

Structure and Reactivity: Prerequisite Knowledge

!!! The concepts presented in this summary are required for lecture and examination!!!

1. Important Principles in Organic Chemistry

In general, structures which can stabilize electrons are favored.

1.1 Electronegativity and "Octet" Rule

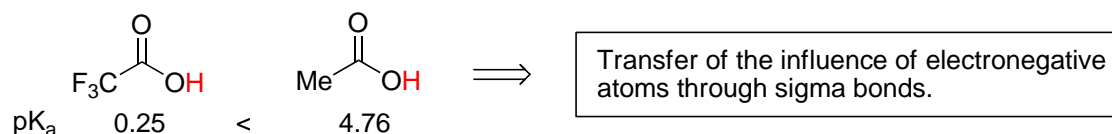
The electronegativity describes the ability of atoms to attract electrons. The nearest to octet (closed shell) the strongest the electronegativity. The electronegativity is weaker for larger atoms.

⇒ On chemical structures and during chemical reactions, the electrons go to the more electronegative element.

example: acidity		Me ₃ CH	Me ₂ NH	MeOH	HF	
pK _a		53	> 36	> 16	> 3.2	⇒
electronegativity		2.5	3.0	3.4	4.0	

The conjugate base is more stable for more electronegative atoms!

Indirect effect: inductive effect



Effect of hybridization:

electron in orbitals with more s characters are more stabilized (more probability next to the nucleus)

example: acidity

	Me ₃ CH		H≡H
pK _a	53	50	24
Hybridization	Sp ³	SP ²	SP

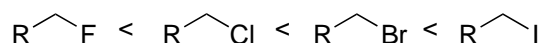
1.2 Stabilization through Delocalization: delocalized charges (electrons) are more stable

1.2.1 Delocalization onto 1 atom: large atoms are more able to stabilize charges (= polarizable)

examples	1) acidity:	HF	HCl	HBr	HI
	pK _a	3.2	> -8	> -9	> -10
	electronegativity	4.0	3.2	3.0	2.7

⇒ Delocalization is more important than electronegativity in this case!

2) leaving group ability in substitution reaction



1.2.2 Delocalization on two atoms: the chemical bond

Important for organic chemistry:

- 1) σ bond is stronger than π bond for C=C bond, but not for C=N and C=O
- 2) Delocalization is better between atoms of the same size (orbital overlap)
- 3) For strong polar bonds: ionic part can become important and compensate the weaker covalent bonds: prediction is more difficult

examples:

	size effects							
σ bond:	C-H	C-C	C-N	C-O	C-F	C-F	C-Cl	C-I
energy in Kcal	99	83	70	86	117	117	81	52
π -bonds	C=C	C=N	C=O			C=O	C=S	
energy in Kcal	64	77	92			92	49	

⇒ Important practical consequence: in organic chemistry, losing C=C and making C=O is often favorable!

1.2.3 Delocalization on more than two atoms: resonance structures

Resonance structure = obtained by moving electron without changing position or connectivity of atoms

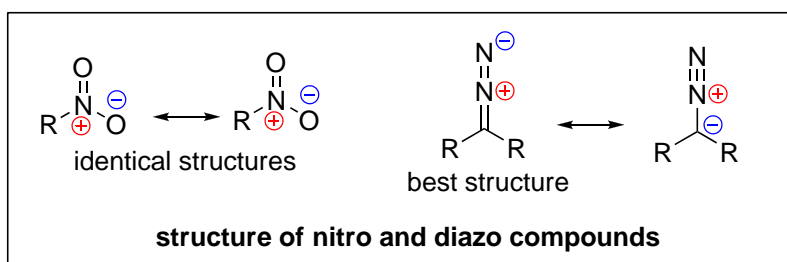
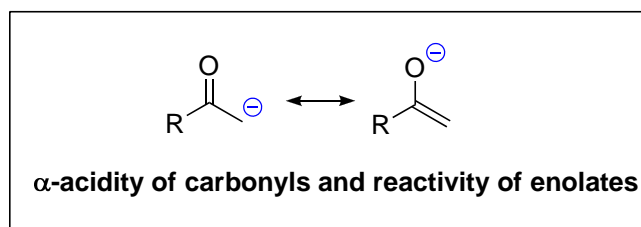
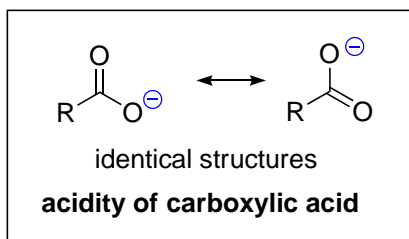
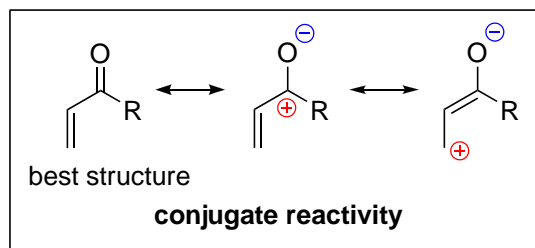
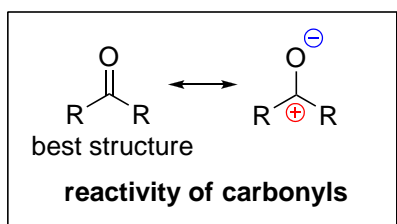
Resonance structures are essential to understand structure and reactivity in organic chemistry!

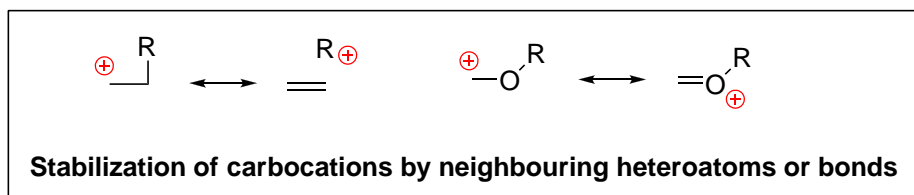
good resonance structure \longleftrightarrow octet rule for 1. row elements, no charges, charges on electronegative atoms, more bonds, "better bonds", aromatic structures

stabilization through resonance (delocalization) is maximal if the **resonance structures are identical**

"reality" = weighted sums of the resonance structures

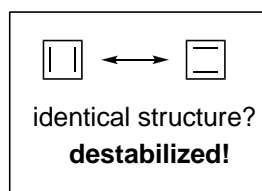
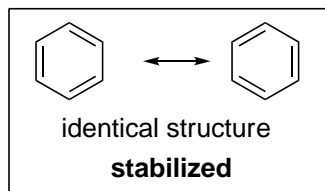
key examples:



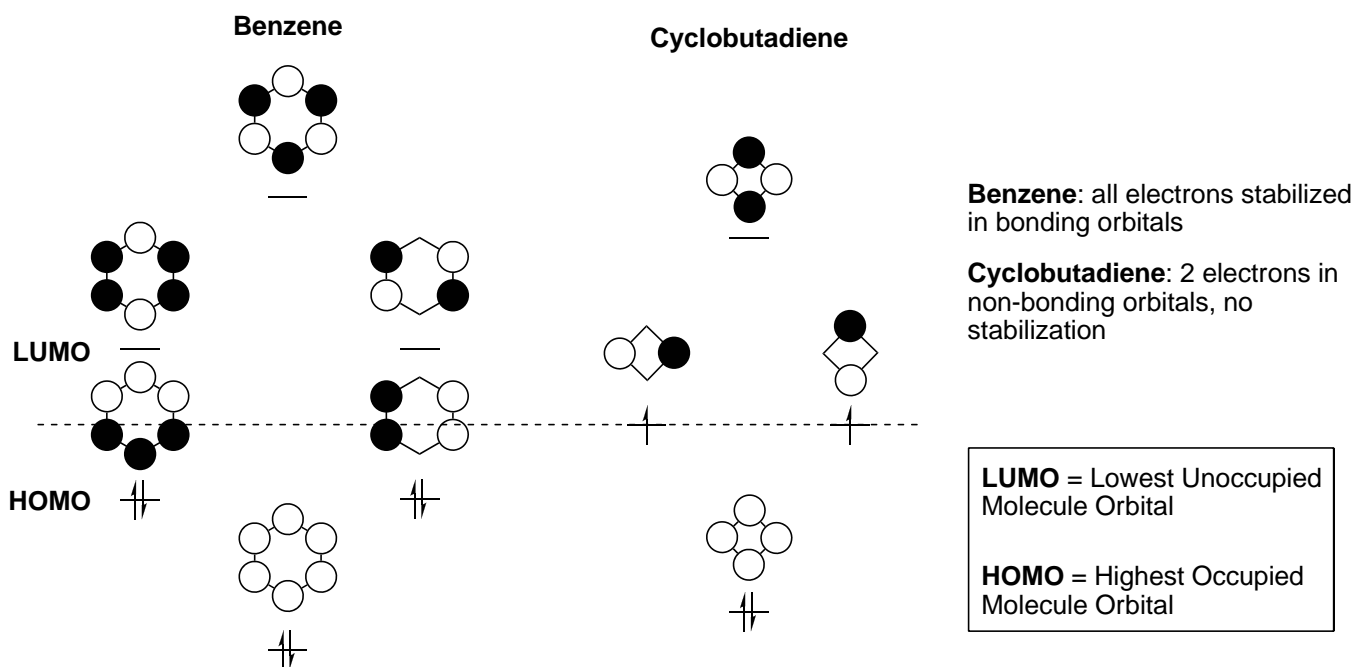


Limitation of resonance structure: description of aromaticity

aromatic stabilization: cyclic conjugate π -system with $4n+2$ electrons (Hückel's rule)



⇒ Higher level model is needed: orbital theory



In organic chemistry, many observations can be explained by FMO (Frontier Molecular Orbital, LUMO and HOMO) considerations. This model is more powerful and precise than resonance/Lewis structure considerations, but need more time to apply.

Test for part 1



Classify this carbonyl compounds in order of increasing reactivity towards nucleophile addition.

2. Important Nucleophiles and Electrophiles in Bachelor Level Organic Chemistry

2.1 Nucleophiles

Heteroatoms	δ^- ROH	δ^- RNH ₂	δ^- RSH	δ^- PR ₃	δ^- R ₂ N-NH ₂	neutral
	alcohols	amines	thiols	phosphines	hydrazines	
	\ominus RO [⊖]	\ominus RNH [⊖]	\ominus RS [⊖]	\ominus X [⊖]		charged
	alcoholates	amides	thiolates	halogen anions		
Hydrides (H ⁻) sources	δ^- NaBH ₄	δ^- LiAlH ₄				
	borohydrides	aluminium hydrides				
C Nucleophiles	δ^- RMgBr	δ^- RLi	δ^- OM R=C δ^-	M = Na, K, Li	δ^- OM R=C δ^- -C(=O)X	
	Grignard	alkyl lithium	enolates		stabilized enolates	
	δ^- NR ₂ R ¹ =C δ^-	\ominus CN	ED C ₆ H ₄ δ^-	ED=C δ^-	ED = Electron-donating group	
	enamines	cyanide	electron-rich aromatic compounds and alkenes			

2.2 Electrophiles

H^+ M^+	RX	O R=C δ^+ X	NR R=C δ^+ X	$\text{R}^+\text{-N-R}$ R=C δ^+ X	EWG C ₆ H ₄ δ^+	EWG=C δ^+
proton metals	alkyl halogenide	carbonyls	imines	iminiums	electron-poor aromatic compounds and alkenes	
					EWG = Electron-withdrawing group	

2.3 Hard and Soft classification of Nucleophiles (Lewis Bases) and Electrophiles (Lewis Acids)

Hard \longleftrightarrow charged, localized electrons, highly electronegative/positive, reaction under charge control
typical hard electrophiles: H⁺, Mg²⁺, RCl, ROTf
typical hard nucleophiles: RMgBr, RLi, RO⁻, RNH⁻, F⁻, O atom of enolates

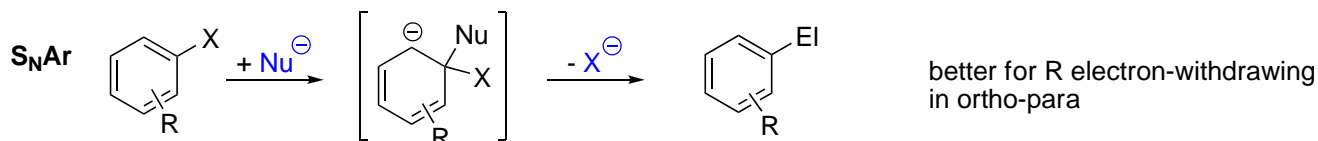
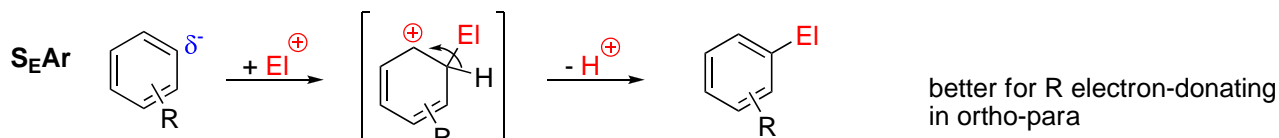
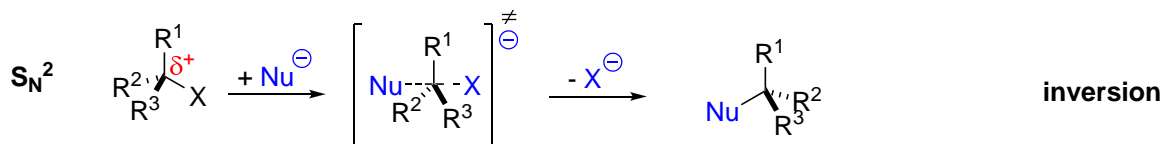
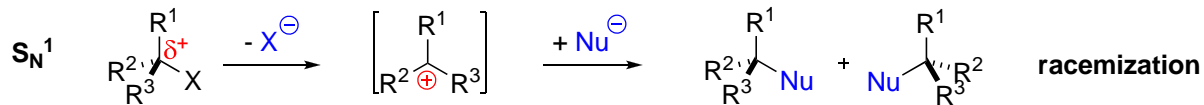
Soft \longleftrightarrow less charged, delocalized electrons, reaction under orbital (HOMO-LUMO) control
typical soft electrophiles: Pd²⁺, carbonyls, electron-poor double bonds and aromatic compounds
typical soft nucleophiles: C atom of enolates, stabilized enolates, electron-rich double bonds and aromatic compounds, I⁻, RNH₂, PR₃

Principle: **Hard-Hard and Soft-Soft interactions are favored!**

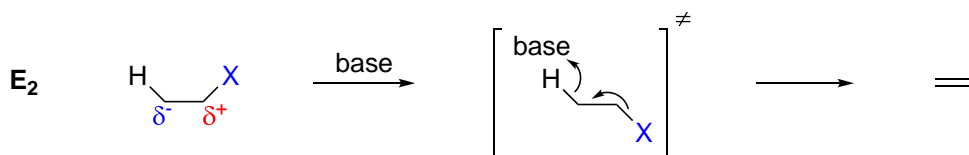
\implies Competition basicity-nucleophilicity: especially hard nucleophiles are usually also strong bases, because proton is hard (hard-hard interaction)

3. Important Classical Reactions in Bachelor Organic Chemistry

3.1 Substitution Reactions



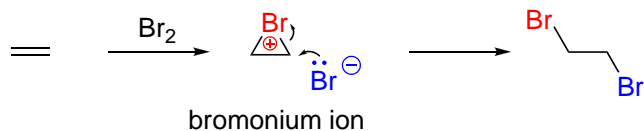
3.2 Elimination Reactions



3.3 Addition to double bonds

In principle: all mechanisms for elimination are possible in the reverse sense!

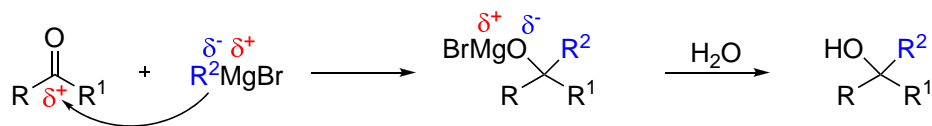
Special case: dibromination



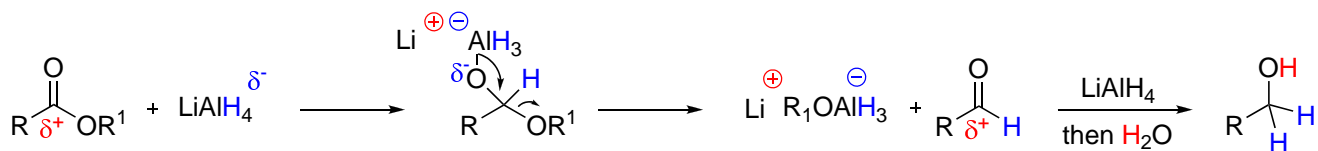
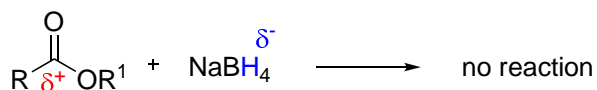
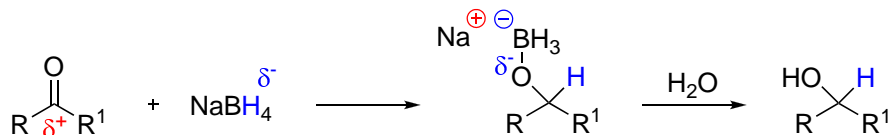
3.4 Chemistry of Carbonyls

3.4.1 Nucleophile Addition

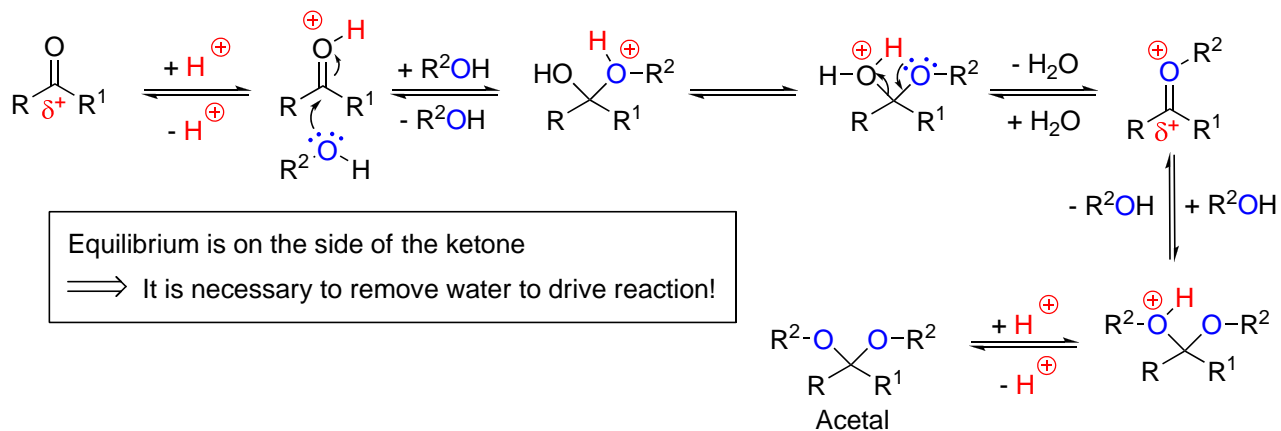
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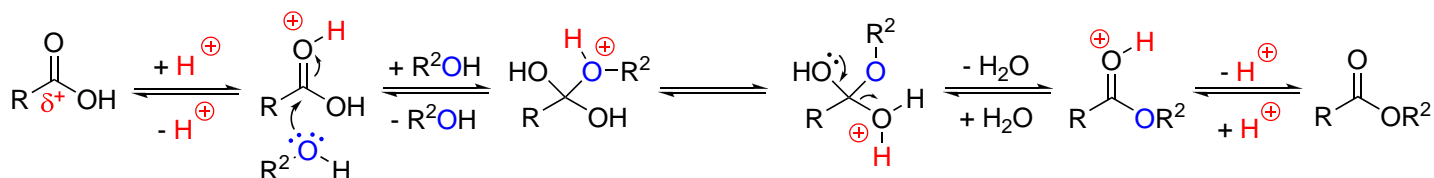
Hydride Reduction



Alcohols: acetal formation under acidic catalysis

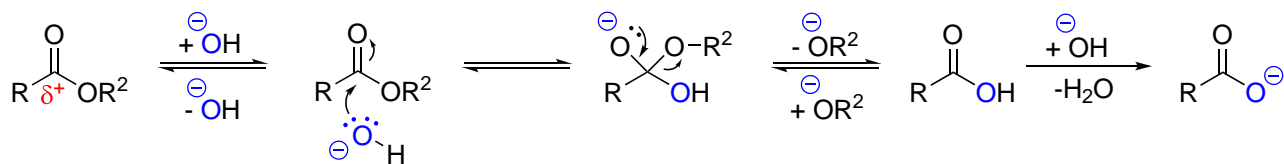


Alcohols: ester formation under acidic catalysis



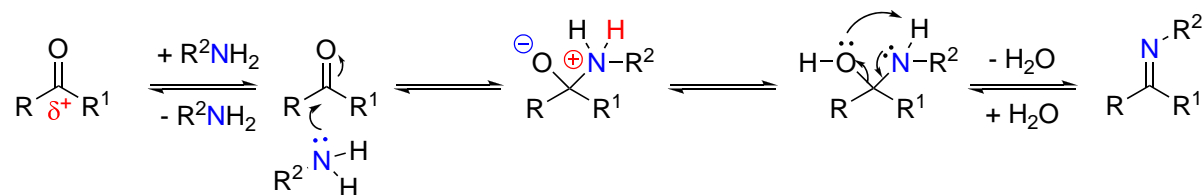
Equilibrium is nearly 1:1
 \implies Use excess alcohol to drive reaction

Ester Hydrolysis



Stability of carboxylate \implies completely on the side of product!

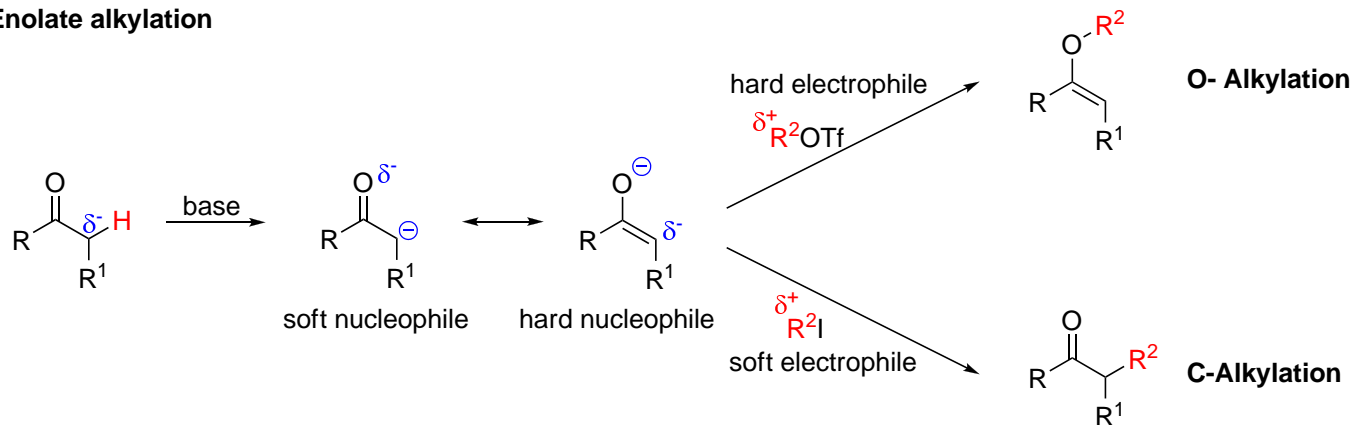
Amine addition and imine formation



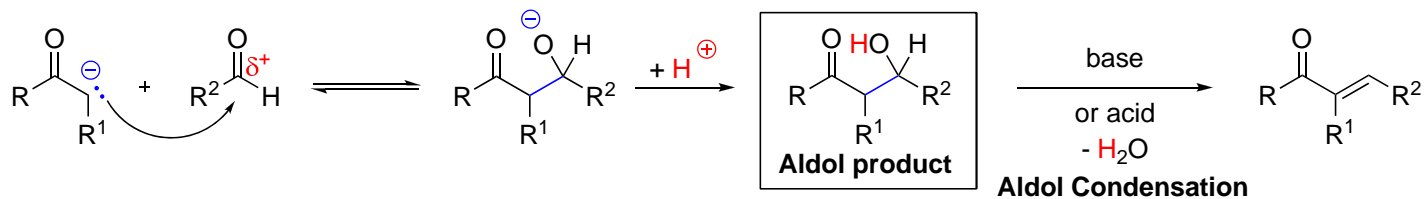
Water removal necessary for ketones, reaction easier with aldehyde

3.4.2 Enolate chemistry

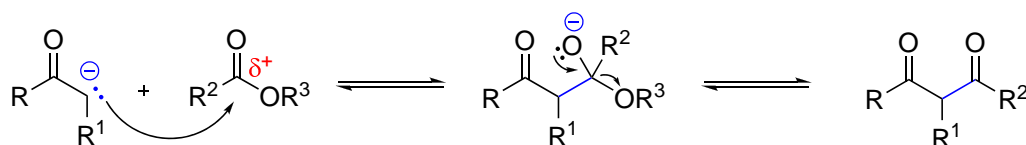
Enolate alkylation



Aldol Reaction

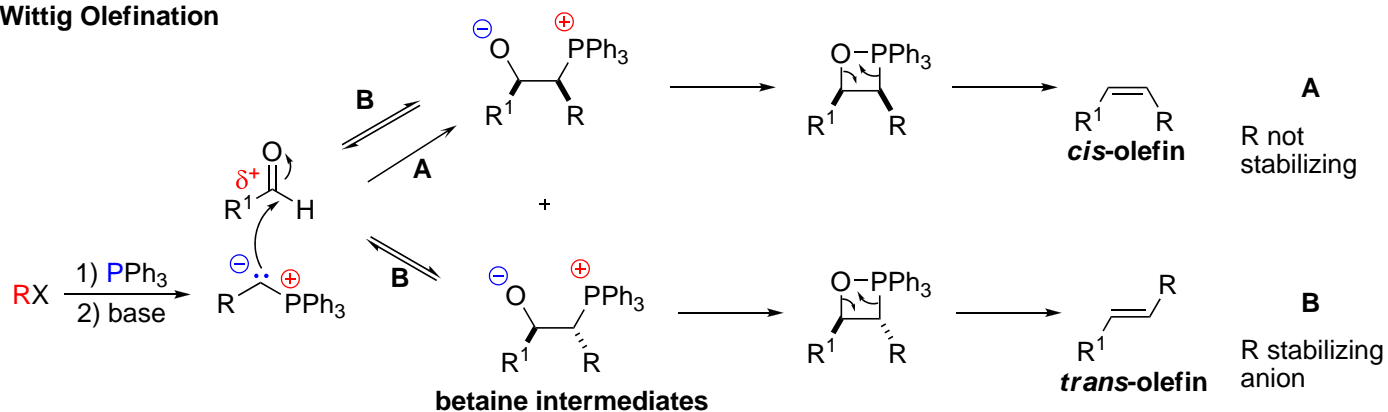


Claisen Condensation



Other related reactions: Knoevenagel condensation, Perkin condensation, Dieckmann condensation.

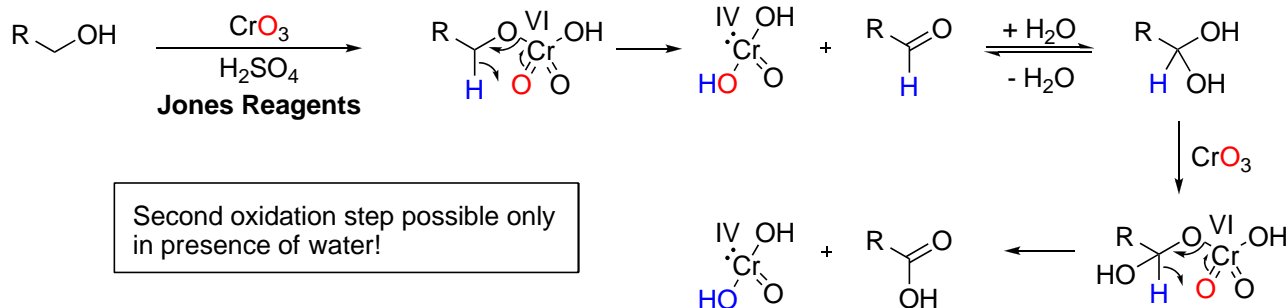
Wittig Olefination



For non-stabilized ylides (**A**), formation of the *cis* betaine is favored and irreversible, leading to *cis* olefin. For stabilized ylides (**B**), an equilibrium leads to formation of the more stable *trans* betaine and finally to *trans* olefin.

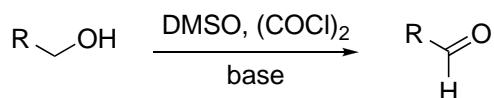
3.5 Oxidation Reactions

Chrom(VI)

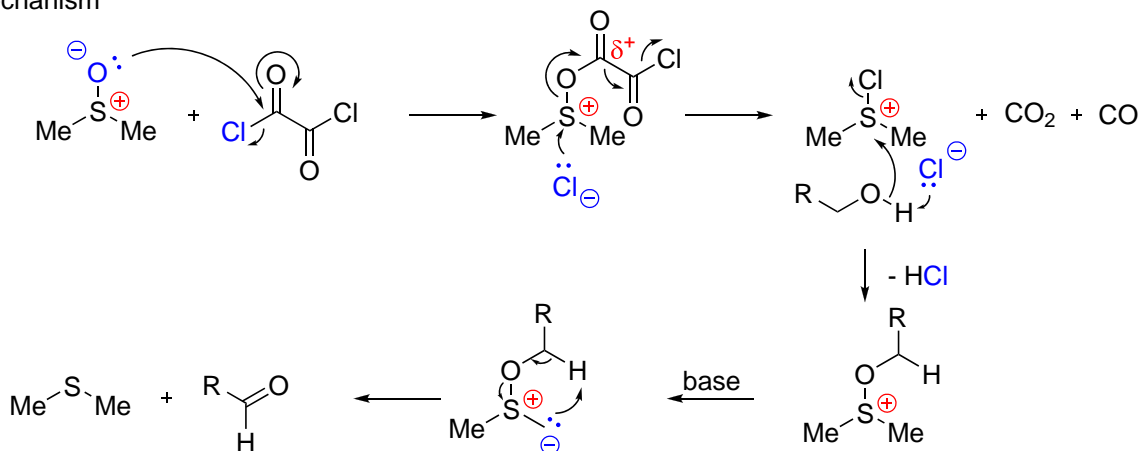


In practice also often used PDC (pyridinium dichromate), PCC (pyridinium chlorochromate)

Moffat-Swern

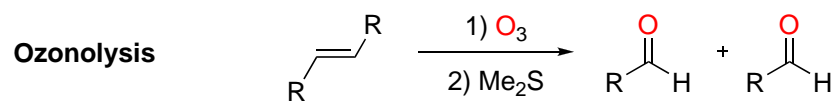


Mechanism



In practice, there are many more methods!

Dihydroxylation, Ozonolysis and Epoxidation



These reactions will be rediscussed in more details in the lecture