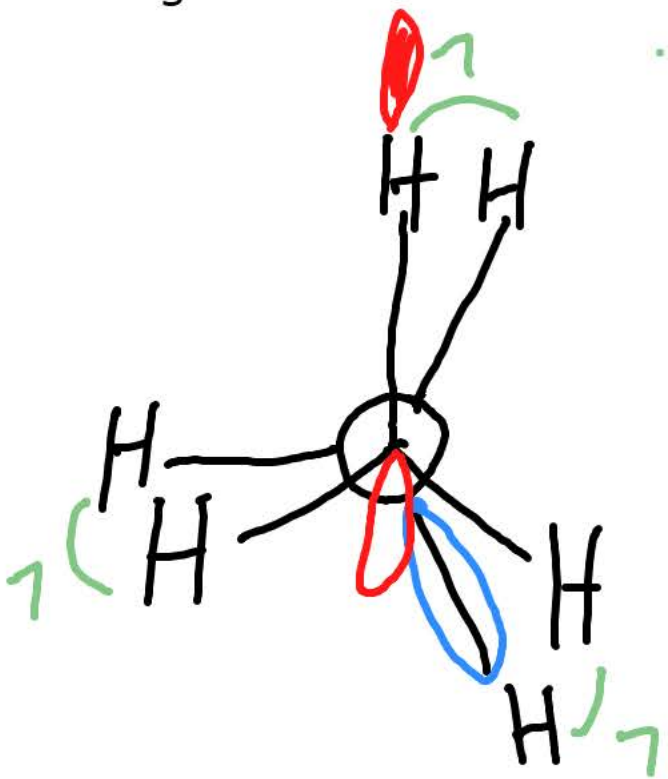




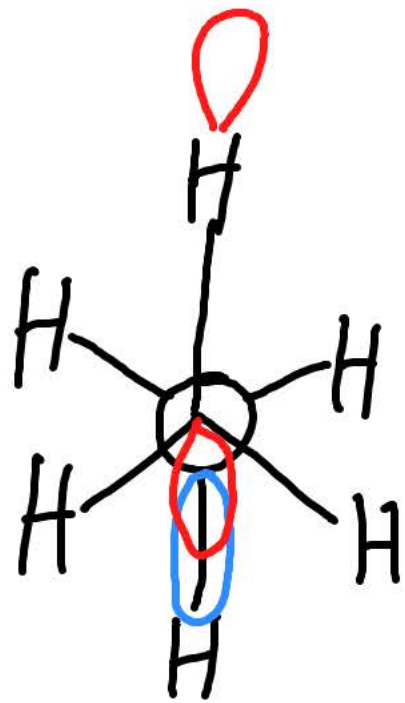
positions 1,2: inversées en passant de Fischer à zigzag

positions 1,3: restent du même côté

origine de la barrière d'énergie pour l'éthane



éclipsée



décalée

3 kcal/mol (mesuré)

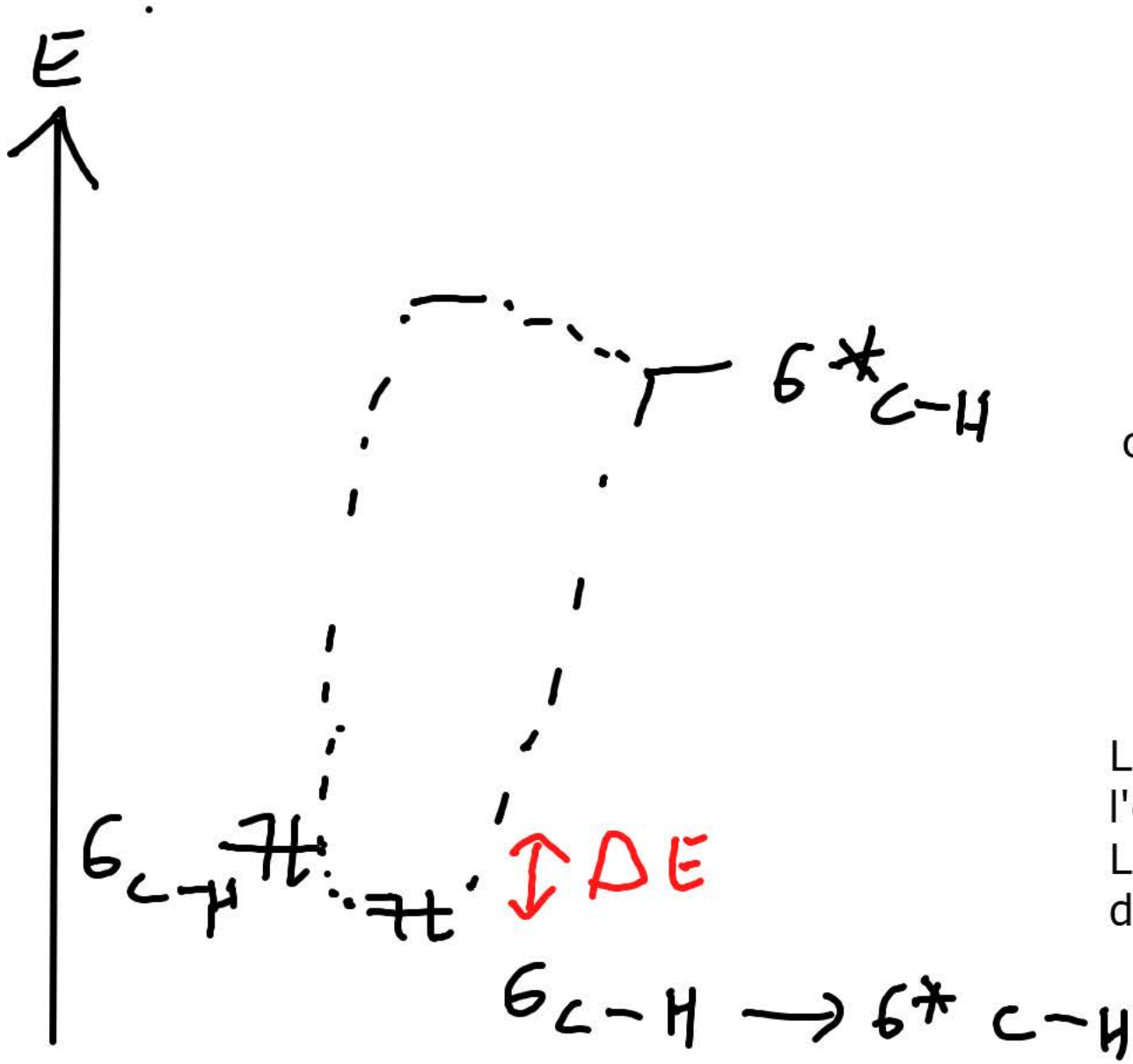
si on mesure le rayon van der Waals des atomes d'hydrogènes, il n'y a pas de contact!

interactions HOMO-LUMO
sigmaC-H et sigma*C-H

HOMO : σ_{C-H}

LUMO : σ^*_{C-H}

interaction uniquement dans la conformation décalée!



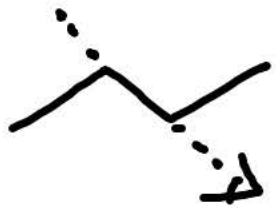
on a 6 fois cette interaction

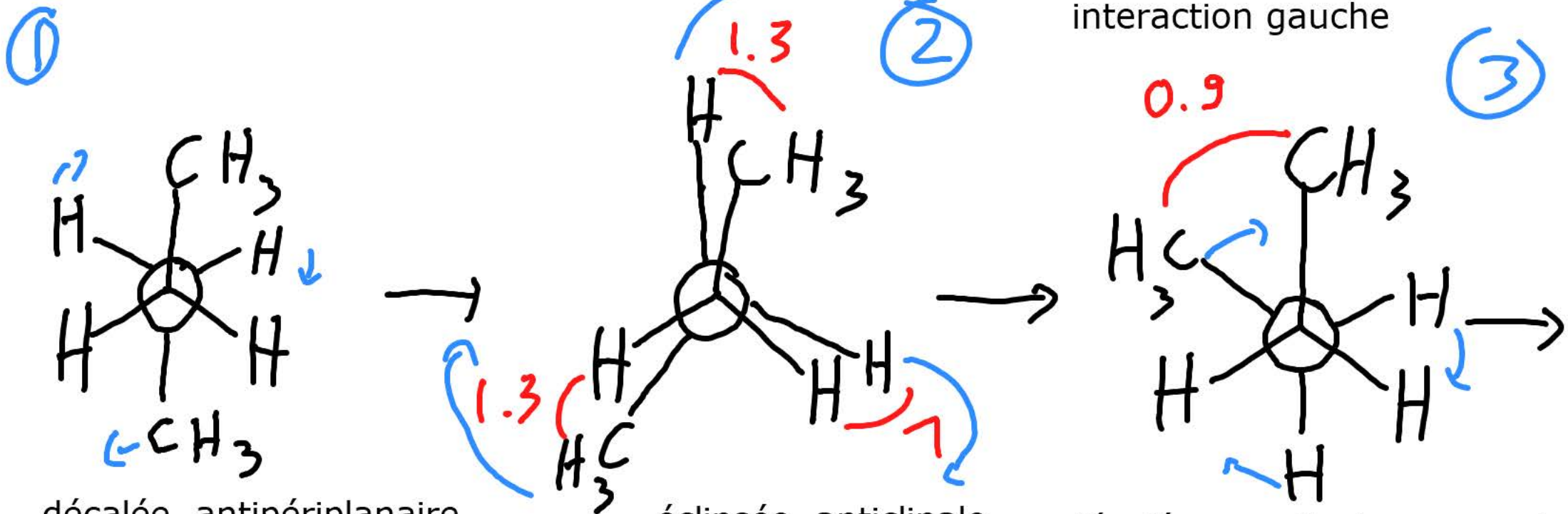
Chaque interaction à 2 électrons

deltaE = 3/12 kcal/mol = 0.25 kcal/mol

Les effets orbitales dominent pour l'éthane.
Les effets stériques commencent avec des atomes de la deuxième période

butane

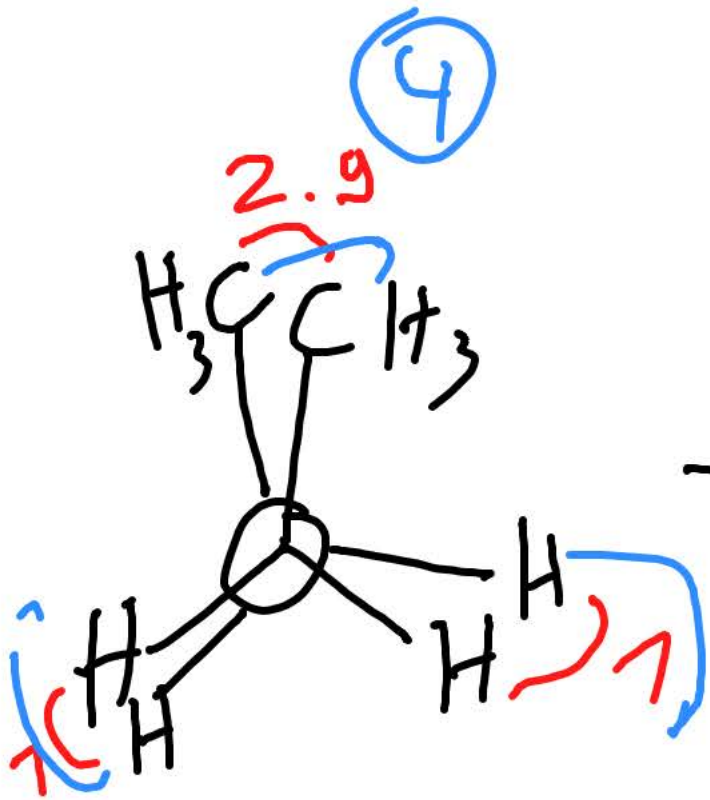




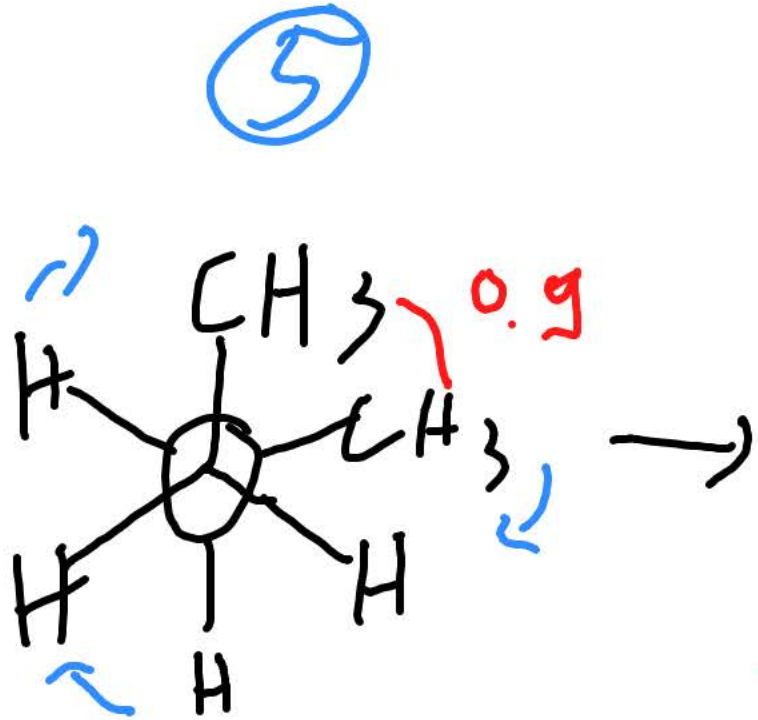
décalée, antipériplanaire
Energie relative = 0

éclipsée, anticlinale
E = 3.6

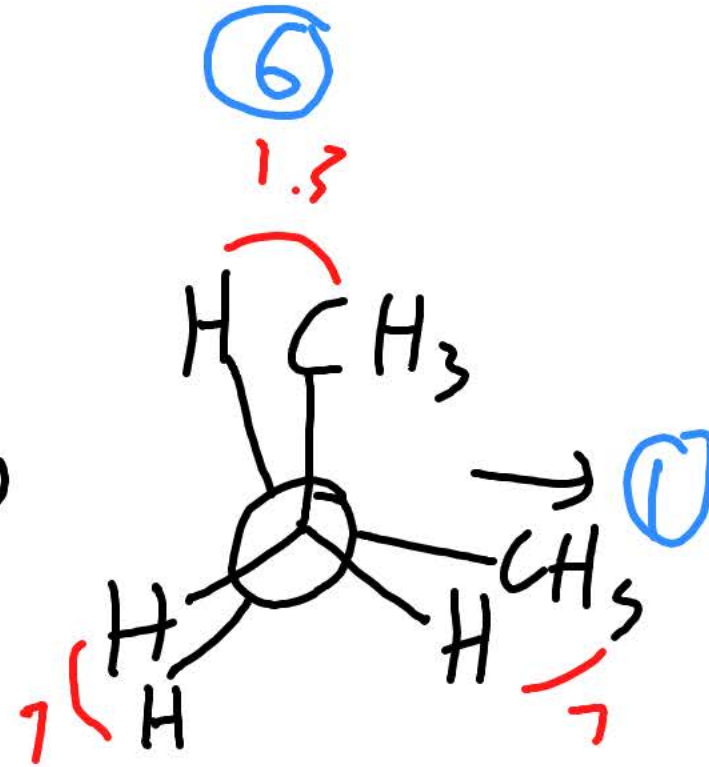
décalée, synclinale ou gauche
E = 0.9



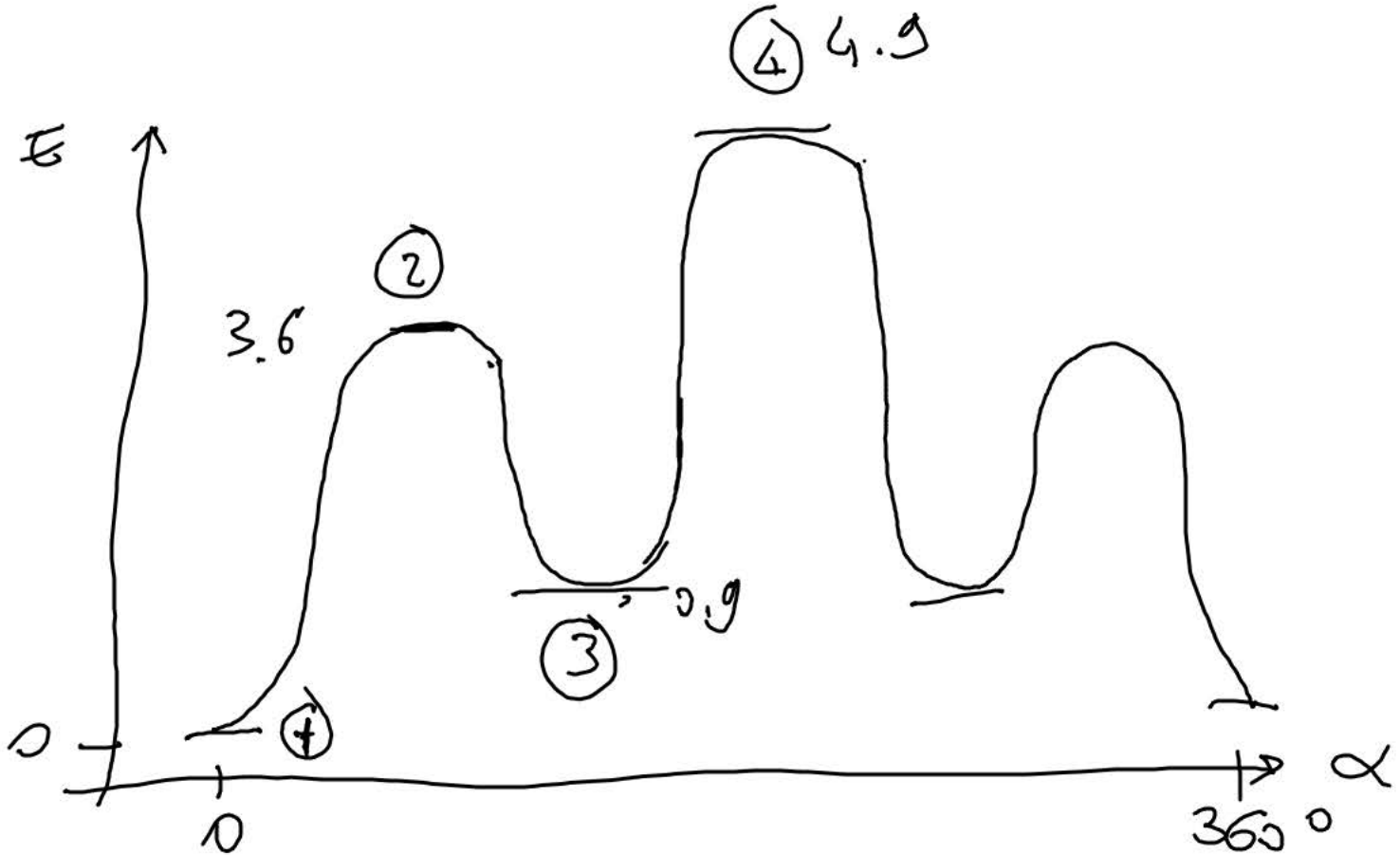
éclipsée, synpériplanaire
E = 4.9



décalée, synclinale ou gauche
E = 0.9



éclipsée, anticlinale
E = 3.6

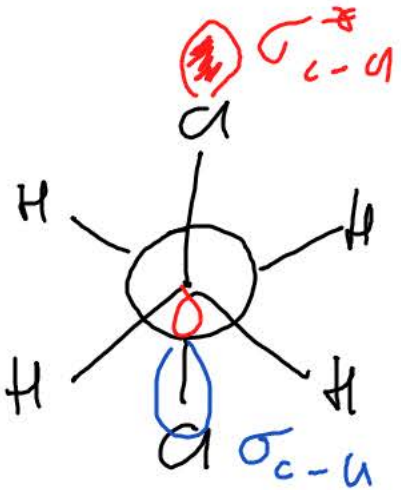

E
4
4.9
2
3.6
3
0.9
1
0
0
360
α

butane

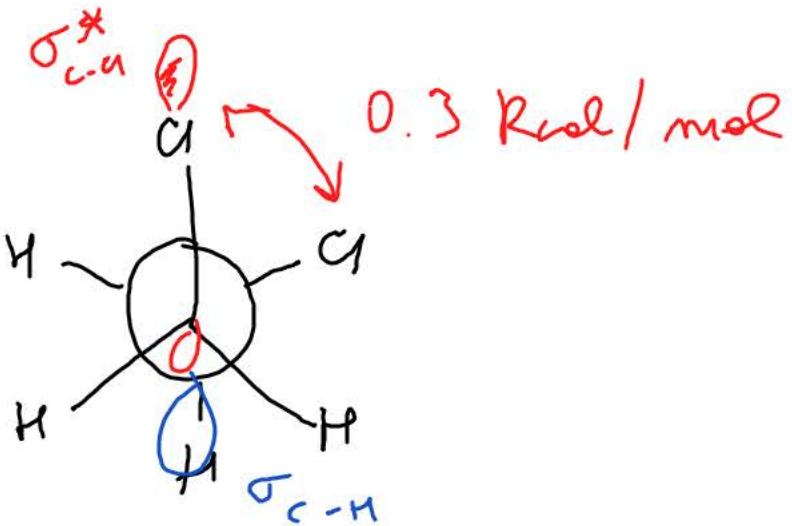
antipériplaire plus stable

1,2-dichloroéthane

gauche plus stable!

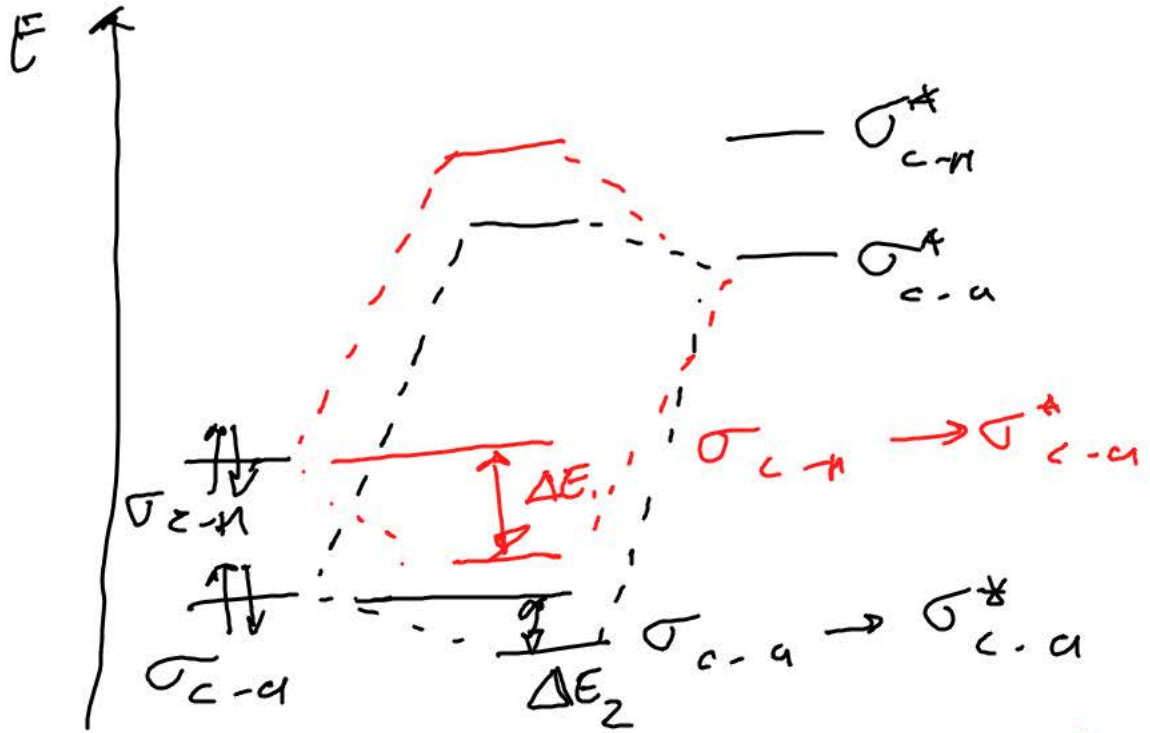


antipériplanaire



gauche

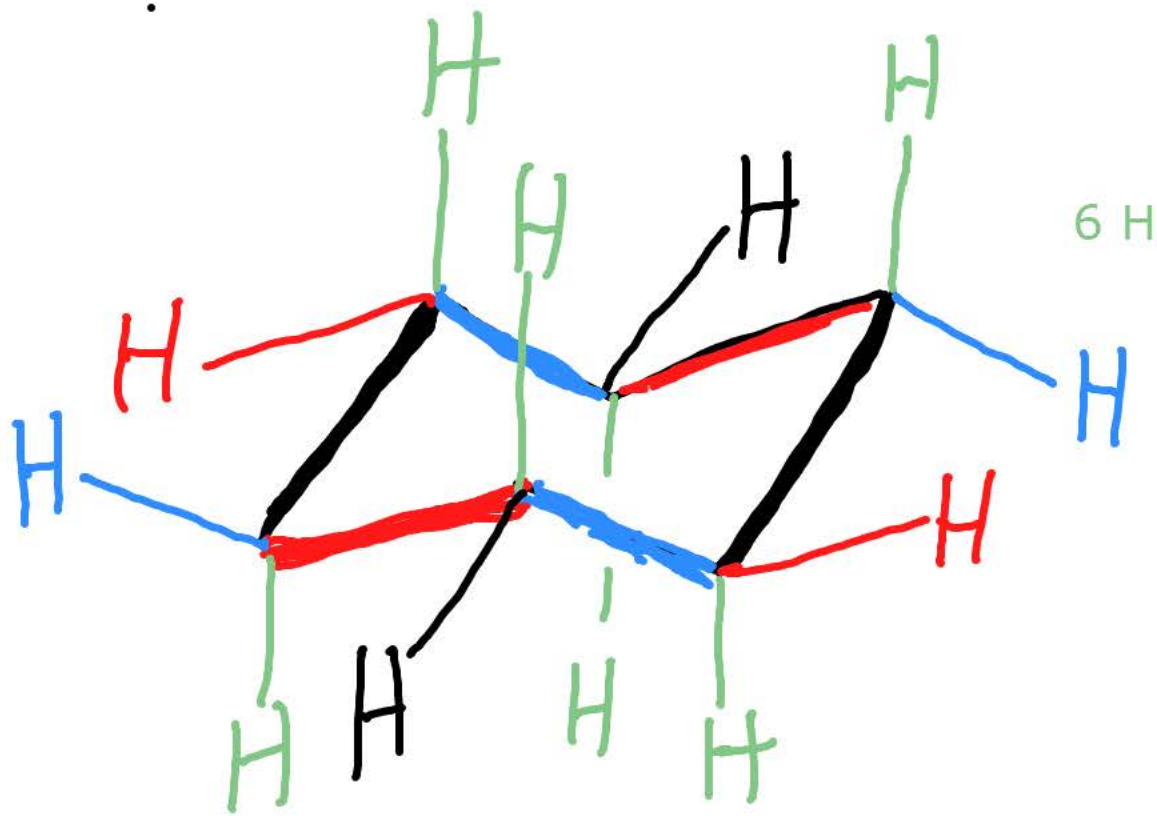
Cl plus EN que H



$\Delta E_1 > \Delta E_2$ ✓

gauche antipéripl.

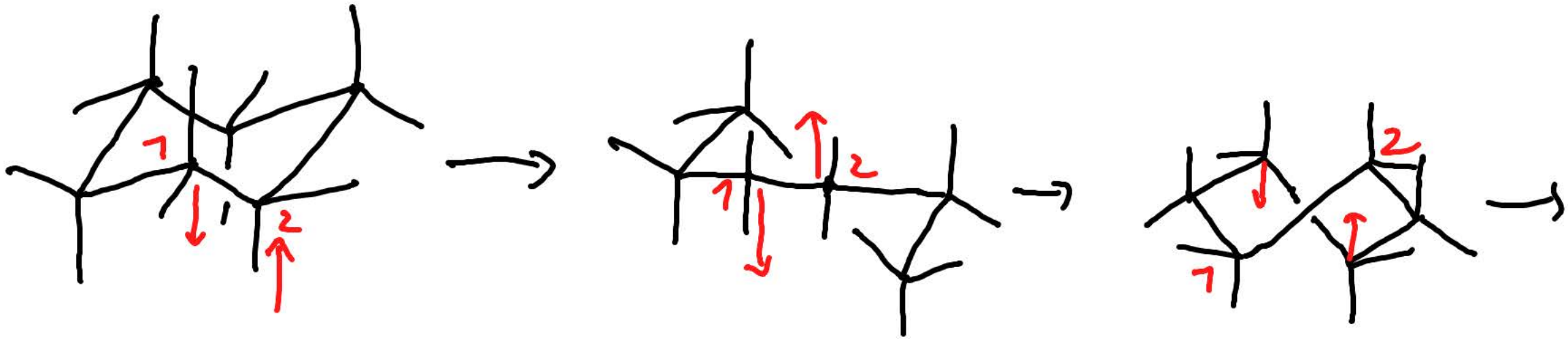
conformation en chaise du cyclohexane



6 H axial

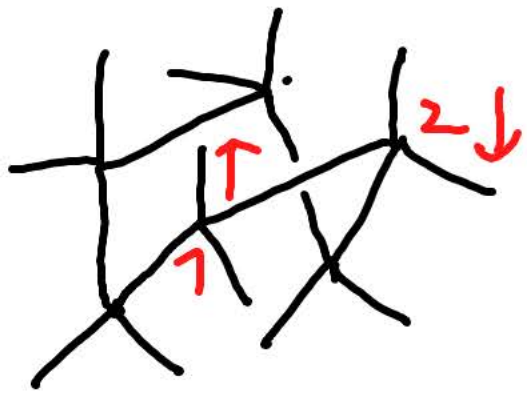
6 hydrogène équatorial
noir, bleu, rouge

Conformères du cyclohéxane



demi-chaise, maximum
E = 10.8 kcal/mol

bateau croisé, twist
minimum
E = 5.5 kcal/mol



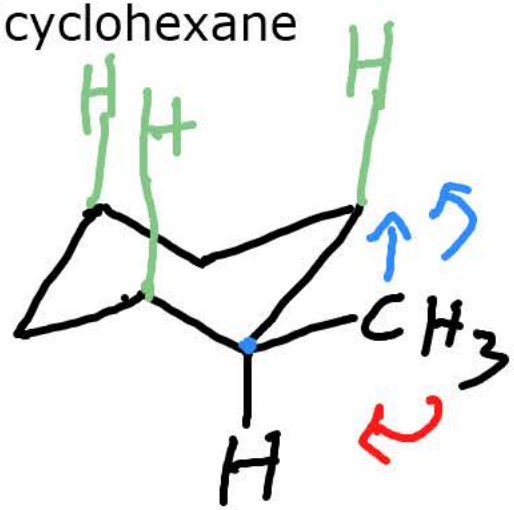
bateau, maximum local
E = 6.9 kcal/mol

→ TWIST → DEMI-CHAISE

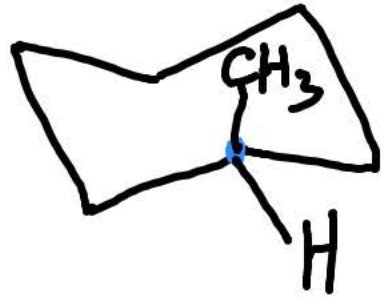
↓

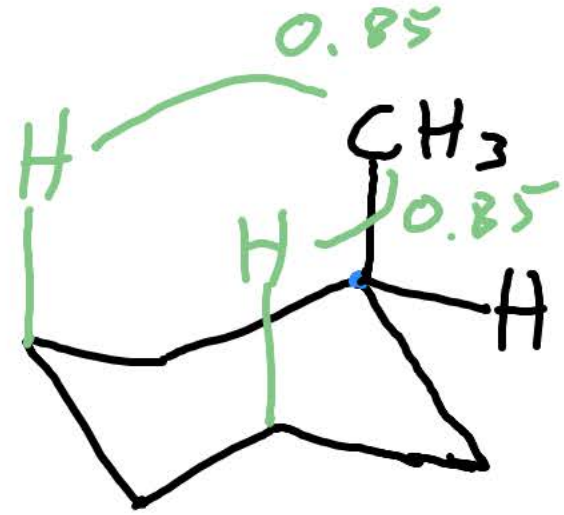
CHAISE

methylcyclohexane



Me équatorial





1) inverser la "perspective"

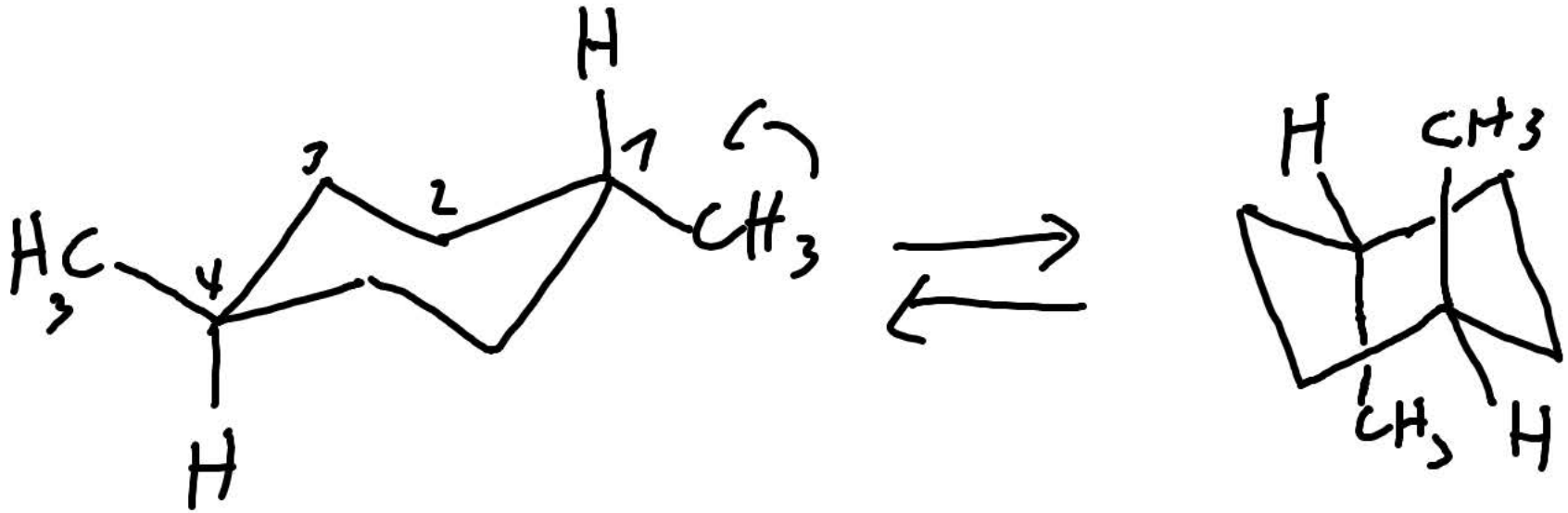
2) monter et tourner

Me axial

méthyl en axial défavorisé pour 1.7 kcal/mol (valeur A du Me)
deltaG = -RT lnK, K = 0.056 (utilser J et K!)
environ 95:5 équatorial:axial
1.4 Kcal = environ 10:1
2.8 Kcal = environ 100:1

:

trans-1,4-diméthylcyclohéxane

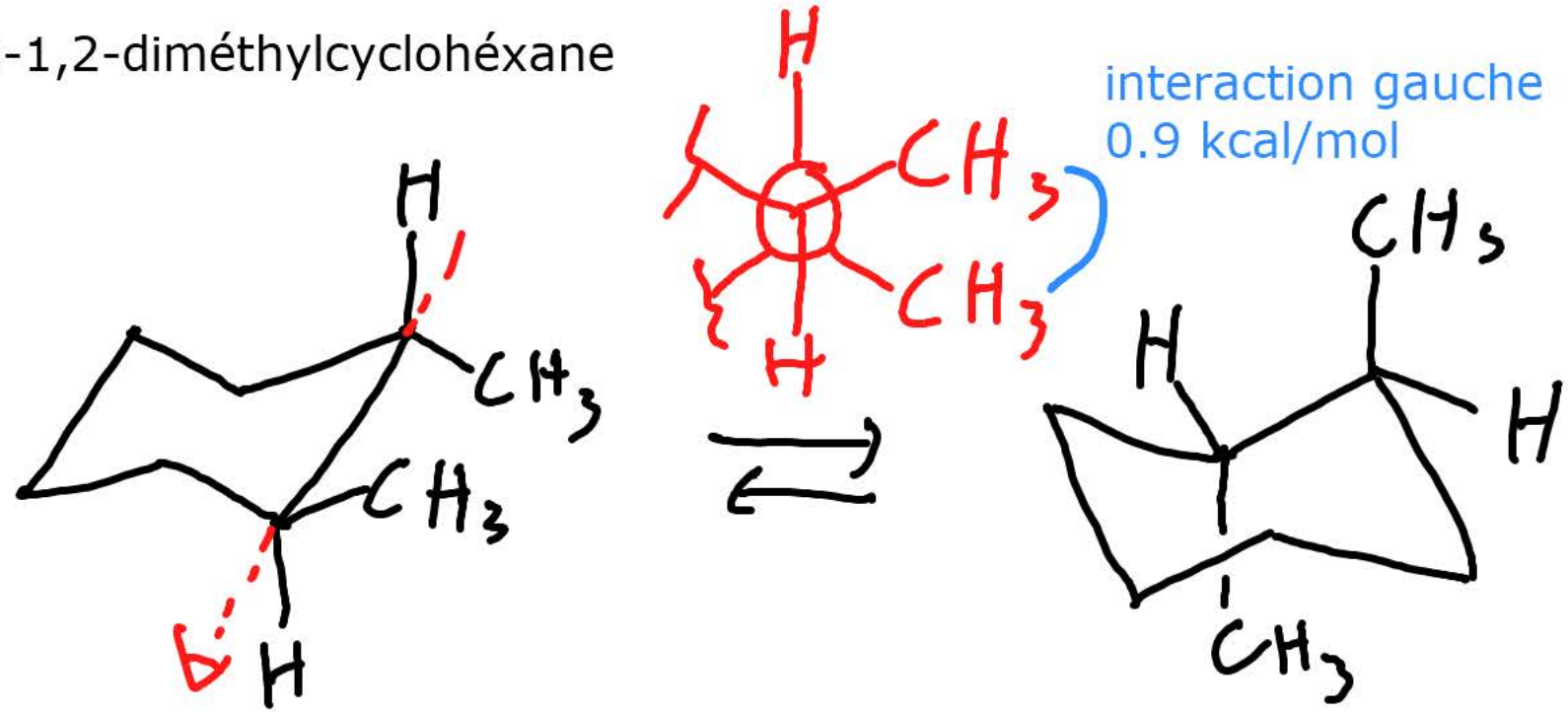


2x méthyl équatorial

2x méthyl axial

deltaG attendu: 2x 1.7 kcal/mol = 3.4 kcal/mol
deltaG mesuré: 3.4 kcal/mol

trans-1,2-diméthylcyclohéxane

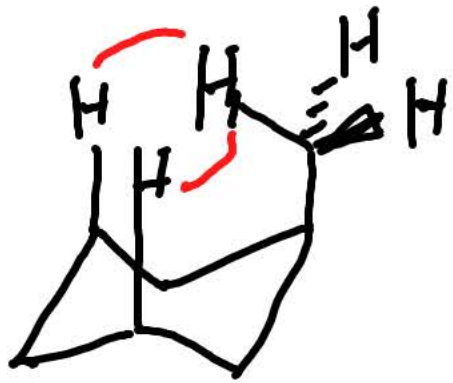


2 méthyl équatorial

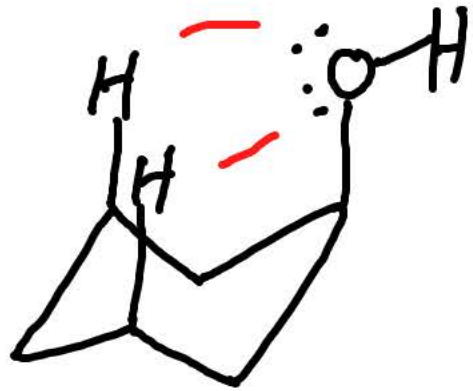
2 méthyl axial

deltaG attendu: 2x1.7 = 3.4 kcal/mol
deltaG mesuré: 2.5 kcal/mol! 0.9 kcal/mol de différence!

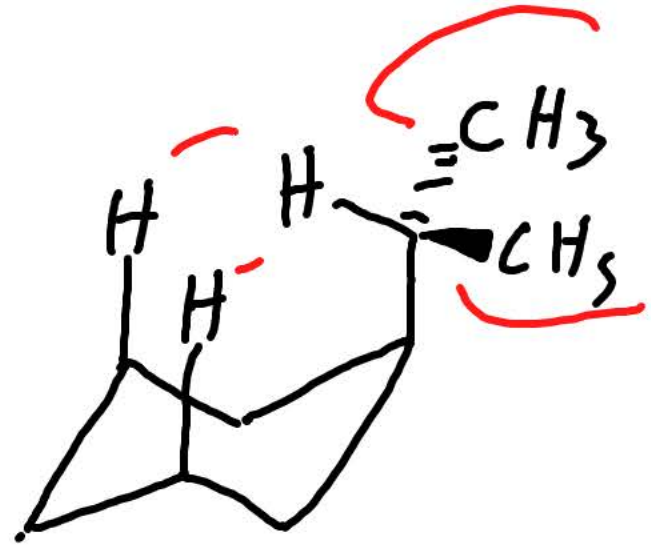
la différence s'explique par une interaction gauche qui défavorise la structure avec 2 méthyls équatorial



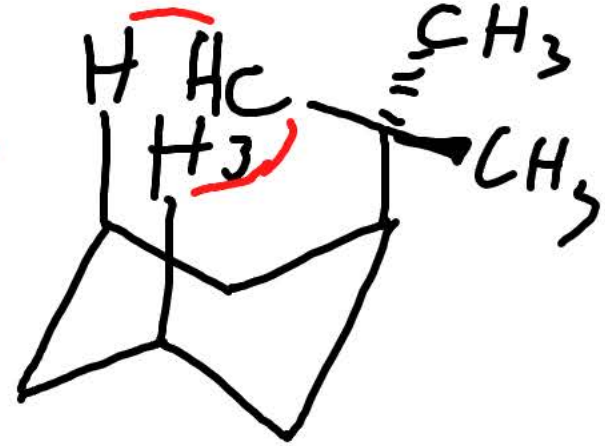
A = 1.7



A = 0.9
paire d'électrons
plus petites



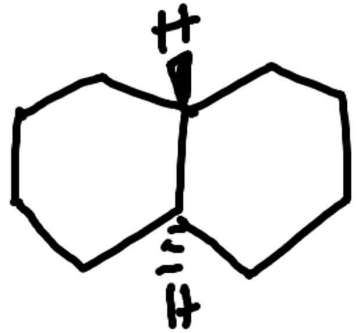
groupe iPr A = 2.2



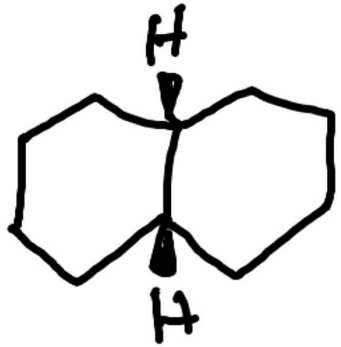
groupe tBu
A = 5
tert-butyl sera "presque
toujours" équatorial

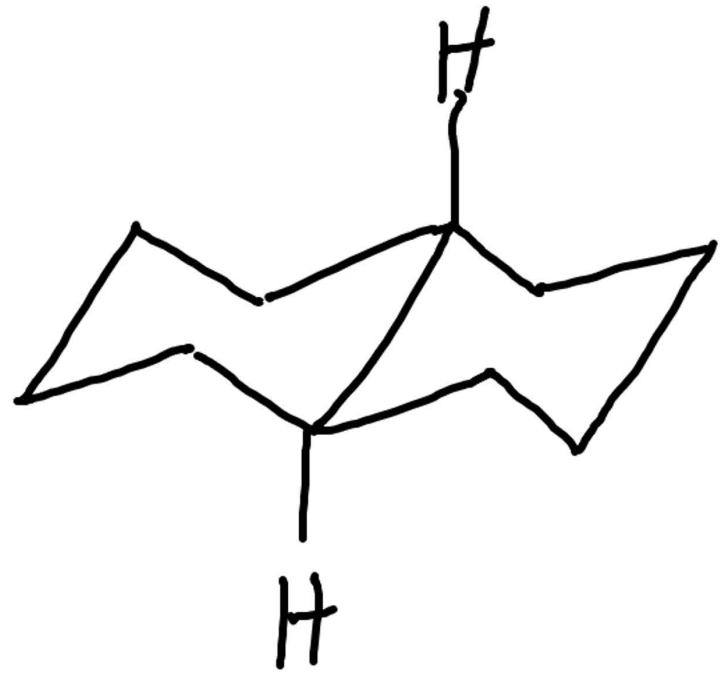
cycles fusionnés: les décalines (10 atomes de C)

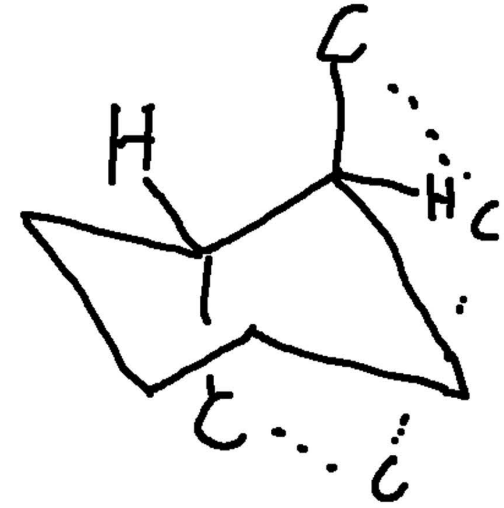
trans-décalines



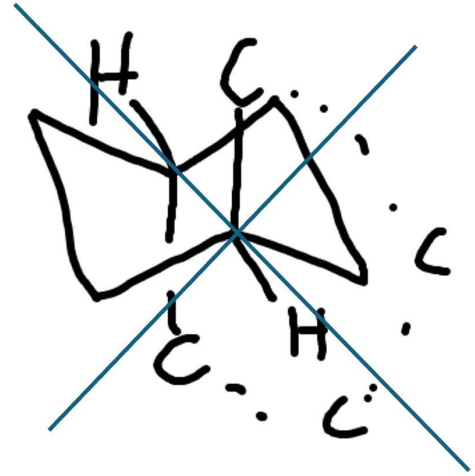
cis-décalines





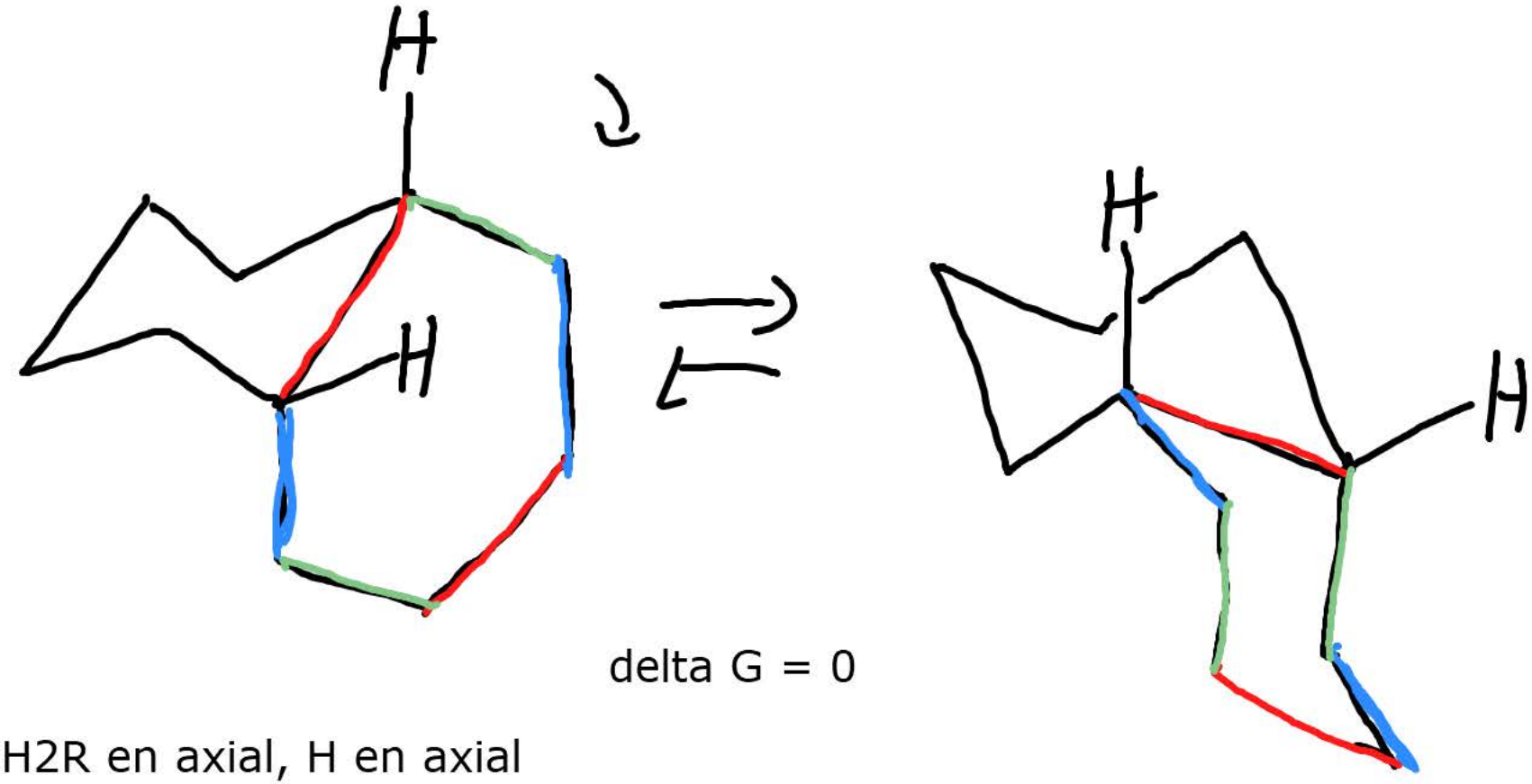


corrected



une seule conformation pour la trans décaline!
Avec tous les C presque dans le même plan

cis-décalines

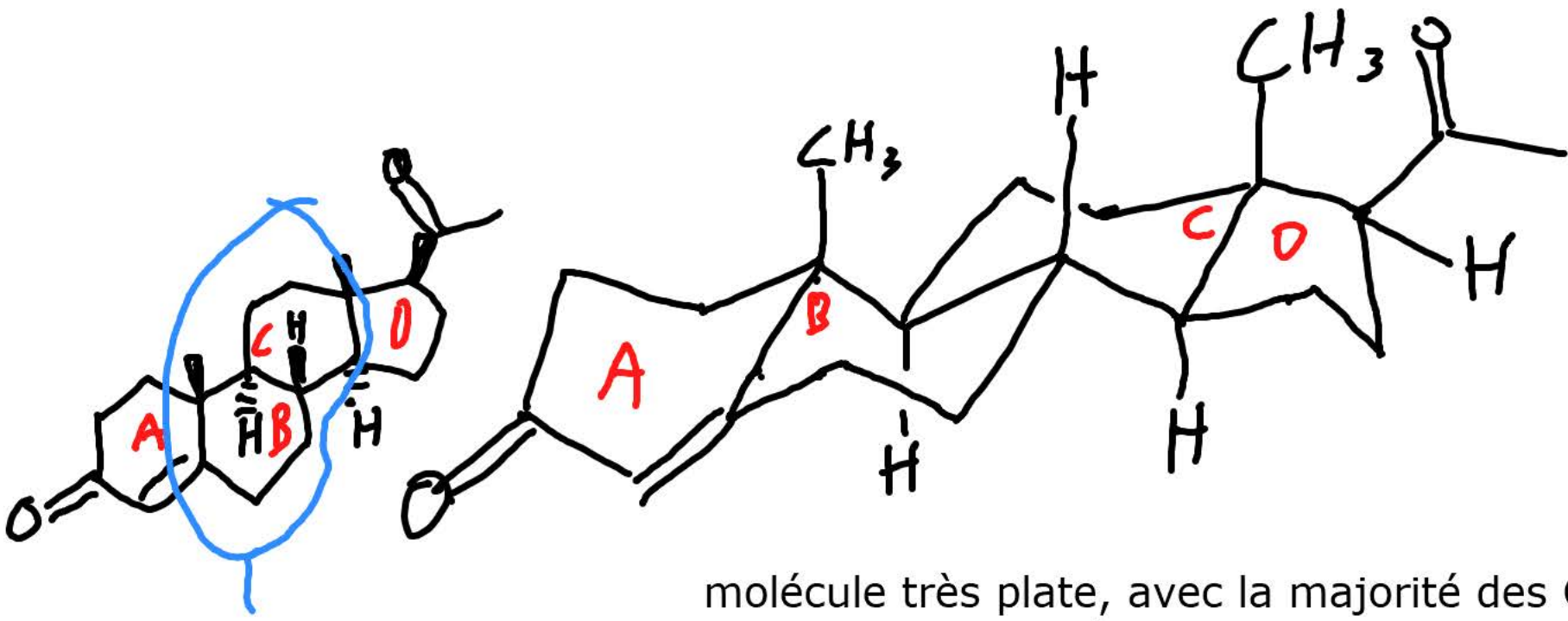


delta G = 0

CH2R en axial, H en axial

CH2R en axial, H en axial

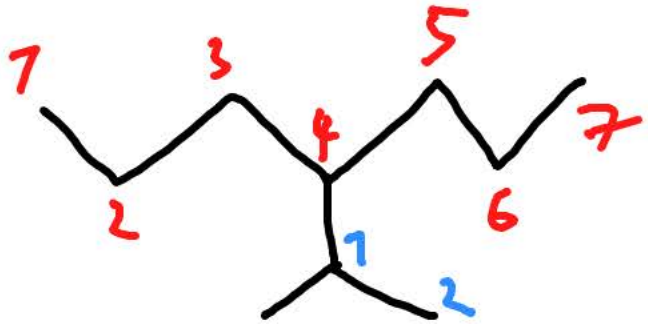
progesterone



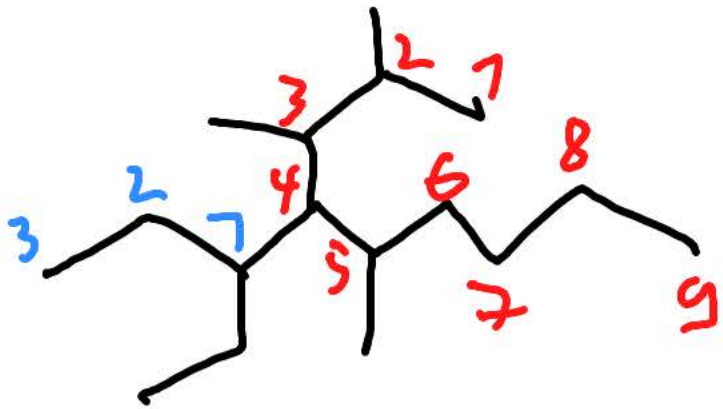
·trans-décaline!

molécule très plate, avec la majorité des C dans les cycles sur le même plan

nomenclature des alcanes



4-(1-methylethyl)-heptane
4-isopropylheptane (non trivial du substituants)



nonane

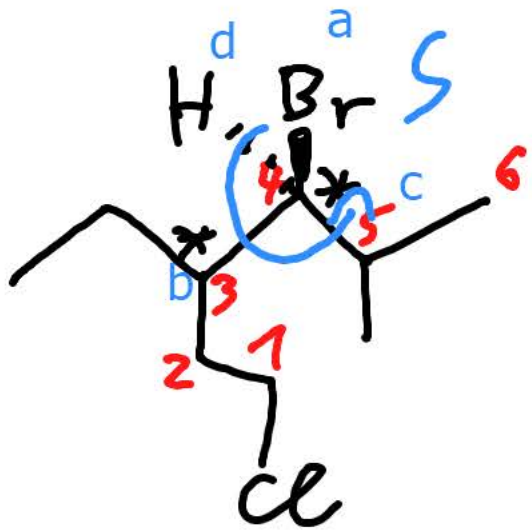
2,3,5-triméthyl

4-(1-ethylpropyl)-

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

Nomenclature

Halogènes: F, Cl, Br, I: toujours comme chaine secondaire avec les préfixes fluoro, chloro, bromo et iodo, sans priorité particulière

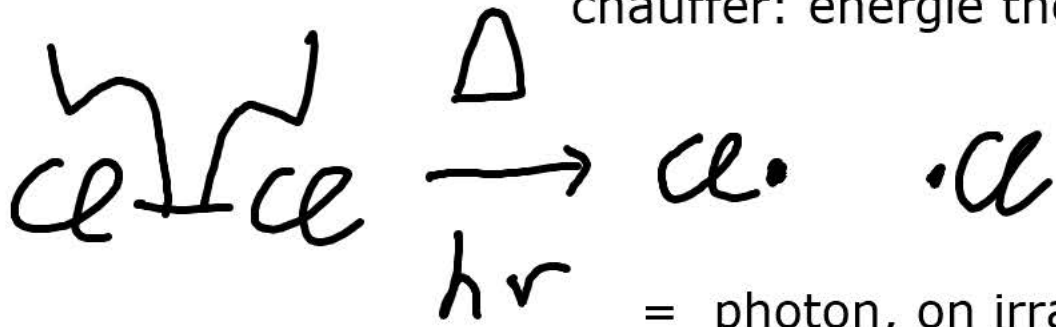


hexane

5-methyl 3-ethyl
4-bromo
1-chloro

(4S)-4-bromo-1-chloro-3-ethyl-5-methylhexane

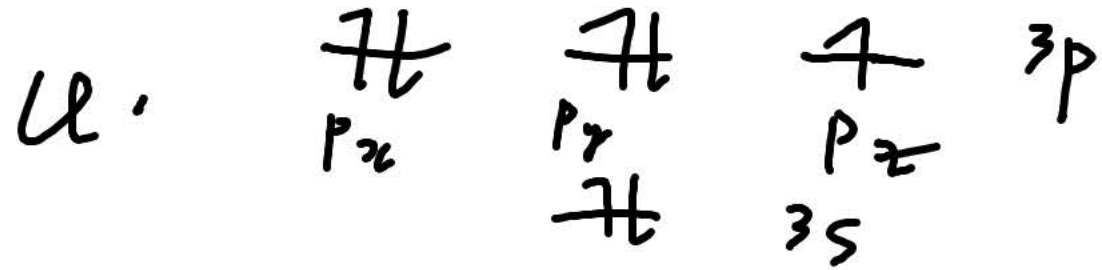
Initiation pour la chlorination du méthane

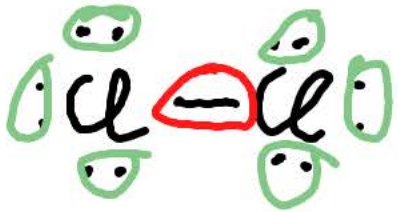


chauffer: énergie thermique

= photon, on irradie lumière UV

pour Cl2: pas de liaison avec C, on fait une liaison sans hybridisation!

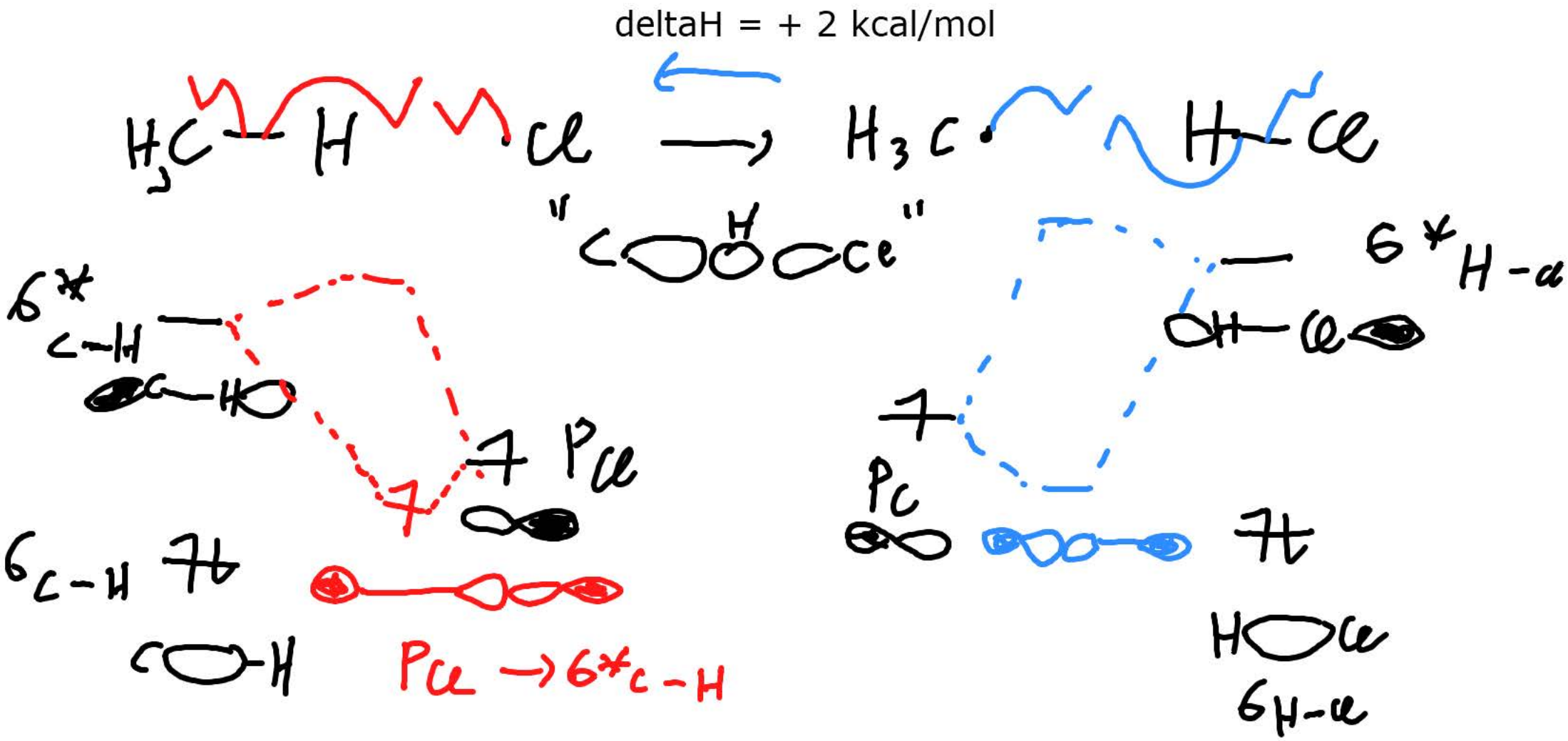




donne la couleur
à la molécule

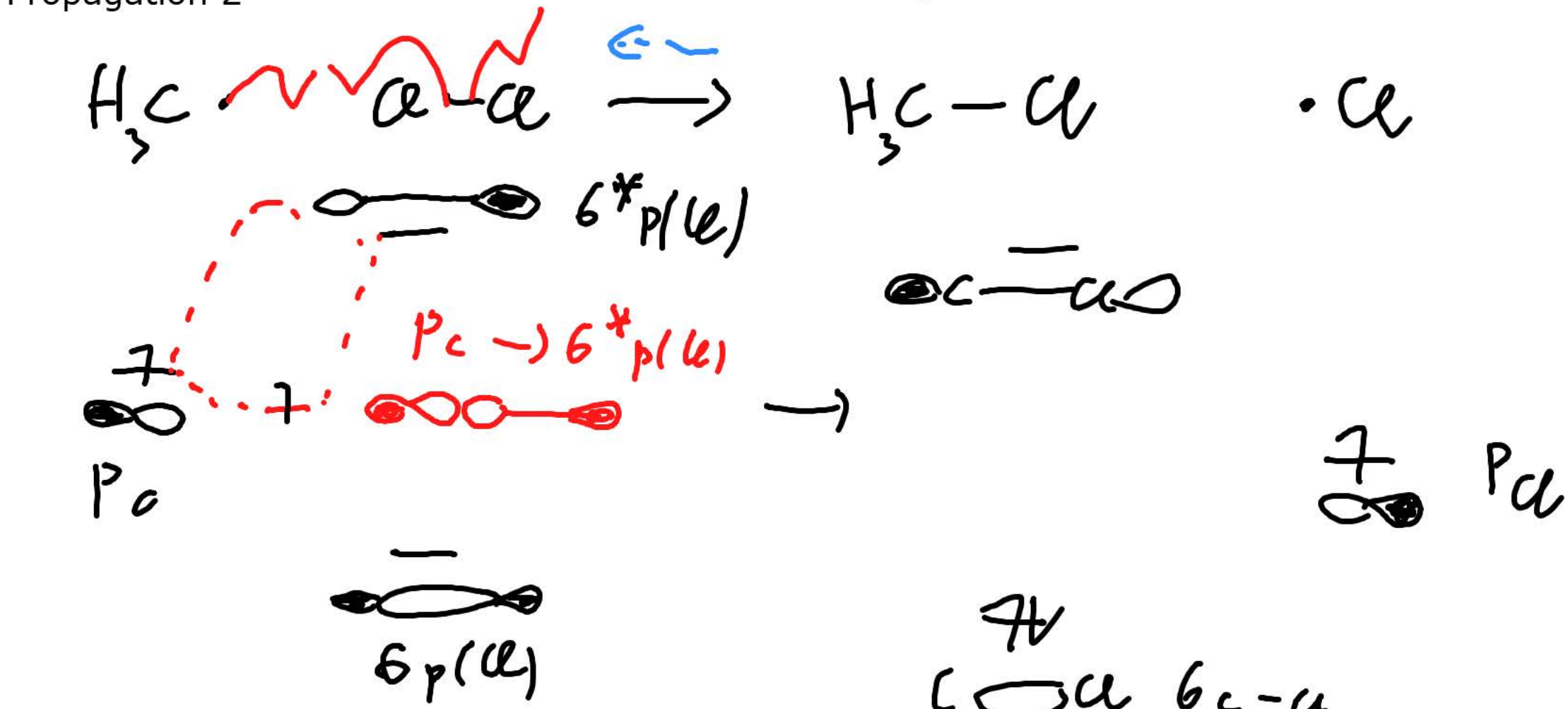
on brise la liaison sigma,
58 kcal/mol
Lumière U

réactions de propagation

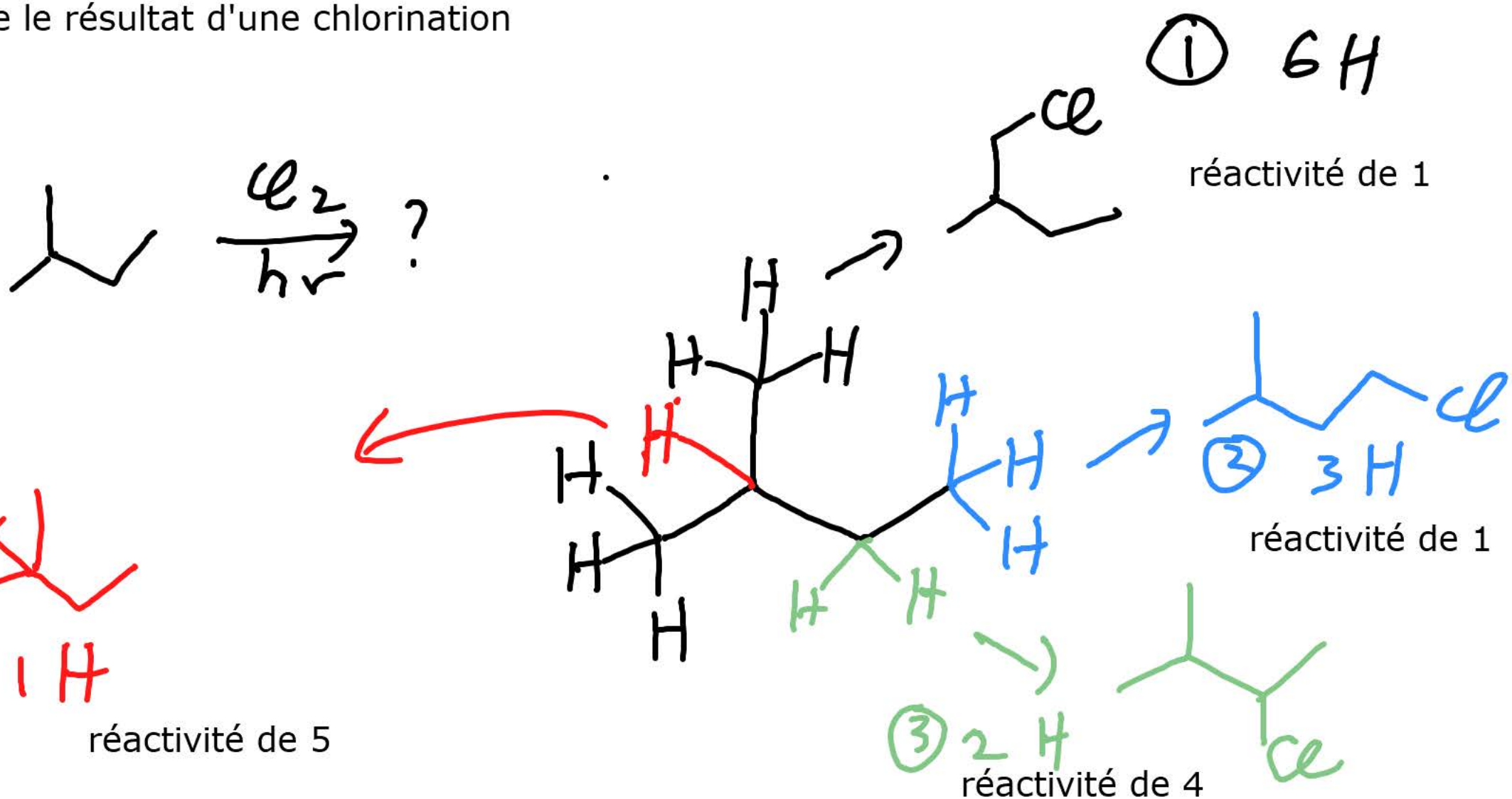


Propagation 2

deltaH = -27 kcal/mol



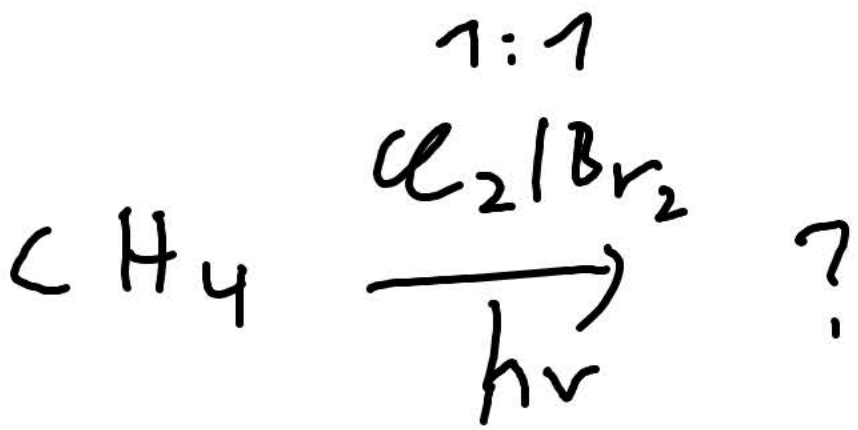
prédire le résultat d'une chlorination



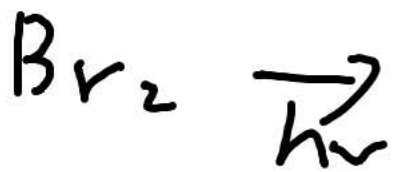
composé	nombre de H	réactivité corrigée	proportion
①	6	$6 \times 1 = 6$	$6/22 = 27\%$
②	3	$3 \times 1 = 3$	$3/22 = 14\%$
③	2	$2 \times 4 = 8$	$8/22 = 36\%$
④	1	$1 \times 5 = 5$	$5/22 = 23\%$
		22	

Autres halogènes?

1) F2? extrêmement réactif, seul le nombre de H compte (toutes les positions réagissent à la même vitesse):
produit 1: produit 2: produit 3: produit 4 = 6:3:2:1
2) Br2: moins réactif, la stabilité du radical détermine le produit
On obtiendra le produit 4 majoritairement. produit 4 > 95%
3) I2: plus réactif du tout, on a pas de réaction.



Initiation



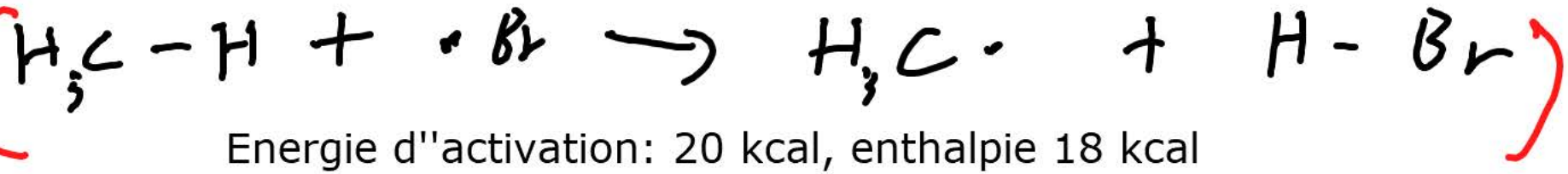
plus rapide

liaison Br2 un peu plus faible, mais les deux liaisons sont activée par UV, deux réactions possibles, un peu plus de radical Br

propagation

1) 

Energie d'activation: 3 kcal, enthalpie: 2 kcal

()

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

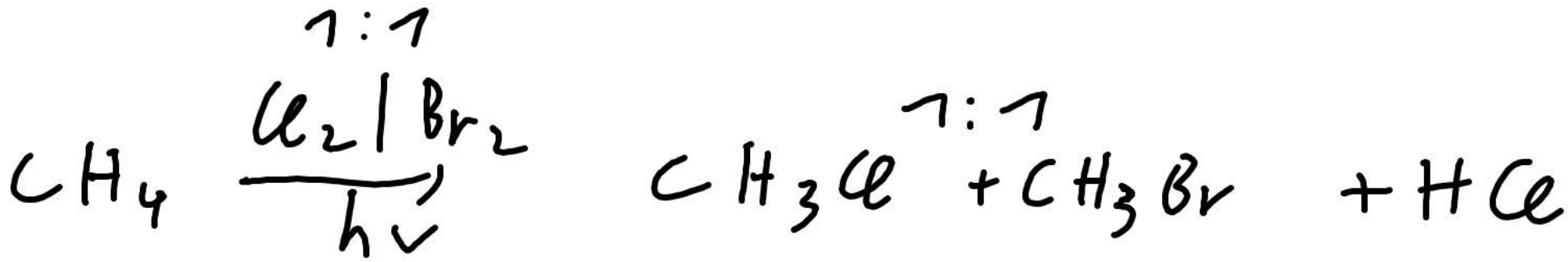
2) 

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

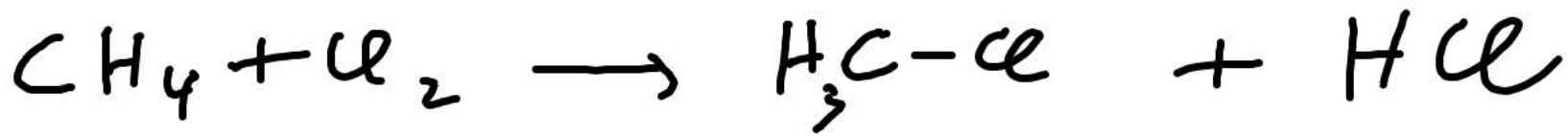
mélange 1:1!

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

Au temps 0, on a



métrique de la chimie verte pour la chlorination



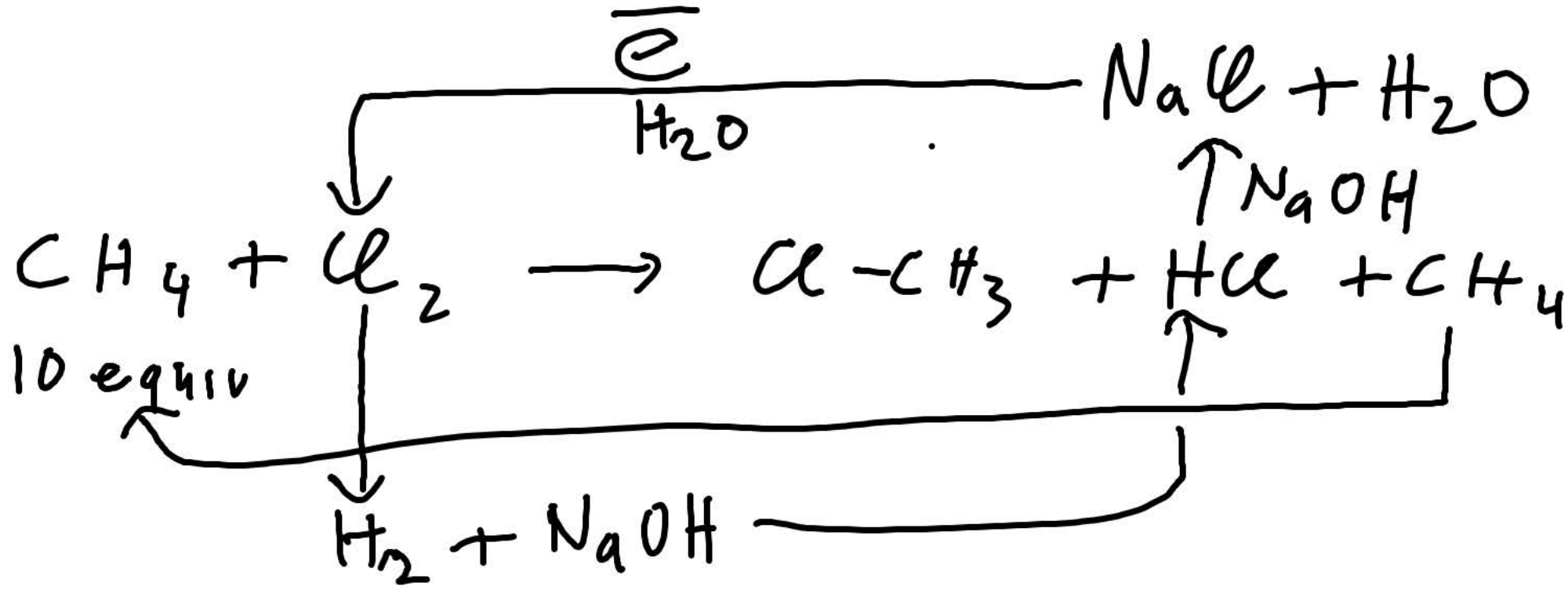
masse moléculaire 16 71 50.5 36.5

économie d'atome: 5/7 = 71%

PMI (produits de départs+solvents/masse des produits (1 kg):
(16+71)/50.5 = 1.7

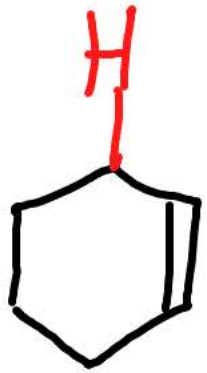
E (masse des déchets/masse des produits):
36.5/50.5 = 0.73

En pratique, on doit utiliser un excès de méthane, sinon on réagit une second fois pour produire du dichlorométhane!

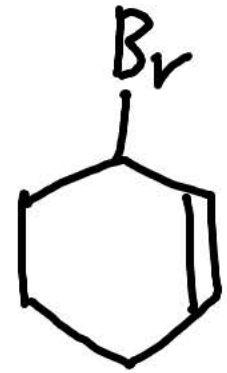


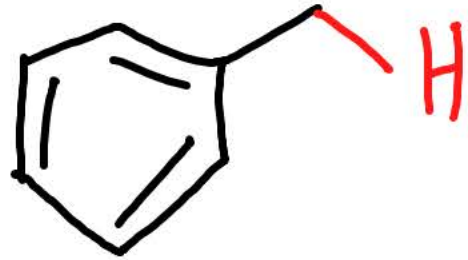
$$H_2O + CH_4 + NaCl \xrightarrow{\overline{e}} ClCH_3 + NaOH + H_2$$

bromination des positions allyliques et benzyliques

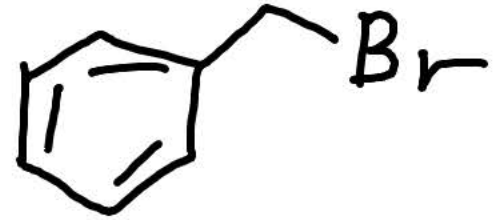


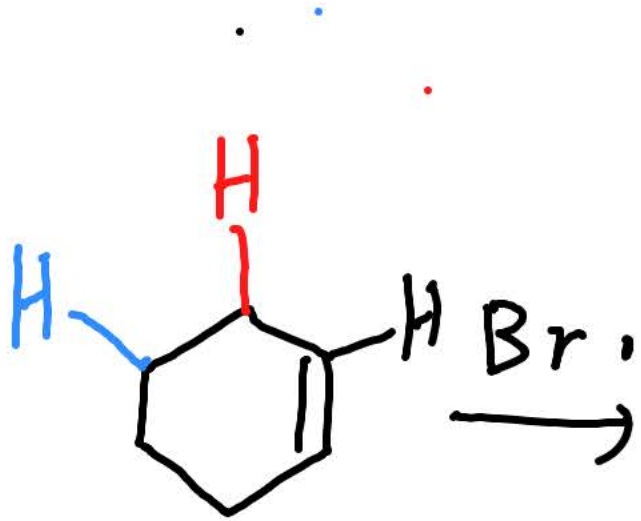
position allylique

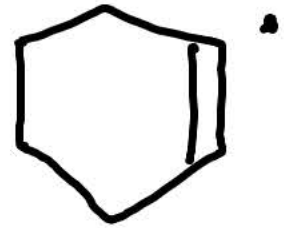




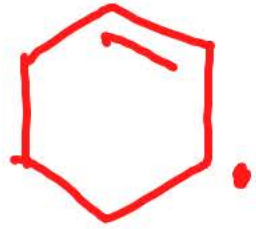
position benzylique

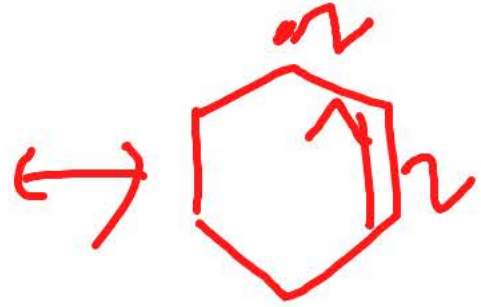






radical hybridisé sp2, moins stable, pas observé

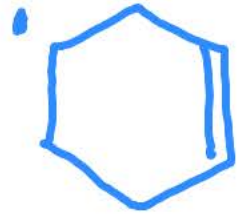




carbon sp2, radical secondaire en orbital p

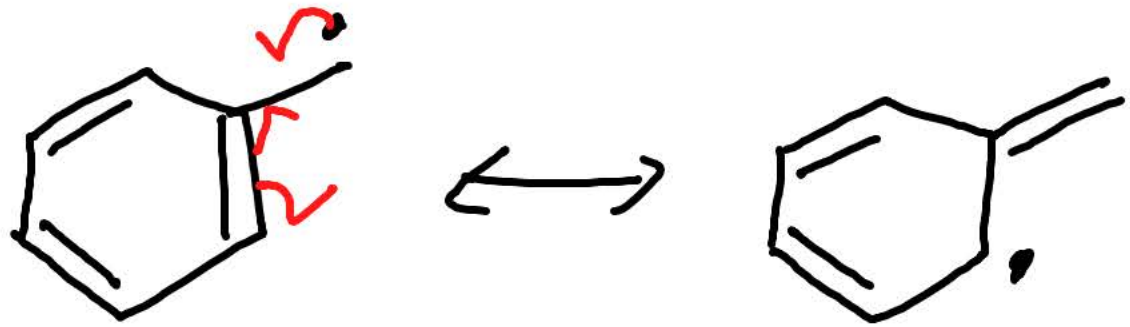
structures de résonances identiques! très stabilisé

uniquement la position allylique réagit!



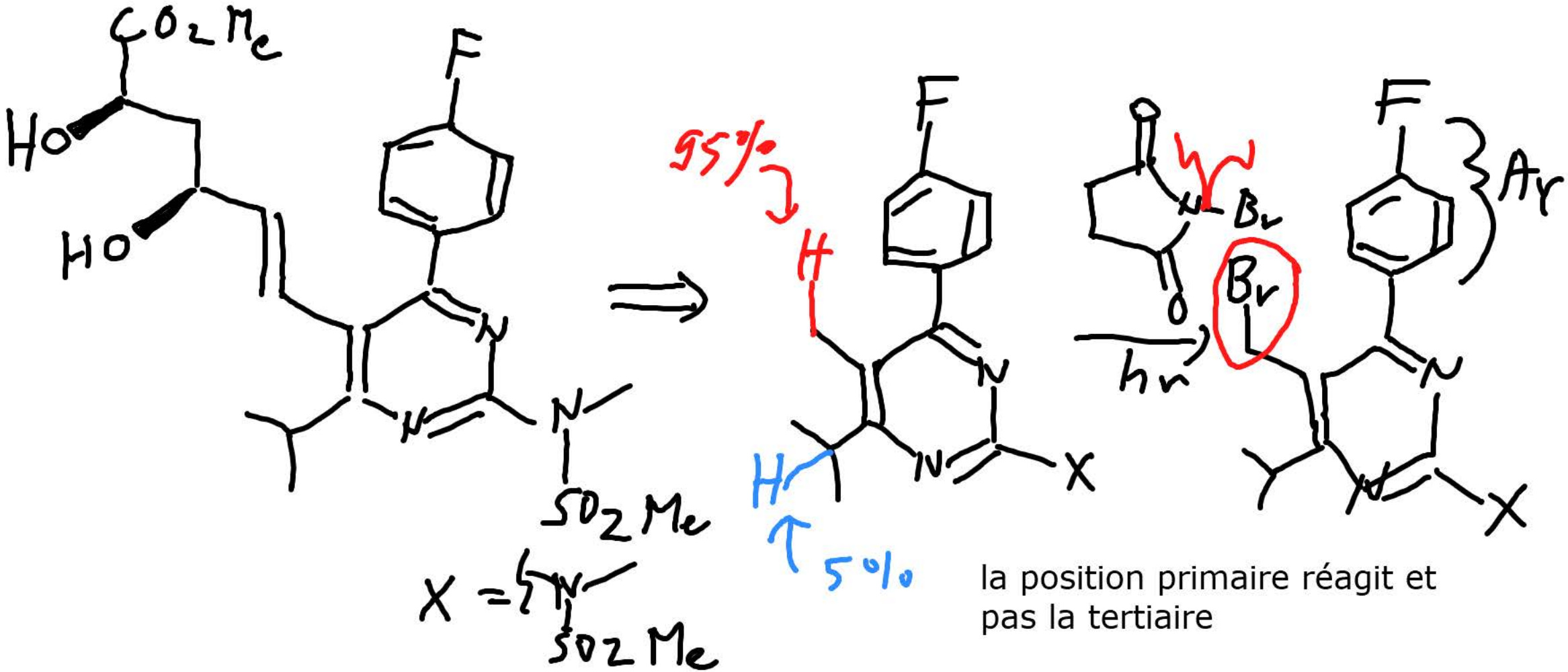
carbon sp2, radical secondaire en orbital p

position benzylique

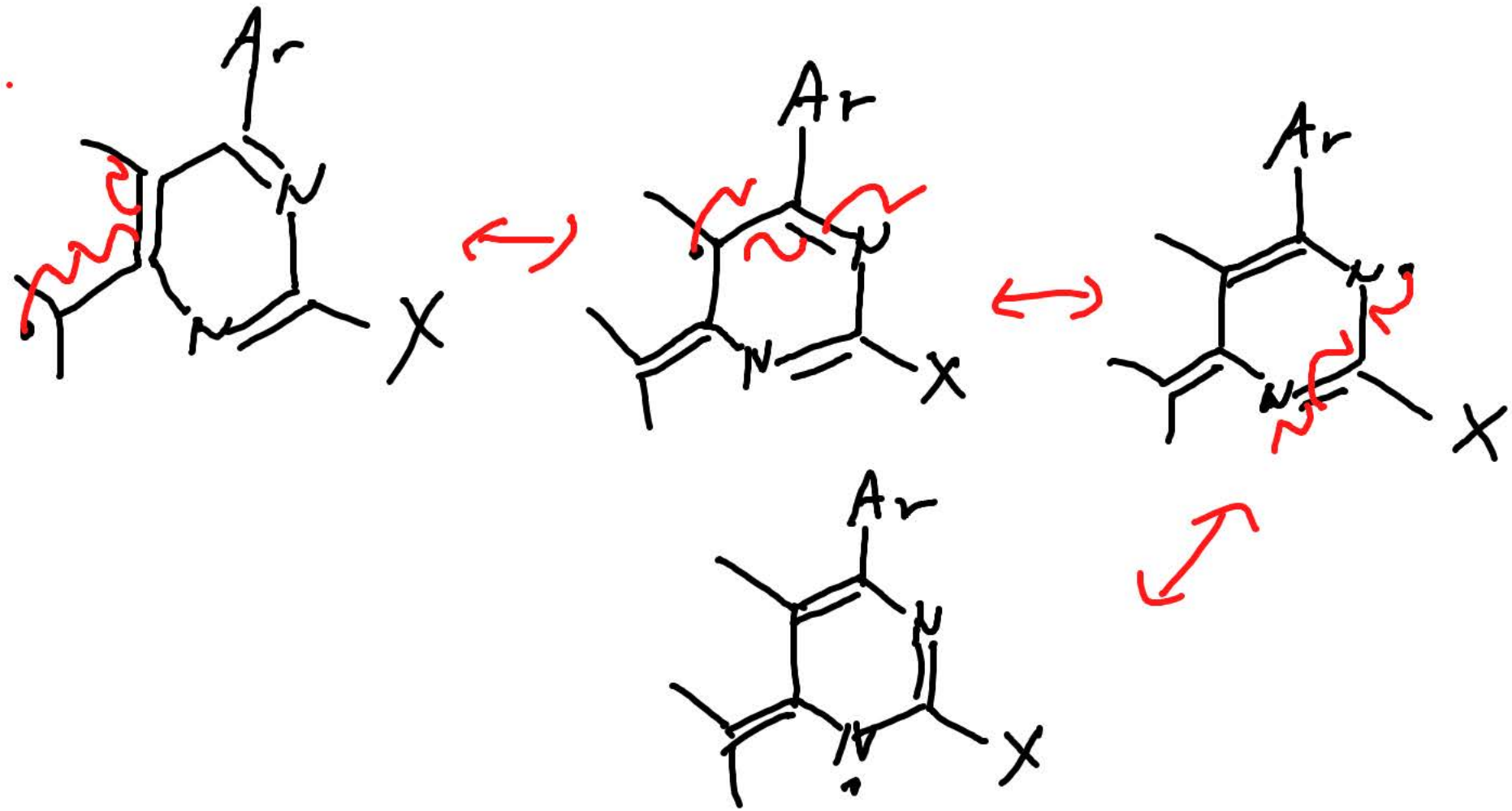


+ 2 autres structures de résonance dans le cycle

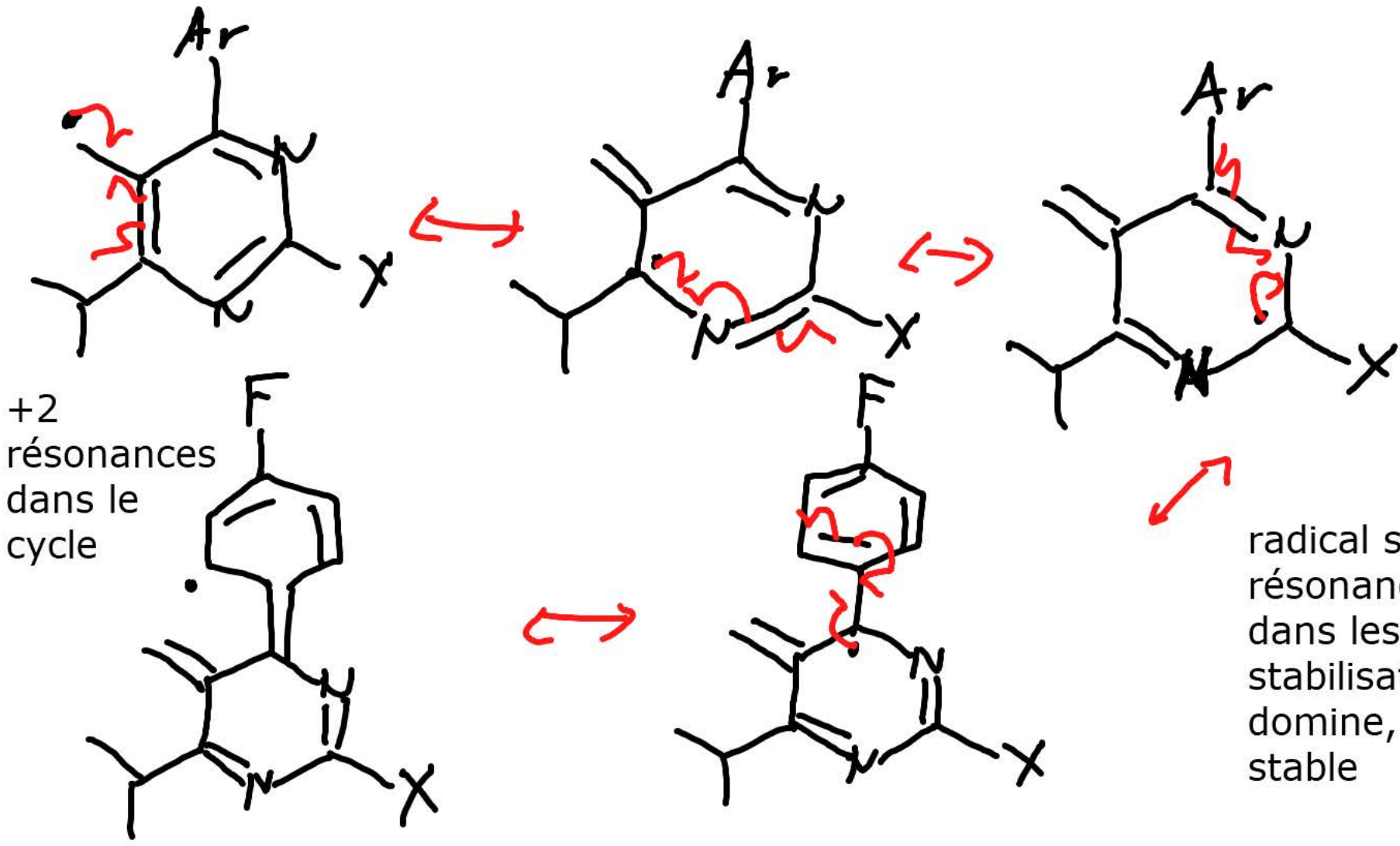
Rosuvastatine (statine, diminue le cholestérol)



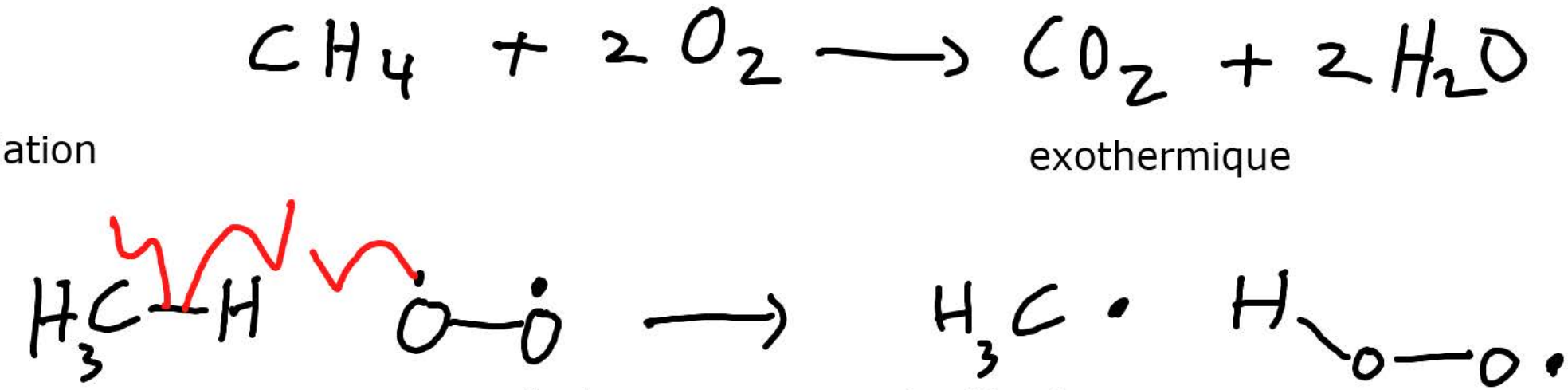
la position primaire réagit et pas la tertiaire



stabilisé par 3 structures de résonance en plus dans le cycle


Ar
X
F
+2 résonances dans le cycle
radical stabilsé par 6 résonances supplémentaires dans les cycles
stabilisation par résonance domine, donc radical plus stable

combustion du méthane

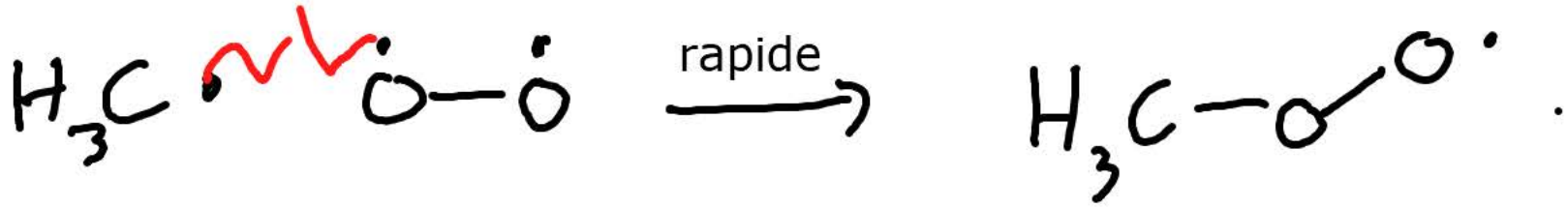


exothermique

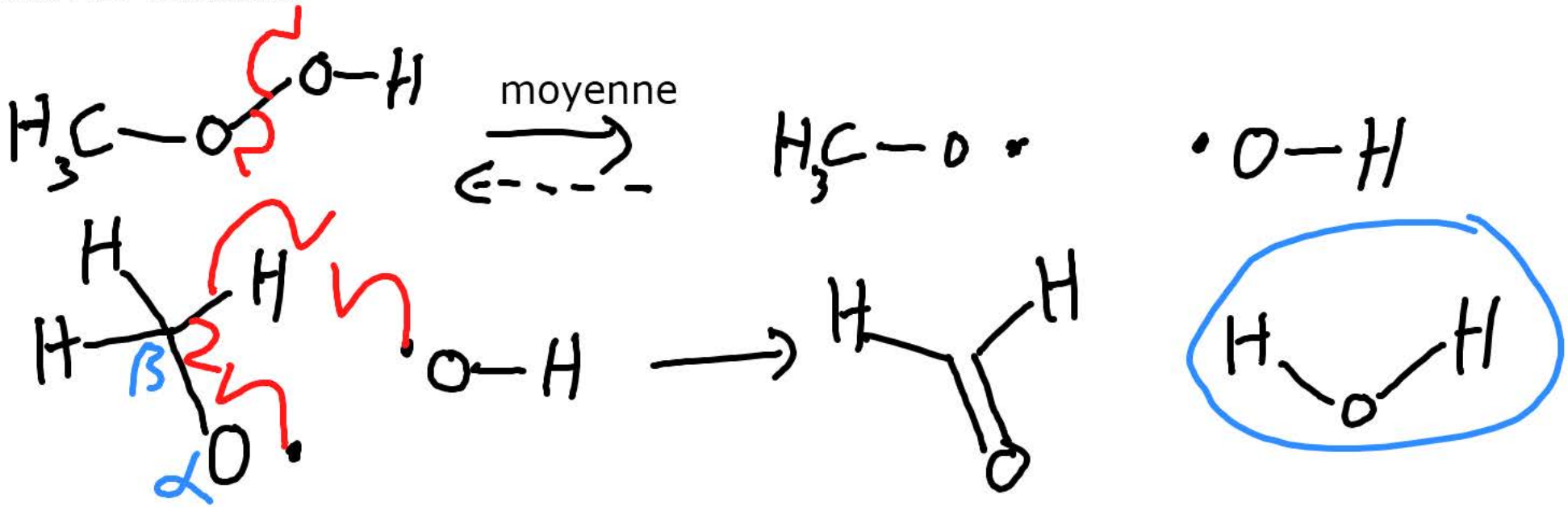
Initiation

très lente, Ea >> 21 kcal/mol

propagation

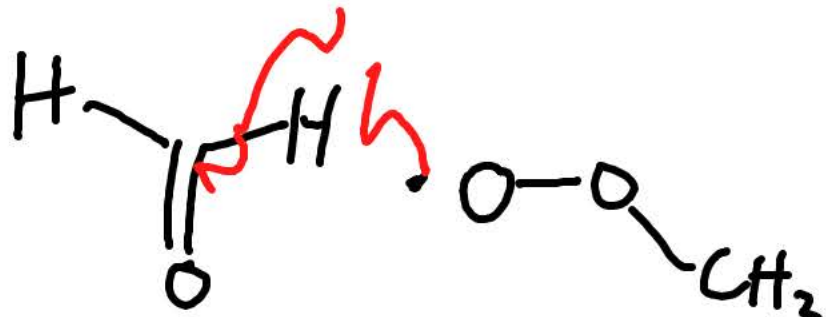


réaction 2: intiation

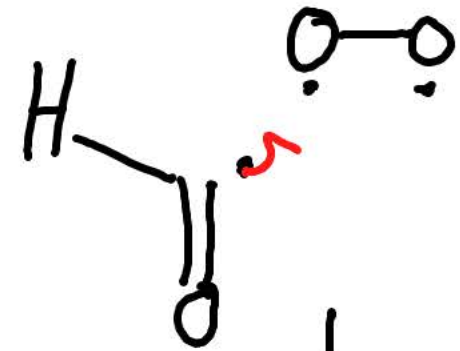


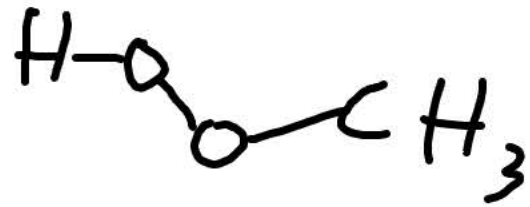
élimination beta (permet des liaisons doubles)

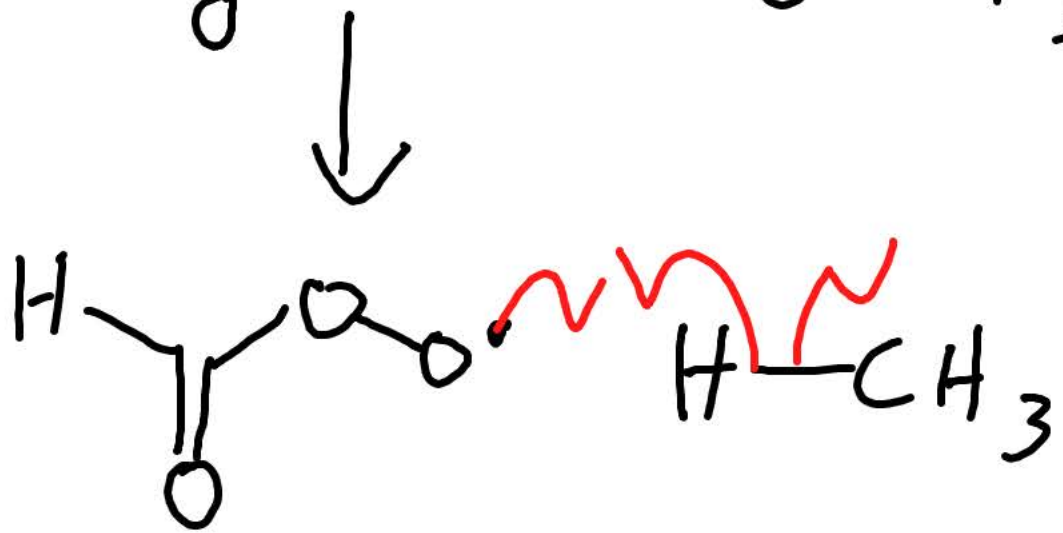
réaction 3

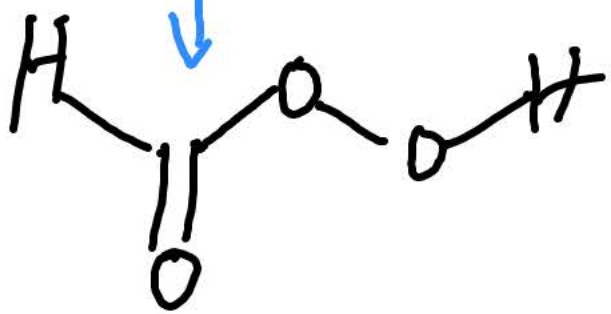


formaldéhyde





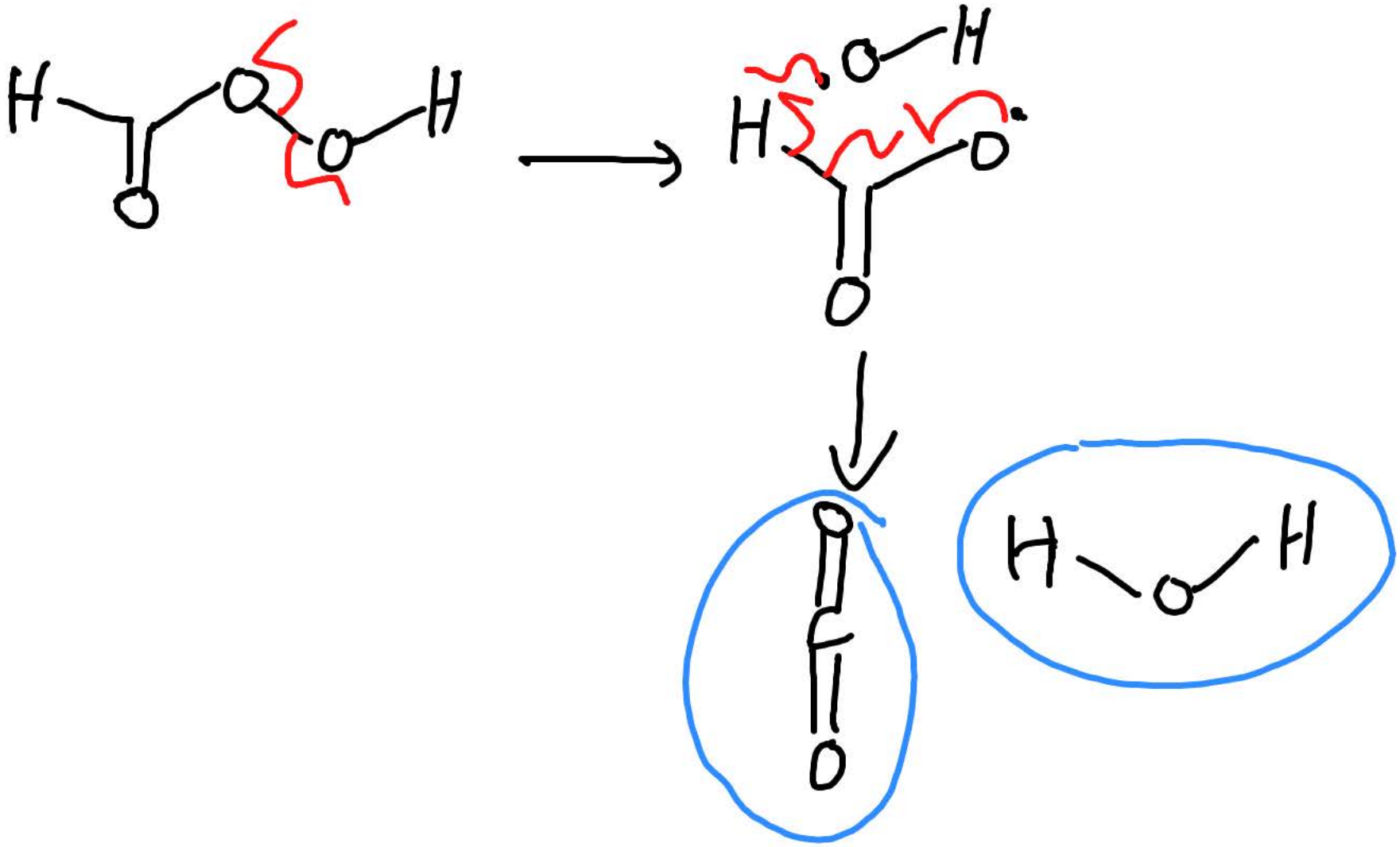




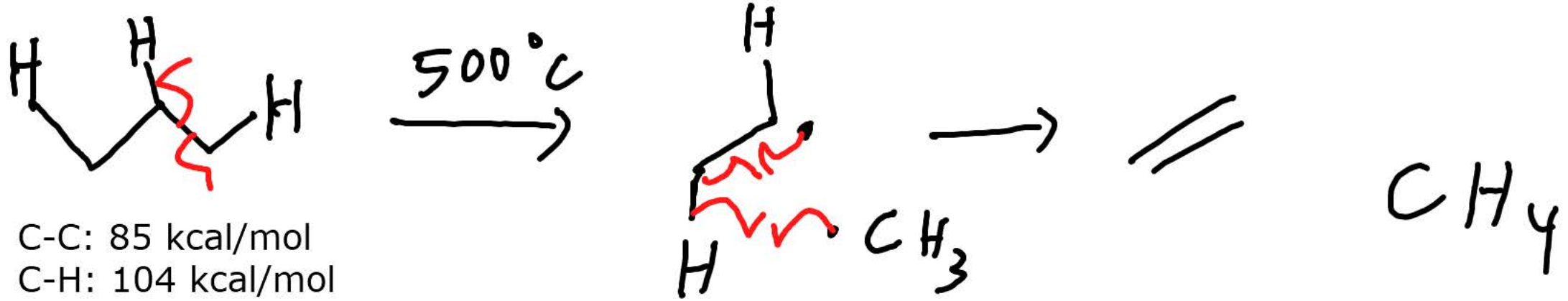
OXIDATION

$\bullet CH_3$

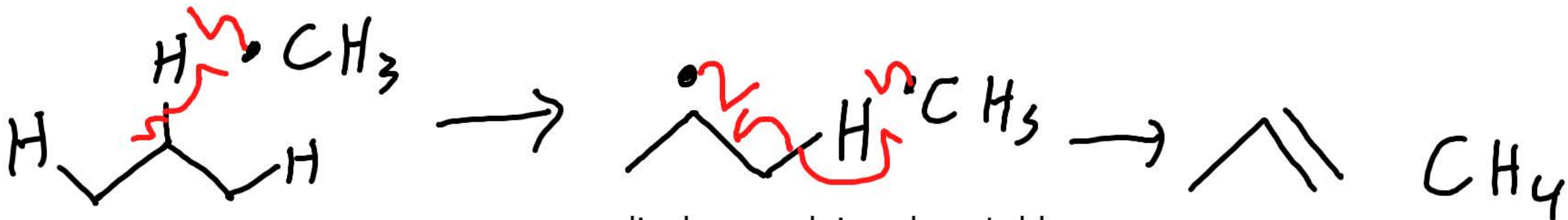
peracide


H
O
O
H
H
O
H
H
O
O
O
H
O
H

cracking du pétrole



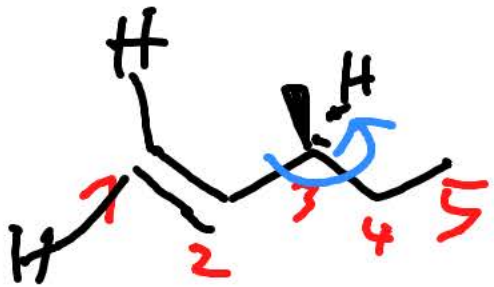
C-C: 85 kcal/mol
C-H: 104 kcal/mol



radical secondaire plus stable

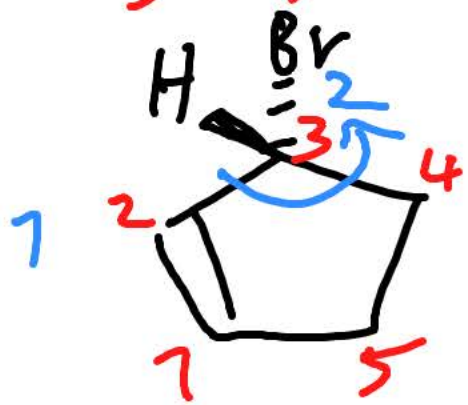
résultat du cracking: des chaines plus courtes et plus d'alcènes!

Nomenclature des alcènes



(S)-3-méthylpent-1-ène

(E)-hept-3-ène

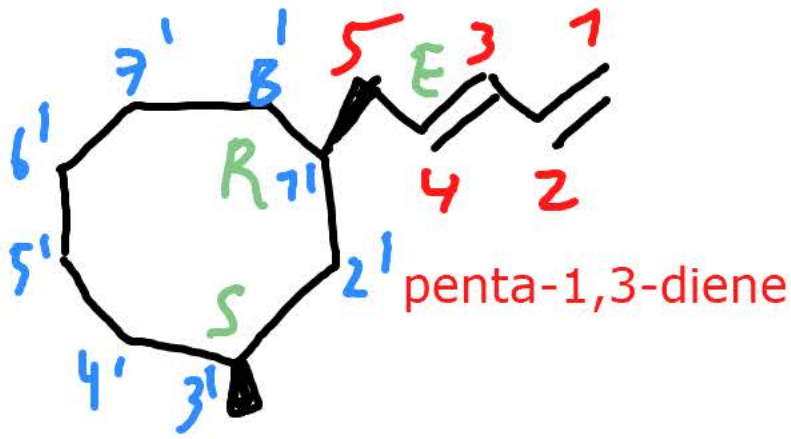


"S" mais H devant: donc R

(R)-3-bromo-cyclopent-1-ène

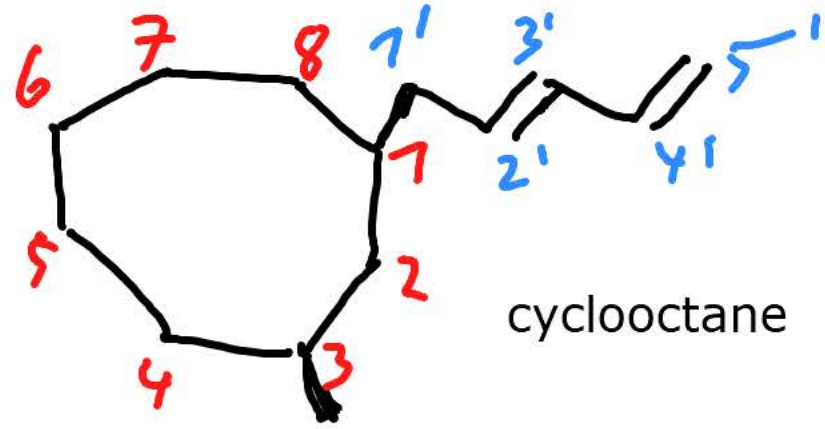
alcène: Z, mais dans le cycle à 5 le E est impossible, donc il n'est pas exigé de l'indiquer

anciennes règles: les insaturations dominent



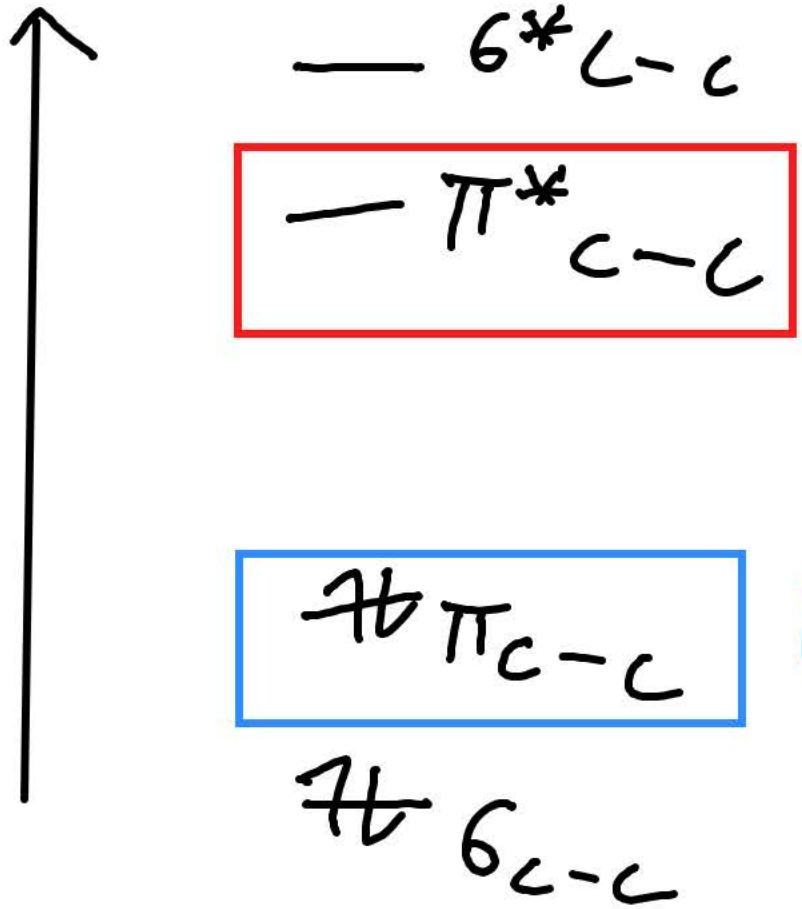
(E)-5-((1R,3S)-3-méthyl-cyclooctyl)-penta-1,3-diène

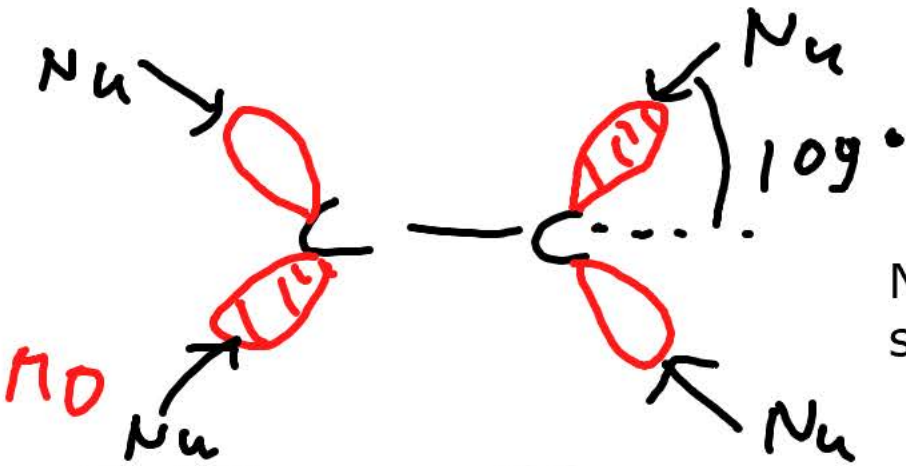
nouvelles règles: 1) cycle, 2) nombre d'atomes 3) insaturations



(1R,3S)-3-méthyl-1-((E)-penta-2,4-diényl)-cyclooctane

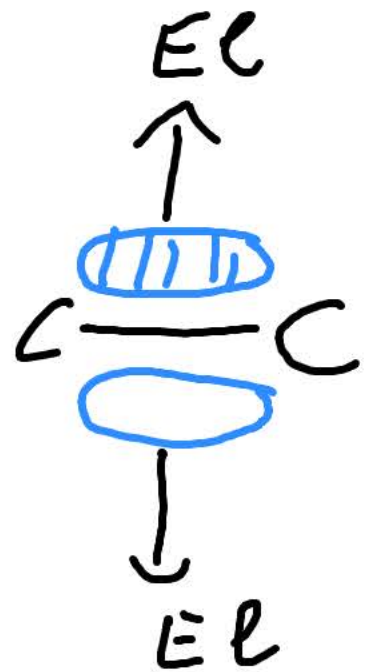
HOMO/LUMO des alcènes





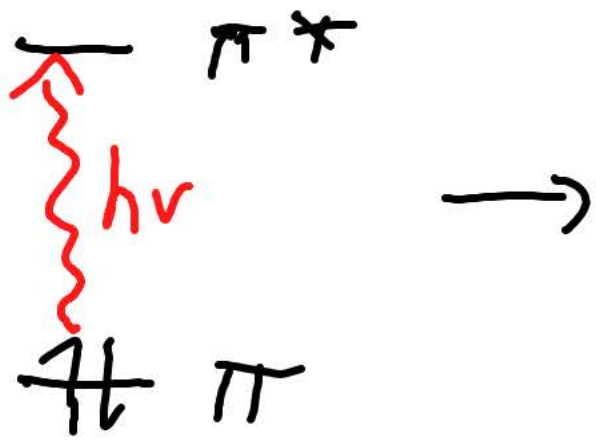
Nu attaque à 109° sur les carbones

Electrophile (El)



El attaque à 90° par rapport à la liaison C-C

photochimie des alcènes



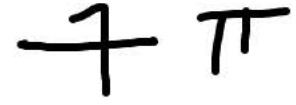
alcène seul: Lumière UV
plusieurs alcènes conjugués:
lumière visible

durée de vie courte

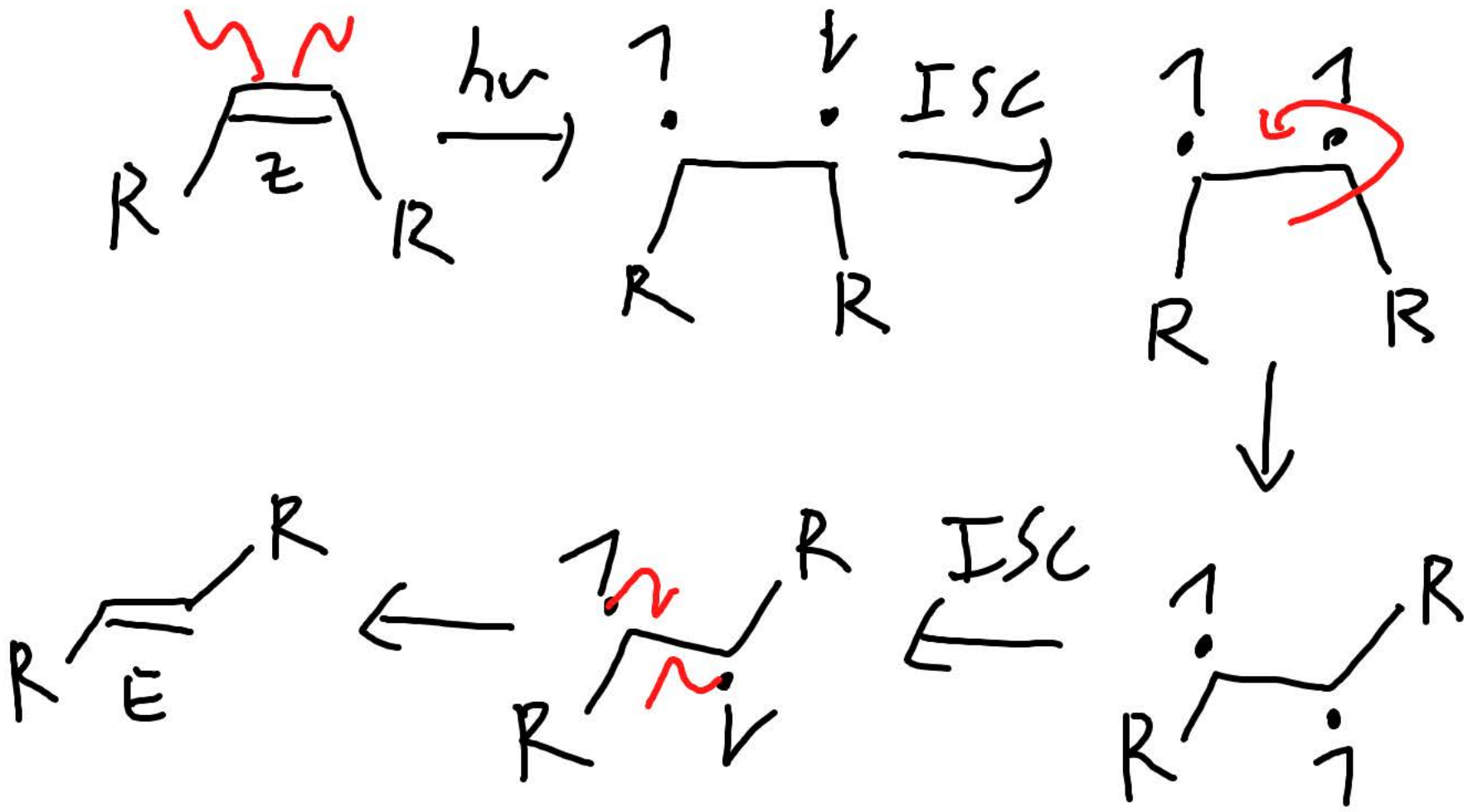
Inter System Crossing (ISC)

singlet (spin opposé)

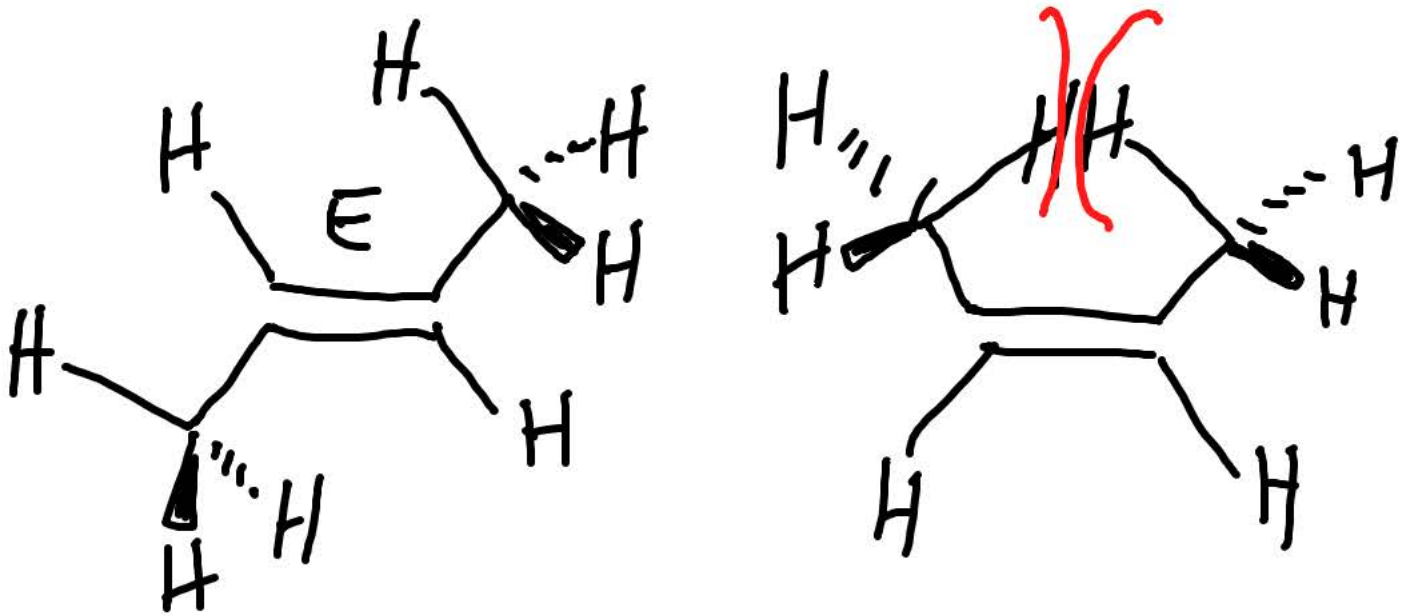
durée de vie plus longue



triplet
spin dans le même sens

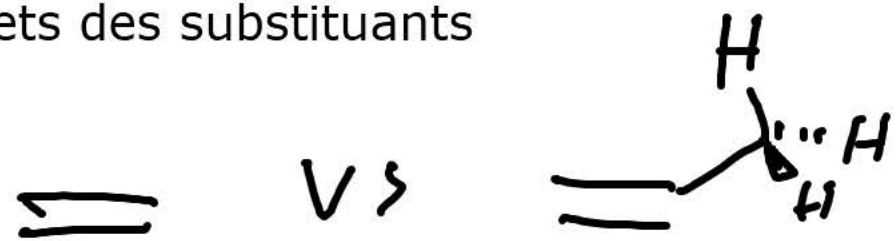

hν
ISC
ISC
Z
E
R
R
R
R
R
R
R
R
R
R

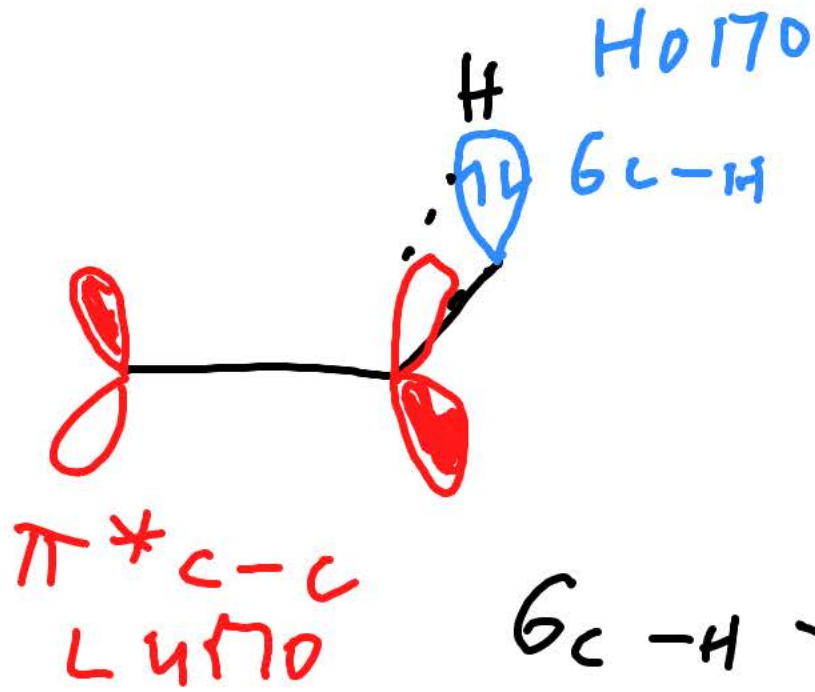
Stabilité des alcènes: E vs Z

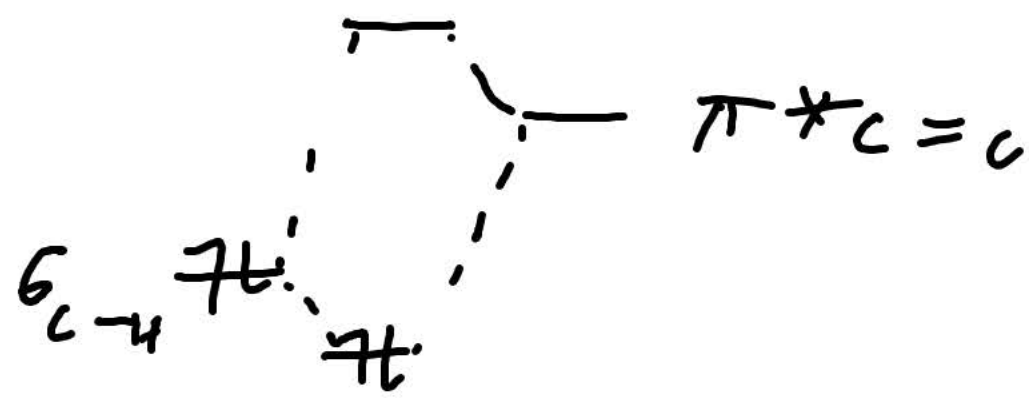


alcène E est plus stable pour des raisons stériques, la différence augmente avec la taille des substituants

effets des substituants



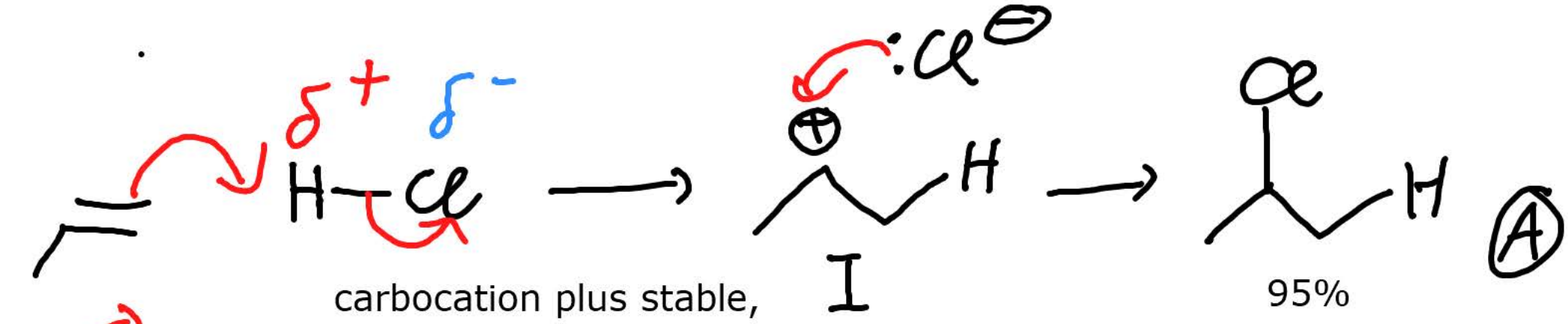




$\sigma_{C-H} \rightarrow \pi^*_{C-C}$

stabilisation par hyperconjugaison des substituants

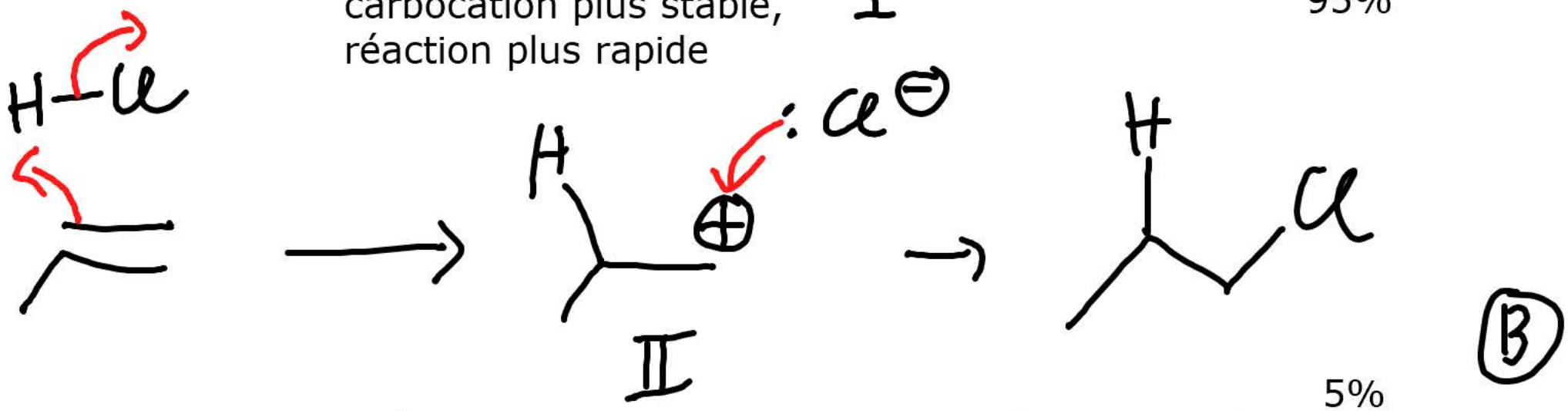
addition des acides forts sur les alcènes



carbocation plus stable,
réaction plus rapide

I

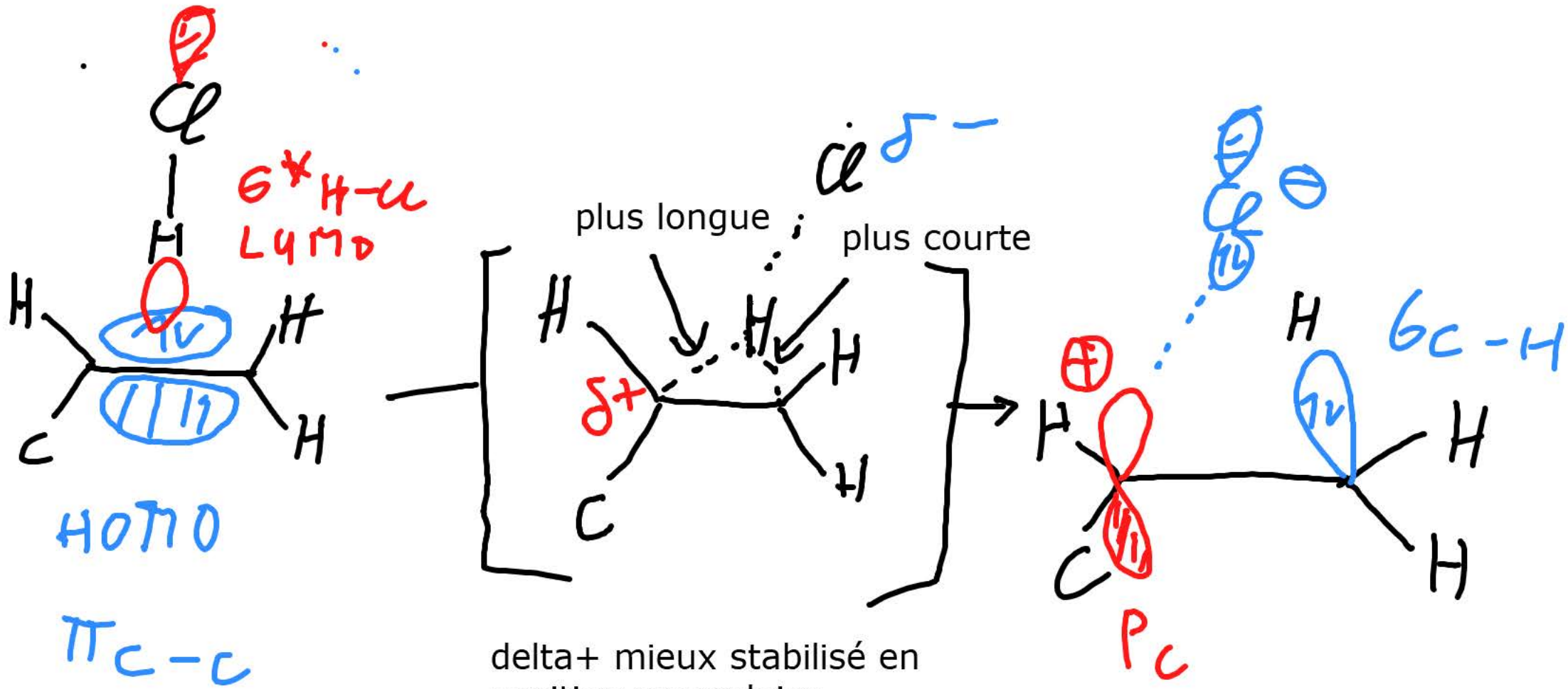
95%



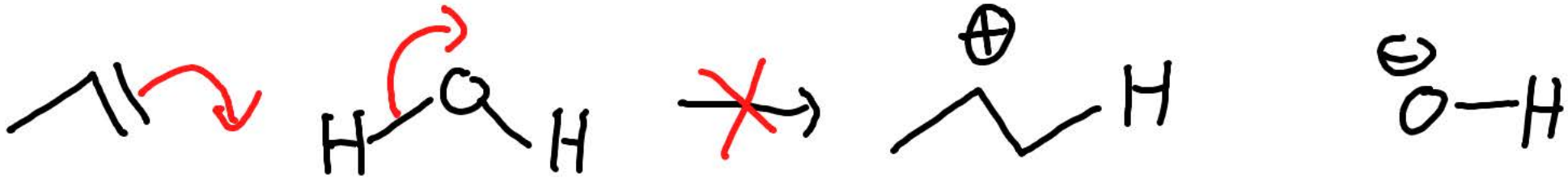
II

5%

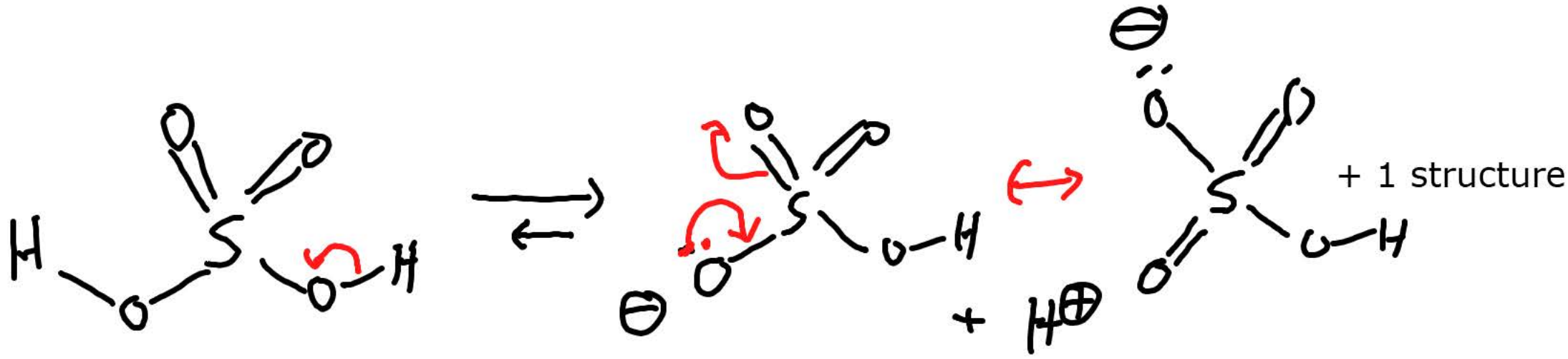
thermodynamique: même liaisons pour A et B, donc même stabilité


σ*H-Cl
LUMO
HOMO
πC-C
plus longue
plus courte
δ+
δ−
σC-H
pC
delta+ mieux stabilisé en
position secondaire

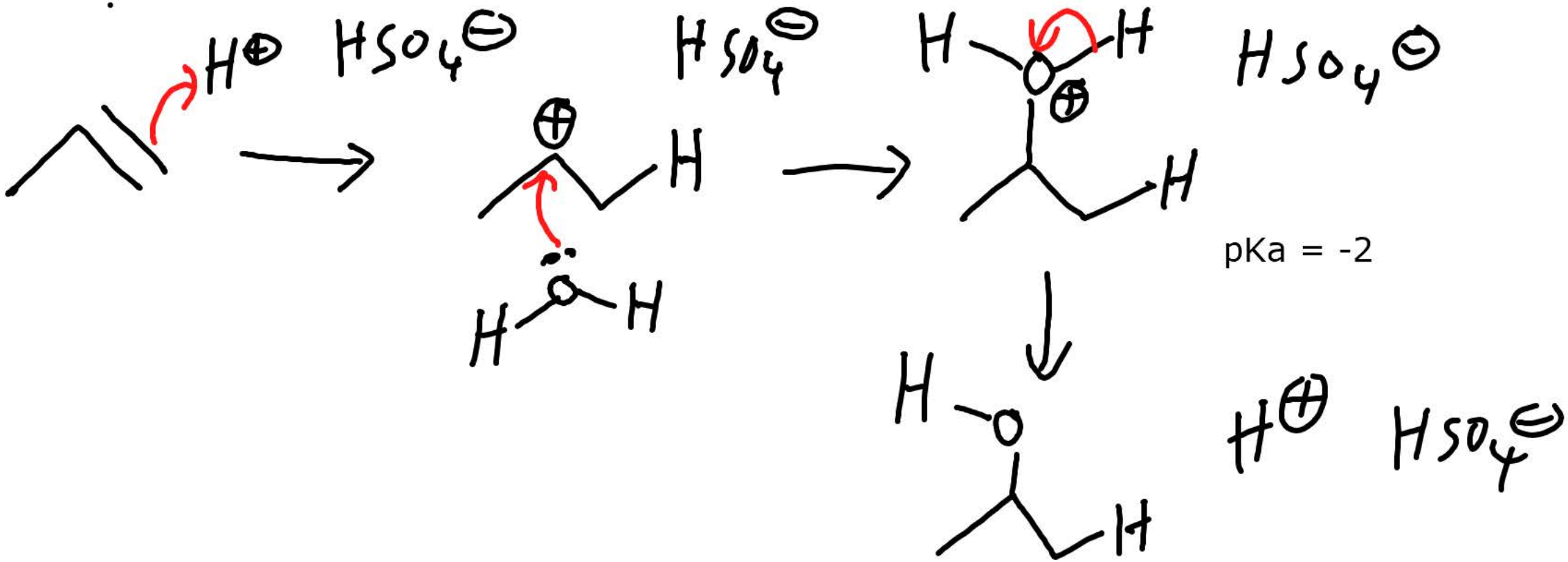
Addition des acides faibles

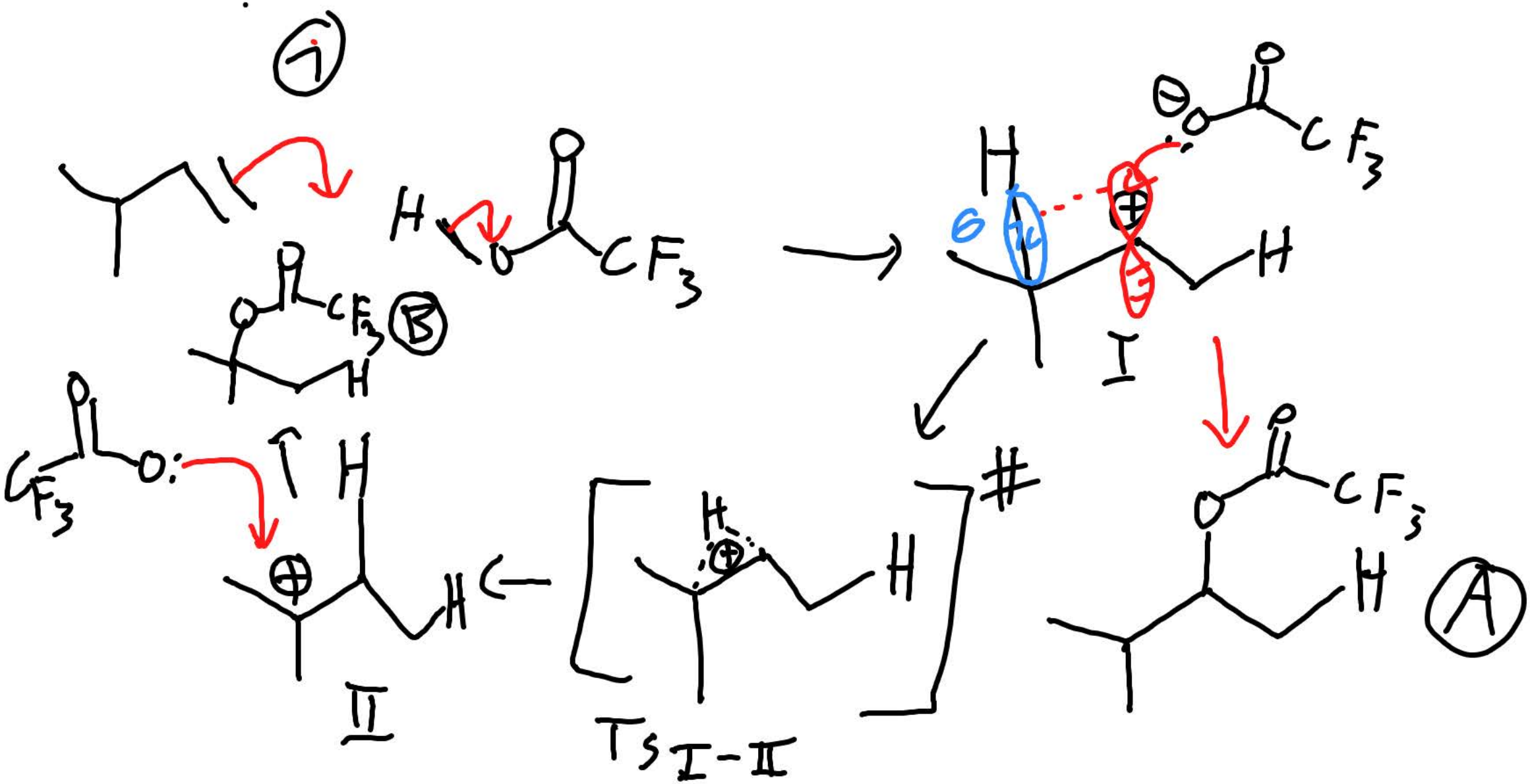


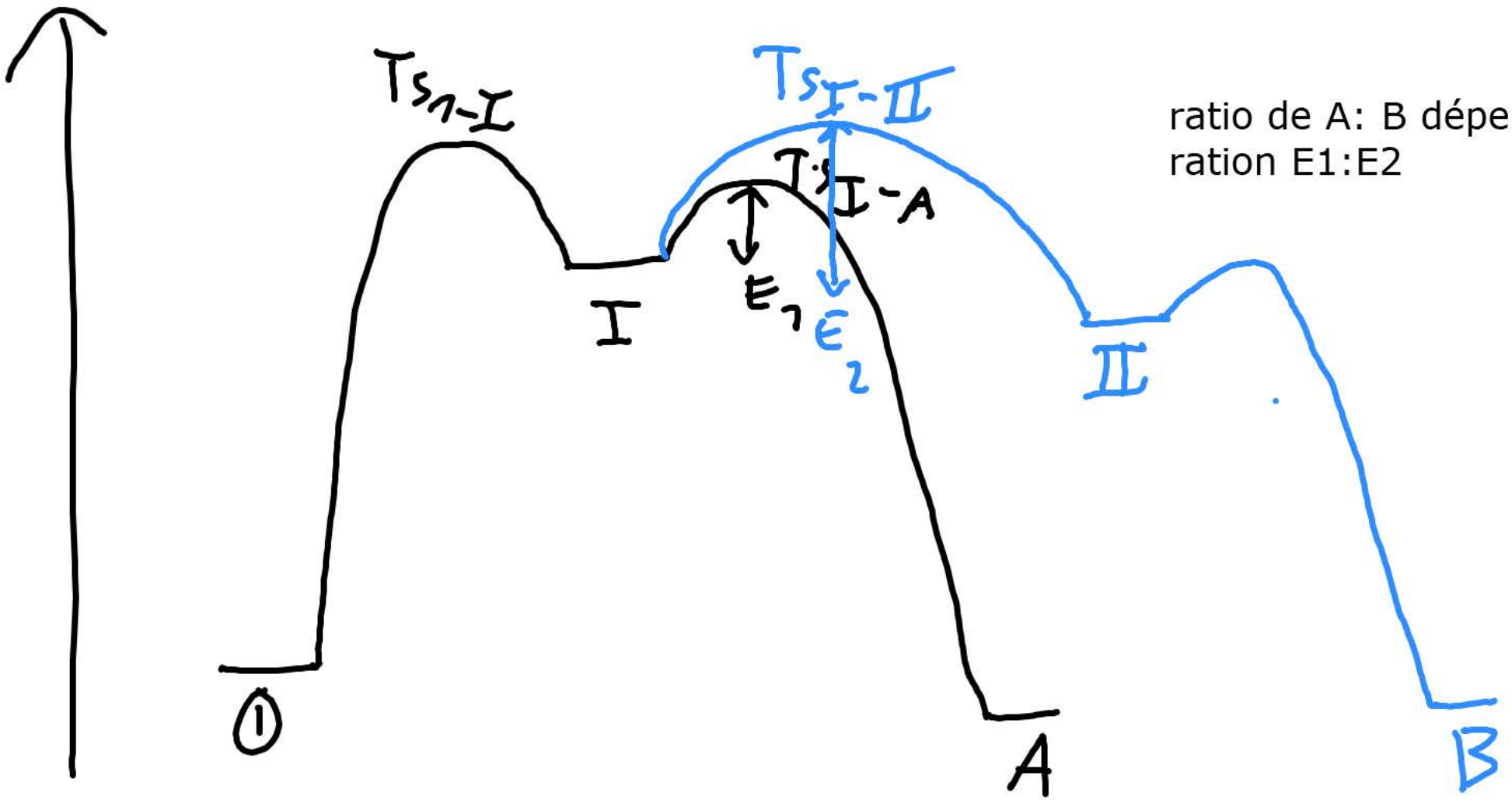
l'eau est trop faible comme acide, pas de réaction (PkA = 14)



acide fort (pkA = -3), base très stabilisée par résonance, mauvais nucléophile

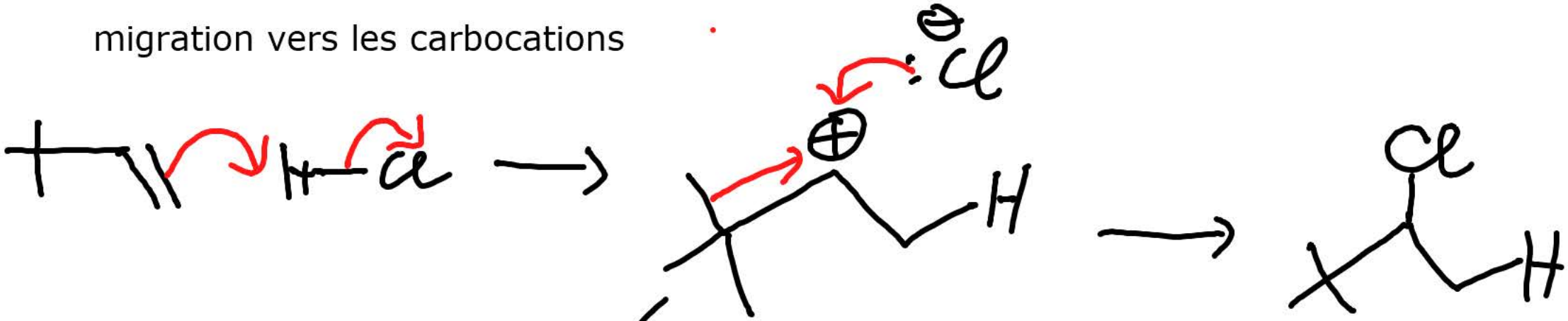

H⊕
HSO4⊖
HSO4⊖
H
H
H
H
H
H
HSO4⊖
pKa = -2
H
H
H⊕
HSO4⊖


1
B
I
II
TS I-II
A

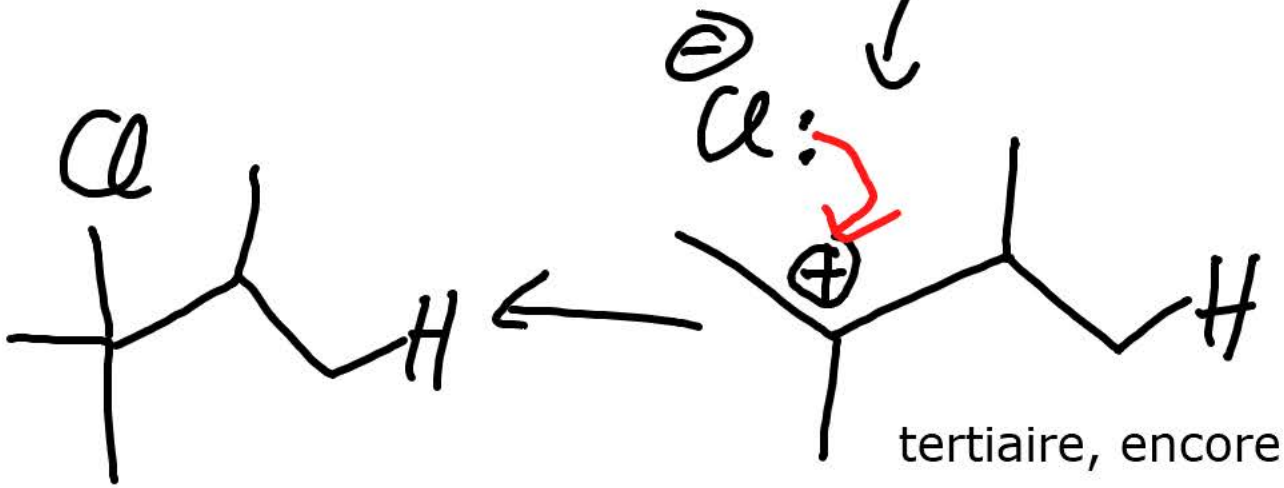


ratio de A: B dépend de la ration E1:E2

migration vers les carbocations



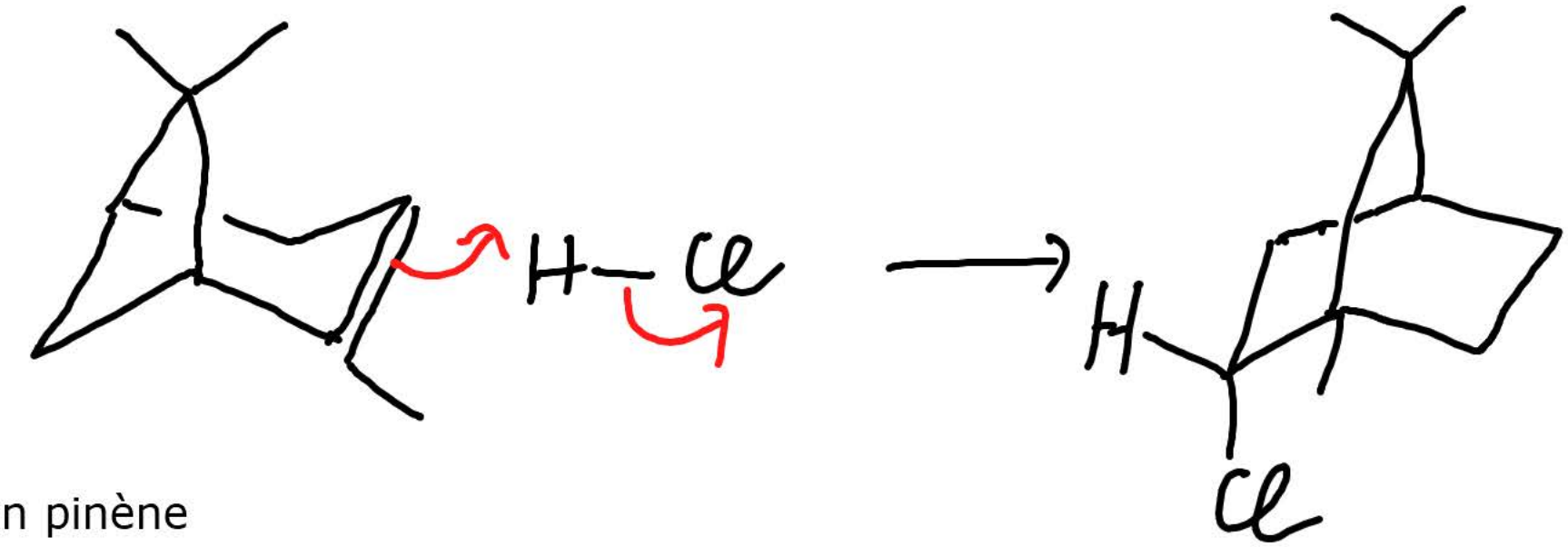
secondaire plus stable



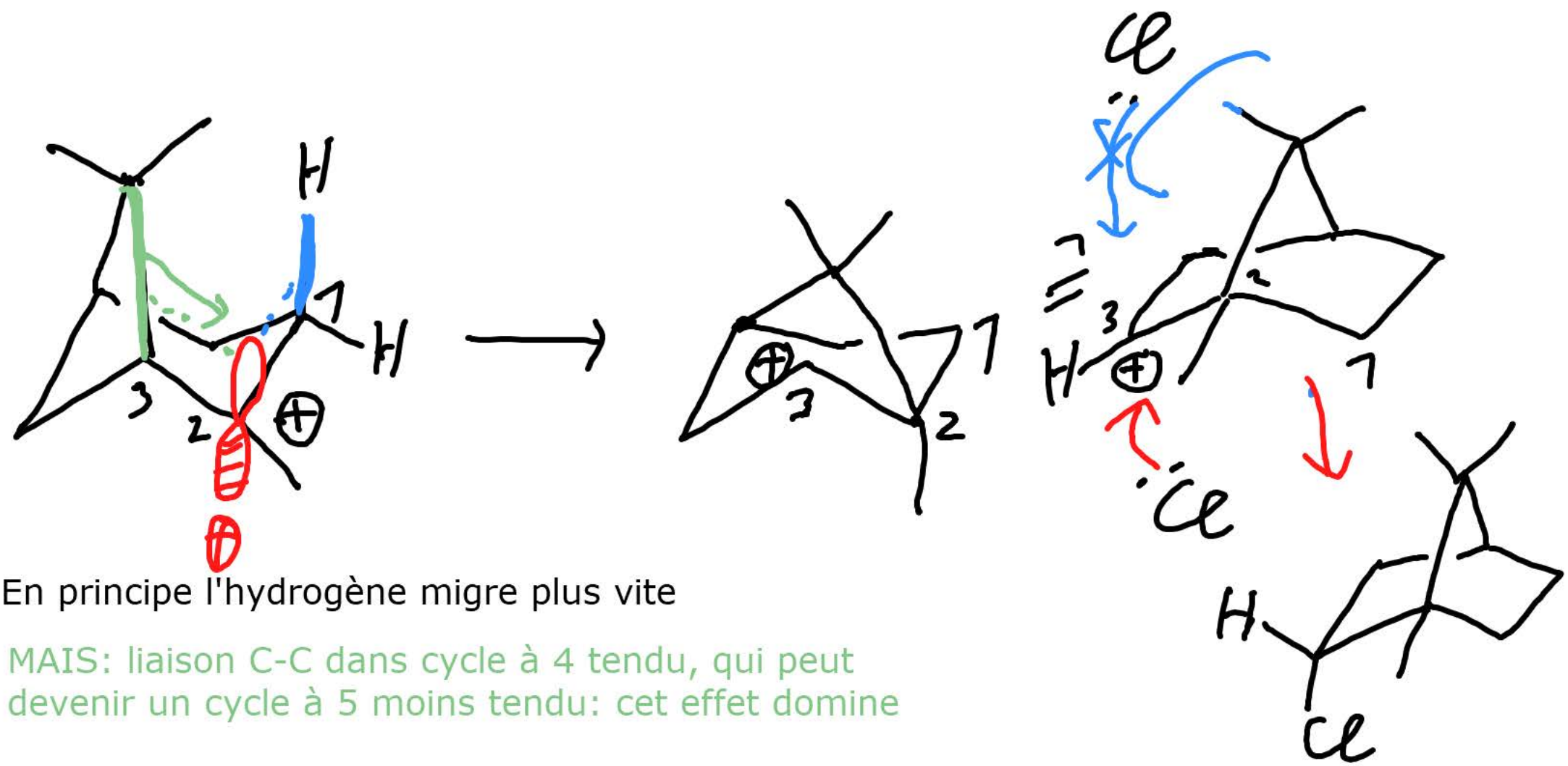
tertiaire, encore plus stable

1) "driving force" aller vers le carbocation plus stable
2) qui migre? le groupe qui stabilise le mieux les charges positives. EN(H) < EN(C), H migre en général plus vite que C

découverte par Wagner-Meerwein (1899)



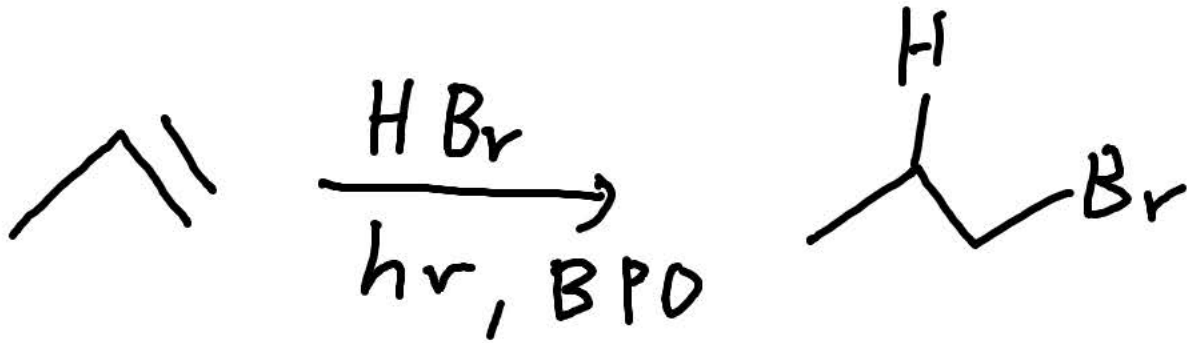
un pinène



En principe l'hydrogène migre plus vite

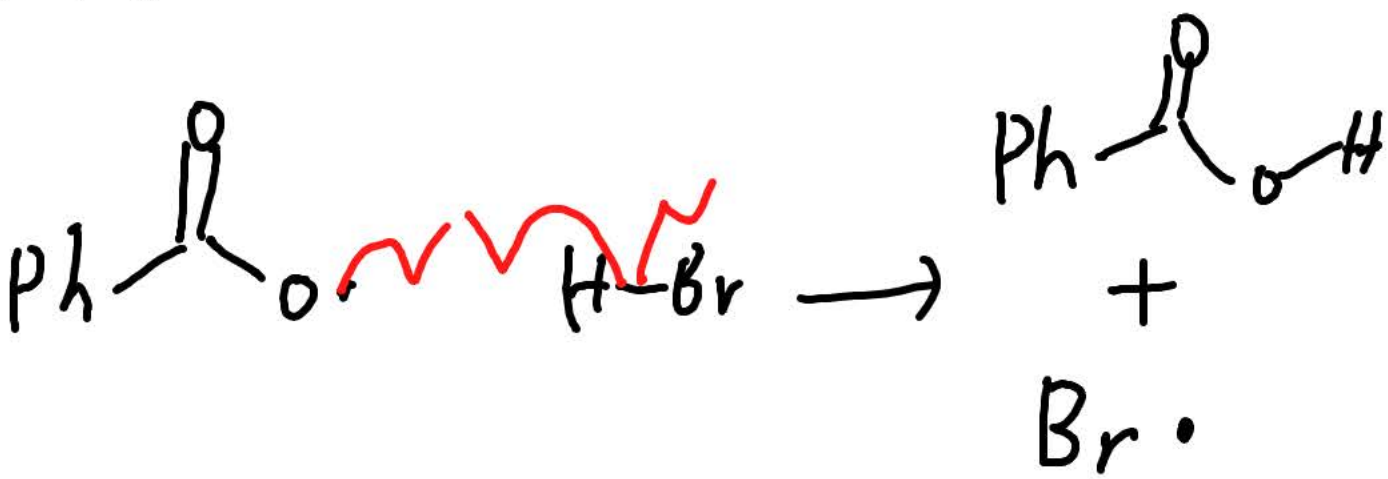
MAIS: liaison C-C dans cycle à 4 tendu, qui peut devenir un cycle à 5 moins tendu: cet effet domine

obtenir le produit anti-markovnikov avec les réactions radicalaires

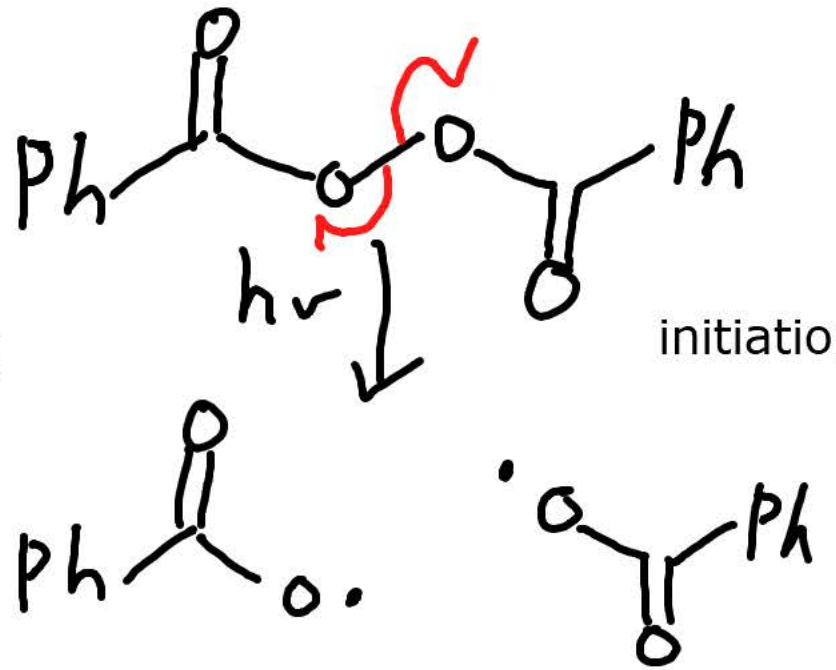


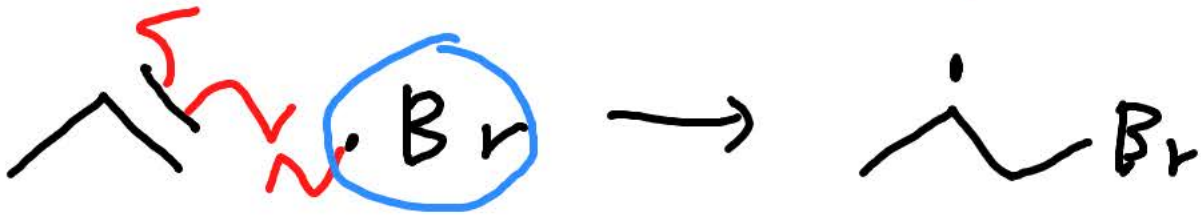
BPO: benzoylperoxide, initiateur

propagation

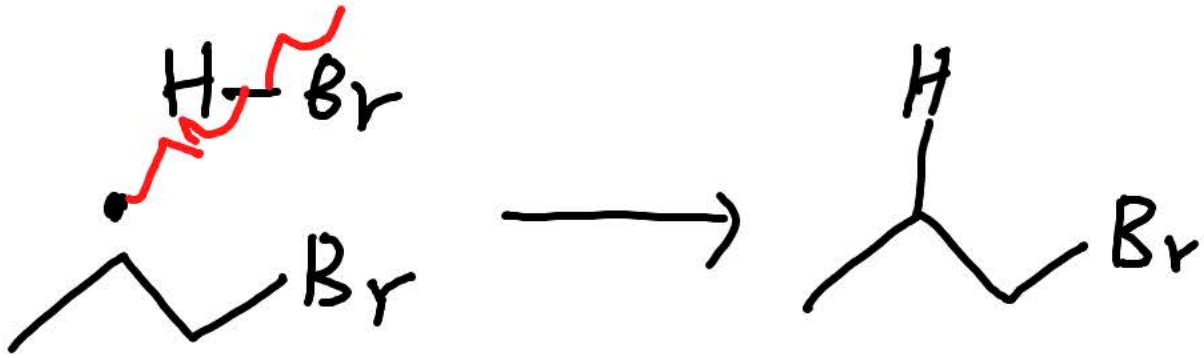


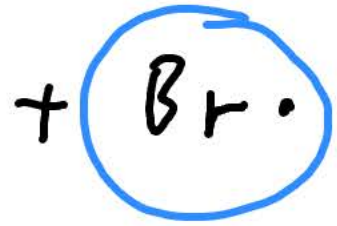
initiation



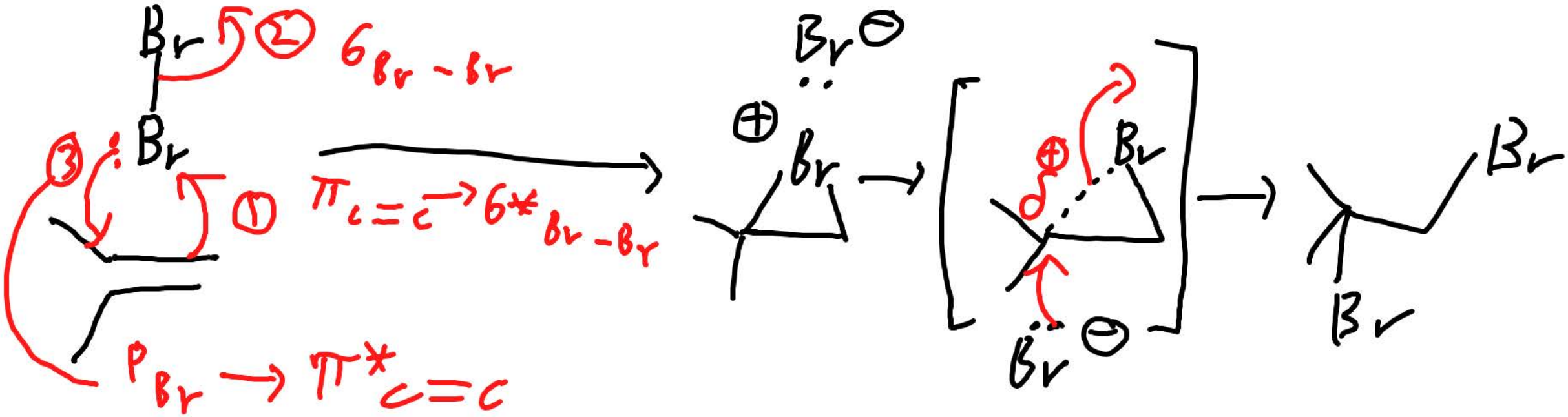


radical en position secondaire
plus stable, favorisé





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



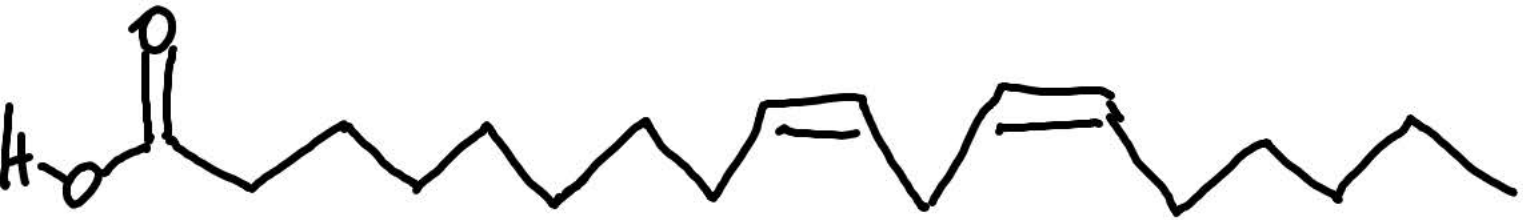
1) alcènes nucléophile, Br2 électrophile

2) on brise la liaison Br-Br

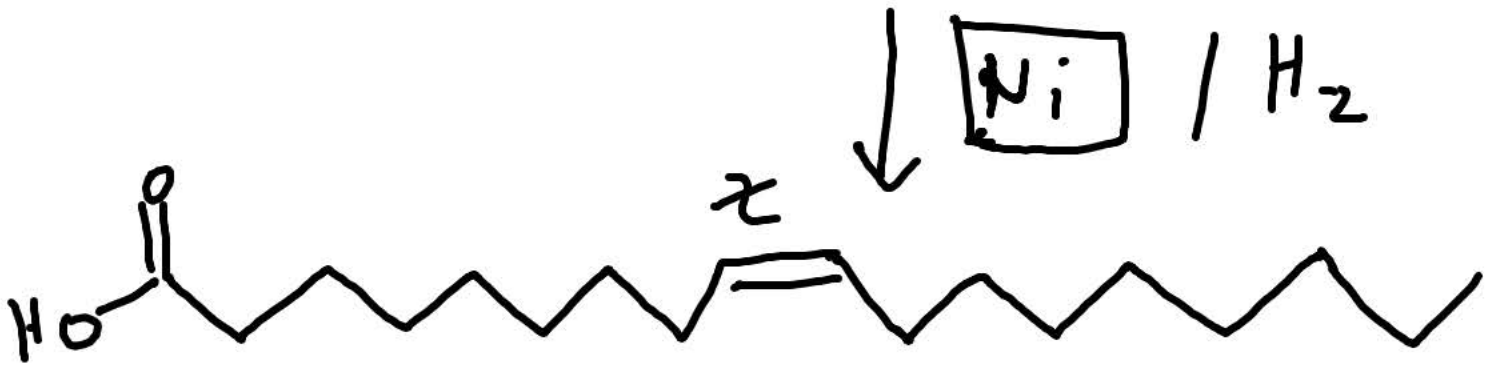
3) paire d'électron nucléophile, alcène électrophile

charge partielle positive, mieux stabilisée en position tertiaire que primaire

example d'hydrogénation: les acides gras

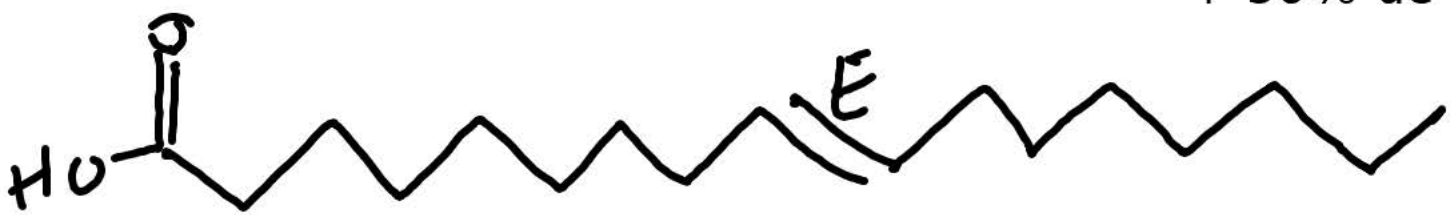


acide linoléique, abondant des les huiles végétales (liquide visqueux)

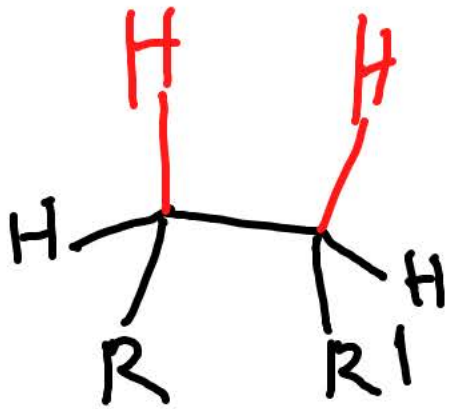


réduction partielle d'un alcène, parafine, solide (facile à utiliser)

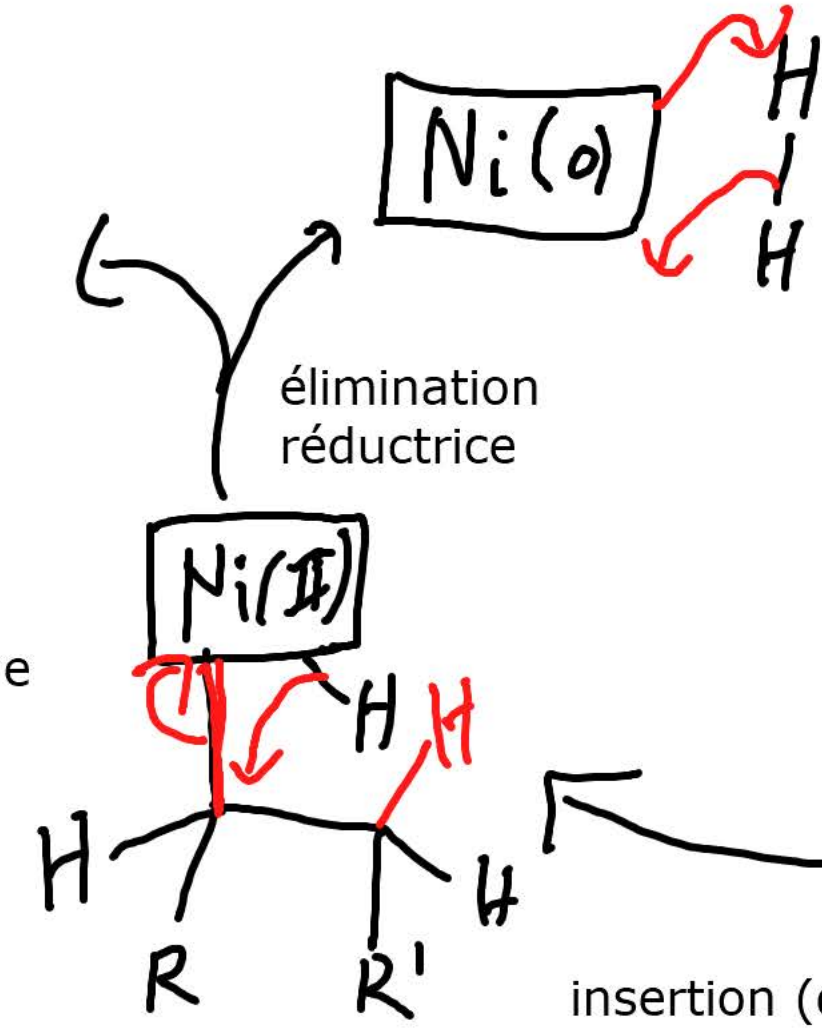
+ 50% de l'autre alcène



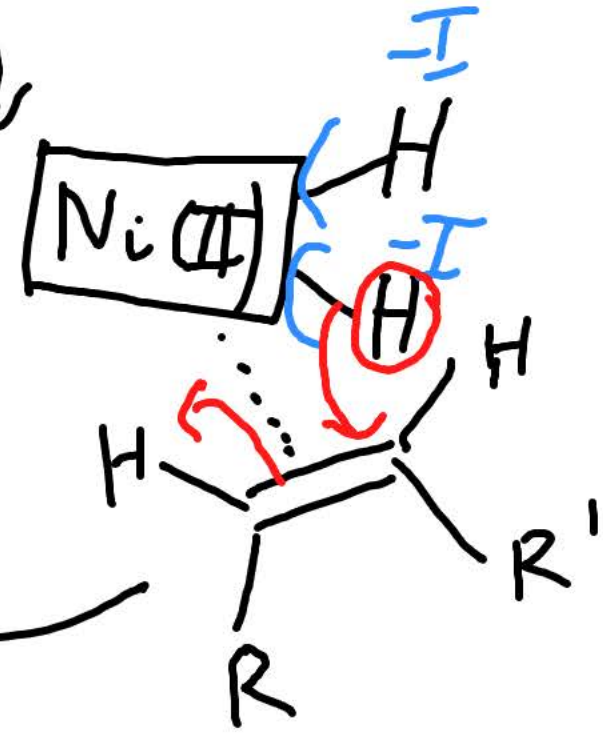
produit secondaire: E/trans "trans-fat", artériosclérose, problème cardiovasculaire



hydrogène du même côté
"syn" ou "cis"

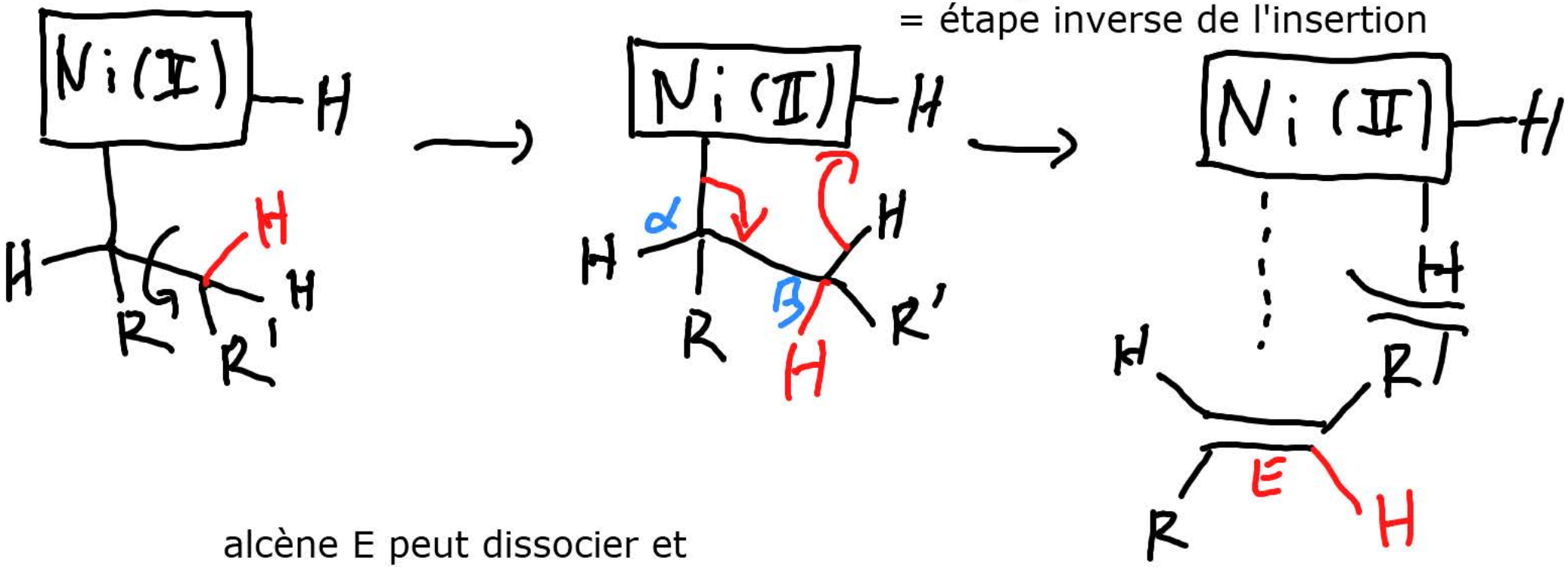


métal oxidé, addition oxidante



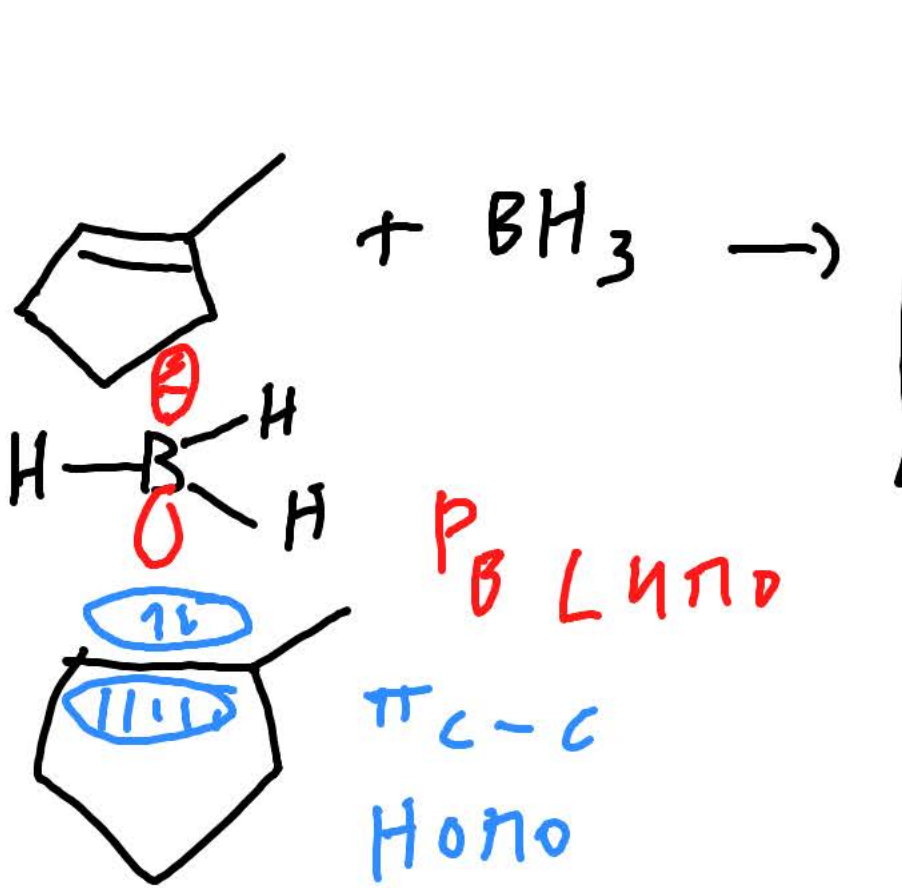
réaction secondaire: isomérisation Z à E

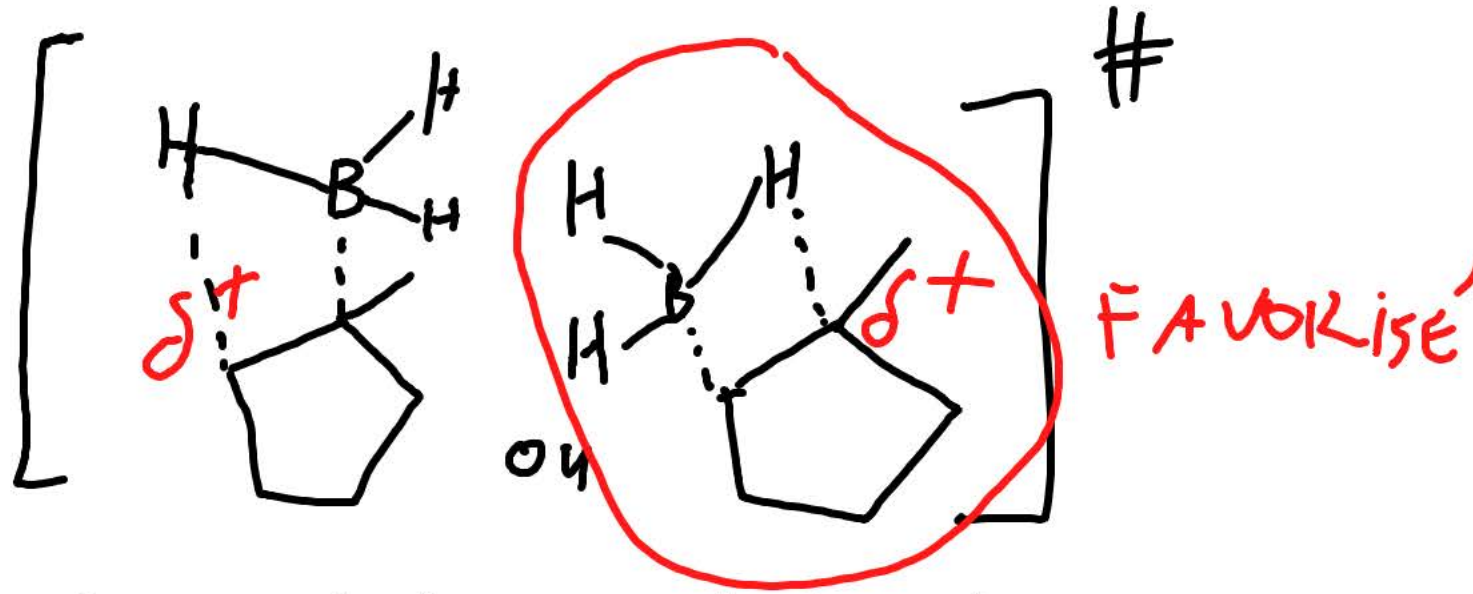
beta-hydride elimination
= étape inverse de l'insertion



alcène E peut dissocier et
s'accumuler!

hydroboration

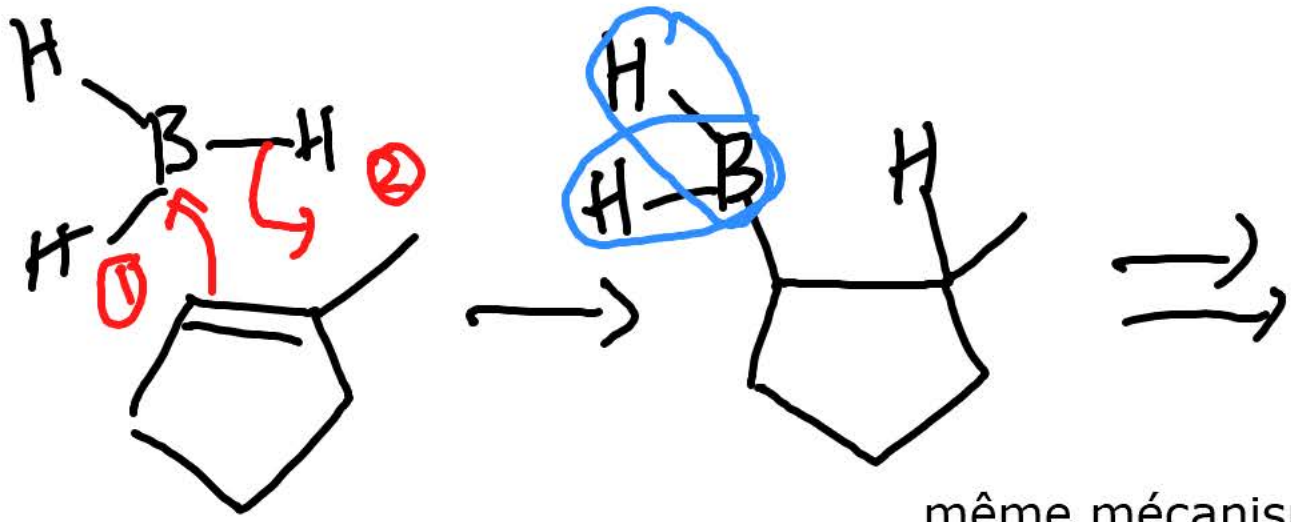




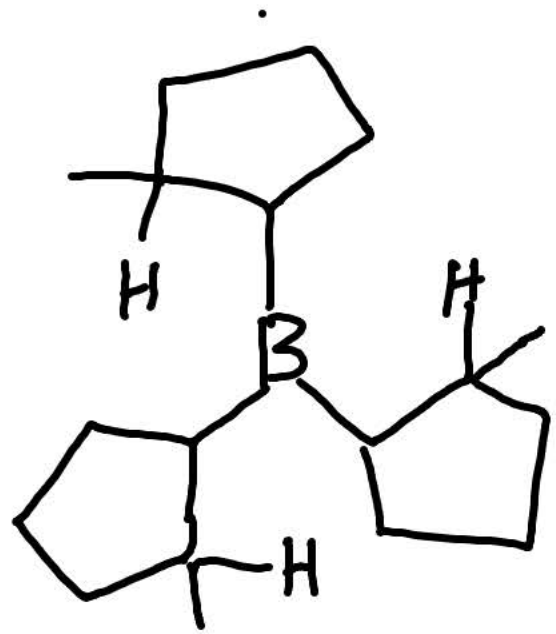
formation de charge partielle, favorisé en tertiaire!

Etat de transition à 4 atomes,
la distance C-B est plus courte
que la distance C-H

une réaction concertée asynchrone

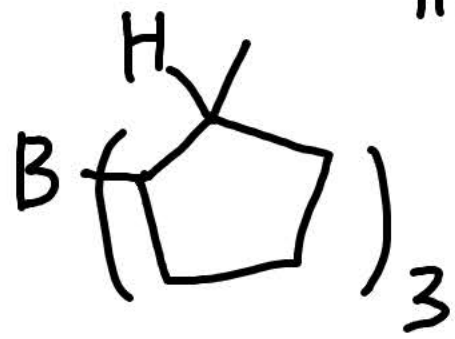


même mécanisme



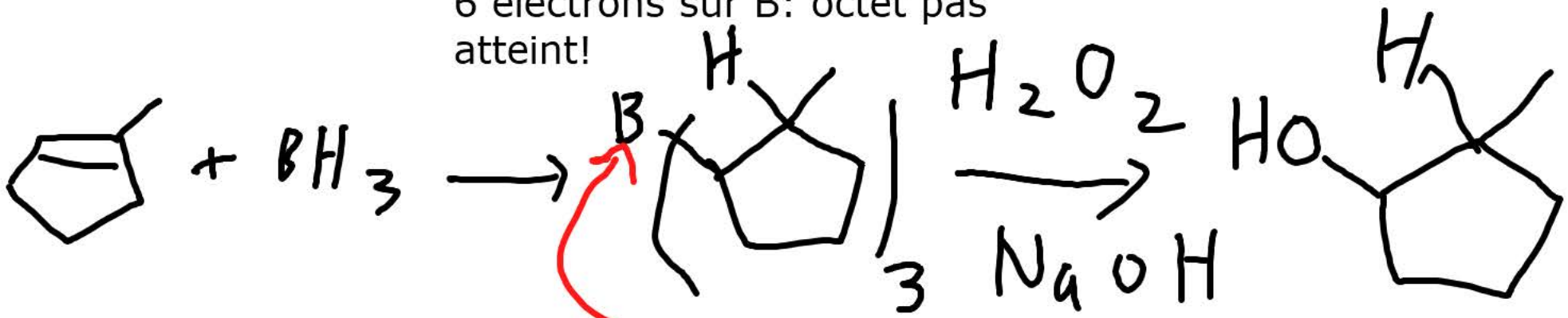
① $\pi_{C-C} \rightarrow p_B$

② $\sigma_{B-H} \rightarrow \pi^*_{C-C}$

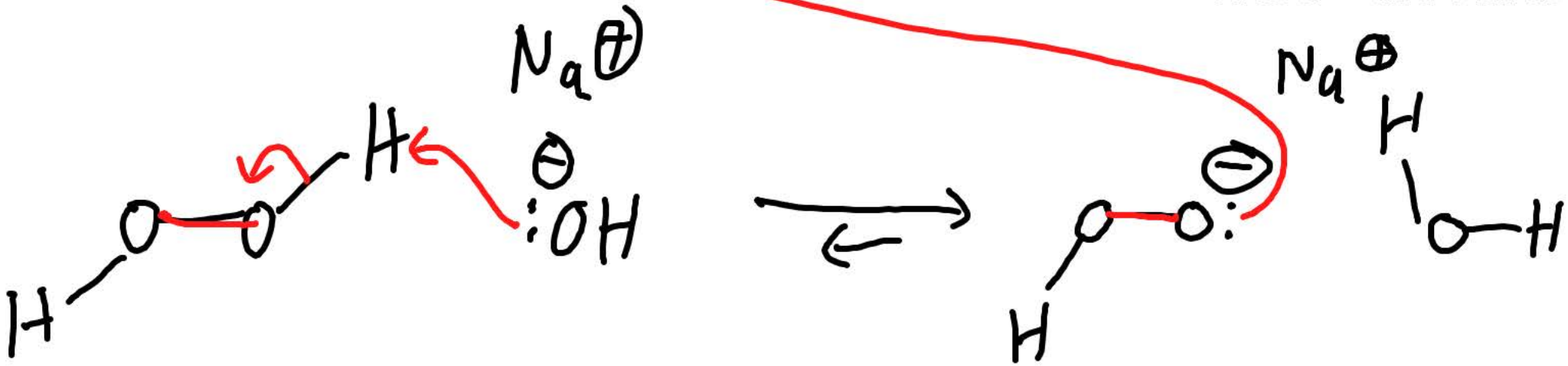


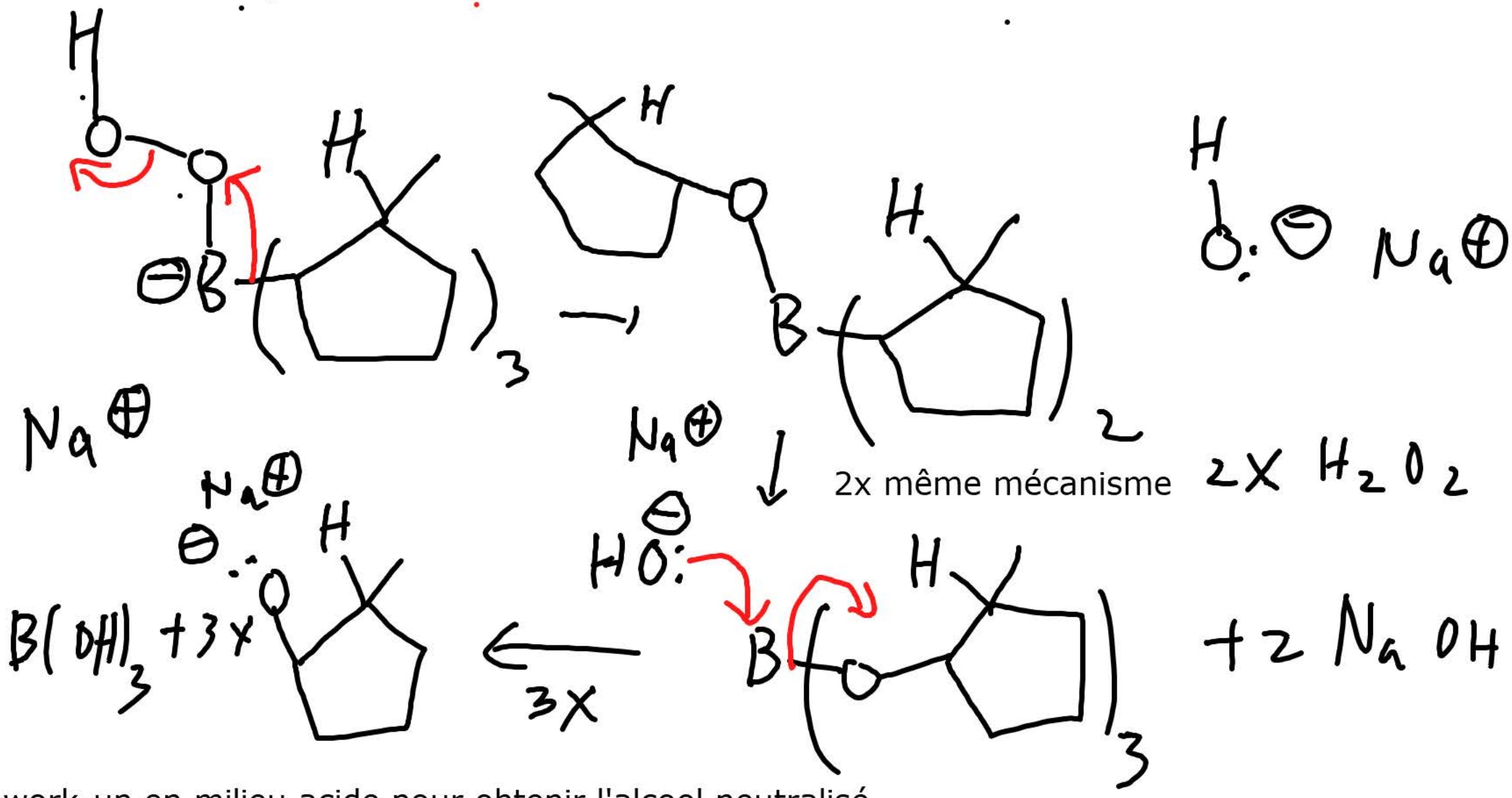
oxidation des liaisons C-B

6 électrons sur B: octet pas atteint!



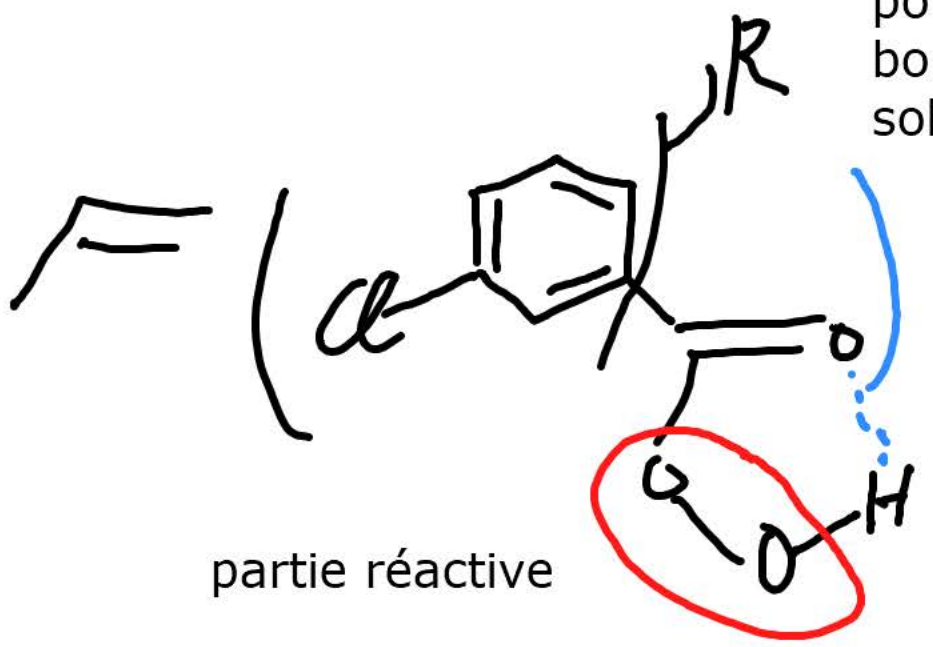
Alcool " anti-Markovnikov"





work-up en milieu acide pour obtenir l'alcool neutralisé

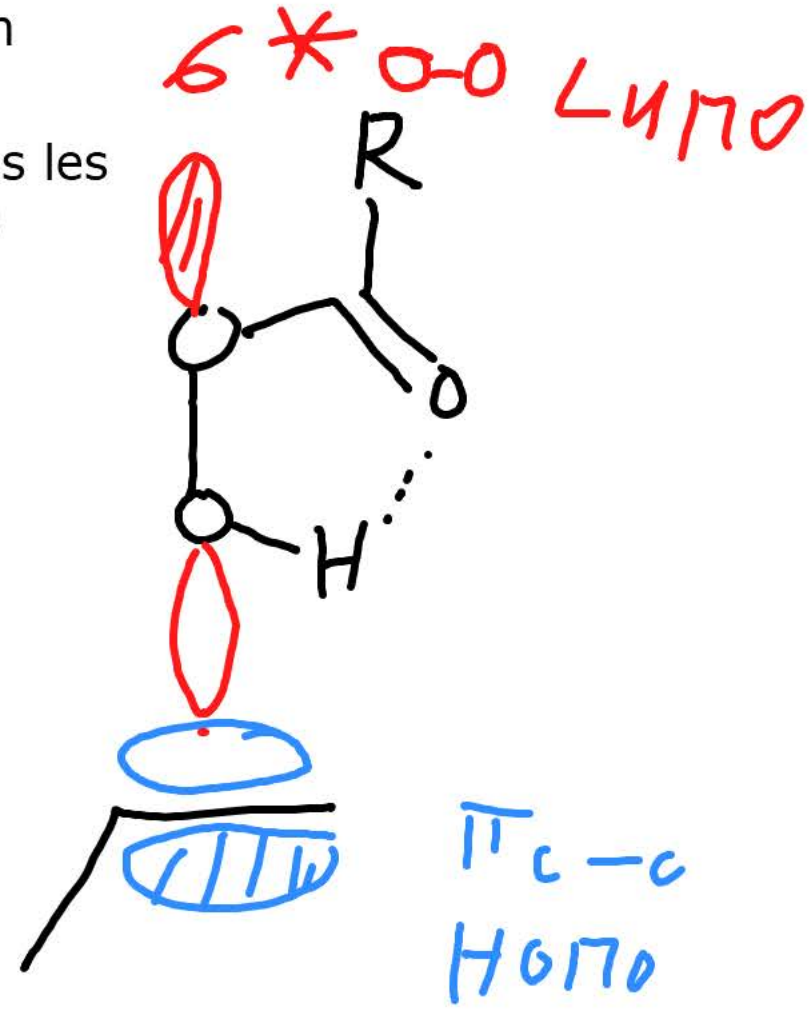
réactions d'oxydation directes des alcènes: 1) époxydation

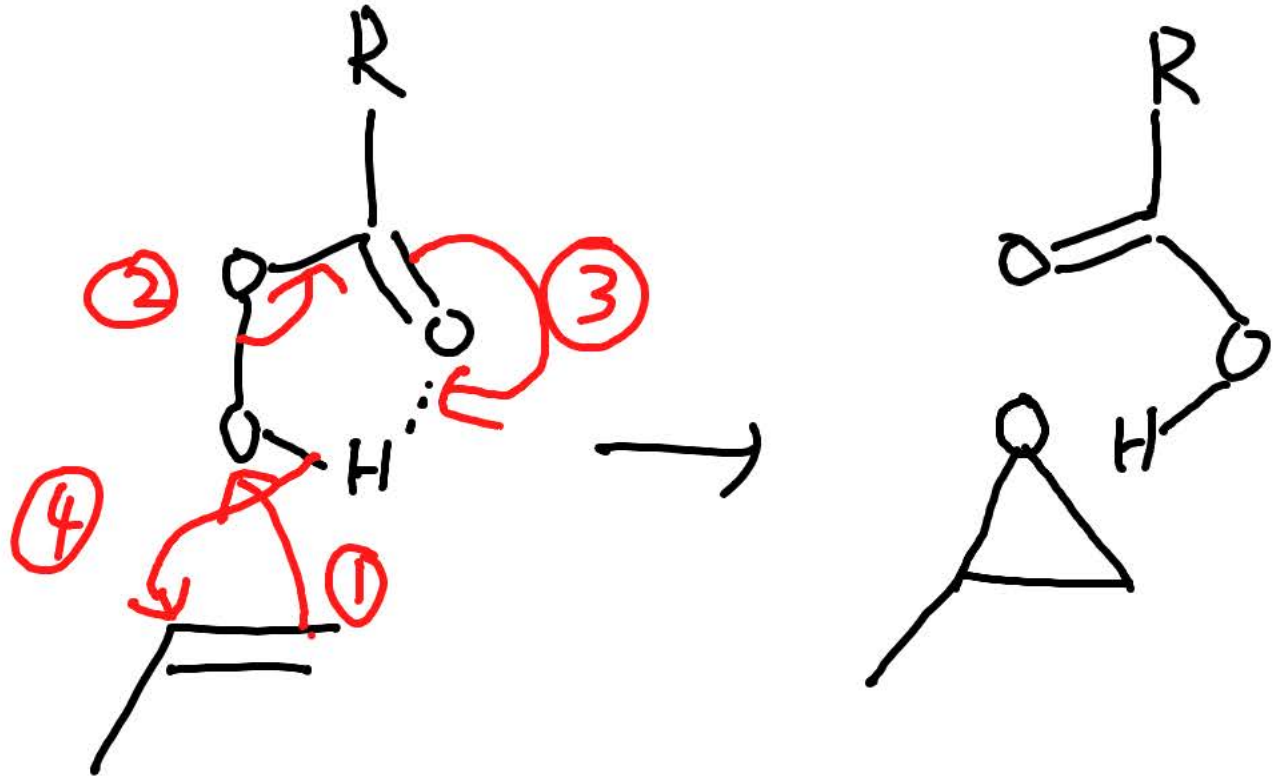


pont hydrogène
bonne solubilité dans les solvants organiques

partie réactive

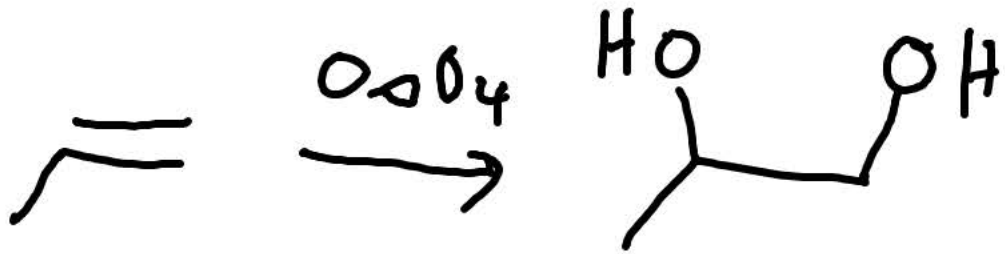
meta-chloroperbenzoic acid
m-CPBA



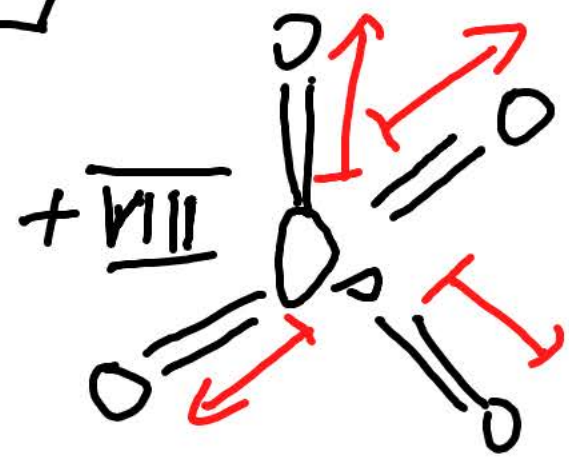


acide: pas de pont hydrogène, moins soluble et précipite.
La molécule qui contient Cl précipite mieux.

oxidation des alcènes: 2) dihydroxylation

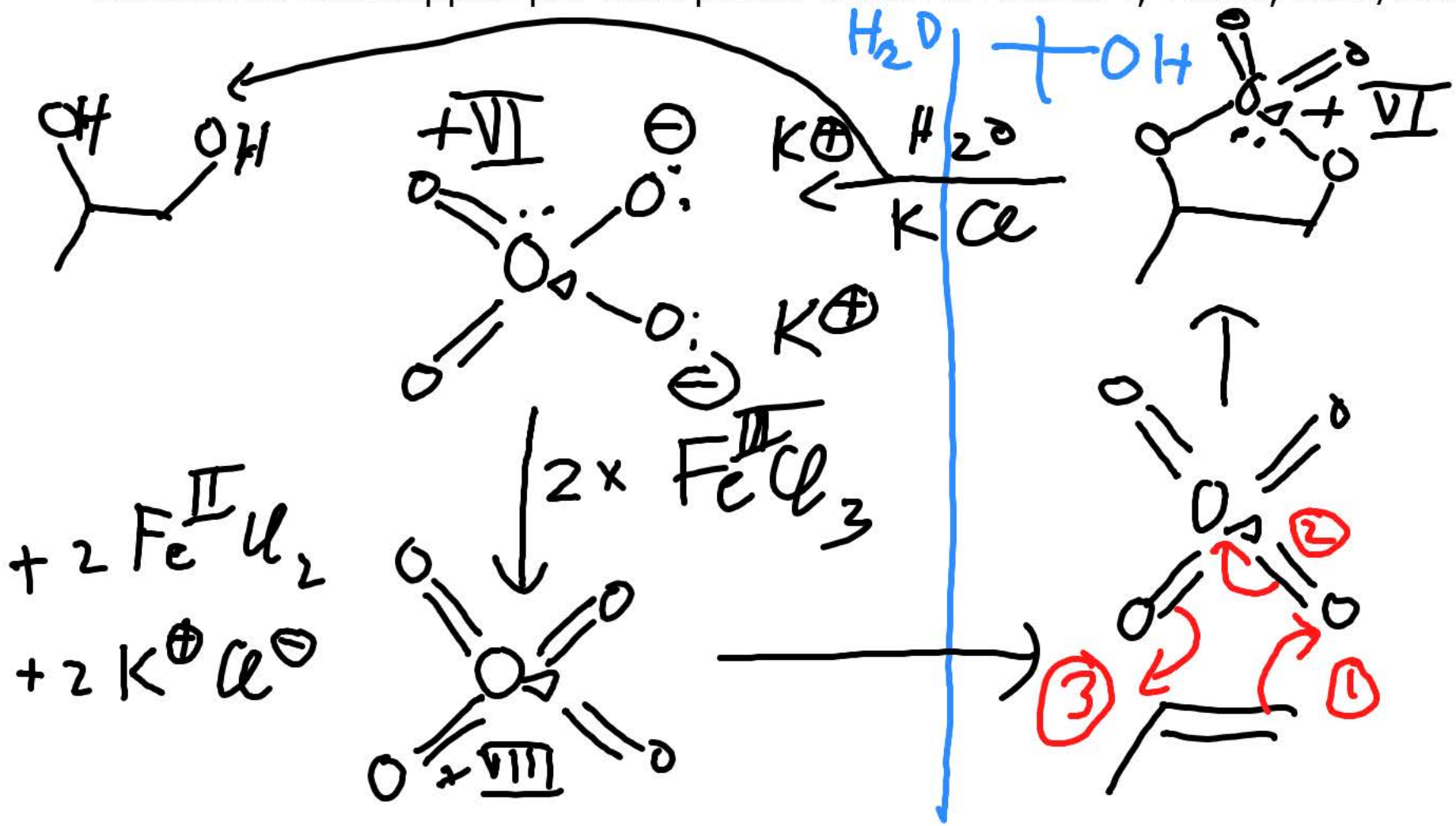


nécessaire de développer une
méthode catalytique!
éviter complètement OsO4

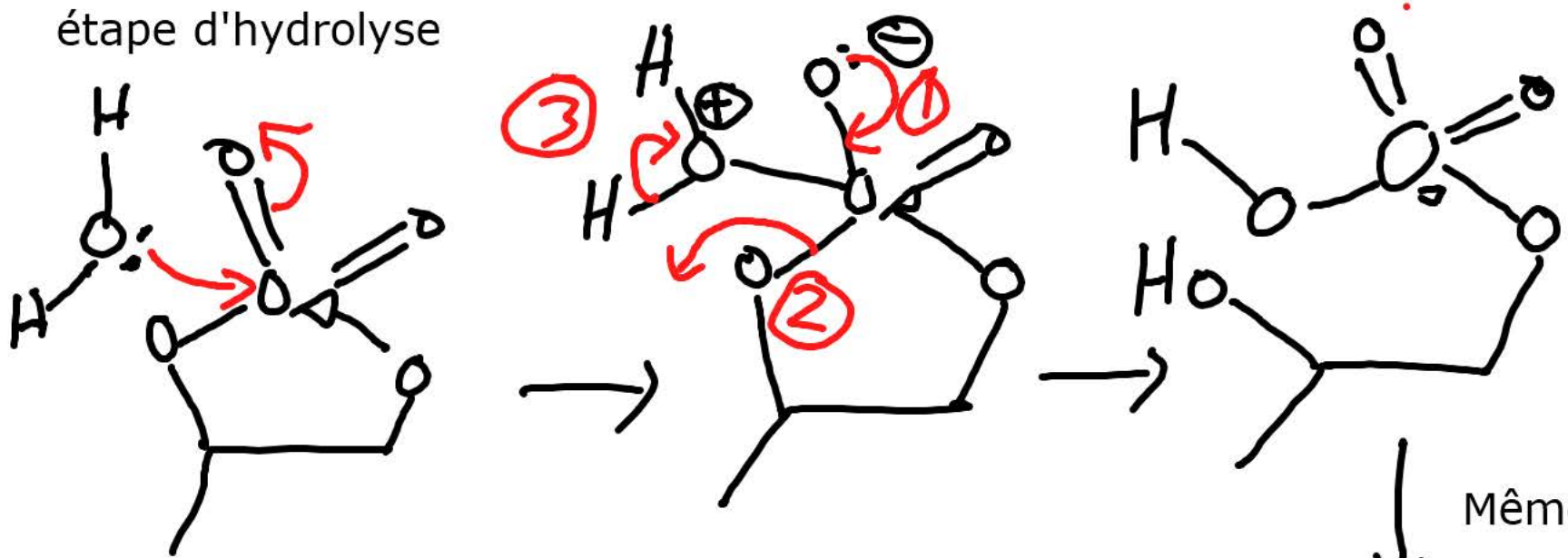


4 substituants, tétrahédrique
dipole globale: 0
lipophilique, passer la barrière sang-cerveau,
sublime facilement
extrêmement toxique!

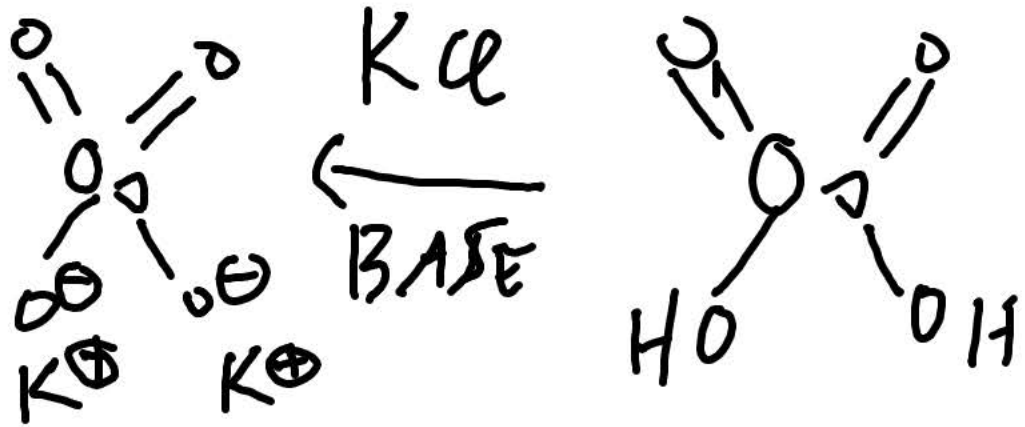
conditions développée par Sharpless: 5 mol% K2OsO4, FeCl3, H2O/tBuOH

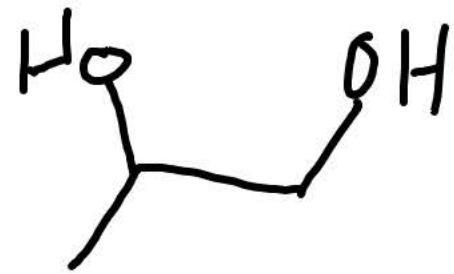


étape d'hydrolyse



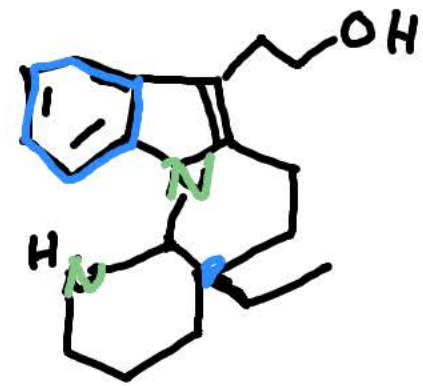
Même mécanisme, H2O

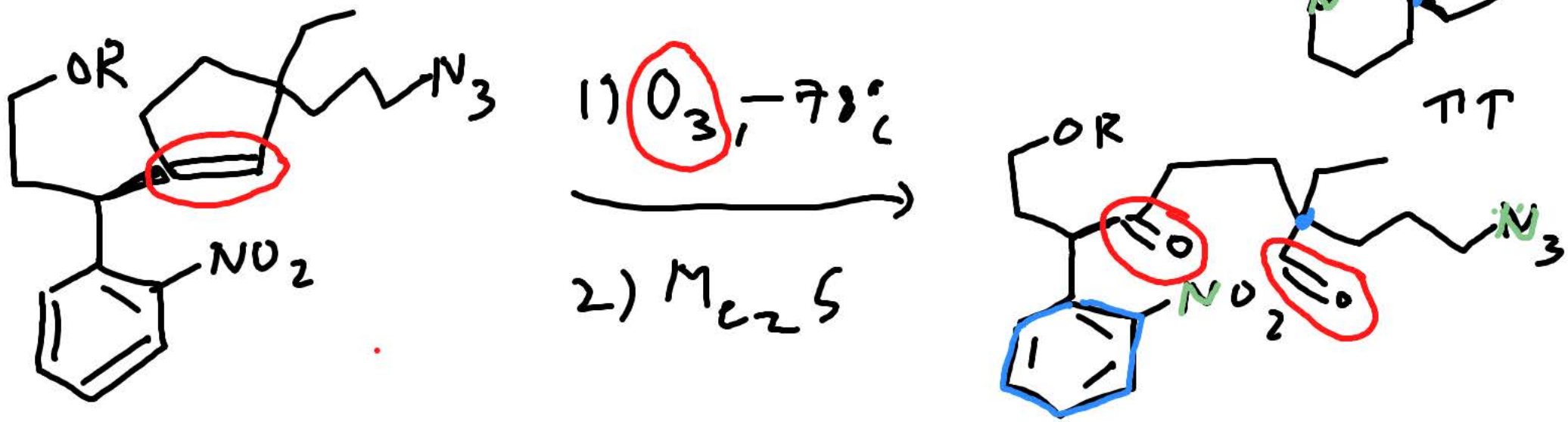


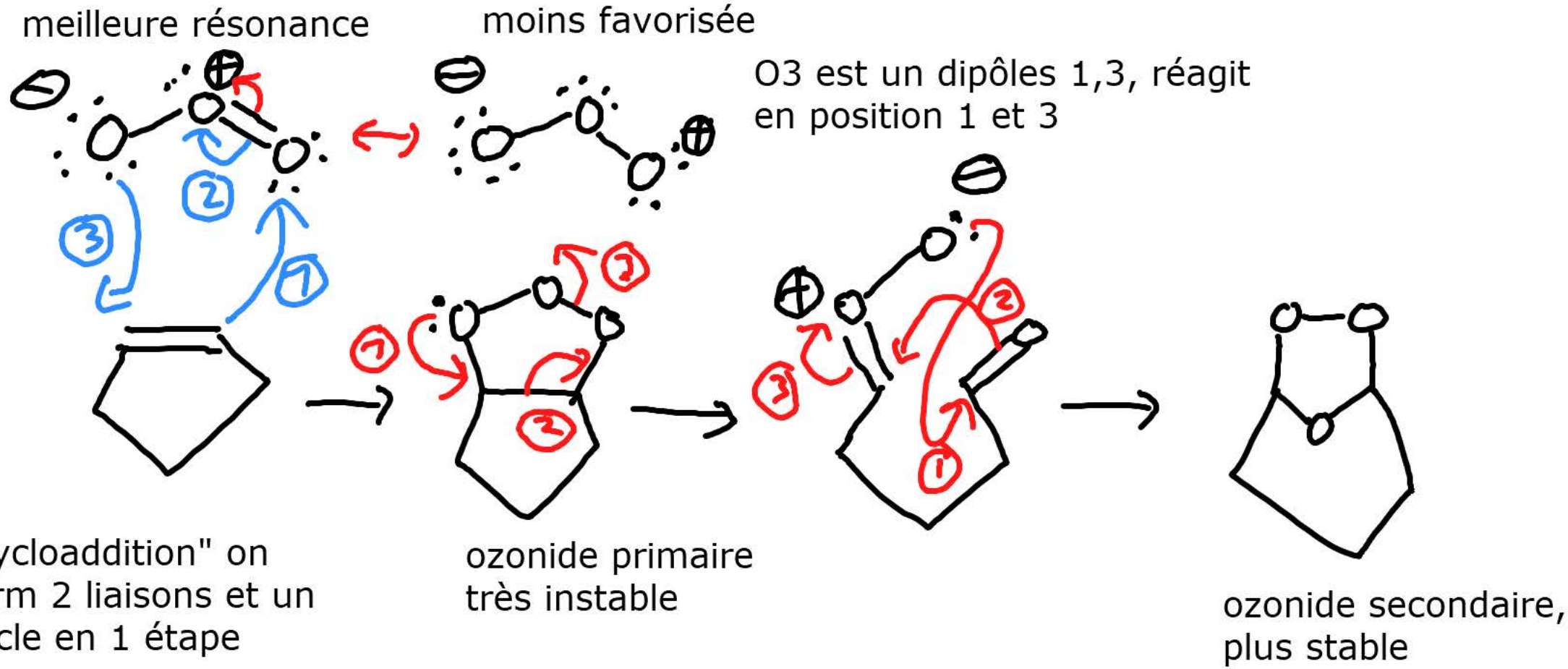


réaction d'ozonolyse. Synthèse de la goniomitine par le groupe de Jieping Zhu (EPFL)

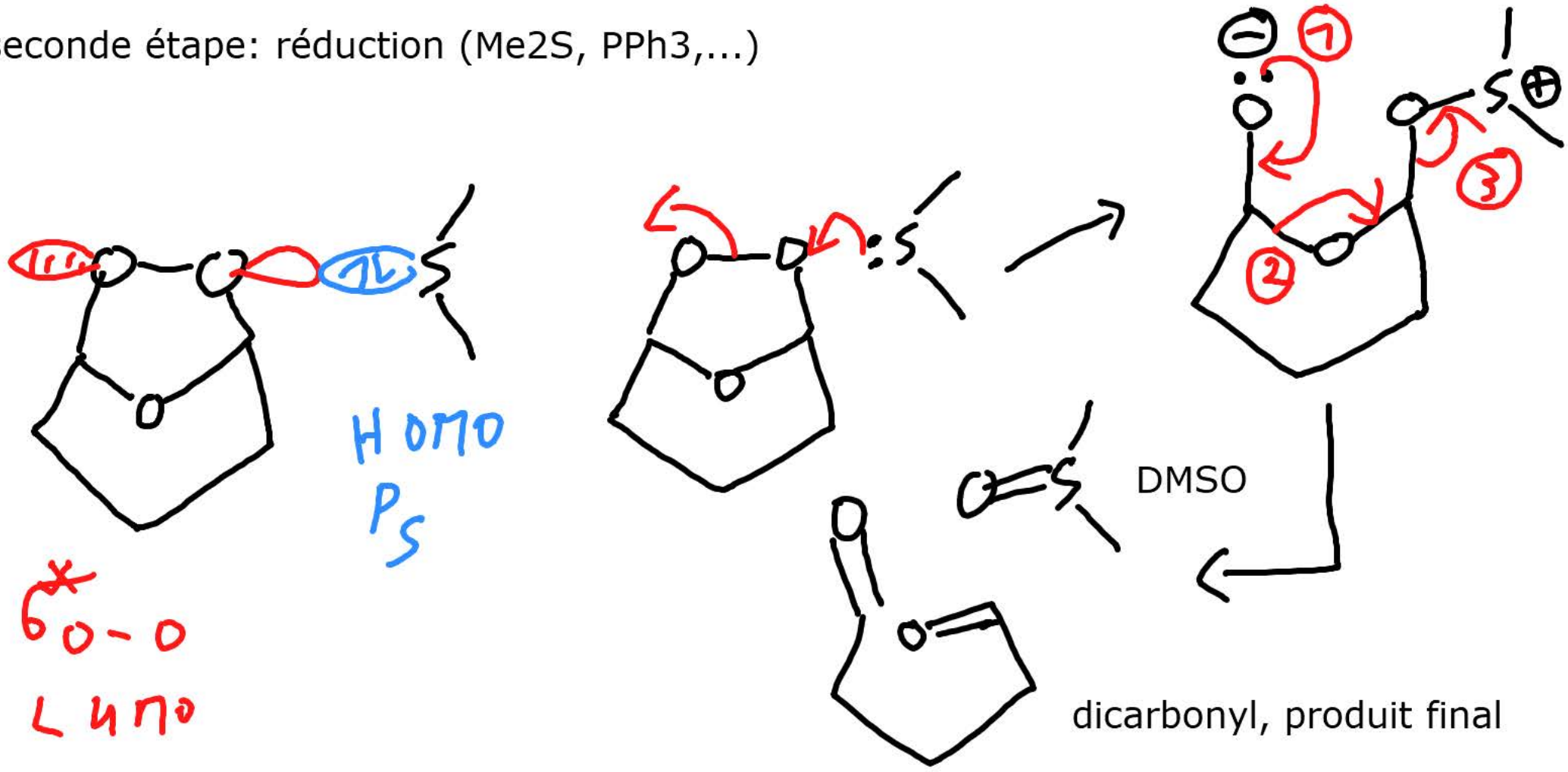
goniomitine



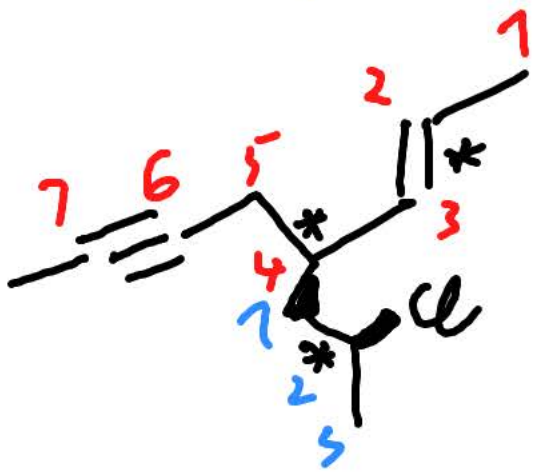



meilleure résonance
moins favorisée
O3 est un dipôles 1,3, réagit en position 1 et 3
"cycloaddition" on form 2 liaisons et un cycle en 1 étape
ozonide primaire très instable
ozonide secondaire, plus stable

seconde étape: réduction (Me2S, PPh3,...)

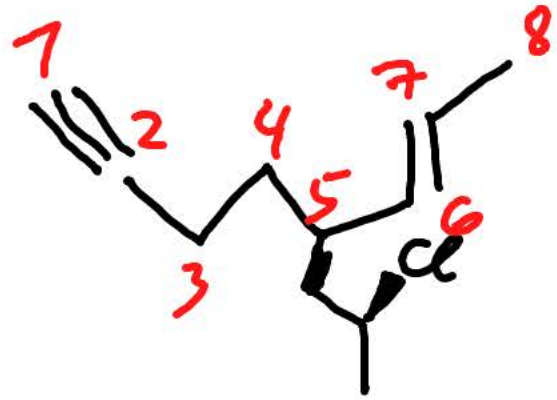


Nomenclature des alcynes: suffixe yne à la fin!



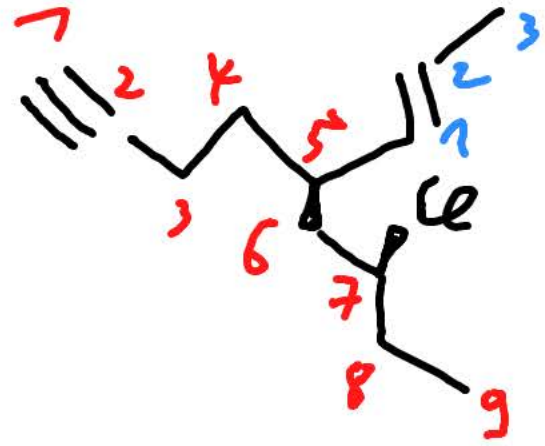
1) la plus longue chaine
2) le plus d'insaturation (alcènes et alcynes compte pour 1 chacun)
3) le chiffre le plus bas doit être donné à l'alcène (alcène domine sur alcynes)

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



chiffre le plus bas pour la première insaturation

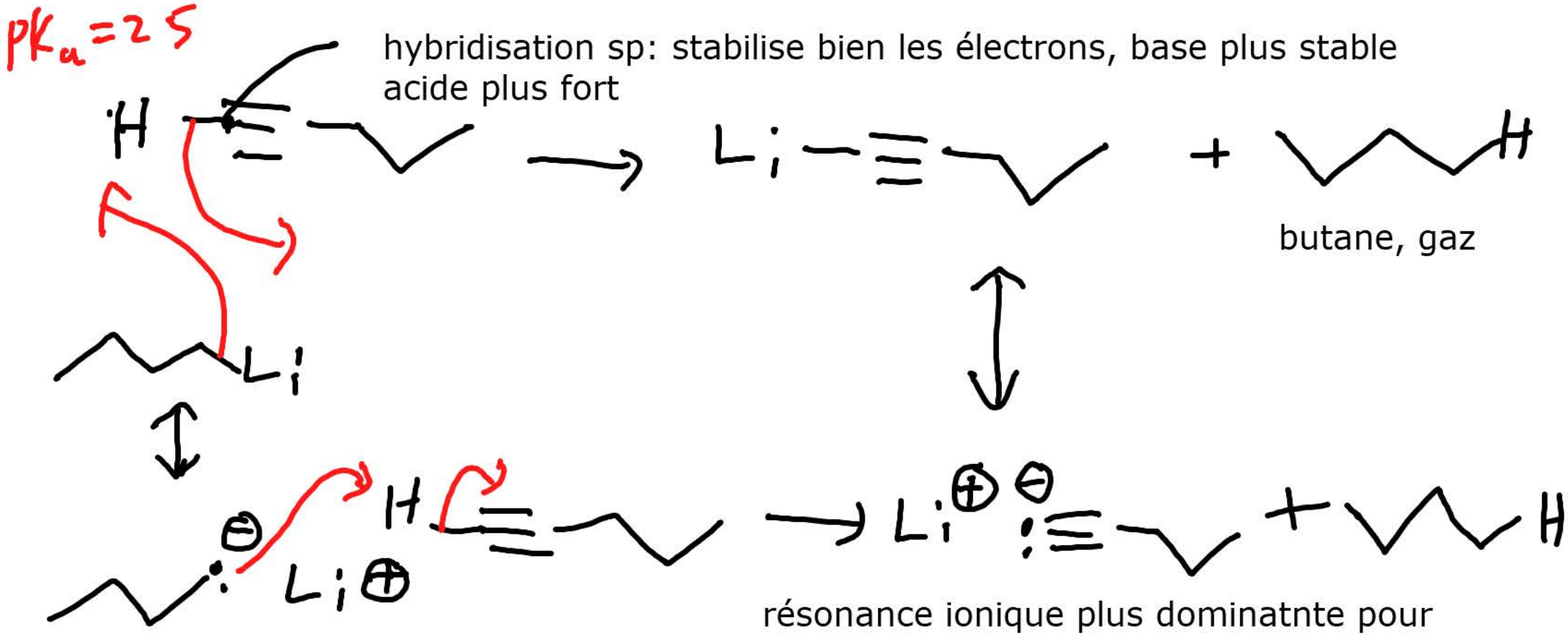
(E,5R)-5-((S)-2-chloropropyl-oct-6-ene-1-yne



chaine la plus longue!

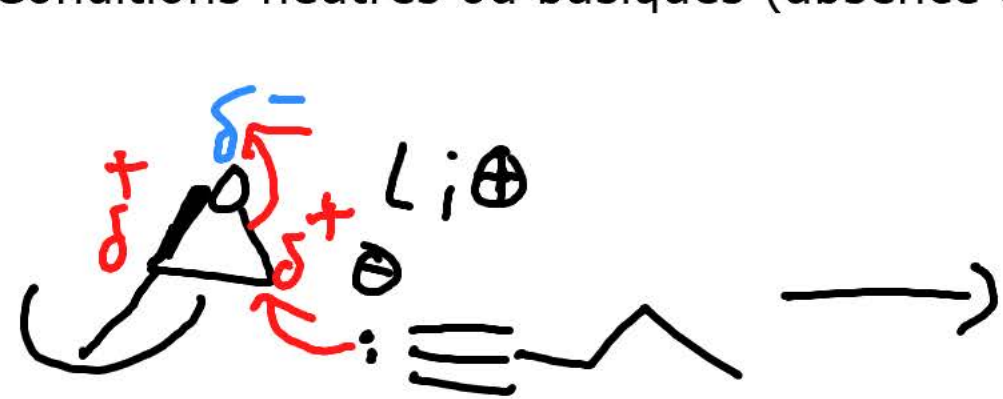
(5R,7S)-7-chloro-5-(E)-prop-1-enyl)-non-1-yne

déprotonation des alcynes et leurs réactions

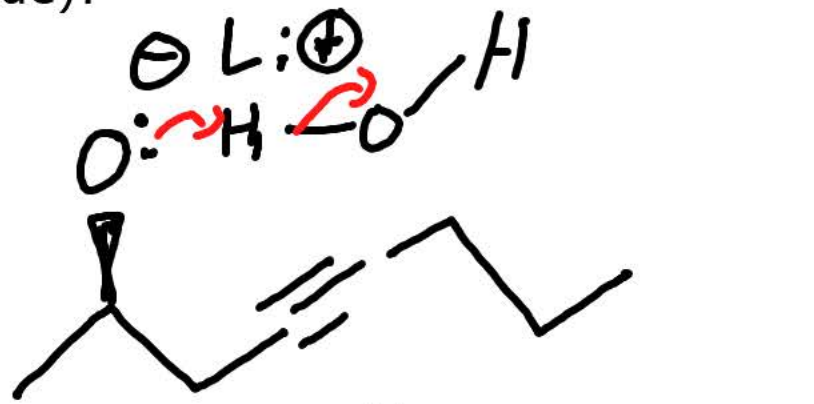


alcynes: réactions avec les époxides

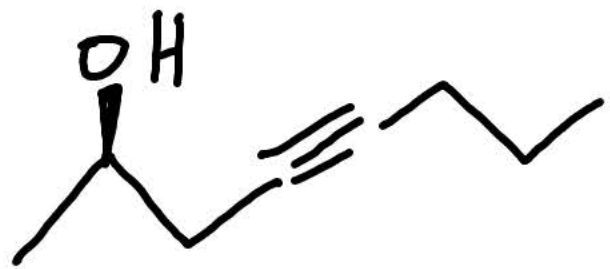
Conditions neutres ou basiques (absence d'acide):



nucléophile

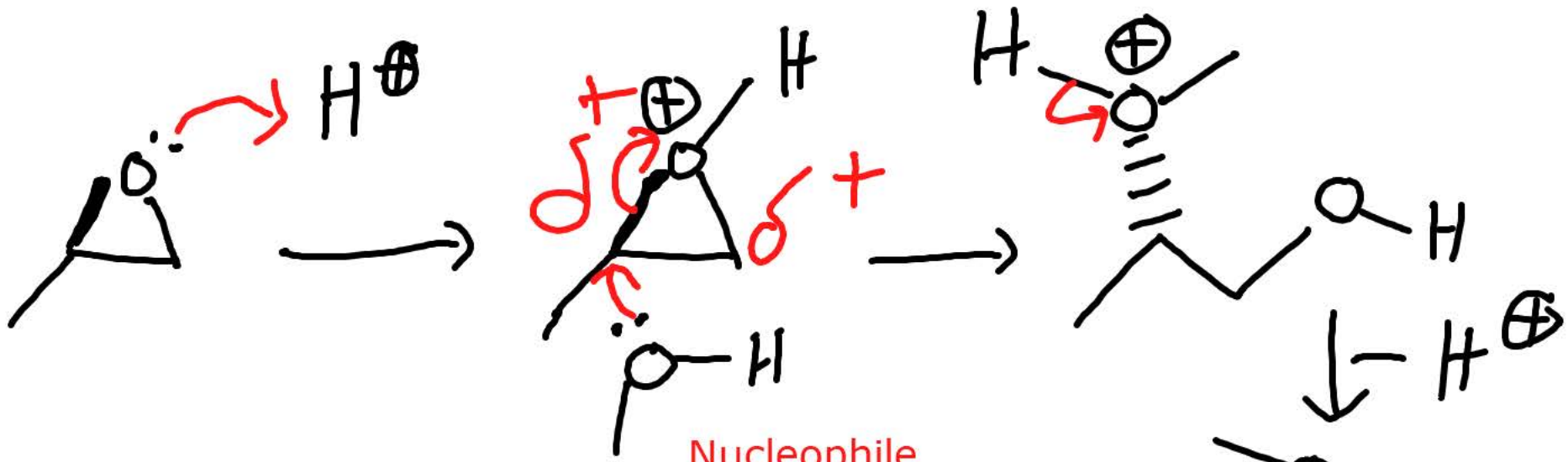


work-up



la réaction est contrôlée par la stérique (taille) des substituents, on attaque en position la moins stubstituée

Conditions acides avec MeOH/H+



Nucleophile

stabilisation des charges
maintenant le plus important
plus stable en position
secondaire que primaire

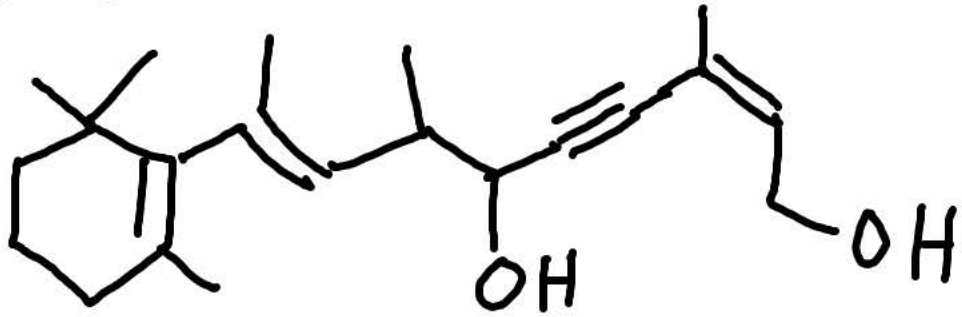
en conditions acides, l'attaque est
contrôlée par la stabilisation des charges

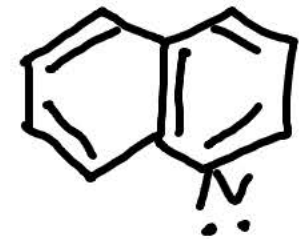
.

réduction des alcyne pour donnes les alcènes

Comment obtenir
selectivement Z ou E?

hydrogénation de Lindlar: Hofman-LaRoche (Bale, 1952)

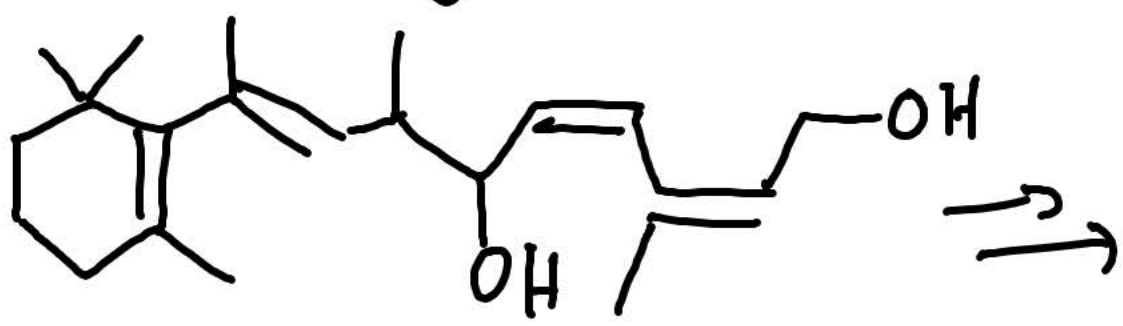




quinoline

H_2 Pd/C/PbSO4/quinoline

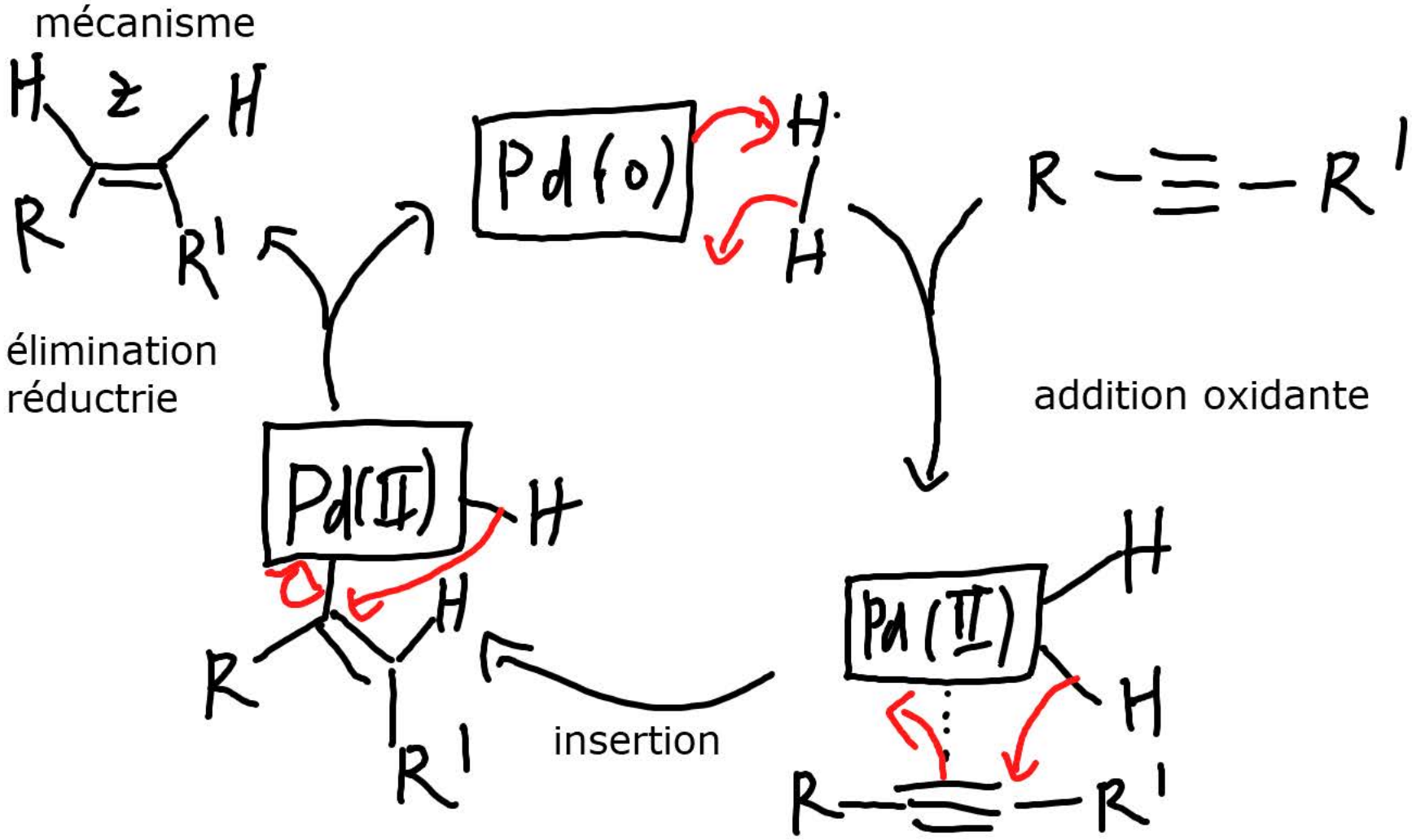
se lie sur la surface du Pd et diminue la réactivité



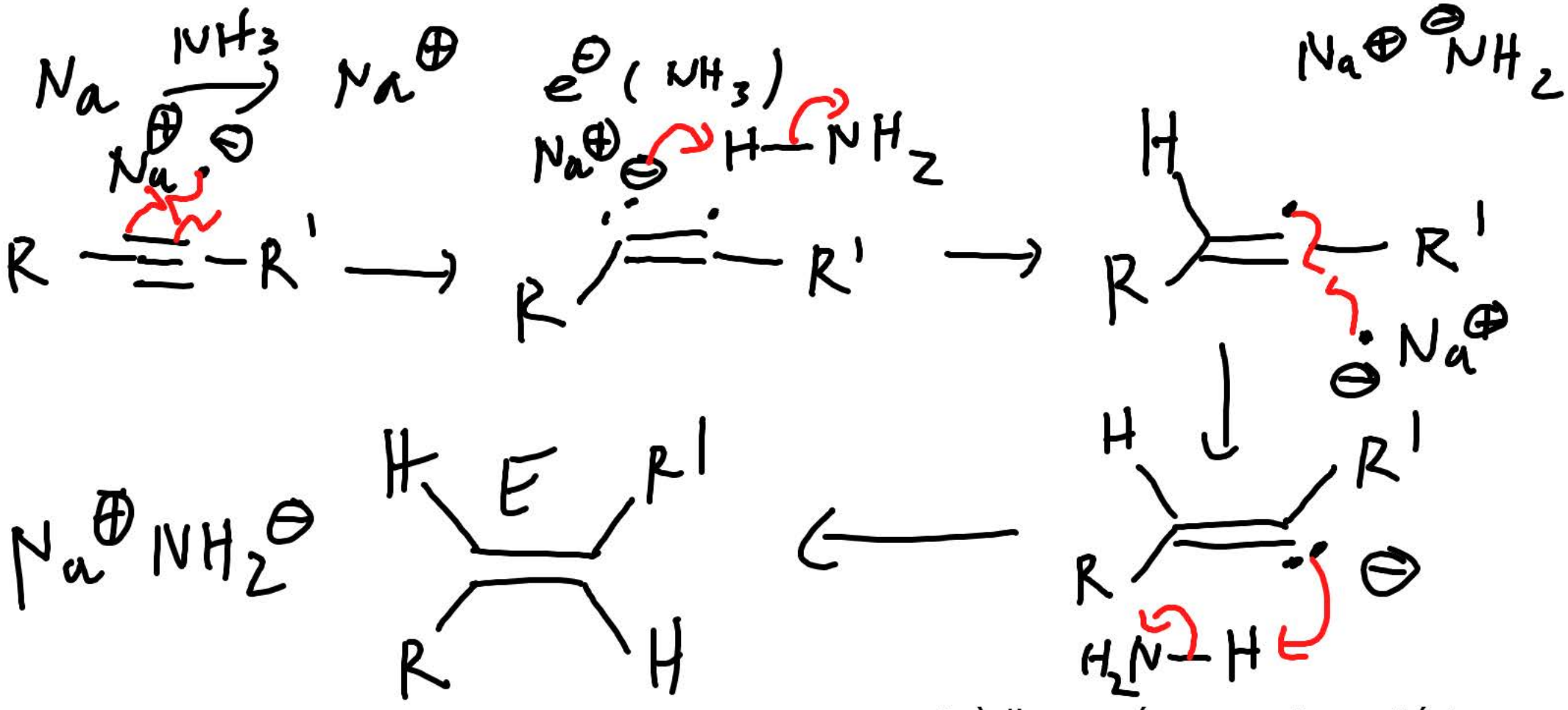
retinol, vitamine A

challenge: comment réduire que la triple liaison et obtenir l'alcène Z?

mécanisme

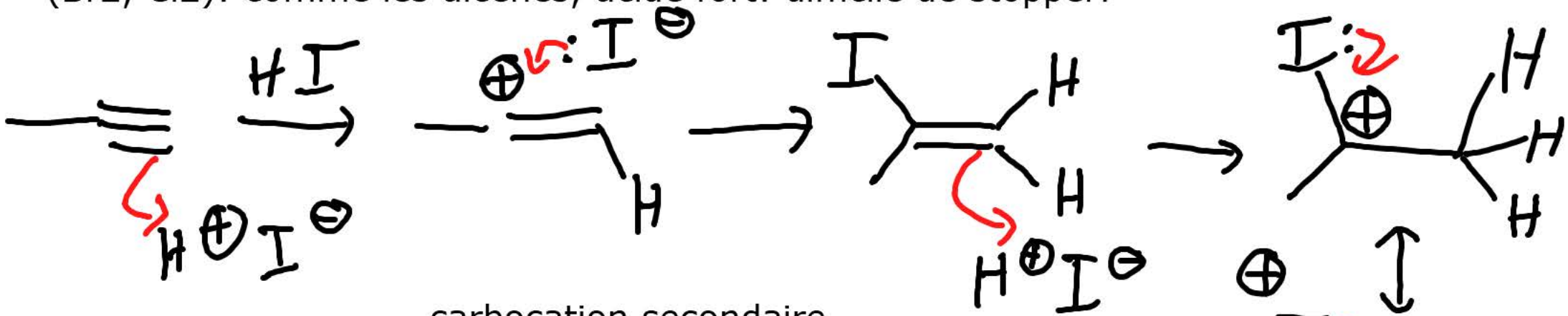

Pd(0)
addition oxidante
Pd(II)
insertion
Pd(II)
élimination
réductrie

Alcène E? Birch: Na/NH3



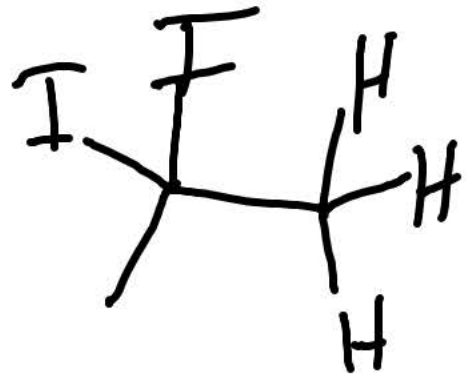
groupe R à l'opposé pour raison stérique

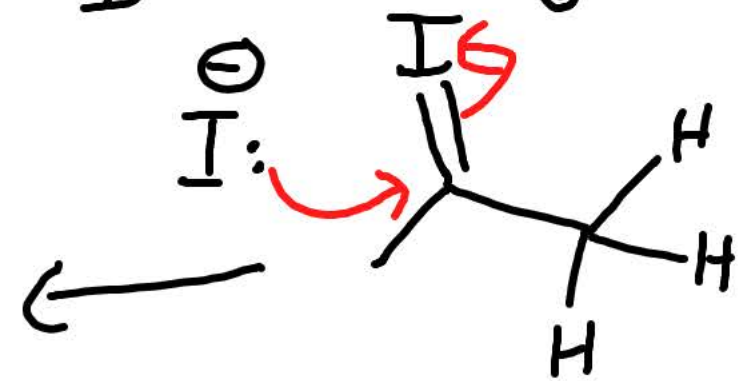
additions des halogènures et des acides forts: halogènures (Br2, Cl2): comme les alcènes, acide fort: difficile de stopper!



carbocation secondaire plus stable

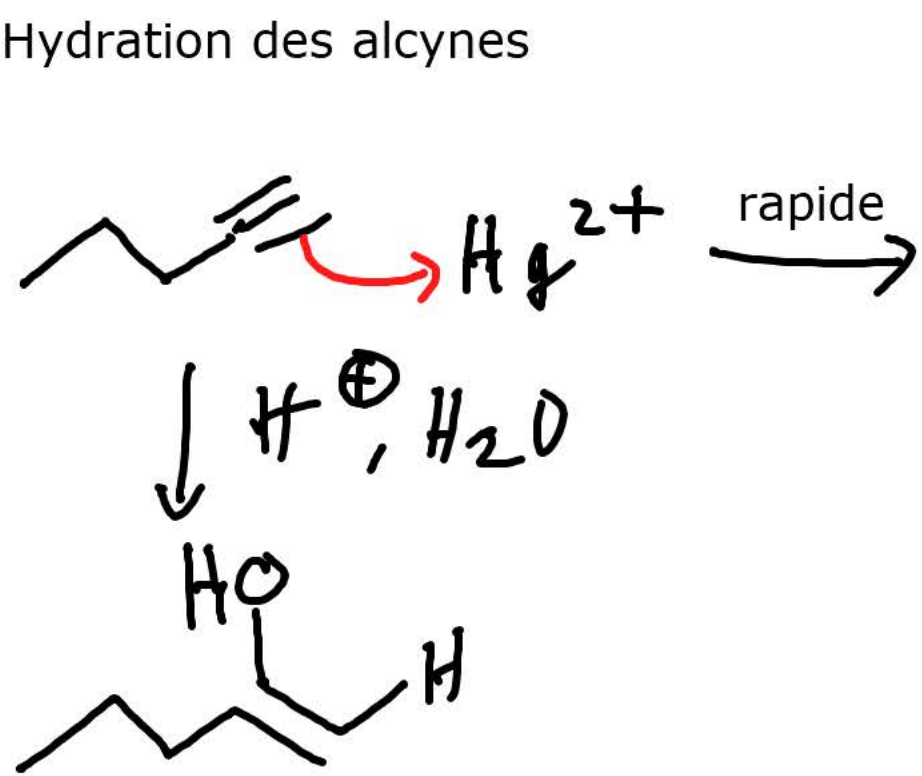
second addition plus rapide que la première, impossible de stopper.



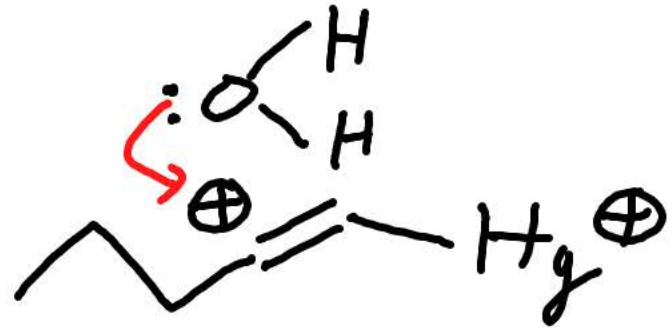


carbocation plus stable

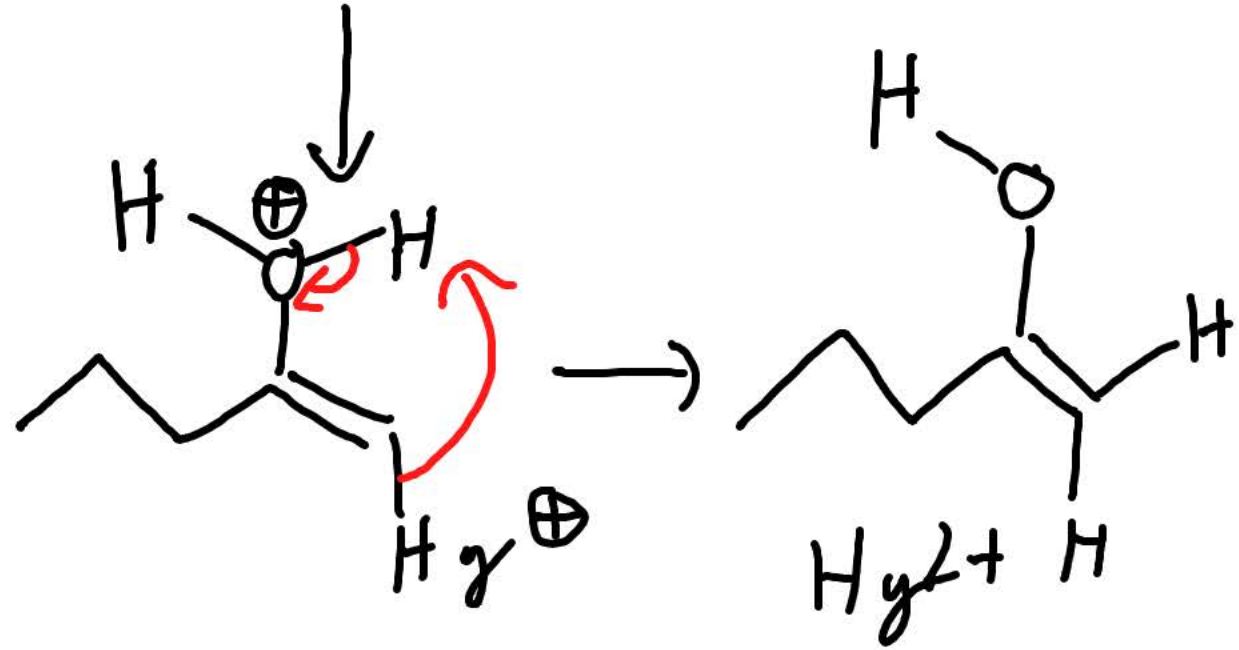
Hydration des alcynes



rapide

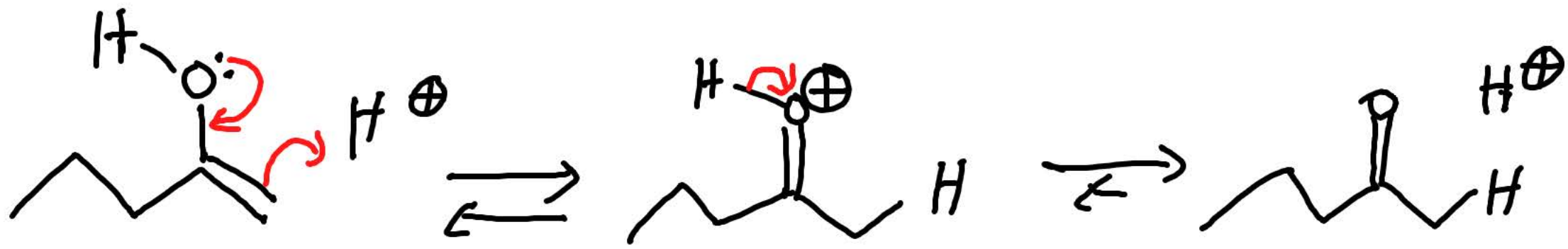


carboction secondaire
plus stable



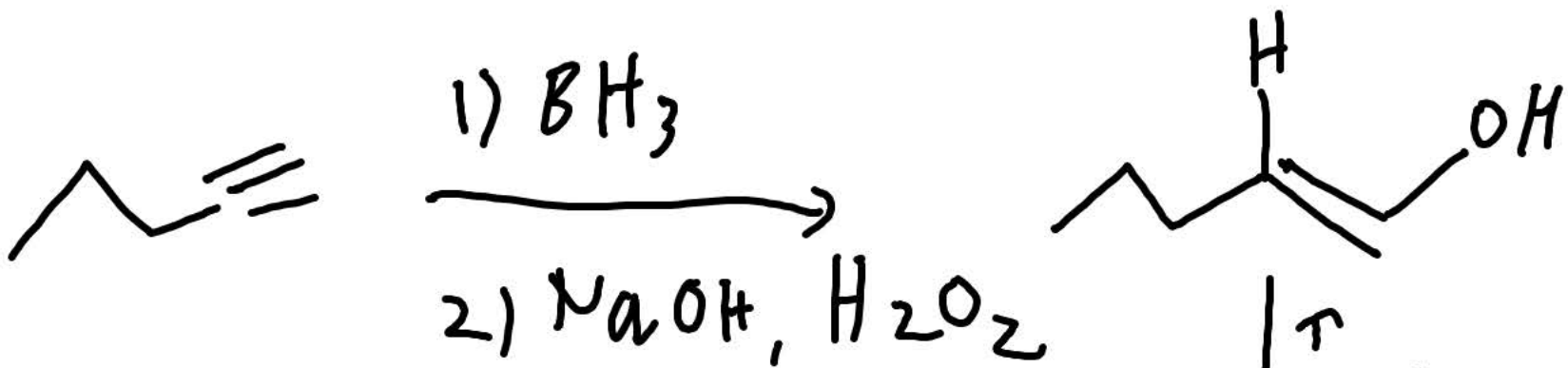
réaction lente, protonation
n'est pas rapide

Hg2+ agit comme catalyseur
pour accélérer la réaction



énol

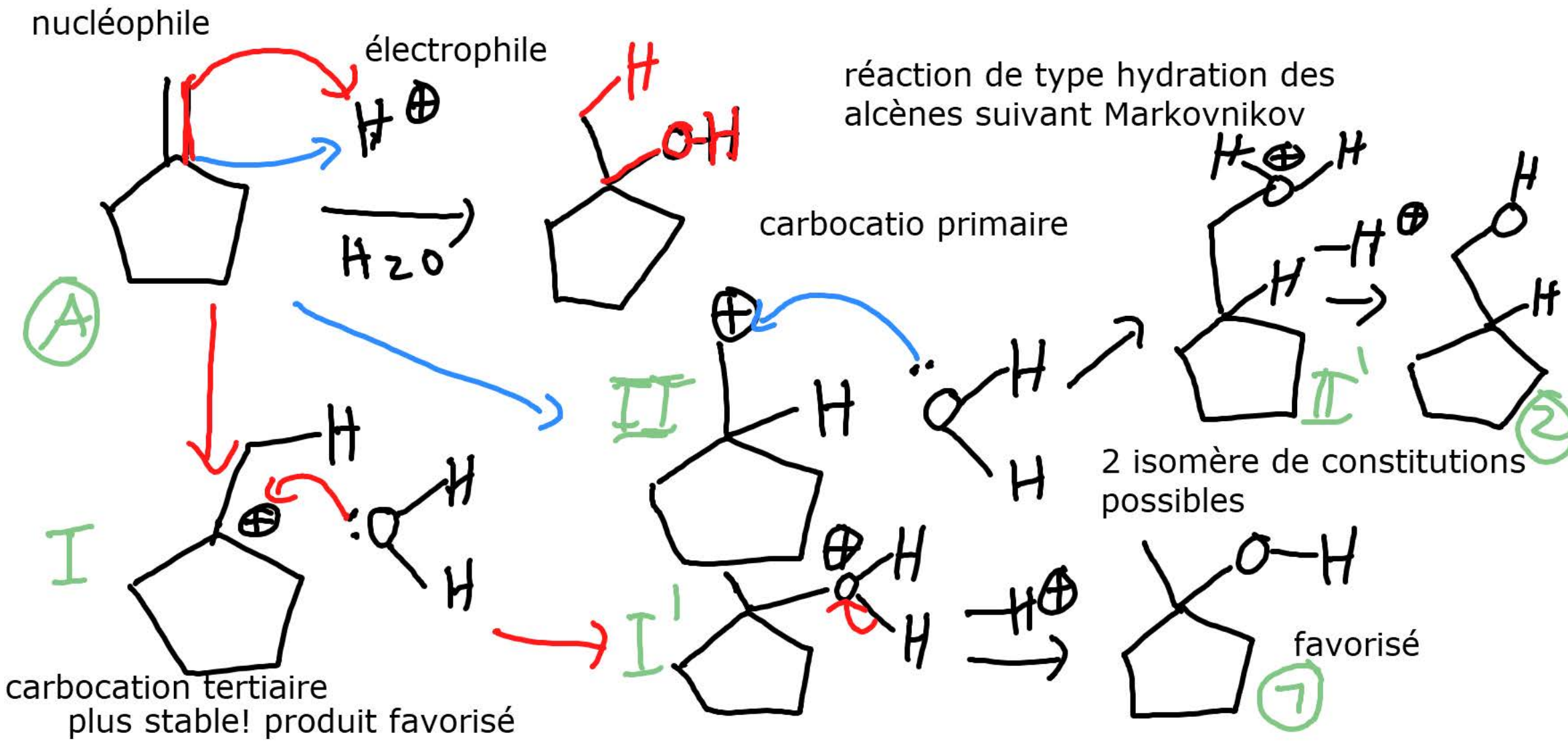
cétone
plus stable
C=O plus stable
que C=C



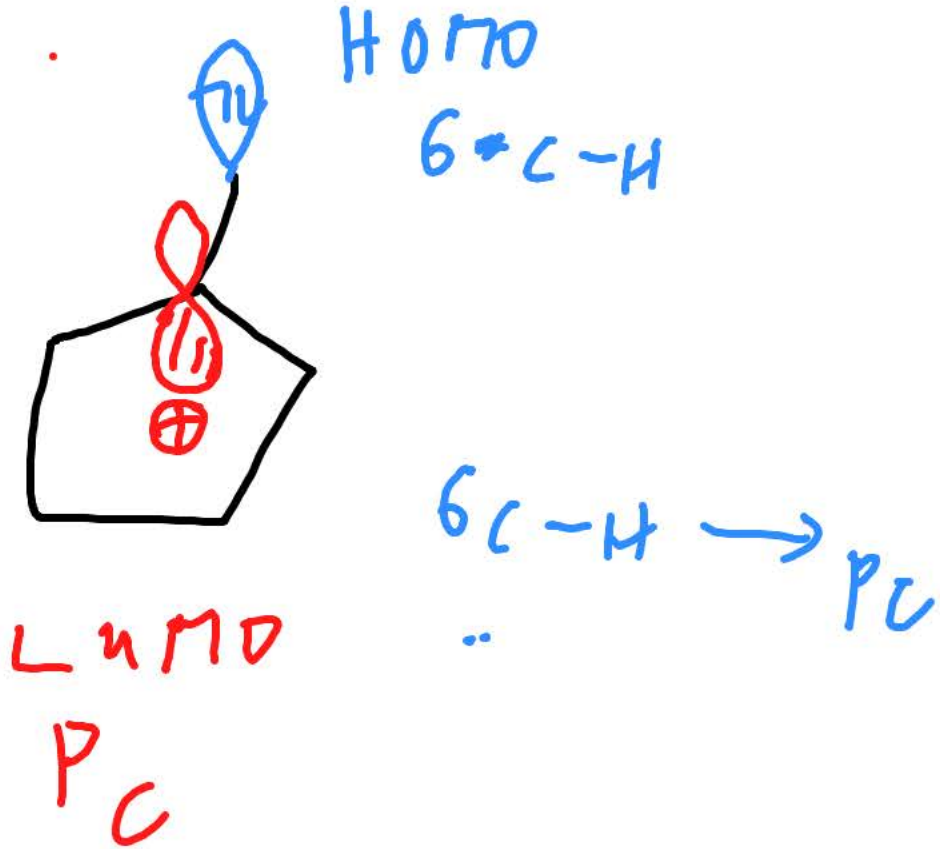
même mécanisme que
pour les alcènes

aldéhydes

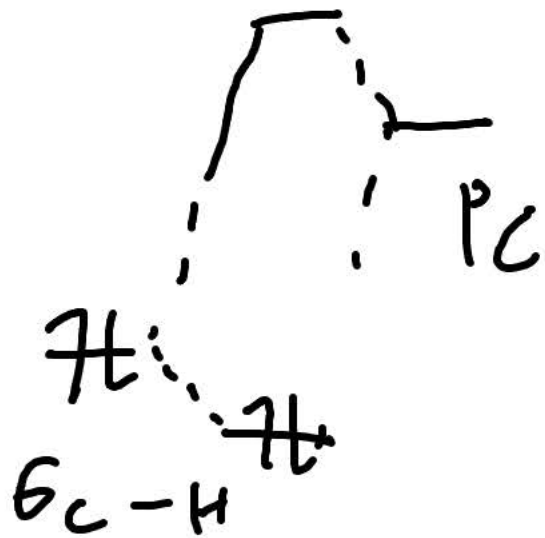
exercice 6.3


nucléophile
électrophile
réaction de type hydration des alcènes suivant Markovnikov
carbocatio primaire
A
I
II
I'
II'
2 isomère de constitutions possibles
favorisé
carbocation tertiaire
plus stable! produit favorisé

orbitales importantes: celles qui expliquent pourquoi le carbocation tertiaire est plus stable!

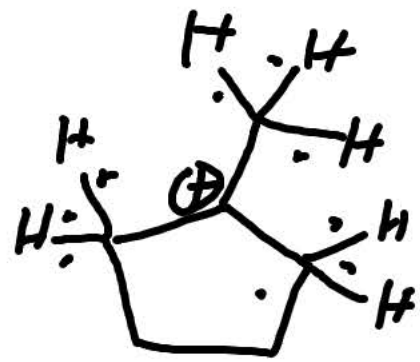


donc carbocation tertiaire plus stable, car plus d'hyperconjugaison



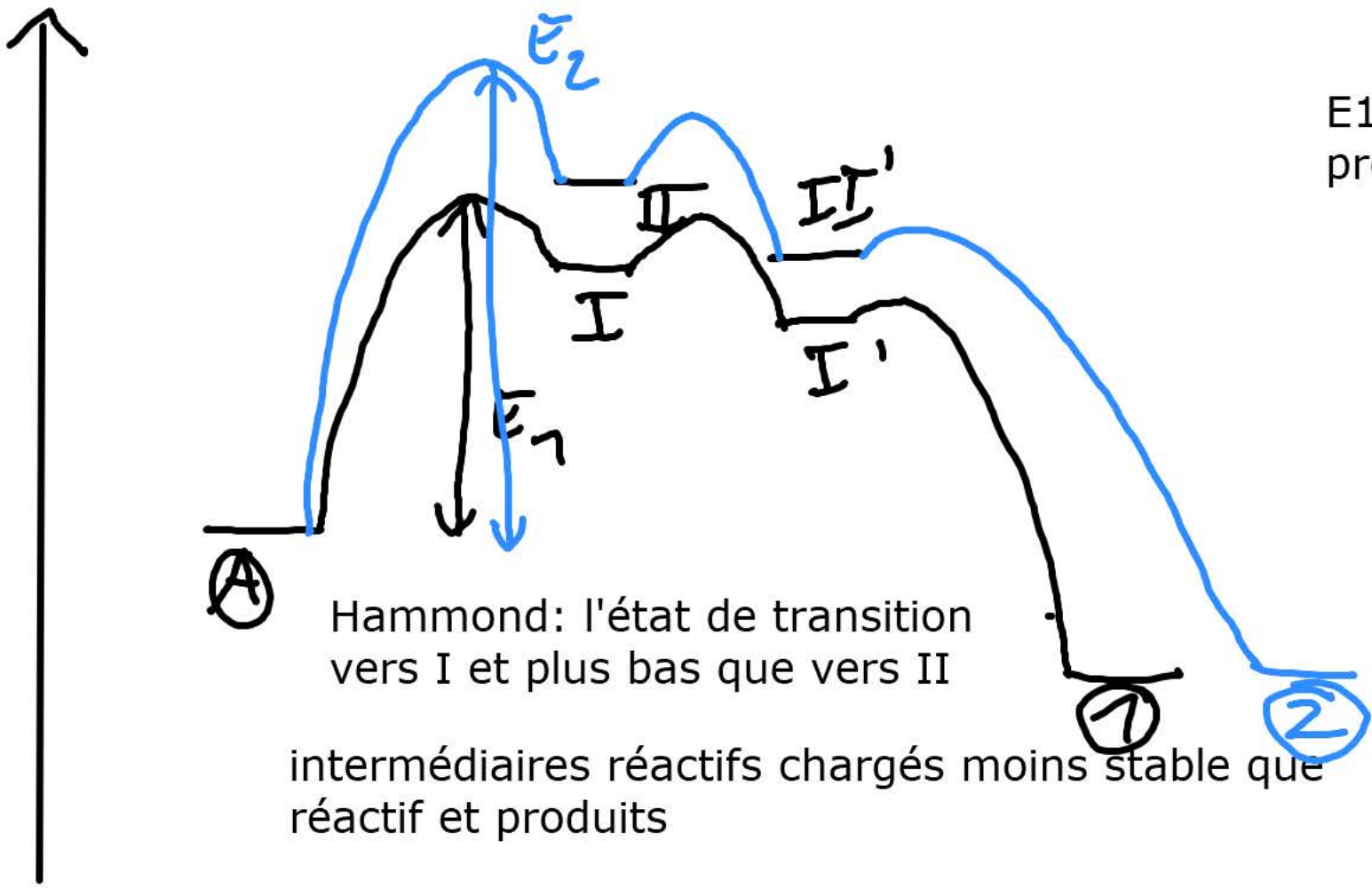
stabilisation par hyperconjugaison

3 liaison possibles pour hyperconjugaison



9 liaisons possibles

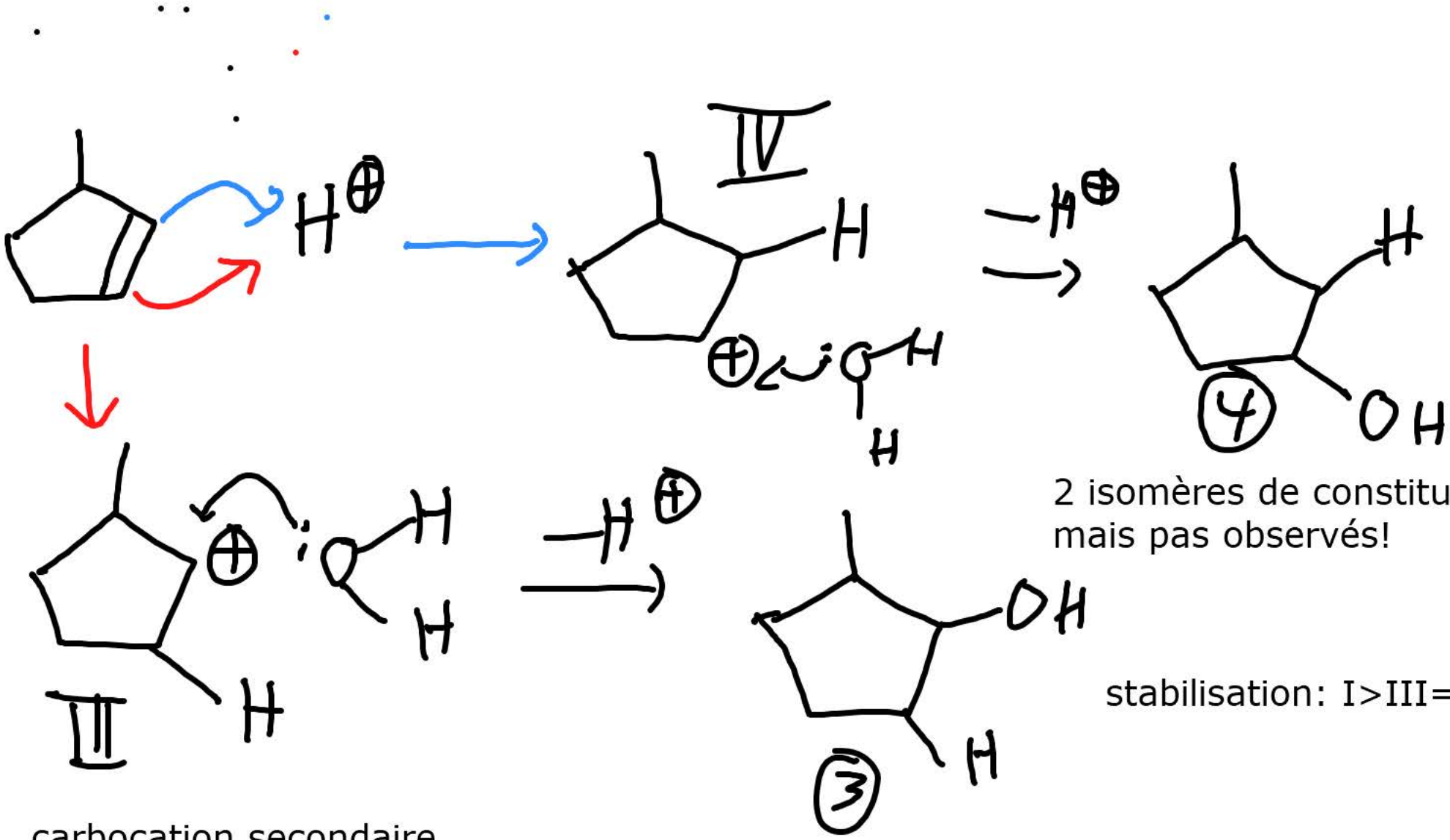
profil d'énergie



E1 < E2, donc on observe le produit 1

Hammond: l'état de transition vers I et plus bas que vers II

intermédiaires réactifs chargés moins stable que réactif et produits

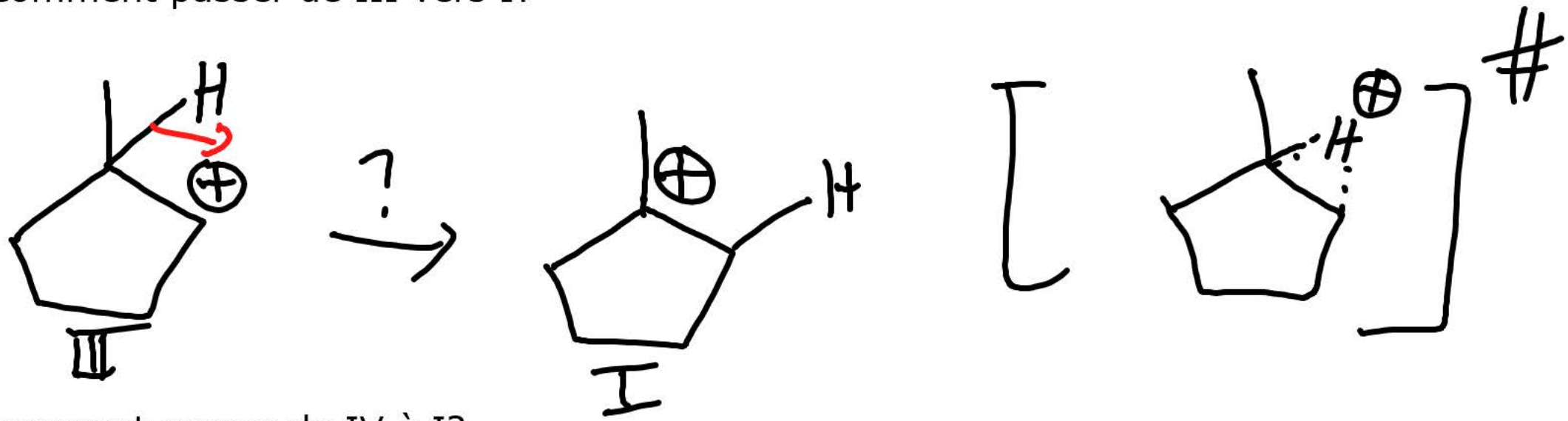


2 isomères de constitutions, mais pas observés!

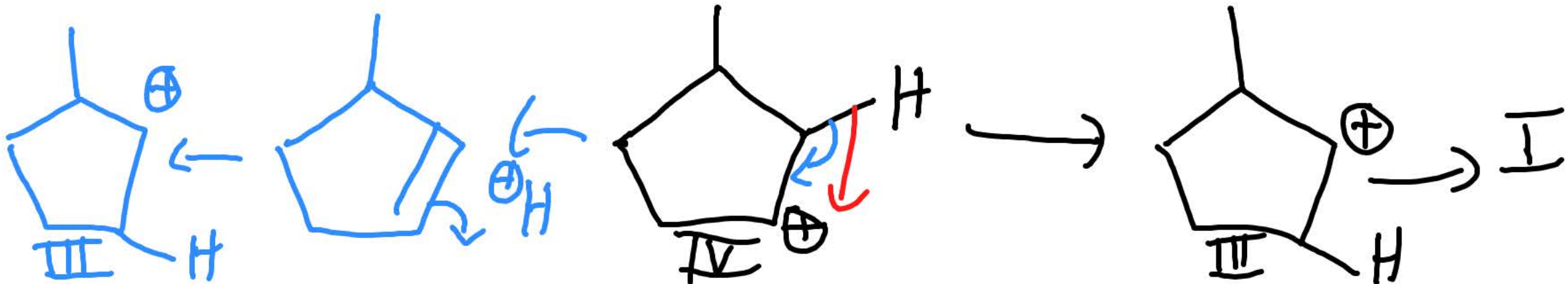
carbocation secondaire

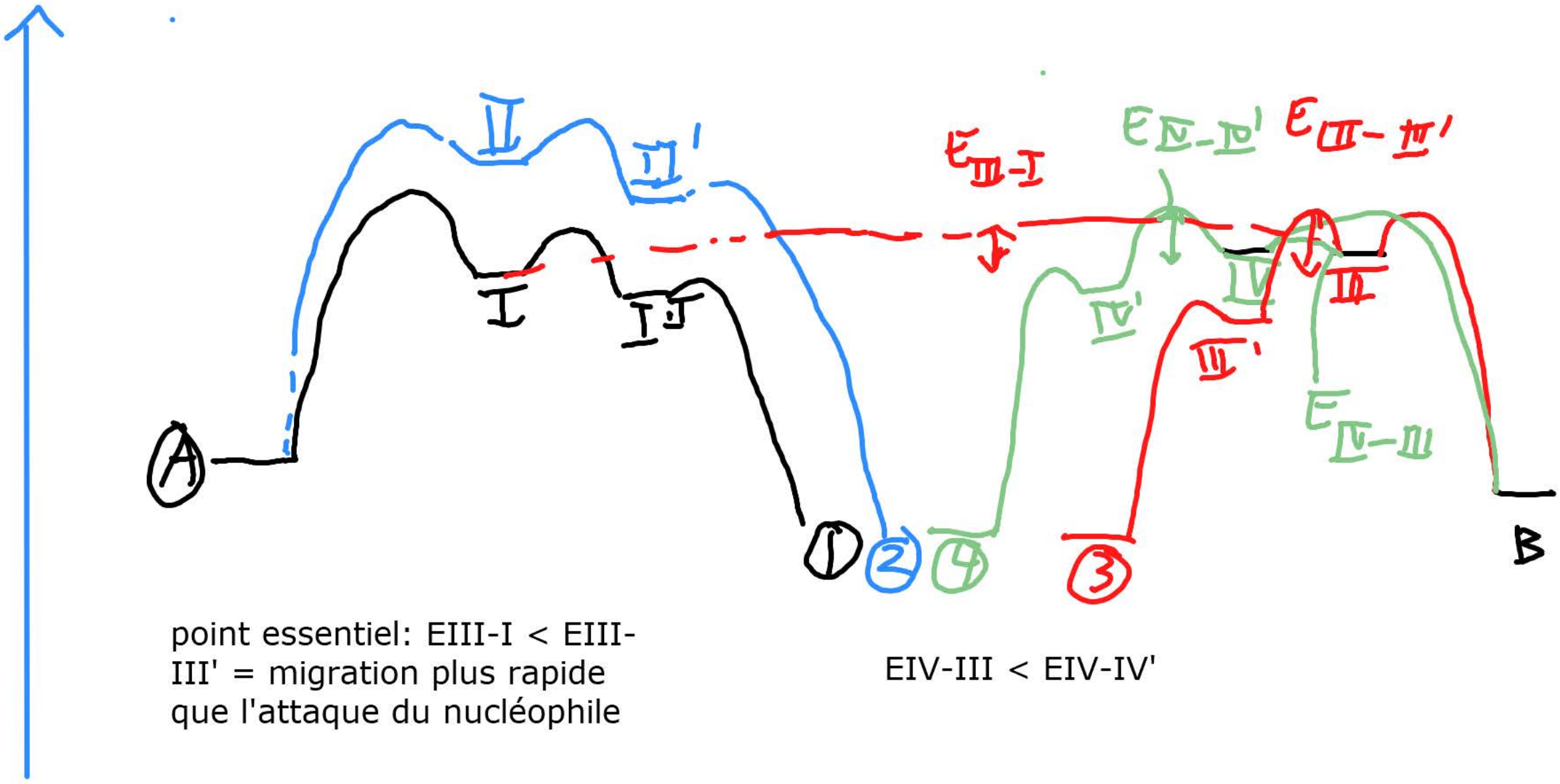
stabilisation: I>III=IV>II

comment passer de III vers I?



comment passer de IV à I?

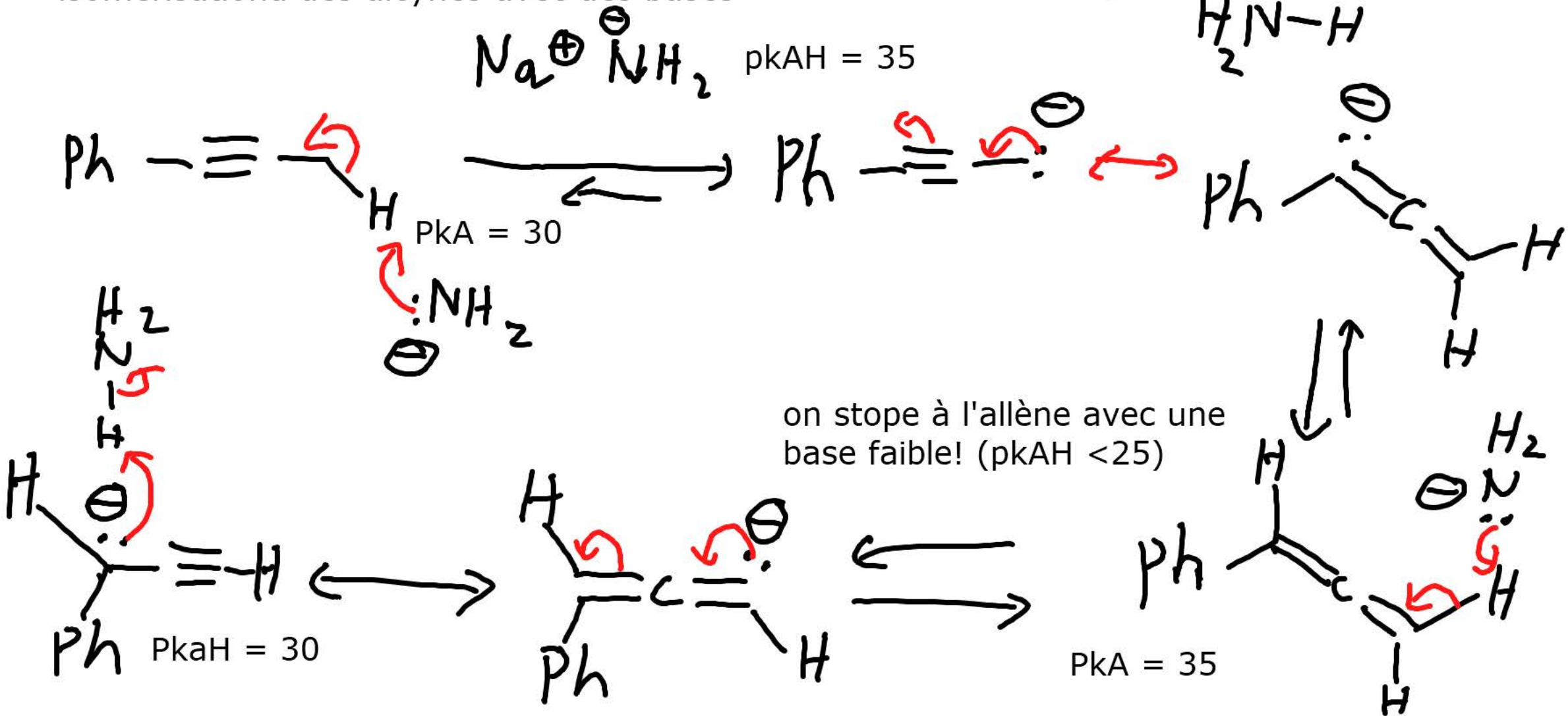


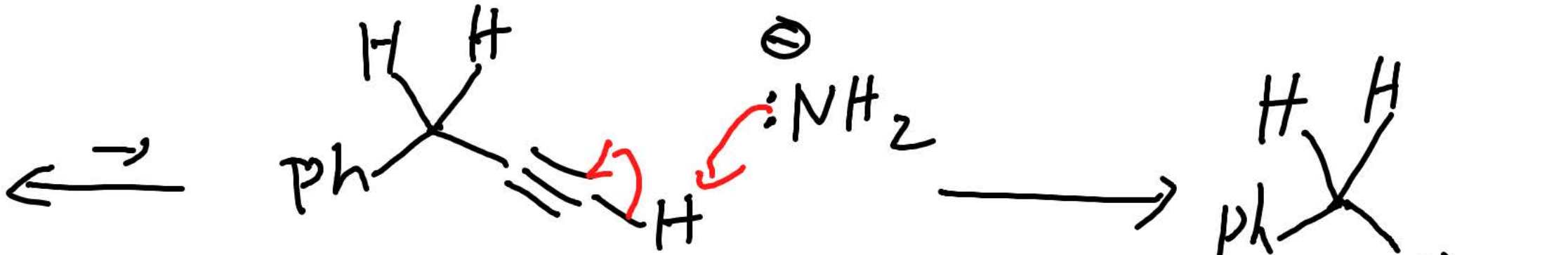


point essentiel: EIII-I < EIII-III' = migration plus rapide que l'attaque du nucléophile

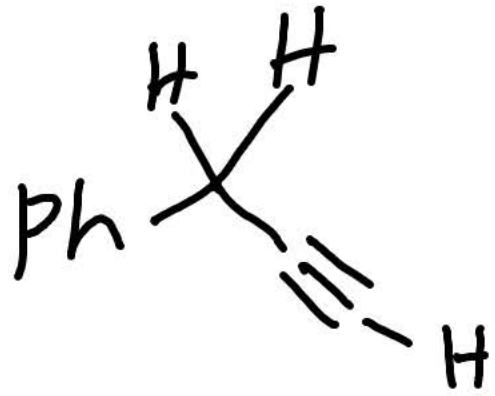
EIV-III < EIV-IV'

isomérisationd des alcynes avec des bases



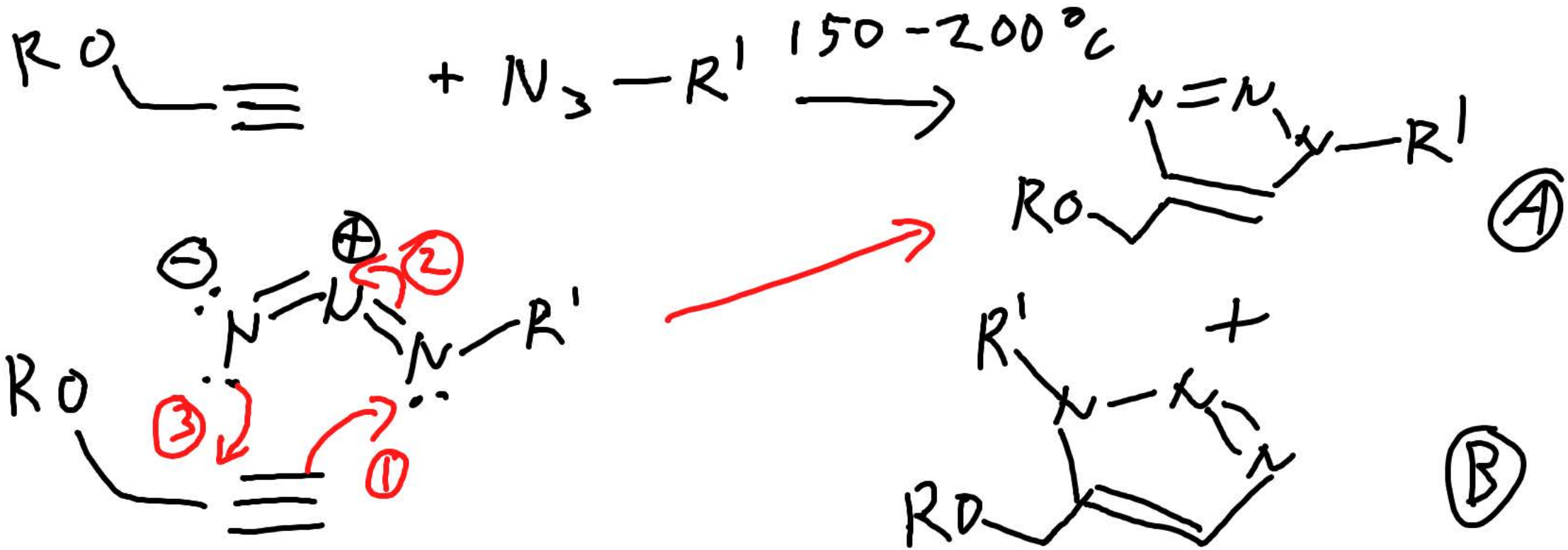


base forte: on peut isomériser
l'alcyne interne en alcyne terminale



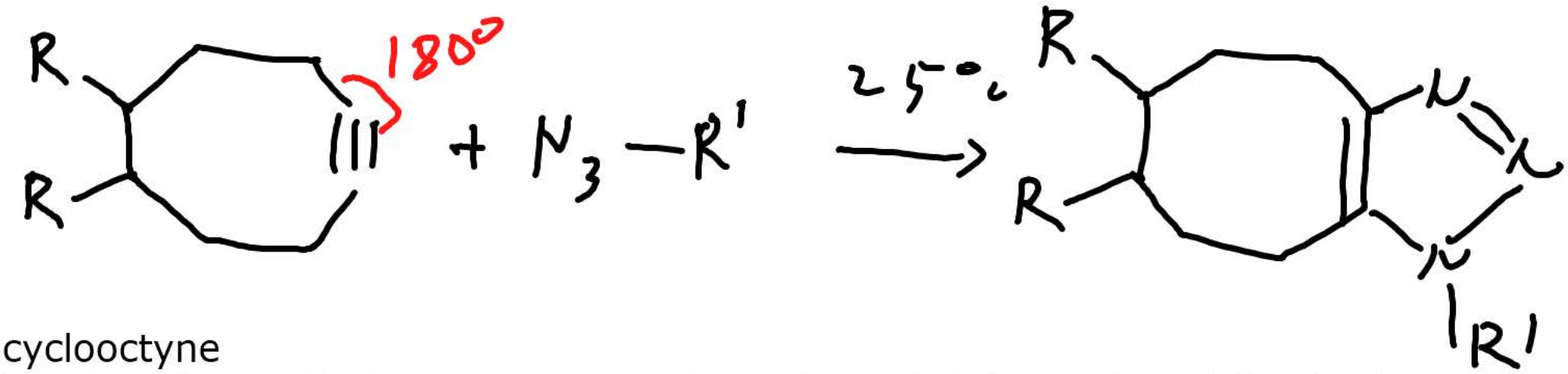
cycloaddition avec les azotures: Sharpless, Medal, Bertozzi (prix Nobel)

Huisgen:



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

Carolyn Bertozzi réaction à 25 °C sans cuivre



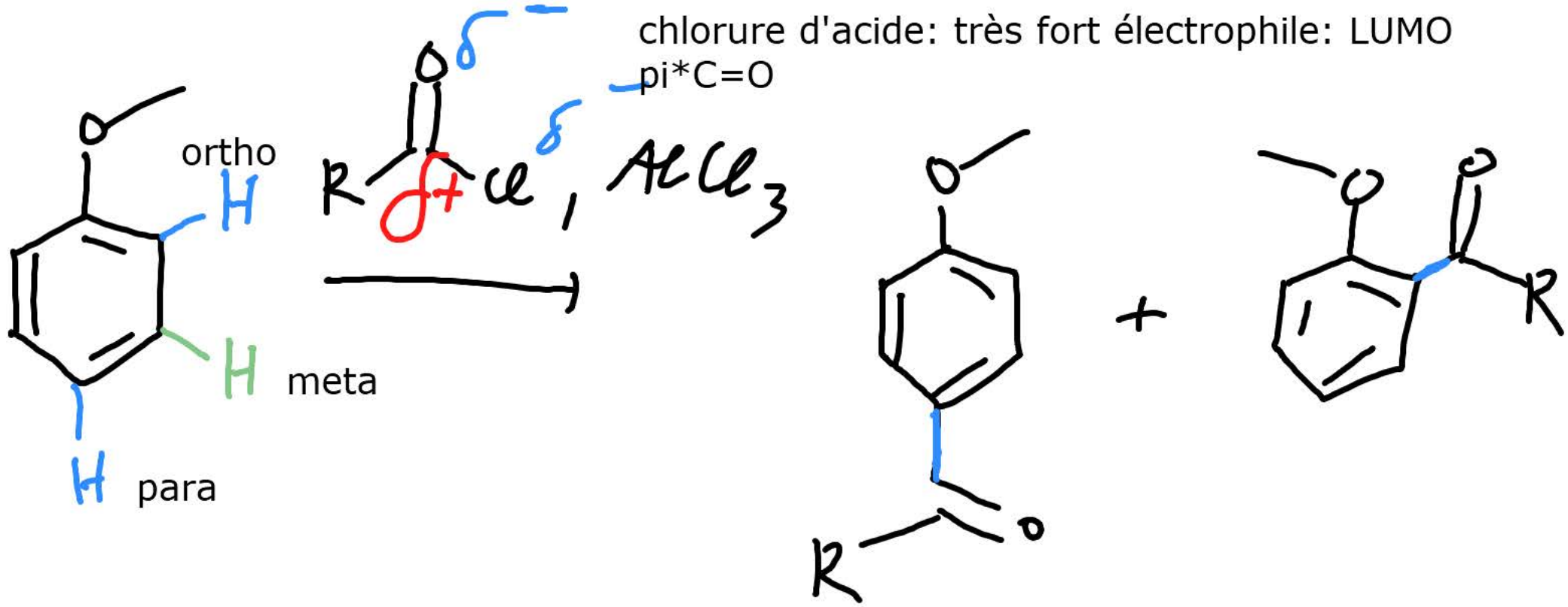
cyclooctyne

l'angle idéal de 180° pour sp ne peut pas être atteint: molécule très réactive

cycle idéa: 8 atomes , 7 atomes: instable, 9 atomes: ne réagit pas assez vite

fonctionne également dans les cellules et organismes vivants

substitution électrophile aromatique: Friedel-Craft

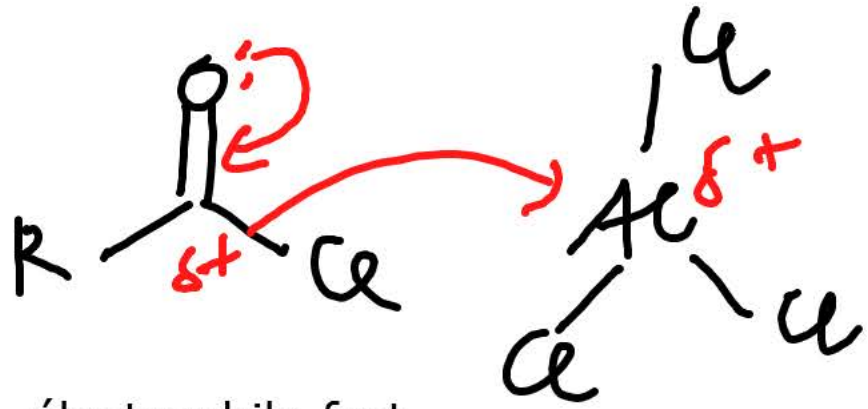


chlorure d'acide: très fort électrophile: LUMO pi*C=O

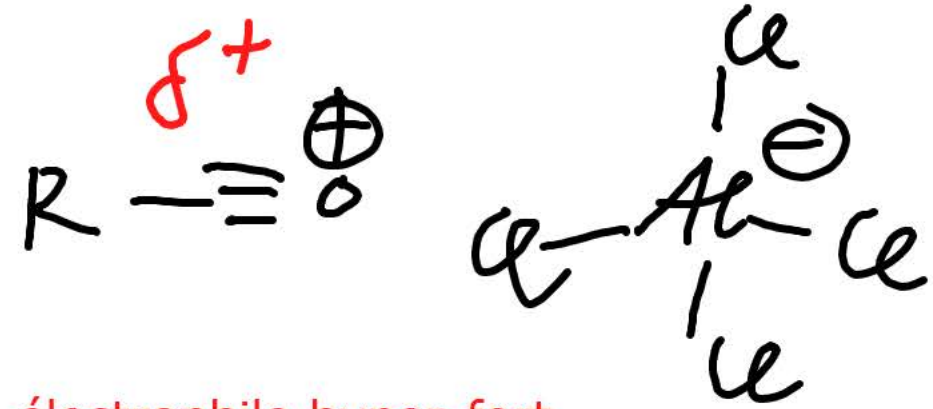
réagit en ortho et para, mais pas méta, pourquoi?

Activation de l'électrophile

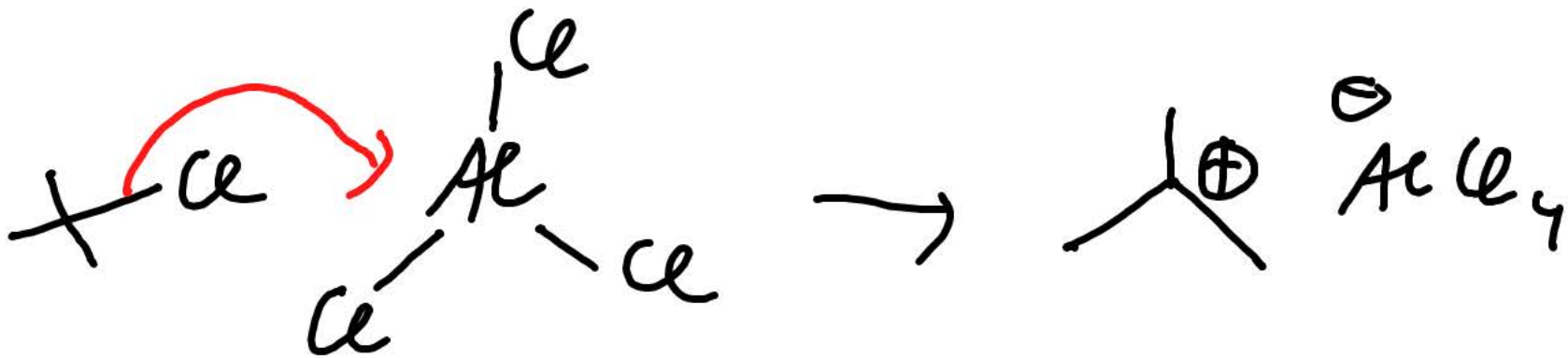
forte affinité de Al3+ pour Cl-!

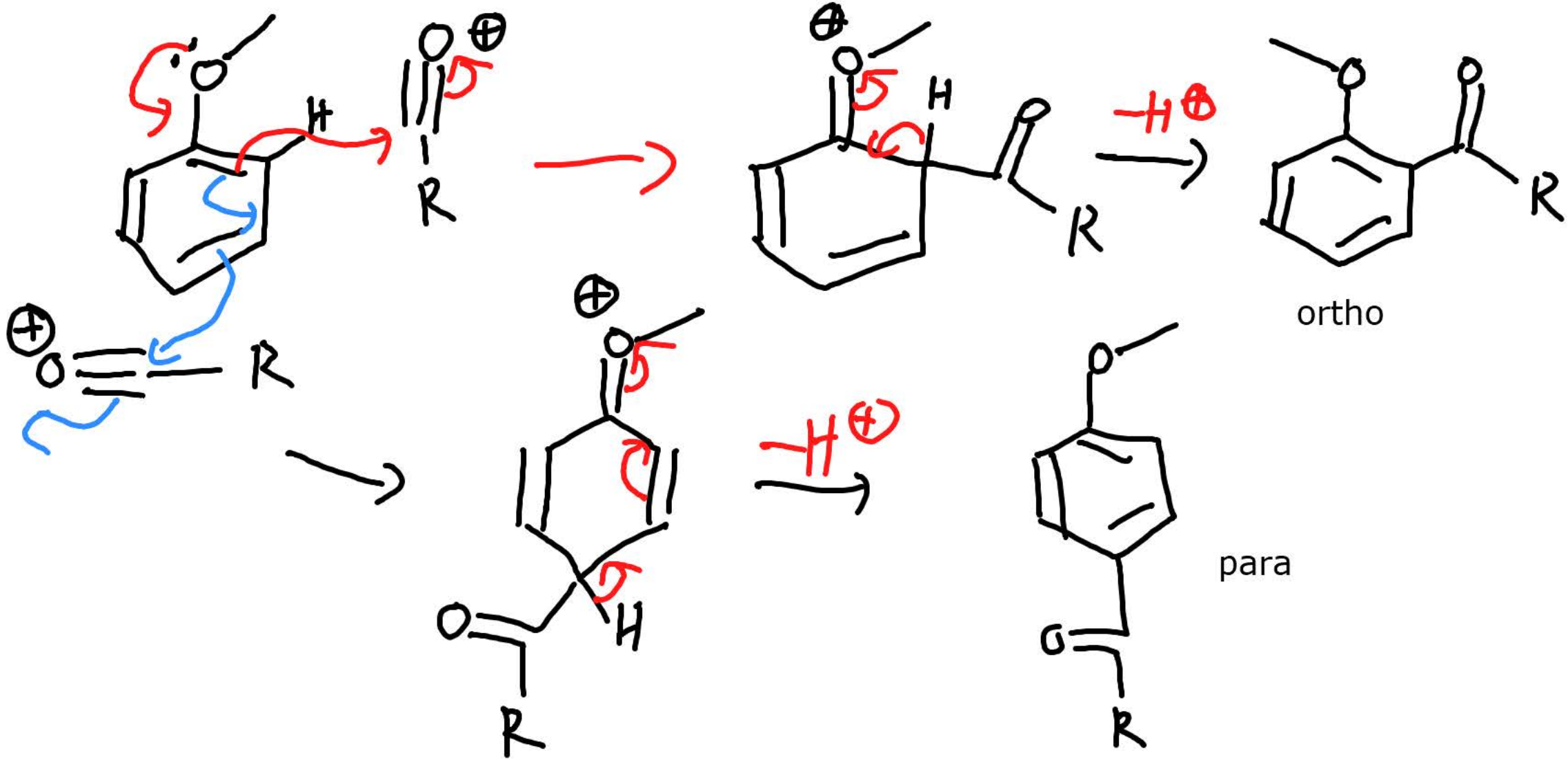


électrophile fort



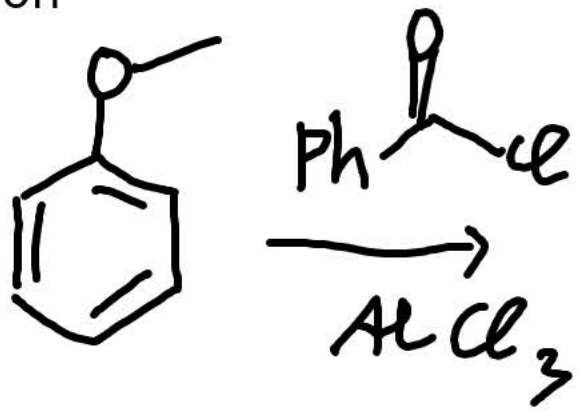
électrophile hyper-fort

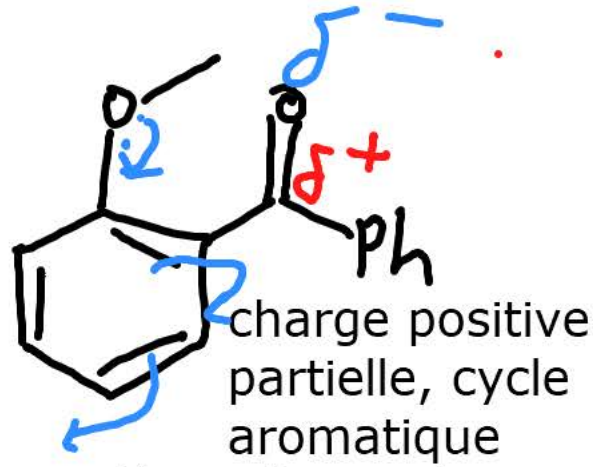



H
R
H
R
H
R
ortho
H
R
para

réaction de Friedel-Craft

acylation

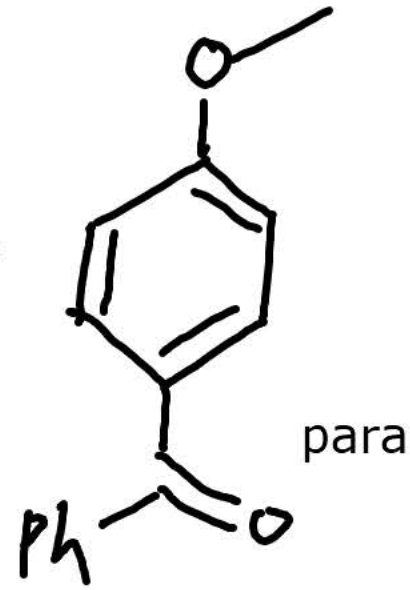




charge positive partielle, cycle aromatique désactivé!

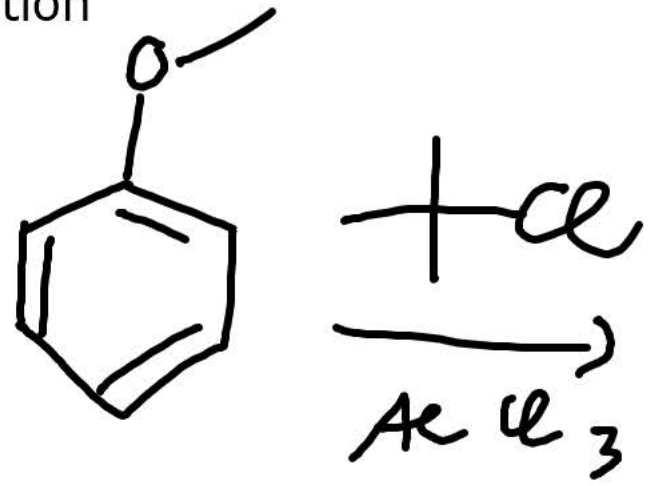
ortho

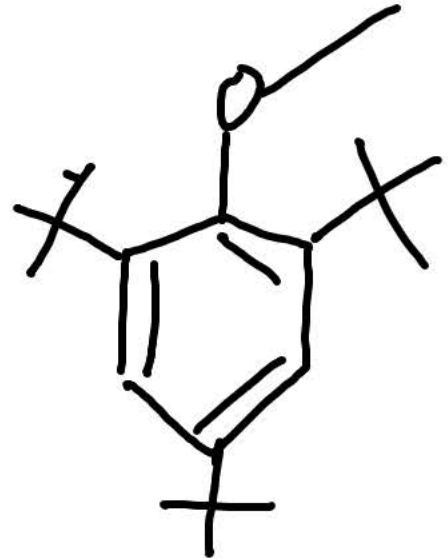
+



para

alkylation

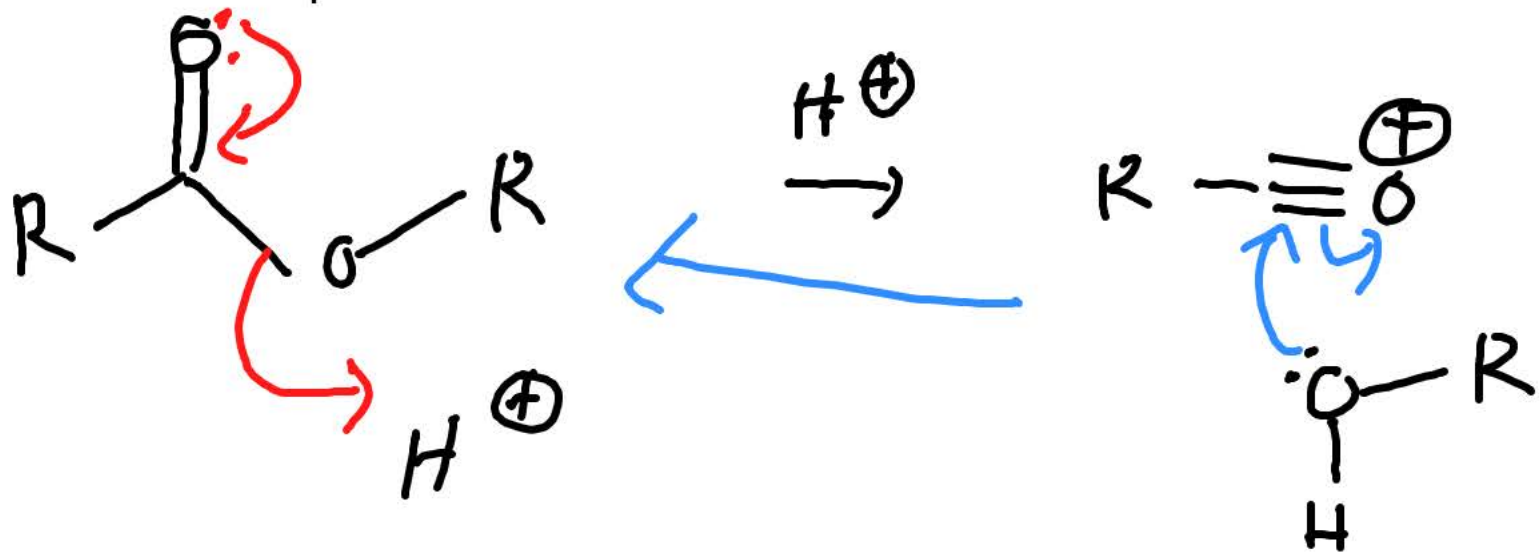




on réagit 3x en ortho et para

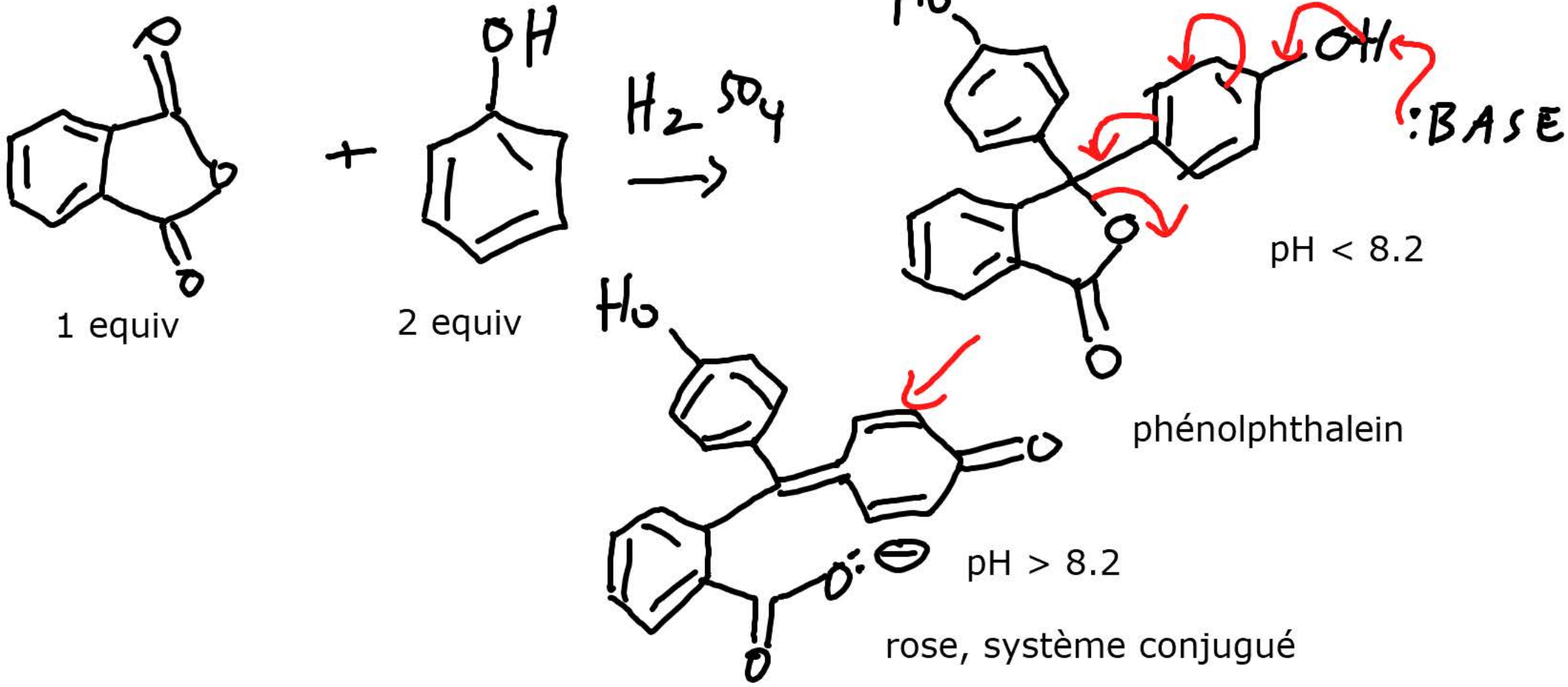
même mécanisme

activation douce pour Friedel-Craft

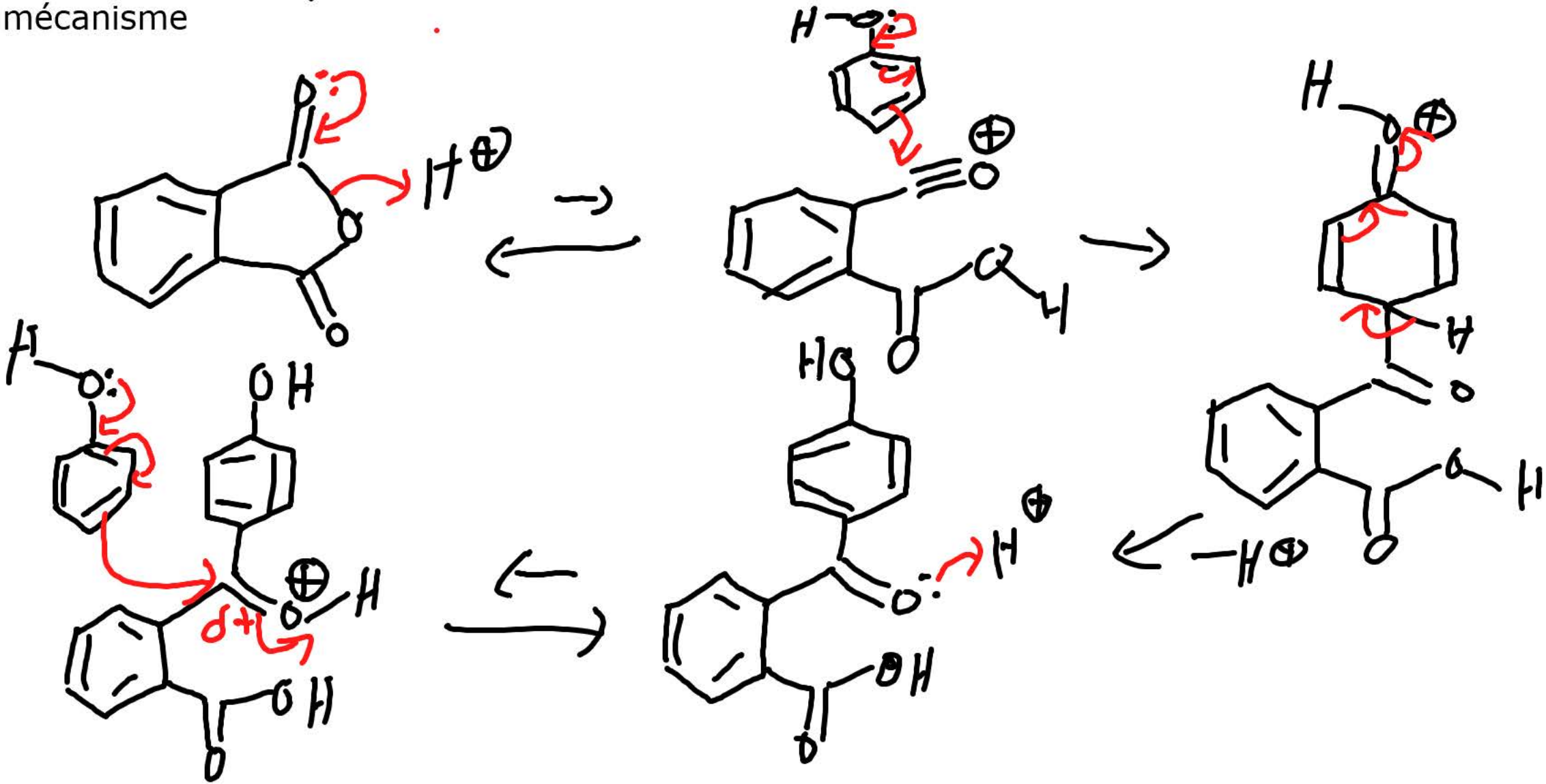


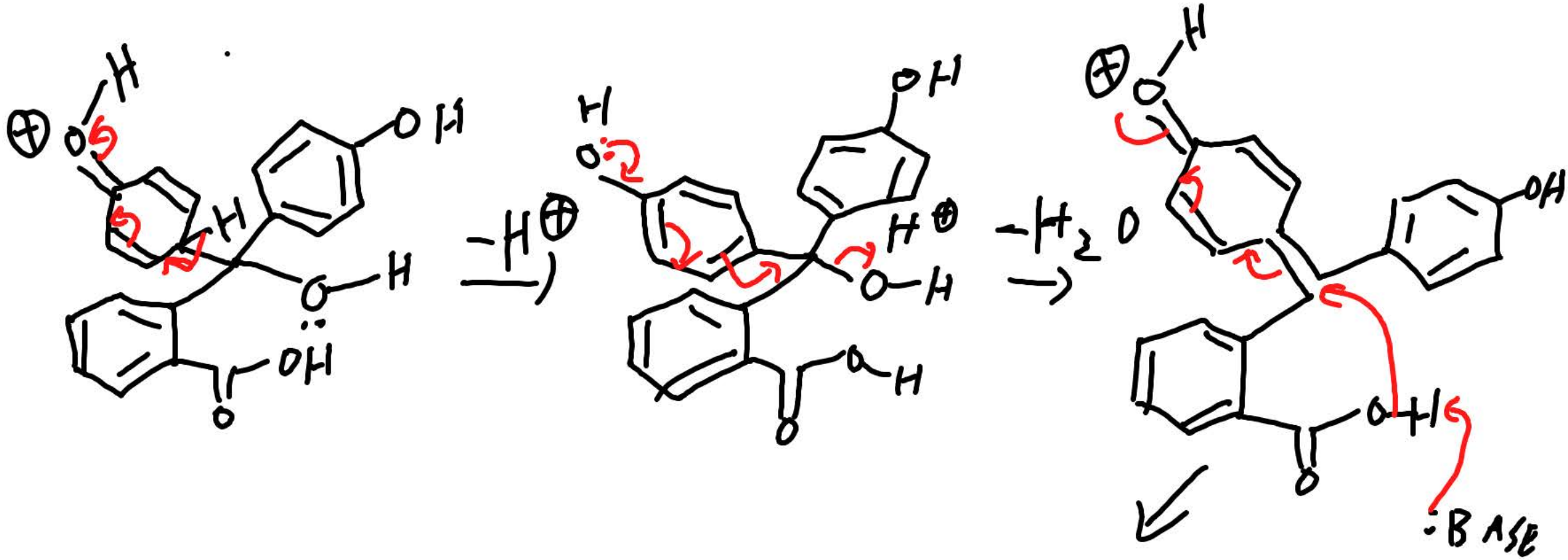
équilibre très défavorisé, juste un peu d'intermédiaire réactif: suffisant seulement pour des nucléophiles excellents (meilleures que l'alcool)

synthèse de la phénolphthalein



mécanisme





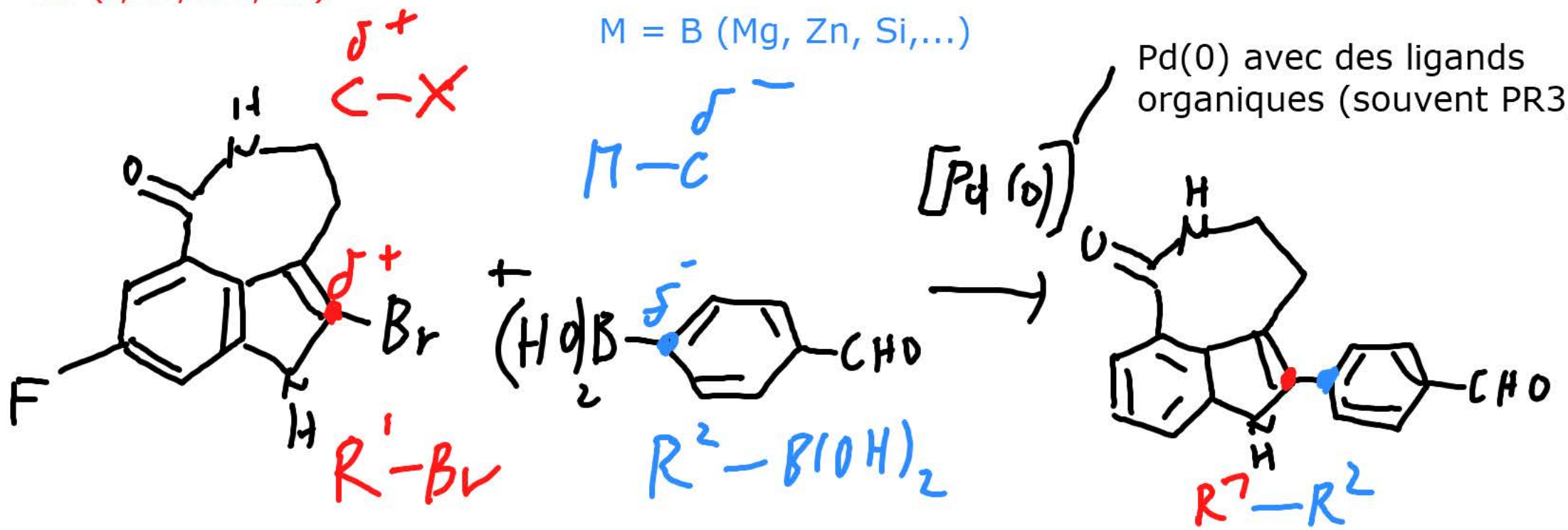
phenolphthalein

Couplage croisé au Pd: synthèse de Rucaparib/Pfizer (cancer des ovaires)

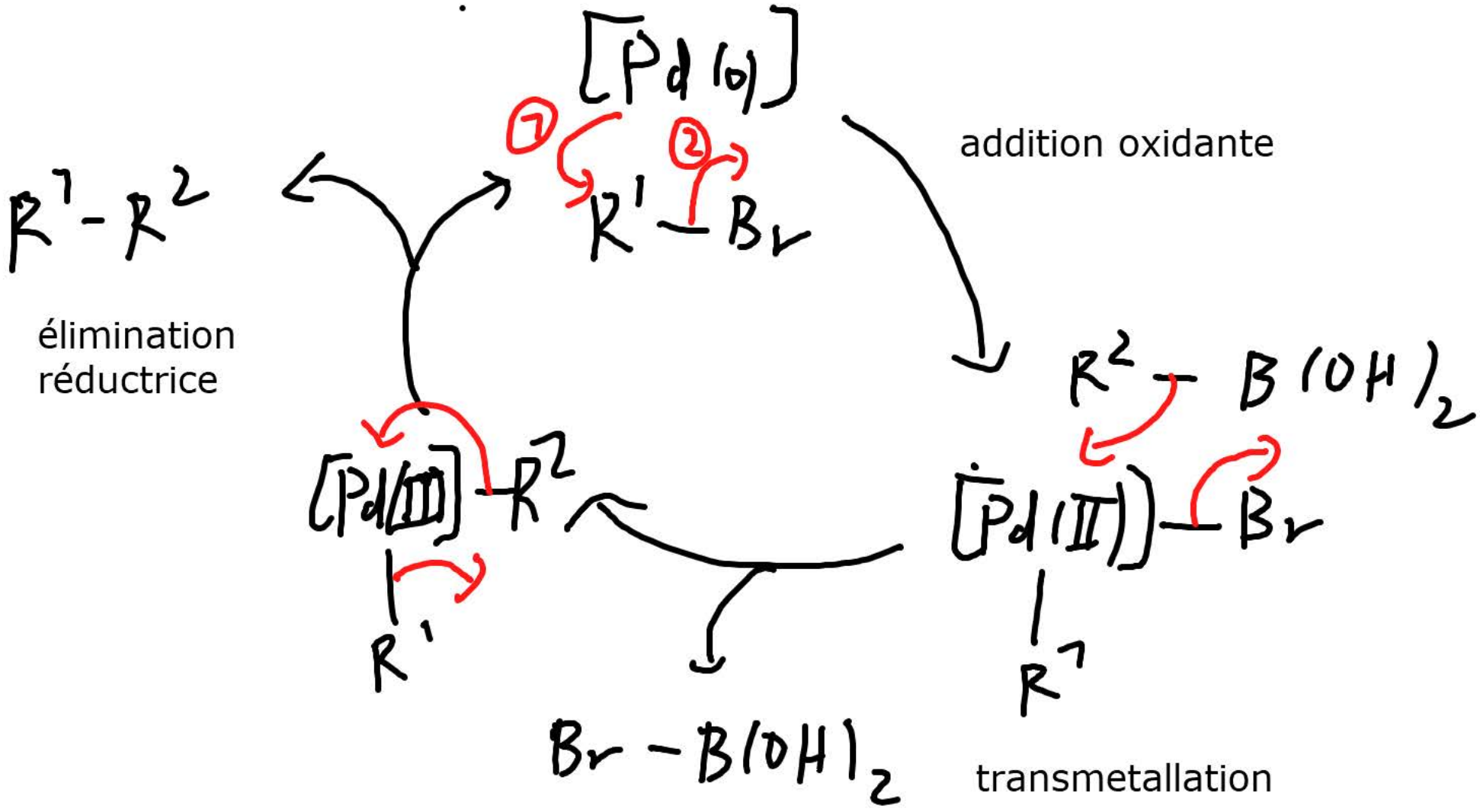
X = Br (I, Cl, OR, ...)

M = B (Mg, Zn, Si,...)

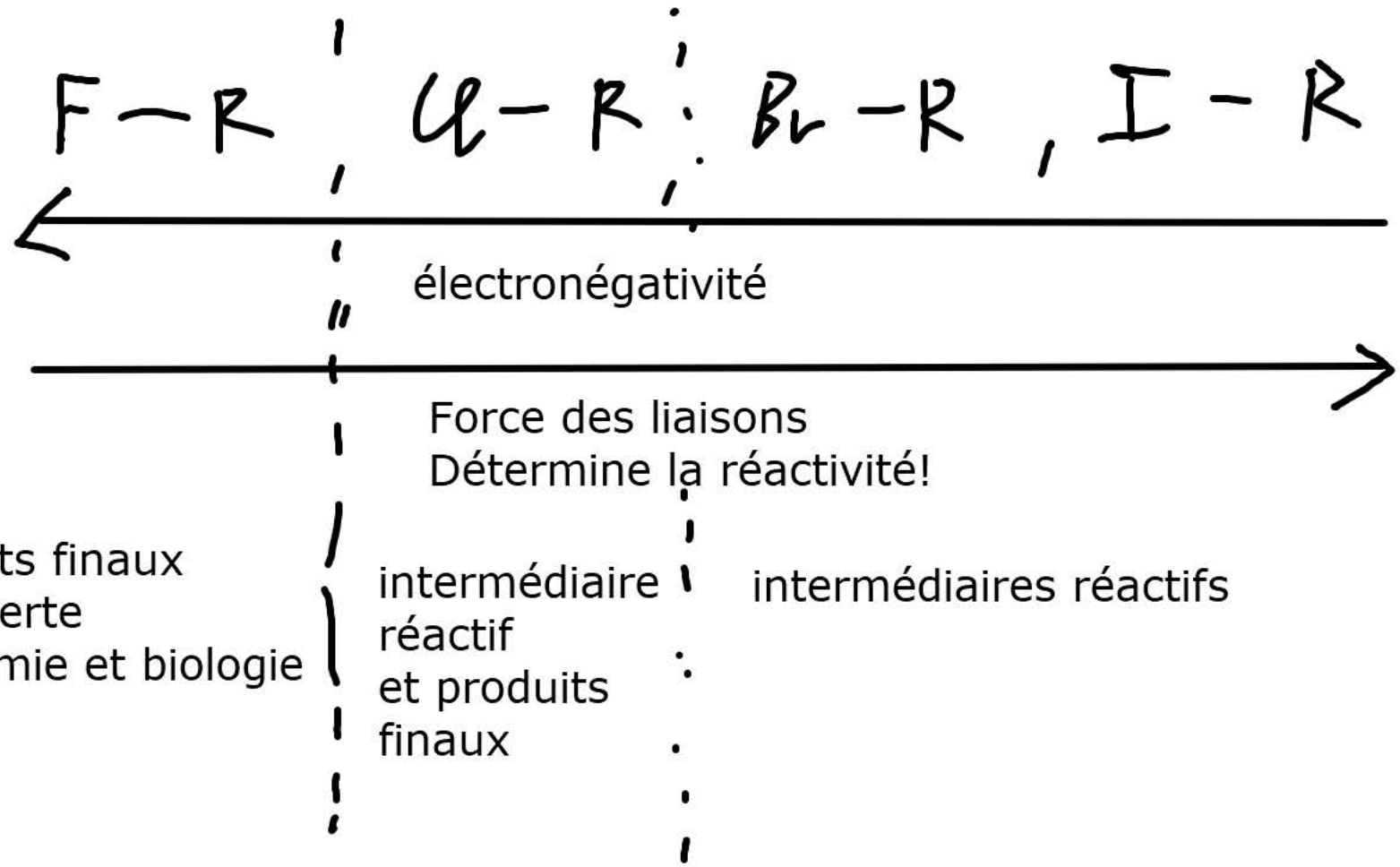
Pd(0) avec des ligands organiques (souvent PR3)



un couplage de 2 carbones, croisé car réagisse l'un avec l'autre

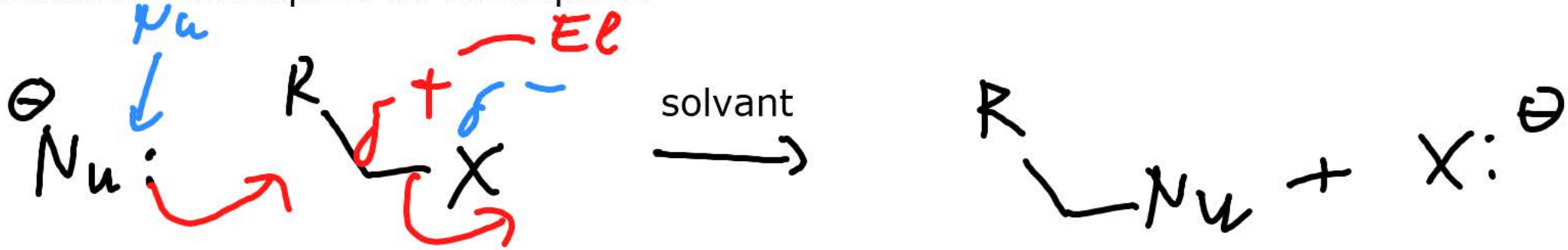

[Pd(0)]
addition oxidante
R¹ – Br
R² – B(OH)₂
[Pd(II)]
transmetallation
Br – B(OH)₂
[Pd(III)]
élimination réductrice
R¹ – R²

composés halogénés



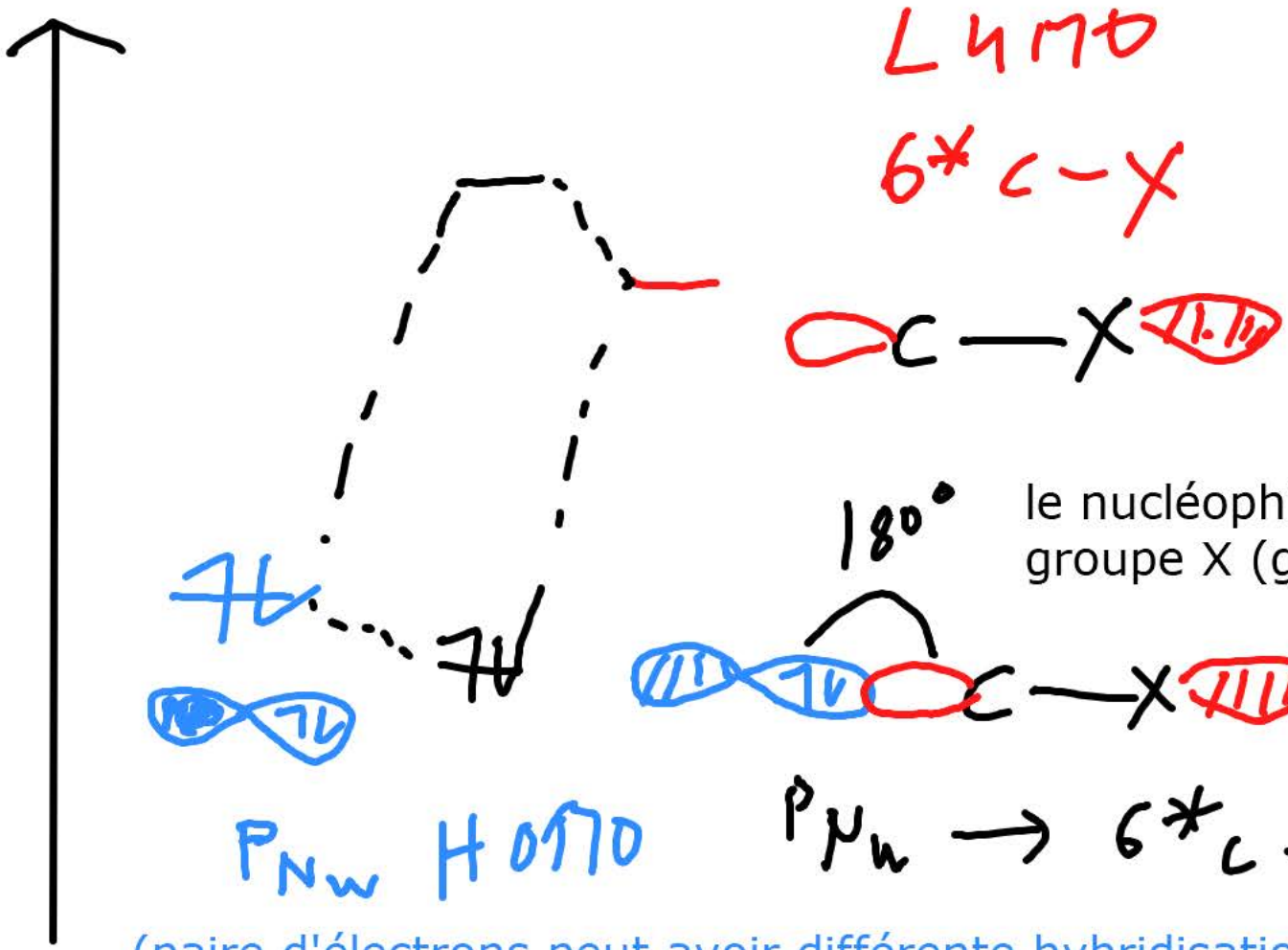
réactions de substitutions nucléophiles

SN2 substitution nucléophile de cinétique 2



$$V_R = k \cdot [Nu] \cdot [R\text{-}CH_2X]$$

analyse des orbitales moléculaires



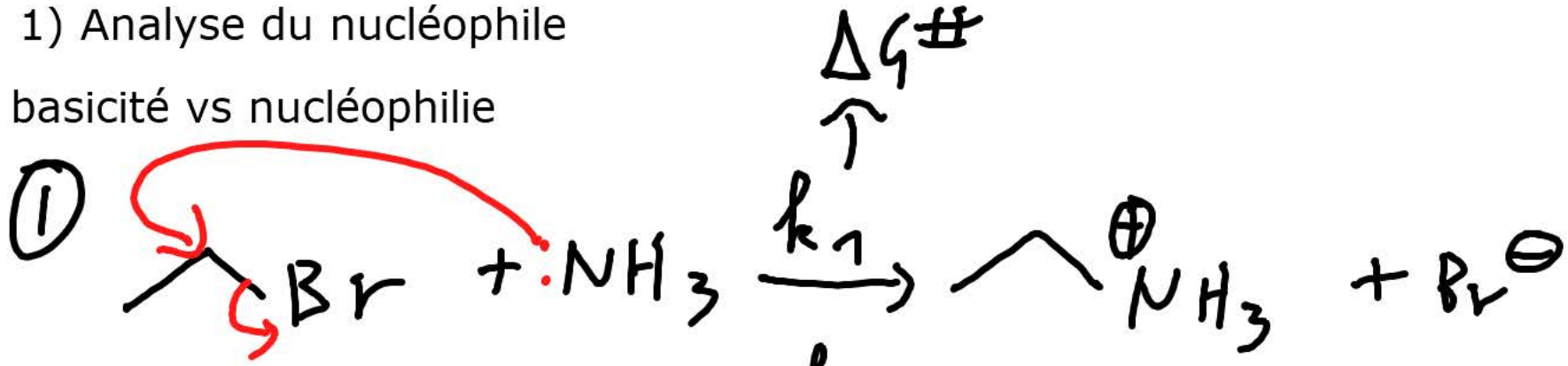
le nucléophile vient à 180°, à l'opposé du groupe X (groupe partant)

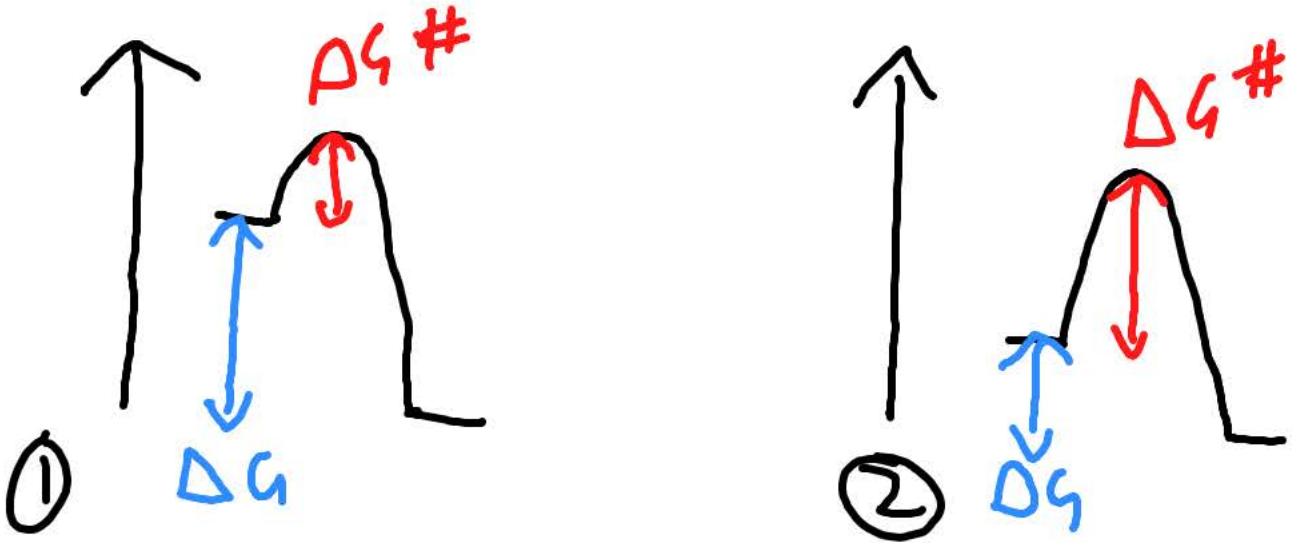
On inverse la stéréochimie sur le carbone!

(paire d'électrons peut avoir différente hybridisation: p, sp, sp2, sp3)

1) Analyse du nucléophile

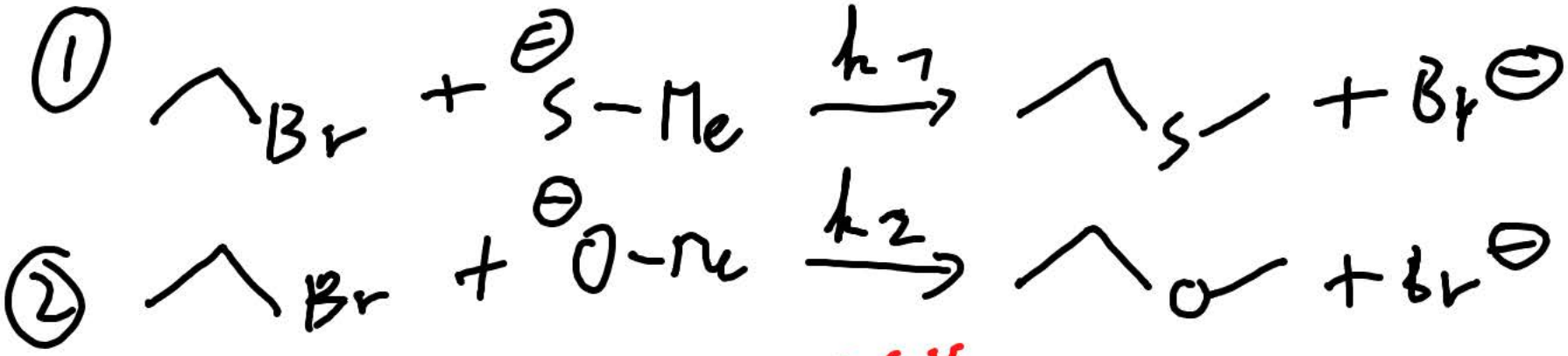
basicité vs nucléophilie

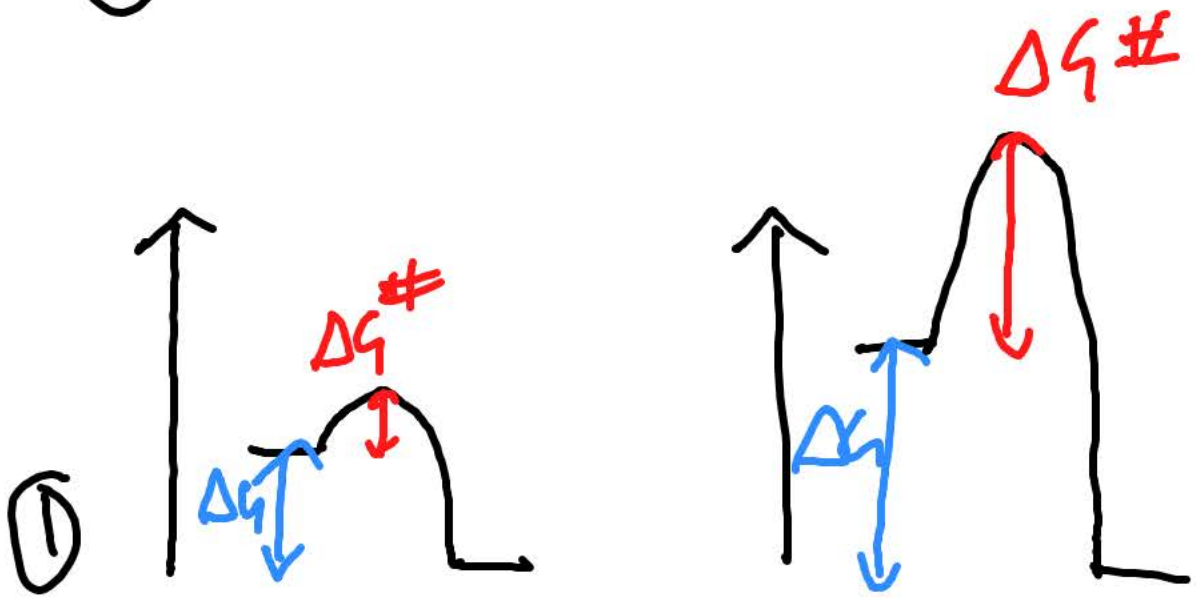




k1>k2, la nucléophilie est corrélée avec la basicité

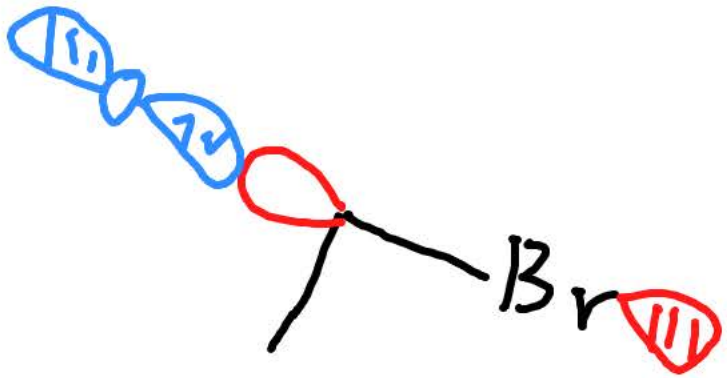
un "accord" entre thermodynamique et cinétique, la réaction la plus favorable va plus vite!



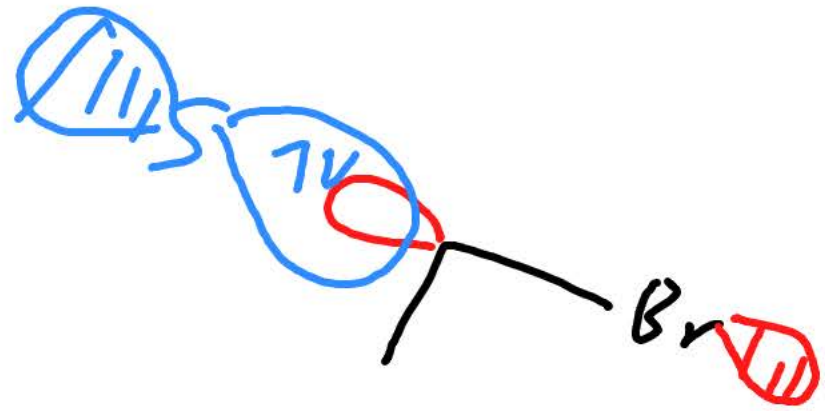


attendu: k2>k1
mesuré: k1>k2!!!

désaccord thermodynamique/cinétique:
la réaction moins favorable va plus vite!



$2p_0 \rightarrow \sigma^*_{C-Br}$

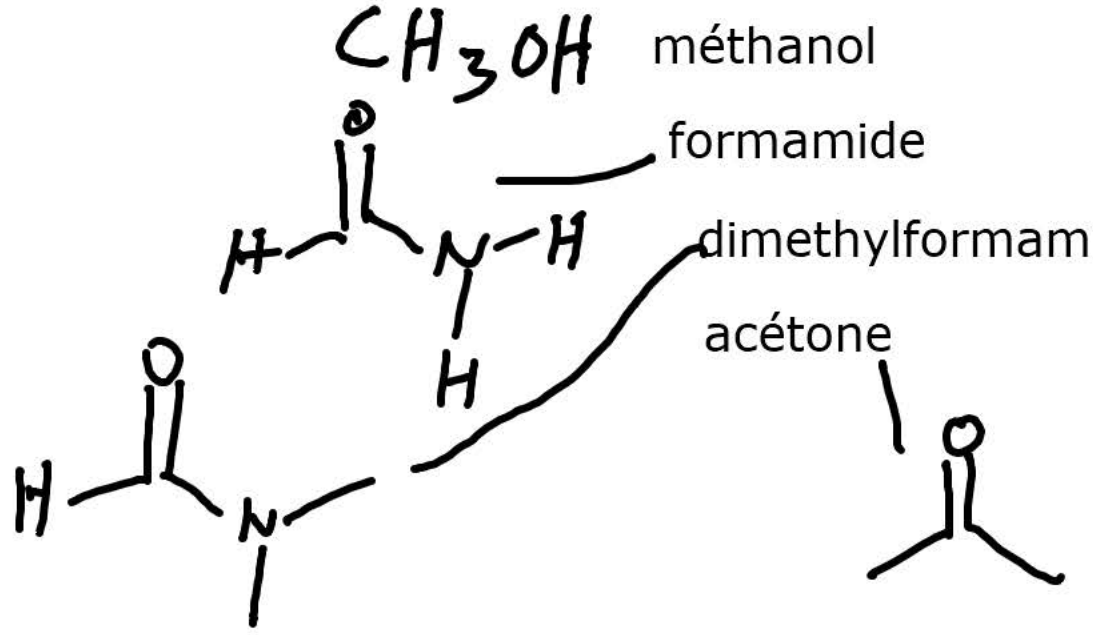


$^3p_S \rightarrow \sigma^*_{C-Br}$

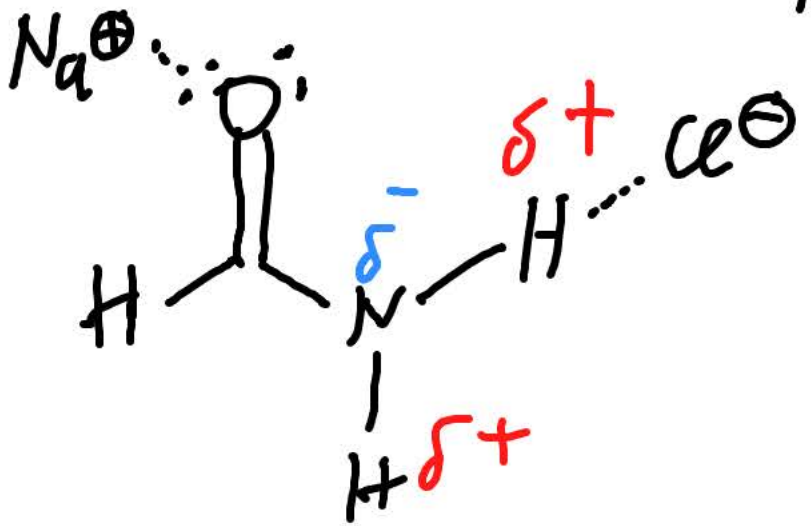
les orbitales du "gros" soufre sont beaucoup plus étendues, et elles peuvent mieux interagir avec l'orbitale antiliante C-Br, l'énergie de l'état de transition baisse, la réaction accélère

Effets du solvant

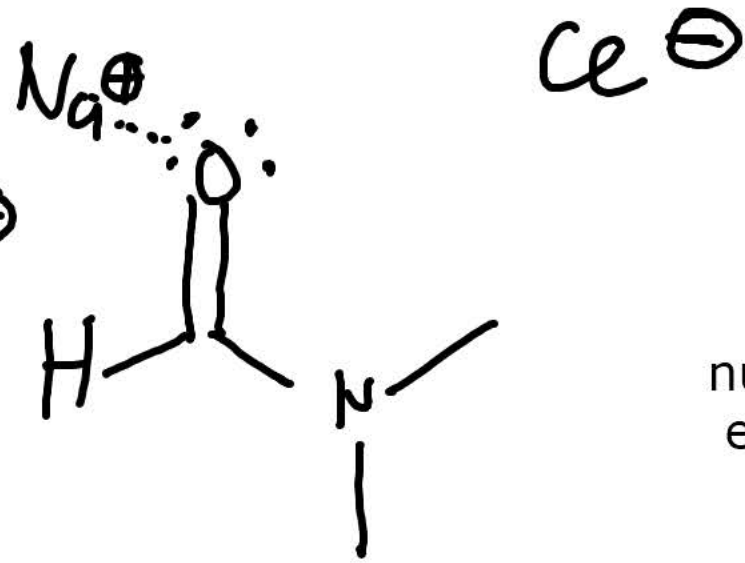
solvant	k
CH_3OH méthanol	1 (relatif)
formamide	12.5
dimethylformamide	1'200'000
acétone	1'500'000



solvants et SN2



formamide: SN2 est lente



DMF: SN2 est rapide

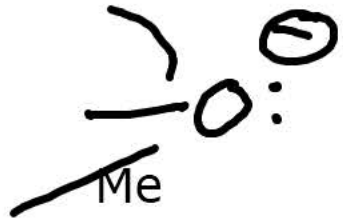
nucléophile Cl- est "libre"
est plus réactif

nucléophile: Na+Cl-

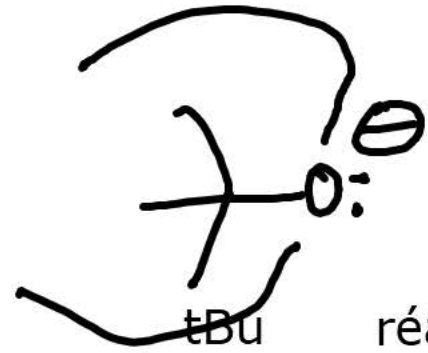
nucléophile Cl- désactivé par ponts hydrogènes

Effet de la taille:

1) Nucléophile

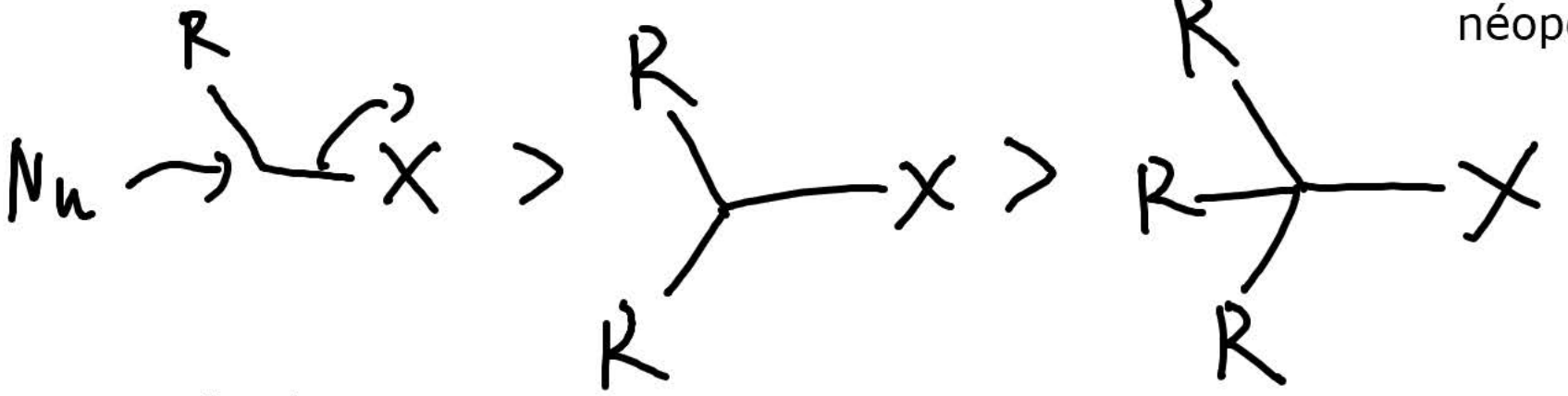


réagit vite



réagit très lentement

2) électrophile



primaire

rapide

secondaire

lente

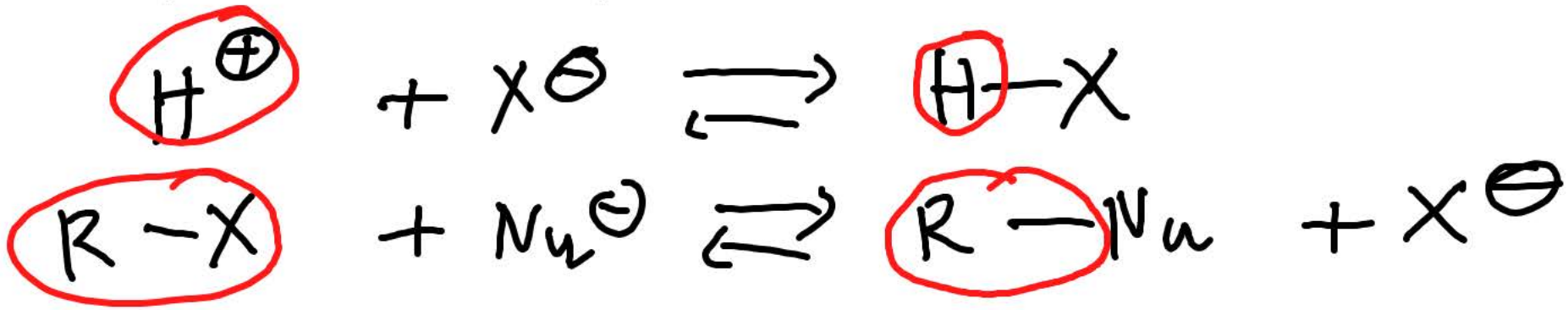
tertiaire

impossible

néopentyl: très lent

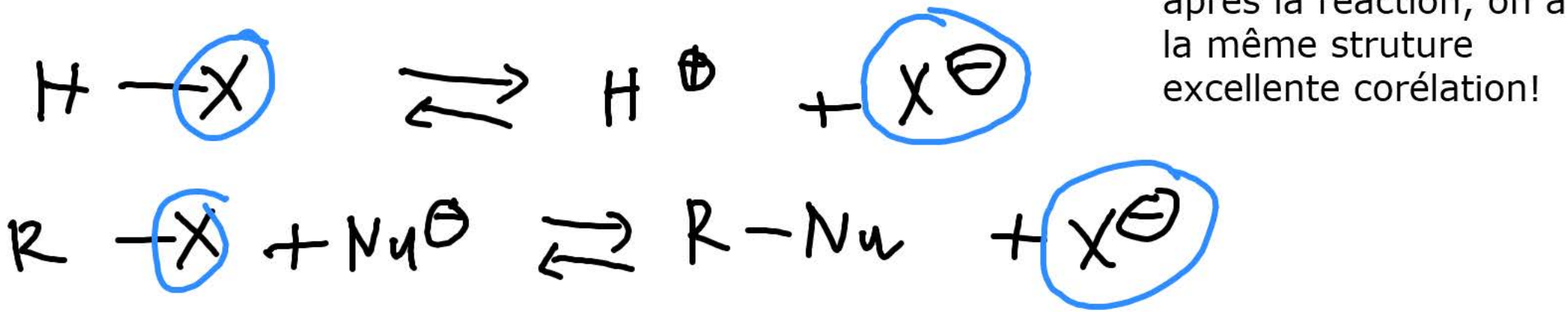
effet du groupe partant

comparaison base/nucléophile



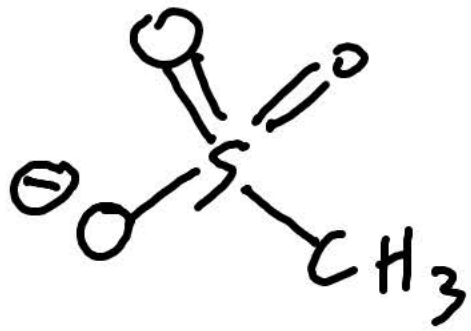
comparaison imparfaite!

comparaison base/groupe partant

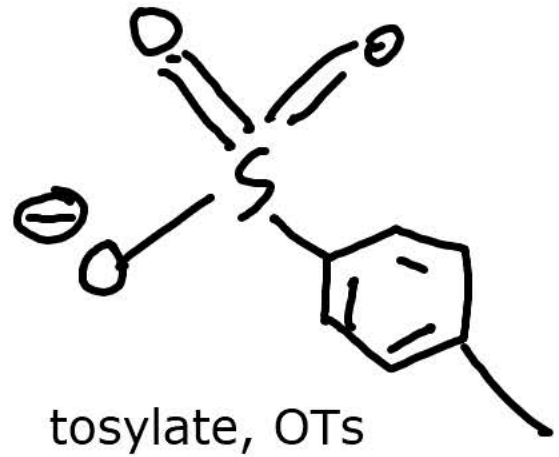


après la réaction, on a la même struture
excellente corélation!

important groupe partants dérivés de l'acide sulfurique
peuvent être obtenus directement des alcools

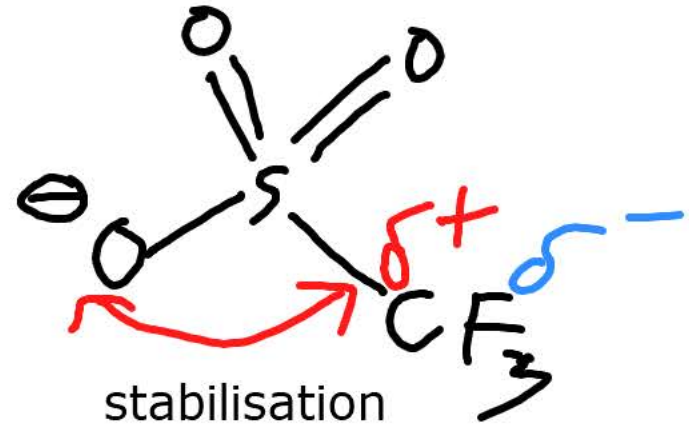


mésilate, OMs



tosylate, OTs

même réactivité

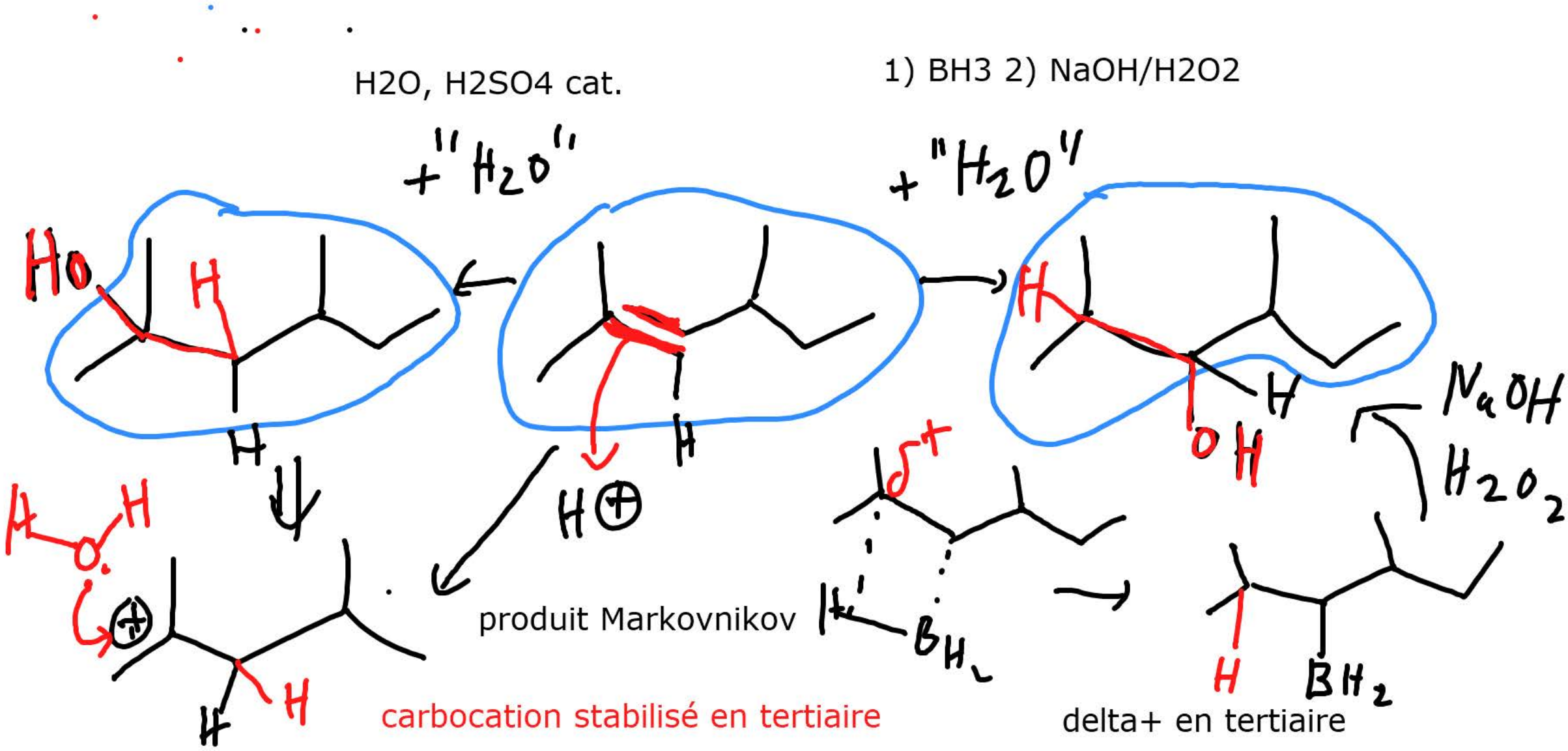


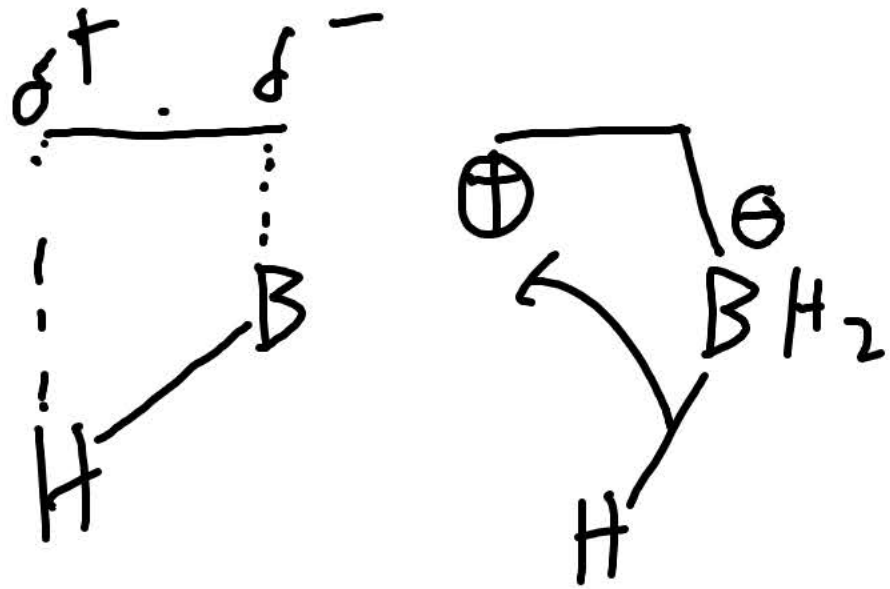
stabilisation

triflate, OTf
plus réactif

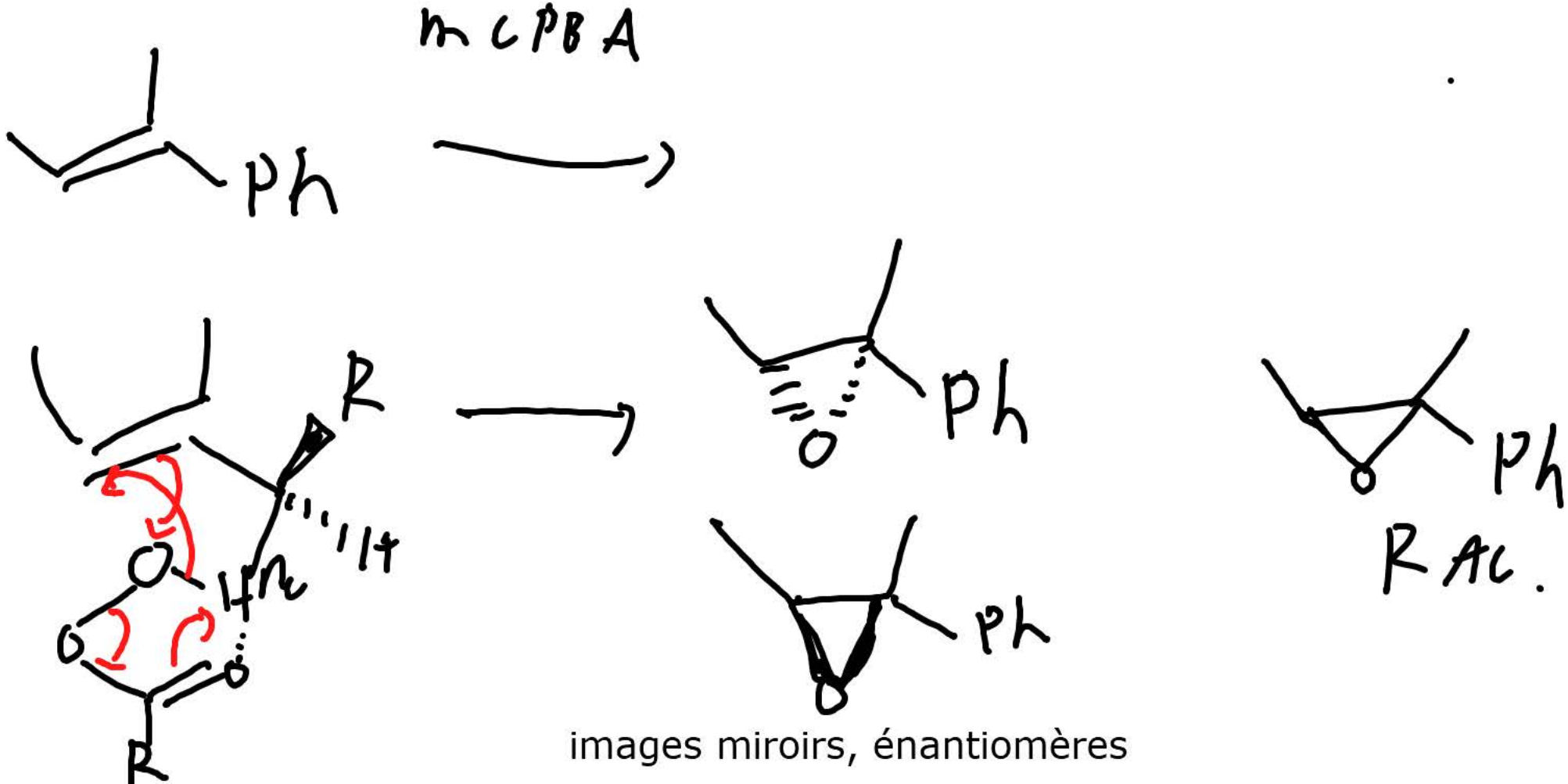
plus économique
en atomes

plus crystallin
(plus facile à purifier)


H2O, H2SO4 cat.
1) BH3 2) NaOH/H2O2
+ "H2O"
+ "H2O"
produit Markovnikov
carbocation stabilisé en tertiaire
delta+ en tertiaire
NaOH
H2O2

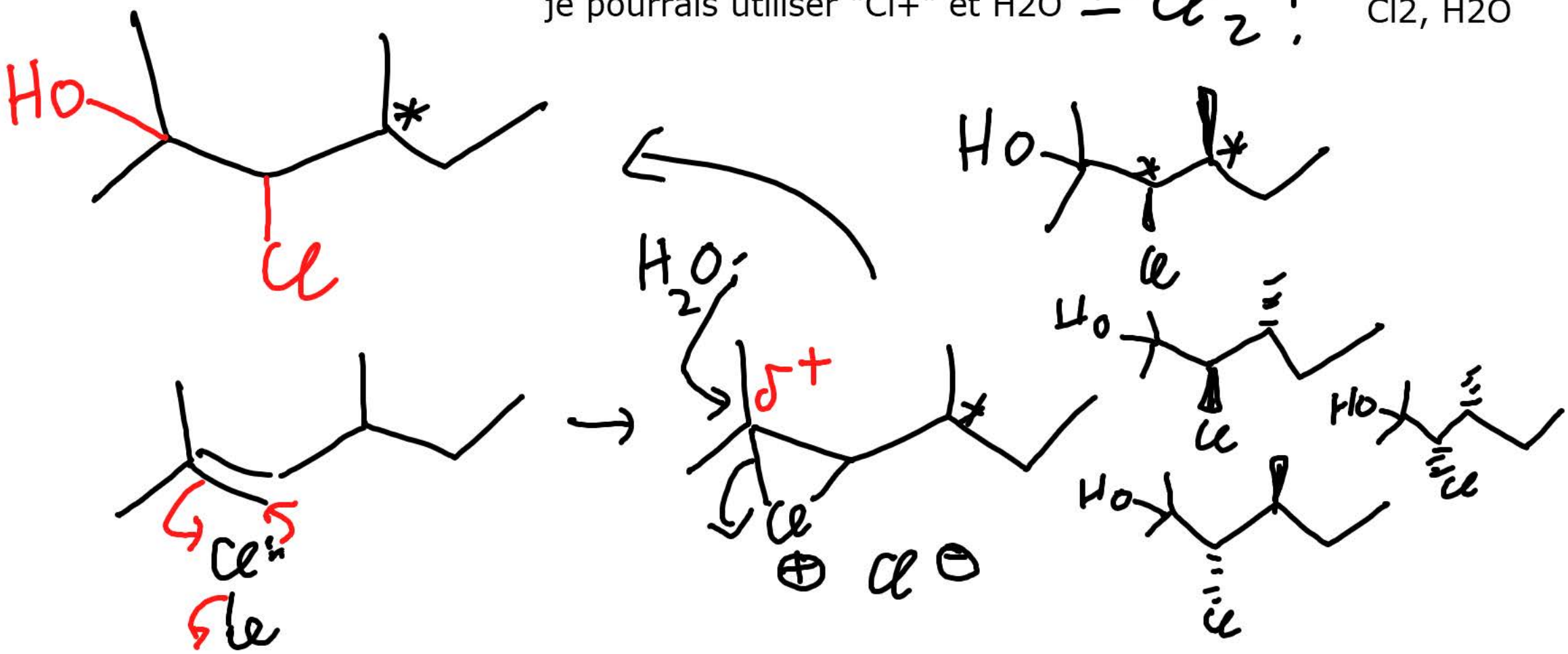

δ+
δ−
B
H
⊕
⊖
BH2
H

exercice 2

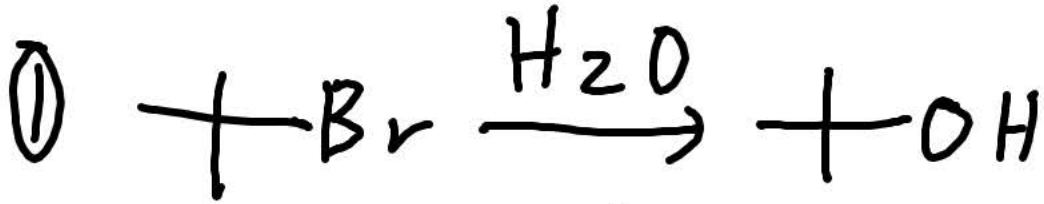


images miroirs, énantiomères

avant: H+ et H2O
je pourrais utiliser "Cl+" et H2O = Cl_2 ! Cl2, H2O

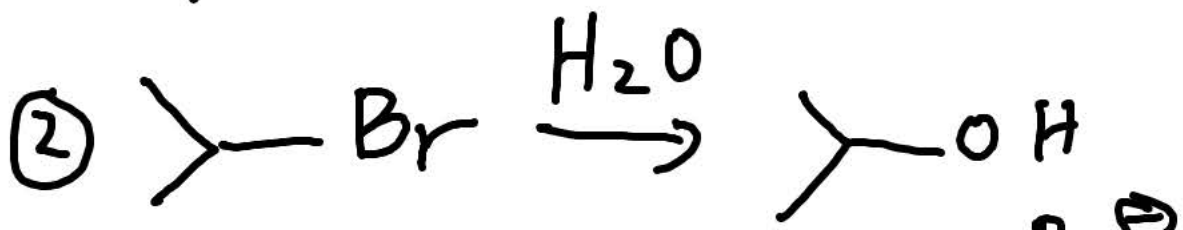


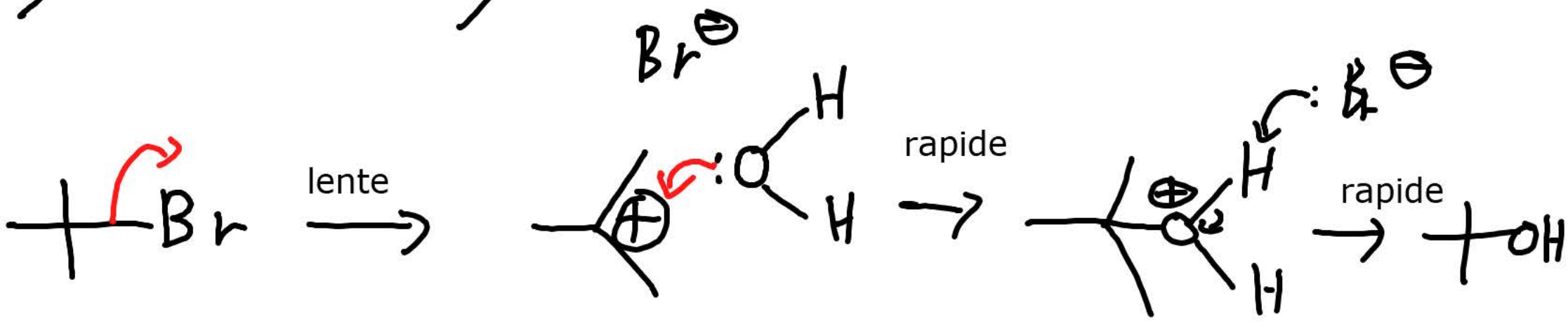
expérience surprenante



attendu 2 plus rapide que 1

observé: 1 plus rapide!



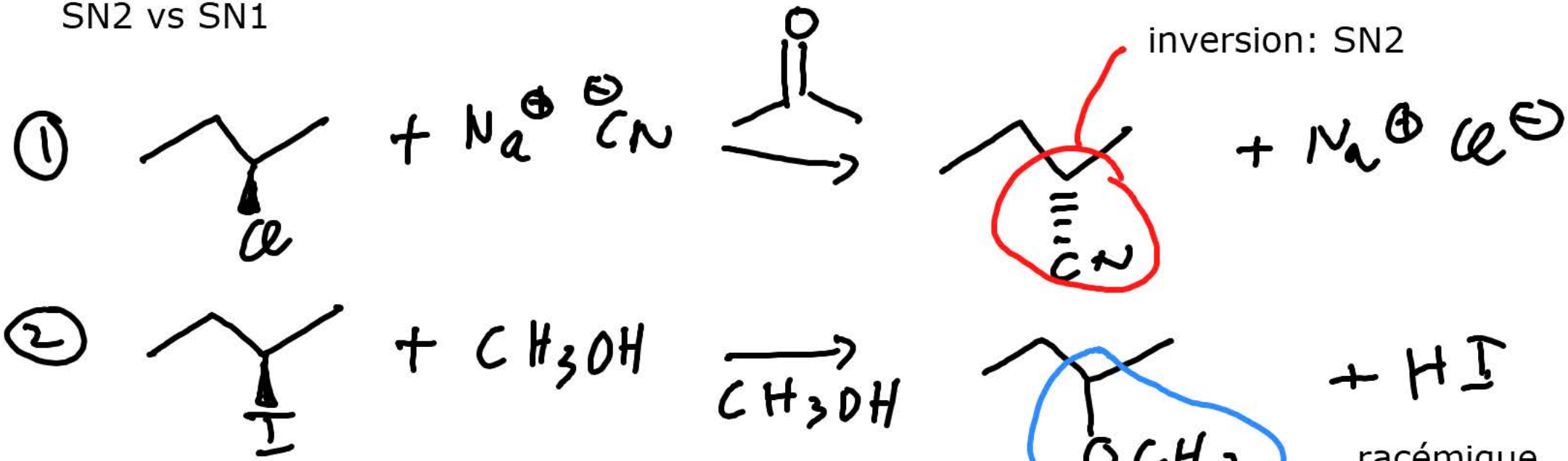


V = k*[tBuBr]

$\Rightarrow$ S_N1

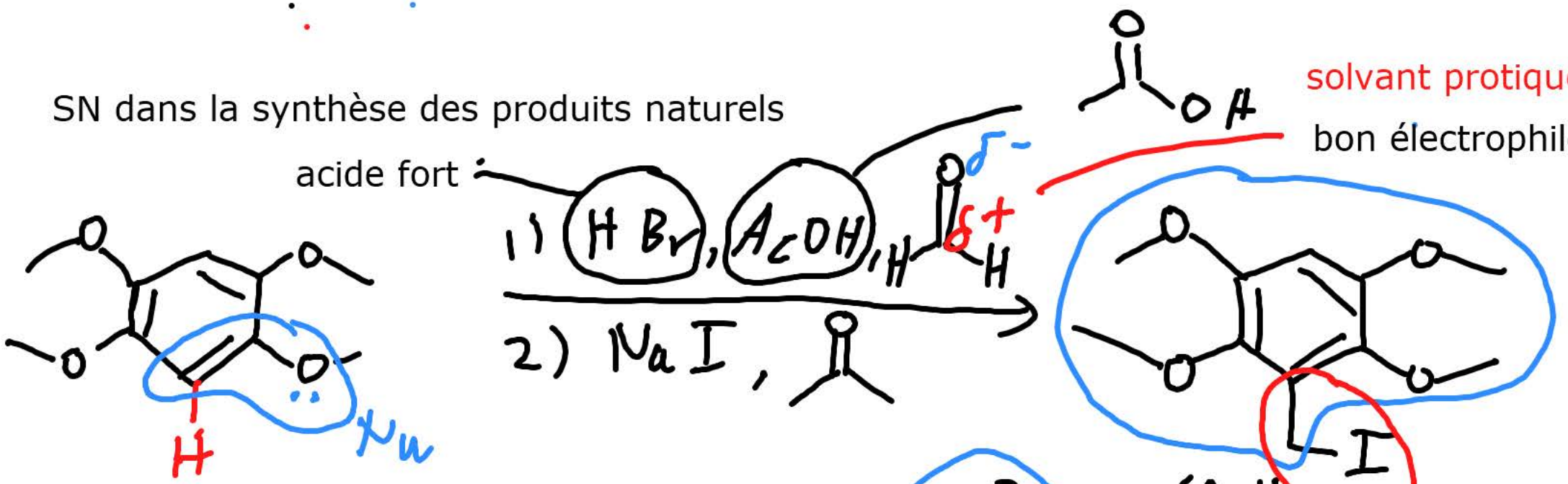
carbocation tertiaire plus stable, plus rapide pour 1 que pour 2

SN2 vs SN1

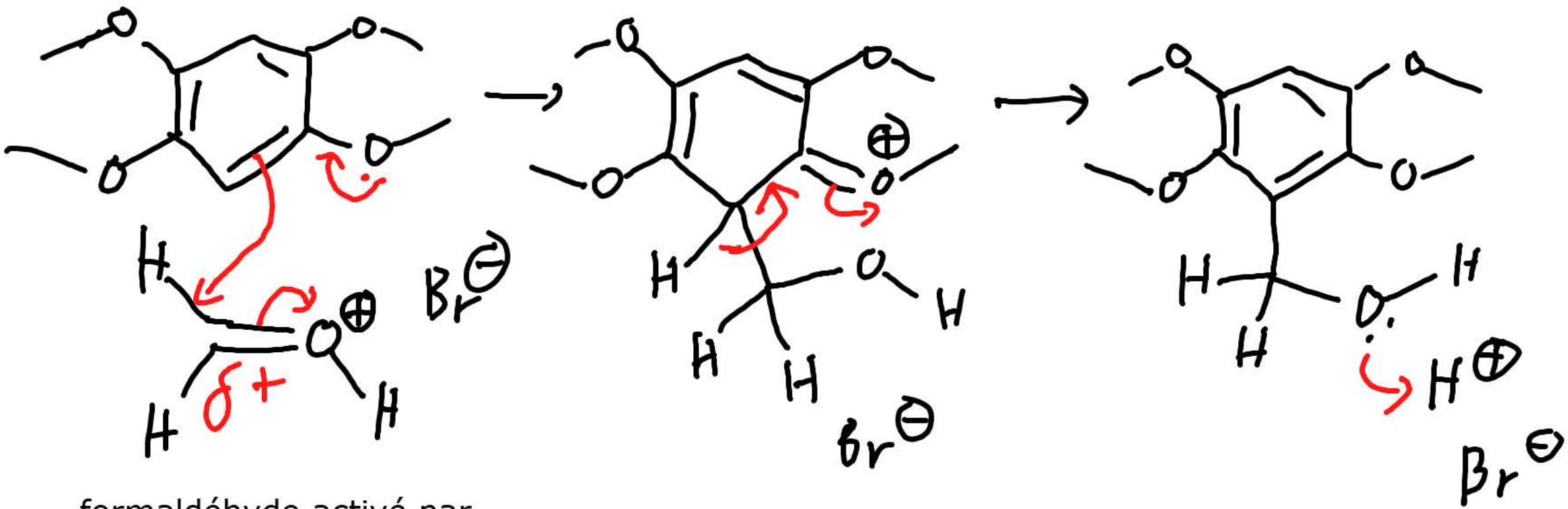


1) substrat: secondaire: SN1 ou SN2: pas de décision possible
2) groupe partant: Cl moyen, I est très bon (pas de décision)
3) Nucléophile: CN- est bon nucléophile chargé, plutôt SN2
MeOH: faible nucléophile neutre, plutôt SN1
4) Solvant: acétone: polaire aprotique, favorise SN2
MeOH: polaire protique, favorise une SN1
points 3 et 4 qui expliquent le résultat observé

SN dans la synthèse des produits naturels

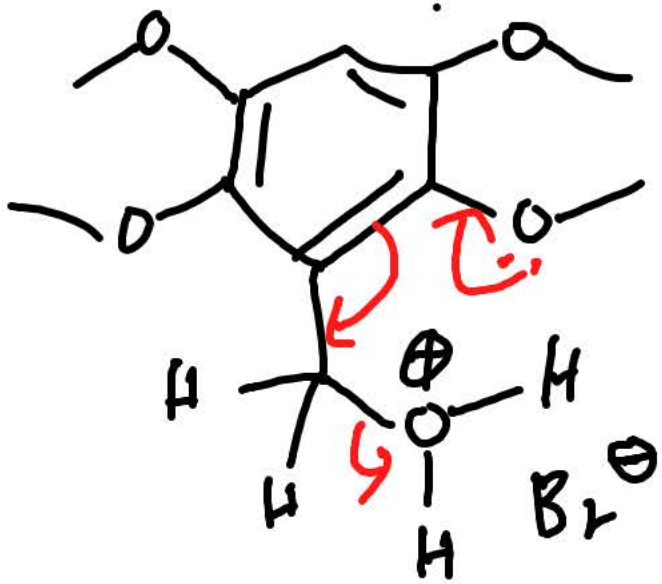


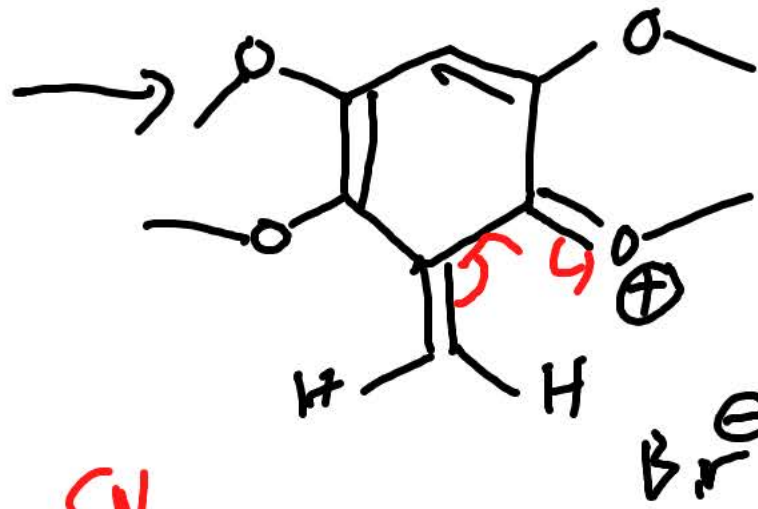
J. Am. Chem. Soc. 2001, 11586.

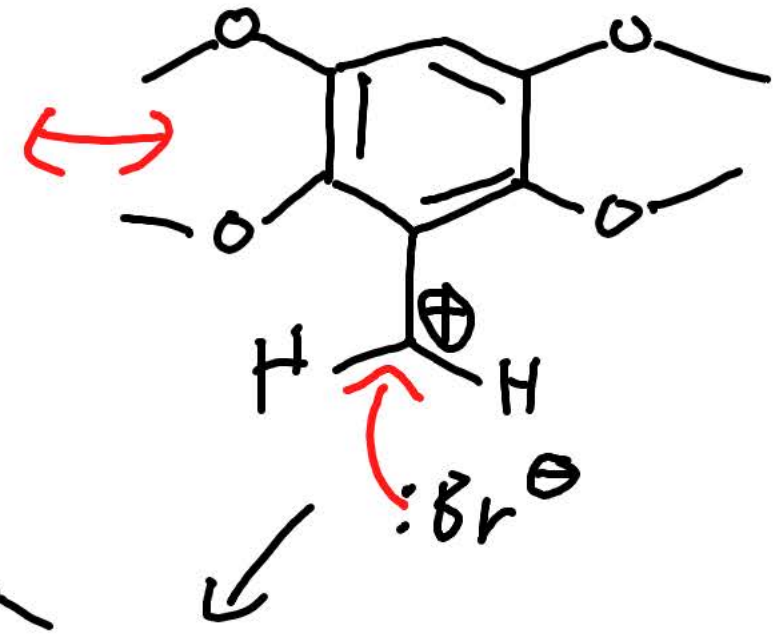


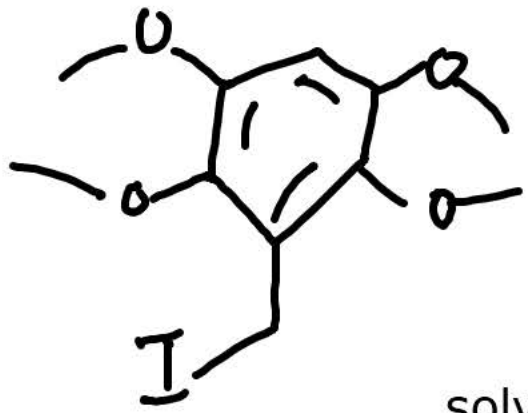
formaldéhyde activé par l'acide

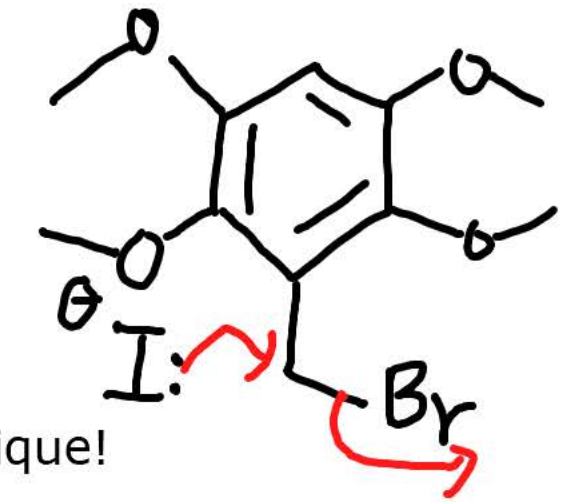
primaire, mais très stabilisé par résonance!







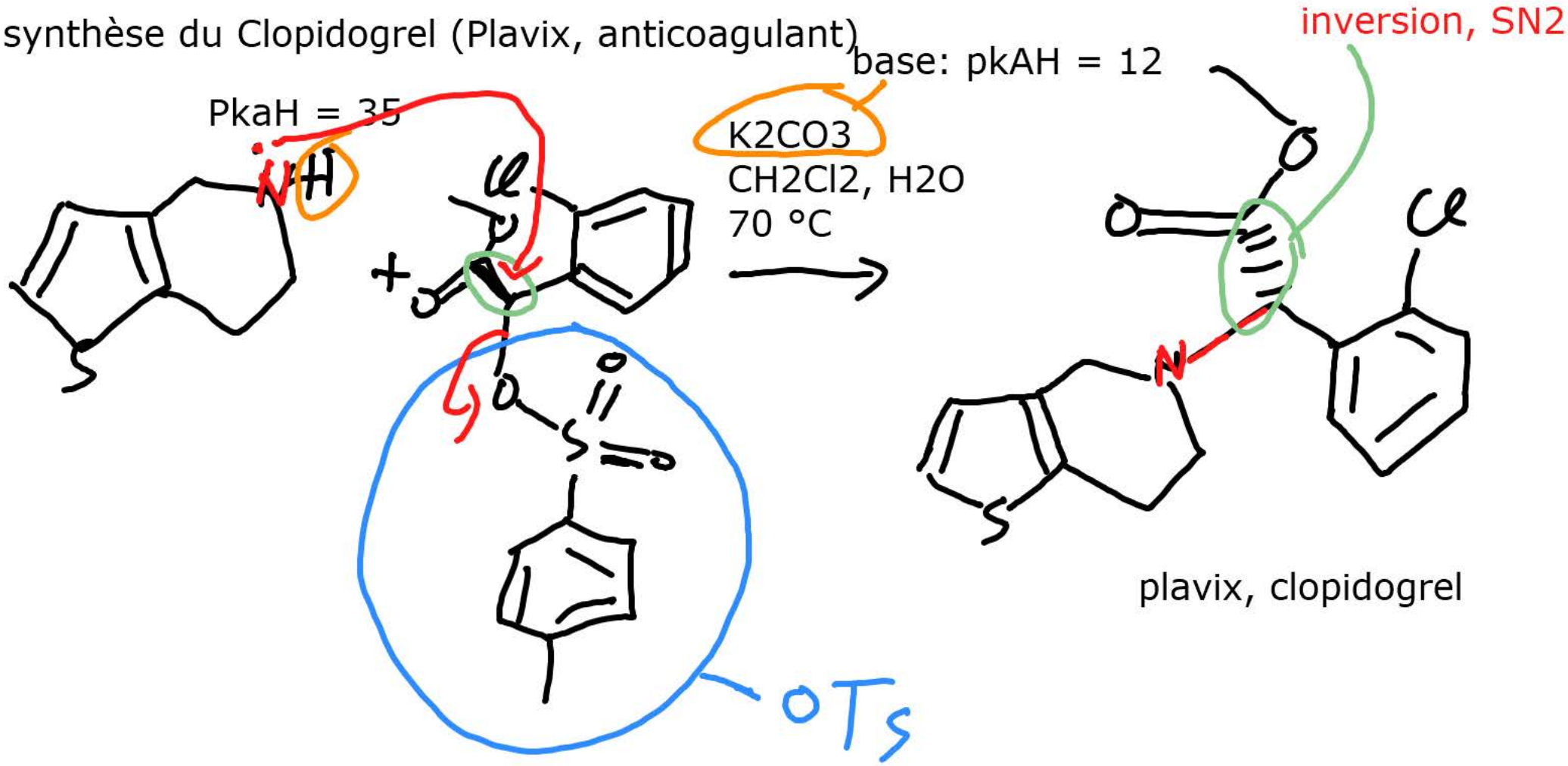




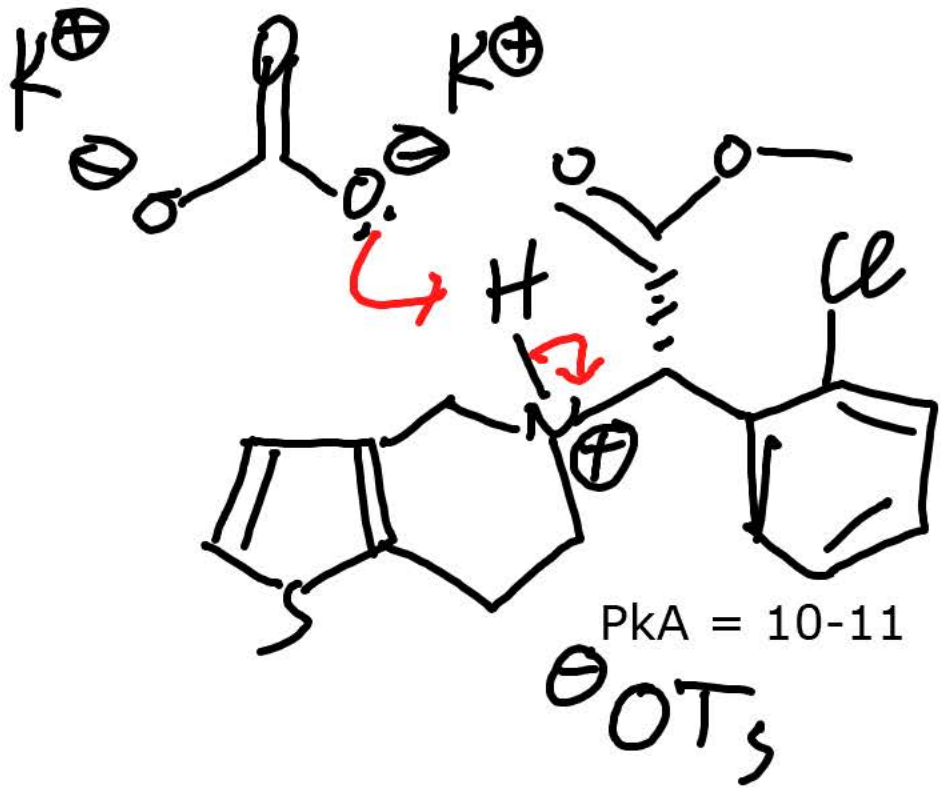
1) substitution aromatique électrophile
2) réaction de SN1

solvant polaire aprotique!

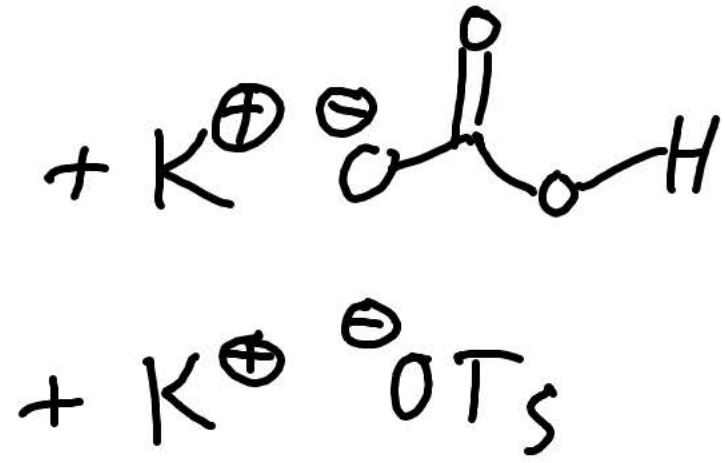
synthèse du Clopidogrel (Plavix, anticoagulant)



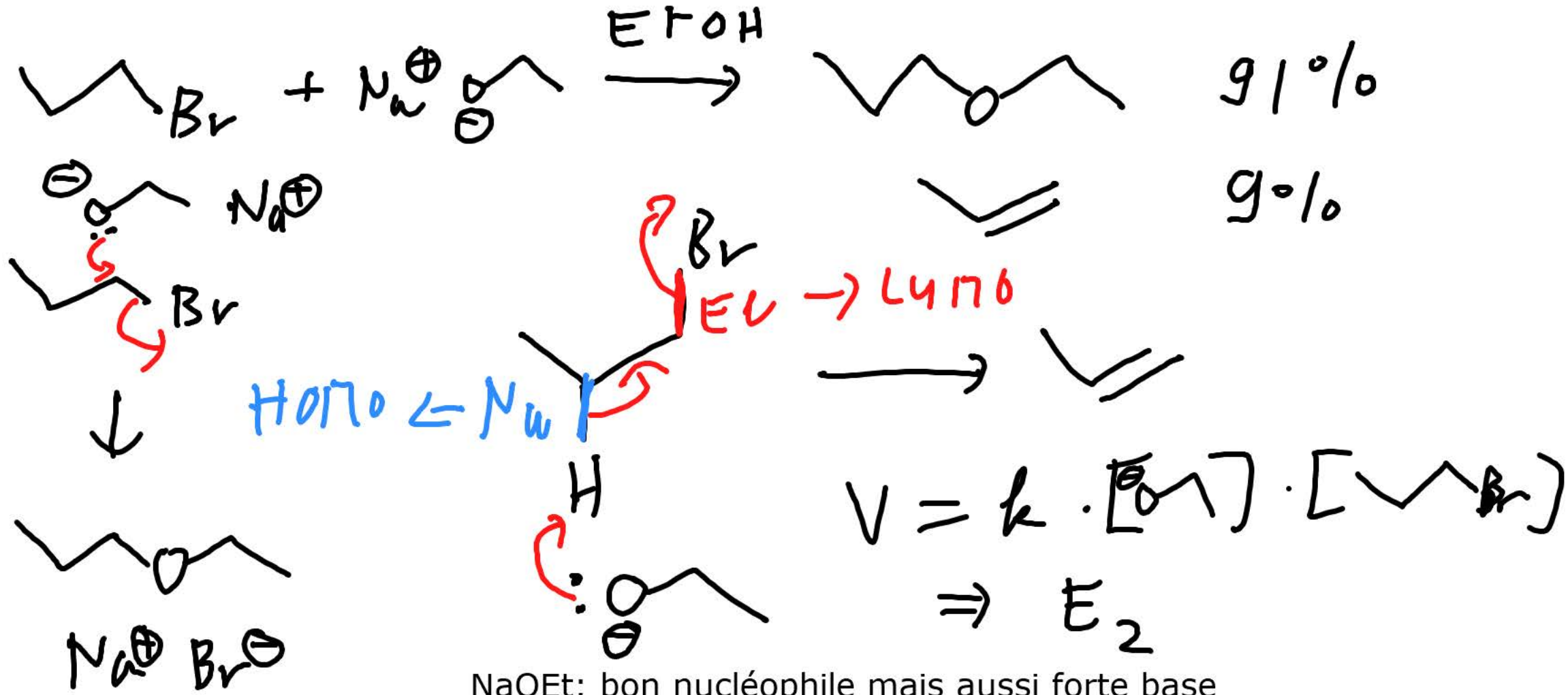
OTs: bon groupe partant (nucléofuge)



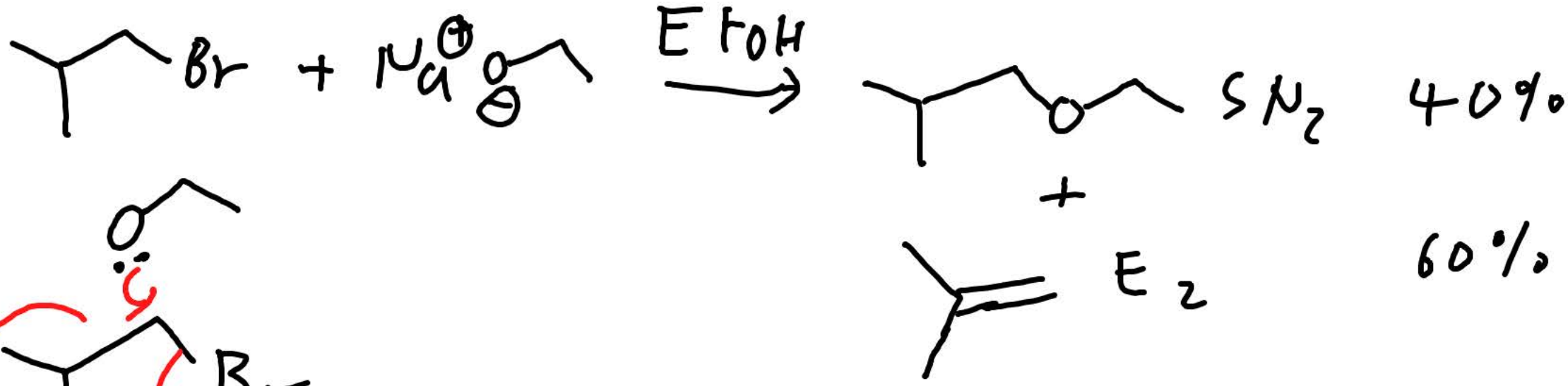
Clopidogrel



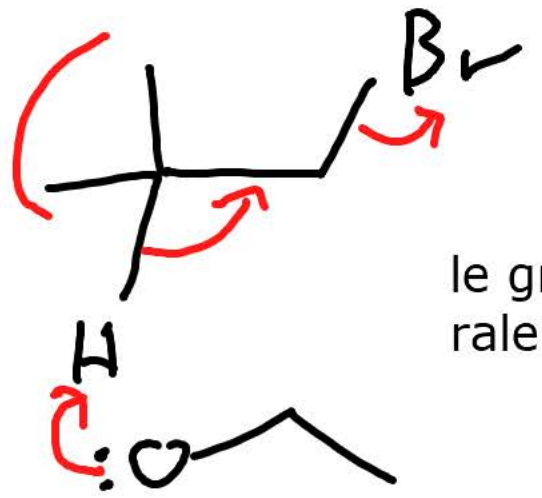
Substitution vs elimination



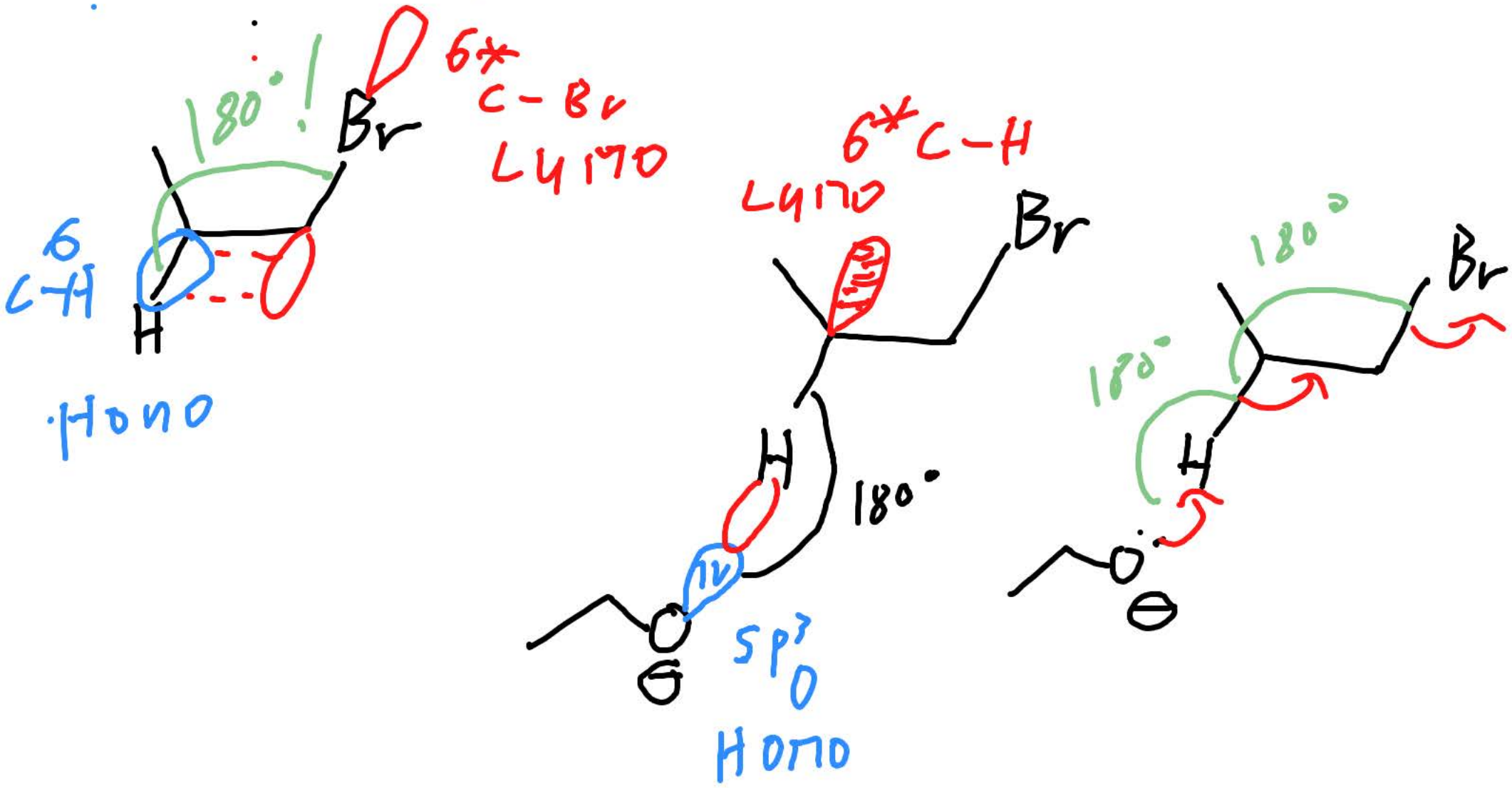
NaOEt: bon nucléophile mais aussi forte base



le groupe Me
ralentit la SN2

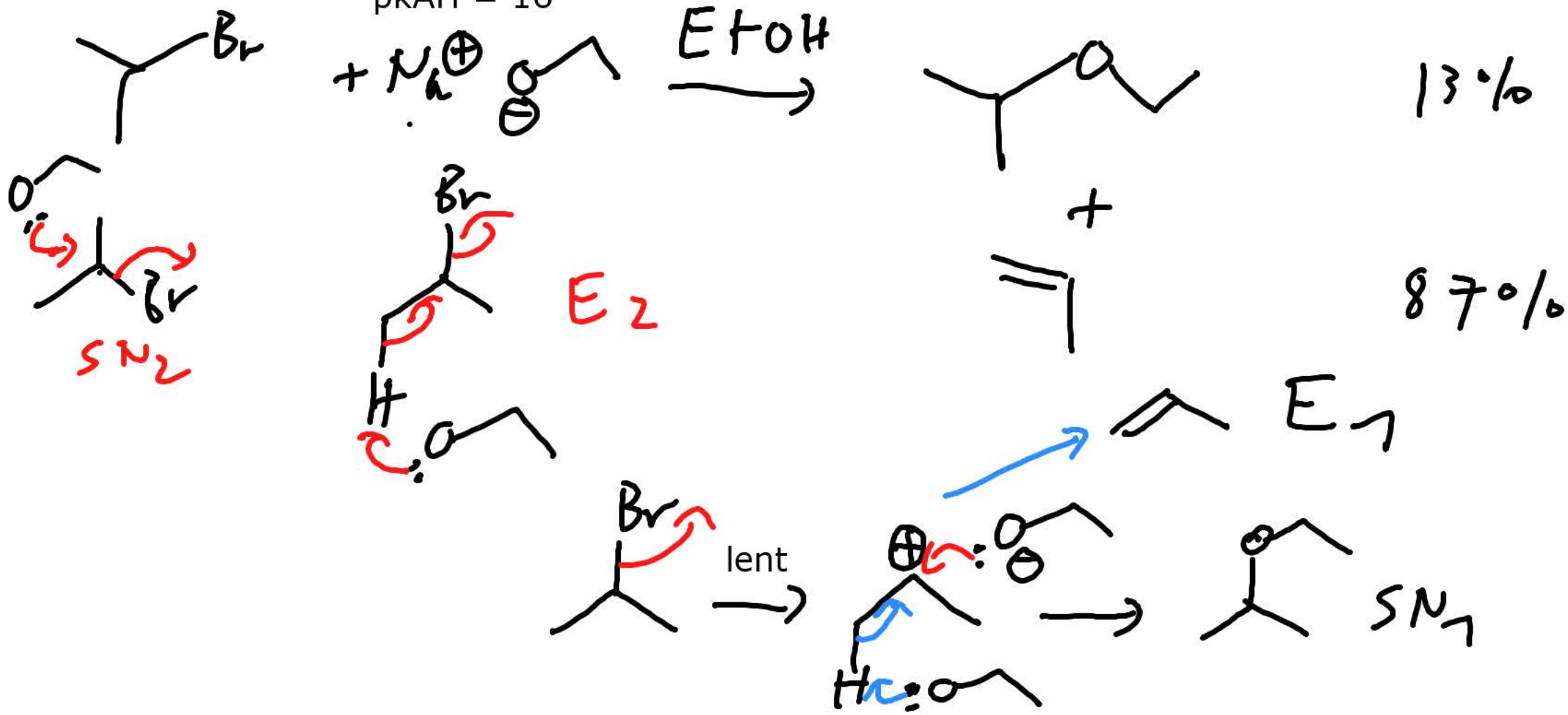


le groupe Me
ralentit beaucoup moins la E2!

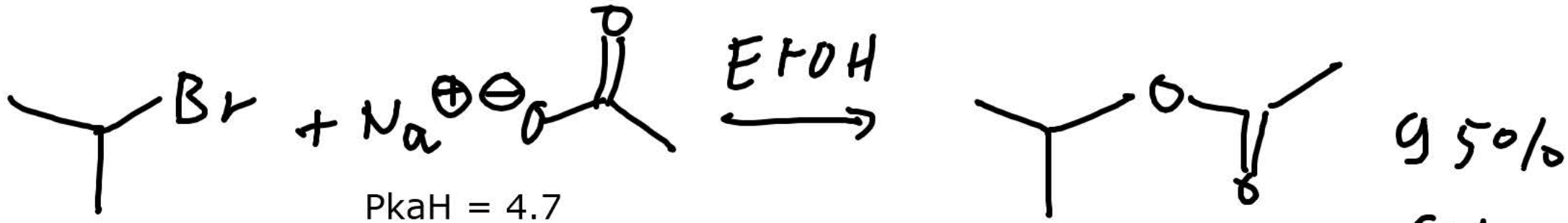

180°
Br
σ*
C-Br
LUMO
σ
C-H
H
HOMO
σ*C-H
LUMO
Br
H
180°
sp³
O
HOMO
180°
180°
Br
H
O

position secondaire

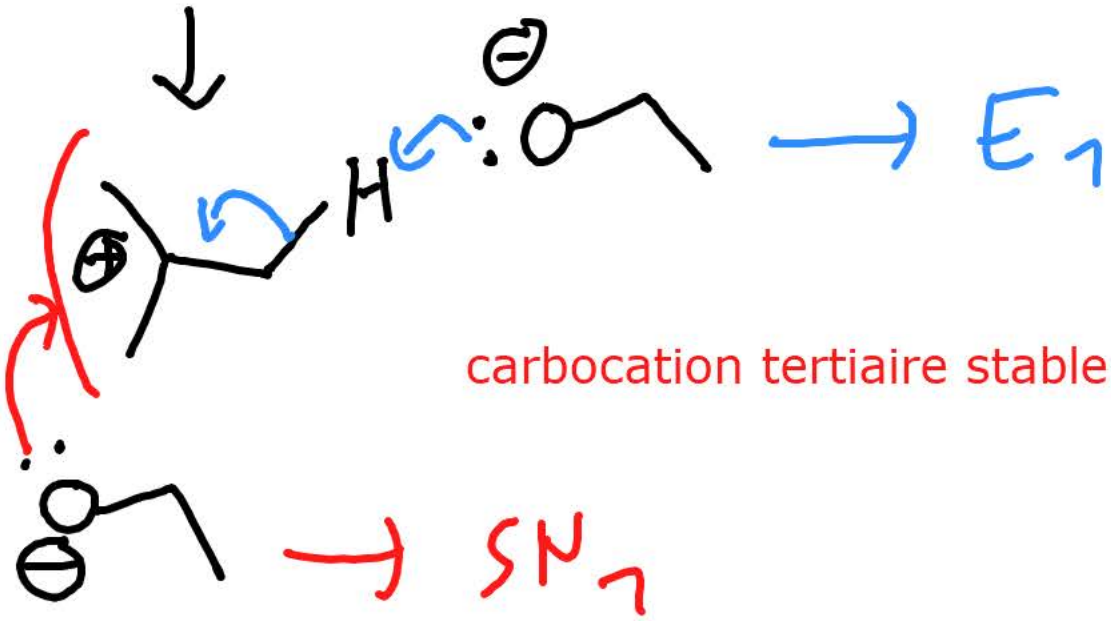
pkAH = 16



Comment favoriser SN? Utiliser un nucléophile moins basique!

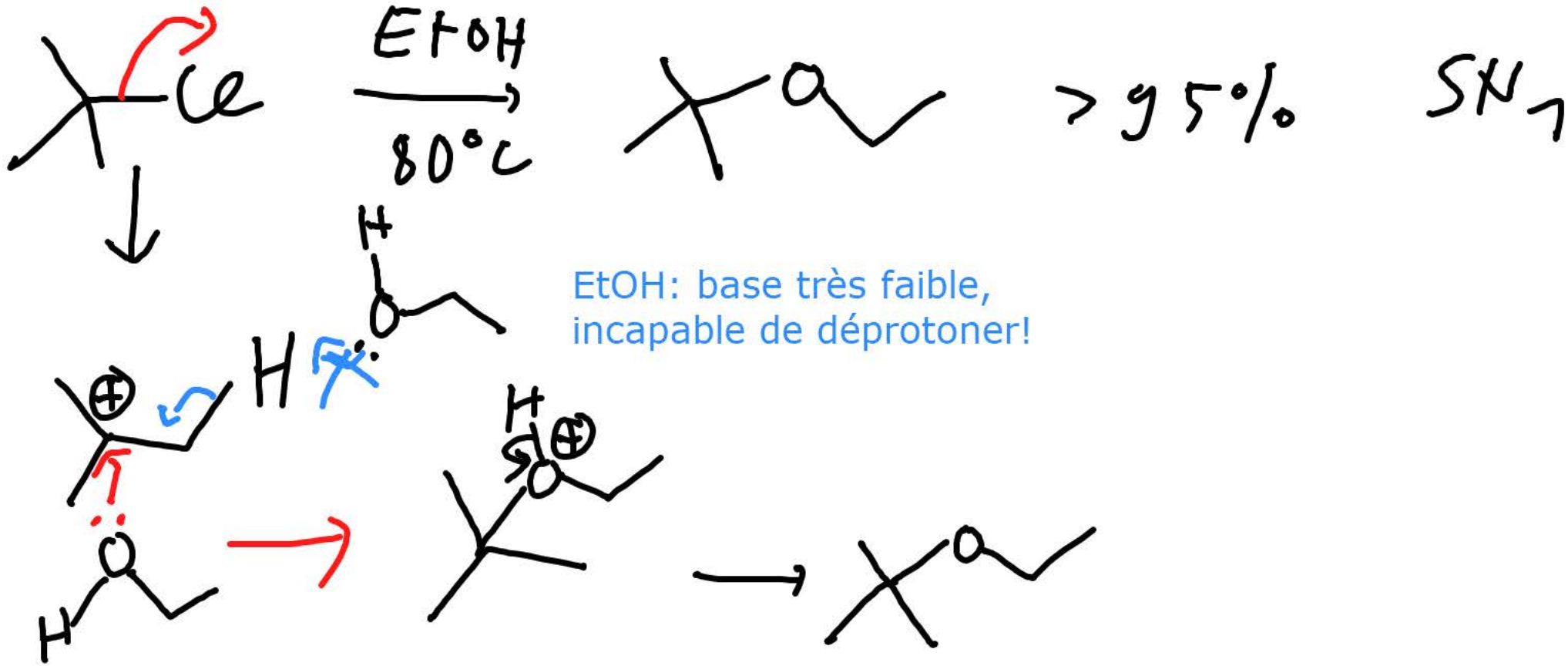


position tertiaire

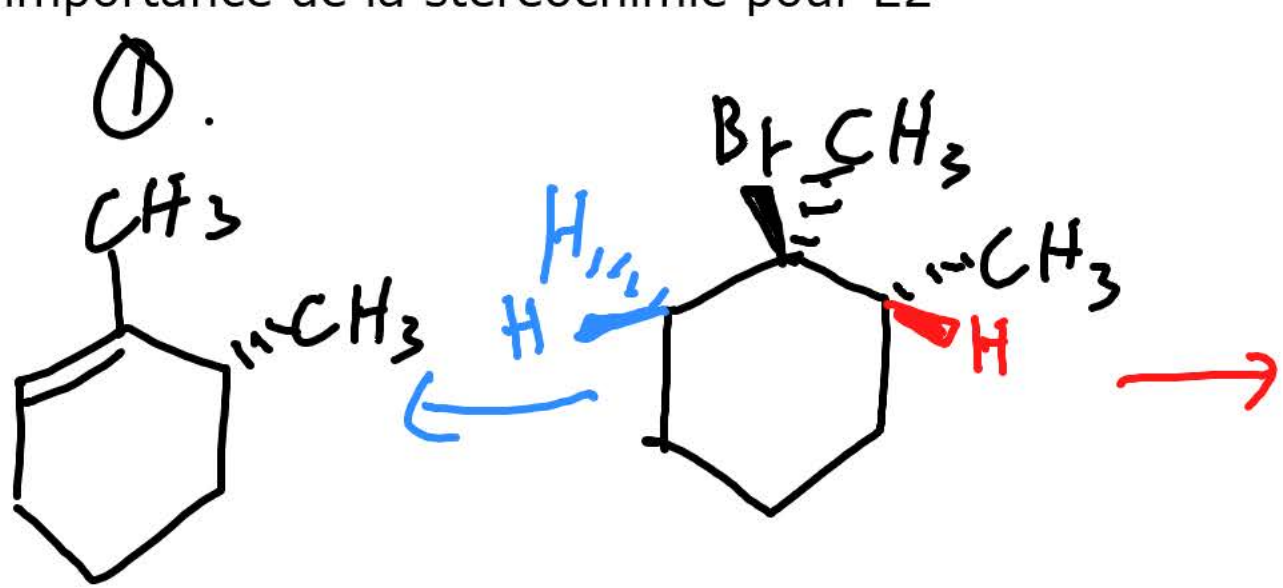


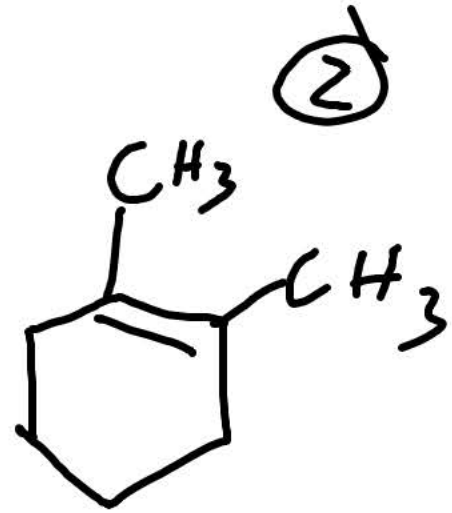
carbocation tertiaire stable

avec la forte base,
l'élimination domine!


EtOH
80°C
> 95%
SN1
EtOH: base très faible,
incapable de déprotoner!

importance de la stéréochimie pour E2





alcène trisubstitué

moins stable

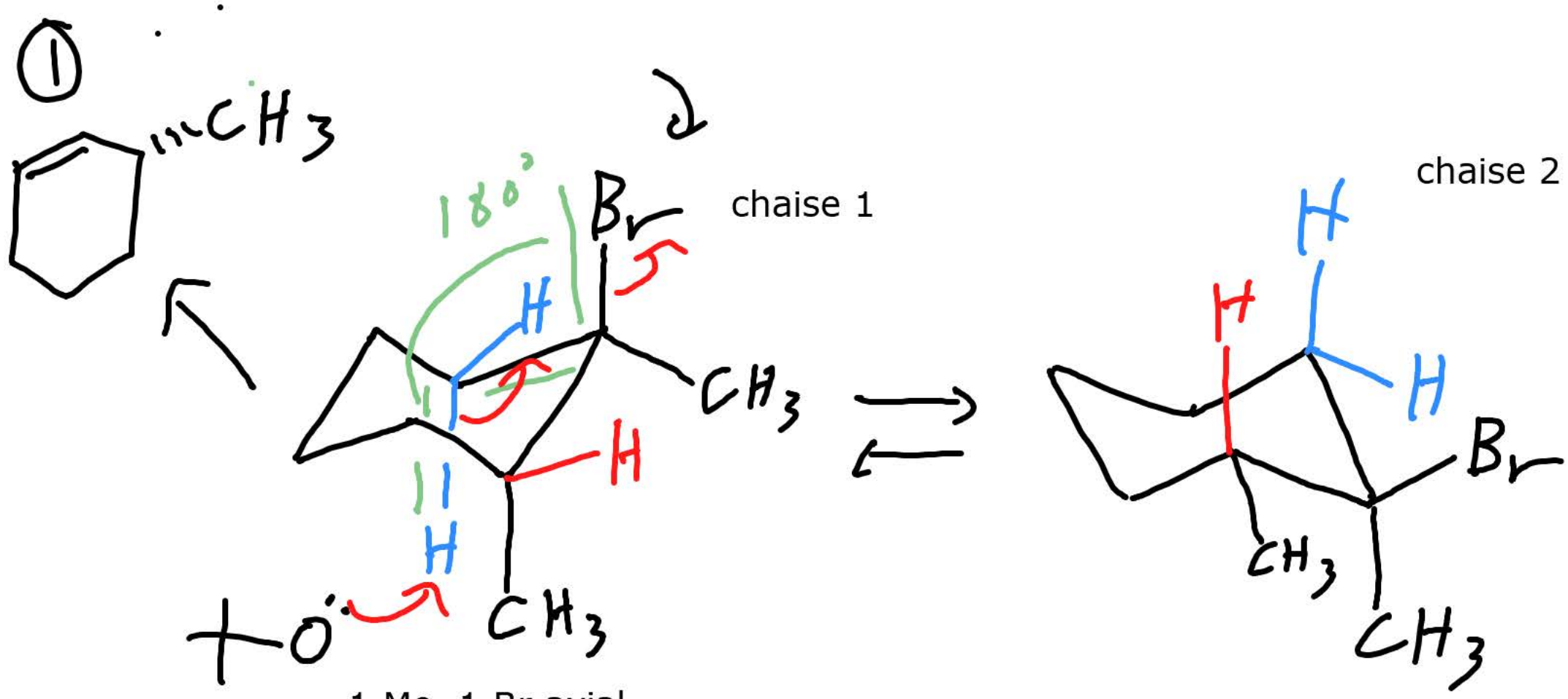
produit cinétique: produit observé!

en présence de KOtBu

alcène tétrasubstitué

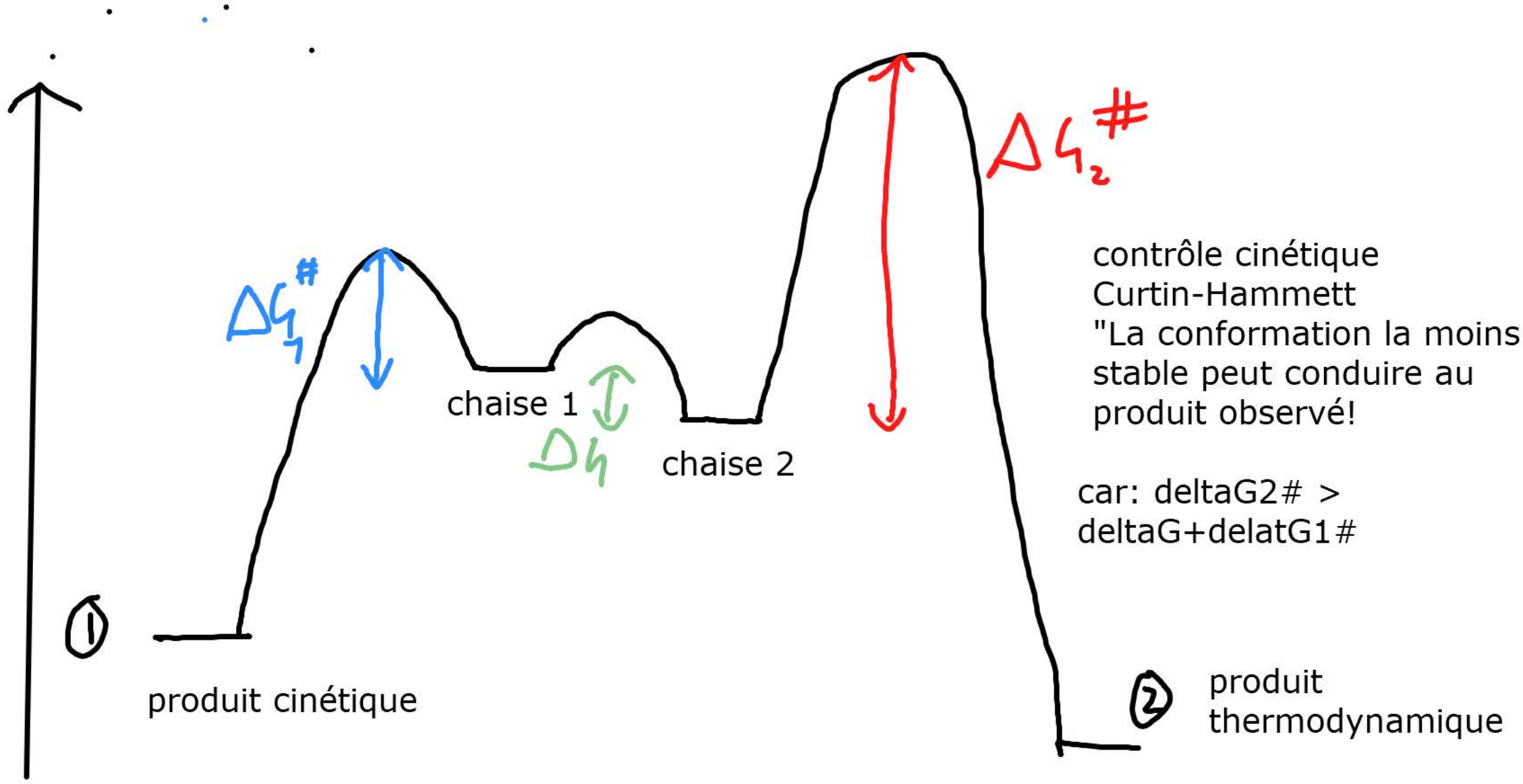
plus stable

produit thermodynamique



1 Me, 1 Br axial
1 Me équatorial

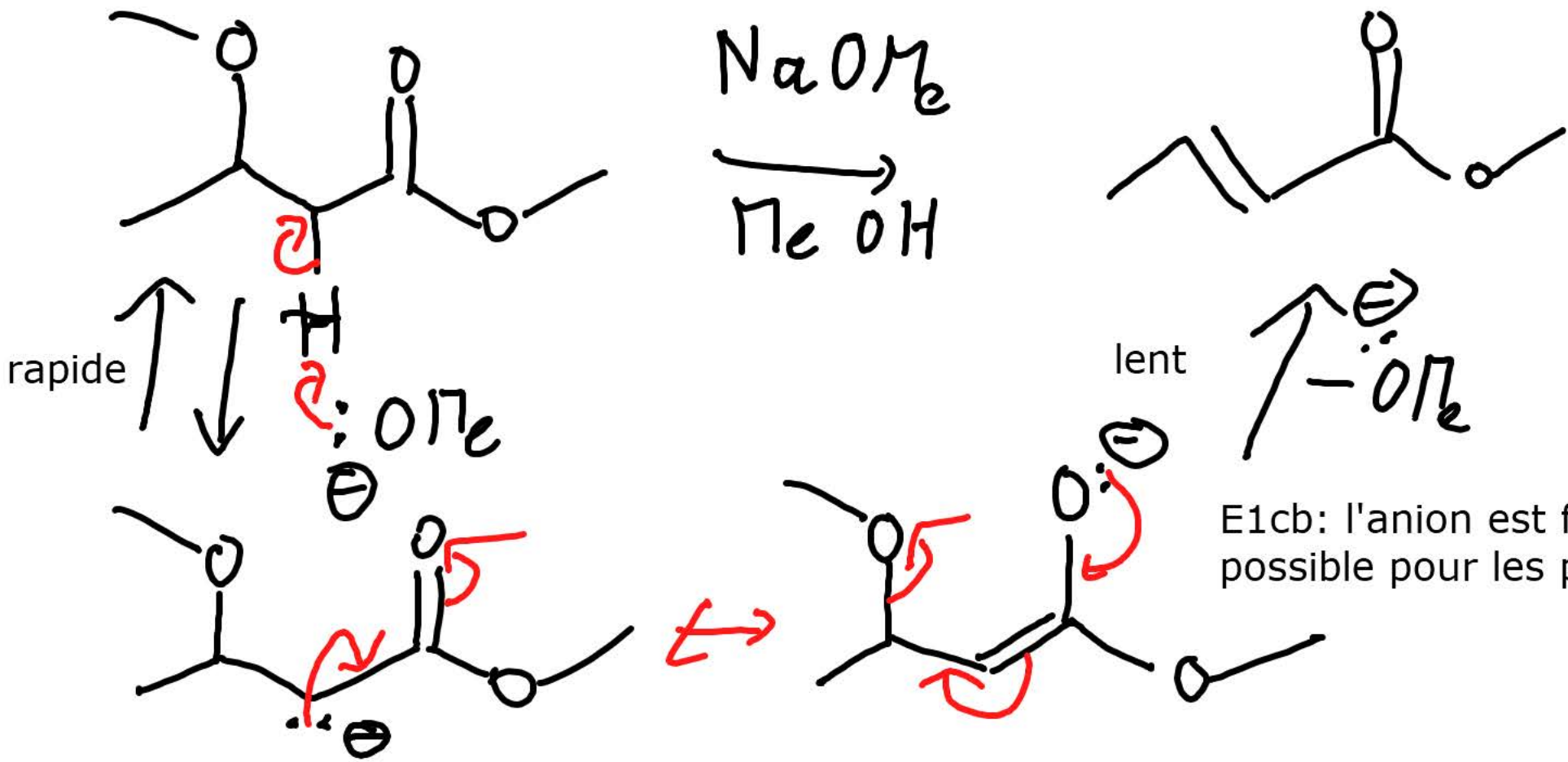
1 Me axial
1 Me et 1 Br équatorial
plus stable!



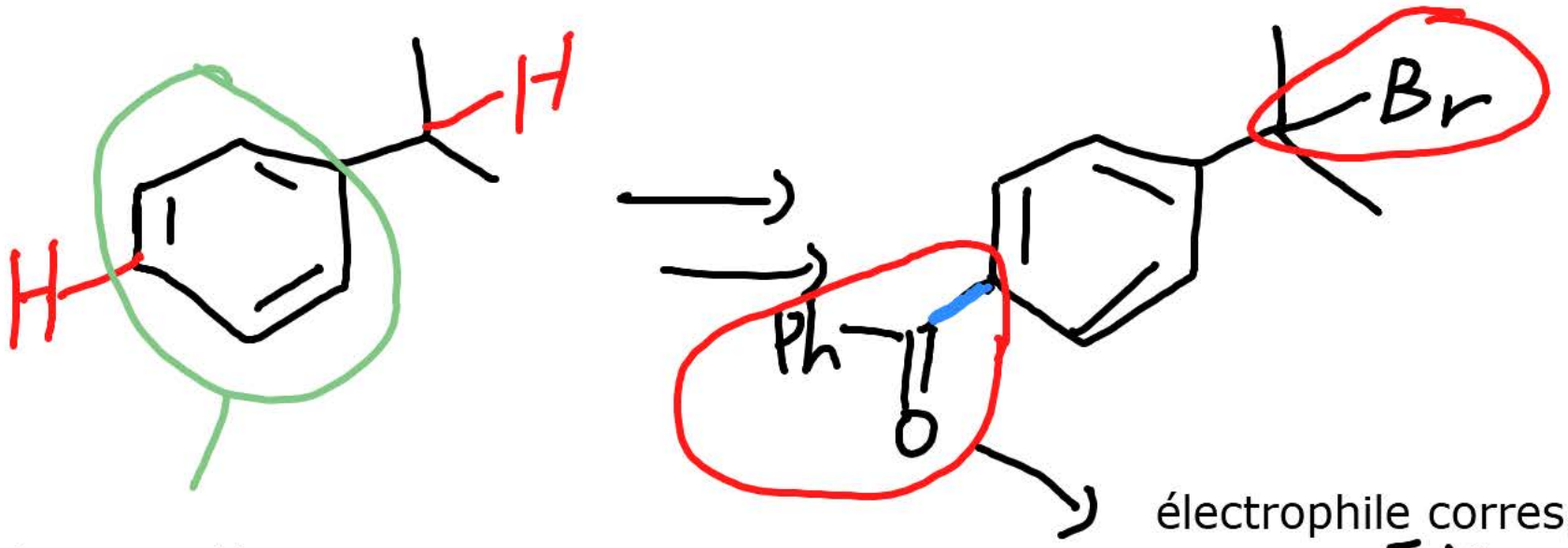
contrôle cinétique
Curtin-Hammett
"La conformation la moins stable peut conduire au produit observé!

car: deltaG2# > deltaG+delatG1#

"5ème mécanisme" élimination E1cb pour les protons acides (cb = conjugated base)

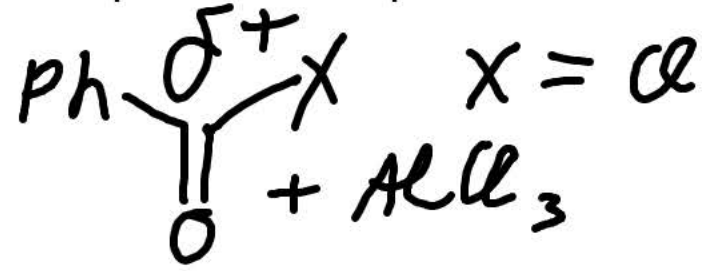


exercice 8.2.3



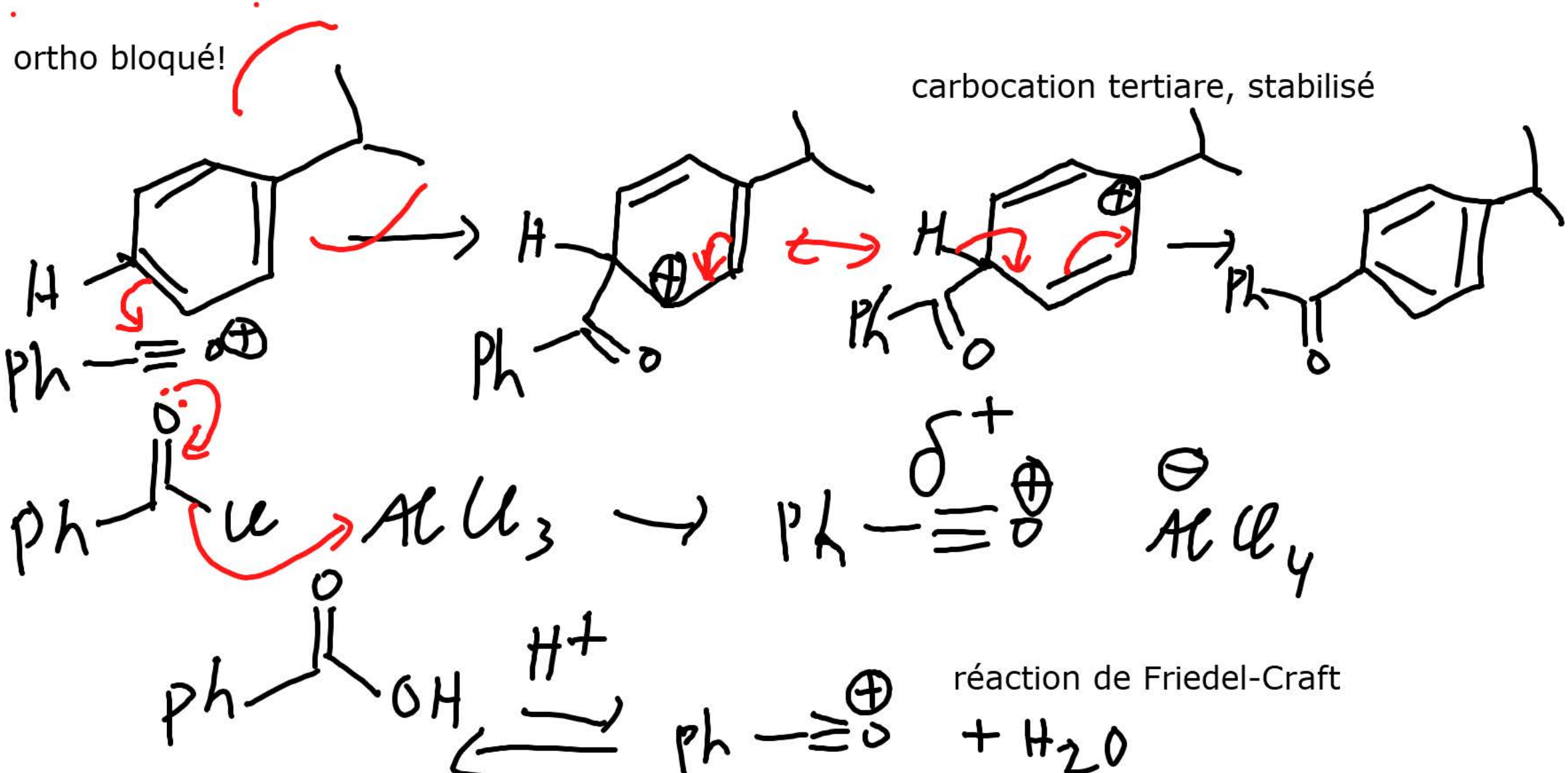
cycle aromatique
Agit comme nucléophile dans les substitutions aromatiques électrophiles

électrophile correspondant?



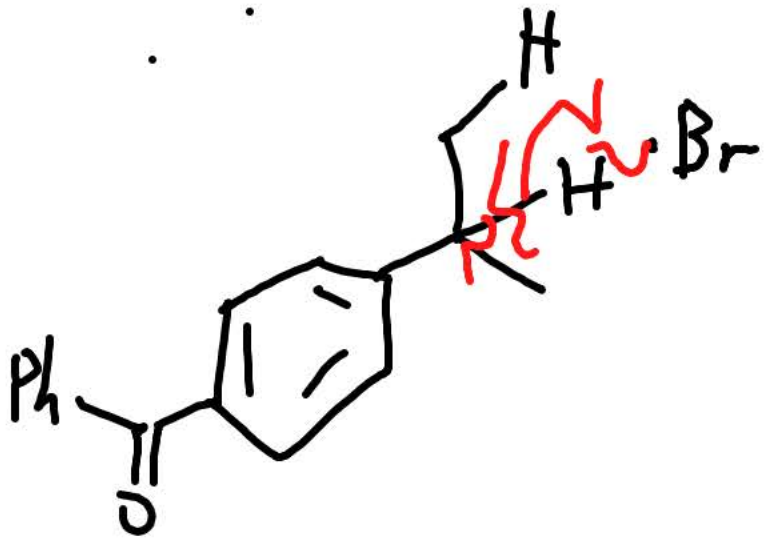
ortho bloqué!

carbocation tertiaire, stabilisé

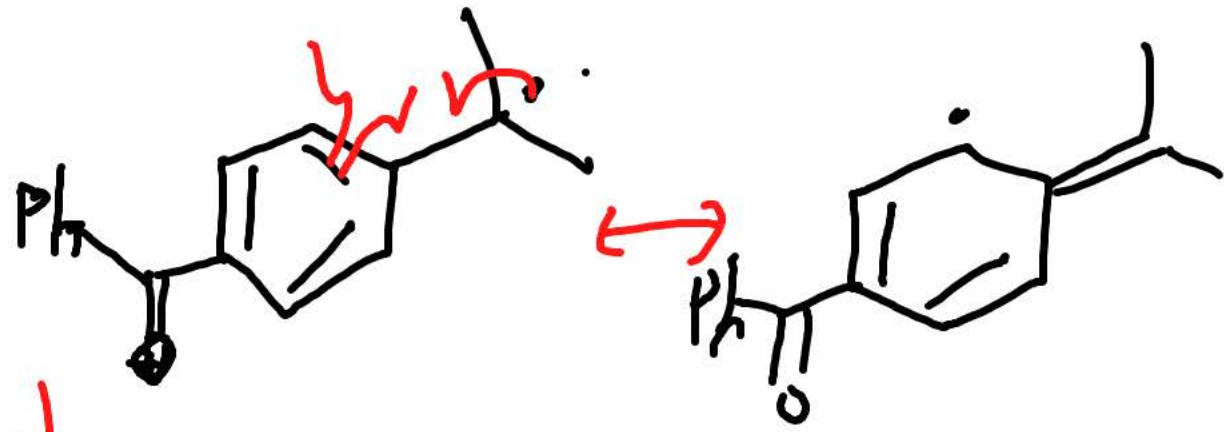


réaction de Friedel-Craft

fonctionne uniquement avec des très bons donneurs (atomes avec pairs d'électrons, O, N)



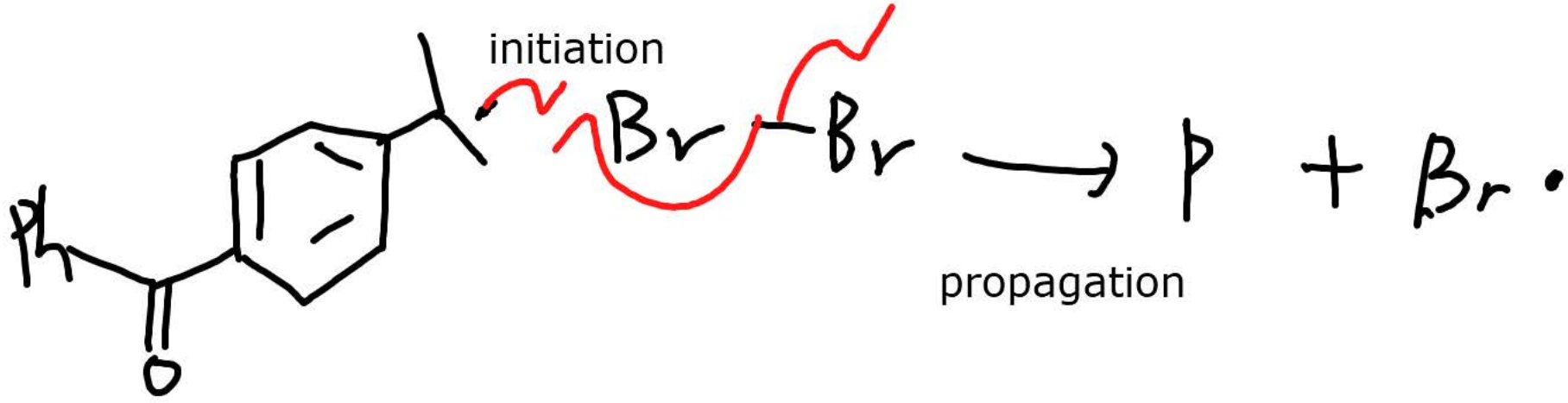
Br_2 / $h\nu$



stabilisé par résonance!

chimie radicalaire!

initiation

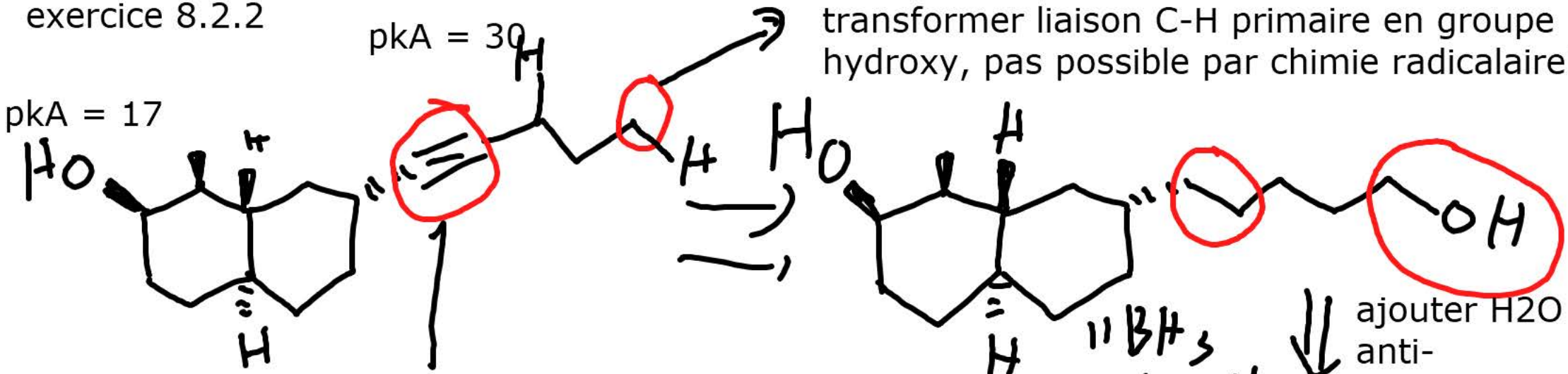


propagation

exercice 8.2.2

pkA = 17

pkA = 30



transformer liaison C-H primaire en groupe hydroxy, pas possible par chimie radicalaire!

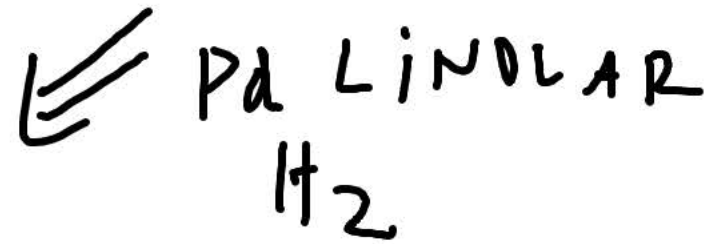
1) BH_3
2) $NaOH/H_2O_2$

ajouter H2O anti-Markovnikov

hydrogénation de la triple liaison pour donner une liaison simple?

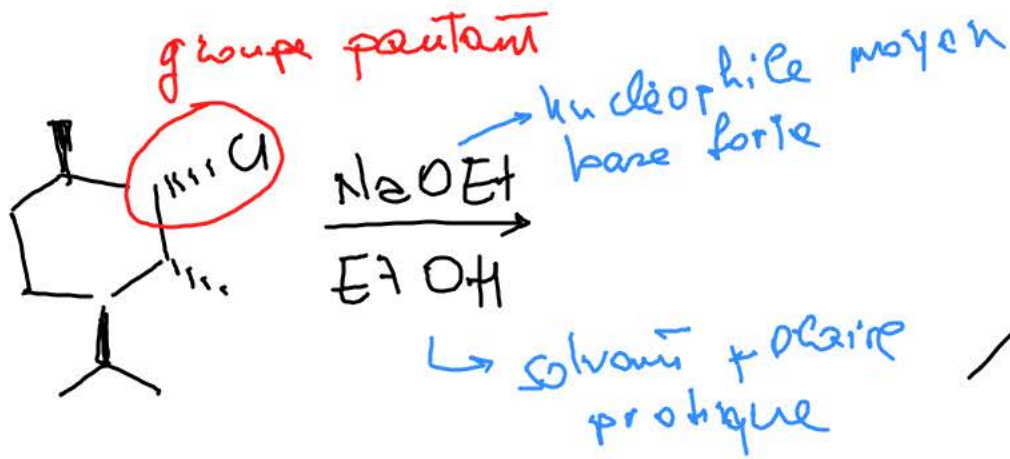
2 equiv NaNH2

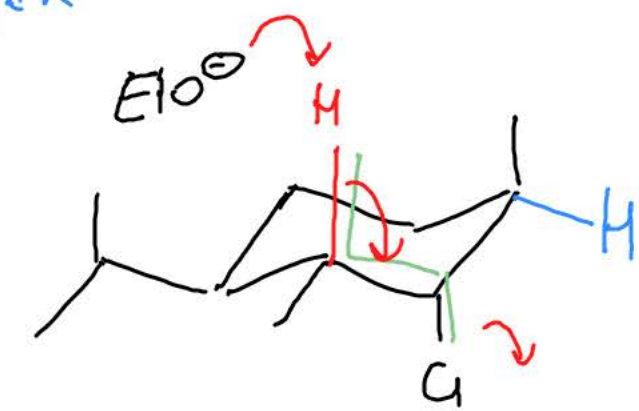
?

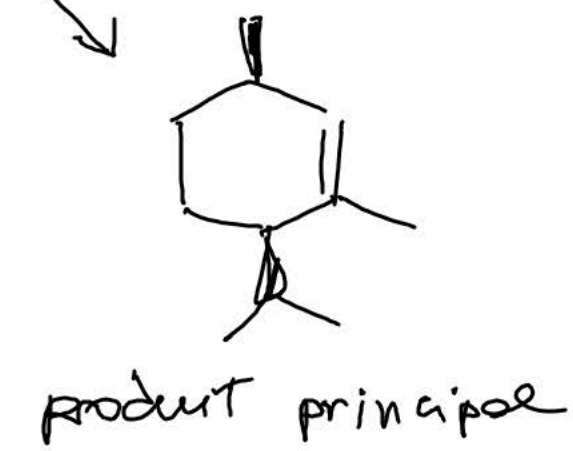


Pd LINDLAR

H_2







produit principal

1) Analyse du substrat : E ou SN

GP en position secondaire

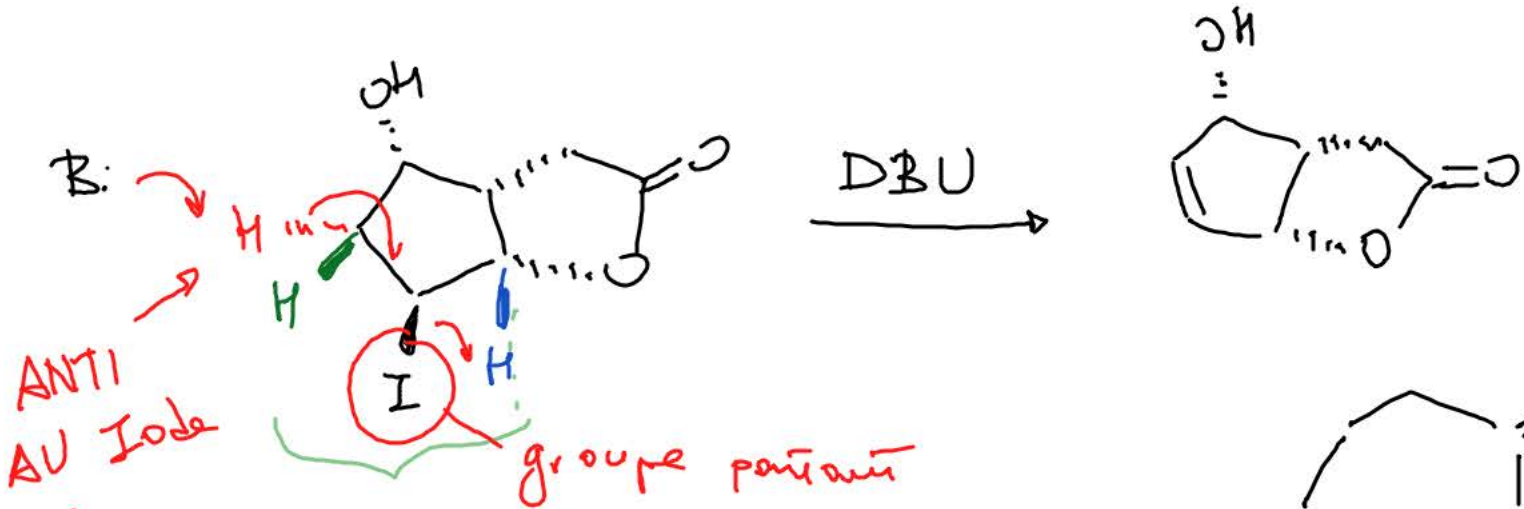
les deux sont possibles

2) conditions : base forte, solv. polaire, protique

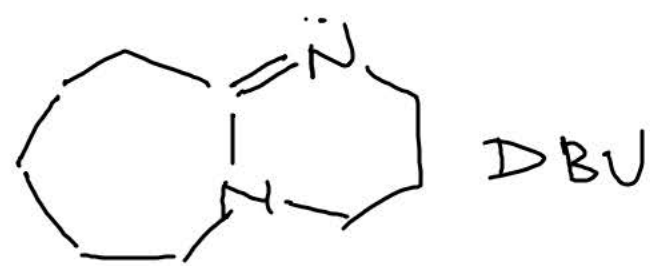
E2 si on peut atteindre l'angle idéal de 180° (anti périplanaire) – sinon E1

Dessin 3D !

synthèse d'un produit naturel : prostaglandines
(hormones naturelles)

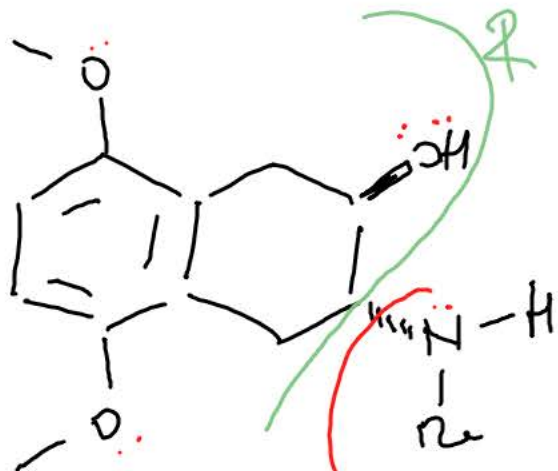


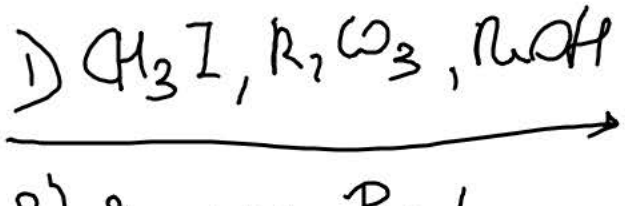
Cycle 5 chaînons, presque plat
seulement l'H en rouge
a le bon angle pour réagir
(anti ou I)

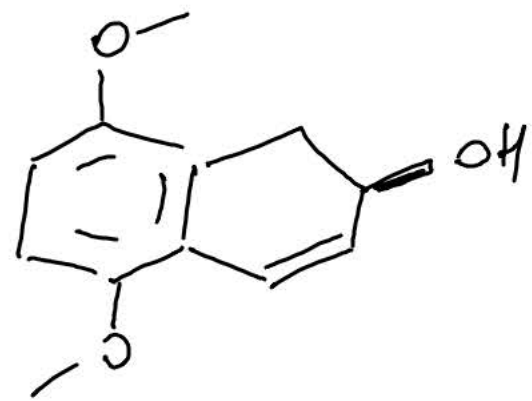


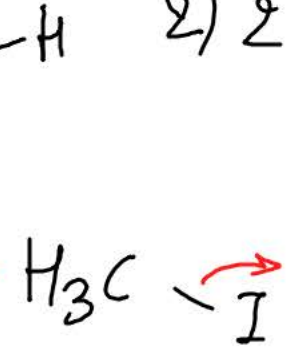
bonne base, acide et
stabilisé par résonance
$pK_A = 16$

Elimination selon Hofmann (à partir des amines)





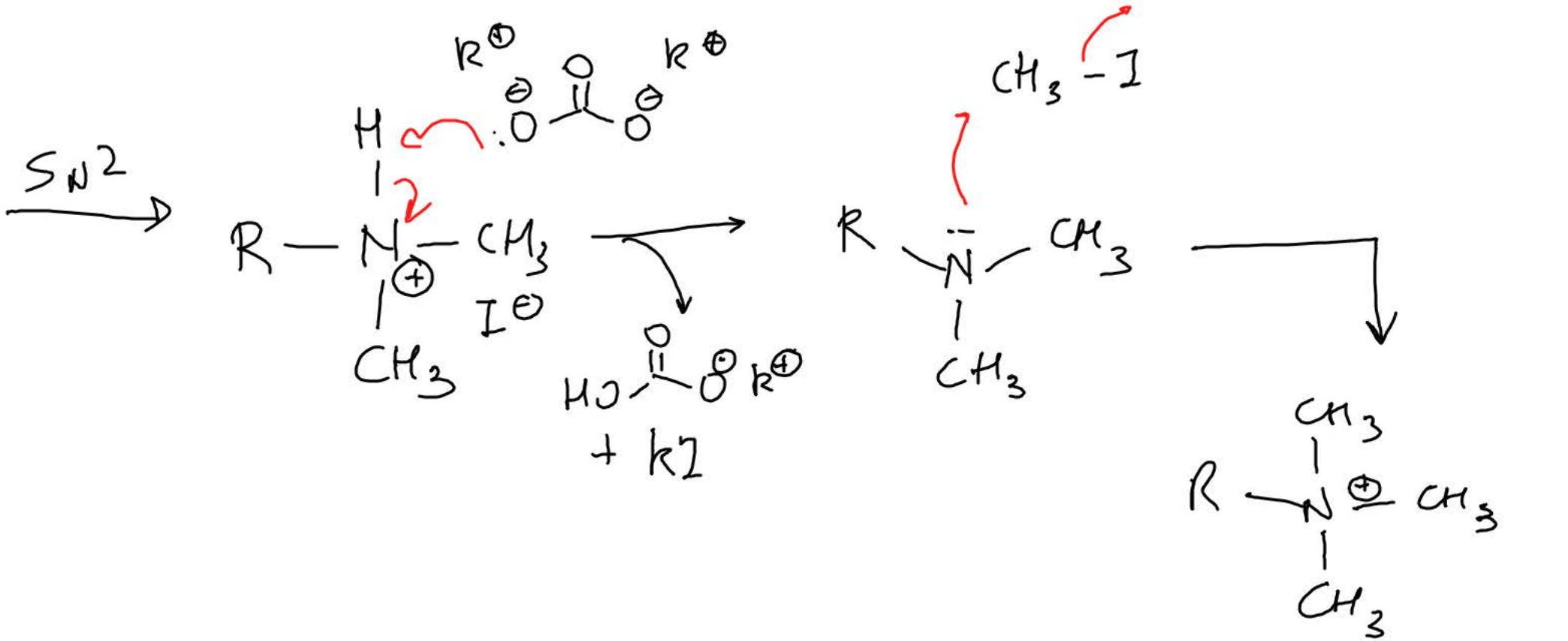


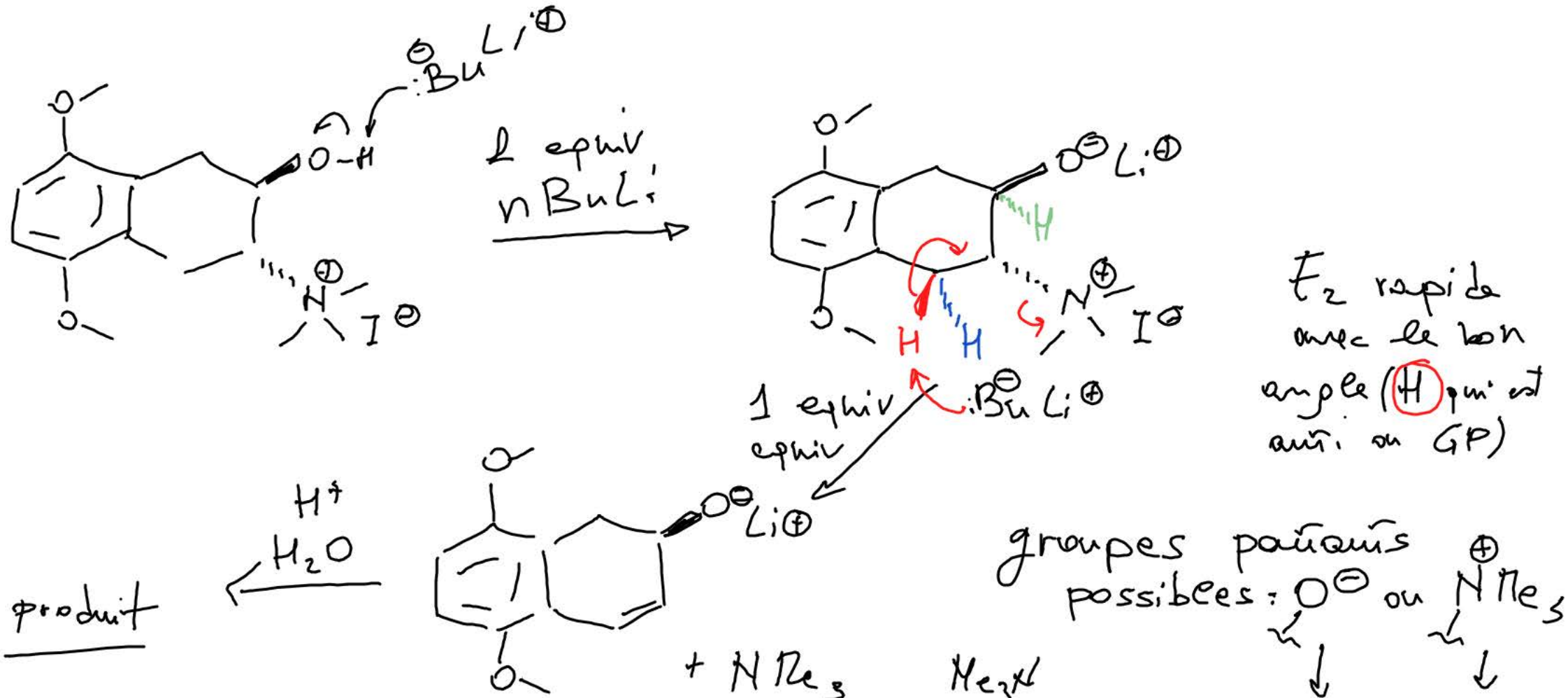


O est plus électronégatif que N

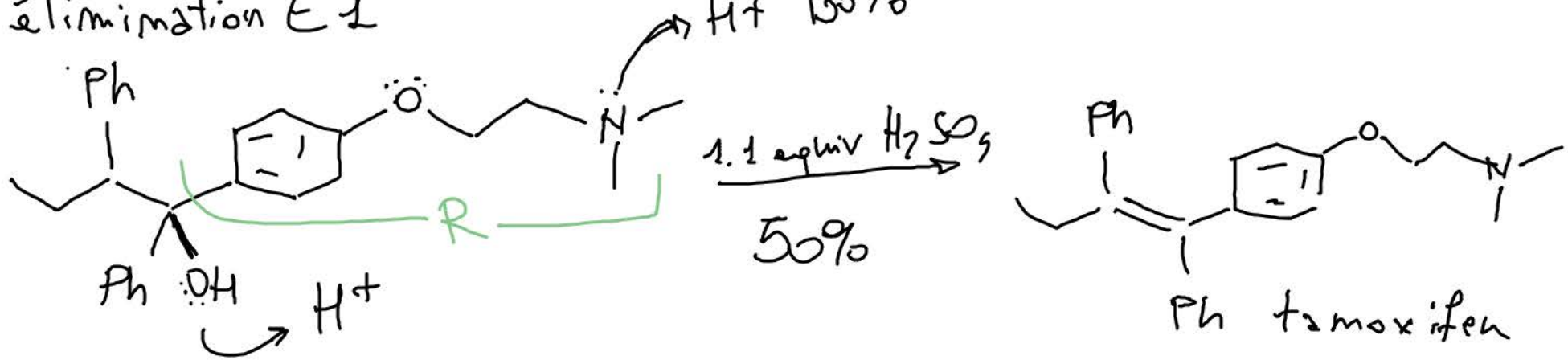
⇒ N plus nucléophile

primaire accessible idéal pour S_N2


SN2
R
N
CH3
I⊖
CH3
H
K⊕
K⊕
HO
K⊕
+ KI
CH3 - I
R
N
CH3
CH3
CH3
R
N
CH3
CH3
sel d'ammonium
quaternaire
la réaction s'arrête

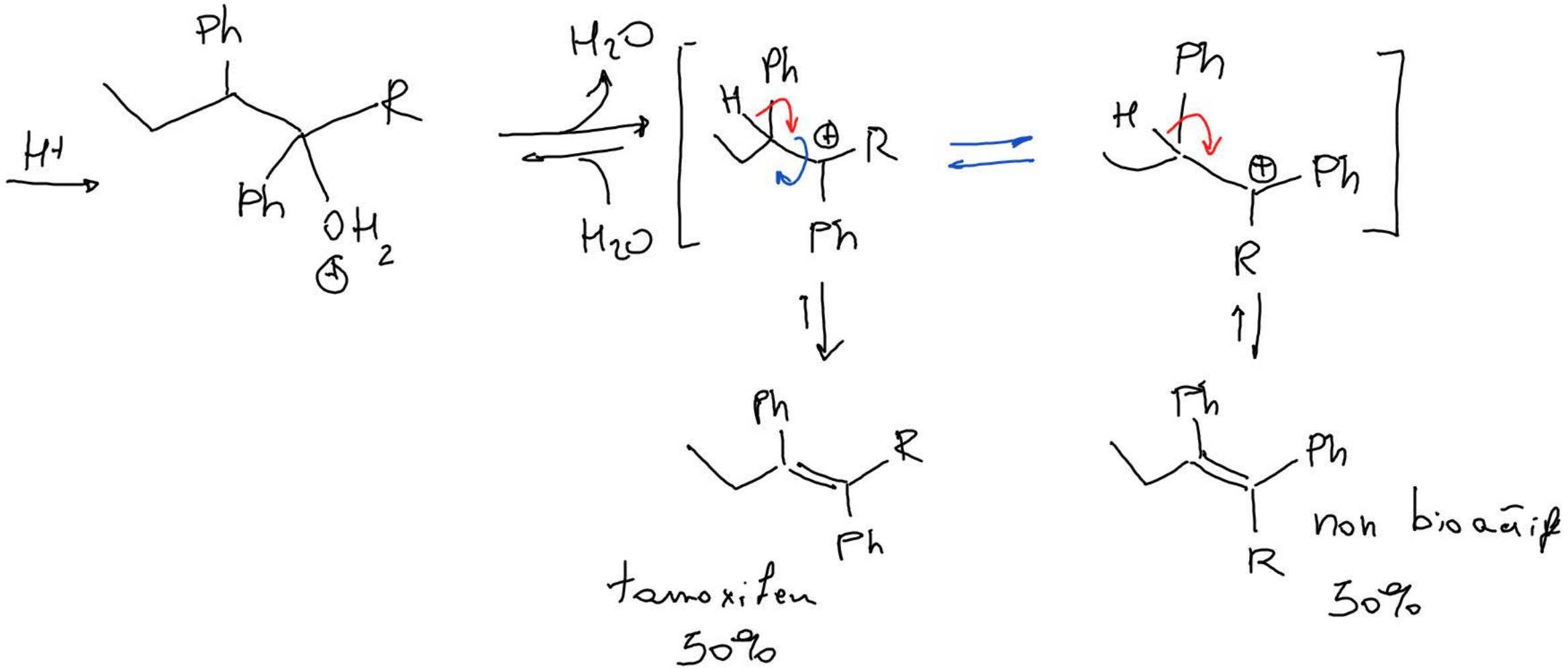

1 equiv
nBuLi
1 equiv
equiv
H+
H2O
produit
+ NMe3
+ Li⊕I⊖
Me3Xl
clairement
meilleur
groupes partants
possibles : O⊖ ou ⊕NMe3
O2-
+NMe3
E2 rapide
avec le bon
angle (H qui est
anti. on GP)

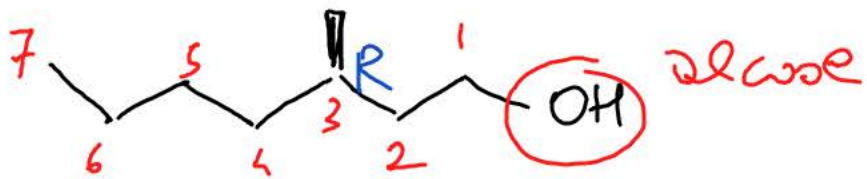
Synthèse du tamoxifen (traitement du cancer du sein)
par élimination E1



O plus électronégatif que N.

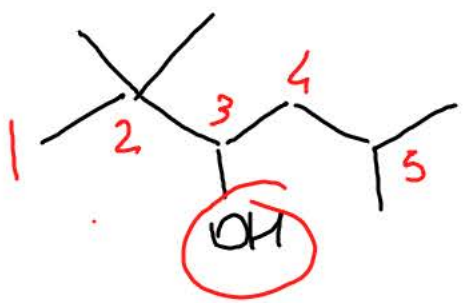
N est plus basique


H+
Ph
Ph
R
OH2
H2O
H2O
Ph
H
R
Ph
Ph
R
Ph
H
Ph
Ph
R
tamoxifen
30%
non bioactif
30%

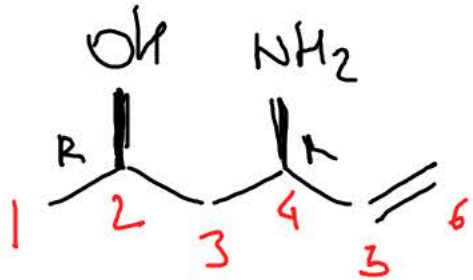


alcool

(R) - 3 - méthyl - heptan - 1 - ol

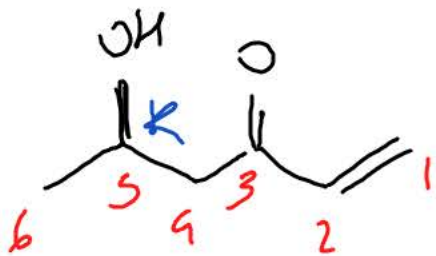


2,2,5 - trimethyl - hexan - 3-ol



alcool > amine

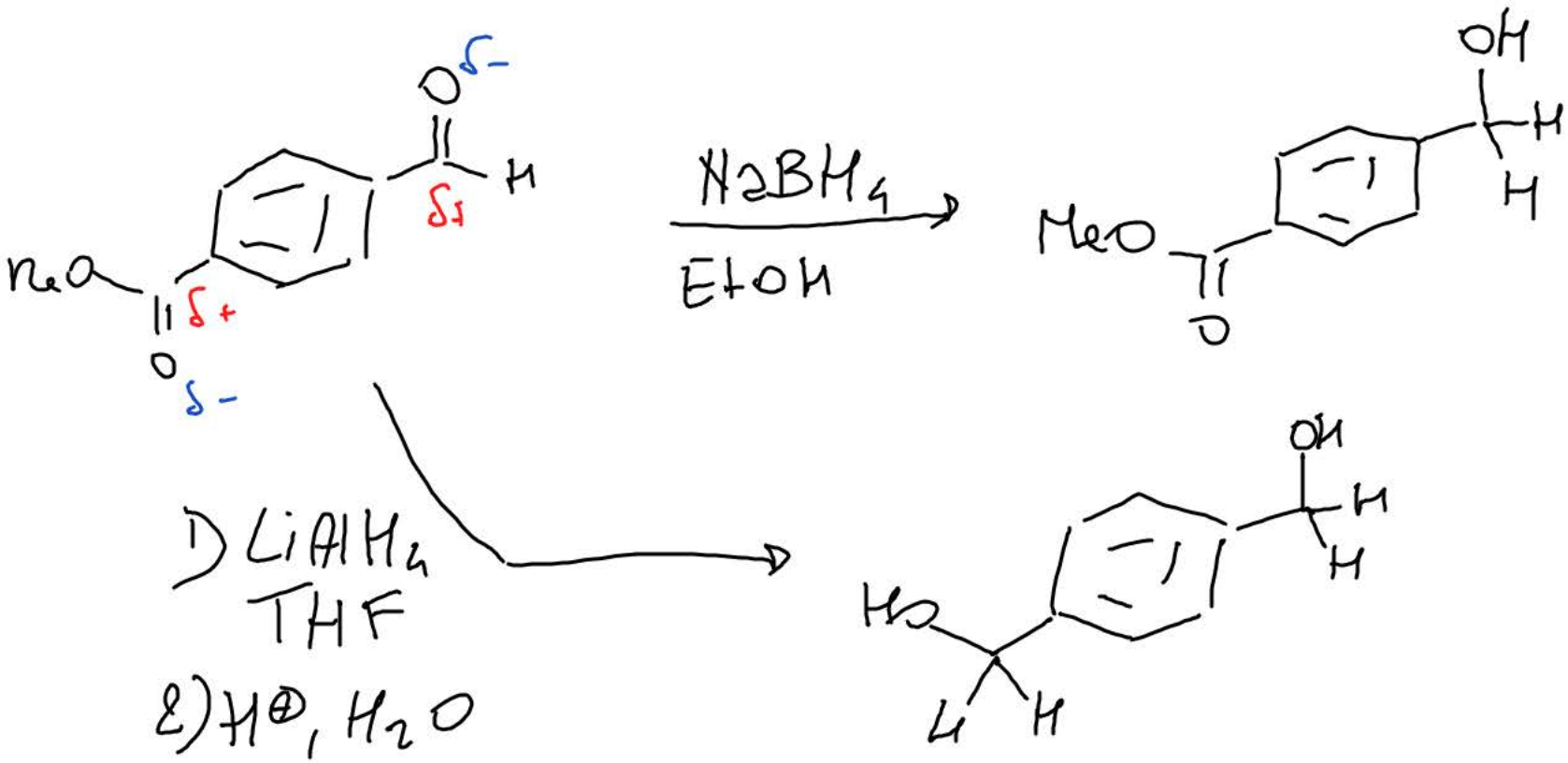
(2R,4R)-4-amino-hex-5-en-2-ol

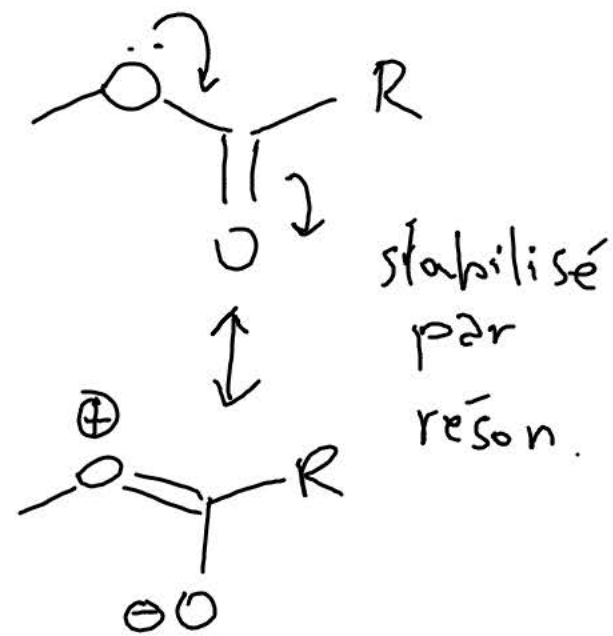


cétone > alcool

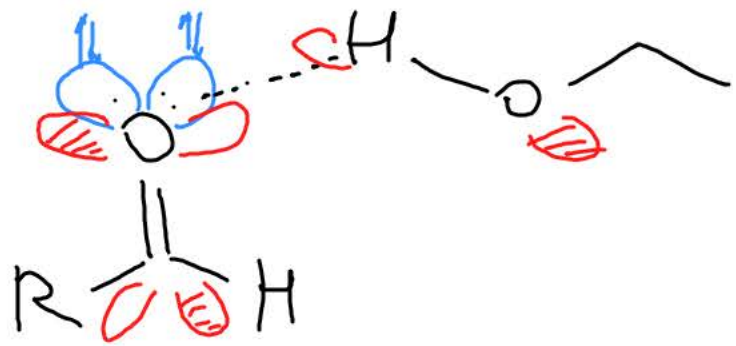
(R)-5-hydroxy-hex-1-en-3-one

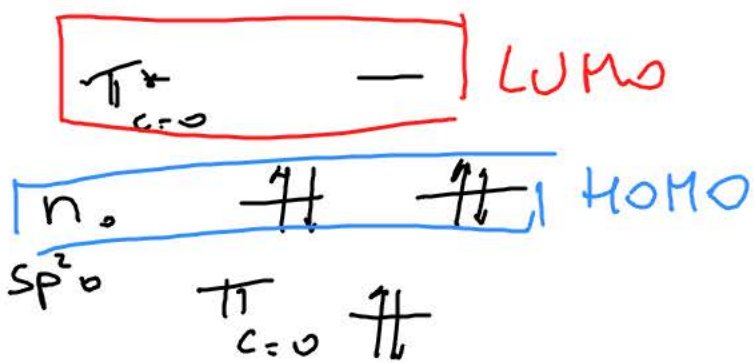
Réduction des carbonyls avec des hydrures





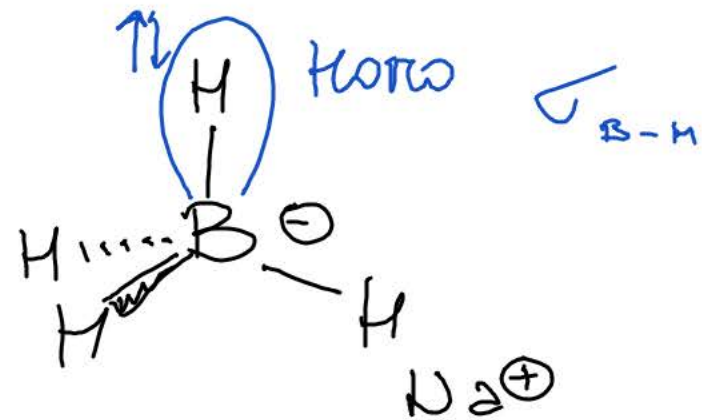
Réduction avec $NaBH_4$

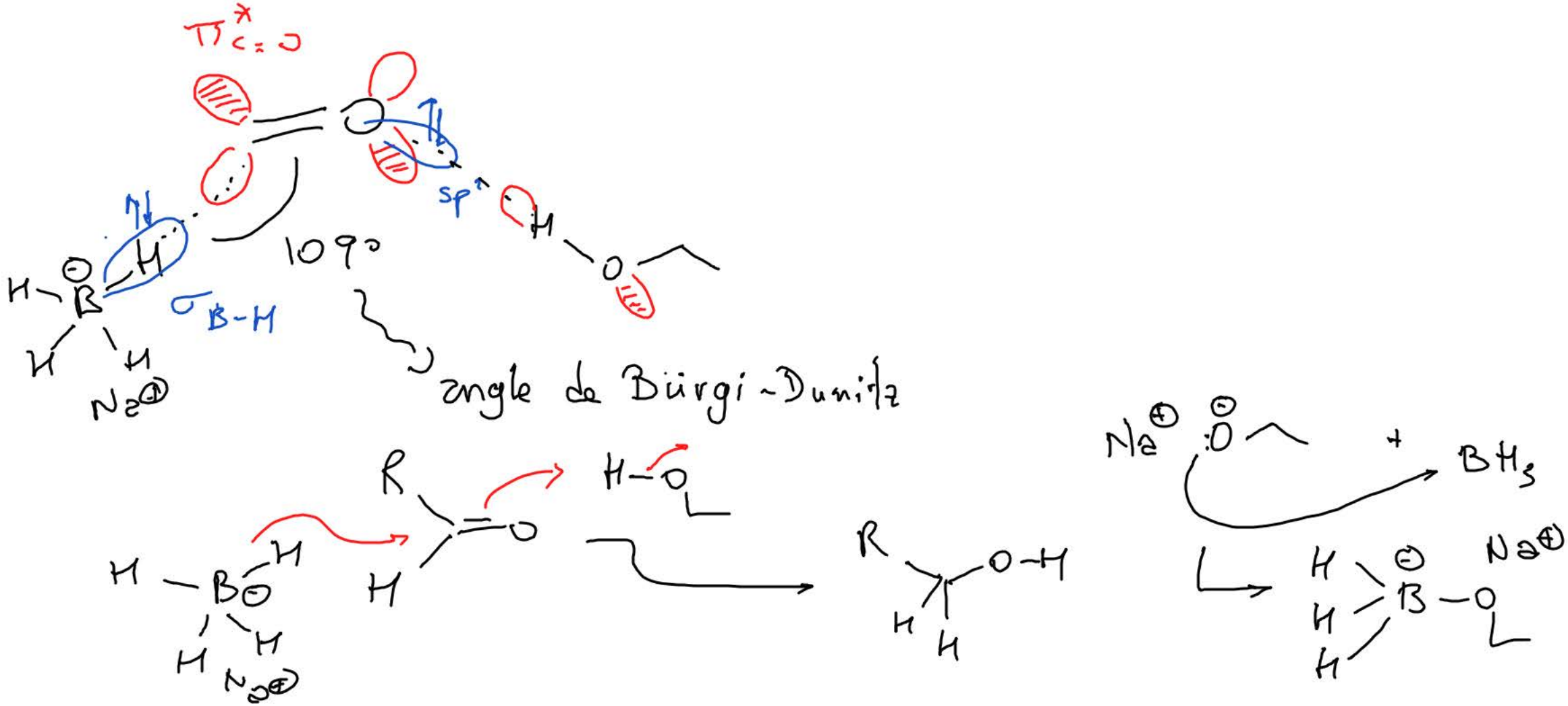




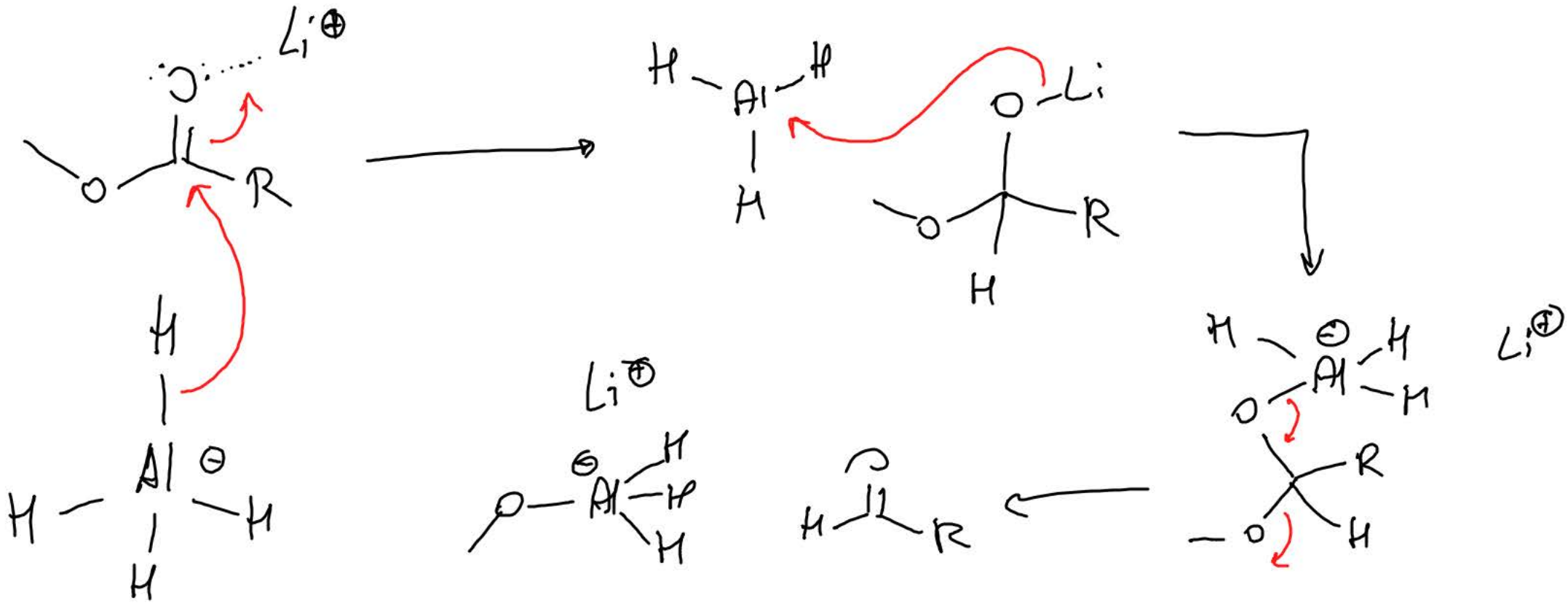
sp^2 O → σ^*_{H-O}

LUMO de l'EtOH

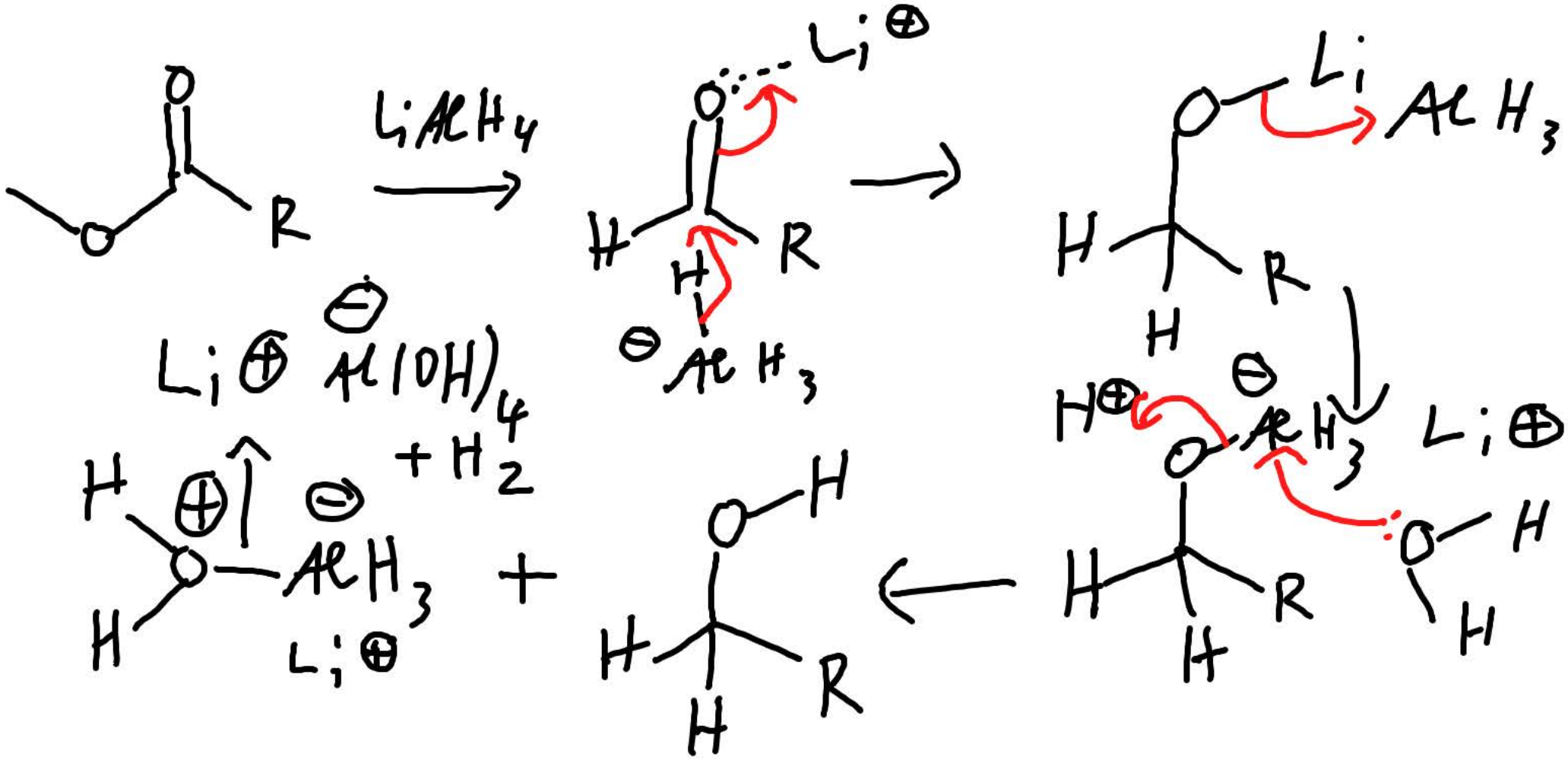


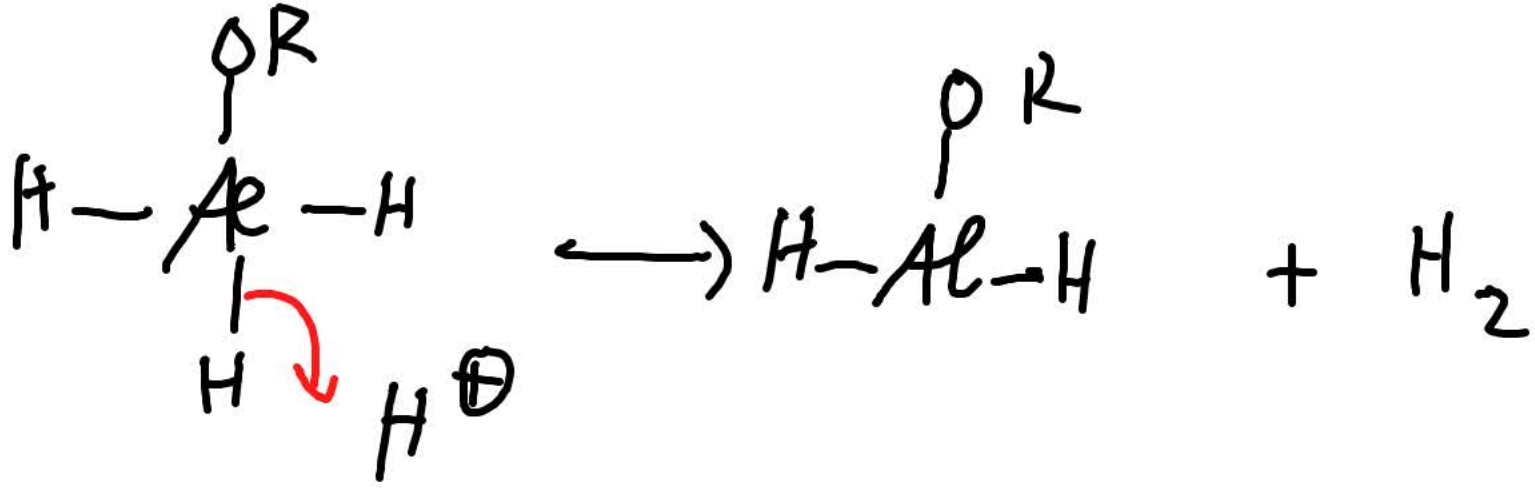

$\pi^*_{C=O}$
sp²
109°
σ_{B-H}
angle de Bürgi-Dunitz

Réduction avec $LiAlH_4$ (dans des solvants not protiques : THF, Et_2O)

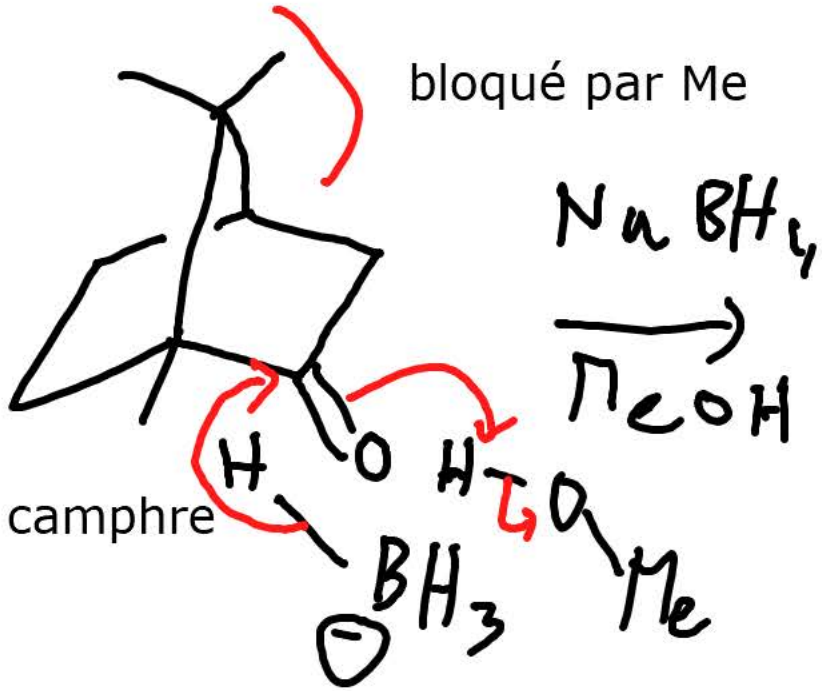


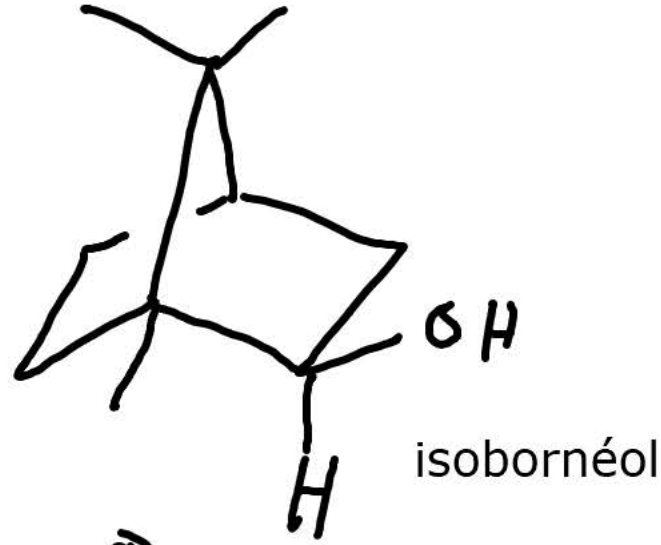
Reduction avec LiAlH4



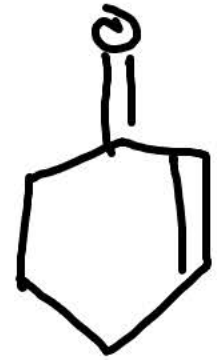


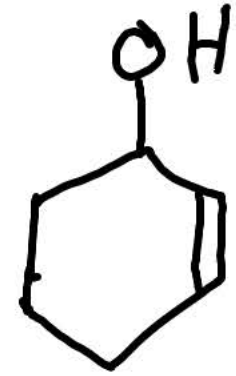
exemples des TP de chimie

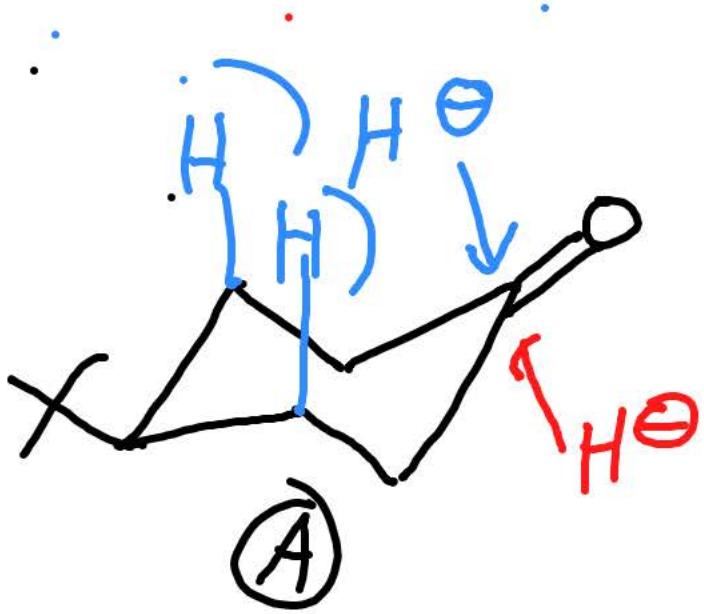




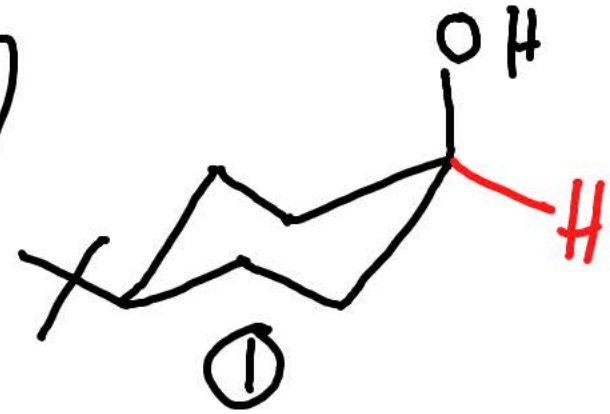
isobornéol

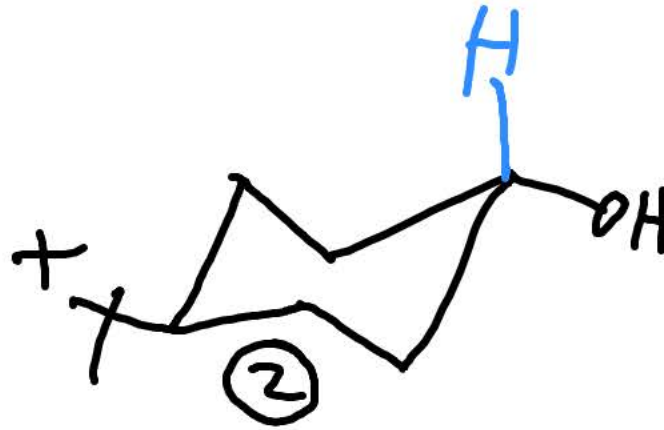






$[H^{\ominus}]$

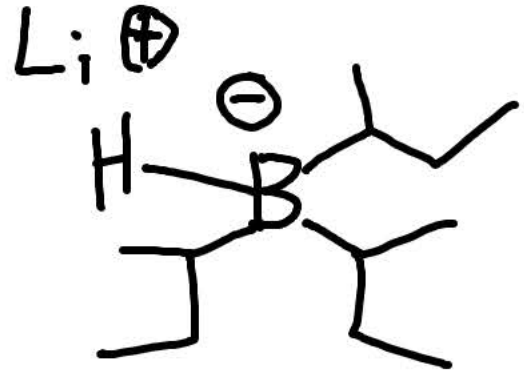




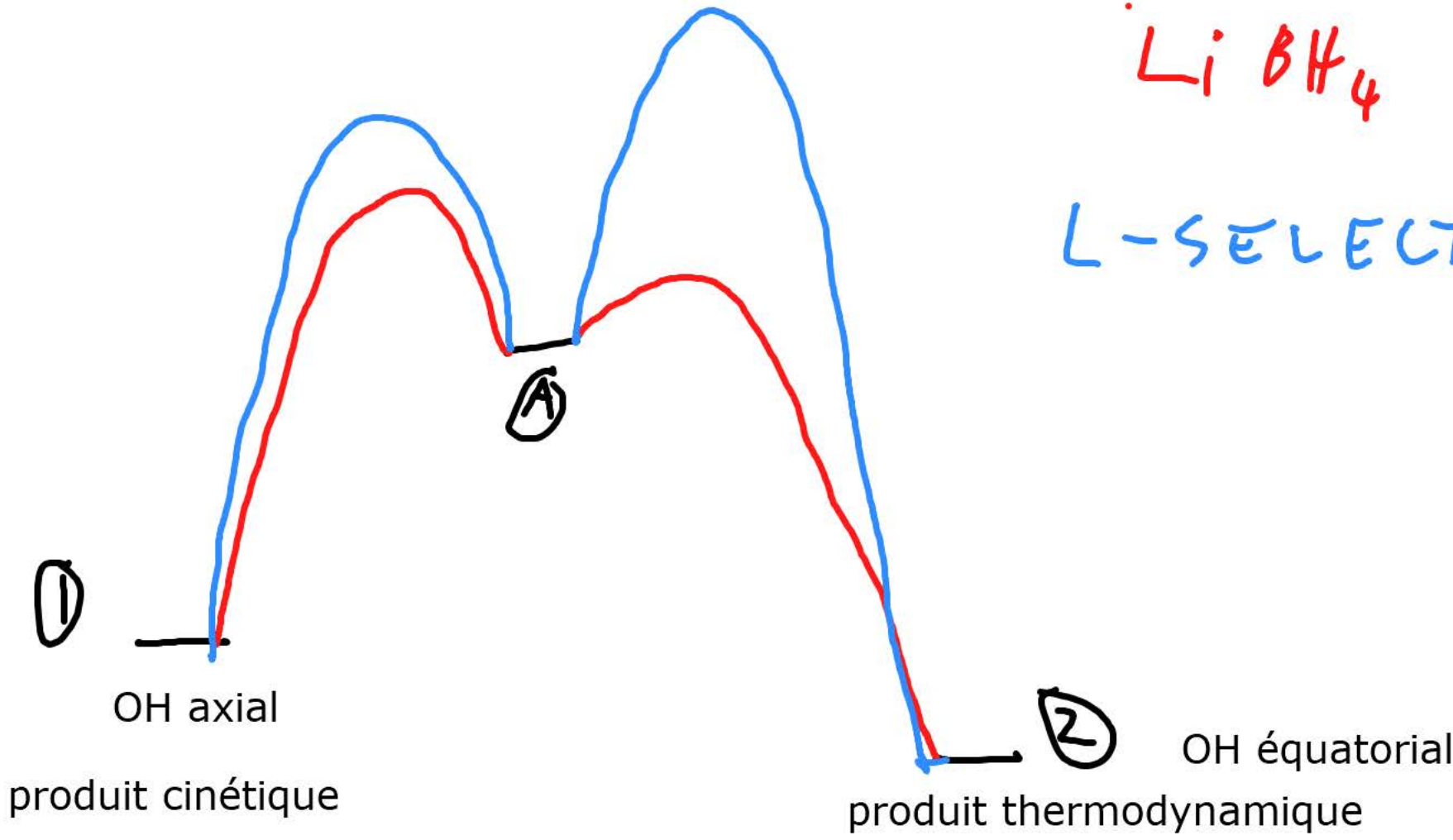
plust stable
car OH équatorial

$[H^{-}] =$ LiBH4: 9:91

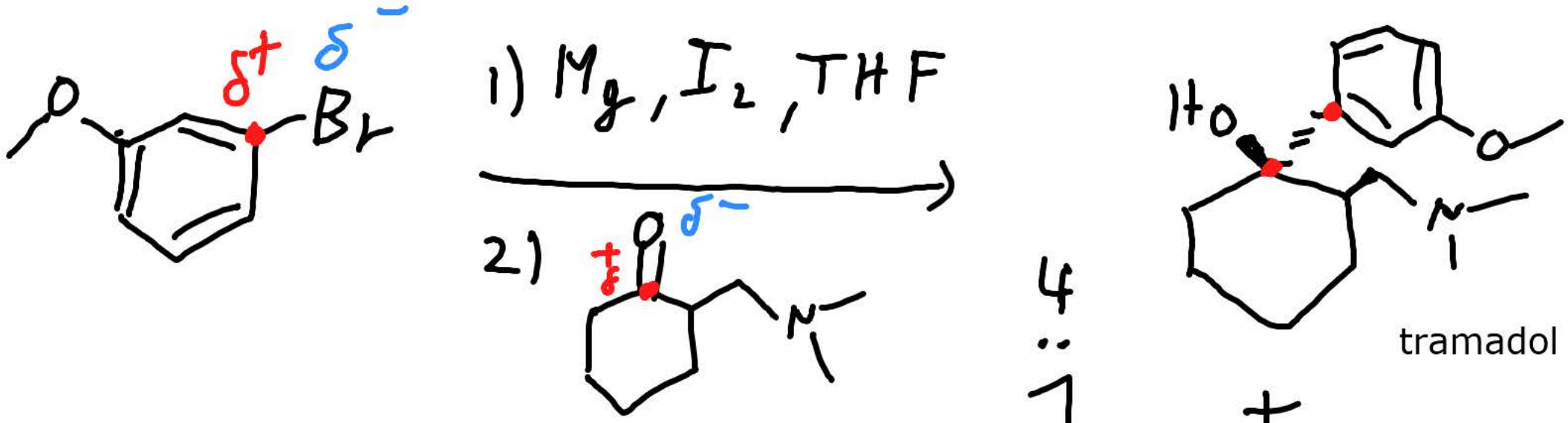
L-Selectride: 86:14



gros réactif, plus difficile
d'attaquer "du haut"

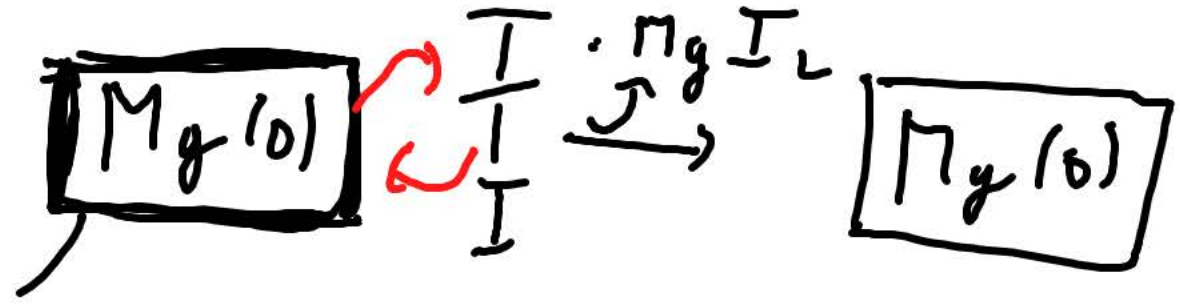

Li BH4
L-SELECTRIDE
1
A
2
OH axial
produit cinétique
OH équatorial
produit thermodynamique

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



mélange de diastéréoisomères,
racémique

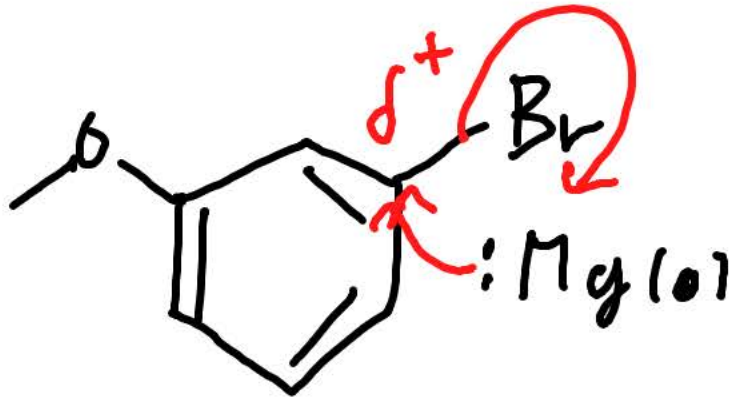
Mg est capable de faire une
"Umpolung" de l'électrophile!



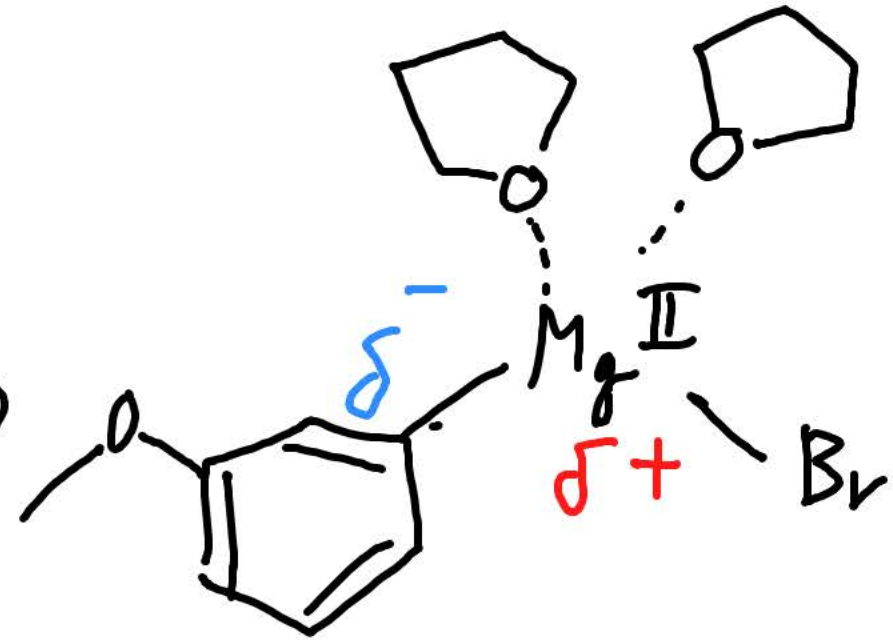
activé

solvant stabilise et rend soluble

couche inerte

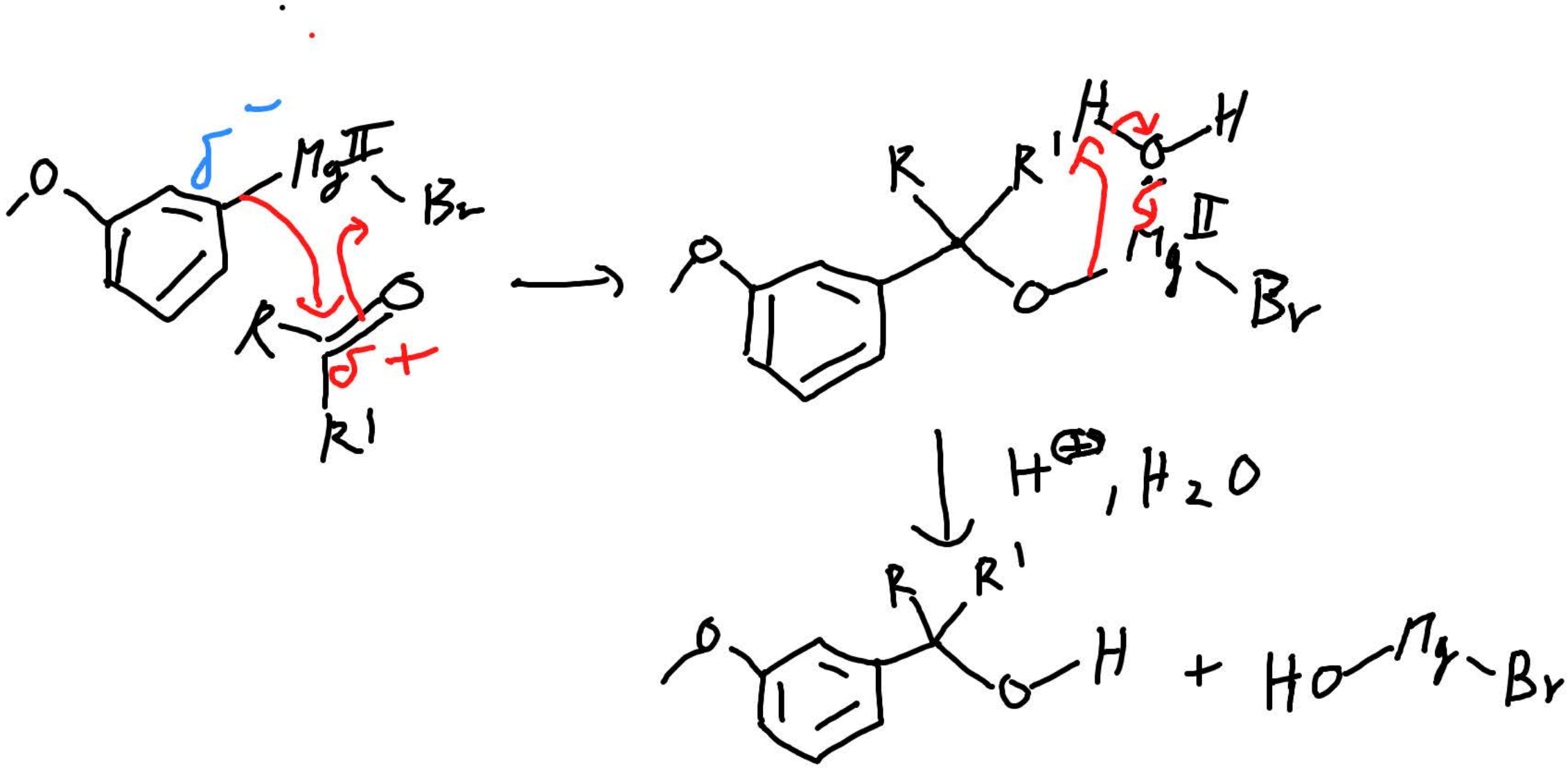


THF

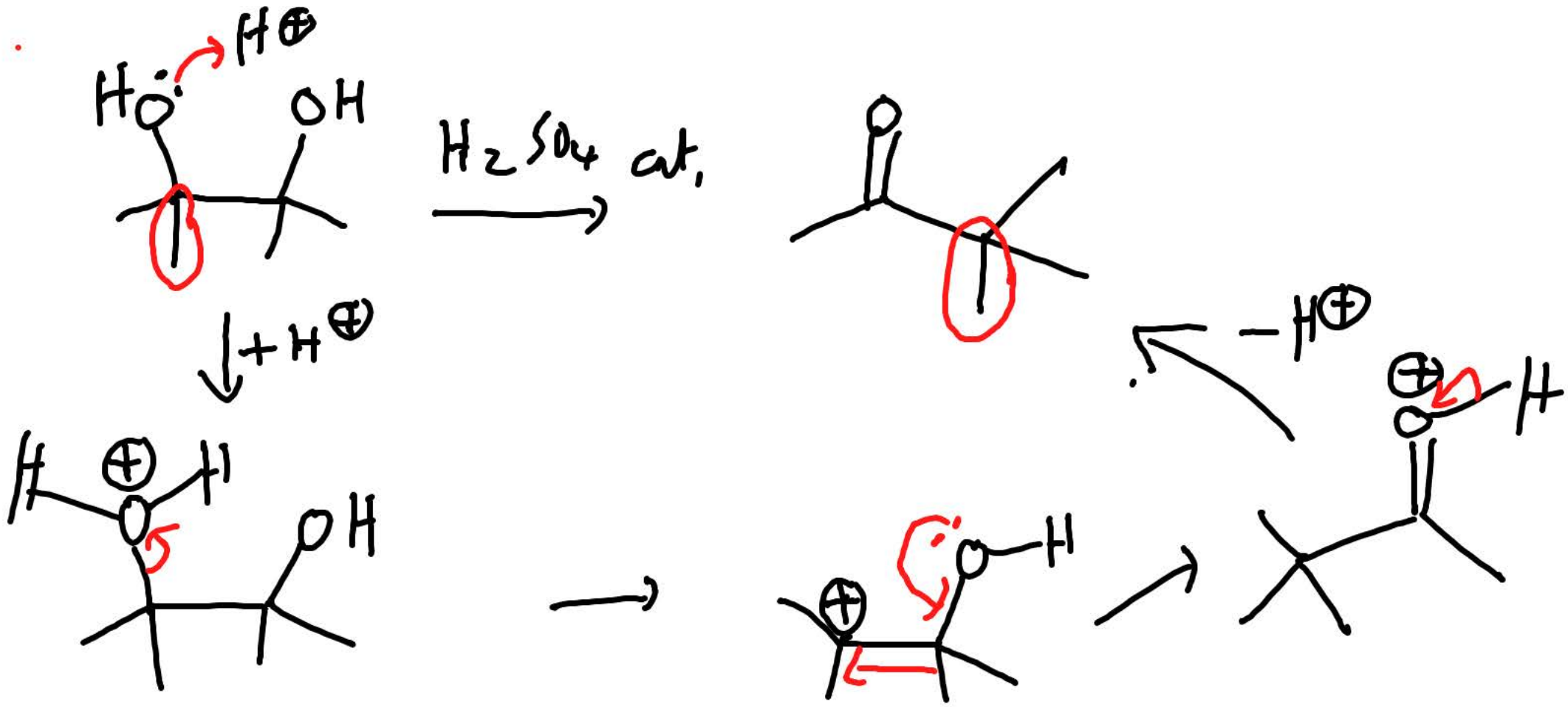


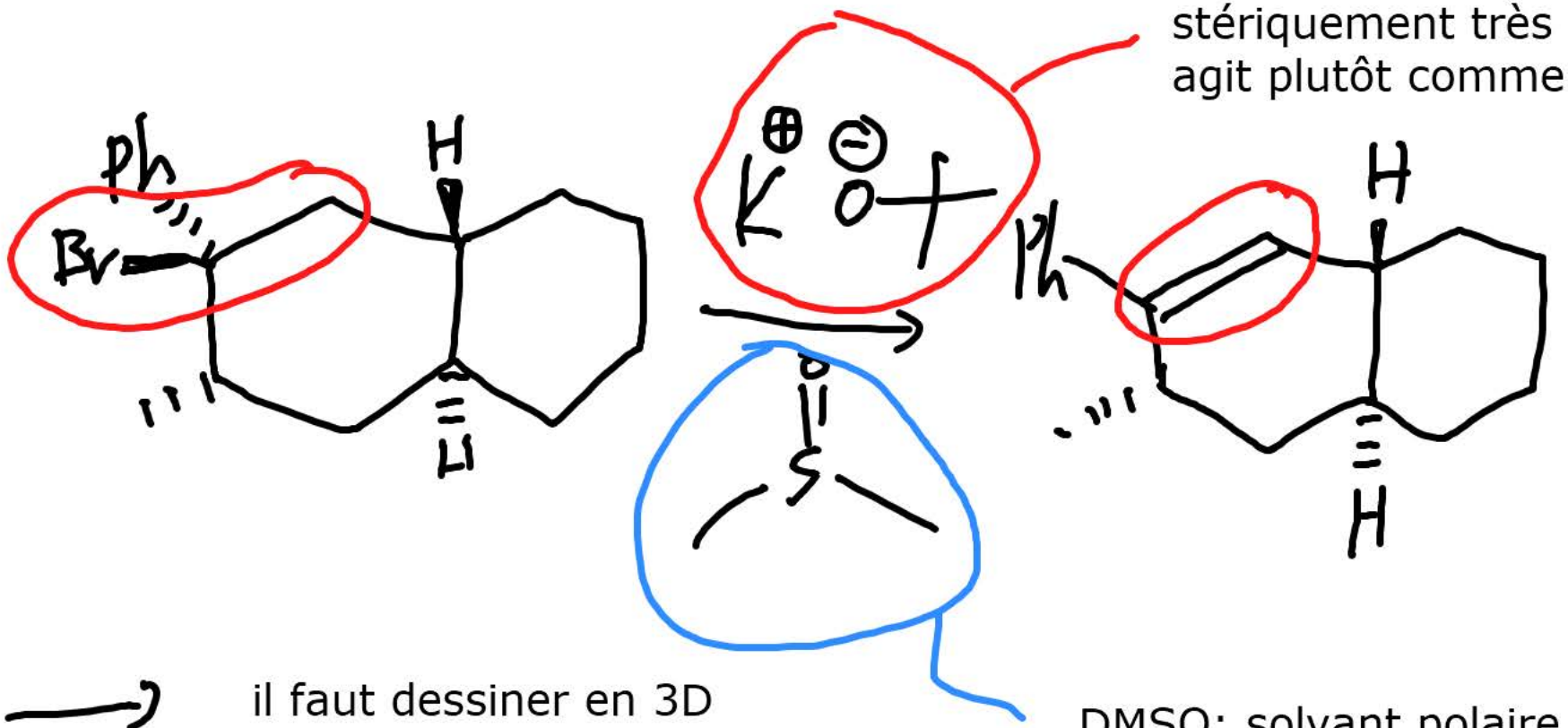
électrophile

nucléophile


δ⁻
MgII
Br
O
R
R1
δ+
H
O
H
R
R1
O
MgII
Br
H⊕, H2O
R
R1
O
H
+
HO
Mg
Br

activation des alcools avec l'acide: réaction de pinacol



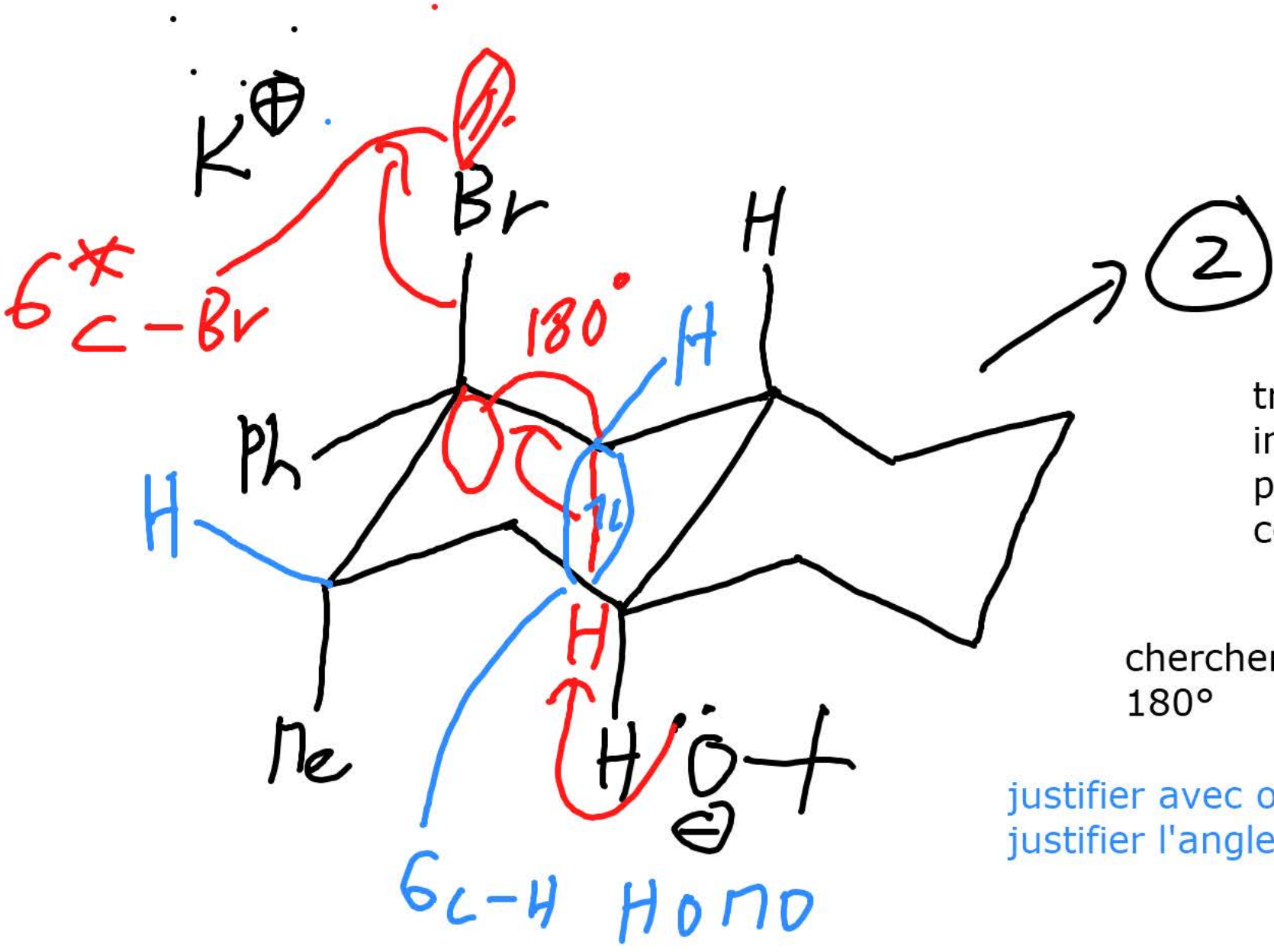


Fort nucléophile ou base, stériquement très encombré: agit plutôt comme base

élimination!
E1 et E2 sont possibles,
DMSO: plutôt E2,
un proton à 180° est nécessaire!

→ il faut dessiner en 3D cyclohexane = chaise

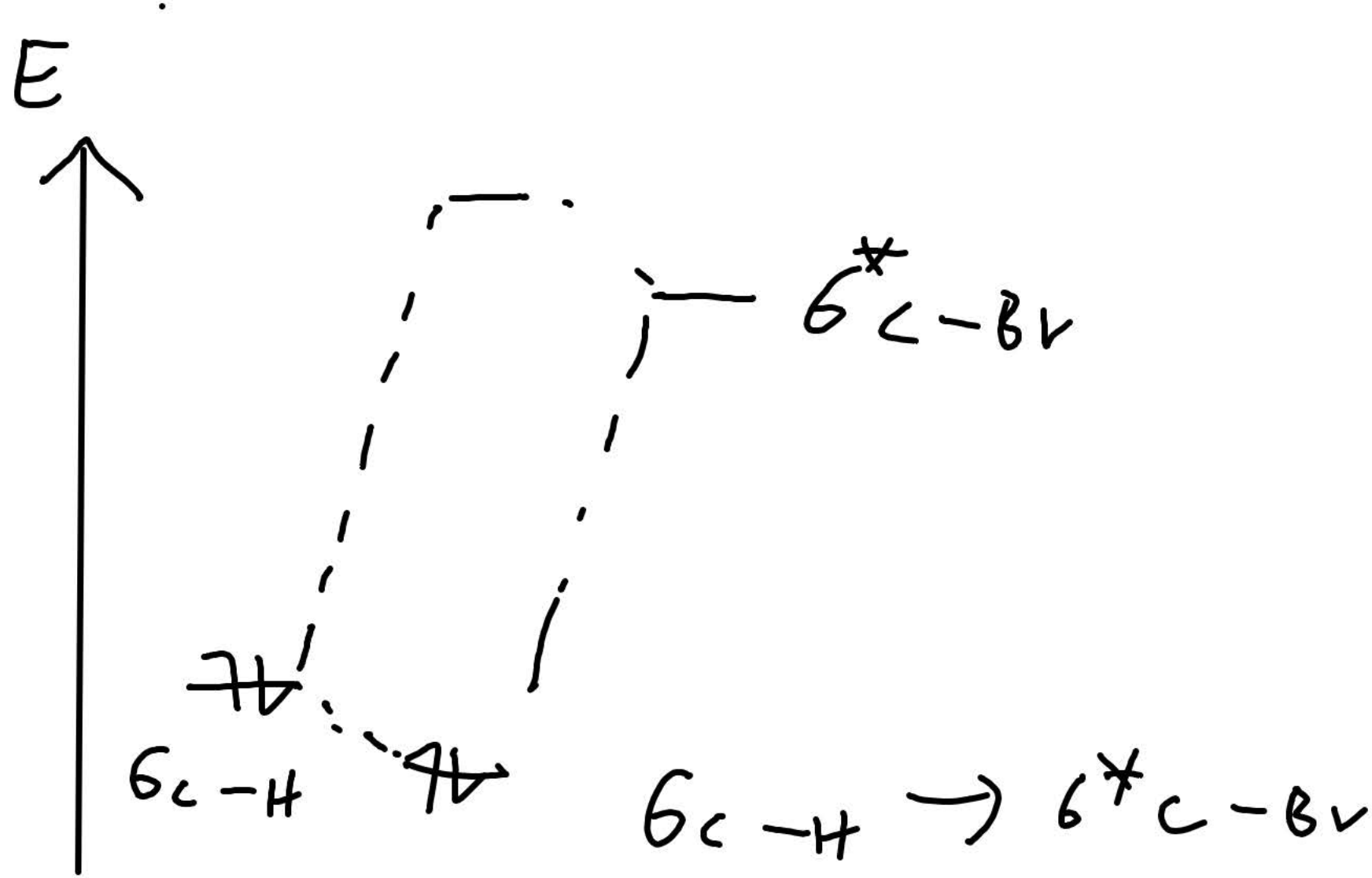
DMSO: solvant polaire aprotique: plutôt E2, SN2, etc...

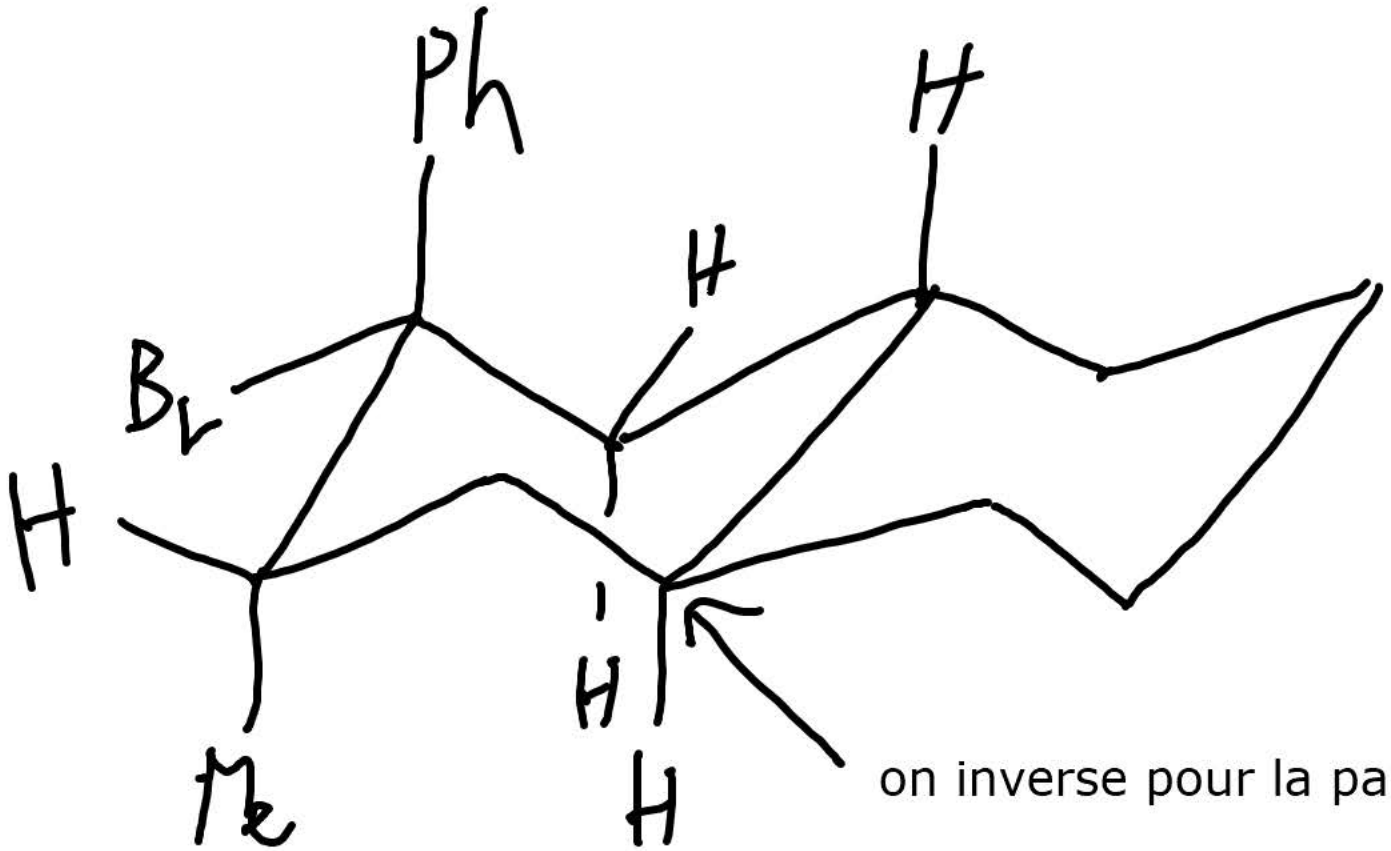


trans-décaline
inversion de la chaise pas possible, une seul conformation!

chercher les H voisin de Br à 180°

justifier avec orbitales? =
justifier l'angle à 180°


E
σ*C-Br
σC-H
σC-H → σ*C-Br



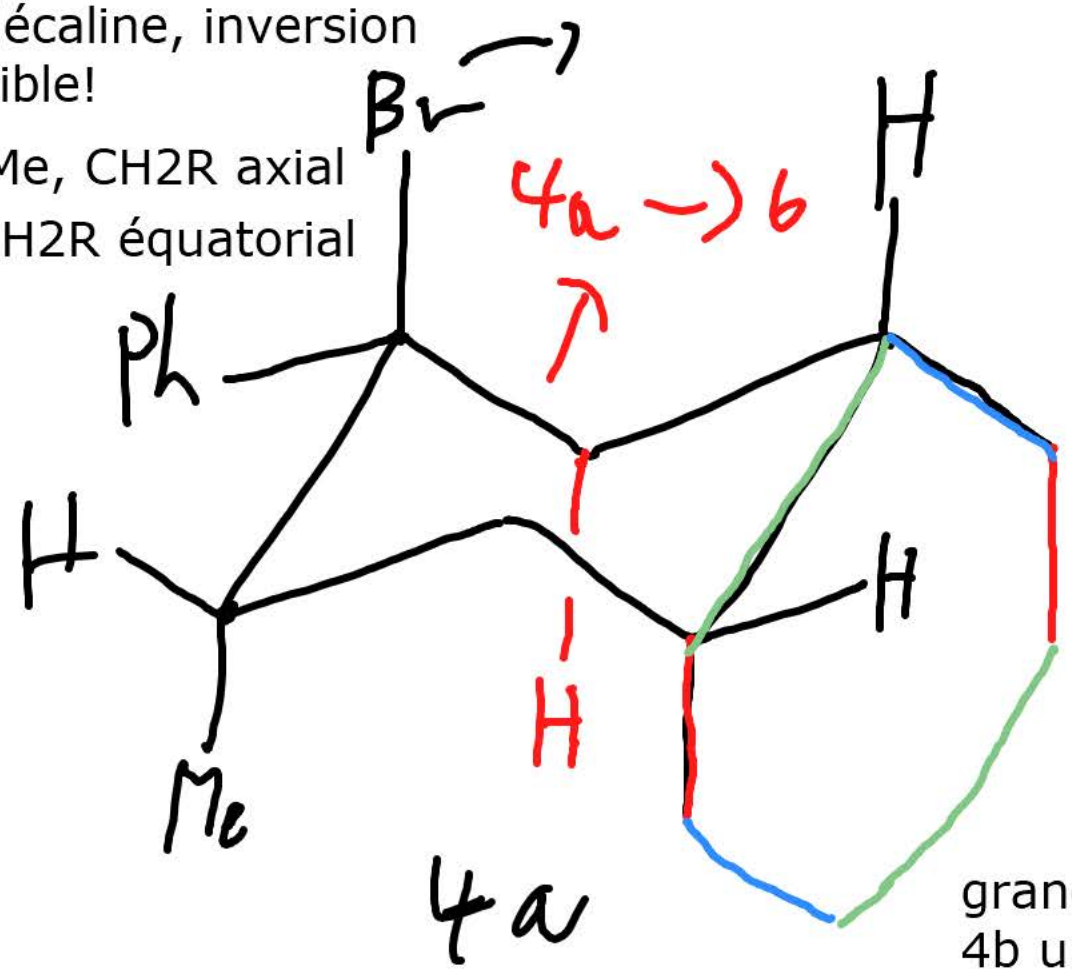
Aucun H à 180°!
Ne réagit pas.

on inverse pour la partie B!

cis-décaline, inversion possible!

Br, Me, CH2R axial

Ph, CH2R équatorial

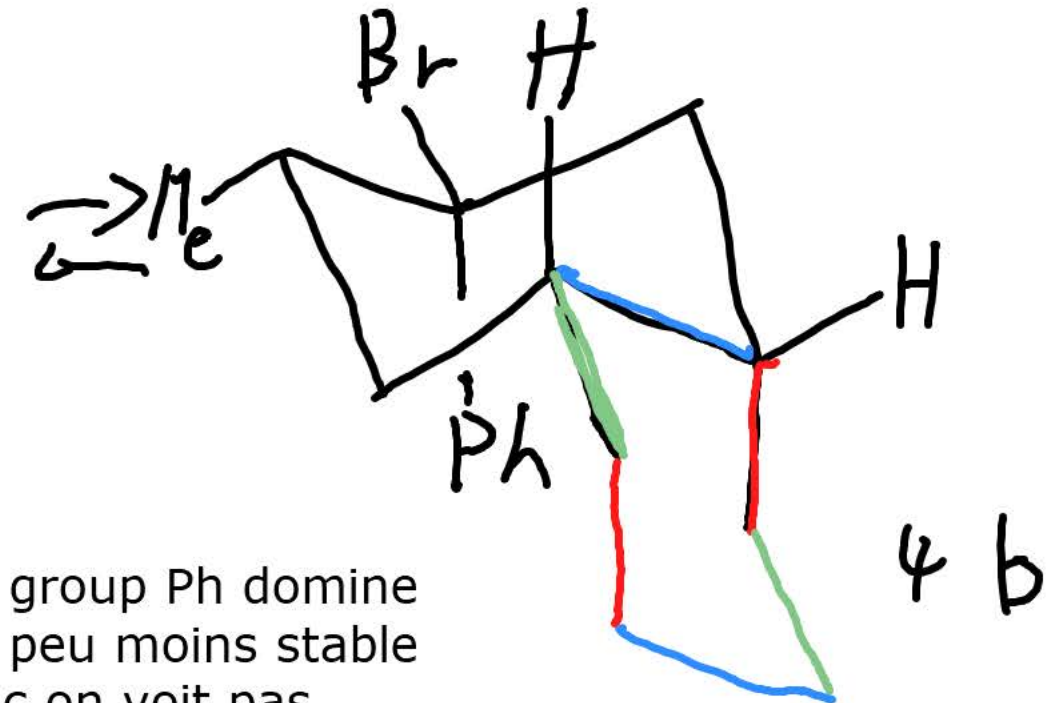


4a

chaise vu de côté et visible

Ph, CH2R axial

Me, Br, CH2R équatorial

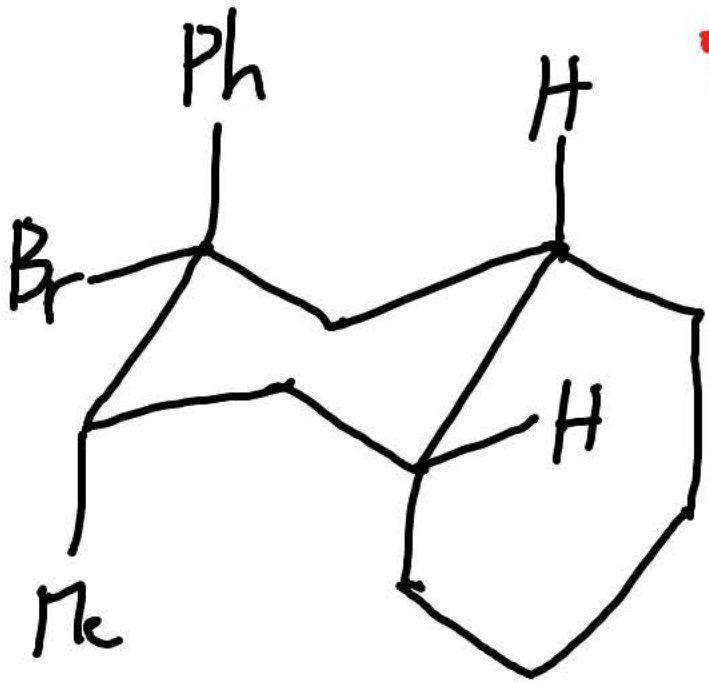


4 b

grand group Ph domine

4b un peu moins stable

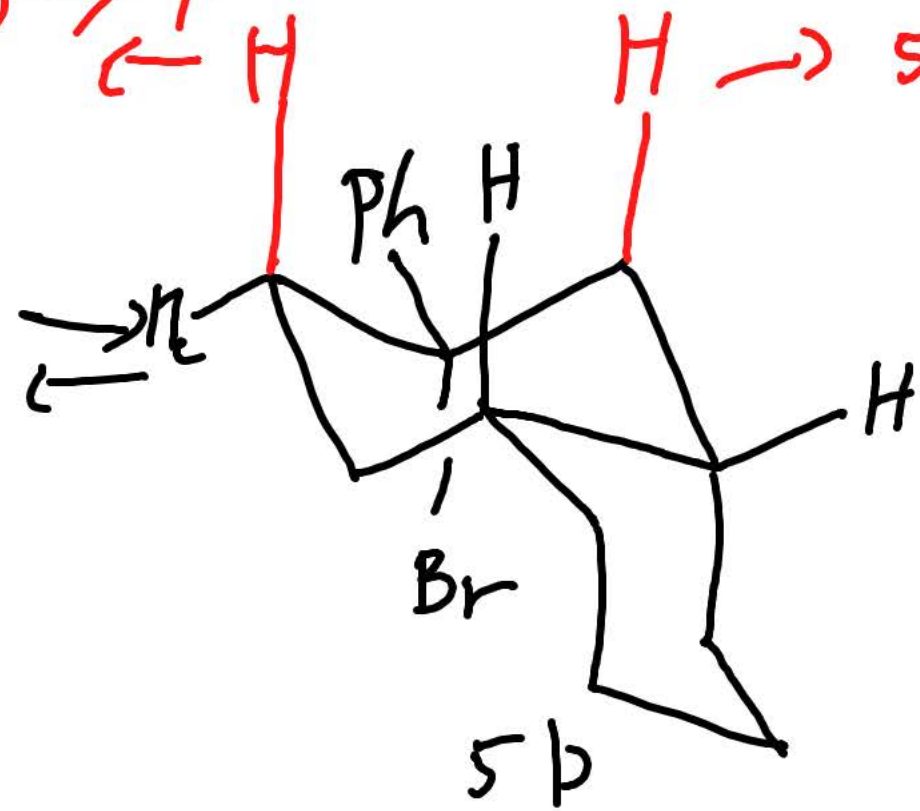
second chaise: apparaitre vue de face, donc on voit pas la structure en chaise!



5a

Ph, CH2R, Me axial
Br, CH2R équatorial

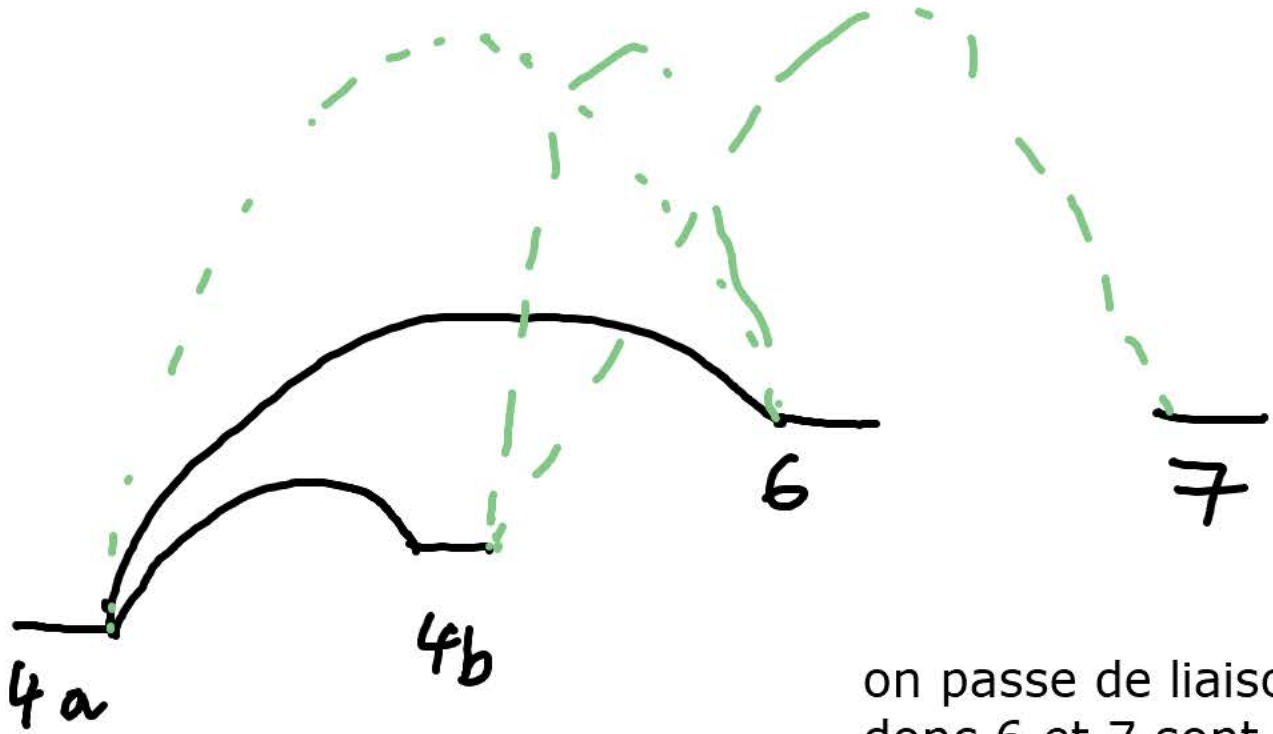
5b → 7



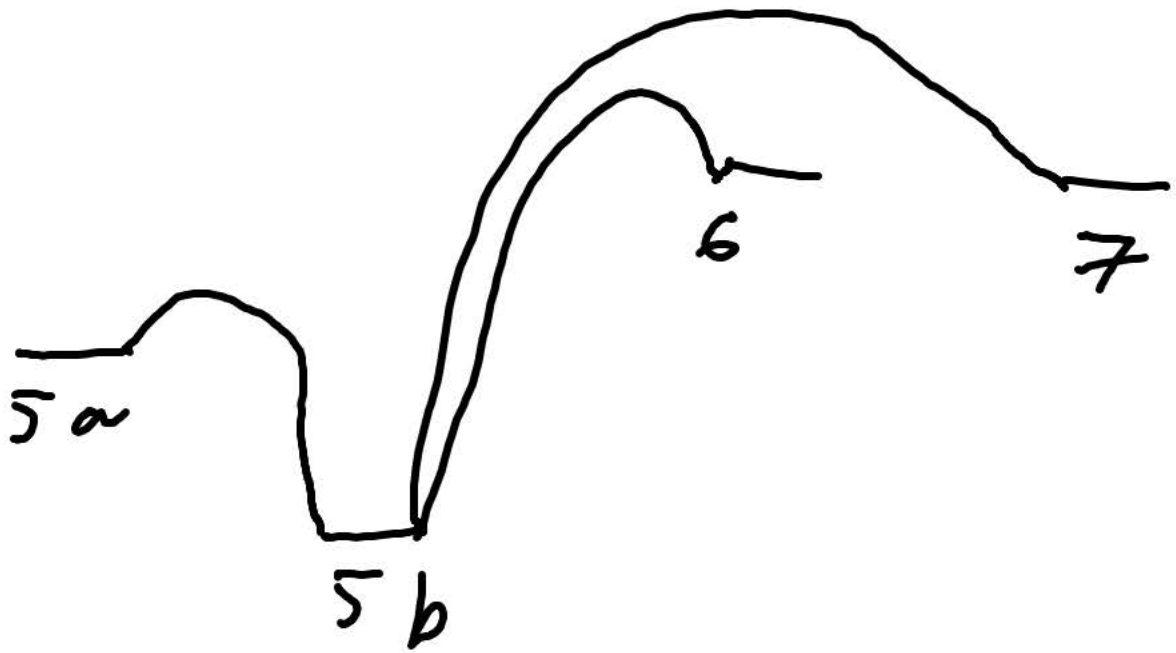
5b

Br, CH2R axial
Me, Ph, CH2R équatorial

5b est clairement plus stable

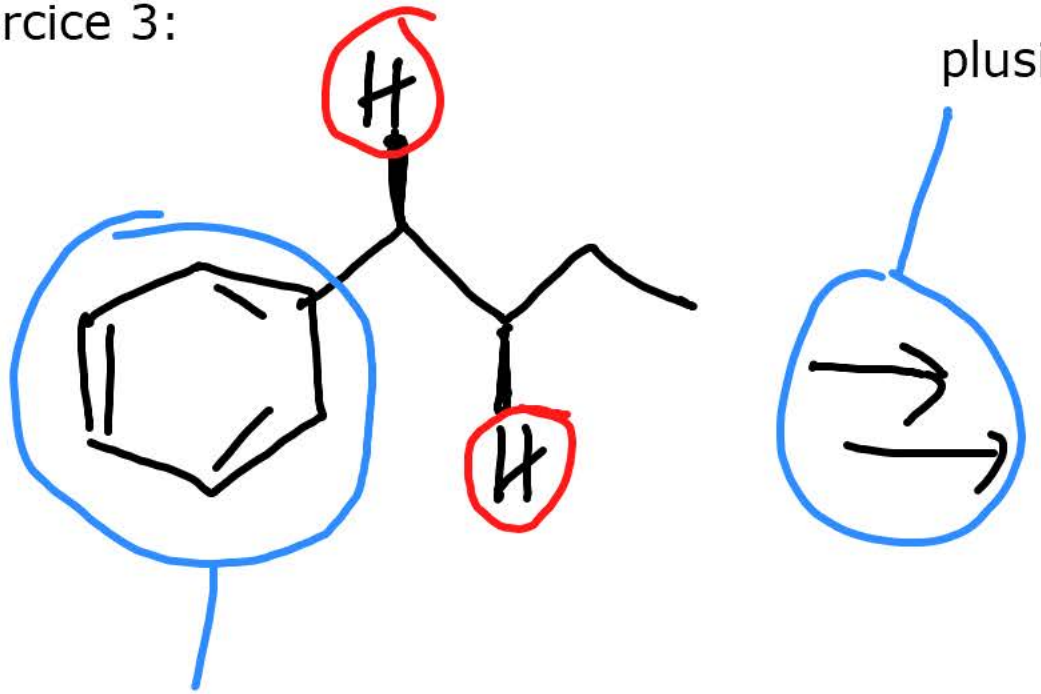


on passe de liaison sigma à pi,
donc 6 et 7 sont moins stables
La réaction globale est
favorisée par la transformation
de KOtBu and KBr et HOtBu


5a
5b
6
7

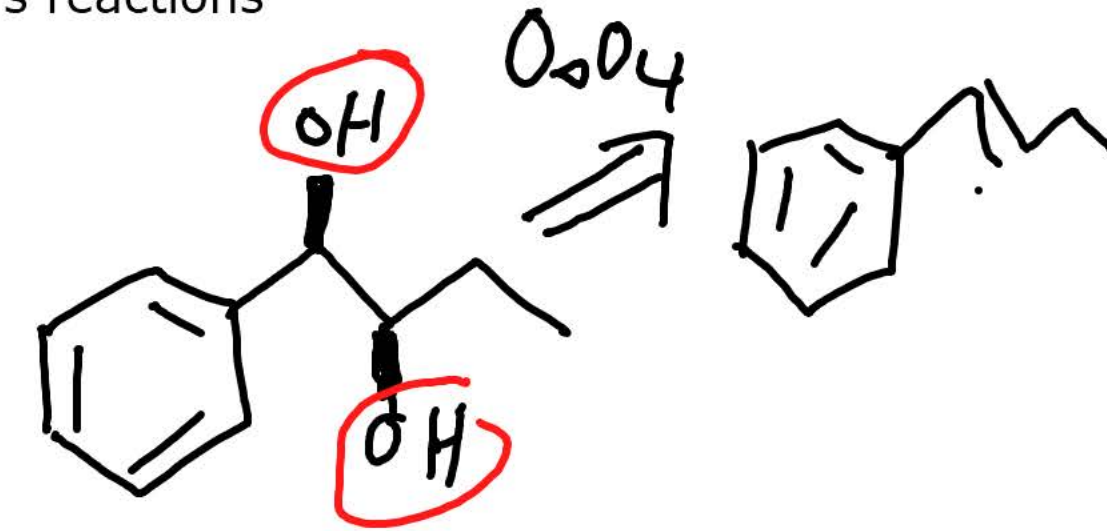
C-H = réactions radicalaires

exercice 3:



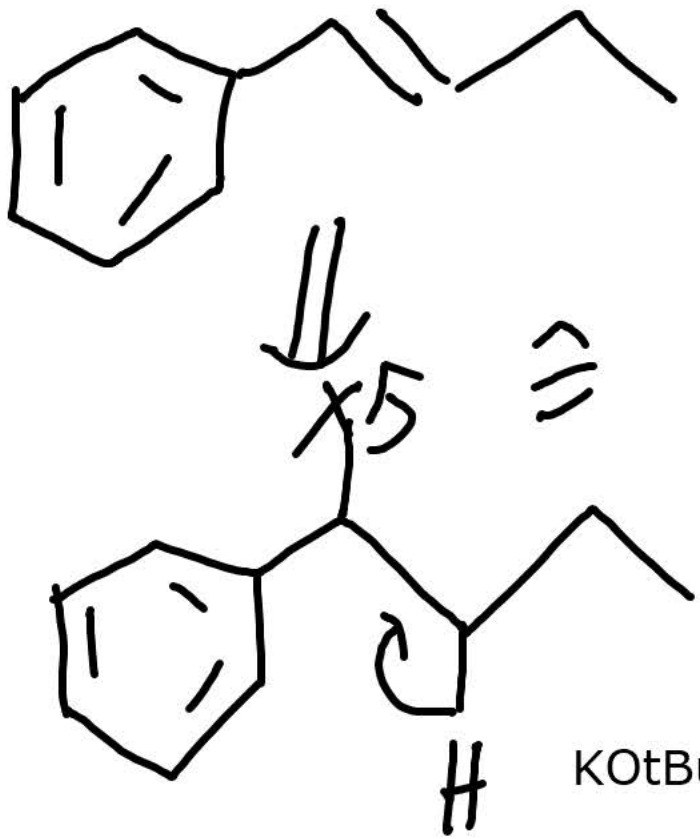
à côté d'un benzène:
stabilisation par résonance
probablement importante

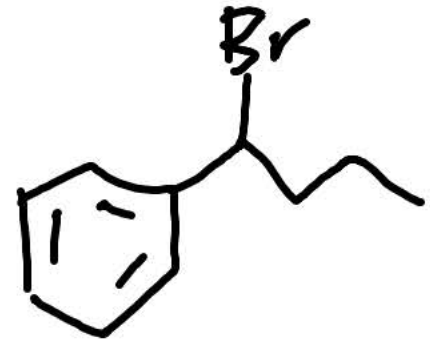
plusieurs réactions



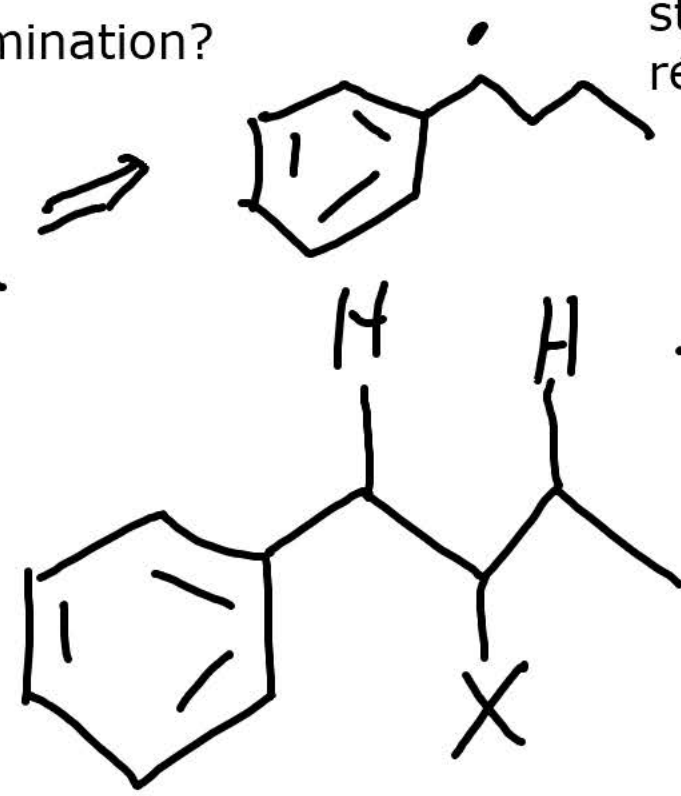
comment obtenir 2 alcools,
syn (= du même côté)
= dihydroxylation des alcènes!

...





alcène = èlimination?



stabilisé par résonance!

(Br2, irradiation)

ou

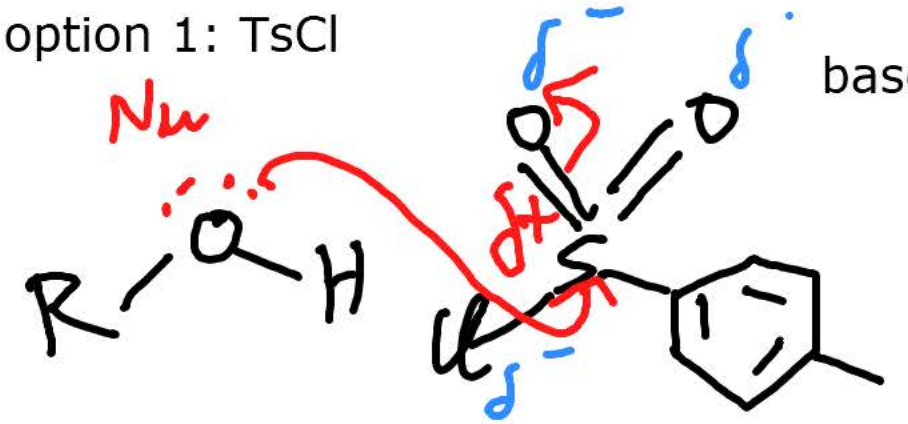
KOtBu, DMSO

Bonne idée

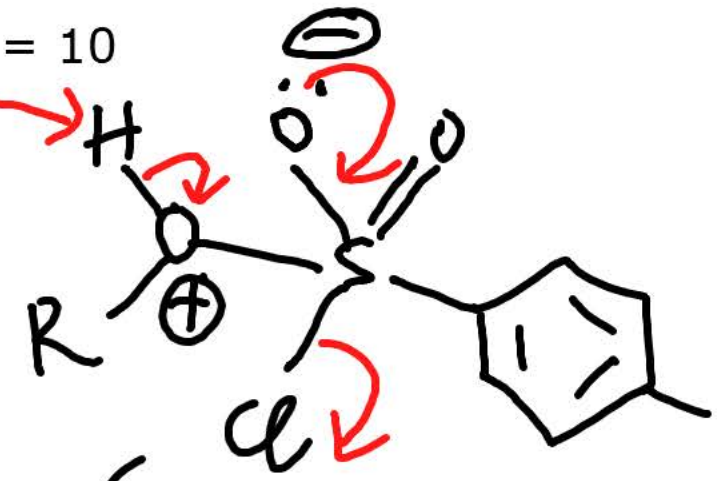
pas bien, peut donner un mélange

réaction directe avec les alcools: nécessite un acide fort (car OH- est un mauvais groupe partant): mélange E1, SN1, E2, SN2, réarrangement)
Solution: introduire un bon groupe partant pour une "activation douce" pour E2 ou Sn2

option 1: TsCl

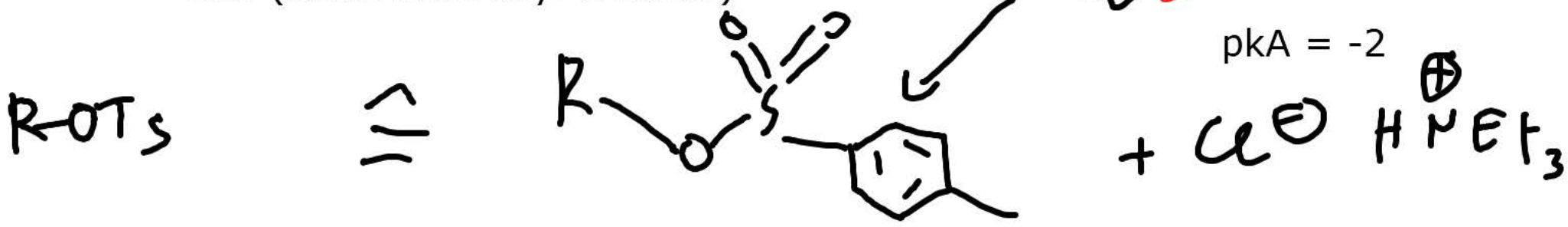


base faible: pkaH = 10

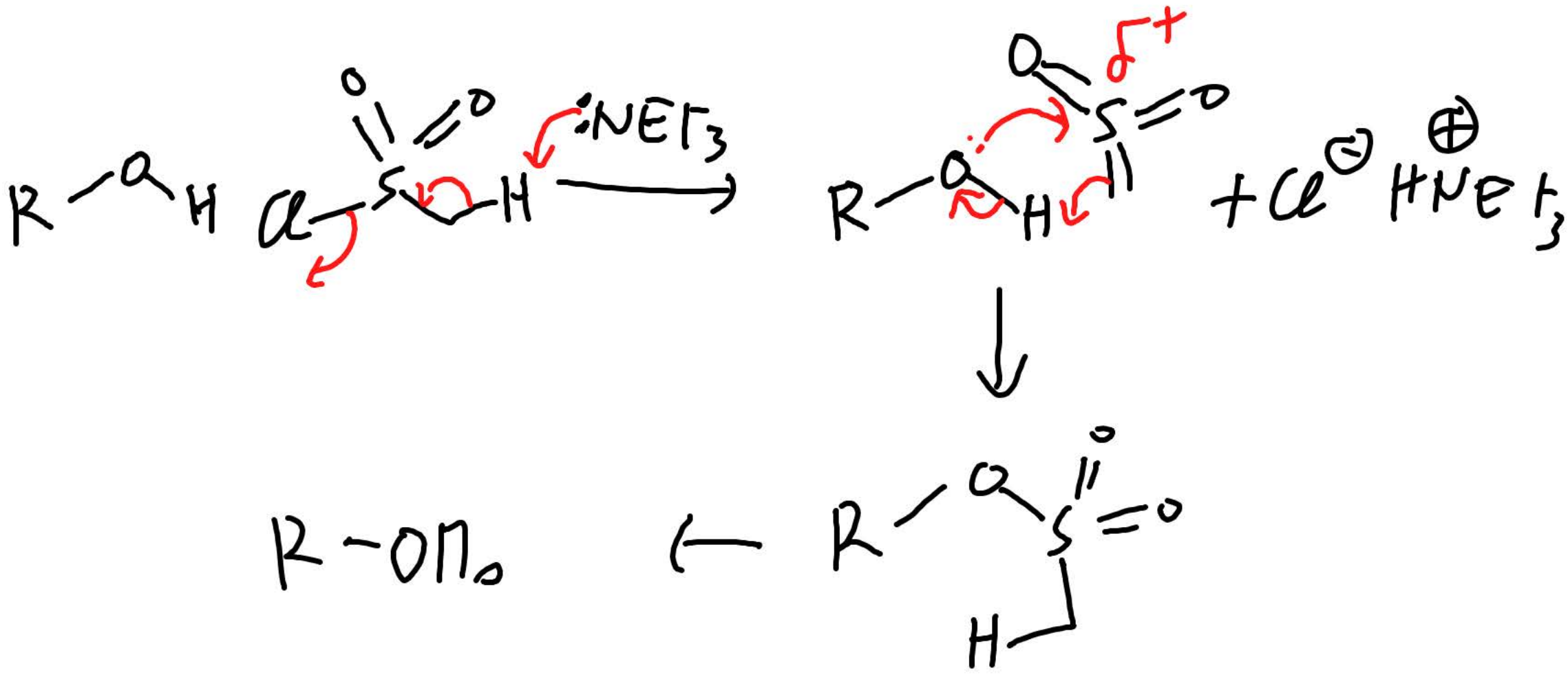


pkA = 16-17 TsCl (toluenesulfonyl chloride)

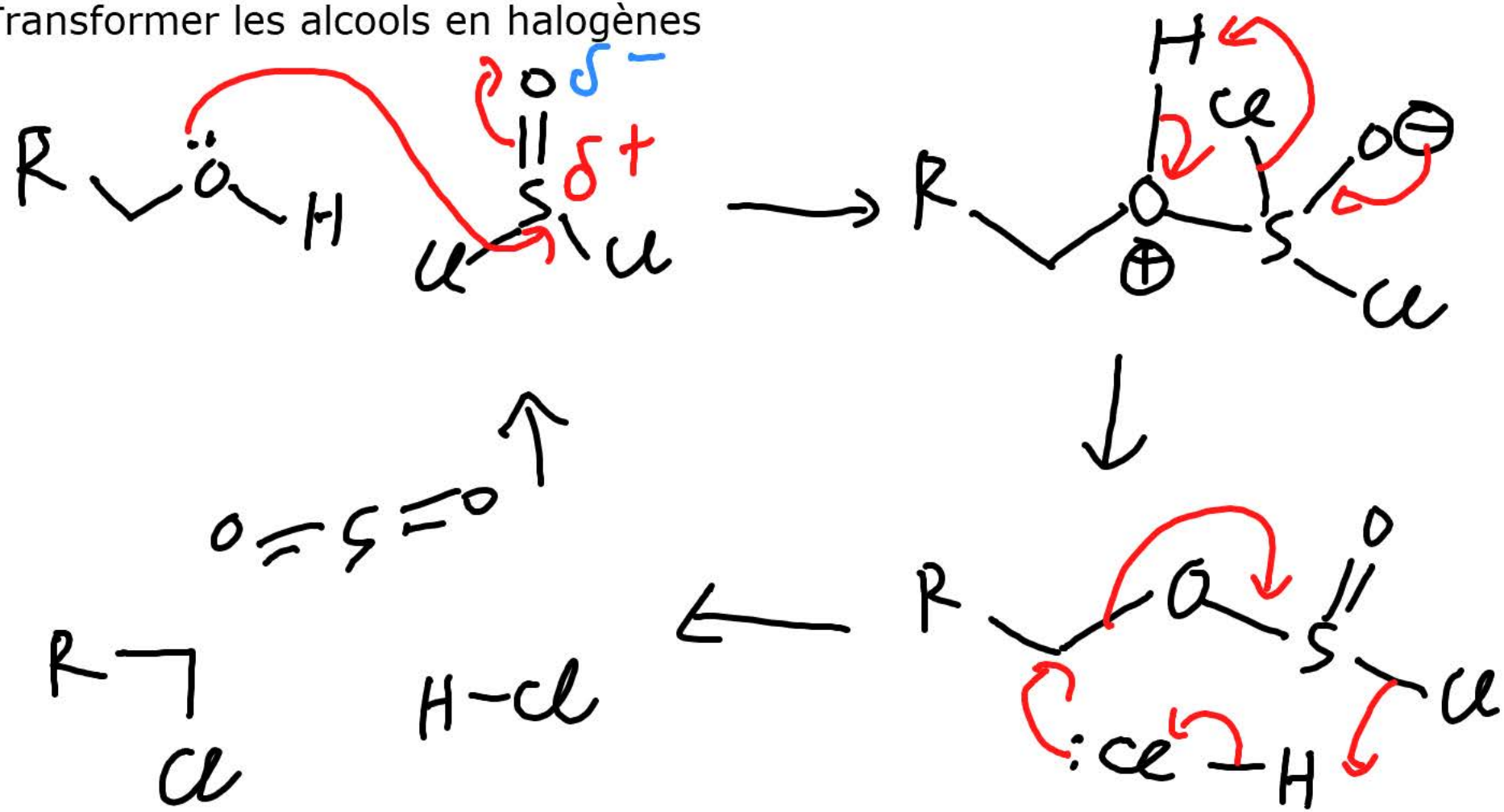
pkA = -2



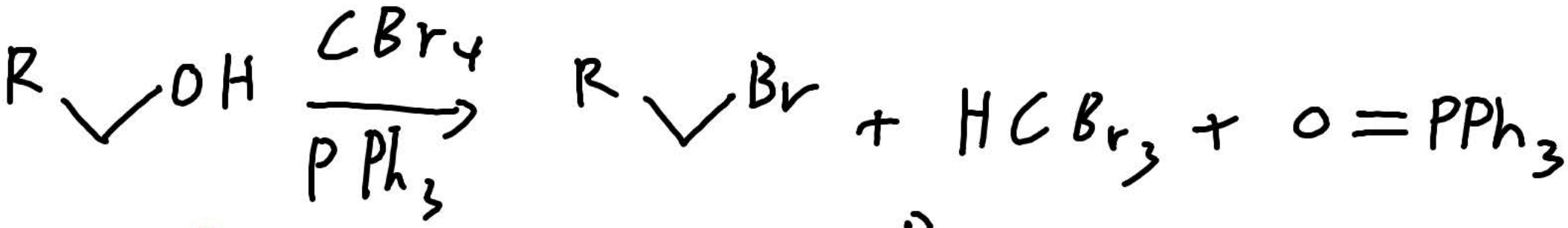
option 2: MsCl

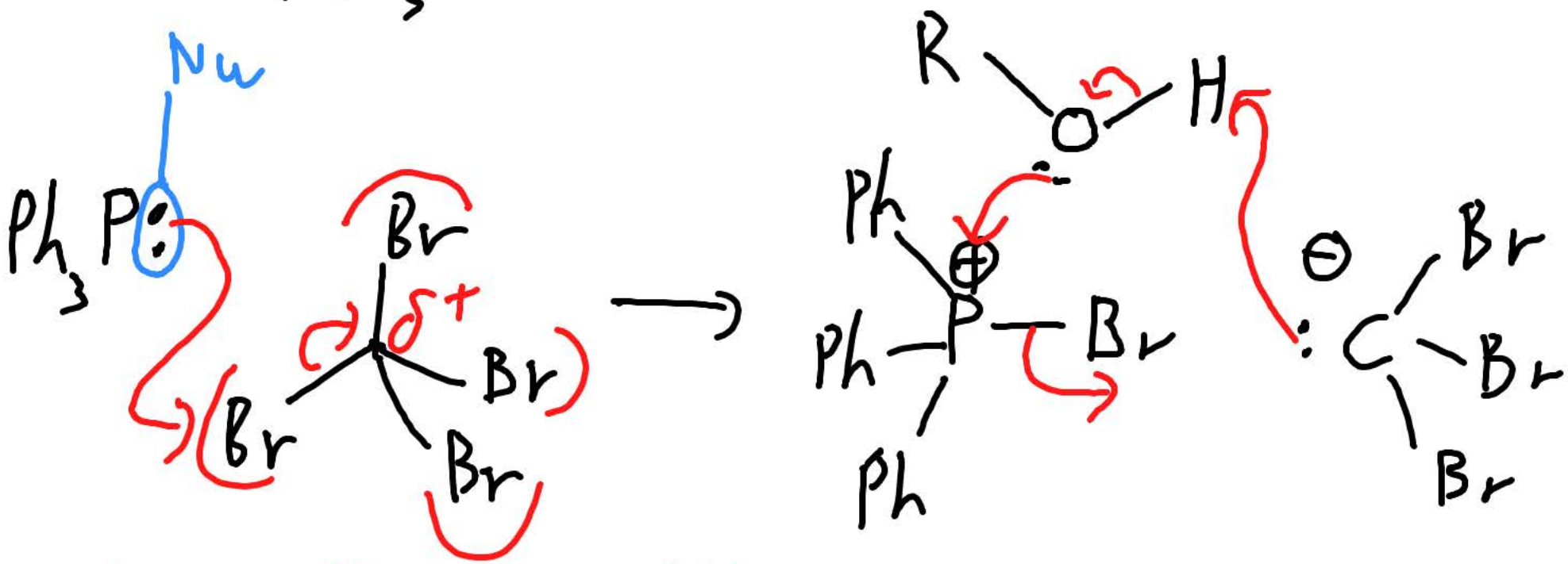


Transformer les alcools en halogènes

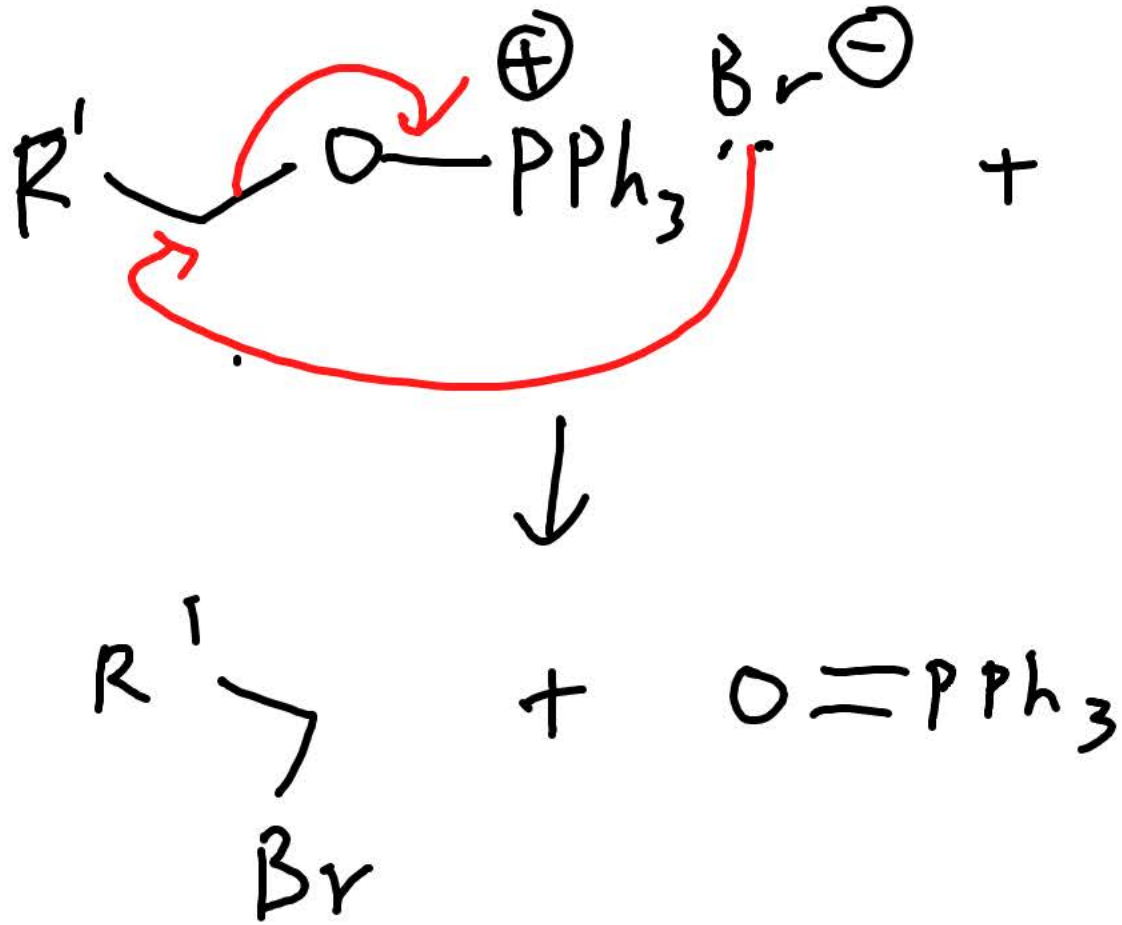


réaction d'Appel

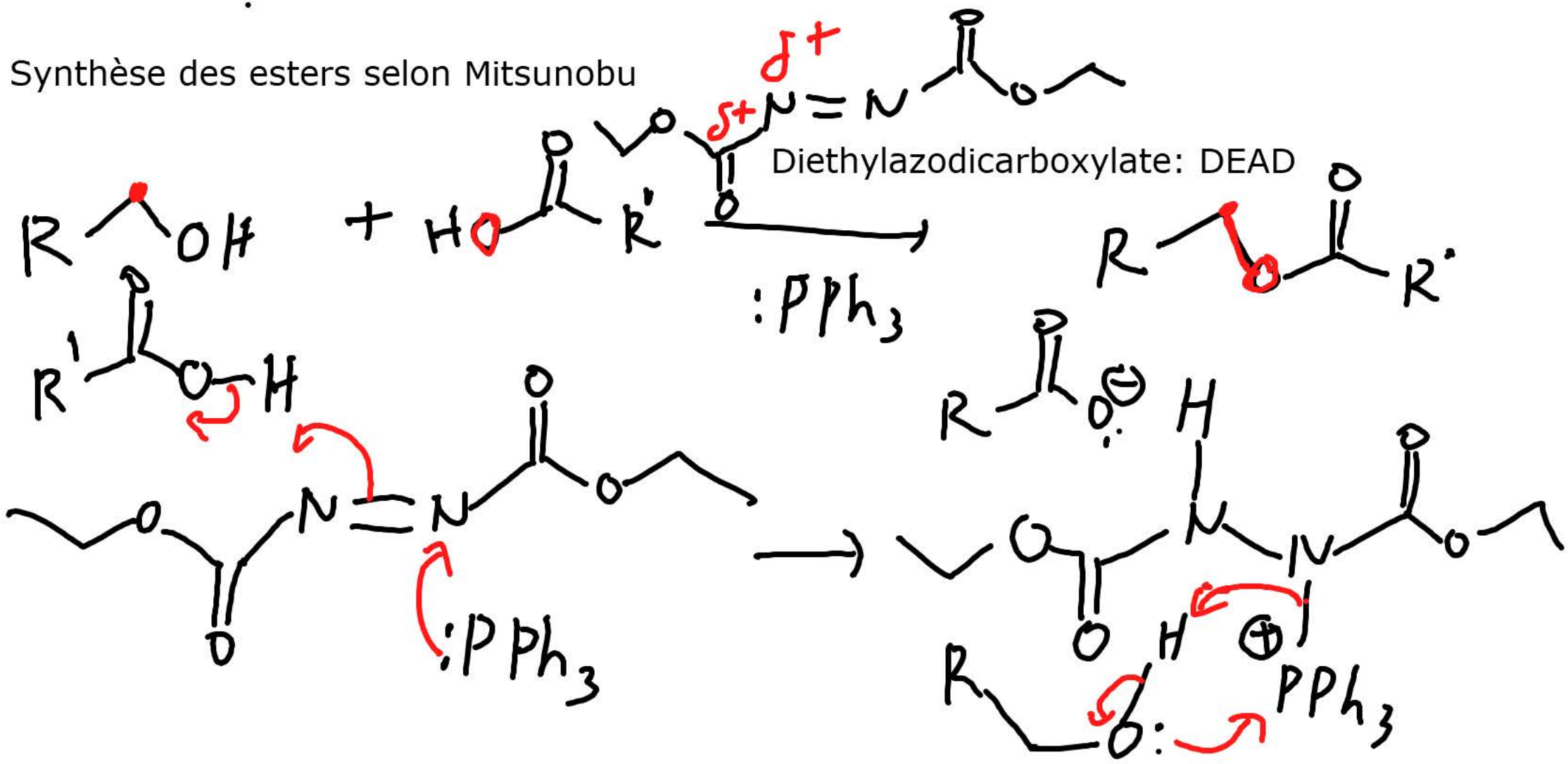


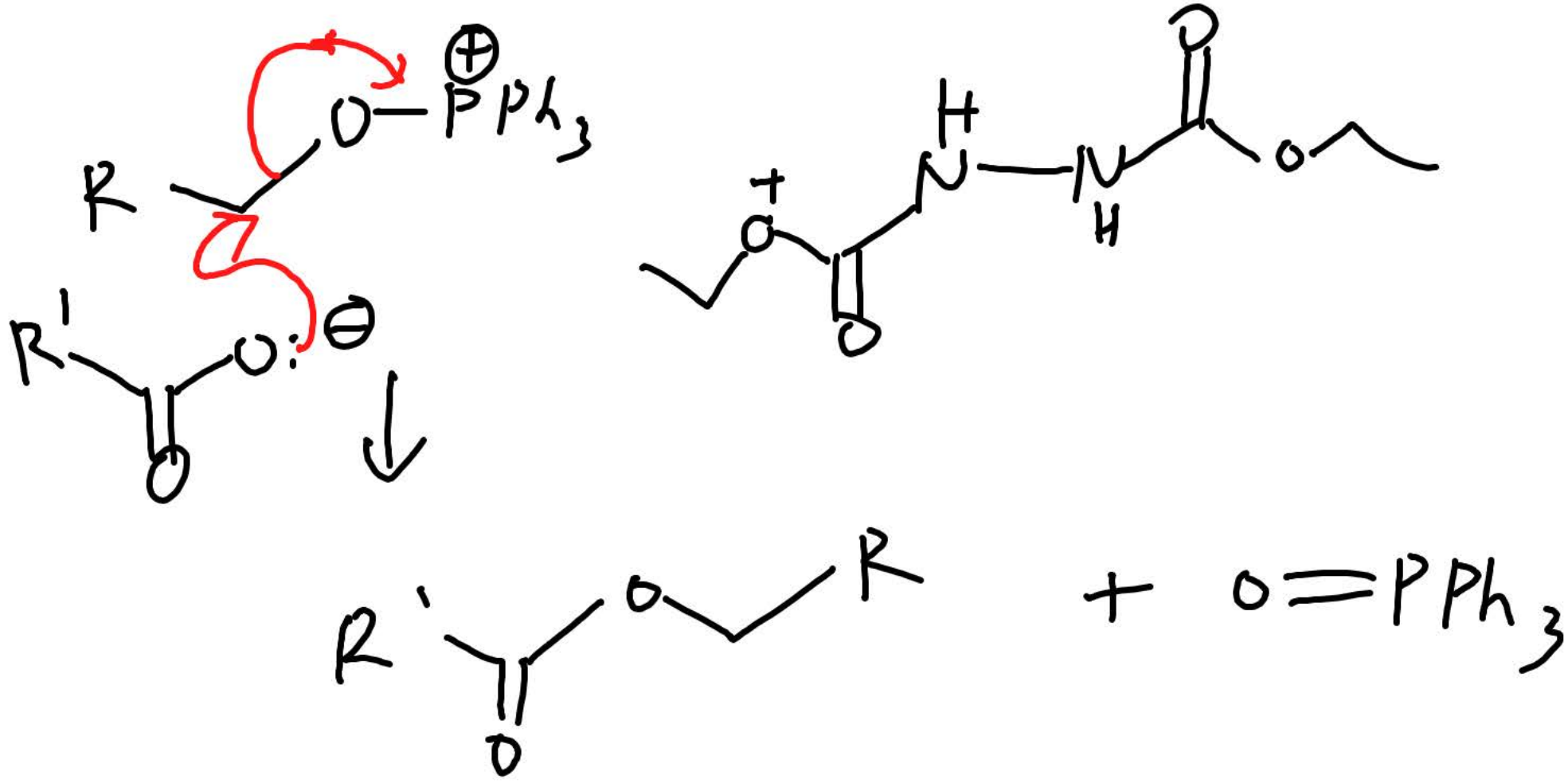


carbone complètement inaccessible!

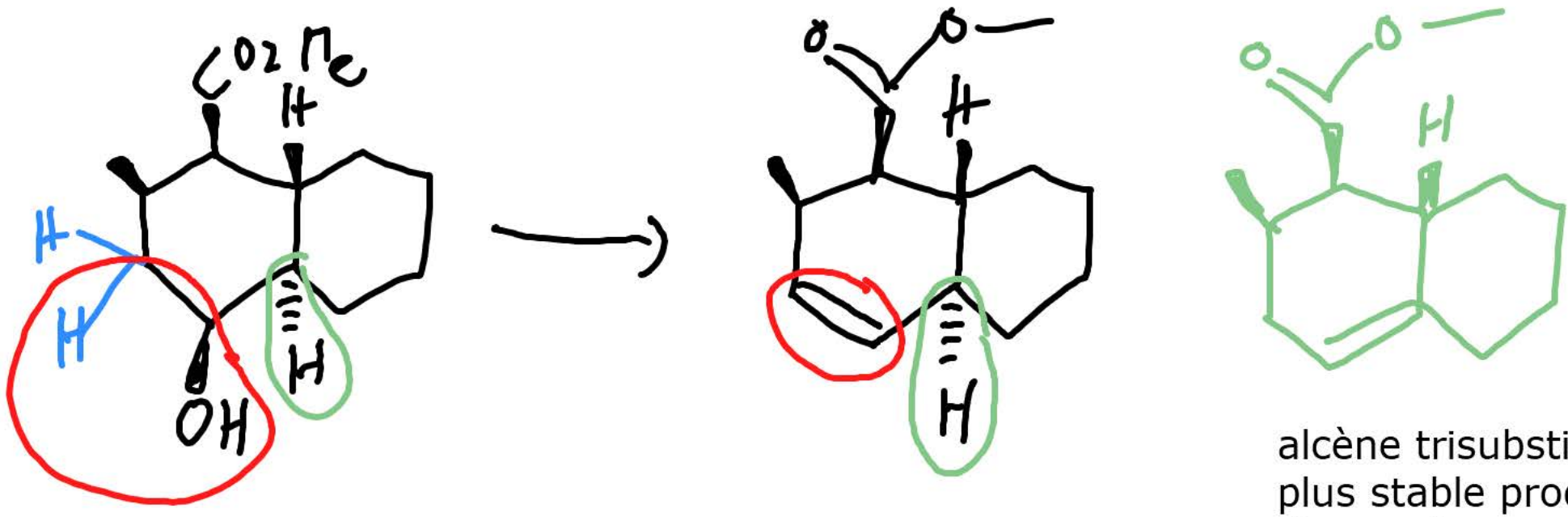

R'
O
PPh3
Br⊖
+ HCBr3
R'
Br
+ O=PPh3

Synthèse des esters selon Mitsunobu

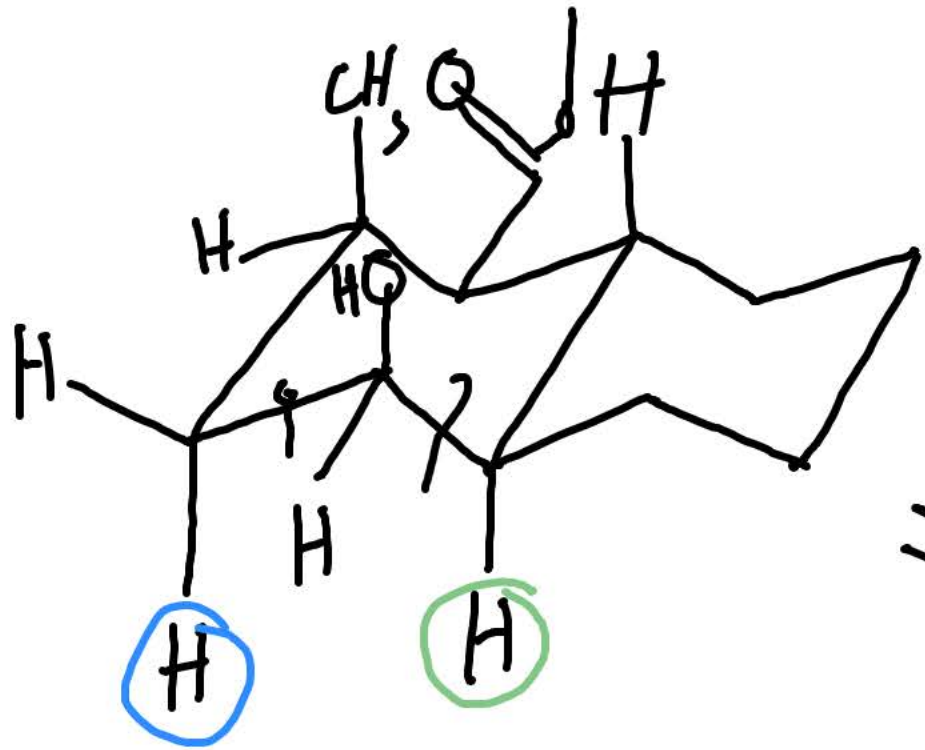




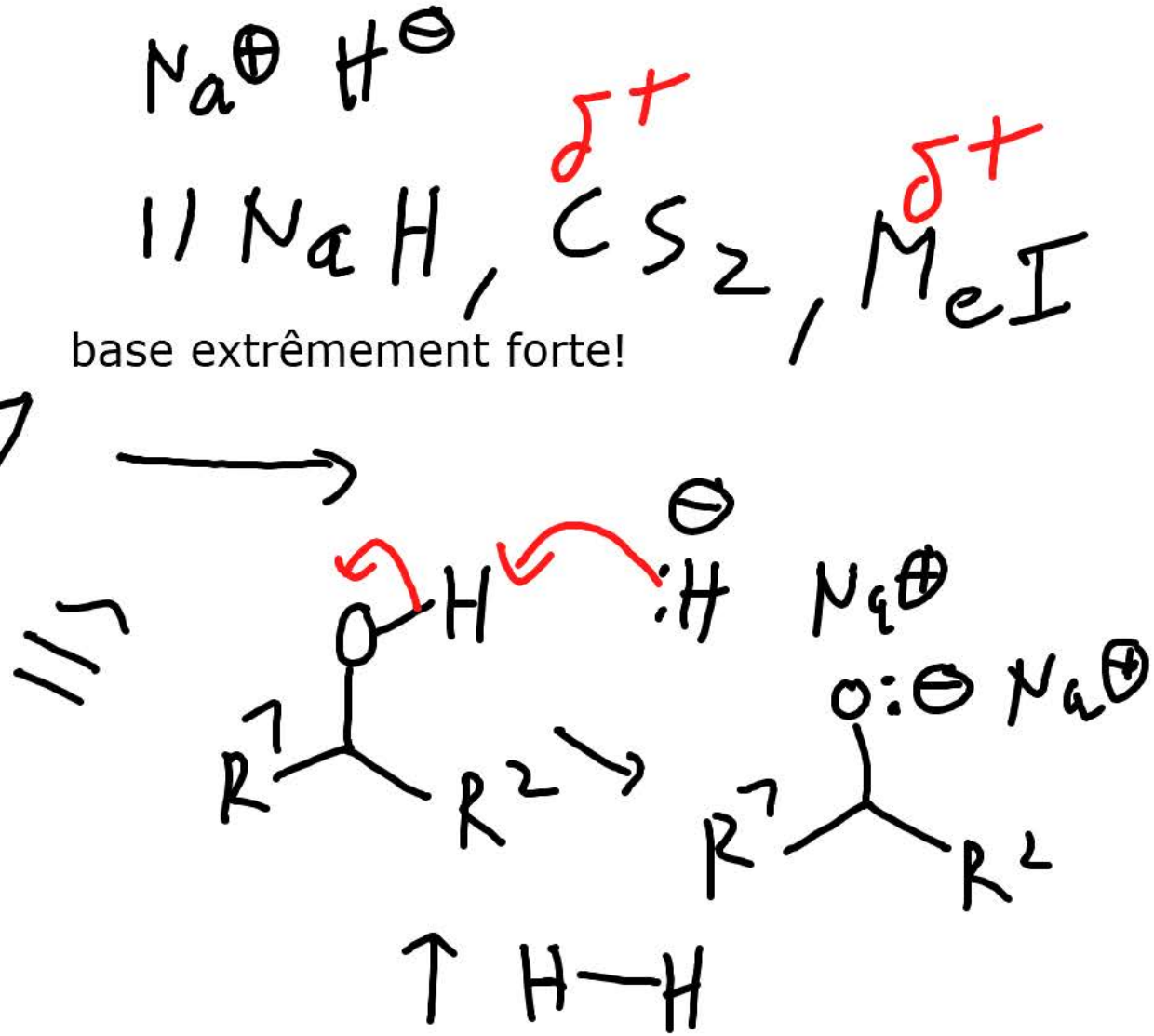
élimination selon Chugaev: application à la synthèse de Solanapyrone E

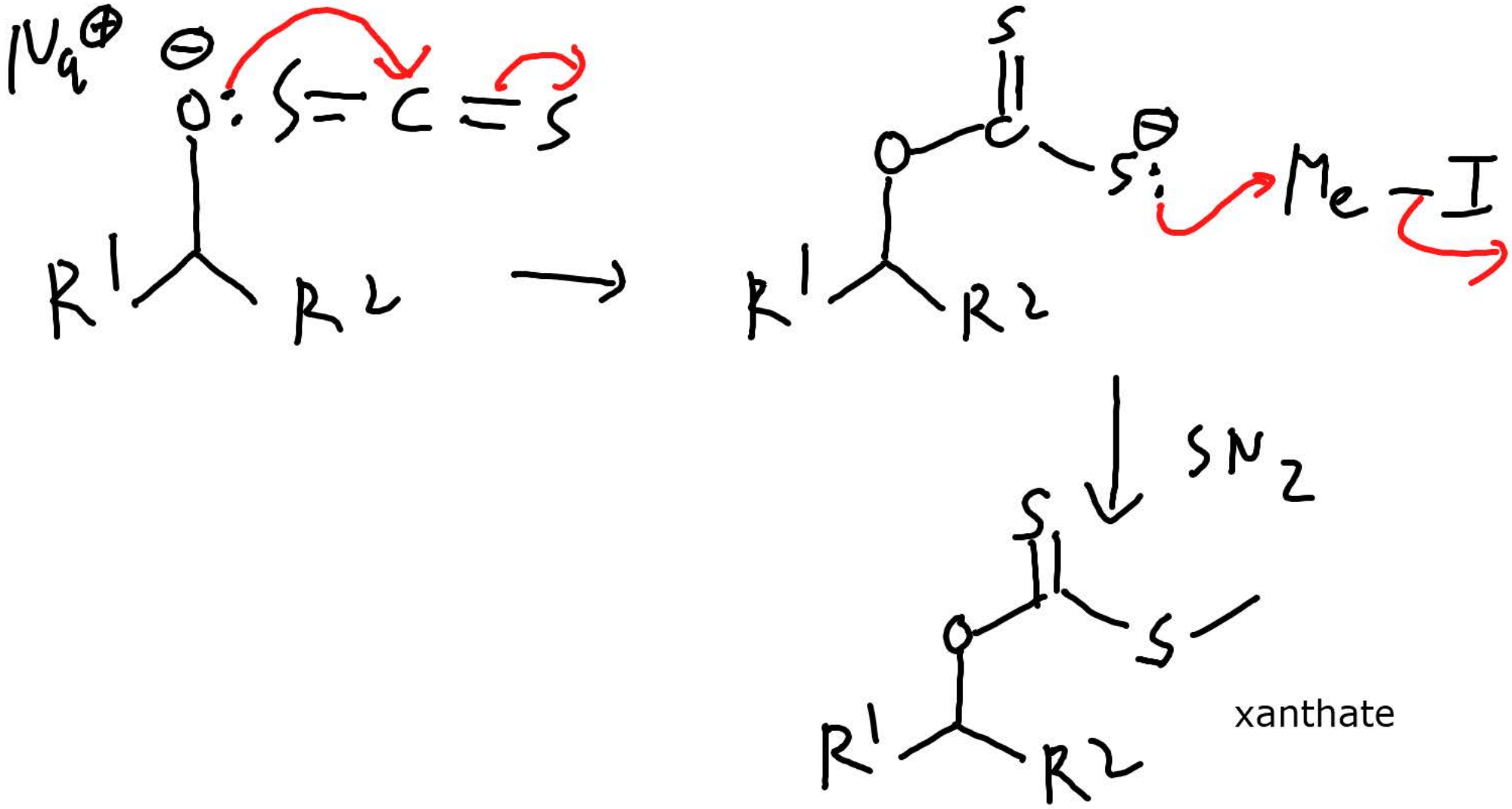


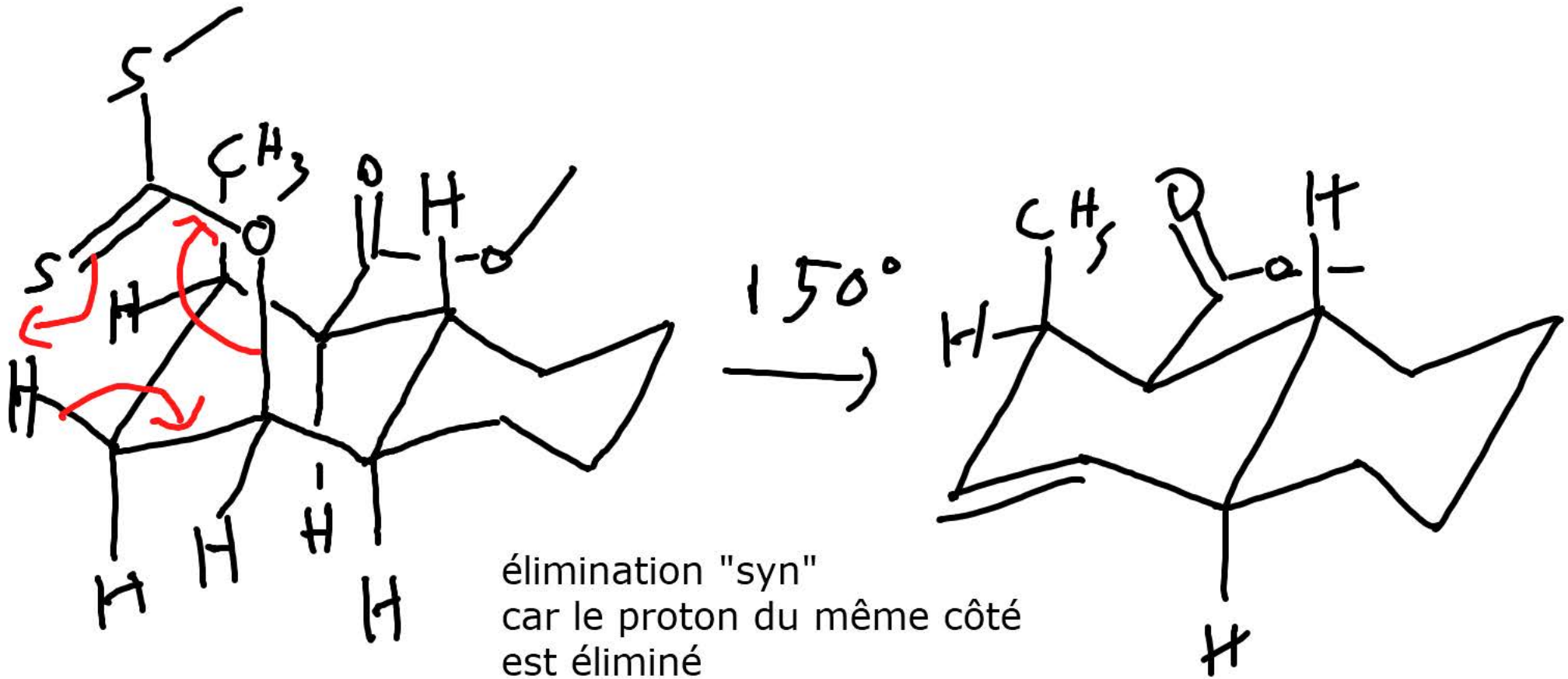
alcène trisubstitué
plus stable produit
thermodynamique: à
éviter!



Les deux H sont à 180°
Une E2 serait non sélective!

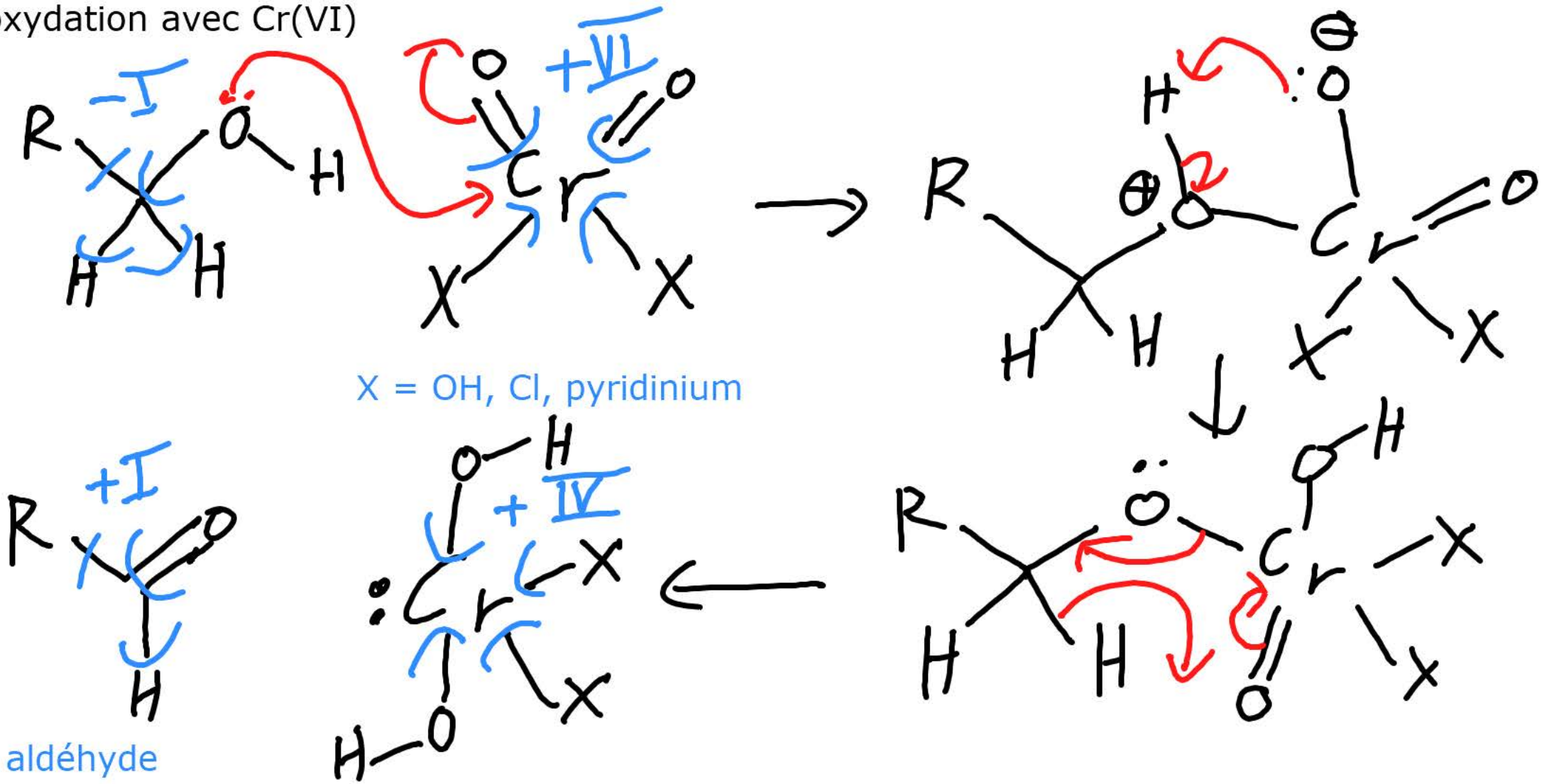



Me
I
SN2
xanthate

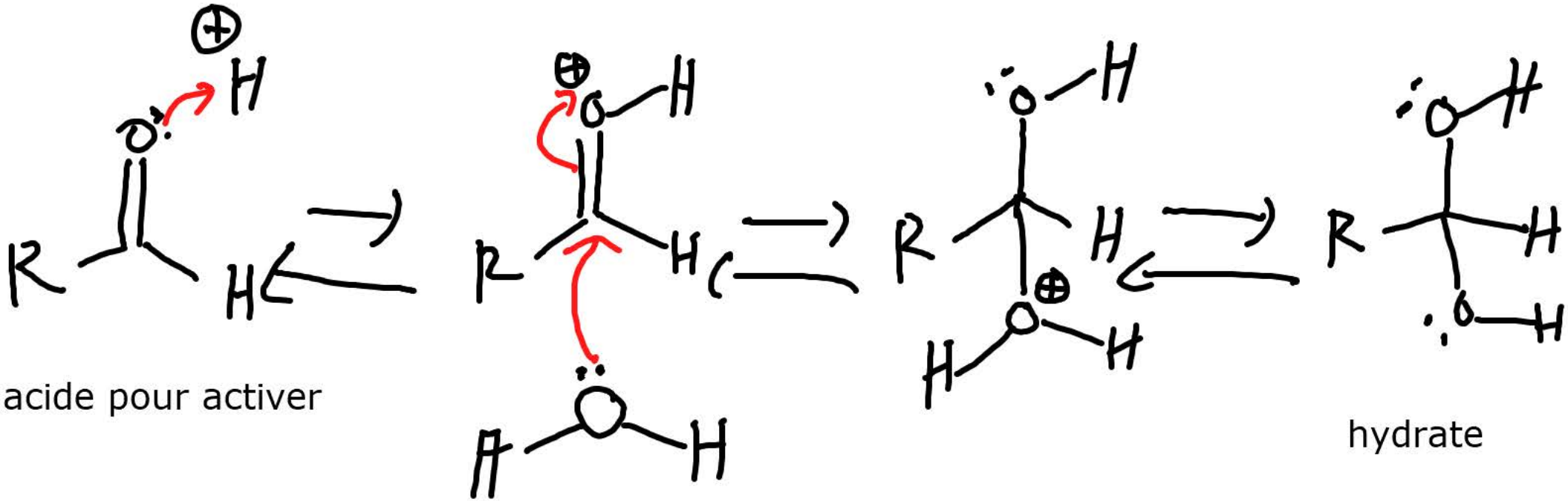


élimination "syn"
car le proton du même côté
est éliminé
(E2 est anti)

oxydation avec Cr(VI)



Oxidation des aldéhydes avec Cr)VI):
en général pas possible, sauf en présence d'acide et d'eau!

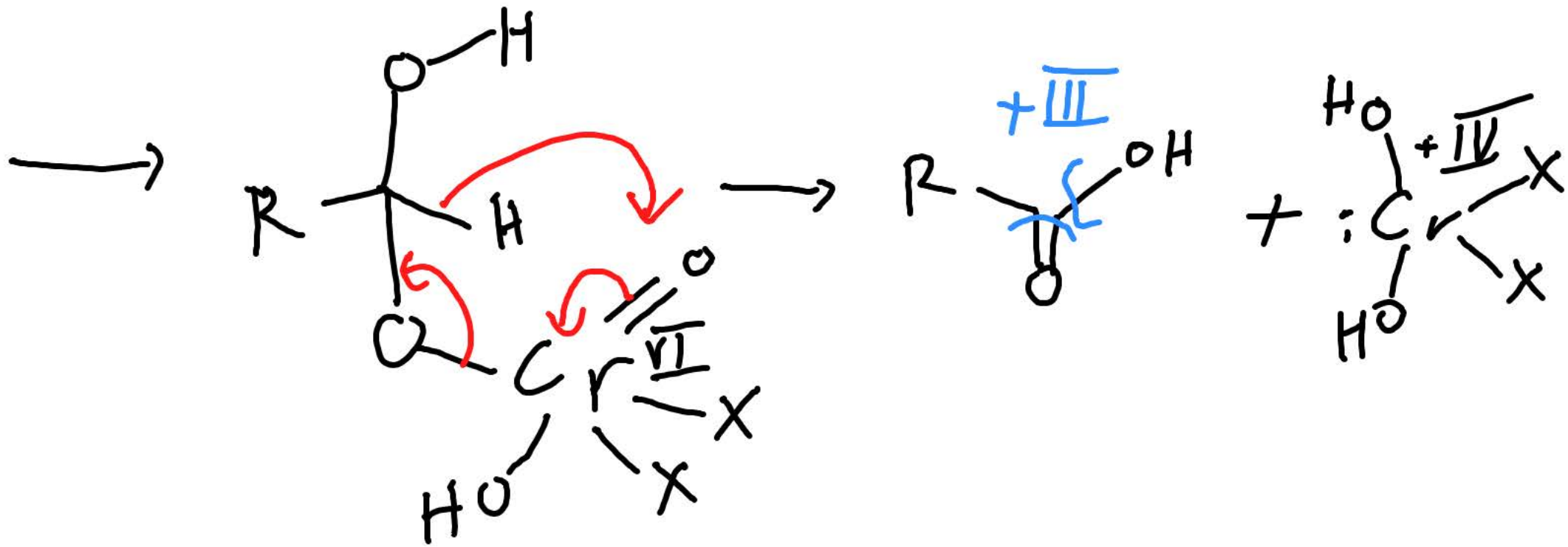


acide pour activer

eau comme nucléophile

hydrate

se lie sur le chrome

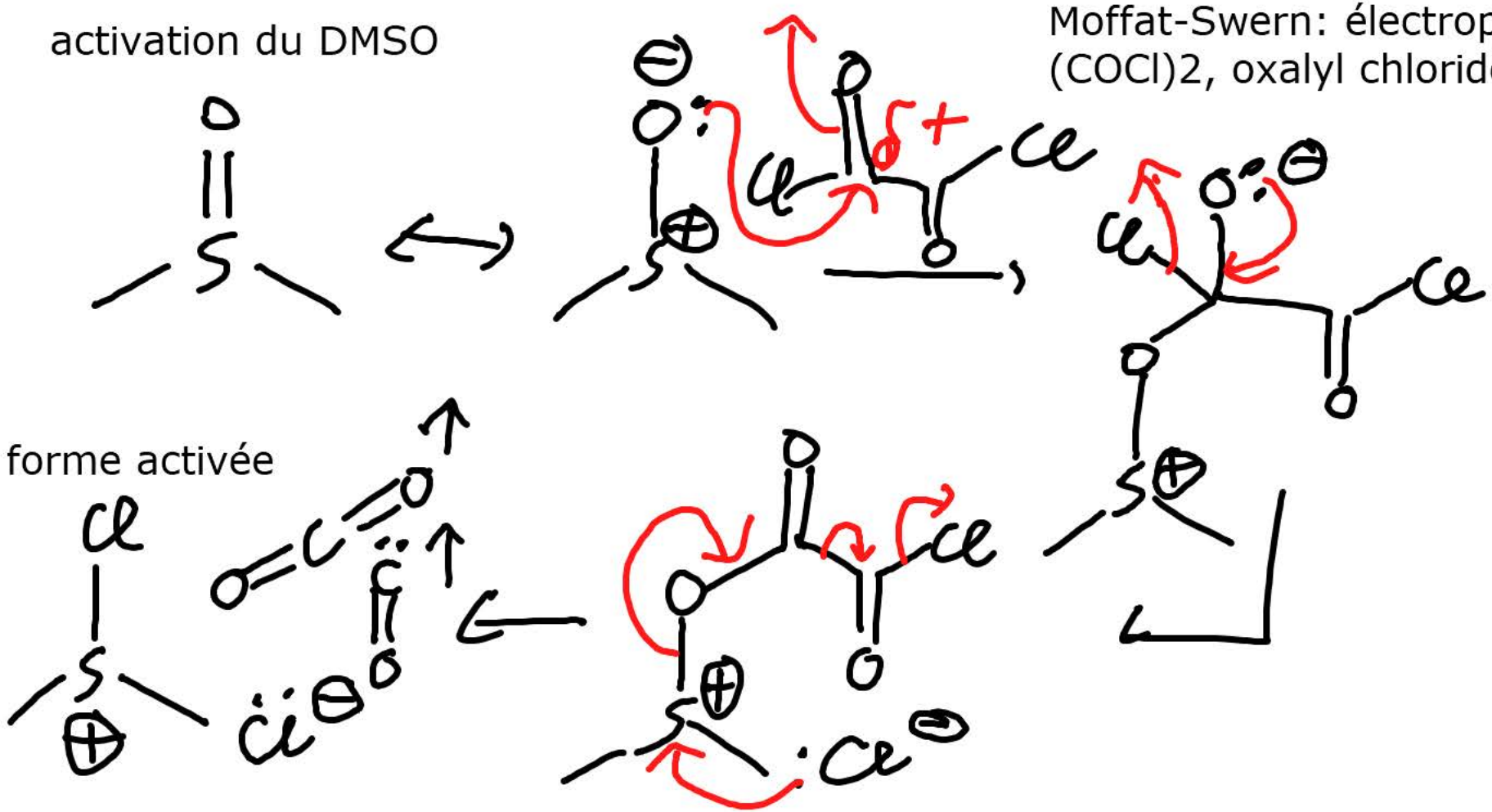


En présence d'eau et d'acide, l'alcool primaire est oxydé jusqu'à l'acide (oxydation de Jones), sinon on stoppe à l'aldéhyde

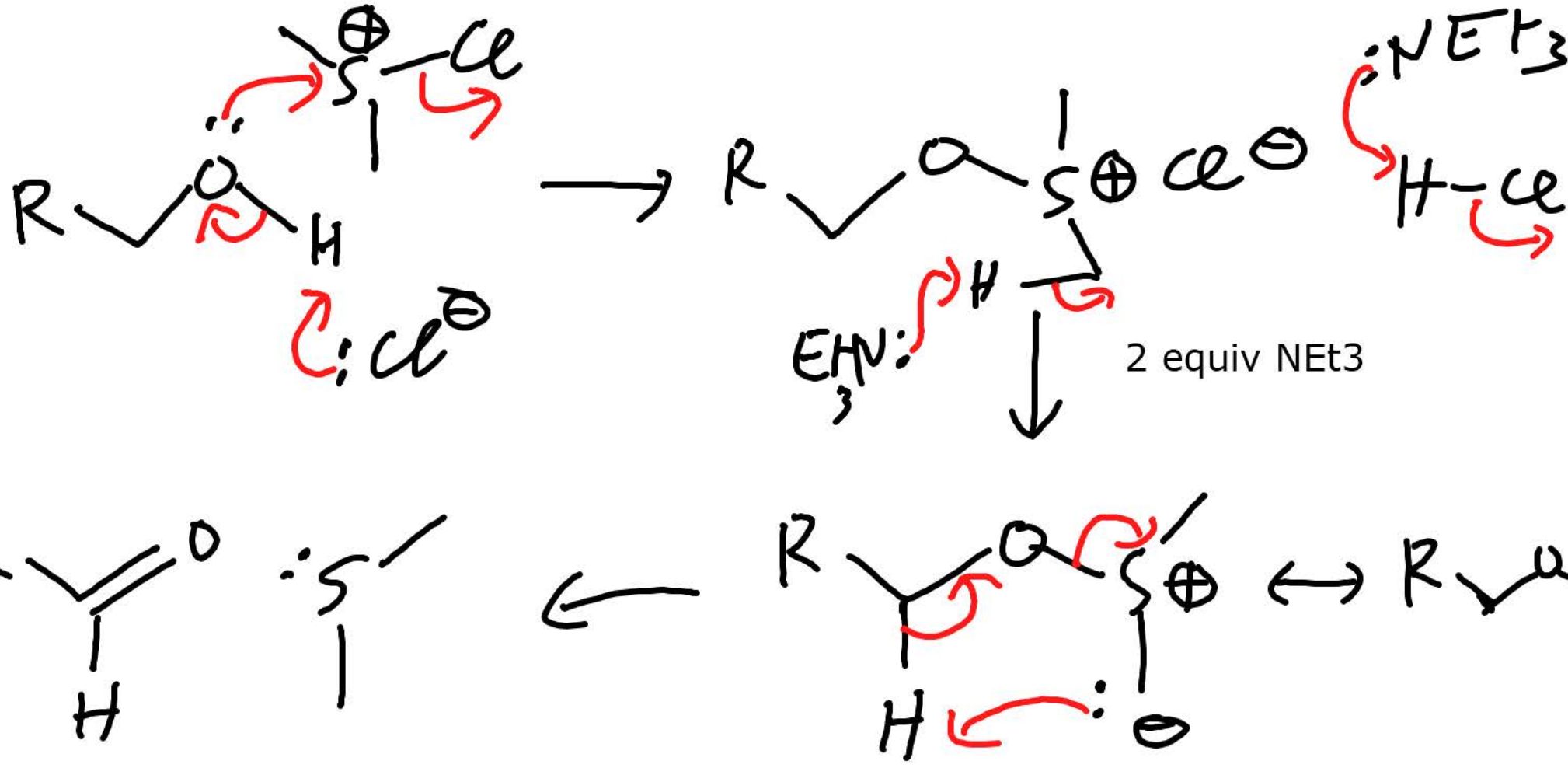
Oxidation de Moffat-Swern: Utiliser le DMSO comme oxidant!

activation du DMSO

Moffat-Swern: électrophile est (COCl)2, oxalyl chloride

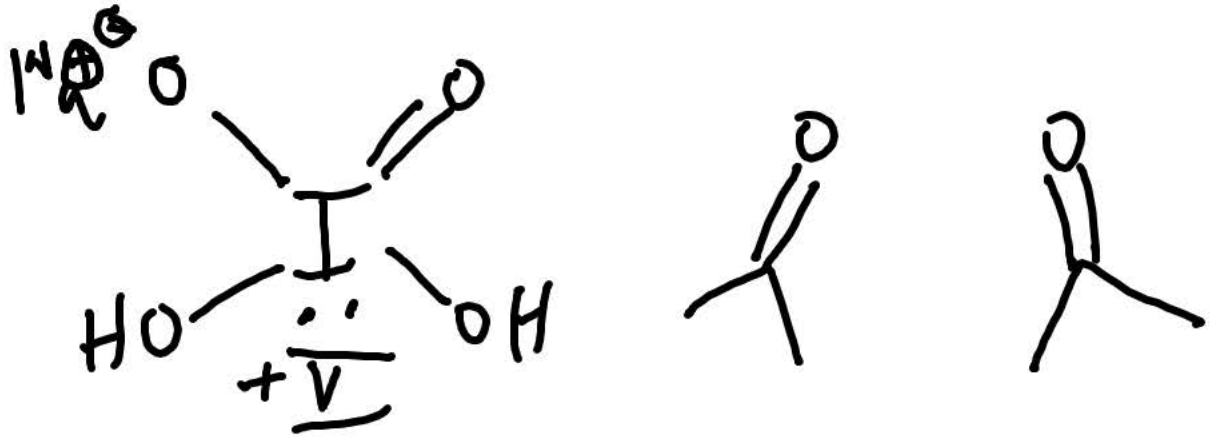


étape d'oxidation



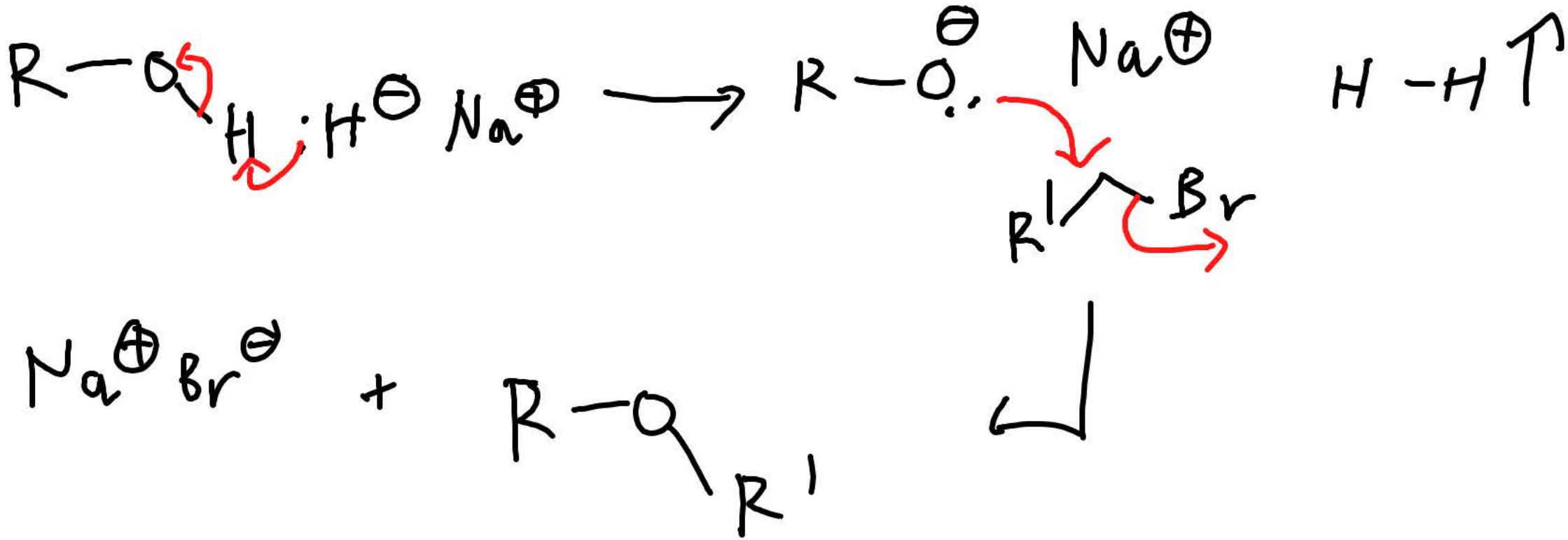
clivage des diols: Pb(OAc)4, NaIO4

nécessaire: un diol 1,2



Les éthers C-O-C

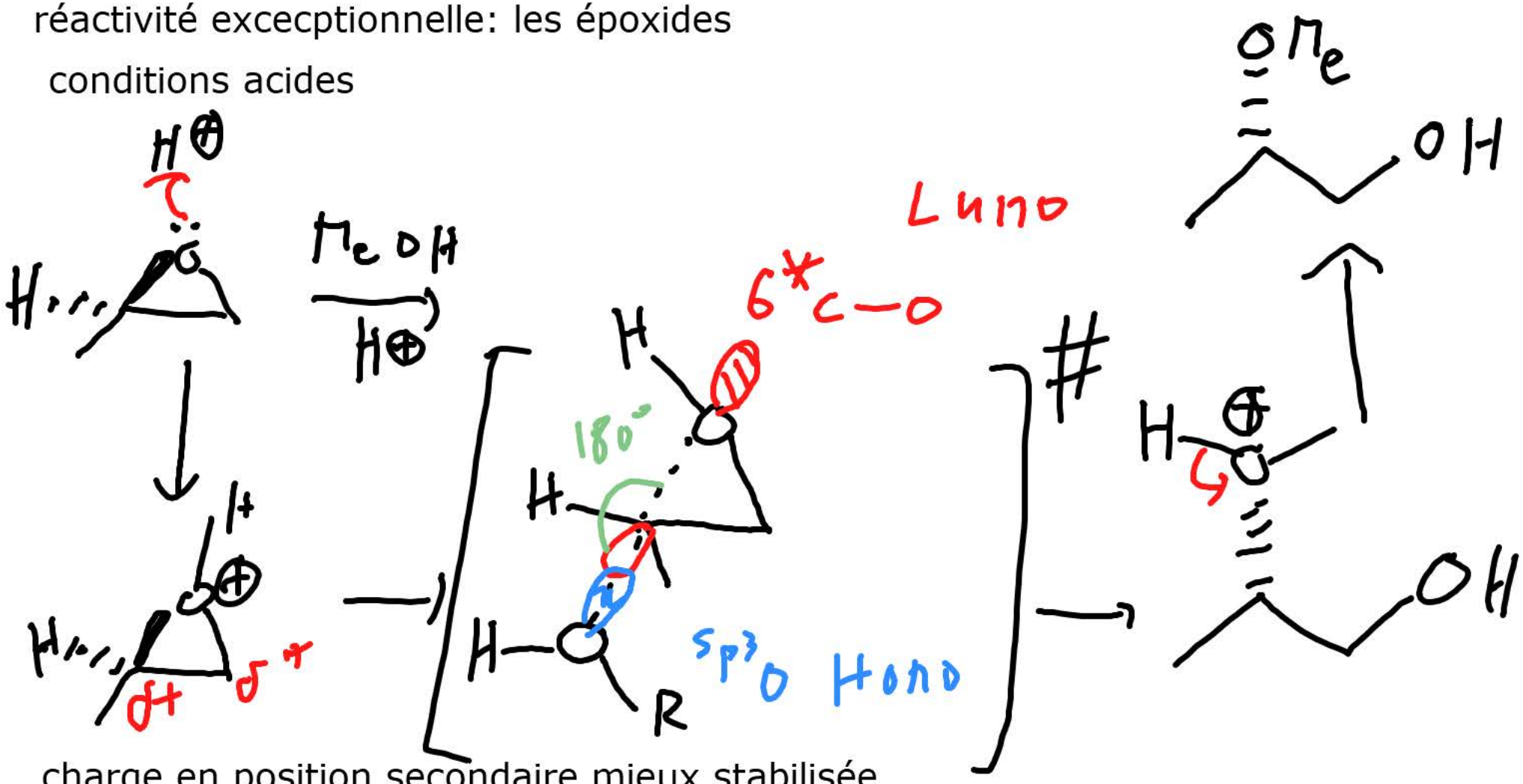
synthèse selon Williamson: déprotonation suivi d'une SN



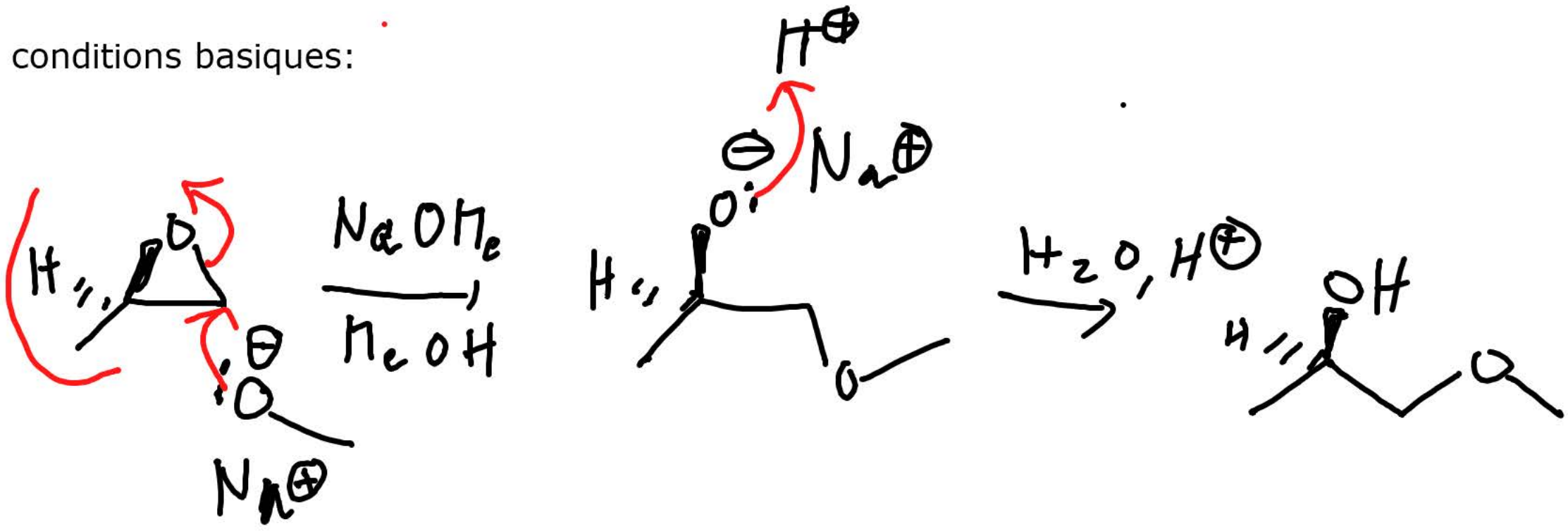
éther, souvent un produit final

réactivité excecptionnelle: les époxides

conditions acides

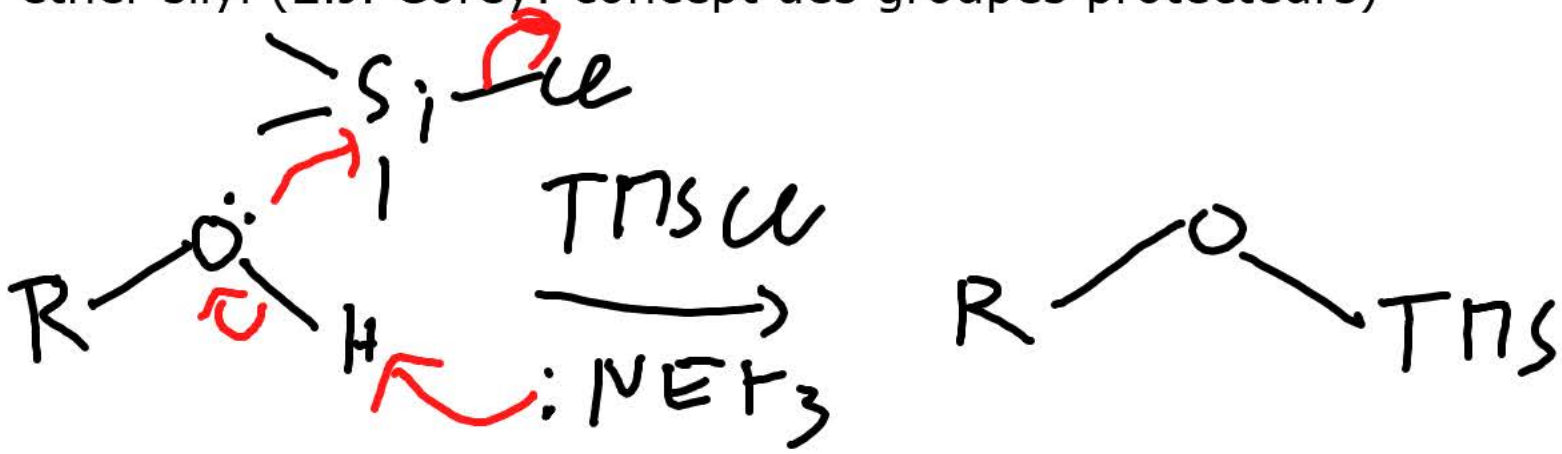


conditions basiques:

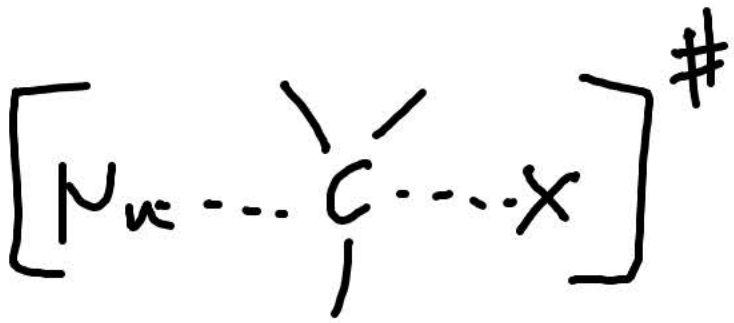


réaction contrôlée par la stérique!

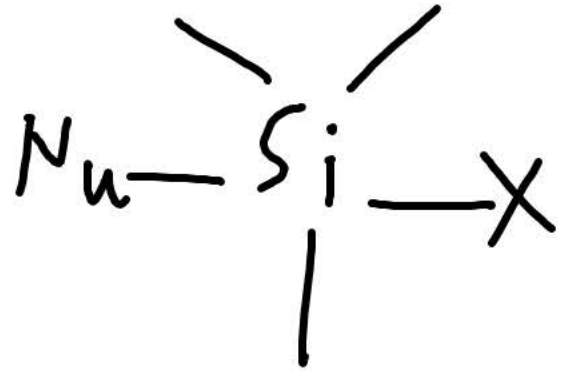
éther silyl (E.J. Corey: concept des groupes protecteurs)



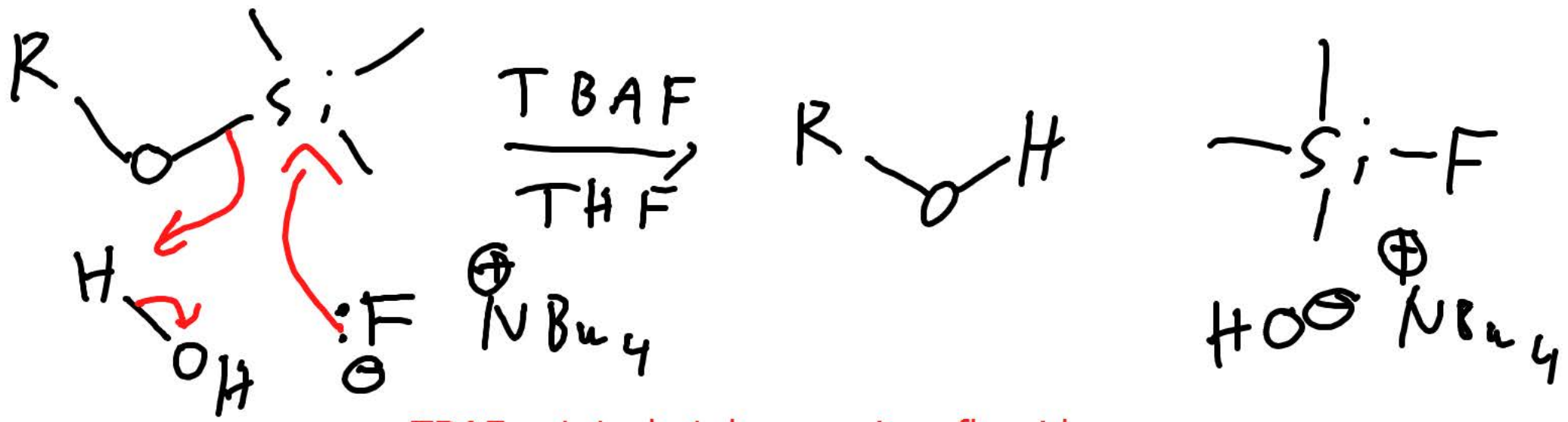
TMS = trimethylsilyl



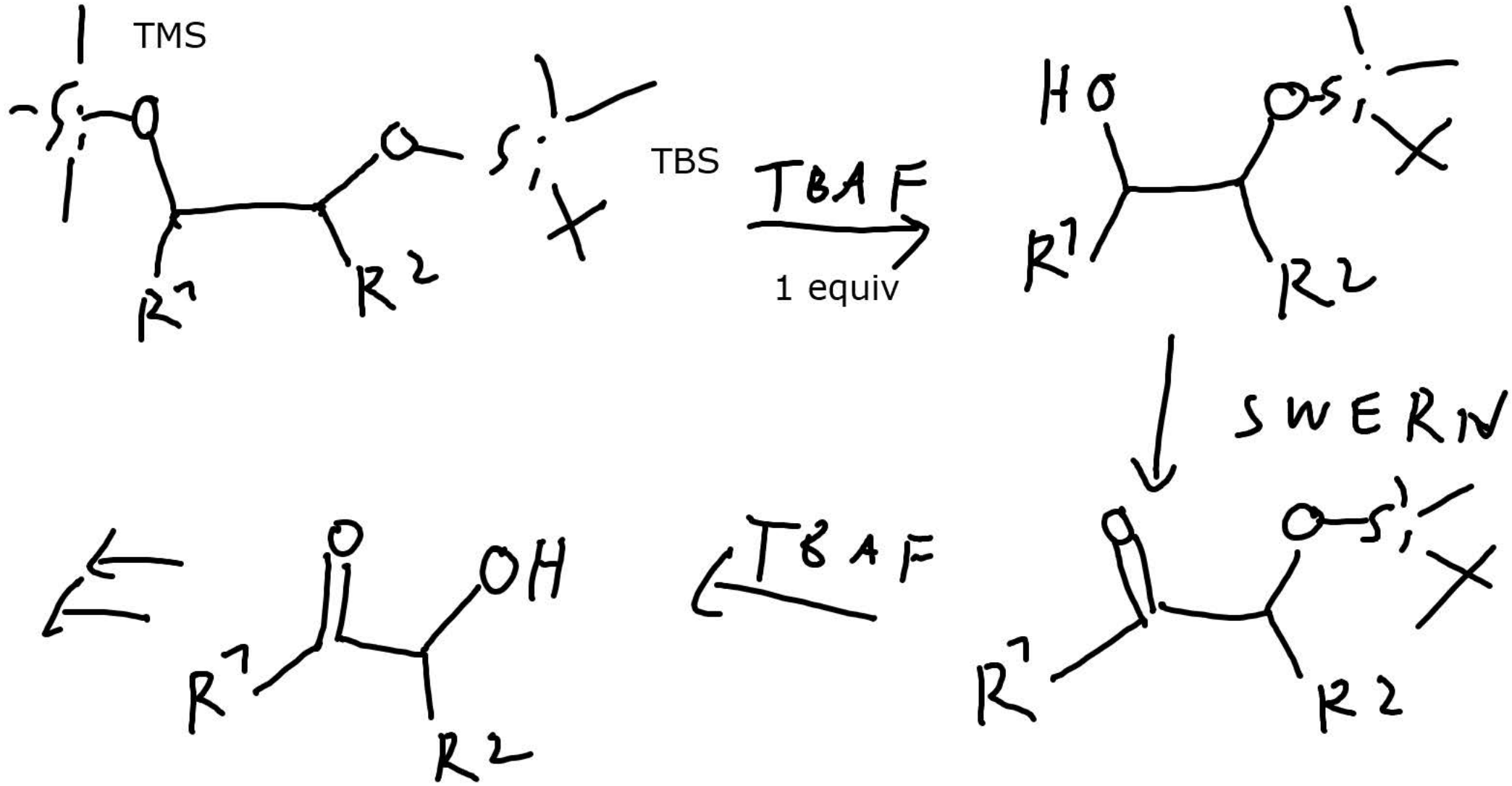
SN2 sur C: état de transition,
on doit respecter l'octet!



intermédiaire,
on peut dépasser
l'octet

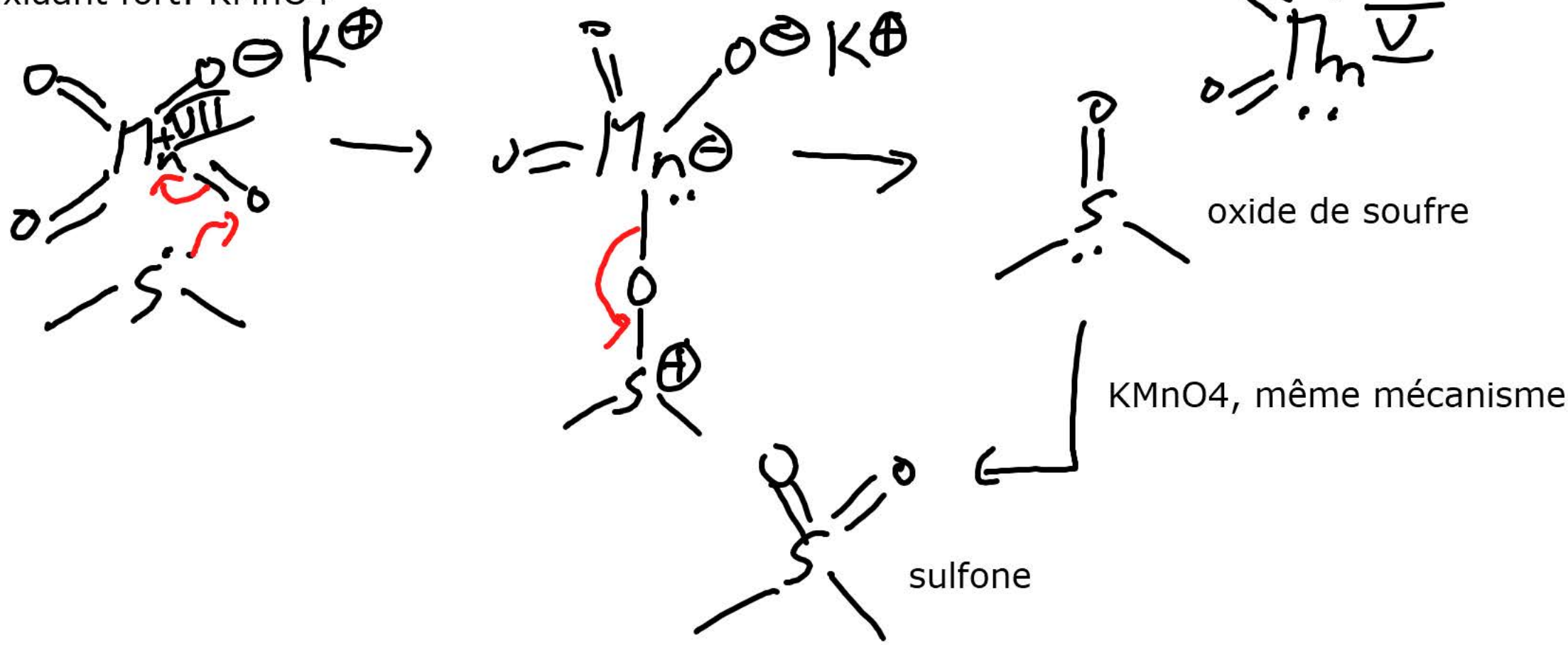


TBAF = tetrabutylammonium fluoride

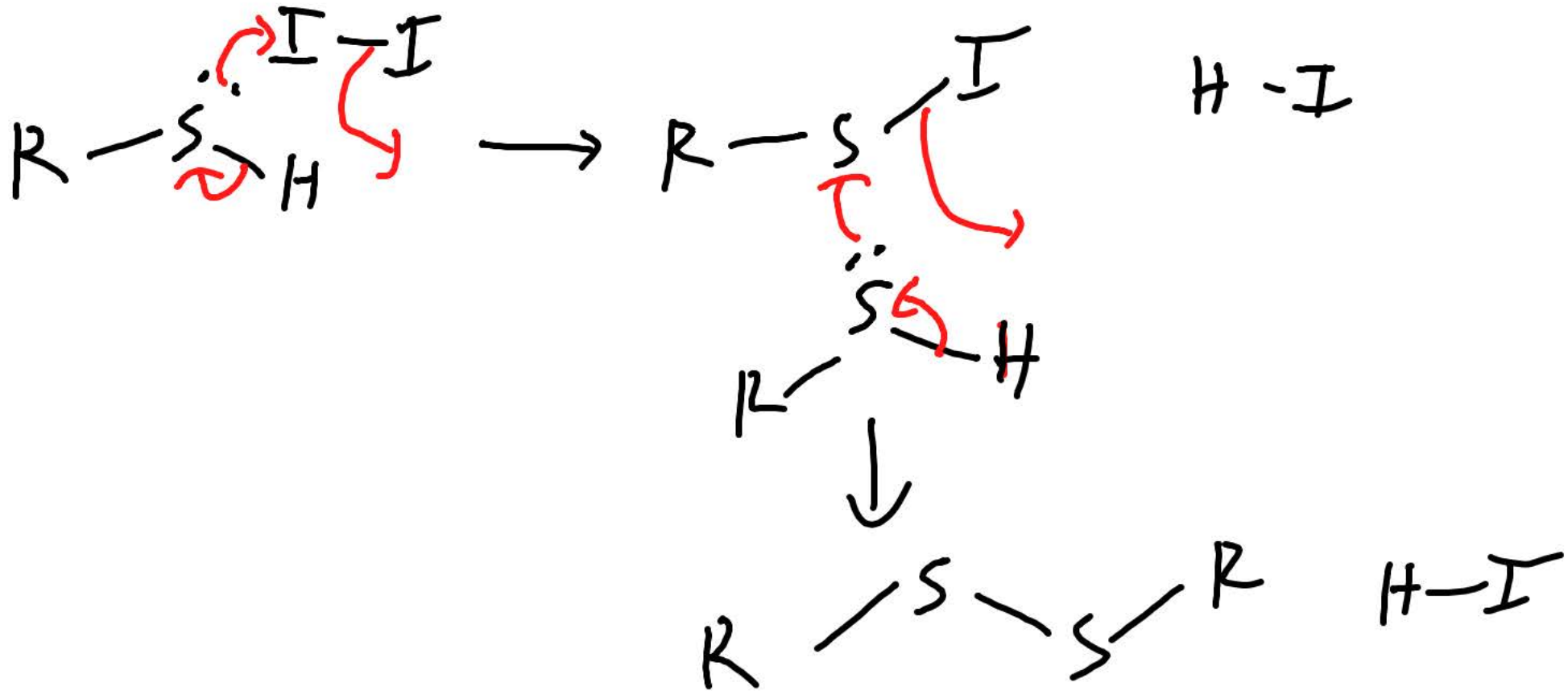

TMS
TBS
TBAF
1 equiv
SWERN
TBAF
OH

chimie spéciale du soufre: oxidation pour dépasser l'octet

1) oxidant fort: KMnO4

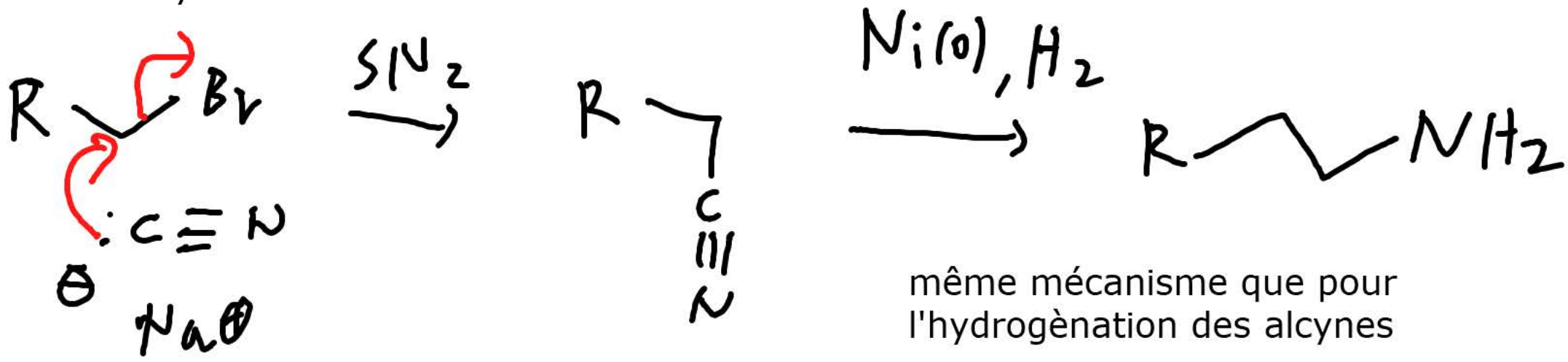


oxidation avec I2, (ou avec oxygen en biologie)



synthèse des amines primaires

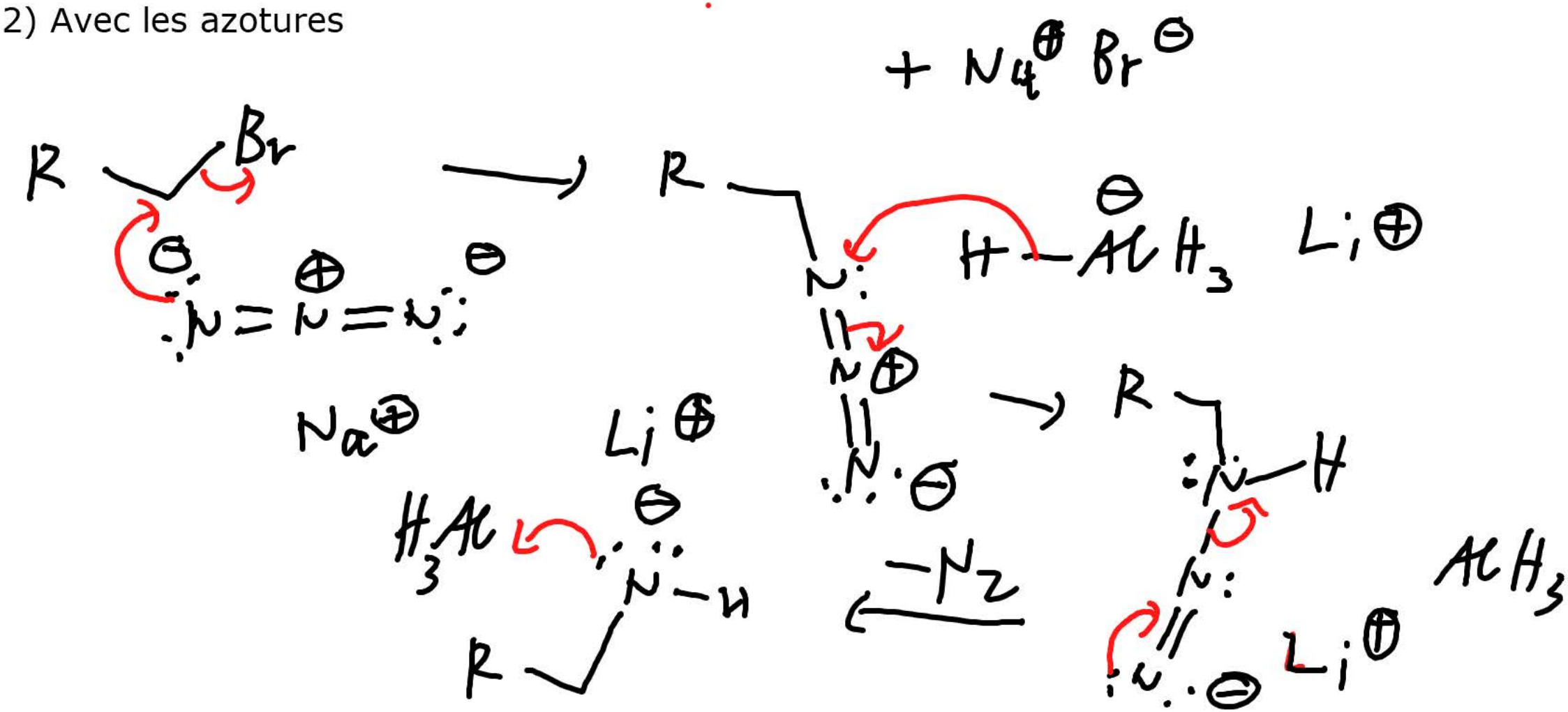
1) avec les cyanures

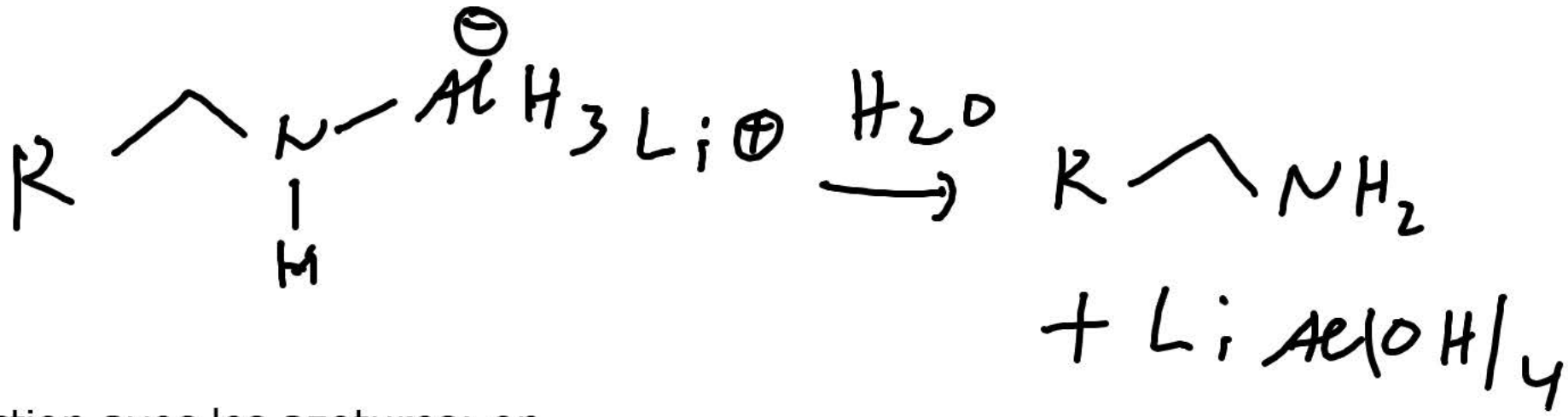


même mécanisme que pour l'hydrogènation des alcynes

on ajouté 1 carbone + 1 azote

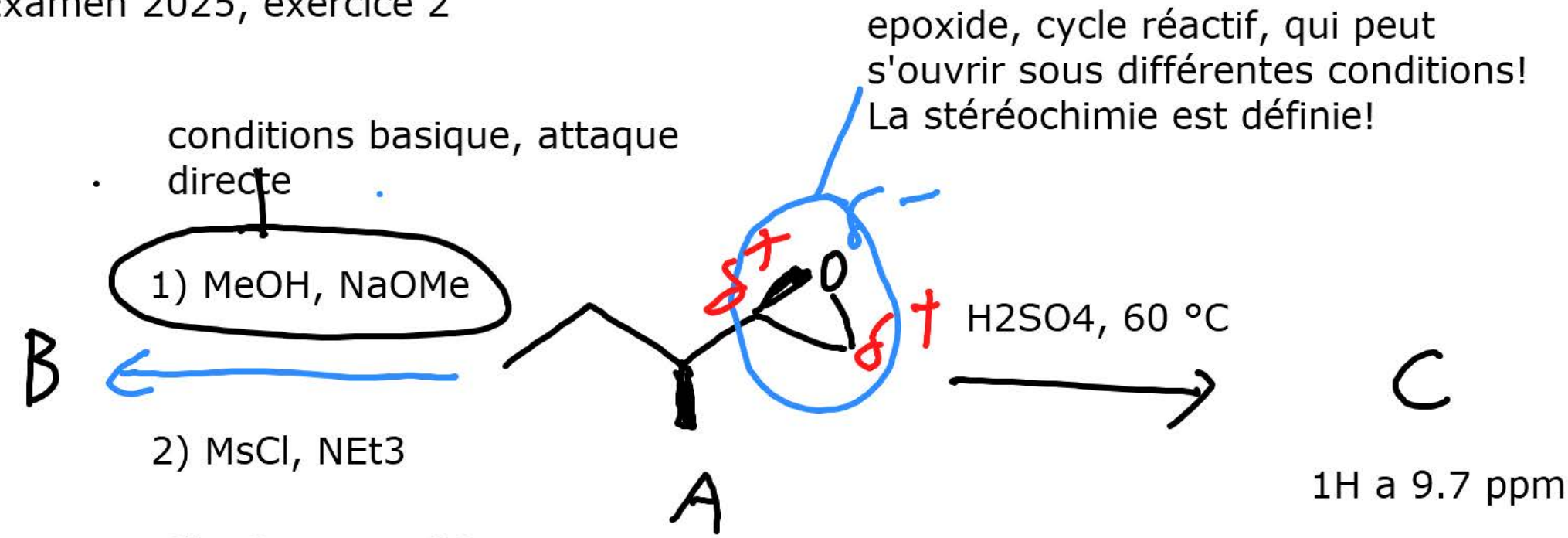
2) Avec les azotures





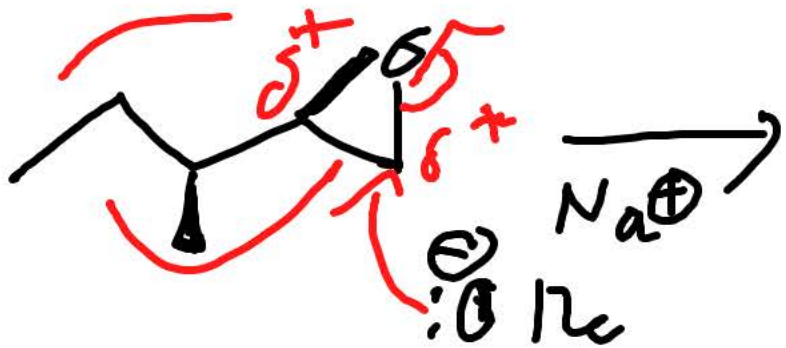
réaction avec les azotures: on ajoute uniquement un atome d'azote

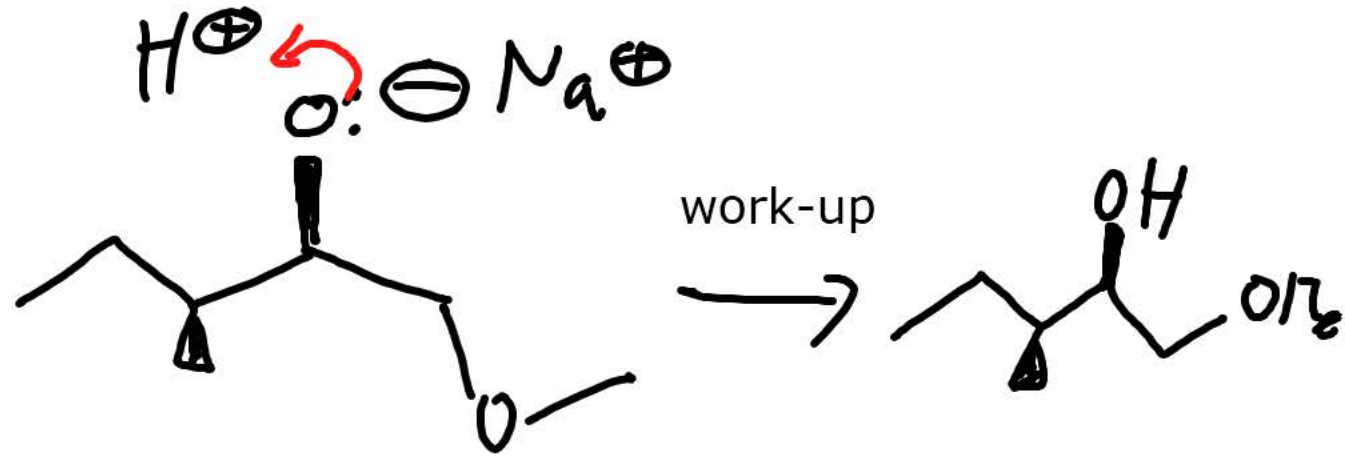
Examen 2025, exercice 2



Me = methyl, tBu= tert-butyl, Ms: Mesyl, Et = ethyl,
DMSO = dimethylsulfoxide, solvant polaire aprotique

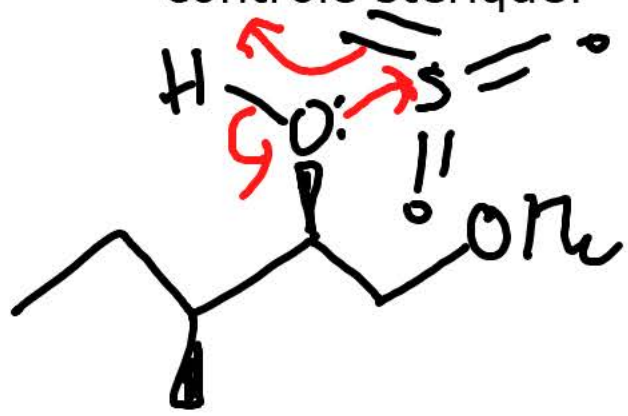
1)

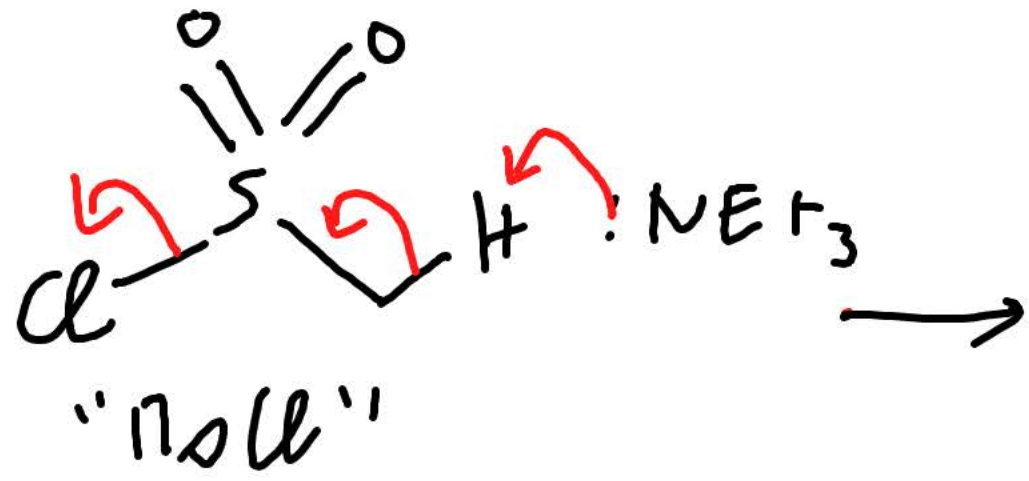


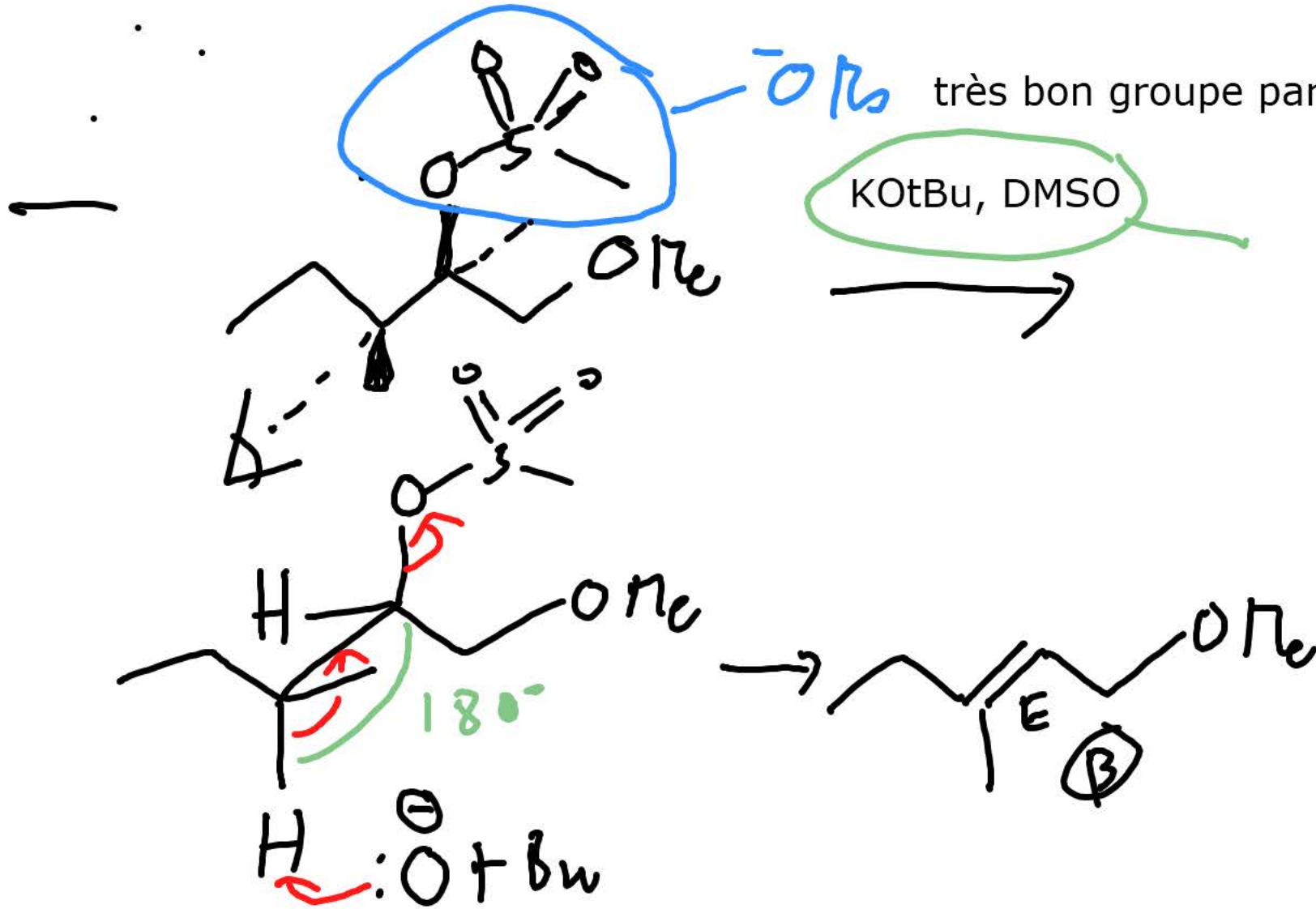


contrôle stérique!

2)



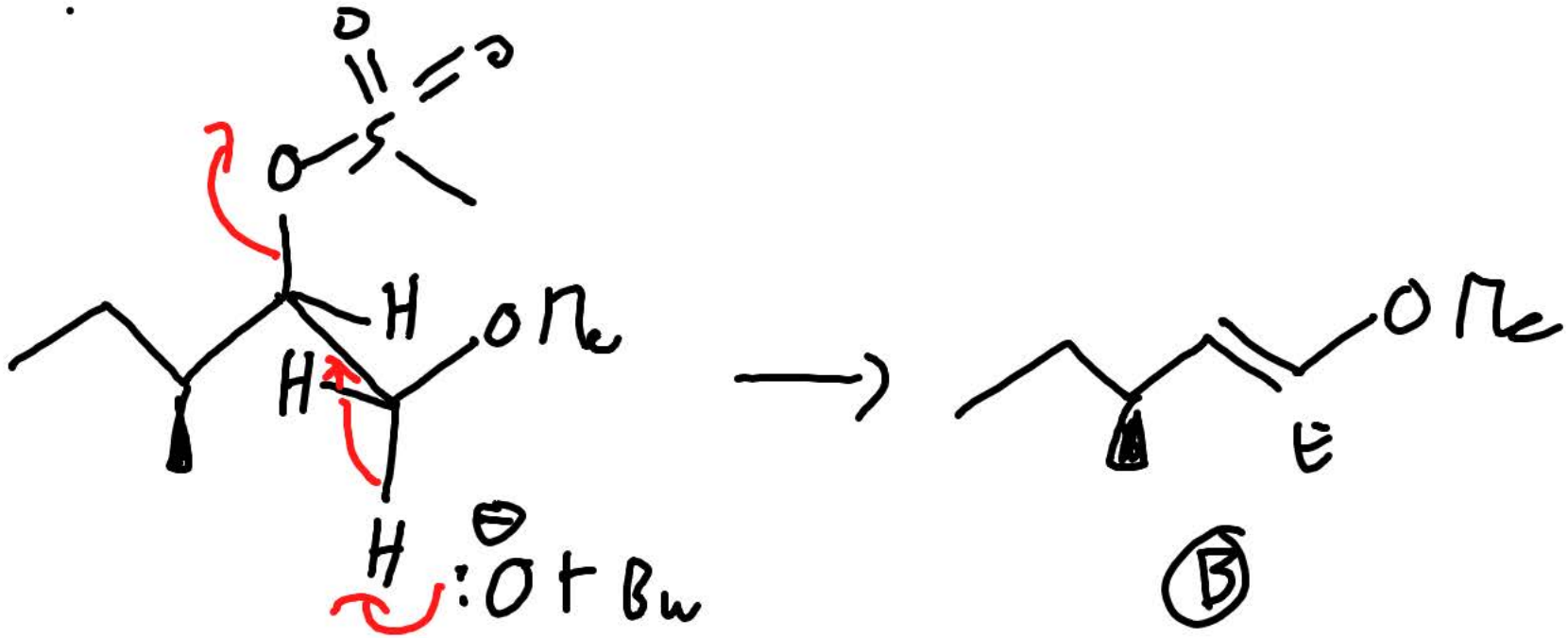




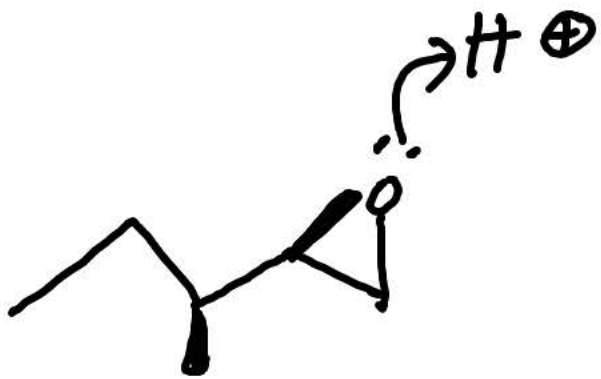
très bon groupe partant: E, ou SN

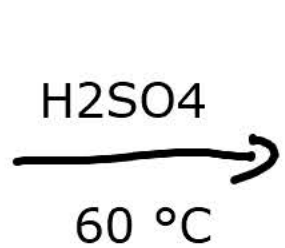
KOtBu, DMSO

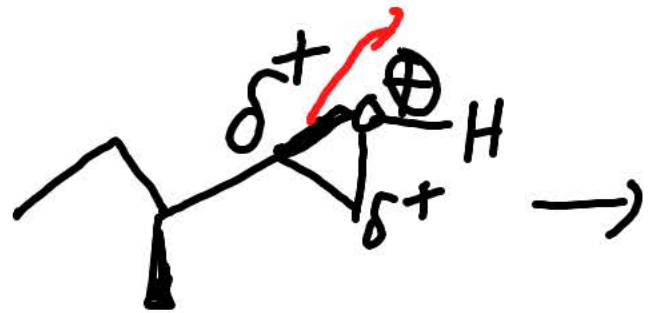
KOtBu, base forte, très encombrée (très mauvais nucléophile): Elimination!
DMSO: solvant polaire aprotique: favorise les mécanisme en une étape (E2, SN2)
Ici on a donc une E2

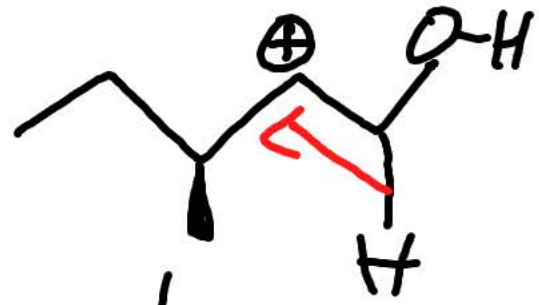


(B)





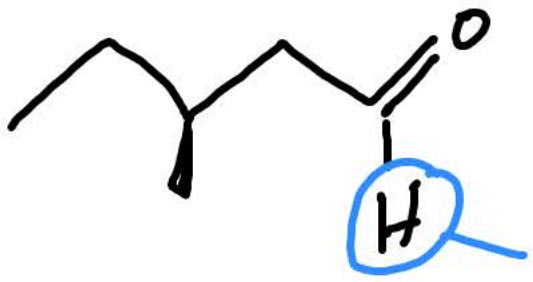




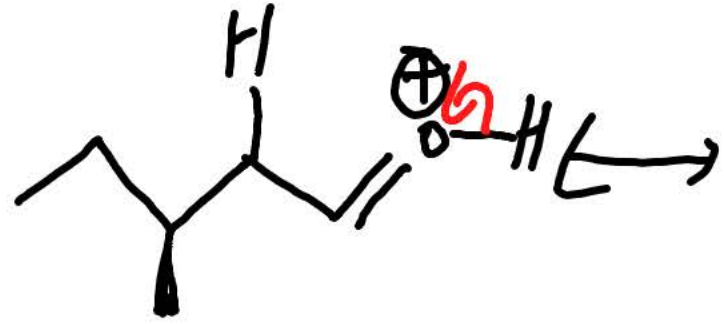
carbocation: 3 possibilité: addition nucléophile (SN1), élimination de proton, ou migration

pas de nucléophile

carbocation secondaire plus stable

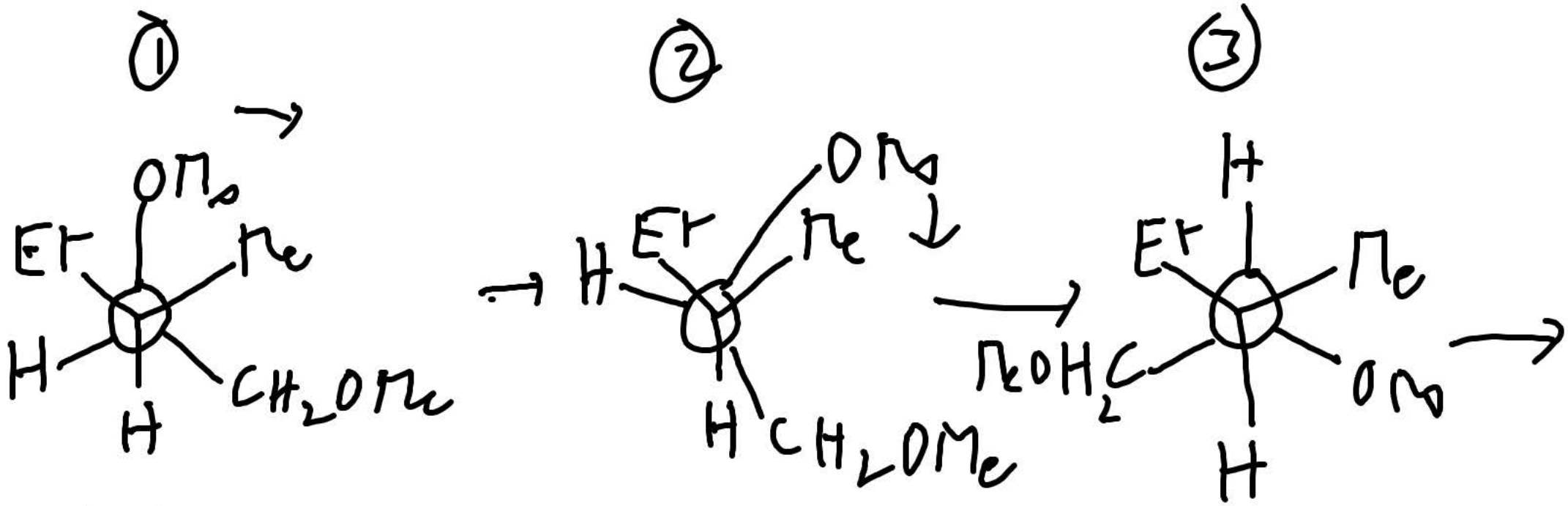


1H a 9.7 ppm!



forte stabilisation par résonance

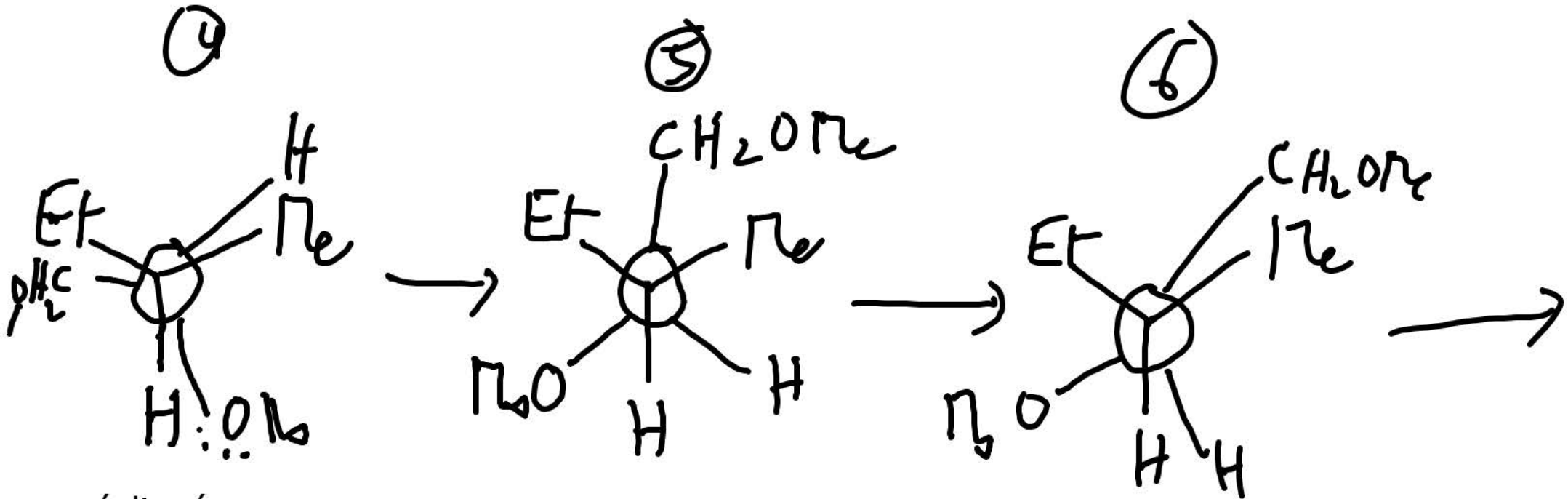
pour 3) Conformation de Newman!



décalée, minimum

éclipsée, état de transition

décalée, minimum

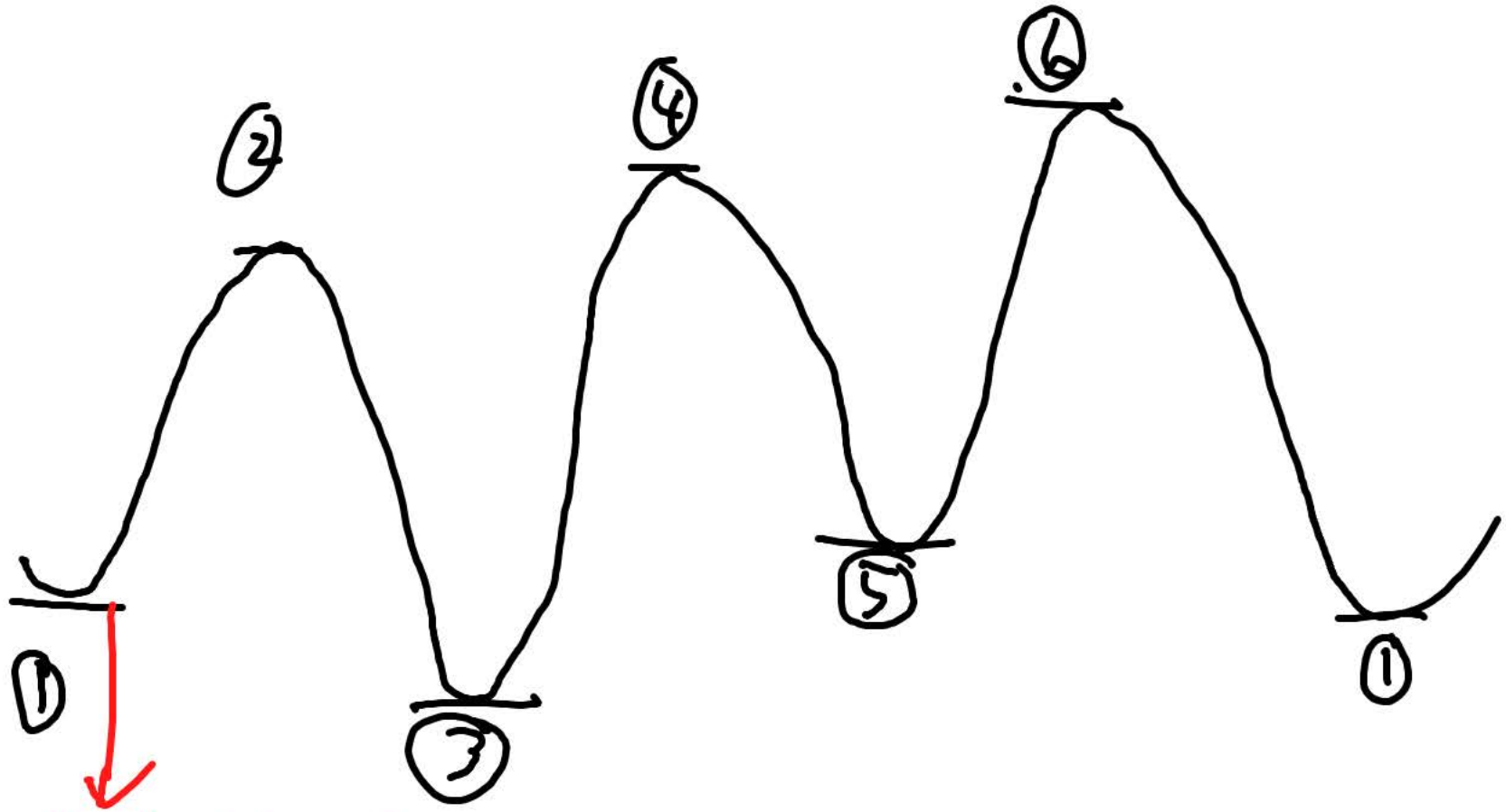


éclipsée décalée éclipsée

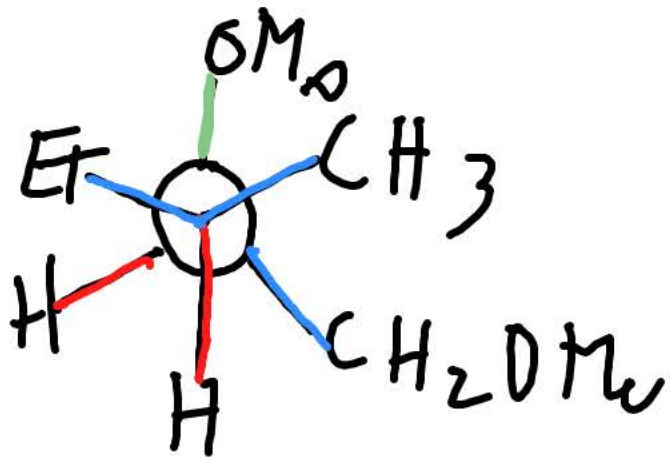
analyser la stérique: Et, CH2OMe >Me>OMs>>H

toujours 6 conformères!

OMs est plus petit car l'atome le plus proche est l'oxygène avec 2 paires d'électrons


2
4
6
1
3
5
0
effet des interactions
orbitalaires

$\sigma_{C-H} \rightarrow \sigma^*_{C-O}$



C-H

C-C

C-O

EN O > C >H

toutes les liaisons sont sigma

σ^*_{C-H}

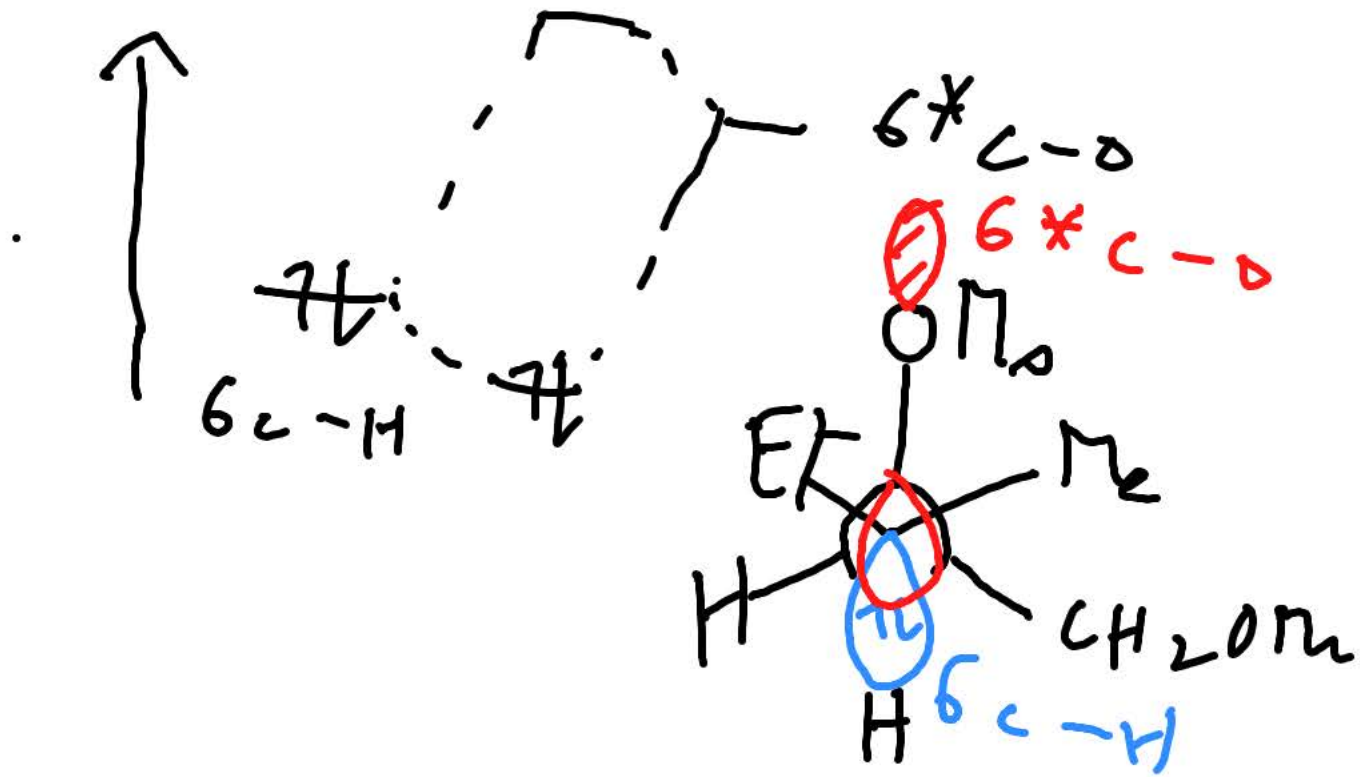
σ^*_{C-C}

σ^*_{C-O} LUMO

σ_{C-H} HOMO

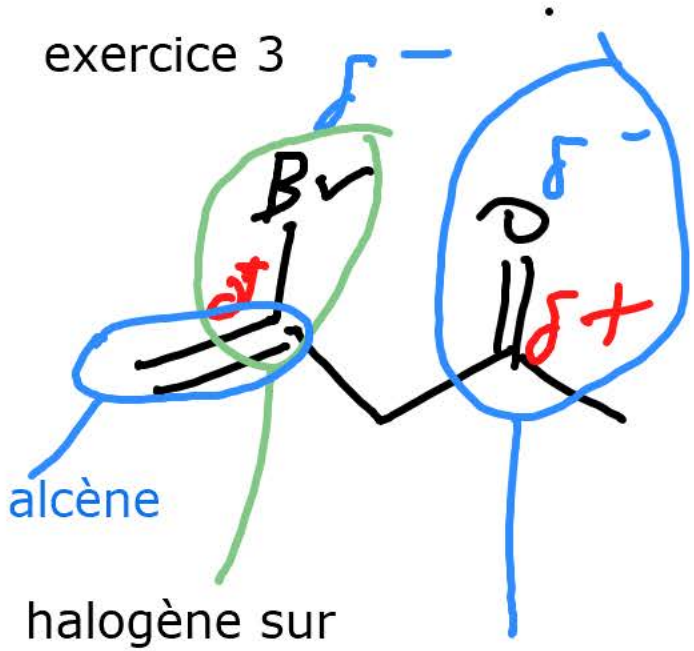
σ_{C-C}

σ_{C-O}



la conformation 1 est stabilisée par cette interaction, elle pourrait devenir la plus stable

exercice 3

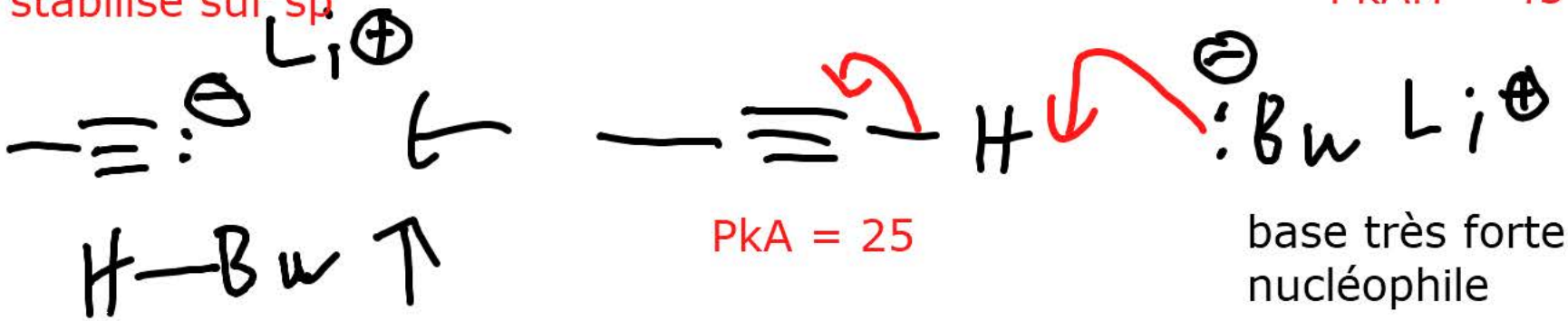


halogène sur carbon sp2
pas de SN...
stabilisé sur sp

carbonyl: bon électrophile de type liaison pi

1) —≡, BuLi

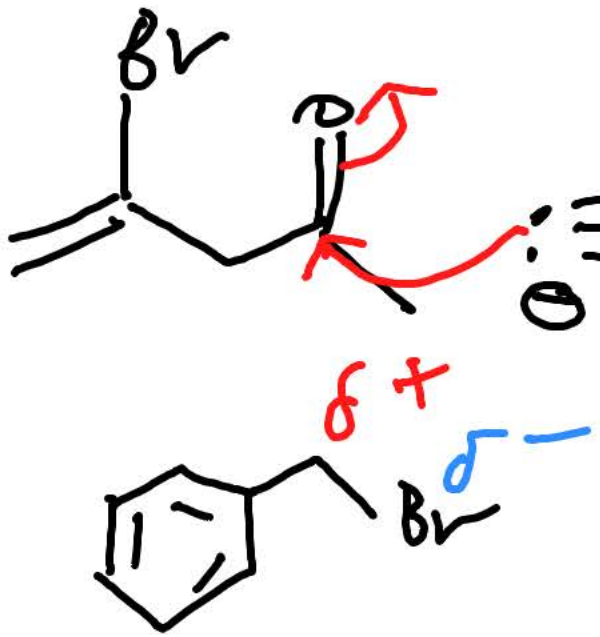
2) A



PkAH = 45

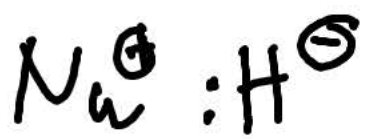
PkA = 25

base très forte, très bon nucléophile



halogen sur sp3:
idéal pour SN!

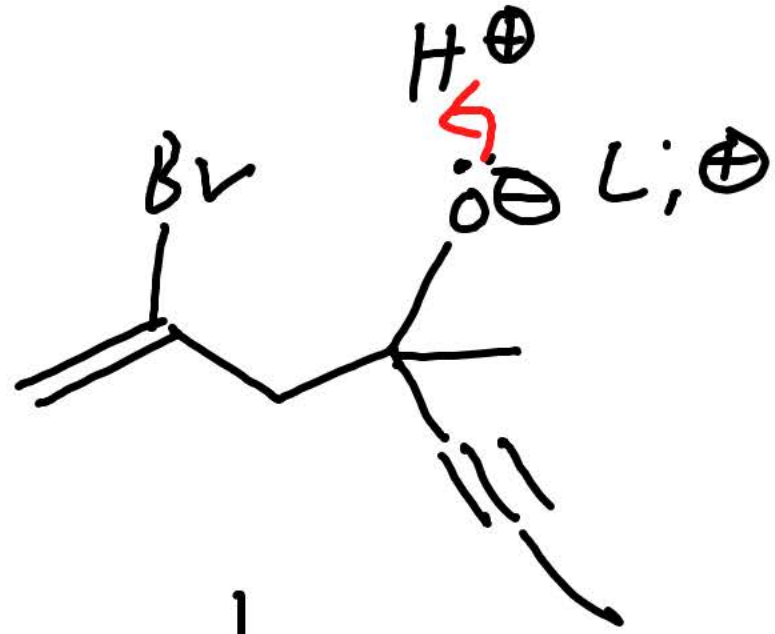
très forte base



pkAH = 40

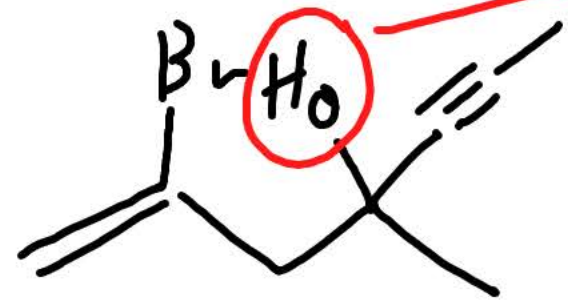
1)NaH, BnBr

2)NaOEt, EtOH

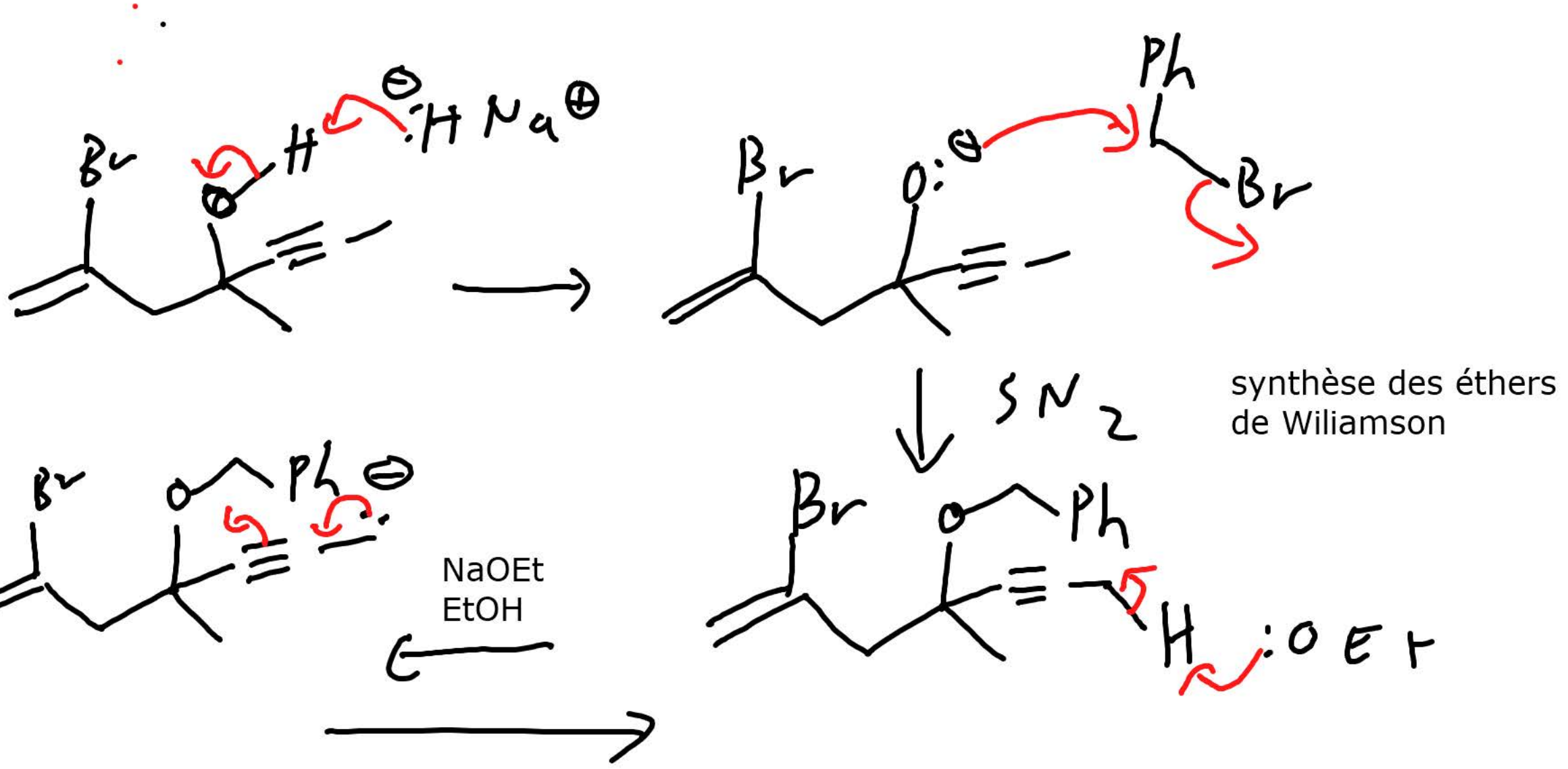


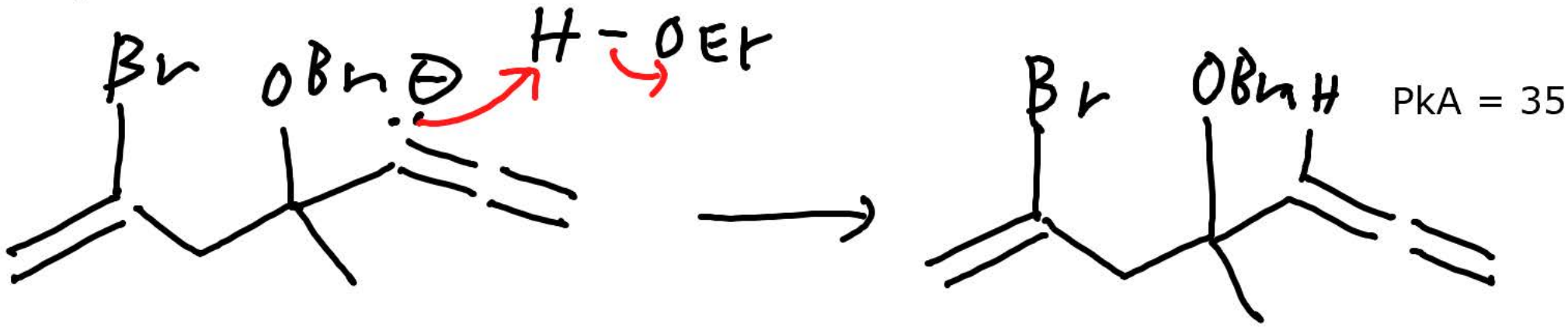
work-up acide

PkA = 17



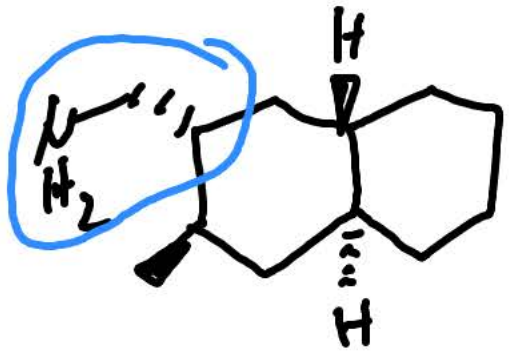
racémique


Br
H
Na
Ph
Br
SN2
synthèse des éthers
de Wiliamson
Ph
NaOEt
EtOH
OEt



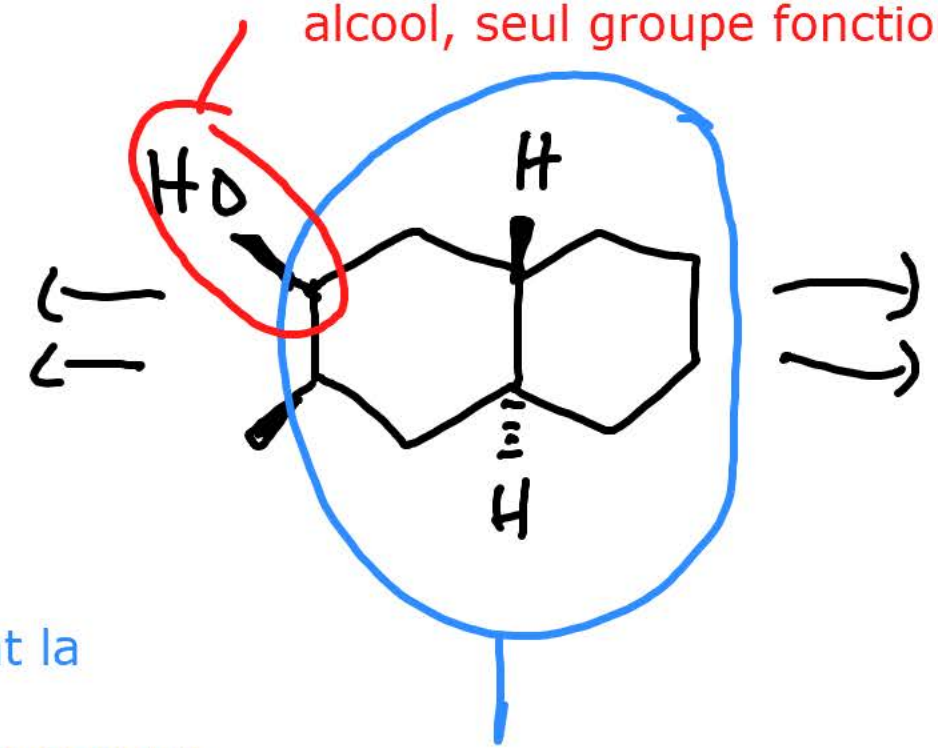
réaction stope ici, base pas assez forte pour déprotoner.

exercice 4



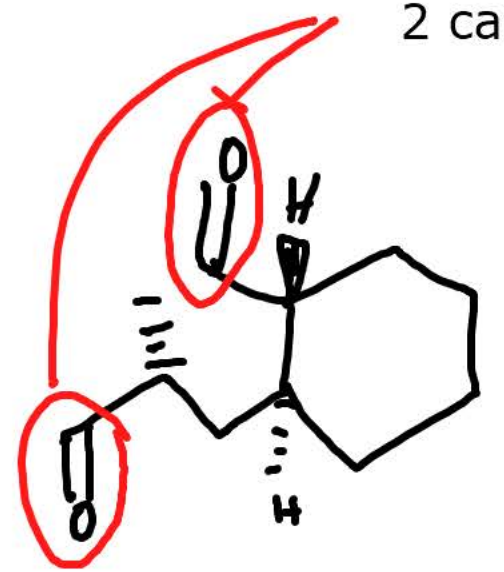
substituer OH par CH2NH2, en inversant la stéréochimie!
- OH n'est pas un bon groupe partant
- CH2NH2 pas un bon nucléophile

alcool, seul groupe fonctionnel



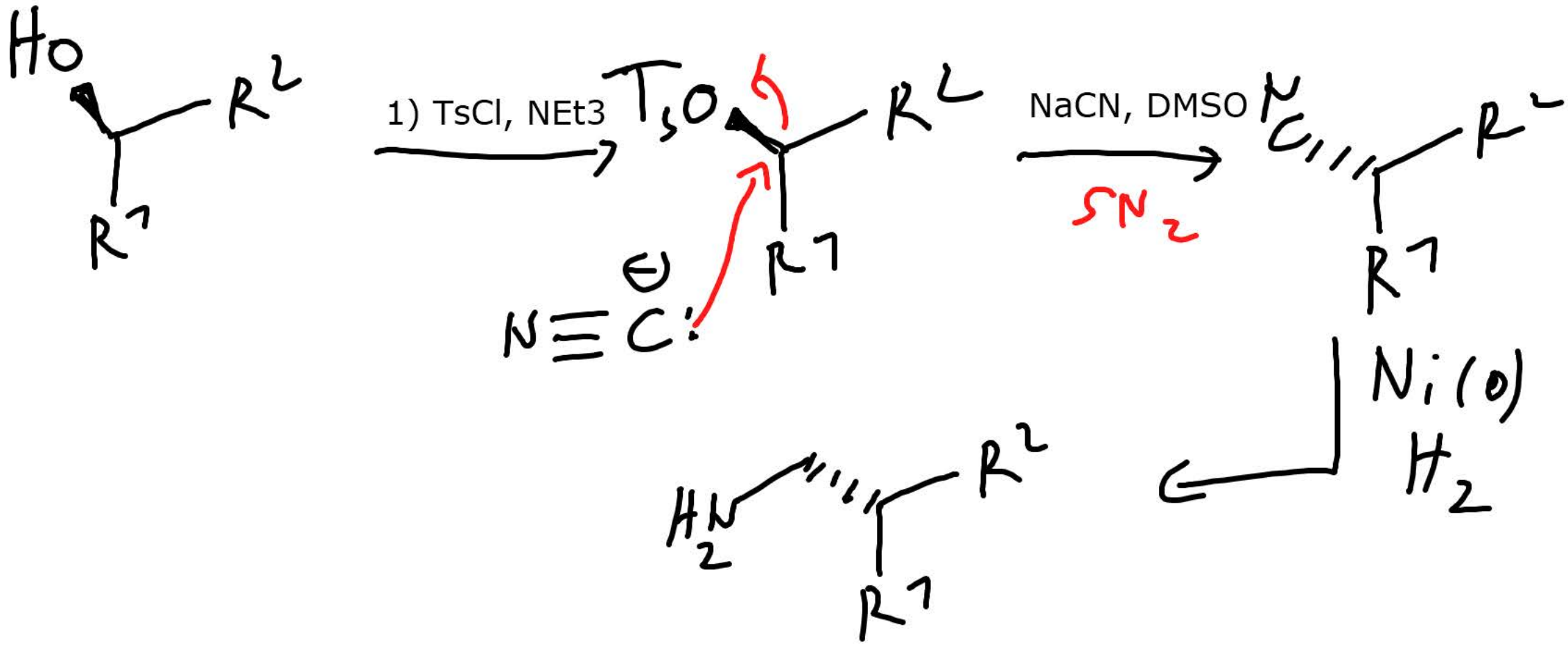
trans-décaline!
2 chaises fusées avec une seule conformation possible!

2 carbonyls

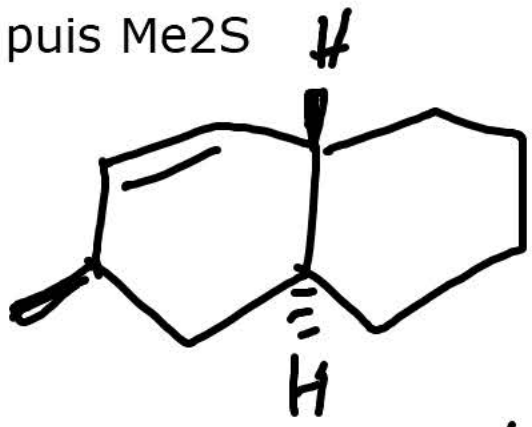


un cycle cassé: il faut briser une liaison C-C
- des alcènes avec ozonolyse
- des diols par oxydation

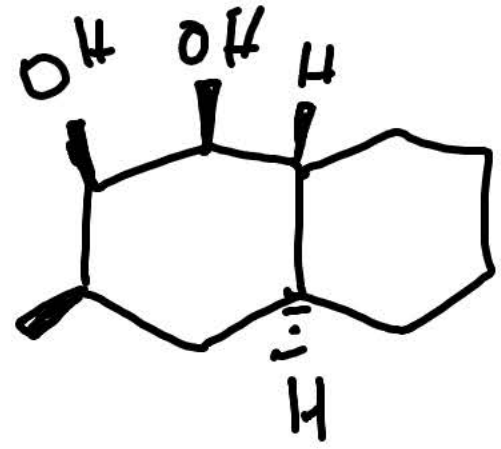
beaucoup d'informations de stéréochimie!


HO
R2
R1
1) TsCl, NEt3
TsO
R2
R1
N≡C⊖
NaCN, DMSO
SN2
NC
R2
R1
Ni(0)
H2
H2N
R2
R1

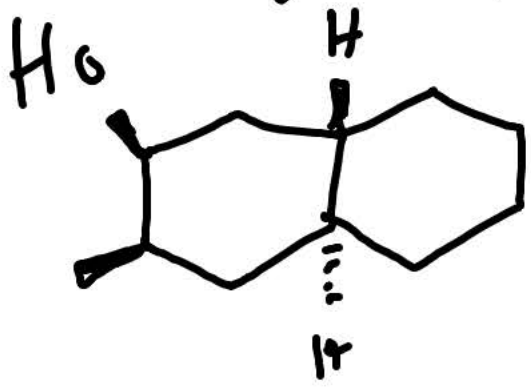
O3, -78 °C, puis Me2S

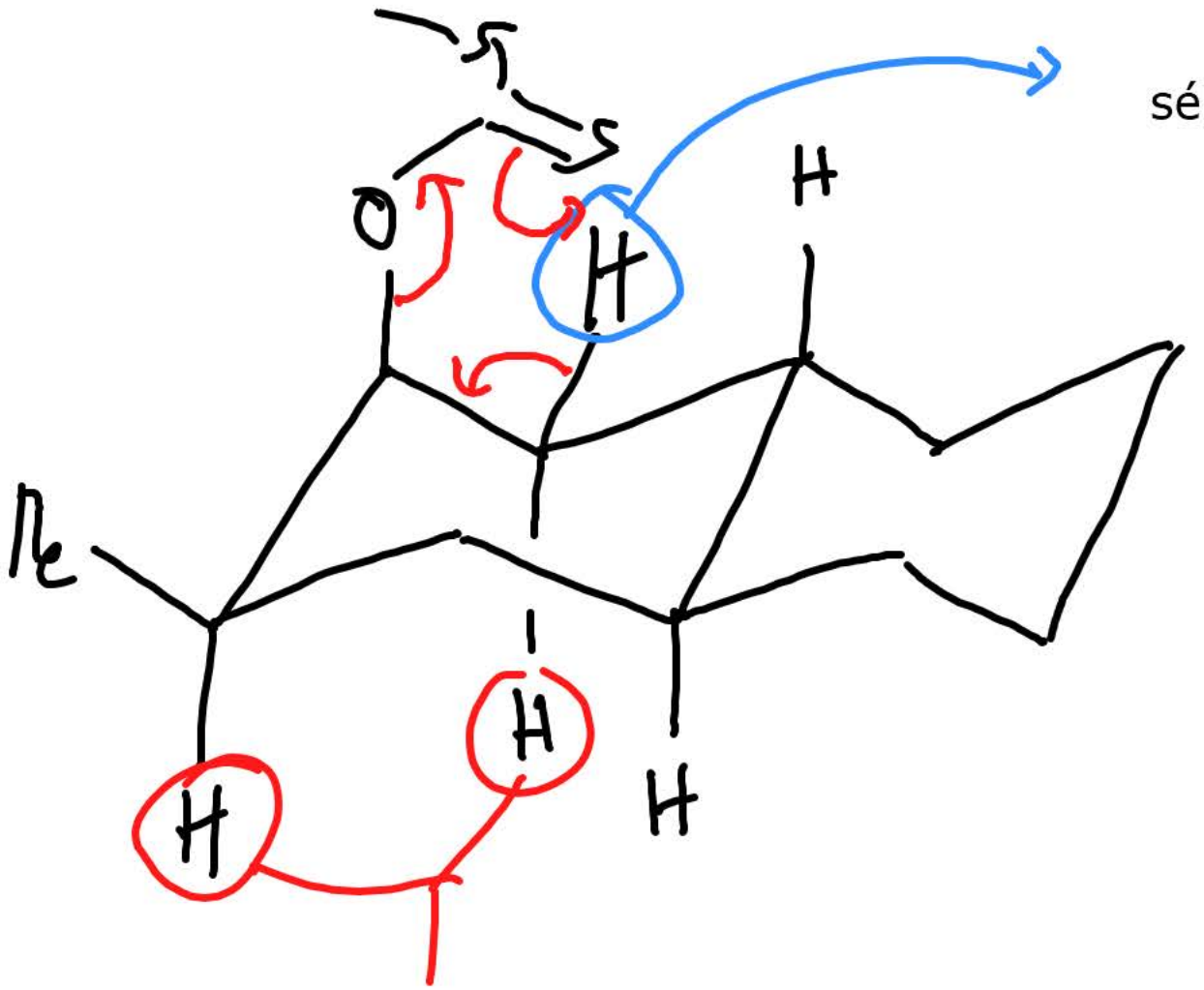


ou



doit être sélective pour donner le bon alcènes





sélectivement pour H en syn

élimination syn, par exemple:
1)NaH, CS2, MeI
2) 150 °C

2 H à 180 °: E2 est une mauvaise idée!