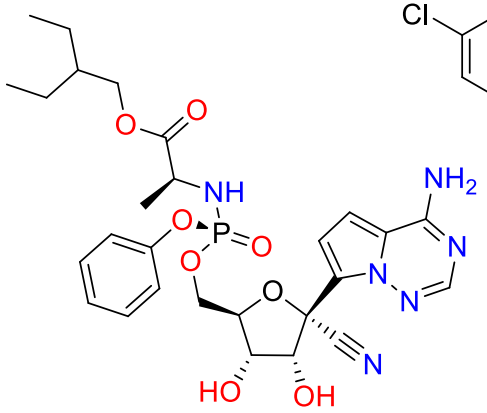
université PARIS-SACLAY | FACULTÉ DE PHARMACIE

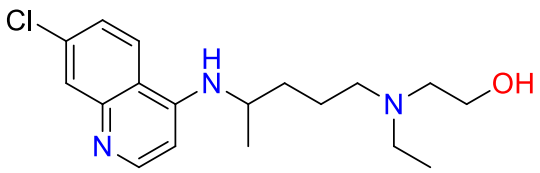
Formation of C-O bonds or C-N bonds

Laurent Ferrié
Chargé de Recherche CNRS-BioCIS
-Université Paris Saclay
laurent.ferrie@universite-paris-saclay.fr

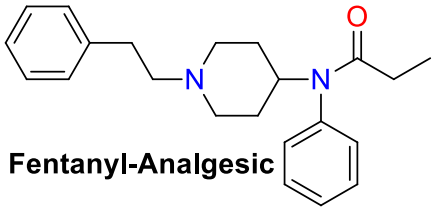
Some C-O and C-N Marketed Drugs



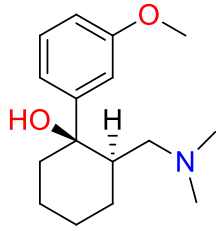
Remdesivir-AntiViral



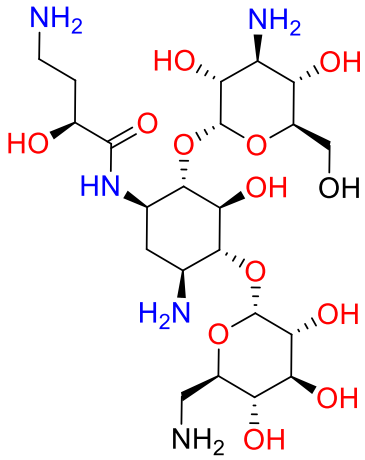
Hydroxychloroquin-antimalarial



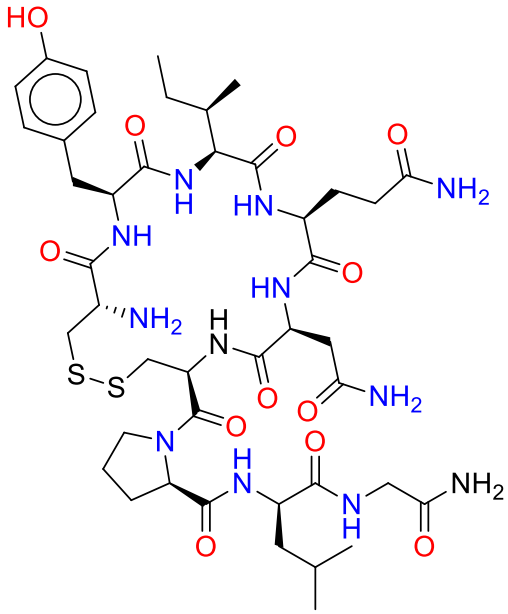
Fentanyl-Analgesic



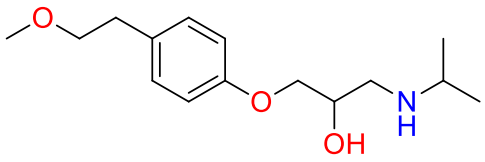
Tramadol-analgesic



Amikacin-Antibiotic

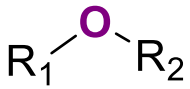


Oxytocyn-Love hormone

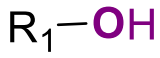


Metoprolol-β1 receptor blocker

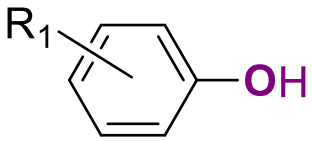
Carbon-Oxygen Functions



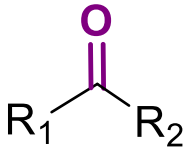
Ether



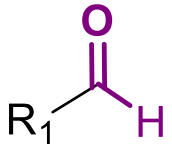
Alcohol



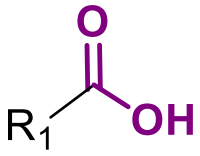
Phenol



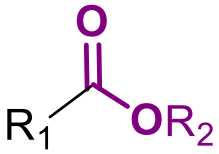
Ketone



Aldehyde

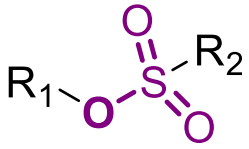


Carboxylic Acid

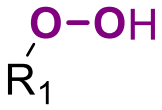


Ester

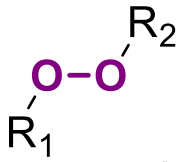
Carbonate



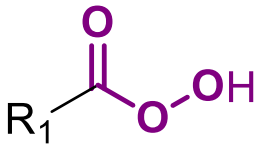
Sulfonate



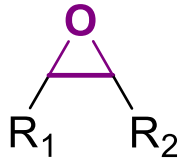
Hydroperoxide



Peroxy ether



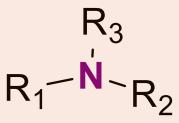
Peracid



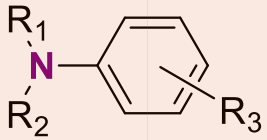
Epoxide

Carbon-Nitrogen Functions

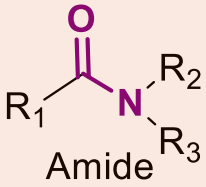
= Fonctions that **must** be known



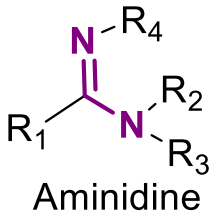
Amine



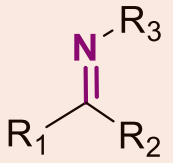
Aniline



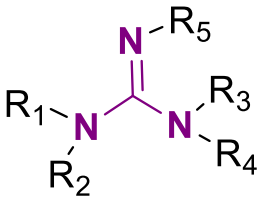
Amide



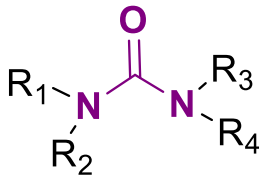
Aminidine



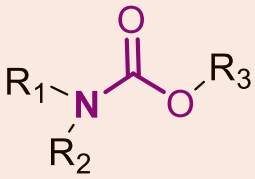
Imine



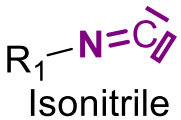
Guanidine



Urea

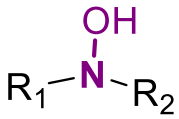


Carbamate

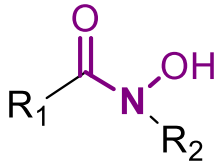


Isonitrile

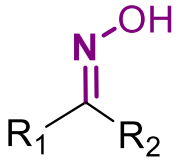
Nitrile



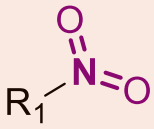
Hydroxylamine



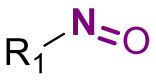
Hydroxamic acid



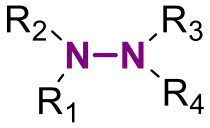
Oxyme



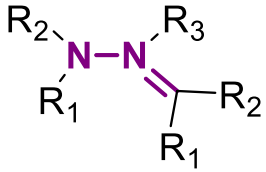
Nitro



Nitroso

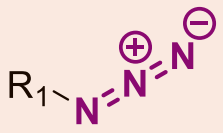


Hydrazine

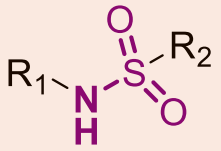


Hydrazones

Azo

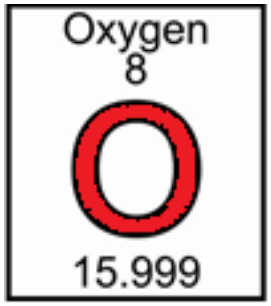


Azide



Sulfonamide

Oxygen Properties

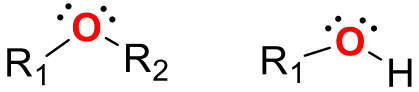


pka = Acid Dissociation Constant:

$HA \leftrightarrow A^- + H^+$ $\quad pKa = -\log Ka = \log [HA]/[A^-][H^+]$

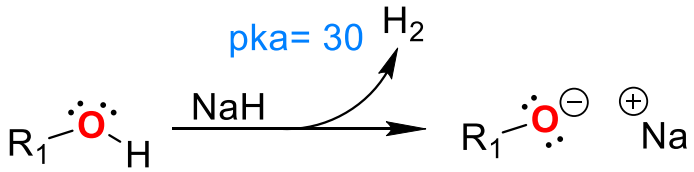
- At pH = pKa, both species are in equal concentration
- pH and pka are logarithmic value (base 10)

eg A pH value 2 higher or lower to pka means that a species (HA or H^+/A^-) is 100x more concentrated.



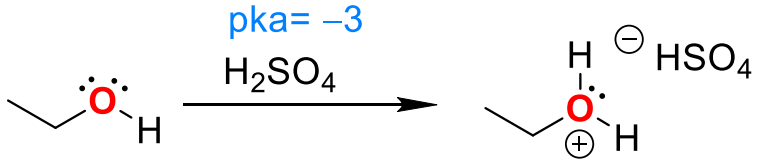
Ethers Alcohols

-2 bonds as neutral
-2 Lone electrons pairs
-Very electronegative
-Weakly nucleophilic and basic



pka= 15
Conjugated base

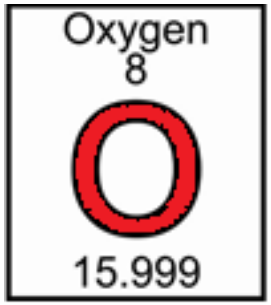
but moderatly acidic :
-**pKa** $ROH_2^+/ROH \approx -1$, **pKa** $ROH/RO^- \approx 15$

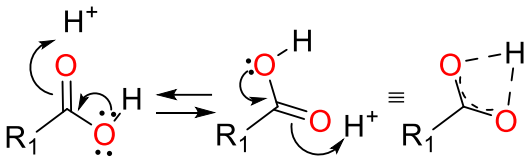


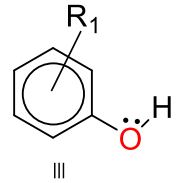
pka= –1
Conjugated acid

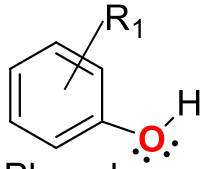
université PARIS-SACLAY

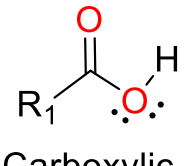
Oxygen Properties: Effect of the Conjugaison

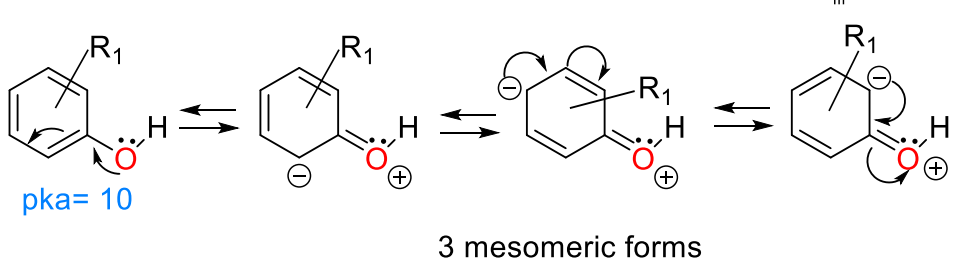










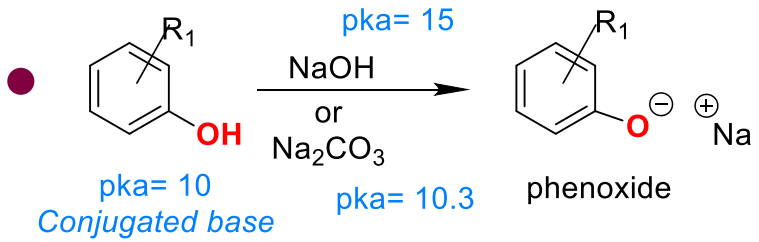


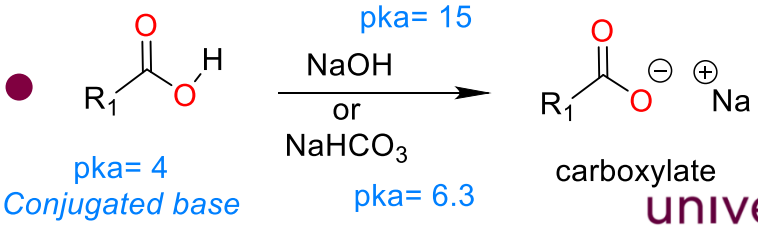
-Lone pairs are participating in the conjugation
with the carbonyl group
or the aromatic ring

→**Lowering pKa**:

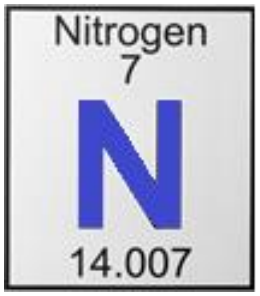
RCOOH/RCOO⁻ ≈ **4**

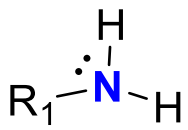
phenol ≈ **10**



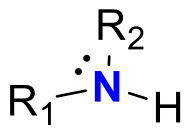


Nitrogen Properties

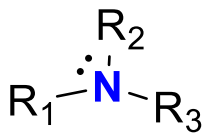




Primary Amine

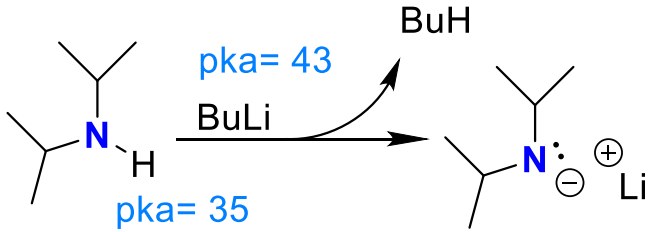


Secondary Amine



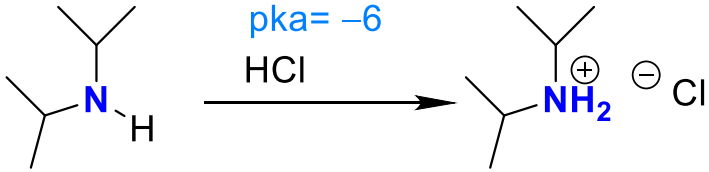
Tertiary Amine

-3 bonds as neutral
-1 Lone electrons pair
-Moderatly electronegative
-**Strongly** nucleophilic and basic but not acidic
-pKa RNH_3^+/ RNH_2 ≈ **10**,
pKa RNH_2 / RNH^- ≈ **35**



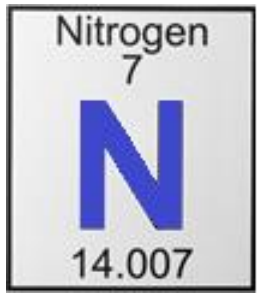
Conjugated base

Lithium Diisopropylamide (**LDA**)

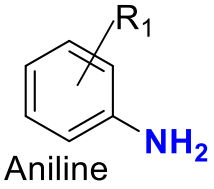


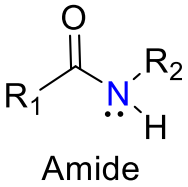
Conjugated acid

Nitrogen Properties: Effect of the Conjugaison



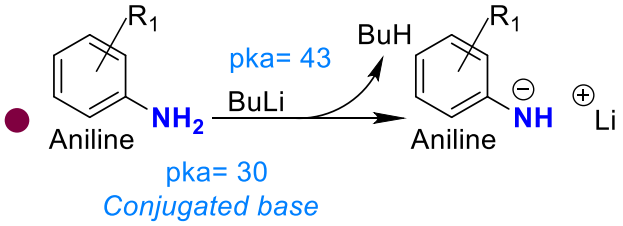
-Lone pairs are participating in the conjugation
→ **Lowering pKa**:

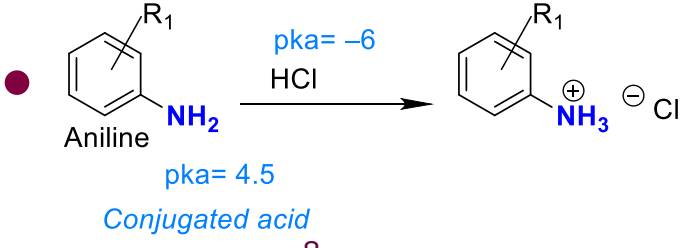


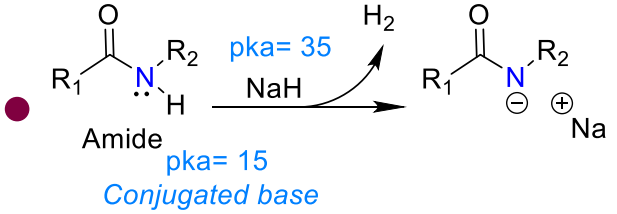


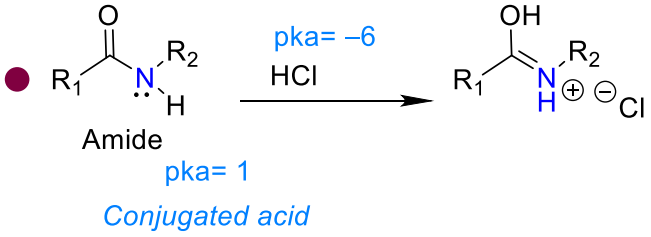
Aniline
$Ar\text{-}NH_3^+/Ar\text{-}NH_2$ ≈ **4.5**
$Ar\text{-}NH_2/Ar\text{-}NH^-$ ≈ **30**

Amide
$RC(O)NH_3^+/R1C(O)NH_2$ ≈ **1**
$RC(O)NH_2$, $RC(O)NH^-$ ≈ **15**



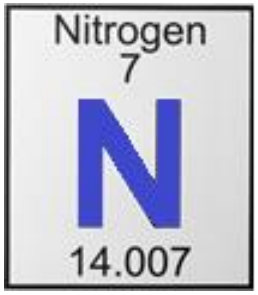






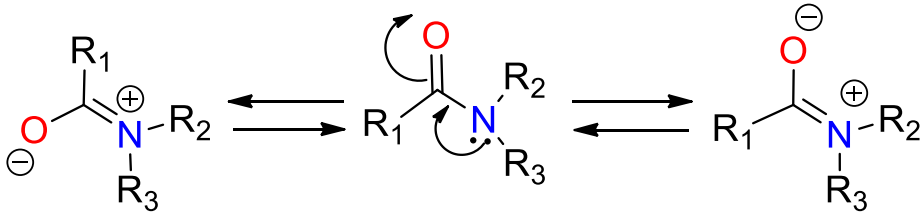
université PARIS-SACLAY

Nitrogen Properties: Donnor Effect

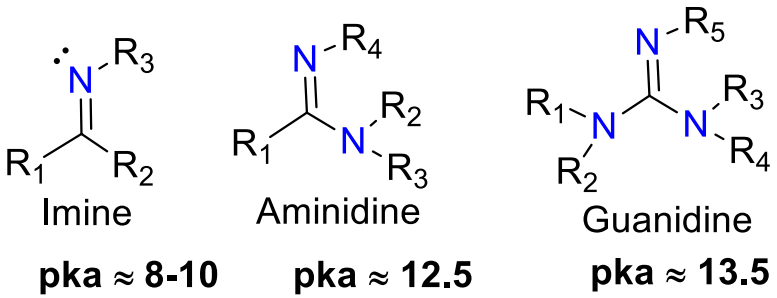


-In contrast, Nitrogen **enhances nucleophilic and basic properties** of carbonyl group or imine group:

Amides , carbamates and ureas are rather good Lewis bases.



Guanidines , amidines are very strong bronsted base.



Electron-Donating groups: Inductive and Mesomeric Effects

Electron-donating effect by induction
Electron-donating effect by mesomerism

↗ **Increases pKa**

Electron Donating effect by induction:

Alkylgroups or silyl (SiR_3) groups

Examples pKa EtOH= 16
iPrOH= 17
tBuOH= 18

Examples

pka $NH_3^{\oplus}$= 9.25, $Me_2NH^{\oplus}$= 10.6

O and N can give both electrodonating effects by mesomerism or electronwithdrawing effects by induction.
For a mesomerism effect, a conjugation is always needed.

⚠ No conjugation = No electron donor effect but EWG effect by induction
(because N and O are electronegative)

pKa $NH_4^{\oplus}$ = 9.25; pka $H_2N^{\delta\ominus}$-$NH_2^{\oplus}$ = 8.1

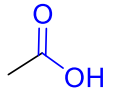
pKa H_2O = 15.7; pka $HO^{\delta\ominus}$-OH = 11.7

Electron Donating effect by mesomerism

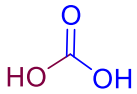
Atoms with a lone pair (or negative charge) in a conjugated system

$R_2\ddot{N}$-, $R\ddot{O}$-, $R\ddot{S}$-

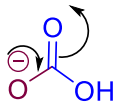
Examples



pka = 4.76

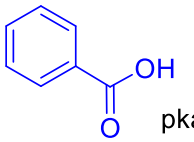


pka = 6.33

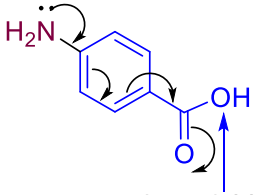


pka =10.33

Examples



pka = 4.2



pka = 4.88

To have a comprehensive tables of pKa values of organic and inorganics species see Bordwells, Williams, and Evans tables at https://organicchemistrydata.org/hansreich/resources/pka/

Electron-withdrawing groups: Inductive and Mesomeric Effects

Electron-withdrawing effect by induction
Electron-withdrawing effect by mesomerism

Decreases pKa

Electron-withdrawing effect by induction

Electronegative Atoms: O, F, Cl, Br, S, "N"

Examples

pKa AcOH= 4.76; $HOCH_2COOH$, pKa =3.83
$ClCH_2COOH$ = 2.86, FCH_2COOH = 2.66

Examples

pKa H-OH =15.7; pKa Cl-OH =7.53;
pKa Br-OH =8.65; pKa I-OH =10.5;
pKa HO-OH =11.75

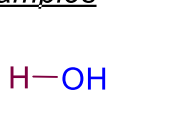
Inductive effect is lost signicatively over distance with acidic group (unlike mesomerism)

pka CF_3CH_2OH = 12.4 / pka $CF_3CH_2CH_2OH$ = 14.1 /
pka $CF_3CH_2CH_2CH_2OH$ = 15.4 / pka EtOH = 16

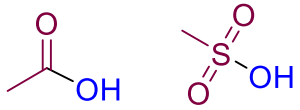
Electron-withdrawing effect by mesomerism

Carbonyl groups
(C=O--> ketone, aldehydes, esters)
Cyanides, Nitro, Sulfones

Examples

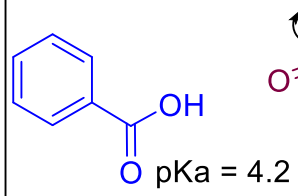


pKa= 15.7 pKa= –1.37

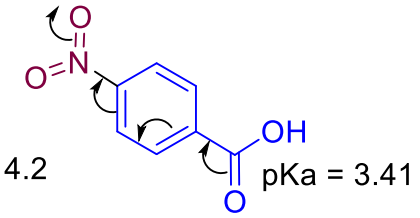


pKa= 4.76 pKa= –1.9

Examples

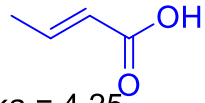


pKa = 4.2

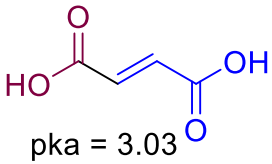


pKa = 3.41

Examples



pka = 4.25



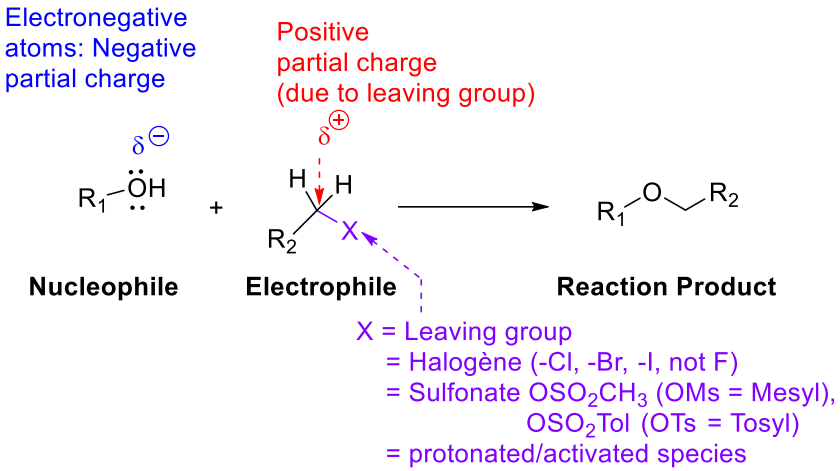
pka = 3.03

To have a comprehensive tables of pKa values of organic and inorganics species see Bordwells, Williams, and Evans tables at https://organicchemistrydata.org/hansreich/resources/pka/

université PARIS-SACLAY

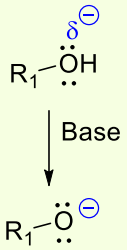
Formation of C-O Bonds: Alkylation/Nucleophilic Substitution (1)

Principle: Organic chemistry is mostly a question of static interactions: **Opposites attract**



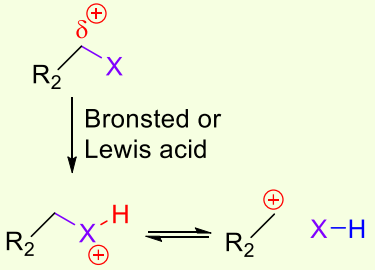
However if the nucleophile and the electrophile are neutral the reaction is very slow (or simply does not work).
→Needs of an activation!

Activation of the nucleophile



Key point:
Transformation of a partial charge into a whole charge makes the reaction possible!

Activation of the electrophile

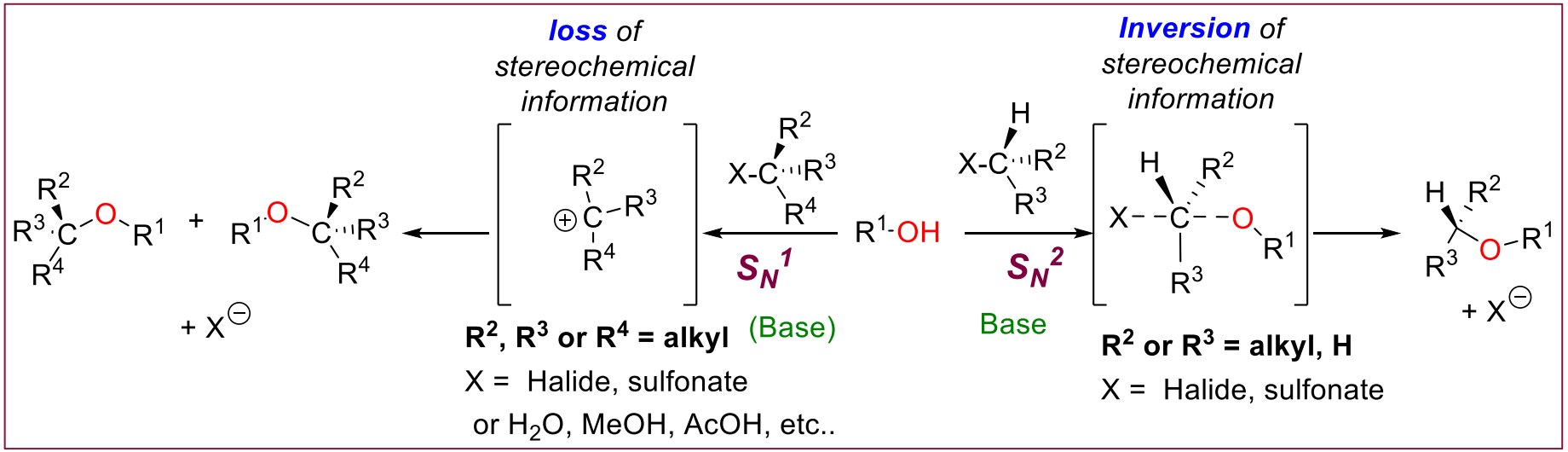


université PARIS-SACLAY

Formation of C-O Bonds: Alkylation (2)

S_N1 is observed on tertiary carbons and in general when the carbocation can be stabilized (e.g. conjugation)

S_N2 is observed on primary or secondary carbons



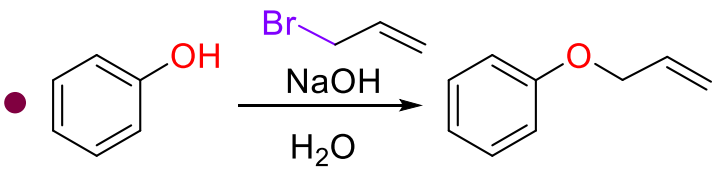
How to determine easily if we are in the S_N1 or S_N2 case?

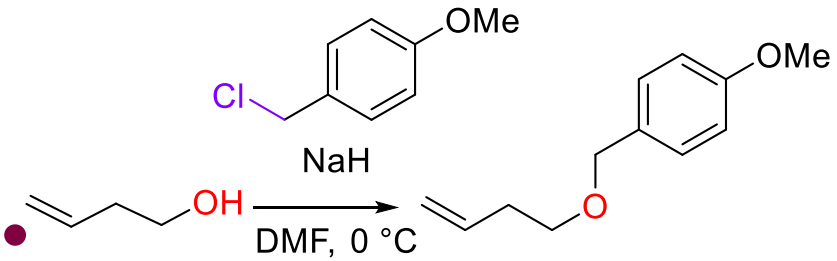
S_N1 reaction always involves acid activation of the electrophile (**carbocation**) and/or a tertiary substrates.

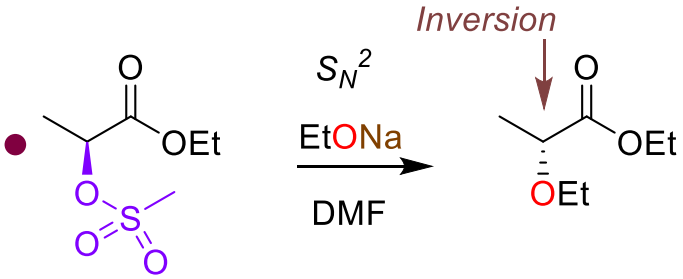
S_N2 reaction always involves base activation of the nucleophile (**anion**) and a primary or secondary substrates

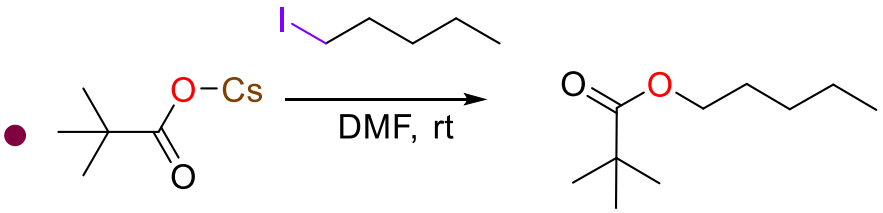
Alkylation with Oxygen Atom: S_N2

S_N2 reactions involve Oxy anions









Leaving Group Effect?

Leaving groups have not the same reactivity in S_N2 reactions

Reactivity scale

OTf > I >Br> Cl

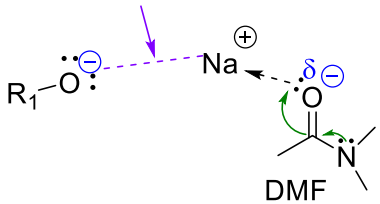
OMs ≈ OTs ≈ Br

CARE, **Fluoride (F)** is not a good leaving group (excepted few cases) because **C-F bond is very strong**!

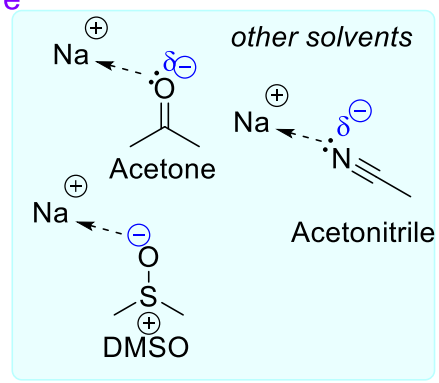
Solvant Effect?

Dissociation of ions:

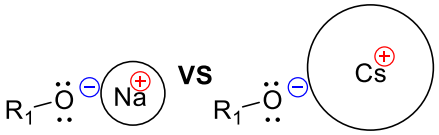
Makes the anion more reactive



Donnor effect of Nitrogen



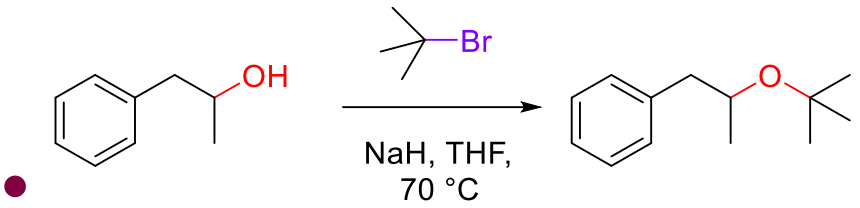
Cation effect ?

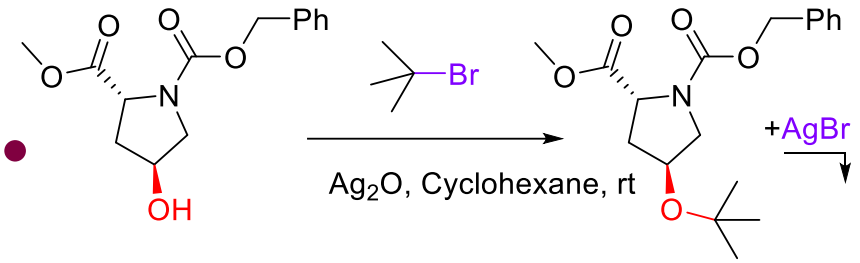


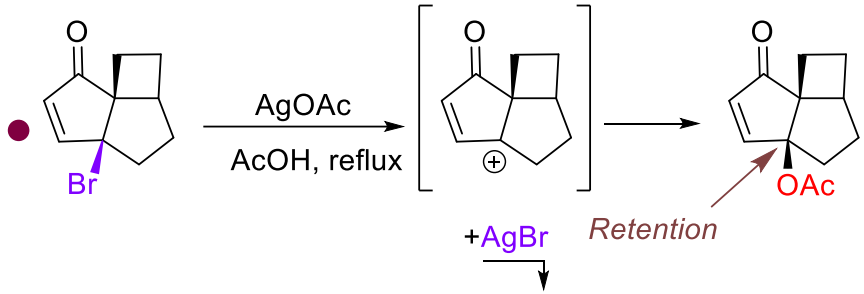
Increasing the size of the cation improves the ionic dissociation, by consequence the reactivity of the anion

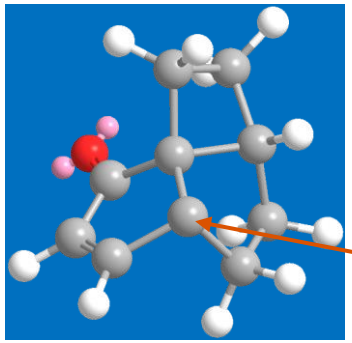
(It increases the distance between the two charges)

Alkylation with Oxygen Atom: S_N1 (Halides)









The stereochemistry can be retained in S_N1 if the conformation of the carbocation only allows addition on one side (here, the concave side is inaccessible).

The Carbocation: the Determining Step

The determining step is the formation of the carbocation.

Carbocation formation can be enhanced by using a cation having a high affinity with halides (usually **Silver (Ag)** or Lead (Pb))

These metals forms insoluble salts which displaced the equilibrium to the carbocation

Anion or not Anion, that is the question

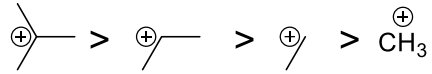
Unlike S_N2, the nucleophile does not necessarily have to be an anion.

In fact, **the carbocation is a very reactive species** and can react directly with OH groups.

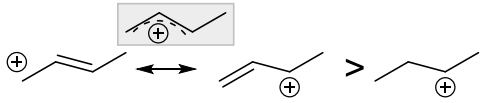
A base with a lower pKa than alcohol can be used to scavange the acid formed.

Stabilization Recipe

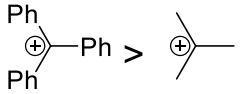
Carbocations are stabilized by the substitution,



Carbocations are stabilized by the conjugaison

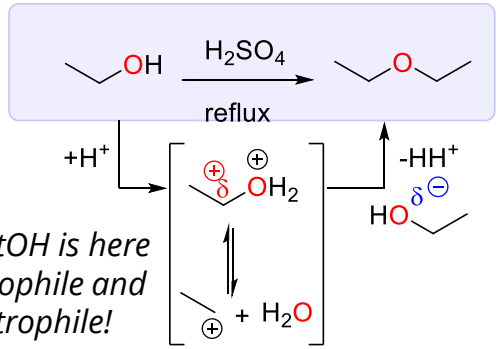


Yellow color due to conjugaison over 16 Carbons



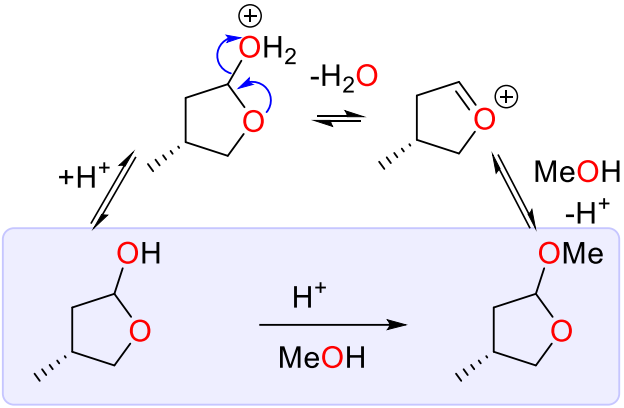
Alkylation with Oxygen Atom: S_N1 (Acid Activation)

Ether Synthesis



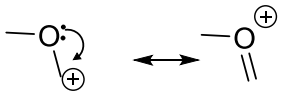
Note: EtOH is here a nucleophile and an electrophile!

Substitution on ketals/acetals

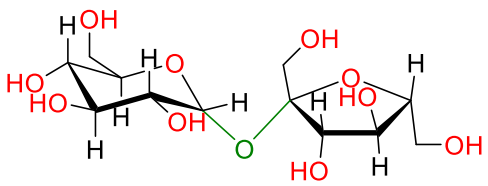


Carbocation Stabilization by Adjacent Heteroatoms

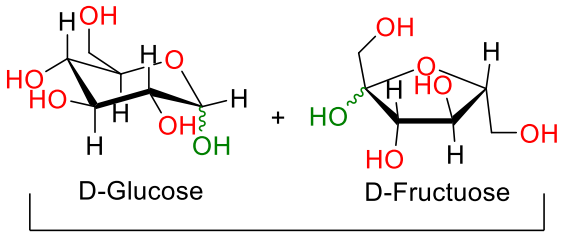
Adjacent oxygen from acetal/ketal functions greatly **stabilizes the carbocation** due to the **donor effect of the oxygen lone pair.**



Works also with N or S atoms



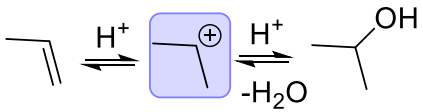
Saccharose / Sucrose



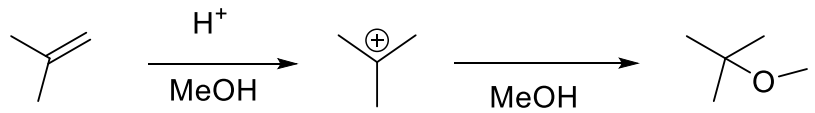
Also called "***inverted sugar syrup***"

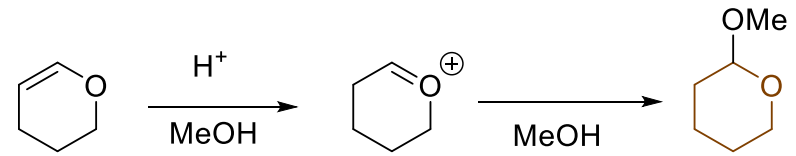
Carbocations from Alkenes

Alkene functions can also provide carbocations by protonation They can be considered like "masked" hydroxy functions



Activation of olefins

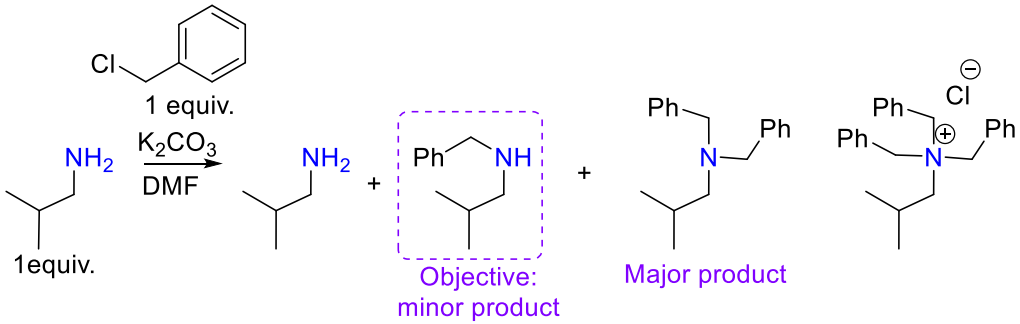




THP protecting group

Alkylation: Examples with Nitrogen Atom

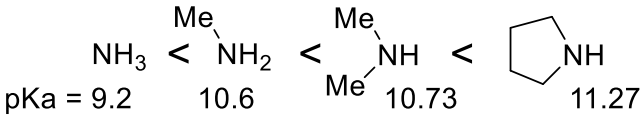
-Direct alkylation is fewly selective with amines.



The Reason Behind the Non-Selectivity

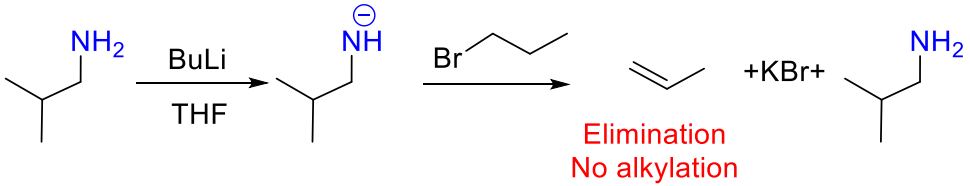
Nucleophilicity of amines are in relationship with their pKa

nucleophily ranking from the least to the most:



*The **more the amine is substituted** by an alkyl group, **the more nucleophilic it is***

*That explains the **leak of selectivity for a direct alkylation***

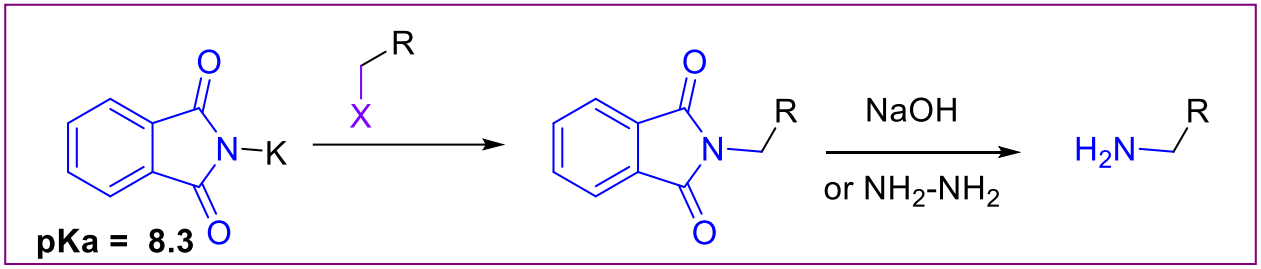


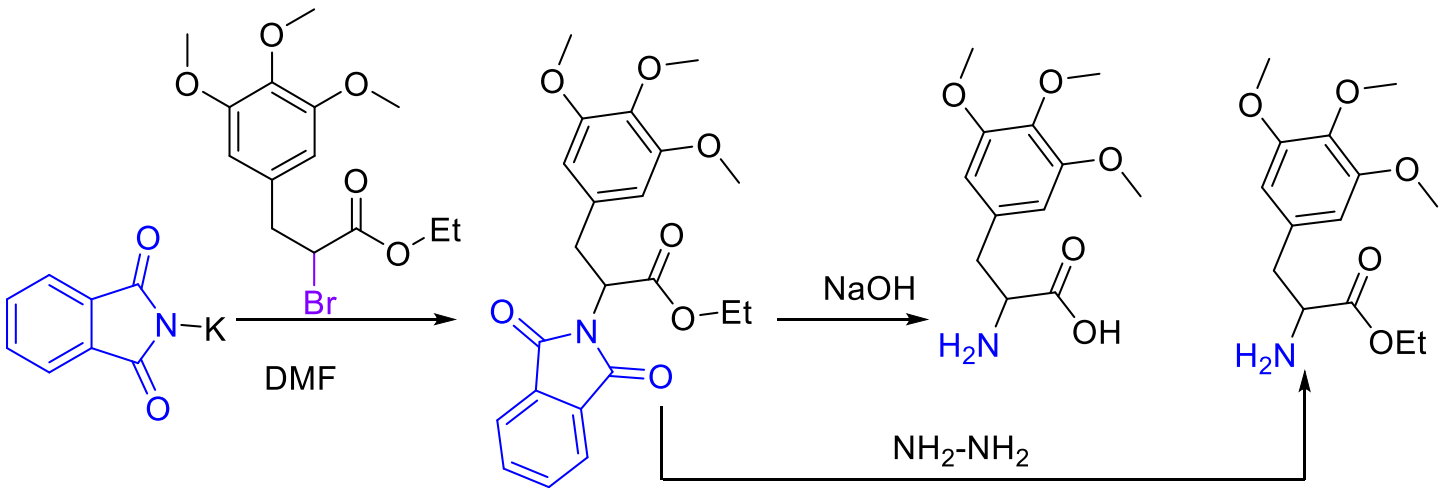
***Amine anions too basic** (pka = 35), thus side reactions are first observed such as the E2-elimination*

Alkylation: Examples with Nitrogen Atom (2)

-The use of an indirect route required:

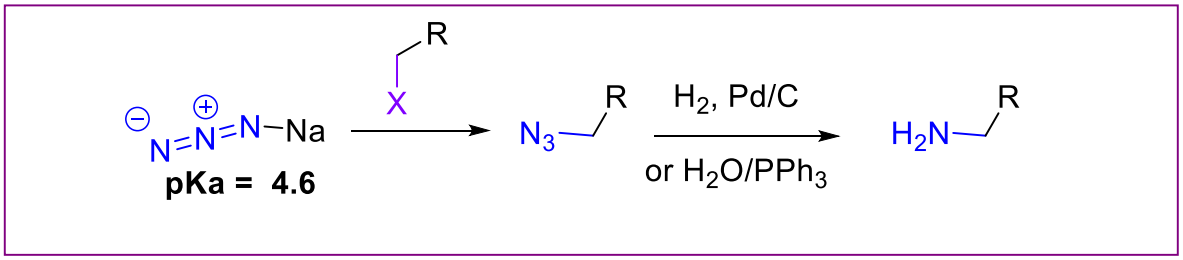
From phtalimides salts:
Gabriel Synthesis (1887)

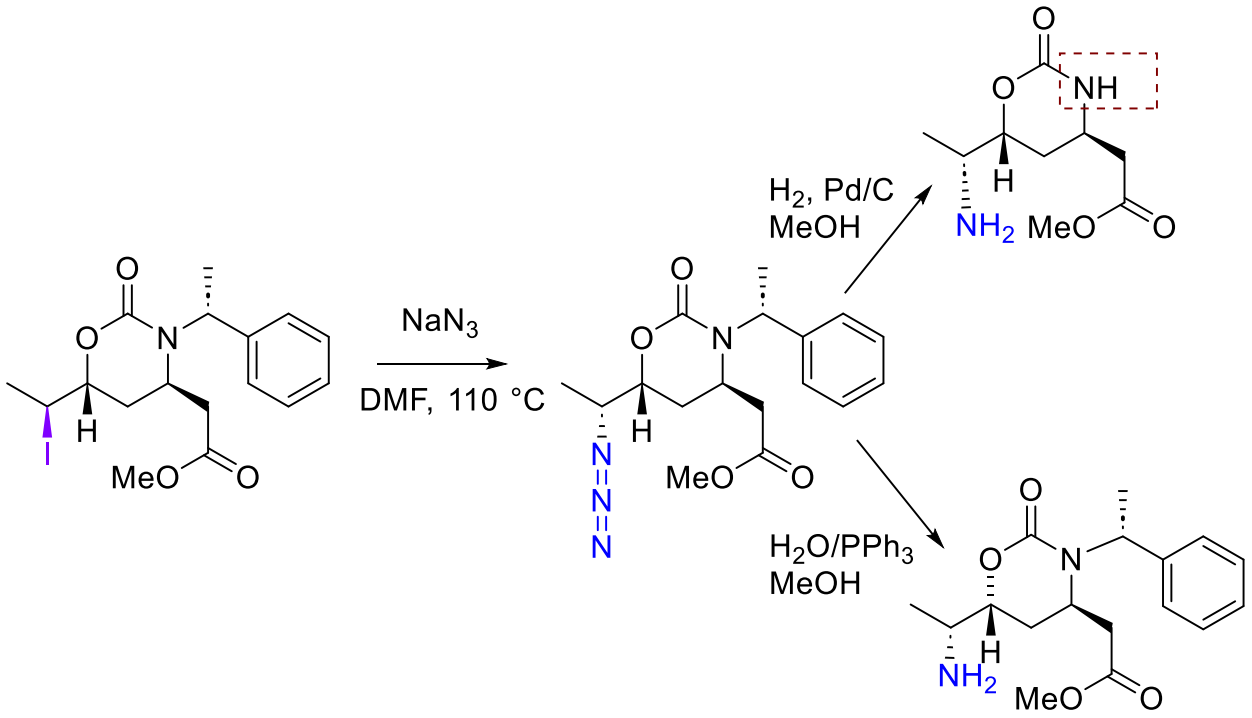




Alkylation: Examples with Nitrogen Atom (3)

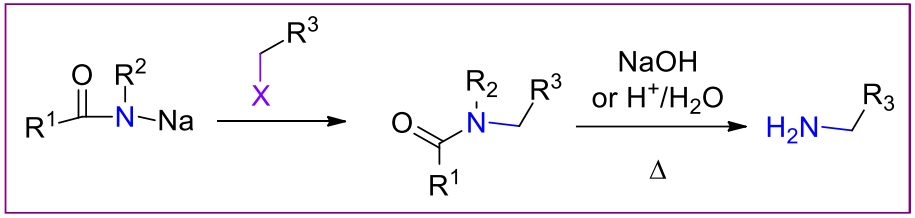
From Azides:

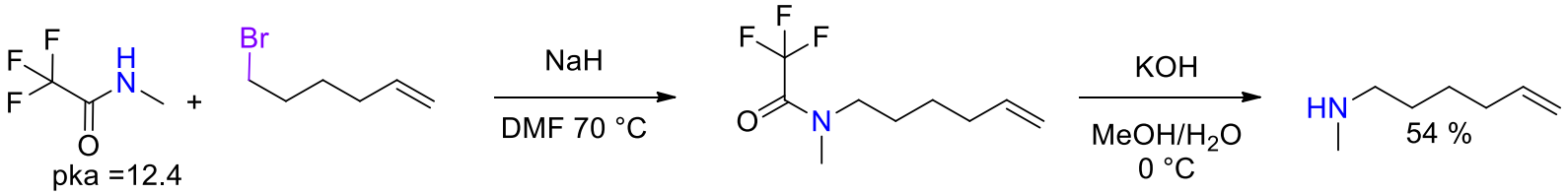




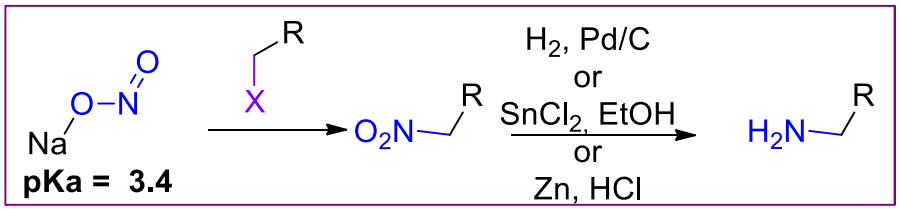
Formation of C-N Bonds: Alkylation (4)

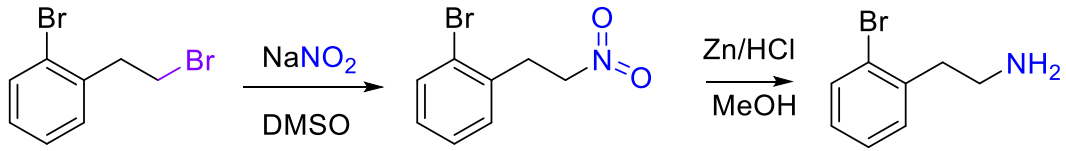
-Formation of Secondary Amides





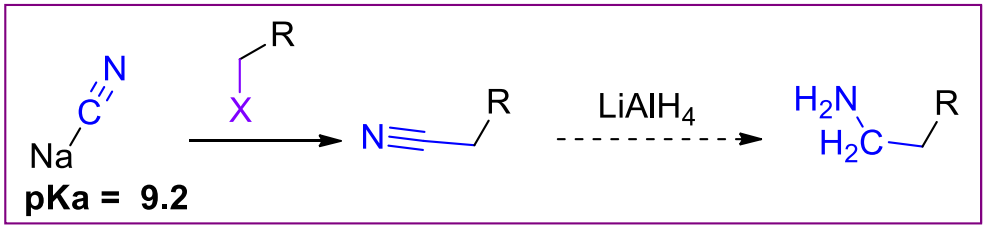
-Formation of Nitroalcanes

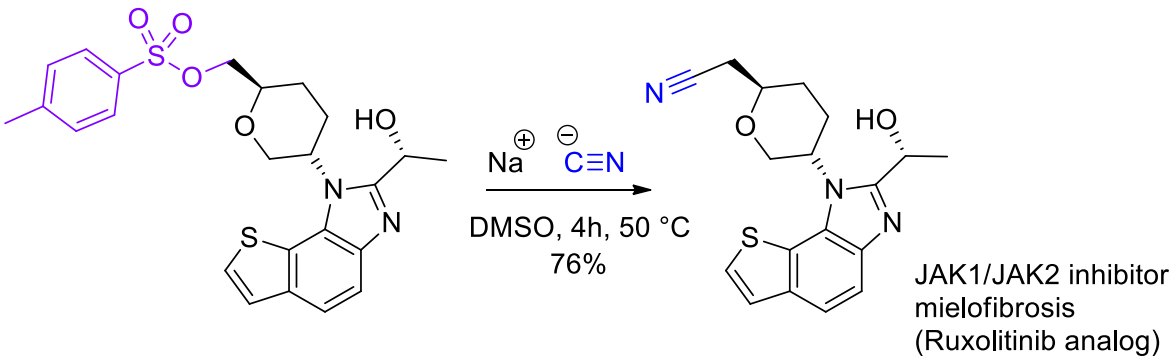




Formation of C-N Bonds: Alkylation (4)

-Formation of Nitriles



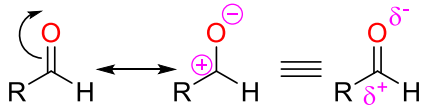


JAK1/JAK2 inhibitor
mielofibrosis
(Ruxolitinib analog)

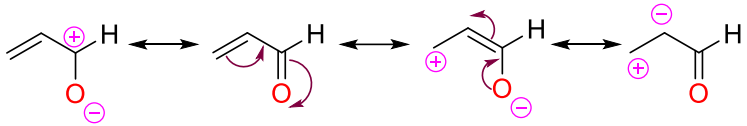
Conjugated Addition: Principle

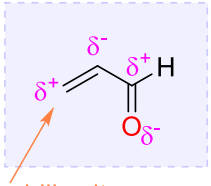
- Amines are better substrates for this transformations than alcohols.
- Conjugated addition is limited to substrates with an electron with-drawing groups (NO_2, CN, ester, ketones, aldehydes, etc...)

Recall: reactivity of carbonyl groups:



Application to a conjugated systems



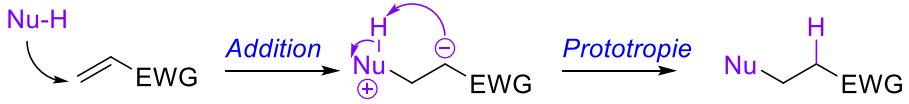


electrophilic site for addition

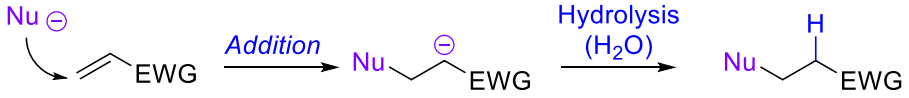
The conjugaison with the carbonyl group (or any electron-withdrawing group) **polarises the alkene function**

→ **make it electrophilic at the β-position**

*With a **neutral** nucleophile*

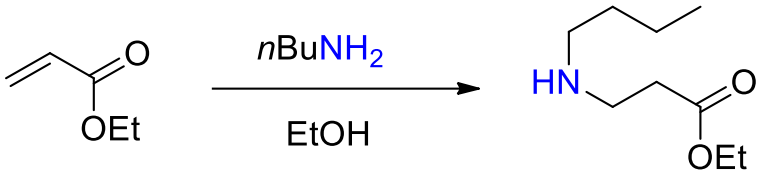


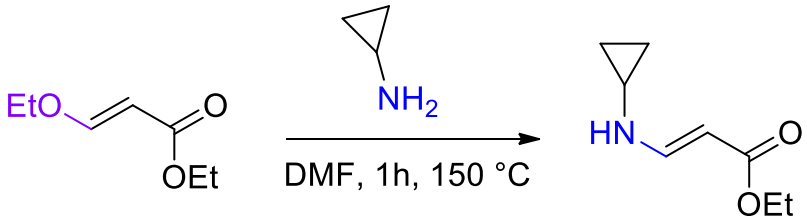
*With an **anionic** nucleophile*



Conjugated Addition: Exemples with Nitrogen and Oxygen

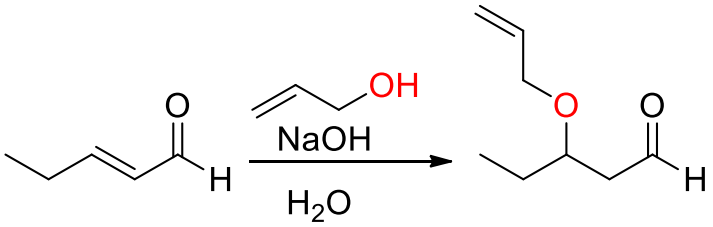
-Addition of amines





E:Z = 83:17

-Addition of alcohols



(works only on enal or enones)

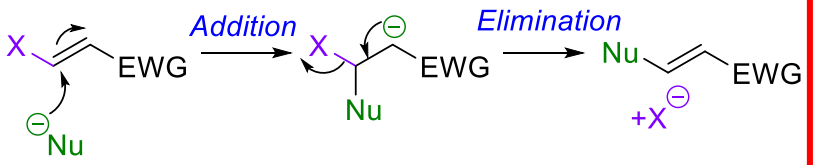
Reactivity Profile

-**Reactivity** of amine and alcohols in conjugated addition is **similar to those observed in alkylation**:

-**Amines reacts as neutral species**, but there is generally less risk of multi-reaction

-**Alcohols needs a base or acid activation**. It is generally **restricted to** unsaturated **aldehyde or ketone**, which are more reactive than the esters.

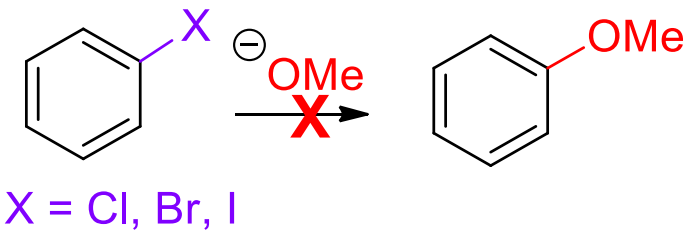
The Case of β-Substituents



-In case of a **heterosubstituent** in β-position, **an elimination proceeds.** (X = Cl, Br, F, I, OR)
-The leaving group (X) should have **better leaving group properties than the nucleophile.**

Aromatic Substitution (1) : Aromatic Nucleophilic Substitution

-Direct Nucleophilic Substitution on aromatic ring and Sp2-carbons are not possible in general.

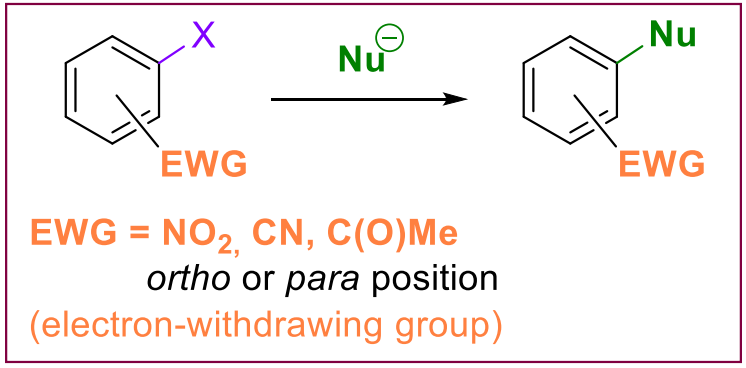


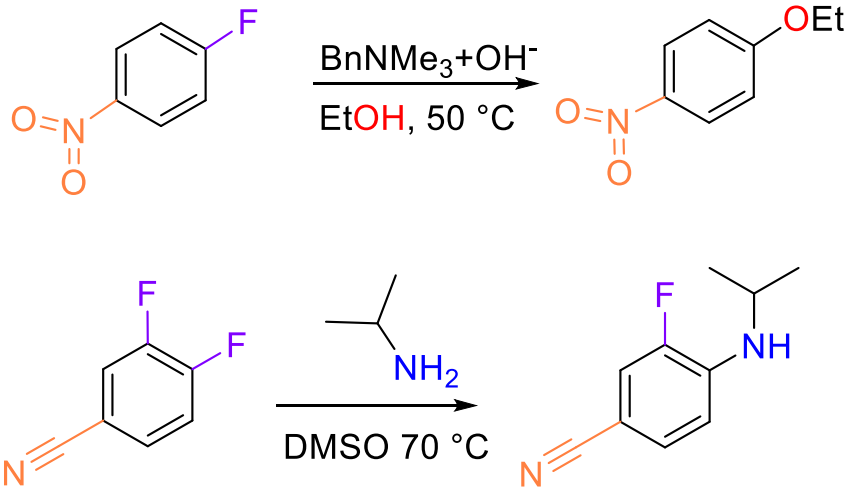
<u>Note:</u> Metal coupling reaction (Pd, Cu, Ni) can mediate sometimes the transformation. It will be viewed further in M2.

-**Aromatic Nucleophilic Substitution**:

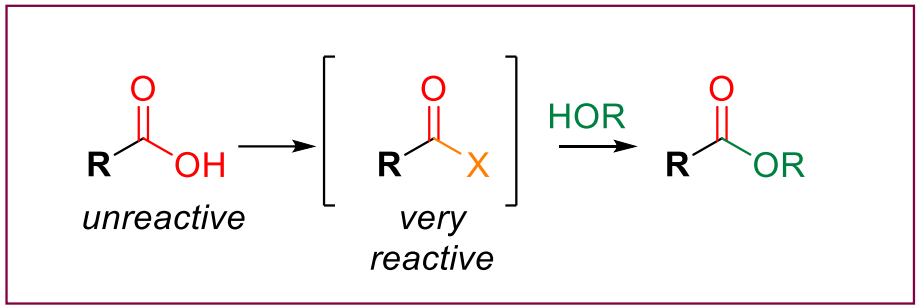
-Works only if a strong electron-withdrawing group is present

-Reactivity of halides is inverse in S_N^{Ar} compared to S_N^2: F>Cl>Br>I

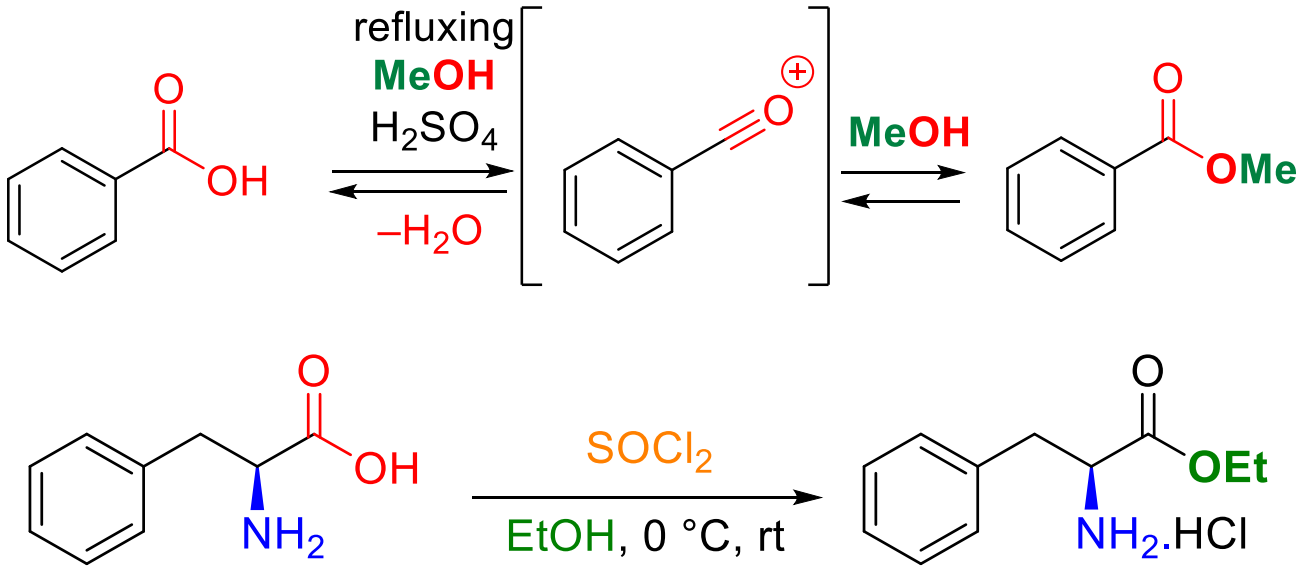




Acylation : Esterification (1)

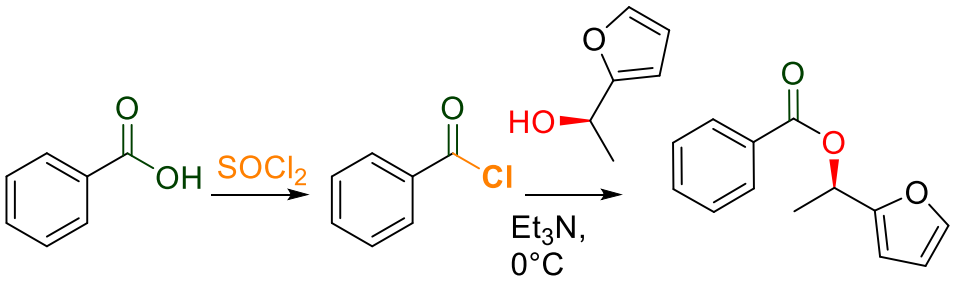


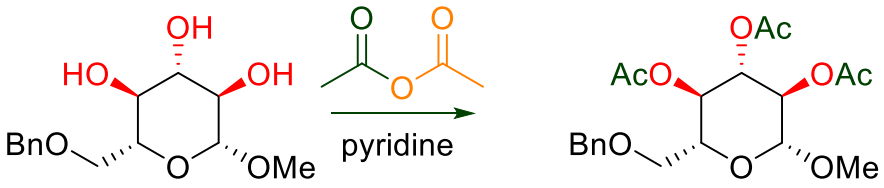
-**Acid catalysis:** It needs a displacement of water or a dehydrating reagent



Acylation : Esterification (2)

-Anhydrides or acyl chlorides

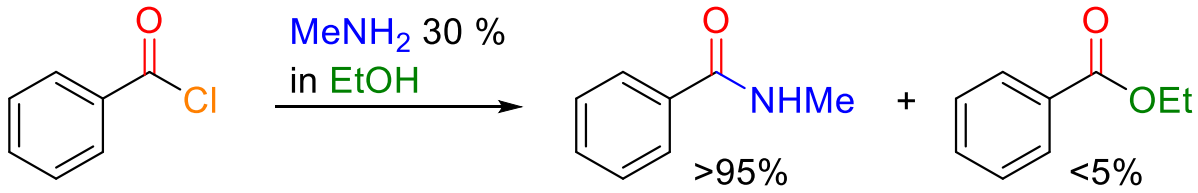




Acylation : Peptide Synthesis (1)

Formation of Amides:

-Amides cannot be prepared by acid catalysis (inactivation of amine by protonation)
-Anhydrides and acyl chlorides are excellent reagents for their formation
-Amines are more reactive than alcohols.



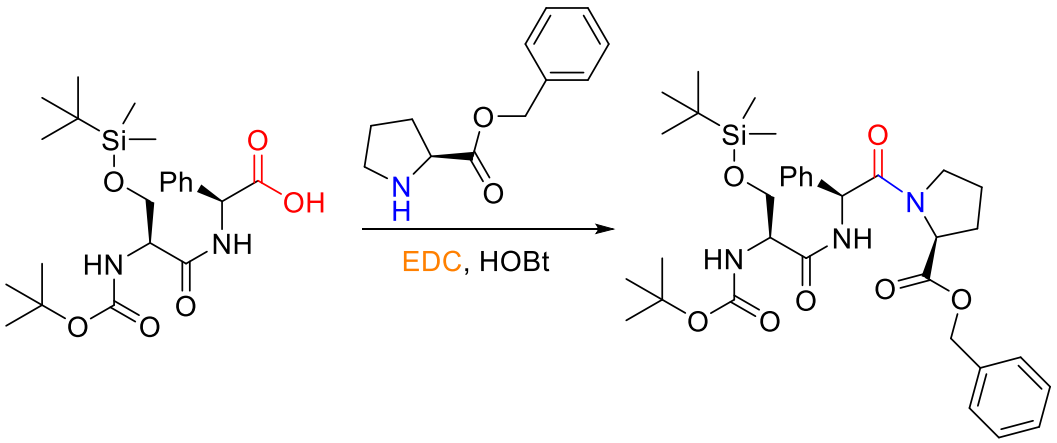
Acylation : Peptide Synthesis (2)

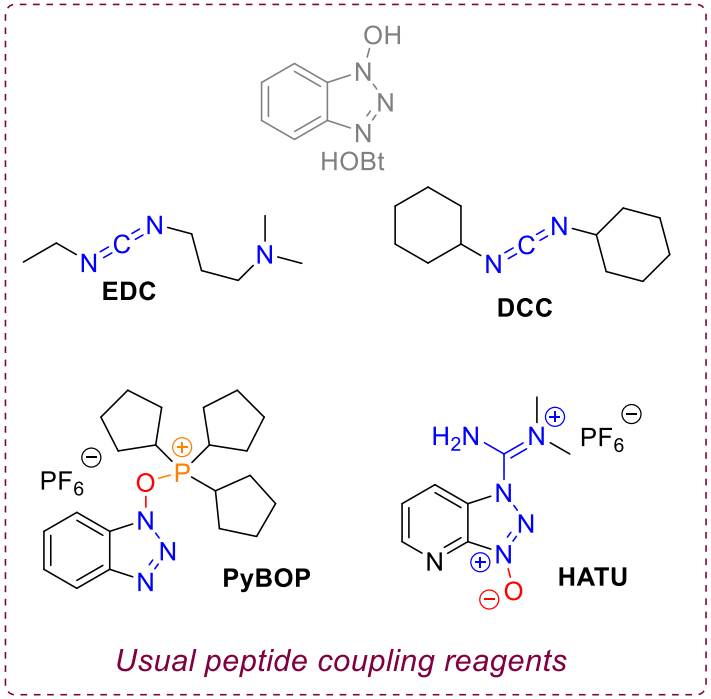
Peptide Synthesis: Needs of Iterative acylation on sensitive substrates.

-Preparation of acyl chloride and anhydrides is not always convenient (acid sensitive group, epimerization).

-Use of special reagents for carboxylic acids activation.

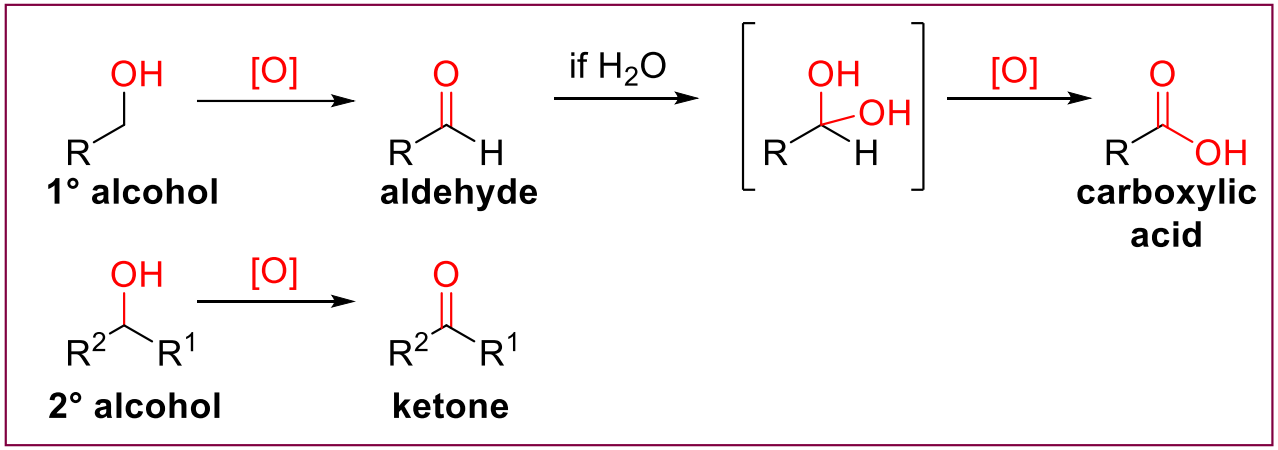
-HOBt generally prevents the epimerization process.



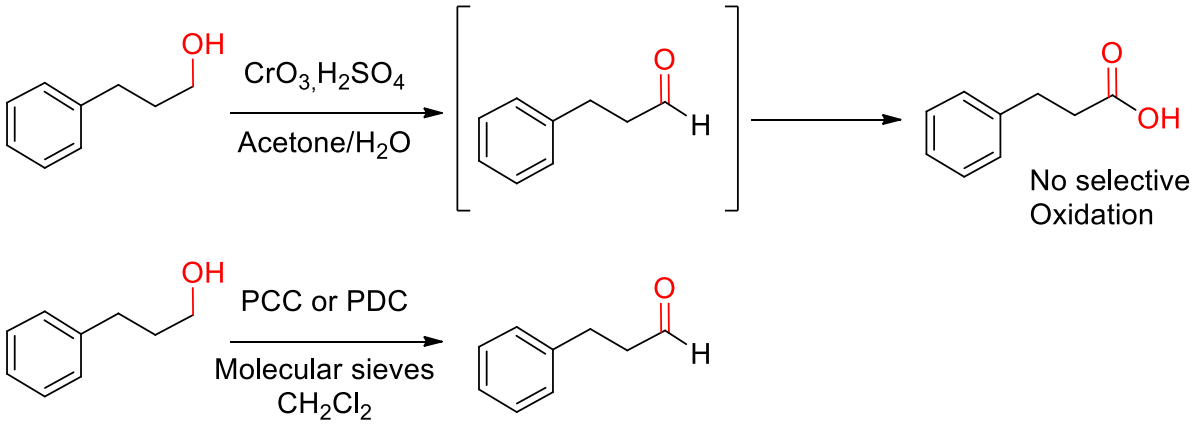


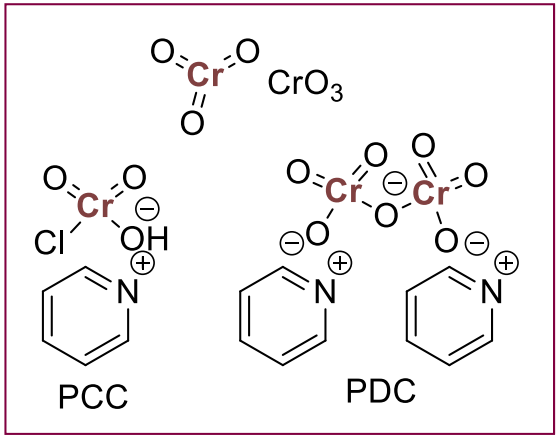
Usual peptide coupling reagents

Oxidations of Alcohols (1)



-**Chromium reagents**: Versatile, cheap but hazardous, no atom economy.
Slight acidic conditions.

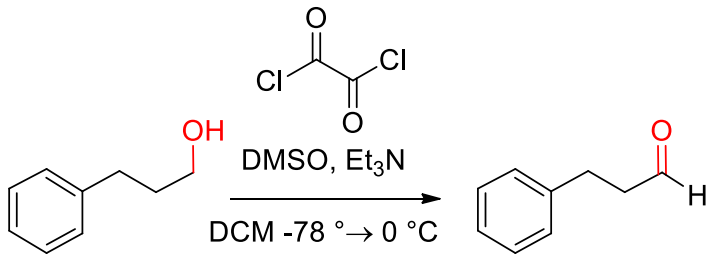


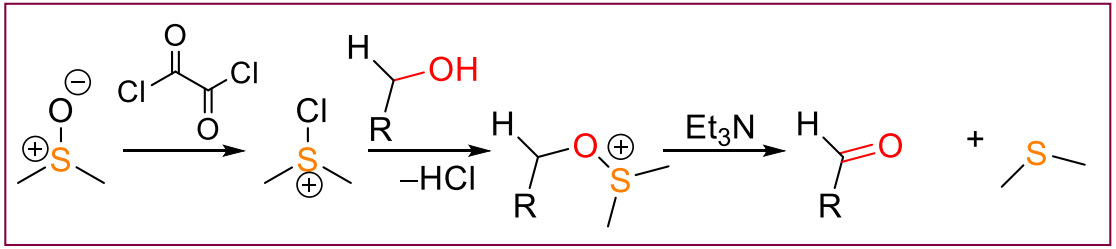


université PARIS-SACLAY

Oxidations of Alcohols (2)

-**Swern Oxidation** and related transformations: cheap, selective but stench (formation of Dimethyl sulfide) byproduct production, no atom economy, Slight basic conditions,

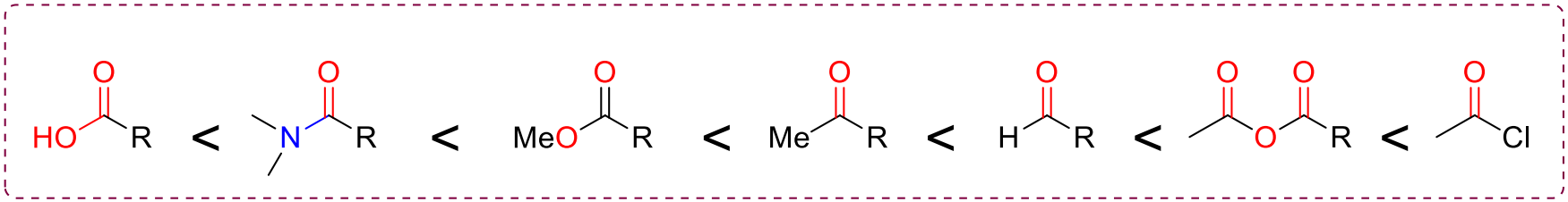




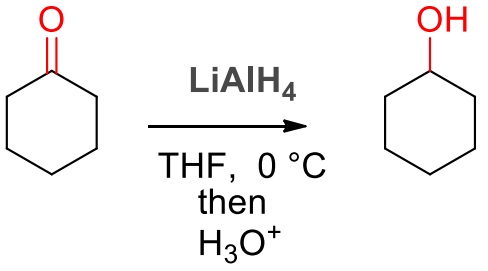
-**Others reagents:** Research on alcohol oxidation is sill under development to to **improve selectivity**, and make **greener process** (TEMPO reagent, metal catalyzed oxidation, etc…)

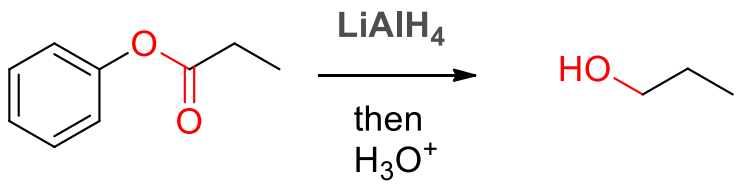
Reduction of Carbonyls: Aluminium Reagents (1)

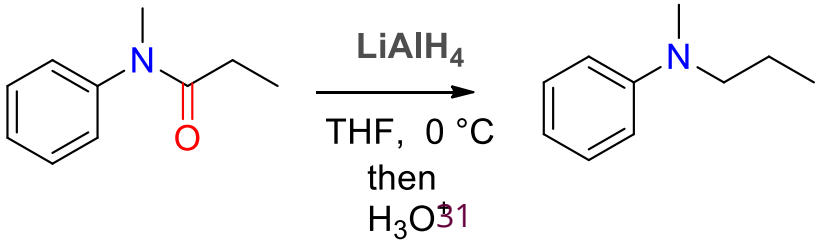
-Reactivity scale: Carbonyl groups have different reactivities. Reagents can be used depending their reactivity.

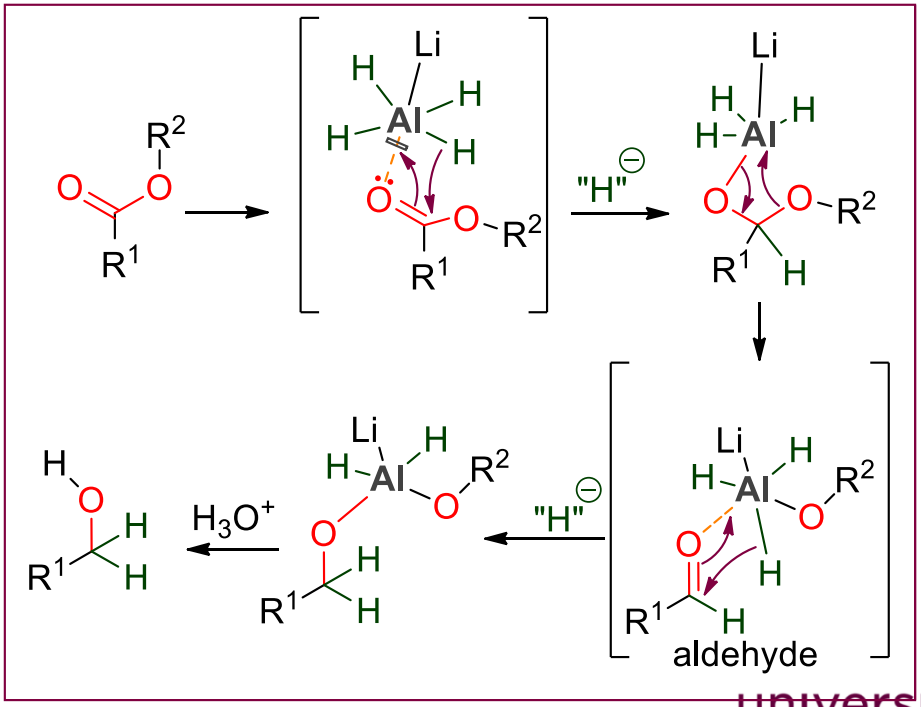


Aluminium reagents: -$LiAlH_4$: The strongest. Reduces every carbonyl group (and beyond). Unselective, hazardous: reacts violently with water.



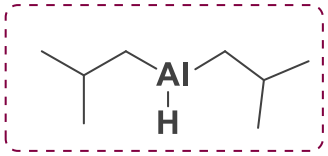






Reduction of Carbonyls: Aluminium Reagents (2)

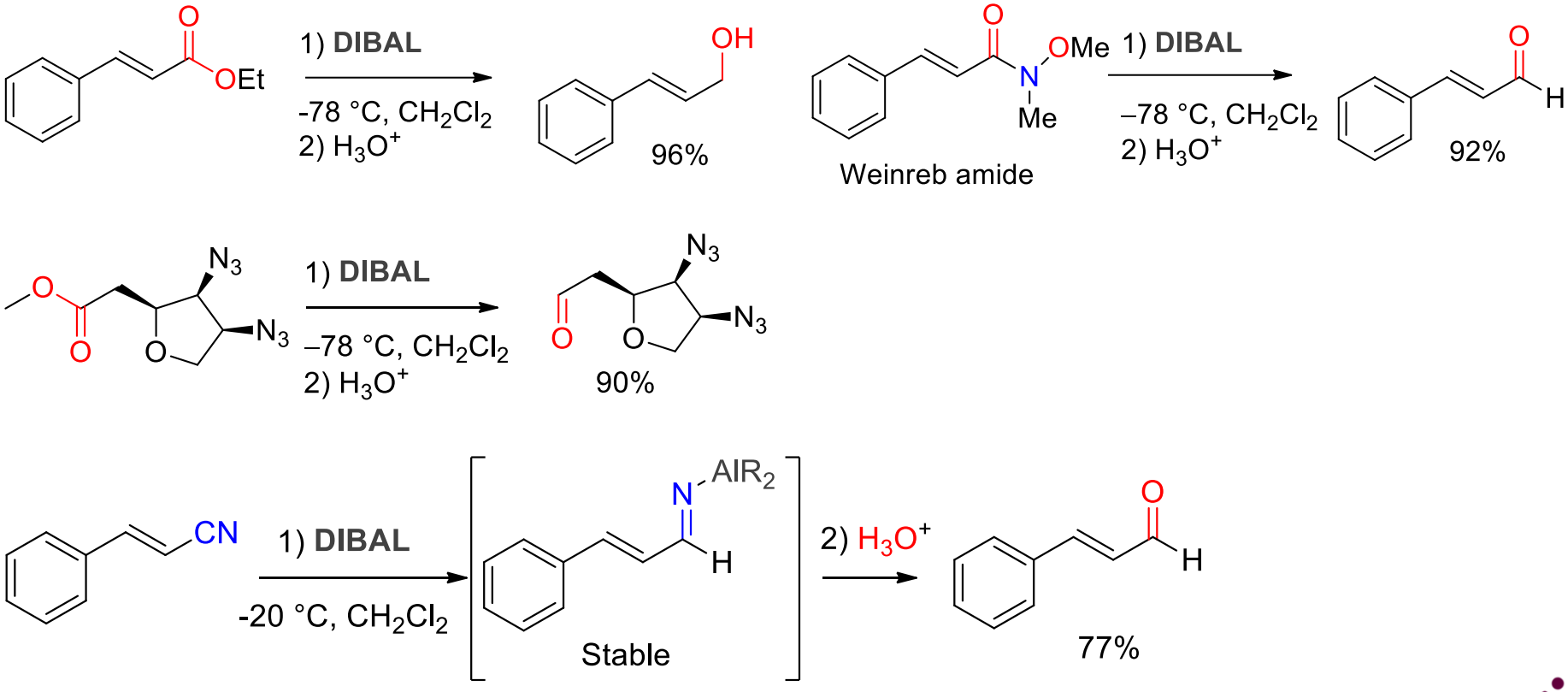
-DIBALH (DiIsoButylALuminium Hydride):



-Reduce most of carbonyl groups

-Can be selective in the transformation of cyanide and amide into aldehyde.

-Sometimes work for esters (substrate dependant)

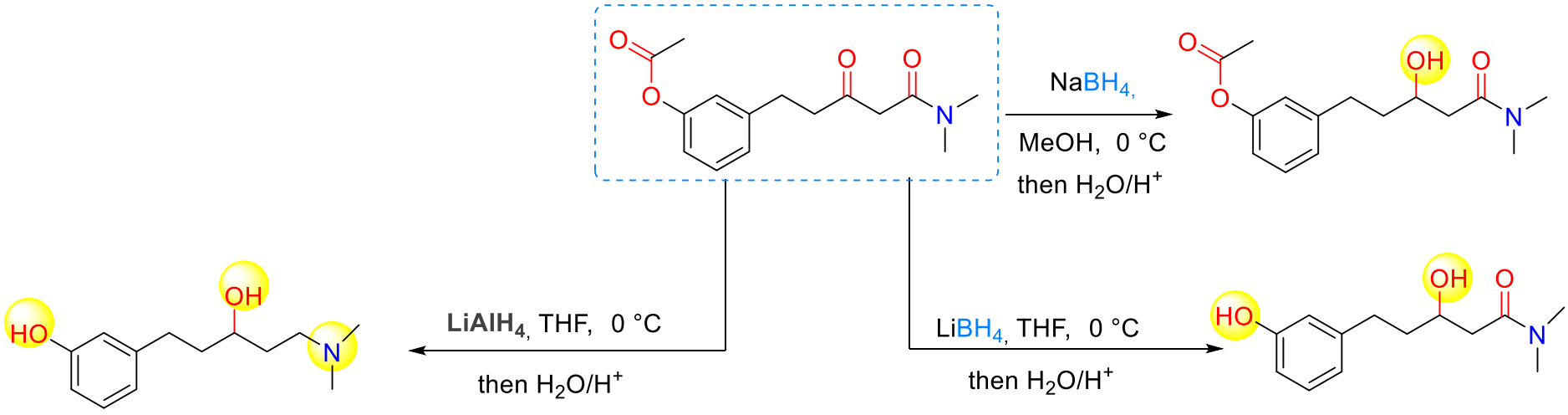


Reduction of Carbonyls: Boron reagents

-Boron reagents:

-$NaBH_4$: Mild Reducing reagent. Selective to **ketones** and **aldehydes**.
Reduce also reactive carbonyl groups such as acyl chlorides or anhydrides.

-$LiBH_4$: reduce also **esters**



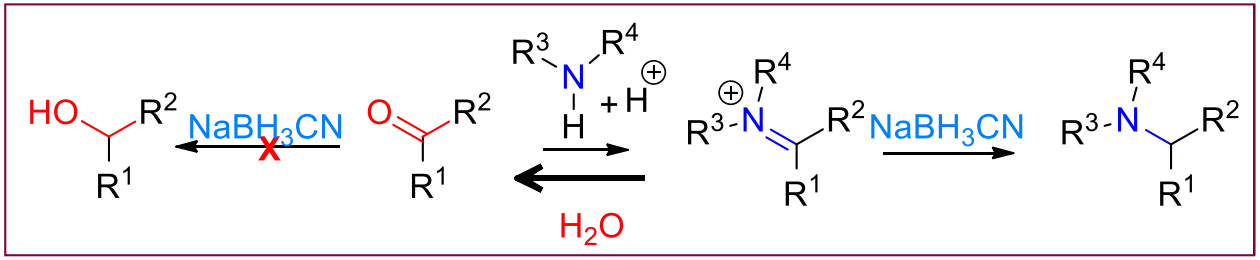
Reduction of Imines: Boron reagents

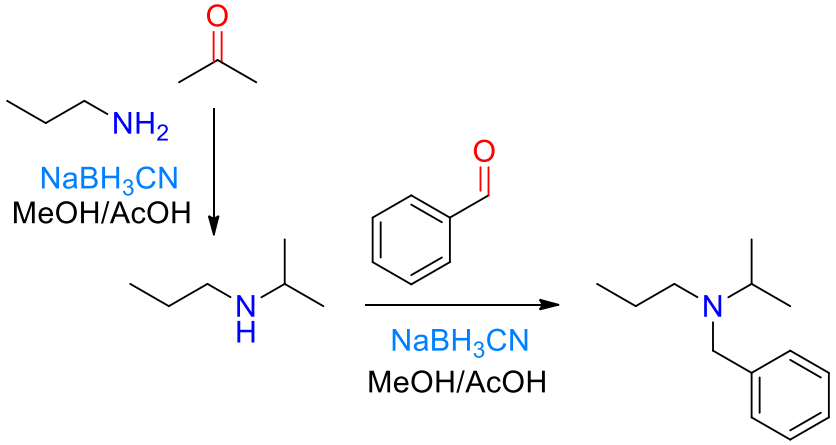
-Reduction of Imines and Imminiums

-$NaBH_3CN$: Reduction of protonated imines and iminiums:

Reductive amination

-Reagents of Choice: $NaBH_3CN$ (poorly reactive towards aldehydes and ketones but specific of iminiums)



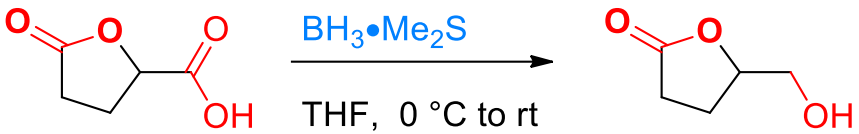


Reduction of Carboxyls: Boron reagents (2)

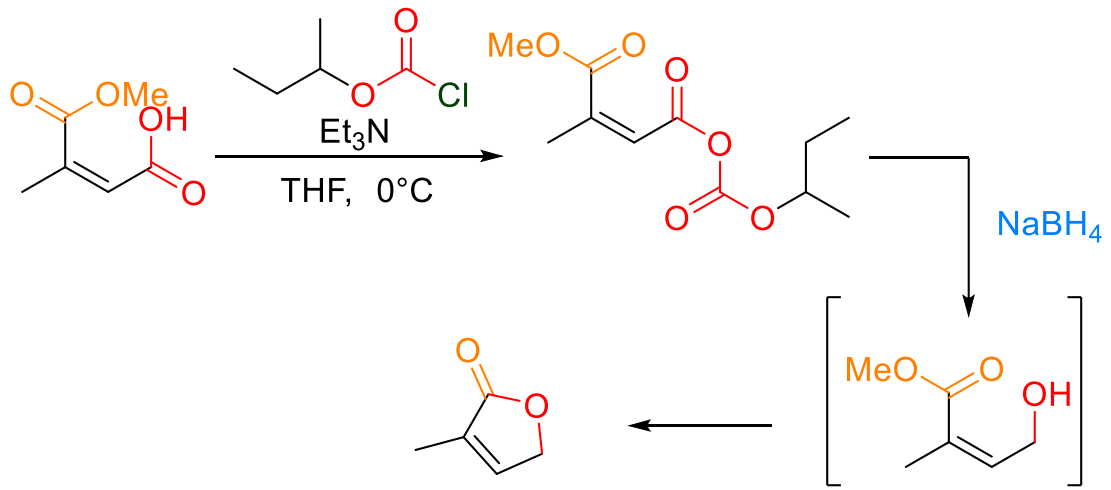
-Selective Reduction of Carboxylic acids:

-BH_3: Unreactive towards cyano, esters or amide groups

Careful: reacts with aldehydes, ketones and alkenes

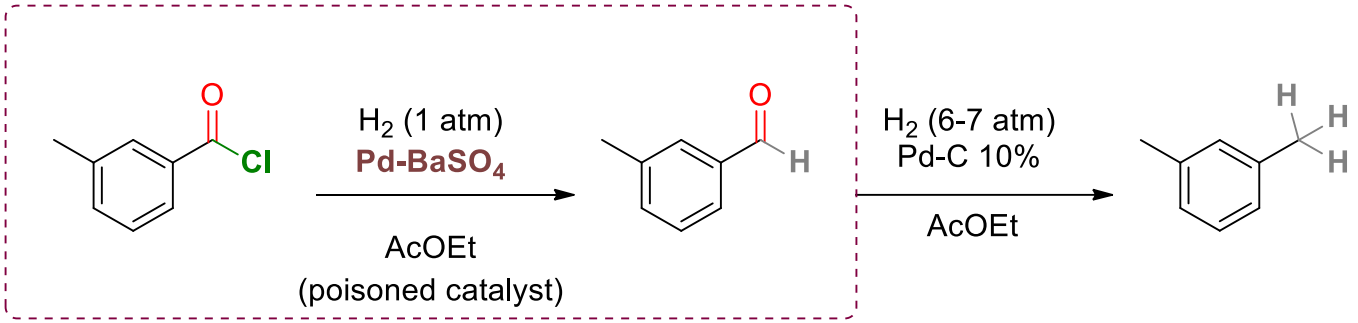


-$NaBH_4$ reduction via **activation** through formation of **mixed anhydride**,



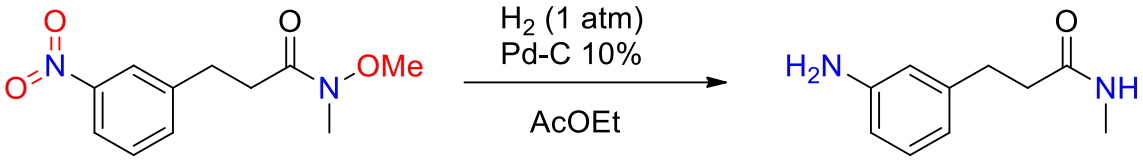
Reduction: Hydrogenation and Metal Reduction

-Acyl chloride (Rosenmund hydrogenation)

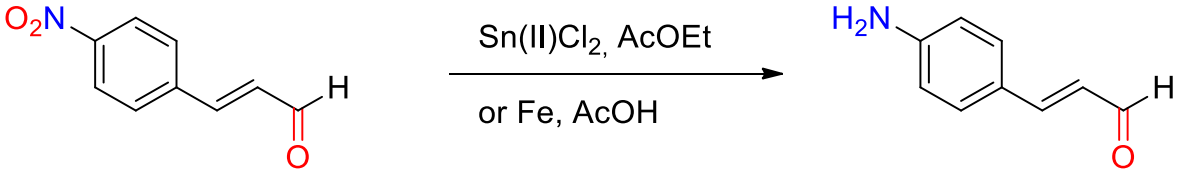


-Nitro groups

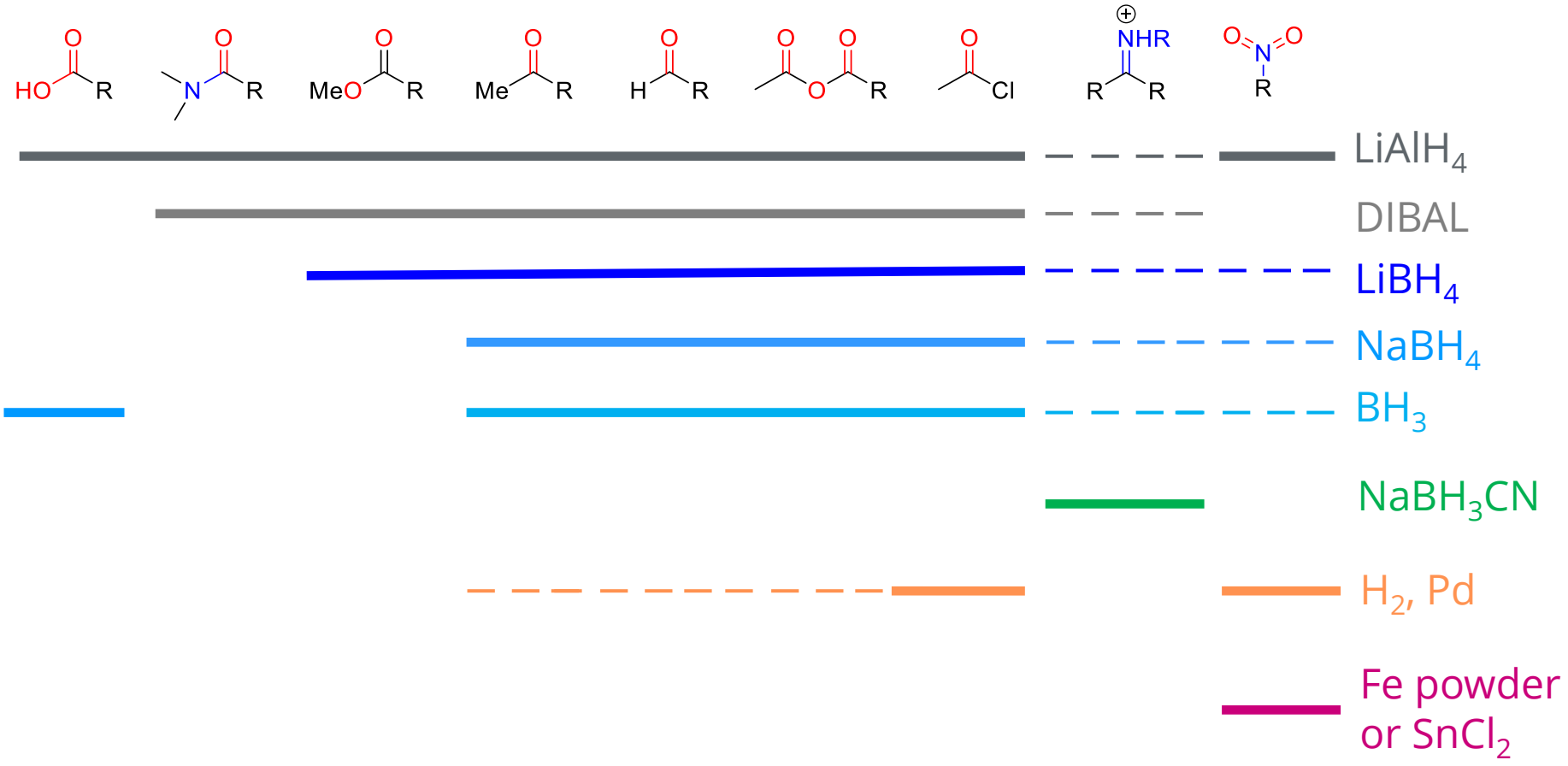
by hydrogenation:



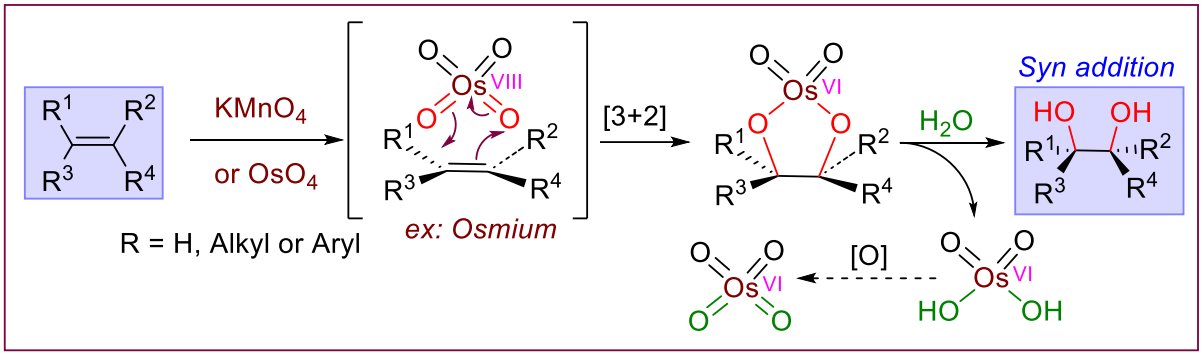
by Metal Reduction



Reduction: Summary



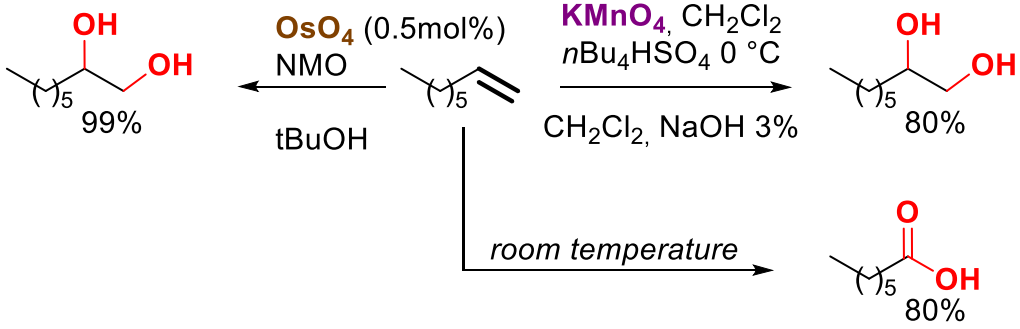
Oxydation of Olefins: Dihydroxylation



Stereospecific transformation

OsO_4: expensive, very selective used in catalytic amount with a co-oxidant

$KMnO_4$: cheap, non selective oxidant,used in stoechiometric amount, non-toxic

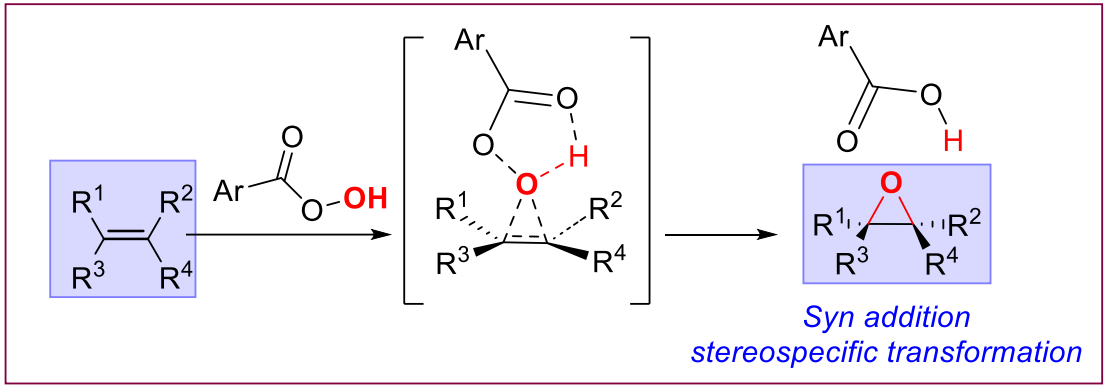


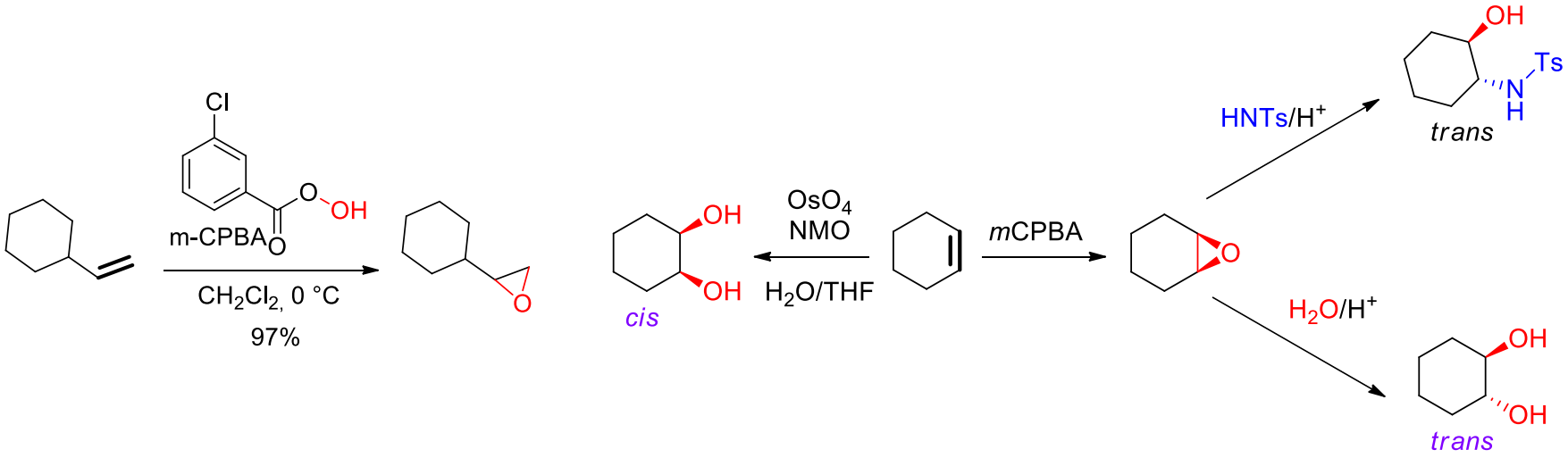
université PARIS-SACLAY

Oxydation of Olefins: Epoxidation (1)

Most popular reagent are peracids, but metal catalyzed epoxidation are also widely used.

-Peracids

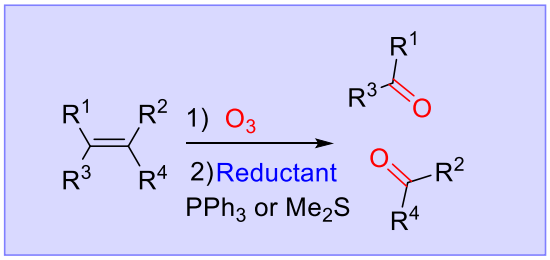


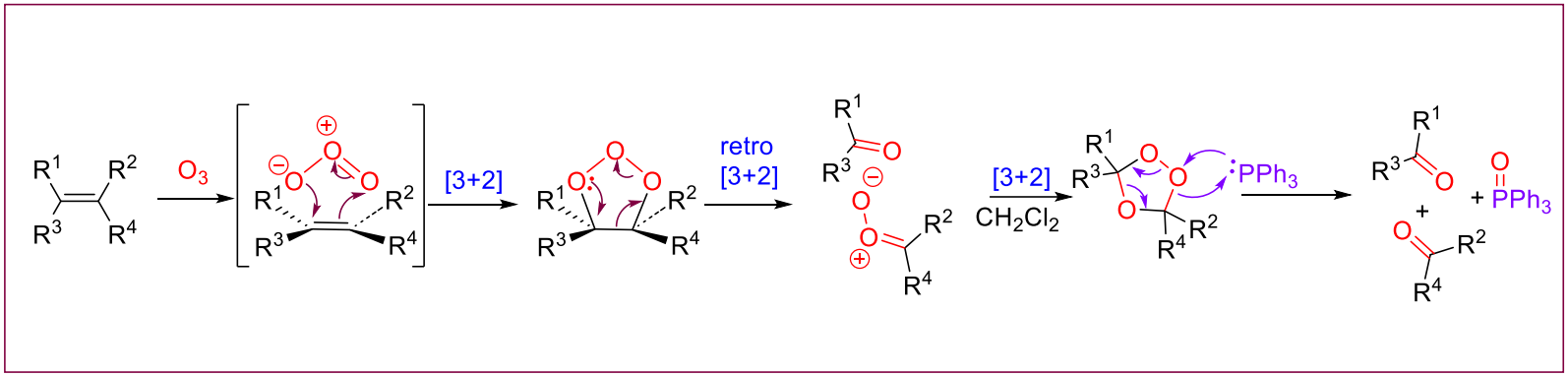


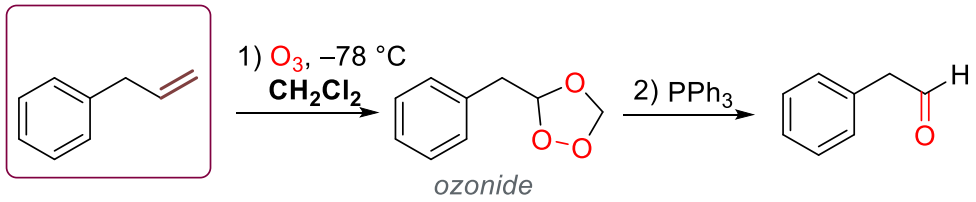
université PARIS-SACLAY

Oxydation of Olefins: Dipolar Cycloaddition (Ozonolysis)

-**Ozonolysis**: Ozone promotes 1,3-dipolar cycloaddition.



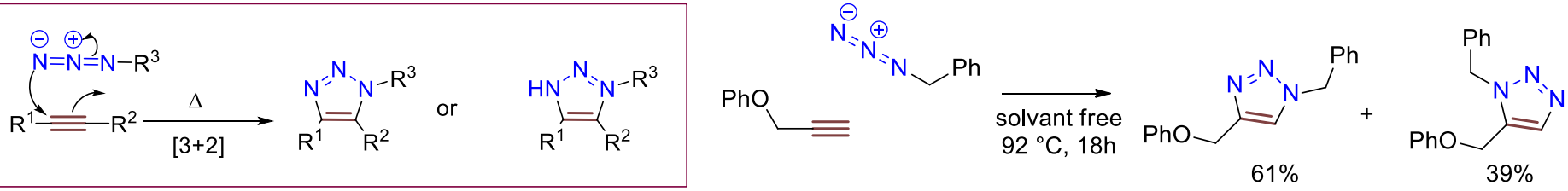




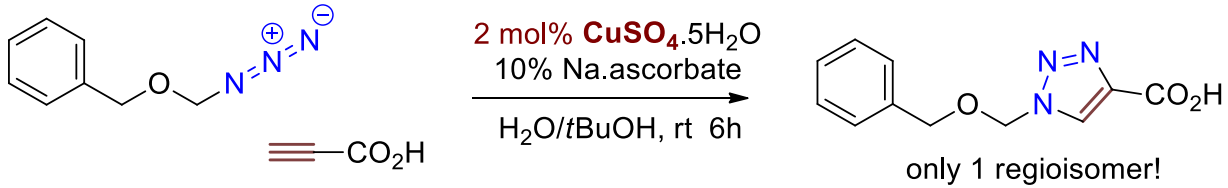
Oxydation of Alkyne: Dipolar Cycloaddition (Huisgen)

-**Nitrogen version of ozonolysis**: <u>the Huisgen cycloaddition.</u>

-requires higher temperature, and longer reaction time, thus it reacts only on alkynes.
-Cycloaddition products are stables leading to triazoles.



-**Copper catalysis** improves the process (low temperature, regioselectivity)

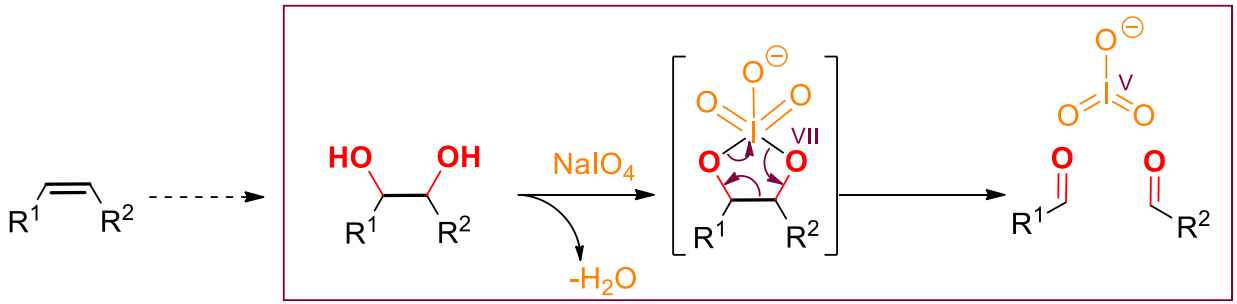


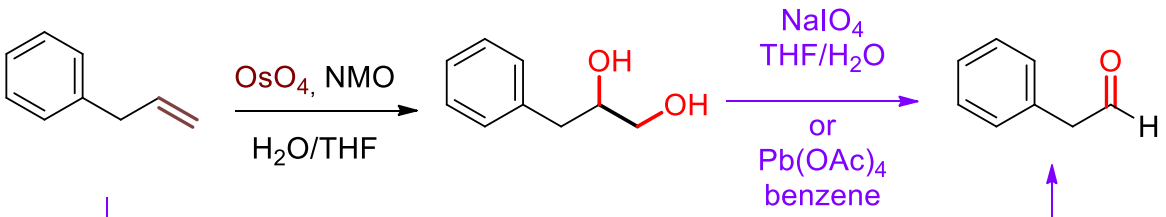
-Widely used in Chemical Biology to insert Fluorescent Probes:

→**<u>Chemistry Nobel prize 2022</u>**

Oxydation of Olefins: Oxidative cleavage

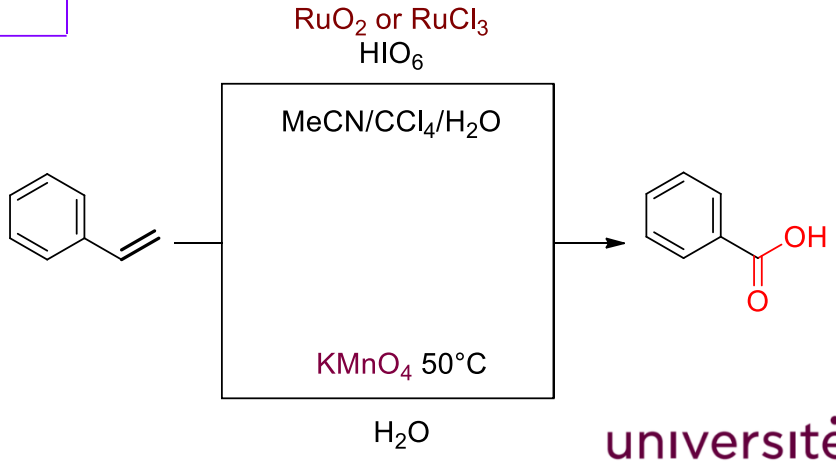
-Alternative to ozonolysis: **Oxidative cleavage**





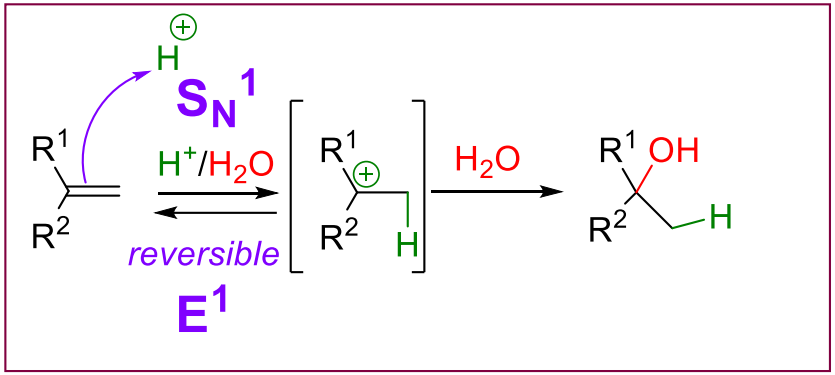
OsO_4, $NaIO_4$, 2,6-lutidine

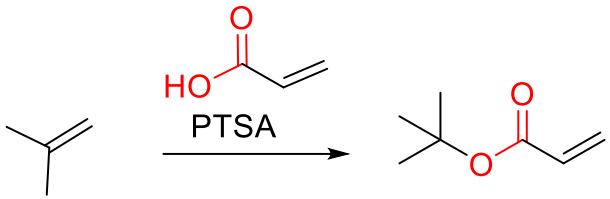
H_2O/THF (one-pot procedure)



Hydratation

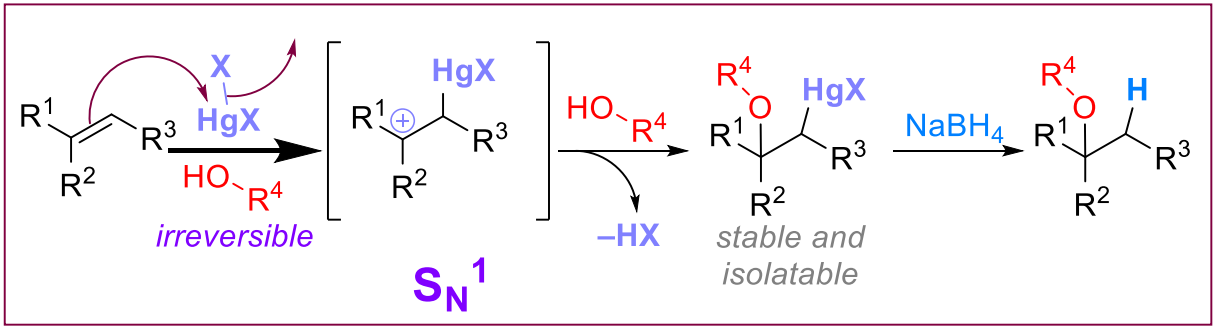
-Hydratation

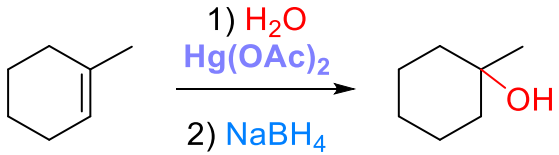


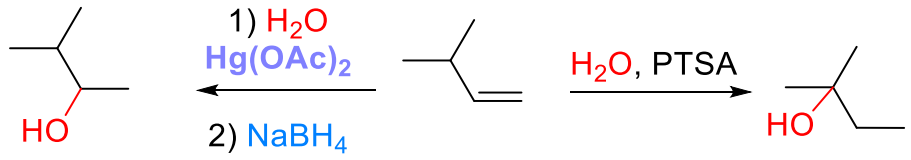


Markovnikov *type Addition.*

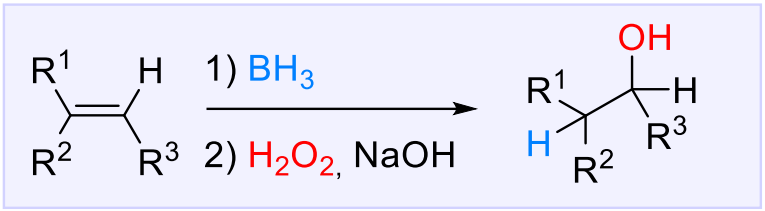
-Oxymercuration





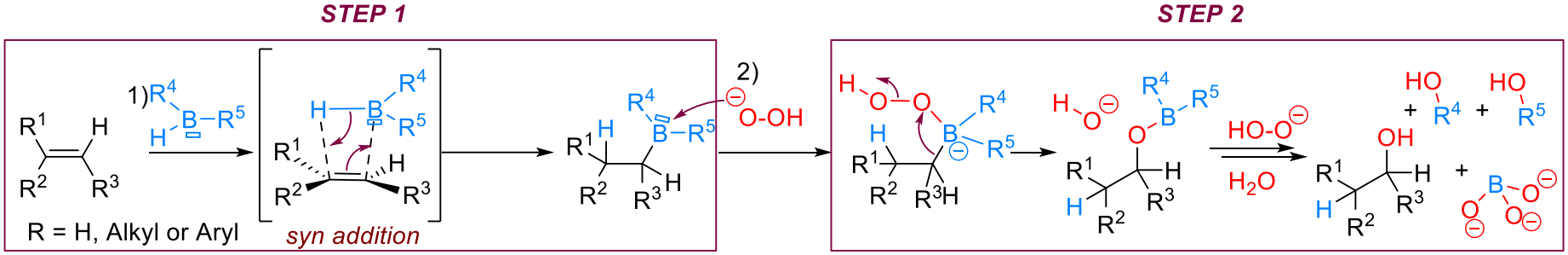


Hydroboration

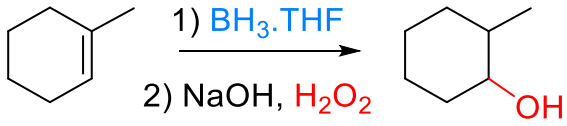


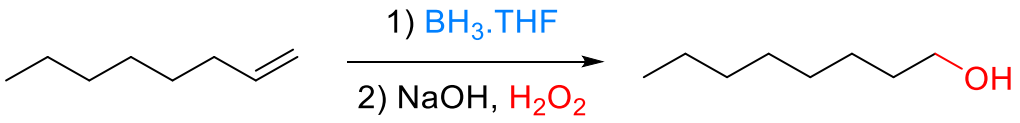
Substitution on the less hindered position

-Hydroboration: Formally an hydratation, but sequentially 1 reductive + 1 oxidation step



C-B bond oxidation

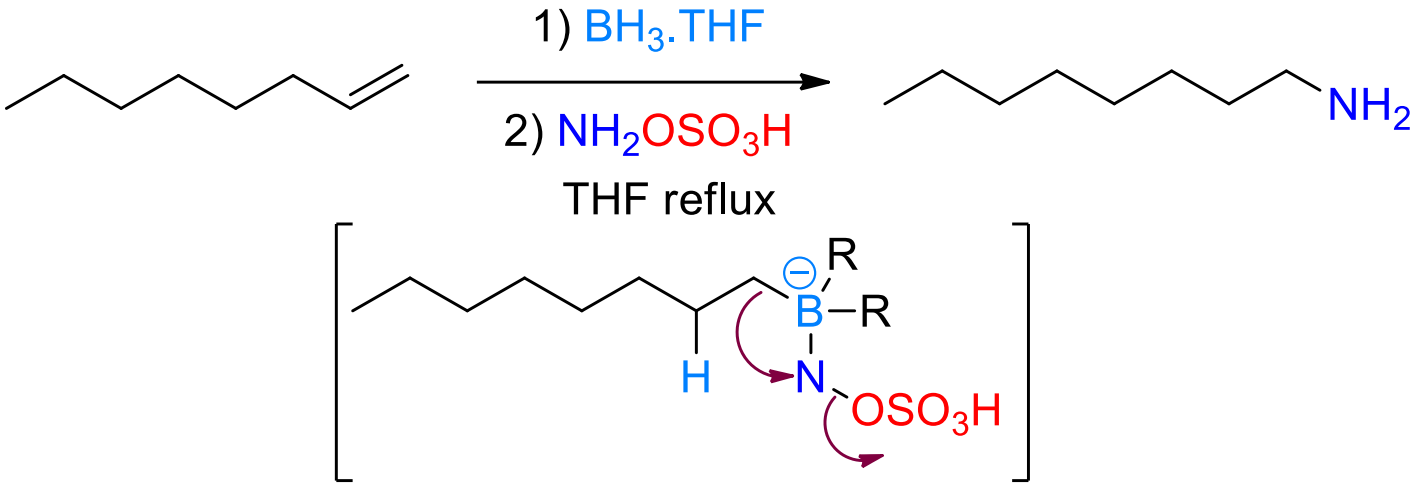




Anti-Markovnikov *type Addition*

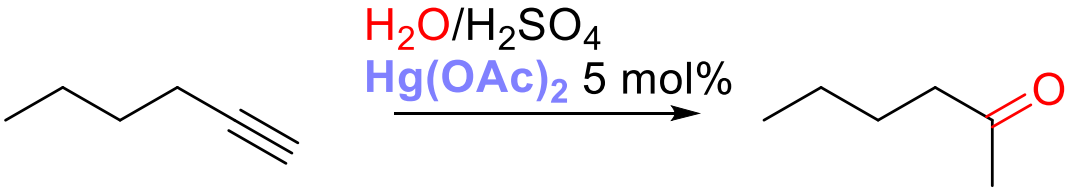
Hydroboration (2)

-Hydroamination : The processus is the same as the one to make alcohol. The oxidative step uses an amino group. Typically a hydroxylamine derivative which includes a leaving group function



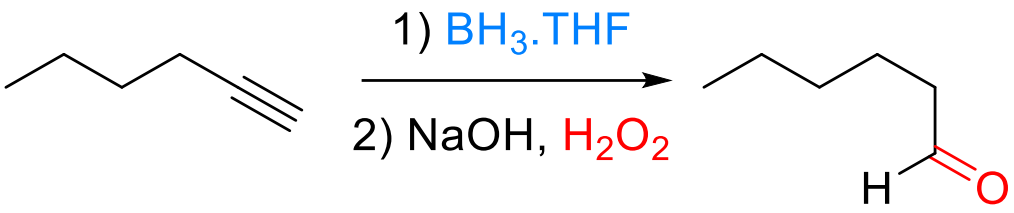
Hydratation/Hydroboration for Alkynes

-Hydratation of Alkyne



no reduction step to remove Mercury

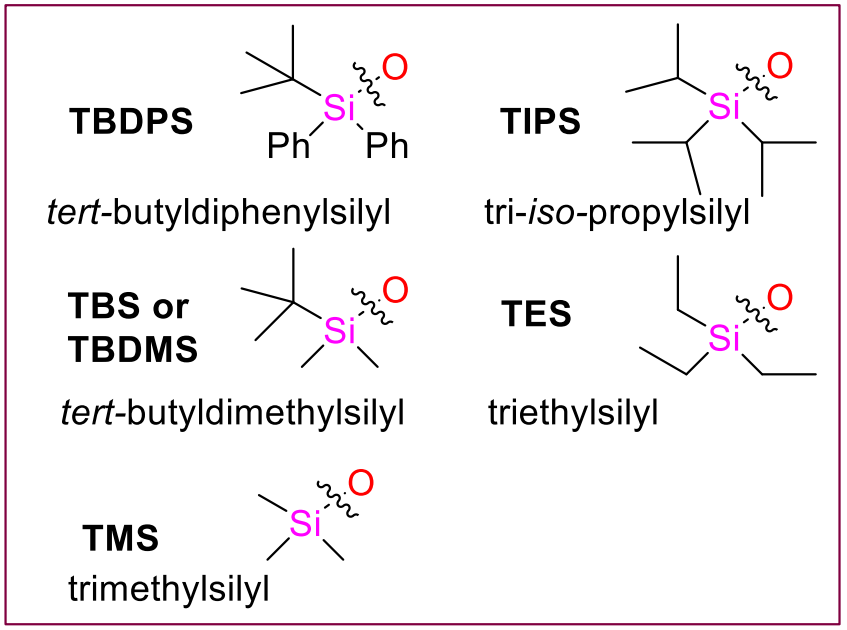
-Hydroboration of Alkyne



Protection of Alcohols: Silyl Ethers (1)

Goal: - Reacting one function chemoselectively in the presence of another one which should have reacted as well
- Being able to discriminate the same functions in the molecule.

Silyl: - Very versatile. Chemoselective deprotection
Ability to remove one silyl group over another one.

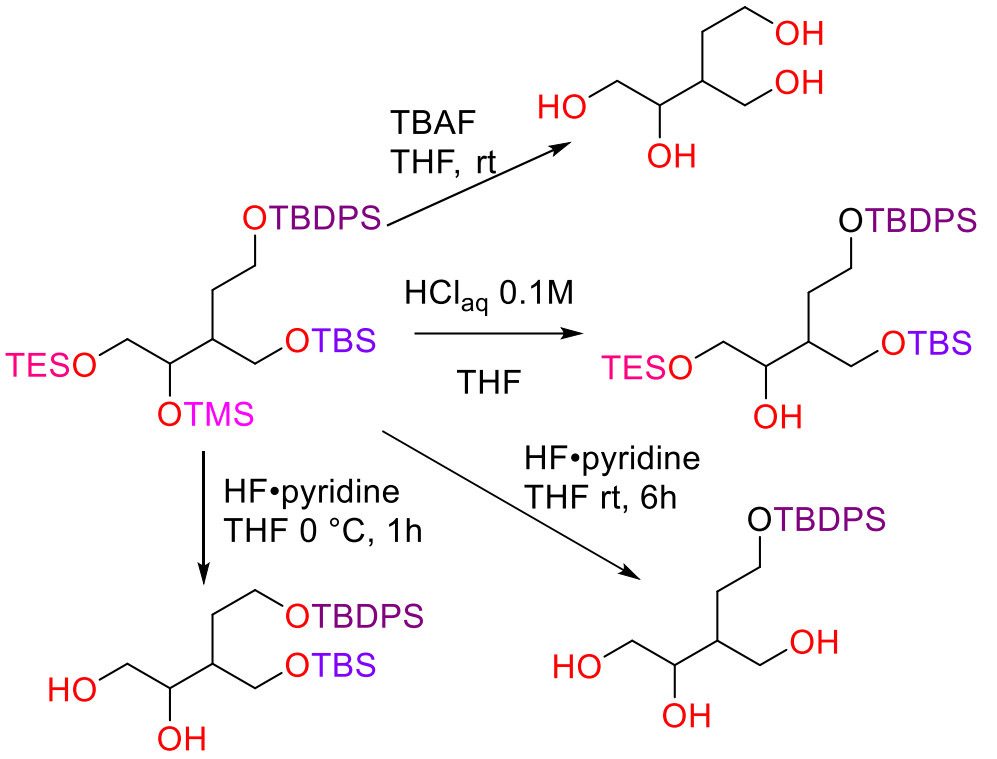


Ease of introduction:
TMS>TES>TBS>TIPS>TBDPS
Ease of cleavage:
TMS>TES>TBS>TIPS~TBDPS

Protection: **SiR_3Cl**, imidazole DMF
or **SiR_3OTf**, 2,6-lutidine-CH_2Cl_2 (for hindered positions)

Cleavage:
-Fluoride source. Usually TBAF (basic conditions)
Or HF•pyridine (for chemoselective deprotection)
-Acid catalysis also works for TMS, TES or TBDMS
Ex: PTSA, MeOH

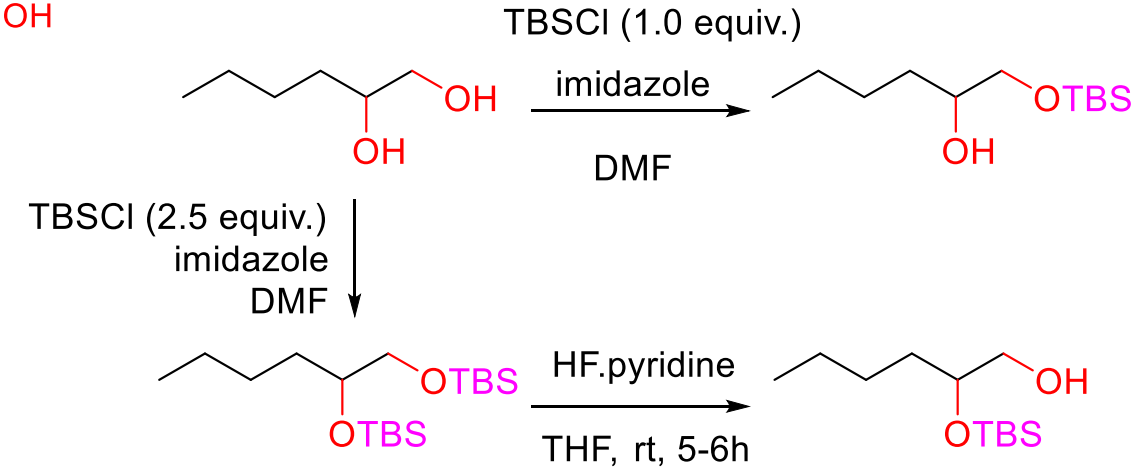
Protection of Alcohols: Silyl Ethers (2)



Ease of cleavage:
TMS>TES>TBS>TIPS~TBDPS

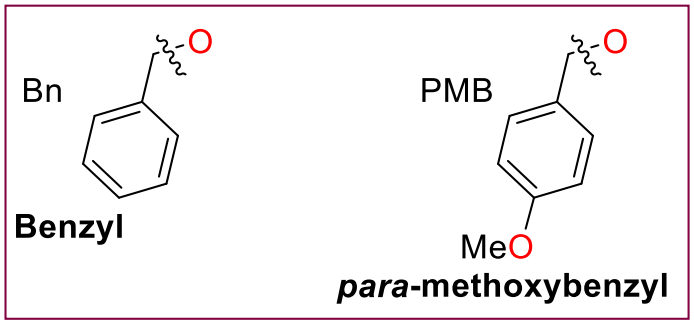
Difference of reactivity

1° > 2° position (steric hindrance)

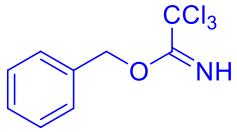


Protection of Alcohols: Benzyl Ethers

-Benzylether: -Chemoselective deprotection
Usually harder to introduce than silyl groups

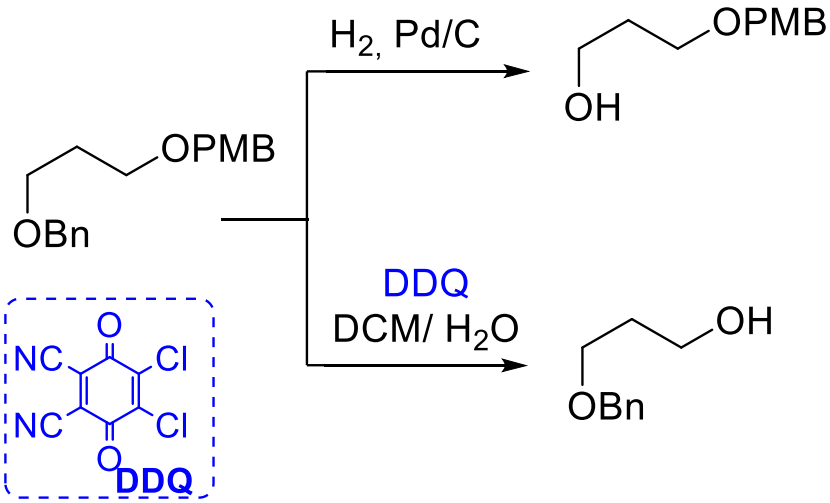


-Protection: BnCl or PMBCl, NaH, TBAI, DMF
or use of trichloroacetimidate, TfOH or $La(OTf)_3$,
CH_2Cl_2,



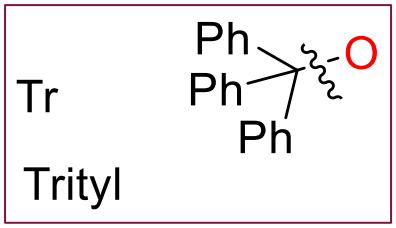
-Cleavage: -Hydrogenation, H_2 Pd/C,
-BCl_3 or Na/NH_3 (Harsh conditions)

<u>Chemoselective cleavage for PMB</u>: Oxydation
DDQ, CH_2Cl_2/ H_2O (10:1) dichlorodicyanoquinone
Or CAN ,MeCN/ H_2O Cerium Ammonium Nitrate



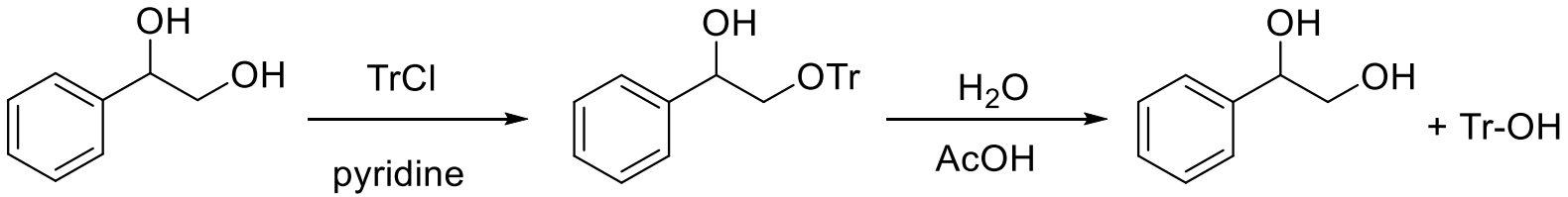
Protection of Alcohols: Triphenylmethyl Ethers

-Tritylether: Can be placed only on primary alcohols



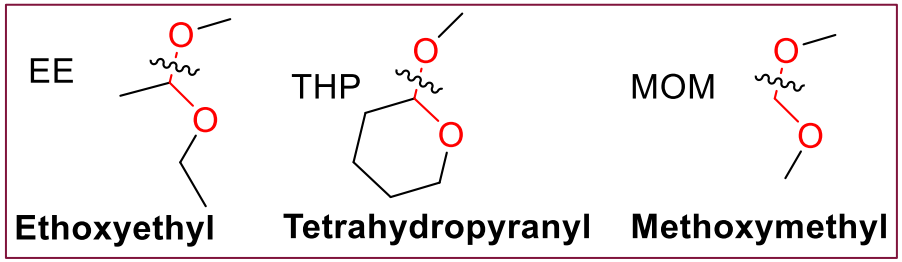
Protection: TrCl in pyridine

Cleavage: -acidic conditions
AcOH/H_2O or HCl, MeOH

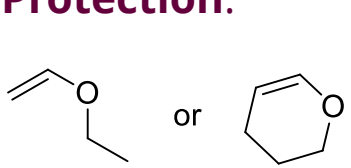


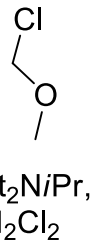
Protection of Alcohols: Acetals

-Acetals: -very robust on basic conditions.
Drawback: Can form mixture of diasteromers (excepted MOM)



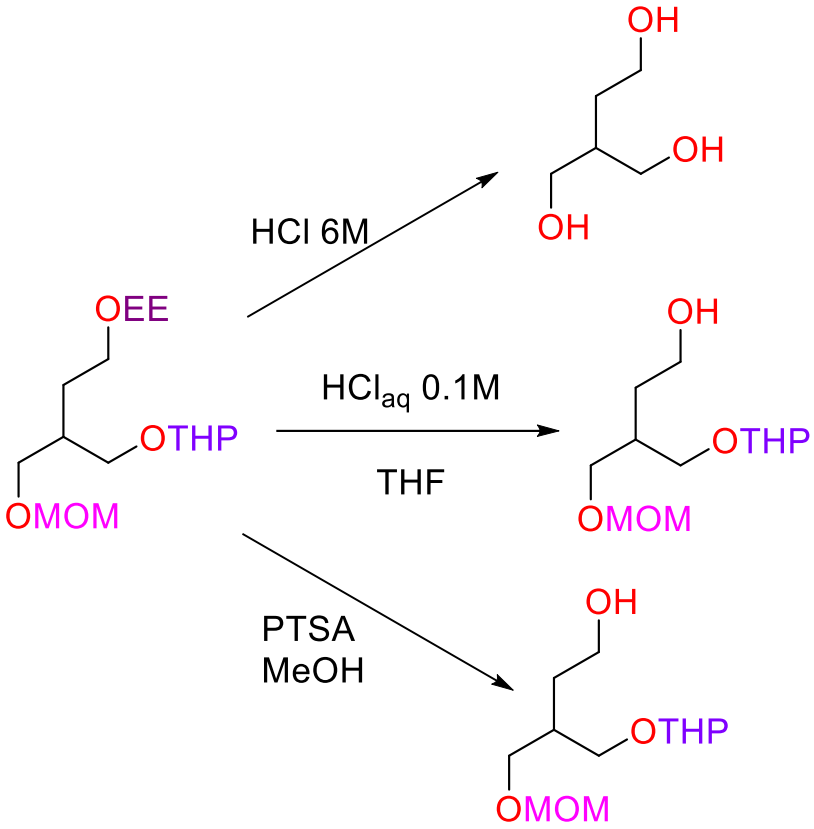
Protection:





Cleavage: -acidic conditions
PTSA, MeOH; HCl 3M for MOM

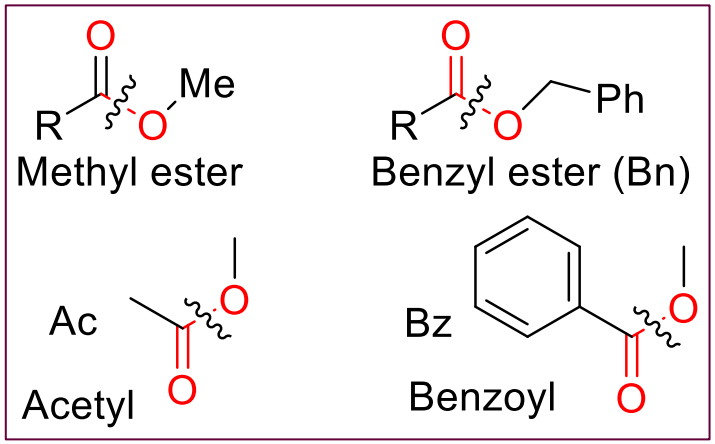
Ease to cleave: OEE > OTHP > OMOM



université PARIS-SACLAY

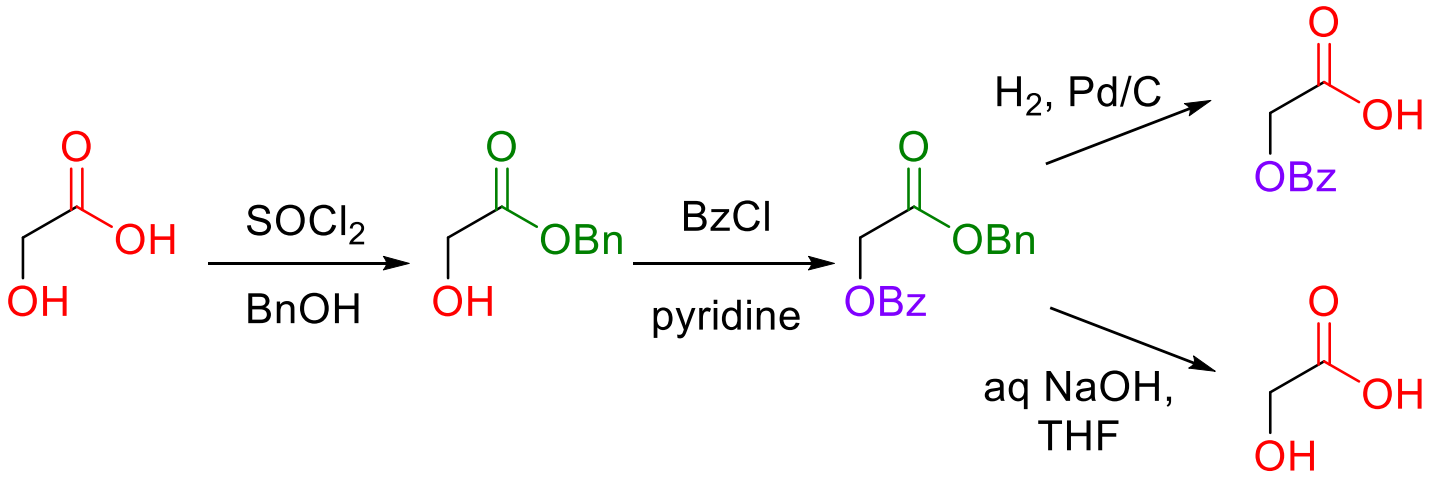
Esters : Protection of Alcohols and Carboxyl groups

-Esters: -Protection of alcohols or carboxylic acids



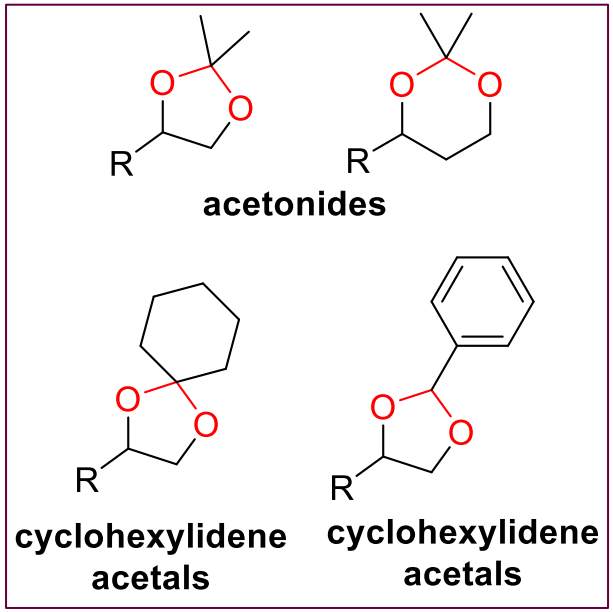
Protection: Acyl chloride or anhydride (ex: Ac_2O or BzCl) with pyridine for alcohols.
Or Carboxylic acid activation (ex: $SOCl_2$ or DCC)

Cleavage: -NaOH, H_2O
Hydrogenation, H_2 Pd/C for Benzyl esters



Acetals: Protection of Diols and Carbonyl groups

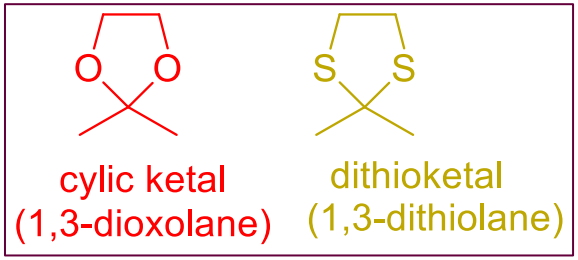
-Diols: protection as cyclic ketal



Protection: -Acetanone, cyclohexanone or benzaldehyde, PTSA, $CuSO_4$ (dry) or molecular sieves 4A
Or 1,2-dimethoxypropane, PTSA

Cleavage: PTSA, MeOH/H_2O

- **Ketones and aldehydes** :
  Protection of ketones and aldehydes

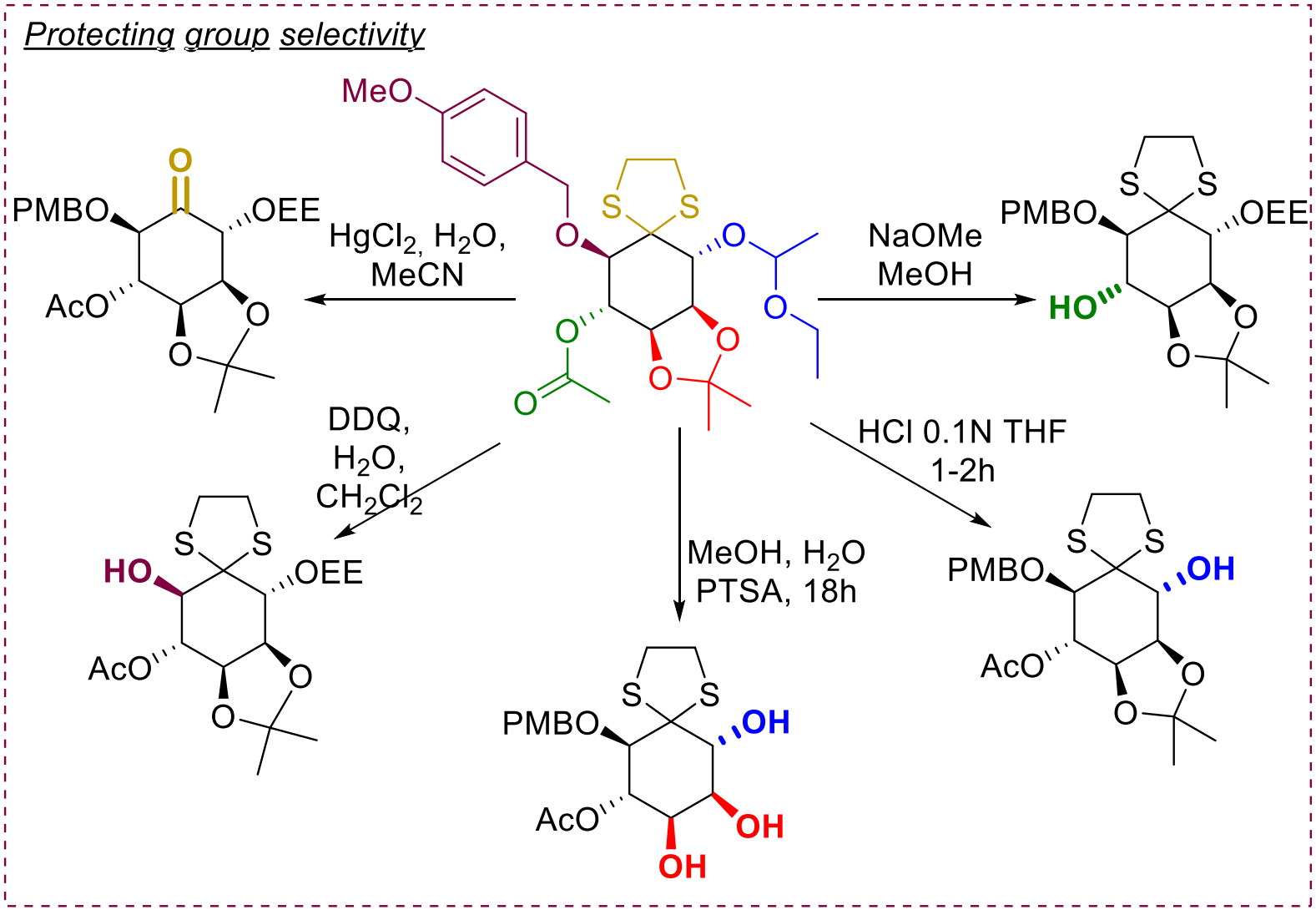


Protection: ethylene glycol PTSA
or Ethanedithiol, $BF_3.OEt_2$

Cleavage: -PTSA, MeOH/H_2O for ketals

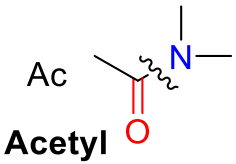
-HgCl, H_2O or NBS, 2,6-lutidine
MeCN/H_2O or MeI $CaCO_3$
MeCN/H_2O for thioketals

Protection of Oxygenated Functions: Selective Cleavage

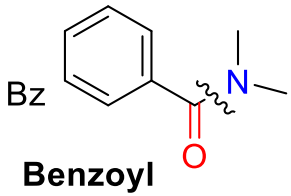


Protection of Amines: Amides and Sulfonamides

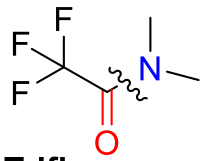
-Amides: equivalent of esters



Acetyl

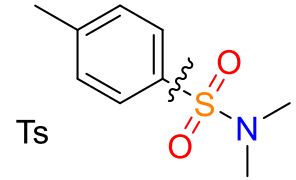


Benzoyl

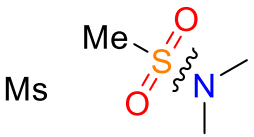


Trifluoroacetyl

-Sulfonamides: easy to make, inert to most conditions (but hard to remove)



***para*-Toluenesulfonyl (Tosyl)**



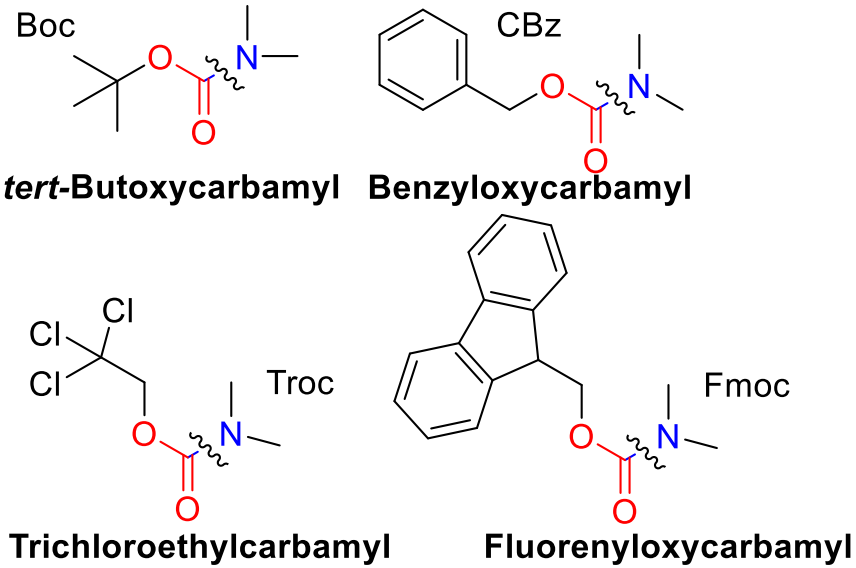
Methanesulfonyl (Mesyl)

Protection: Acyl chloride or anhydride (ex: Ac_2O or BzCl) with pyridine
Cleavage: $-H^+$, H_2O 100 °C 16-24h
Trifluoroacetate: KOH/H_2O 0 °C

Protection: TsCl or MsCl, Et_3N
Cleavage: Reduction with strong reducing agents
-Na/NH_3 or Sodium naphtalenide

Protection of Amines: Carbamates

-Carbamates: the most used protecting groups for amines. Versatile deprotection conditions



Protection: ROC(O)Cl, Et_3N or $[ROC(O)]_2O$ (for Boc)

Cleavage:

-Boc: *acid conditions*. Usually, 6N HCl or CF_3COOH
-Cbz: *hydrogenolysis*. H_2, Pd/C
-Fmoc: *Basic conditions*. Usually DBU or pyrrolidine.
-Troc: *Reductive conditions.* Usually Zn, aq NH_4OAc, THF