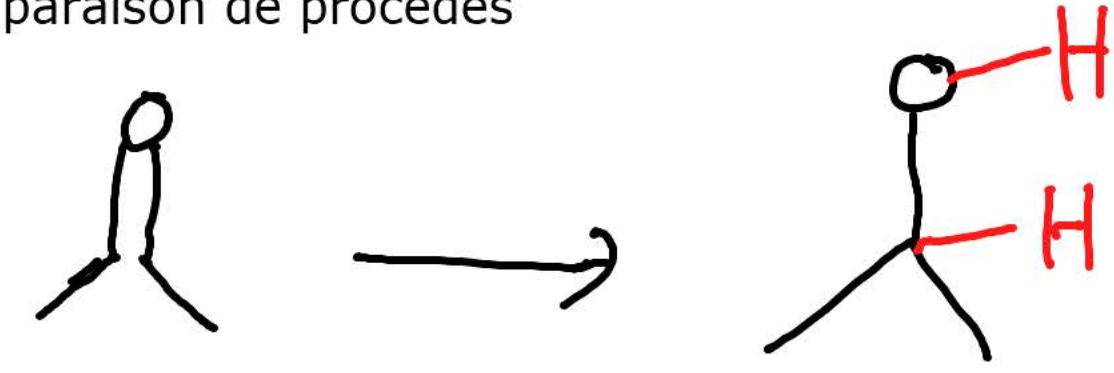
comparaison de procédés

réduction des cétones



cétone

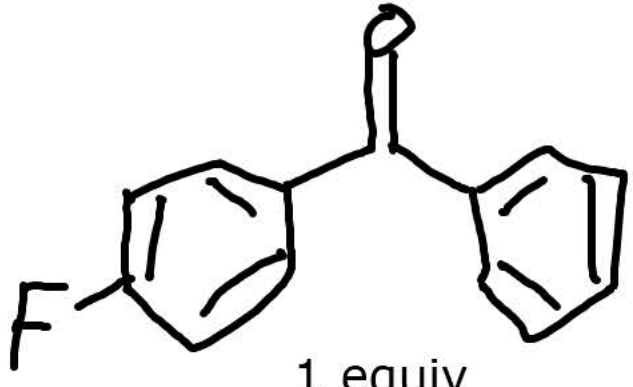
Alcool

① $NaBH_4$

② H_2 , Ru cat.

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

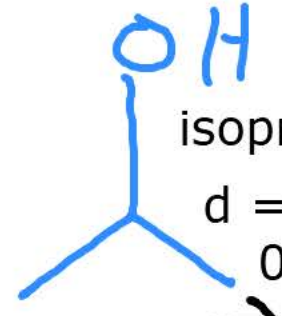
C13H9FO: 24 atomes



1 equiv
200 g/mol

6 atomes

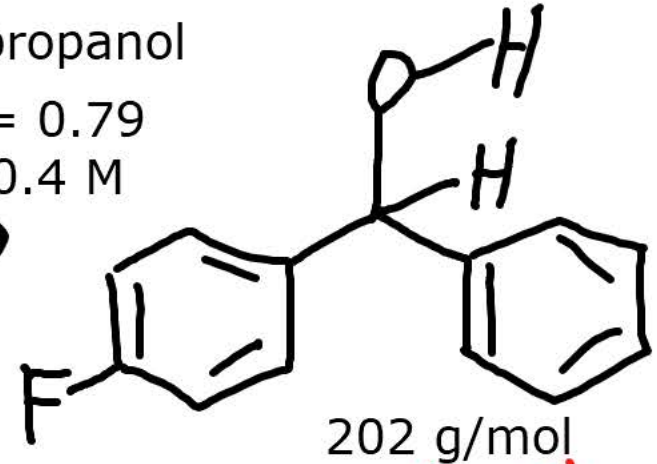
0.38 equiv
37.8 g/mol



isopropanol
d = 0.79
0.4 M

98%

C13H11FO: 26



202 g/mol

économie d'atome 26/(24+6) = 87%

purification: extraction:
acétate d'éthyle: 1 volume (égal à isopropanol), d = 0.90
Eau: 1.5 volume, d = 1.0
0.200 Kg/Kg Na2SO4 (pour sécher le produit)

0.20 Kg/Kg
(Kg de déchet par Kg de produit)

Bilan de masse pour produire 1 kg de produit

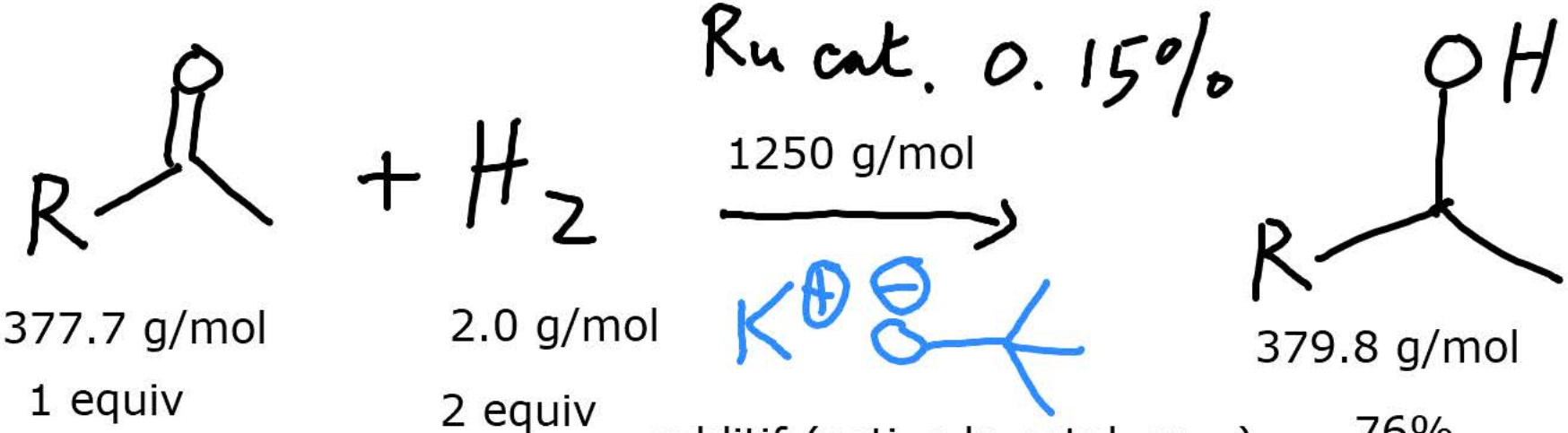
1000/202 = 4.95 mol de produit
98% de rendement, donc 4.95/0.98 = 5.05 mol de produit de départ = 1.01 Kg
NaBH4: 0.38*37*5.05 = 73 g, 0.073 Kg
NaB(OH)4 = 0.200 Kg
Solvant: 0.4 M d'isopropanol, 5.05/0.4 = 12.6 L, 10 Kg

Extraction:
acétate d'éthyle: 1 volume, 12.6 L, 11.3 Kg
Eau: 1.5 volume, 18.9 L, 18.9 Kg
Na2SO4: 0.200 Kg

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

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

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



377.7 g/mol

1 equiv

2.0 g/mol

2 equiv

additif (active le catalyseur)

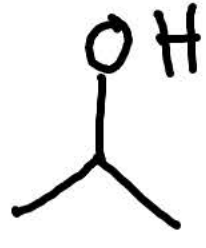
112.2 g/mol, 0.5 equiv

379.8 g/mol

76%

économie d'atome: 100%

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



1.5 M, d = .079
solvant

Bilan de masses:
1 Kg produit: 2.63 mol
Produit de départ: 76% de rendement, donc 3.46 mmol, 1.30 Kg

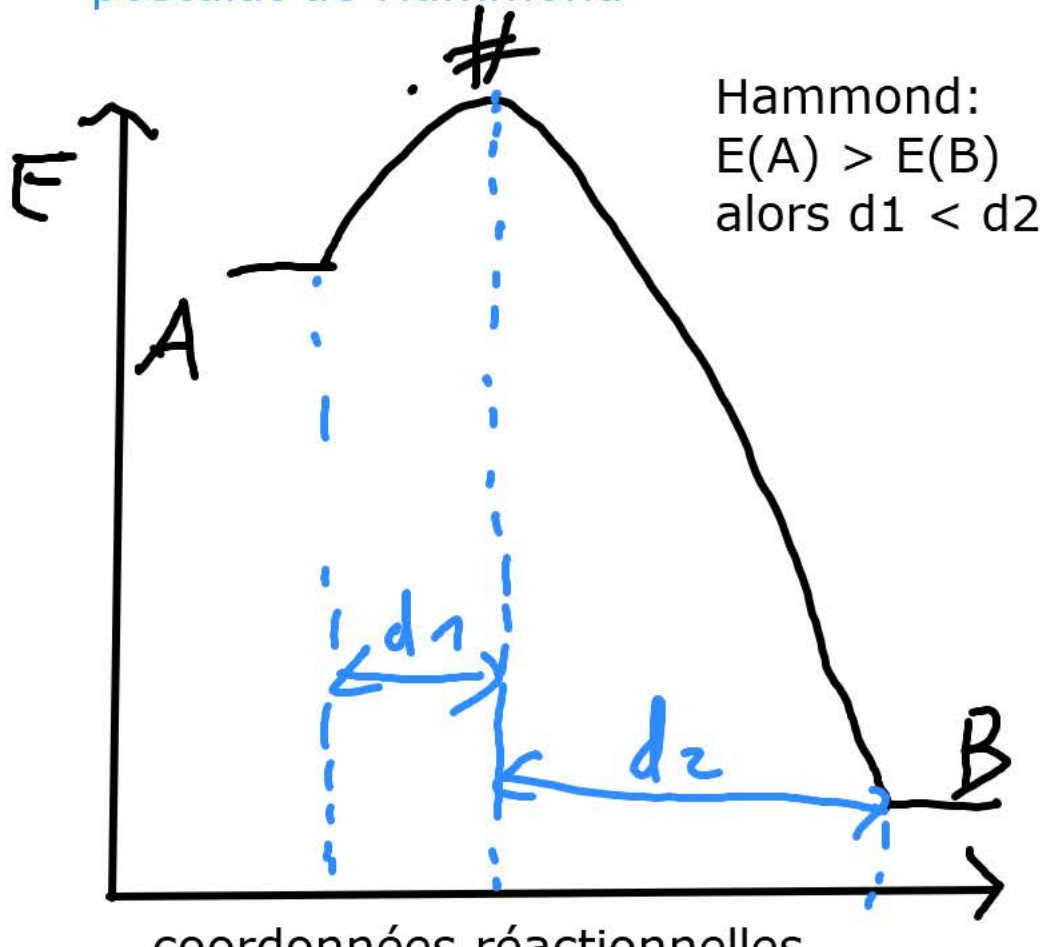
H2: 0.015 Kg
Ru cat: 0.0065 Kg
KOtBu: 0.12 Kg
Isopropanol: 2.3 L, 1.8 Kg
Toluene: 6.5 volume, 13 Kg
Eau, 6.5 volume, 15 Kg

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

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

moitié de l'hydrogène non utilisé!

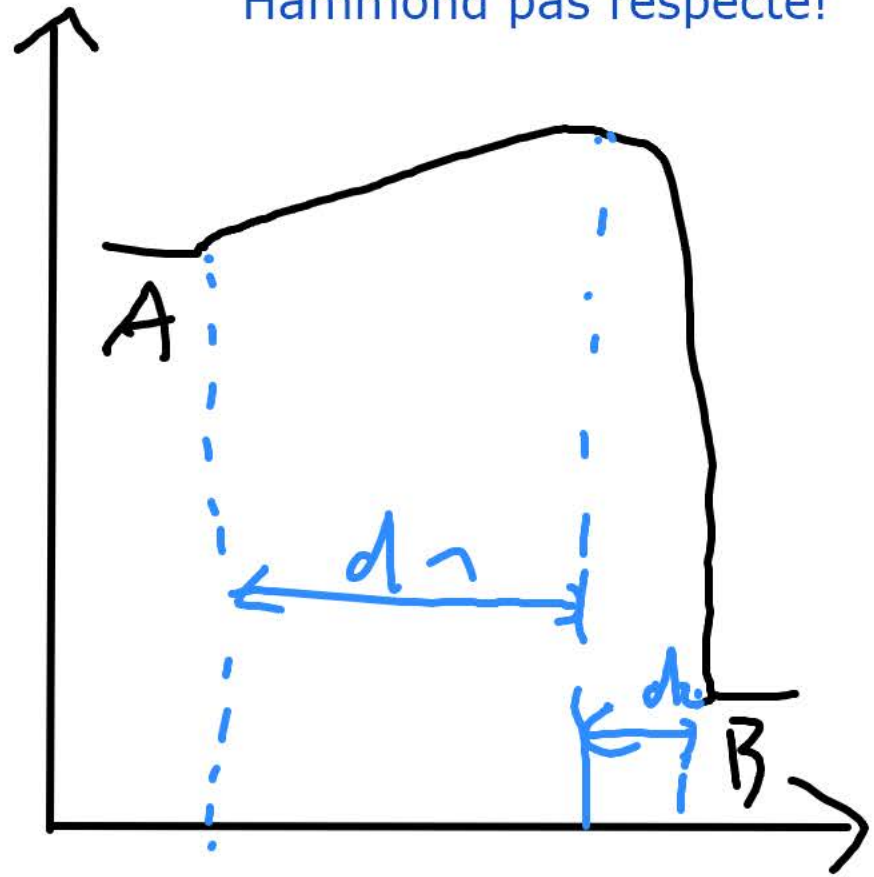
postulat de Hammond



Hammond:
E(A) > E(B)
alors d1 < d2

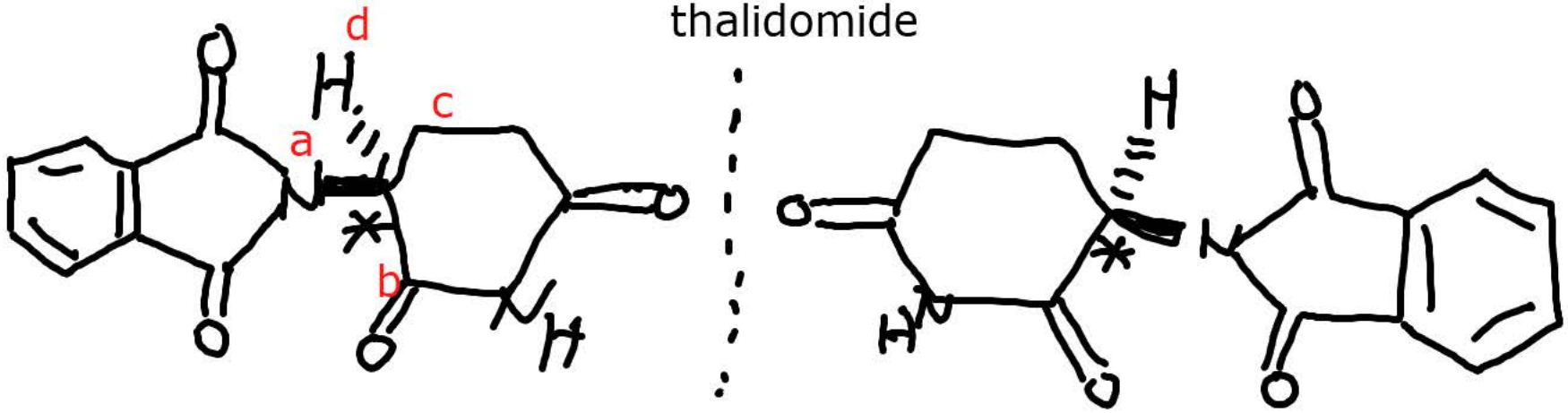
coordonnées réactionnelles
= changement de structure

Hammond pas respecté!



Importance de la chiralité

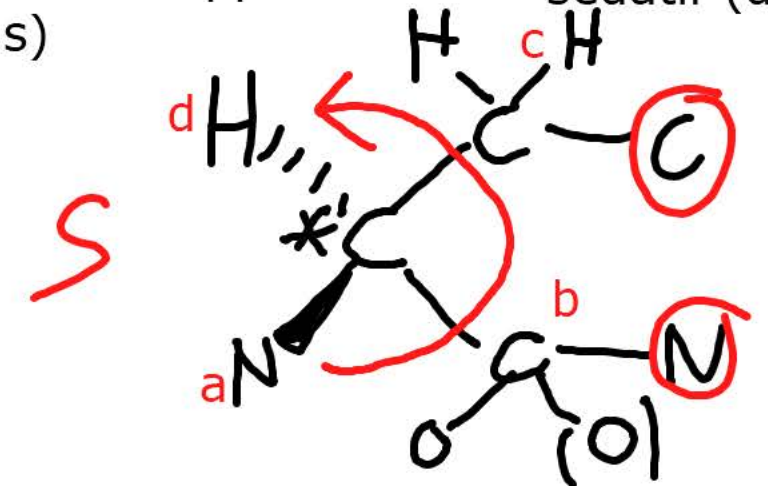
bioactivité différente



thalidomide

tératogène (empêche le développements des membres du foetus)

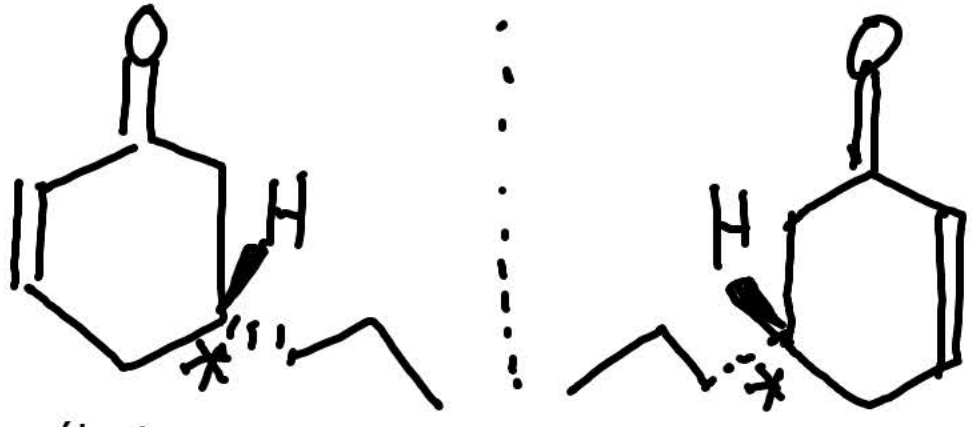
sédatif (donné aux femmes enceintes)



mettre d derrière

configuration absolue: S

odeurs/gouts

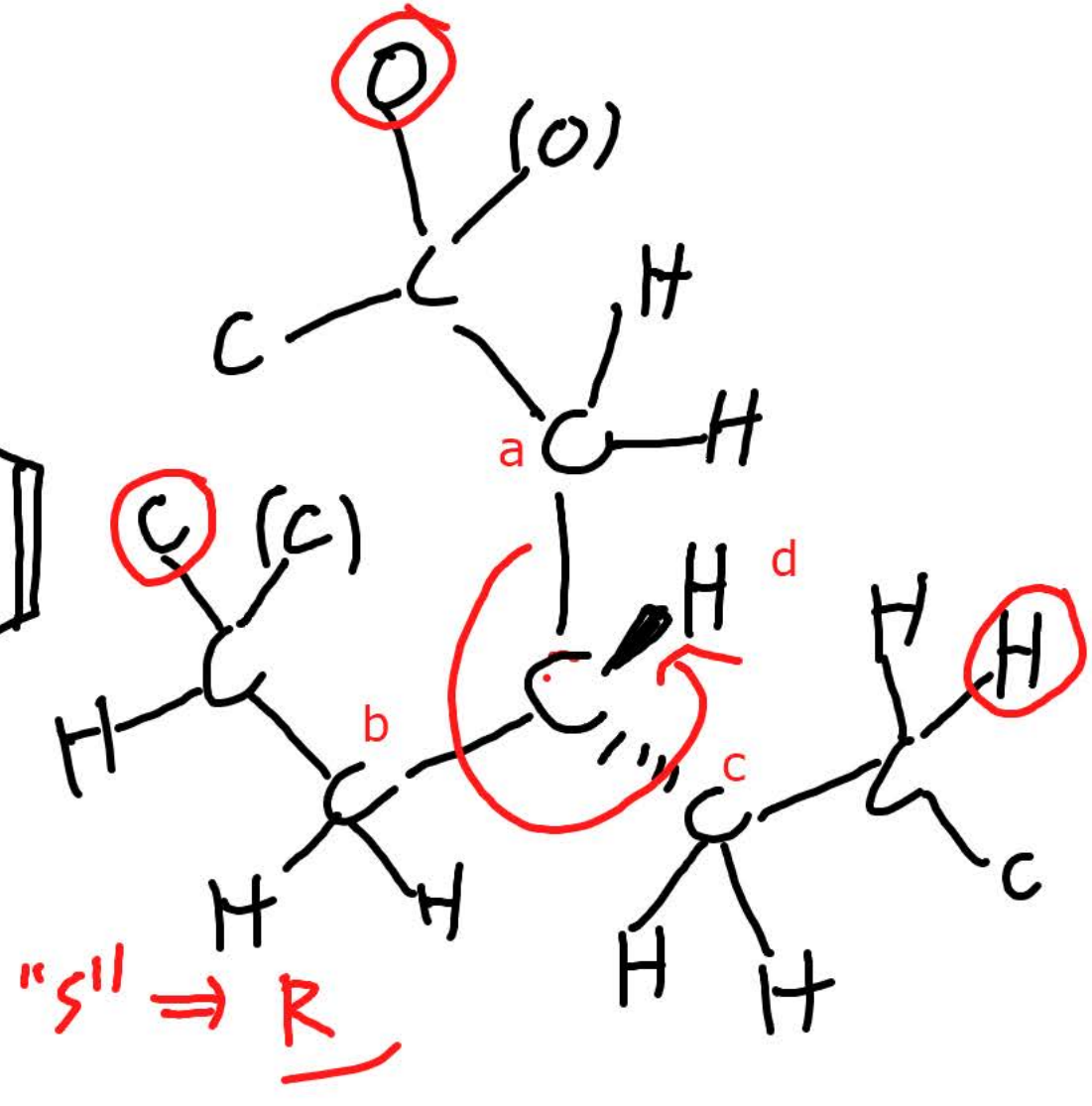


céleri

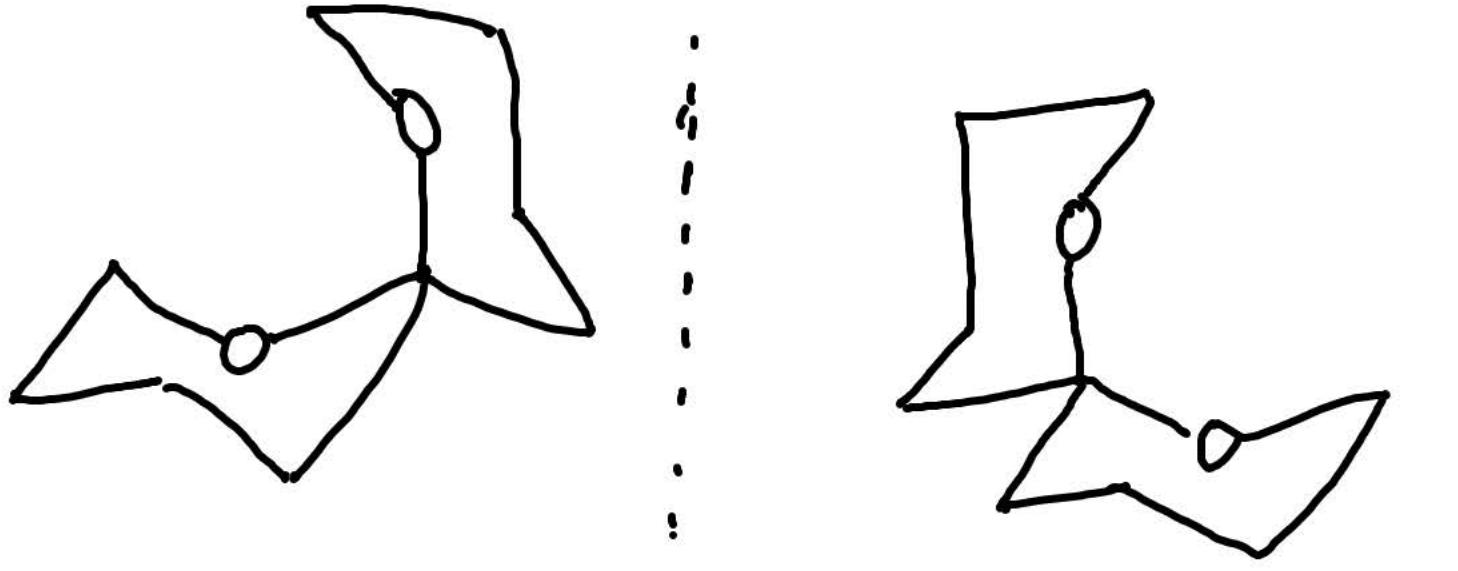
anis

d doit être derrière: ici devant,

"S" mais H (d) devant, donc la molécule a R

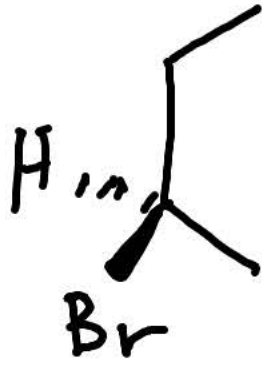


phéromone



attire les insectes mâles

attire les insectes femelles



Mesure au polarimètre:
+ 20°

pour la substance pure: alpha = +23.1 °

pureté optique: 20/23.1 = 87%

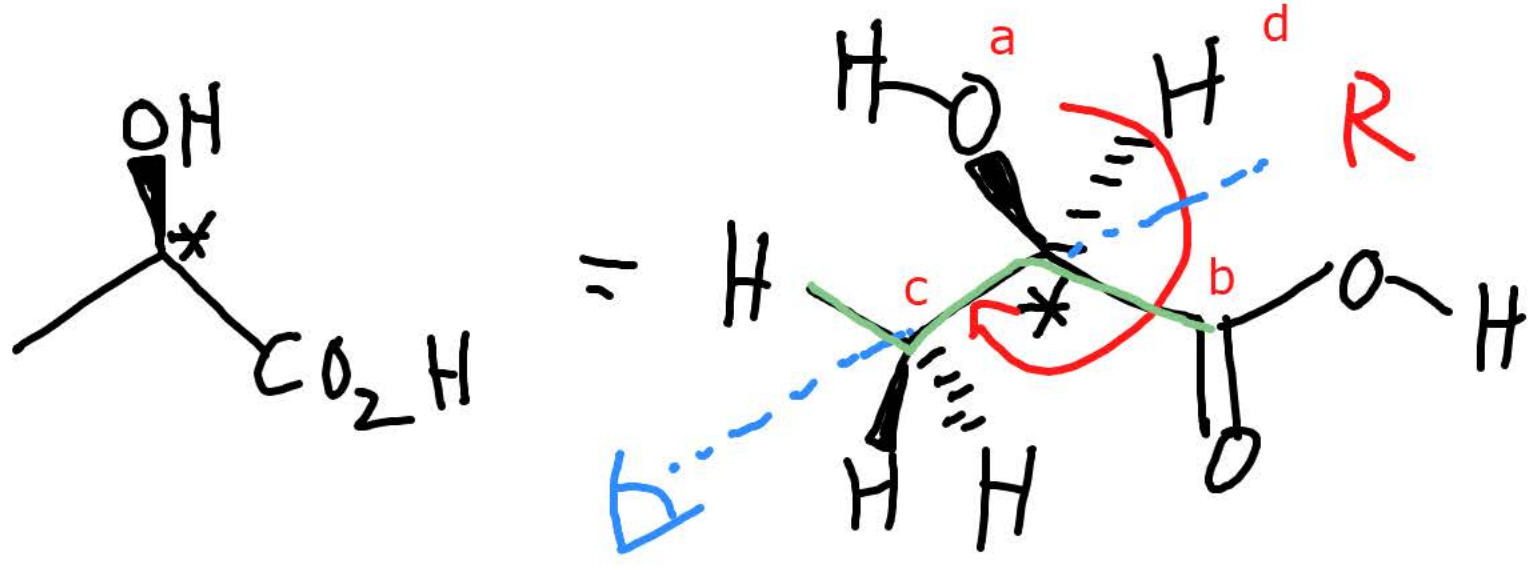
excès énantiomérique = pureté optique = 87% ee

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

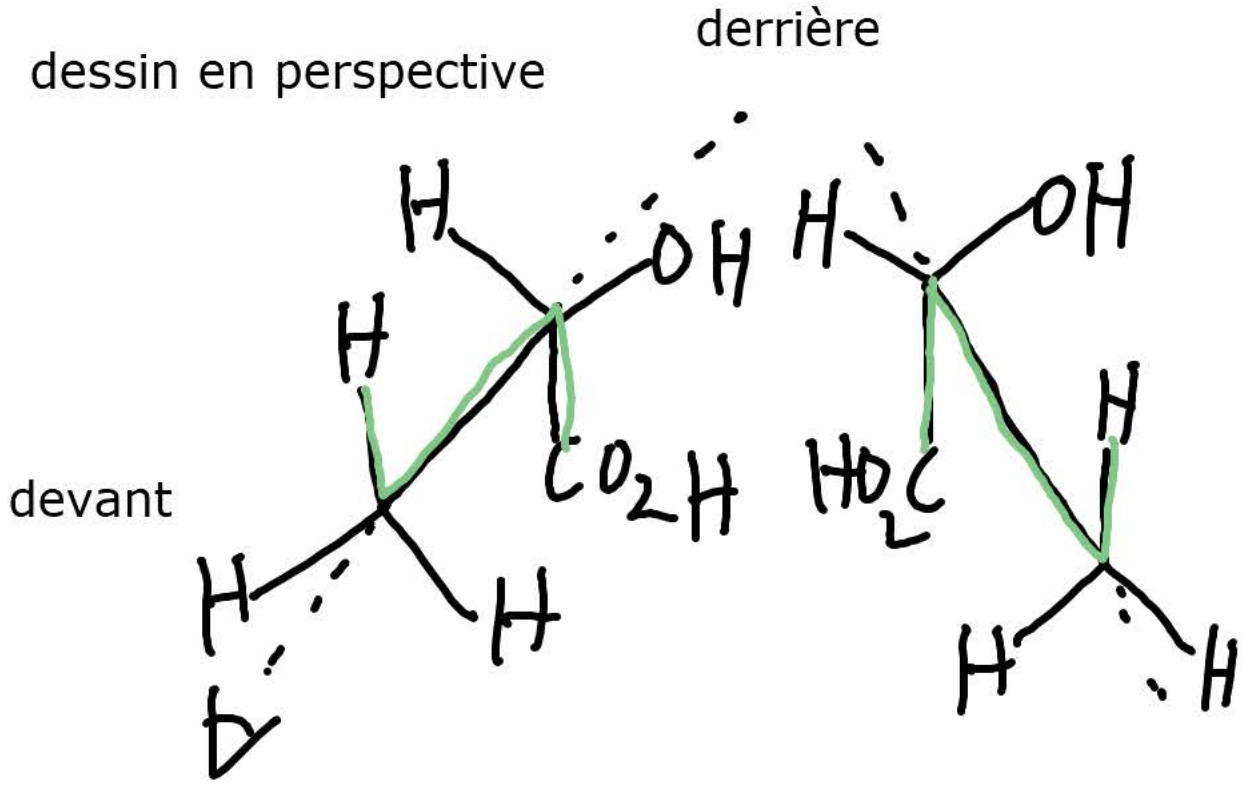
techniques de dessin en chimie organique

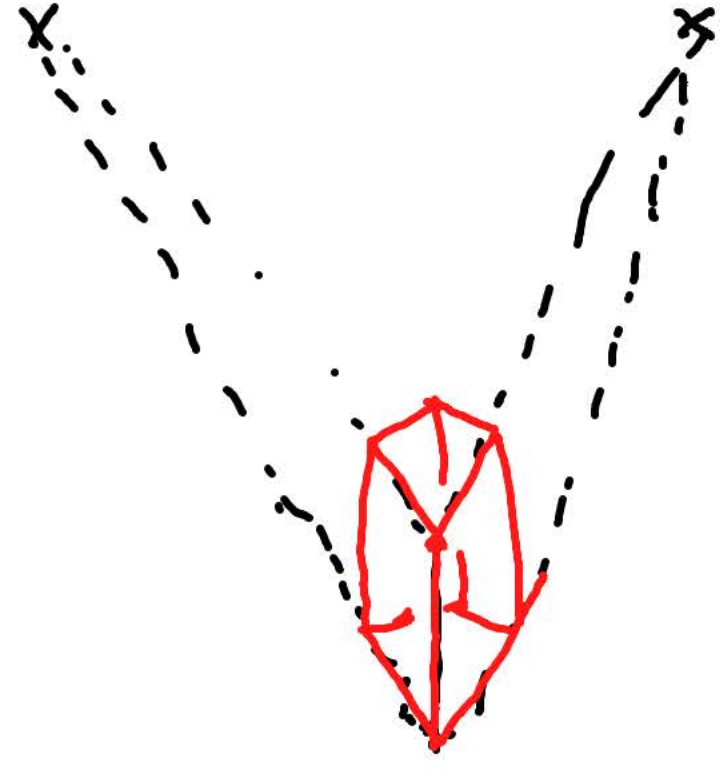
acide lactique

("d" derrière, OK)

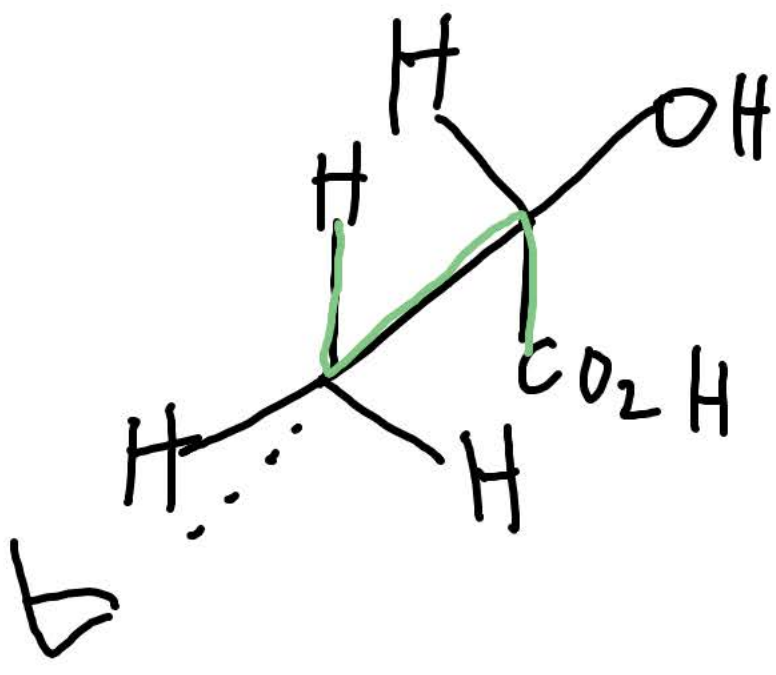


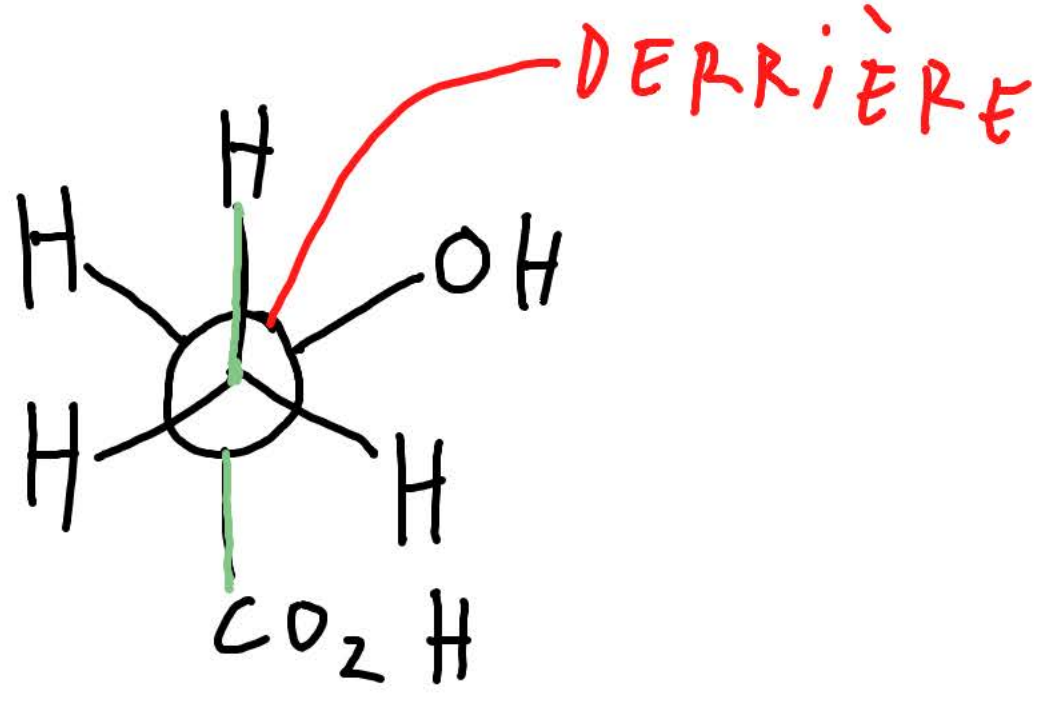
dessin en perspective

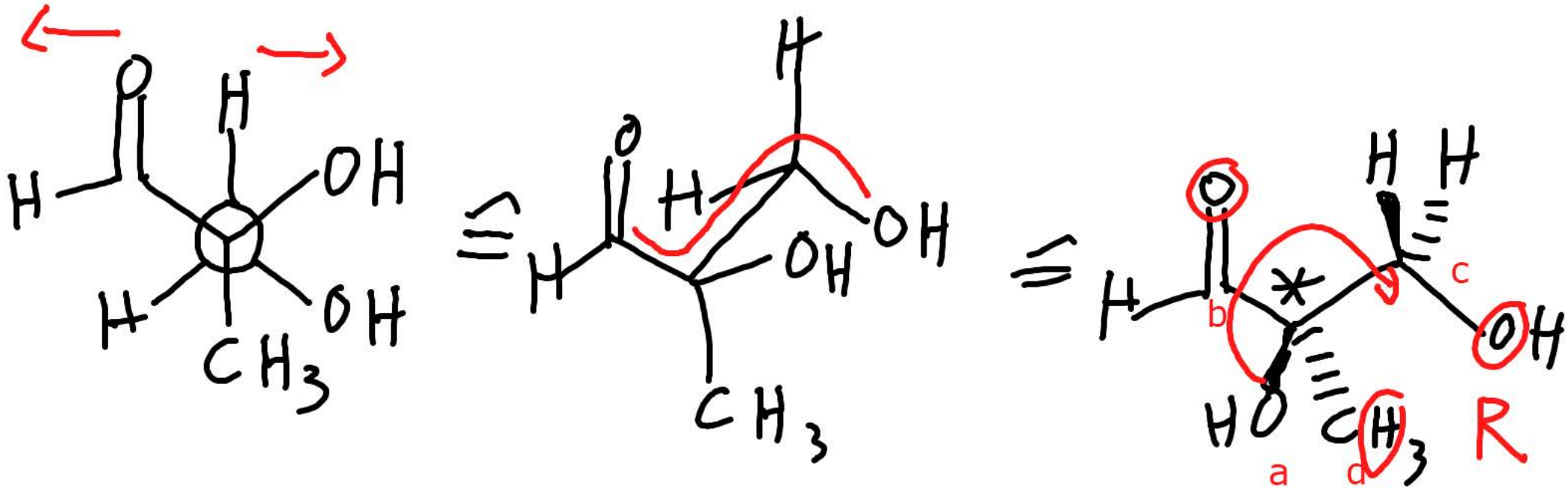




projections de Newman

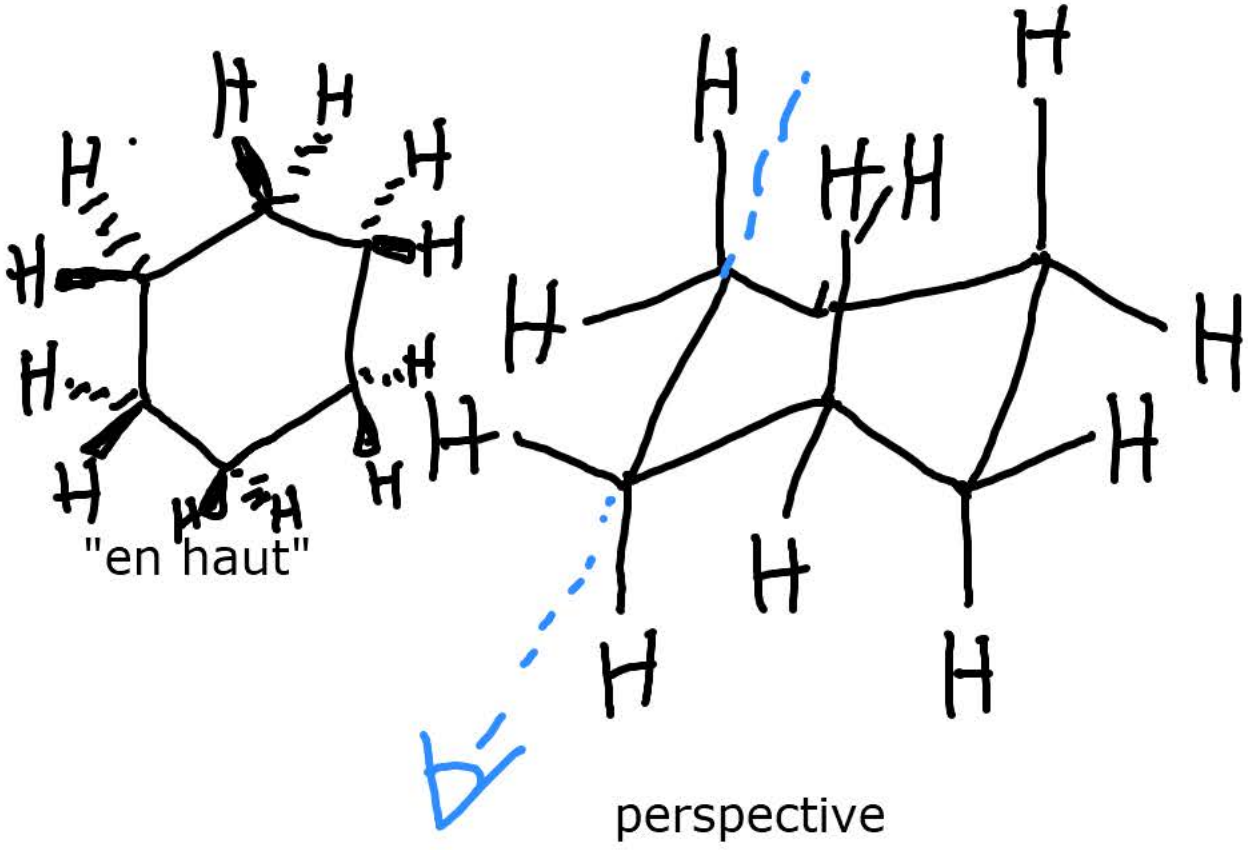


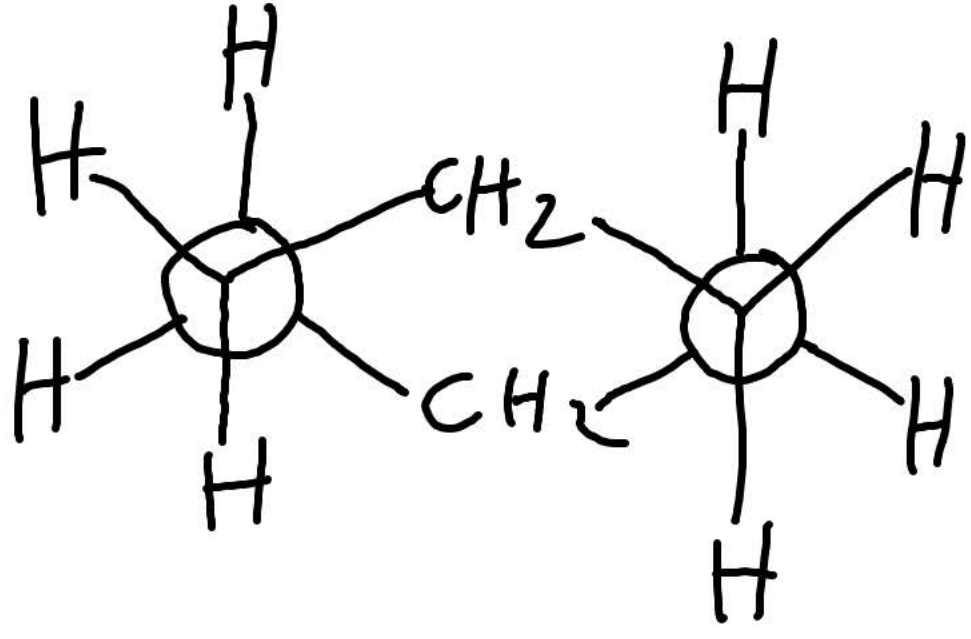




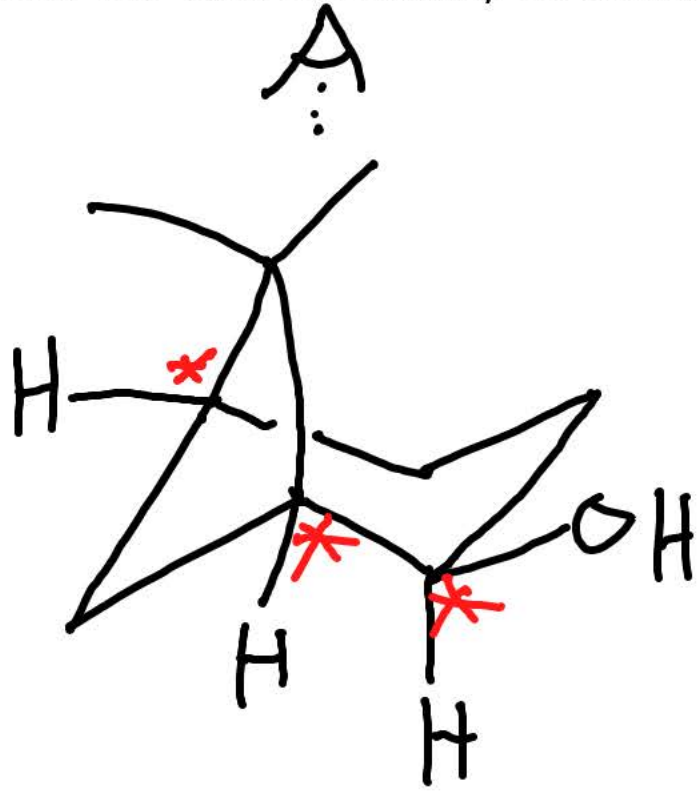
d derrière, OK

stéréocentre sur les molécules cycliques



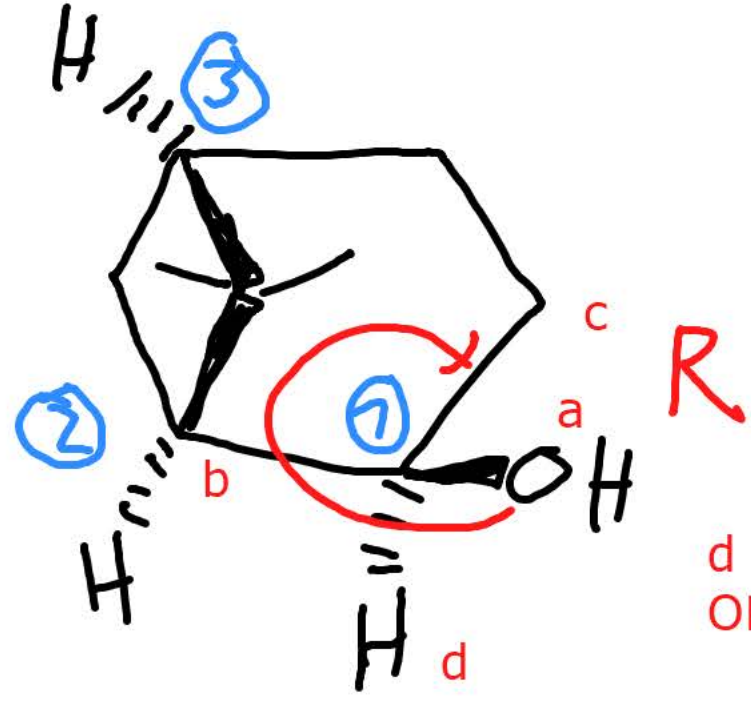


identifier les stéréocentre, et déterminer la configuration absolute (R ou S)

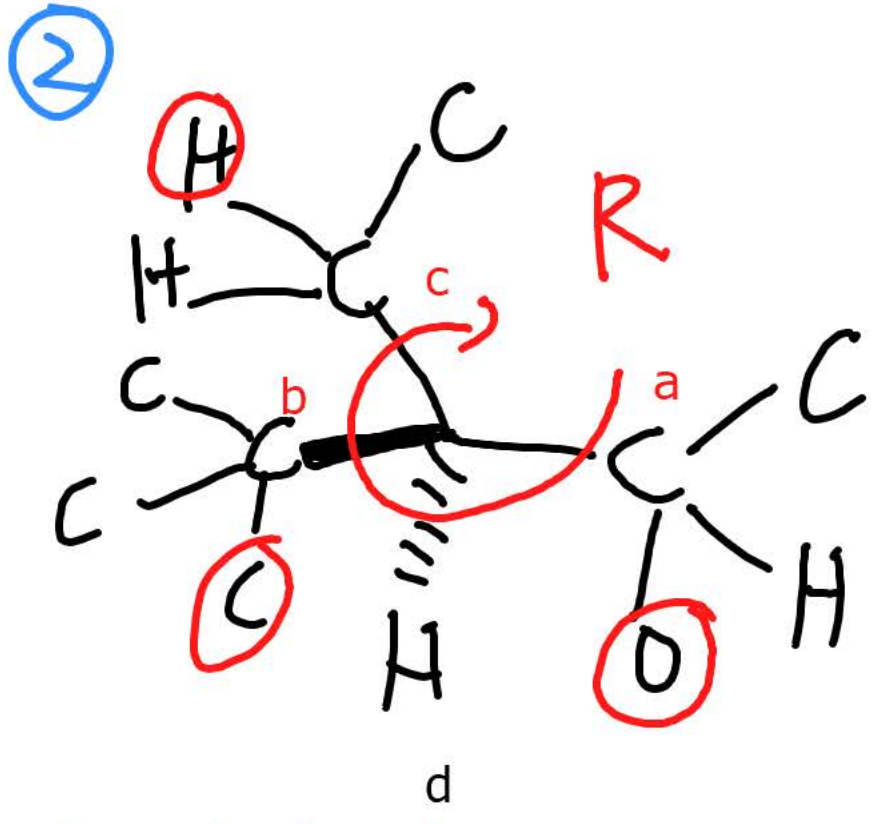


3 stéréocentre

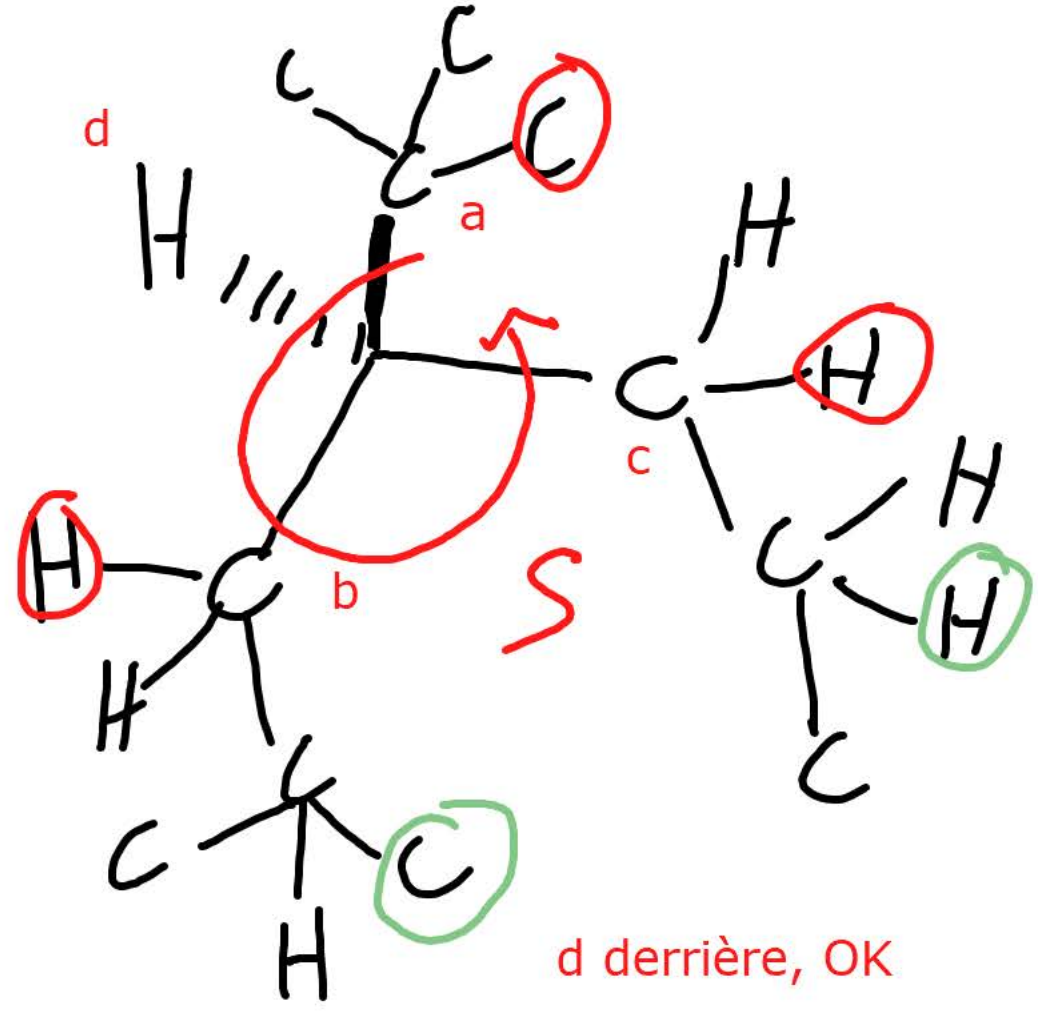
≅



d est derrière
OK

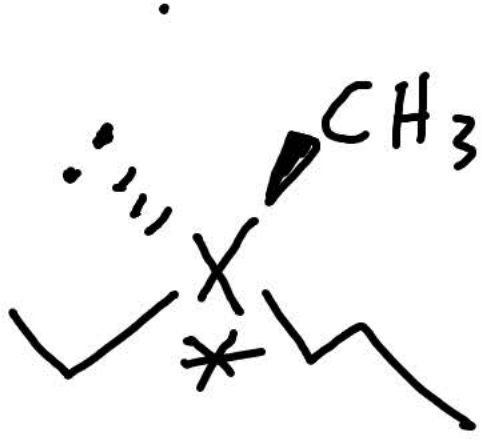


d est derrière: OK



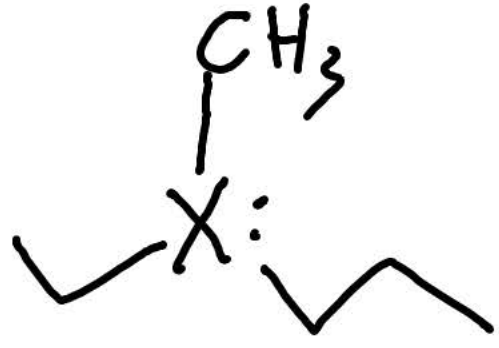
d derrière, OK

cas particulier des hétéroatomes avec paires d'électrons



sp3, chiral

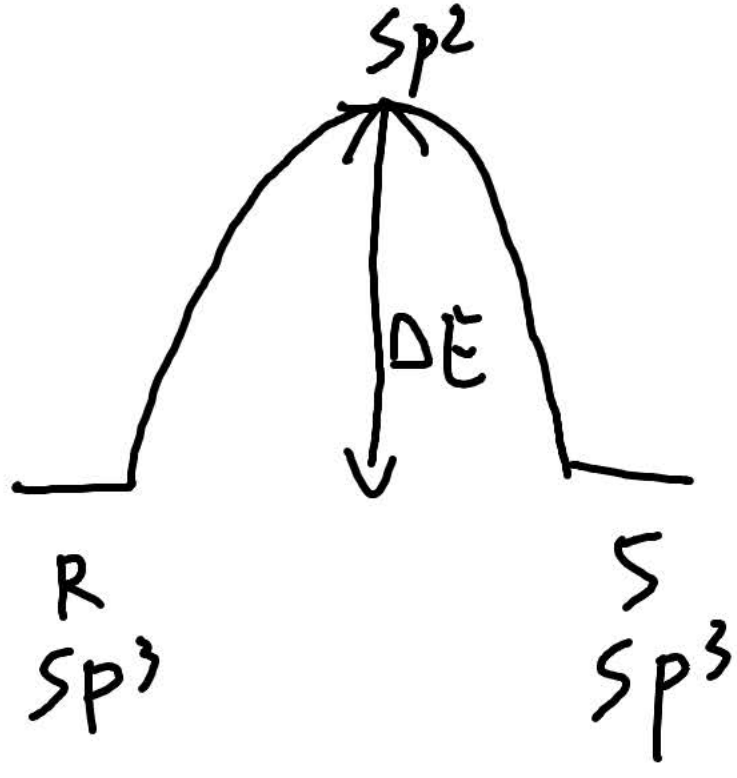
favorisé selon vsepr



sp2, non chiral

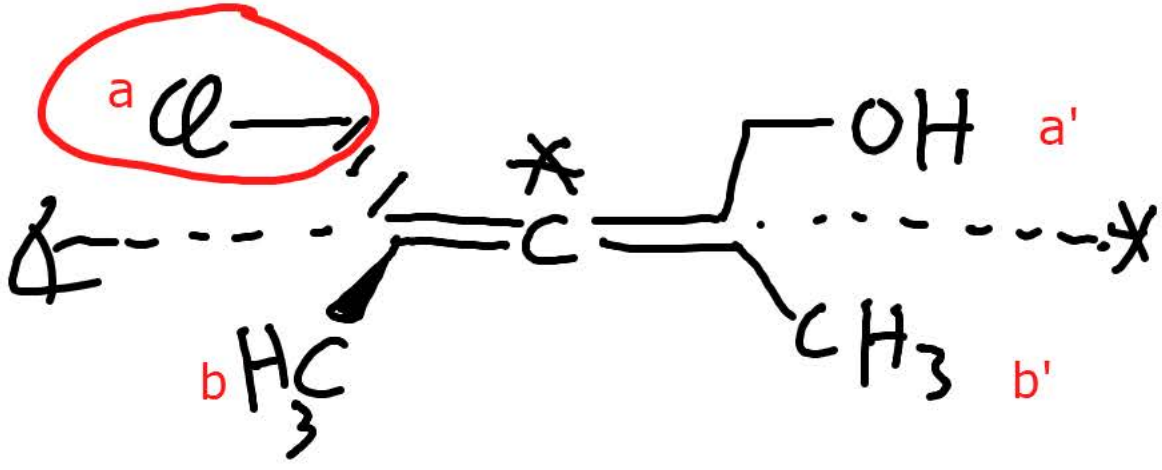
plan de symétrie

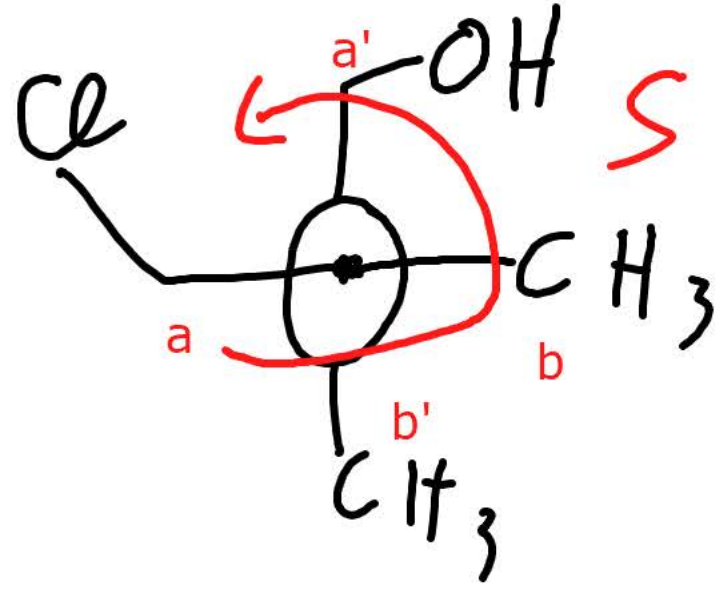
X = P, alpha non égal à 0
X = N, alpha = 0 (pas de chiralité! à 25 °C)



pour P: deltaE = 25 kcal/mol
(> 21 kcal/mol)
Pour N: deltaE = 10 kcal/mol
(< 21 kcal/mol)

pour la 2ème période: pas de stéréocentre sur les hétéroatomes avec un paire d'électron
pour la 3ème période: il y a un stéréocentre!
à température ambiante



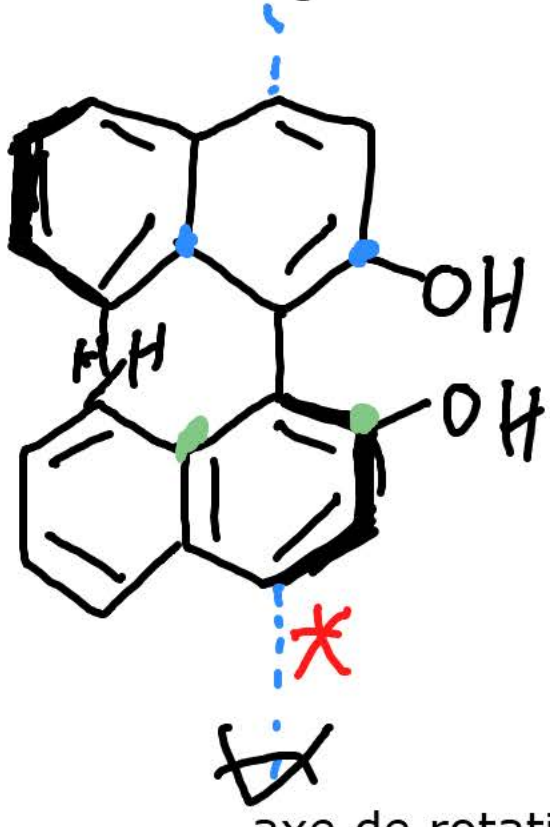


axe S

1 1) on regarde depuis le plus grand le long de l'axe

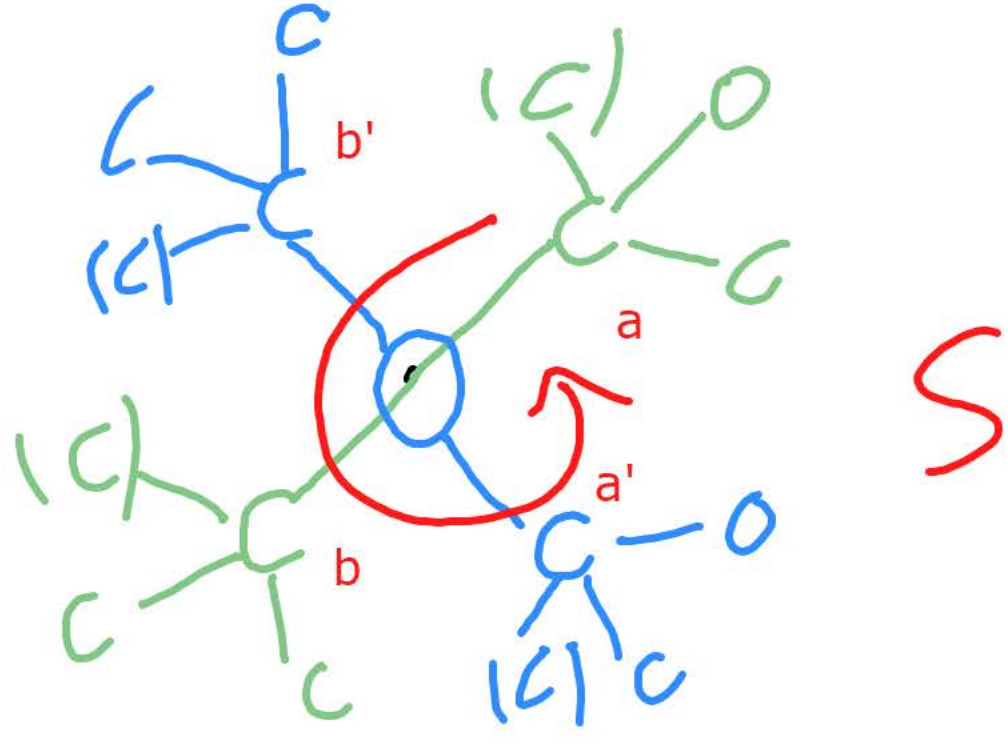
2) on tourne dans le sens:
grand devant, petit devant,
grand derrière

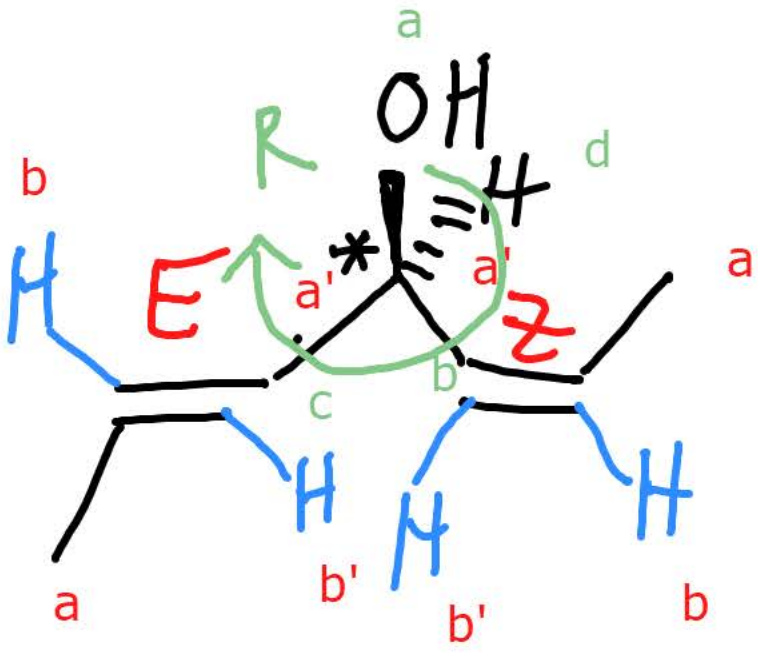
axe de chiralité le long d'une liaison simple qui ne peut pas tourner



Binol

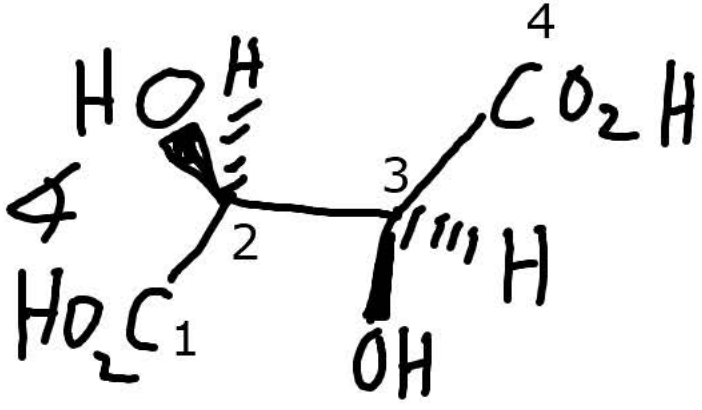
axe de rotation





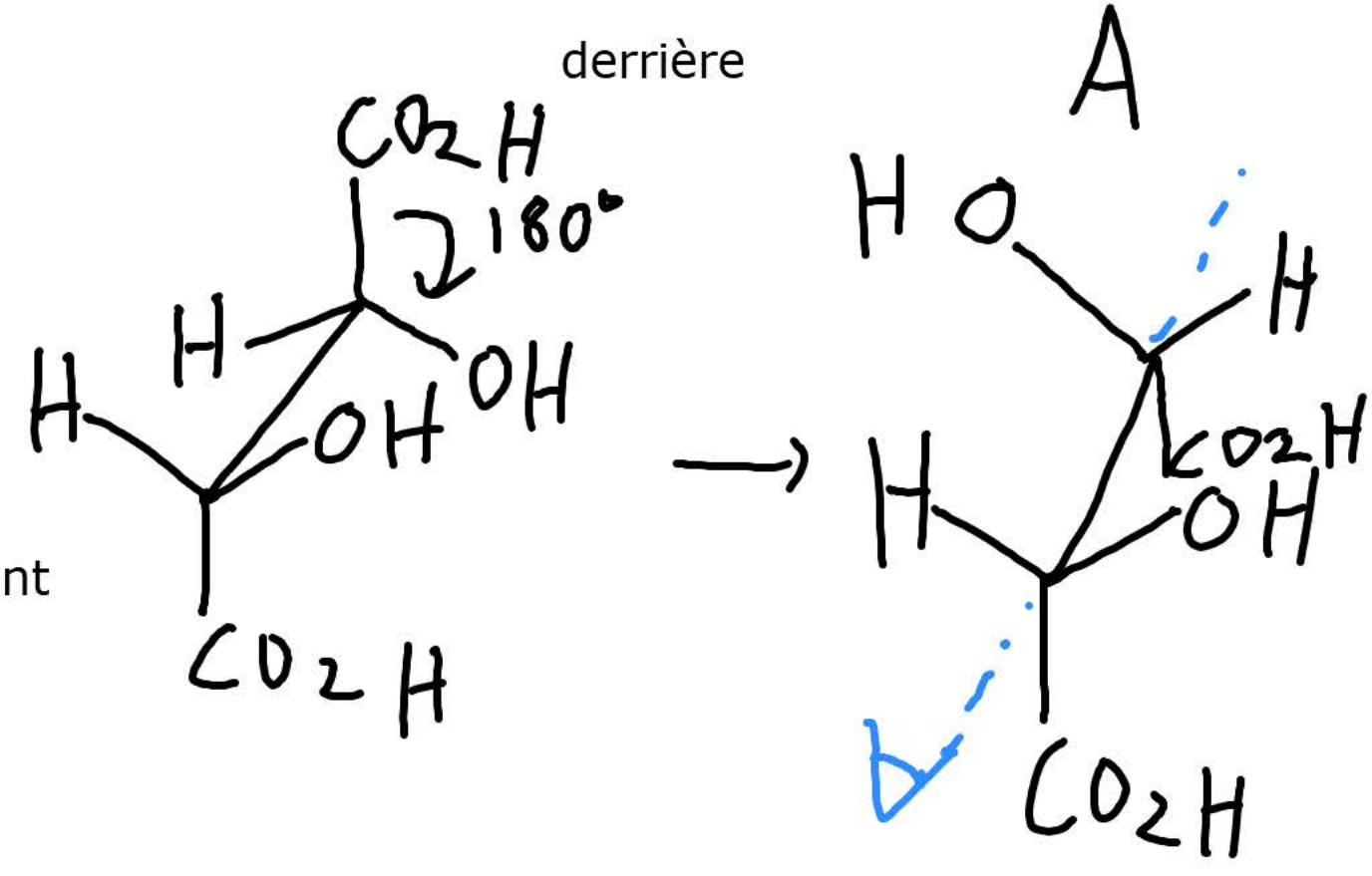
régle: Z à la priorité E

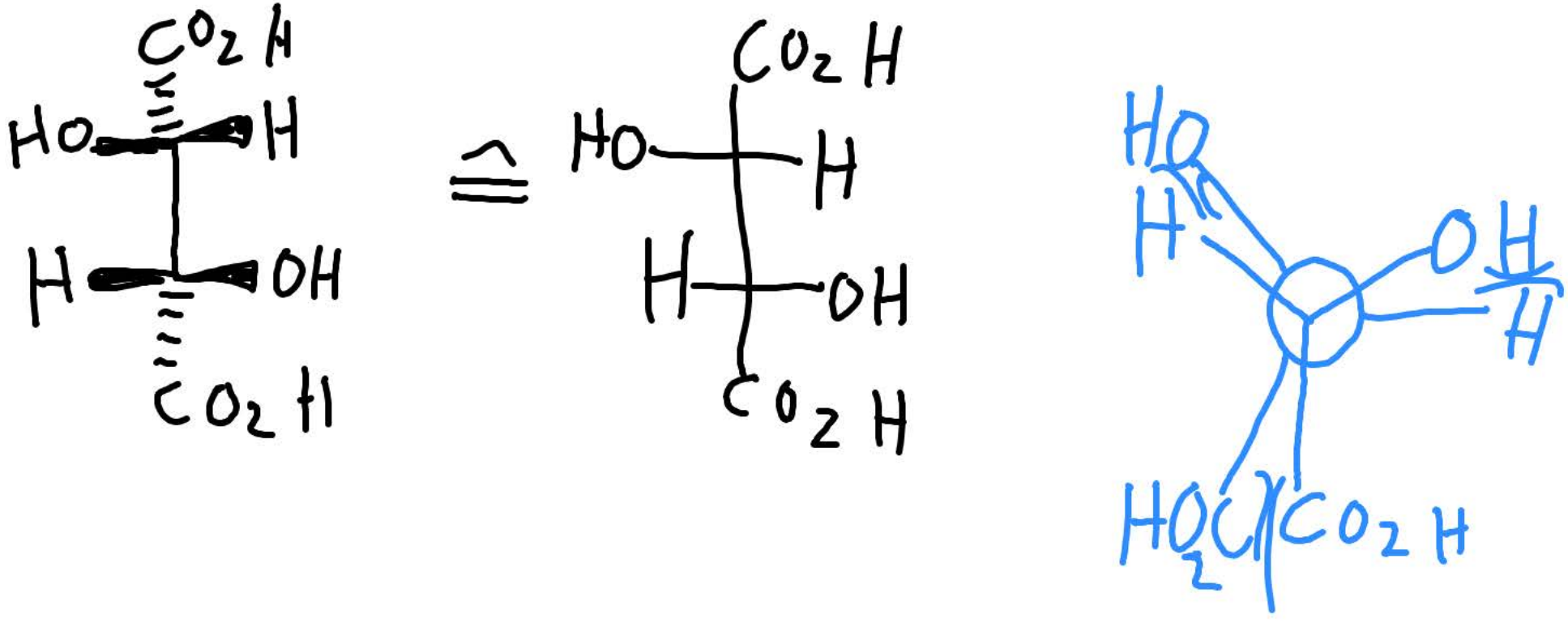
acid tartrique



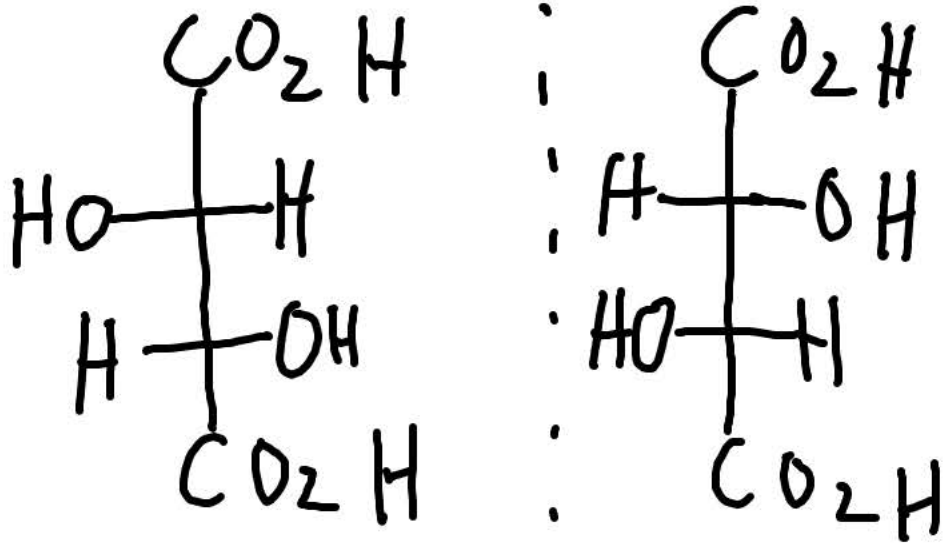
(-)-(2S,3S)

alphaD = -12°





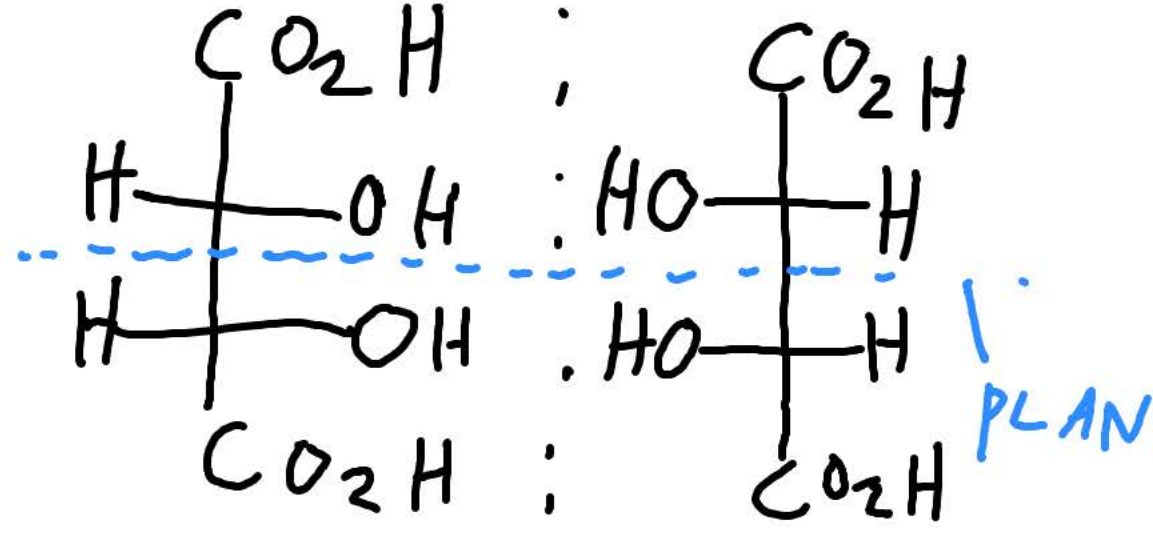
situation pas favorable, Fischer ne correspond pas une conformation favorisée de la molécule!



(-)-(2S,3S)

(+)-(2R,3R)

la molécule contient un plan de symmétrie interne et est non chirale!



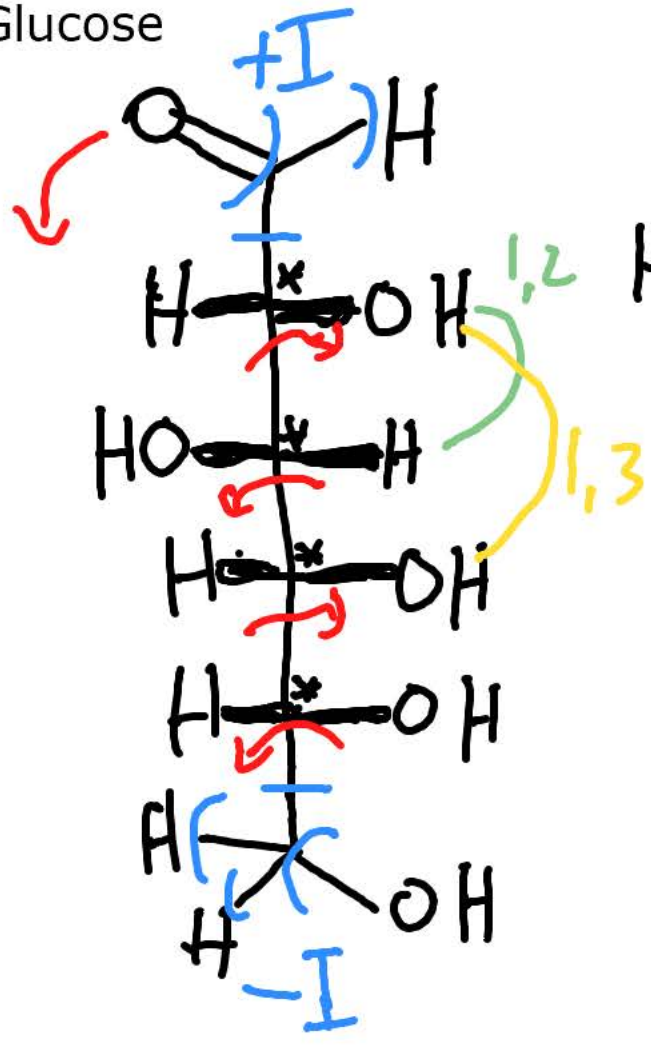
molécules identiques!

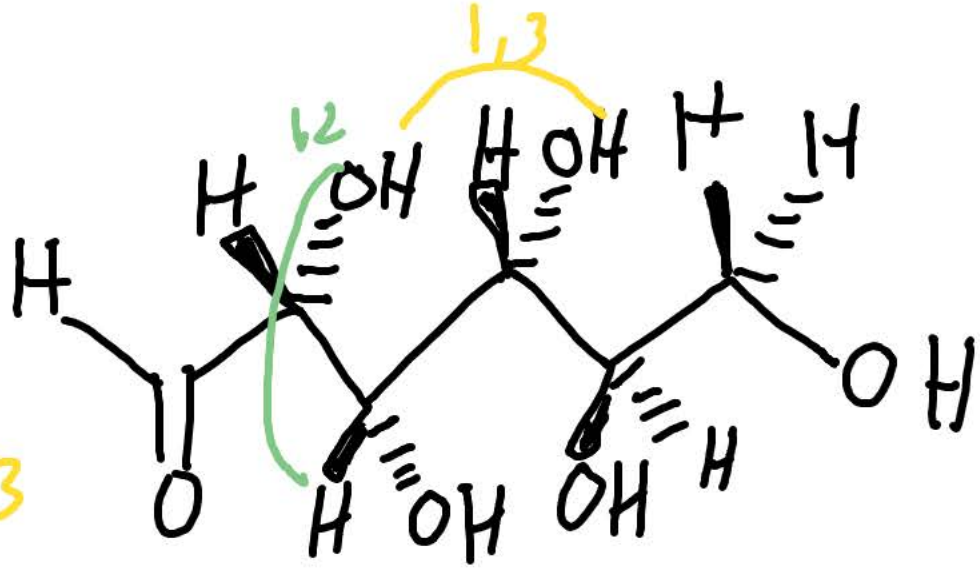
(2S,3R)

(2R,3S)

alphaD = 0

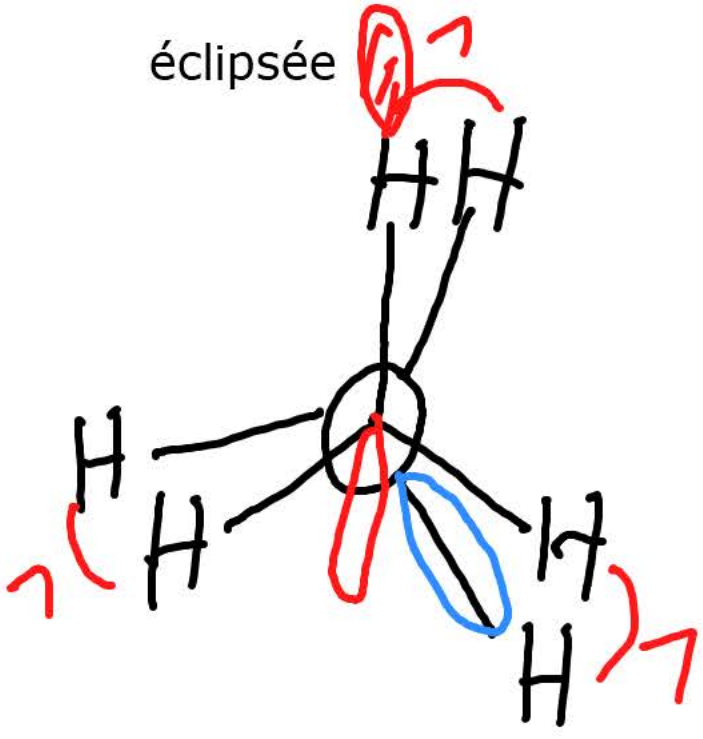
Glucose





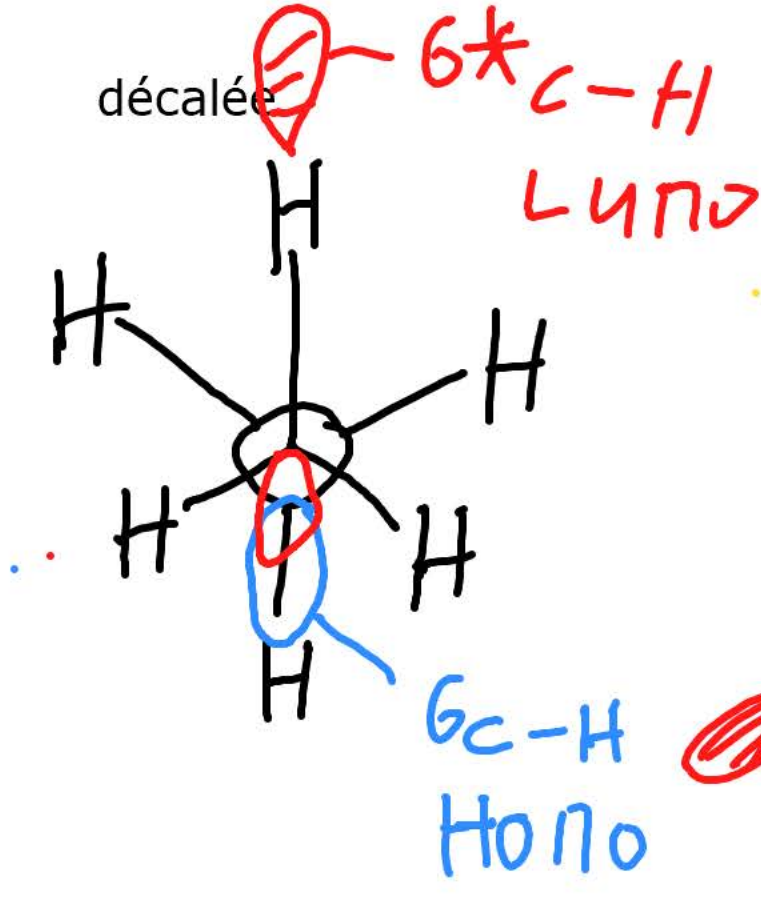
positions 1,2: inversées en passant de Fischer à zigzag
positions 1,3 restes du même côté

origine pour la barrière pour l'éthane

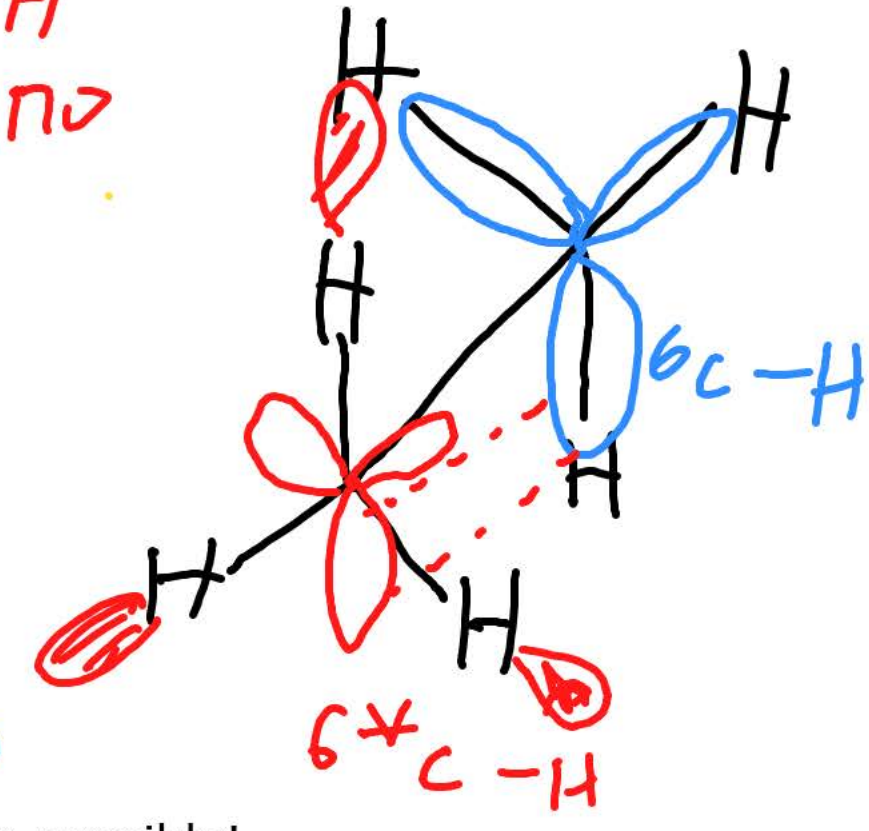


3 kcal, pas d'effet stérique
(H trop petit!)

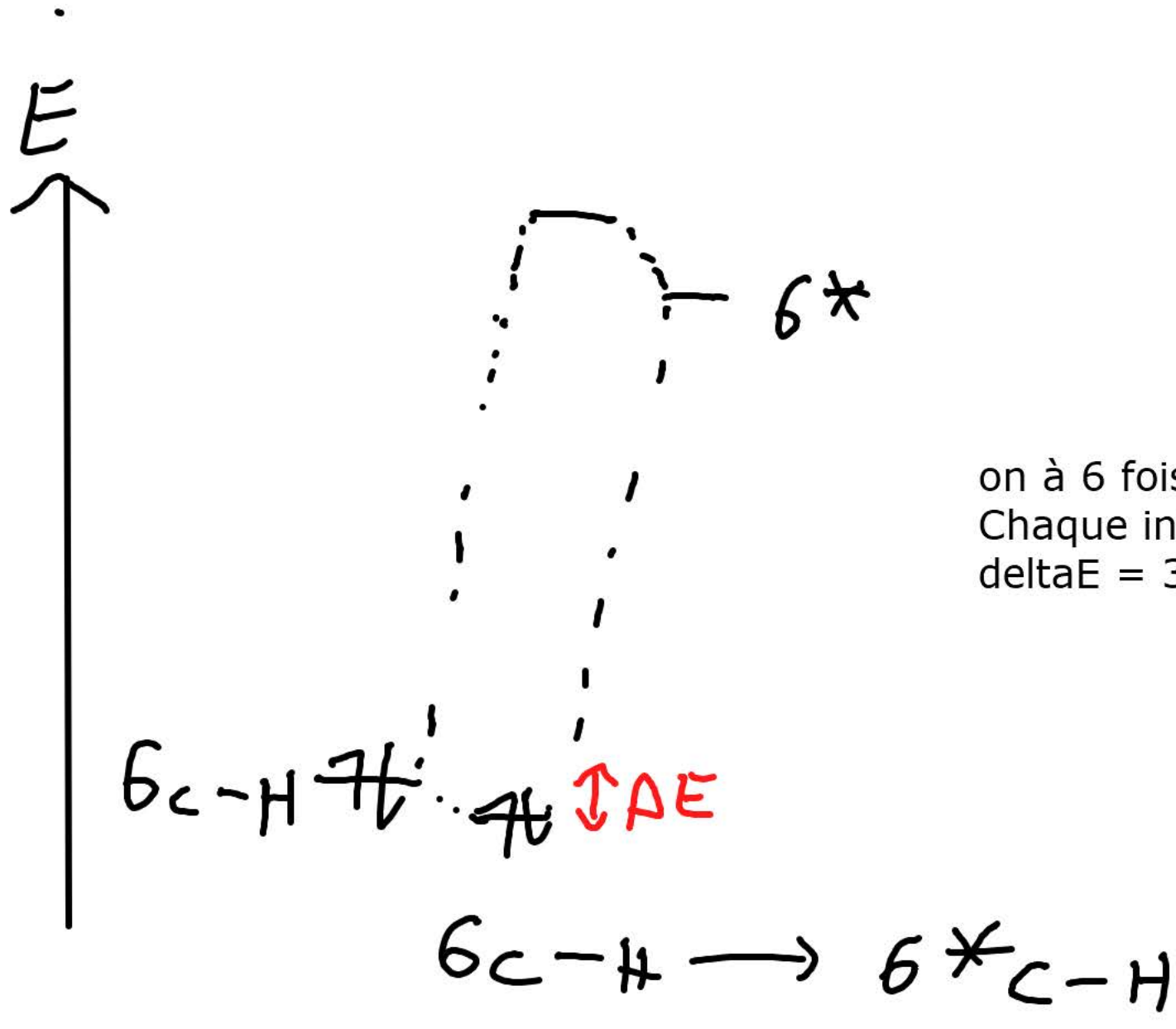
pas de superposition, pas d'interaction!



interaction orbitalaire possible!

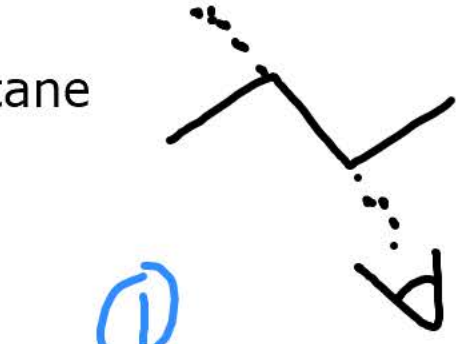


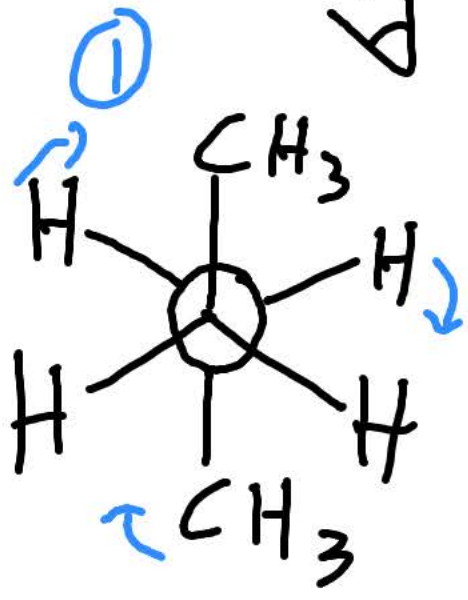
un total de 6 interactions



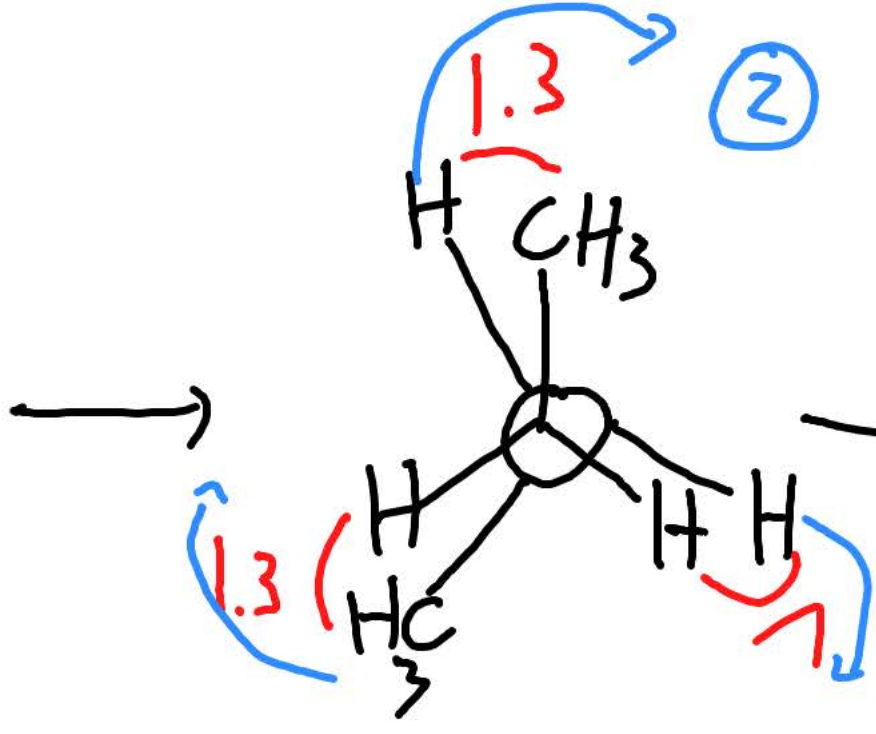
on à 6 fois cette interaction,
Chaque interaction à 2 électrons
deltaE = 3/12 kcal/mol = 0.25 Kcal/mol

butane

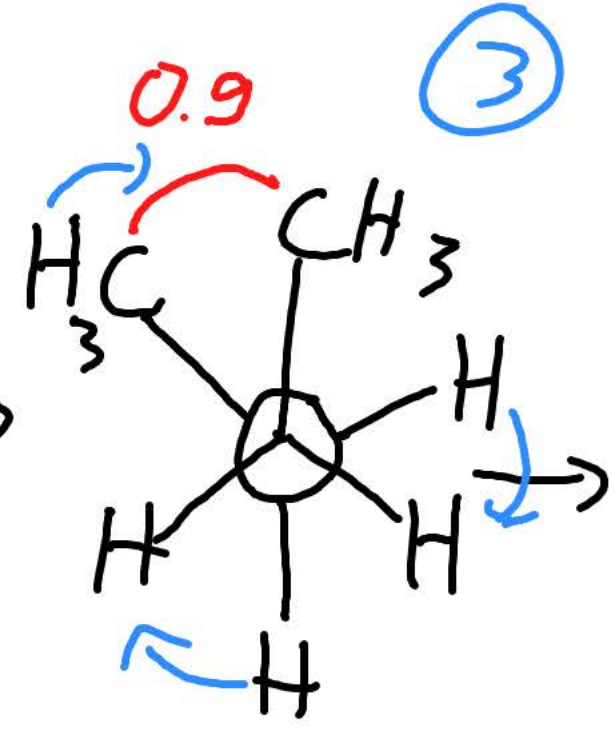




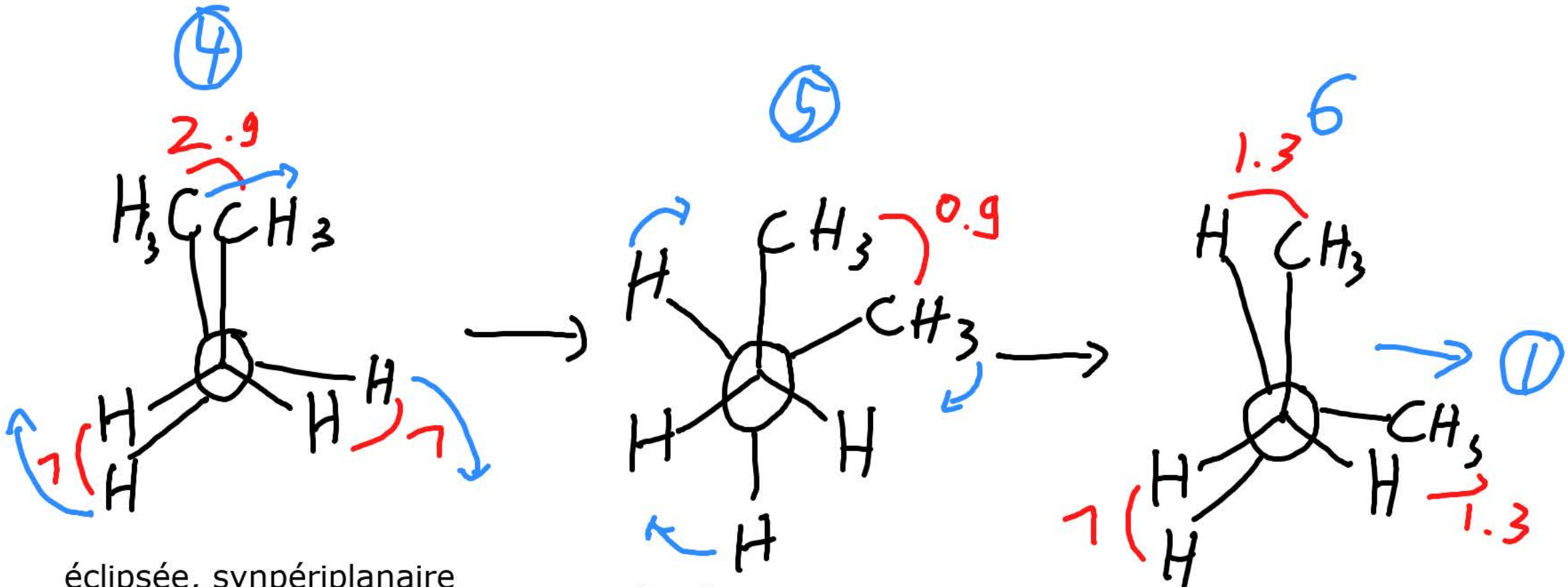
décalée, antipériplanaire
E = 0



éclipsée, anticlinale
E = 3.6



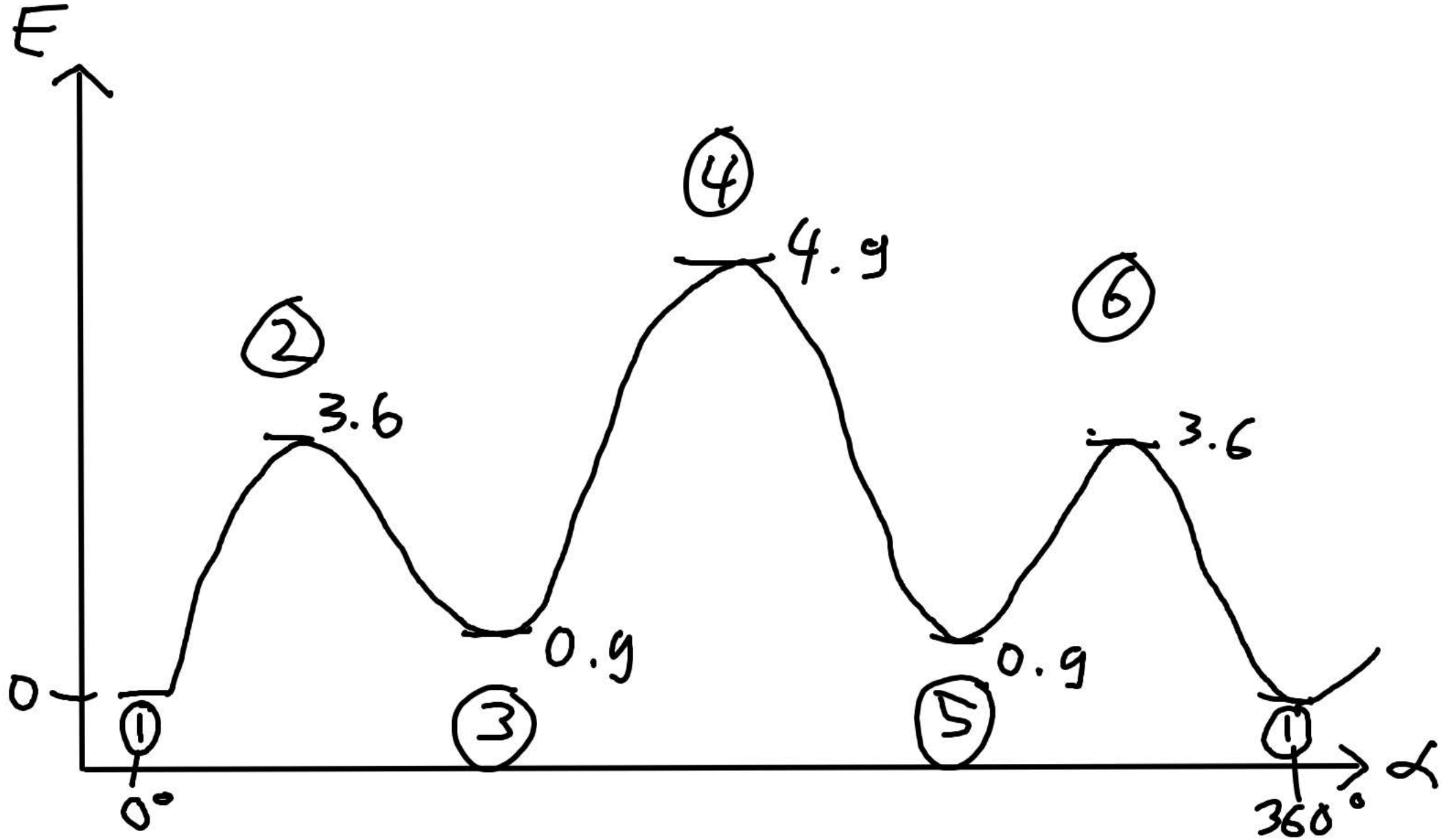
décalée, synclinale ou
gauche, E = 0.9



éclipsée, synpériplanaire
E = 4,9

décalée, synclinale ou gauche
E = 0.9

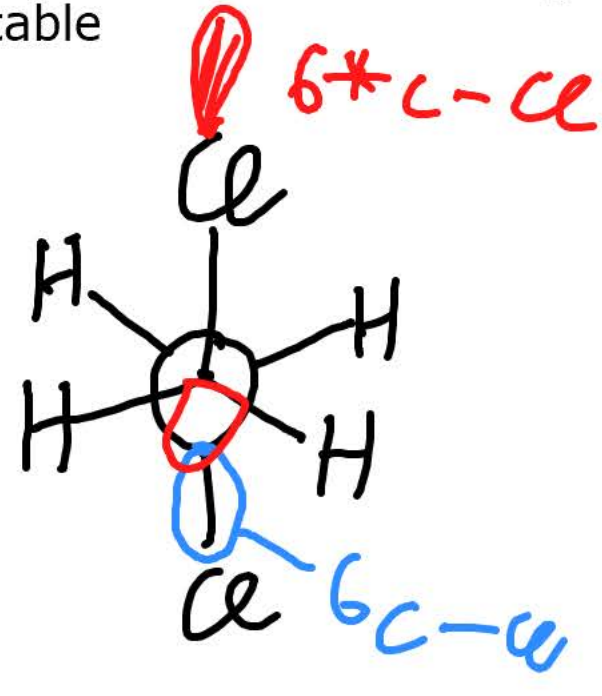
éclipsée, anticlinale
E = 3.6


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

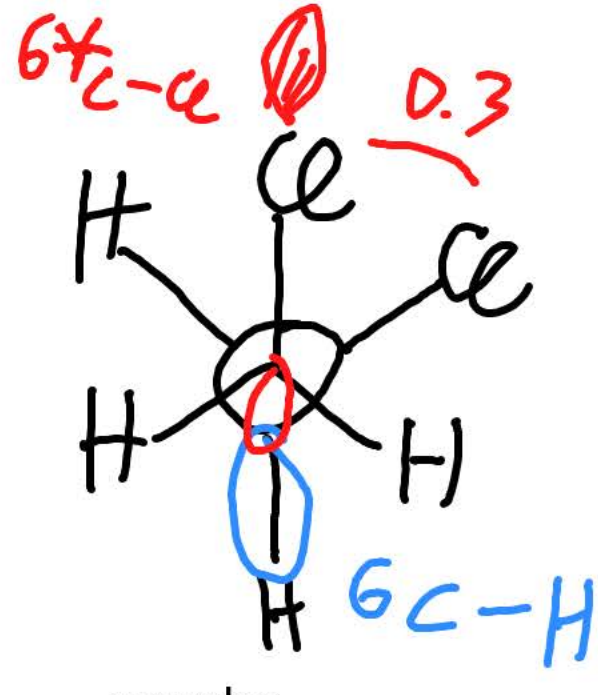
comparer le butane et le dichloroéthane

antipériplanaire est le plus stable

gauche/synclinale est la plus stable!

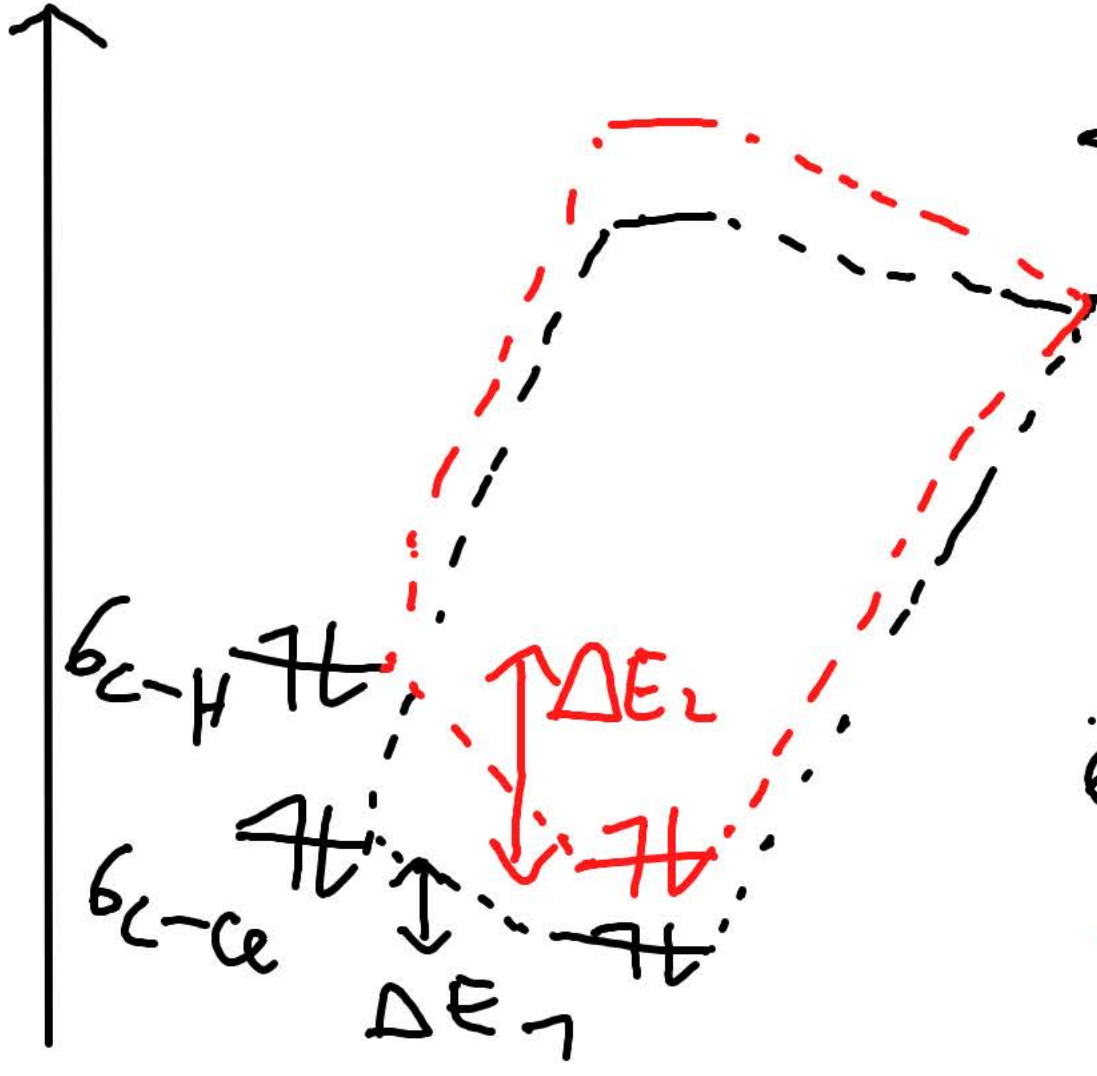


antipériplanaire



gauche

Cl plus petit que CH3
0.3 au lieu de 0.9



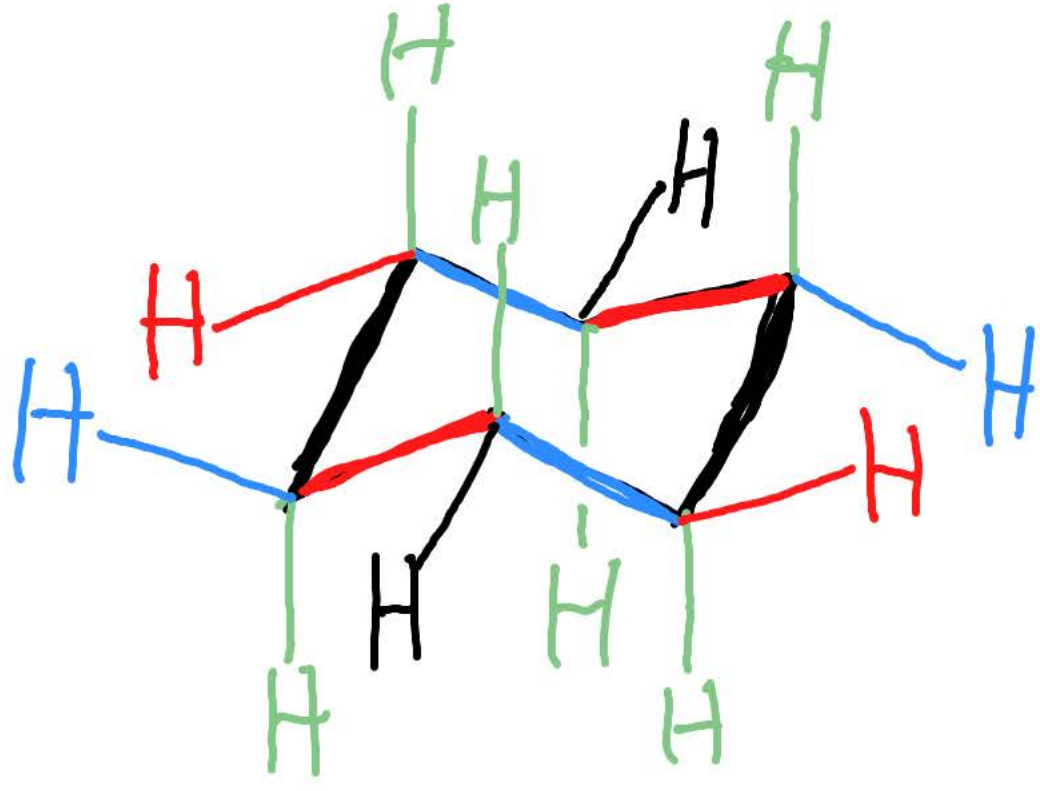
Cl plus EN que H

delta E2 > deltaE1, car les orbitales sont plus proches en énergie (gauche est plus stable pour 1 kcal, donc la différence est 1.3 kcal/mol)

$\sigma_{C-Cl} \rightarrow \sigma^*_{C-Cl} : \Delta E_1$

$\sigma_{C-H} \rightarrow \sigma^*_{C-Cl} : \Delta E_2$

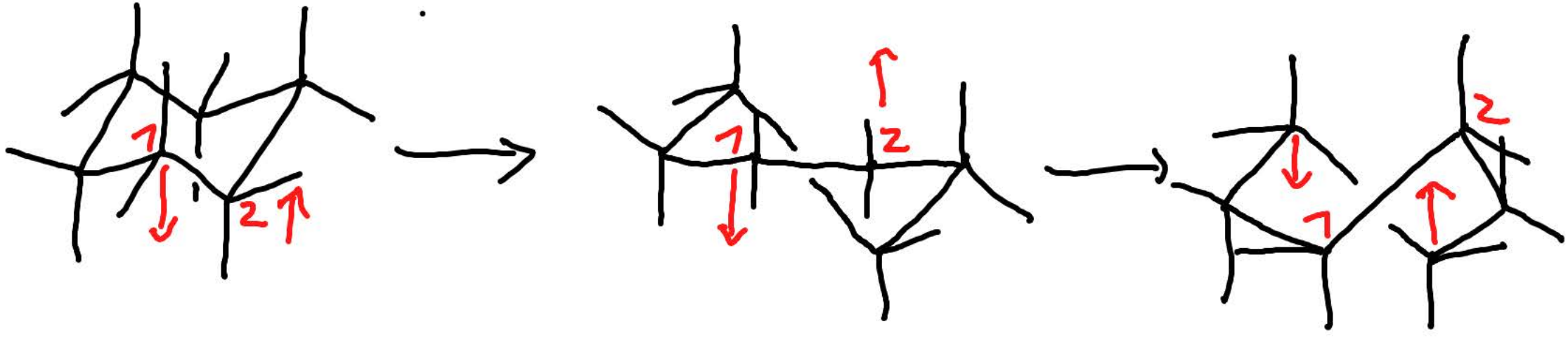
conformation en chaise du cyclohexane



6H AXIAL

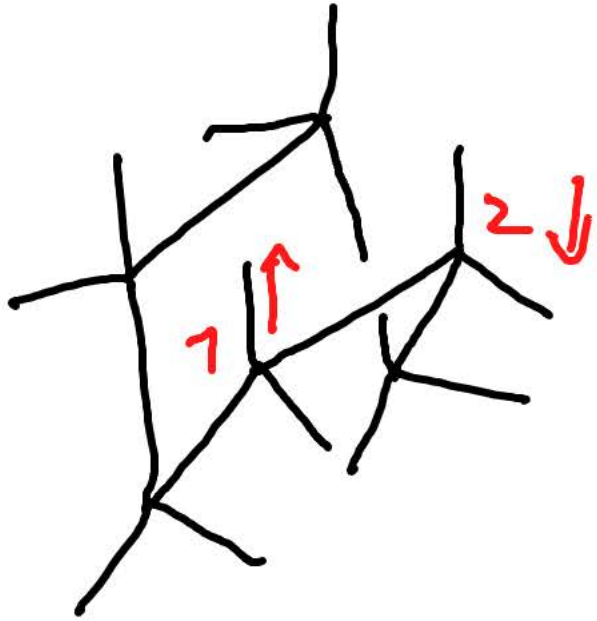
6 H équatorial (rouge, bleu, noir)

Conformères de la chaise



demi-chaise, maximum
E = 10.8 kcal/mol

bateau croisé/twist, minimum
E = 5.5 kcal/mol



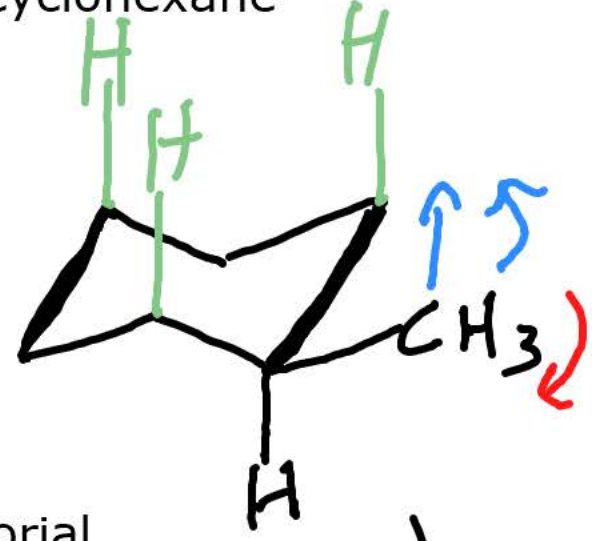
bateau E = 6.9 kcal/mol
maximum local

→ TWIST → DEMI-CHAISE

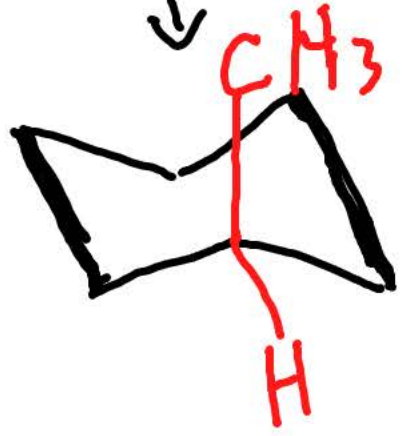
↓

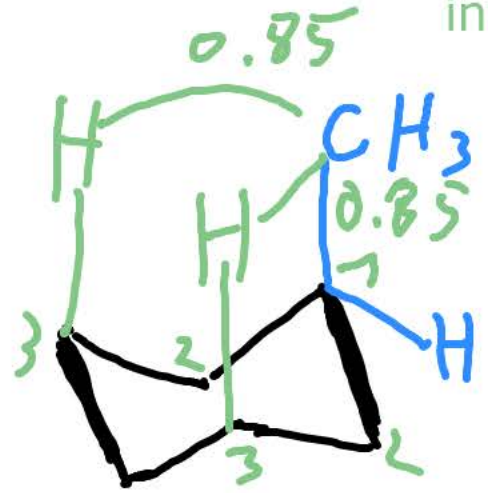
CHAISE

methylcyclohexane



Me équatorial





Me axial

interactions 1,3-diaxiales

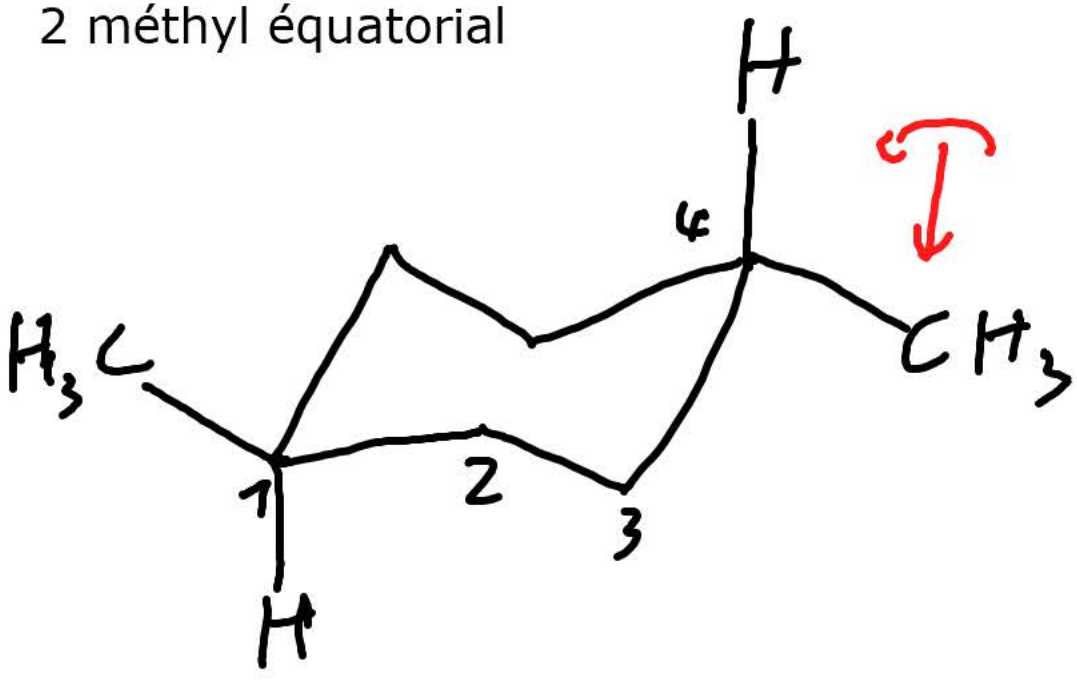
1)inverser la "perspective"

2) monter et tourner

Le méthyl en axial est défavorisé pour 1.7 kcal/mol! (valeur A du groupe Methyl)
delta G = RT LnK
mélange 95:5 équatorial:axial

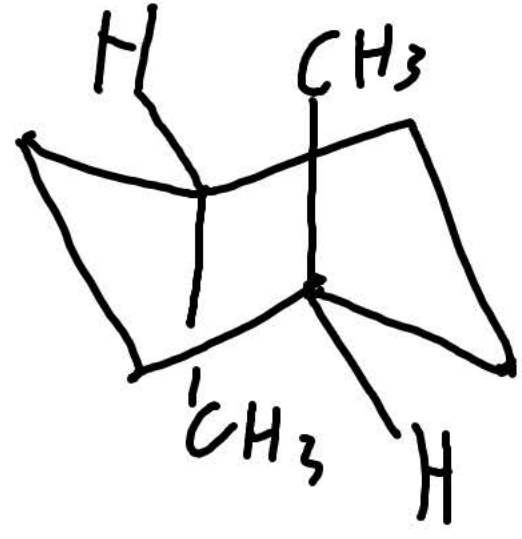
trans-1,4-diméthylcyclohexane

2 méthyl équatorial



delta G?

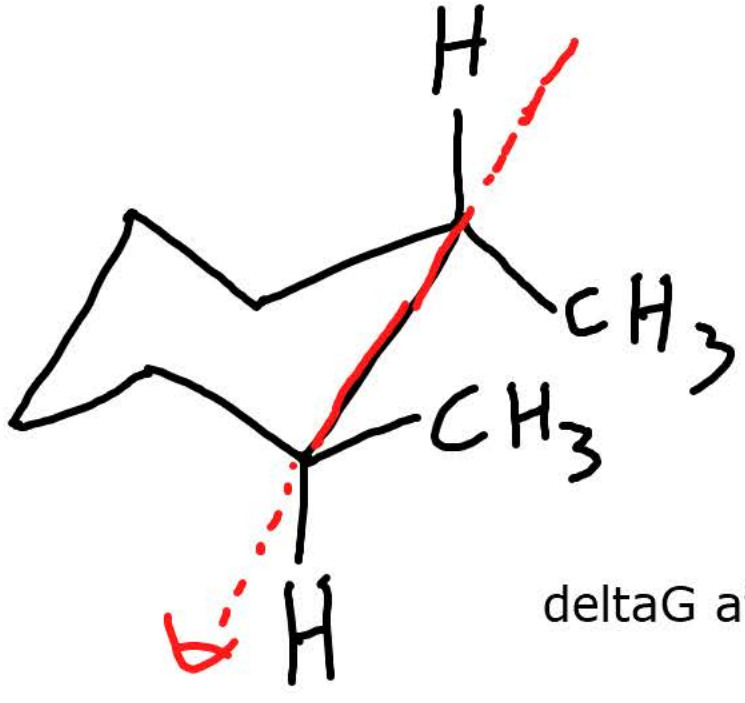
2 méthyl axial



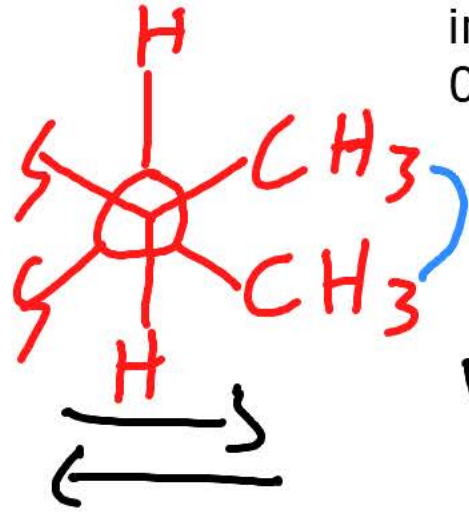
trans = côté opposé du cycle
cis = même côté du cycle

deltaG = 2x1.7 = 3.4 kcal/mol

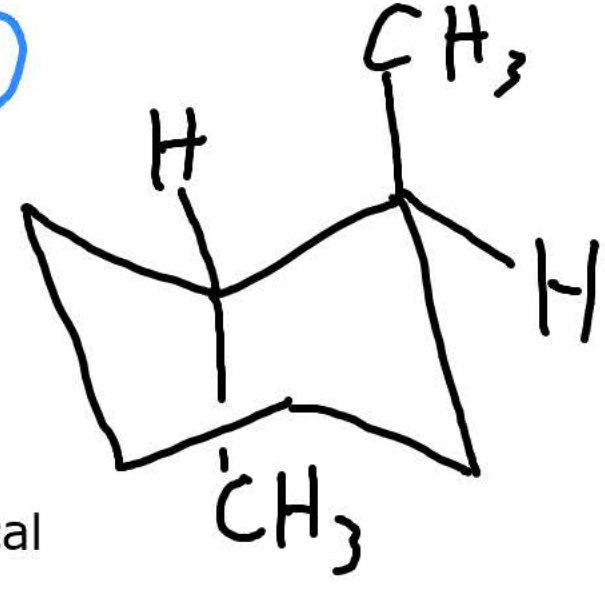
trans-1,2-diméthylcyclohexane



2 méthyl équatorial



interaction gauche:
0.9 kcal/mol!



2 méthyls axiales

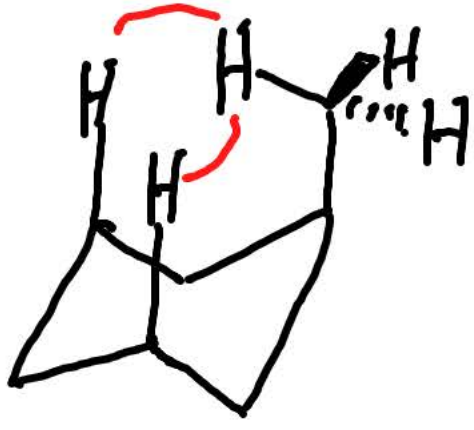
deltaG attendu 2x1.7 = 3.4 kcal

deltaG mesuré: 2.5 kcal/mol!

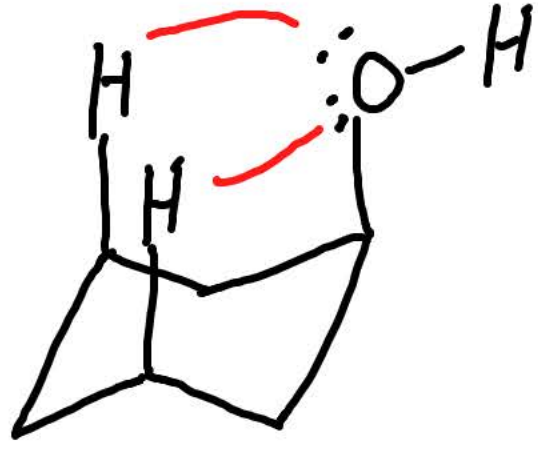
en considérant l'interaction gauche: 2x1.7-0.9 = 2.5 kcal/mol: OK

.

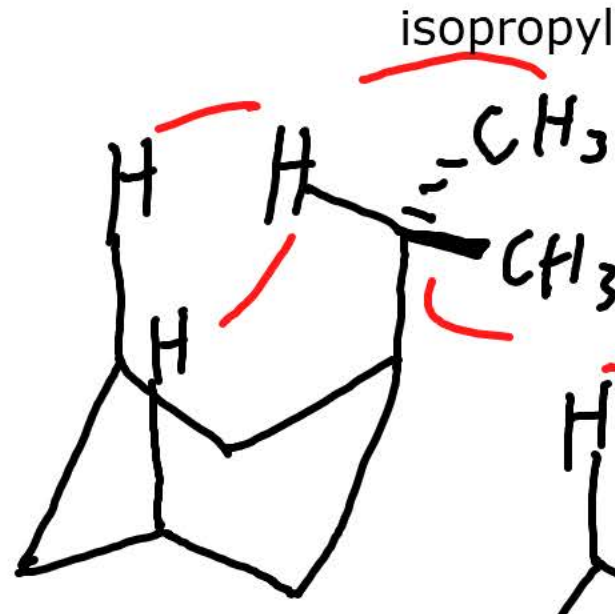
exemples de valeur A



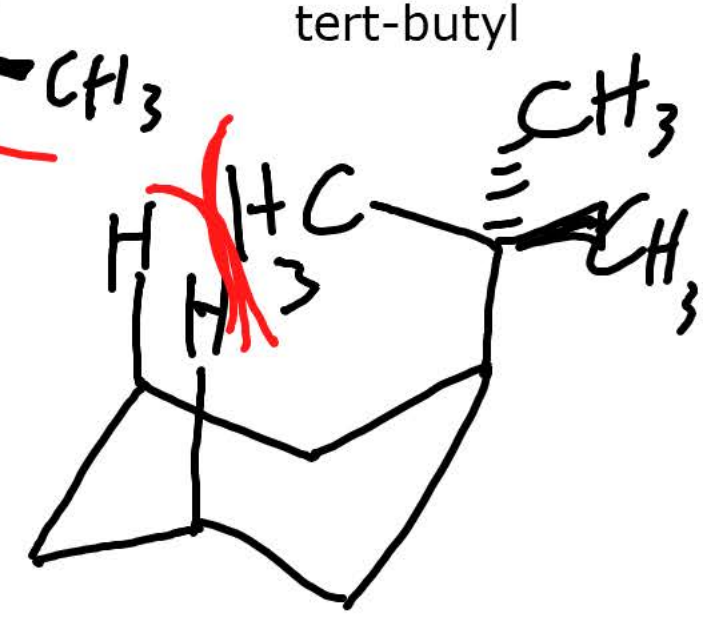
A = 1.7



A = 0.9
(paire d'électons
plus petite)



A = 2.2



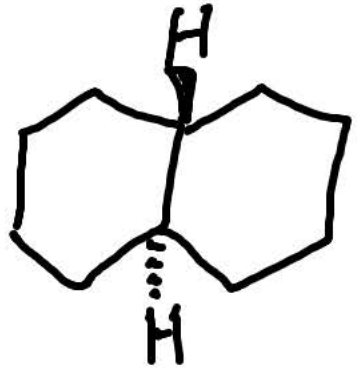
A = 5

tert-butyl "presque toujours"
en équatorial!

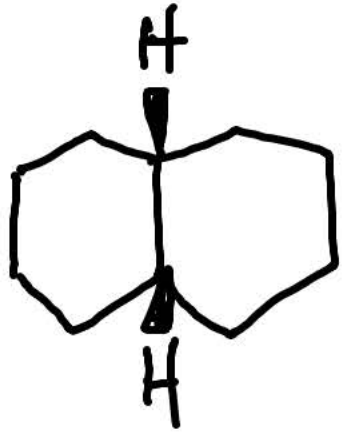
.

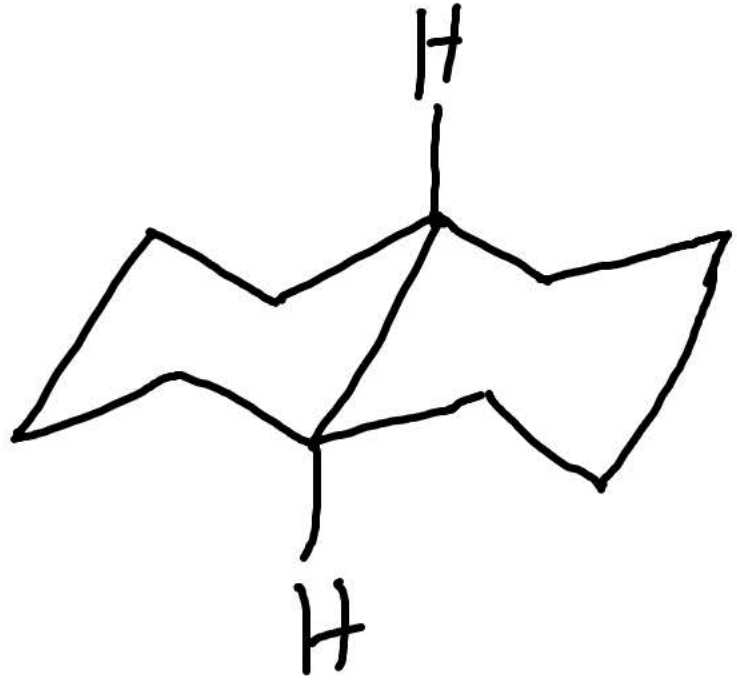
cycles fusionnés: les décalines (10 atomes de C)

trans-décalines



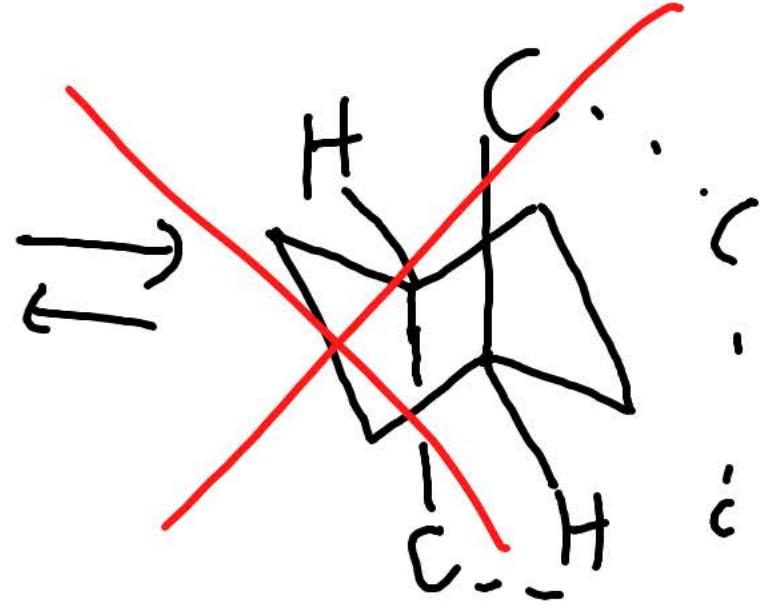
cis-décalines



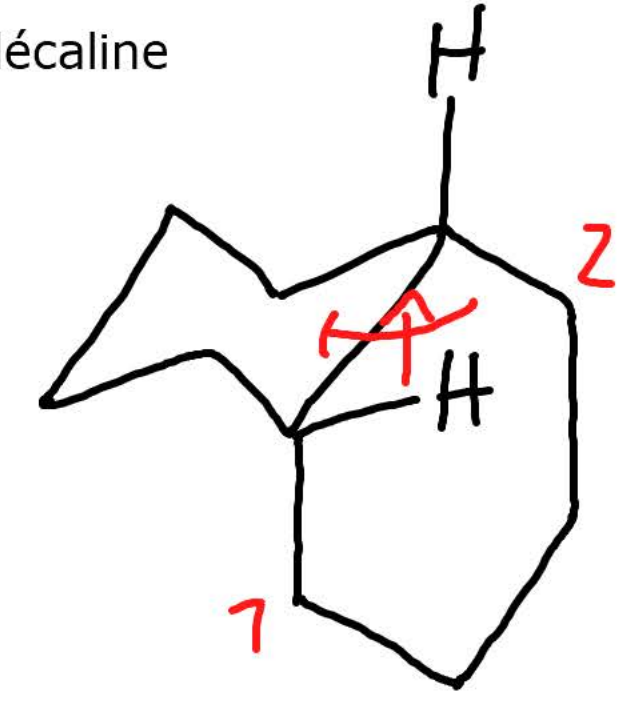


un seul conformère pour la trans-décaline!
structure presque plate

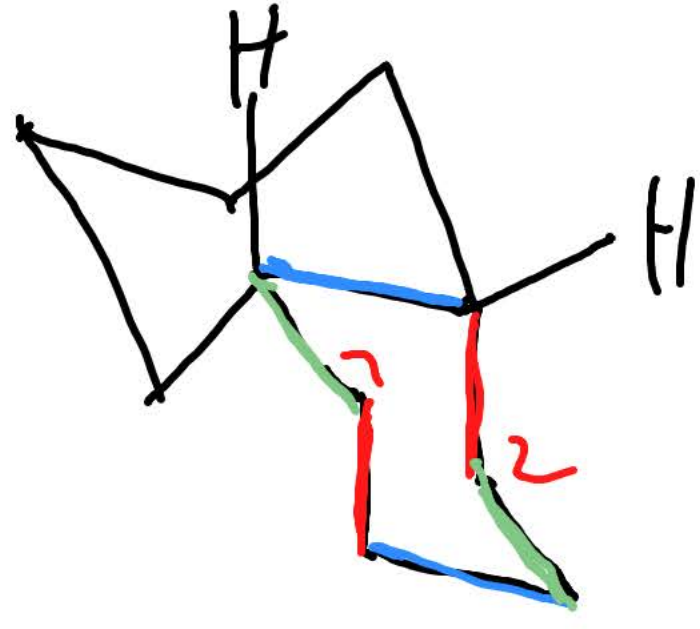
trop loin, pas possible de joindre avec seulement 3 liaisons!



cis-décaline



deltaG = 0



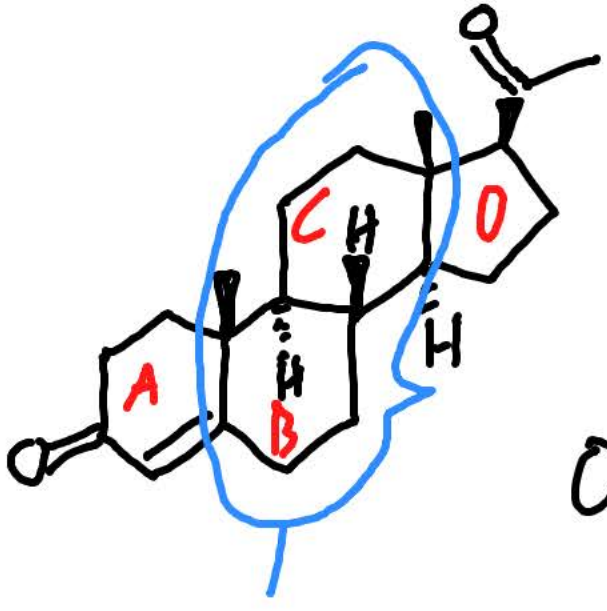
+ CH2R en axial, 1 H en axial

1 CH2R axial, 1 H axial

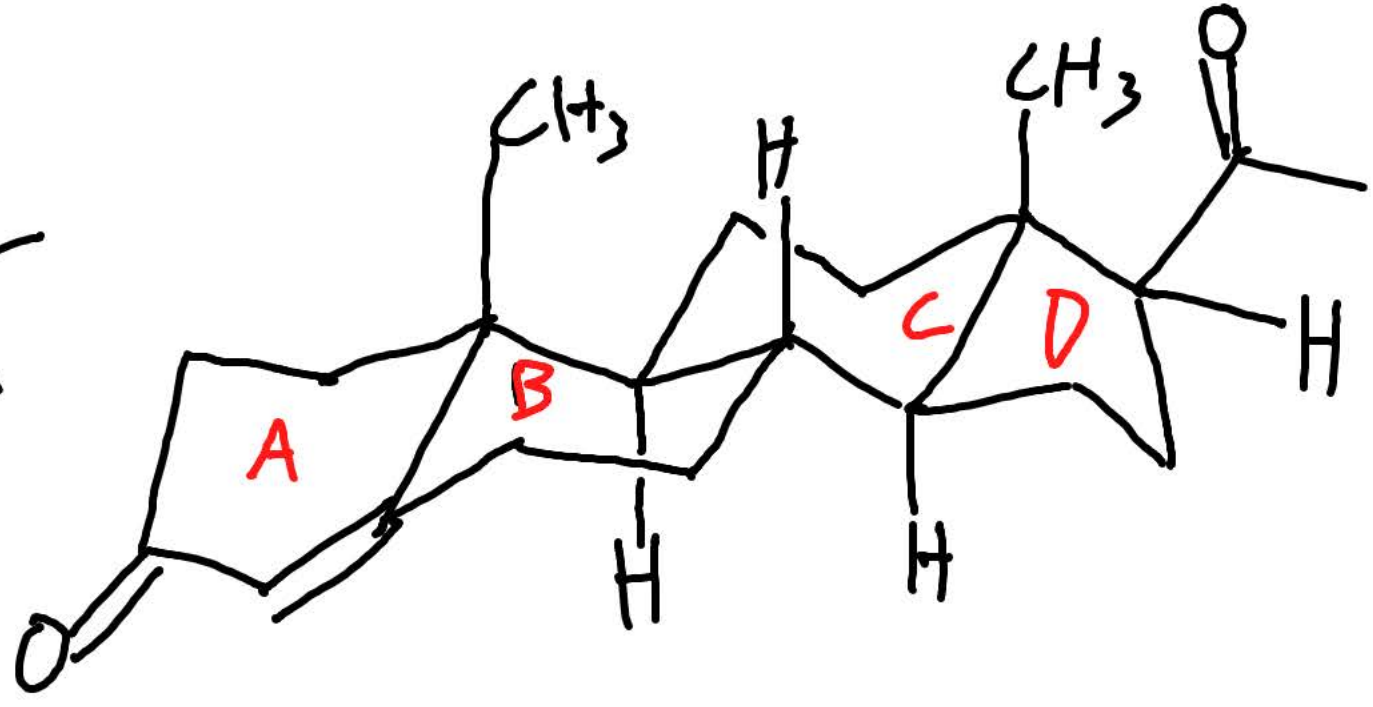
cis-décaline: est flexible, et elle est coudée

progesterone

commencer par le cycle "idéal": le cyclohéxane qui contient uniquement des centres sp3: C

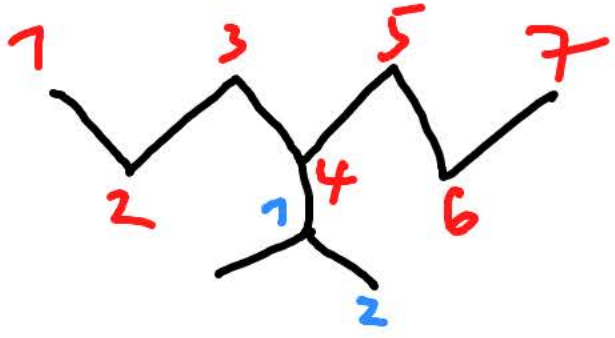


trans-décaline

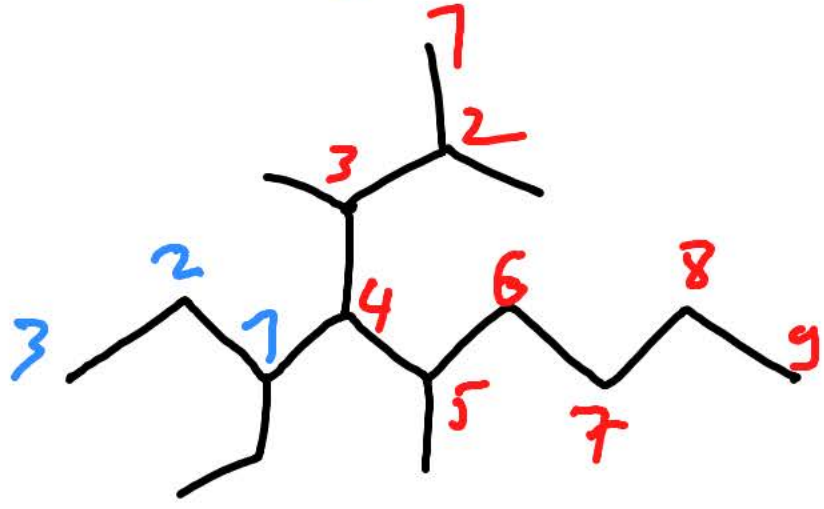


molécule très plate

nomenclatures des alcanes



4-(1-méthyléthyl)-heptane
4-isopropylheptane



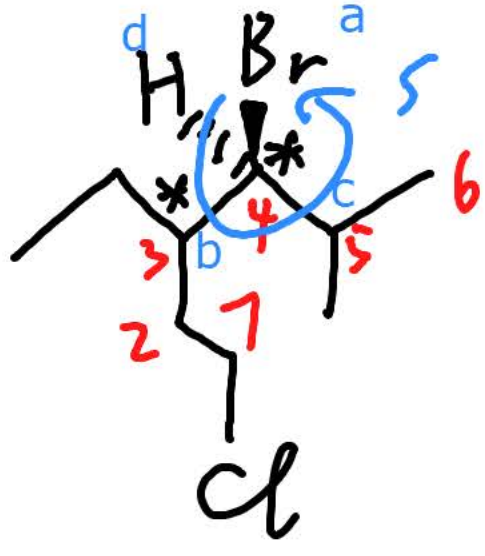
nonane

2,3,5-triméthyl

4-(1-éthylpropyl)-

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

halogènes: F, Cl, Br, I: toujours comme chaine secondaire, avecl les préfixes fluoro, chloro, bromo et iodo

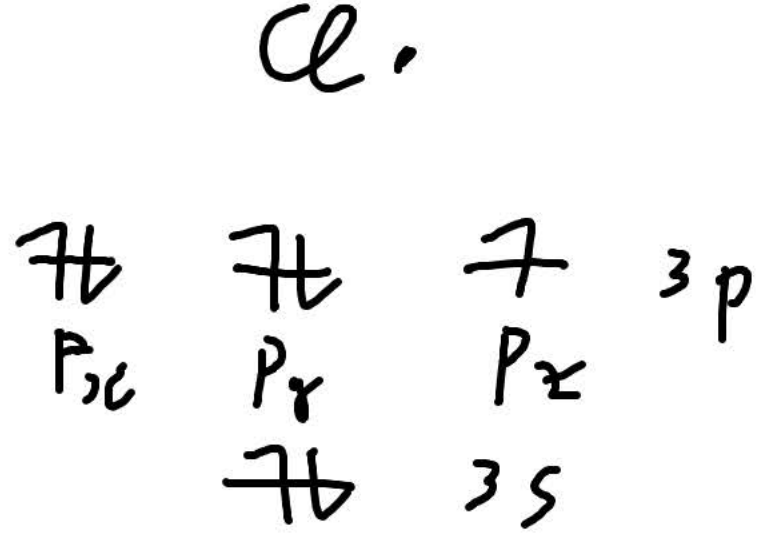


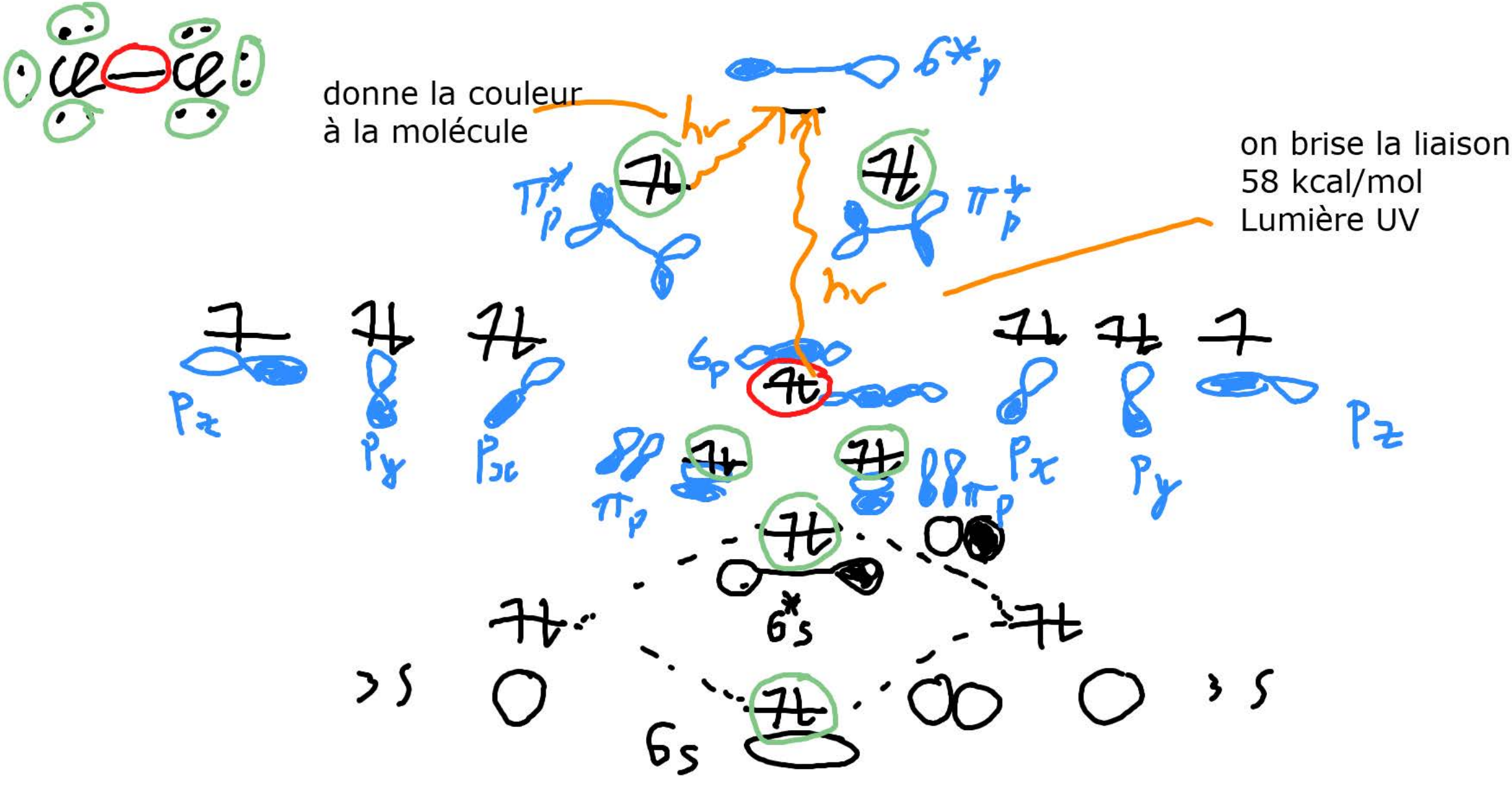
(4S)-4-bromo-1-chloro-3-éthyl-5-méthylhexane

chlorination du méthane: détails du mécanisme

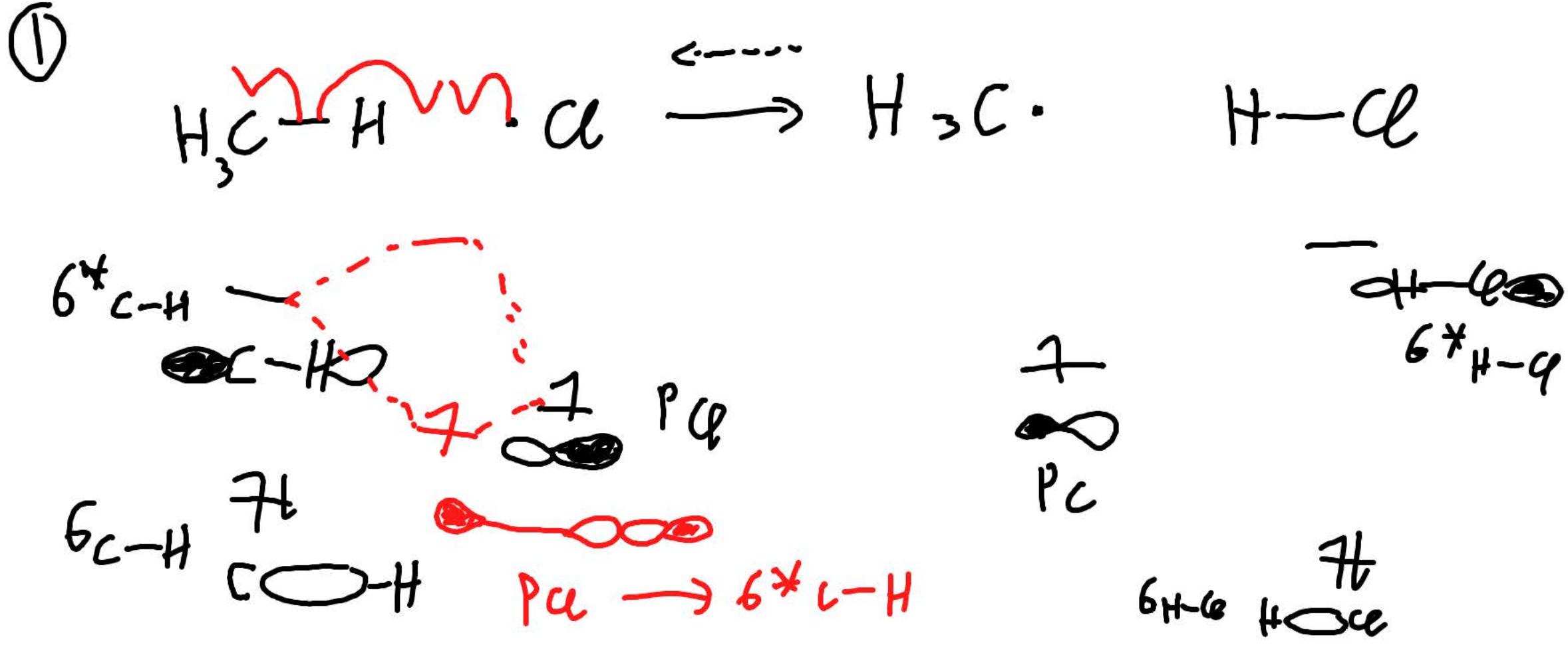
1) initiation

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

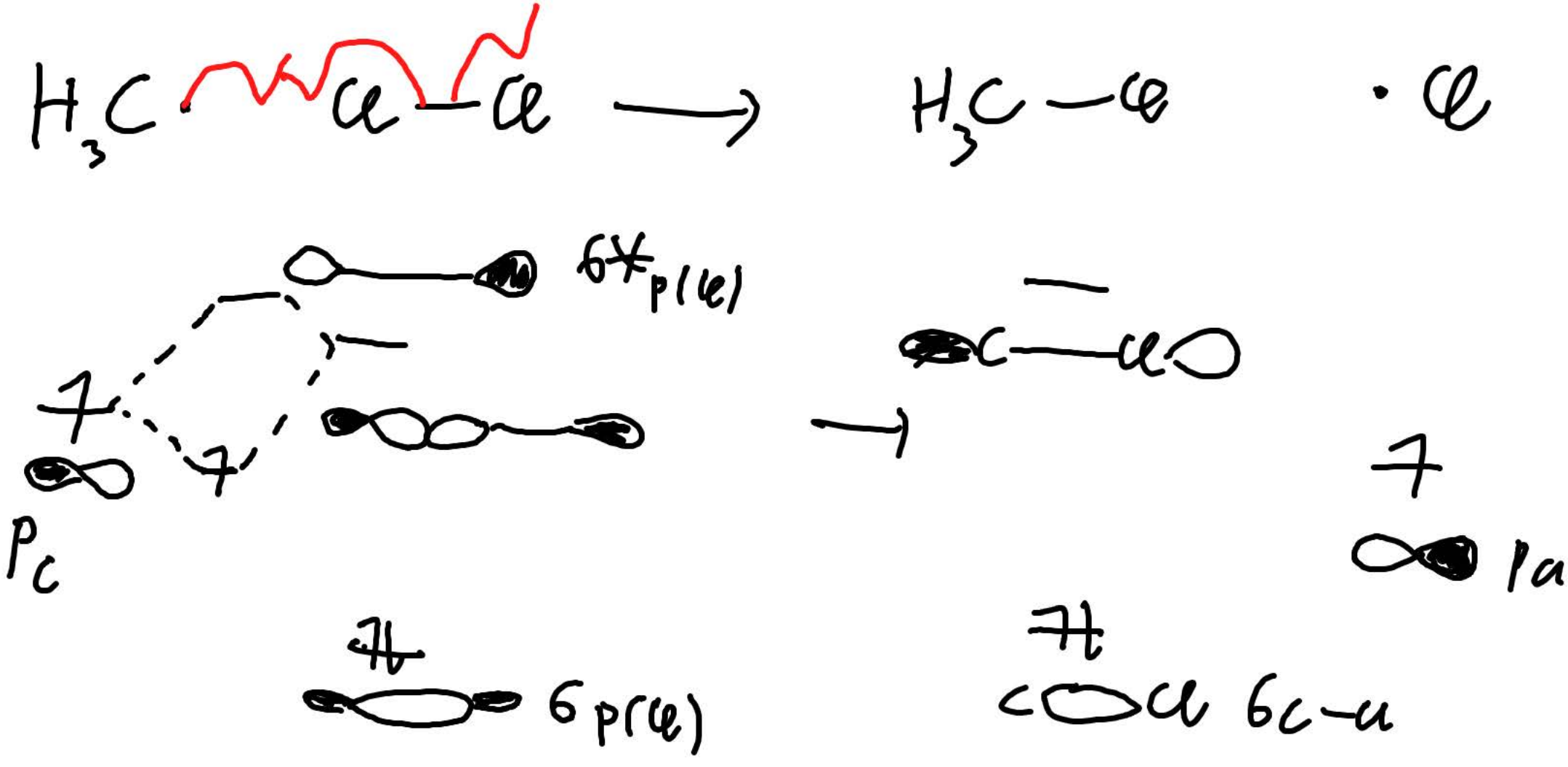



donne la couleur
à la molécule
on brise la liaison
58 kcal/mol
Lumière UV

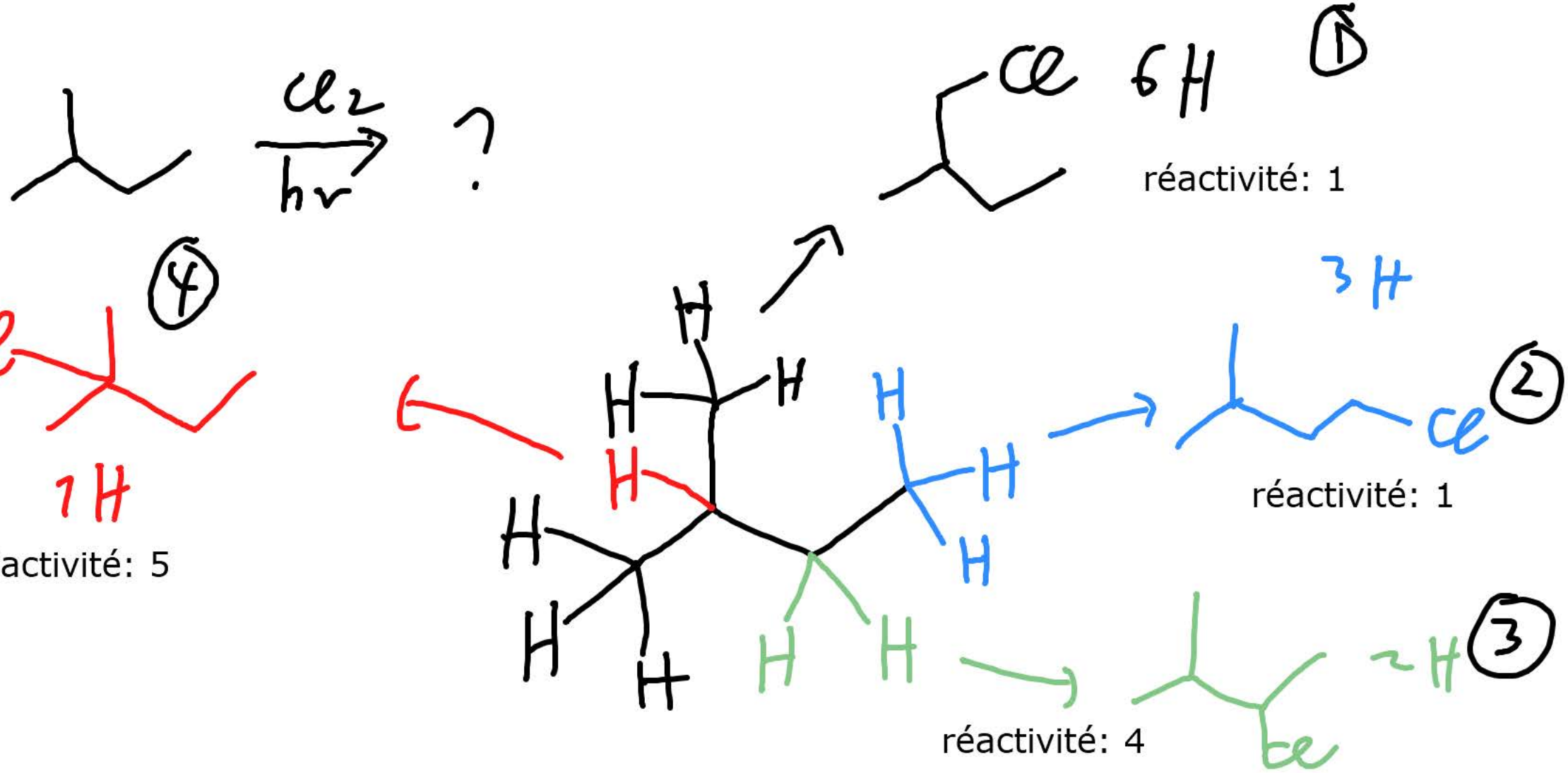
propagation 1 et 2



propagation 2:



prédire le résultat d'une chlorination



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

Que se passe-t-il avec F2?
extrêmement réactif, seul le nombre de H va compter (réagissent tous à la même vitesse):
produit 1: produit 2:produit 3: produit 4 = 6:3:2:1

Que se passe-t-il avec Br2?
moins réactif, la stabilité du radical détermine la sélectivité, on aura:
produit 1: produit 2:produit 3: produit 4 = <1%, <1%, <5%, >95%

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

CH_4 Cl_2 | Br_2 1:1 $\xrightarrow{h\nu}$?

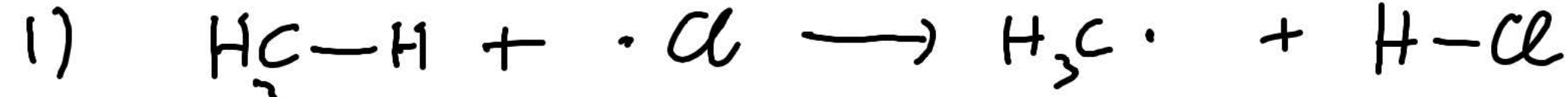
intiation

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

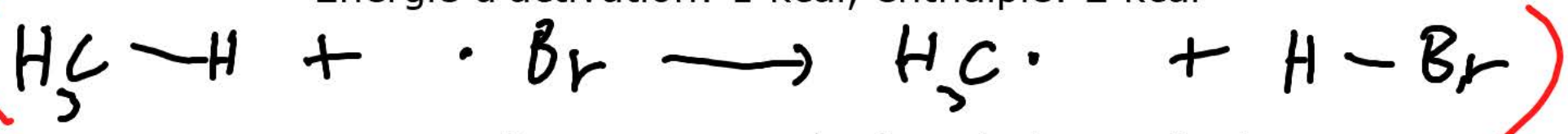
$$Br_2 \xrightarrow{h\nu} Br\cdot + Br\cdot$$ plus rapide

les deux sont possibles, plus de Br.

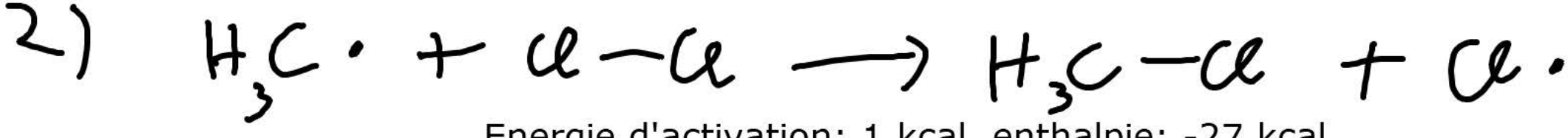
propagation:

1) 

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

négligeable 

Energie d'activation: 20 kcal, enthalpie 18 kcal

2) 

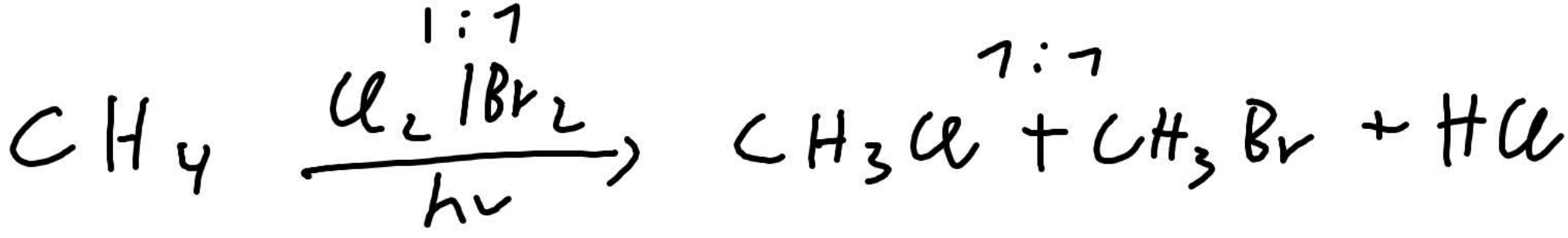
Energie d'activation: 1 kcal, enthalpie: -27 kcal

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

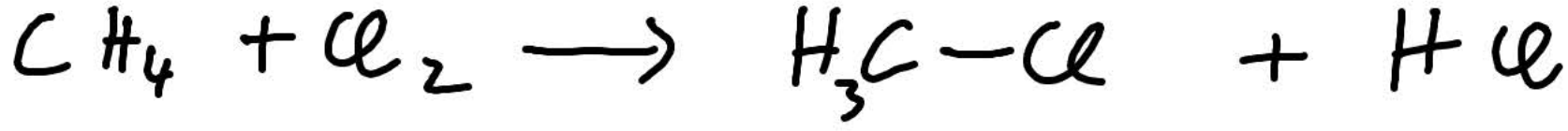
ici mélange 1:1

-

Au temps zéro de la réaction on a:



métriques de chimie verte pour la chlorination



masse moléculaire	16	71	50.5	36.5

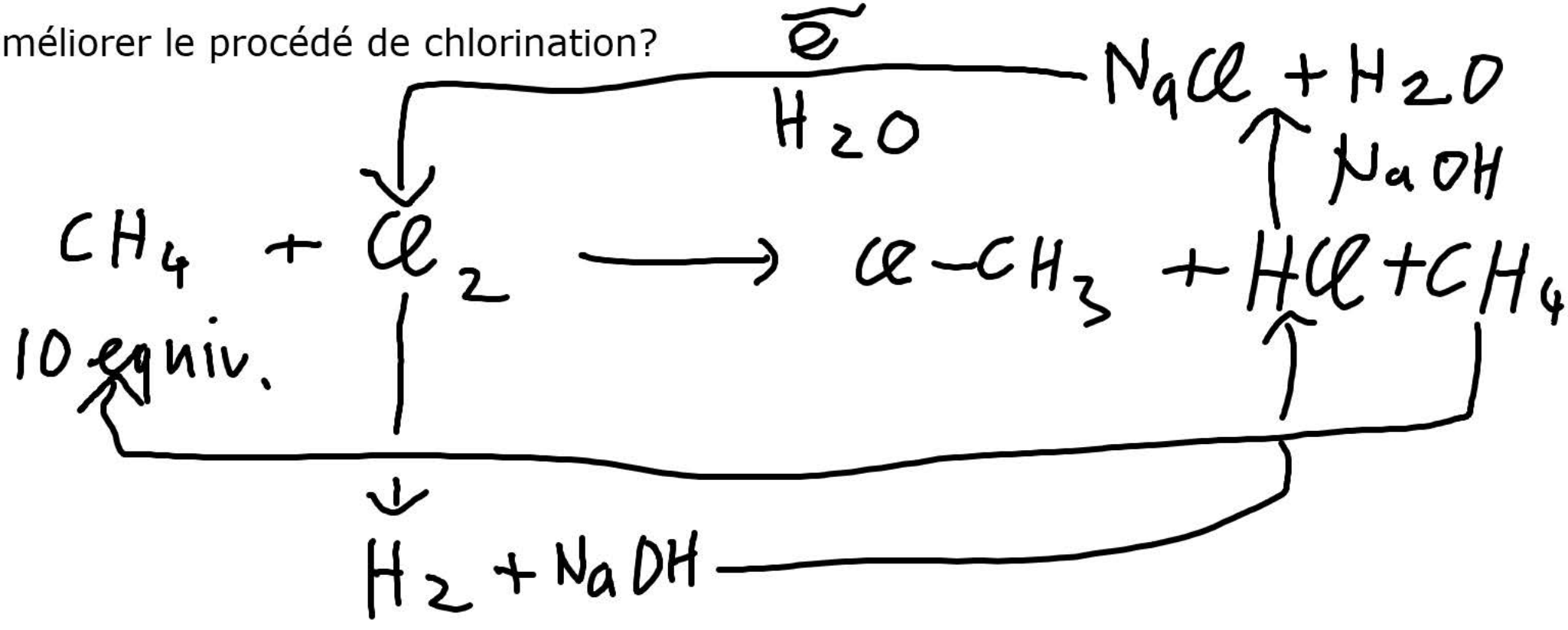
économie d'atomes: 5/7 = 71%

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

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

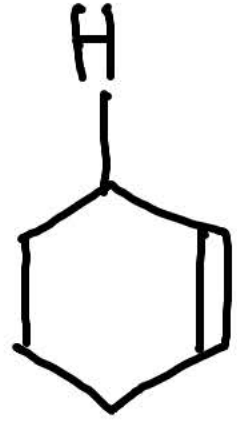
En pratique: on doit utilise un excès de méthane! Sinon on réagit une second fois et produit du dichlorométhane!

comment améliorer le procédé de chlorination?

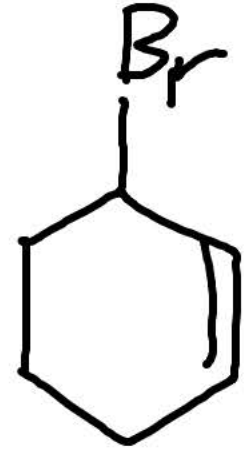


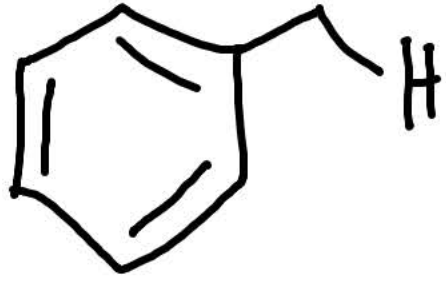
$$H_2O + CH_4 + NaCl \xrightarrow{\grave{e}} ClCH_3 + NaOH + H_2$$

bromination des positions allyliques et benzyliques

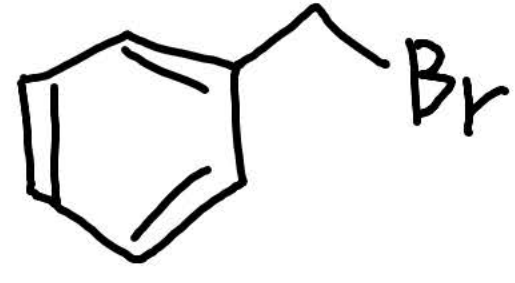


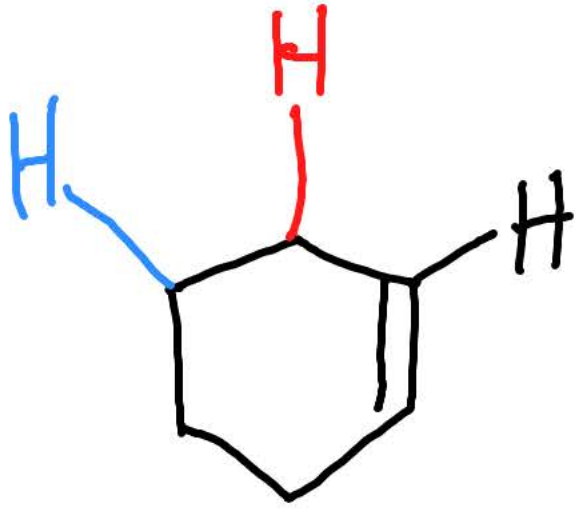
position allylique



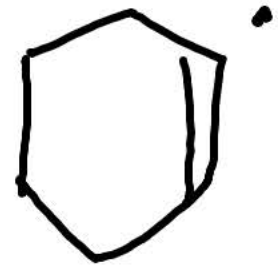


position benzylique

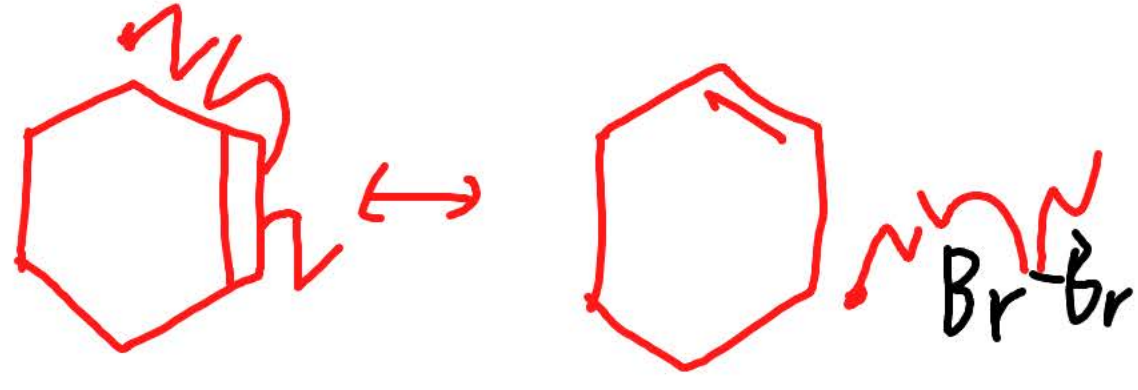


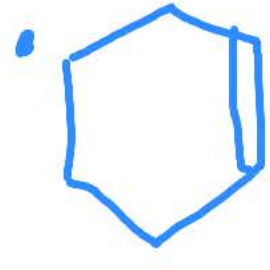


radicaux sp3
plus stables

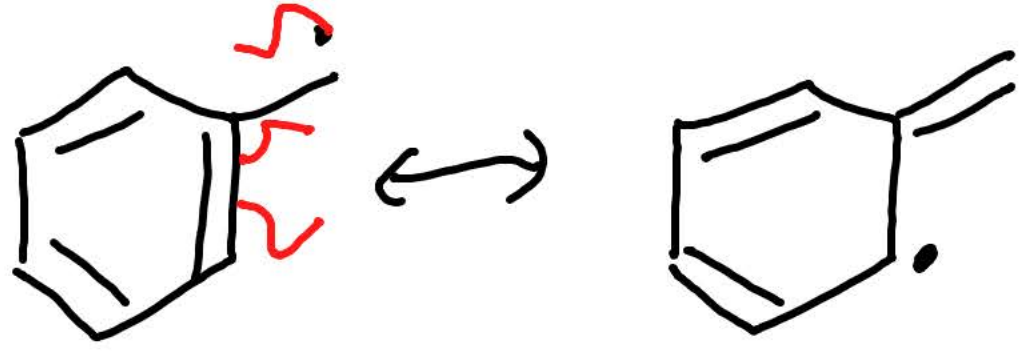


radical hybridisé sp2,
moins stable, pas observé



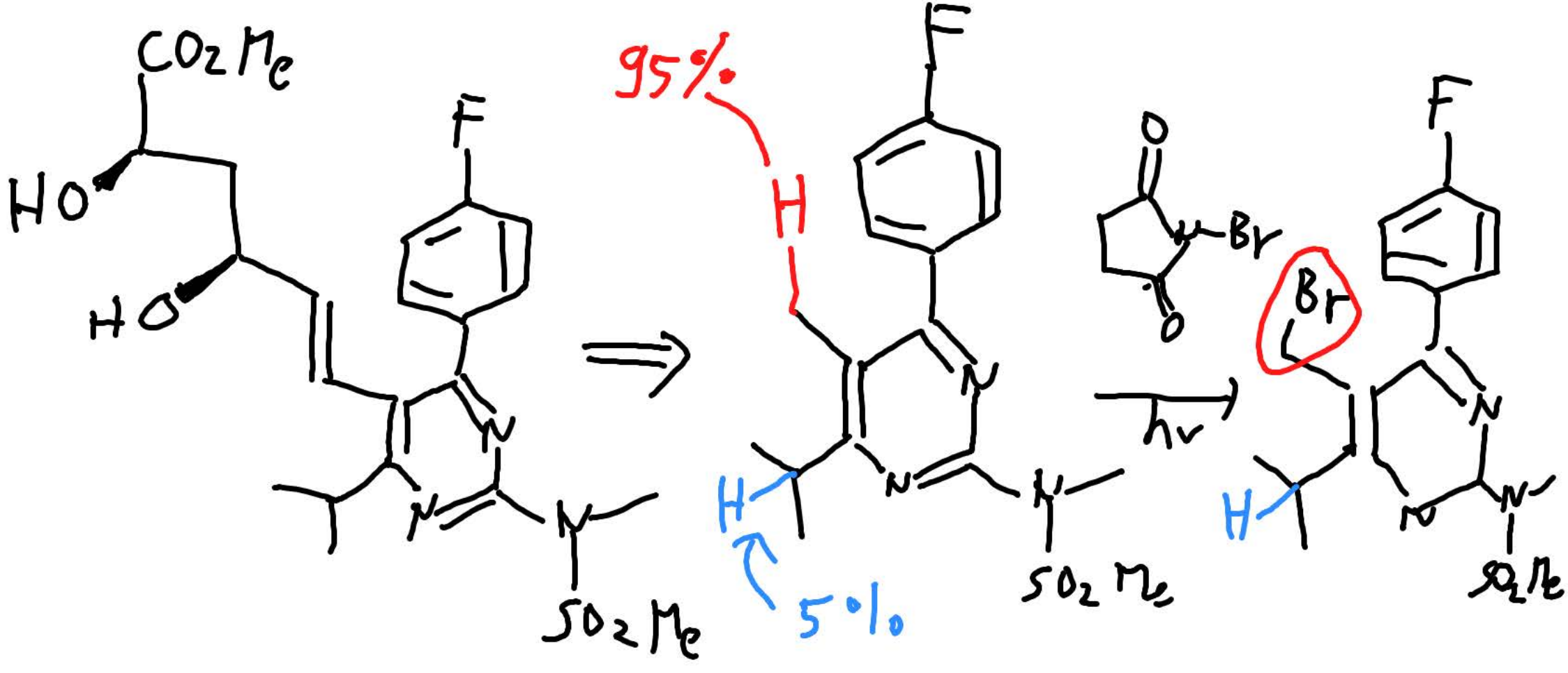


résonances identiques,
excellente stabilisation
radical très stabilisé

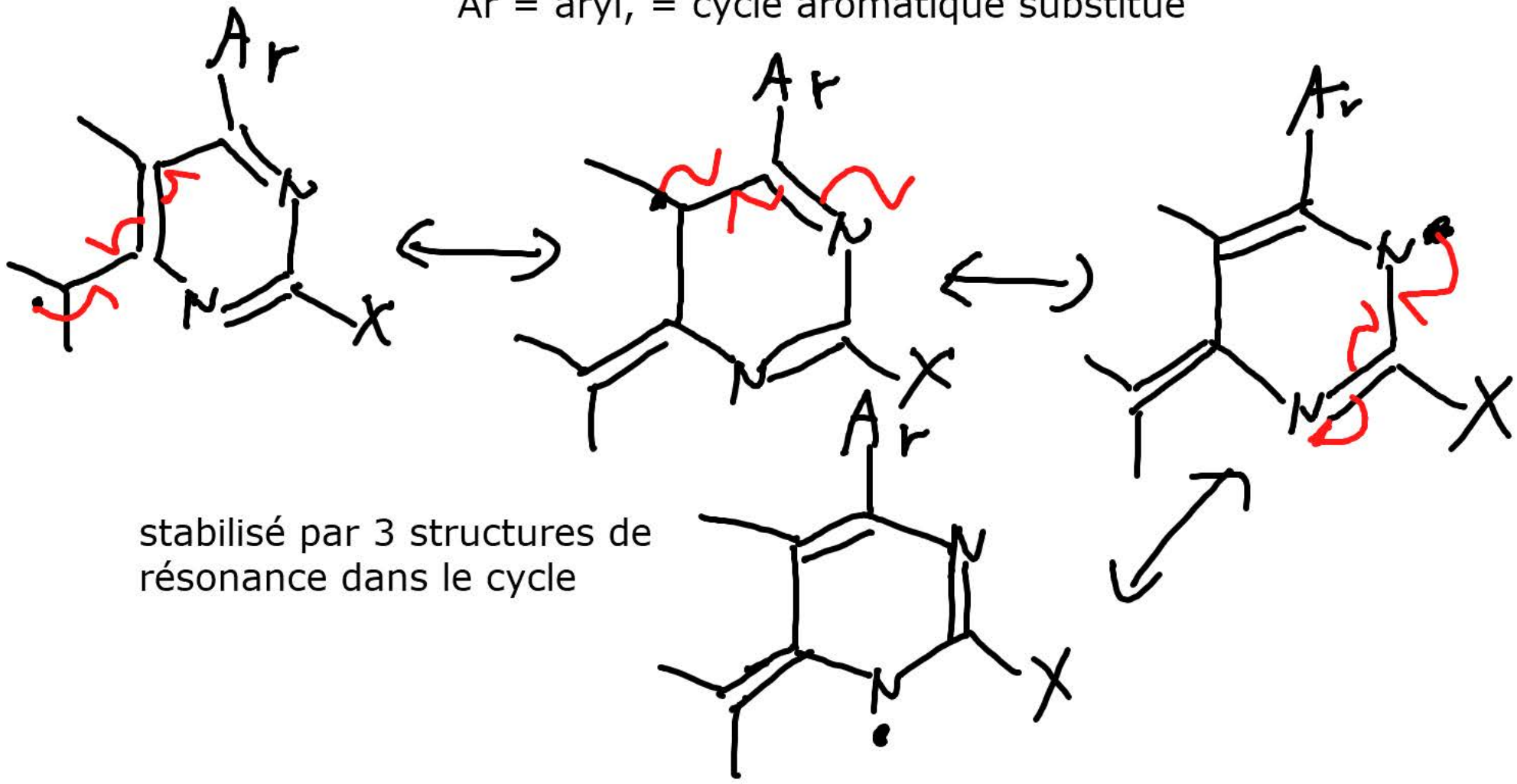


+ 2 autres résonances dans le cycle

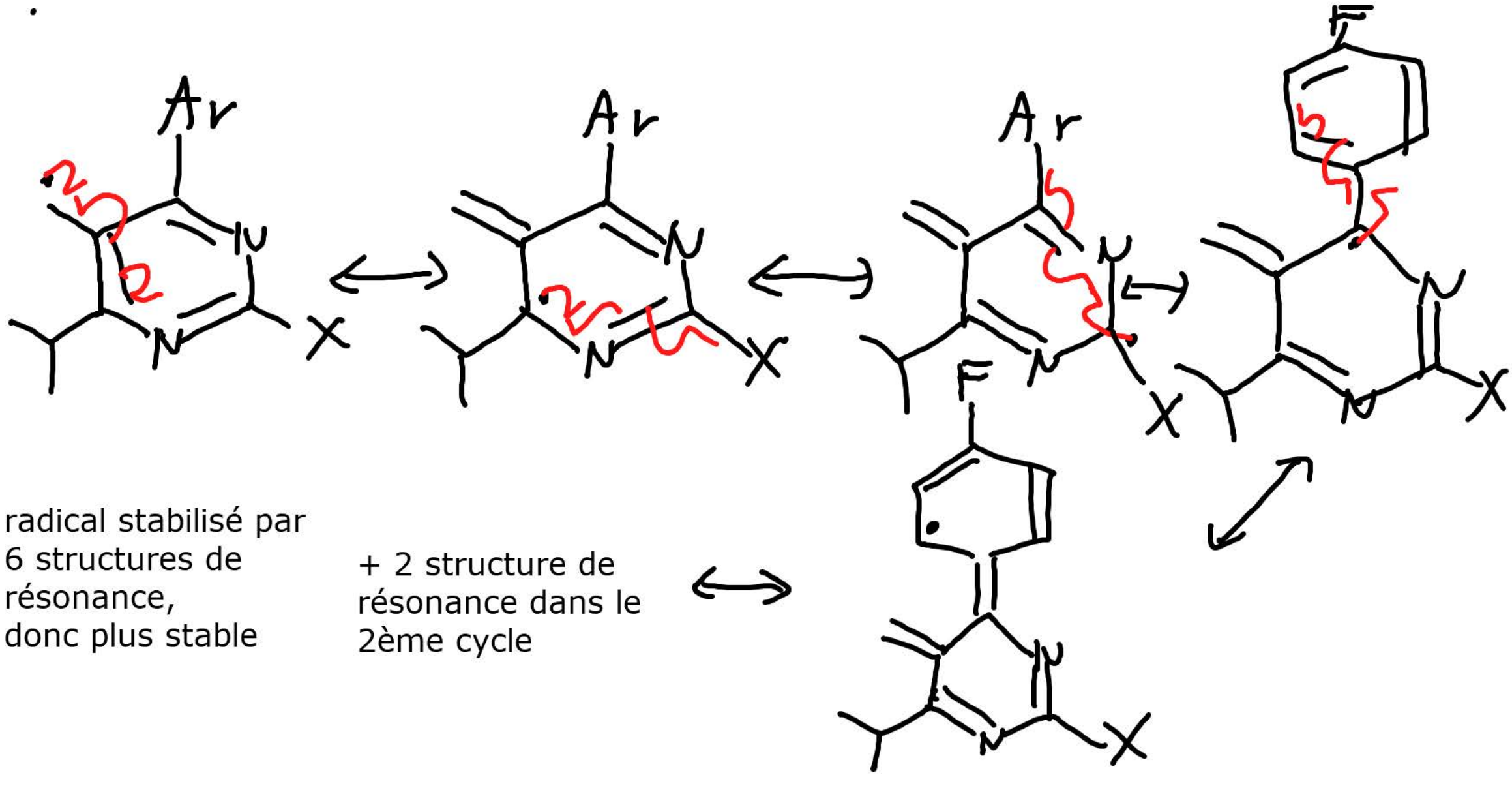
Rosuvastatine (diminue le cholestérol)



Ar = aryl, = cycle aromatique substitué



stabilisé par 3 structures de résonance dans le cycle



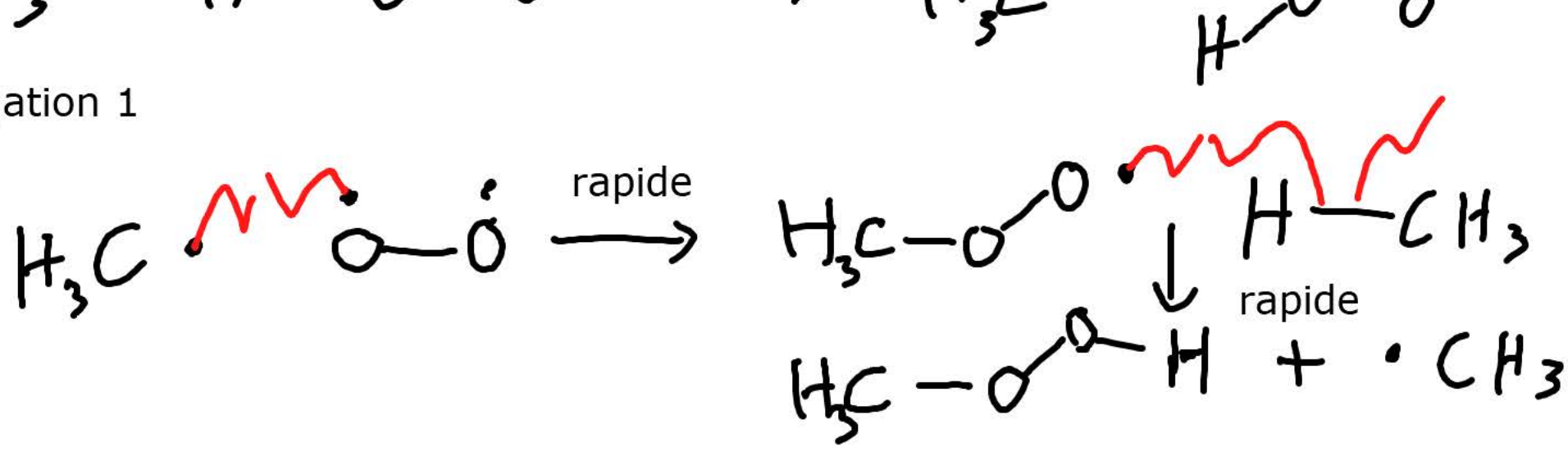
radical stabilisé par 6 structures de résonance, donc plus stable

+ 2 structure de résonance dans le 2ème cycle

combustion du méthane

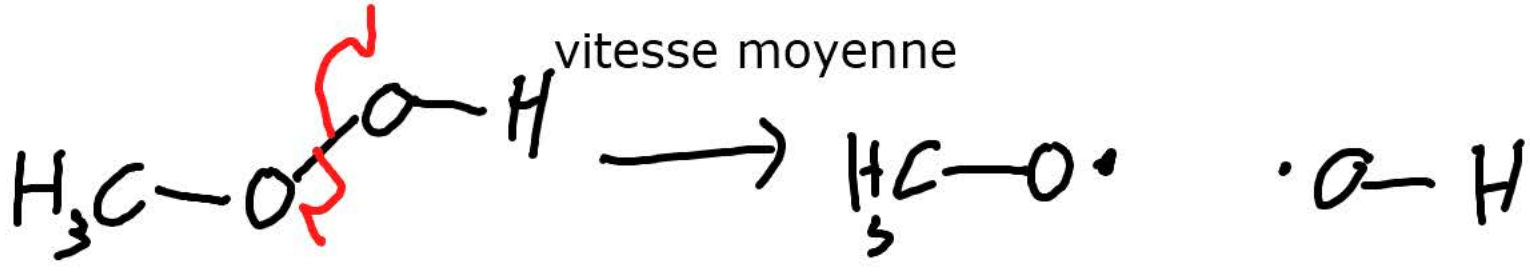
Initiation

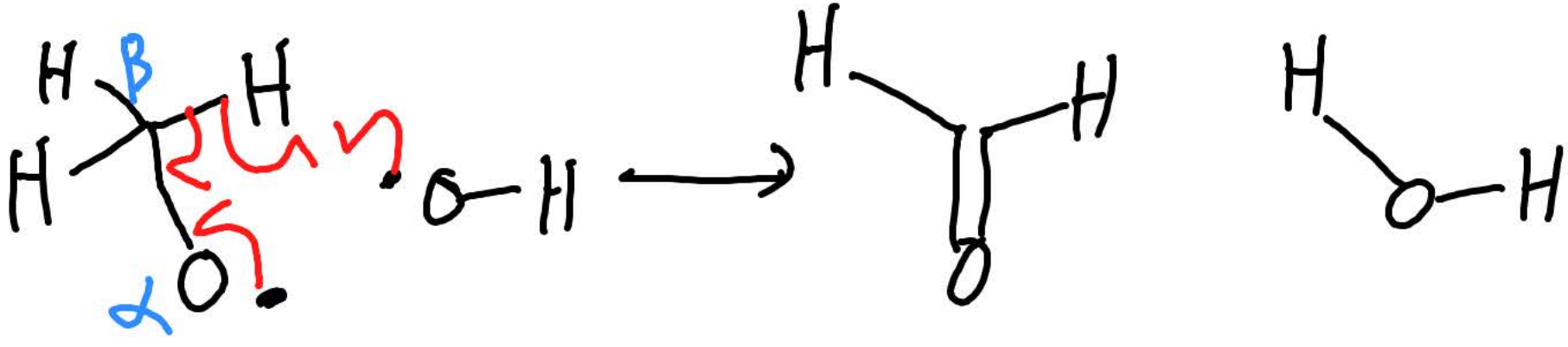
propagation 1



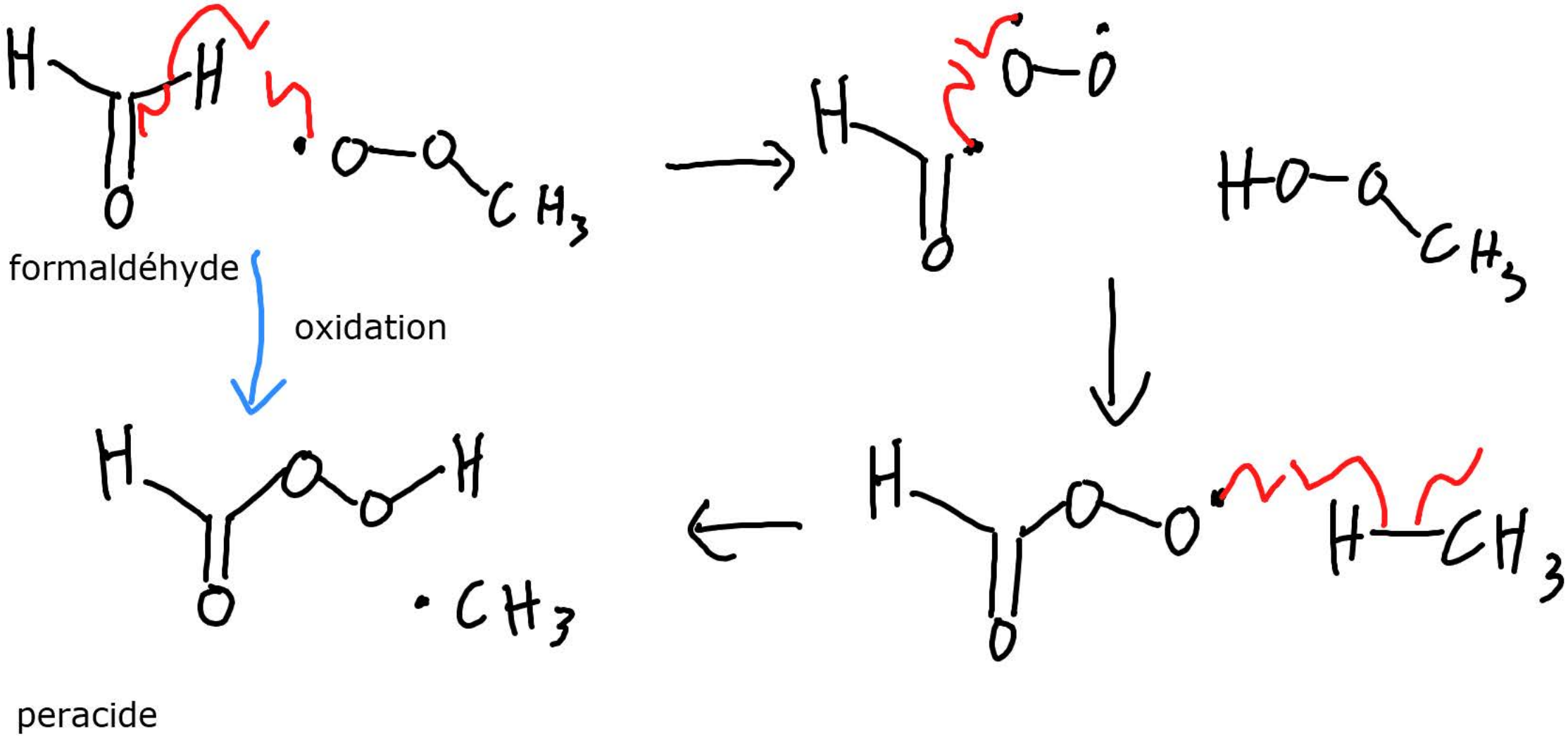
initiation

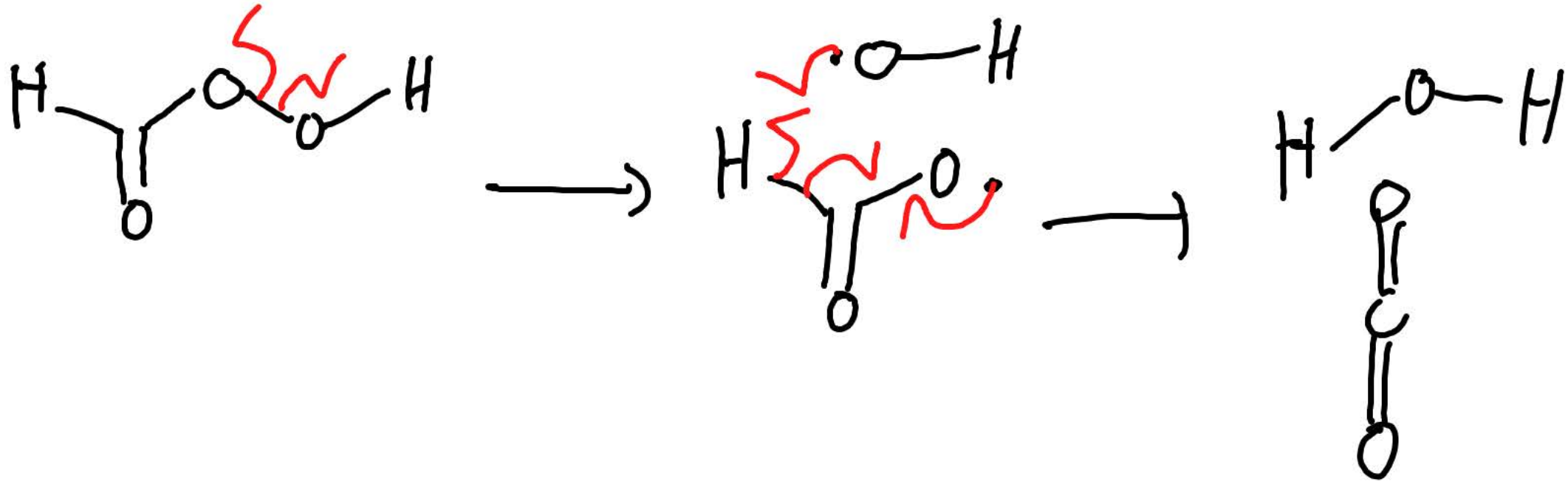
vitesse moyenne



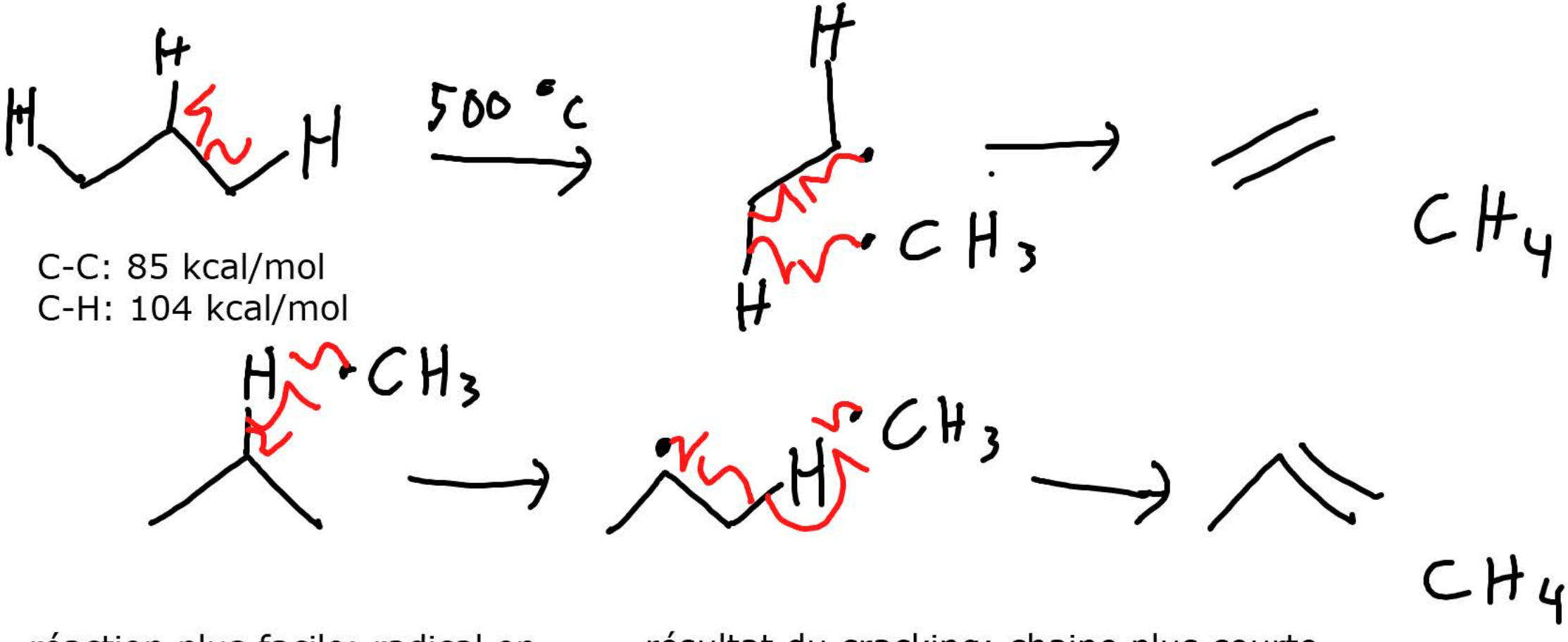


élimination beta


formaldéhyde
oxidation
peracide



cracking du pétrole

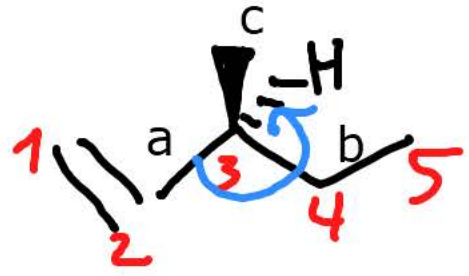


C-C: 85 kcal/mol
C-H: 104 kcal/mol

réaction plus facile: radical en position secondaire plus stable

résultat du cracking: chaine plus courte, contiennent plus d'alcènes

nomenclature des alcènes



(S)-3-méthylpent-1-ène

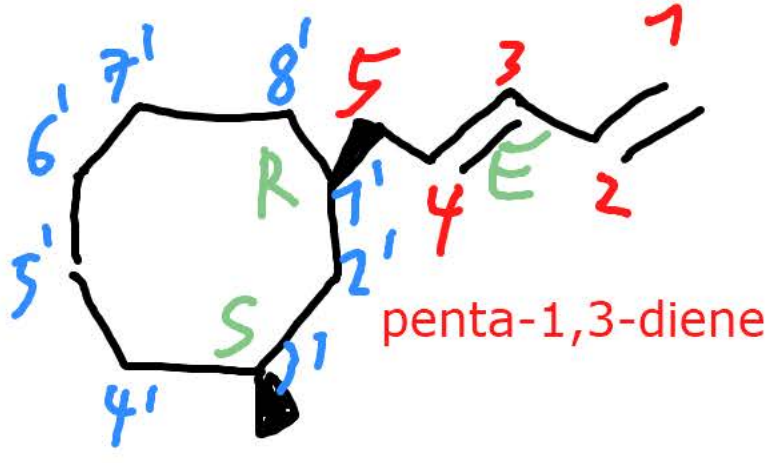
(E)-hept-3-ène

"S" mais H devant
donc R

(R)-3-bromo-cyclopent-1-ène

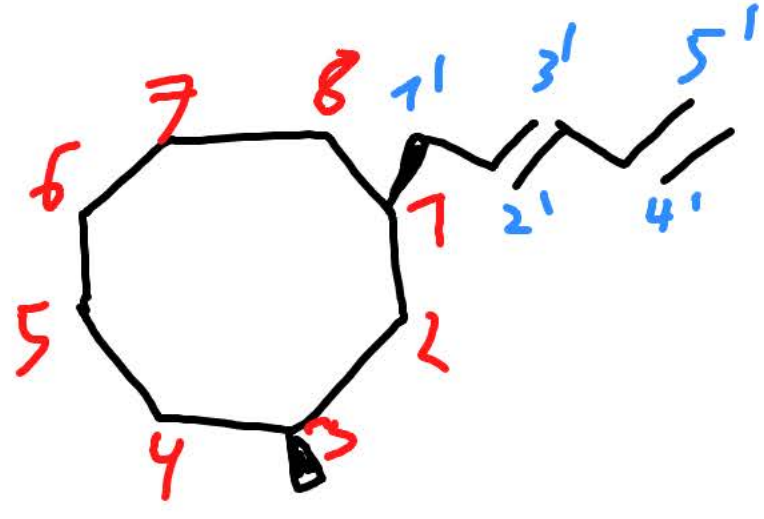
.

ancienne règle: les insaturations dominent



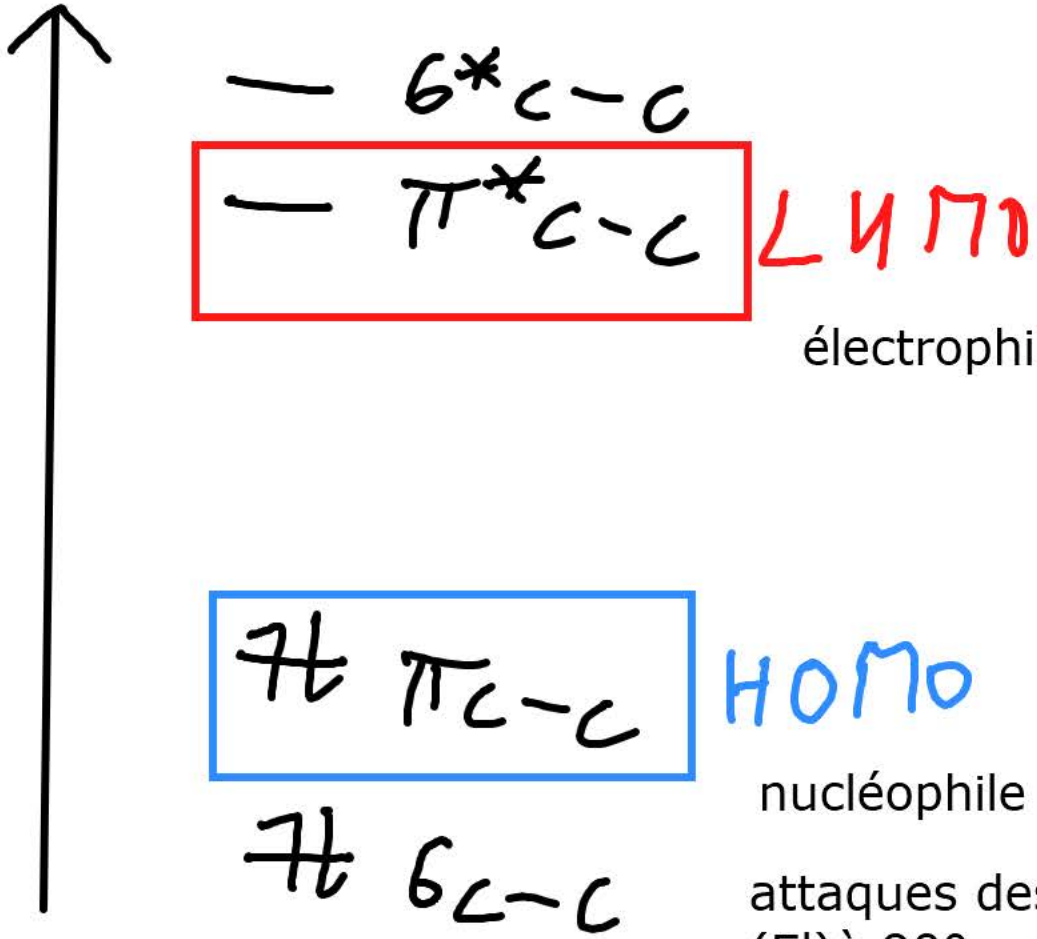
(E)-5-((1R,3S)-(3-méthyl-cyclooctyl))-penta-1,3-diène

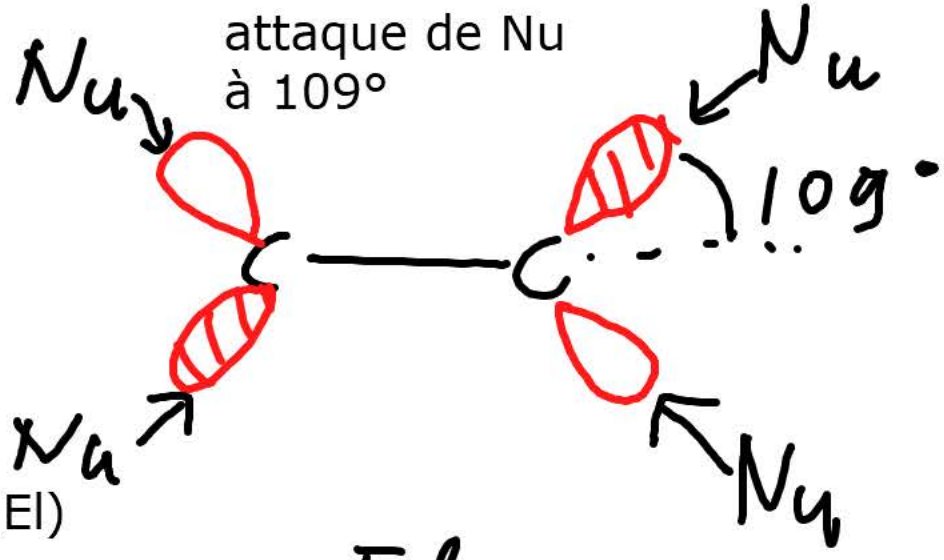
nouvelles règles: 1) cycle 2) nombre d'atome, 3) insaturations

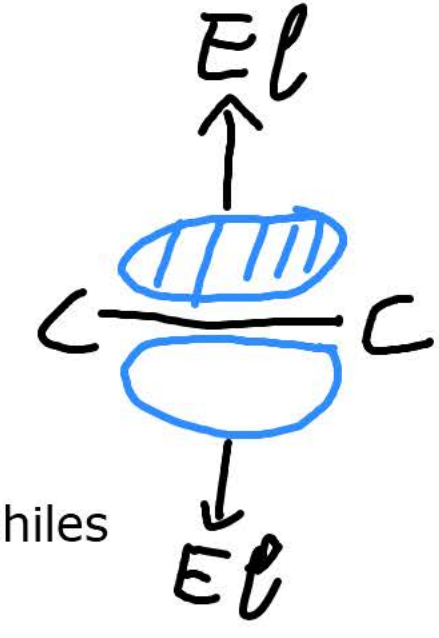


(1R,3S)-3-méthyl-1-((E)-penta-2,4-diényl)-cyclooctane

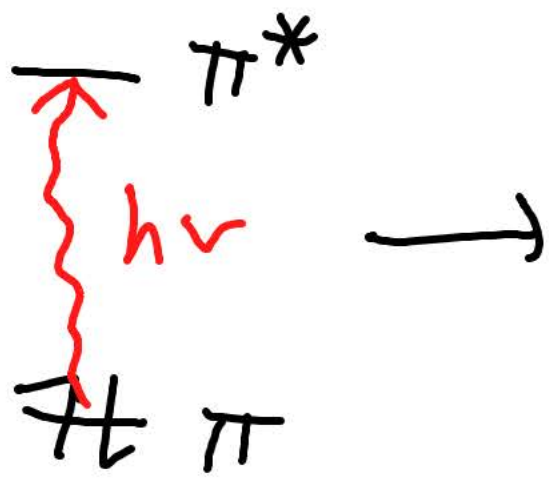
HOMO/LUMO des alcènes



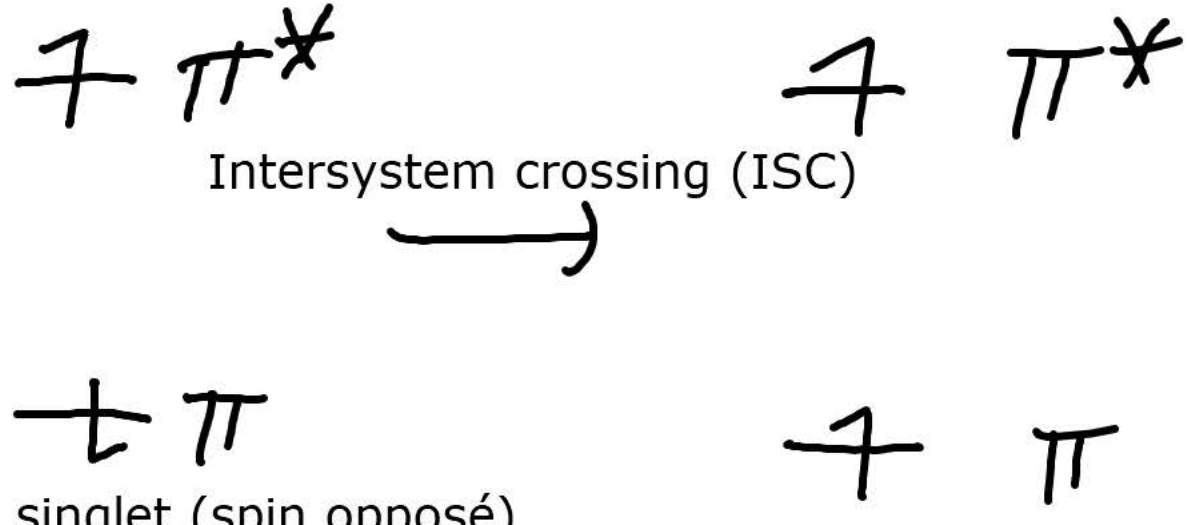




photochimie des alcènes

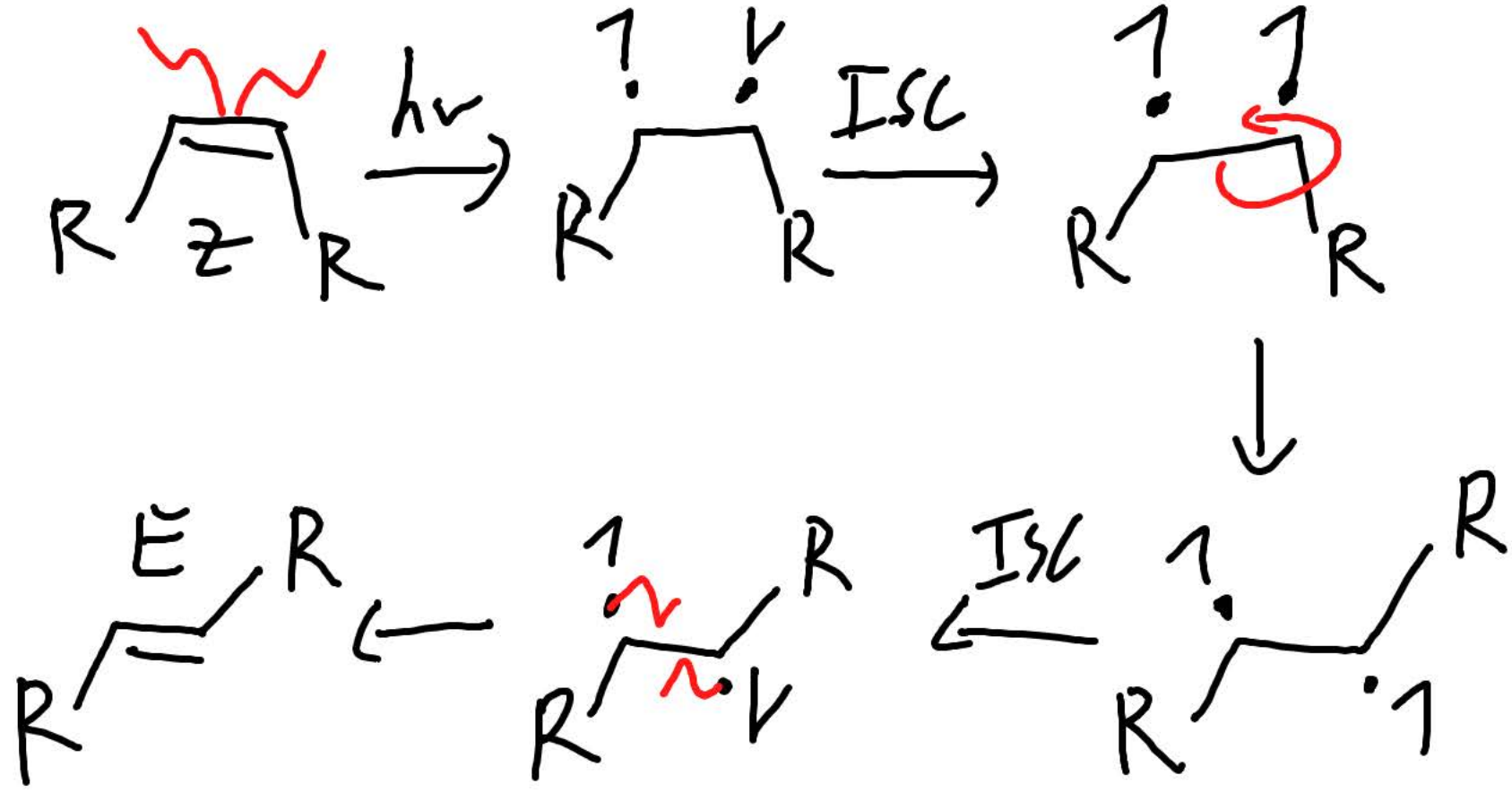


alcène seul: lumière UV
plusieurs alcènes conjugués: lumière visible

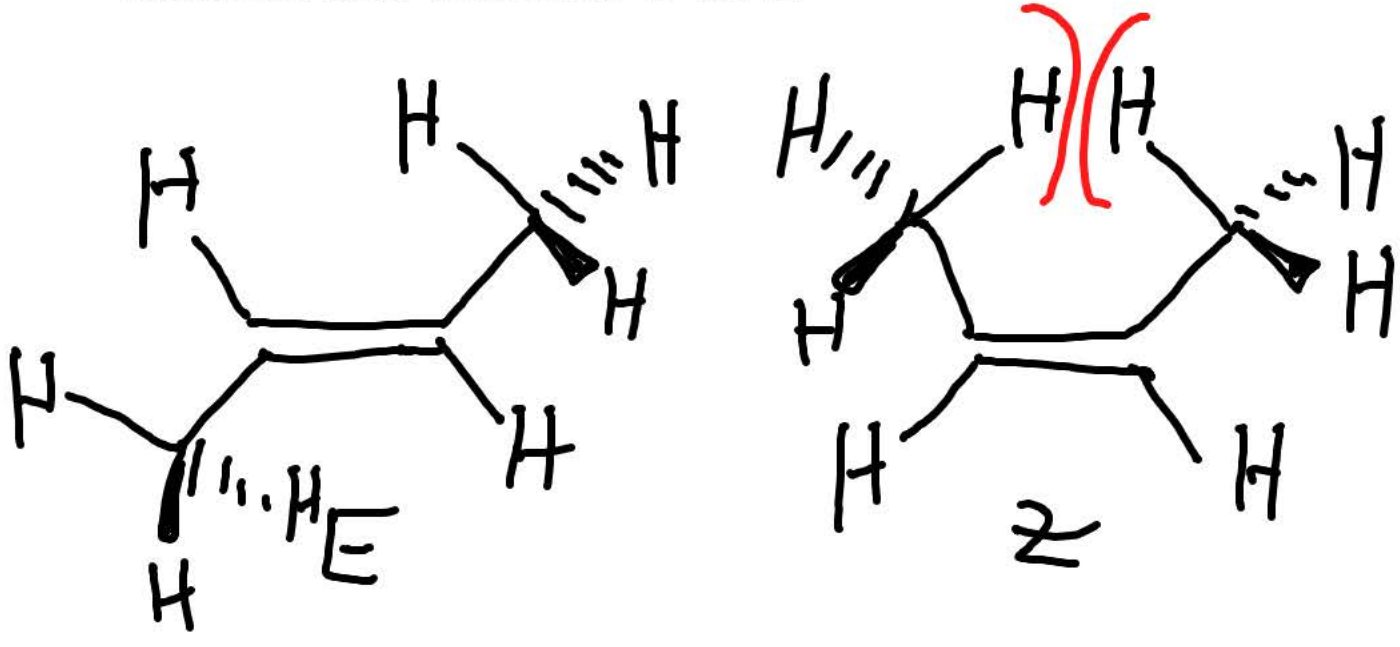


singlet (spin opposé)

triplet (spin parallèles) plus stable

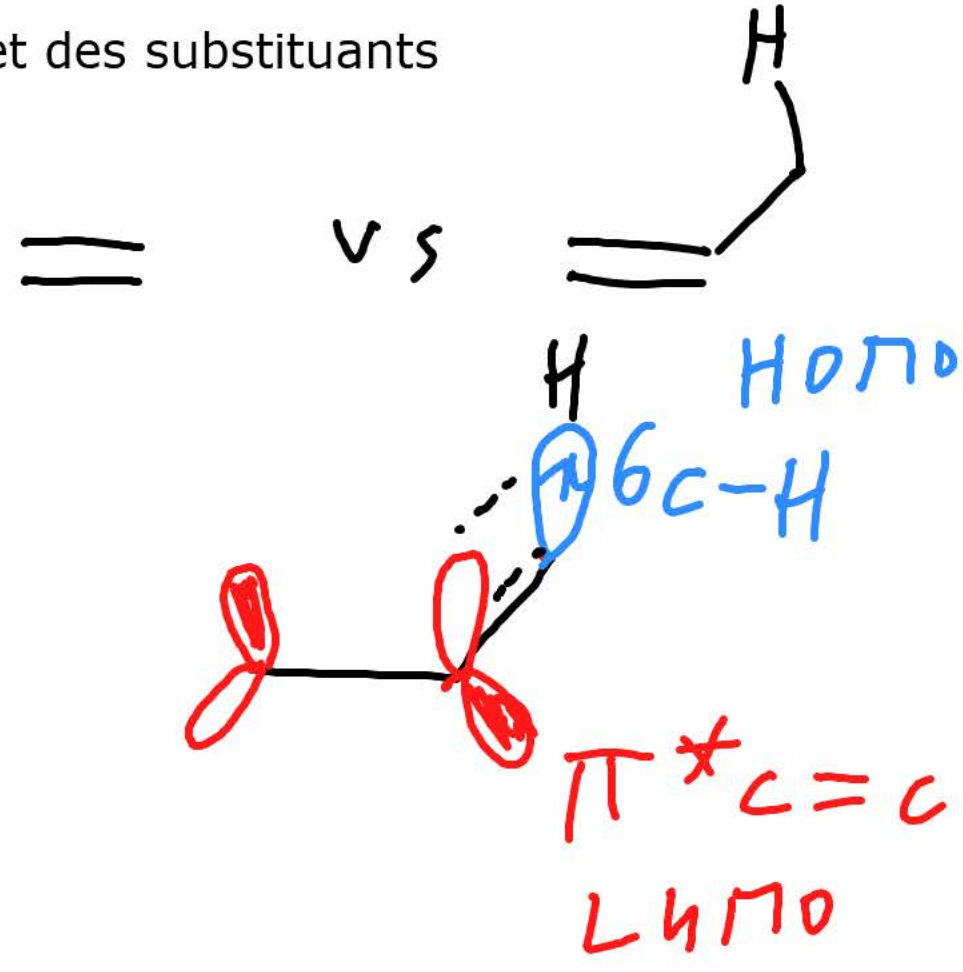

R
Z
R
hν
R
R
ISC
R
R
R
E
R
R
R
hν
ISC
R
R
R

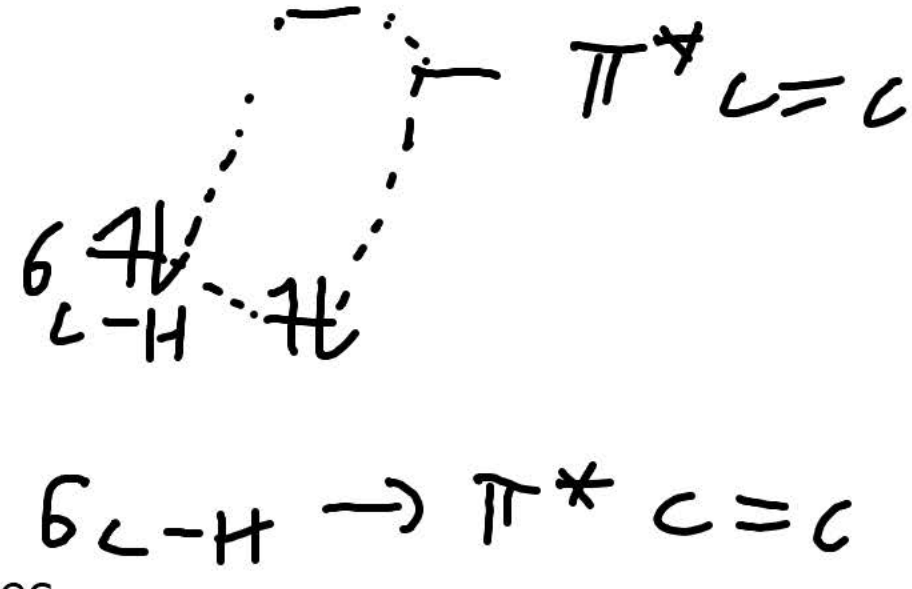
stabilité des alcènes: E vs Z



alcéne E est plus stable pour des raisons stériques, plus les substituants sont grands, plus la différence est grande

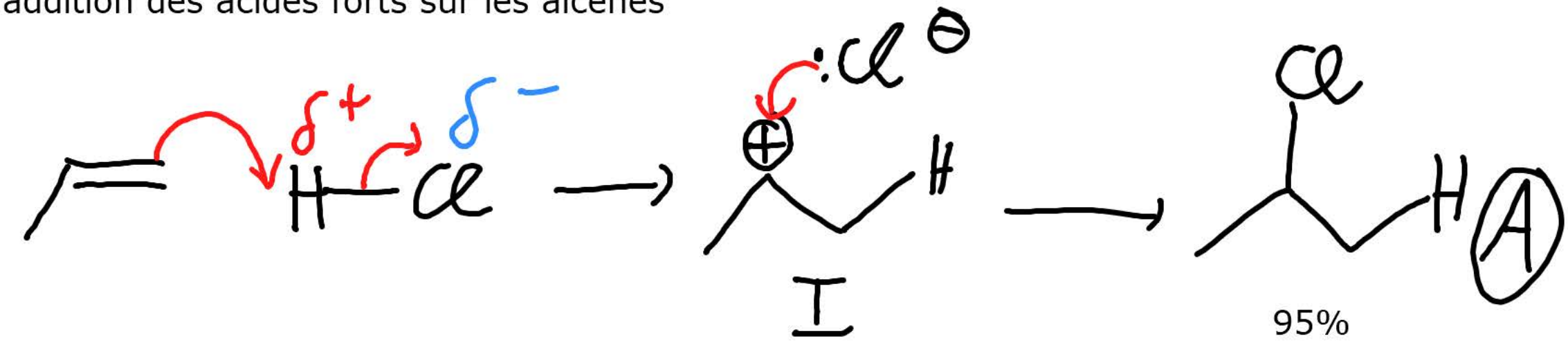
effet des substituants



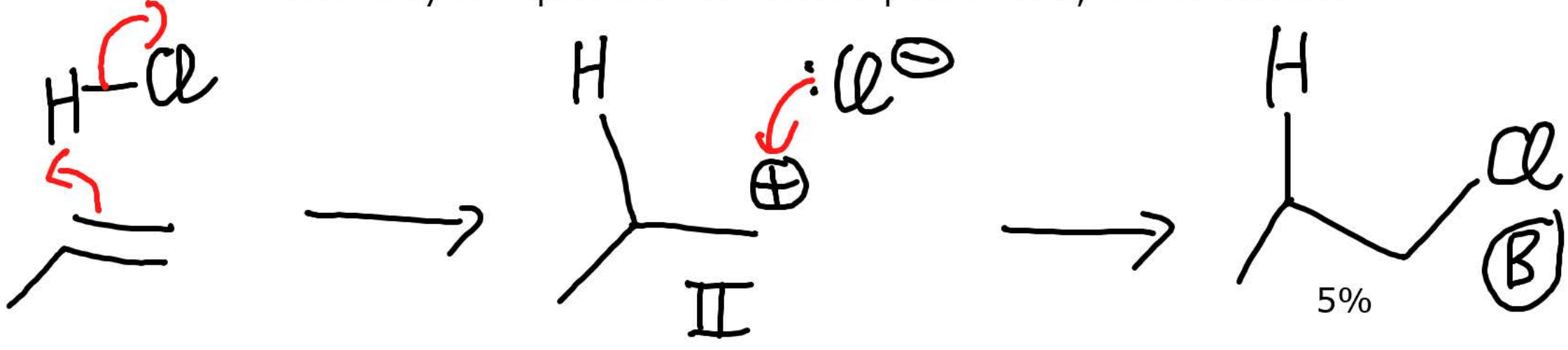


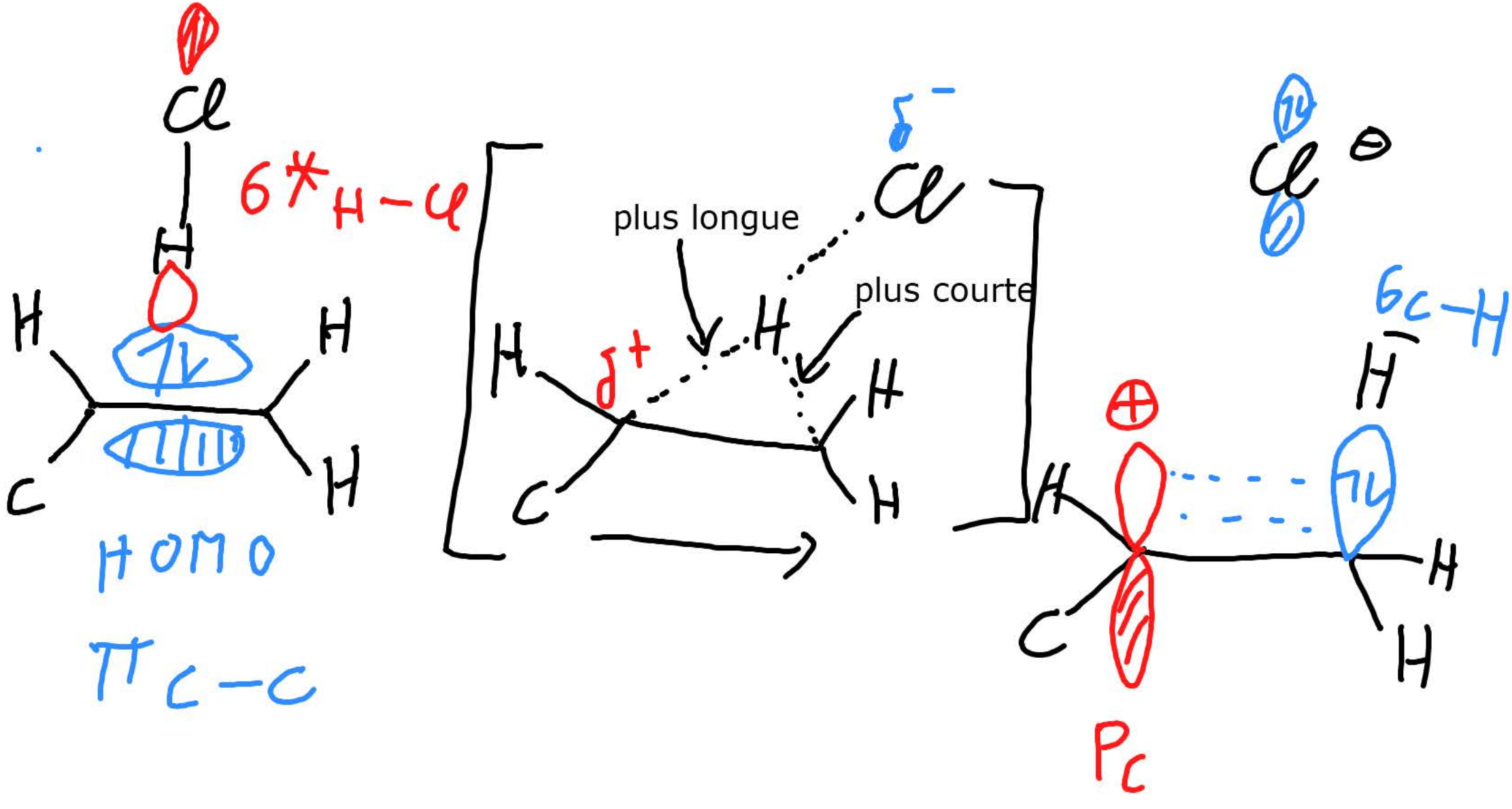
chaque substituant peut stabiliser par interactions avec la LUMO de la double liaison

addition des acides forts sur les alcènes

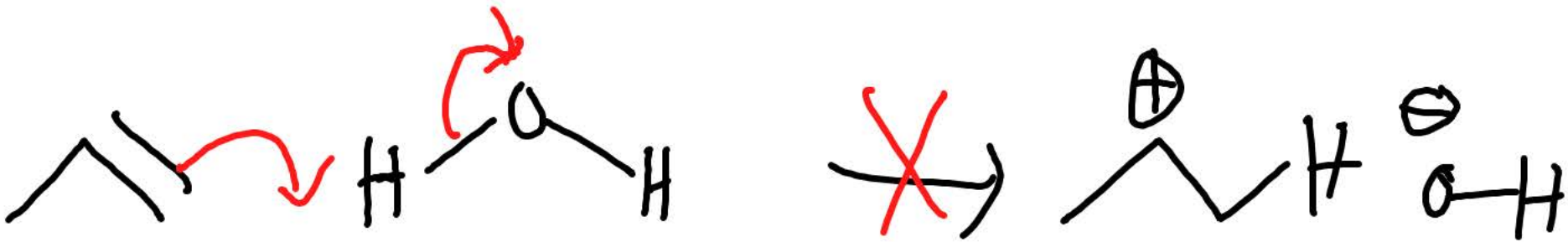


thermodynamique: mêmes liaisons pour A et B, même stabilité

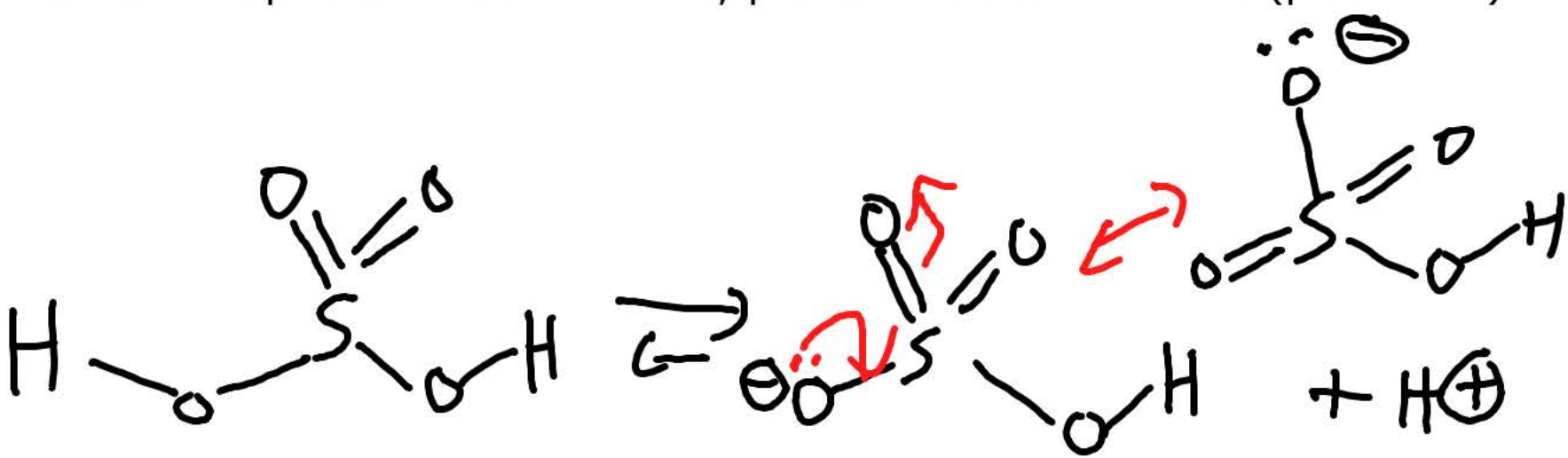



Cl
H
H
H
H
C
HOMO
π_{C-C}
σ^*_{H-Cl}
plus longue
plus courte
δ^-
δ^+
Cl
H
H
H
H
C
Cl
H
H
H
H
C
σ_{C-H}
P_C

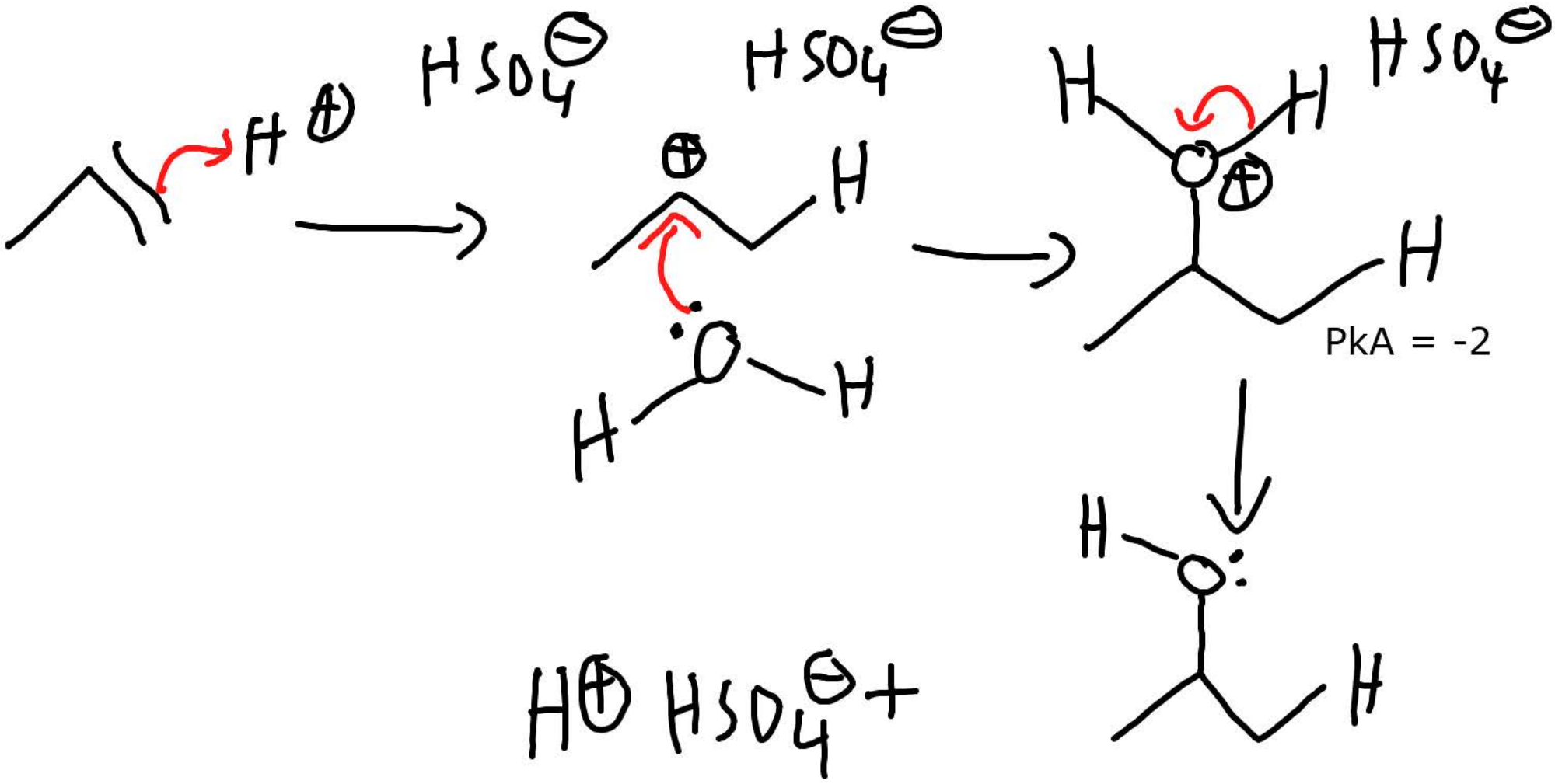
addition des acides faibles



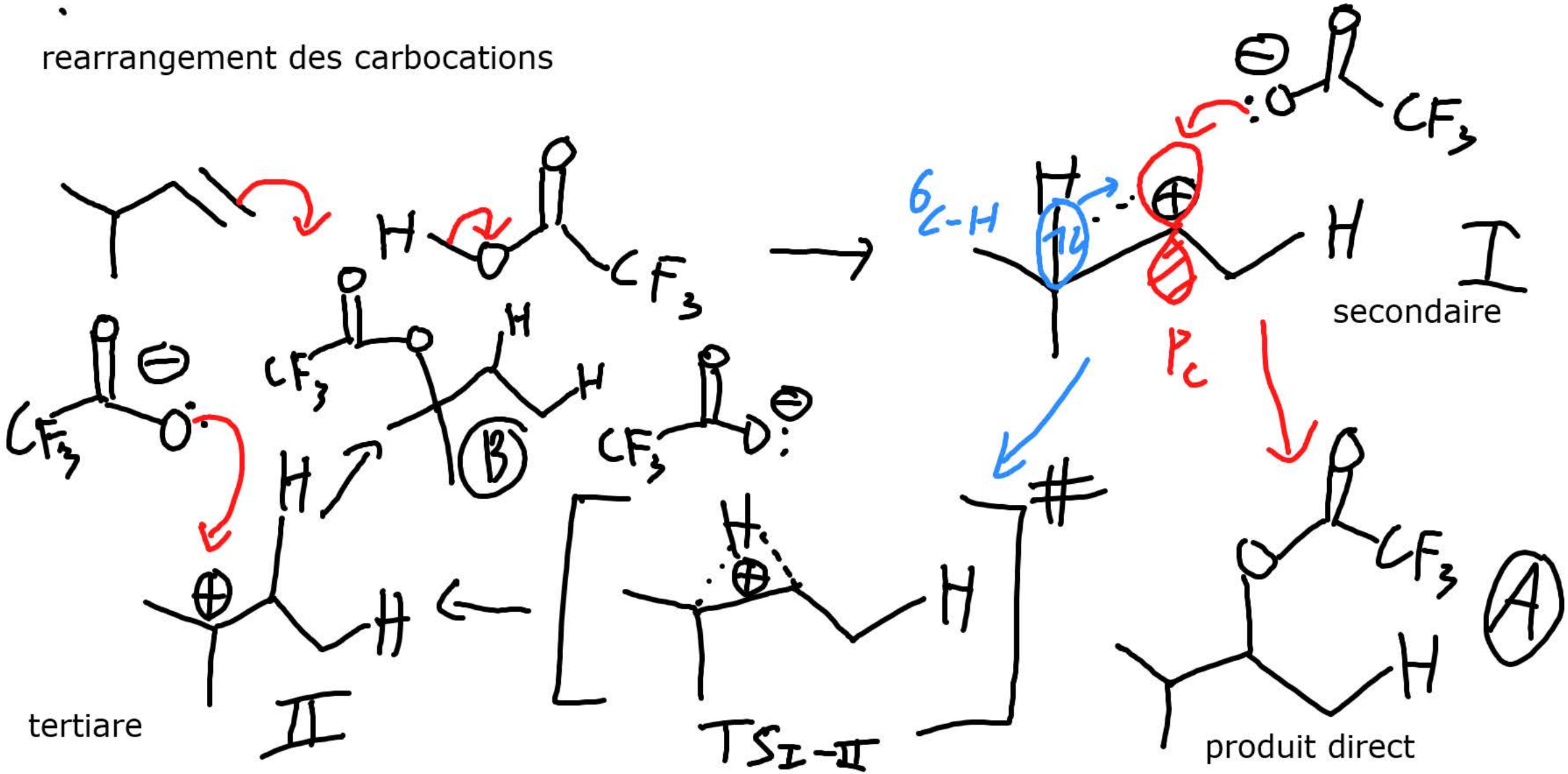
l'eau est trop faible comme acide, pas de réaction directe! (pKa = 14)

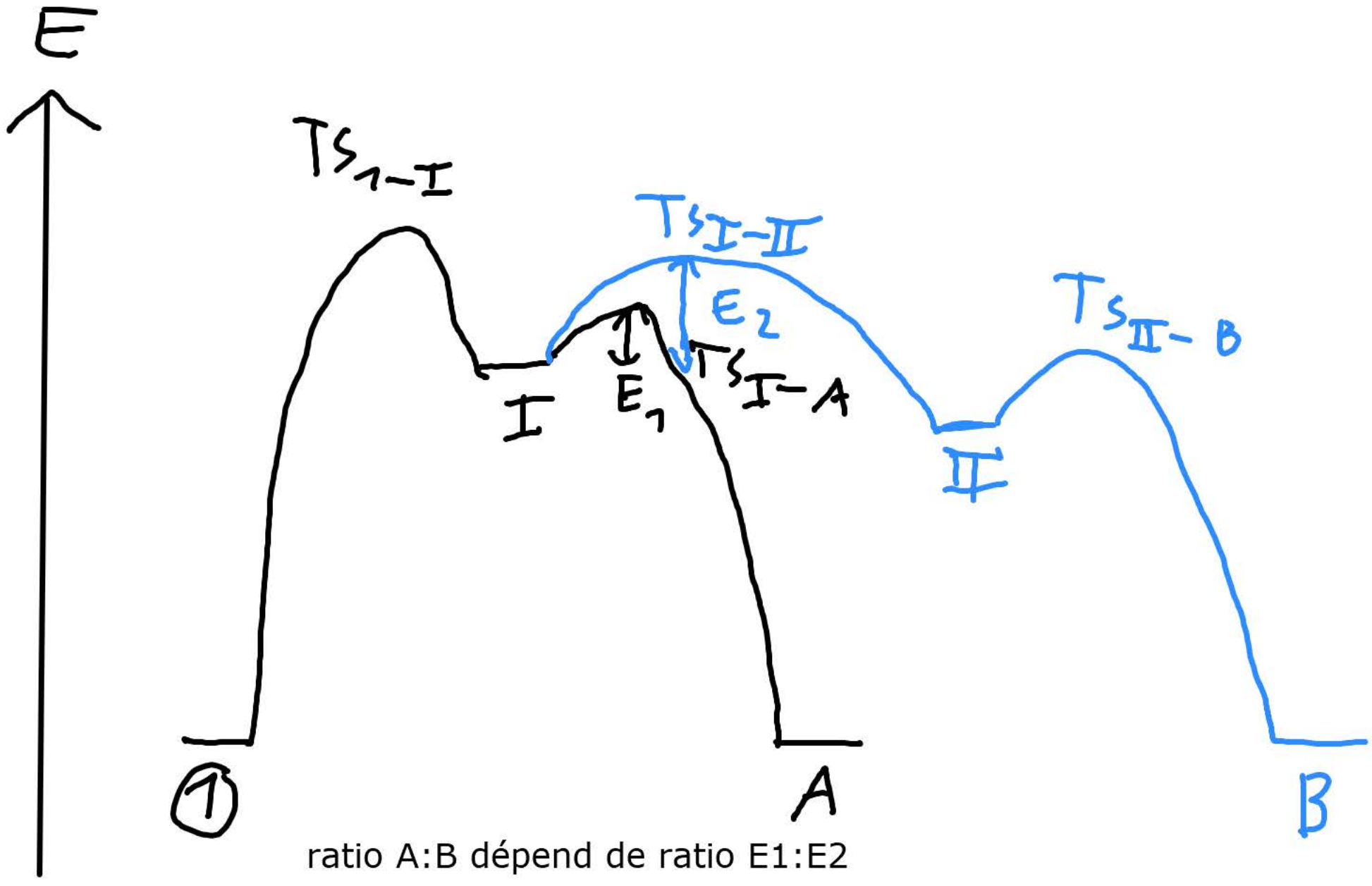


acide fort (pKa = -3) base très stabilisée par résonance, mauvais nucléophile

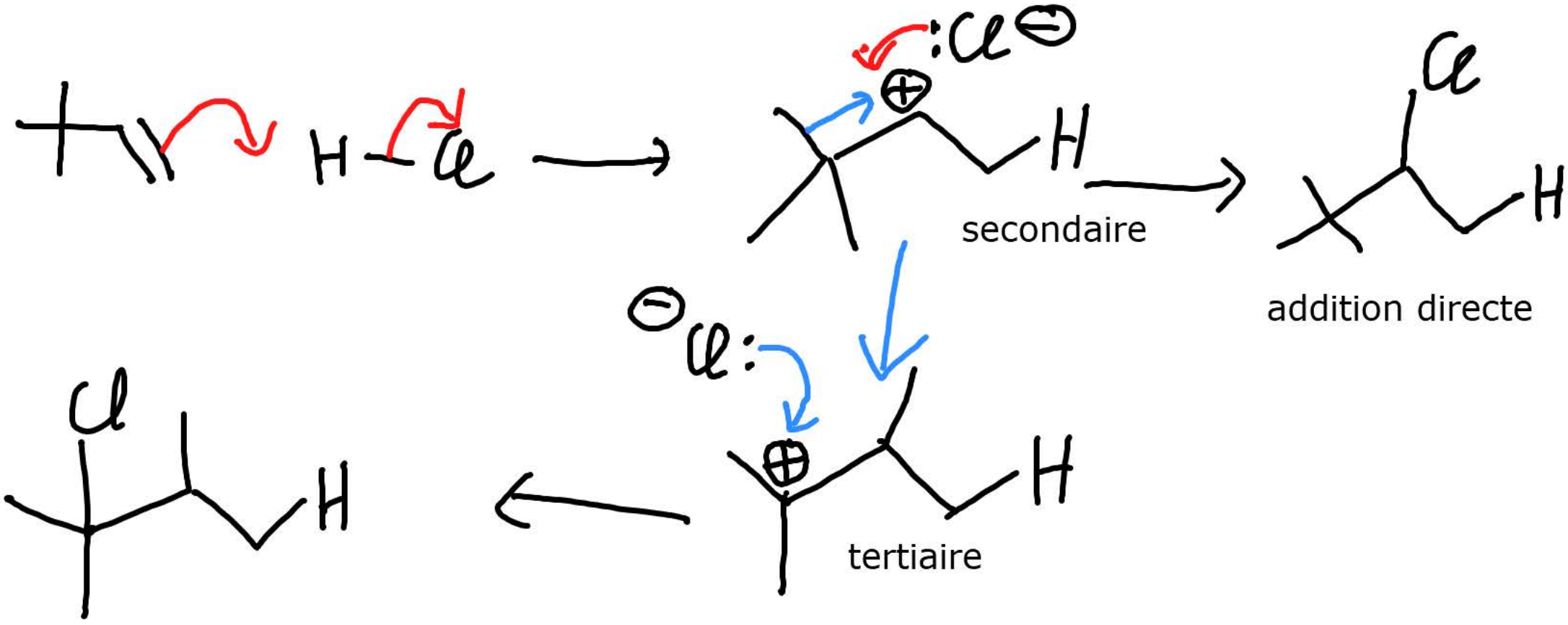

HSO4⊖
HSO4⊖
HSO4⊖
PkA = -2
H⊕ HSO4⊖ +

rearrangement des carbocations





ratio A:B dépend de ratio E1:E2

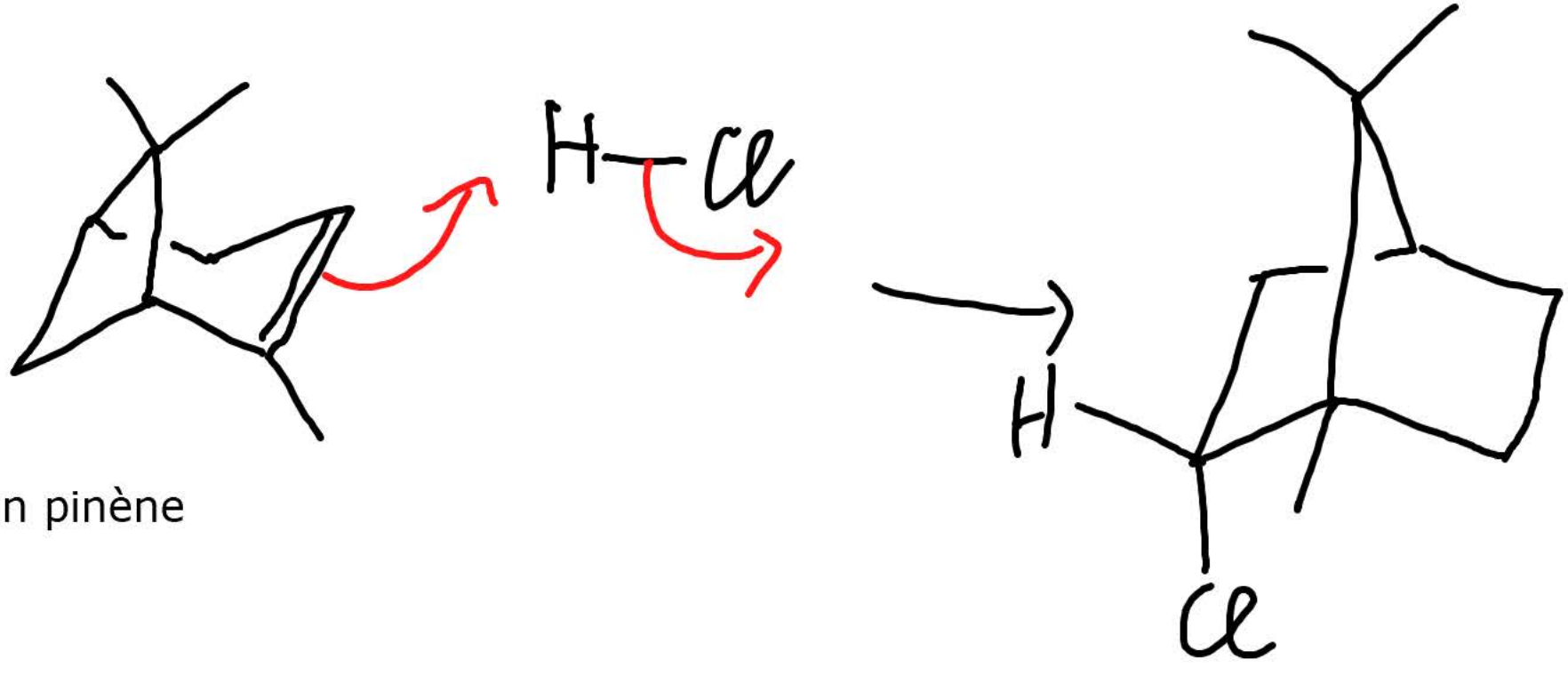


réarrangement

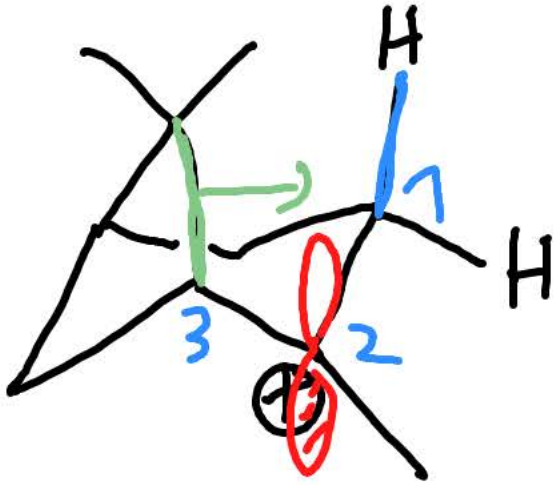
réarrangement favorable si le carbocation obtenu est plus stable

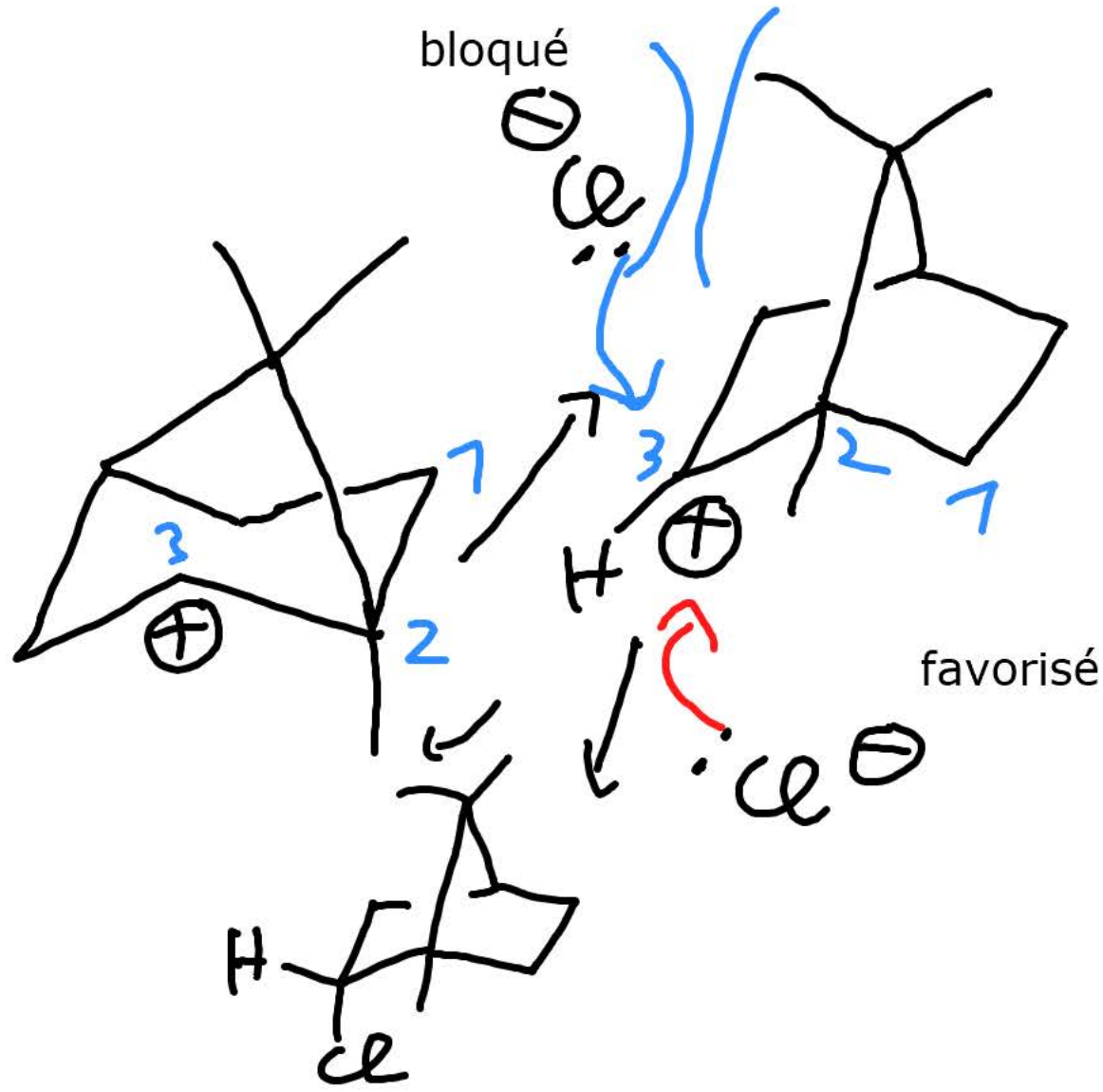
Le groupe qui stabilise le plus le carbocation va migrer
EN(H) < EN(C), donc H migre plus vite

découverte par Wagner-Meerwein (1899)



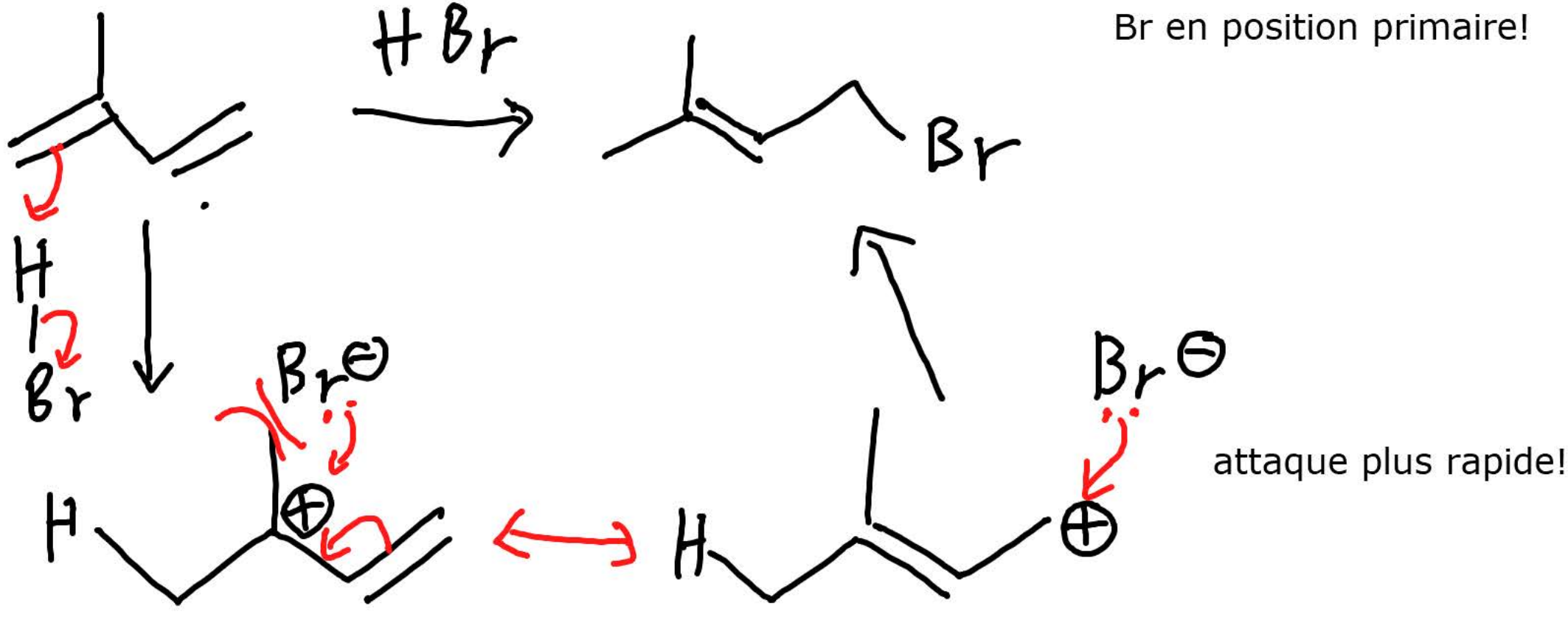
un pinène





En principe H migre plus vite,
mais ici c'est C!
en migrant C, on passe d'un cycle à 4 à un cycle à 5 = plus stable

exception à Markovnikov



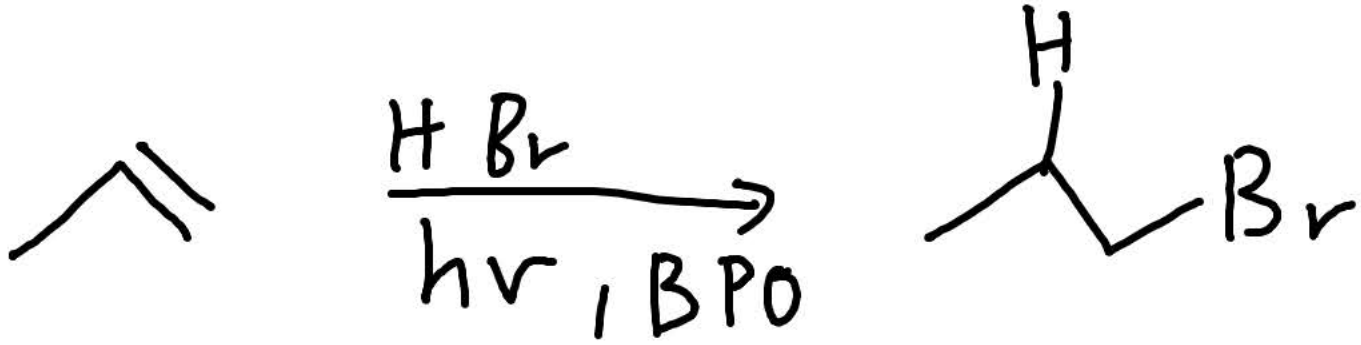
Br en position primaire!

attaque plus rapide!

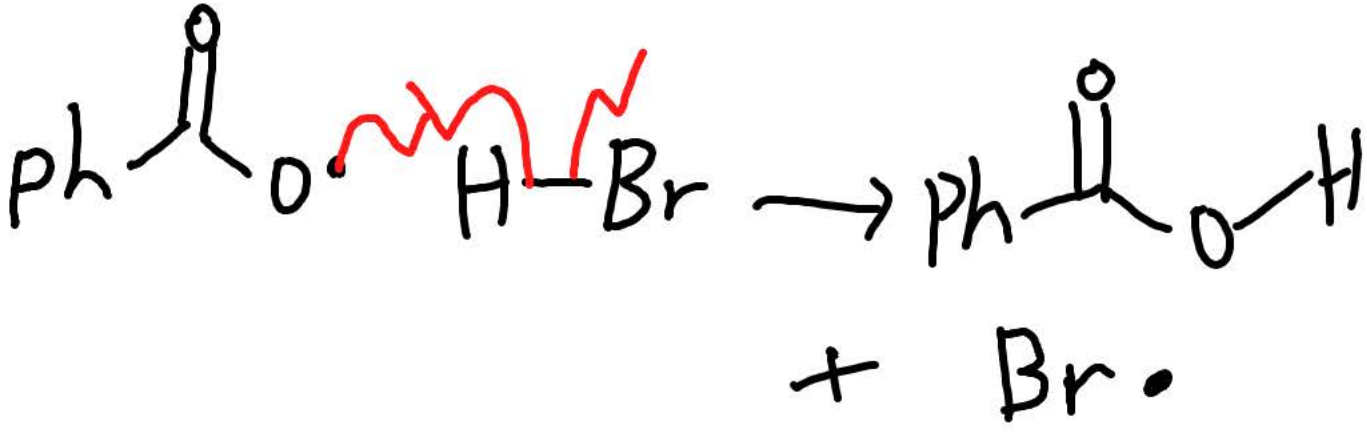
tertiaire

structure de résonance

Comment synthétiser le produit anti-markovnikov: utiliser les radicaux

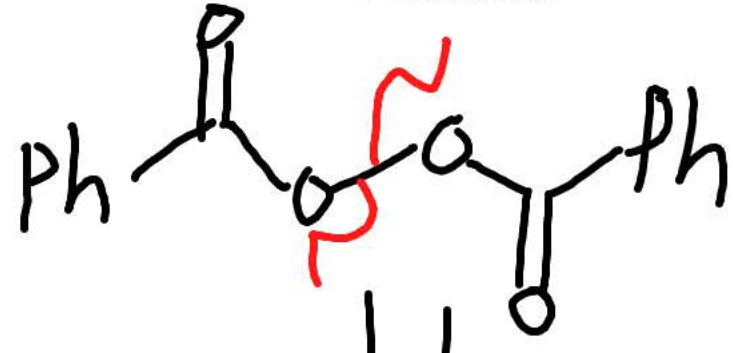


propagation

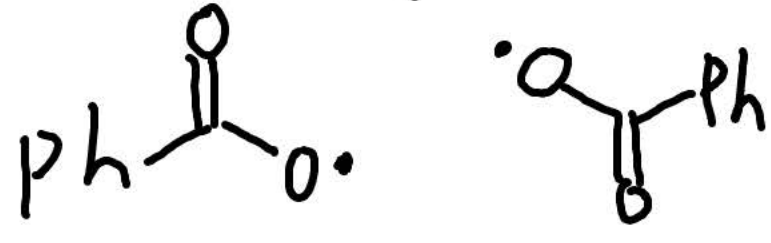


BPO: benzoylperoxide

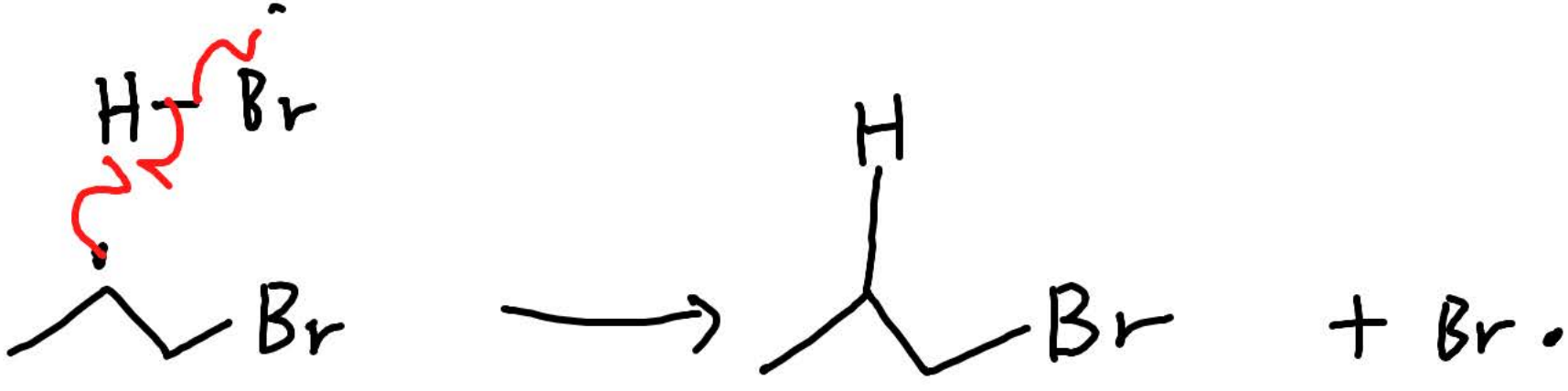
initiateur



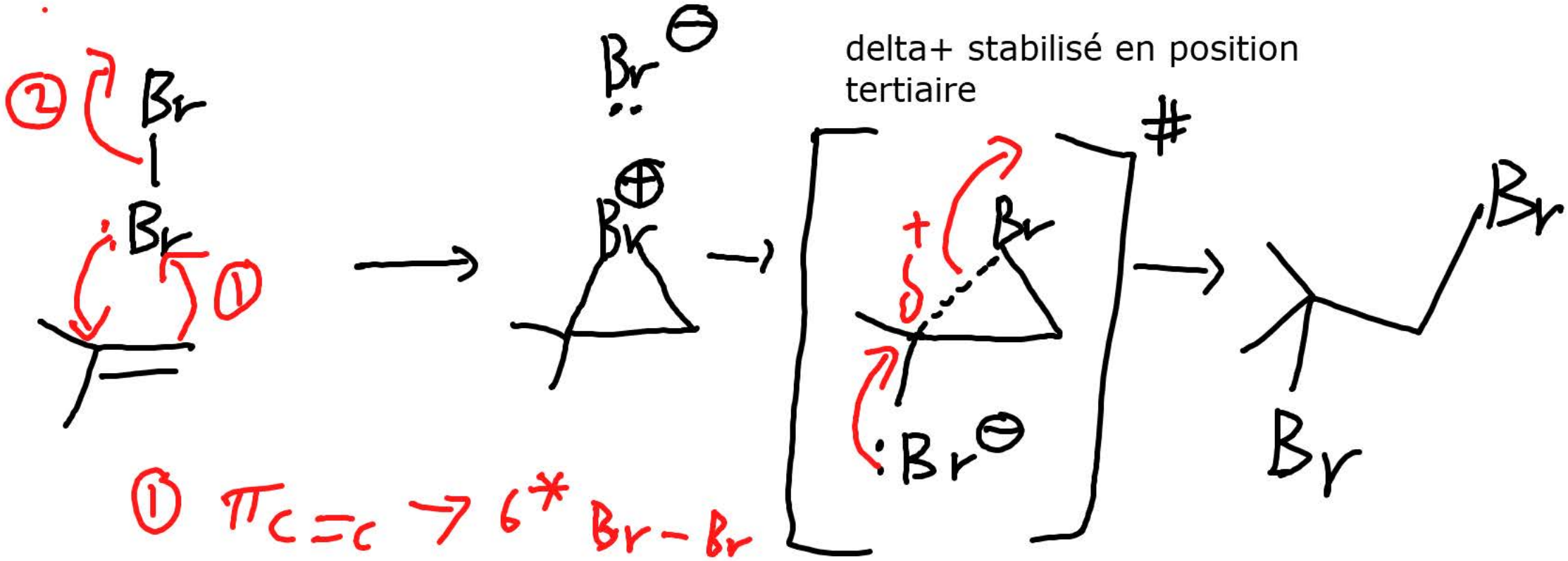
initiation



radical secondaire plus stable, favorisé



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



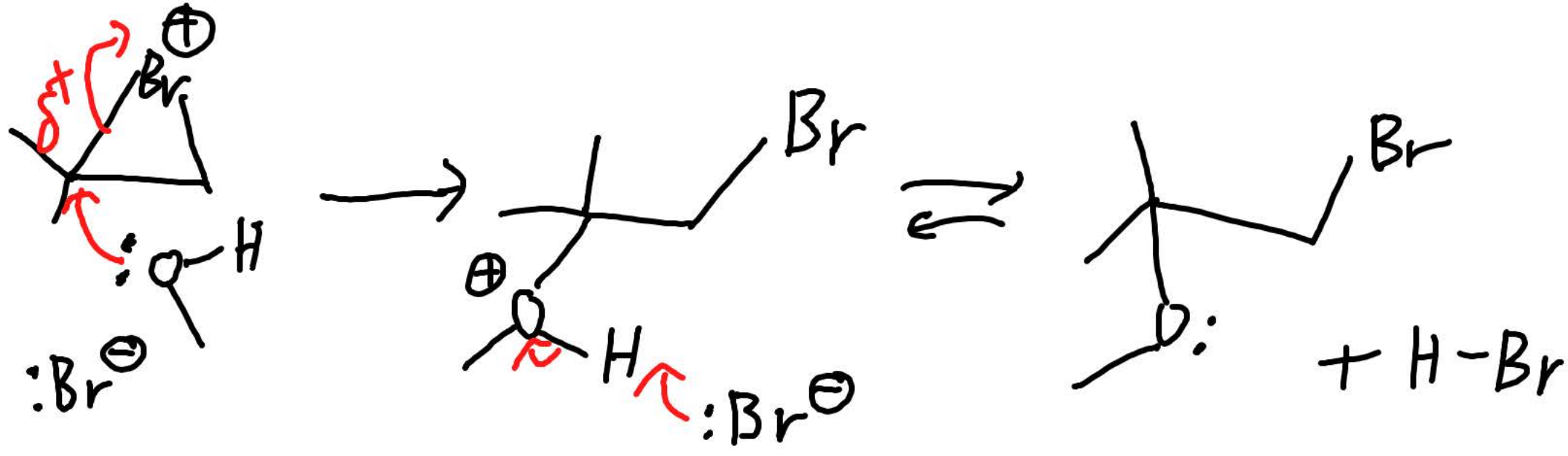
① $\pi_{C=C} \rightarrow \sigma^*_{Br-Br}$

② σ_{Br-Br} brisée

③ $n_{Br} \rightarrow \pi^*_{C=C}$

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

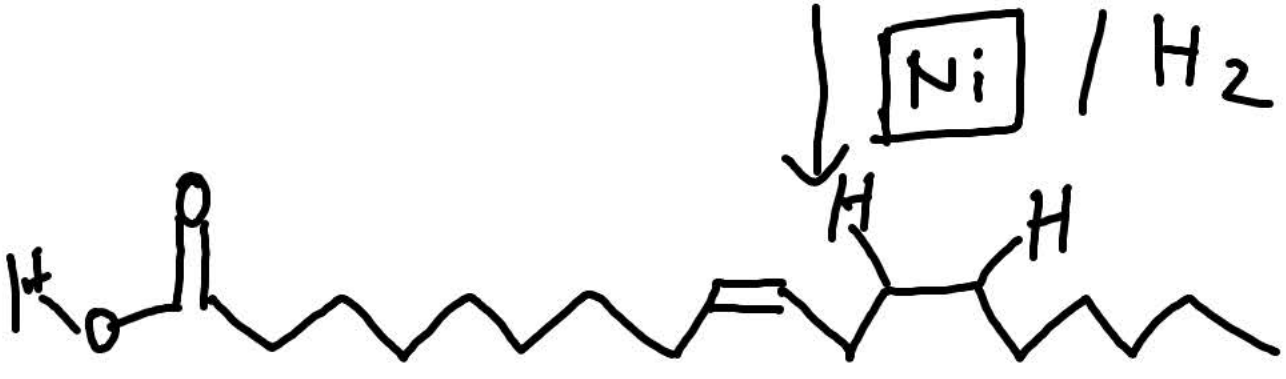
réaction dans le méthanol



compétition entre 2 nucléophiles: Br- et MeOH, Br- est meilleur, mais l'utilisation du méthanol comme solvant "surcompense"

example d'hydrogénation: les acides gras

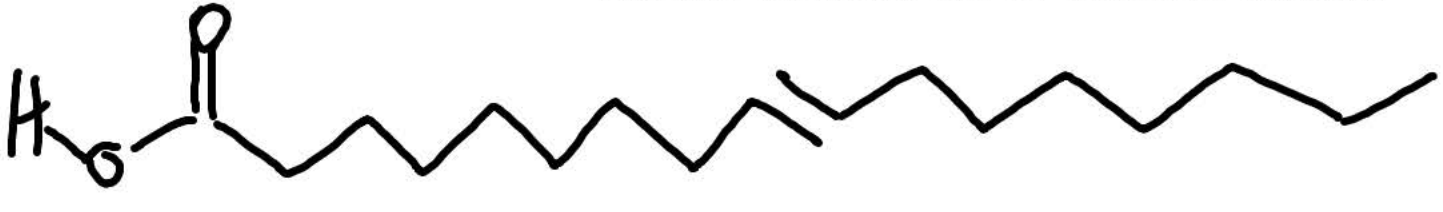
acide linoléique: abondant dans les huiles végétales (liquide visqueux)



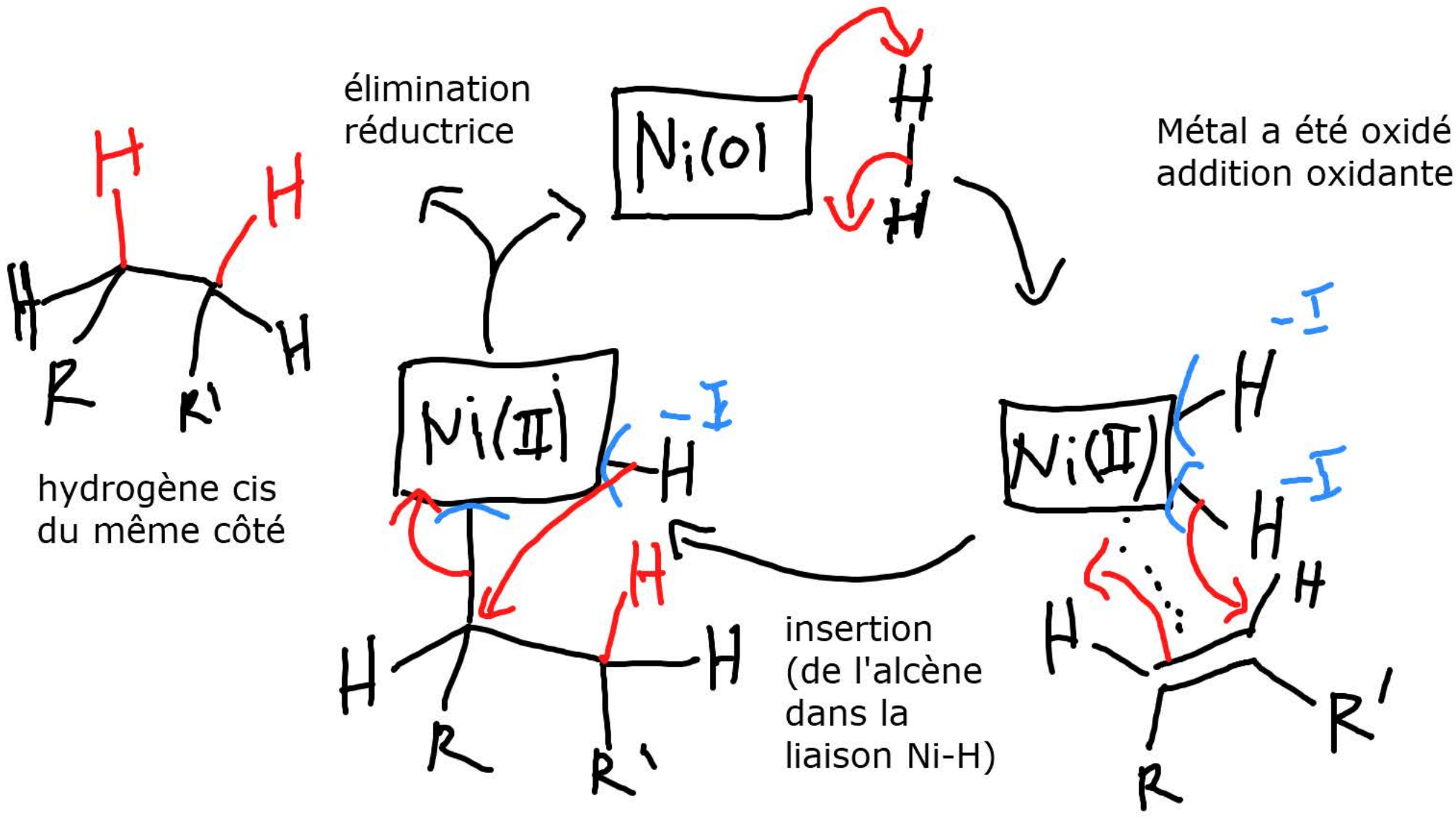
réduction partielle d'une alcènes
parafine, solide (facile à utiliser)

produit secondaire:

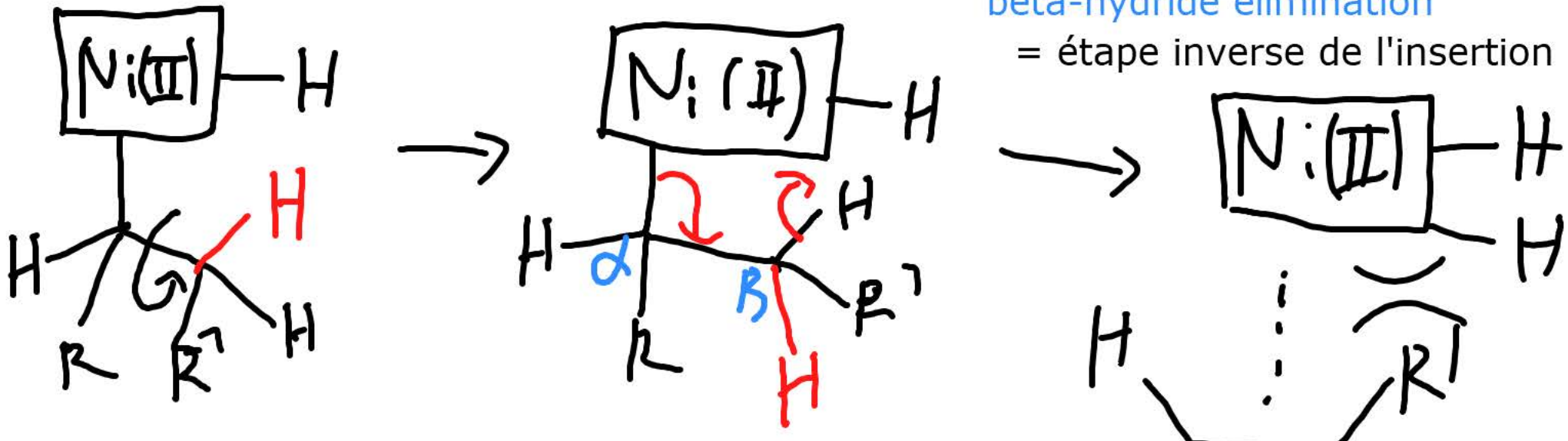
isomérisation de la double liaison



E/trans, trans-fat
athériosclérose, problème vasculaire


élimination
réductrice
Ni(0)
Métal a été oxidé
addition oxidante
hydrogène cis
du même côté
Ni(II)
Ni(II)
insertion
(de l'alcène
dans la
liaison Ni-H)

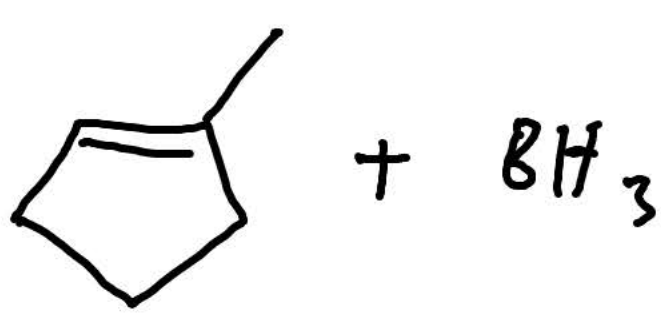
réaction secondaire:
isomérisation



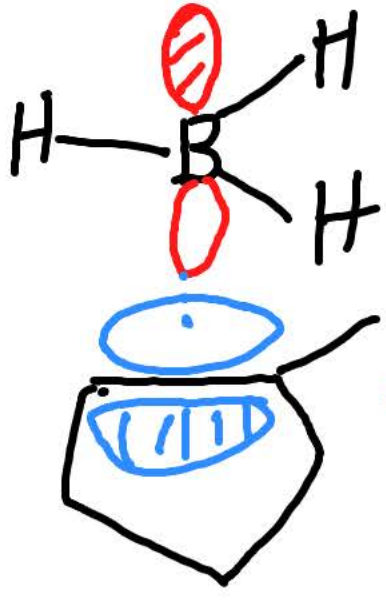
beta-hydride élimination
= étape inverse de l'insertion

oléfine trans peut se dissocier et s'accumuler

hydroboration



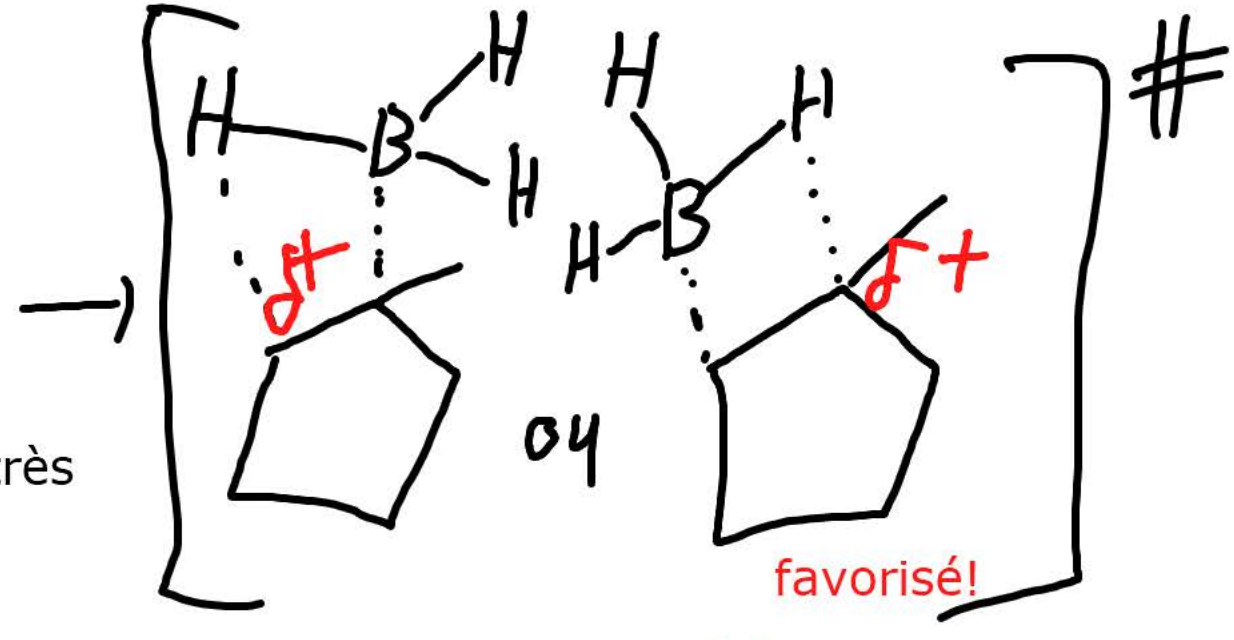
+ BH_3



6 electrons sur B, très électrophile

p_B LUMO

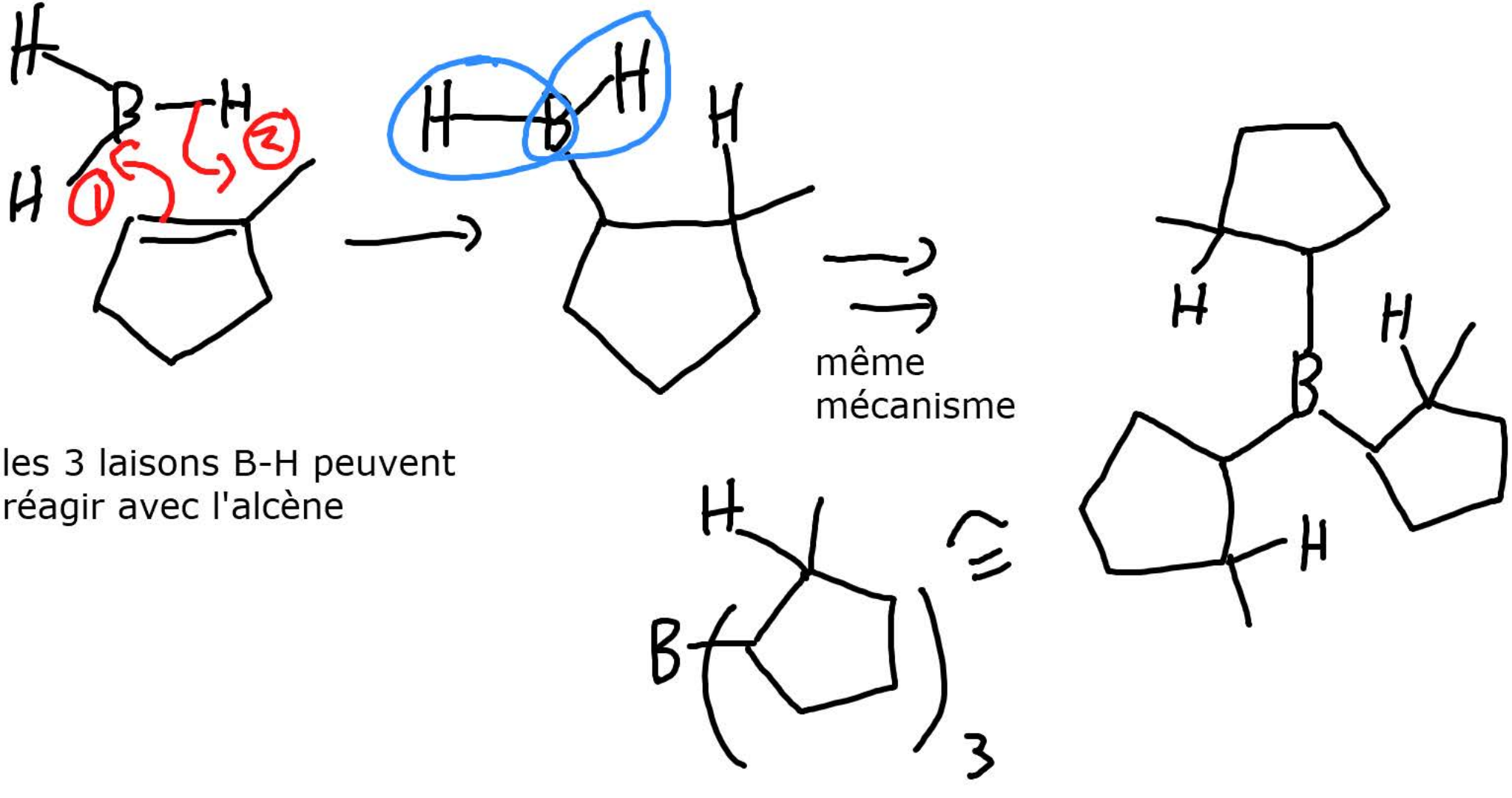
π_{C-C} HOMO



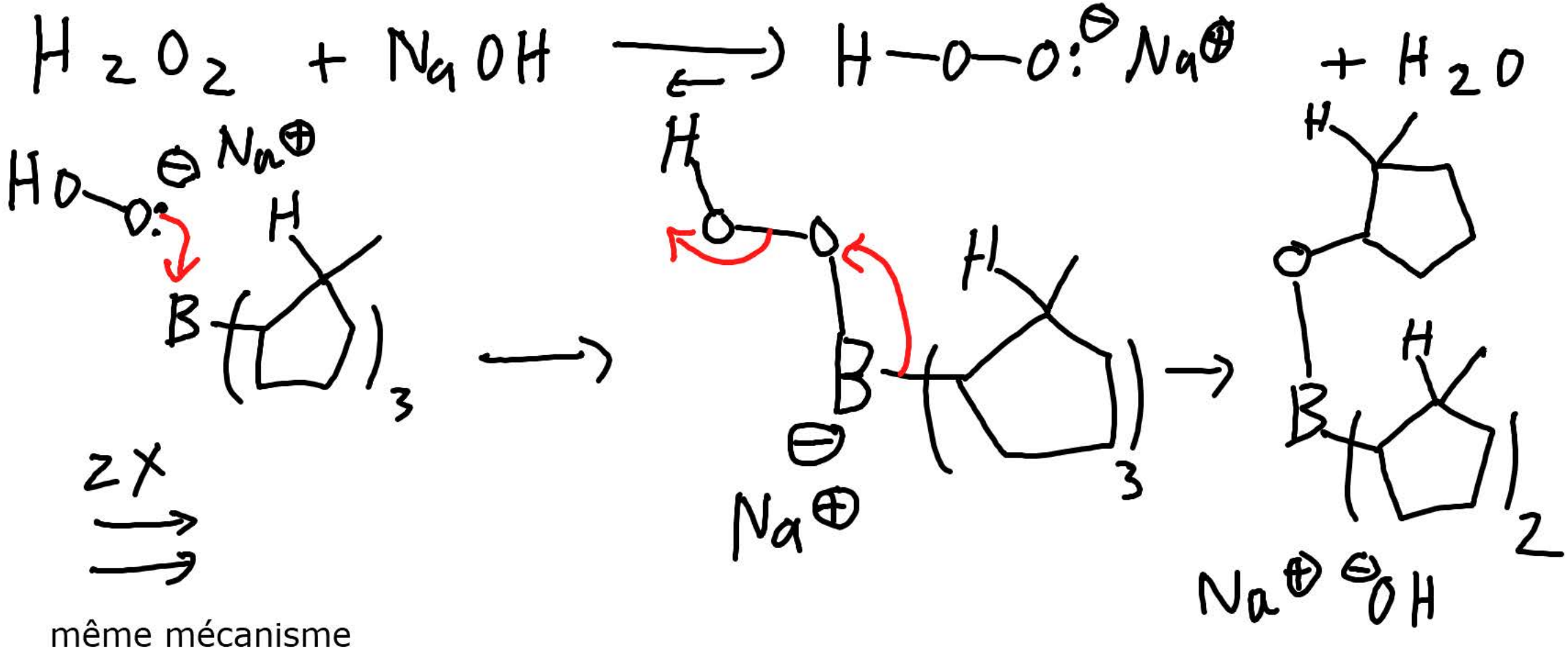
favorisé!

delta+ en tertiaire

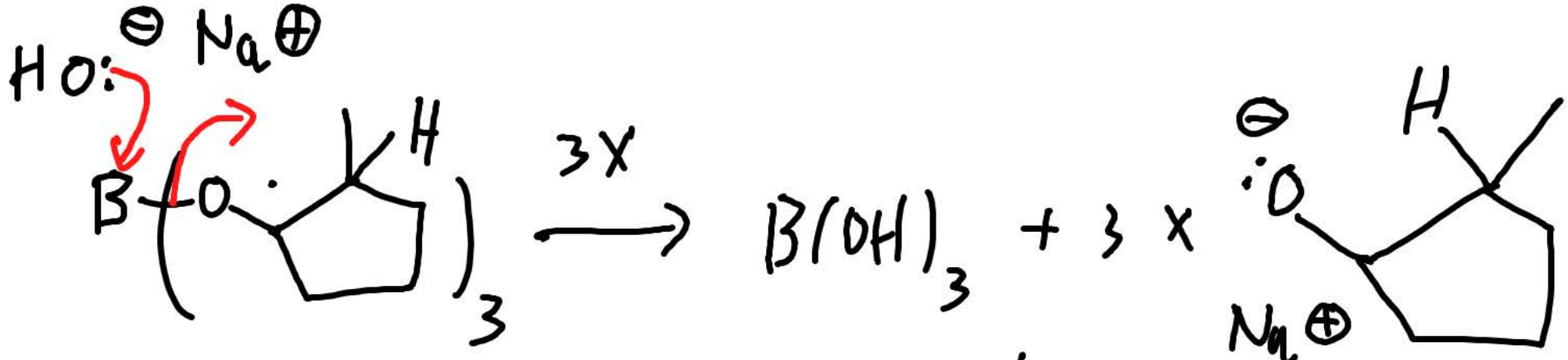
état de transition à 4 atomes
La distance C-B est plus courte que la distance C-H dans l'état de transition


même
mécanisme
les 3 laisons B-H peuvent
réagir avec l'alcène

étape d'oxidation



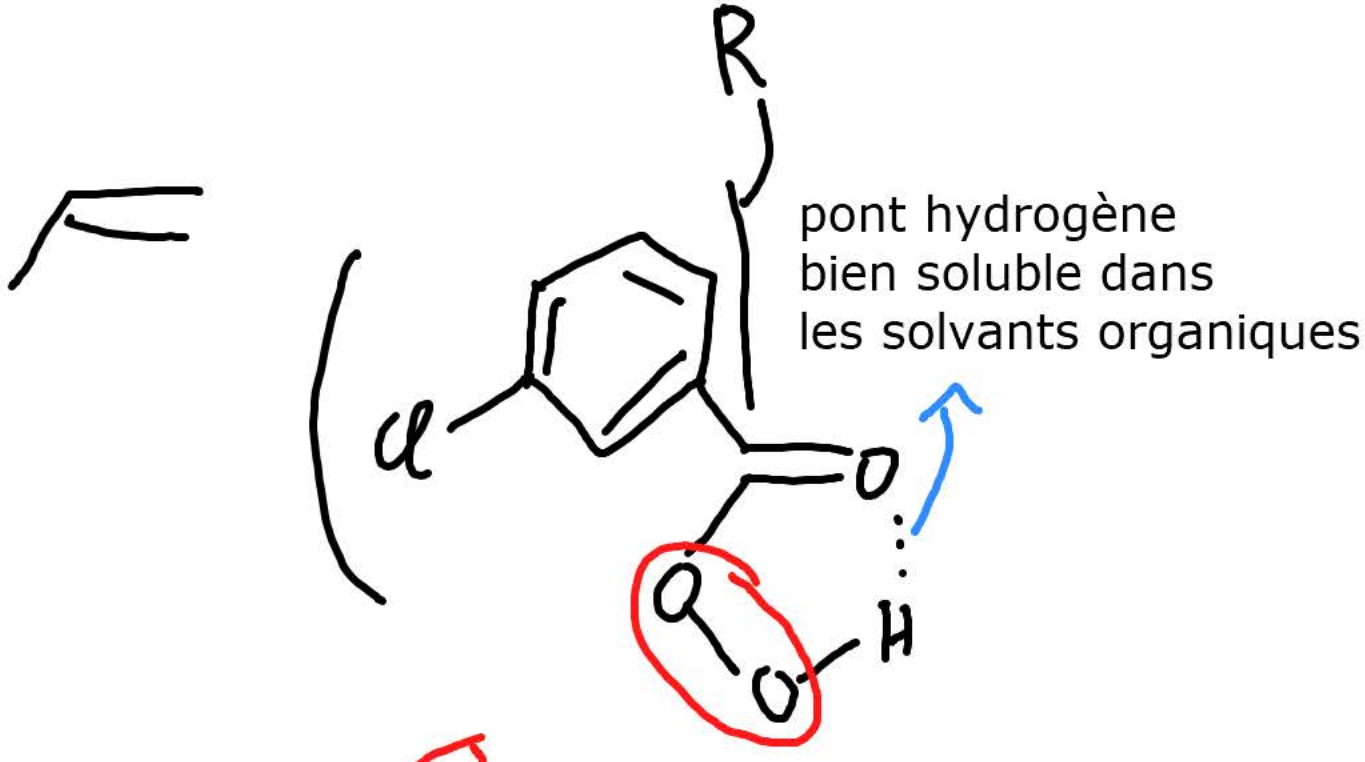
même mécanisme



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

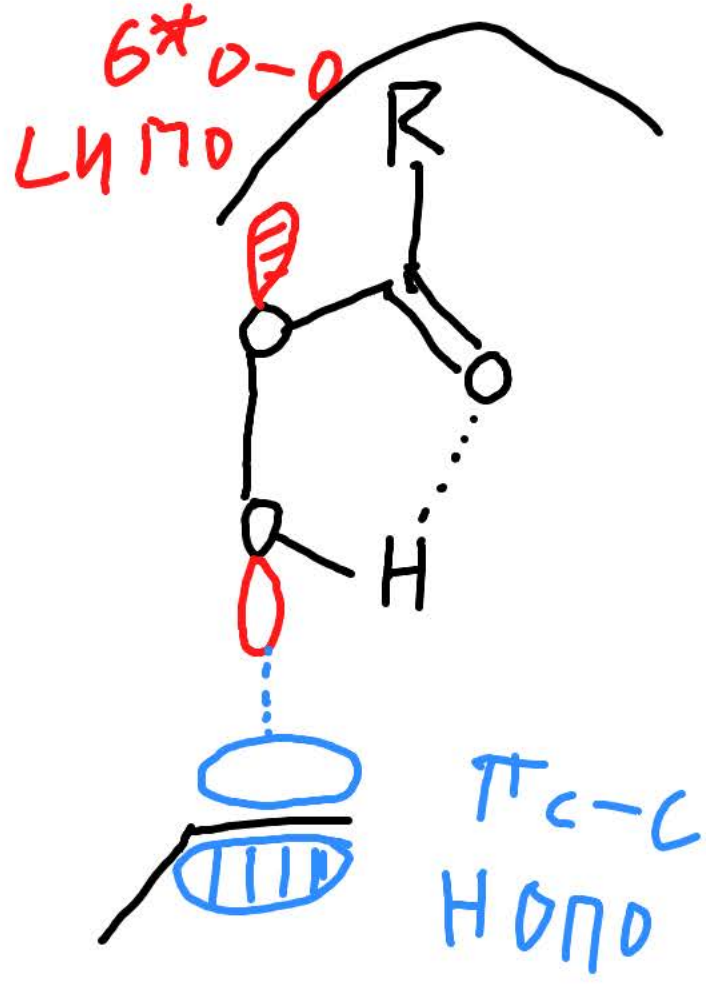
au total: addition de H2O sur
alcène, mais anti-Markovnikov

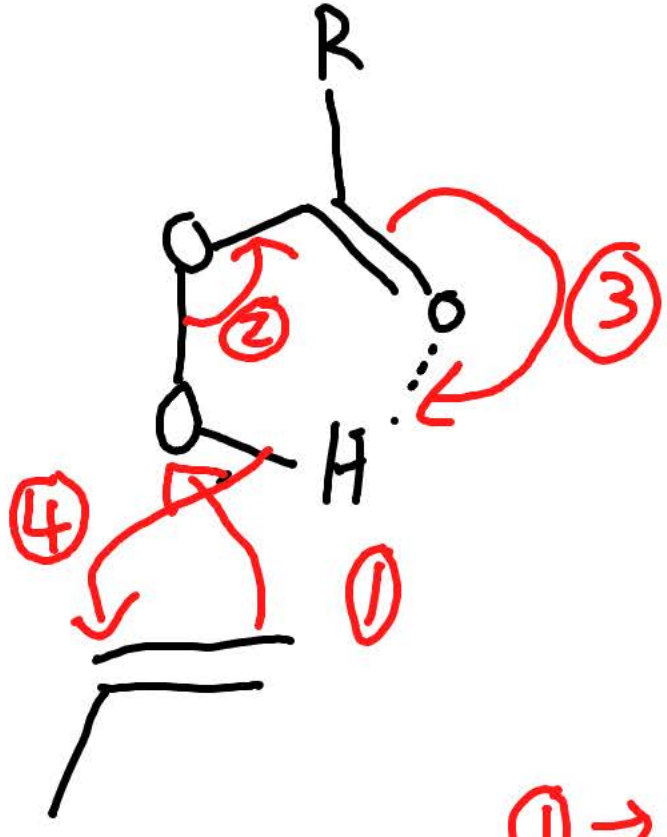
époxidation avec les péroxides

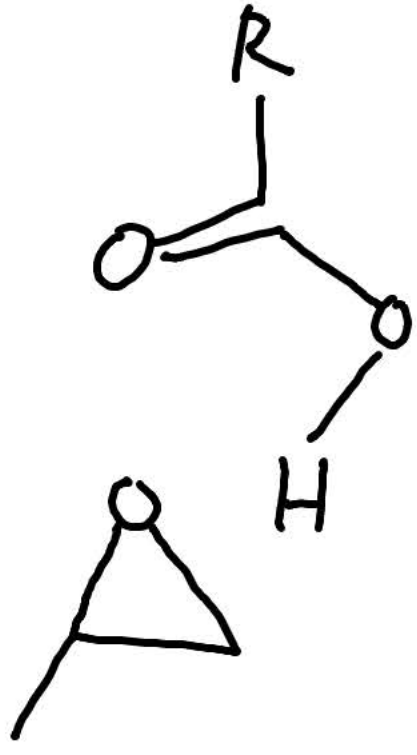


pont hydrogène
bien soluble dans
les solvants organiques

meta-chloroperbenzoic acid
m-CPBA







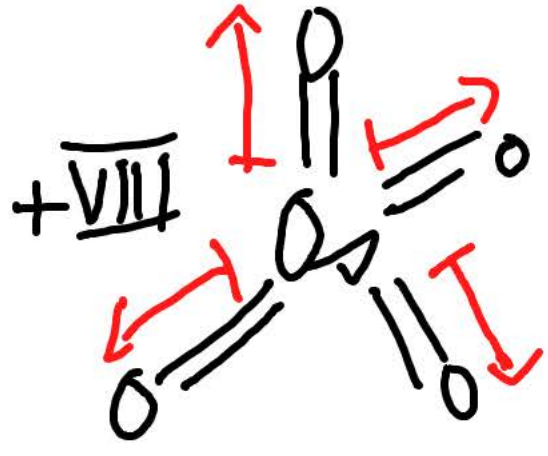
acide: pas de pont hydrogène
moins soluble, précipite

① → π_{C-C}

↓

σ^*_{O-O}

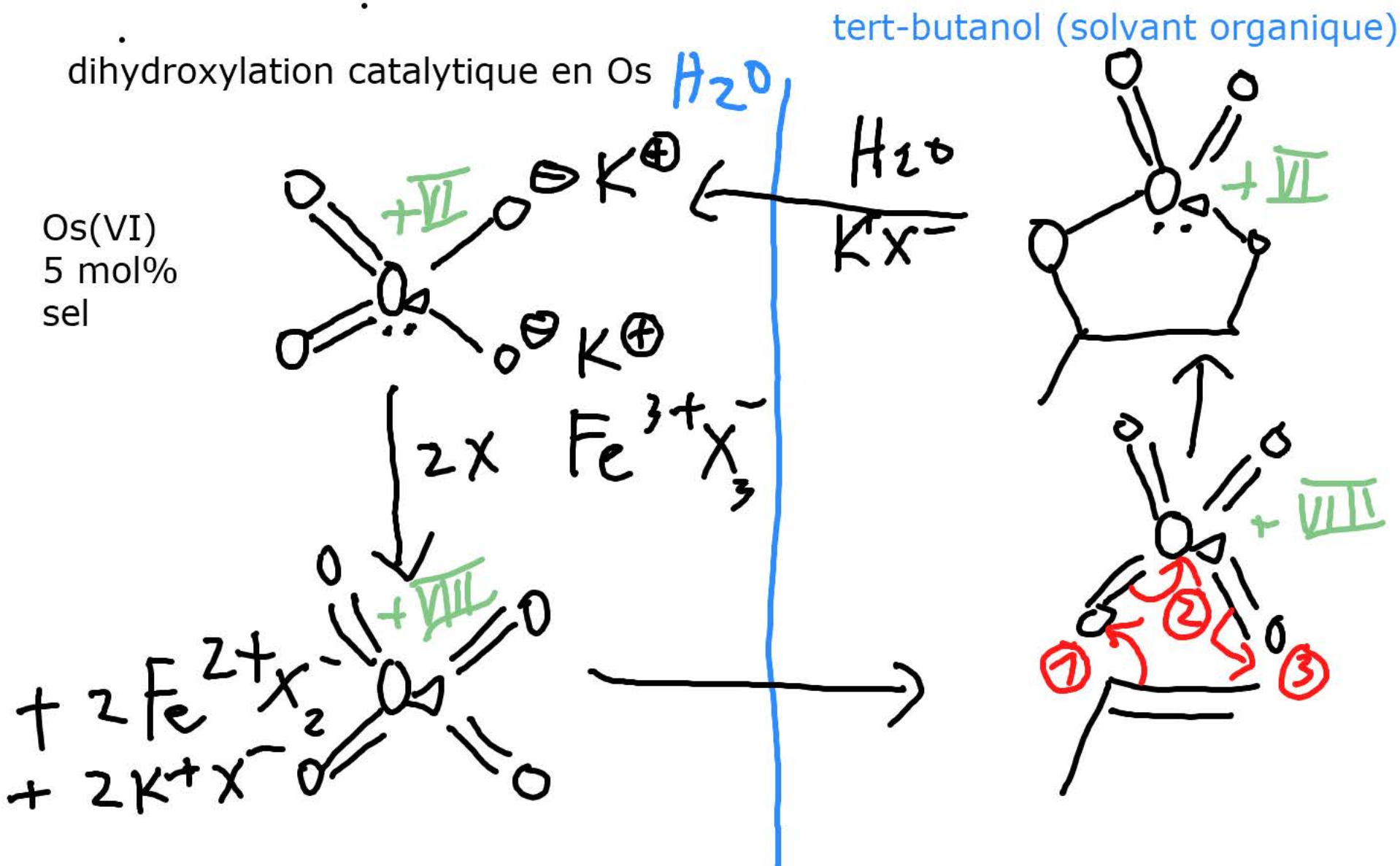
réaction de dihydroxylation avec OsO4



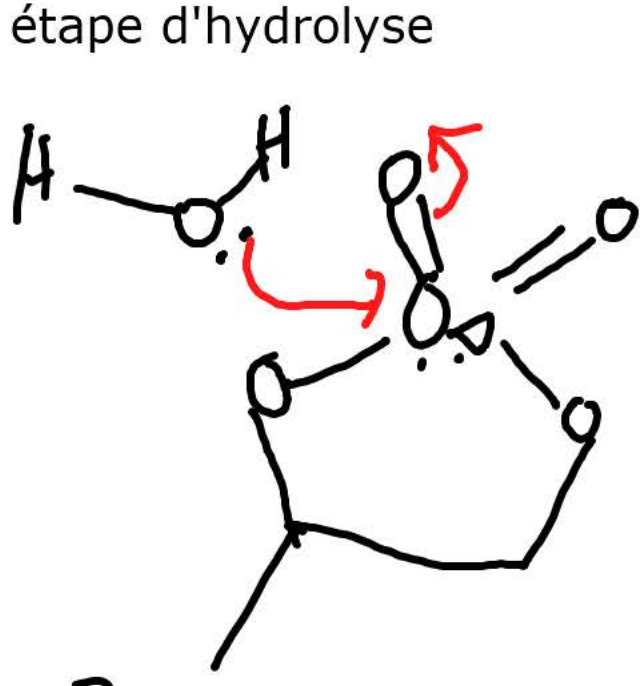
dipole globale: 0
lipophilique: passer la barrière sang-cerveau
sublime facilement

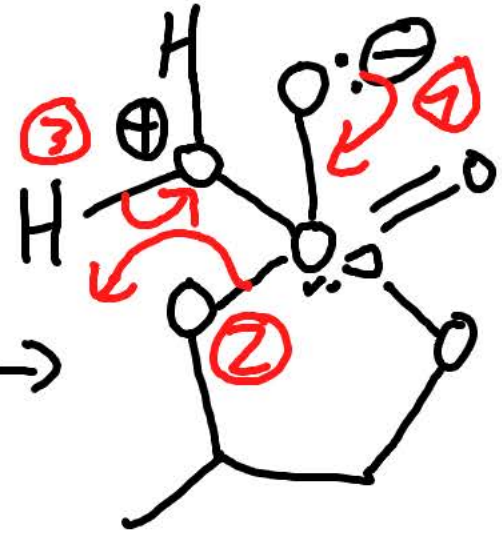
4 substituants, tétraédrique

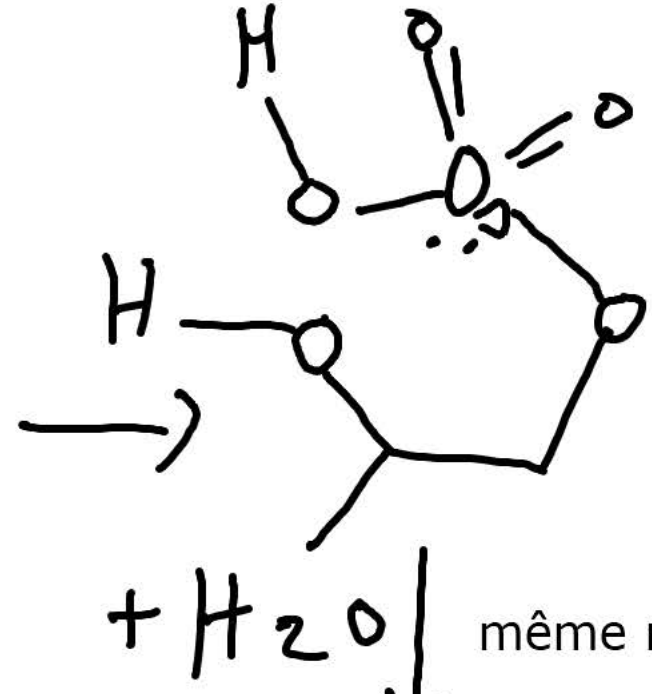
dihydroxylation catalytique en Os



étape d'hydrolyse

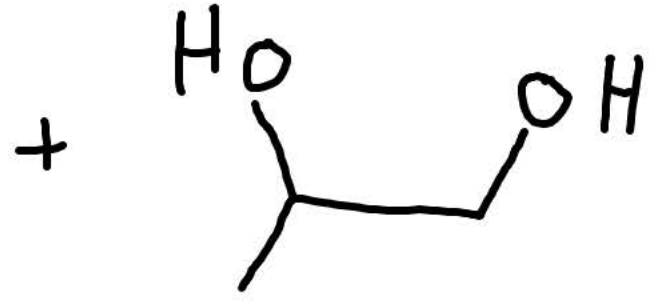


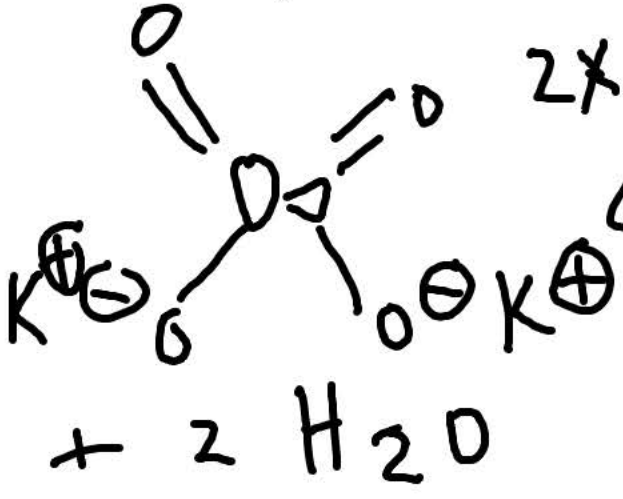




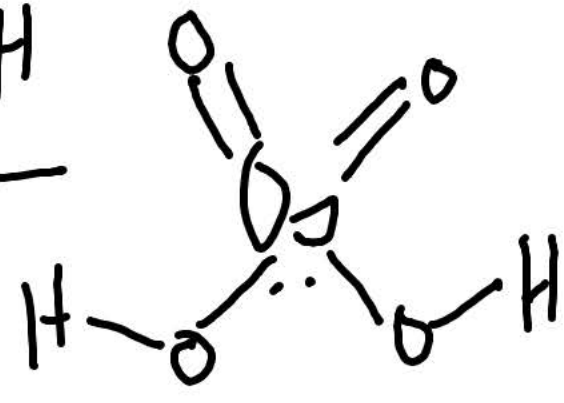
+ H_2O

même mécanisme



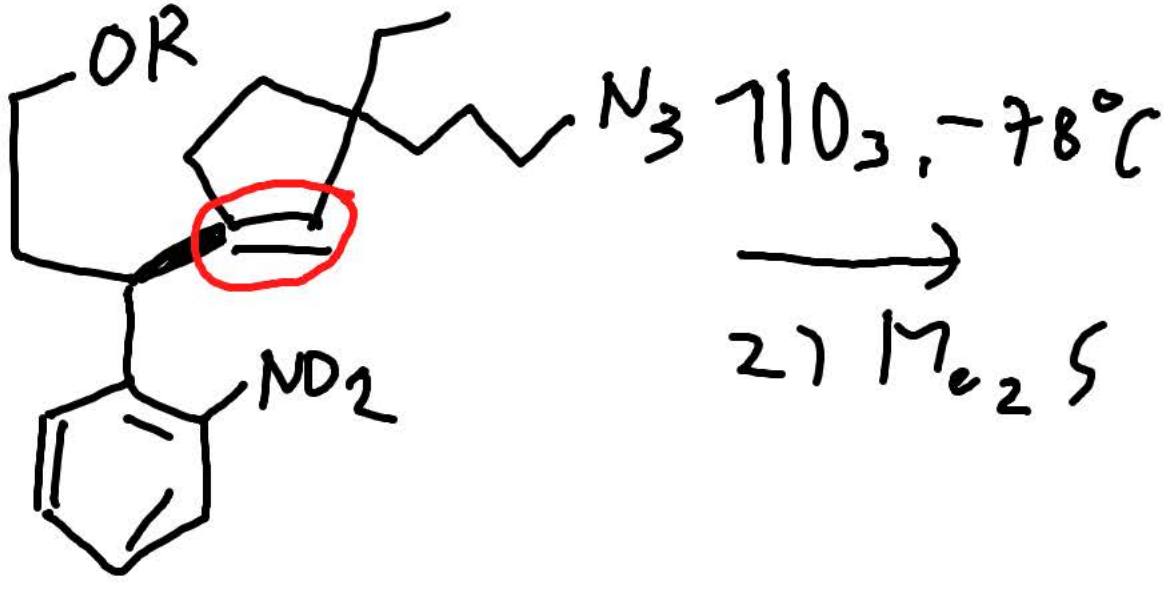


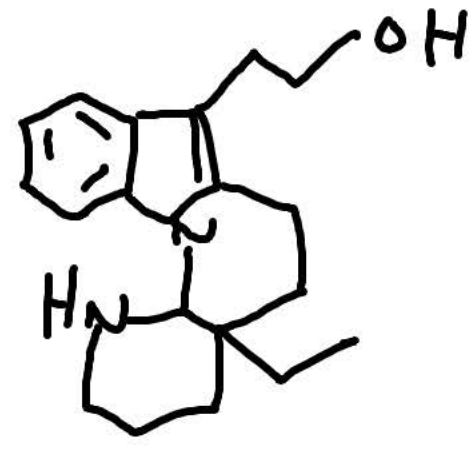
2 x KOH

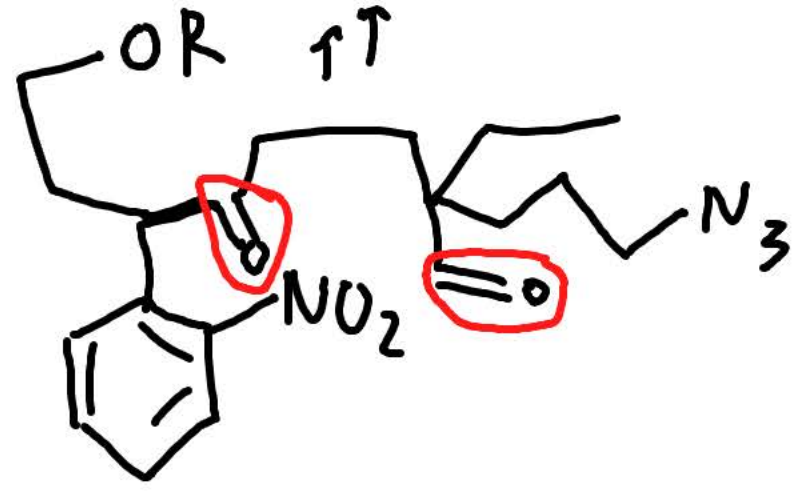


+ 2 H_2O

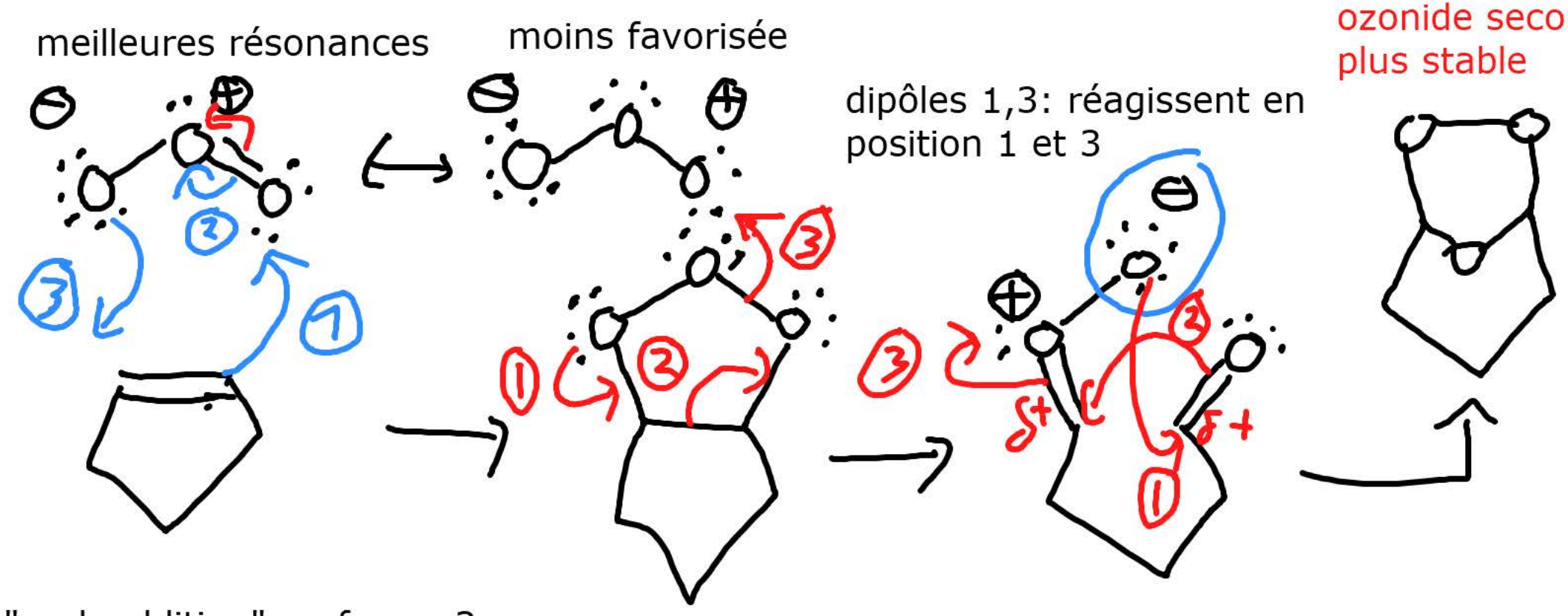
réaction d'ozonolyse: synthèse de la goniomitine par le groupe de Jieping Zhu (EPFL)







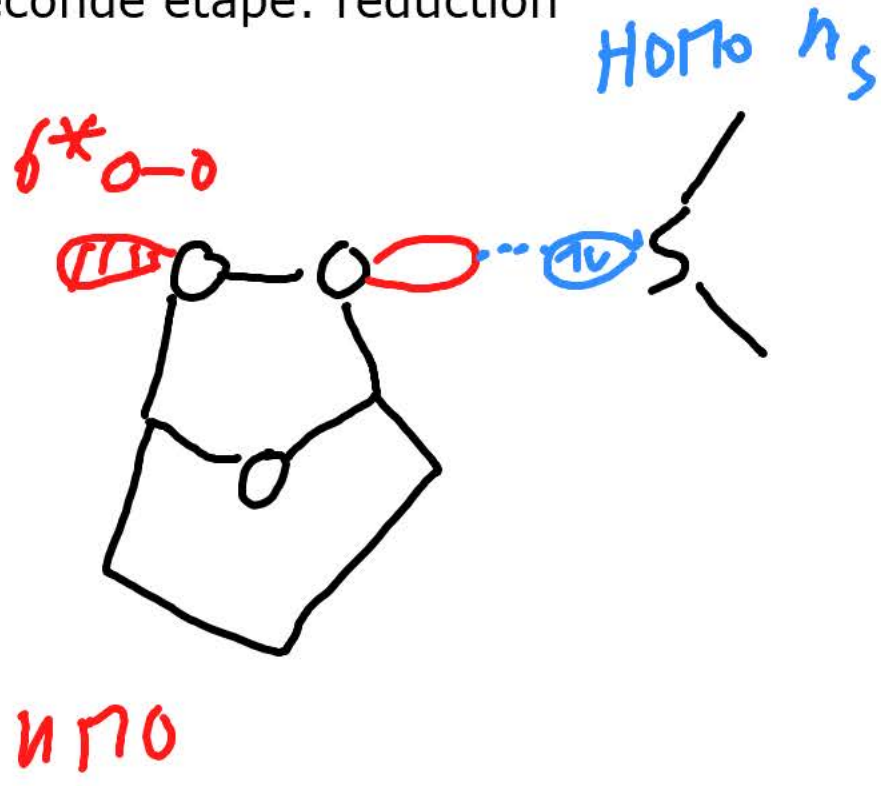
mécanisme

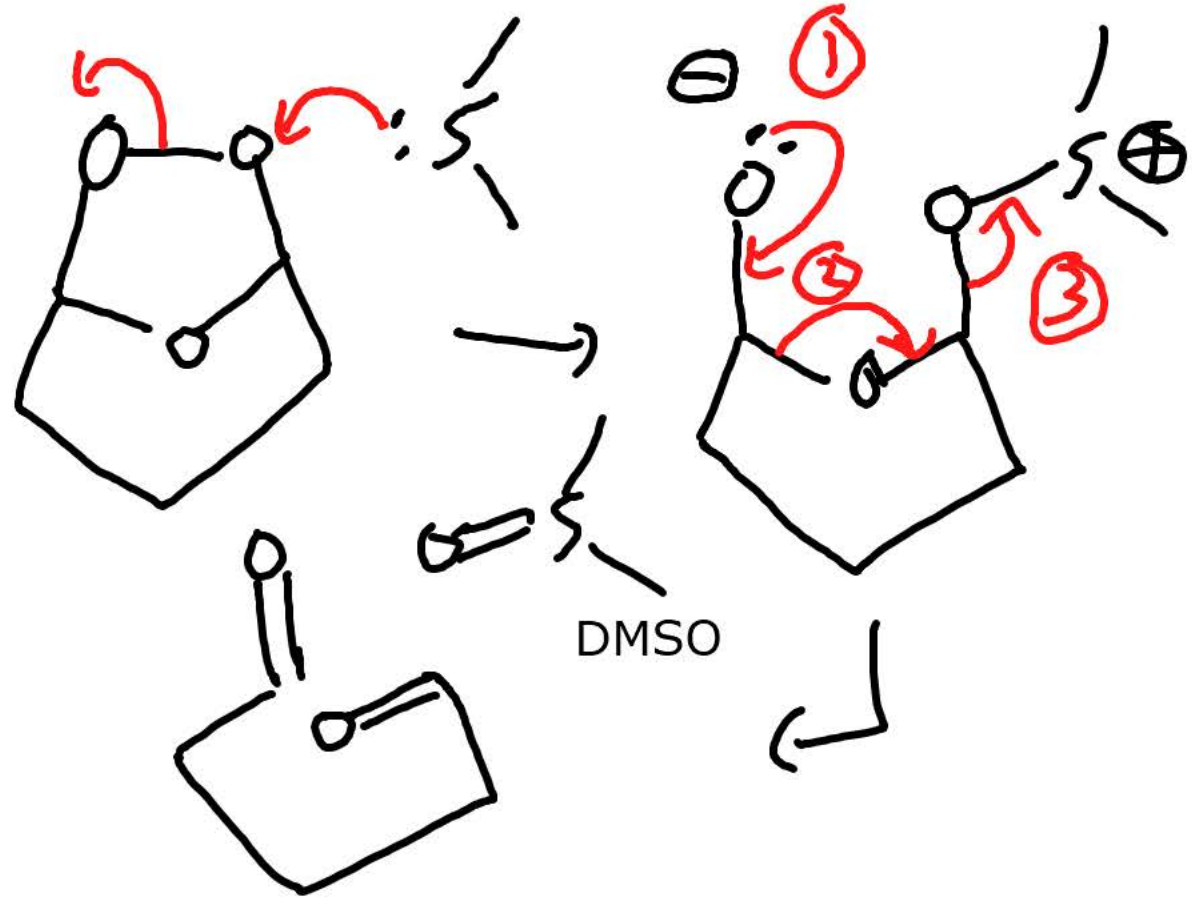


"cycloaddition" on forme 2 liaisons et un cycle en 1 étape

ozonide primaire:instable
2 liaisons O-O!

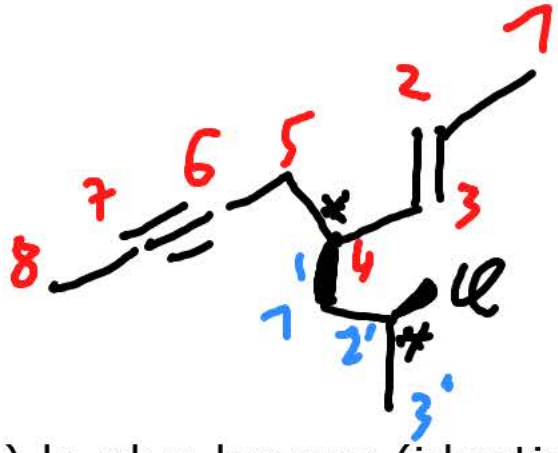
seconde étape: réduction





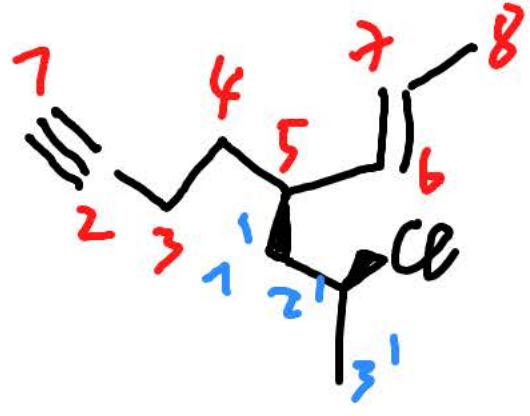
dicarbonyl,
produit final

nomenclature des alcynes



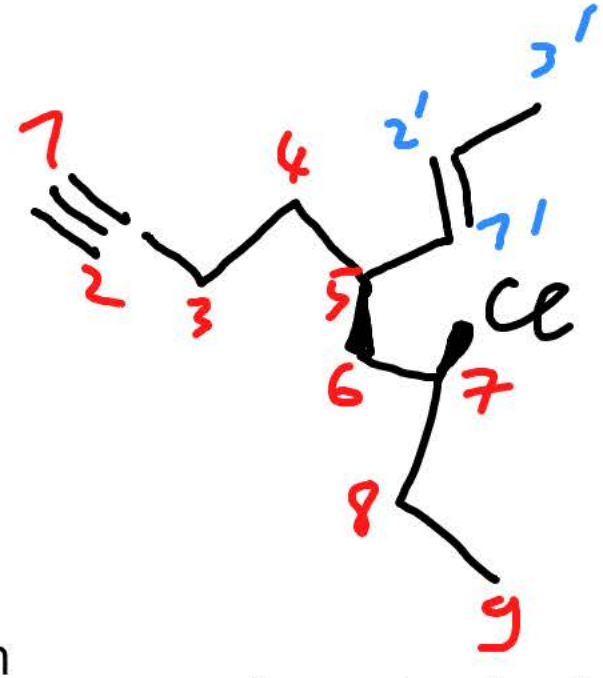
1) la plus longue (identique)
2) le plus d'insaturation
3) le chiffre le plus bas pour alcènes

(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

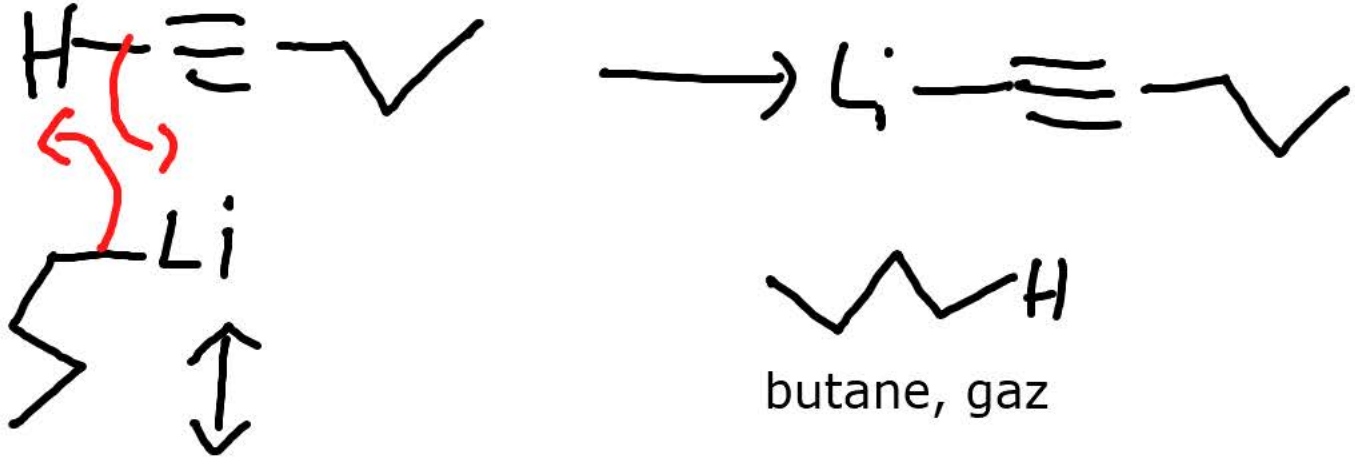


chaine la plus longue!

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

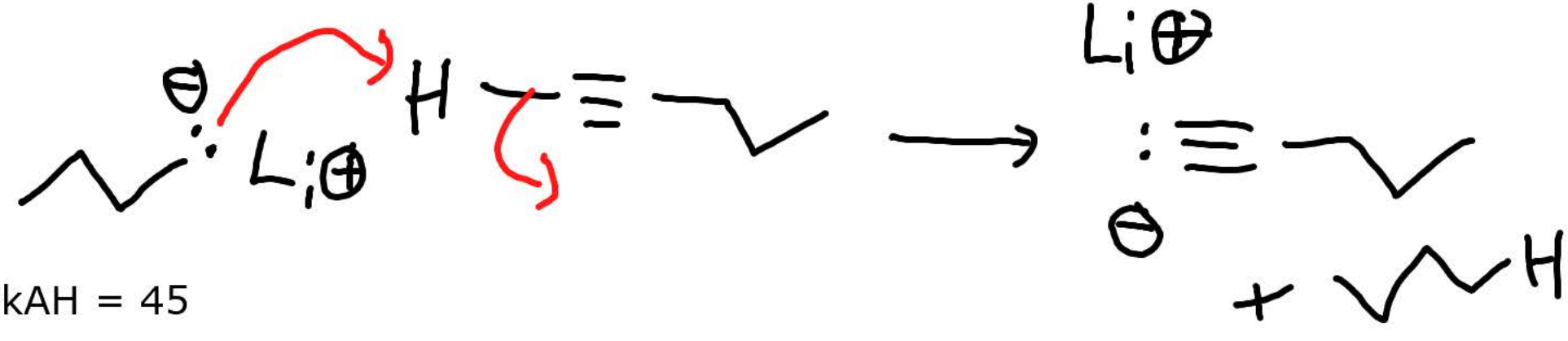
déprotonation et réaction des alcynes

PkA = 25



butane, gaz

forme ionique plus importante dans le cas des alcynes

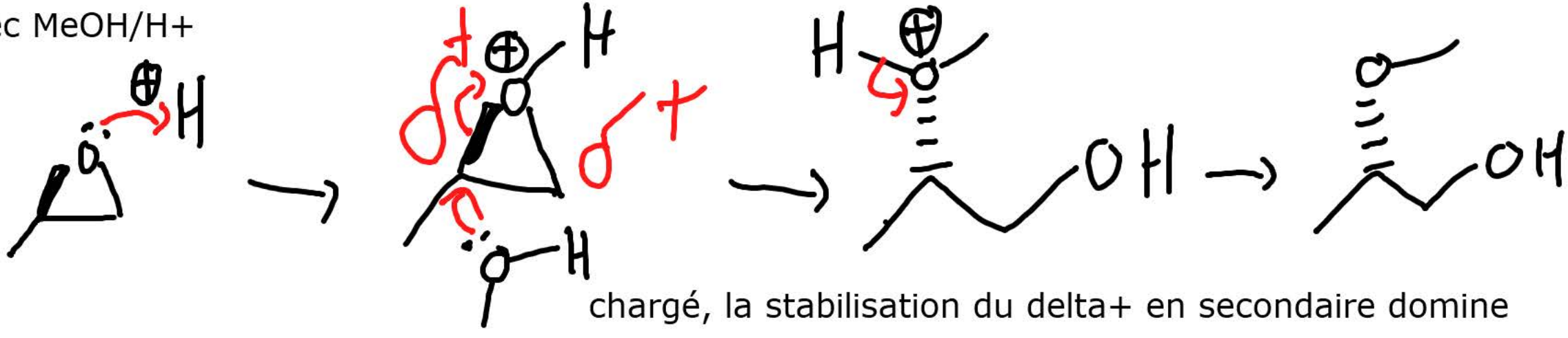


BuLi, PkAH = 45

réaction avec l'époxide

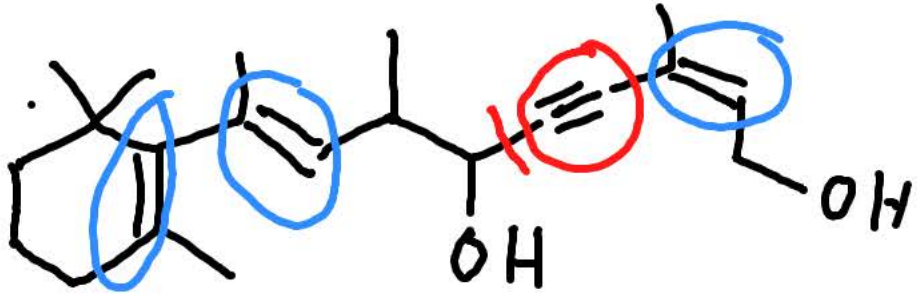
neutre: la stérique domine

avec MeOH/H+



chargé, la stabilisation du delta+ en secondaire domine

Hydrogénation de Lindlar: Hofman-LaRoche (Bale)

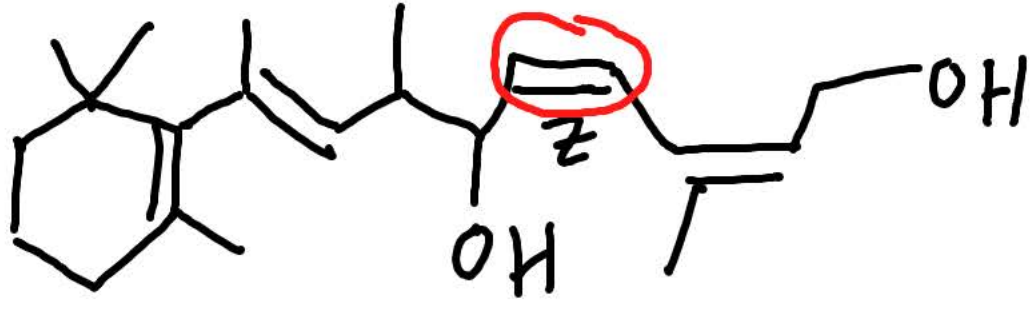


H_2

Pd/C/PbSO4/quinoline

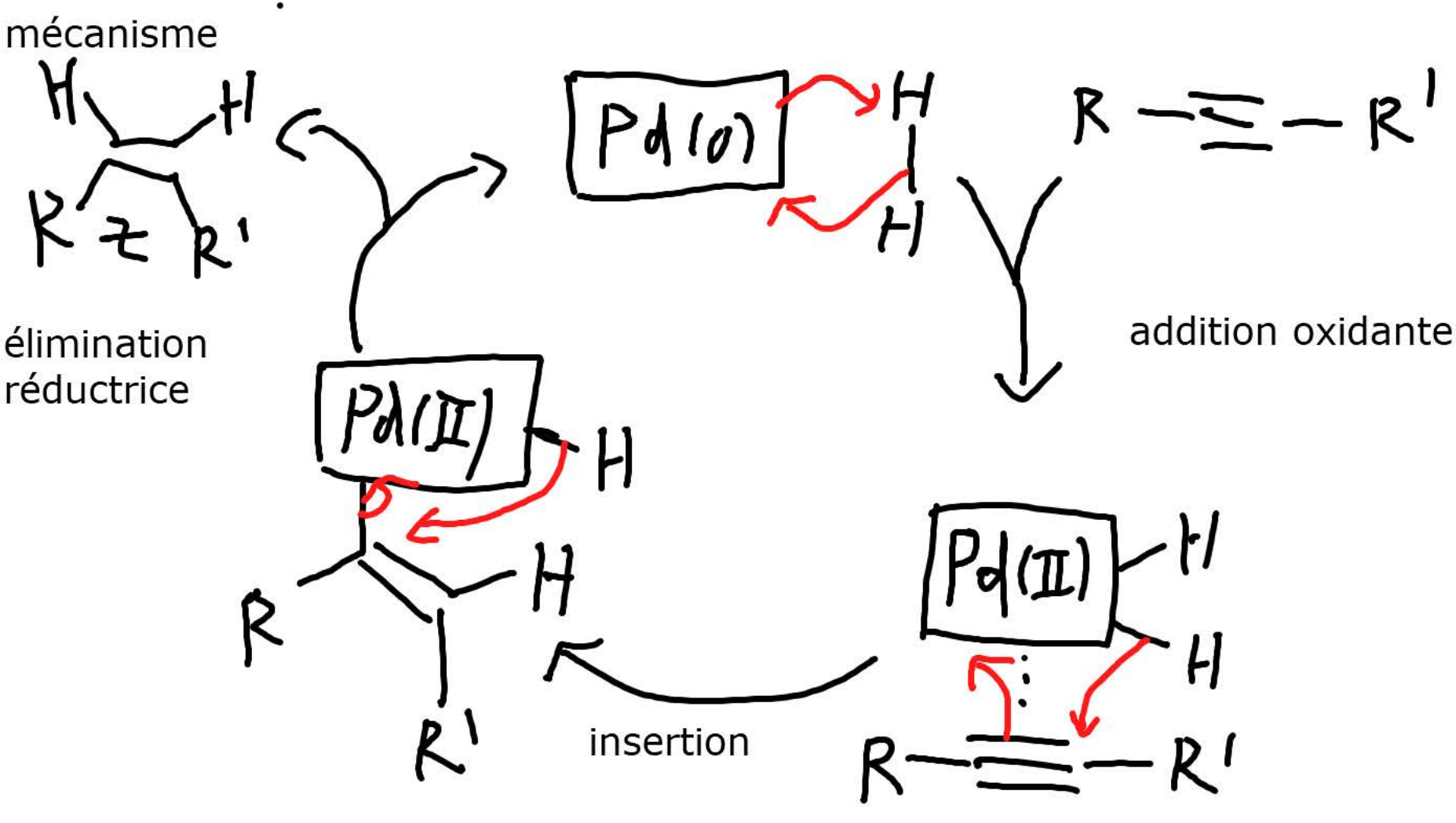
quinoline

se lie sur la surface du Pd et diminue la réactivité

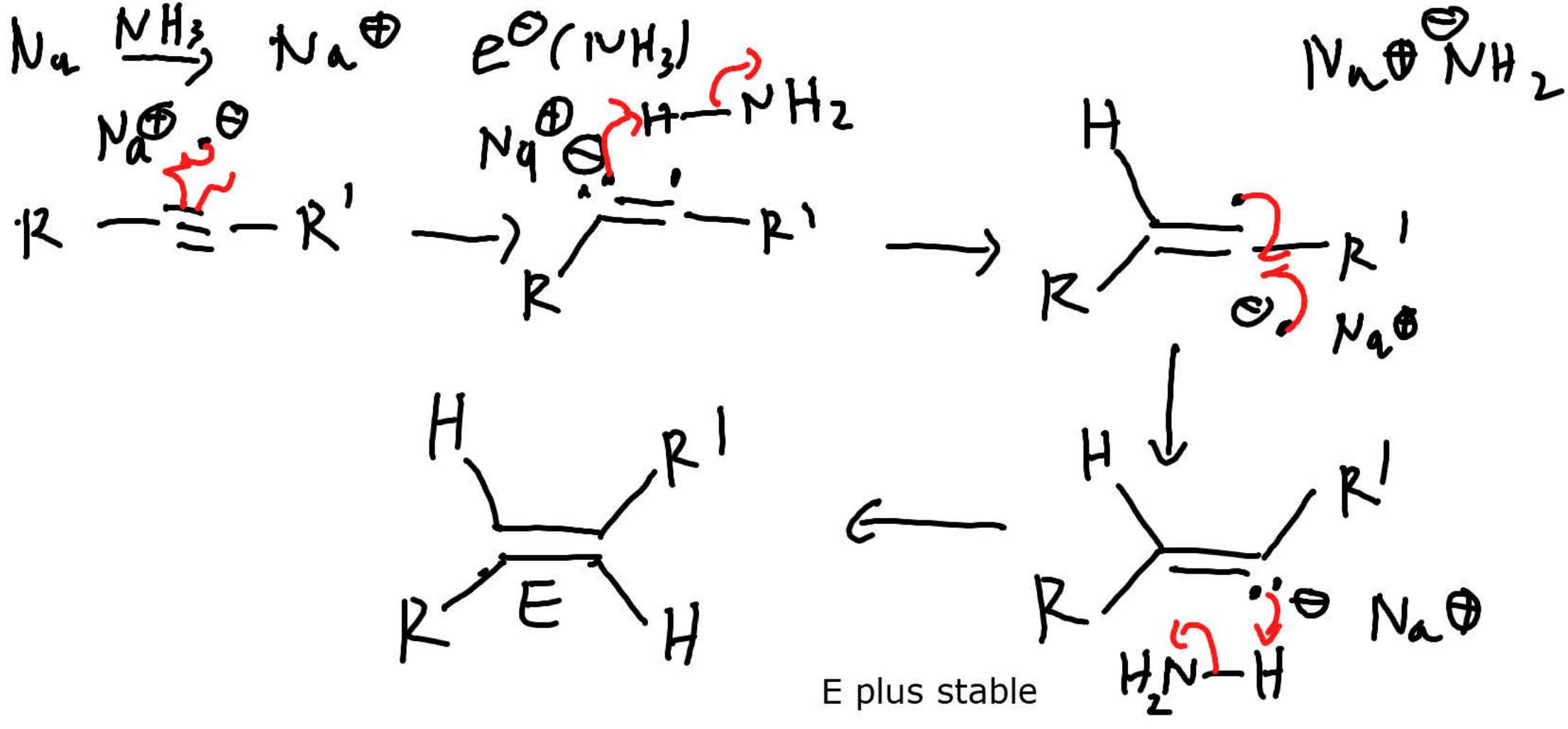


rétinol/vitamine A

mécanisme

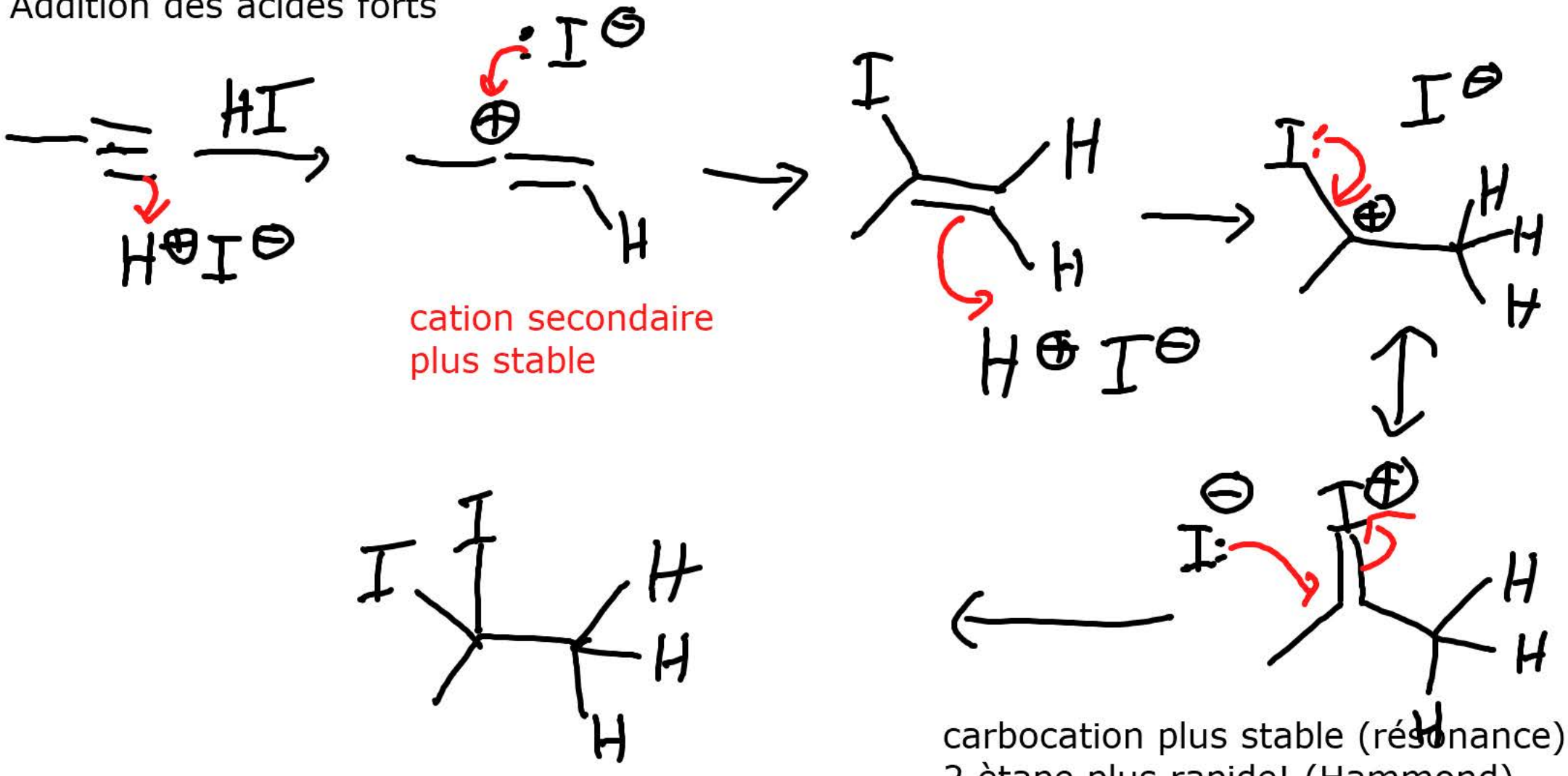

Pd(0)
addition oxidante
Pd(II)
élimination
réductrice
insertion
Pd(II)

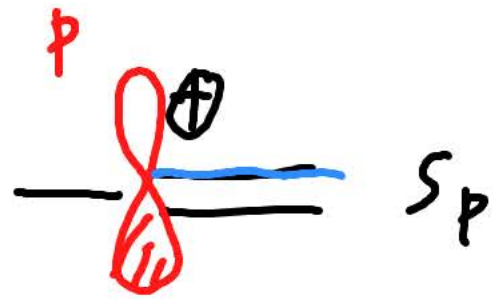
Na/NH3 (Birch)



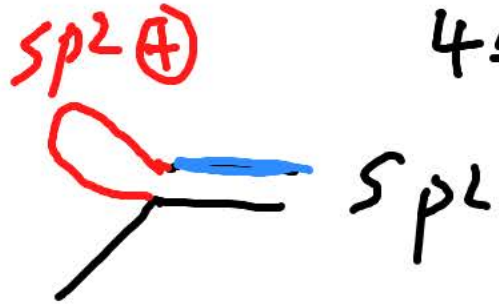
E plus stable

Addition des acides forts

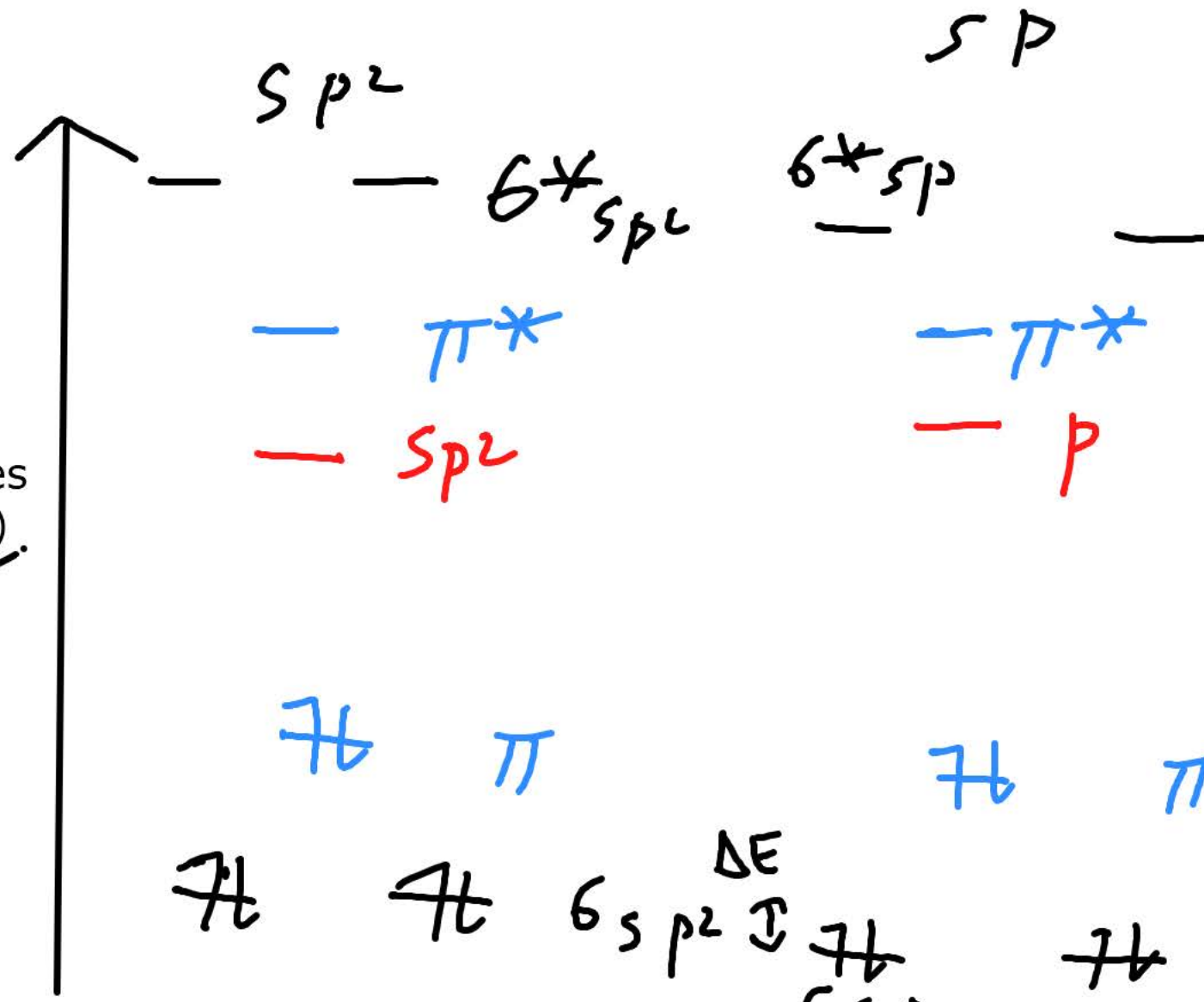




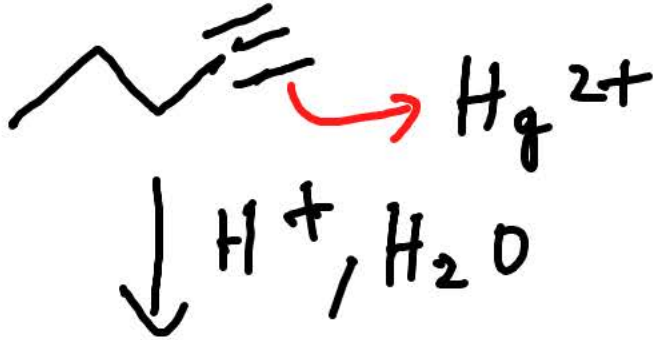
sp est plus stable (stabilisation des électrons dans liaisons sigma-sp!)

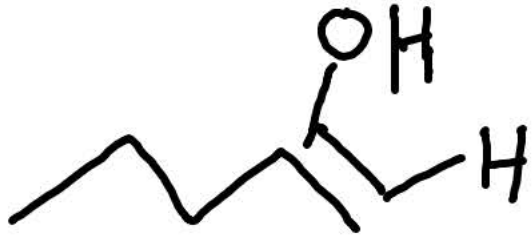


4ΔE

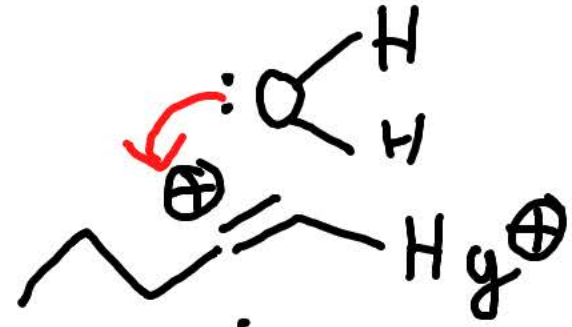


Hydration des alcynes

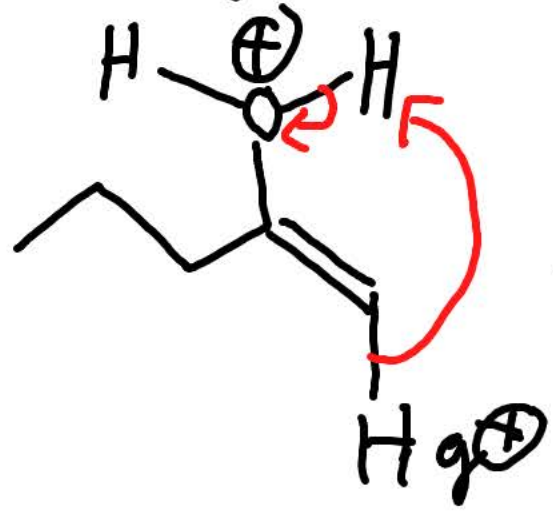


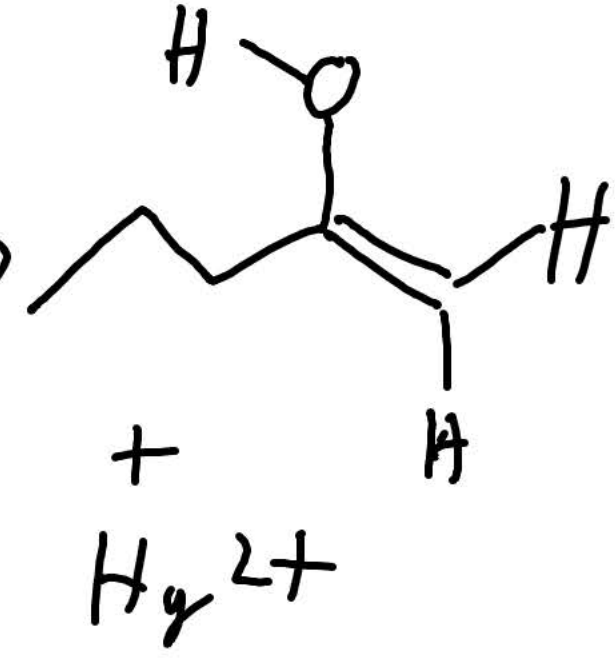


réaction très lente,
protonation de l'alcyne lente
Hg2+ réagit très vite

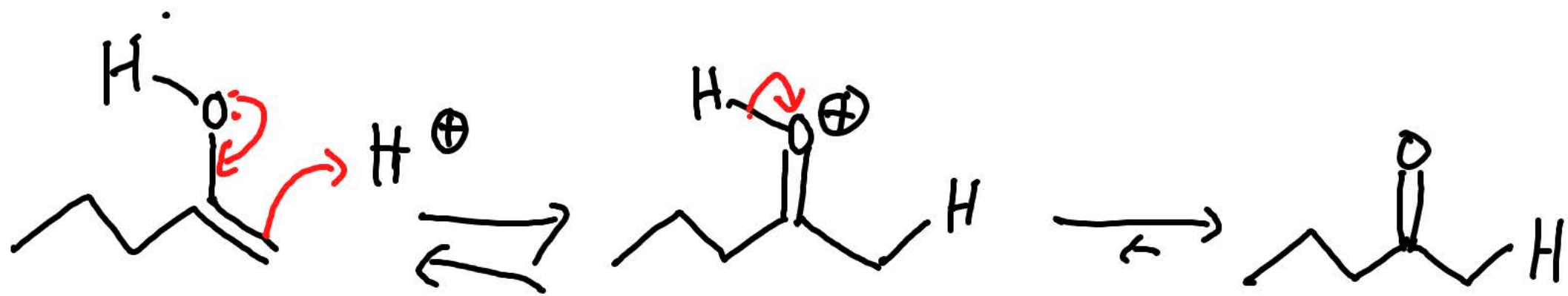


secondaire, plus stable
réaction rapide





catalytique en Hg2+

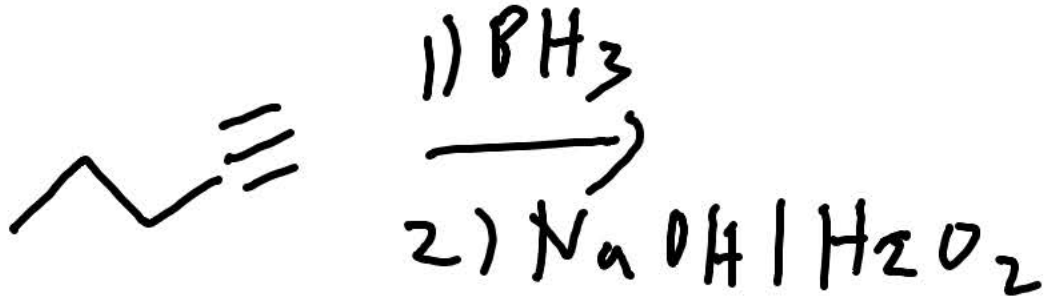


enol

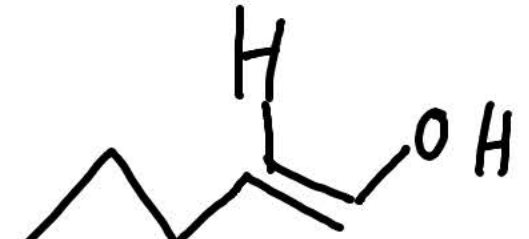
très rapide

procédé de tautomérisation

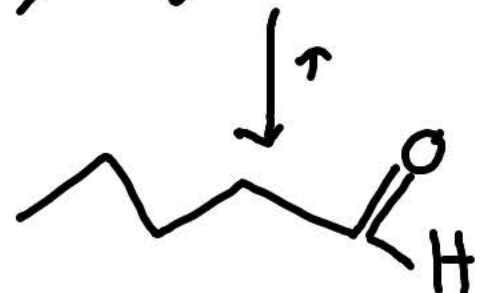
cétone
plus stable
double liaison C=O plus stable que C=C



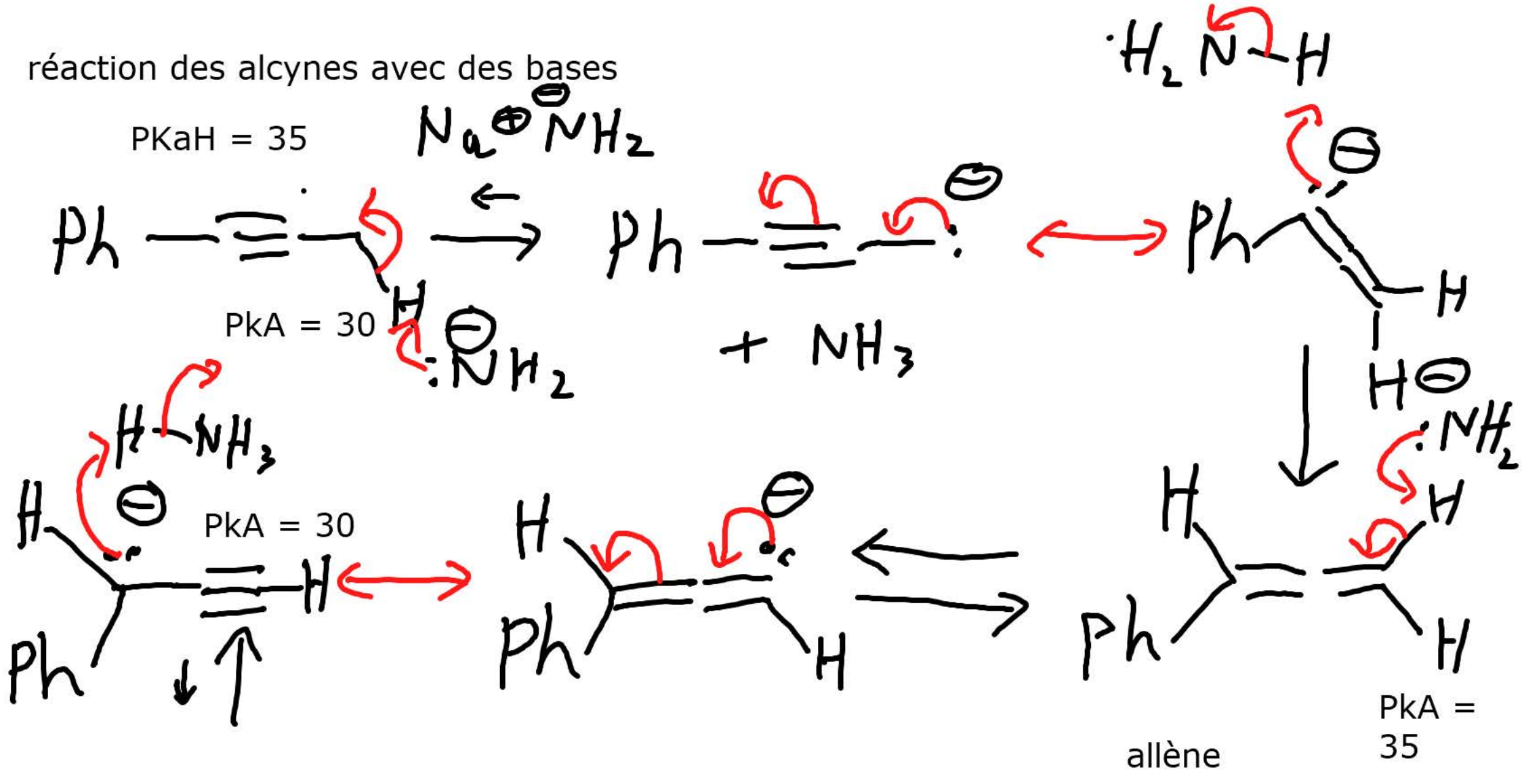
aldéhyde

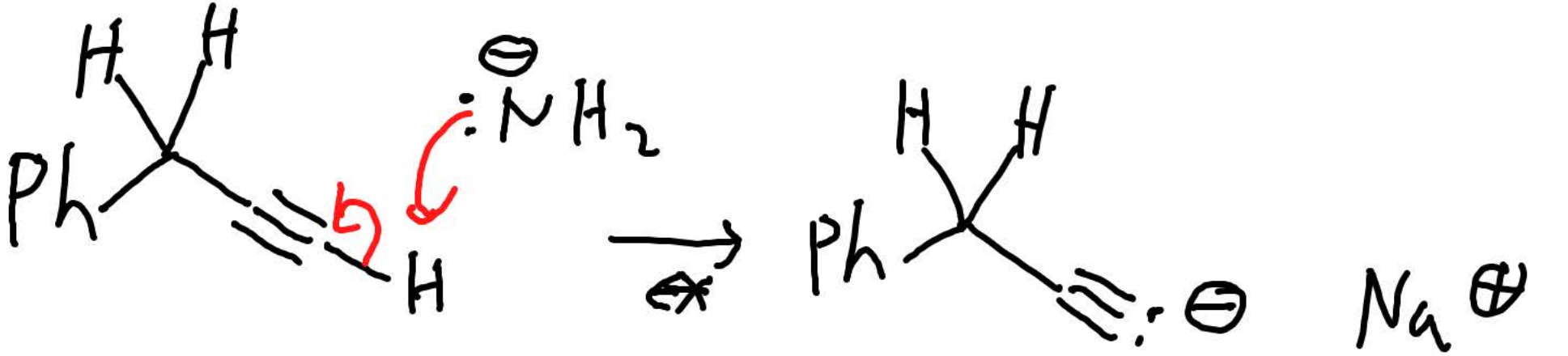


énol



réaction des alcynes avec des bases

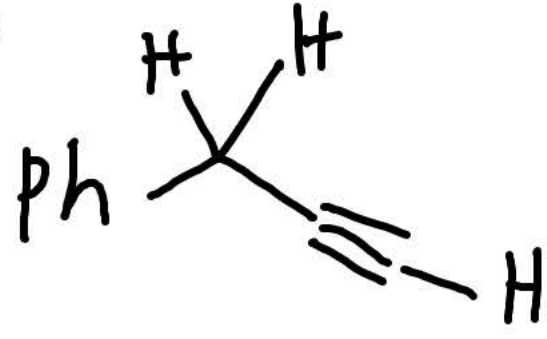




charge sur carbone sp, très stabilisée: PkaH = 25

work-up
HCl, H2O

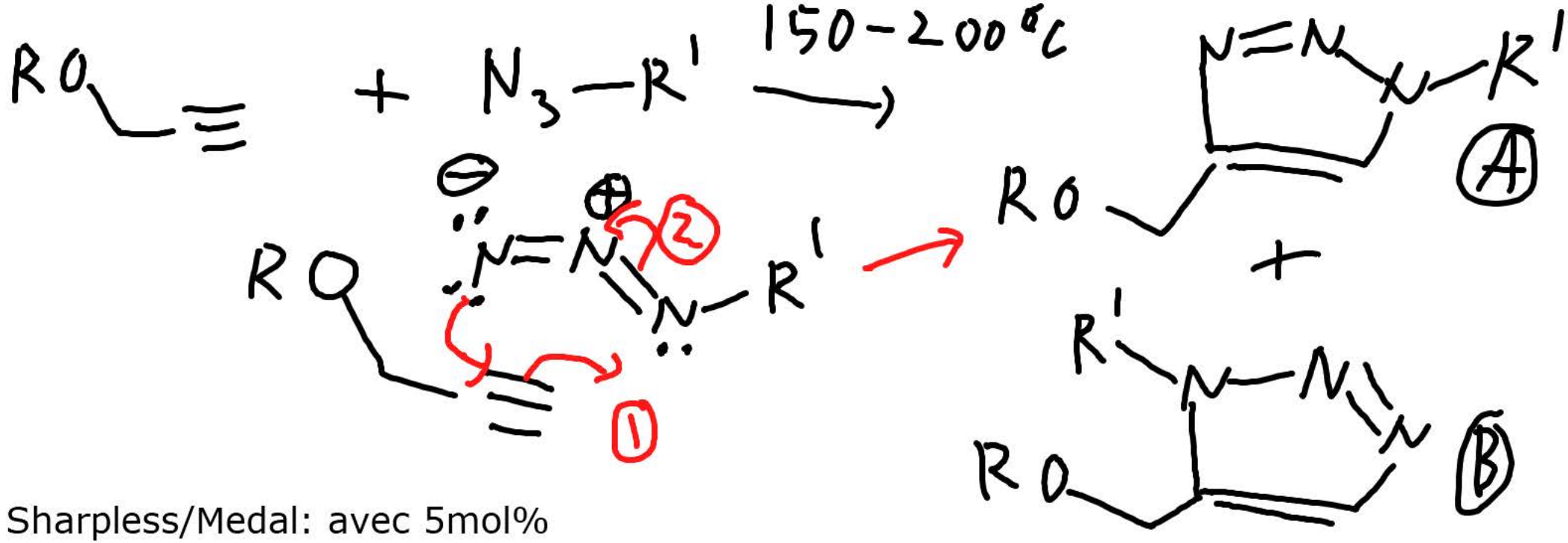
produit obtenu avec base forte
PkAH > 30



base plus faible <30
on stope à l'allène

Cycloaddition avec les azotures: Sharpless, Medla, Bertozzi (prix Nobel)

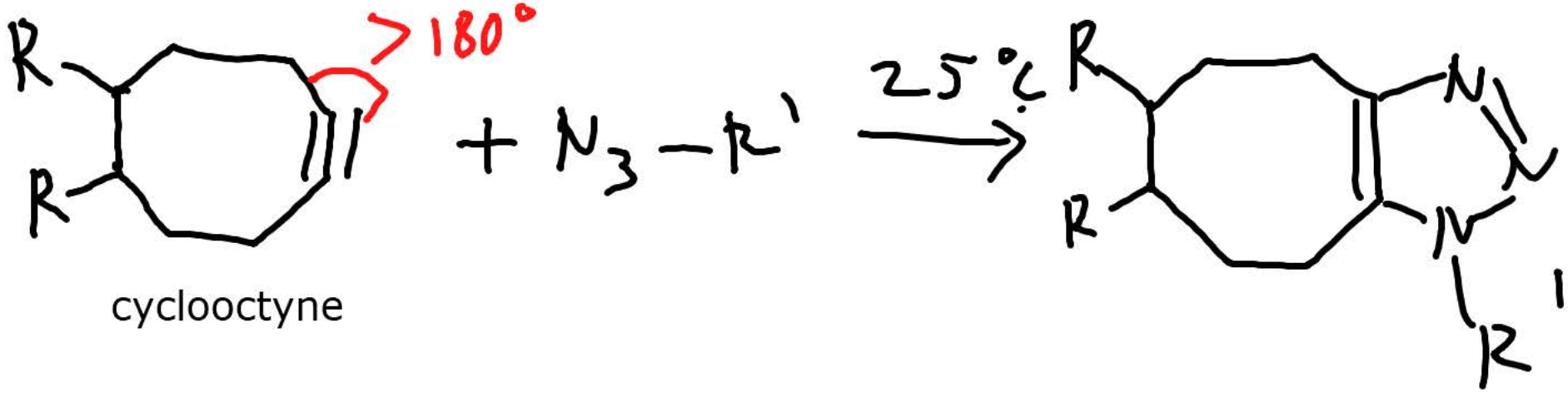
Huisgen



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

triazoles, très stables/aromatiques

Carolyn Bertozzi: réaction à 25 °C sans cuivre



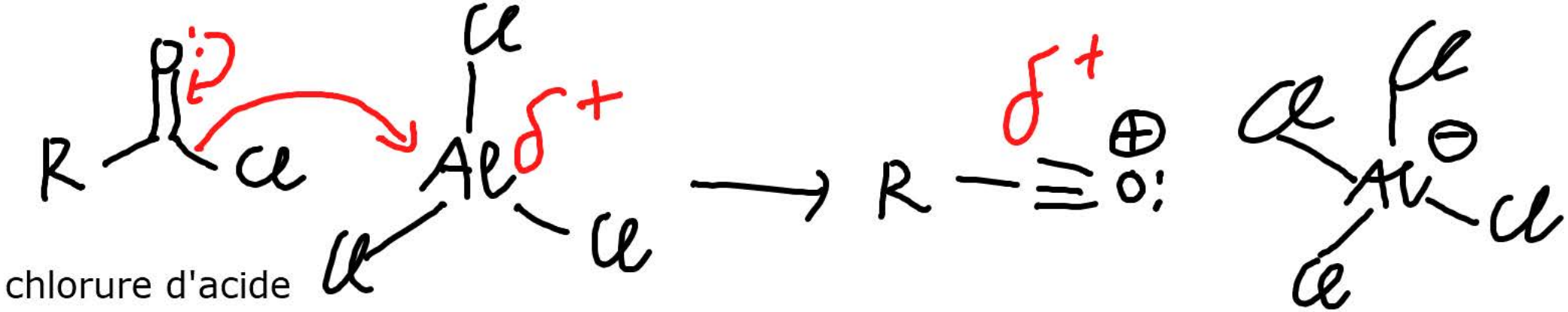
cyclooctyne

angle idéal de 180 ° n'est pas possible à cause du cycles: l'alcyne est beaucoup plus réactif
Cycle idéal: 8 atomes: 7 atomes la molécule est instable, et à 9 atomes la molécule n'est pas assez réactive

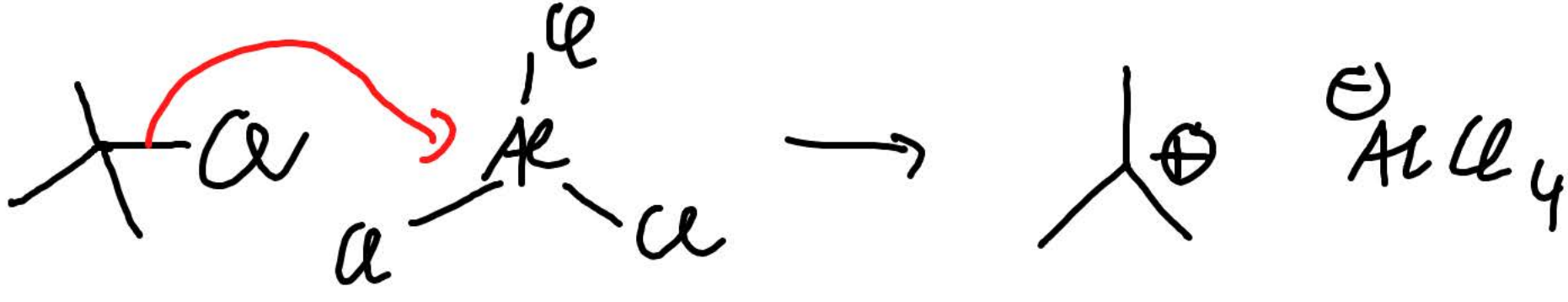
Réaction de Friedel-Craft

1) activation de l'électrophile

1.1): approche 1: chlorure d'acide avec AlCl3

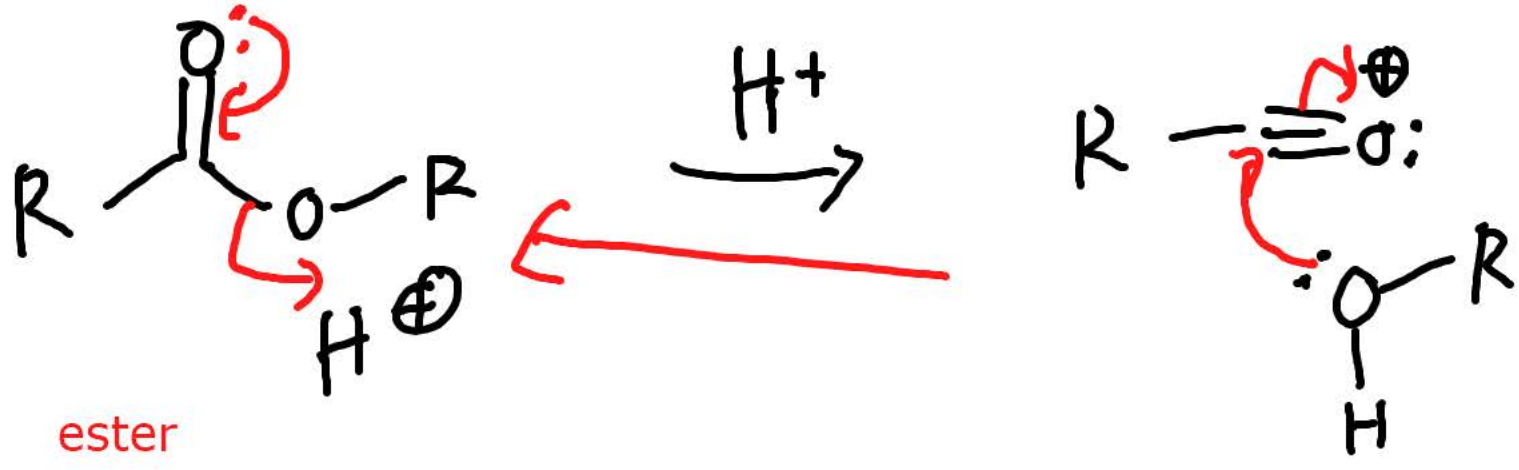


chlorure d'acide



.

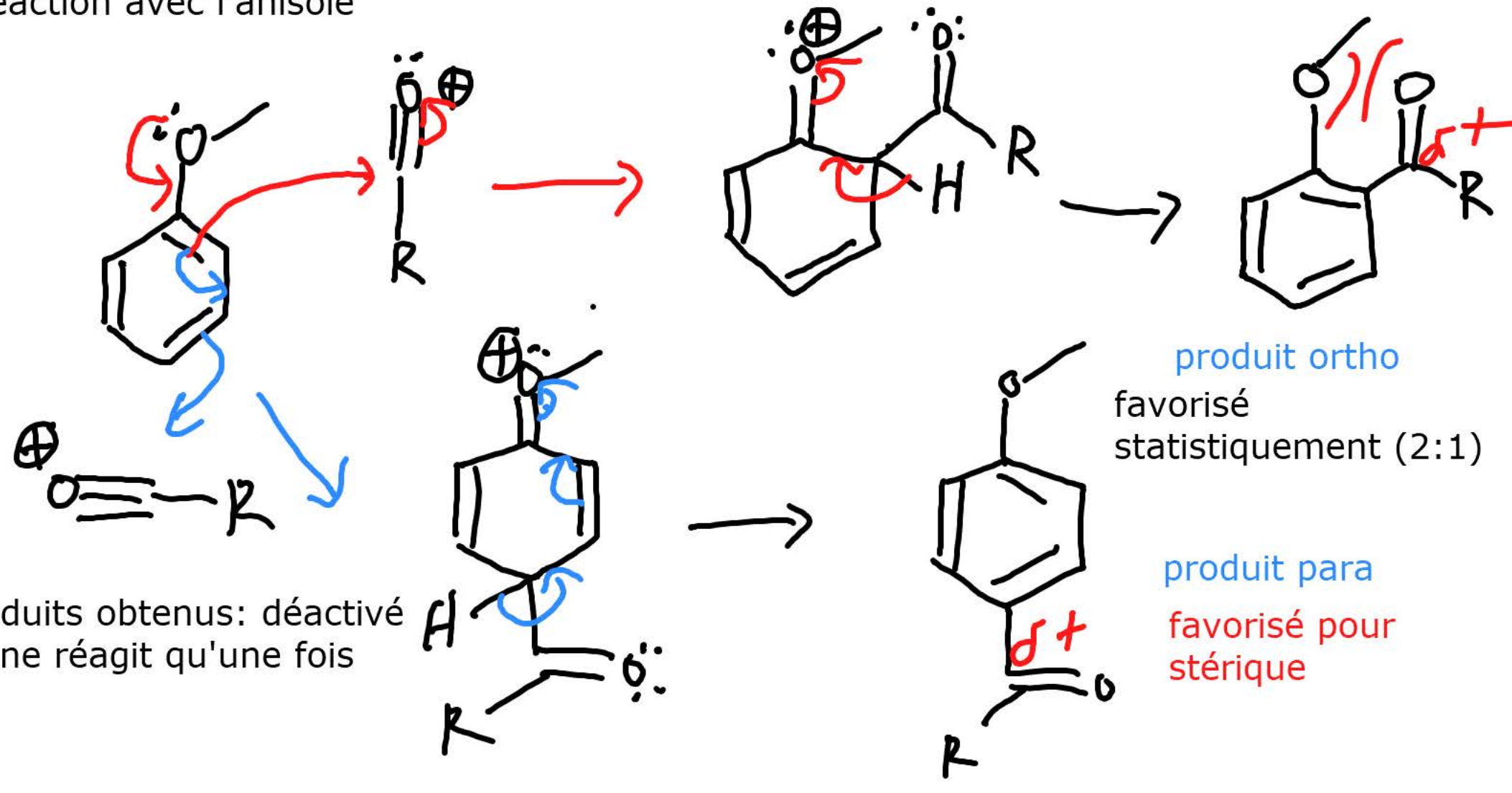
1.2 Approche 2: plus douce



ester

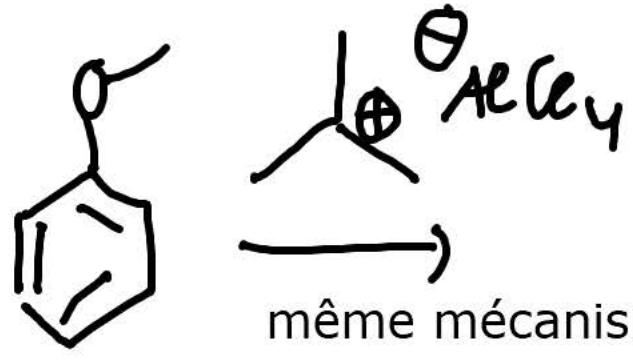
équilibre très défavorisé, mais suffisant pour avoir "un peu" d'intermédiaire réactif

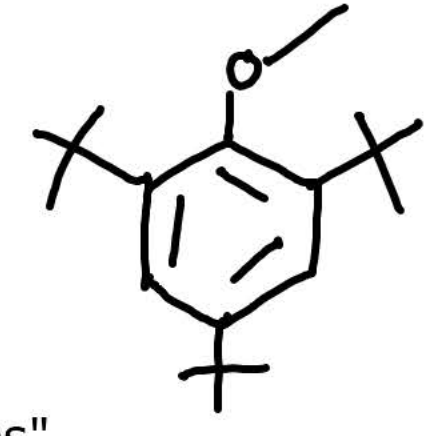
réaction avec l'anisole



produits obtenus: déactivé
on ne réagit qu'une fois

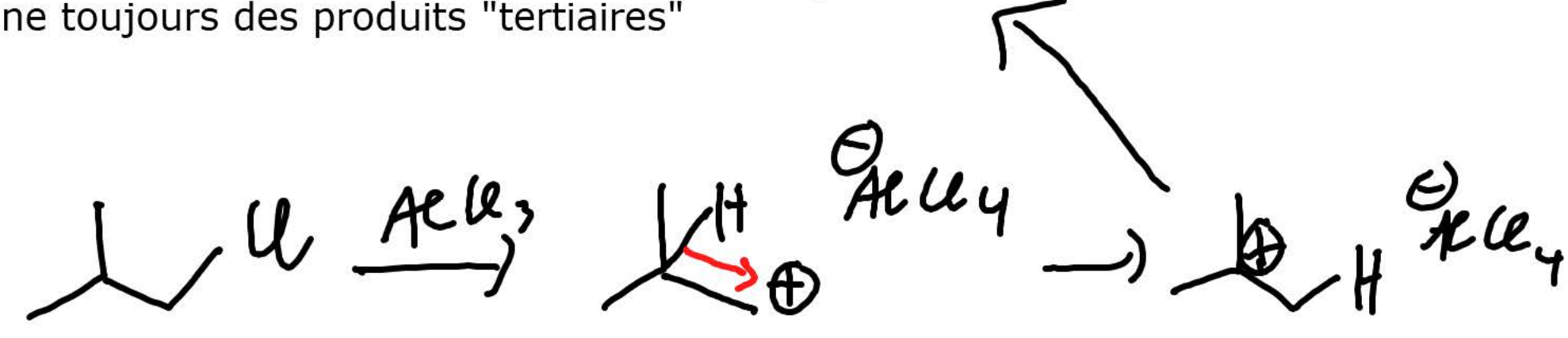
alkylation de Friedel-Craft



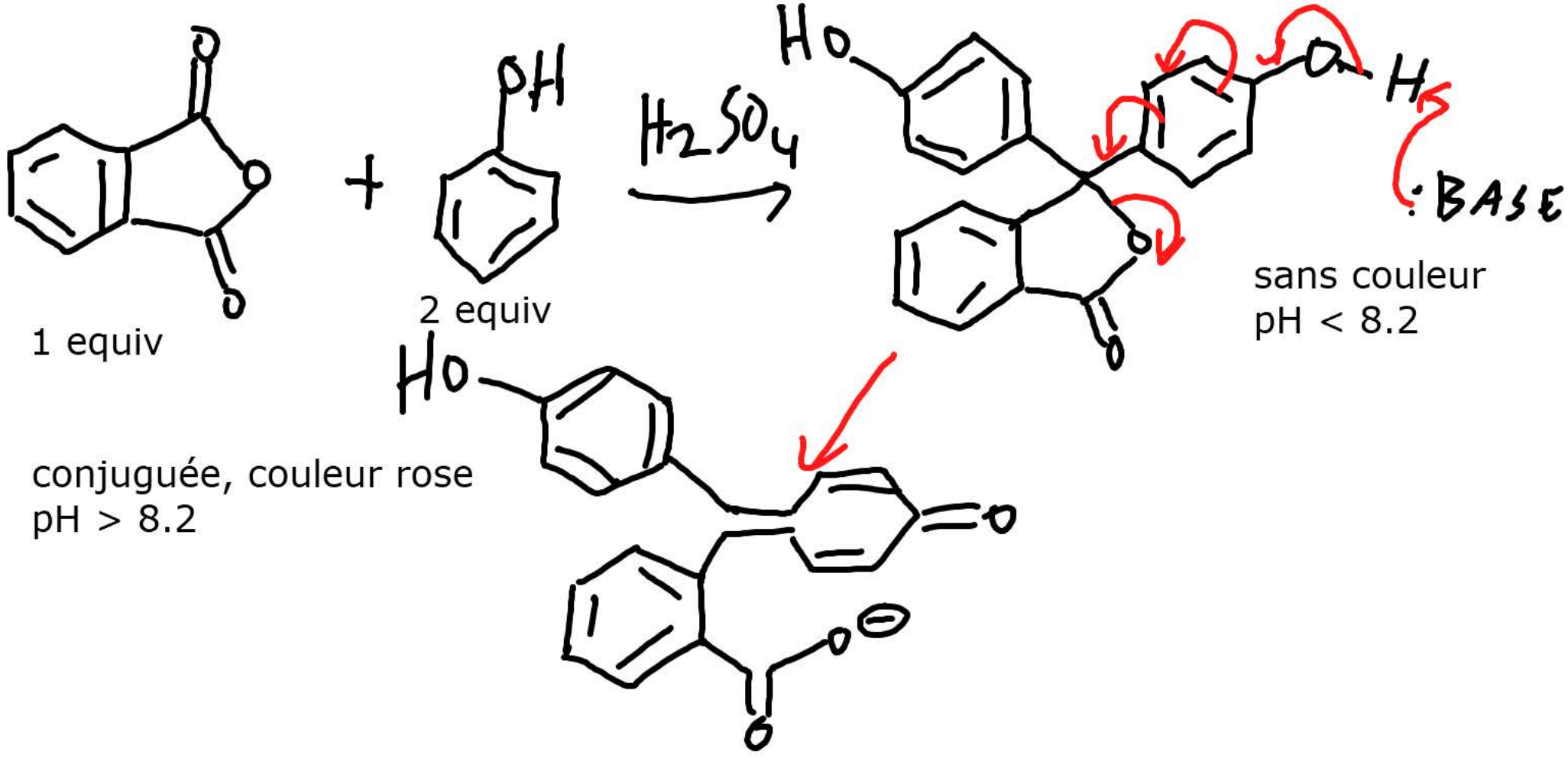


groupe tBu riche en électrons
Le cycle est activé et réagit 3 fois, puis stoppe pour des raisons stériques

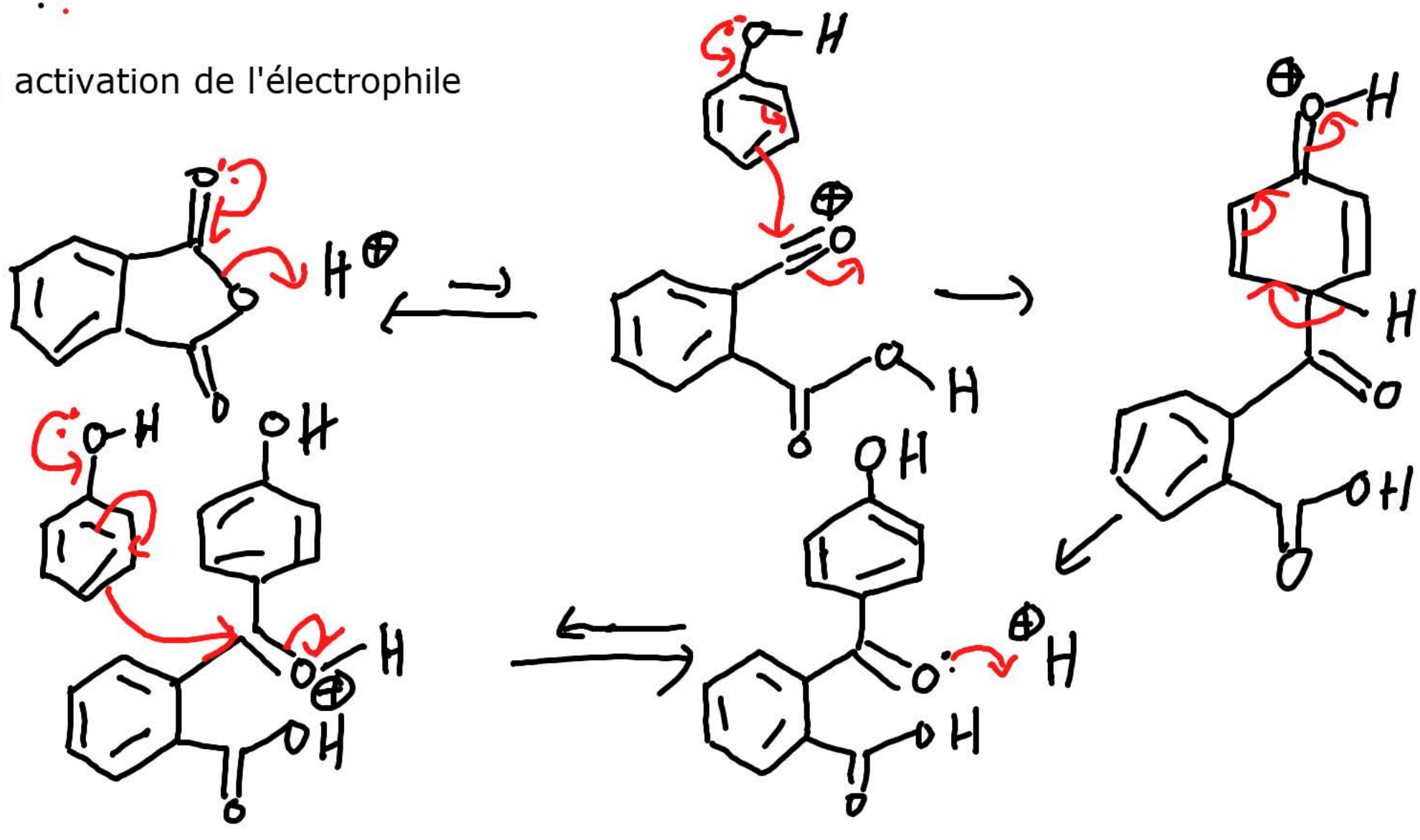
donne toujours des produits "tertiaires"

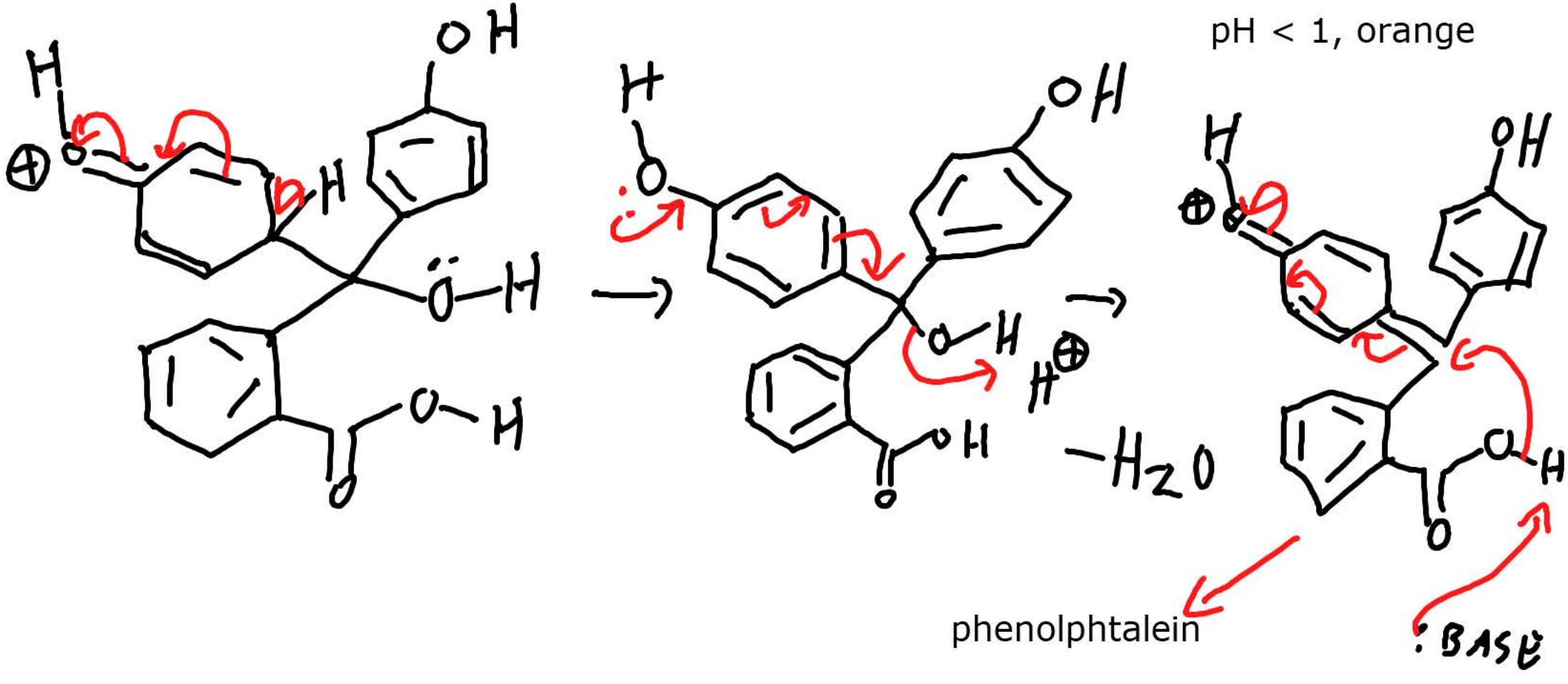


synthèse de la phénolphtalein

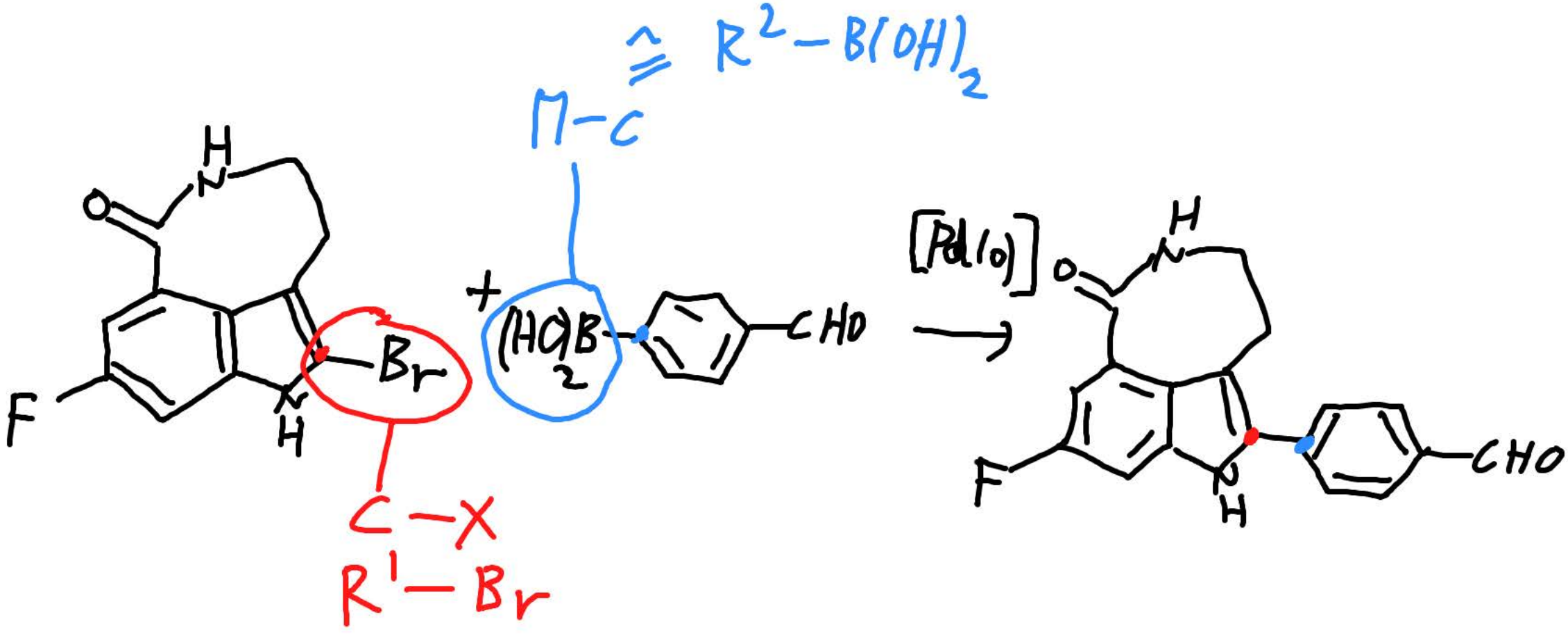


1) activation de l'électrophile

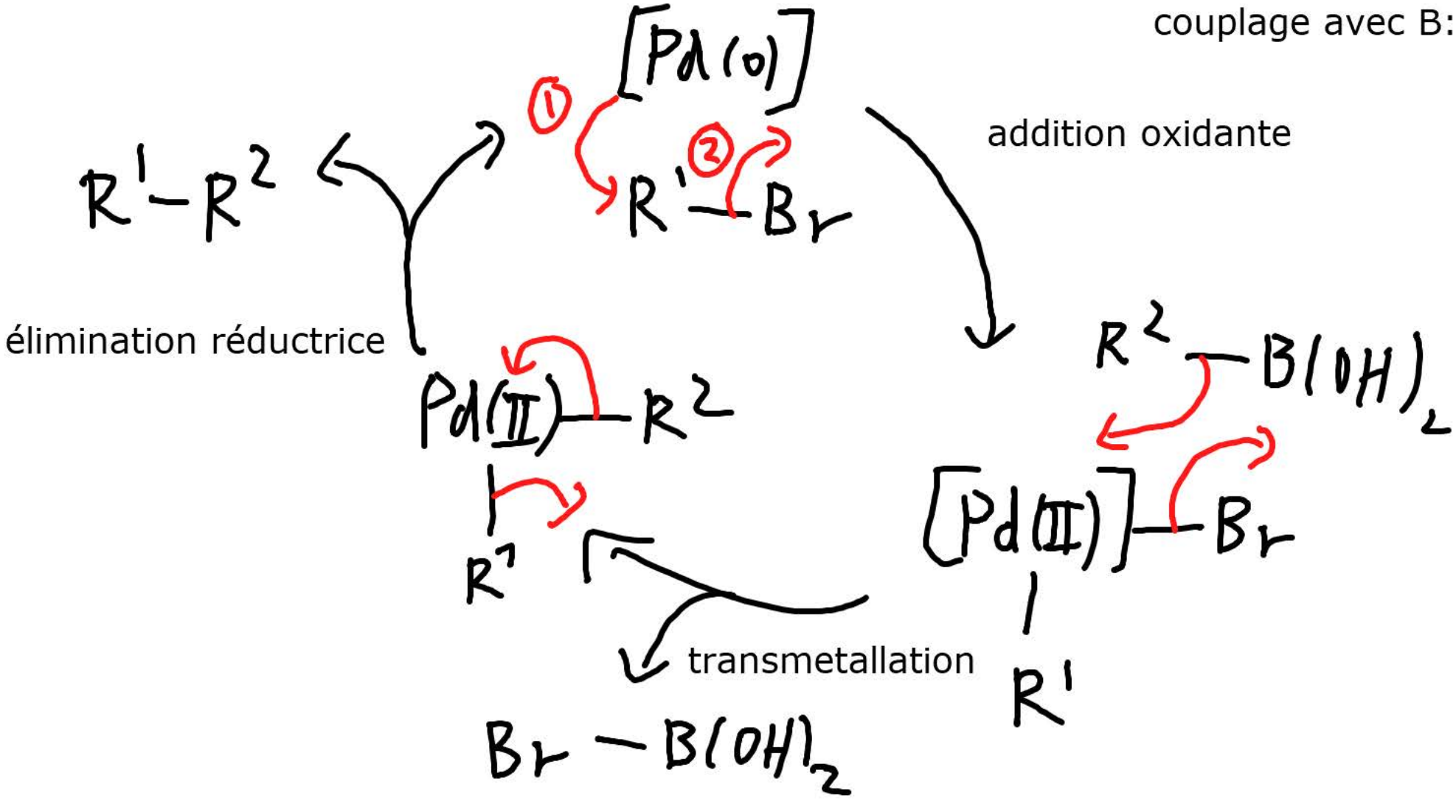



pH < 1, orange
phenolphtalein
BASE

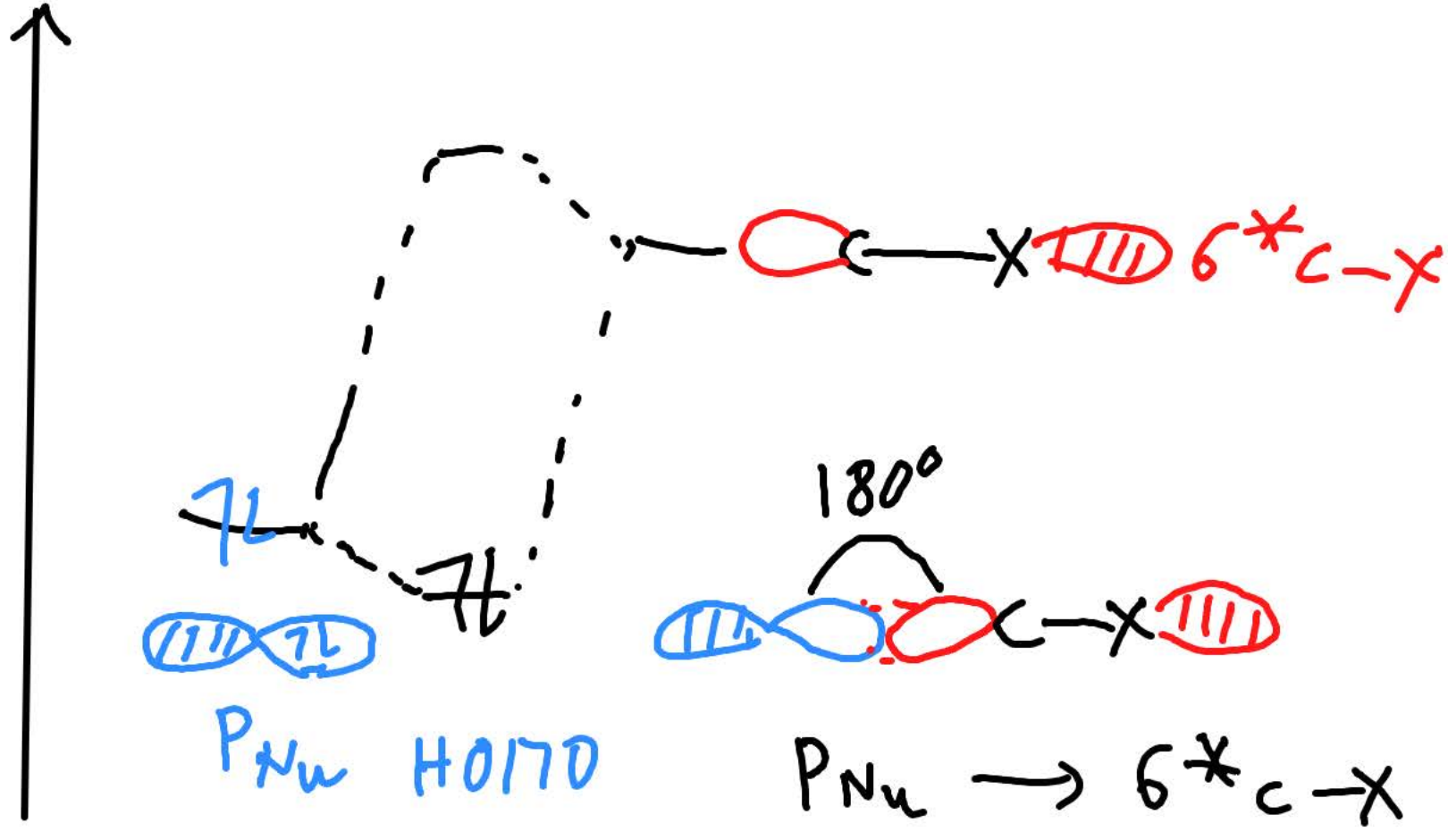
Couplage croisé au Pd: synthèse de Rucaparib/Pfizer, traitement du cancer des ovaires



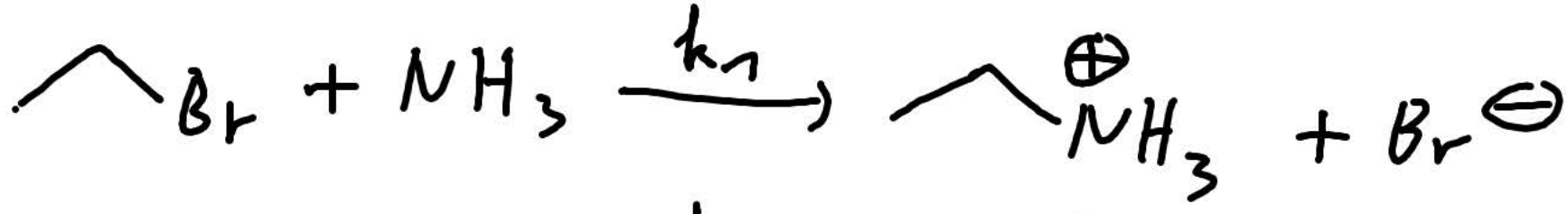
couplage avec B: Suzuki



mécanisme SN2 avec orbitales moléculaires

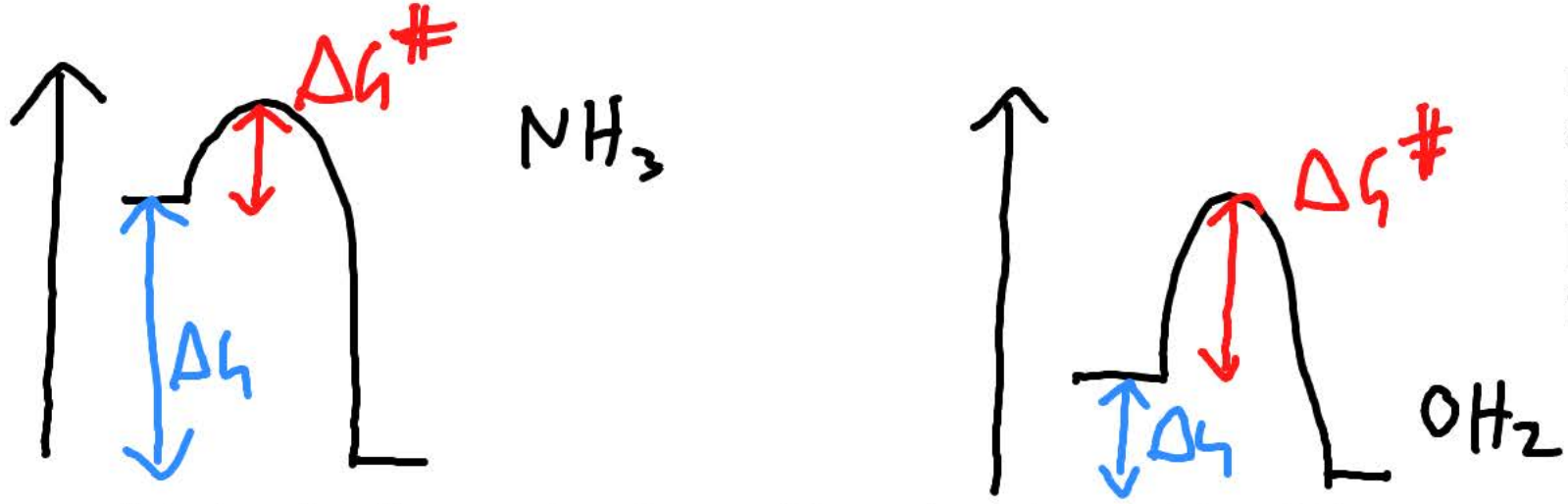


basicité vs nucléophilie



NH3:
PkAH = 9

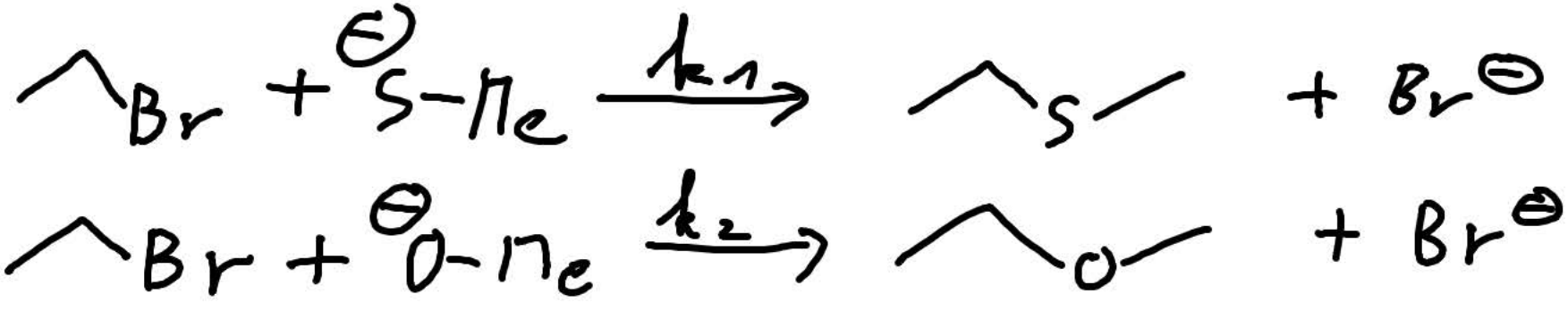
H2O:
PkAH = 0



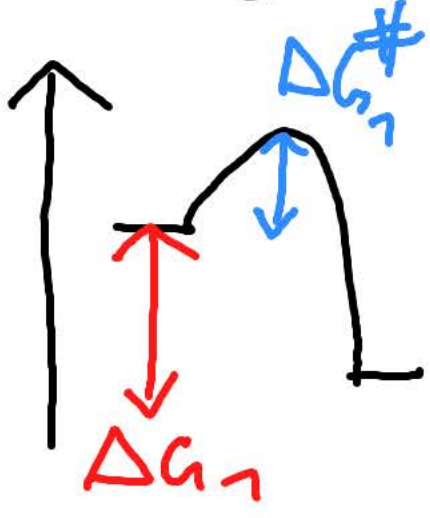
nucléophilie corrèle avec l'énergie d'activation
la basicité avec la thermodynamique

ici: la réaction moins favorable est moin rapide: OK

basicité vs nucléophilie

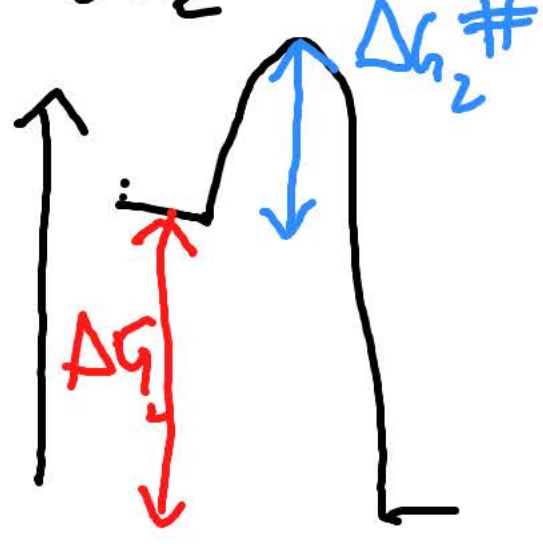


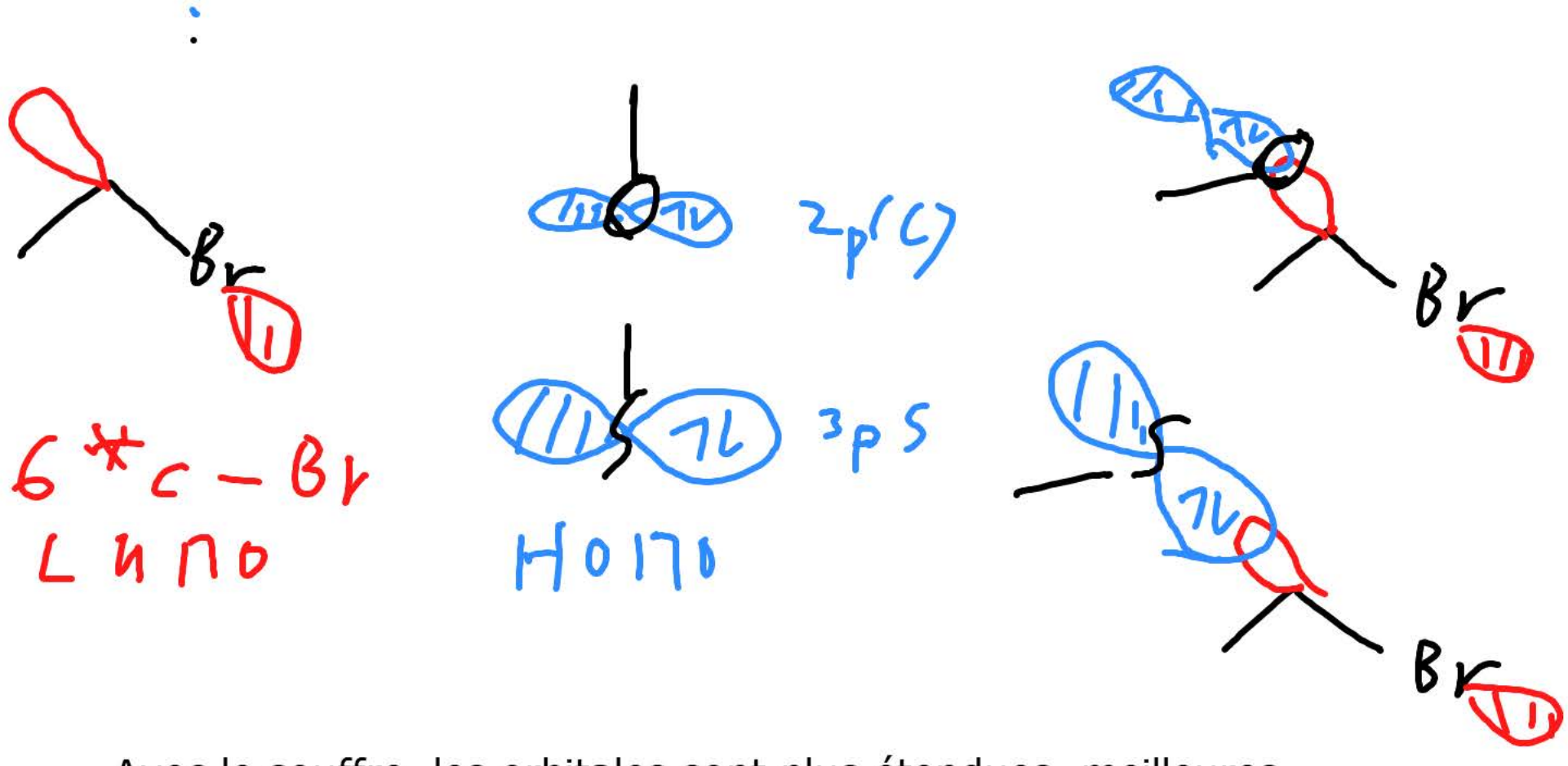
PkAH = 8



PkAH = 16, on s'attend: k2 > k1
mais on mesure le contraire! k1 > k2

la réaction moins favorable est plus rapide!

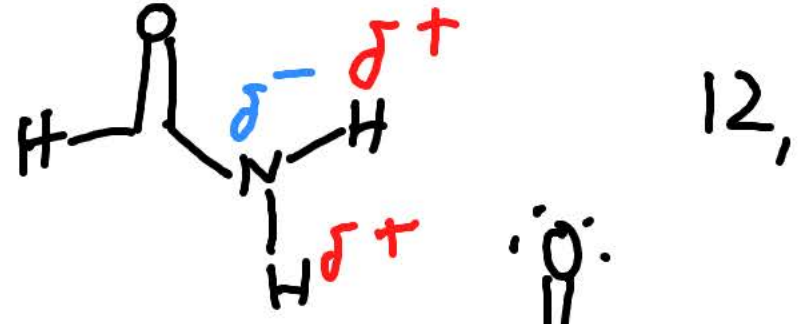


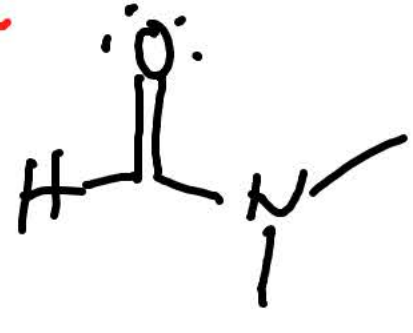


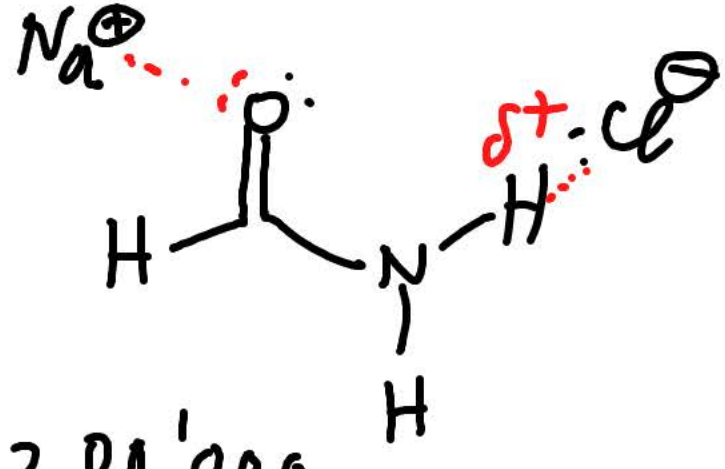
Avec le souffre, les orbitales sont plus étendues, meilleures superpositions, l'énergie de l'état de transition diminue et la réaction accélère

effets du solvant

Solvant	k
methanol	1
formamide	12,5
dimethylformamide (DMF)	1'200'000
acétone	1'500'000







synthèse des iodures

soluble

soluble

approche de Finkelstein

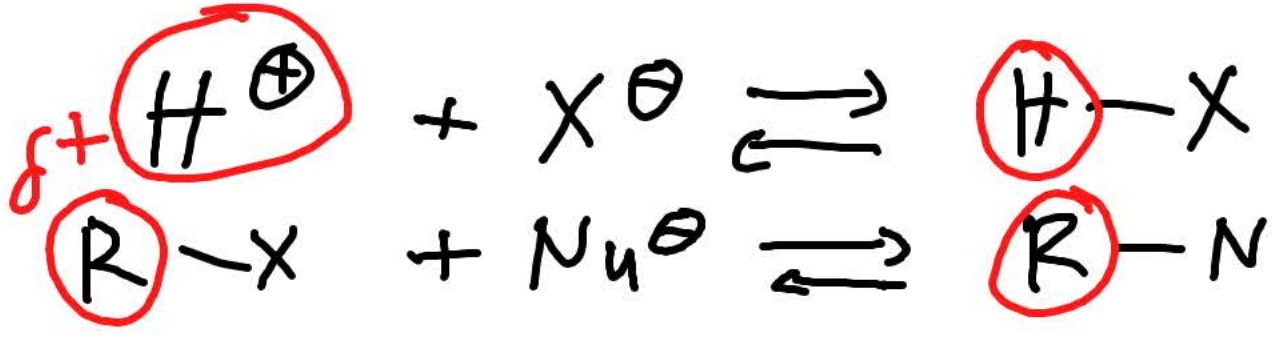
non soluble

soluble

principe de Le Chatelier "on pousse la réaction en enlevant un réactif"

comparaison base/nucléophilie vs base/groupe partant

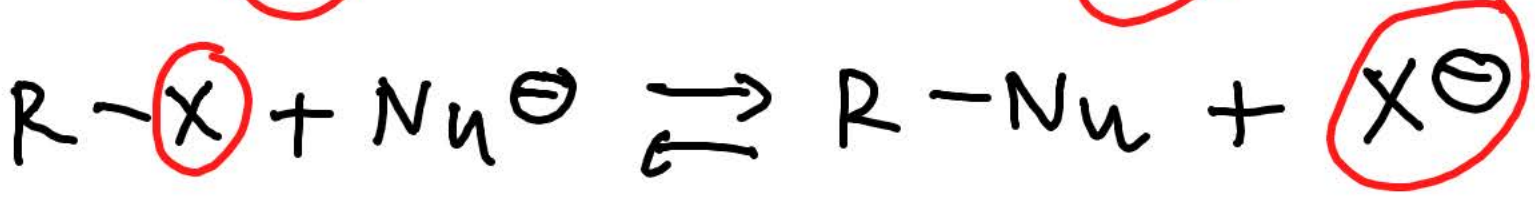
comparaison base/nucléophilie vs base/groupe partant



comparaison base/nucléophilie

comparaison pas idéal car R différent de H

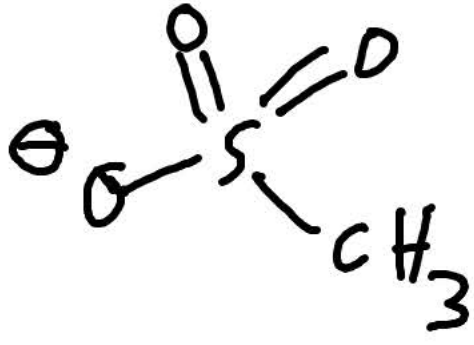
comparaison groupe partant/base



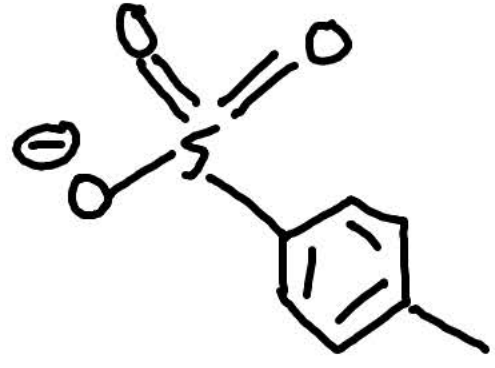
bonne comparaison: car la structure du groupe partant et identique à la structure de la base, excellent corélation

importants groupes partants dérivés de l'acide sulfurique

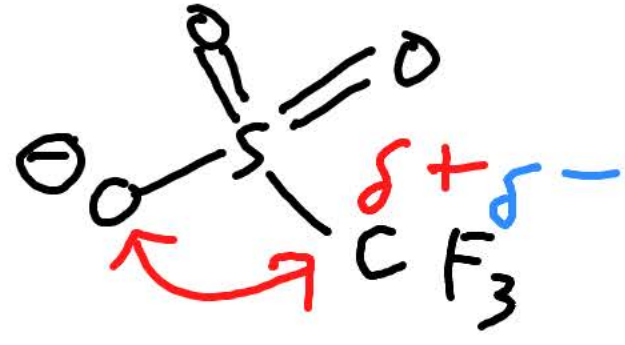
stabilisé par effet inductif
base est plus stable
le groupe partant est meilleur



mésylate, OMs



tosylate, OTs



triflate, OTf

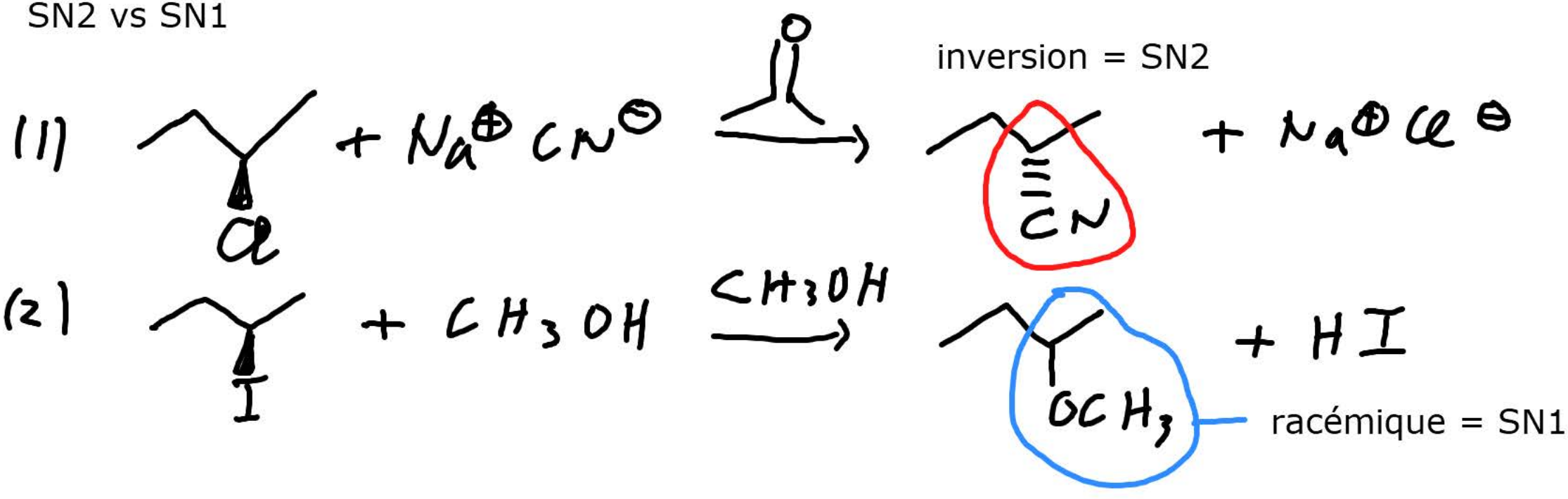
même réactivité

plus économique
en atome

plus crystallin
(plus facile à purifier)

plus réactif

SN2 vs SN1



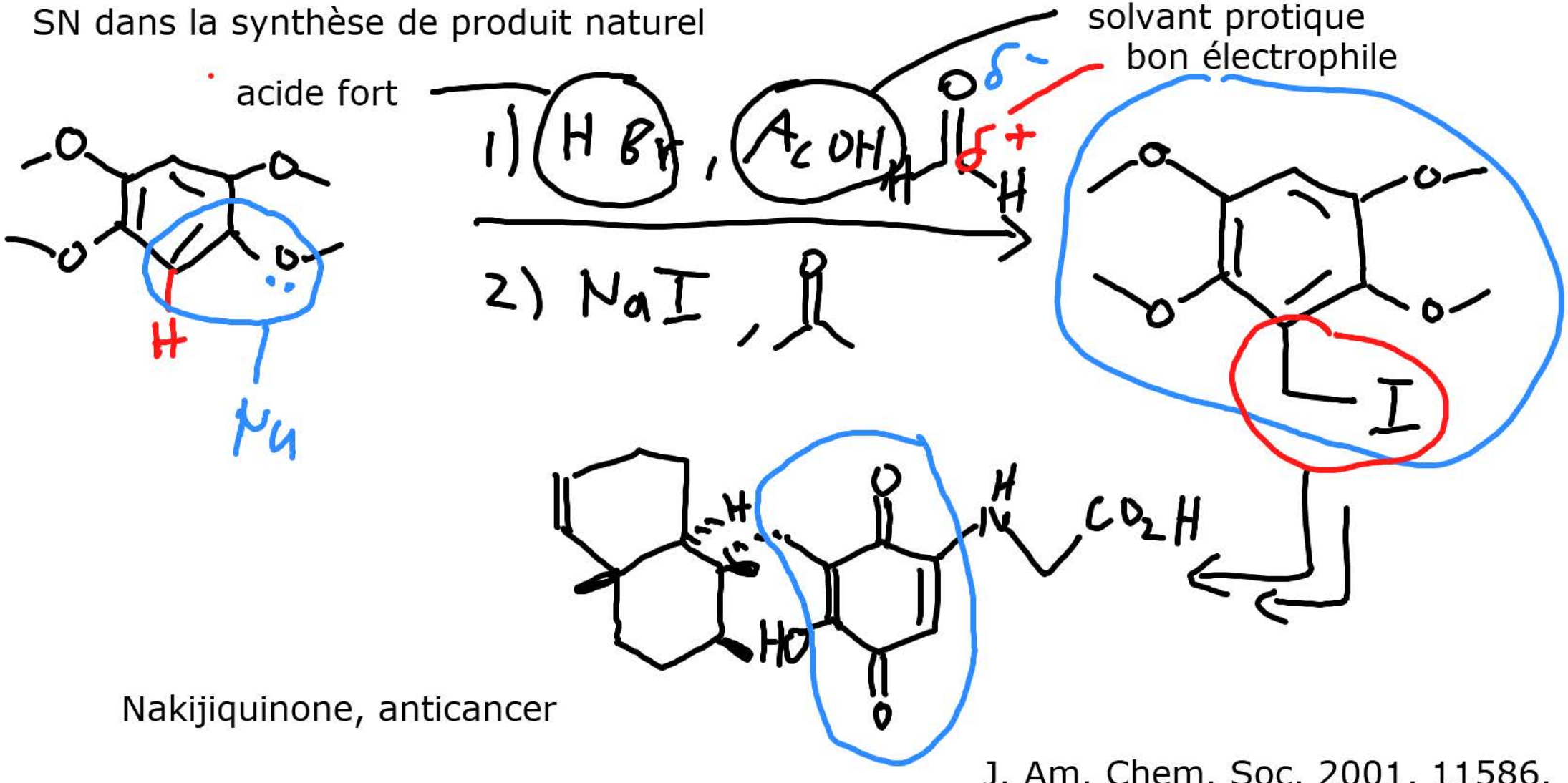
1) substrat: secondaire: SN1 ou SN2 (pas de décision)
2) groupe partant: Cl moyen, I est très bon (pas de décision)
3) Nucléophile: CN- est un bon nucléophile chargé, plutôt SN2
MeOH = faible nucléophile, favorise plutôt une SN1
4) Solvant: acétone: polaire aprotique, favorise une SN2
MeOH = polaire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

SN dans la synthèse de produit naturel

acide fort

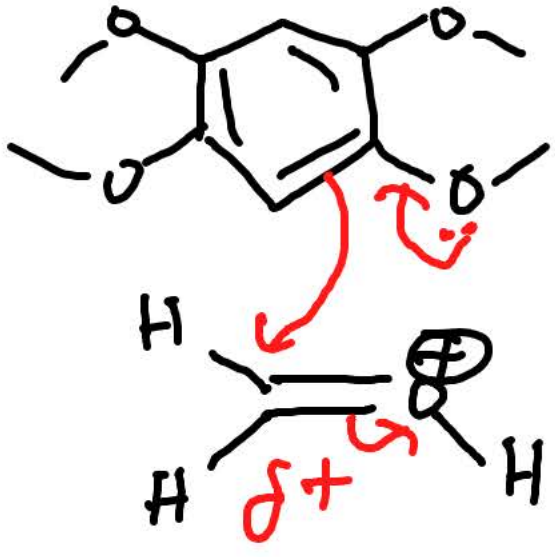
solvant protique

bon électrophile

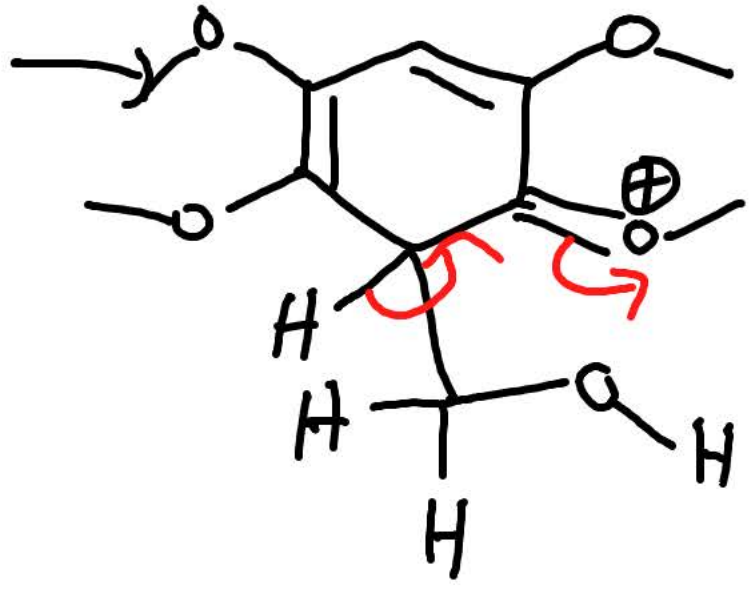


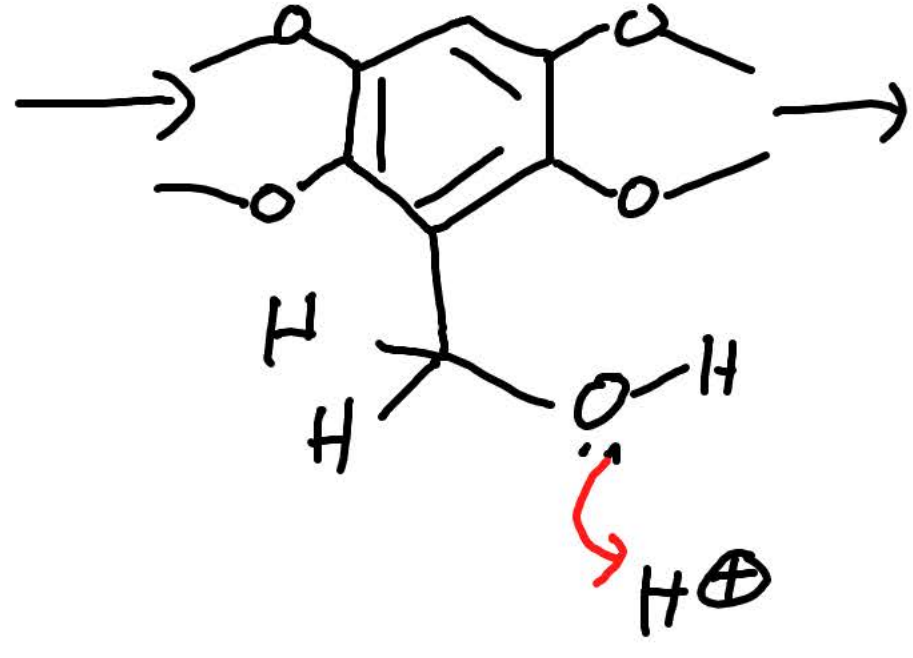
Nakijiquinone, anticancer

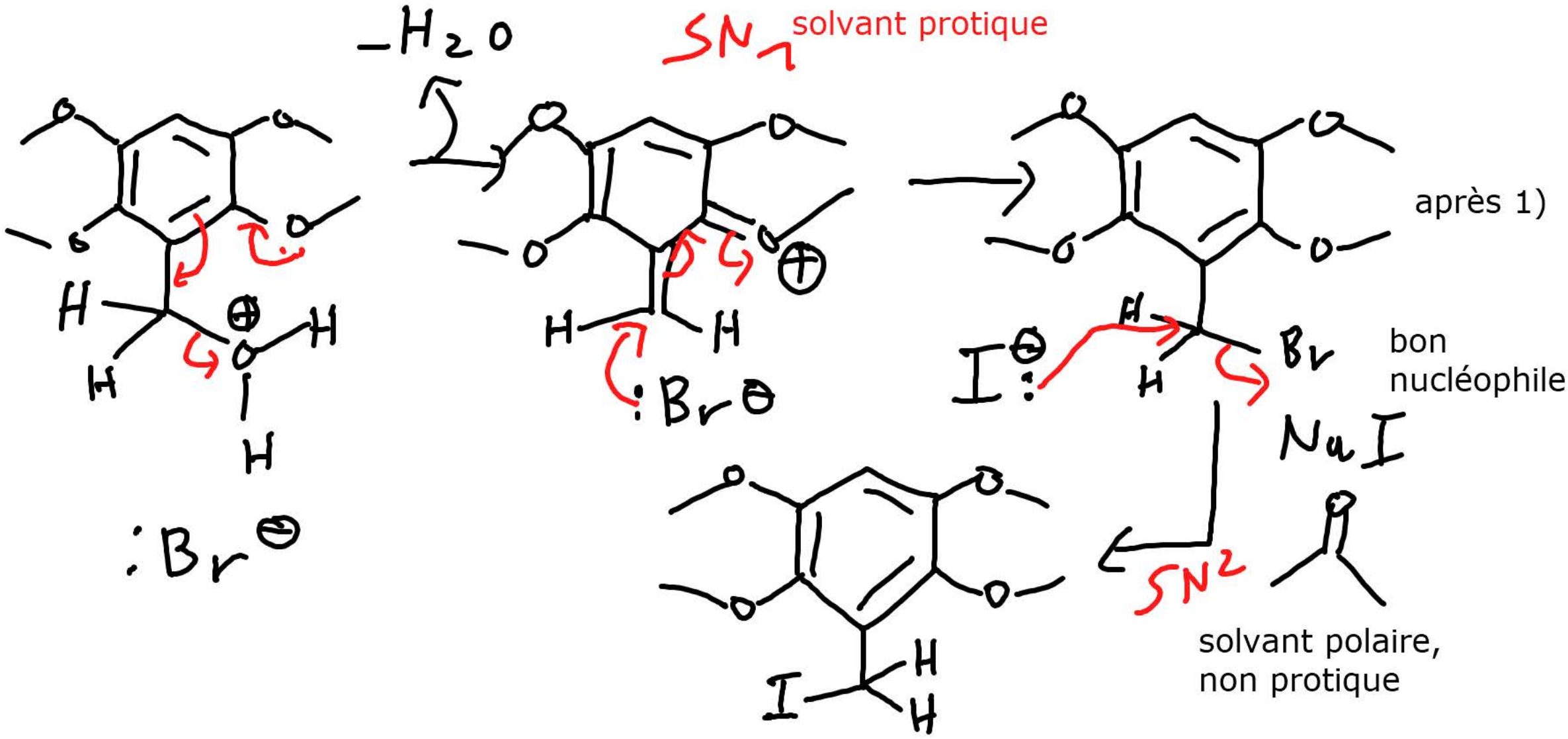
J. Am. Chem. Soc. 2001, 11586.



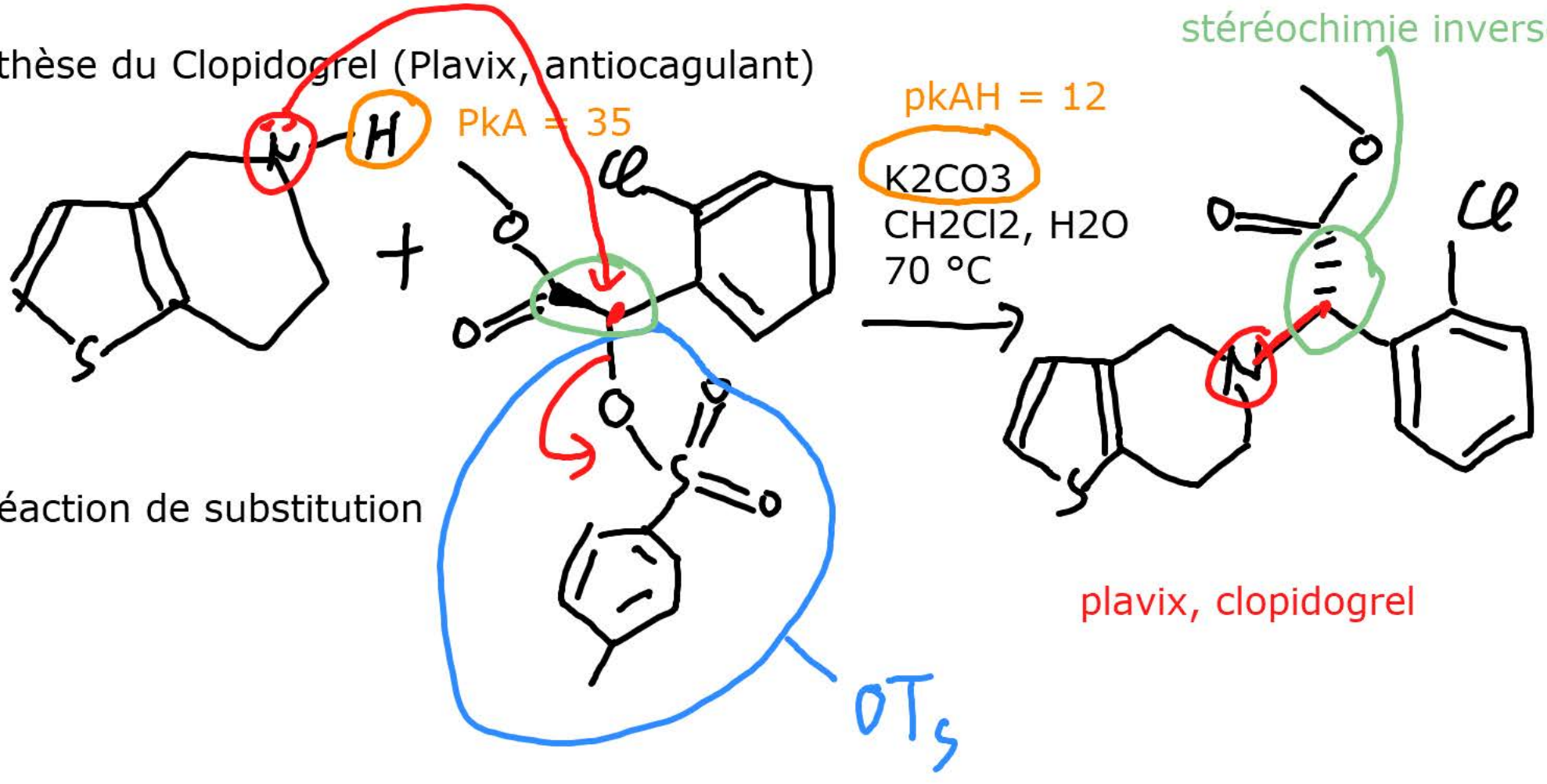
activé par l'acide






$-H_2O$
SN1
solvant protique
après 1)
bon
nucléophile
NuI
SN2
solvant polaire,
non protique

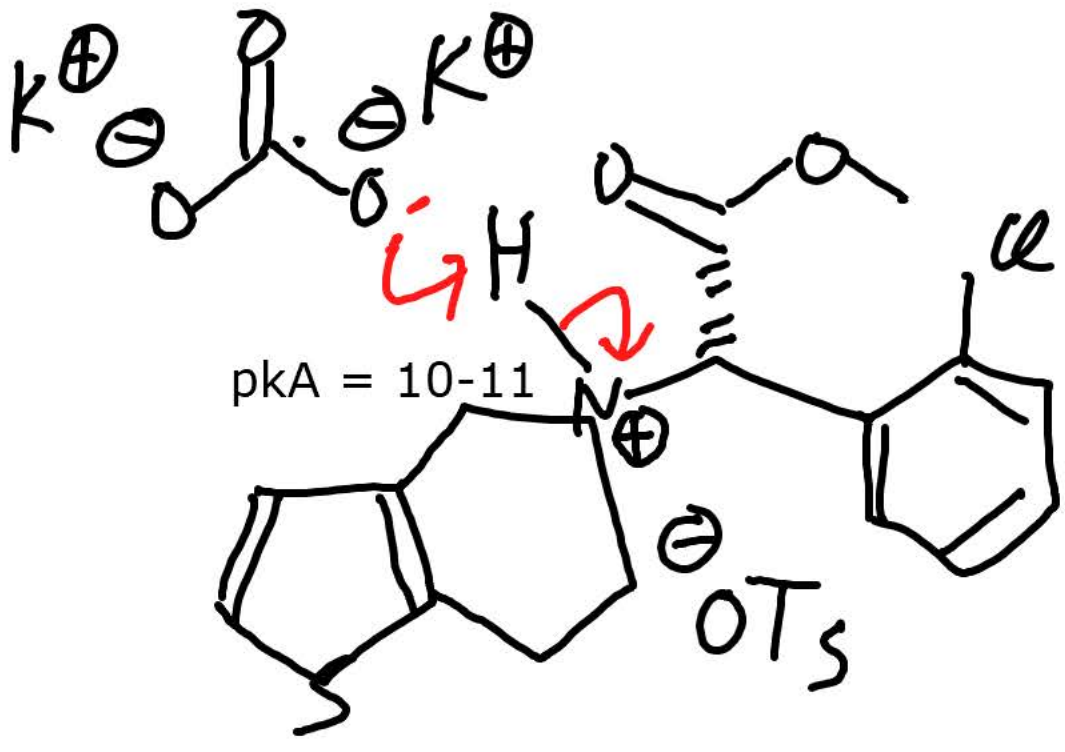
synthèse du Clopidogrel (Plavix, antiocagulant)



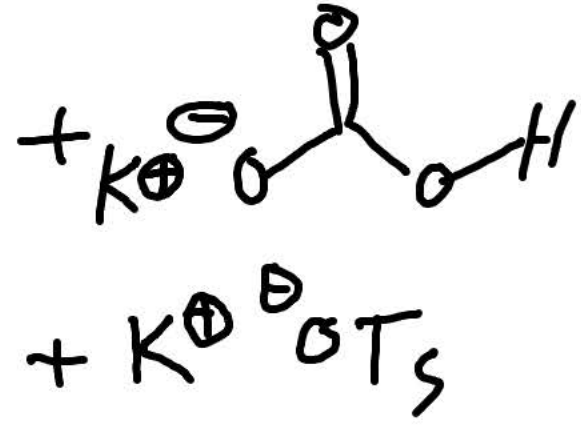
réaction de substitution

plavix, clopidogrel

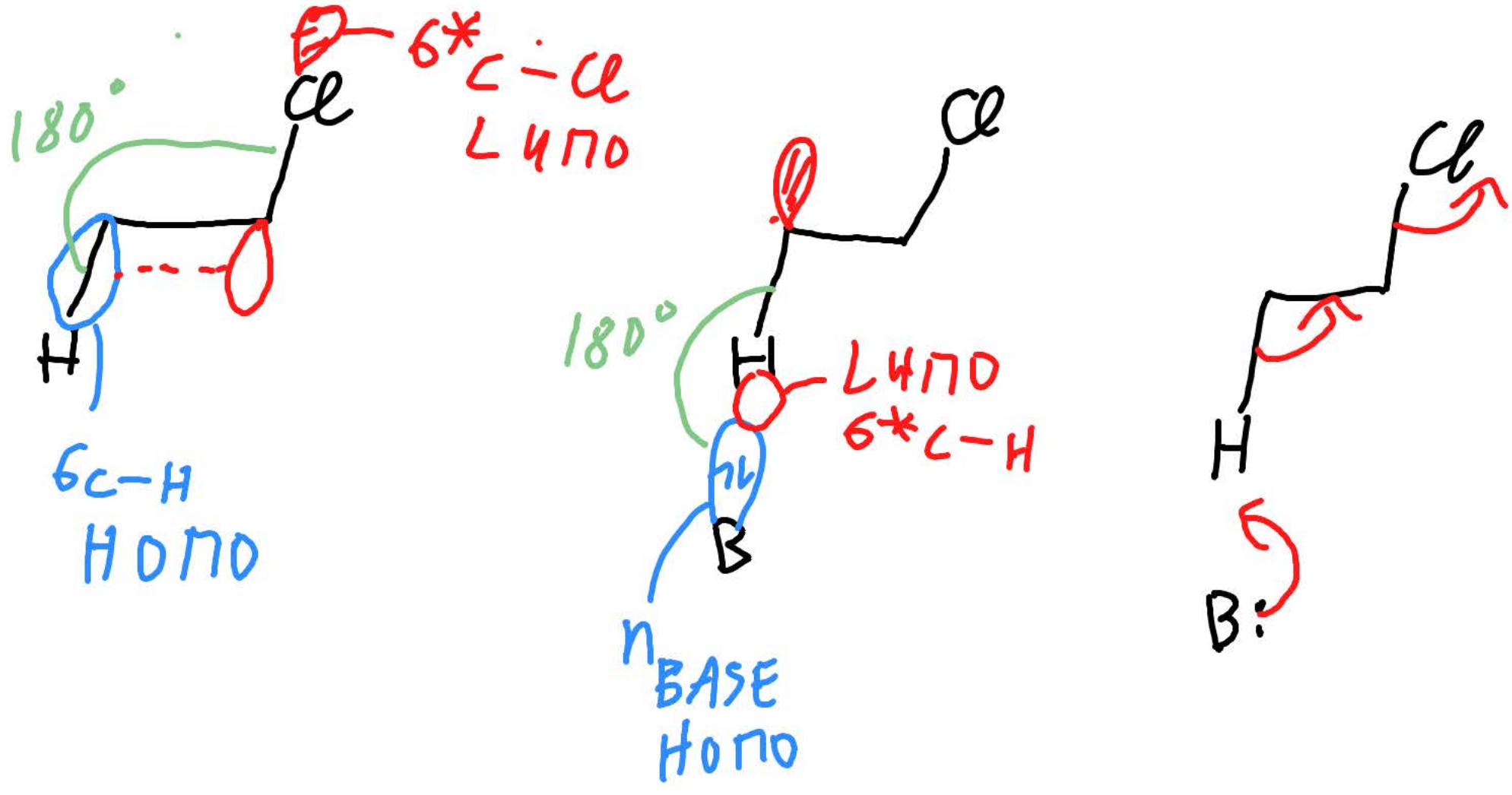
OTs: bon group partant (nucléofuge)

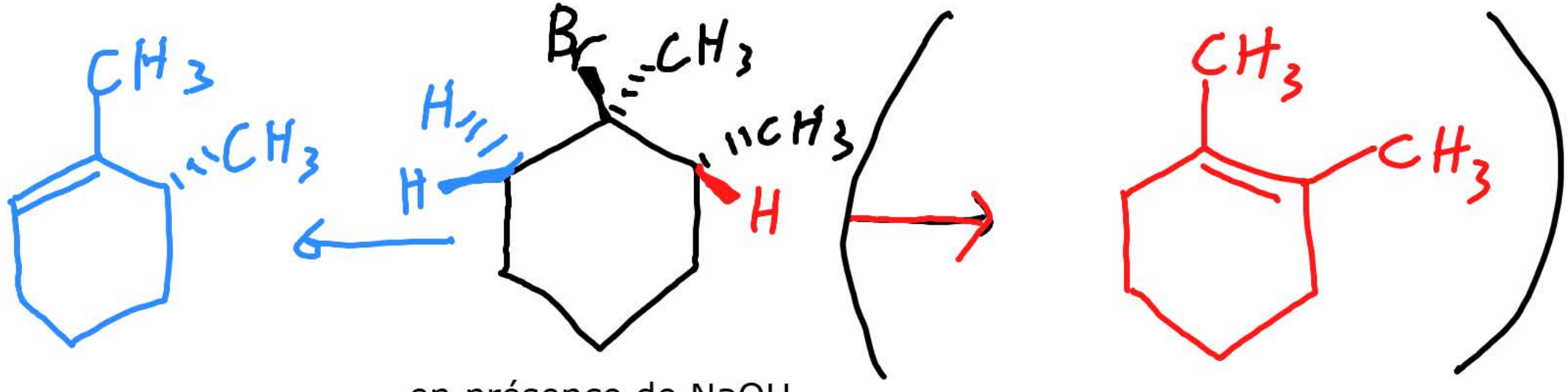


clopidogrel



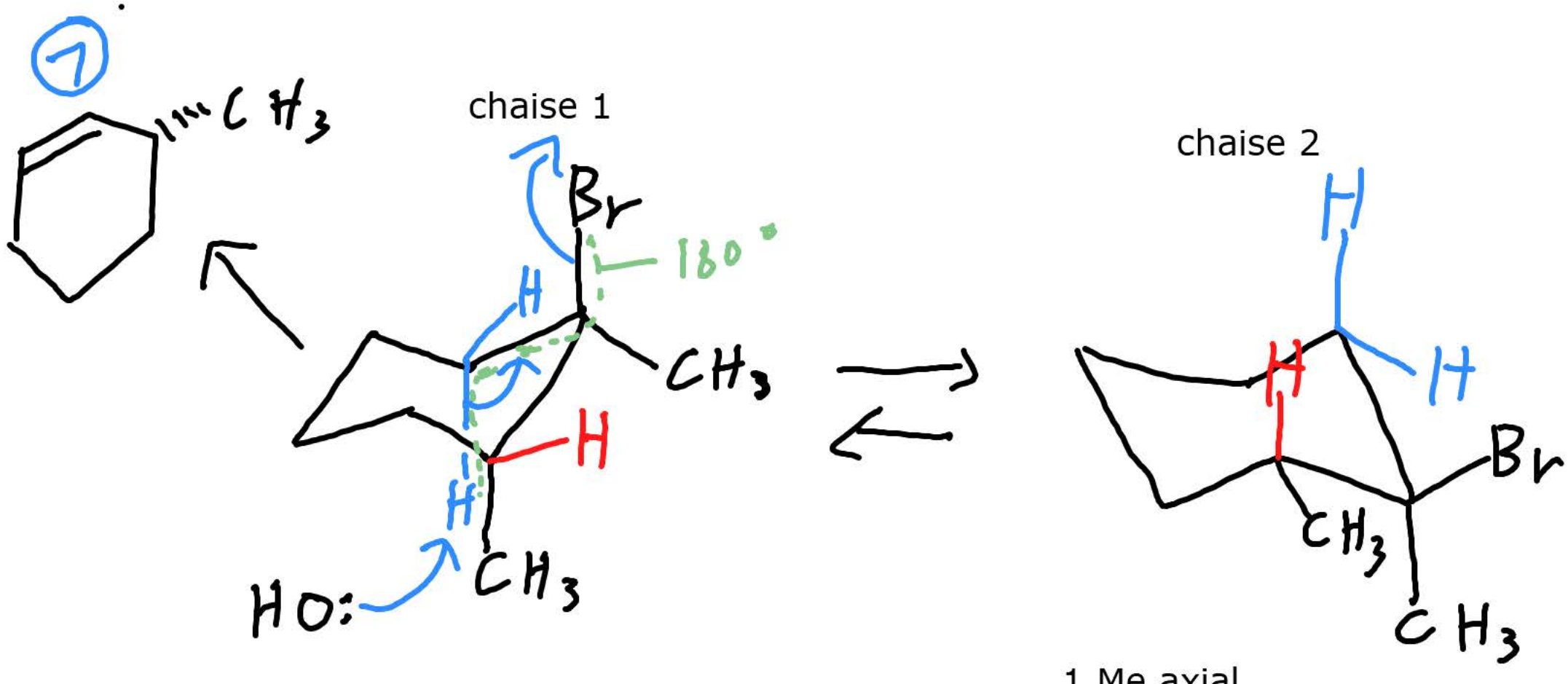
élimination E2, orbitales moléculaires





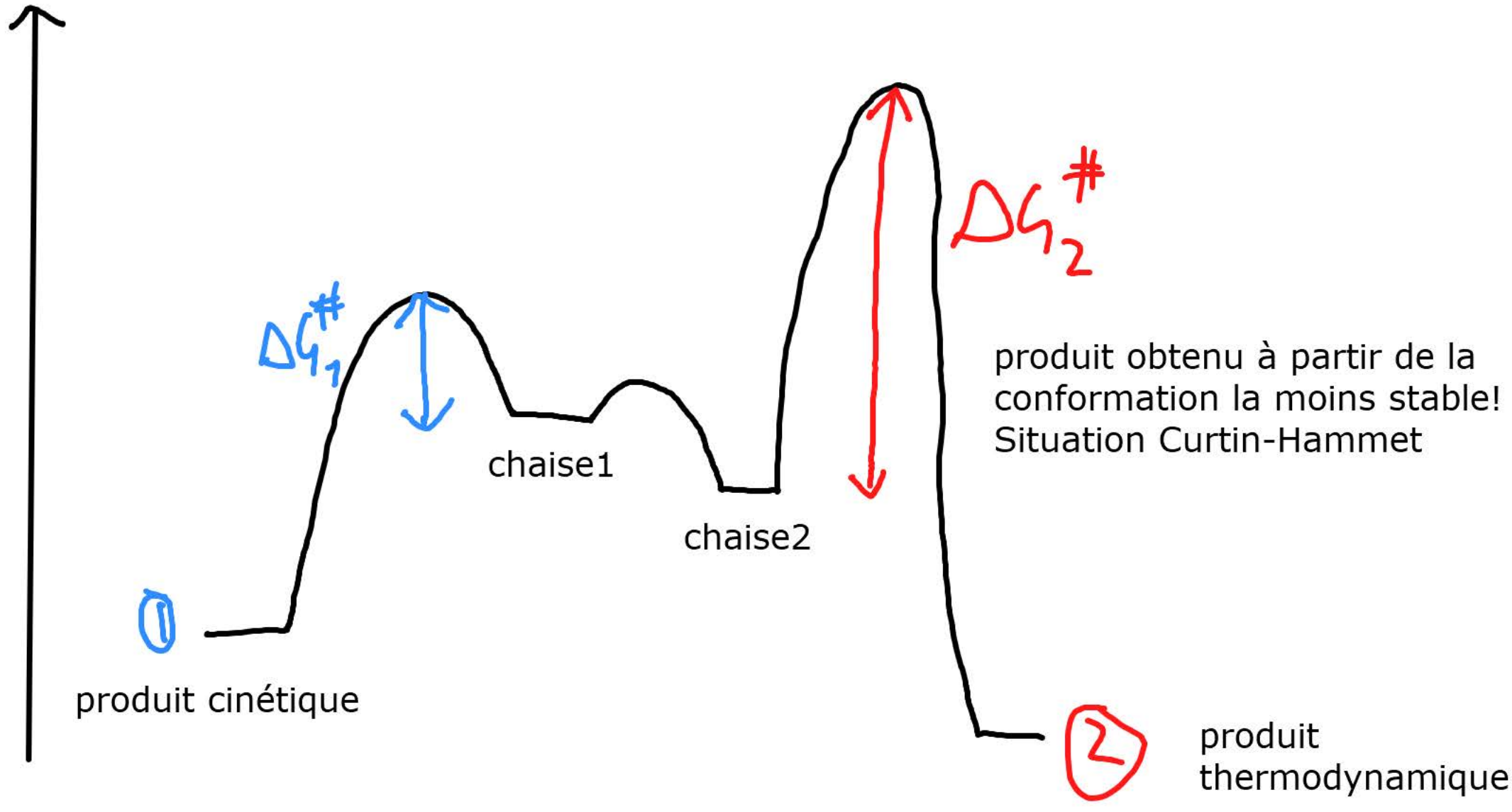
alcène trisubstitué
moins stable
produit observé!
Produit cinétique.

alcène tétrasubstitué
plus stable
produit thermodynamique

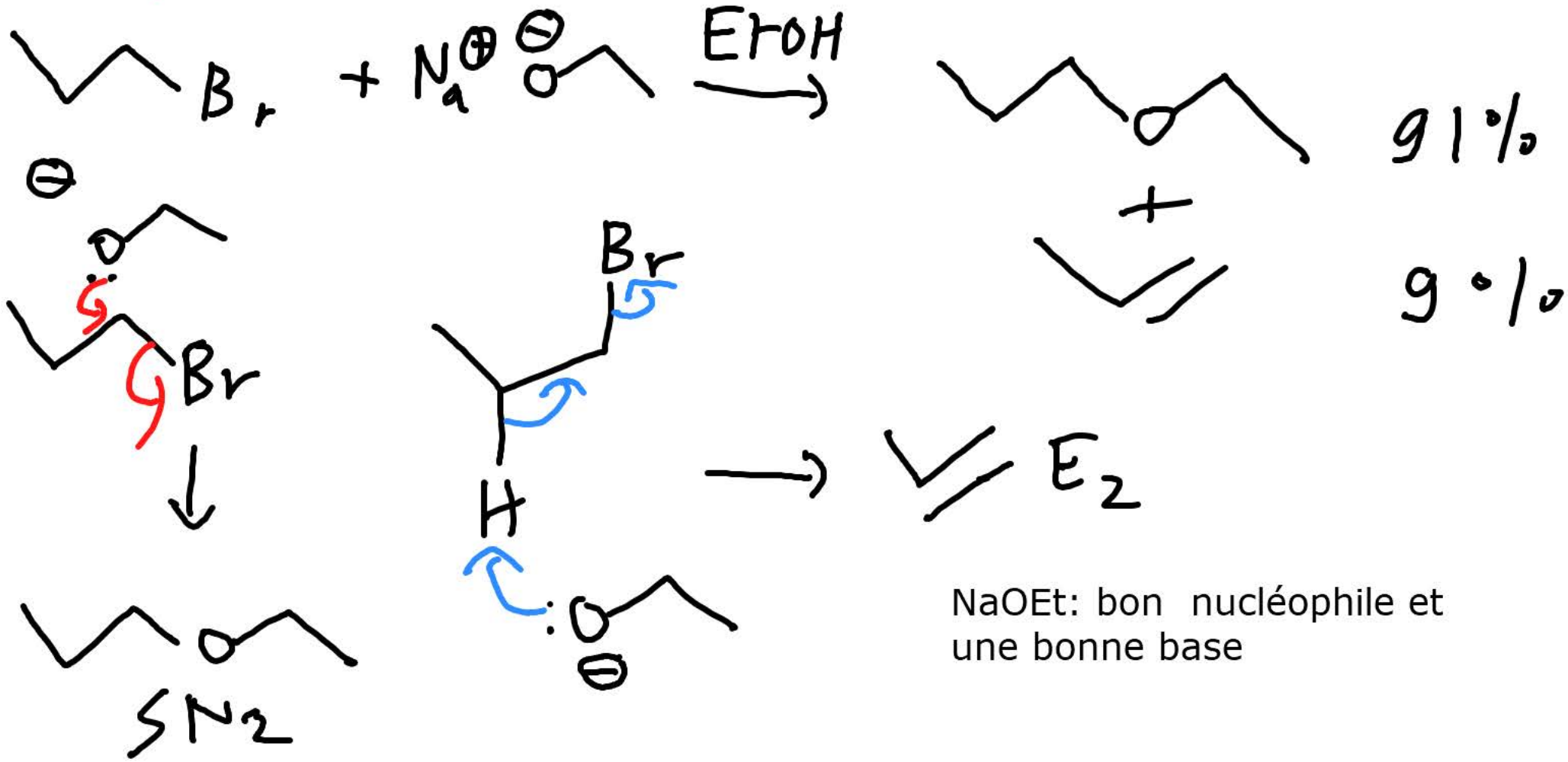


1 Me, 1 Br axial
1 Me équatorial

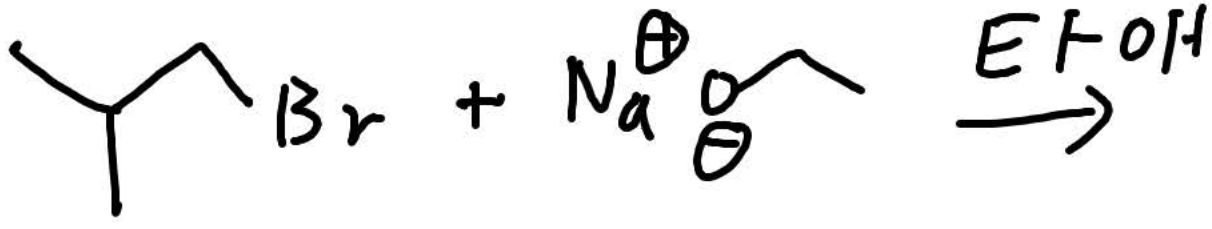
1 Me axial
1 Me et 1 Br équatorial
plus stable!


$\Delta G_1^{\#}$
$\Delta G_2^{\#}$
chaise1
chaise2
1
2
produit cinétique
produit obtenu à partir de la conformation la moins stable! Situation Curtin-Hammet
produit thermodynamique

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



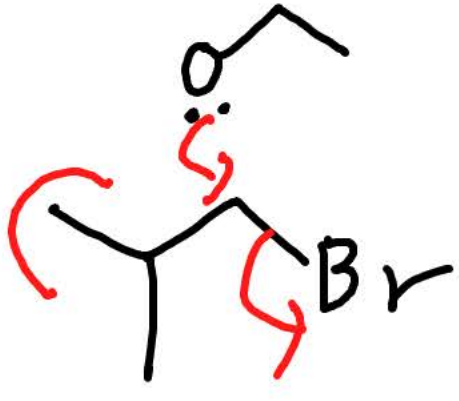
NaOEt: bon nucléophile et une bonne base



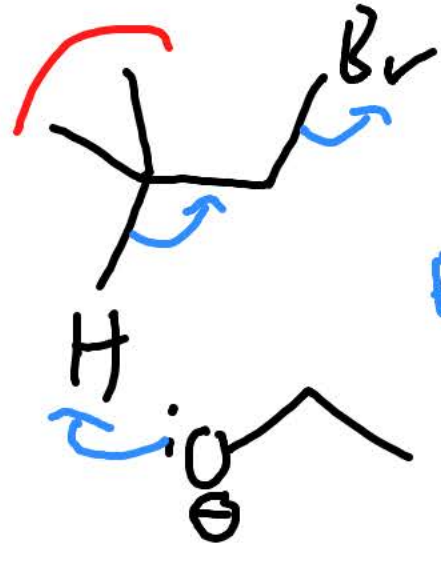
S_N2 40%

+

E_2 60%



S_N2



E_2

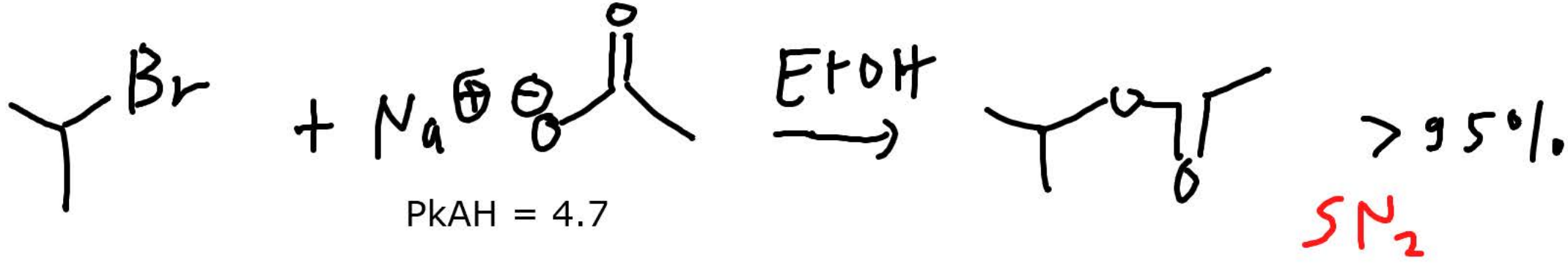
Sn est plus sensible à l'effet du group stérique que E! on devrait augmenter la proportion d'E2.

position secondaire

PkAH = 16

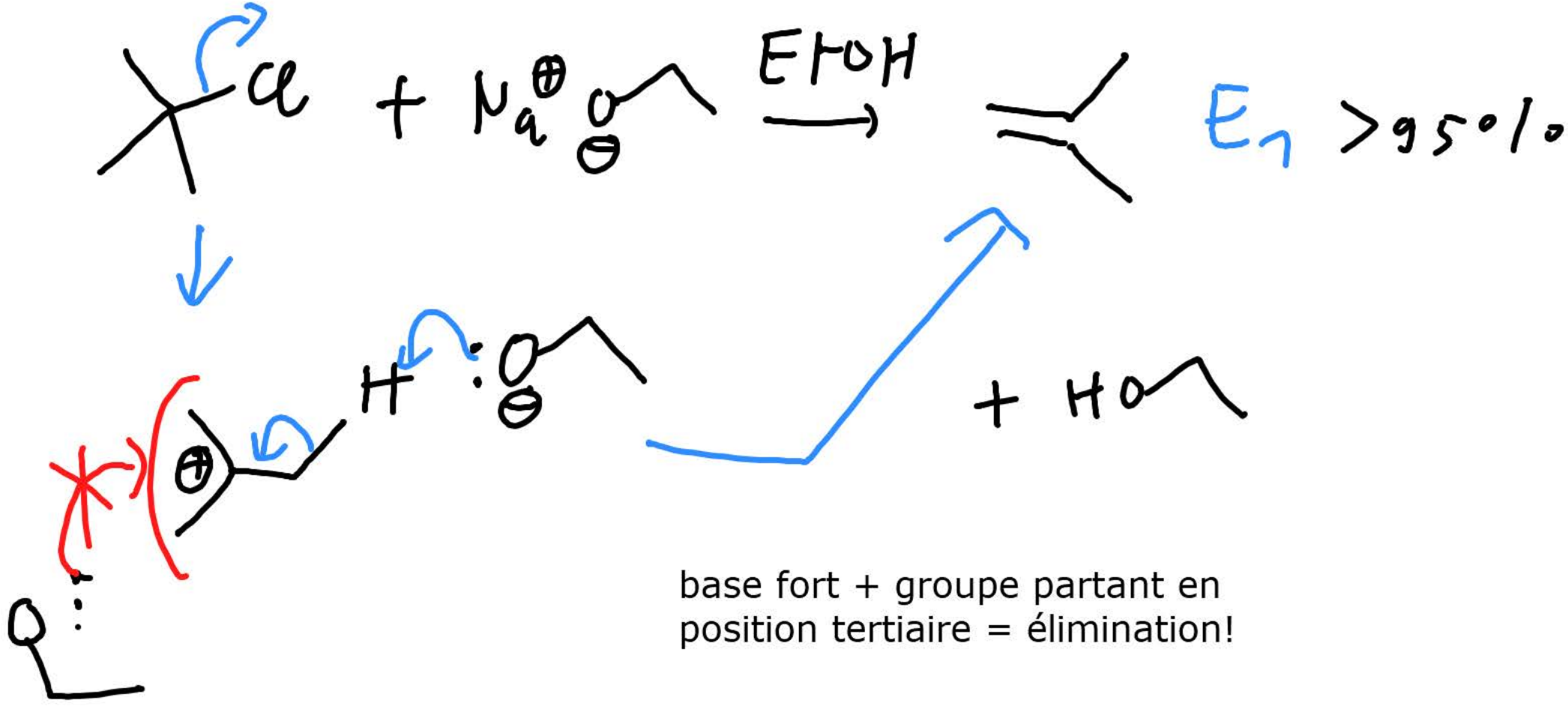
secondaire avec forte base:
E1/2 domine!

pour favoriser SN: il faut diminuer la basicité!

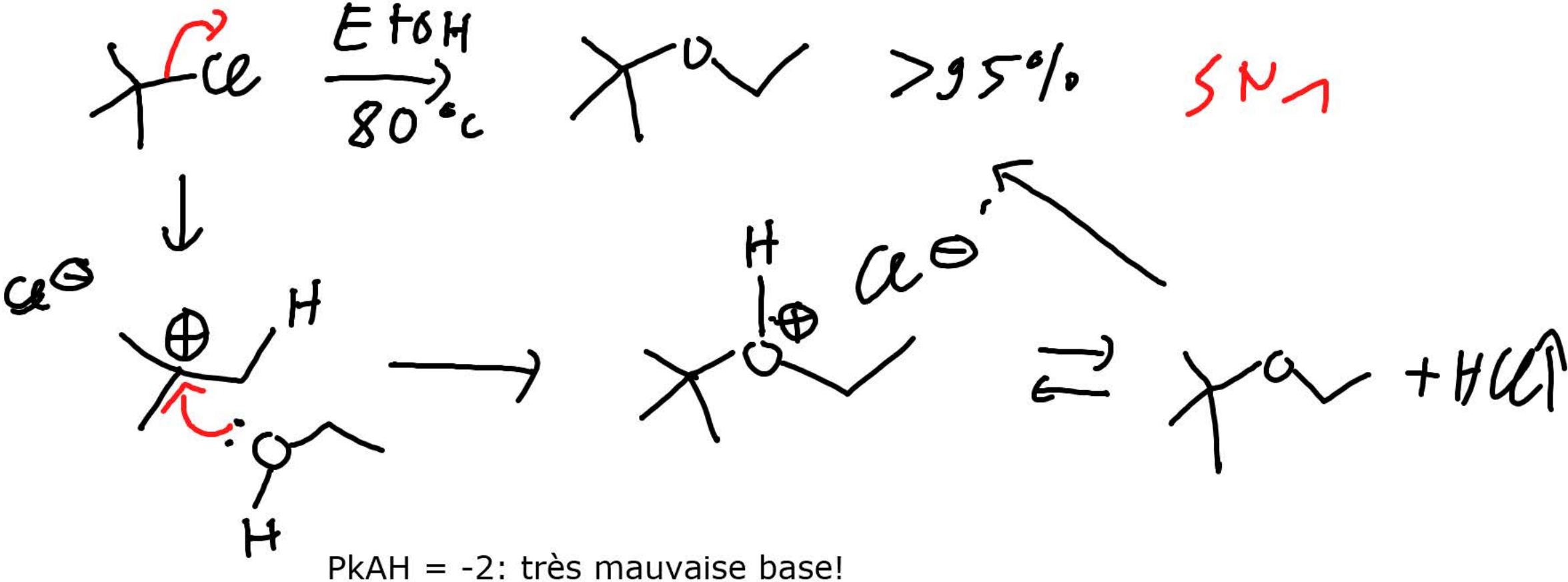


PkAH = 4.7

position tertiaire: E1 our SN1

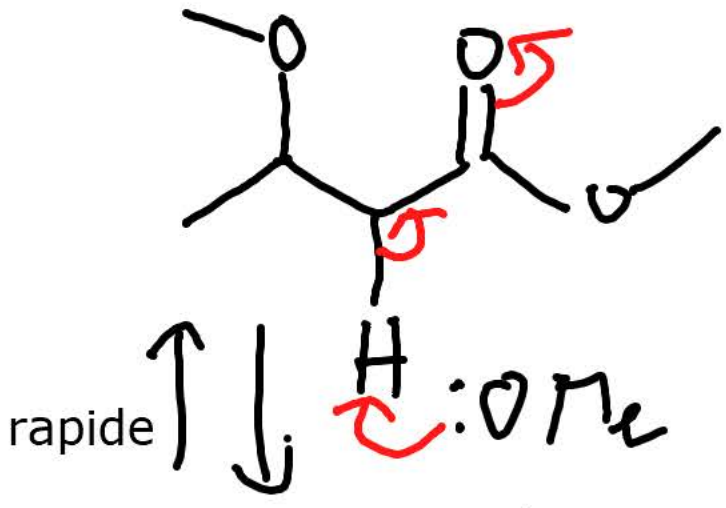


Pour SN1: réaction en absence de base

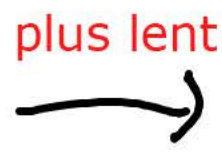


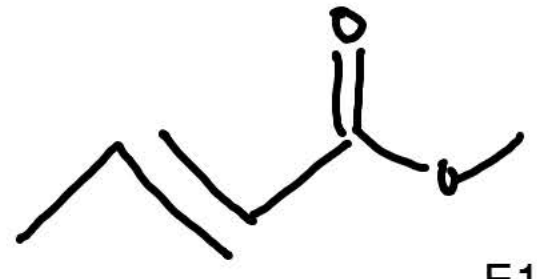
PkAH = -2: très mauvaise base!

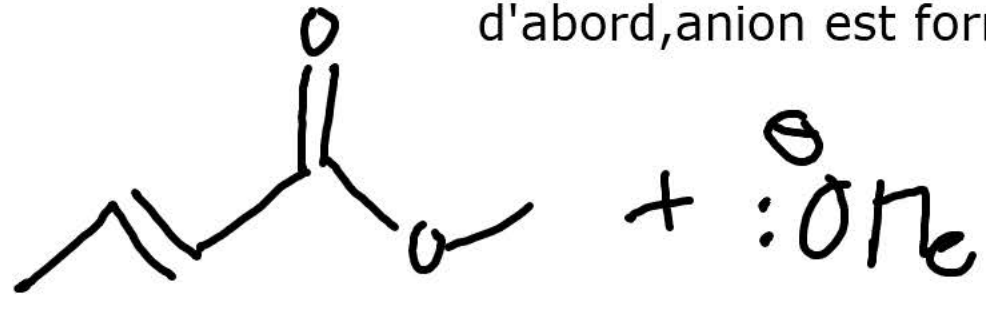
"5ème mécanisme" cas particulier E1cb des protons acides



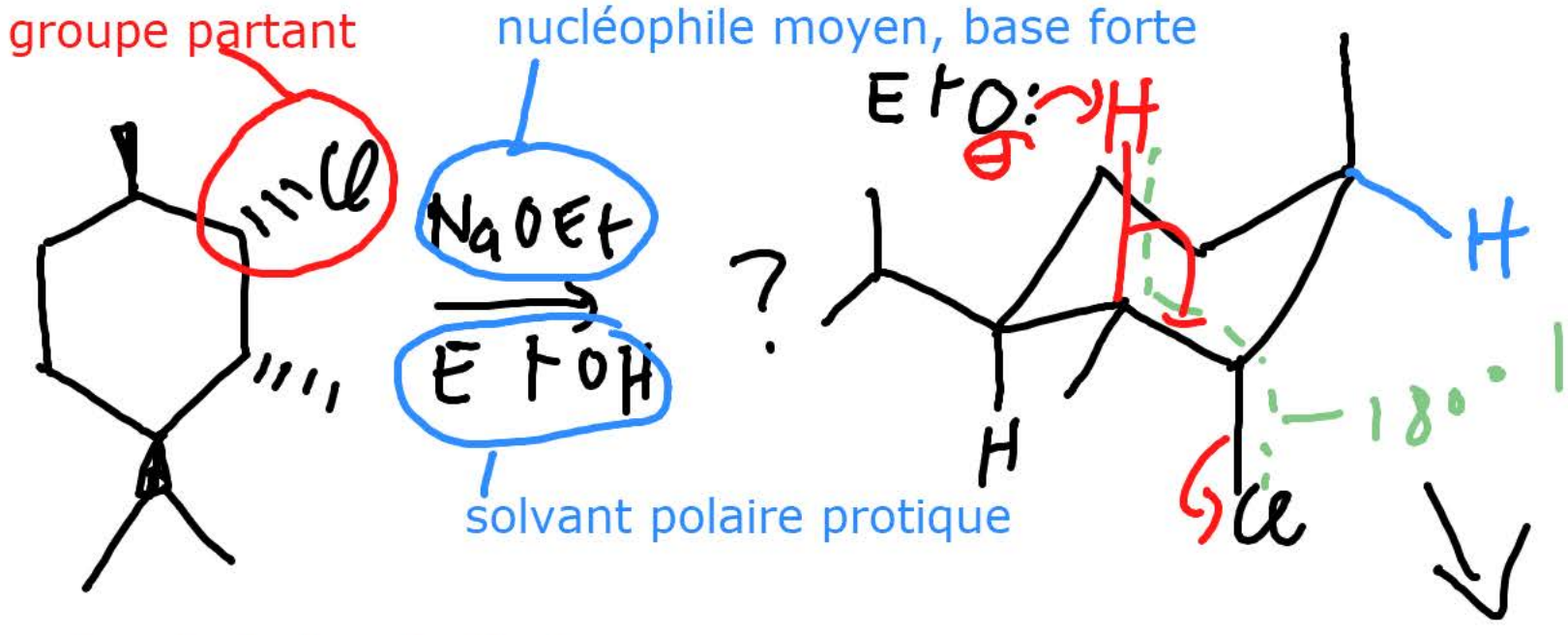
anion comme intermédiaire







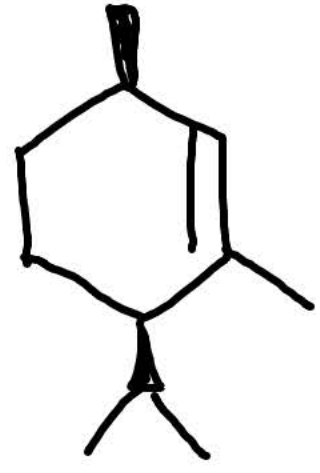
E1 : group partant d'abord, cation est formé
E1cb: déprotonation d'abord,anion est formé



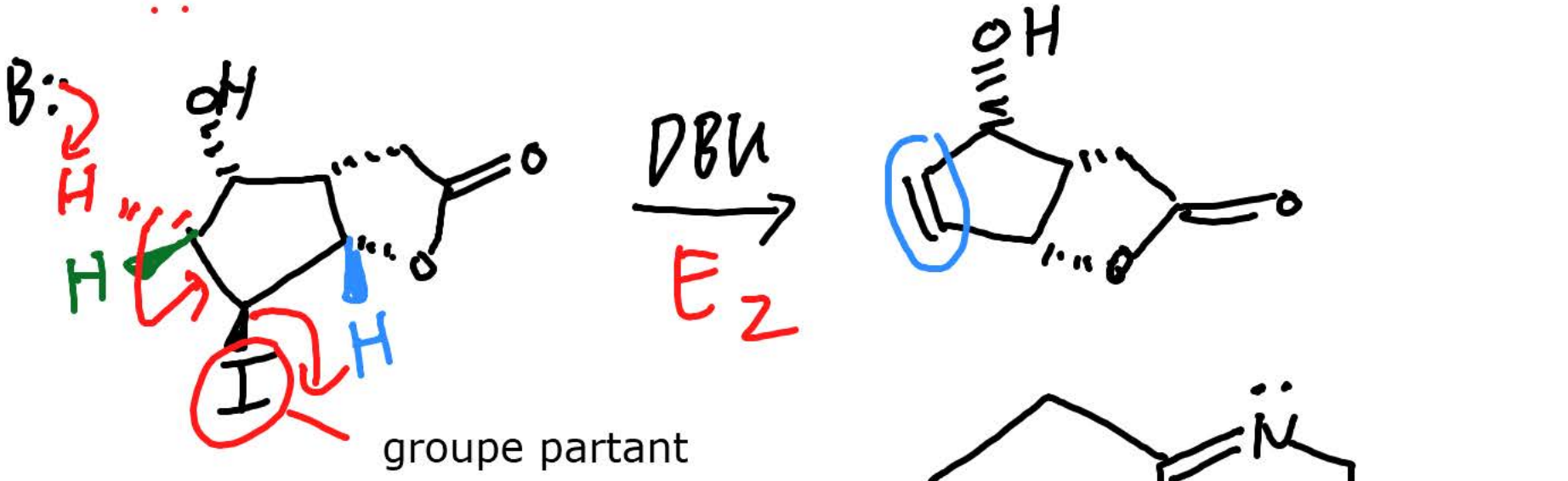
1) analyser le substrat: substitution ou élimination? position secondaire: les 2 possibles

2) conditions: forte base, solvent polaire protique: favorisent élimination: E2 si on peut atteindre l'angle idéal de 180°, sinon plutôt E1: on doit dessiner en 3D!

produit principal

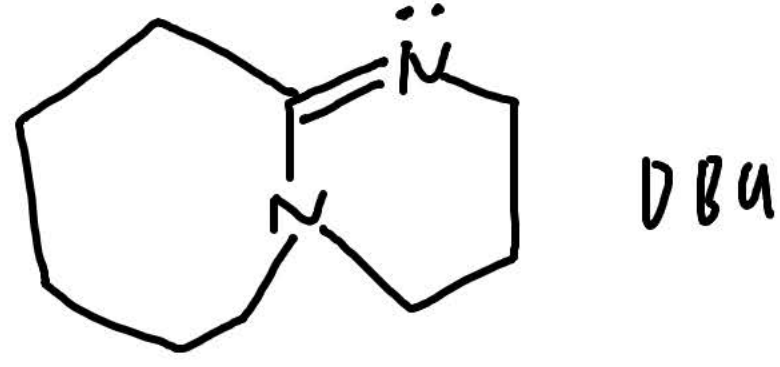


synthèse de produit naturel: prostaglandines (hormones naturelles)



groupe partant

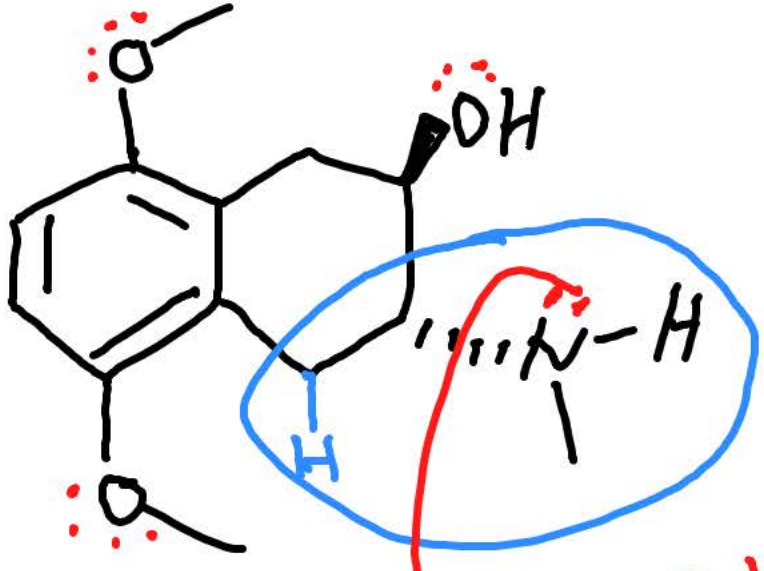
cycle à 5 presque "plat", seul l'hydrogène rouge en trans/anti à le bon angle pour réagir.



DBU

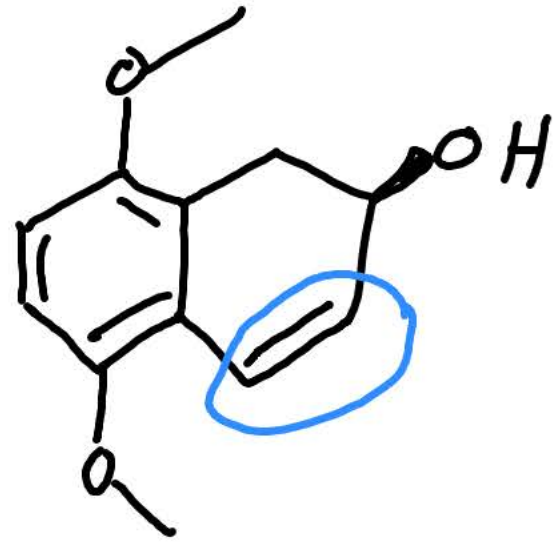
bonne base, acide stabilisé par résonance, PkaH = 14

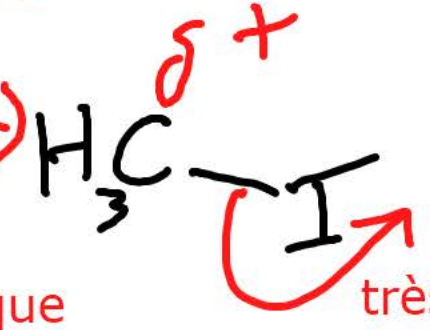
Elimination selon Hofmann (à partir des amines)



1) CH3I, K2CO3, MeOH

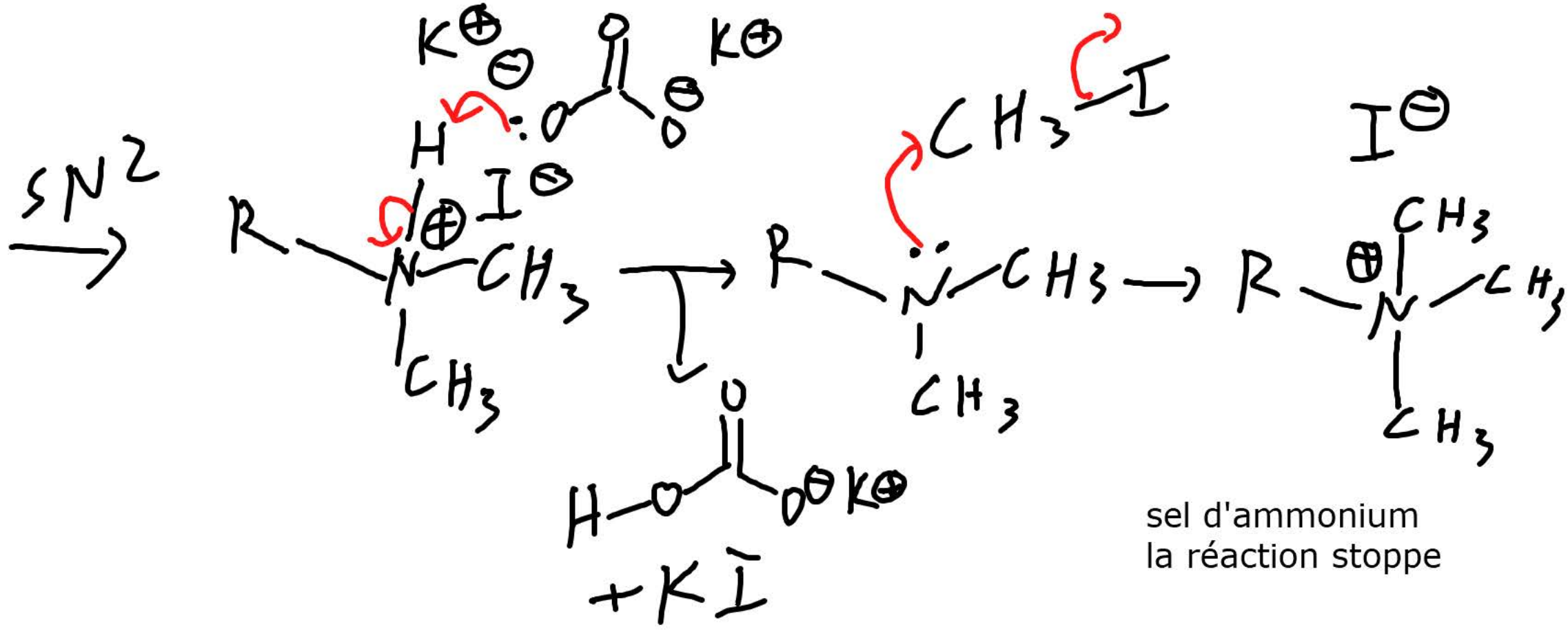
2) 2 equiv. BuLi

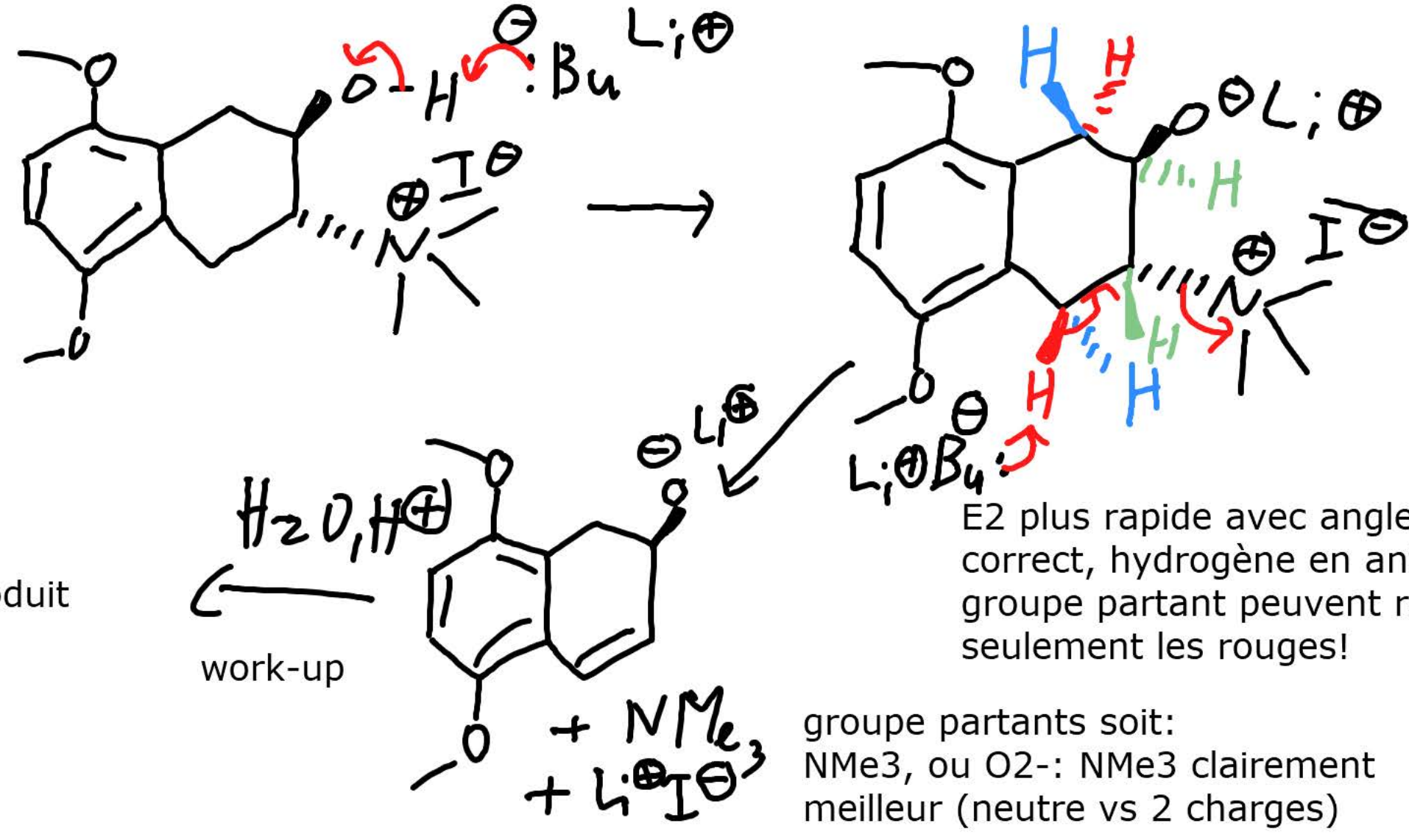




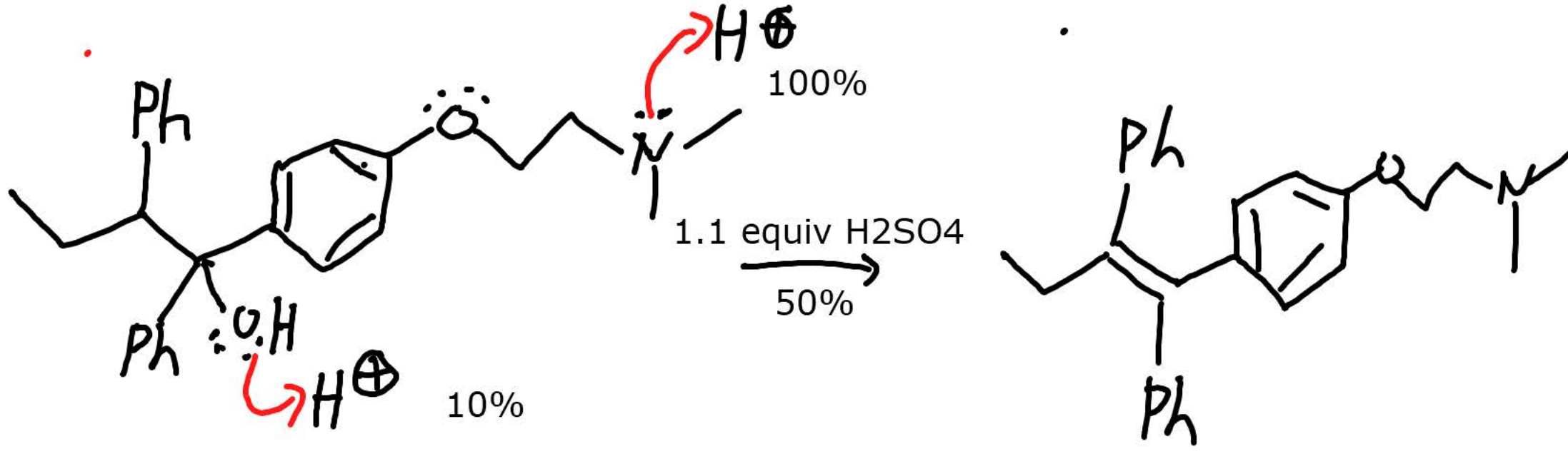
O est plus électronégatif que N, donc N plus nucléophile

très accessible, idéal pour SN2


SN2
sel d'ammonium
la réaction stoppe

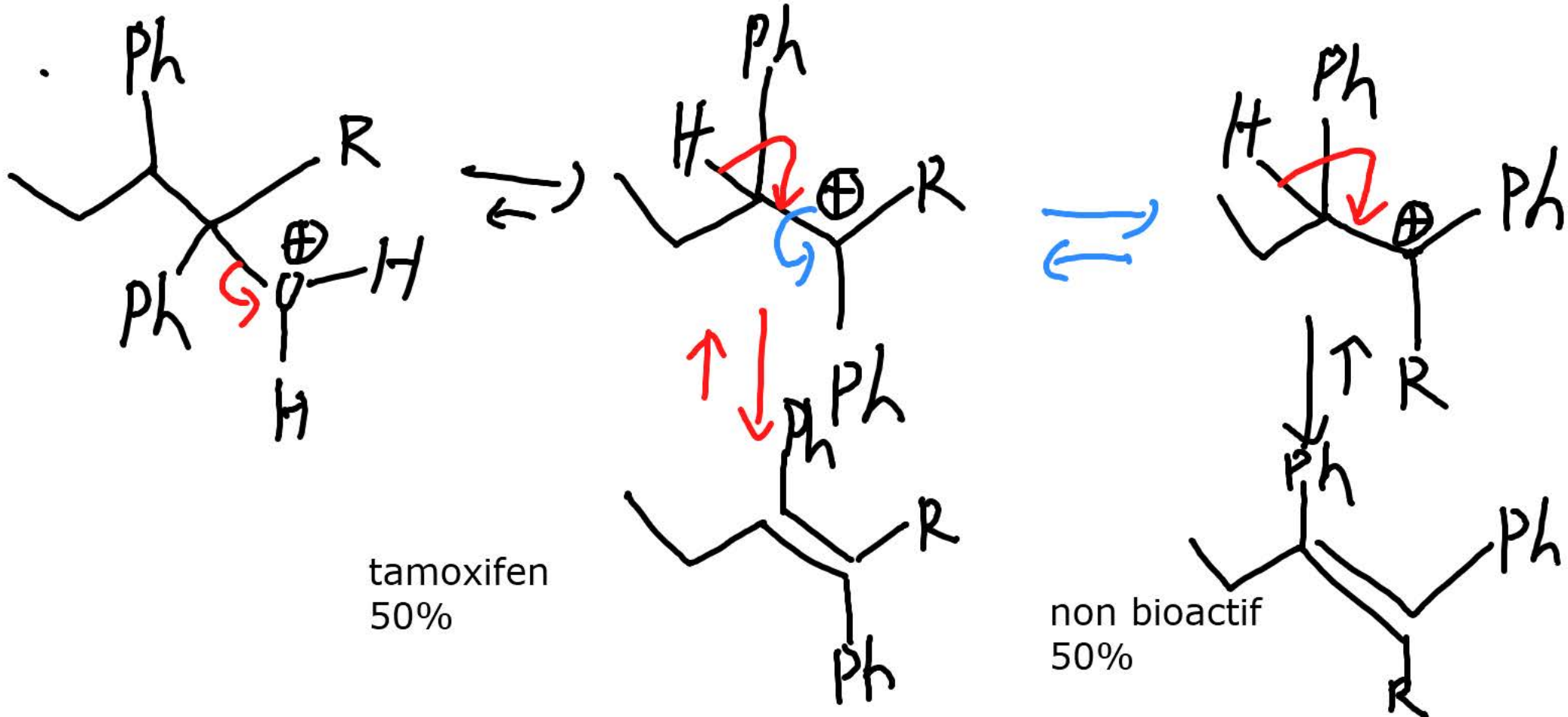

produit
work-up
E2 plus rapide avec angle correct, hydrogène en anti du groupe partant peuvent réagir: seulement les rouges!
groupe partants soit:
NMe3, ou O2-: NMe3 clairement meilleur (neutre vs 2 charges)

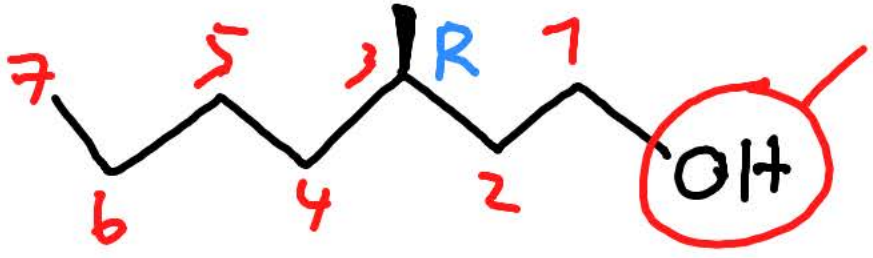
synthèse du tamoxifen (traitement du cancer du sein) par élimination E1



O plus électronégatif que N,
donc N plus basique

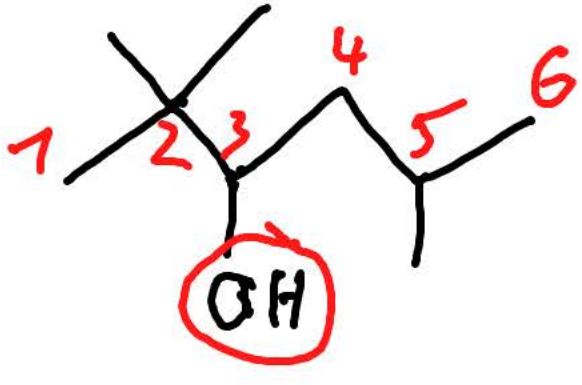
tamoxifen


Ph
R
Ph
H
H
Ph
R
H
Ph
Ph
R
Ph
tamoxifen
50%
Ph
H
Ph
R
Ph
R
non bioactif
50%

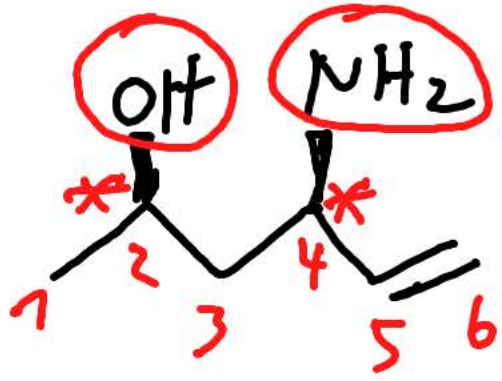


alcool

(R)-3-méthyl-heptan-1-ol

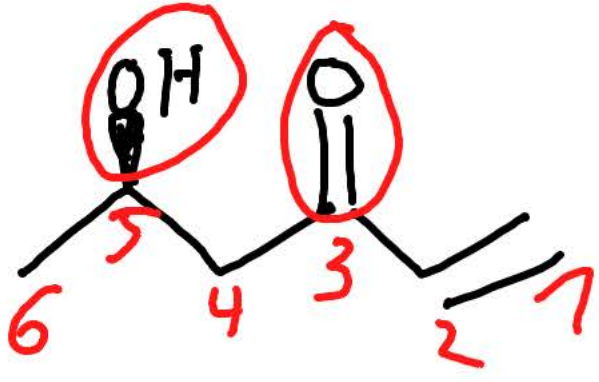


2,2,4-triméthyl-hexan-3-ol



alcool > amine

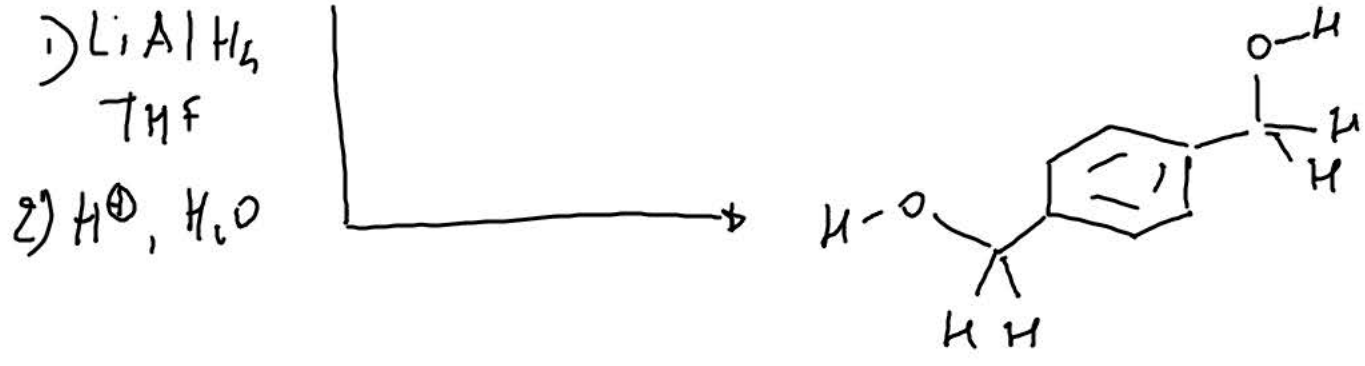
(2R, 4R)-4-amino-hex-5-en-2-ol

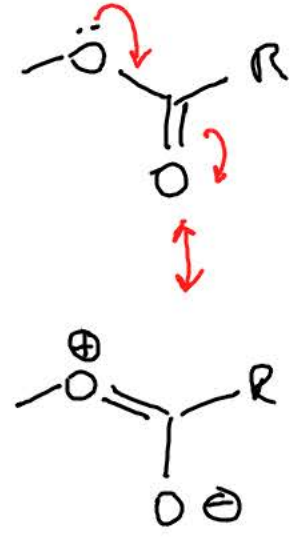


cétone > alcool

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

Réduction des carbonyls avec des hydrures

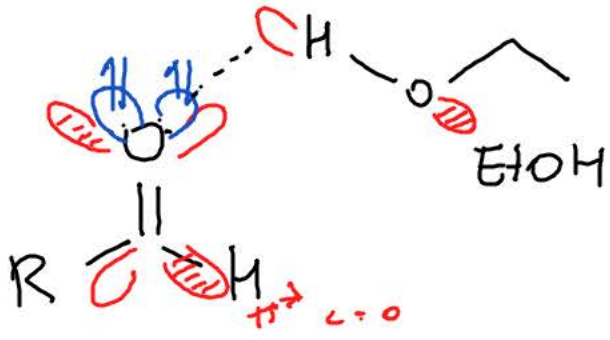




ester stabilisé par réson.

2> moins réactif

Réduction avec $NaBH_4$ (en EtOH)

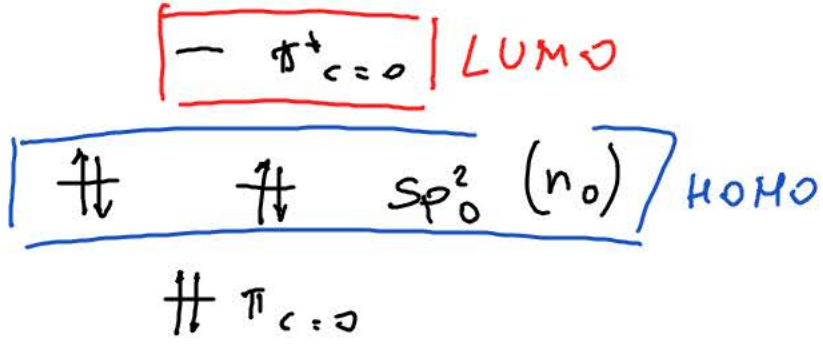


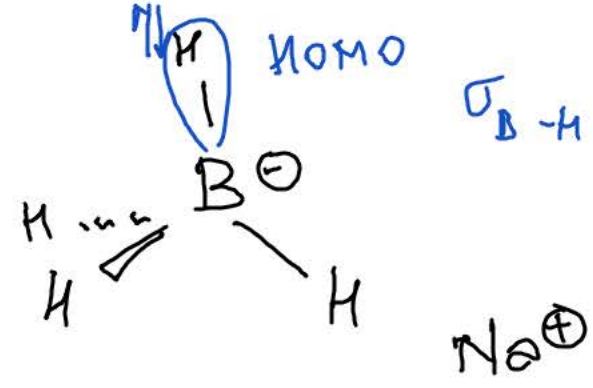
$Sp^2O \rightarrow \sigma^*_{H-O}$

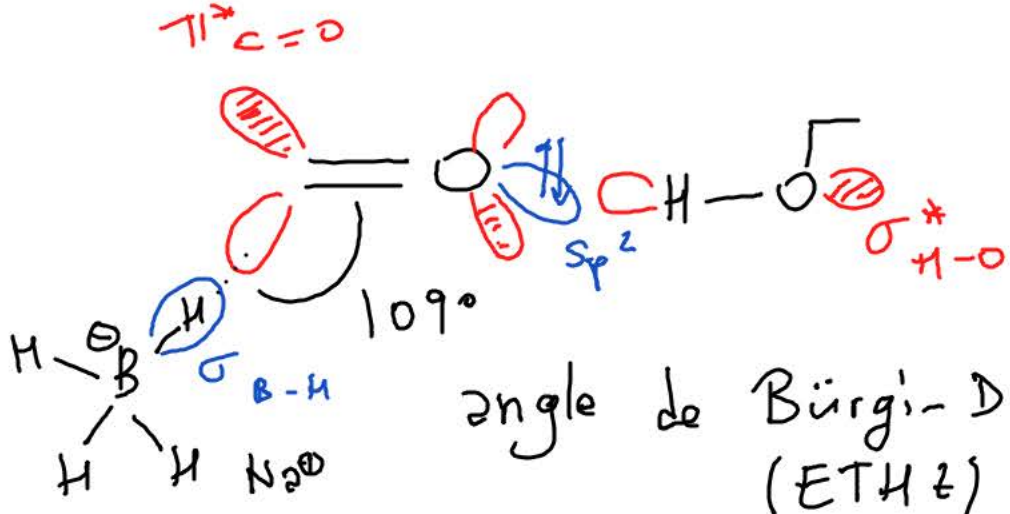
LUMO EtOH

pont hydrogène

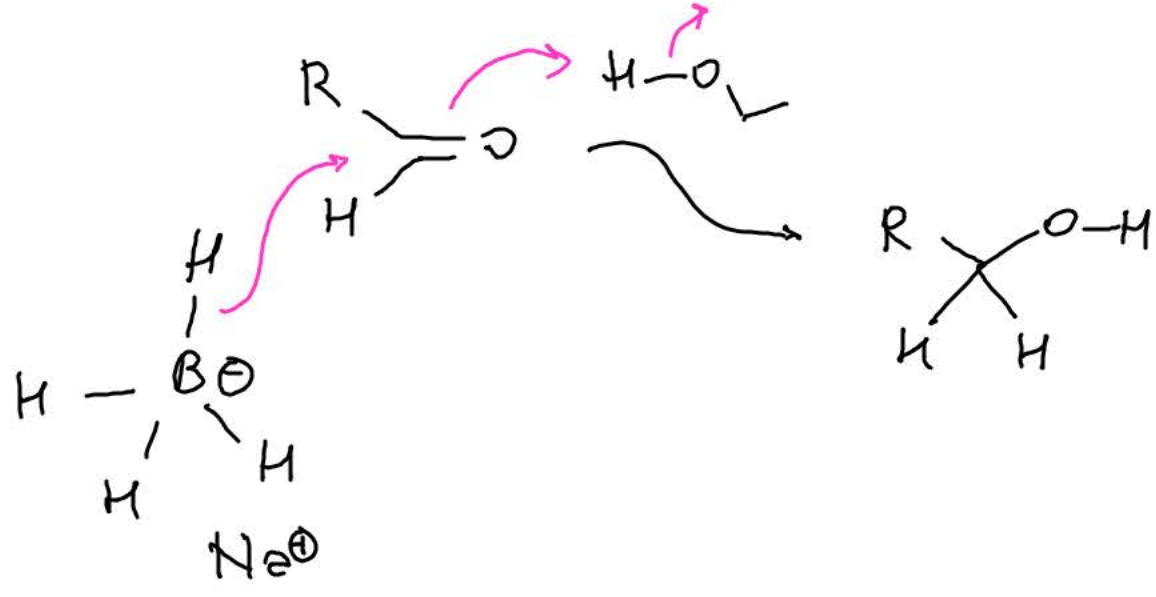
aldéhyde → solvant

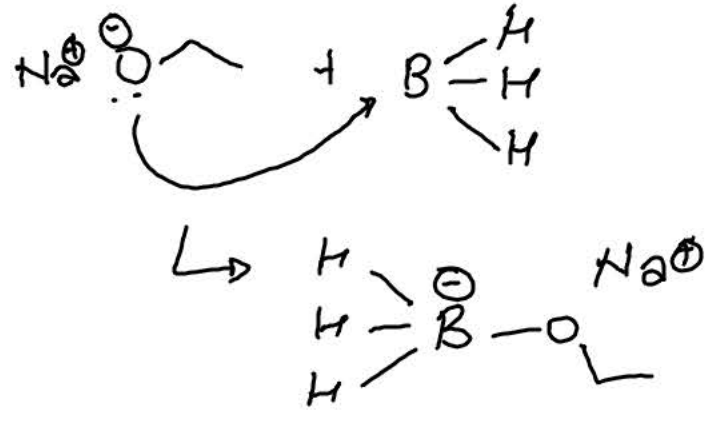






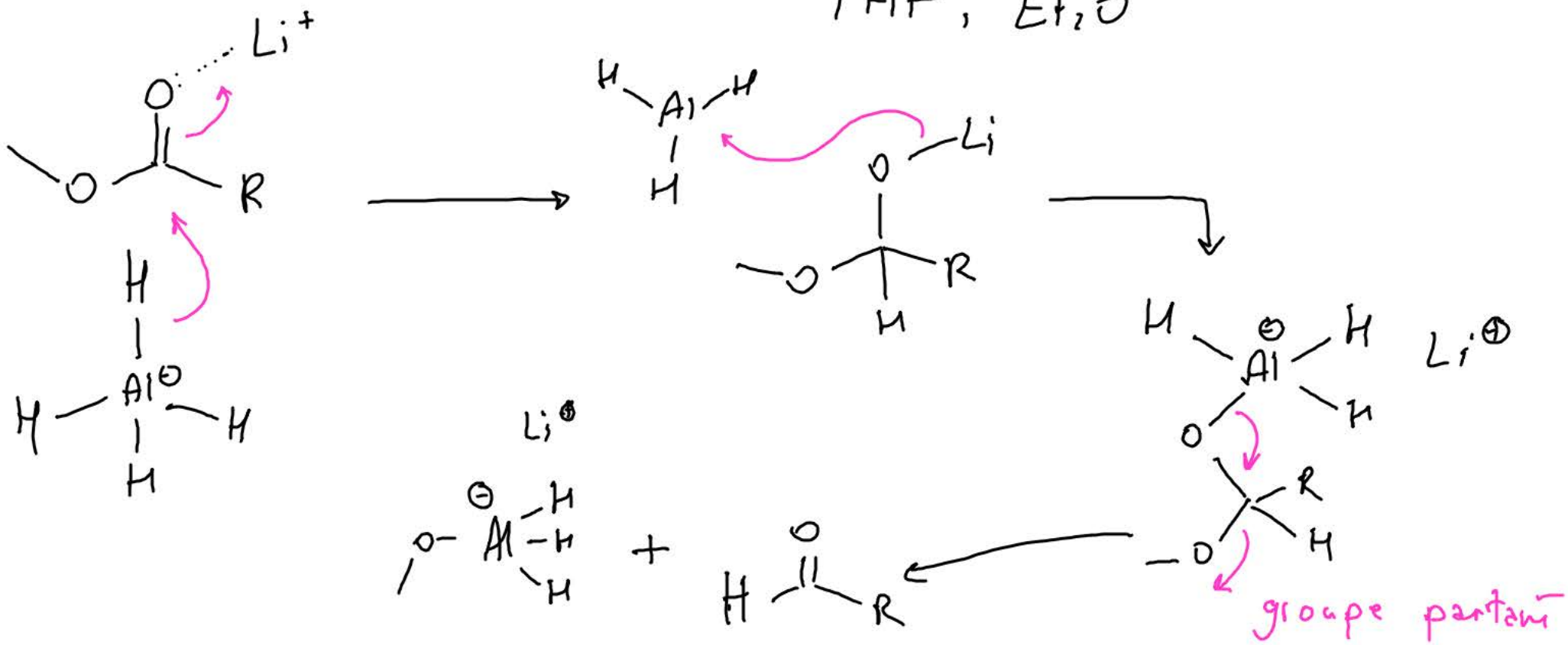
angle de Bürgi-Dunitz
(ETHz)





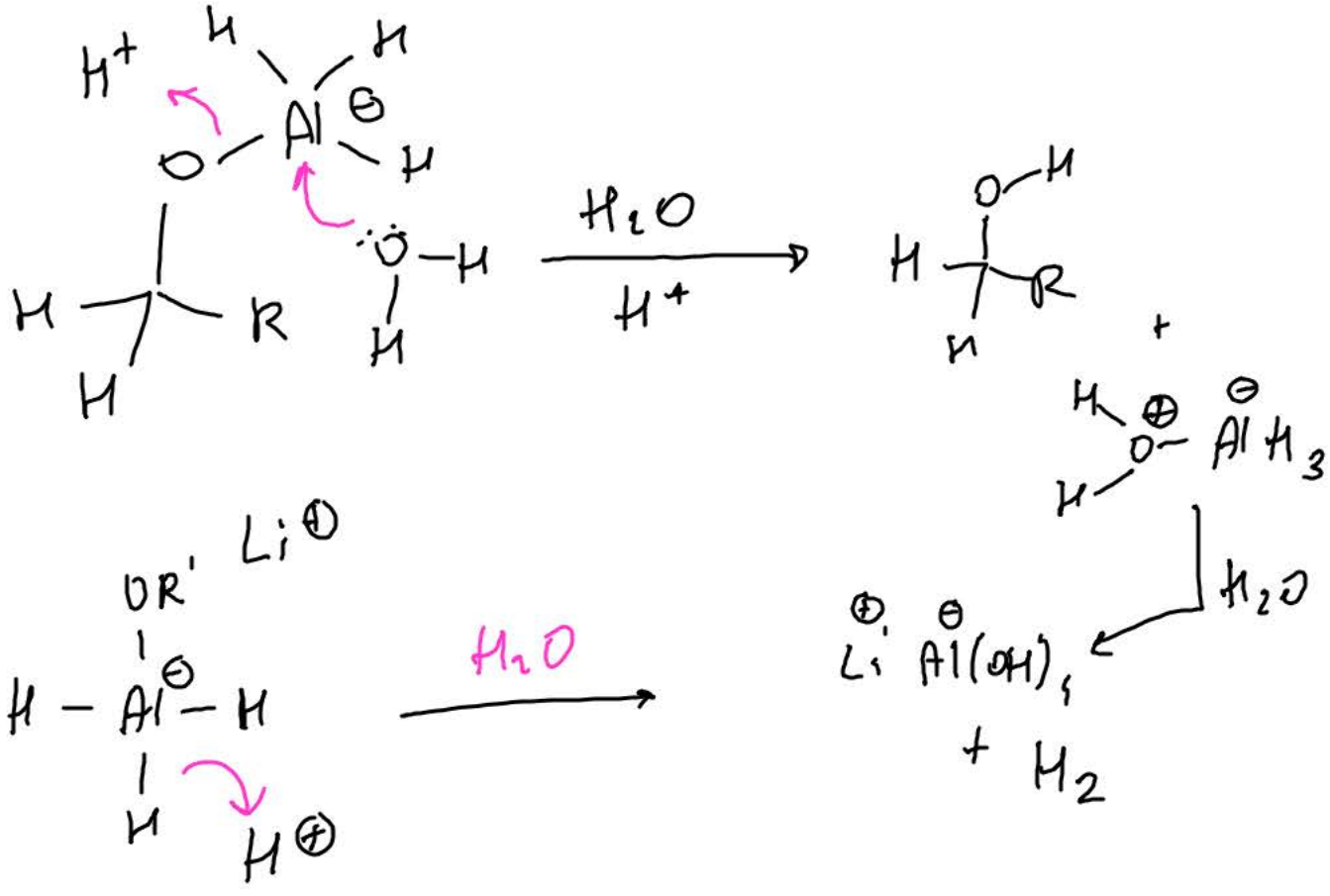
Réduction avec $LiAlH_4$ (dans un solvant not protique)

THF, Et_2O

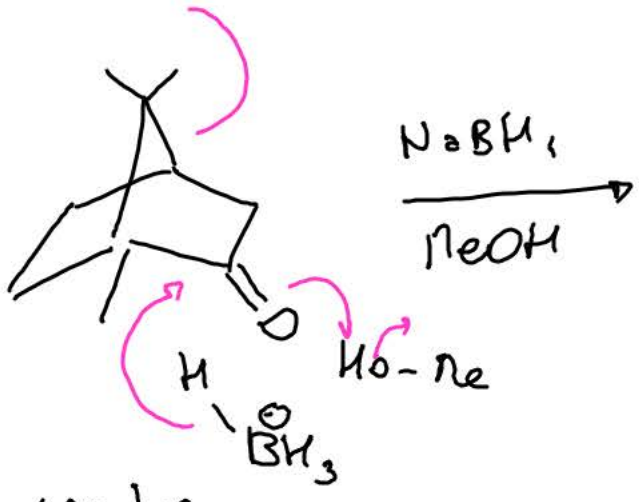


même

mécanisme



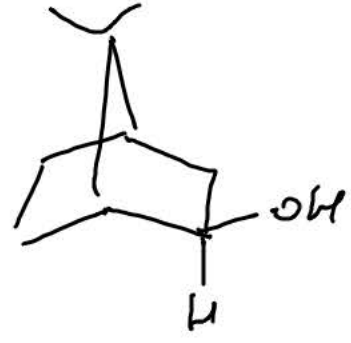
Exemples des TP chimie



camphre

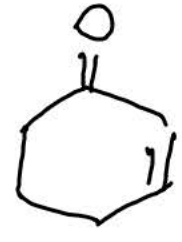
$NaBH_4$

MeOH



en bas

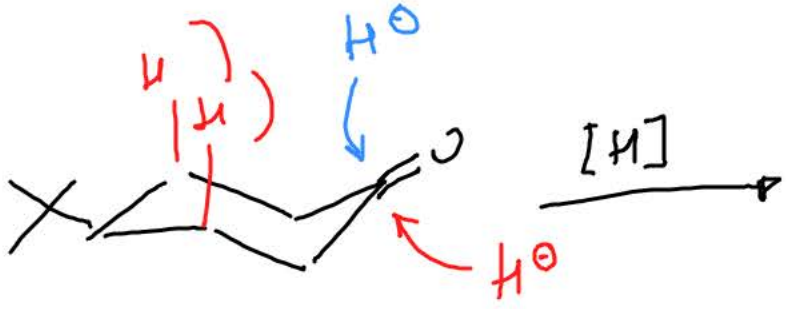
isobornéol

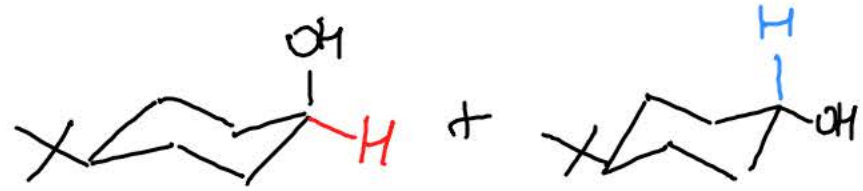


$LiAlH_4$

THF

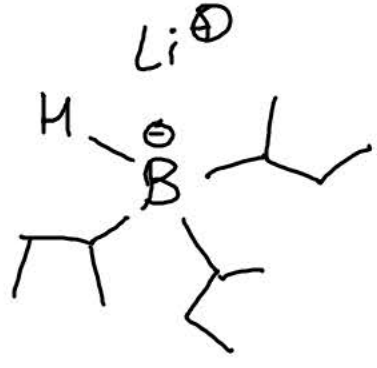
cyclohexenone

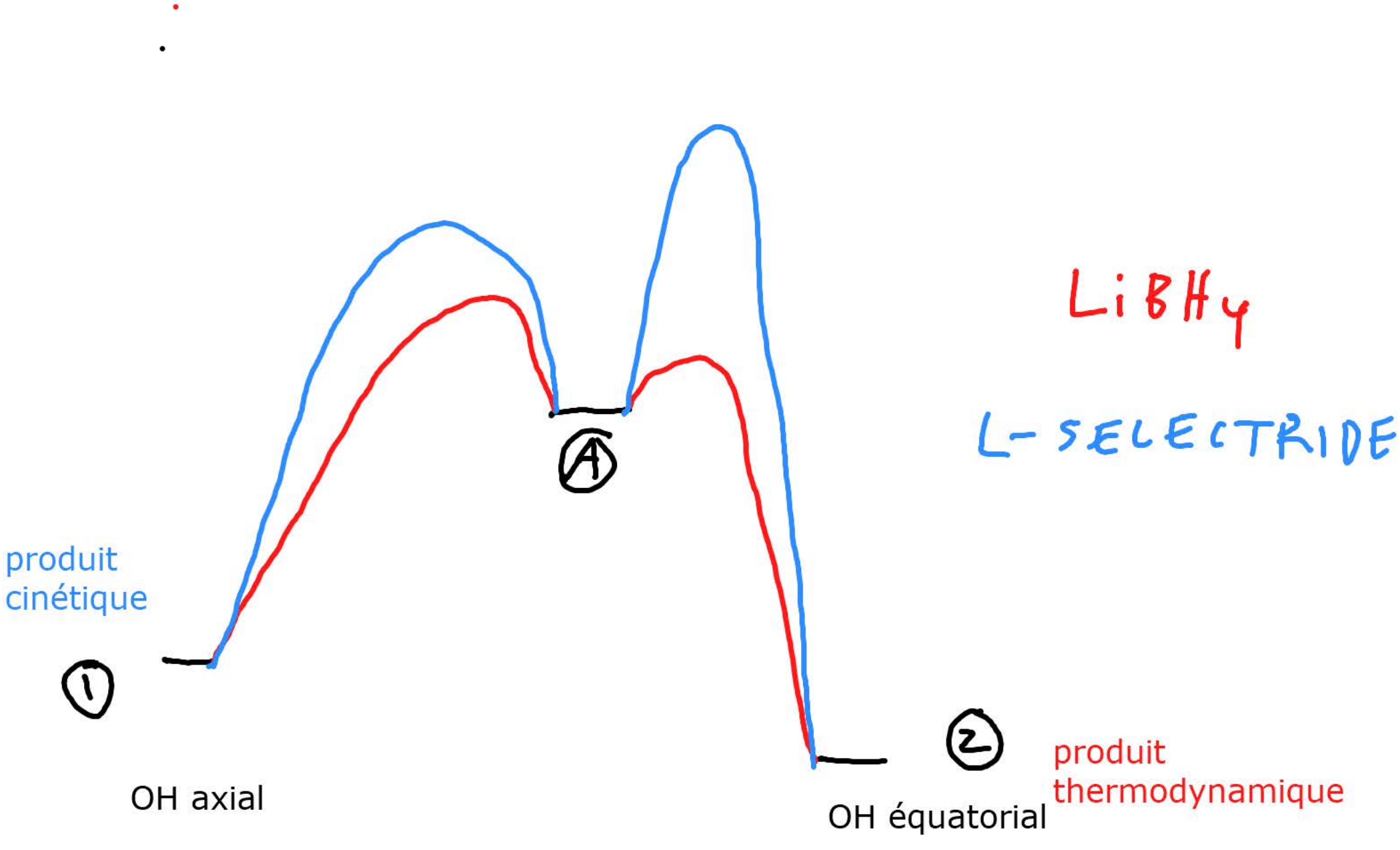




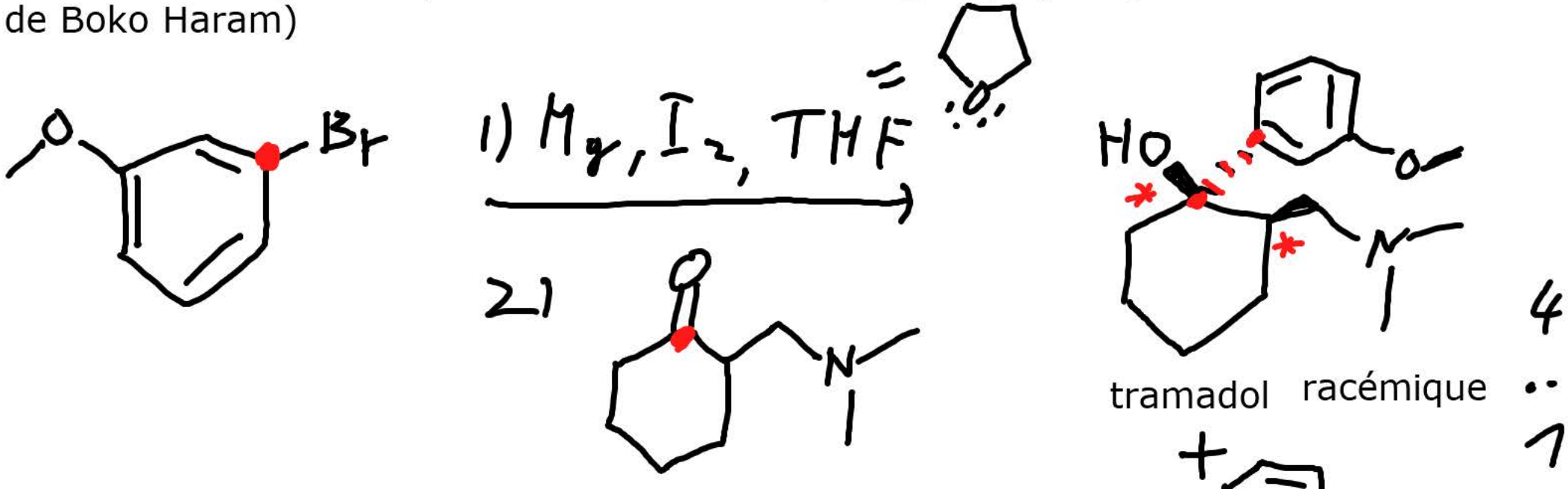
[H] = $LiBH_4$ 9 : 91

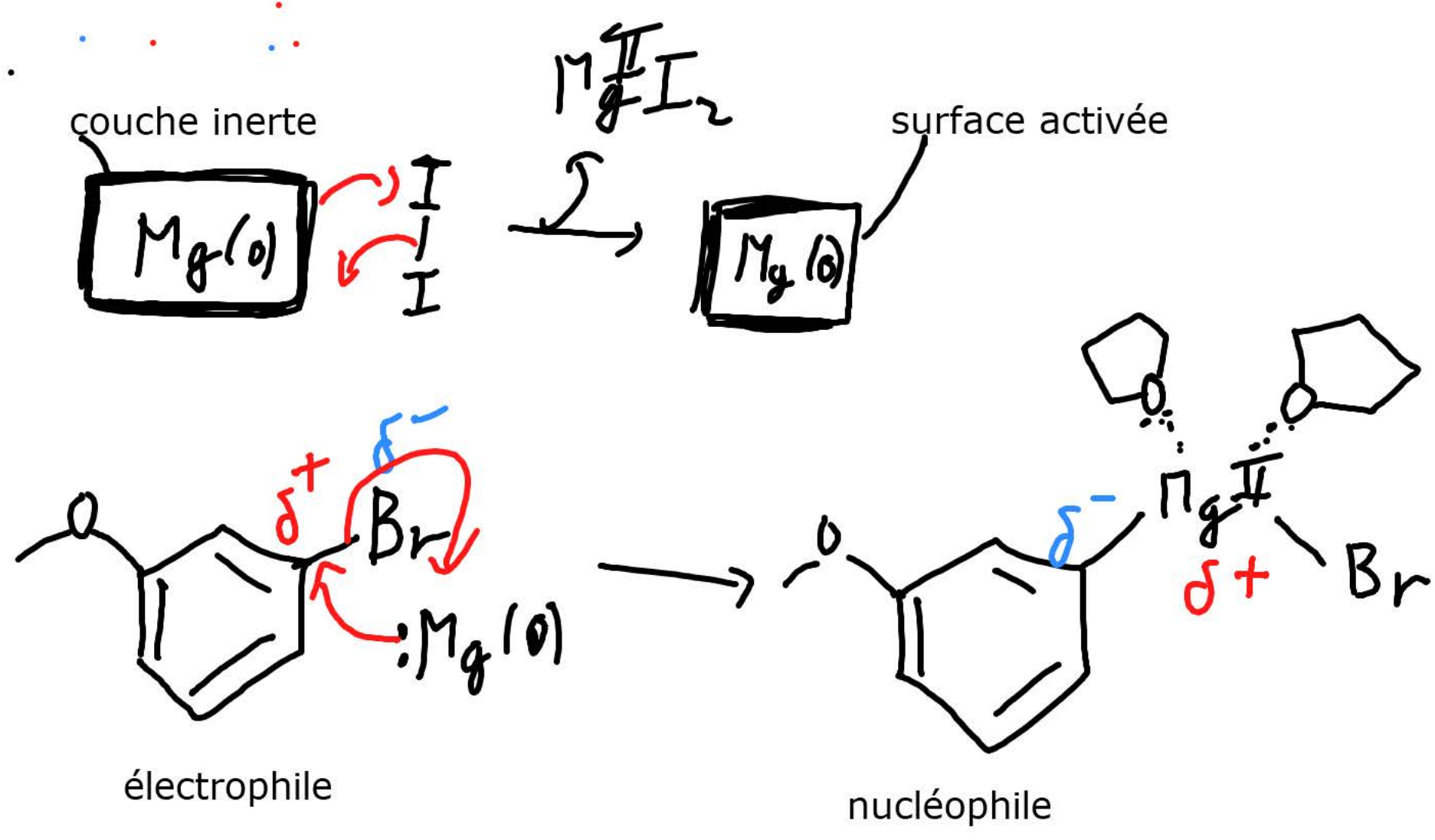
L - selectride 86 : 14



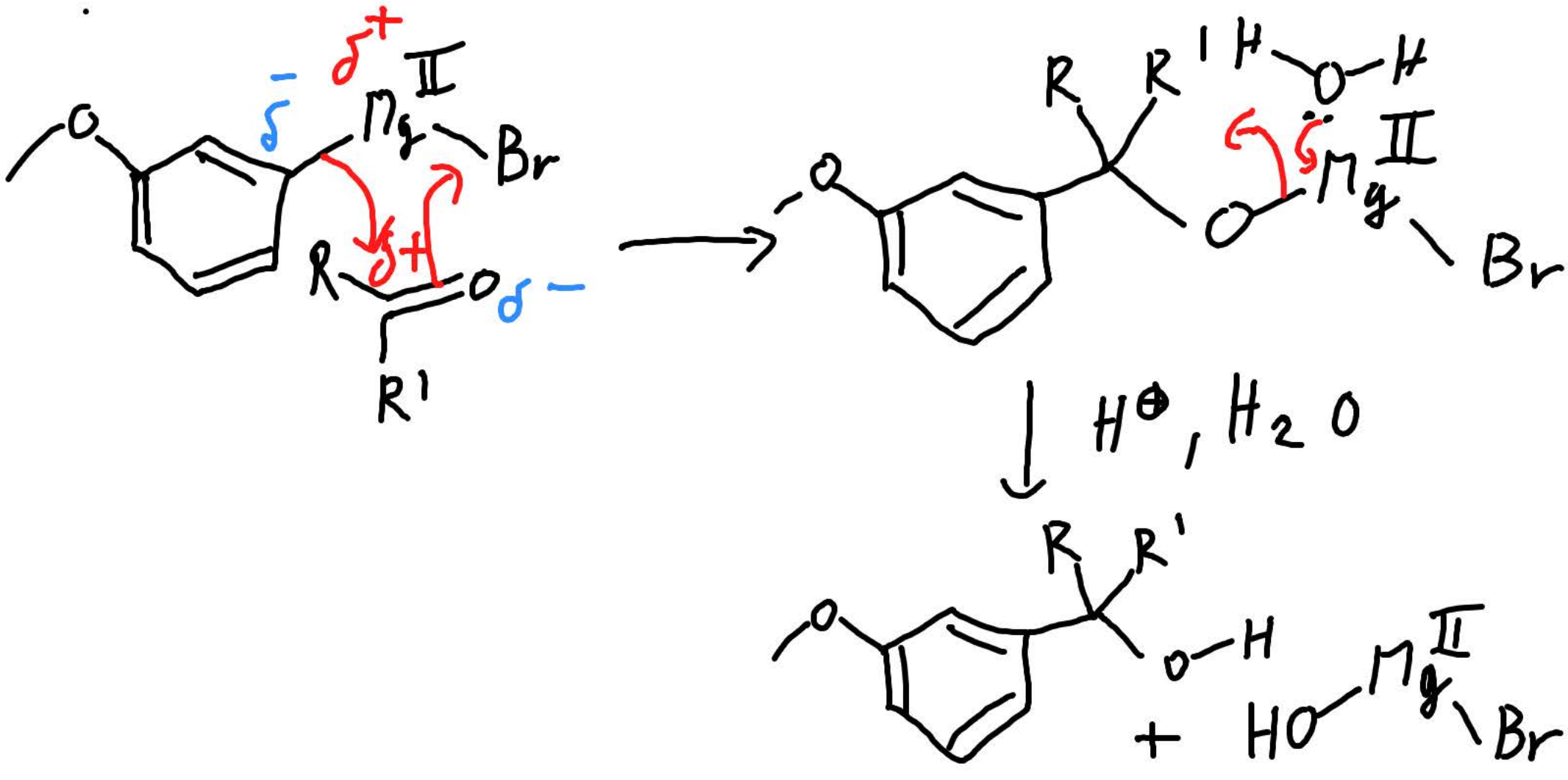

produit
cinétique
1
A
2
produit
thermodynamique
OH axial
OH équatorial
LiBH4
L-SELECTRIDE

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

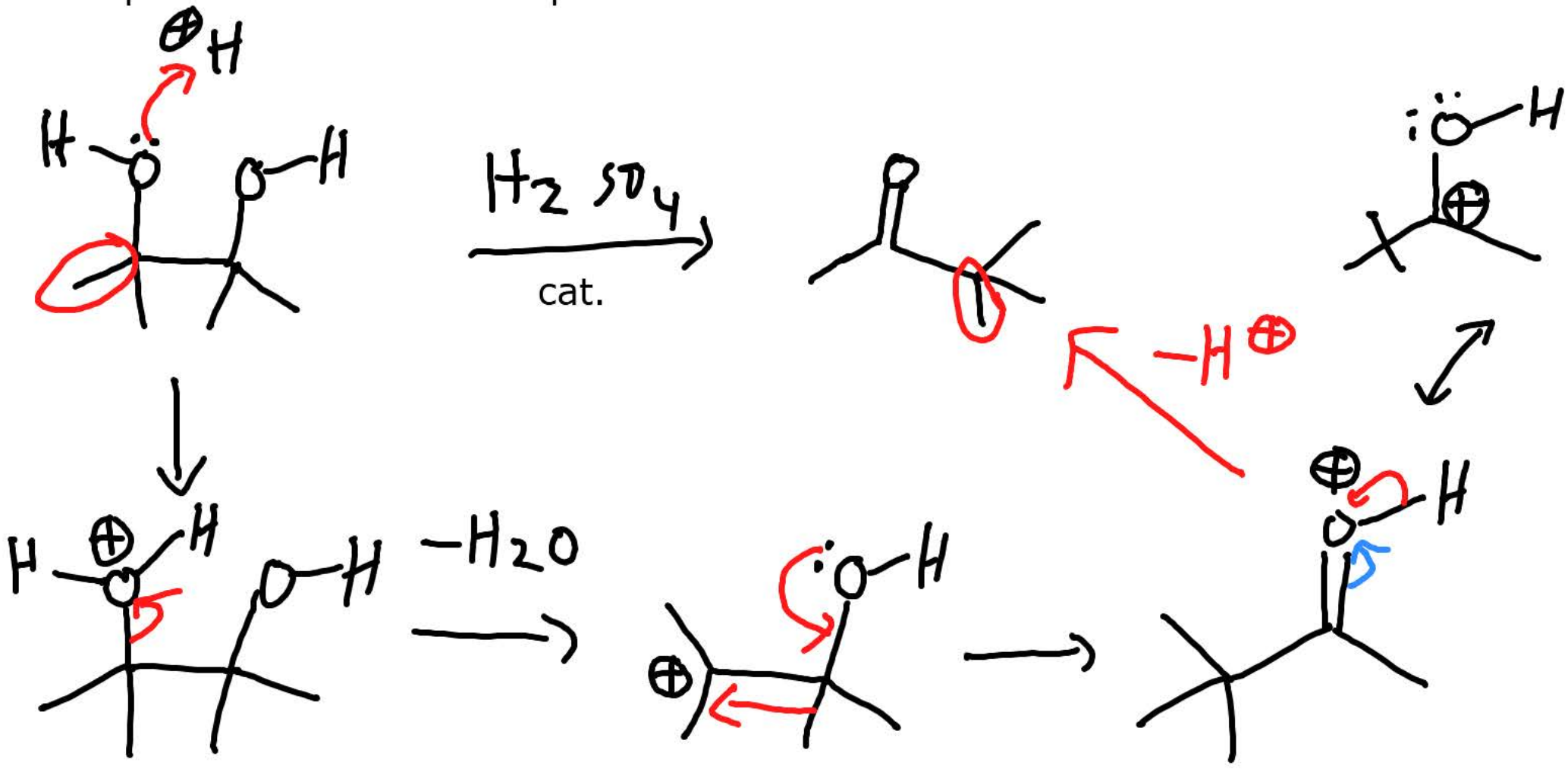




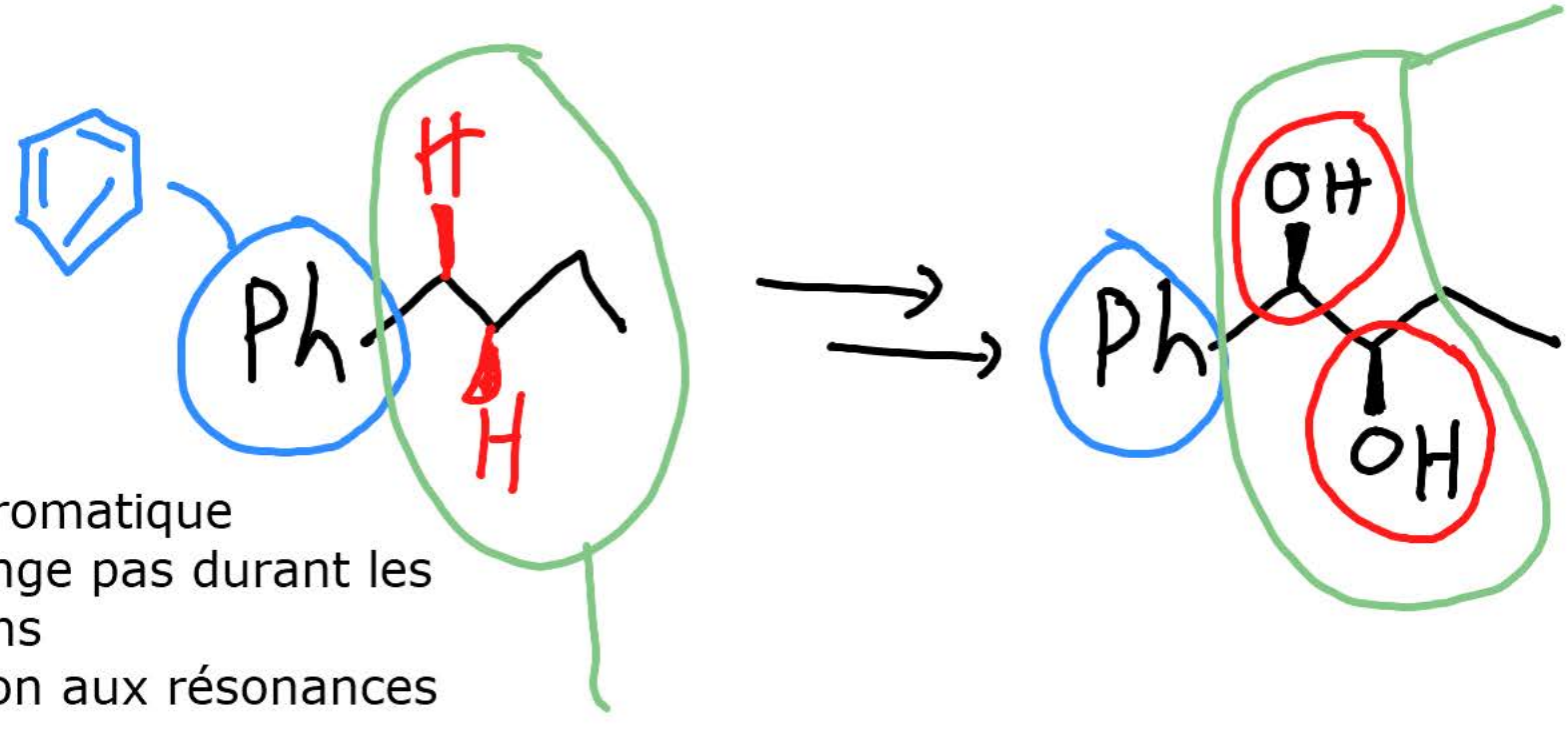
La réactivité est inversée (Umpolung)


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

cas particulier: réaction de pinacol



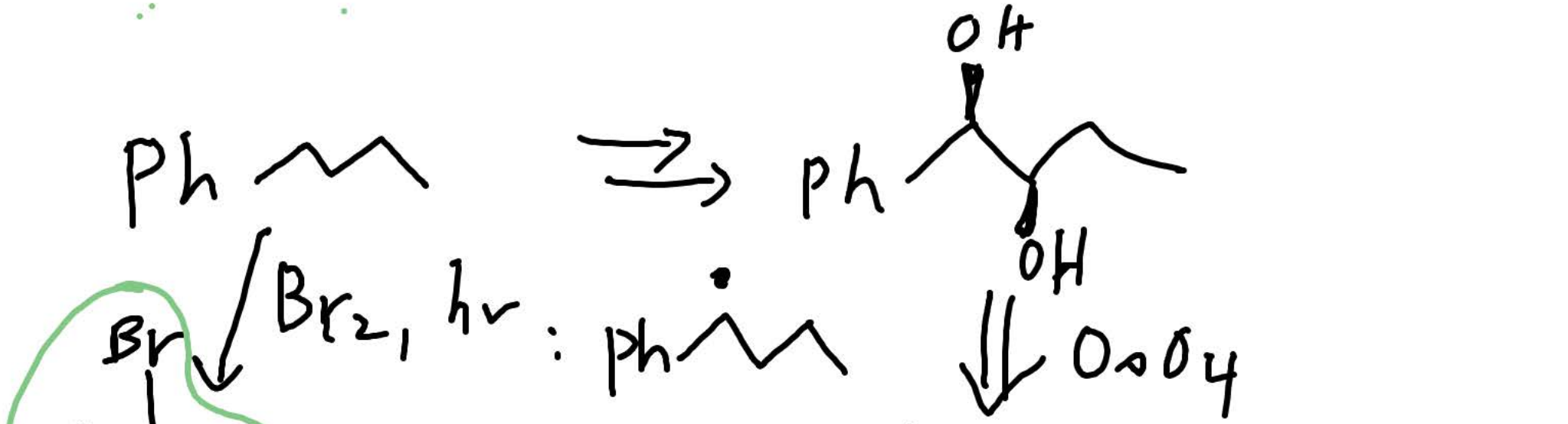
synthèse d'alcools multi-étapes



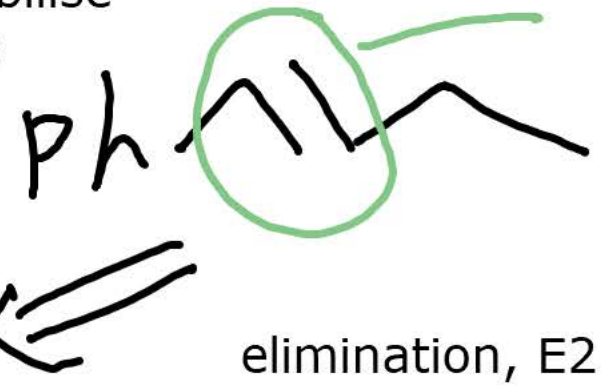
cycle aromatique
ne change pas durant les réactions
Attention aux résonances

liaisons C-H, peu de réactions possibles
Chimie radicalaire

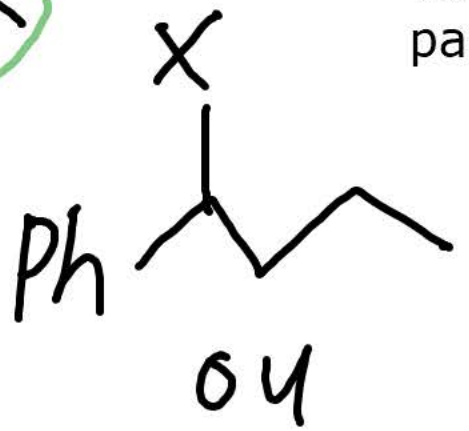
2 alcools
en position 1,2- syn
"signal" pour une dihydroxylation des alcènes avec OsO4



via radical stabilisé
par résonance



double liaison
élimination?

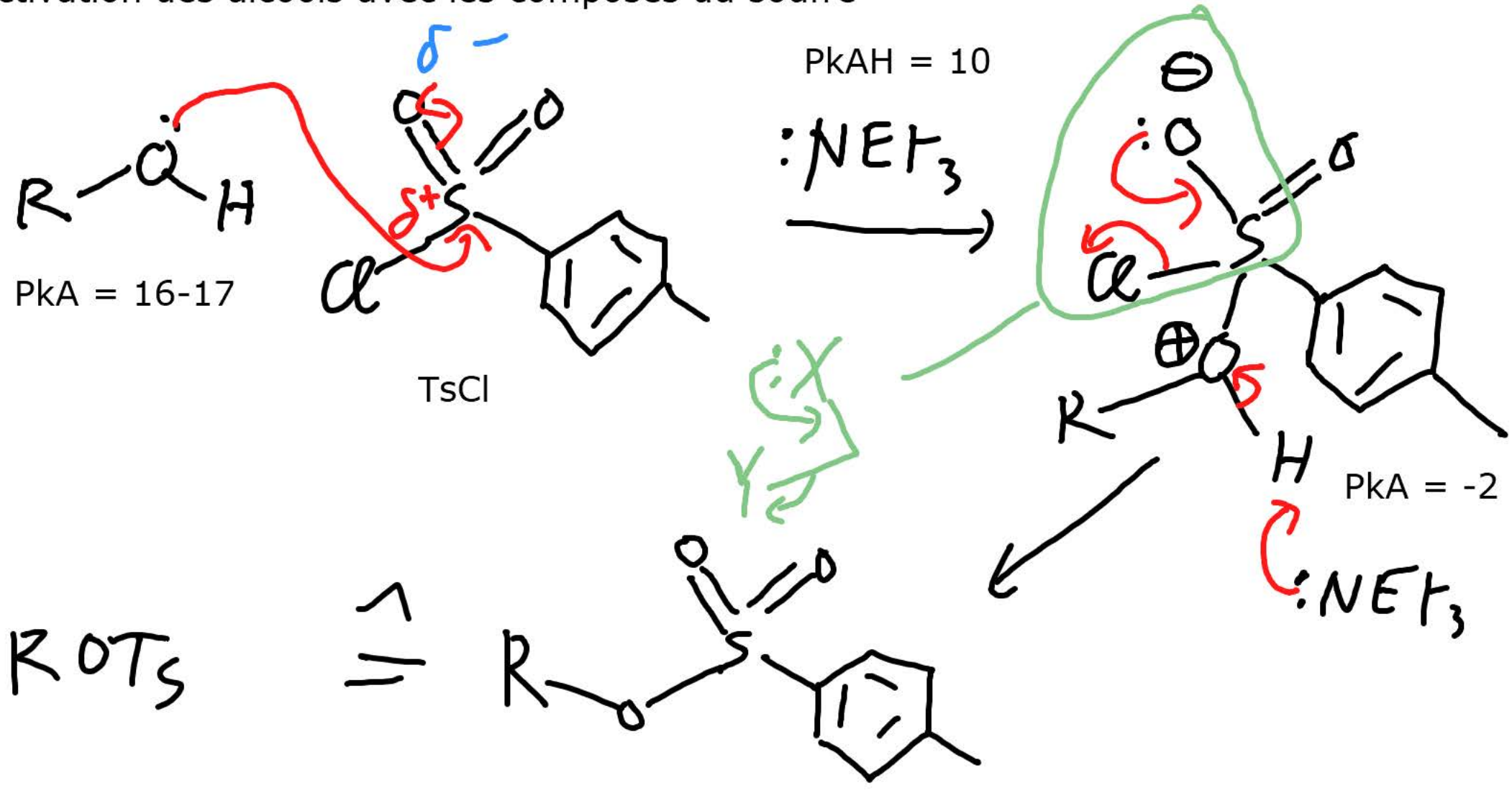


elimination, E2

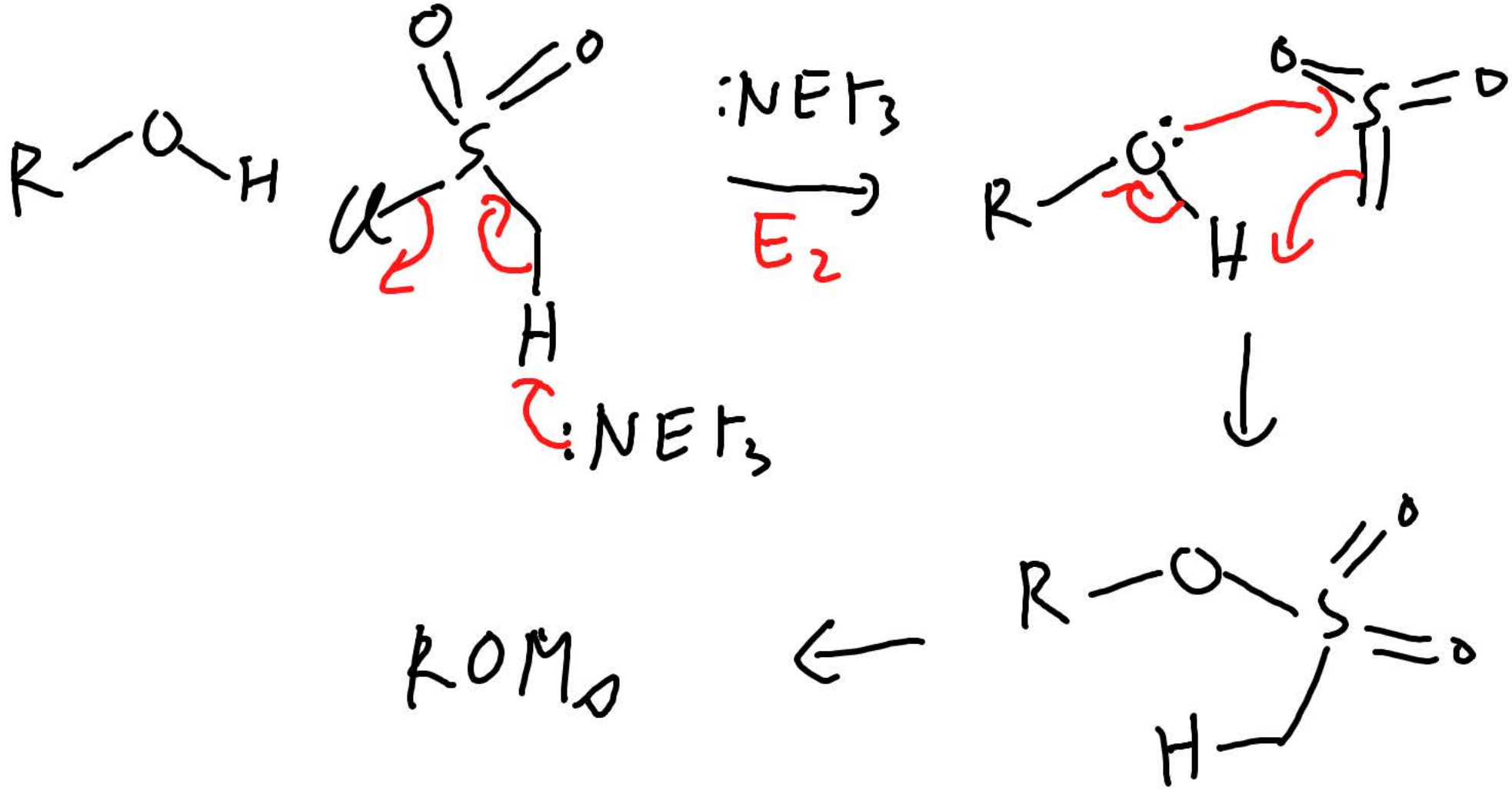
choix de la position et de la
nature de X?

chimie radicalaire introduit halogènes, bon
groupes partants

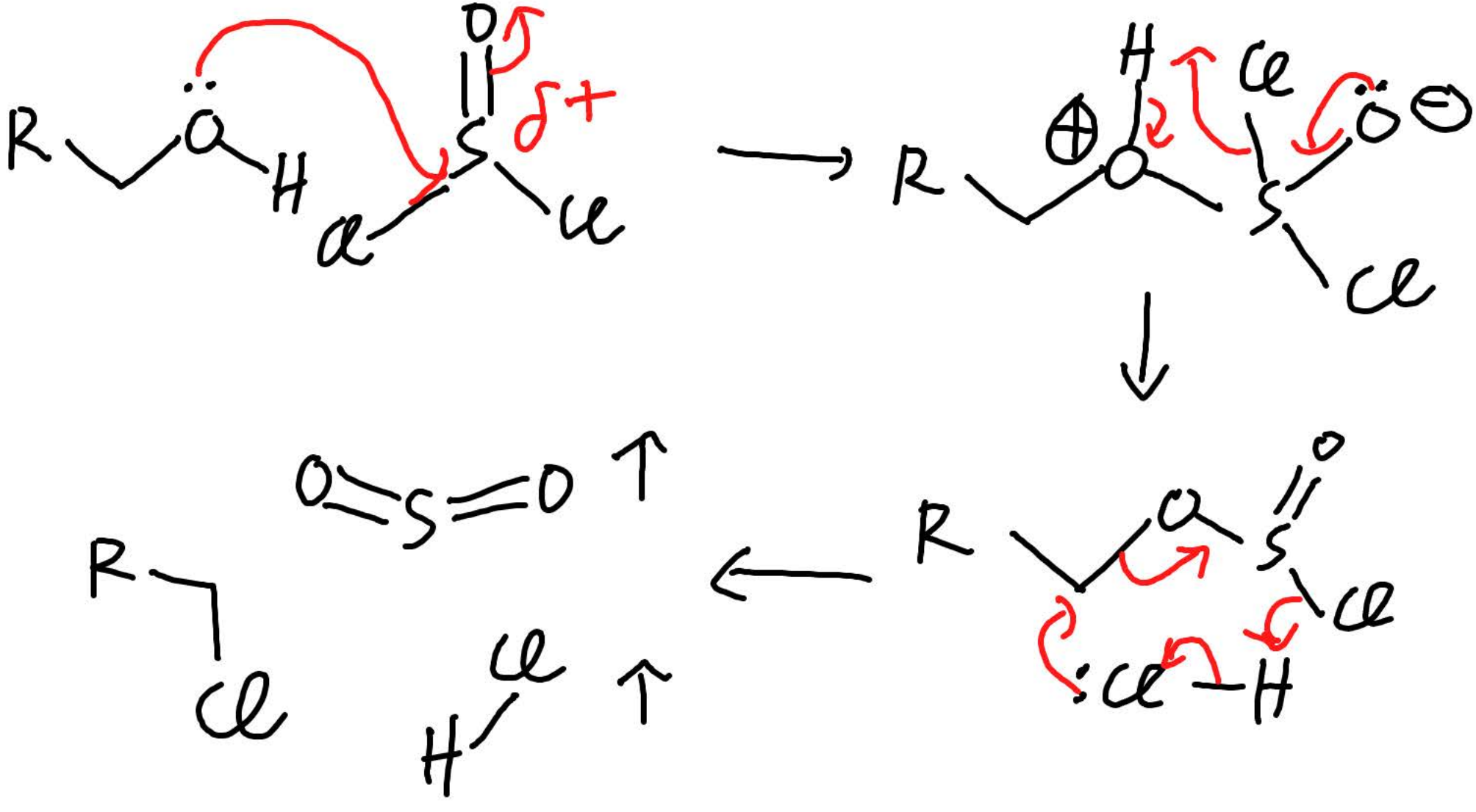
activation des alcools avec les composés du soufre



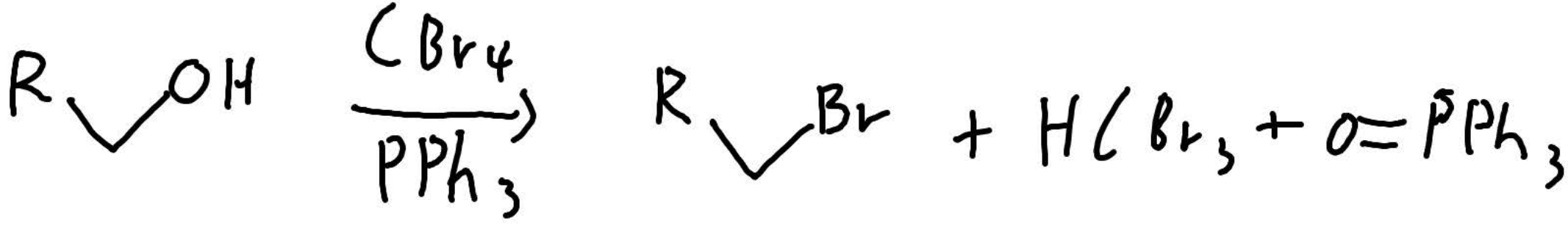
Avec MsCl

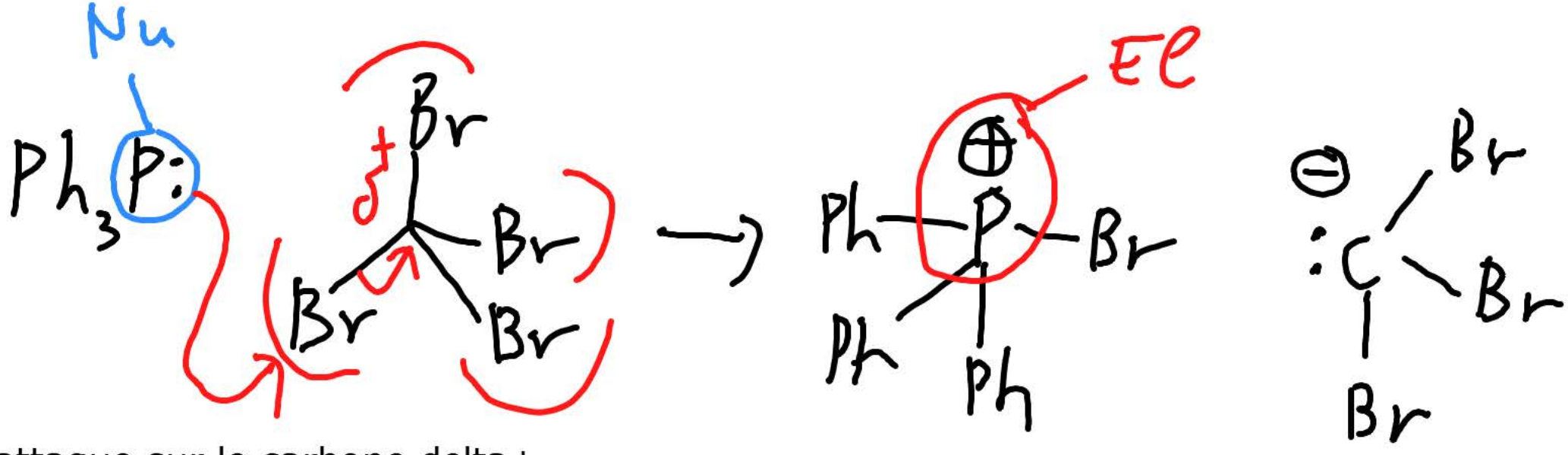


réaction avec SOCl2

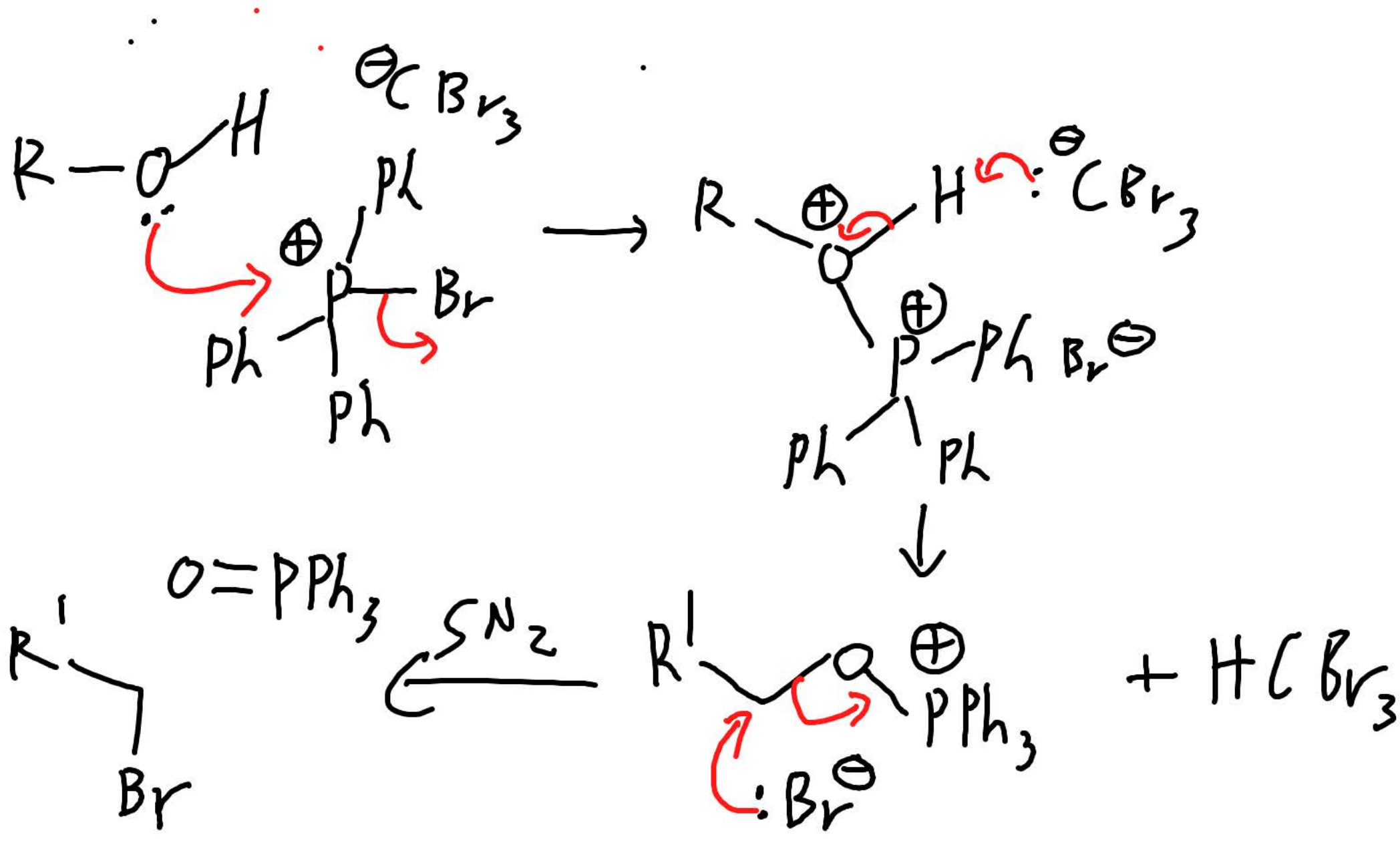


réaction d'Appel

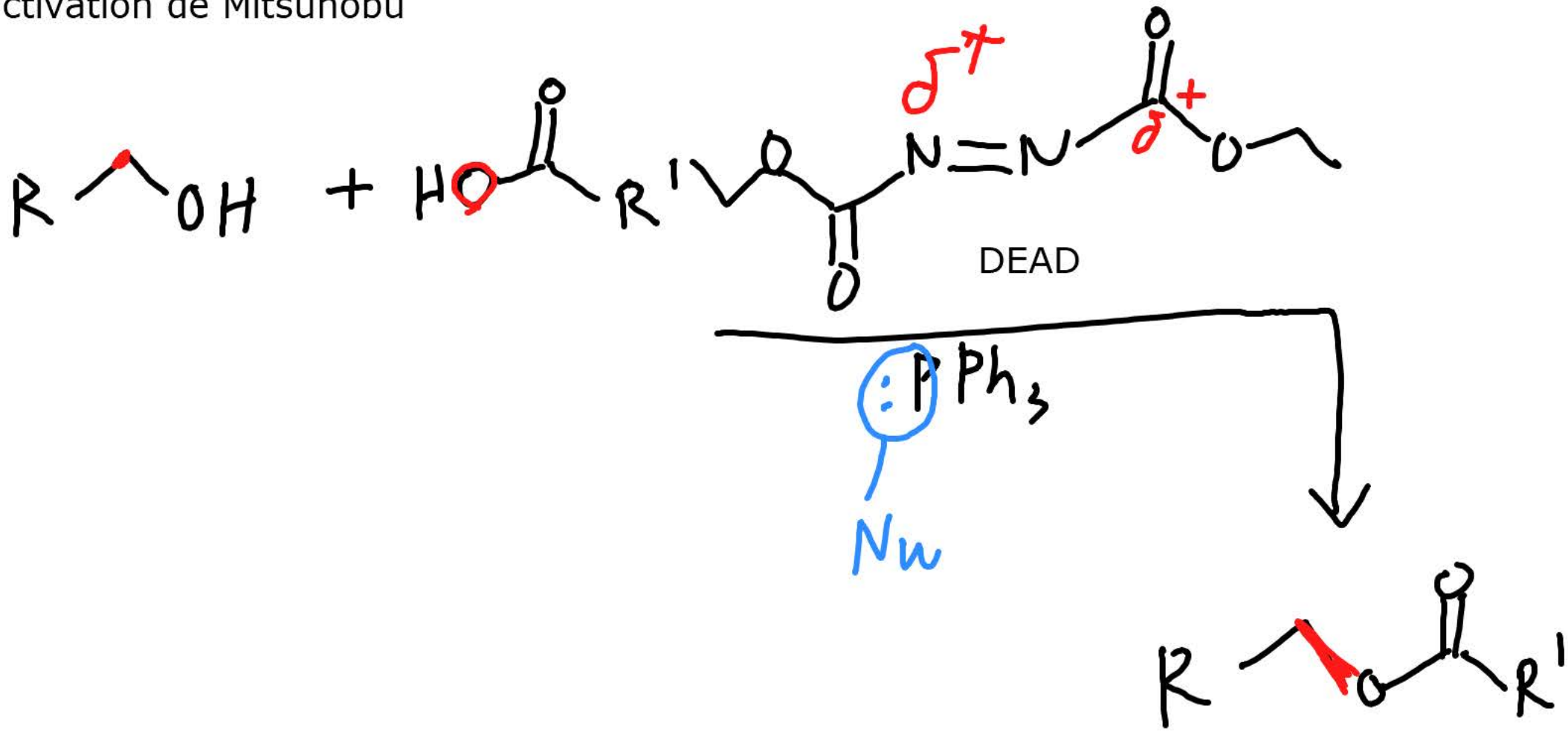


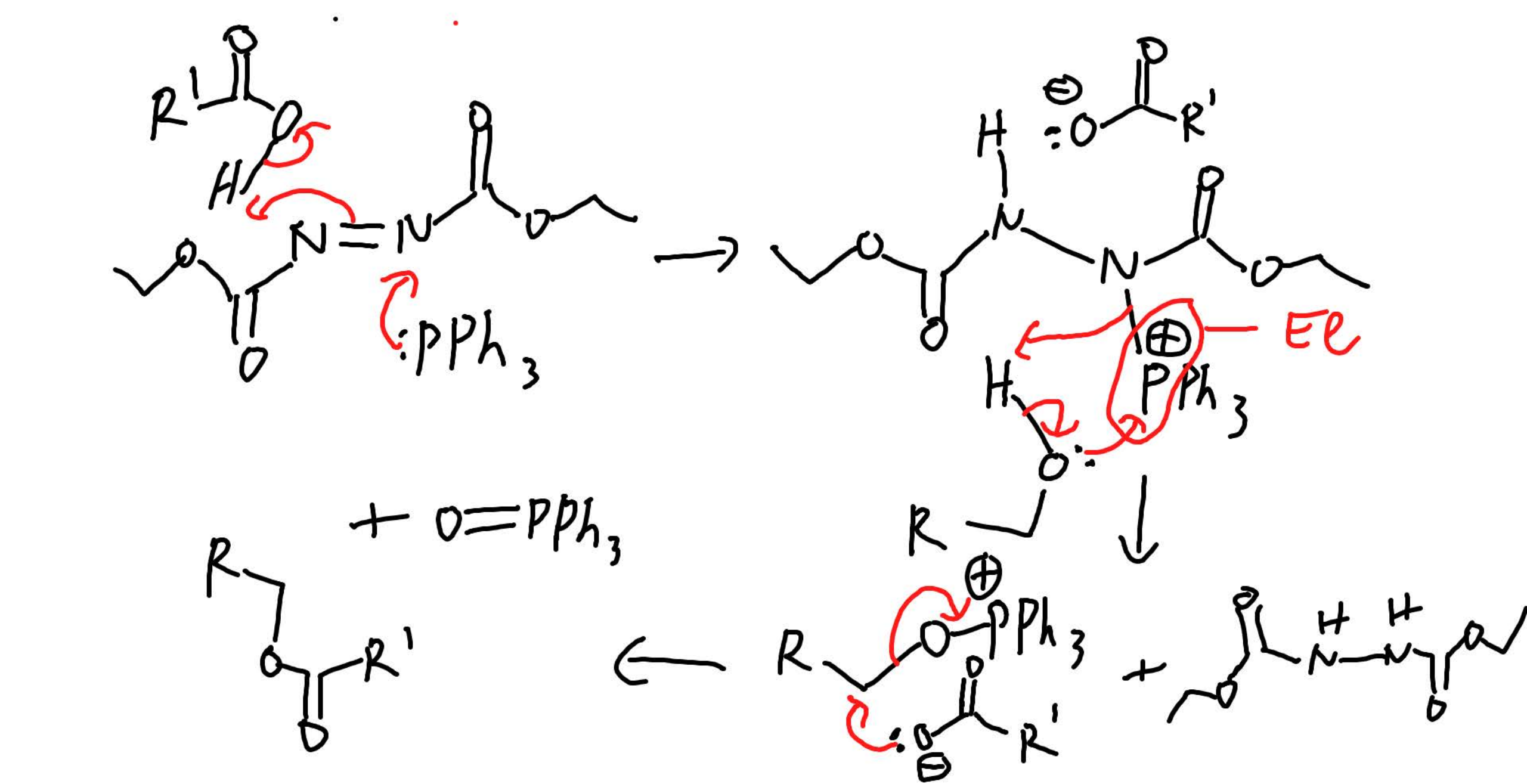


attaque sur le carbone delta+
bloquée! rare exception

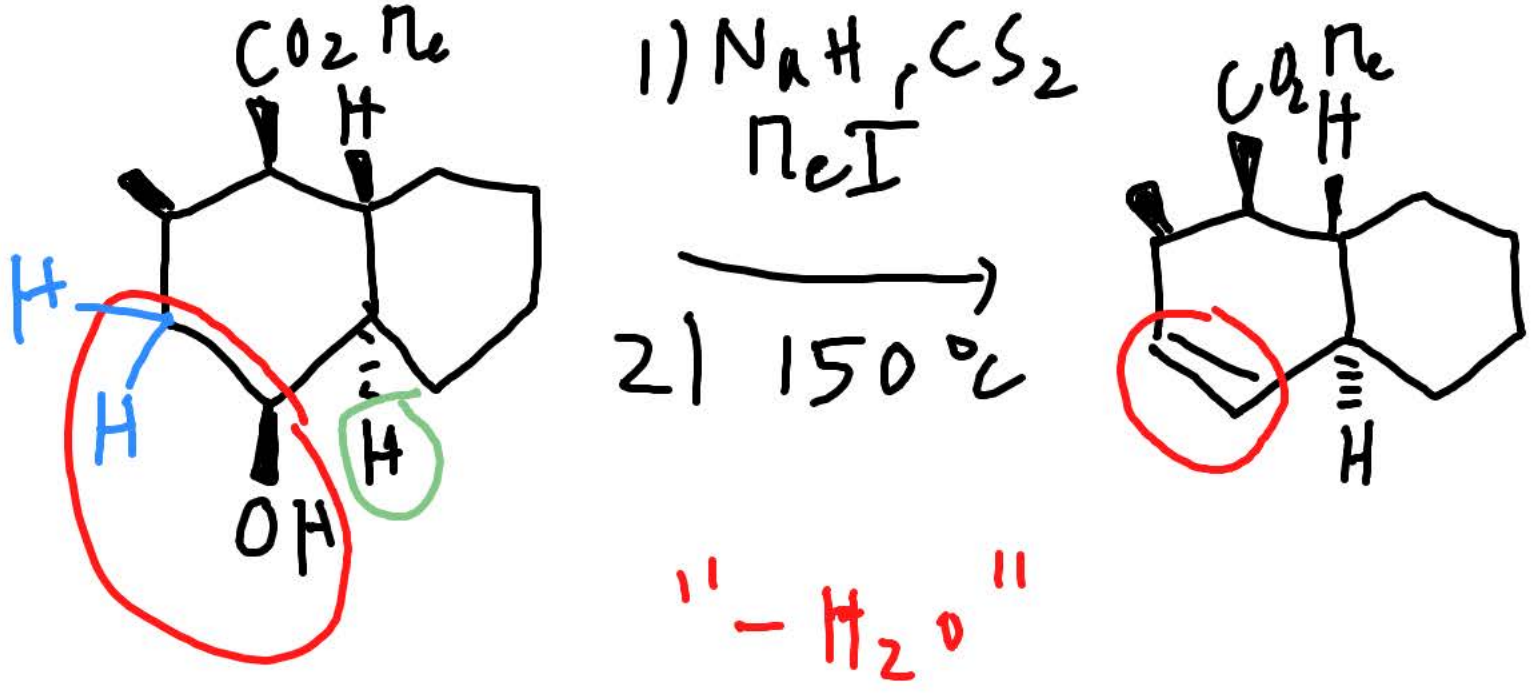

R
O
H
$^{\ominus}CBr_3$
Ph
P
Br
Ph
Ph
$^{\oplus}$
$H^{\ominus}:CBr_3$
$Br^{\ominus}$
$O=PPh_3$
S_N2
R'
Br
PPh_3
$:Br^{\ominus}$
$+ HCBr_3$

activation de Mitsunobu



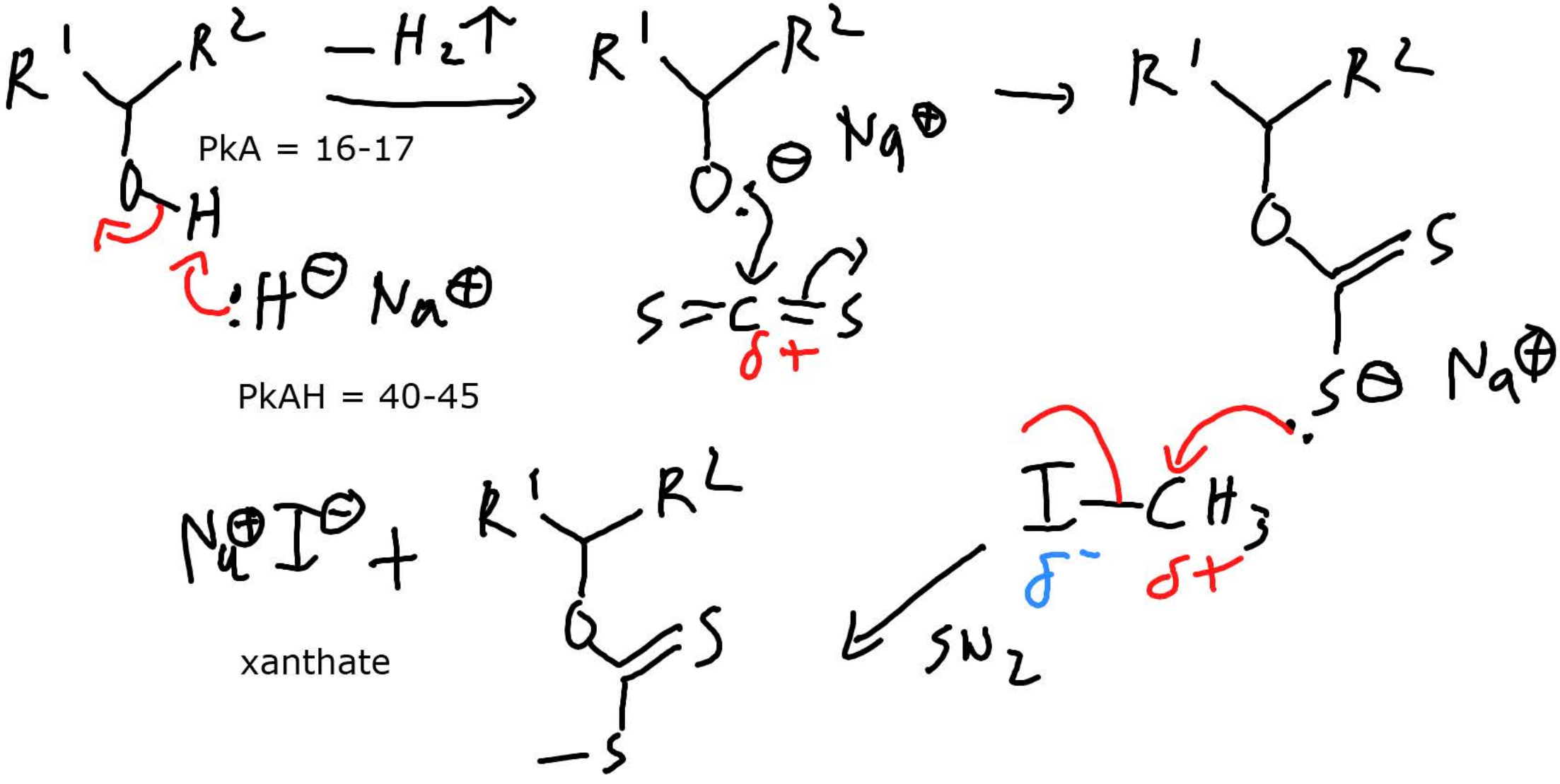

R1
H
N=N
:PPh3
H
R'
Et
PPh3
R
+ O=PPh3
R
R'
R
PPh3
R'

élimination selon Chugaev, application à la synthèse de Solanapyrone E

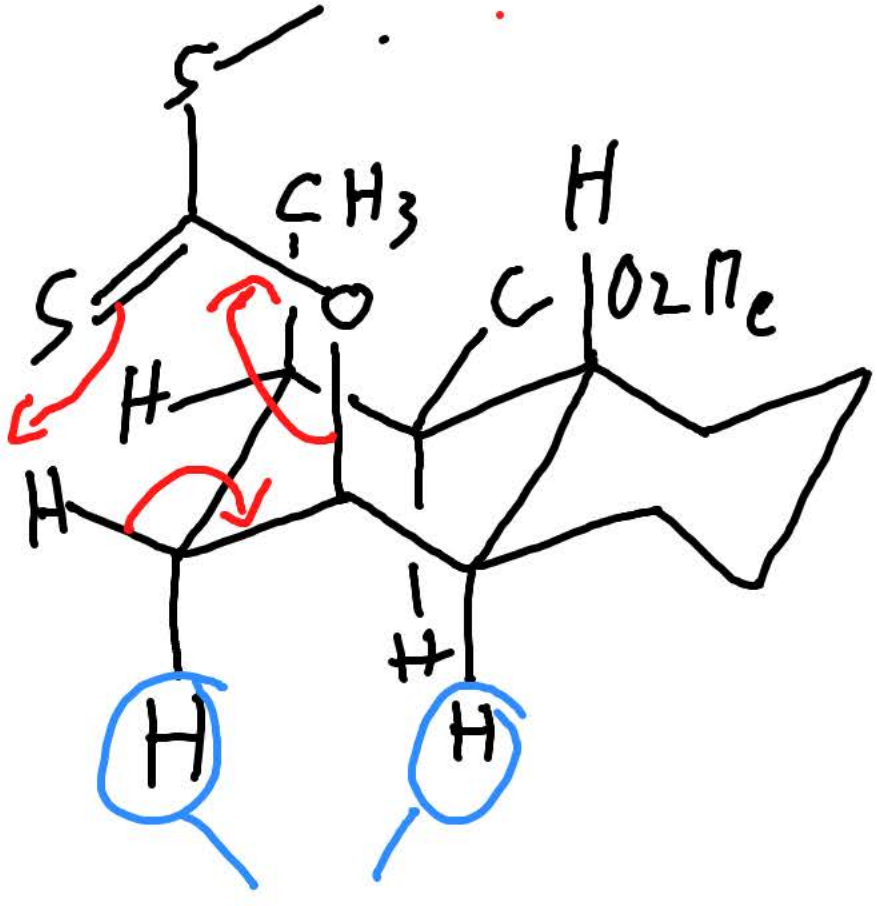


élimination d'eau

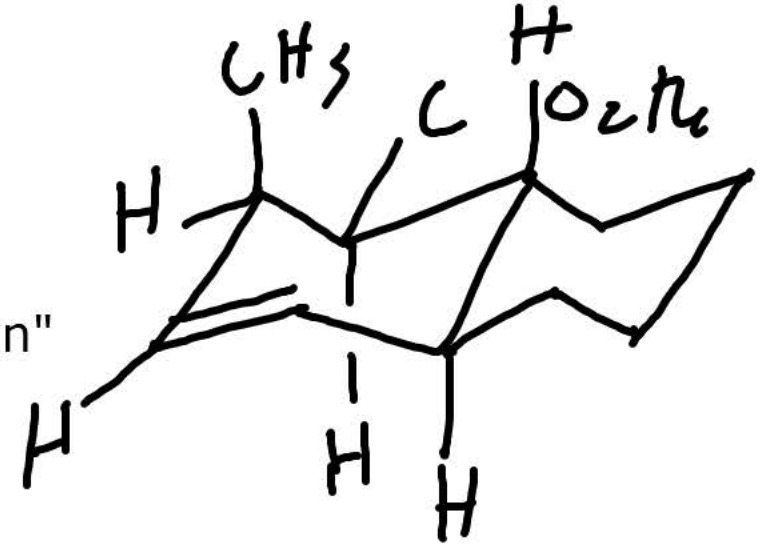
1) étape d'activation



élimination avec situation de trans-decaline

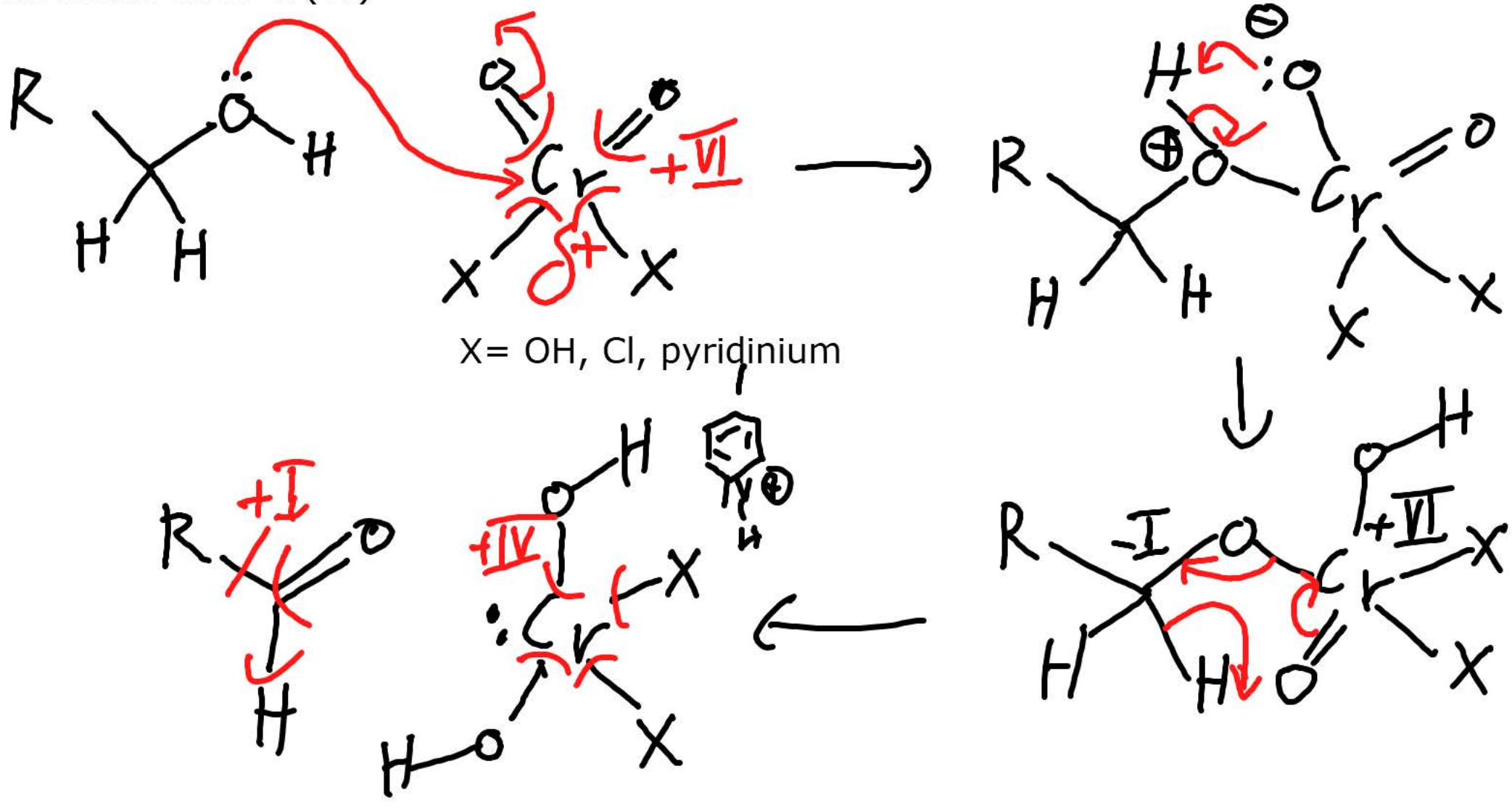


élimination "syn"



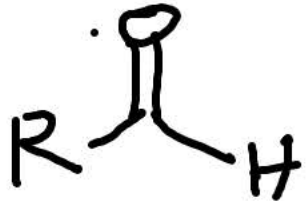
angle idéal pour E2, mais très
loin de S=C

oxidation avec Cr(VI)

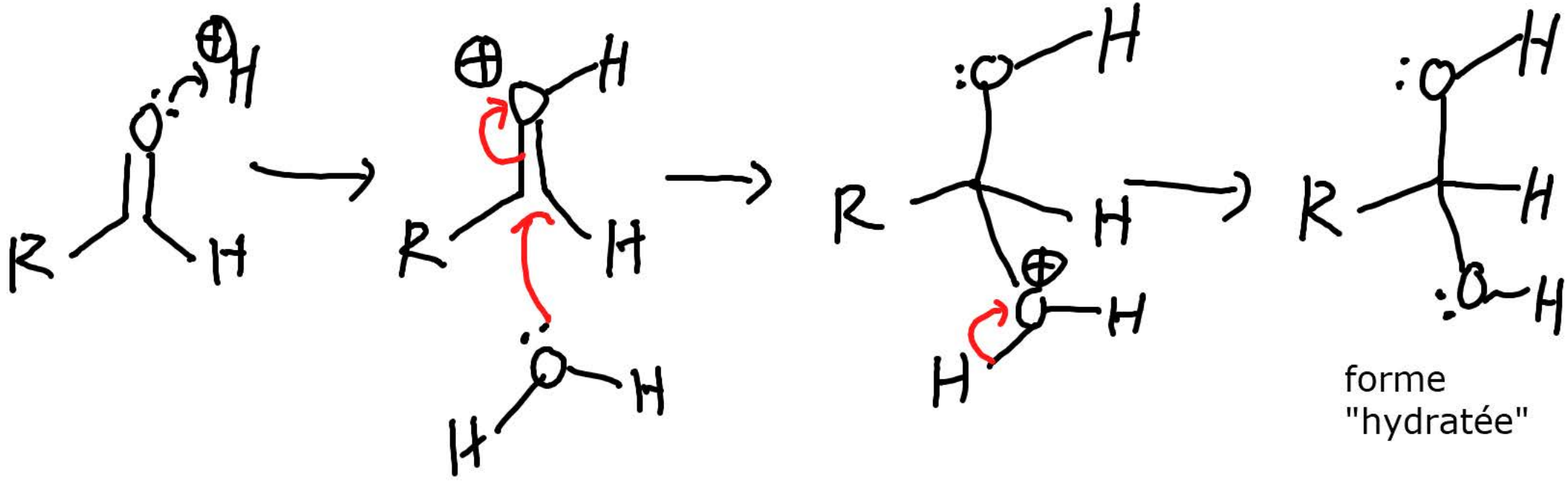


X= OH, Cl, pyridinium

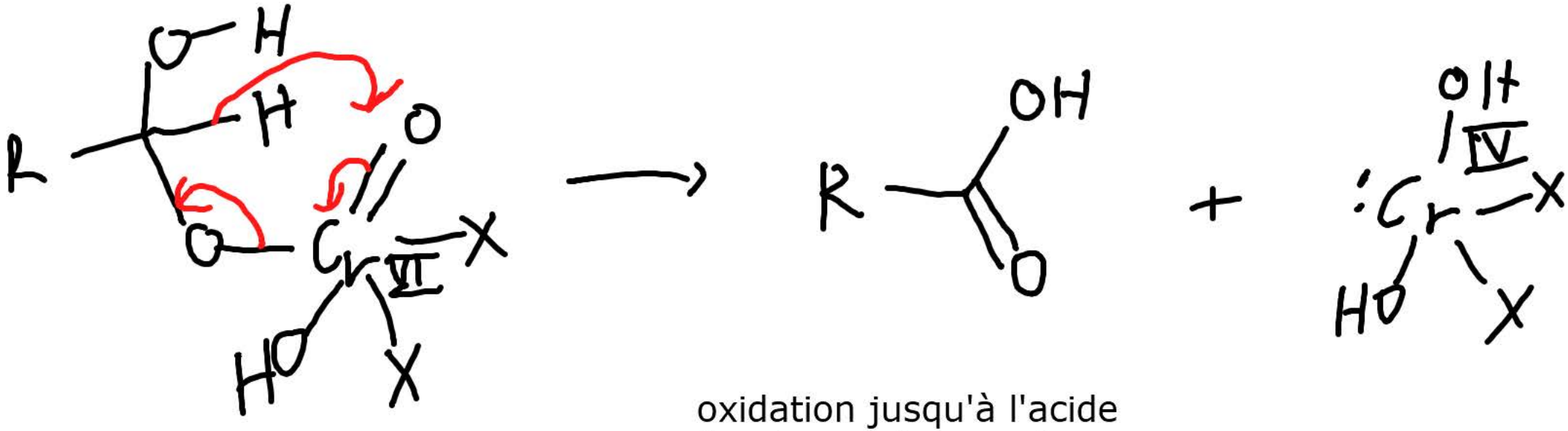
Oxidation des aldéhydes avec Cr(VI)



en général pas oxidés par Cr(VI), sauf en présence d'acide et d'eau



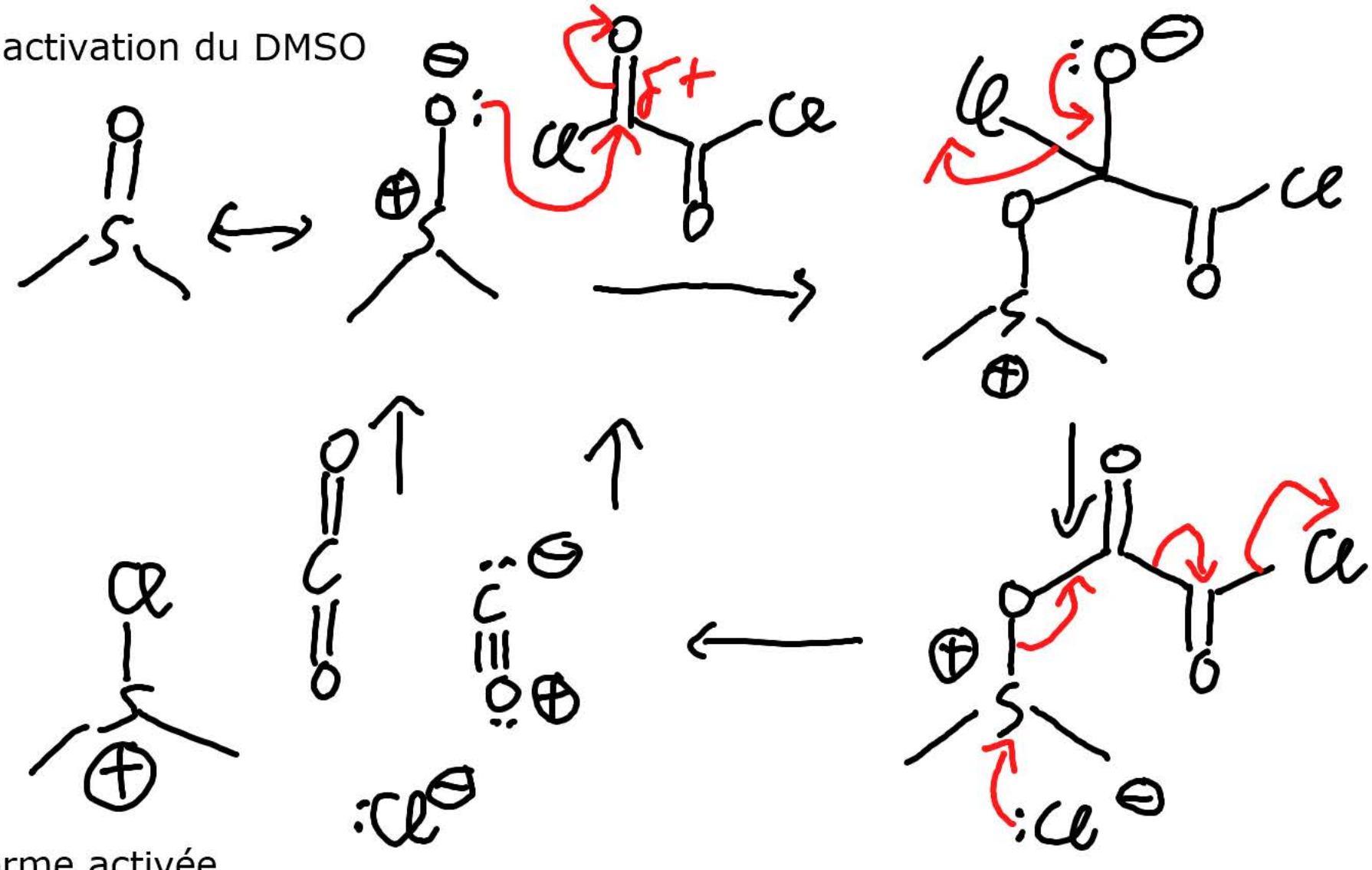
forme "hydratée"



oxidation jusqu'à l'acide
(oxidation de Jones)

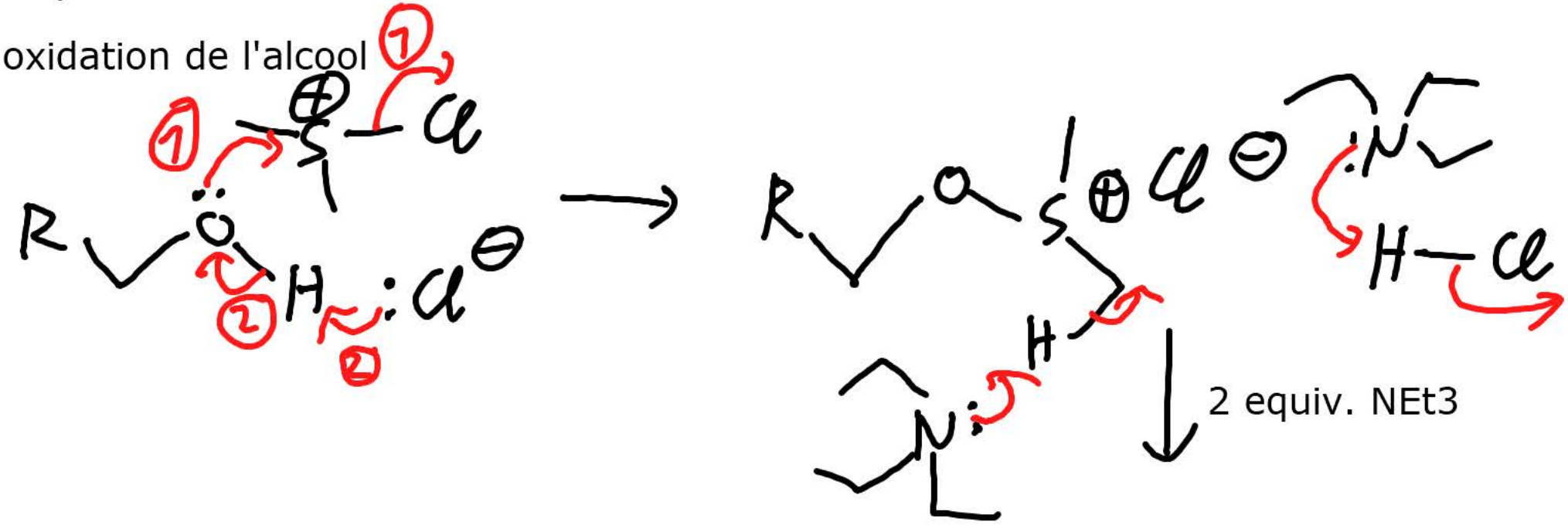
oxidation de Moffat-Swern: Le DMSO comme oxidant

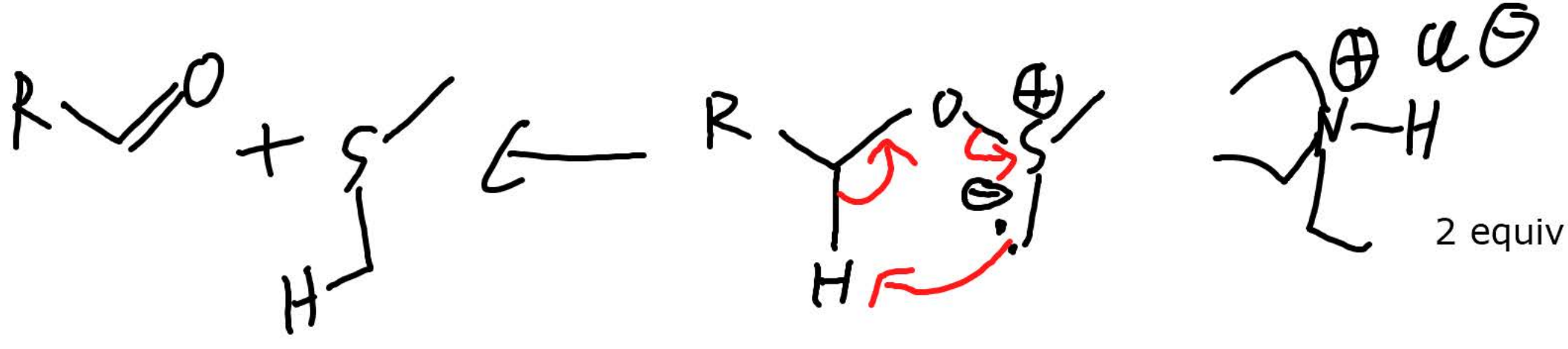
1) activation du DMSO



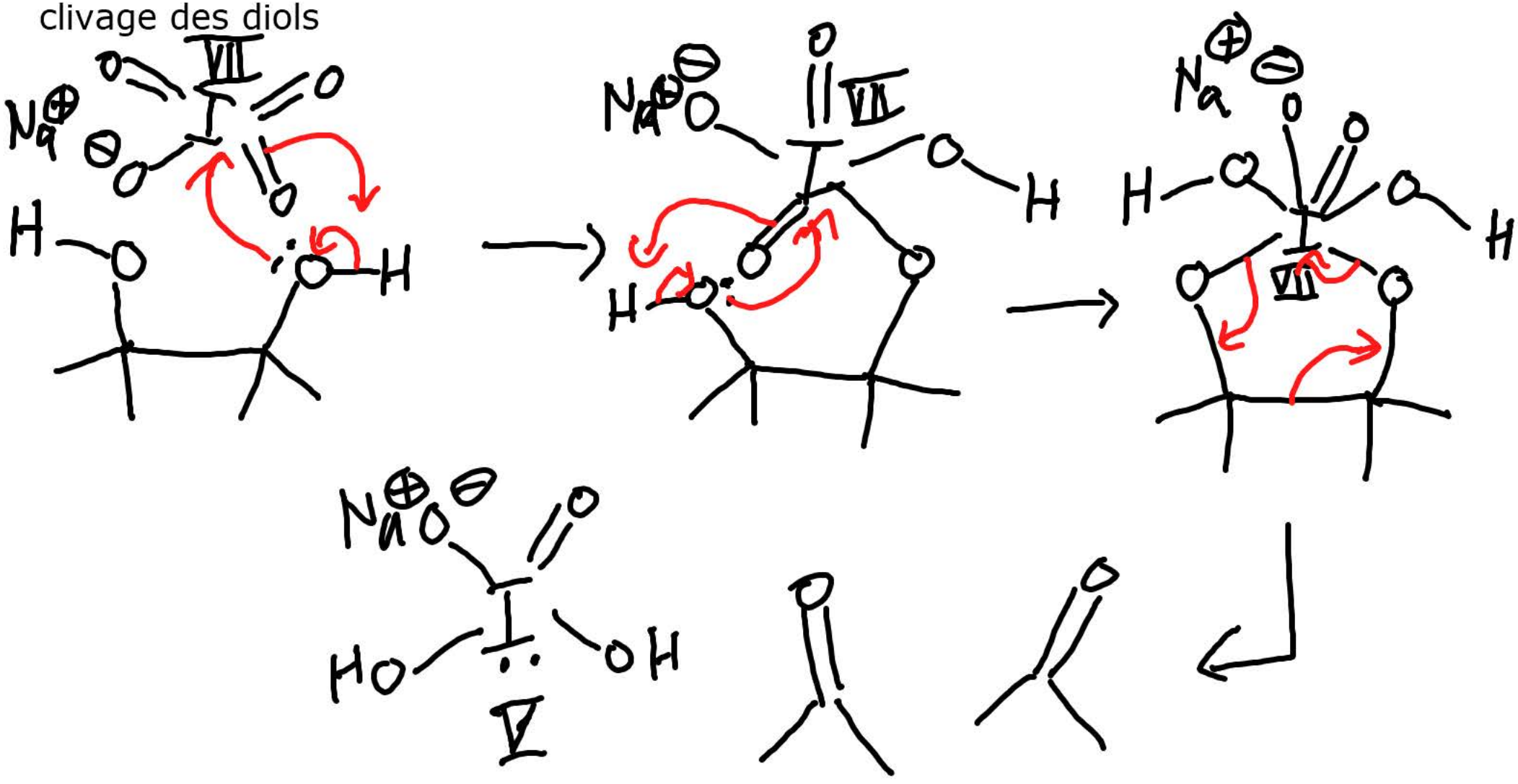
forme activée

2) oxidation de l'alcool



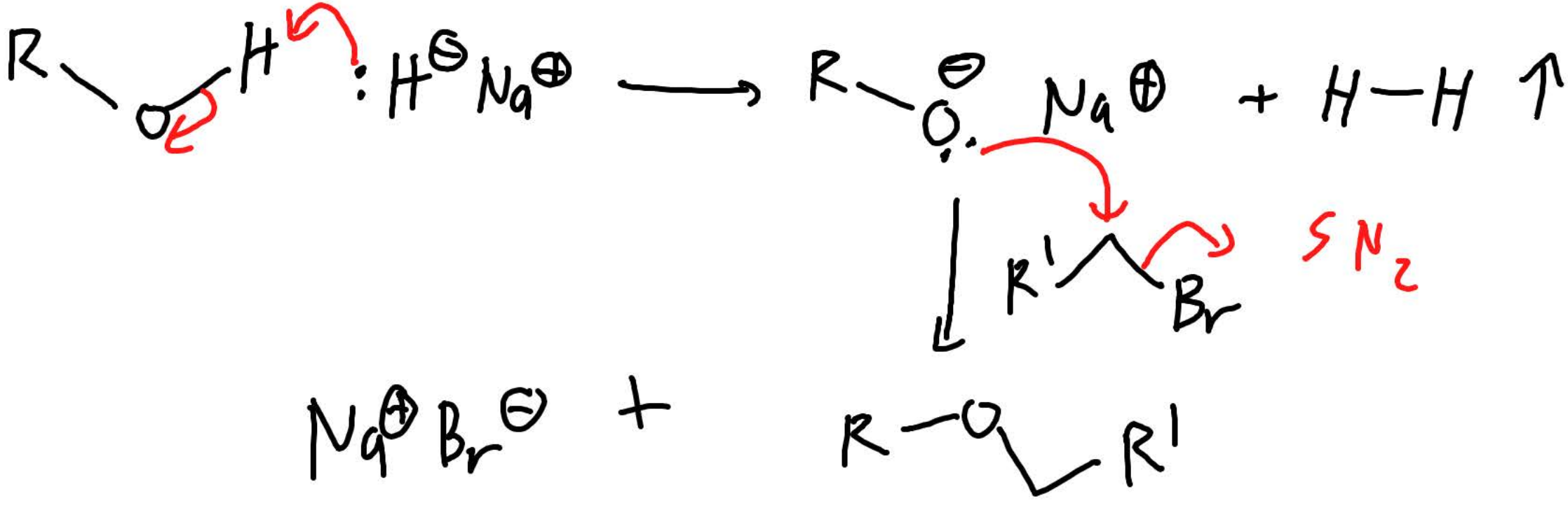


clivage des diols

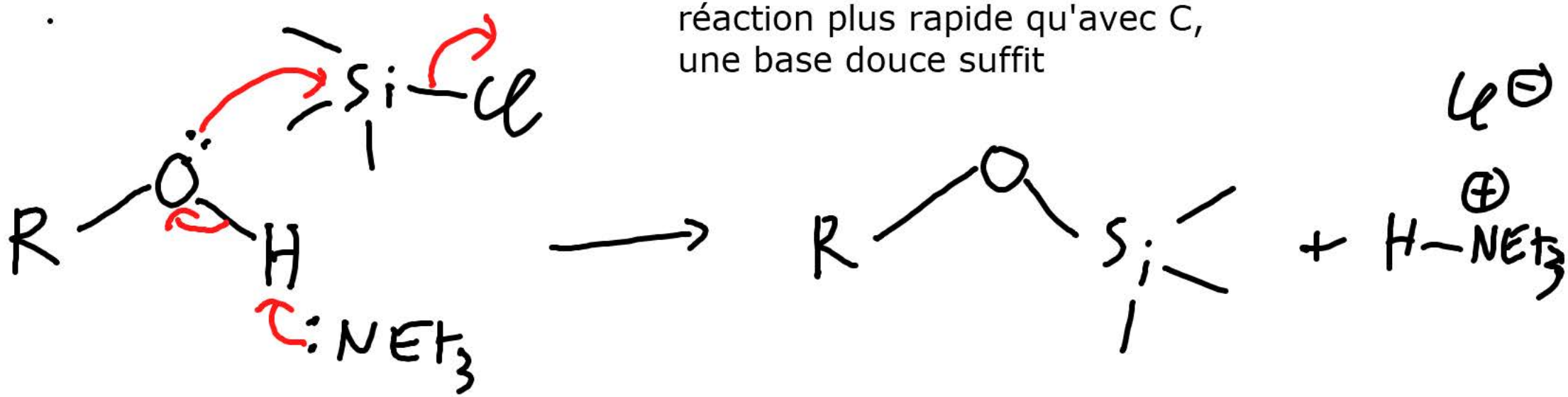


oxidation des cis-1,2-diols

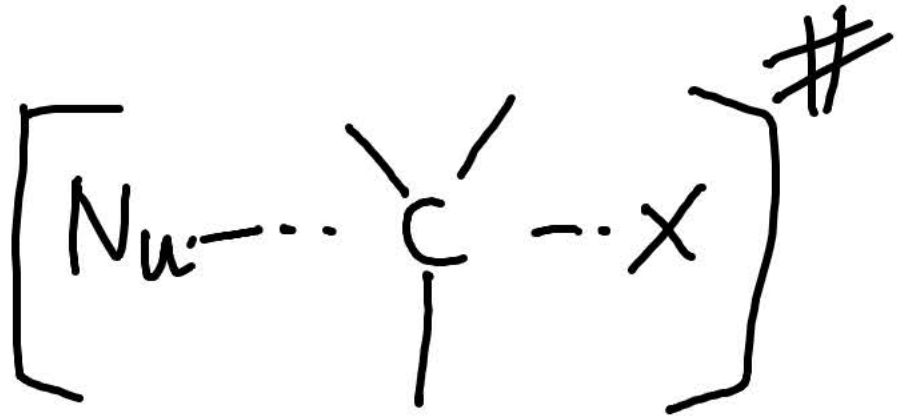
synthèse des éthers de Williamson



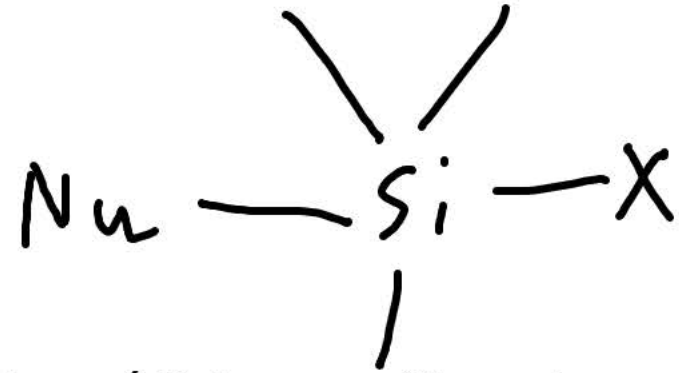
éther de silyl: 1) installation



réaction plus rapide qu'avec C,
une base douce suffit

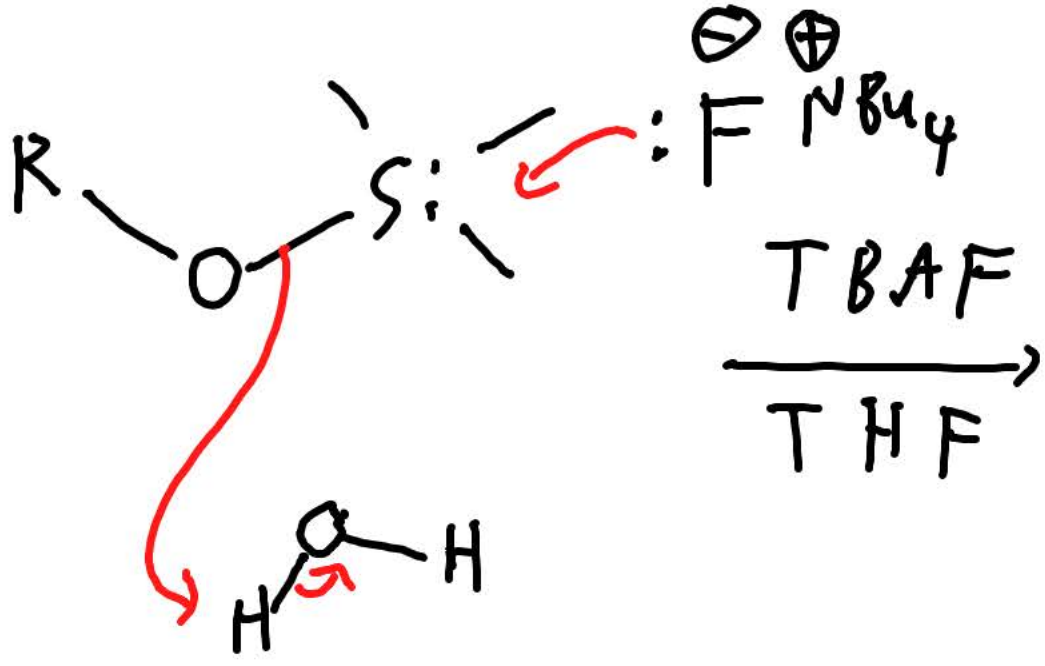


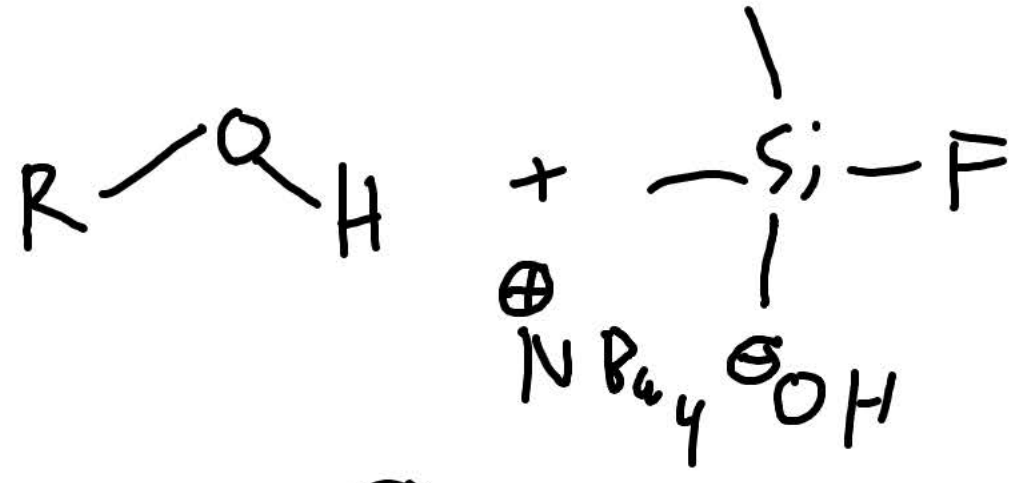
SN2 sur C: état de transition, on ne peut pas dépasser l'octet



intermédiaire, car Si peut dépasser l'octet

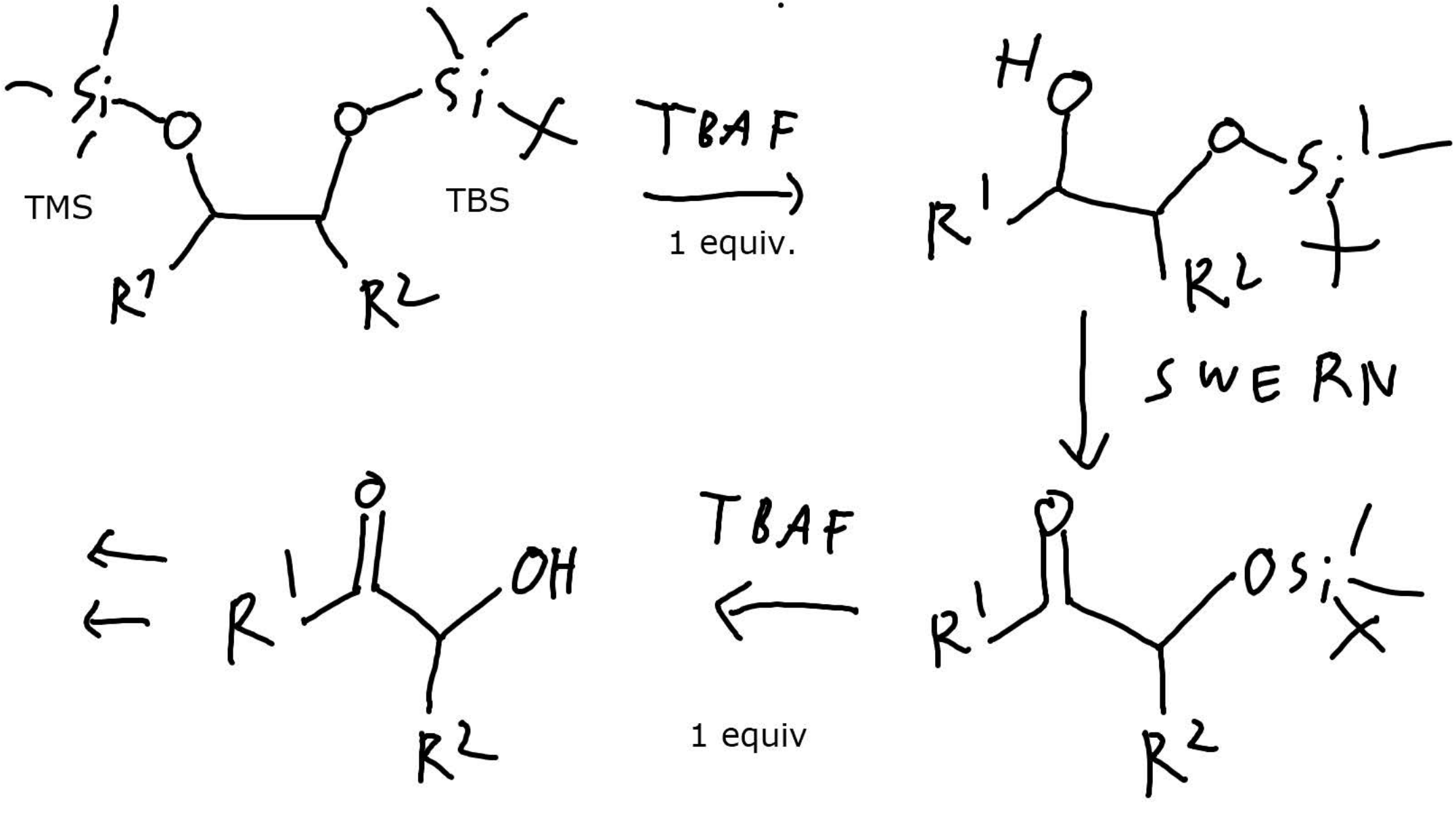
2) déprotection: avec le fluorure



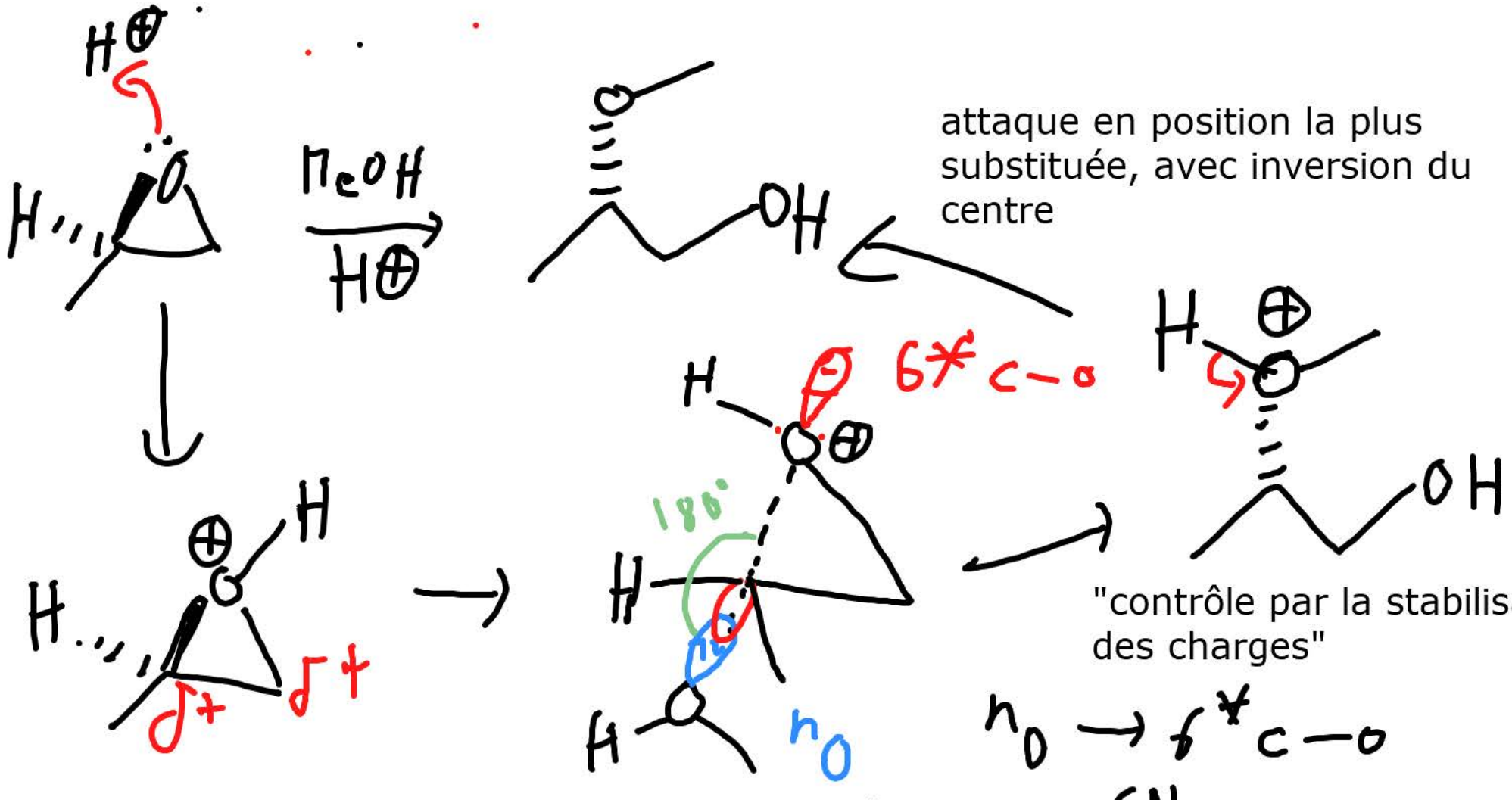


TBAF: tétrabutylammonium fluoride

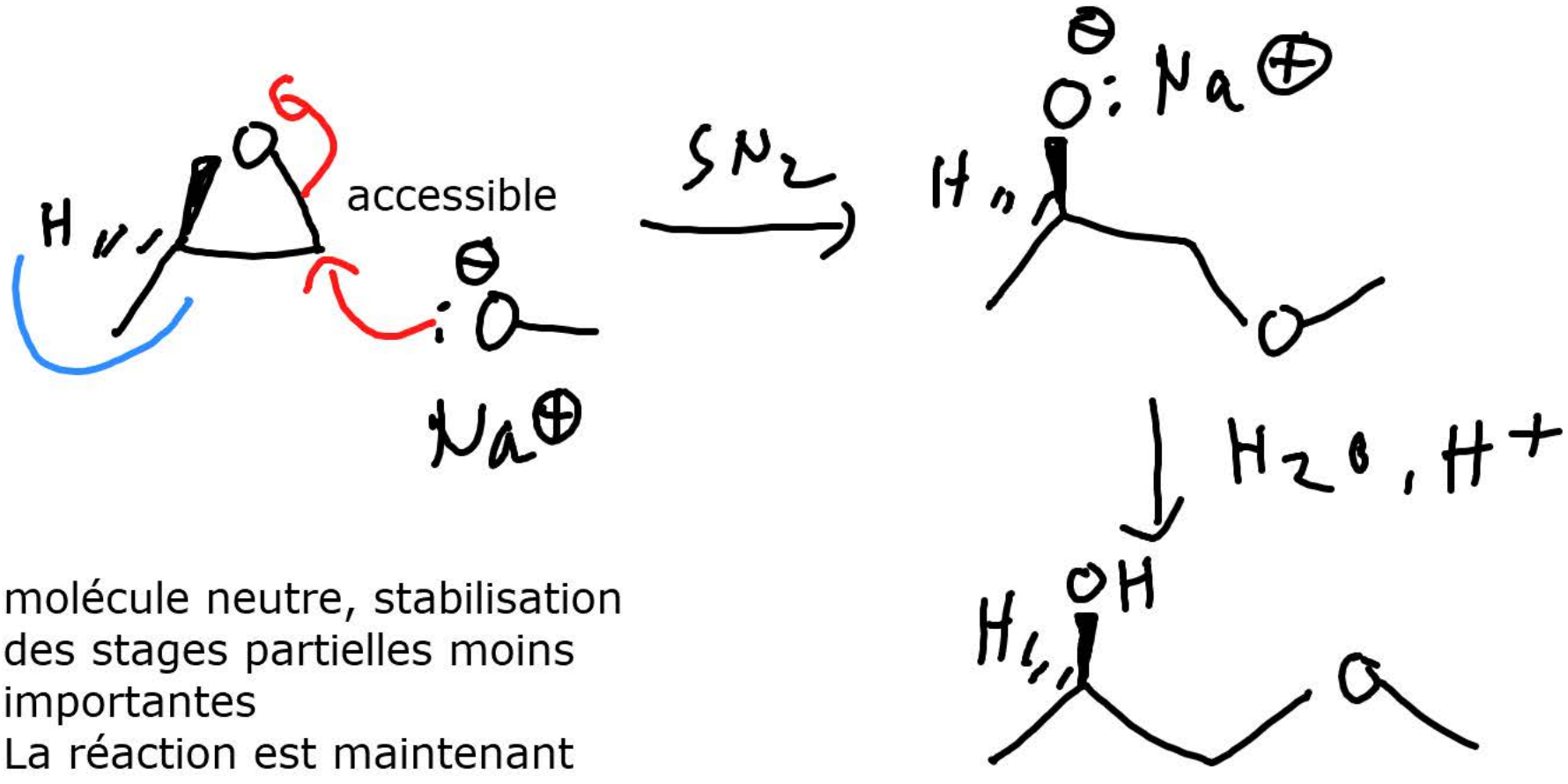
forme de fluorure soluble dans les solvants organiques


TMS
TBS
TBAF
1 equiv.
SWERN
TBAF
1 equiv

réactivité des époxides: 1) conditions acides

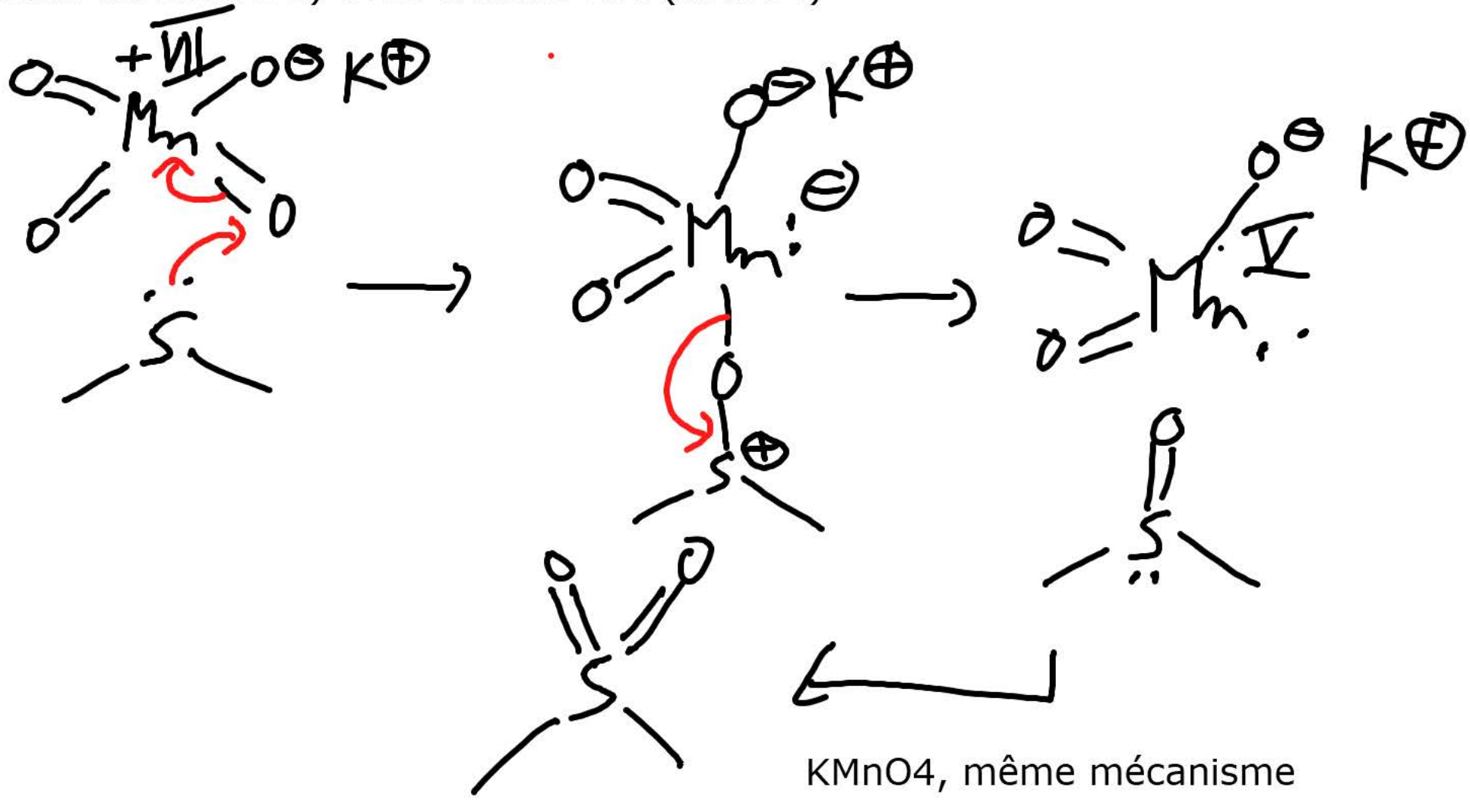


2) conditions basiques



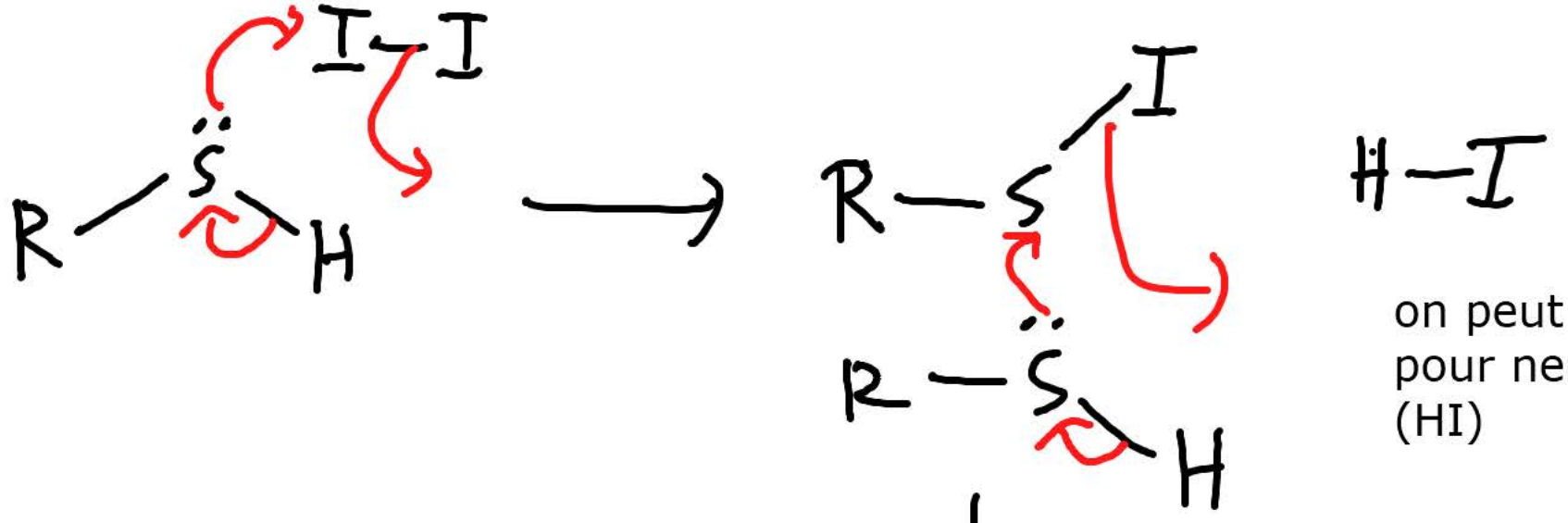
molécule neutre, stabilisation des stages partielles moins importantes
La réaction est maintenant contrôlée pas les effets stériques

oxidation du soufre 1) avec oxidant fort (KMnO4)



KMnO4, même mécanisme

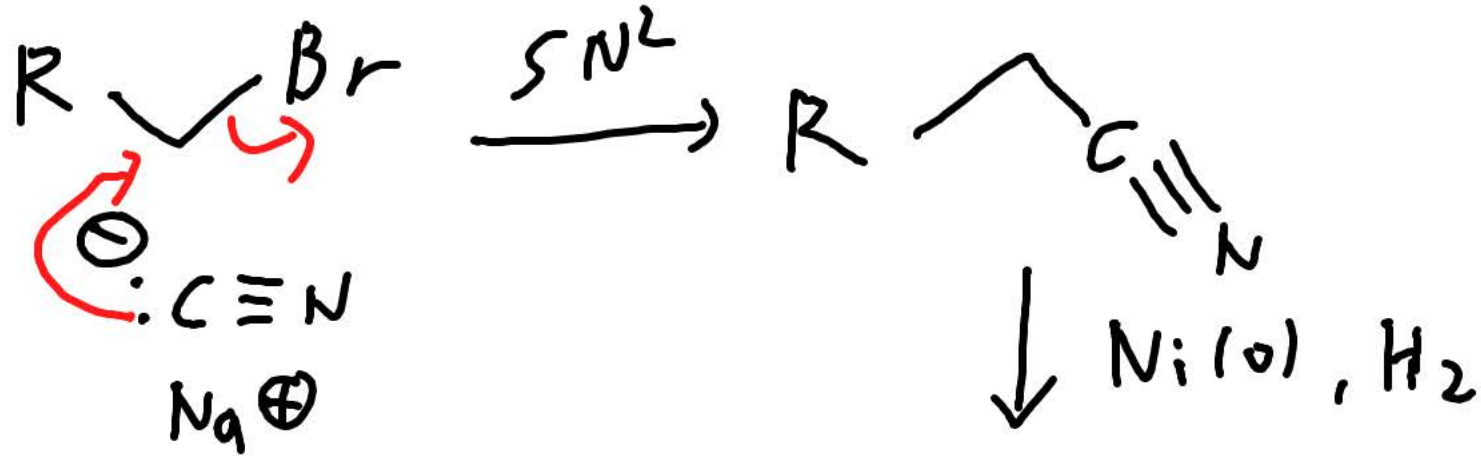
Oxydation des thiols avec l'iode



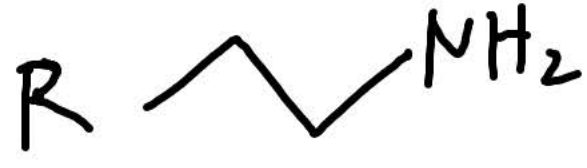
on peut ajouter une base pour neutraliser l'acide fort (HI)

seconde réaction plus rapide

synthèse des amines avec les nitriles

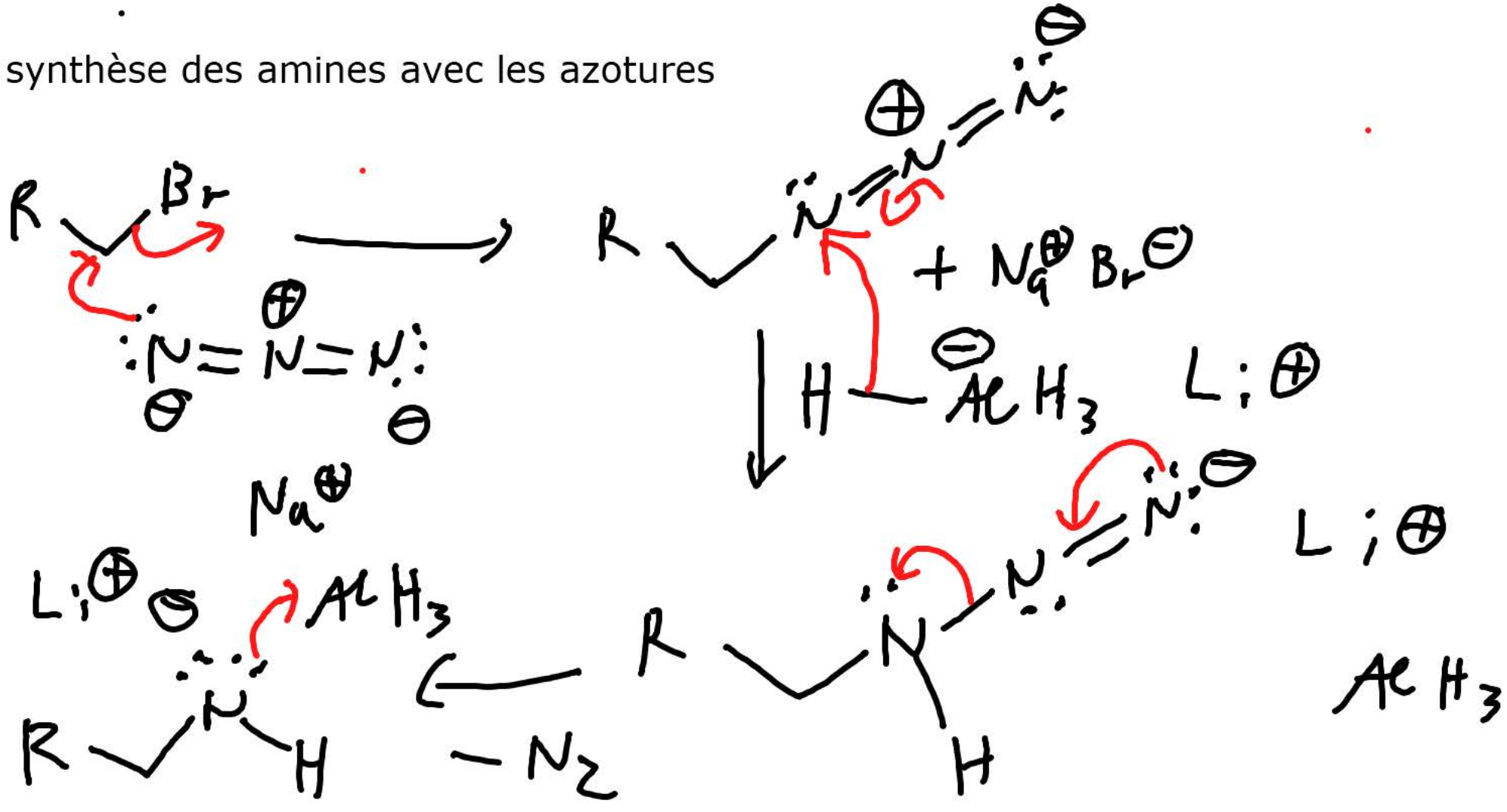


même mécanisme que pour les alcynes/alcènes

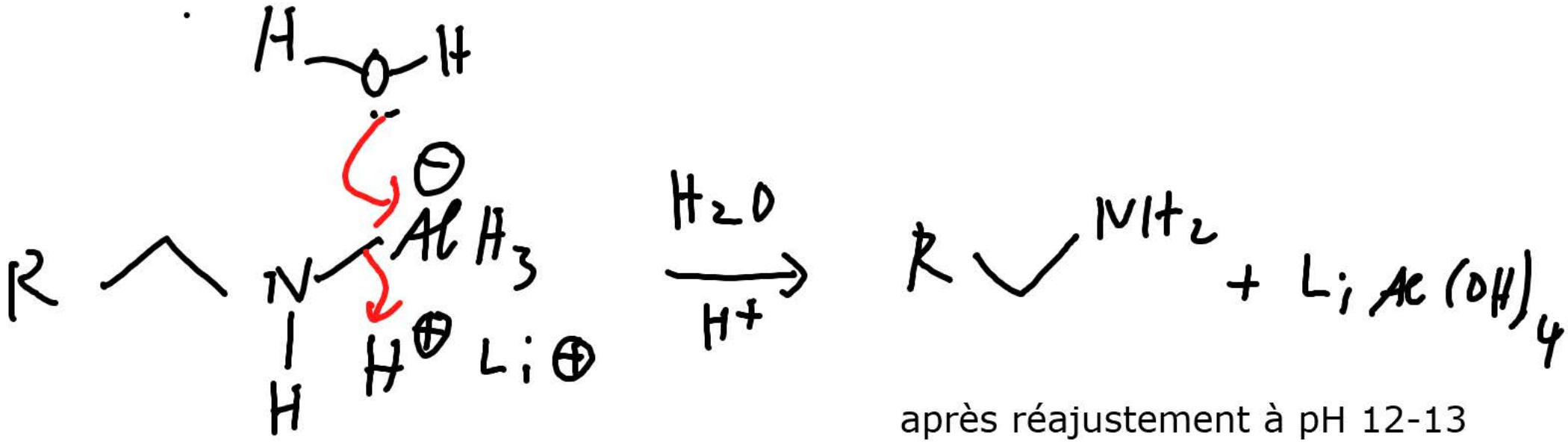


on introduit l'amine en rallongeant la chaine d'un carbone

synthèse des amines avec les azotures

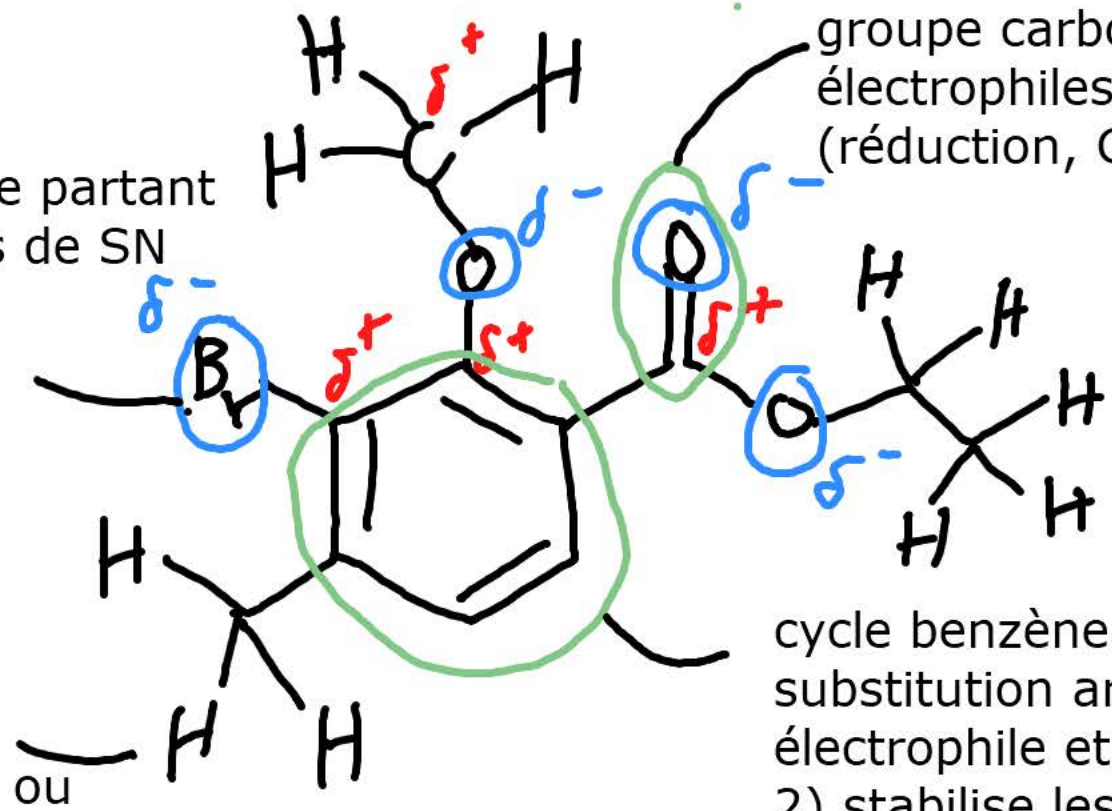


formation d'azote favorisée



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

Examen 2024, exercice 3



groupe carbonyl: un des meilleures électrophiles en chimie organique (réduction, Grignard,...) ✓

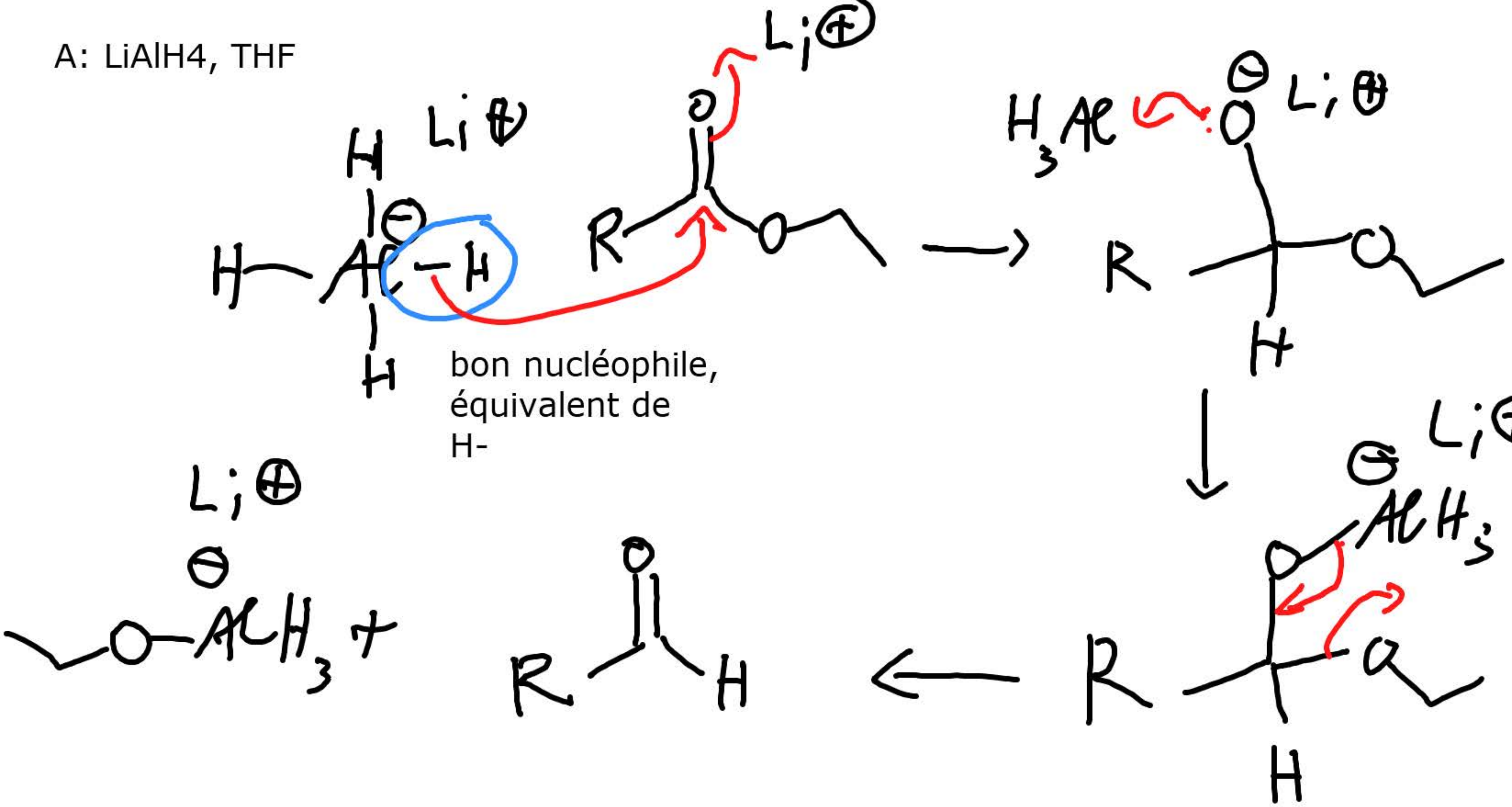
Br: halogène, groupe partant mais attentions: pas de SN sur les centres sp2

cycle benzène: 1) réagit en substitution aromatique électrophile et couplage au Pd ✓
2) stabilise les intermédiaires adjacents par résonance

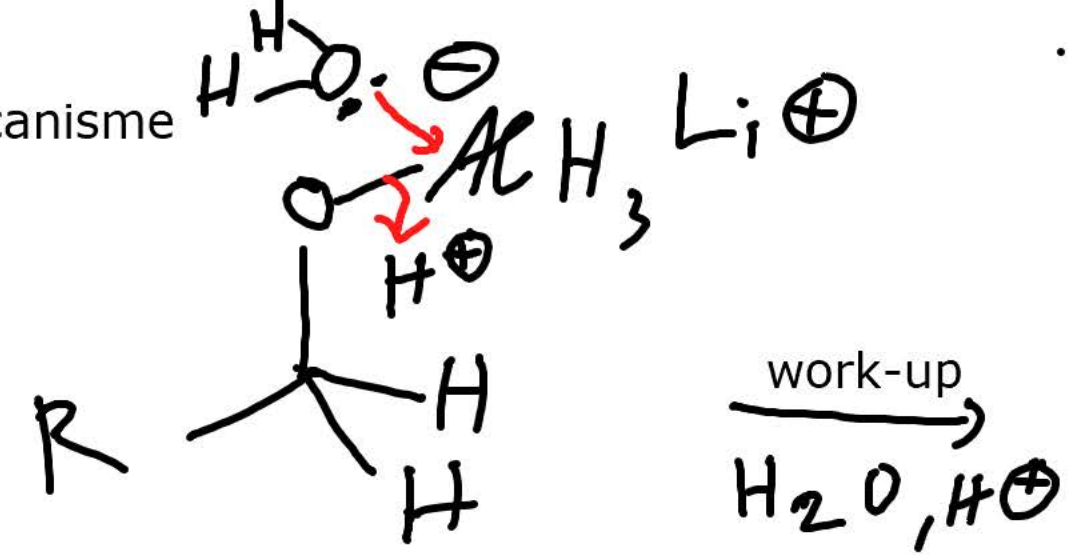
liaisons C-H:
réaction radicalaires ou déprotonation si suffisamment acide

double liaison très souvent plus réactive que les liaisons simples

A: $LiAlH_4$, THF

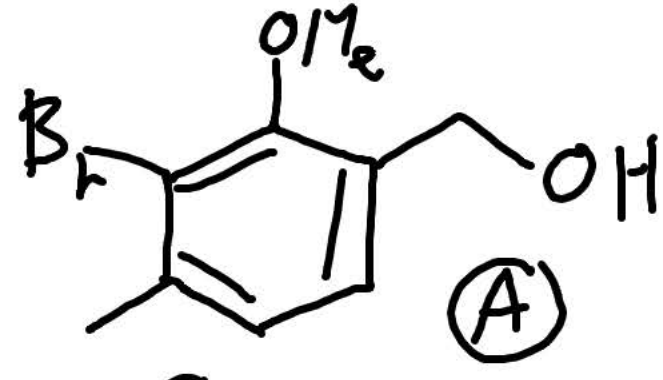


même mécanisme



work-up

$H_2O, H^{\oplus}$



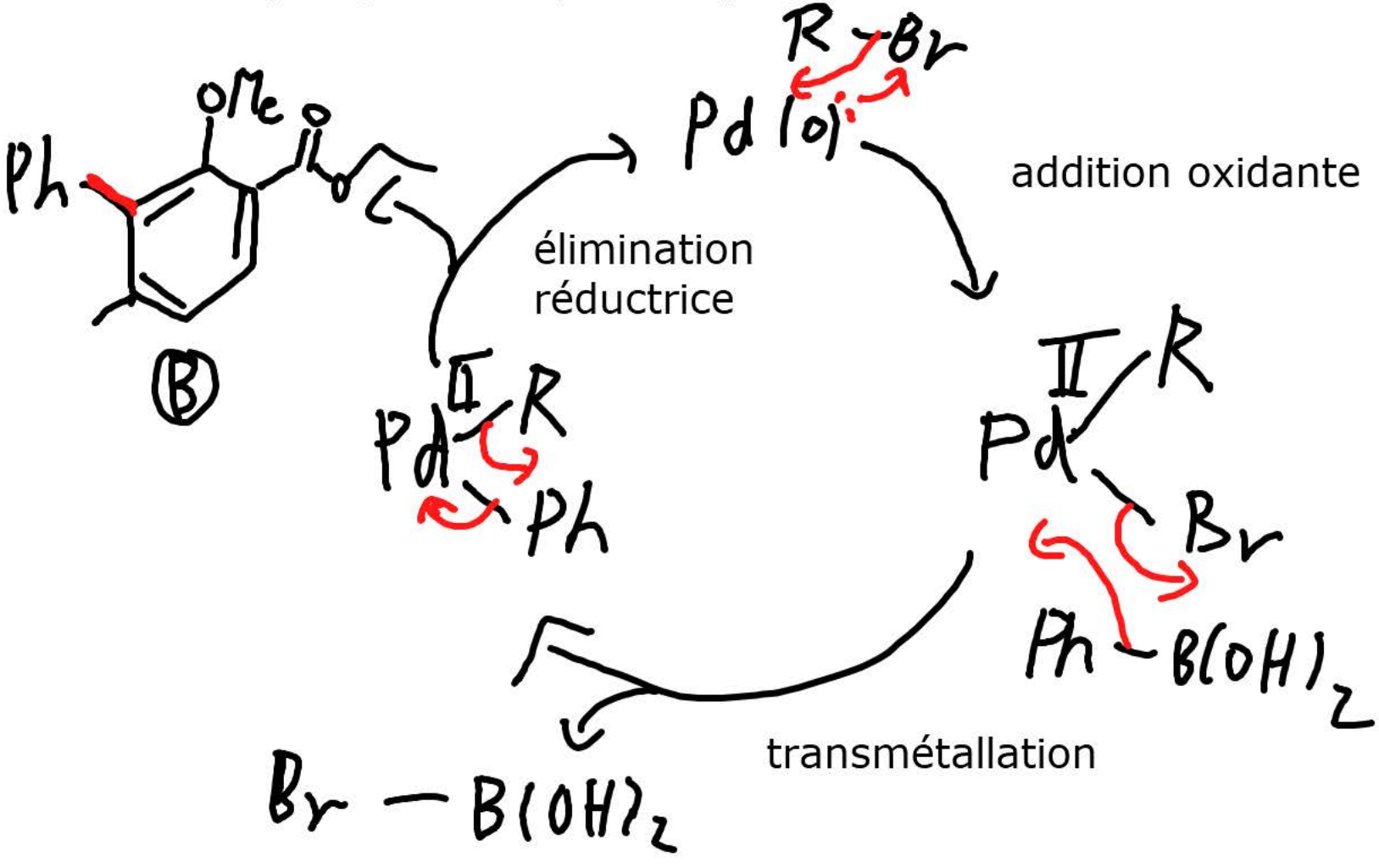
$Li^{\oplus}\,{}^{\ominus}AlH(OH)H_3$

$\downarrow H_2O, H^{\oplus}$

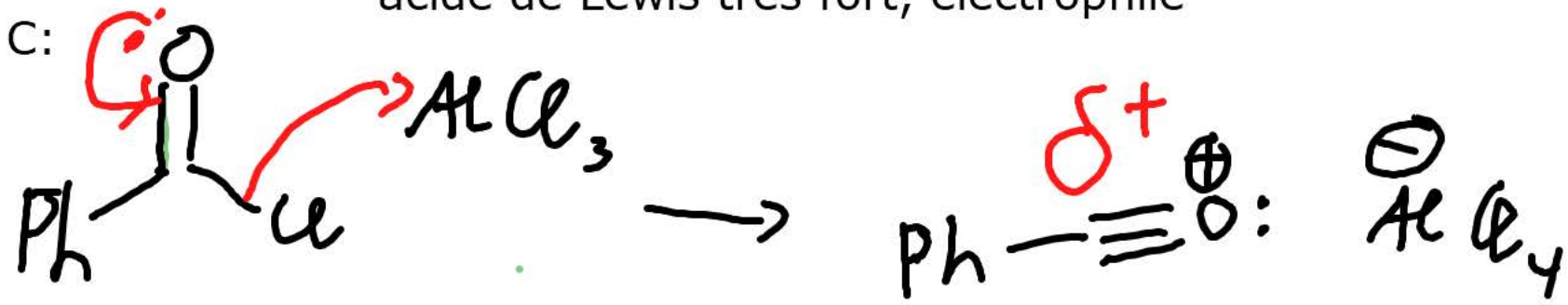
$Li^{\oplus}\,{}^{\ominus}Al(OH)_4 + H_2$

B: Pd(0) cat., PhB(OH)2

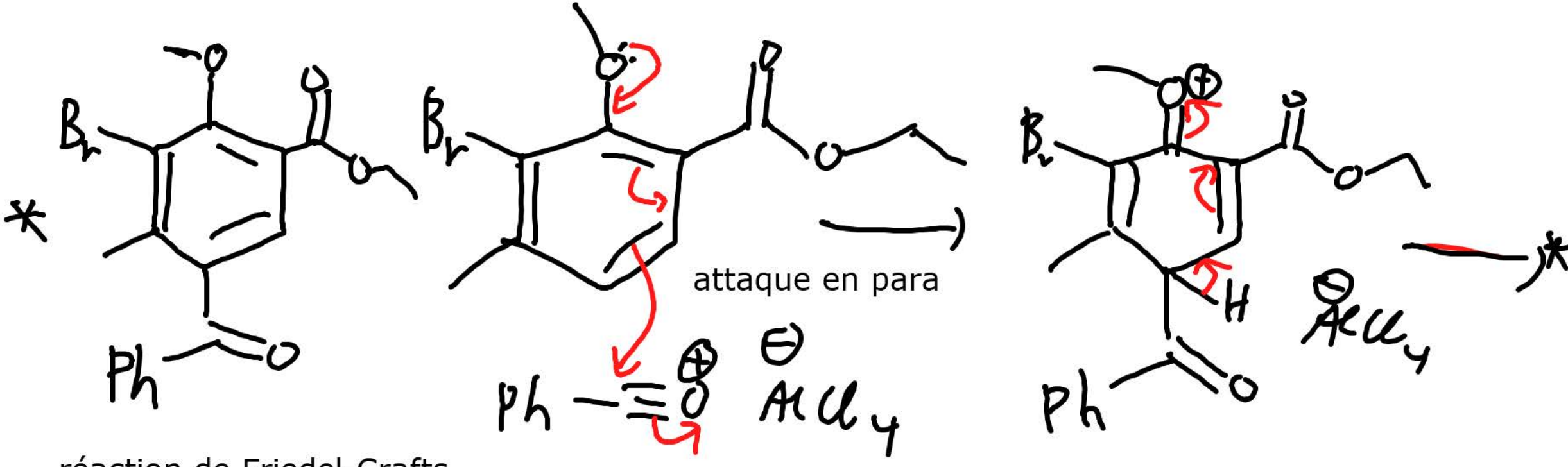
Pd: hydrogénations, ou couplage croisés



acide de Lewis très fort, électrophile



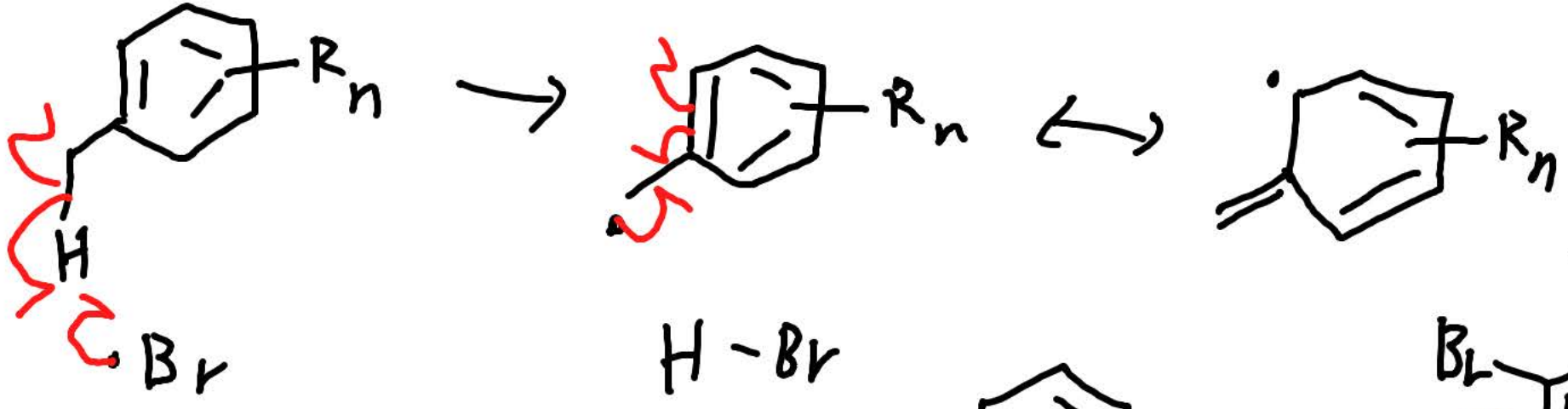
électrophile très fort!



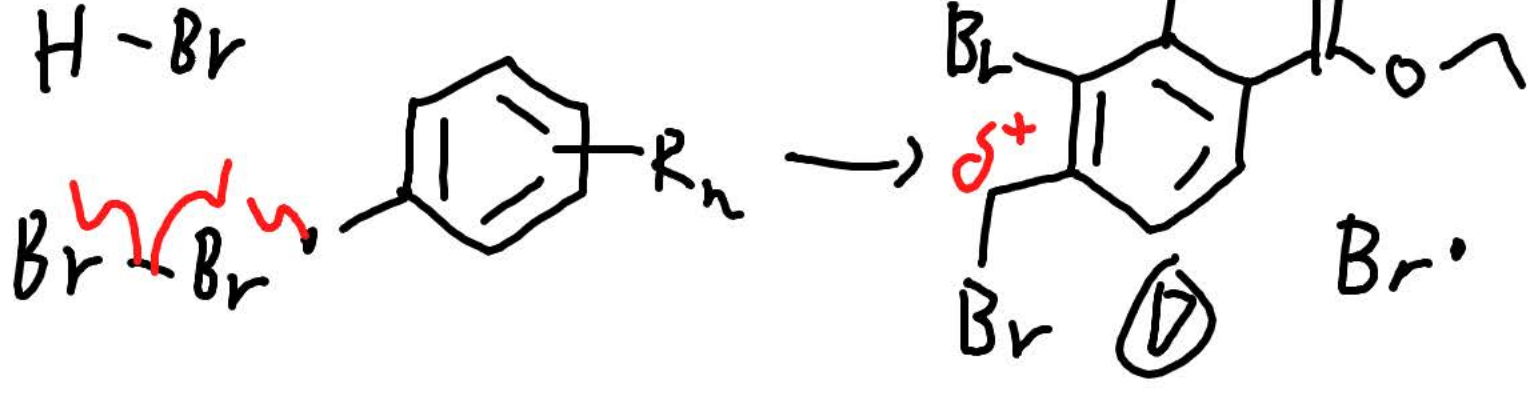
réaction de Friedel-Crafts

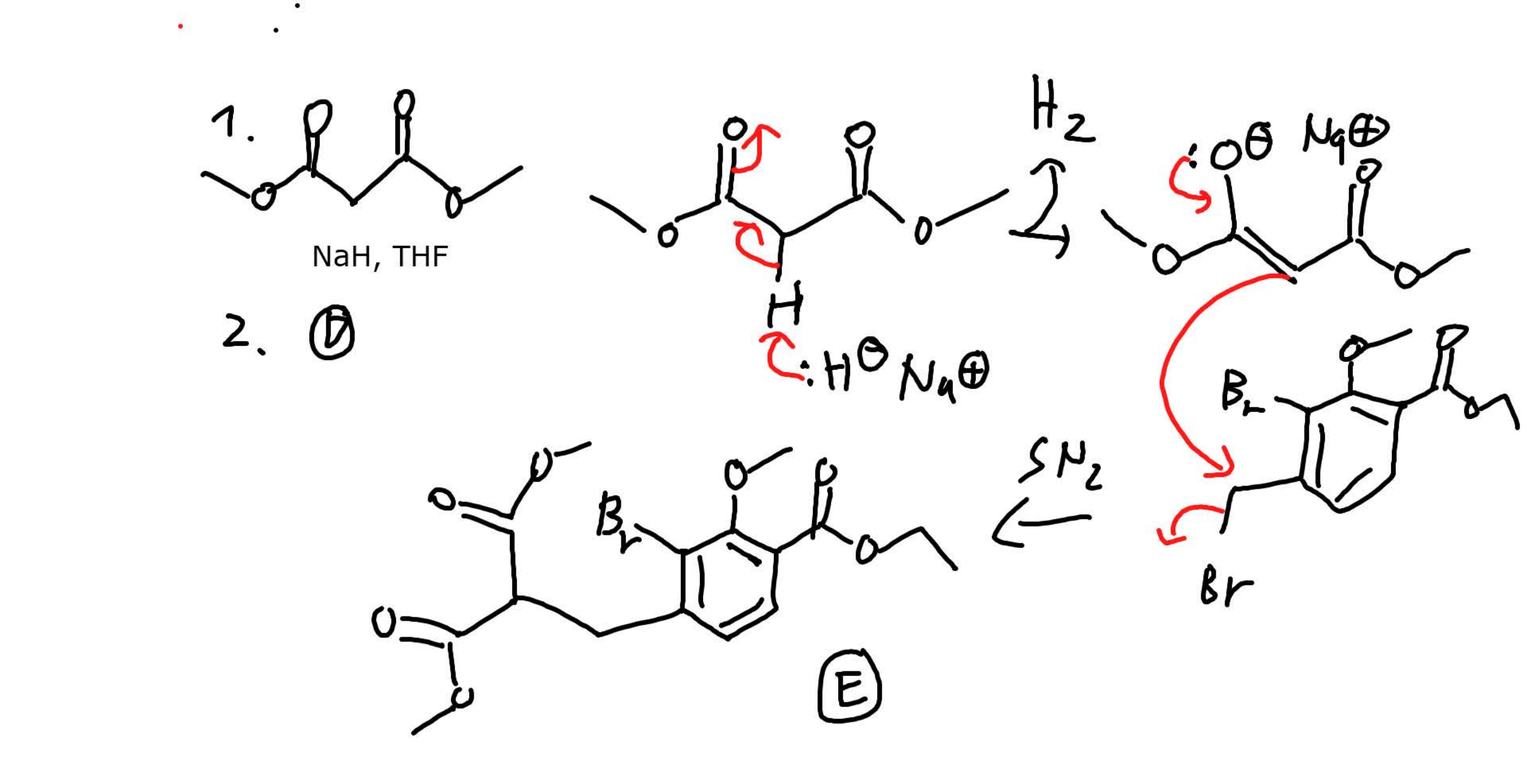
hv, Br2

réactivité des radicaux:
1) abstraction des H si le radical obtenu est stable
2) addition sur les alcènes

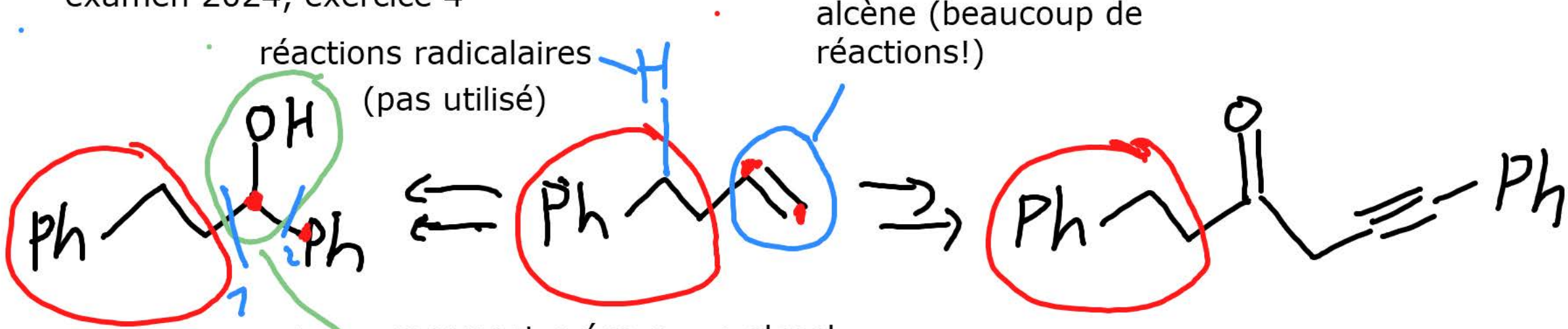


+2 résonance dans le cycle

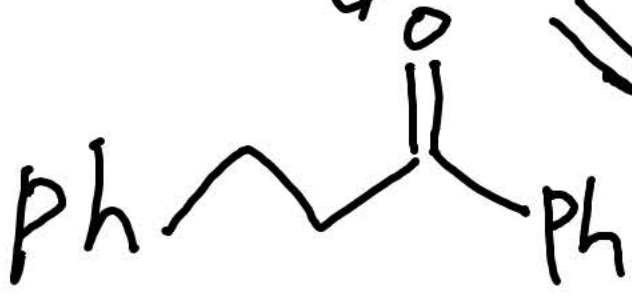



1.
NaH, THF
2.
D
H2
SN2
Br
Br
E

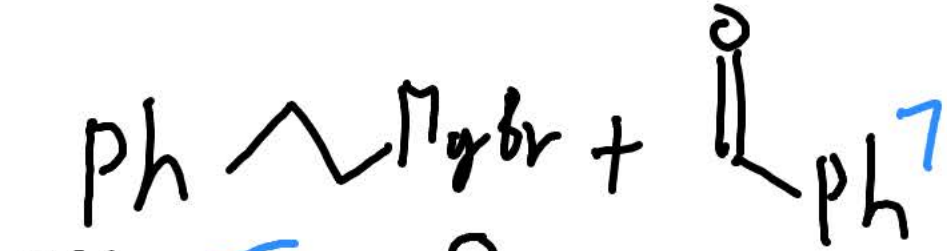
examen 2024, exercice 4



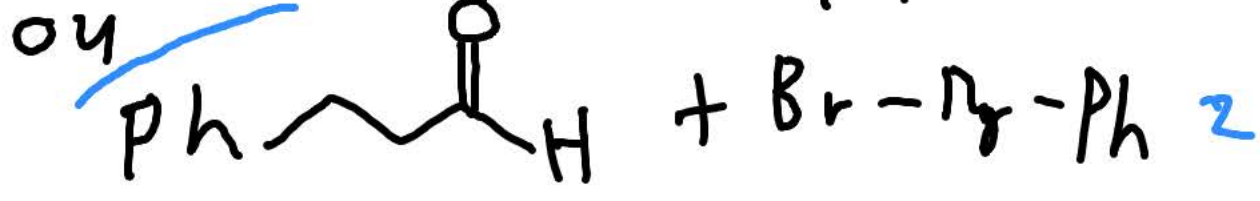
comment préparer un alcool
réduction, addition de
Grignard, réaction des alcènes

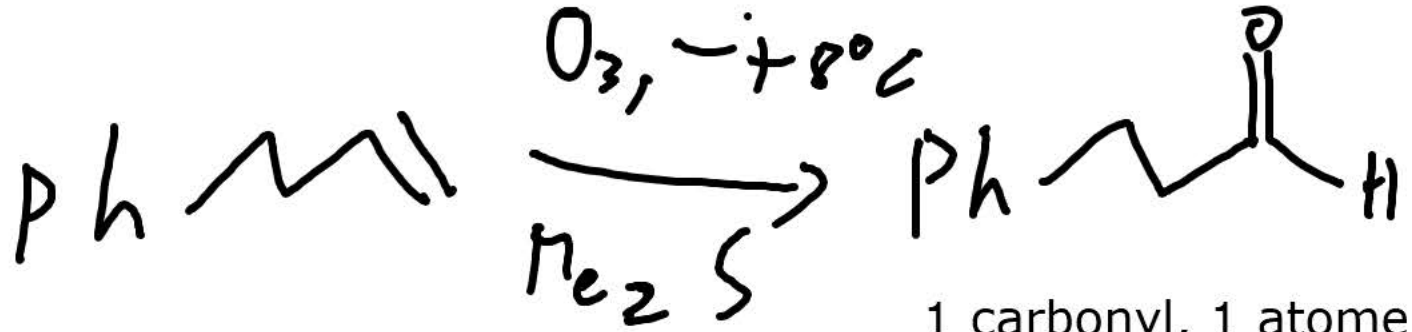


avec une réduction



réaction de
Grignard

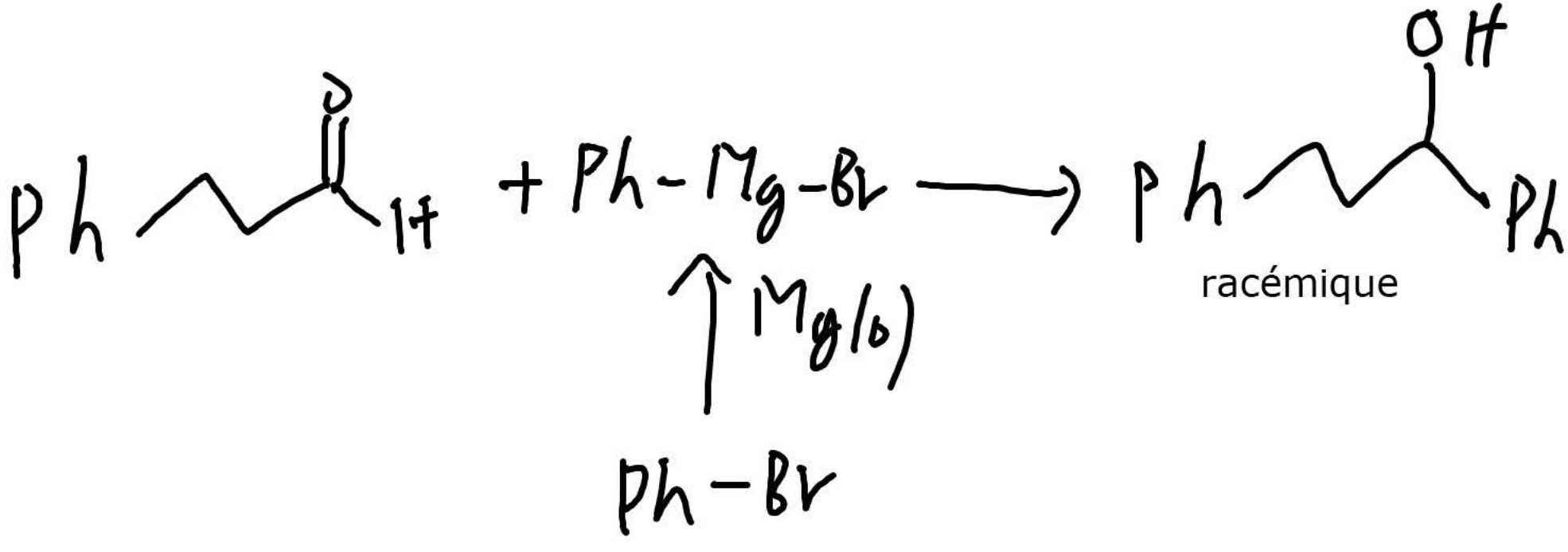




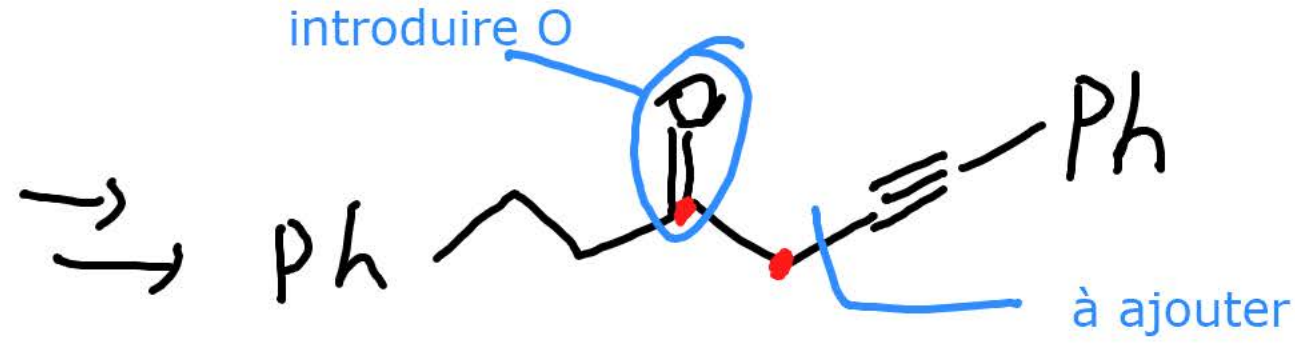
Ou: 1)OsO4
2) NaIO4

alternative acceptée

1 carbonyl, 1 atome perdu:
ozonolyse des alcènes!



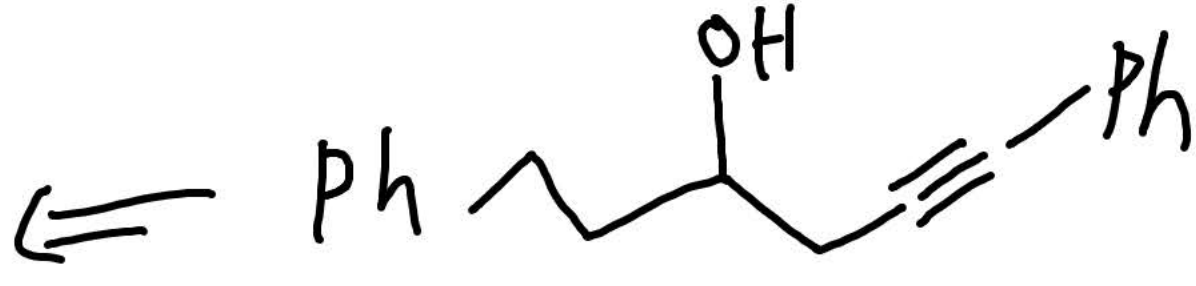
racémique



"indication pour oxidation des alcènes"

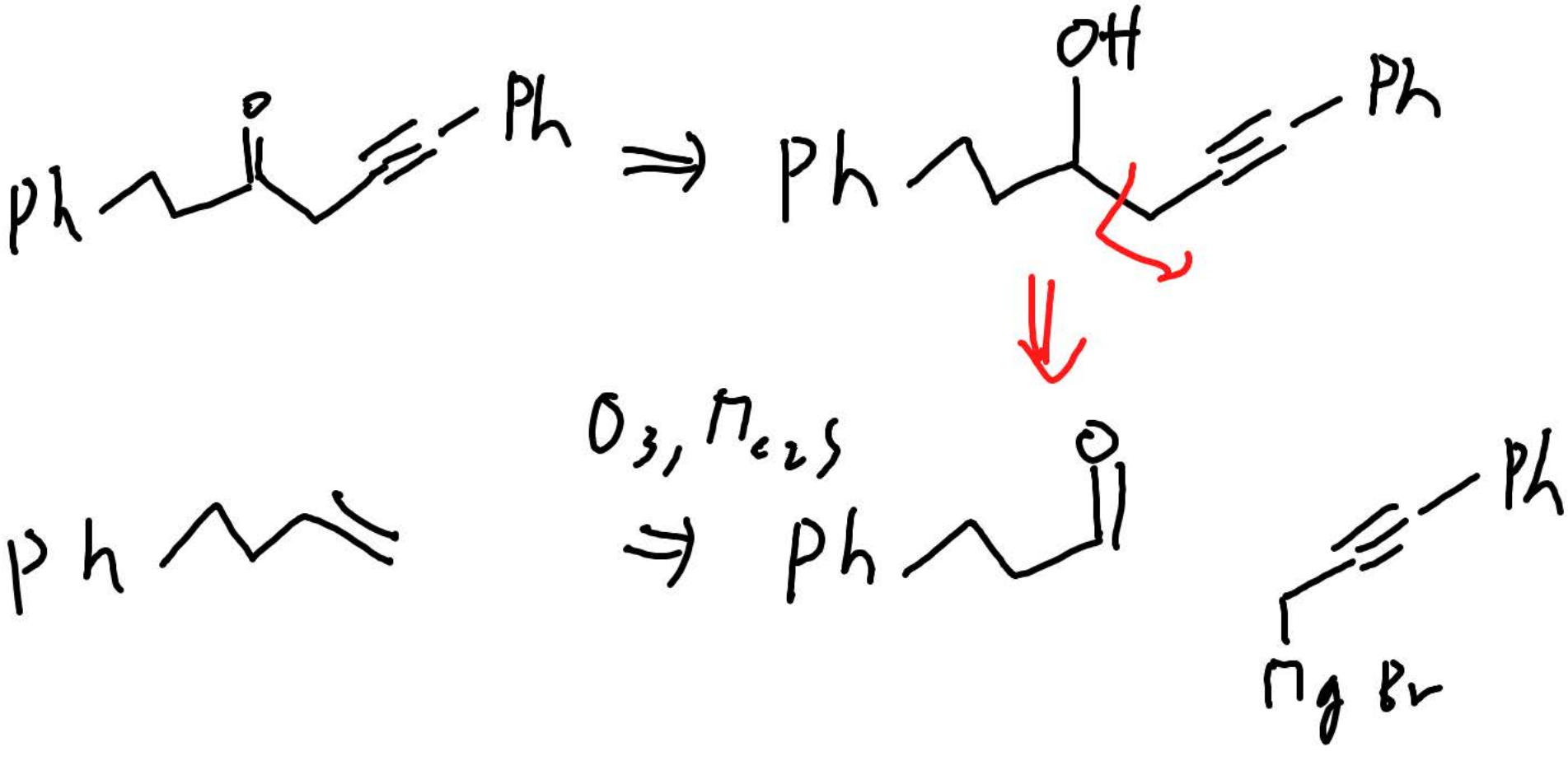
cétone: peut être obtenu par oxidation des alcools

bon nucléophile, facile à générer



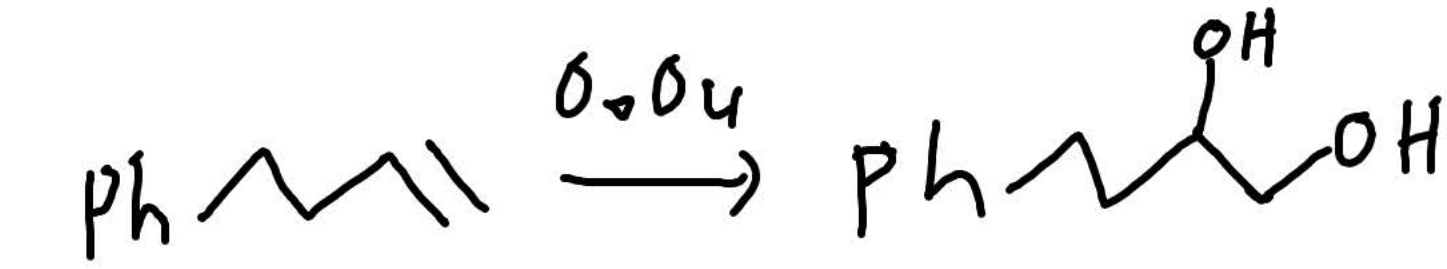
alcool à côté d'un nucléophile: peut être accédé par addition sur les époxides

alternative proposée à l'examen

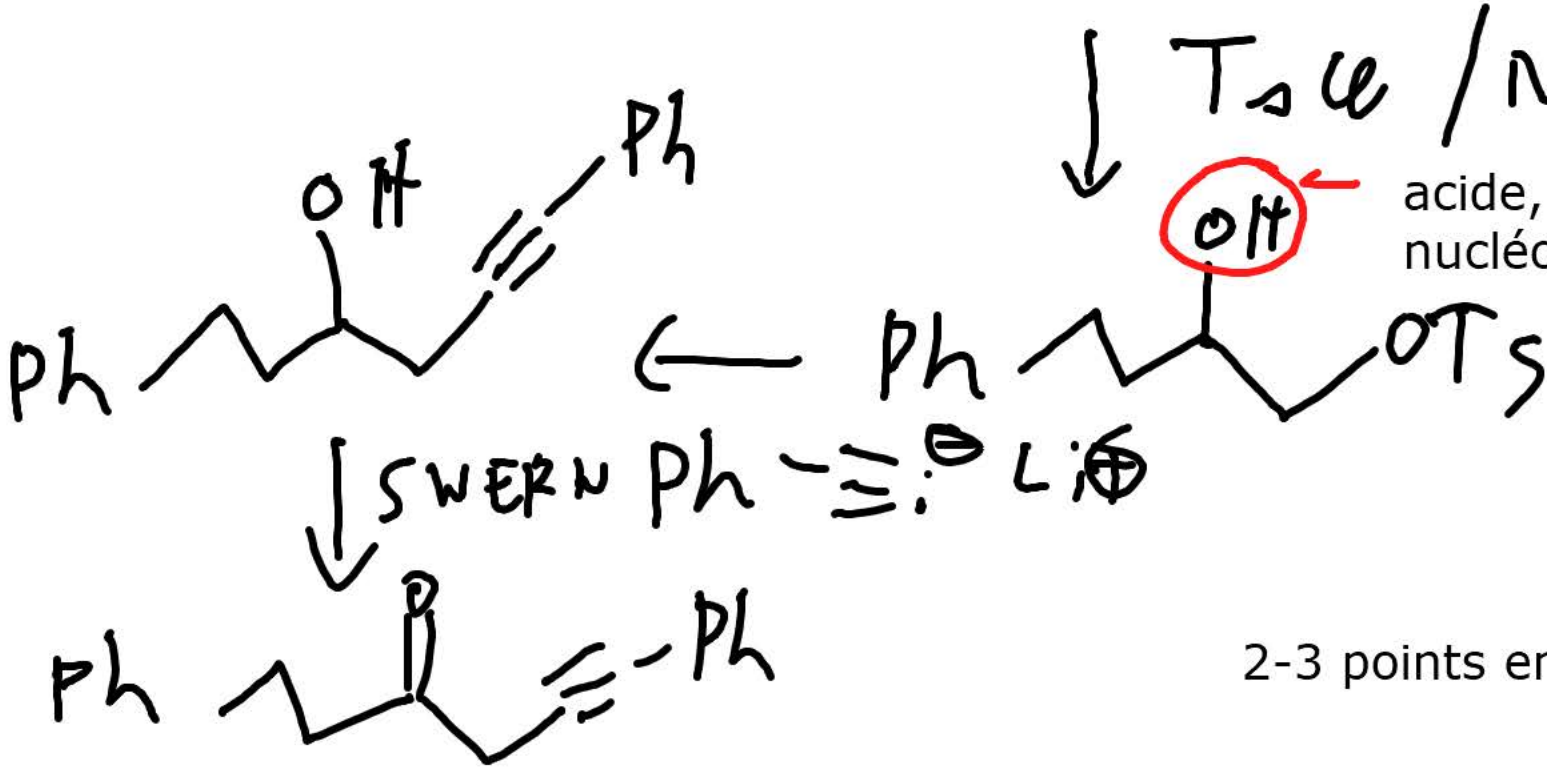


100% des points

autre alternative:



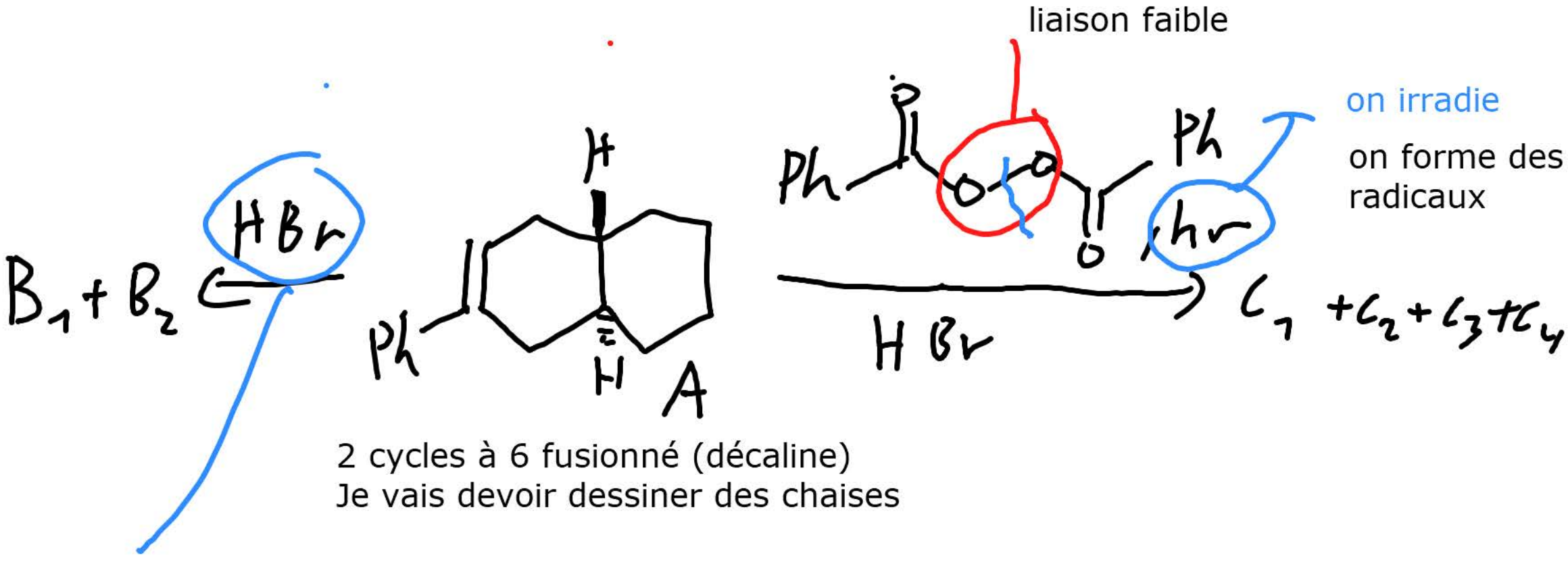
sélectivité: 2 alcools



acide, peut réagir avec le nucléophile

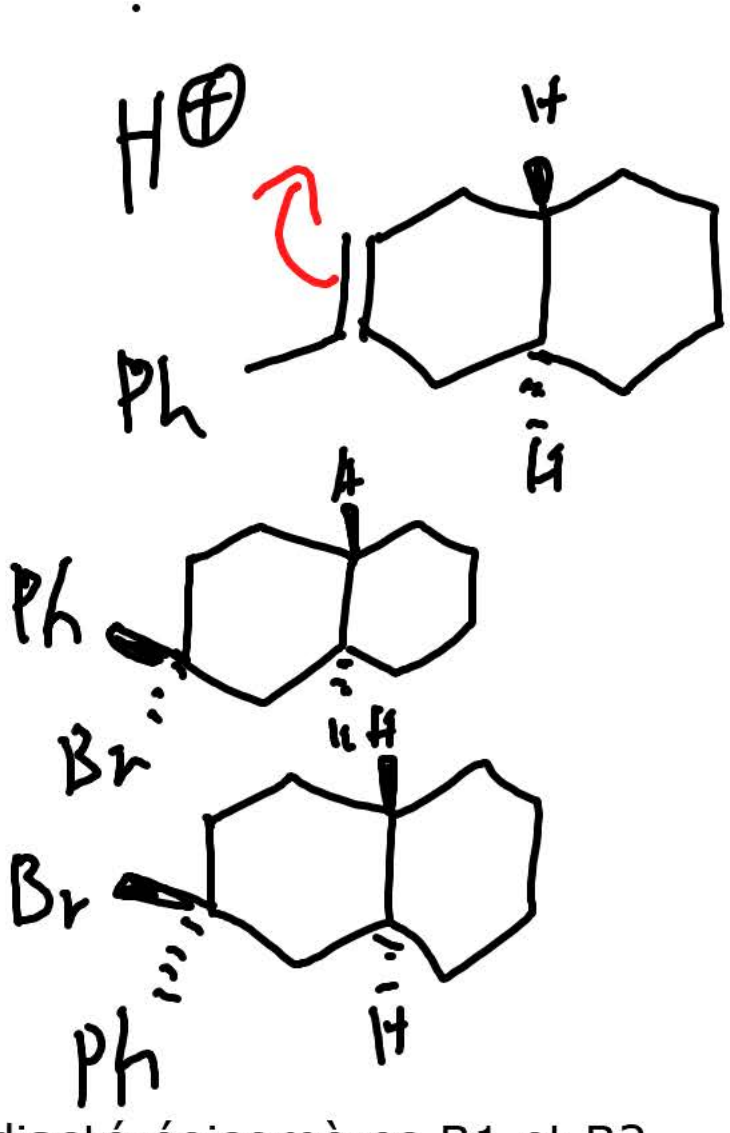
2-3 points en moins

examen 2024, exercice 2: "mécanisme détaillé"

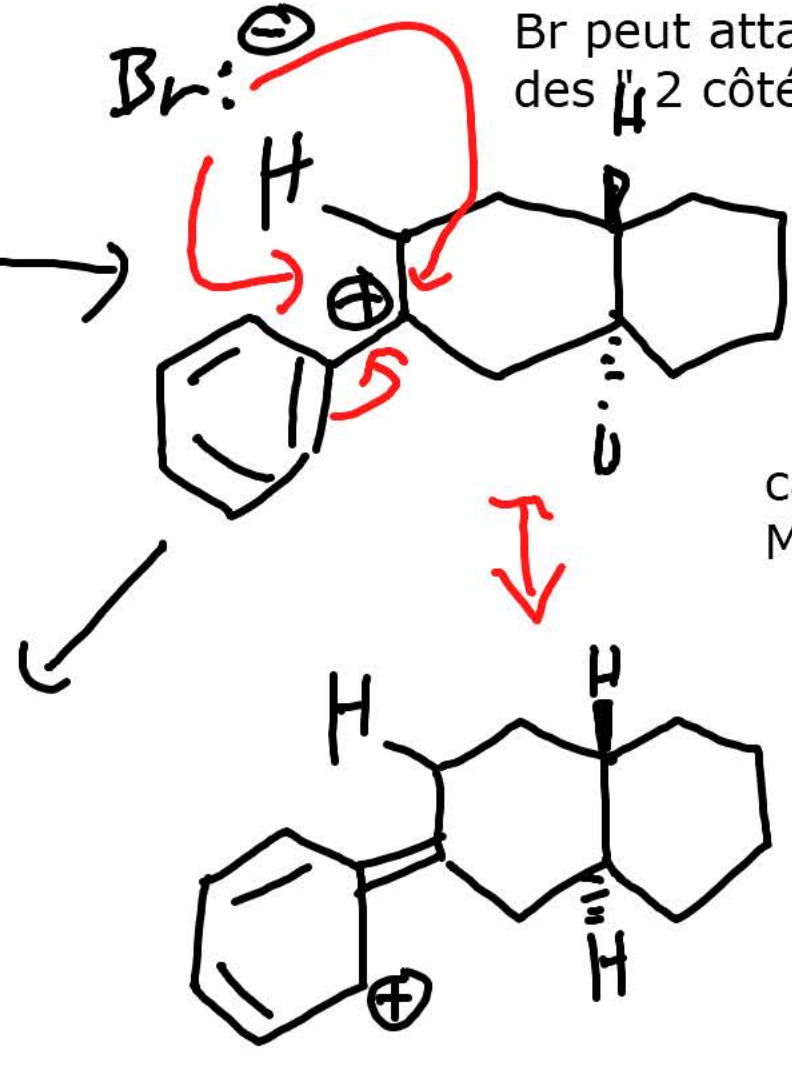


2 cycles à 6 fusionné (décaline)
Je vais devoir dessiner des chaises

Acide fort, avec base nucléophile



2 diastéréoisomères B1 et B2

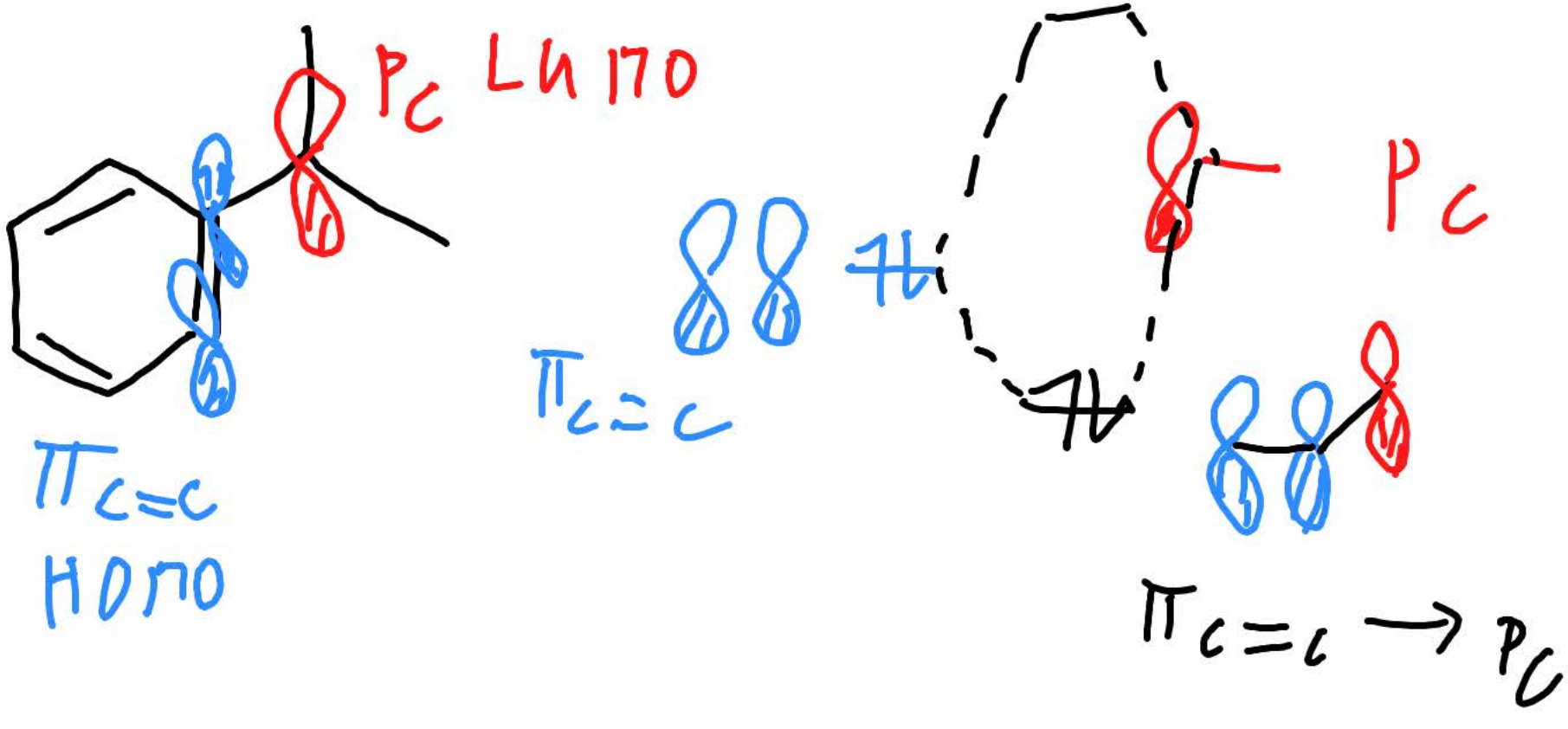


Br peut attaque le carbocation des "2 côtés"

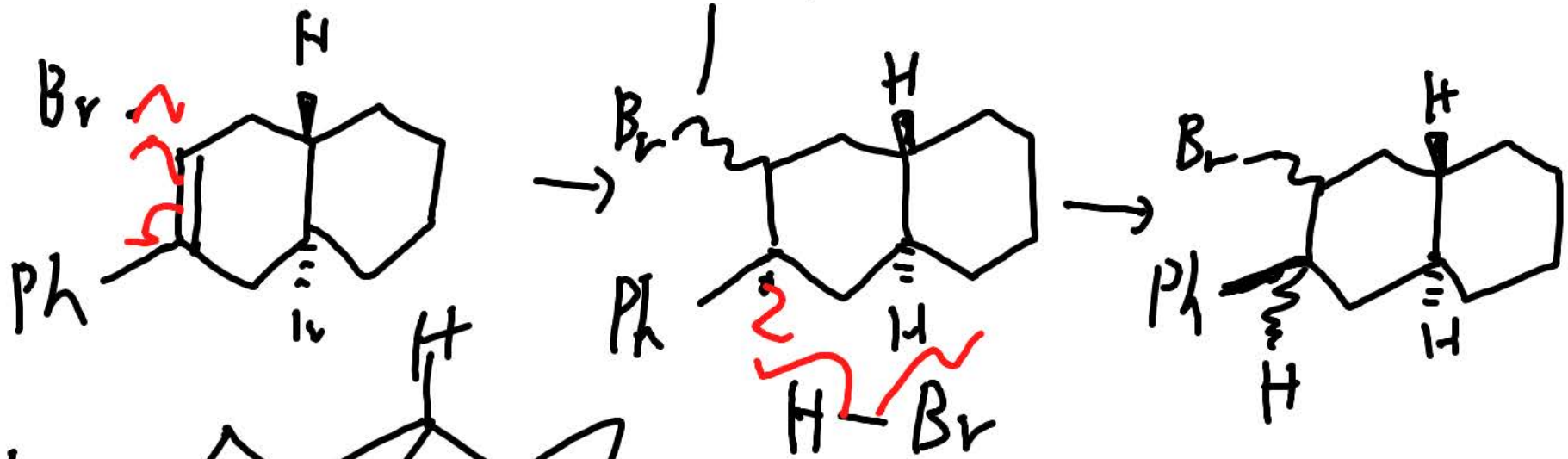
carbocation plus stable Markovnikov

+ 2 résonance dans le cycle

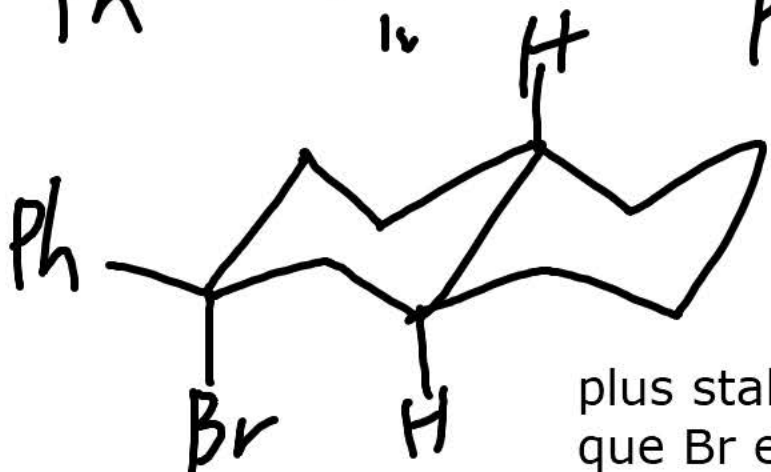
rationaliser la sélectivité avec des interactions orbitalaires=
interactions orbitalaires qui stabilisent le carbocation



attaque en haut et en bas



4 différents diastéréoisomères sont obtenus



plus stable, car ph plus grand que Br en équatorial