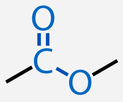
4.5 Nucleophilic Reactions on Carbonyl Groups (S_{AE}, A_N)

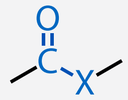
Carbonyl Compounds

carbonyl function

carboxyl function



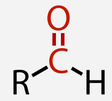
carboxyl derivative



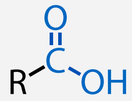
X = O, S, NH, Hal ...

carbonyl compounds

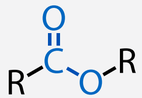
carboxyl compounds



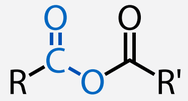
aldehyde



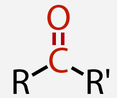
carboxylic acid



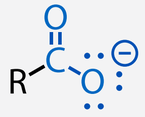
ester



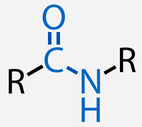
anhydride



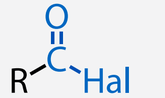
ketone



carboxylate



amide

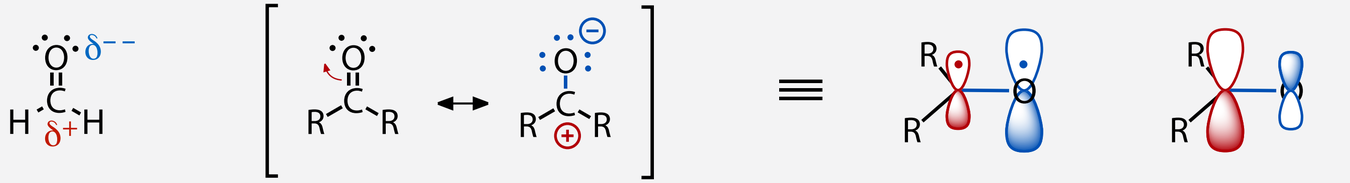


acyl halide

- carbonyl compounds are all compounds contains a carbonyl (C=O) function
- carboxyl compounds have additional bond to an electronegative element (leaving group!)

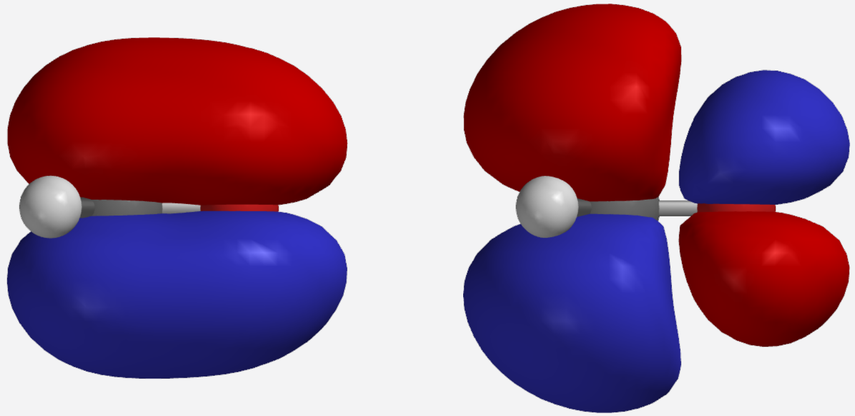
Carbonyl Compounds are Electrophiles

- carbonyl carbon atoms are inherently very reactive electrophilic centers



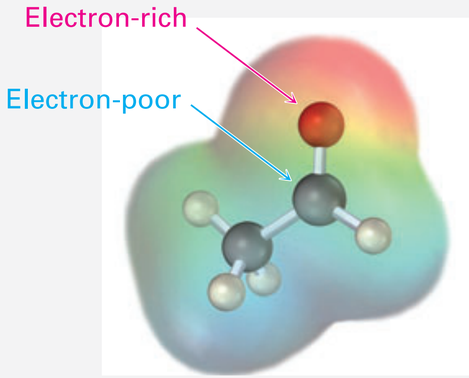
π (HOMO)

π* (LUMO)



π

π*

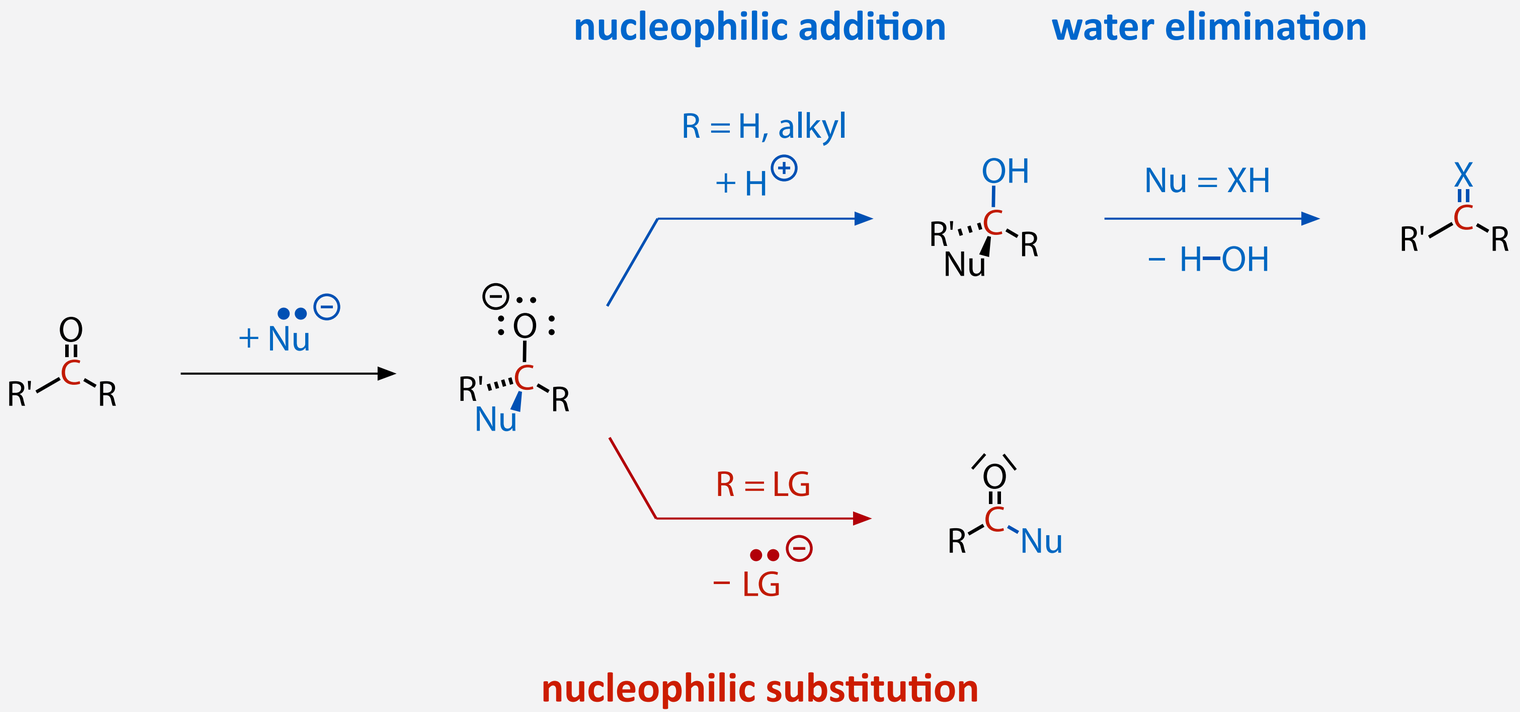


electrostatic potential

- oxygen (high electronegativity) gives positive partial charge (–I effect)
- resonance structures of the C=O π-bond give additional positive formal charge (–M effect)
- empty π* orbital (LUMO) has large lobe on carbon protruding from molecular plane

Overview of Nucleophilic Reactions on the Carbonyl Compounds

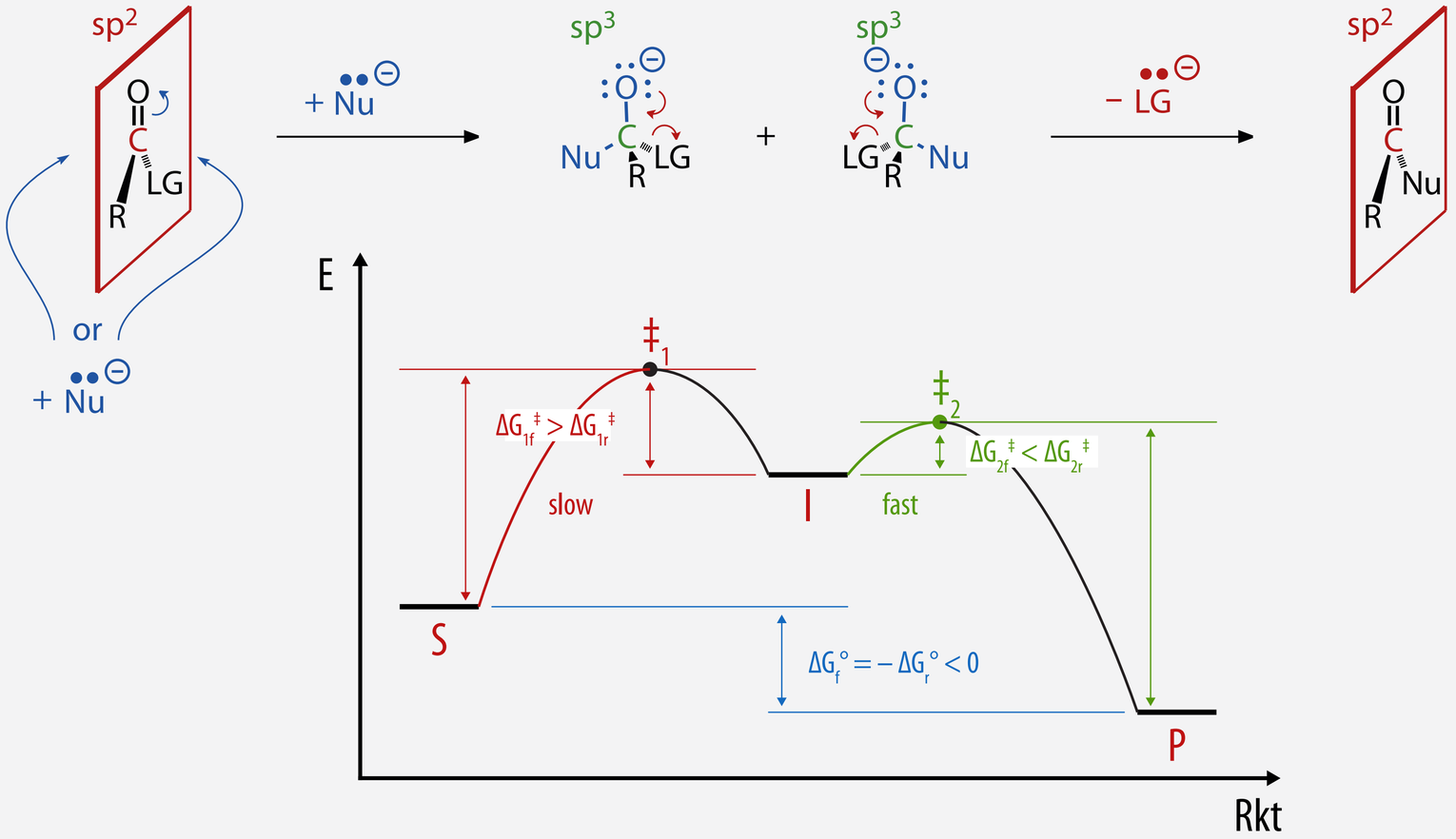
- all reaction sequences start with nucleophilic attack on the electrophilic carbonyl carbon



- **if one substituent is a leaving group (LG), nucleophilic substitution is preferred (Nu for LG)**
- **if no substituent is a leaving group (H, alkyl), nucleophilic addition occurs (of H–Nu)**
- **if the nucleophile carries an additional hydrogen (XH), subsequent water elimination occurs**

Nucleophilic Substitutions

Nucleophilic Substitution: Addition–Elimination Mechanism (S_{AE})

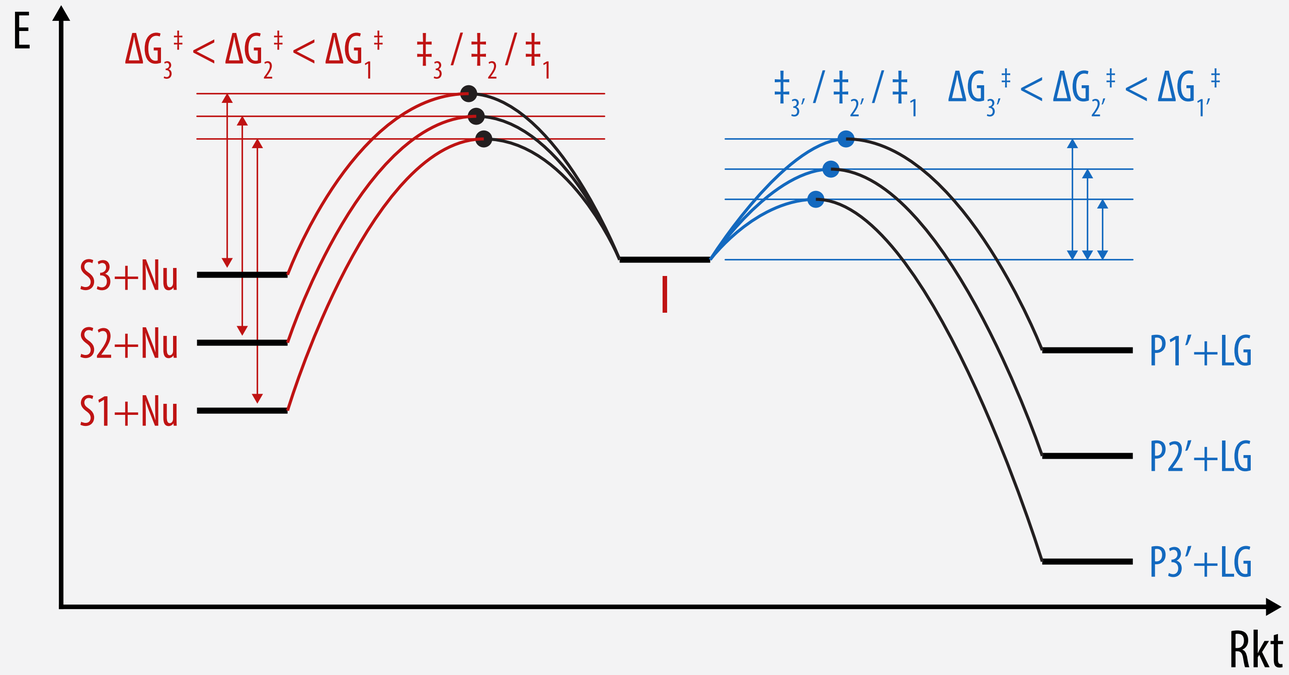


- carbonyl carbons are tetravalent, but sp² hybridized and coordinatively unsaturated
- stable intermediate by addition of nucleophile prior to cleavage of leaving group is possible
- nucleophile addition results in racemic intermediate, but no consequences for product

Factors Favoring Kinetically / Thermodynamically the S_{AE} Reaction

- more electrophilic carbonyl carbon
- (stronger nucleophile)

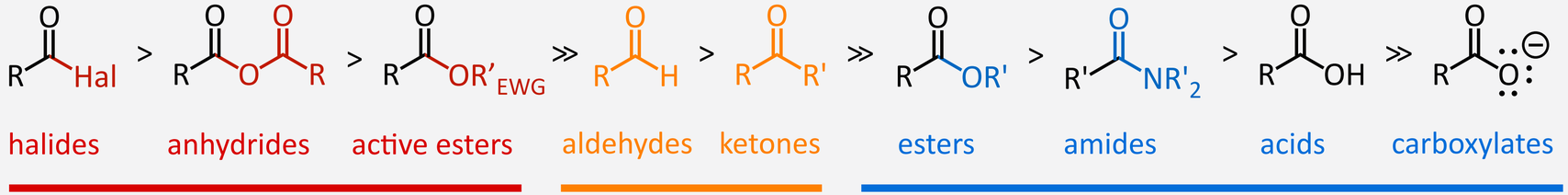
- better leaving group
- (more stable product)



- carbonyl carbons are tetravalent, but sp^2 hybridized and coordinatively unsaturated
- stable intermediate by addition of nucleophile prior to cleavage of leaving group is possible
- nucleophile addition results in racemic intermediate, but no consequences for product

Reactivity of Carbonyl Group as an Electrophilic Center

- carbonyl carbon **electrophilicity** increased by electron-withdrawing carbonyl substituents:

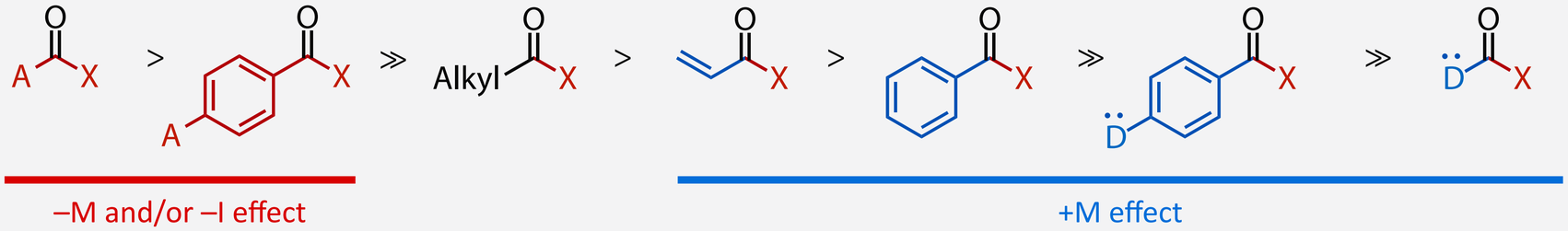


undergo electrophilic attack in first step (and good leaving group for second step)

undergo electrophilic attack (no leaving group!)

less susceptible for electrophilic attack (poor leaving group in second step)

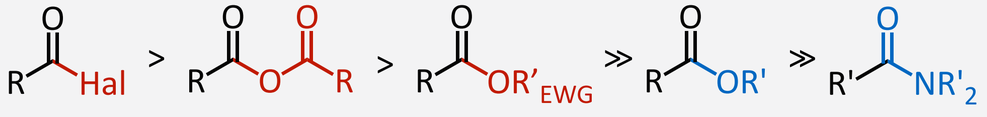
- **both** substituents relevant, residue R tunes reactivity of the electrophilic center for given X:



- **amides, acids, carboxylates have poor leaving groups, do not easily undergo substitution**
- **aldehydes, ketones have no leaving groups (H, R') but are reactive for nucleophile addition!**

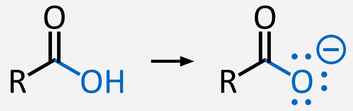
Reactivity of the Leaving Group in Carbonyl Compounds

- reactivity in second step depends on leaving group quality (see S_N1) of carbonyl substituent:



halides	anhydrides	active esters	esters	amides
HCl	RCOOH	$R'_{EWG}OH$	R'OH	R'_2NH
pK_A –7	pK_A 4	pK_A 6–10	pK_A 18	pK_A 18–30

- carboxylic acids undergo deprotonation



acids	carboxylates
H_2O	OH^-
pK_A 15.6	pK_A 30

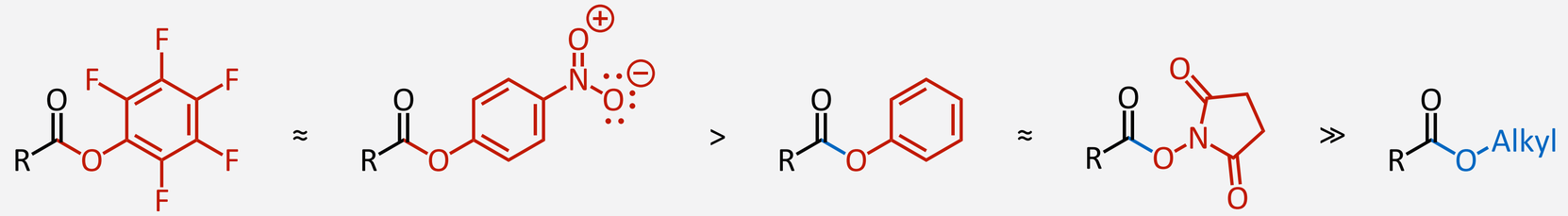
- aldehydes, ketones have no leaving group

aldehydes	ketones
H_2	CH_4
pK_A 35	pK_A 48

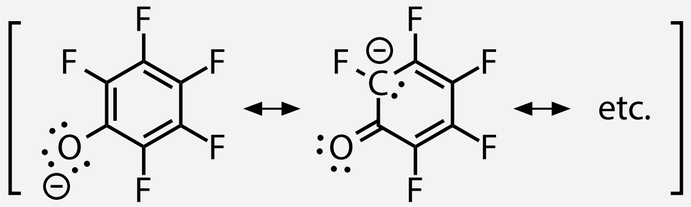
- **amides, acids, carboxylates have poor leaving groups, do not easily undergo substitution**
- **aldehydes / ketones have no leaving groups, cannot complete nucleophilic substitution**

Reactivity of Active Ester Leaving Group

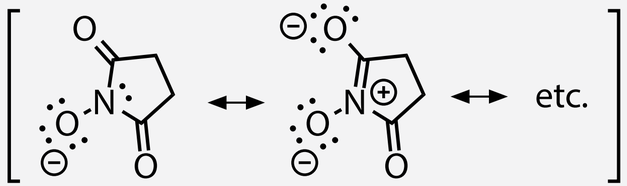
- active esters are formed from alcohols/phenols with strongly electron-withdrawing residues



pentafluorophenyl	nitrophenyl	phenyl	*N*-succimidyl	regular esters
C_6F_5OH	NO_2-C_6H_4OH	C_6H_5OH	SuOH	ROH
pK_A 6	pK_A 7	pK_A 10	pK_A 10	pK_A 18



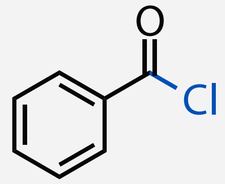
pentafluorophenyl esters



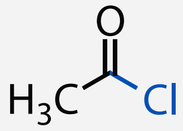
N-succinylimidyl esters

- **regular esters have poor alcoholate leaving groups**
- **active esters result in well stabilized phenolate/alcoholate leaving groups (–M / –I effects)**

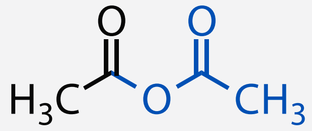
Trivial Names and Acronyms of Important Reactants



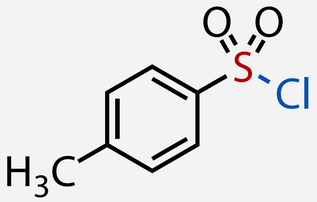
benzoyl chloride
(BzCl)



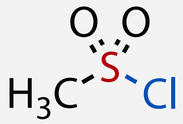
acetyl chloride
(AcCl)



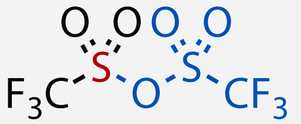
acetic anhydride
(AcOAc, Ac_2O)



tosyl chloride
(TsCl)

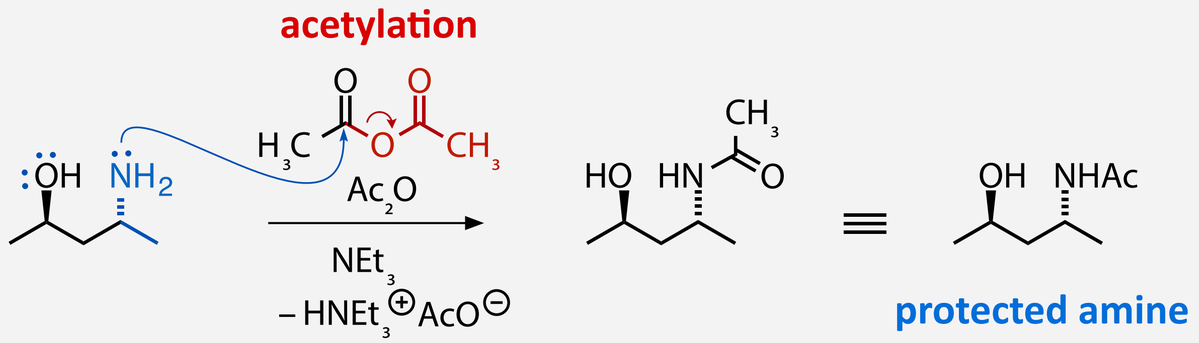


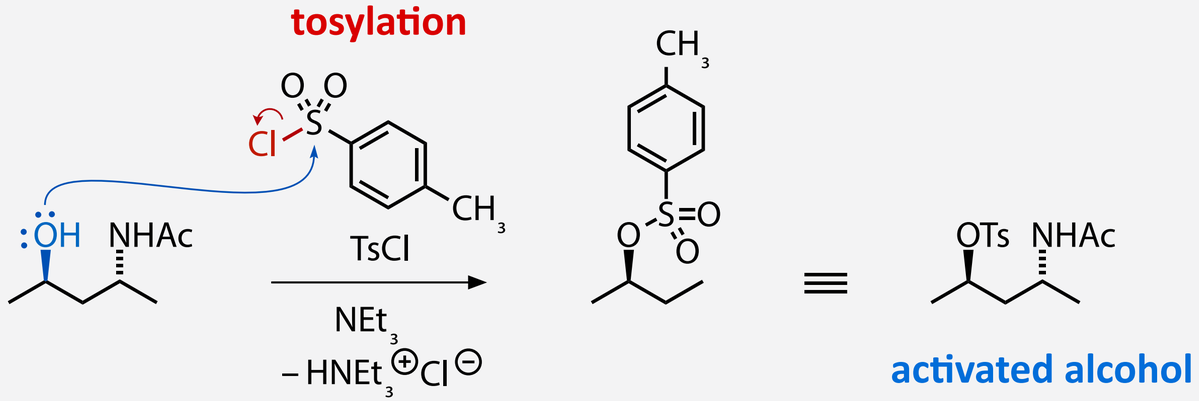
mesyl chloride
(MsCl)

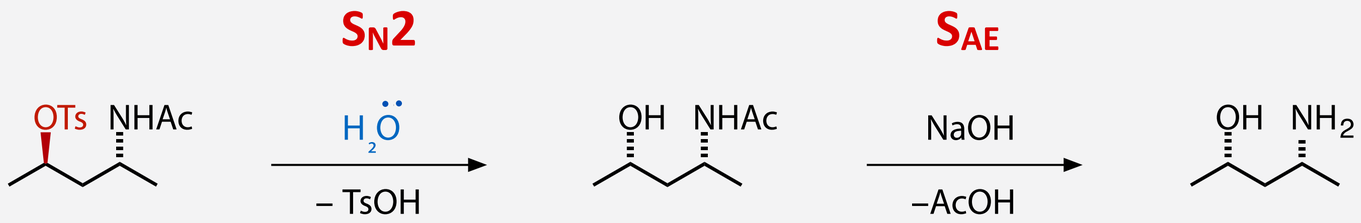


Triflic anhydride
(TfOTf, Tf_2O)

Example: Protection by Acetylation, Electrophilic Activation by Tosylation

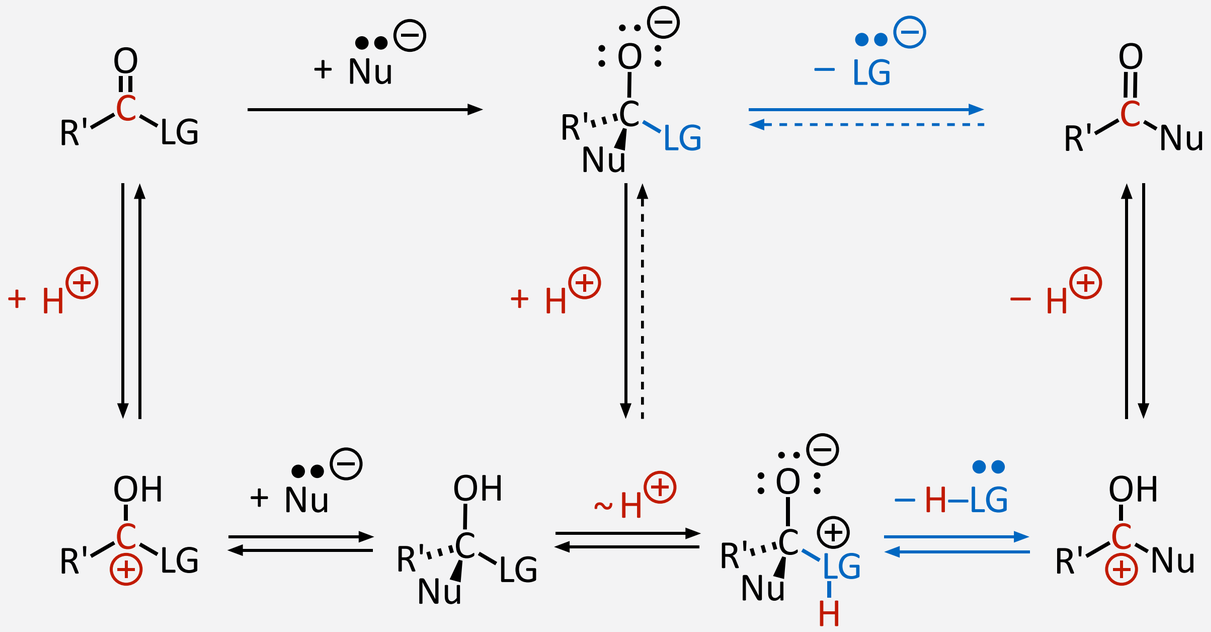






Electrophilic Activation

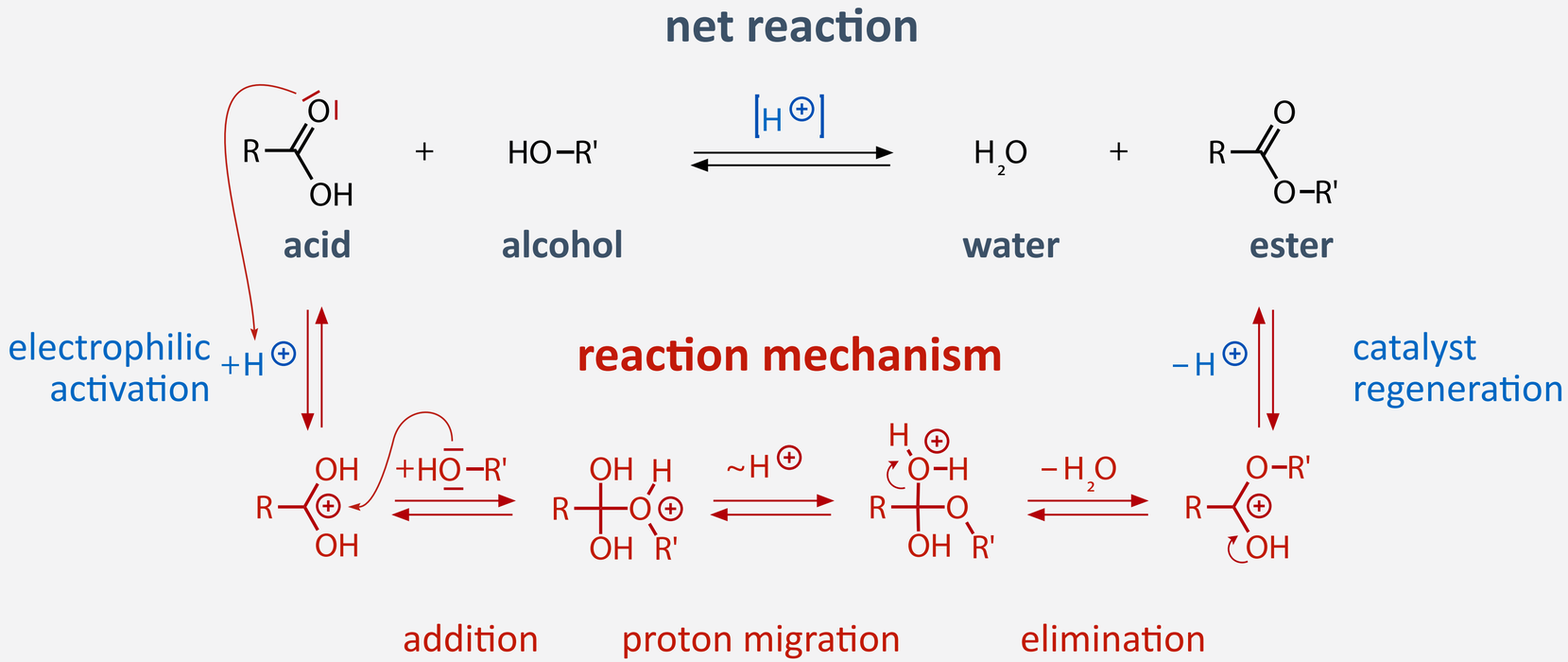
- **electrophilic intermediates can be activated by even better electrophiles (Lewis or Brønsted acids)**



- Lewis acid (e.g., $ZnCl_2$, $AlCl_3$, BF_3) or Brønsted acid ($H^{\oplus}$) adds to carbonyl oxygen
- **carbonyl carbon obtains formal positive charge, becomes more electron-deficient**
- **different leaving group (conjugate acid of original leaving group) with lower pKA, much better**
- **electrophilic catalysis: new sequence with two additional steps but overall lower activation energies**

Example: Esterification

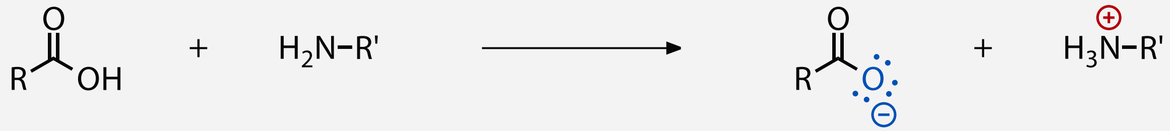
- esterifications are typically performed using acid catalysts for electrophilic activation



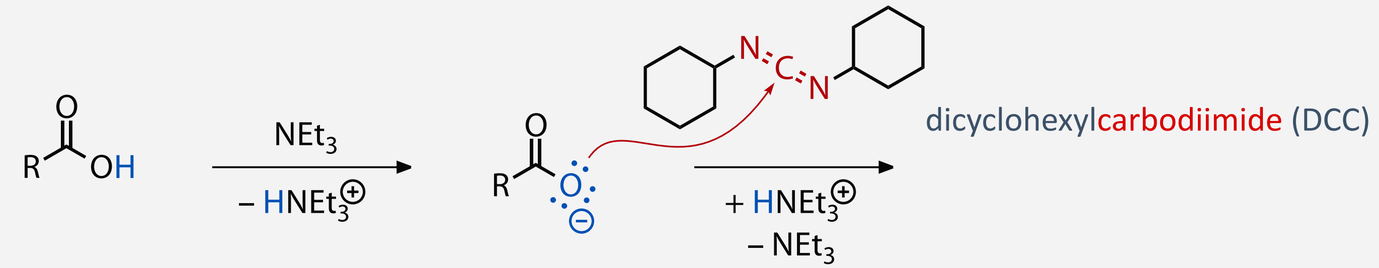
- **since OH^- is a very poor leaving group, acid catalysis is required for electrophilic activation**
- **reaction proceeds under proton migration, any oxygen of the starting material can leave**
- **equilibrium means that reverse reaction (“ester hydrolysis”) is equally well possible**
- **equilibrium in closed system typically 60% ester, can be shifted in open system (product removal)**

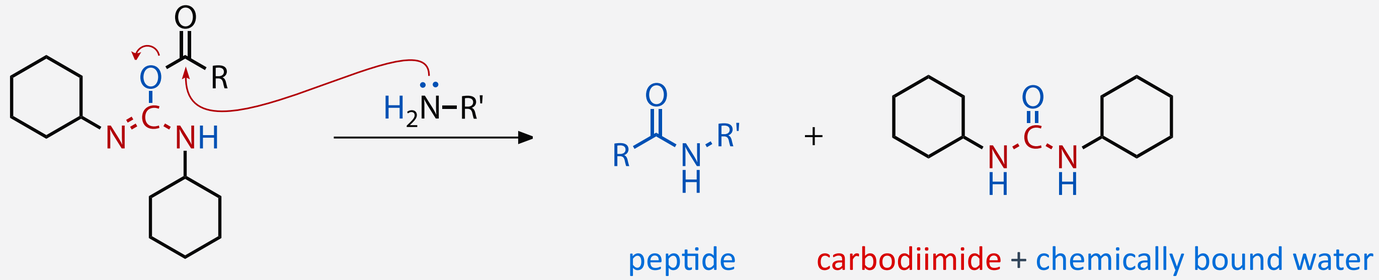
Example: Peptide Coupling Reactions

- problem: no amide (peptide) formation between carboxylic acid and amine:



- solution: electrophilic activation with peptide coupling reagents



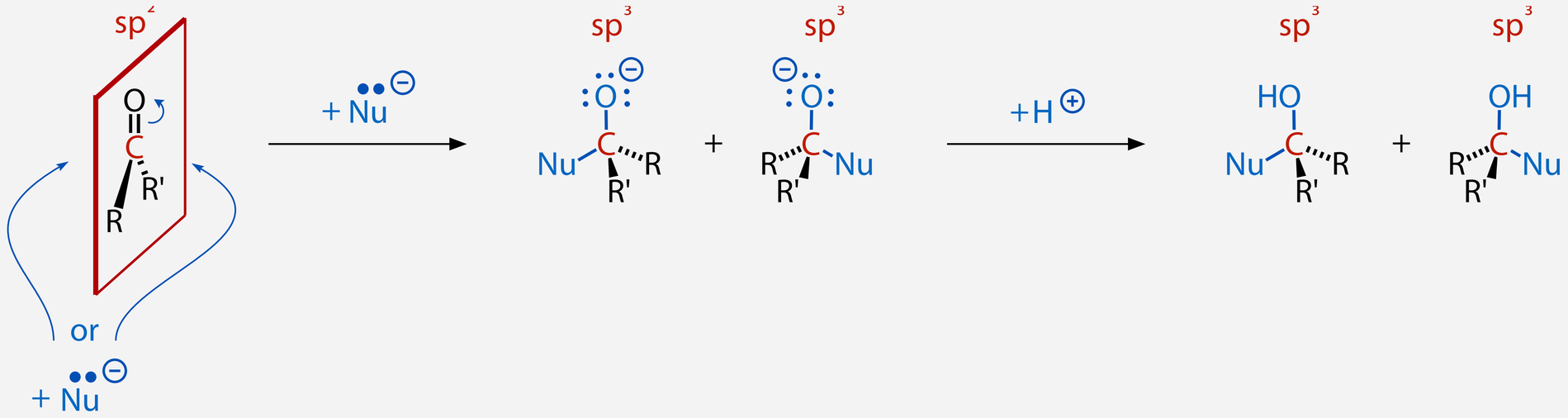


- **peptide coupling agents are Lewis acid for electrophilic activation of the acid component**
- **peptide coupling agents "chemically remove" (bind) water**

Nucleophilic Additions

Mechanism of Nucleophilic Additions (A_N)

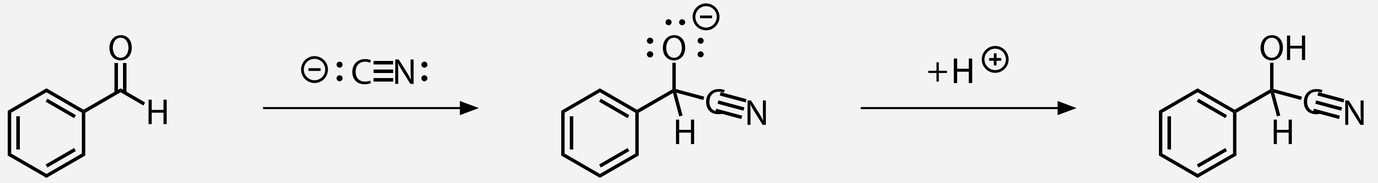
- if the carbonyl group has no leaving group, nucleophilic substitution is impossible!



- **instead, addition of the nucleophile followed by addition of an electrophile (typically $H^{\oplus}$)**
- **product remains tetrahedral, becomes chiral if R ≠ R', but is generated as racemic mixture**
- **the reaction is also a reduction of the carbonyl carbon (to lower oxidation state)**

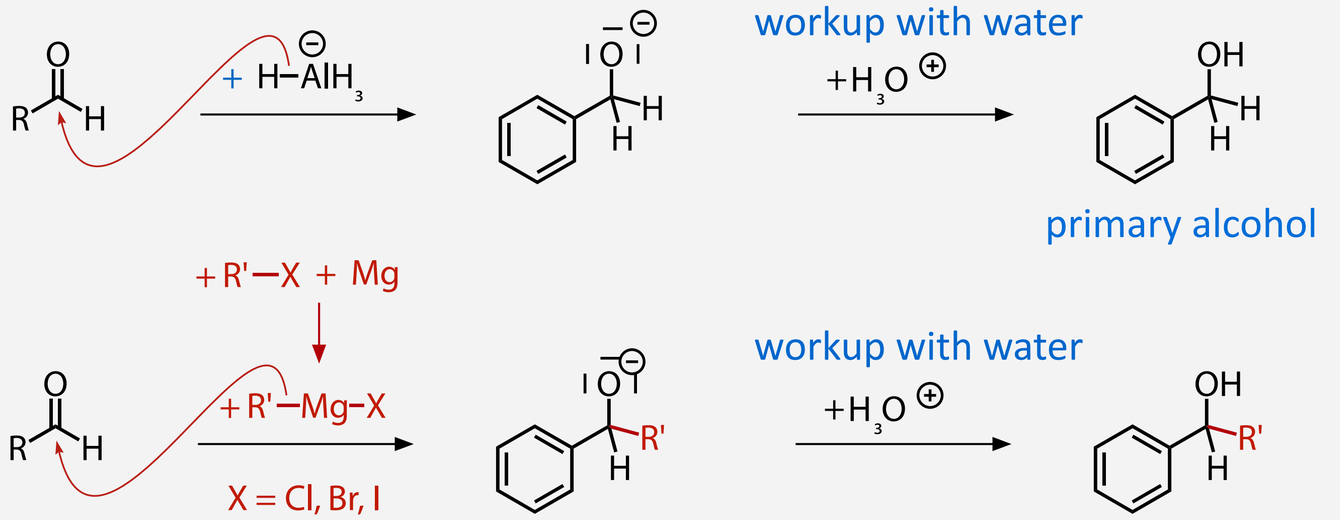
Examples: Nitrile Addition and Reductions

- cyanide anion (CN^-) is a strong nucleophile, results in formation of organic nitriles (R–CN)



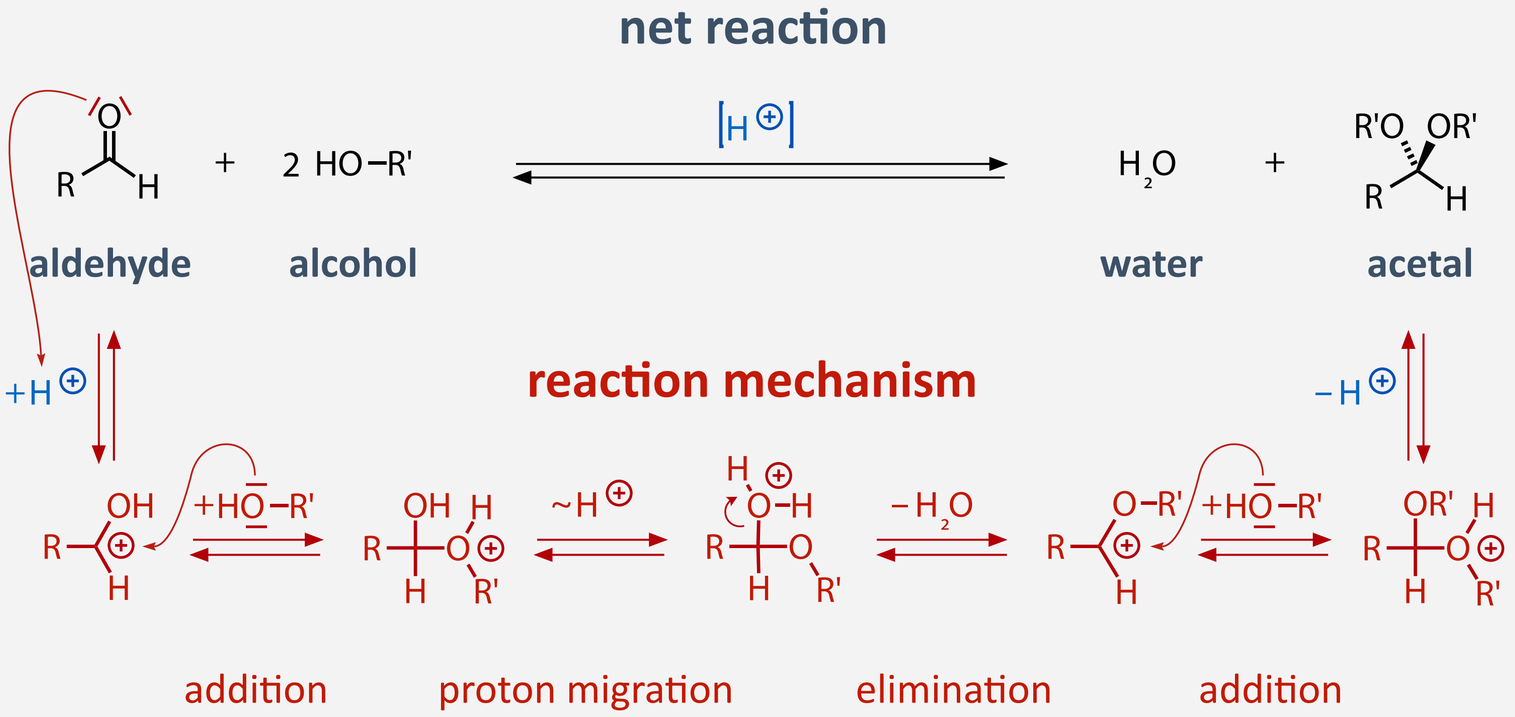
mandelonitrile
(bitter almond)

- reduction with hydride (H^-) sources ($NaBH_4$, $LiAlH_4$) or Grignard reagents (R–Mg–X)



A Peculiar Example: Acetalization of Aldehydes or Ketones

- acetalization of aldehydes and ketones typically using acid catalysts for electrophilic activation



- **reaction similar to esterification but path diverges because H^- is not a leaving group at all**
- **electrophilic activation and proton migration convert carbonyl oxygen into leaving group**
- **reaction sequence is terminated with a second addition of an alcohol molecule**

Learning Outcome

- **carbonyl carbon atoms are inherently very reactive electrophilic centers**
- **reactivity can be enhanced by electrophilic activation**
- **all reactions start with nucleophilic attack on the electrophilic center**
- **reaction sequence then dominated by presence/absence of leaving group**
  - if leaving group present, nucleophilic substitution is preferred
  - if no leaving group present, nucleophilic addition occurs