(Non exhaustive) List of tips and reactions to know for FROI

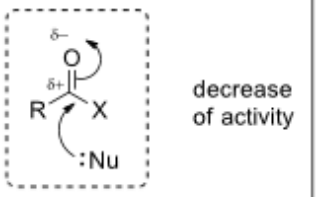
Learn your course and all the exercise session correction…everything is more detailed!

For relative acidity and basicity, you have to compare:
-electronic effect (EWG, EDG, inductive effect (& electronic density), mesomery...) and steric (hindrance, ortho effect...)
-to compare pKa = compare stability of conjugated base (more stable = more acidic = lower pKa)
-to compare basicity = compare stability of conjugated acid (more stable = more basic), or
-in some cases, for base you can also compare the availability of the doublet (for amine, or alcoolate)
-see TD examples to understand the different cases and what should be compared
-Compare relative electronegativity difference (nitrogen is less electronegative than oxygen so its doublet is more available and minus charge will be less stabilized)

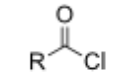
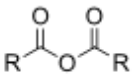
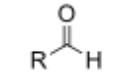
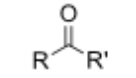
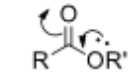
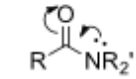
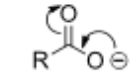
-A lot of examples are explained in the different exercise sessions!

General comments:
-a carbocation is more stabilize when it is more substituted (tertiary > secondary > primary), and/or in alpha of EDG or conjugated with double bonds (alkenes, aryl, ...)
-a carbanion is more stabilize when it is less substituted (primary > secondary > tertiary), and/or in alpha of EWG

Carbonyl electrophilicity:



decrease of activity

	X	Effect	Activity
	Cl, Br (acyl halide)	-I	strongly increase
	OCOR (anhydride)	-I	increase
	H (aldehyde)	none	none
	Alkyl (ketone)	+I	slighly decrease
	OAlkyl (ester)	-I, +C (-I << +C)	decrease
	NHAlkyl (amide)	-I, +C (-I << +C)	decrease
	O- (carboxylate)	-I, +C (-I << +C)	strongly decrease

Notes:

I : inductive effect

C: conjugative effecet

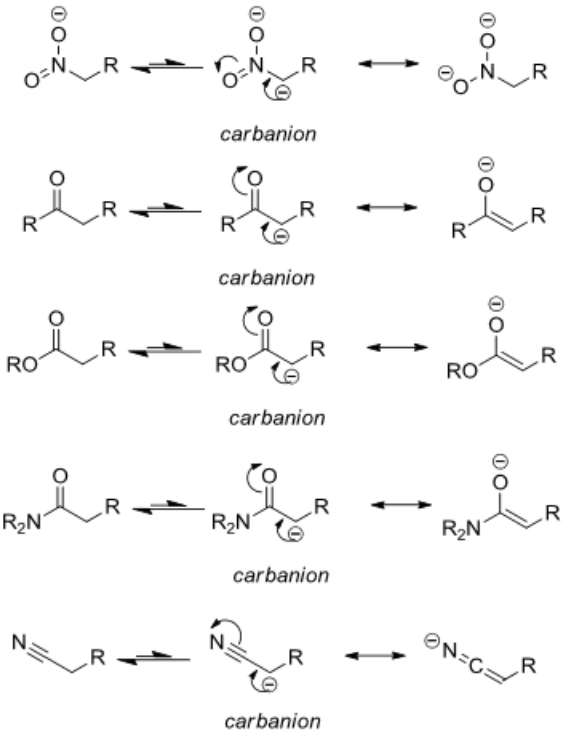
- : withdrawing electron

+: donating electron

Some anion stabilization:

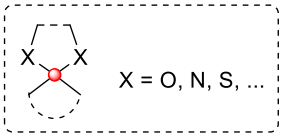
Acidicity of C-H at α possition is dependent on the ability to stabilize carbanion of functional group.

NO2 > COR > CN ~ COOR > SO2R > SOR > Ph ~ SR > H > R



RO and R_2N, conjugating to C=O as well, can "interfere" the stablization of carbanion. Therefore, acidity of C-H (ketone) > (ester) > (amide)

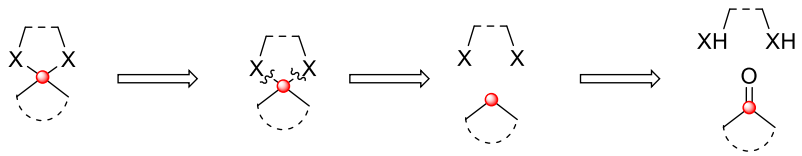
Disconnection of acetal and related compounds:



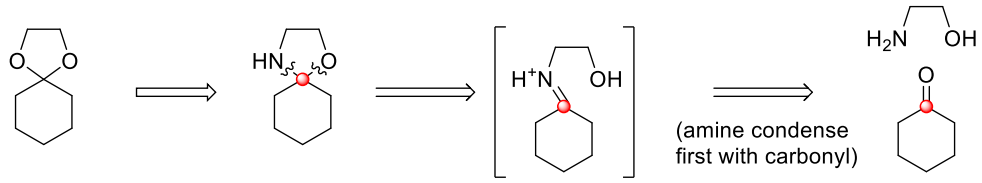
1) Find the carbon linked to the two heteroatoms

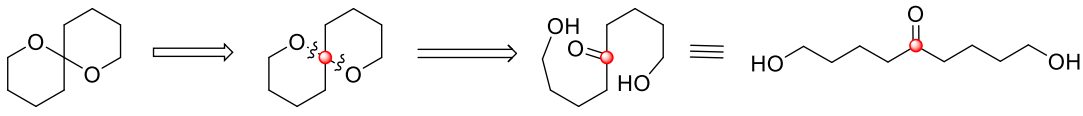
2) Cut the two bonds between THIS carbon and the two heteroatoms

3) Add a carbonyl on the carbon & add H to the two X



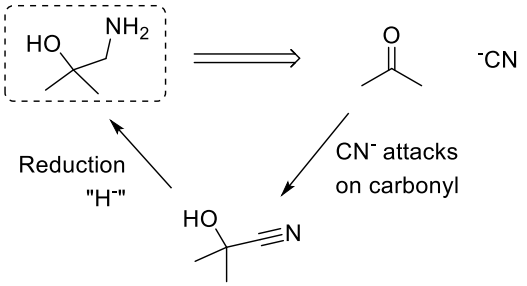
Examples:





Reminder: Mechanism for acetal protection and deprotection is the same... just not in the same way.
Removal or addition of alcohol/water or acetone will displace the equilibrium toward one side

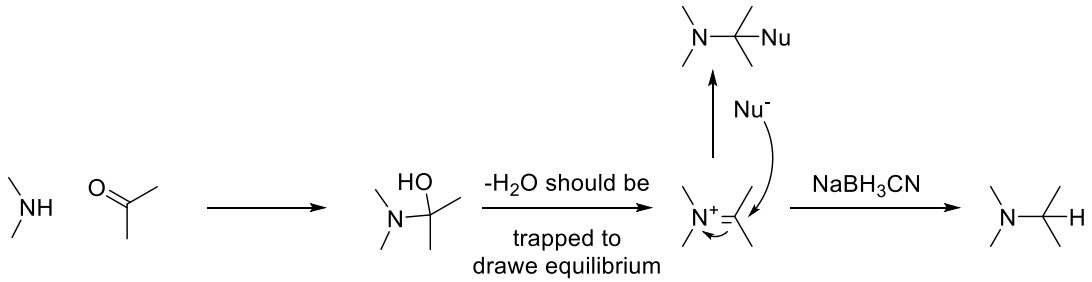
Other building block to recognize (different from the acetal, here there are two carbone between O and N):



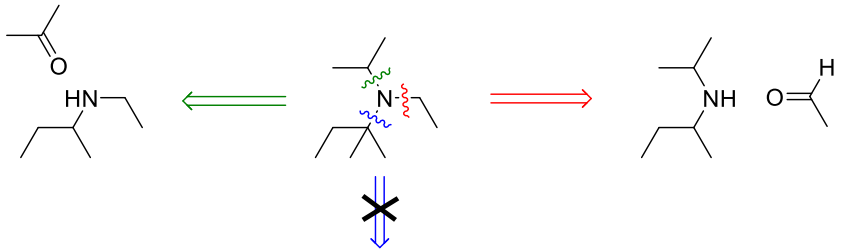
-R-CN are converted to R-CO_2H by acidic hydrolysis (cf mechanism TD_5)
-R-CO_2H could be esterified to R-CO_2Me with H^+, reflux in MeOH
-RCO_2R' could be hydrolysed to R-CO_2H with H^+, heating in water, or by saponification ("basic hydrolysis") with NaOH or LiOH or KOH

Imine = good electrophile on the carbon, so nucleophile will attack the carbon
Possible Nu = H^- (reduction), $^-$CN, ROH, ...

Reductive Amination = Imine/iminium formation (condensation of the carbonyl and the amine)
+ reduction of the imine/iminium with mild reductant ($NaBH_3CN$ or $NaBH(OAc)_3$...)



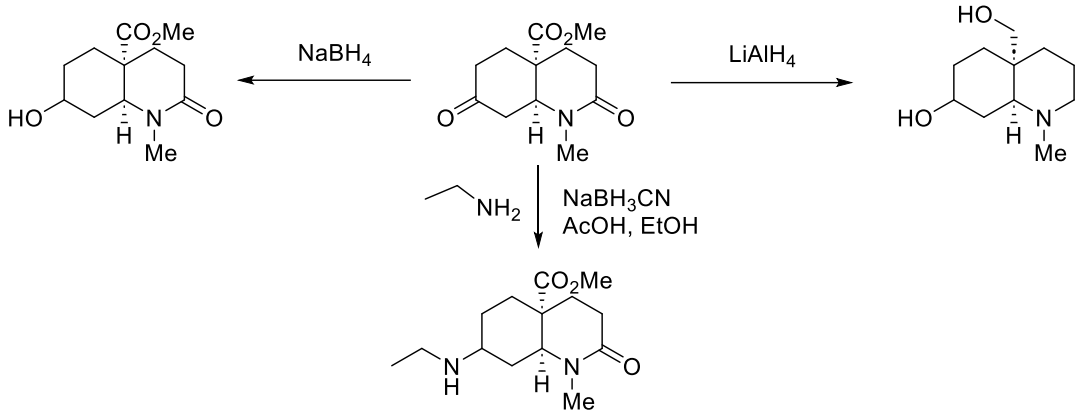
Example of retrosynthetic disconnection: often several possibilities

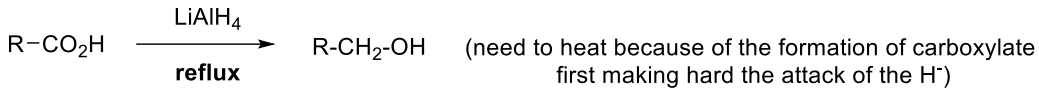


impossible because no possibility to form the
imine to be reduced (no H on the attached carbon)

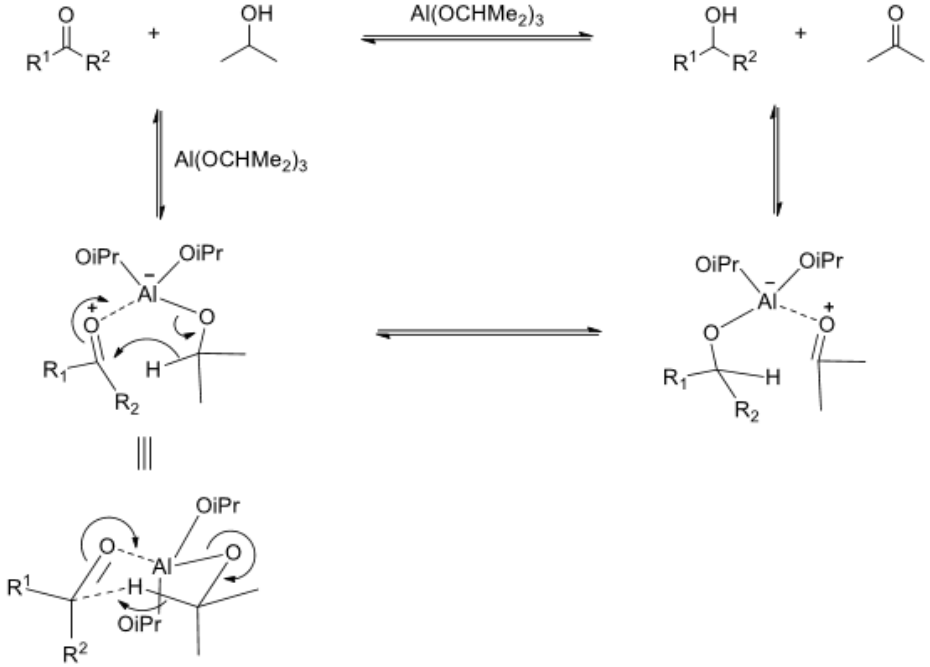
Reduction: all reductants have different reactivity in terms of strengh:
-strong reactivity of LAH (=$LiAlH_4$) reduced everything ;
-intermediate reactivity with $NaBH_4$ reduced ketones and aldehydes;
-mild reactivity with $NaBH_3CN$, $NaBH(OAc)_3$.. only reduced imine).

Those reductants are hydride donor: Metal-H equivalent to nucleophilic "H^-".

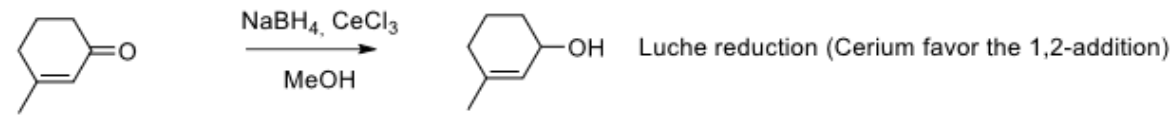




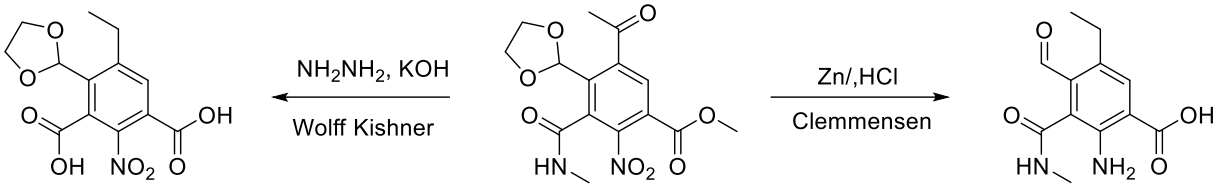
MPV reduction and Oppenauer oxidation:



Luche reduction for conjugated ketones:

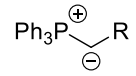


Reduction of ketone to CH_2: tolerance of functional groups



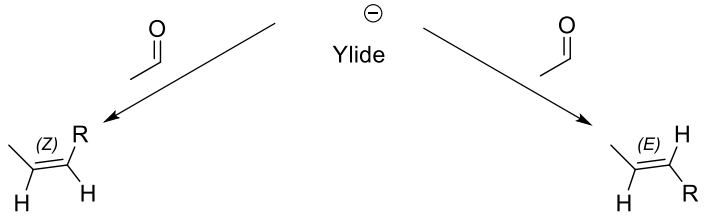
Wittig:

R=Alkyl, EDG → unstabilized ylide → (Z) selectivity

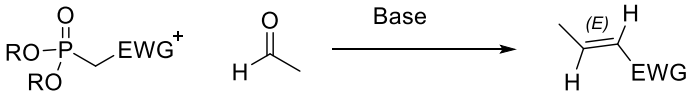


R=EWG → stabilized ylide → (E) selectivity

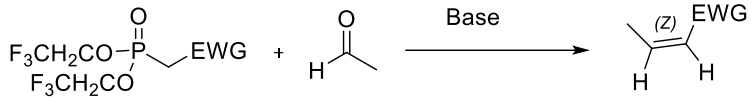
Ylide



Horner-Wadsworth-Emmons olefination: generally, (E) selectivity with EWG

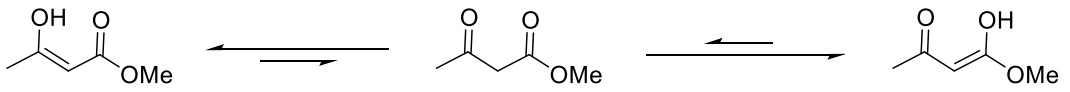


Still Gennari modification: generally, (Z) selectivity with EWG

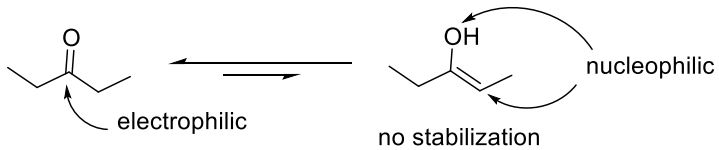


All those reaction are also feasible with ketone instead of aldehyde.

keto/enol tautomerization:



conjugation of the full system — no conjugation — conjugation of the full system



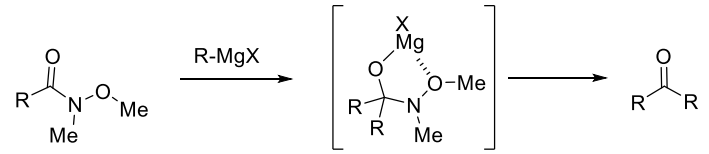
no stabilization

preferred form

(Same thing with imine/enamine tautomerization)

Addition of R-Mg-X:

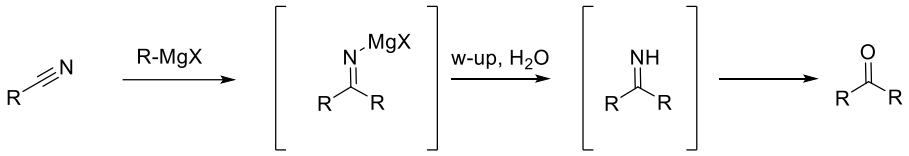
(can't stop at any intermediate, each one being more reactive than the previous one)



Weinreb amide

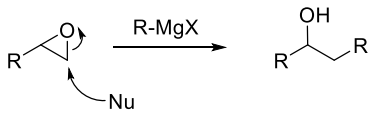
stable until work-up

(similarly reduction with $LiAlH_4$ of Weinreb amide stop after one addition)



stable until work-up

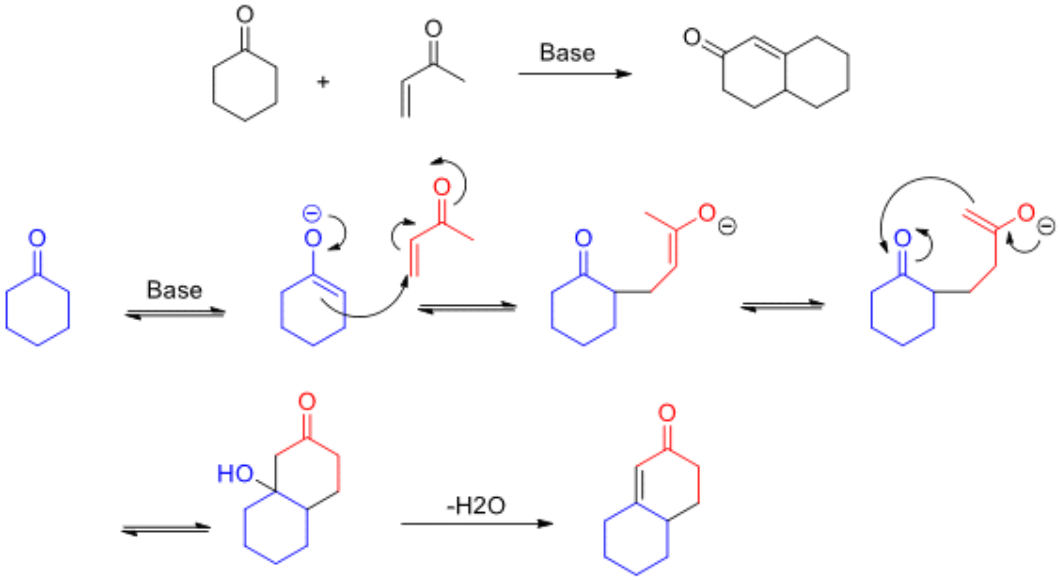
imine is unstable in water, hydrolyzed to ketone



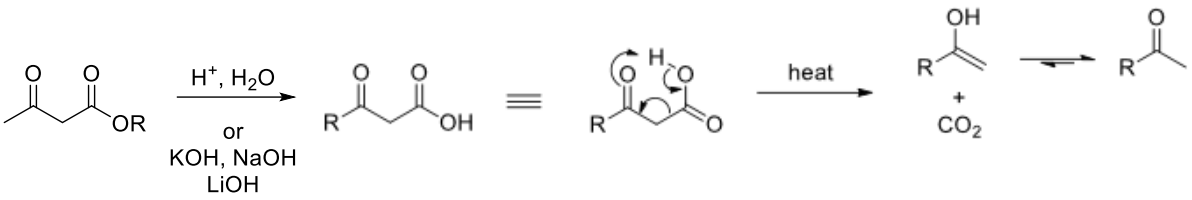
epoxide are activated towards nucleophilic addition (strain + leaving group)

works similarly with any Nucleophile

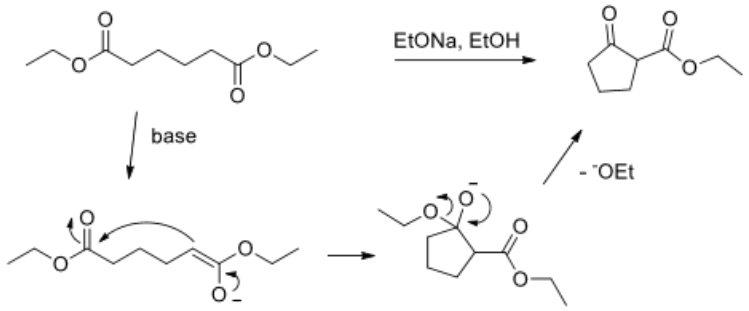
Robinson annulation:



Notes: β–ketocarboxylic acid can be easily decarboxylated by heating to generate ketone

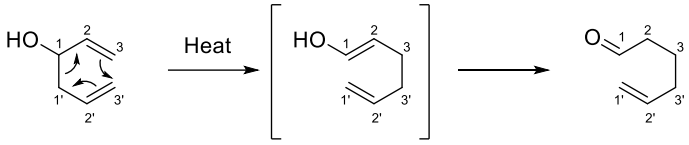


Claisen/Dieckmann (=intramolecular Claisen reaction): (Thorpe-Ziggler is similar but with CN groups instead of esters)



[3,3]-sigmatropic rearrangement (Cope, oxy-Cope, Claisen, Johnson-Claisen, ...): Think to number your atoms !!

Example: Oxy-Cope



(Don't forget at the end to tautomerize your enol if you have one...)

Pinacol/Semi-pinacol rearrangement: formation of cation and bond migration towards the more stabilized carbocation