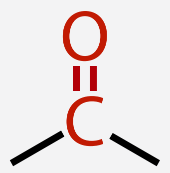
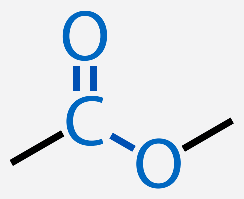
4.5 Nucleophilic Reactions on Carbonyl Groups (S_{AE}, A_N)

Carbonyl Compounds

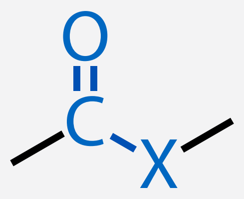
carbonyl function



carboxyl function



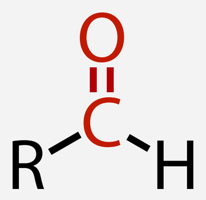
carboxyl derivative



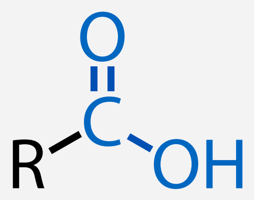
X = O, S, NH, Hal ...

carbonyl compounds

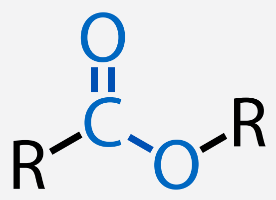
carboxyl compounds



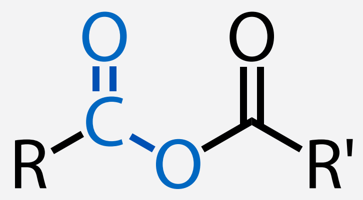
aldehyde



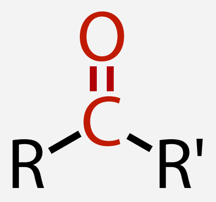
carboxylic acid



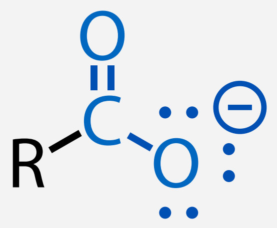
ester



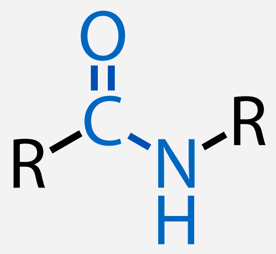
anhydride



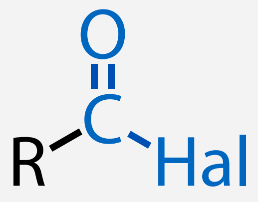
ketone



carboxylate



amide

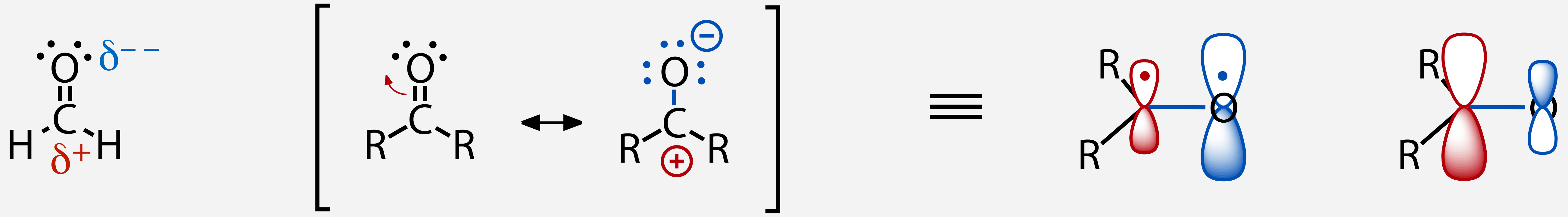


acyl halide

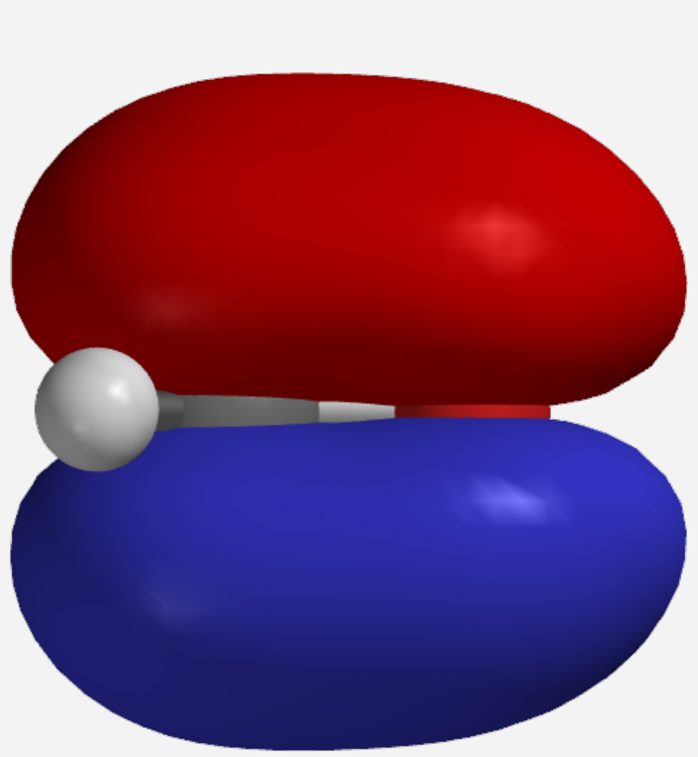
- carbonyl compounds are all compounds contains a carbonyl (C=O) function
- carboxyl compounds have additional bond to an electronegative element (leaving group!)

Carbonyl Compounds are Electrophiles

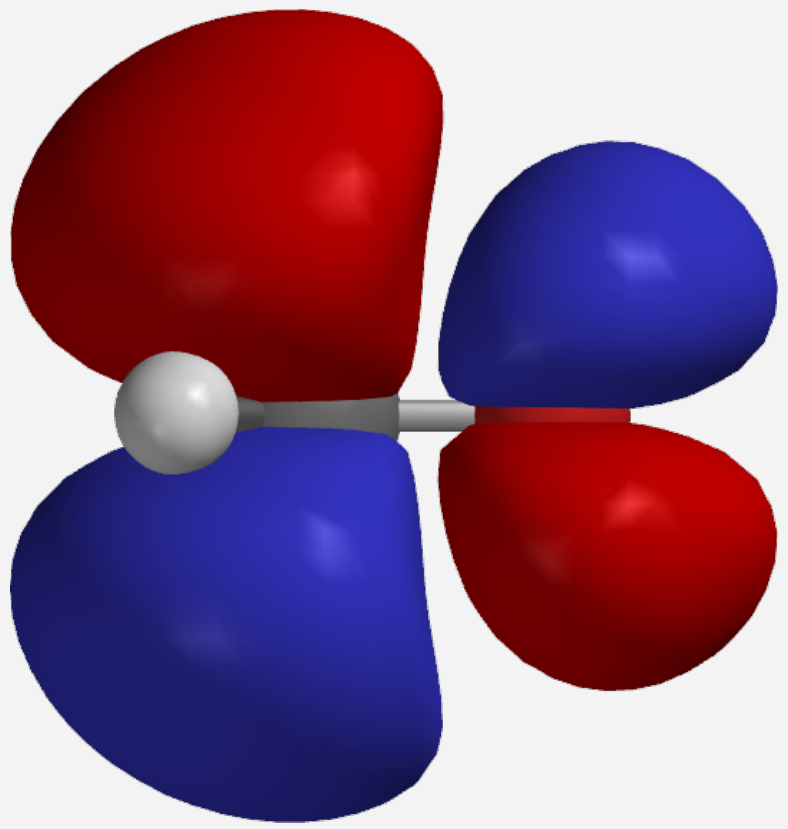
- carbonyl carbon atoms are inherently very reactive electrophilic centers



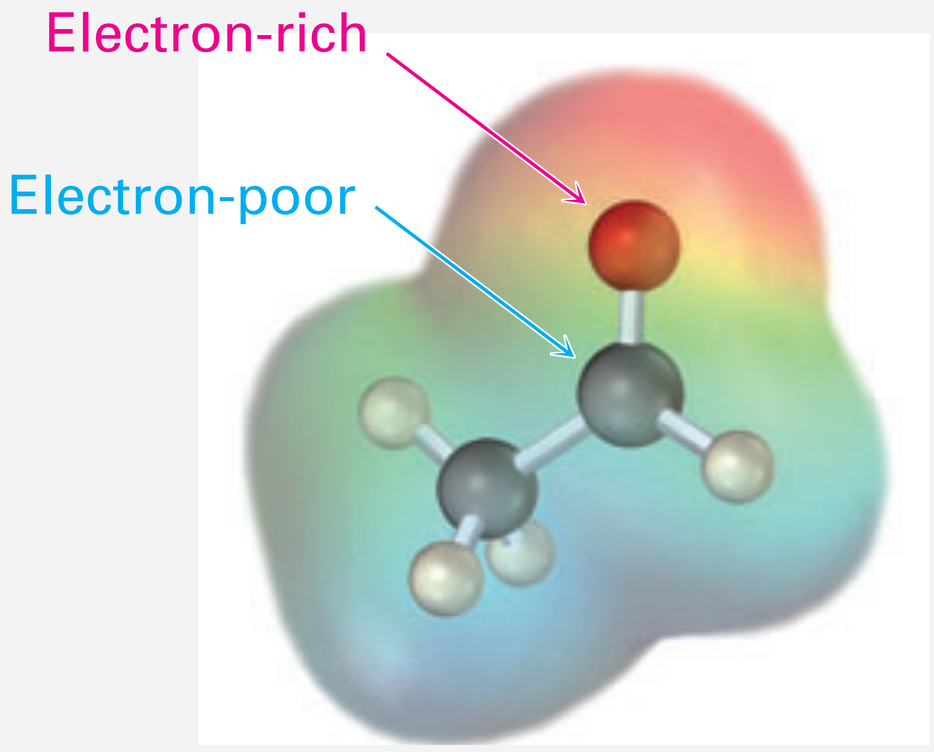
π (HOMO) **π* (LUMO)**



π



π*



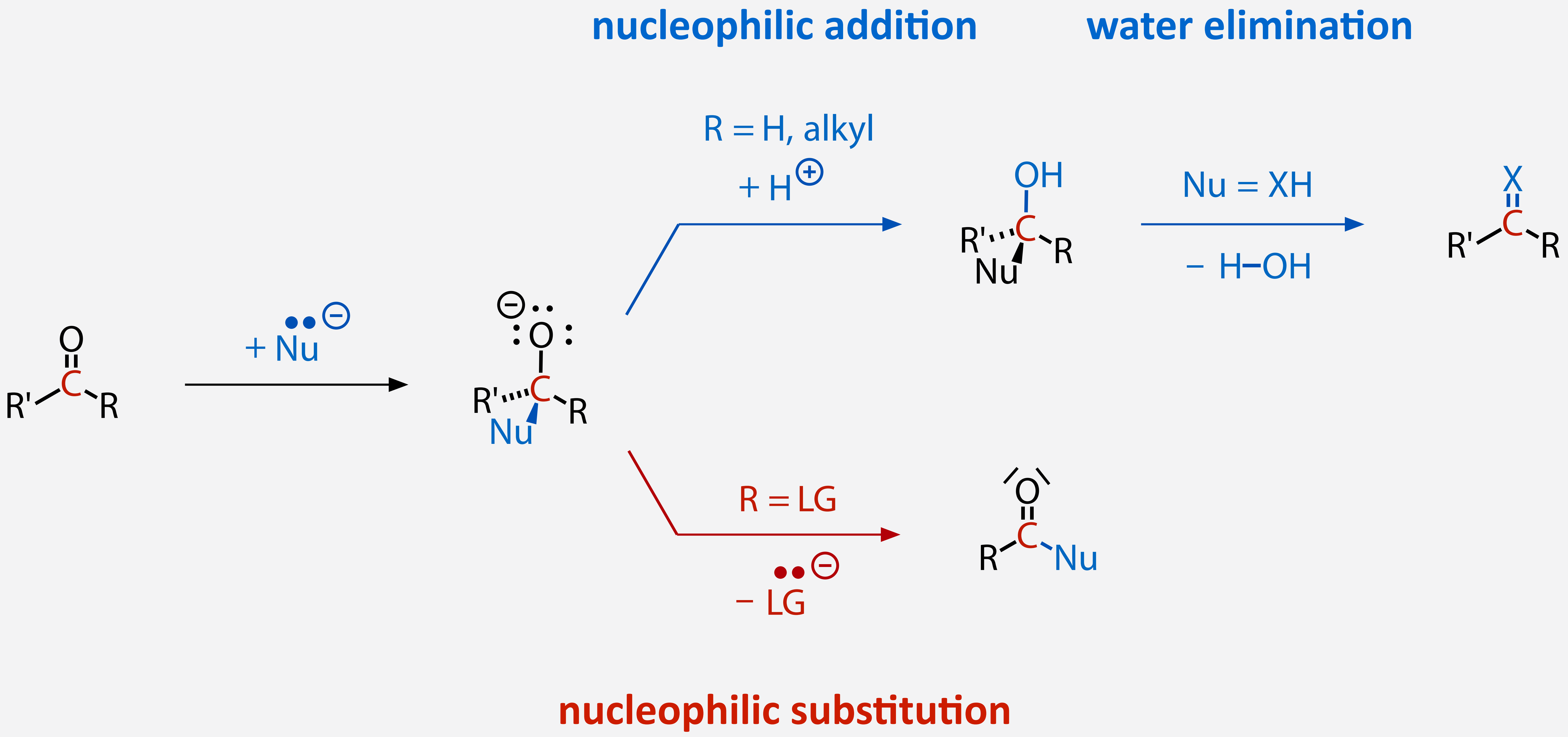
electrostatic potential

- **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**

see also chapters 2.2, 2.3, 2.4

Overview of Nucleophilic Reactions on the Carbonyl Compounds

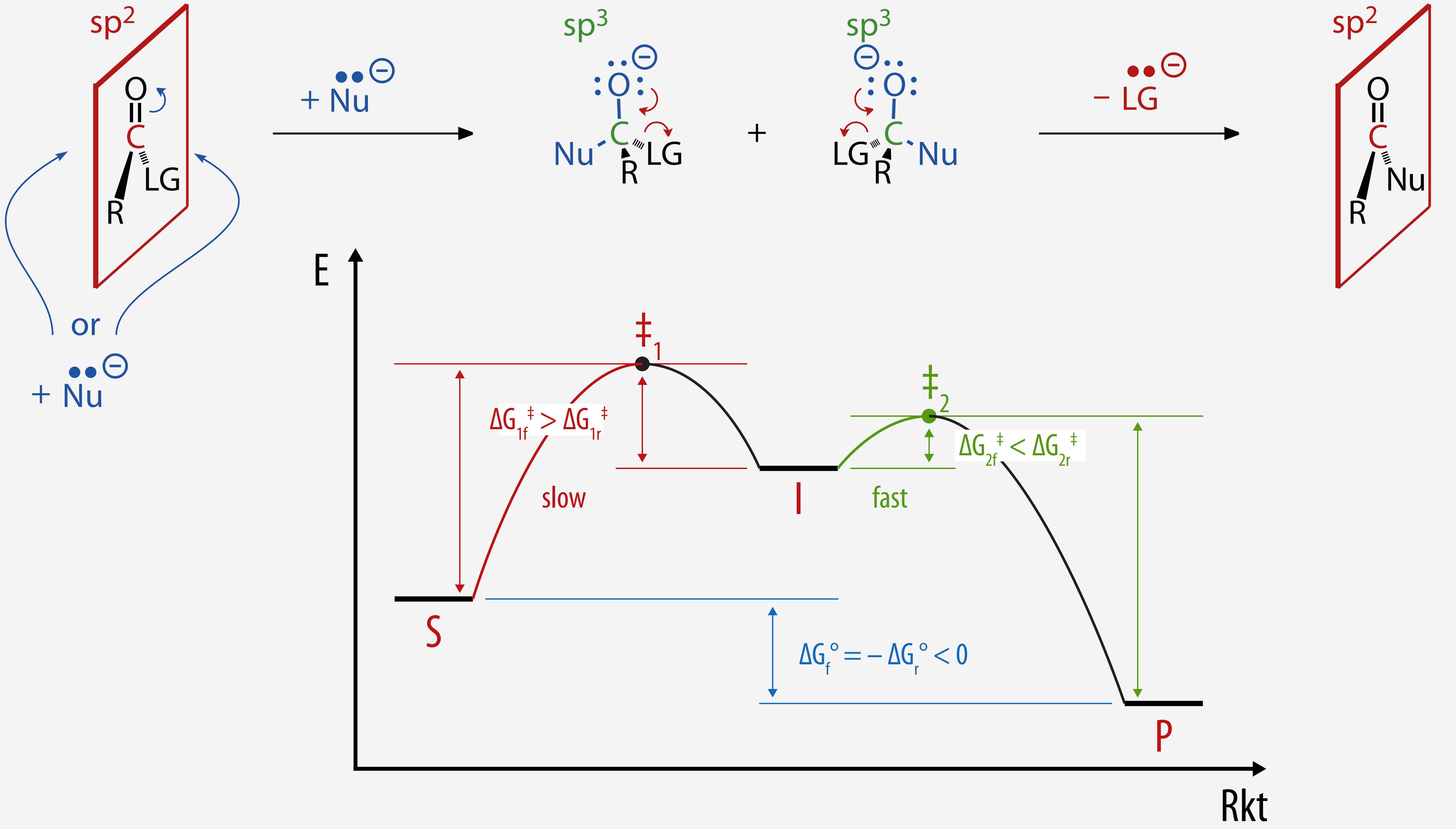
- all reaction sequences start with nucleophilic attack on the electrophilic carbonyl carbon



- **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})

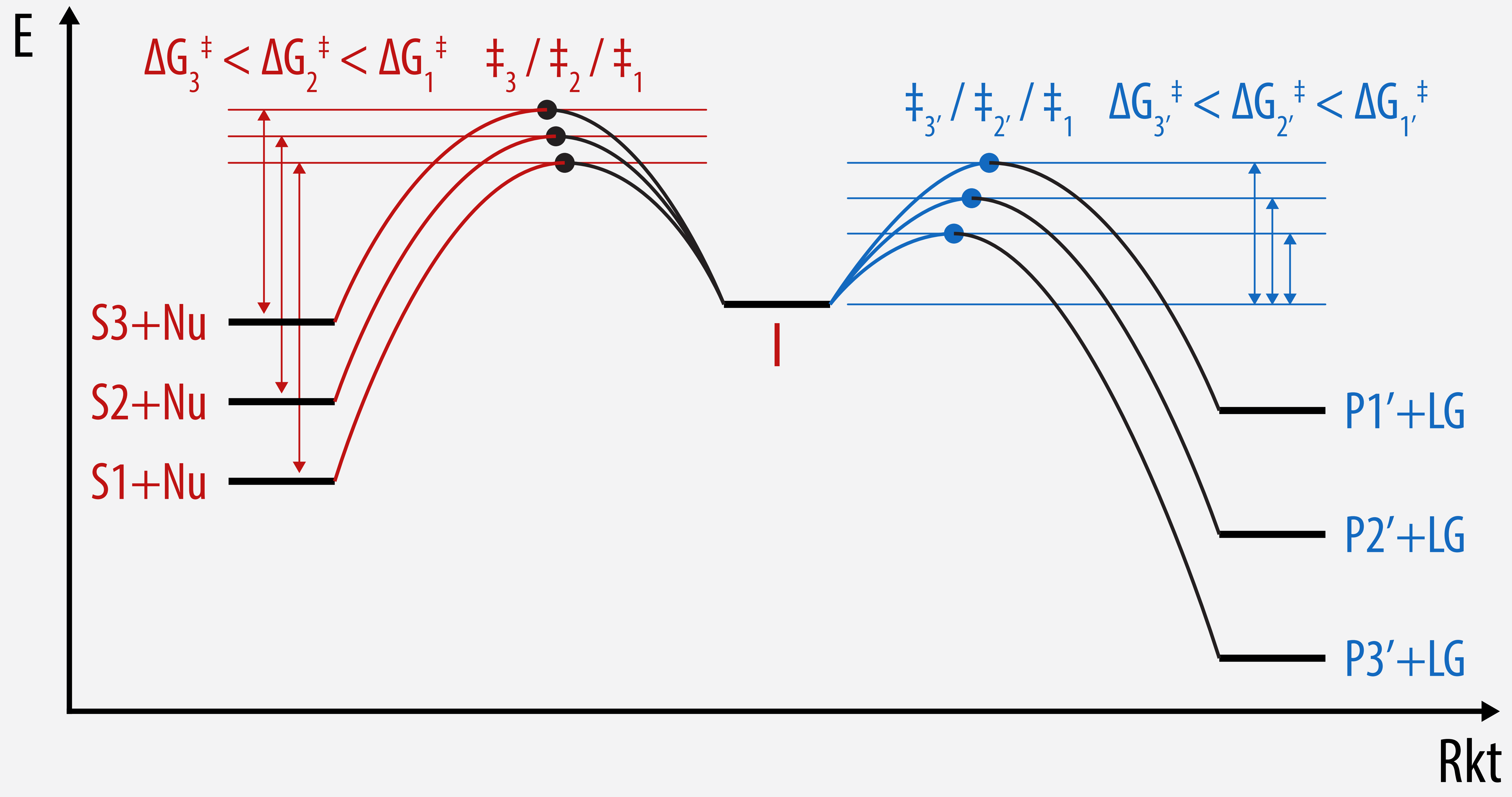


- **carbonyl carbons are tetravalent, but sp² hybridized and coordinatively unsaturated**
- **stable intermediate by addition of nucleophile prior to cleavage of leaving group is possible**

Factors Favoring Kinetically / Thermodynamically the S_{AE} Reaction

- more electrophilic carbonyl carbon
- (stronger nucleophile)

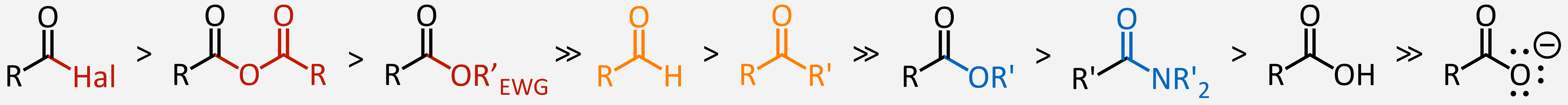
- better leaving group
- (more stable product)



- 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

Reactivity of Carbonyl Group as an Electrophilic Center

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



halides anhydrides active esters aldehydes ketones esters amides acids carboxylates

–M and/or –I effect

no effect

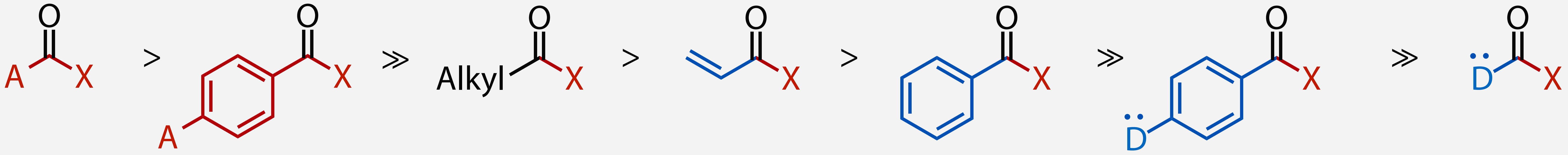
+M effect

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:



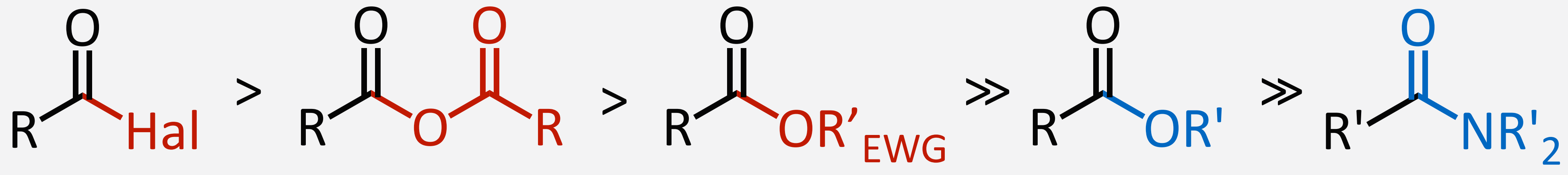
–M and/or –I effect

+M effect

- **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!**

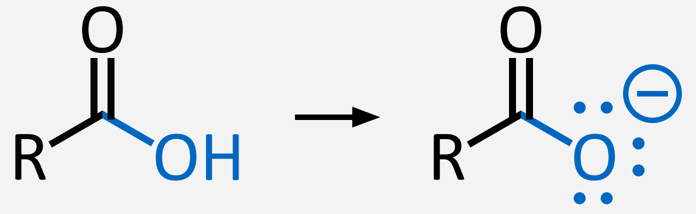
Reactivity of the Leaving Group in Carbonyl Compounds

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



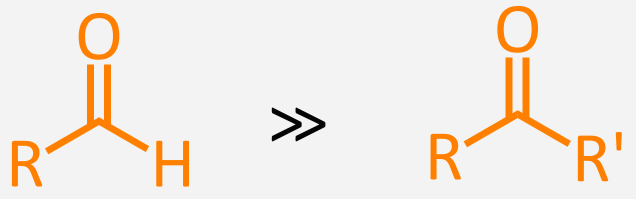
halides	anhydrides	active esters	esters	amides
HCl pK_A –7	RCOOH pK_A 4	$R'_{EWG}OH$ pK_A 6–10	R'OH pK_A 18	R'_2NH pK_A 18–30

- carboxylic acids undergo deprotonation



acids	carboxylates
H_2O pK_A 15.6	$OH^–$ pK_A 30

- aldehydes, ketones have no leaving group

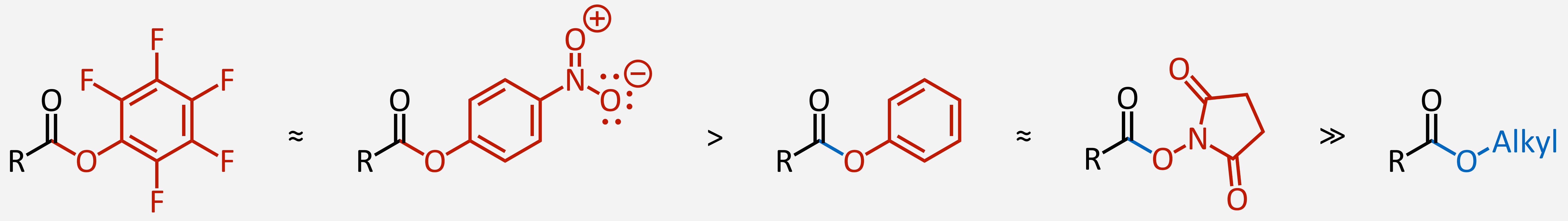


aldehydes	ketones
H_2 pK_A 35	CH_4 pK_A 48

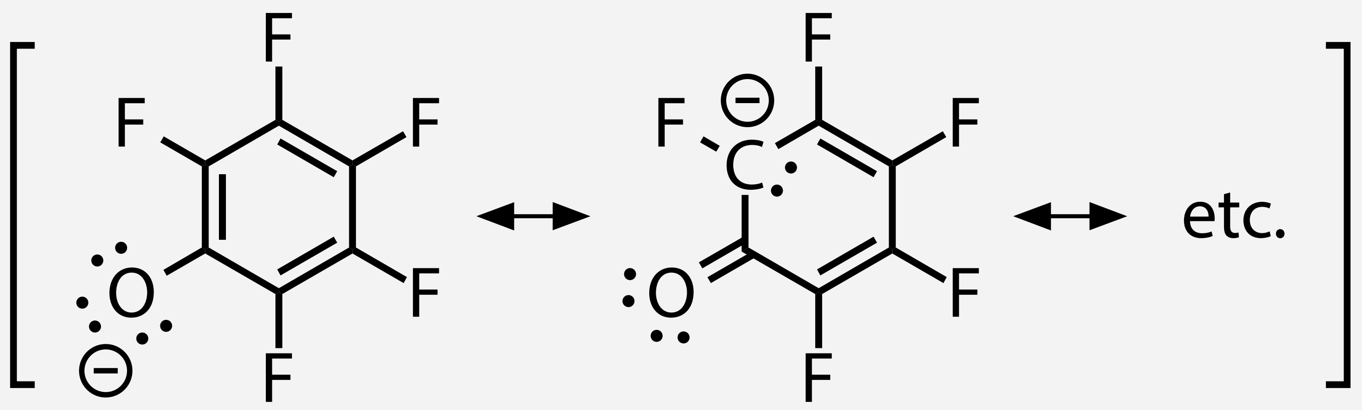
- **amides, acids, carboxylates have poor leaving groups, do not easily undergo substitution**
- **aldehydes / ketones have no leaving groups, cannot complete nucleophilic substitution**

Reactivity of Active Ester Leaving Group

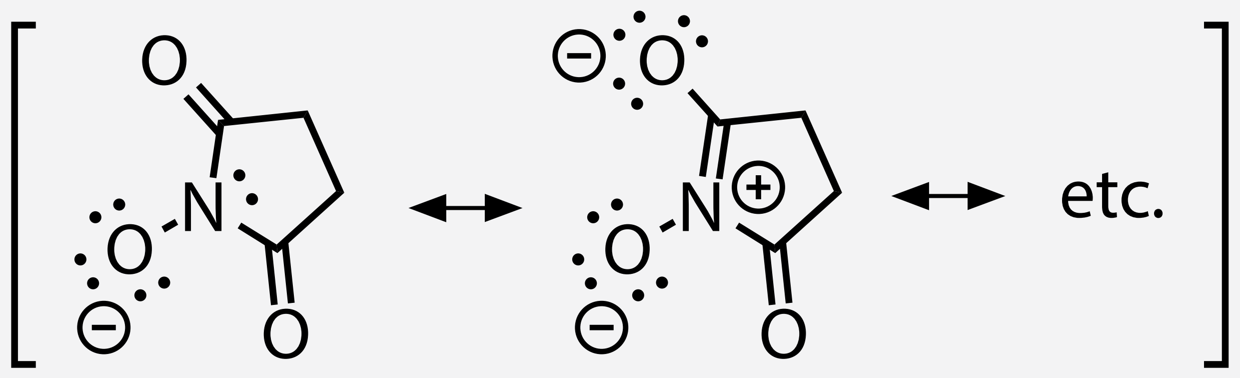
- active esters are formed from alcohols/phenols with strongly electron-withdrawing residues



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



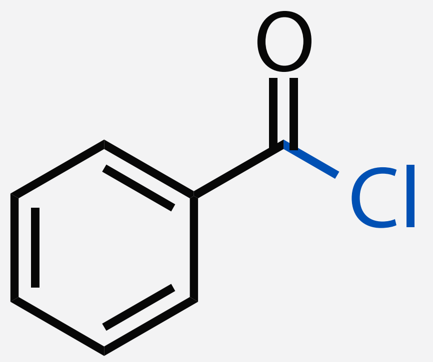
pentafluorophenyl esters



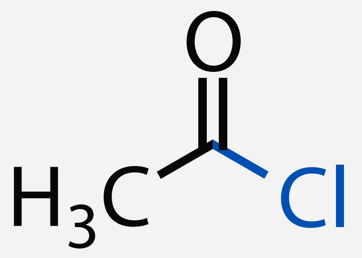
N-succinylimidyl esters

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

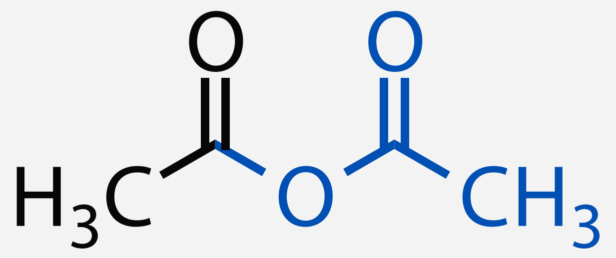
Trivial Names and Acronyms of Important Reactants



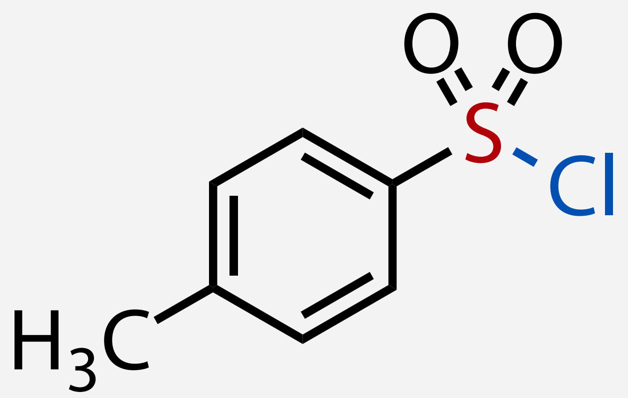
benzoyl chloride
(BzCl)



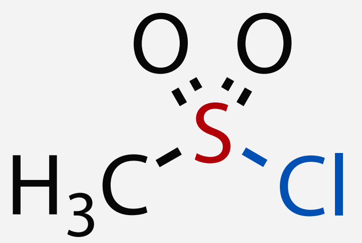
acetyl chloride
(AcCl)



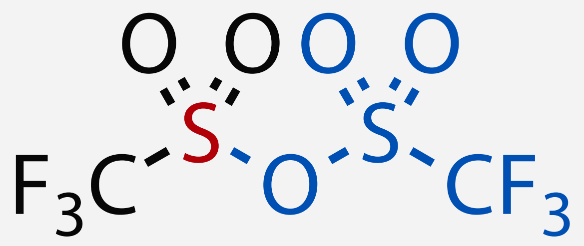
acetic anhydride
(AcOAc, Ac_2O)



tosyl chloride
(TsCl)



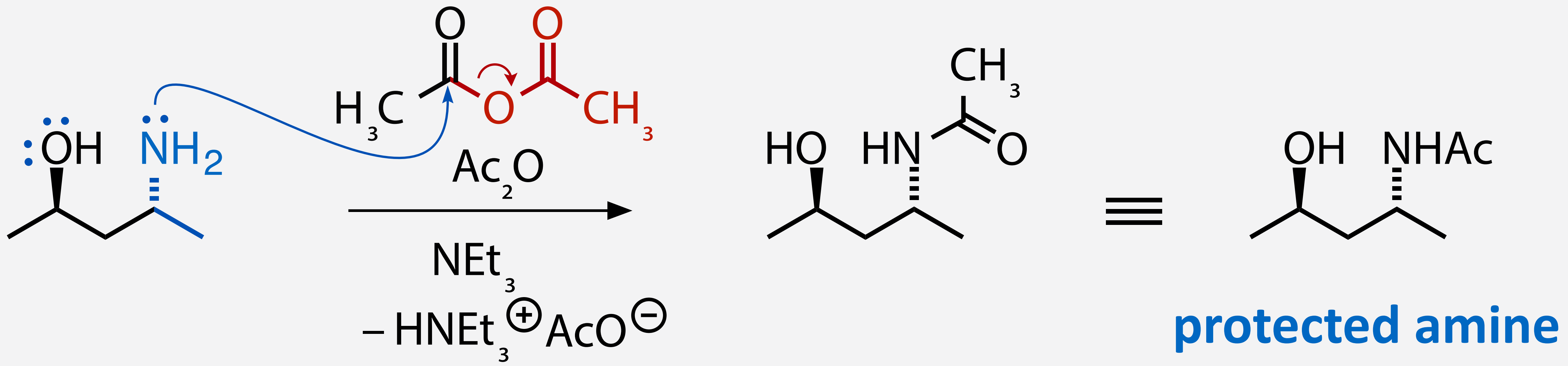
mesyl chloride
(MsCl)



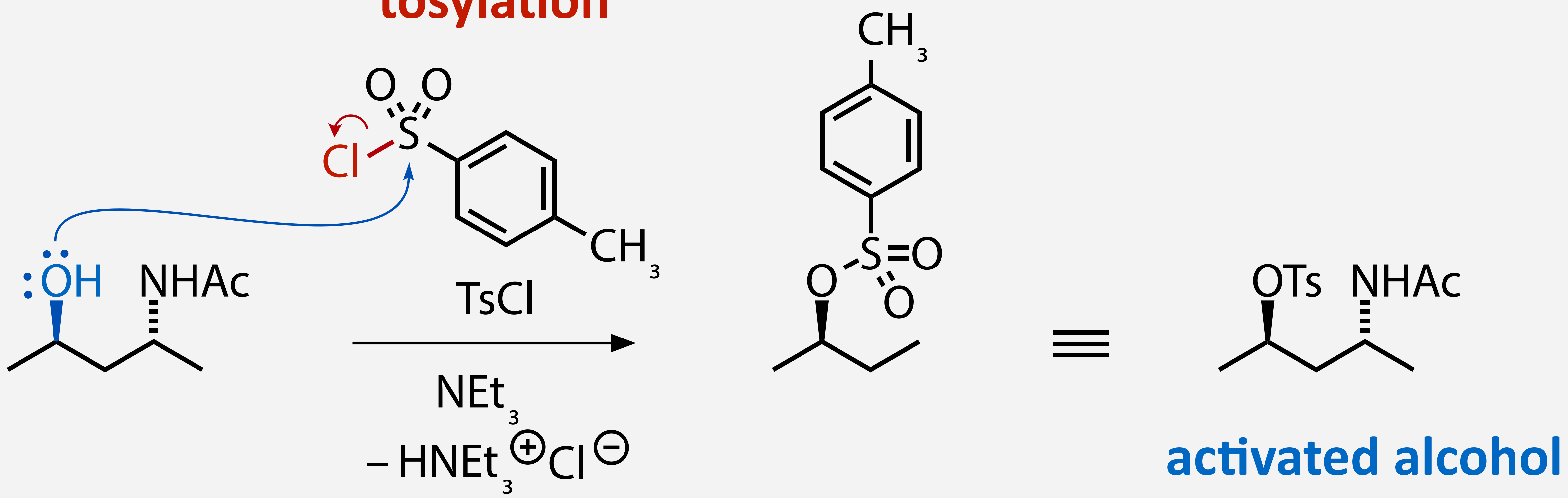
Triflic anhydride
(TfOTf, Tf_2O)

Example: Protection by Acetylation, Electrophilic Activation by Tosylation

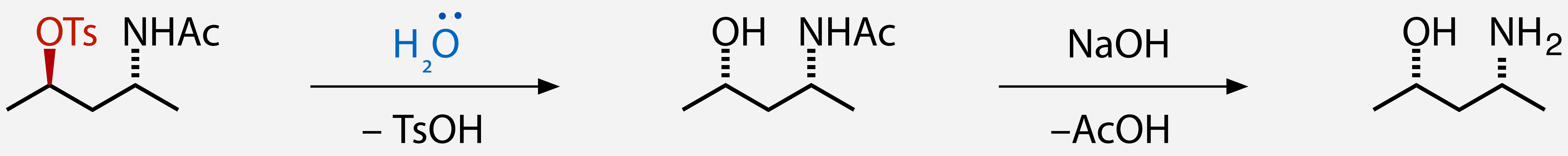
acetylation



tosylation

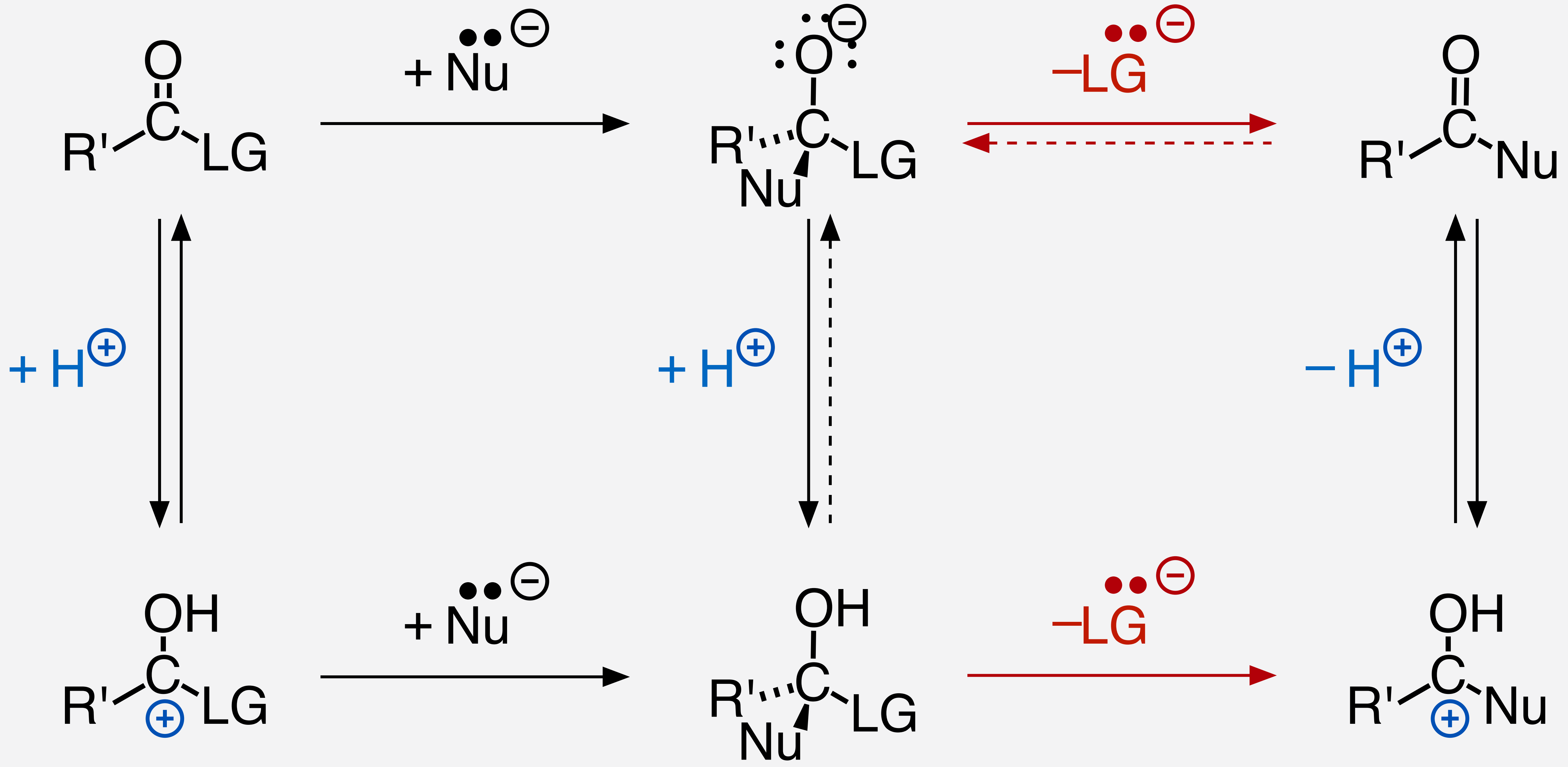


S_N2 **S_{AE}**



Electrophilic Activation

- Lewis or Brønsted acids makes the electrophilic carbonyl carbon more reactive

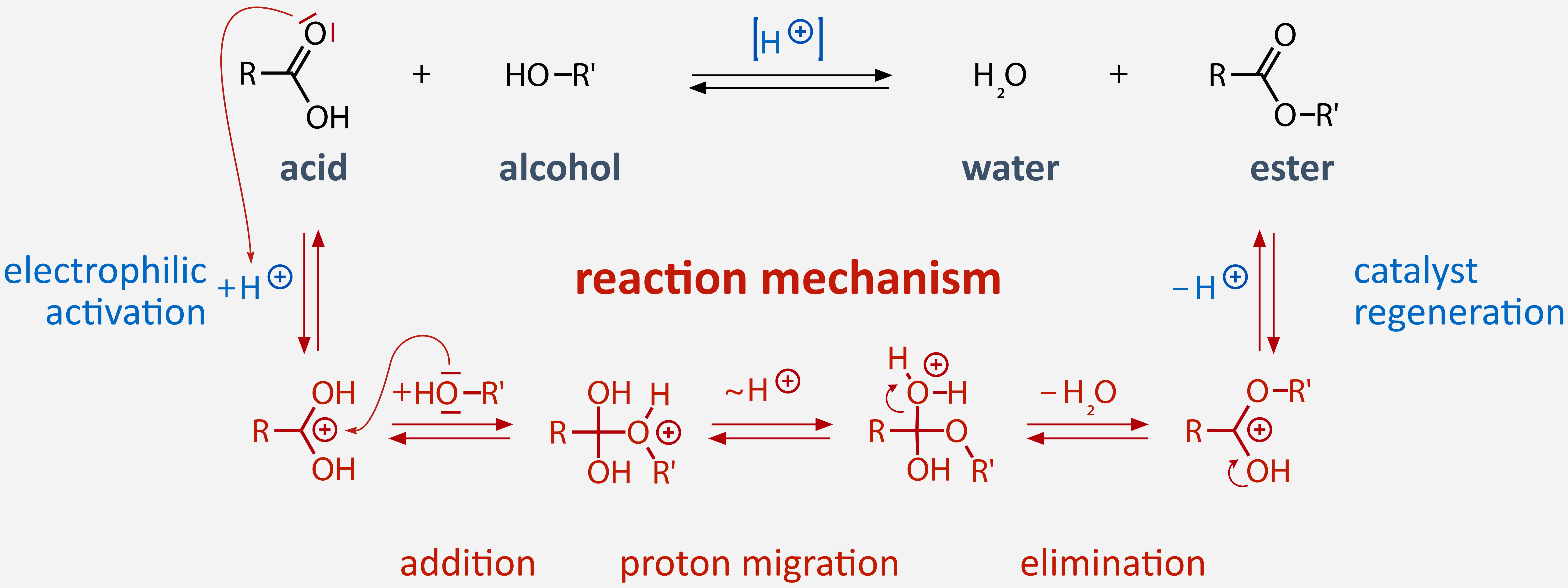


- **Lewis acid (e.g., $ZnCl_2$, $AlCl_3$, BF_3) or Brønsted acid ($H^\oplus$) adds to carbonyl oxygen**
- **carbonyl carbon obtains formal positive charge, becomes more electron-deficient**

Example: Esterification

- esterifications are typically performed using acid catalysts for electrophilic activation

net reaction

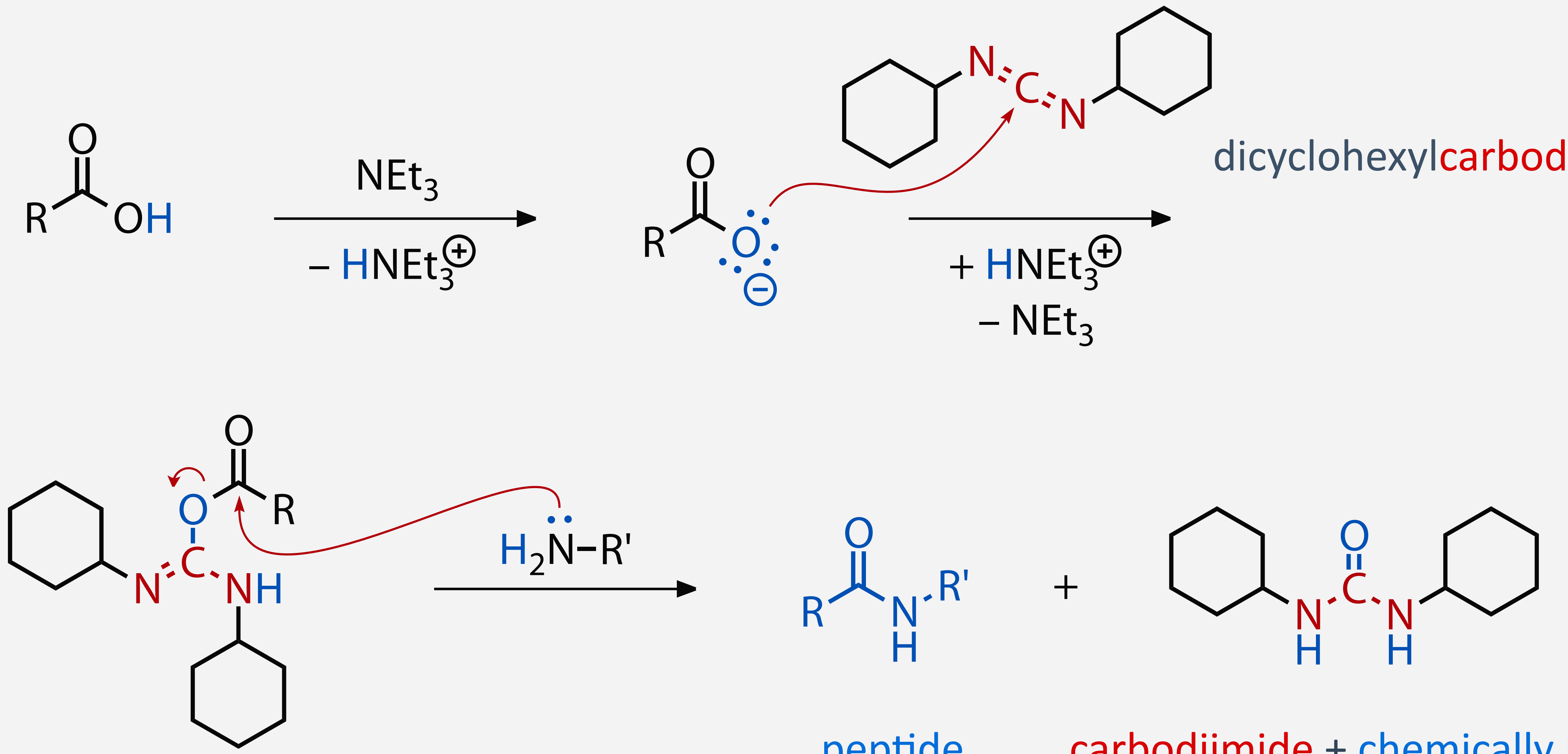


- **since OH⁻ is a very poor leaving group, acid catalysis is required for electrophilic activation**
- **reaction proceeds under proton migration, any oxygen of the starting material can leave**

Example: Peptide Coupling Reactions

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

- solution: electrophilic activation with peptide coupling reagents



dicyclohexylcarbodiimide (DCC)

peptide

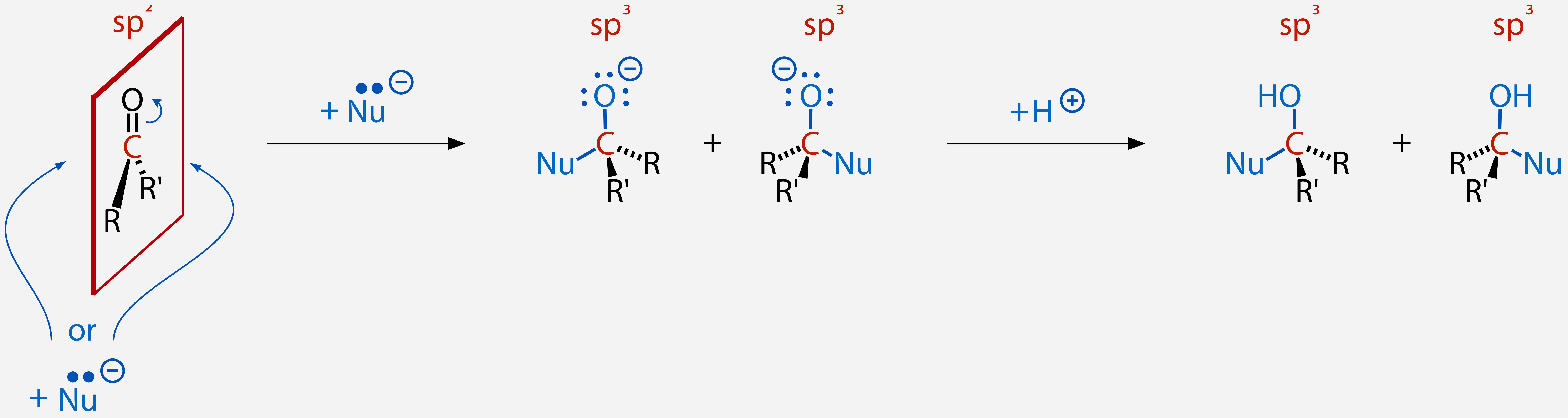
carbodiimide + chemically bound water

- **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)

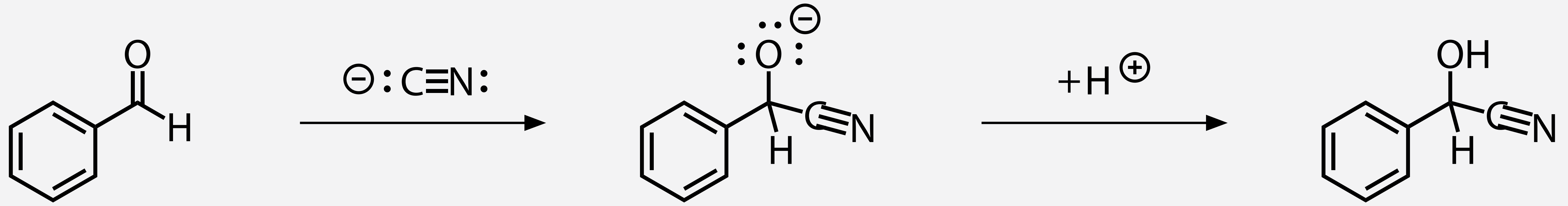
- if the carbonyl group has no leaving group, nucleophilic substitution is impossible!



- **instead, addition of the nucleophile followed by addition of an electrophile (typically H⊕)**
- **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)**

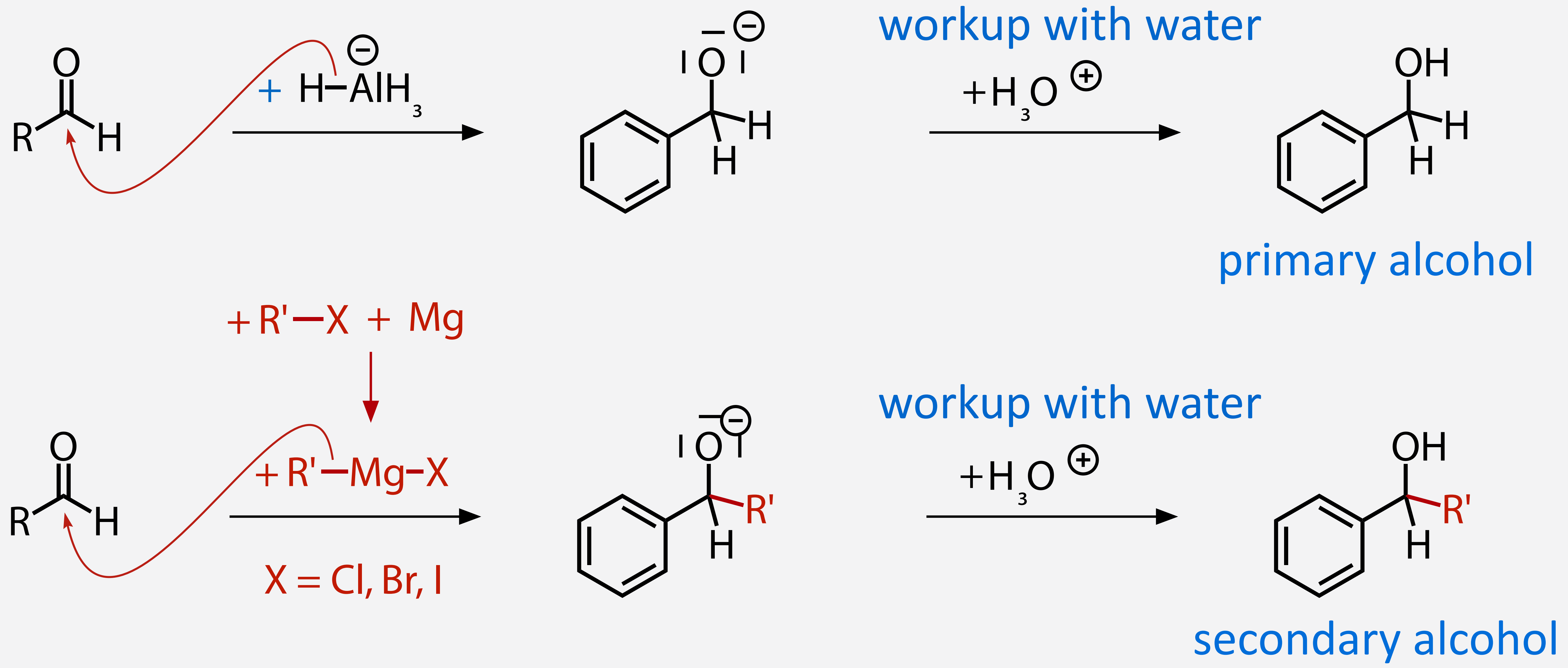
Examples: Nitrile Addition and Reductions

- 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)



workup with water

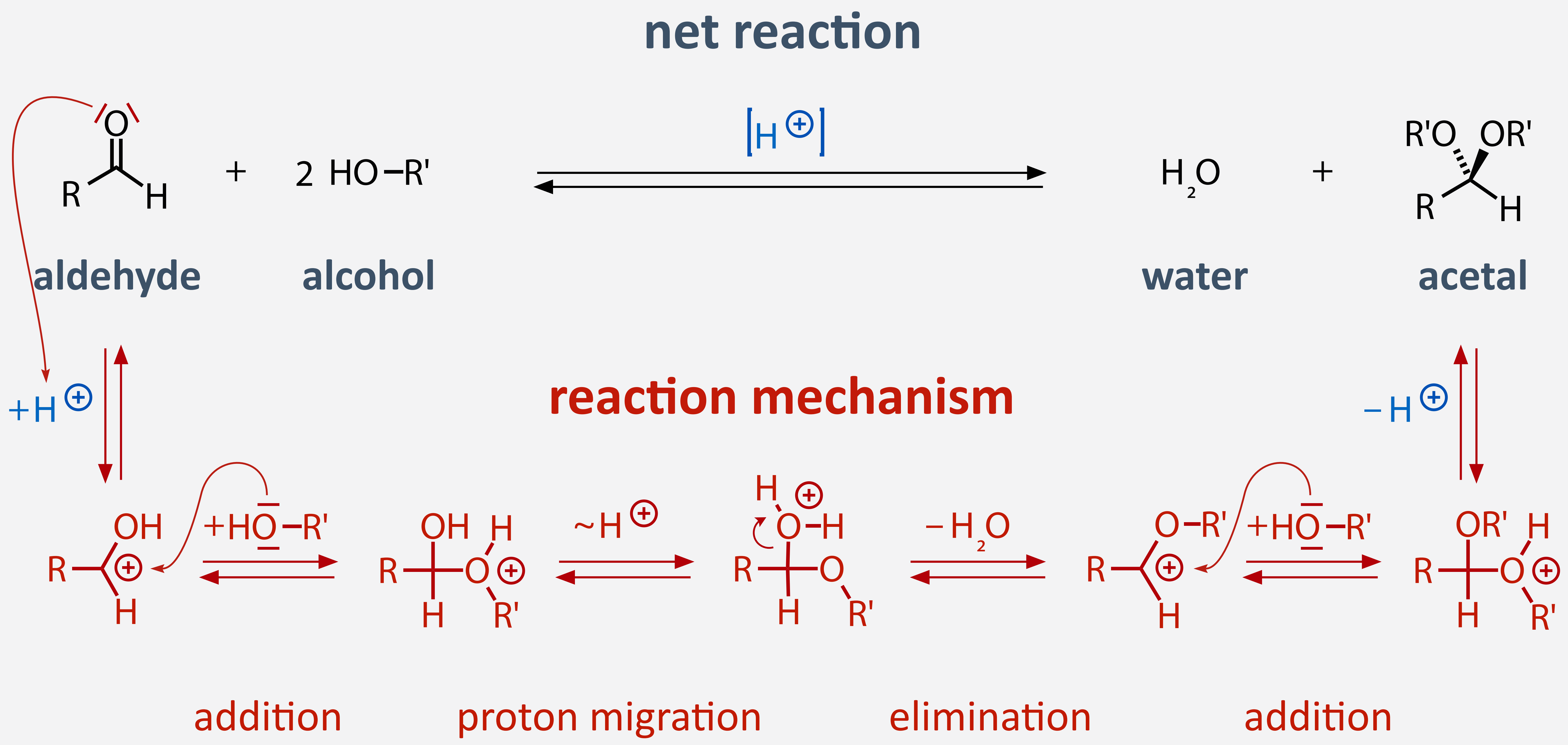
primary alcohol

workup with water

secondary alcohol

A Peculiar Example: Acetalization of Aldehydes or Ketones

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



net reaction

reaction mechanism

- **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