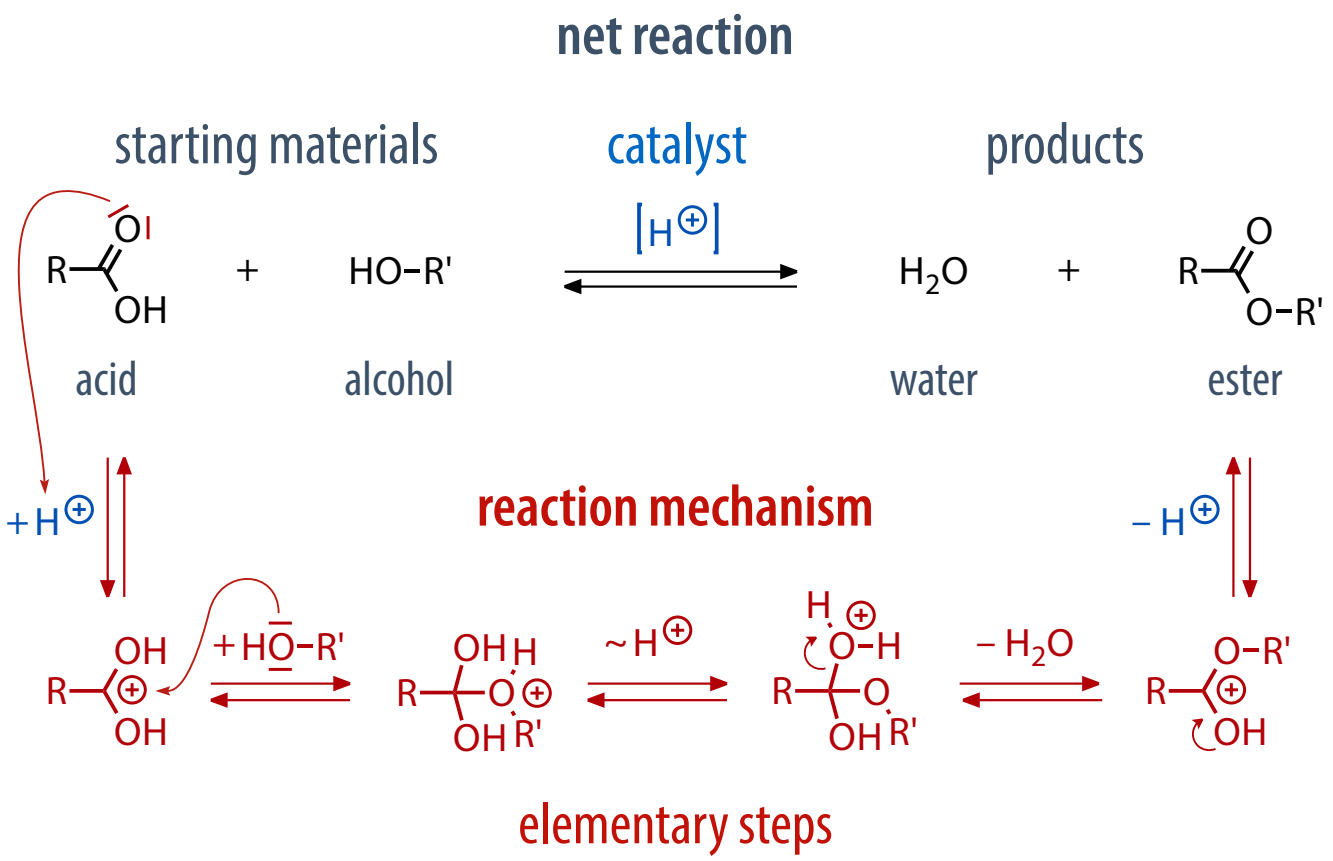
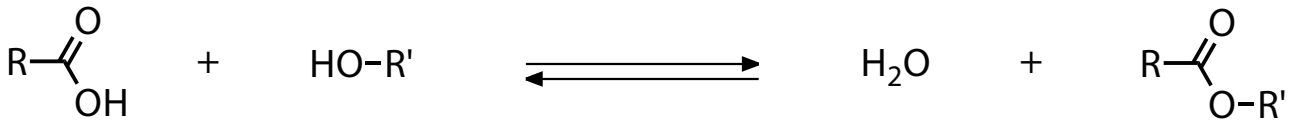
Chapter 3
Mechanisms of Organic Reactions

3.1
Reaction Thermodynamics and Kinetics



- **net reaction** describes the starting materials and the products of a reaction
- **reaction mechanisms** describes the individual elementary steps of the reaction
- **catalyst** takes part in the reaction mechanism but is retained unchanged

- **thermodyamics** are concerned with the energy balance of chemical reactions



$$\Delta G_R = \Delta G_R^{\ominus} + RT \ln \frac{[\text{R–COOR'}]\,[\text{H}_2\text{O}]}{[\text{R–COOH}]\,[\text{R'–OH}]}$$

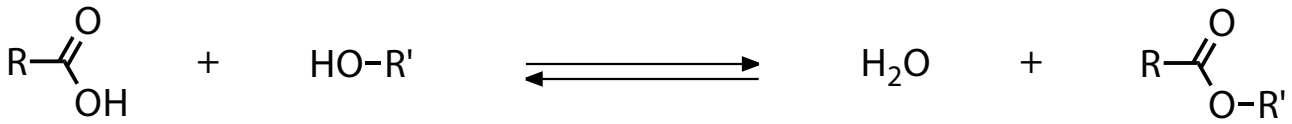
$\Delta G_R > 0$ **endergonic reaction**, runs from right to left

$\Delta G_R = 0$ **reaction is in equilibrium**

$\Delta G_R < 0$ **exergonic reaction**, runs from left to right

- **Gibbs' free reaction energy ΔG_R** determines whether and in which direction the reaction runs
- **standard Gibbs' free reaction energy ΔG°_R** at standard conditions (1 bar, 25°C, reactants 1 mol/L)

- **thermodyamics** are concerned with the energy balance of chemical reactions



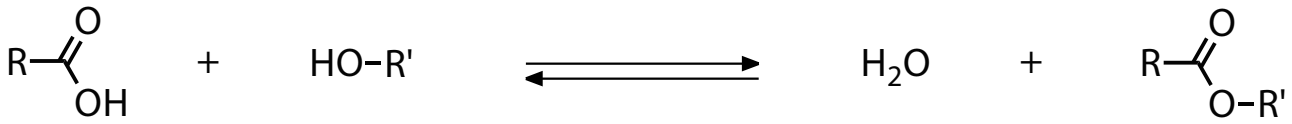
$$\Delta G_R = \Delta G_R^{\ominus} + RT \ln \frac{[\text{R–COOR'}]_{eq}[\text{H}_2\text{O}]_{eq}}{[\text{R–COOH}]_{eq}[\text{R'–OH}]_{eq}} = 0$$

$$K_R = \frac{[\text{R–COOR'}]_{eq}[\text{H}_2\text{O}]_{eq}}{[\text{R–COOH}]_{eq}[\text{R'–OH}]_{eq}} \qquad pK_R = -\log K_R$$

$$\Delta G_R^{\ominus} = -RT \ln K_R \qquad pK_R \propto \frac{\Delta G_R^{\ominus}}{RT}$$

- **equilibrium constant K_R** is the ratio of reactant concentrations in equilibrium
- **standard free reaction enthalpy $\Delta G°_R$** determines the position of the equilibrium (at given temp.)

- **thermodyamics** are concerned with the energy balance of chemical reactions



$$\Delta G_R^{\ominus} = \Delta H_R^{\ominus} - T\Delta S_R^{\ominus}$$ **Gibbs-Helmholtz Equation**

$\Delta H_R^{\ominus} < 0$ **exothermic reactions**, sum of all bond energy changes negative

$\Delta H_R^{\ominus} > 0$ **endothermic reactions**, sum of all bond energy changes positive

$\Delta S_R^{\ominus} < 0$ **exotropic reactions**, disorder, degrees of freedom decrease

$\Delta S_R^{\ominus} > 0$ **endotropic reactions**, disorder, degrees of freedom increase

- **standard reaction enthalpy $\Delta H°_R$** is negative (advantageous) if bonds in products are stronger
- **standard reaction entropy $\Delta S°_R$** is positive (advantageous) if the disorder increases

- **reaction kinetics** refers to "how fast reactions proceed", i.e., the **reaction rates**
- **rate laws** describe the relation between substrate concentrations and reaction rates

first order	monomolecular		monomolecular	first order
$r_{1f} = k_{1f} \cdot [A]$	A	⇌	B	$r_{1r} = k_{1r} \cdot [B]$
second order	bimolecular		bimolecular	second order
$r_{2f} = k_{2f} \cdot [A][B]$	A + B	⇌	C + D	$r_{2r} = k_{2r} \cdot [C][D]$
third order	trimolecular		monomolecular	first order
$r_{3f} = k_{3f} \cdot [A][B][C]$	A + B + C	⇌	D	$r_{3r} = k_{3r} \cdot [D]$
third order	trimolecular		bimolecular	second order
$r_{4f} = k_{4f} \cdot [A]^2[C]$	2 A + B	⇌	2 C	$r_{4r} = k_{4r} \cdot [C]^2$

- **reaction rates *r*** are proportional to the product of the concentrations of all reactants
- **rate constants *k*** are the proportionality factors
- **reaction order** is the sum of all exponents of the concentrations of all reactants in the rate law
- **molecularity** is the number of molecules actually involved in an elementary reaction
- **for simple, single-step reactions, the molecularity determines the reaction order**

- in thermodyamic equilibrium, concentrations of reactants do not change anymore
- forward and reverse reaction are equally fast

$r_{2f} = k_{2f} \cdot [A][B]$ A + B ⟷ C + D $r_{2r} = k_{2r} \cdot [C][D]$

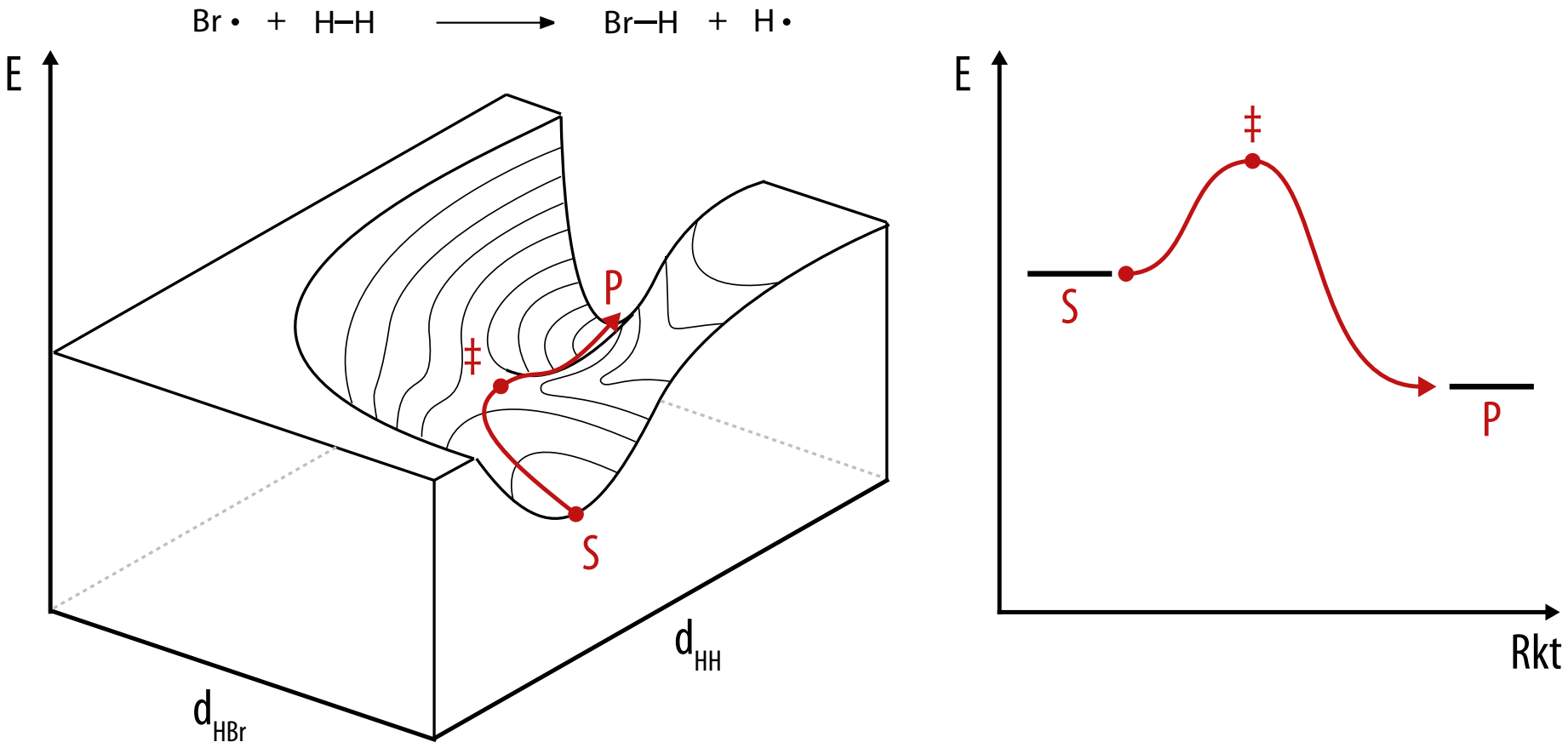
$$r_{2f} = r_{2r}$$

$$k_{2f} \cdot [A][B] = k_{2r} \cdot [C][D]$$

$$\frac{k_{2f}}{k_{2r}} = \frac{[C][D]}{[A][B]} = K$$

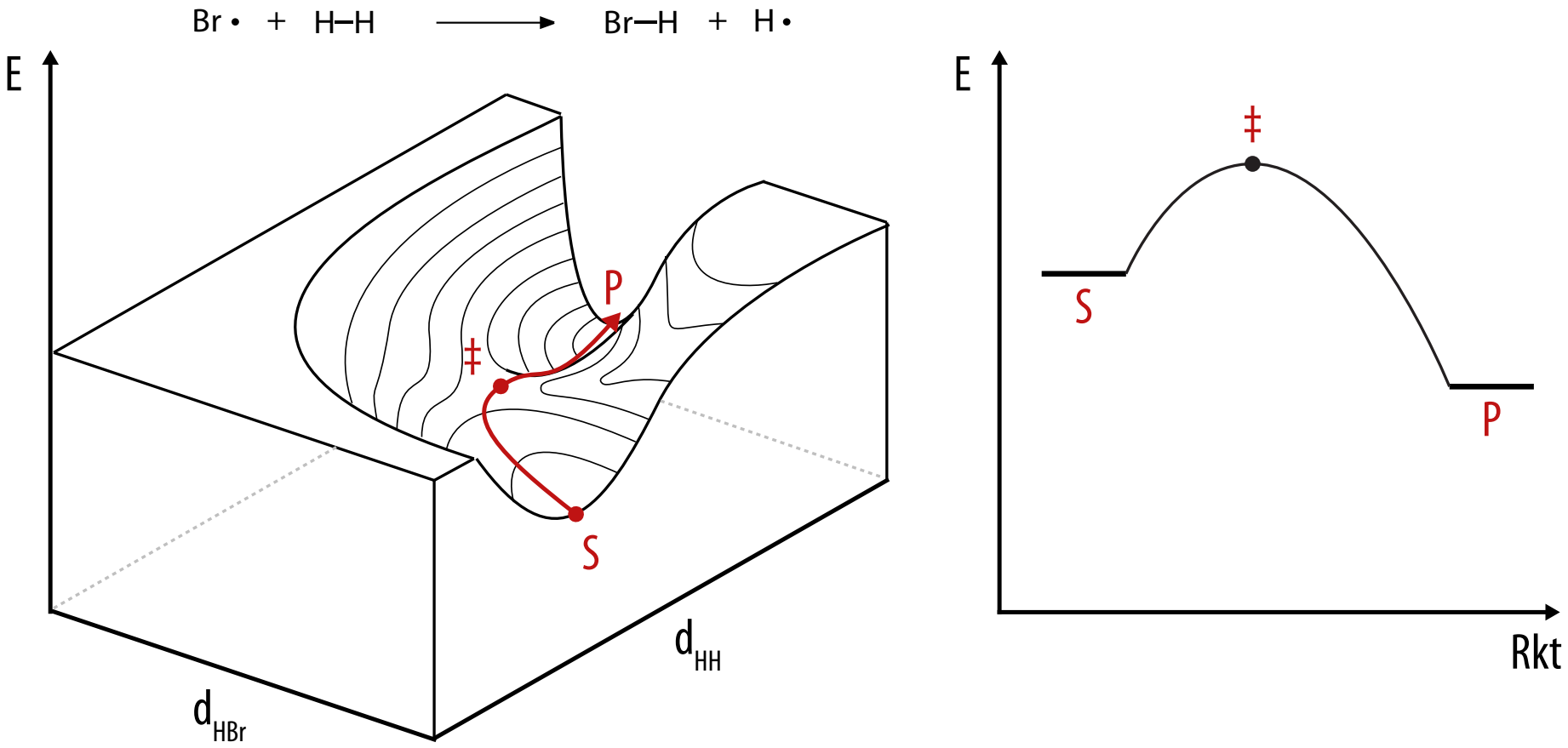
- the **ratio** of rate constants of forward and reverse reactions determines equilbrium constant K
- the faster the forward reaction (relative to reverse), the larger is K
- the faster the forward (relative to reverse) reaction, the more the equilibrium is on product side

- **reaction profiles** are simplified energy diagrams of chemical reactions, following the lowest energy path from the starting materials to the products in the **energy hypersurface**



- starting materials (S) and products (P) are stable compounds, i.e., energetic minima
- transition states (‡) are saddle points in the energy hypersurface, maxima in the reaction profile

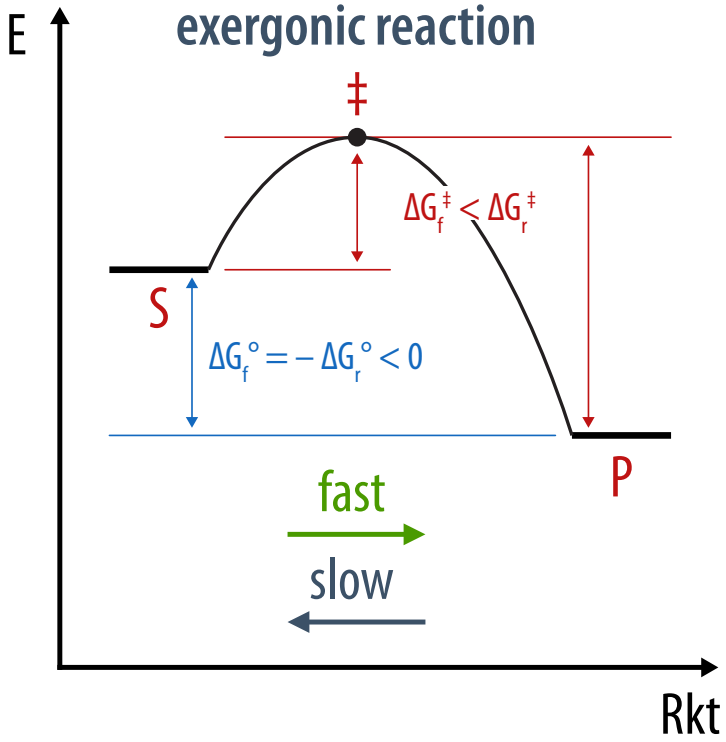
- **reaction profiles** are simplified energy diagrams of chemical reactions, following the lowest energy path from the starting materials to the products in the **energy hypersurface**

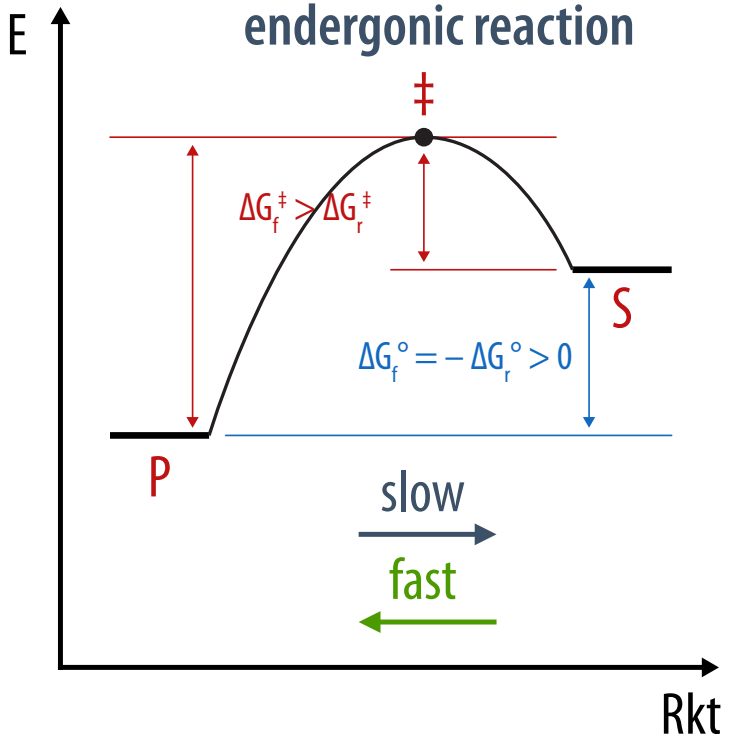


- starting materials (S) and products (P) are stable compounds, i.e., energetic minima
- transition states (‡) are saddle points in the energy hypersurface, maxima in the reaction profile

- **Boltzmann distribution of molecular thermal energies**

$$E_{A,f} \approx \Delta G_f^{\ddagger} = -RT \ln k_f \qquad E_{A,r} \approx \Delta G_r^{\ddagger} = -RT \ln k_r$$





$$\Delta G_R^{\ominus} = \Delta G_f^{\ddagger} - \Delta G_r^{\ddagger}$$

$$K_R = \frac{k_f}{k_r}$$

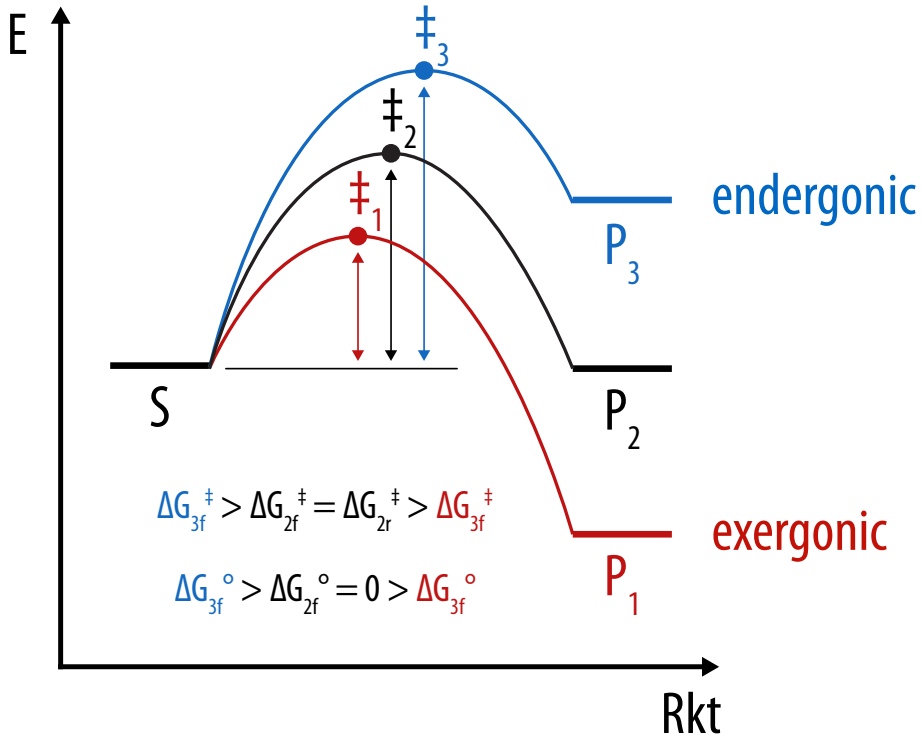
$$r_f = r_r \qquad k_f \cdot \Pi[\mathrm{S}]_{\mathrm{eq}} = k_r \cdot \Pi[\mathrm{P}]_{\mathrm{eq}}$$

$$\frac{k_f}{k_r} = \frac{\Pi[\mathrm{P}]_{\mathrm{eq}}}{\Pi[\mathrm{S}]_{\mathrm{eq}}} = K_R$$

- Polanyi Principle and Hammond Postulate for mechanistically similar, single-step reactions

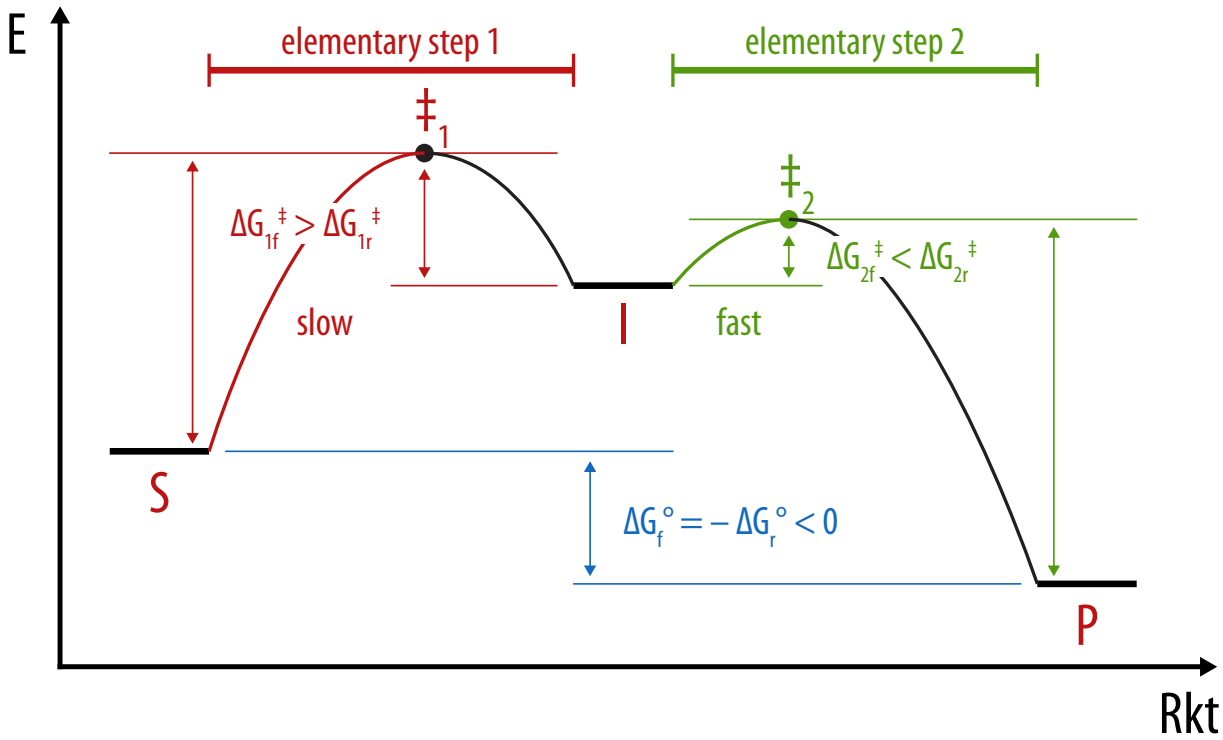
"late" transition state
higher activation energy

"early" transition state
lower activation energy



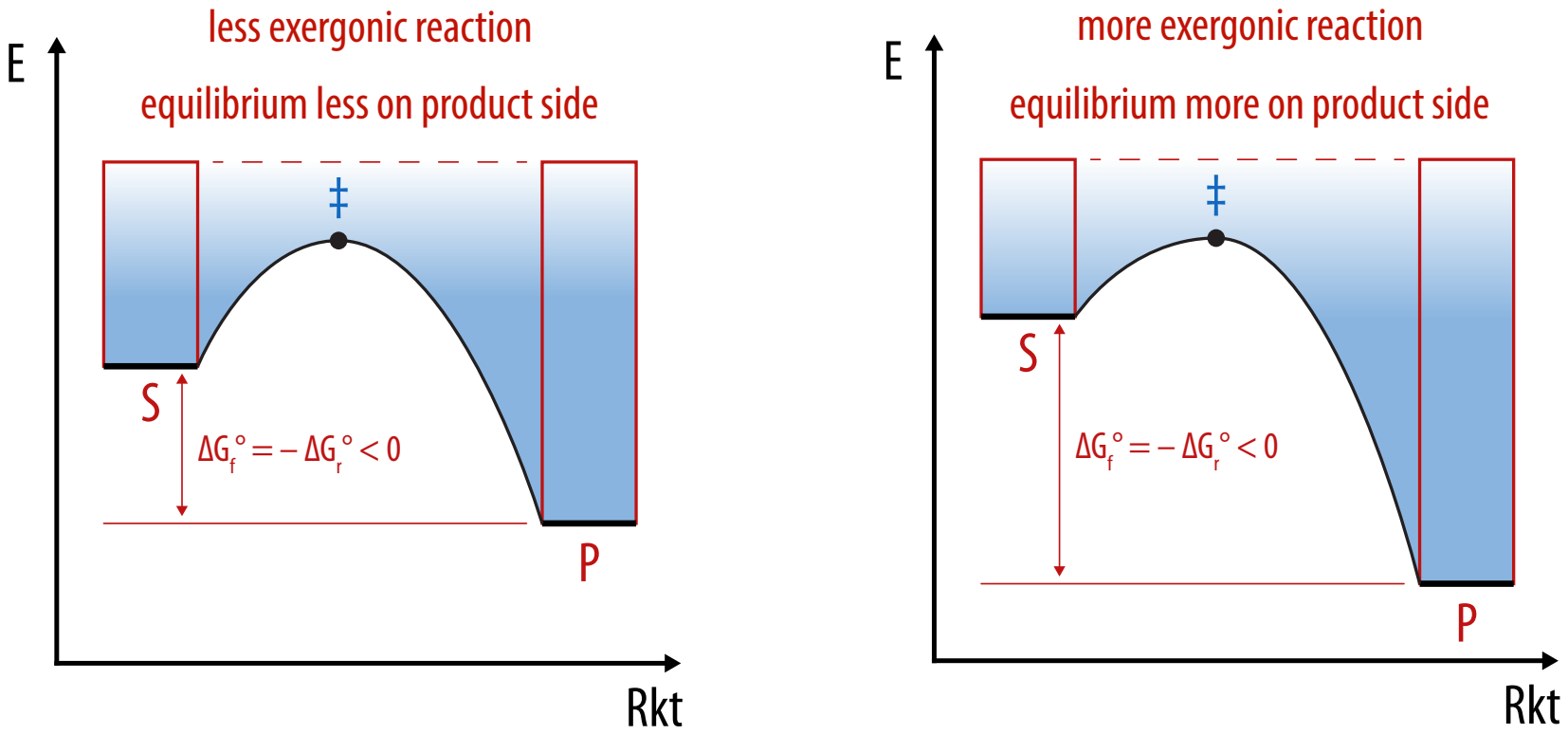
- **Polanyi Principle:** Difference in activation energies proportional to difference in free enthalpies
- **Hammond Postulate:** Energetically more similar states are also geometrically more similar

- elementary reactions are steps between the minima in the reaction profile, i.e., between starting materials (S), intermediates (I), and products (P), seprated by transition states (‡).



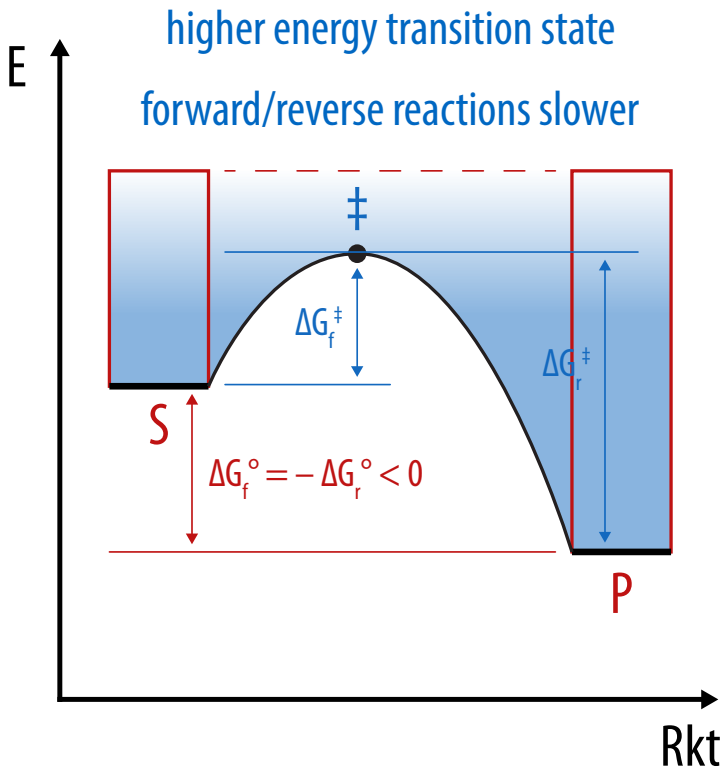
- overall reaction rate and molecularity are controlled by slowest, **rate-determining step**
- typically, the generation of the **reactive intermediate** is the rate-determining step
- intermediate is a good approximation for the transition state of the rate-determining step

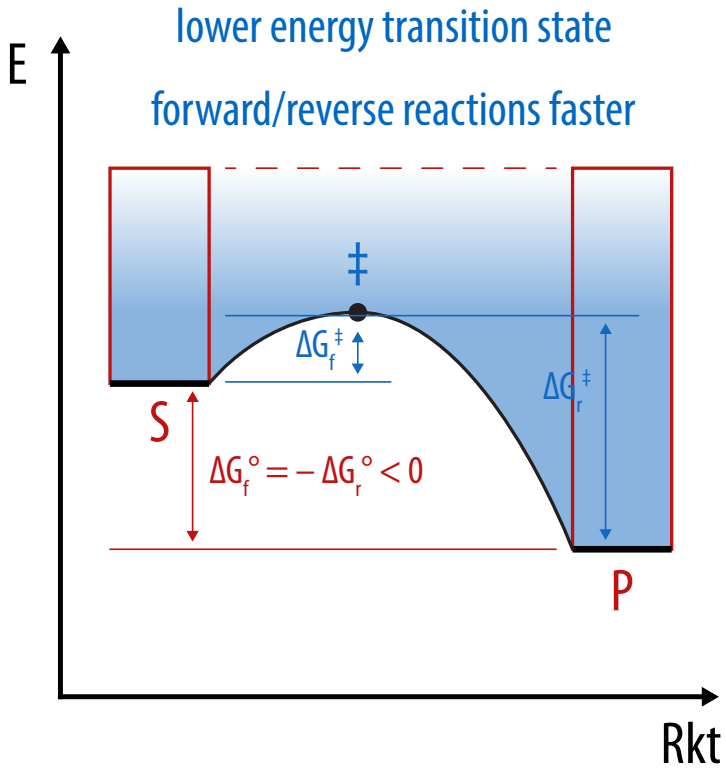
$$\Delta G_R^{\ominus} = -RT \ln K_R$$



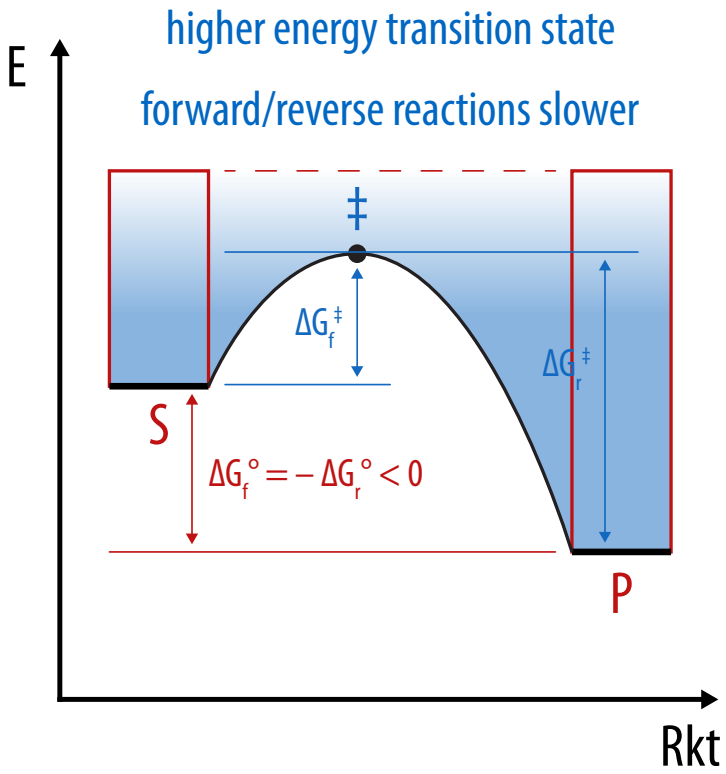
- change in standard Gibbs free reaction energy $\Delta G°_R$ leads to change of equilibrium concentrations
- in reality, even more drastic because ln $K \sim \Delta G°_R$

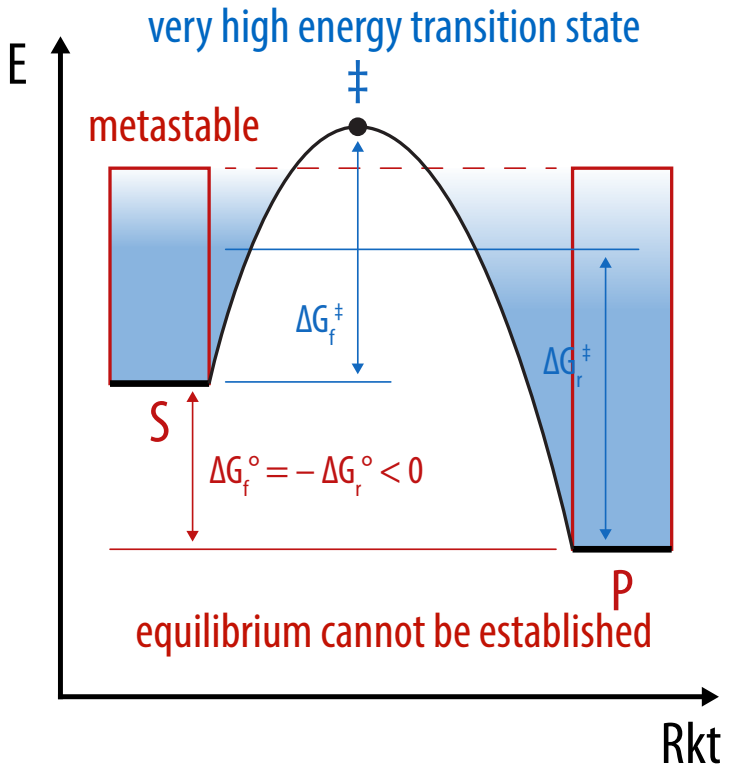
$$\Delta G_f^{\ddagger} = -RT \ln k_f \quad \text{and} \quad \Delta G_r^{\ddagger} = -RT \ln k_r$$



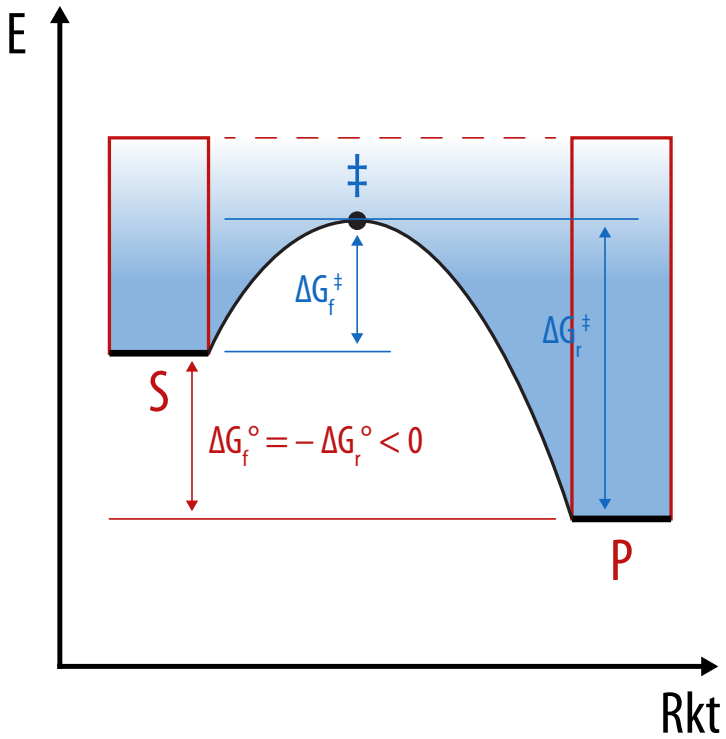


- change in Gibbs free energy of transition state ΔG‡ leads to change in reaction rates
- in reality, even more drastic because ln *k* ~ ΔG‡


higher energy transition state
forward/reverse reactions slower
E
‡
$\Delta G_f^{\ddagger}$
$\Delta G_r^{\ddagger}$
S
$\Delta G_f^{\circ} = -\Delta G_r^{\circ} < 0$
P
Rkt

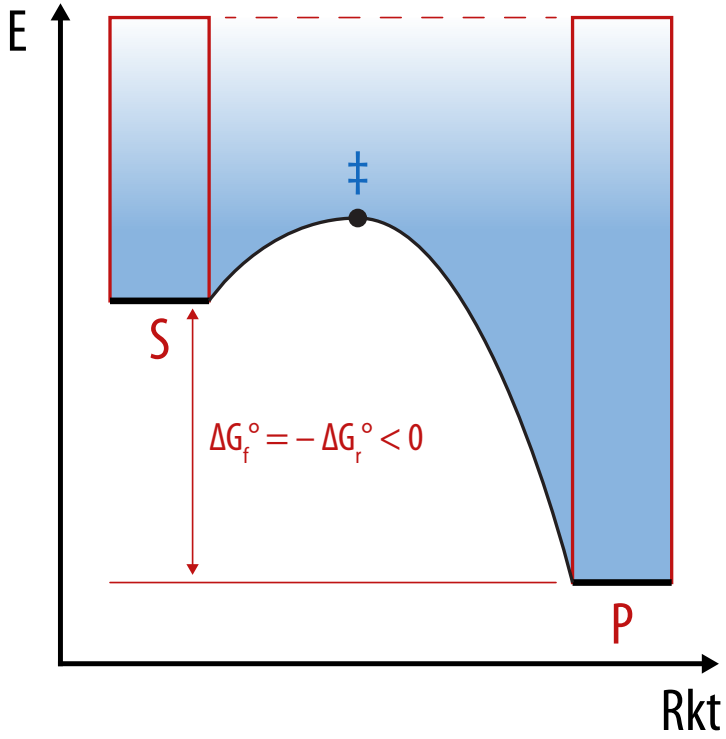

very high energy transition state
E
‡
metastable
$\Delta G_f^{\ddagger}$
$\Delta G_r^{\ddagger}$
S
$\Delta G_f^{\circ} = -\Delta G_r^{\circ} < 0$
P
equilibrium cannot be established
Rkt

lower temperature
forward/reverse reactions slower



for endotropic reaction (ΔS>0):
equilbrium less on the product side

higher temperature
forward/reverse reactions faster

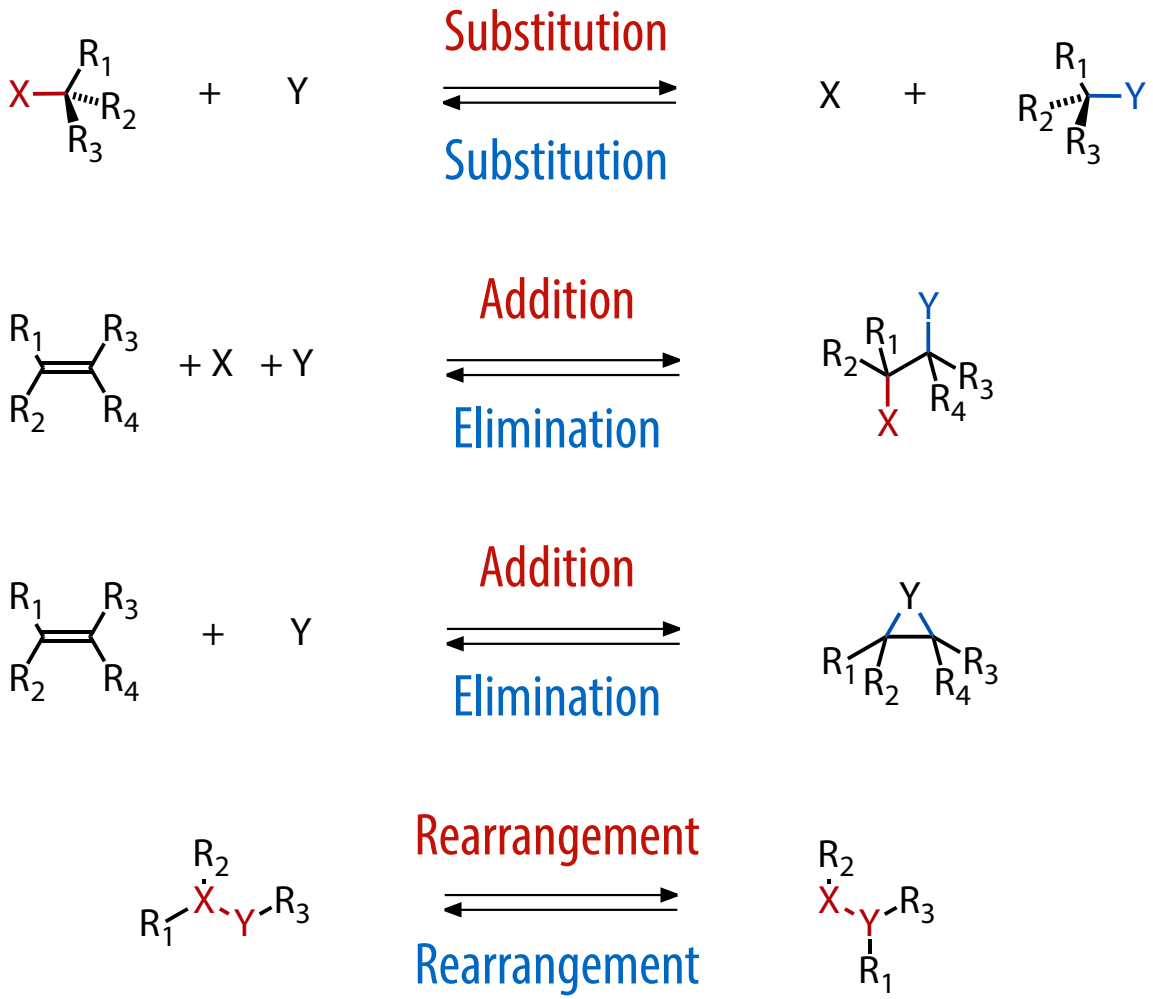


for endotropic reaction (ΔS>0):
equilbrium more on the product side

- change in temperature changes equilbrium (due to Gibbs-Helmholtz equation $\Delta G = \Delta H - T\,\Delta S$)
- change in temperature also causes reaction rates because of thermal energy of molecules

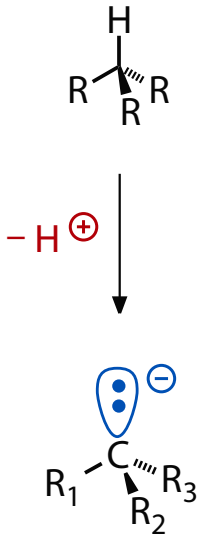
3.2
Classification of Organic Reactions

- classification according to **reaction type**, i.e., the type of changes to molecular topology

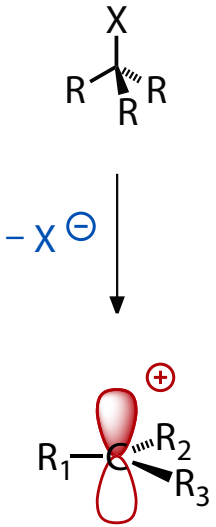


- classification according to **reactive intermediate**

bond heterolysis



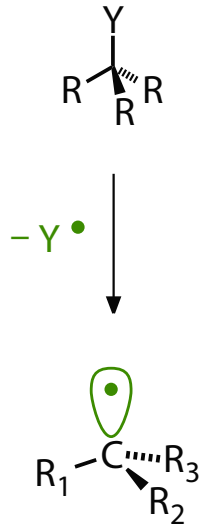
carbanion
sp^3
pyramidal



carbocation
sp^2
planar

polar mechanisms
nucleophiles or electrophiles

bond homolysis

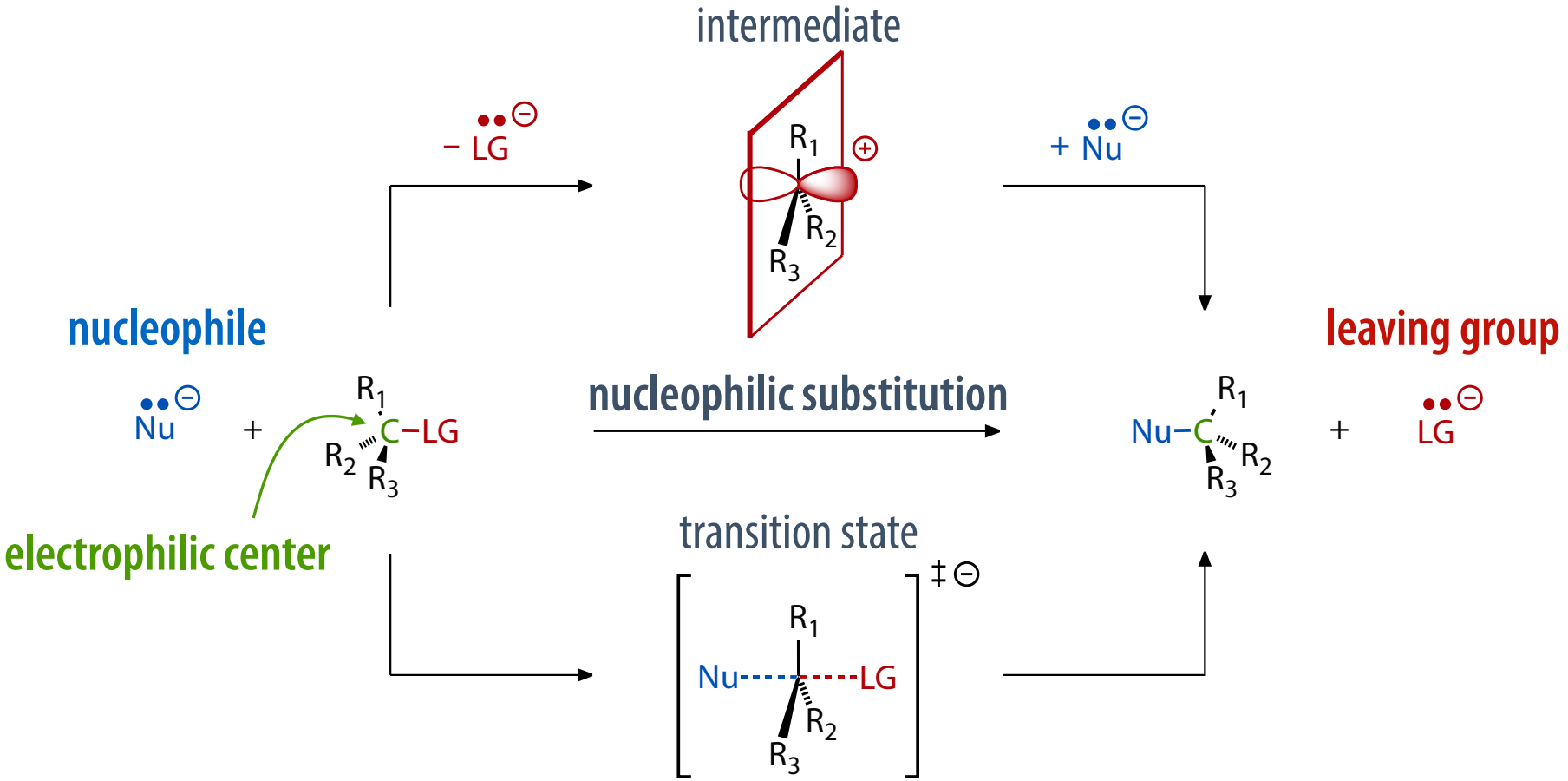


carbon radical
sp^2 or sp^2 or in between
planar or pyramidal

radical mechanisms
radical starters

3.3
Nucleophilic Substitutions (S_N Reactions)

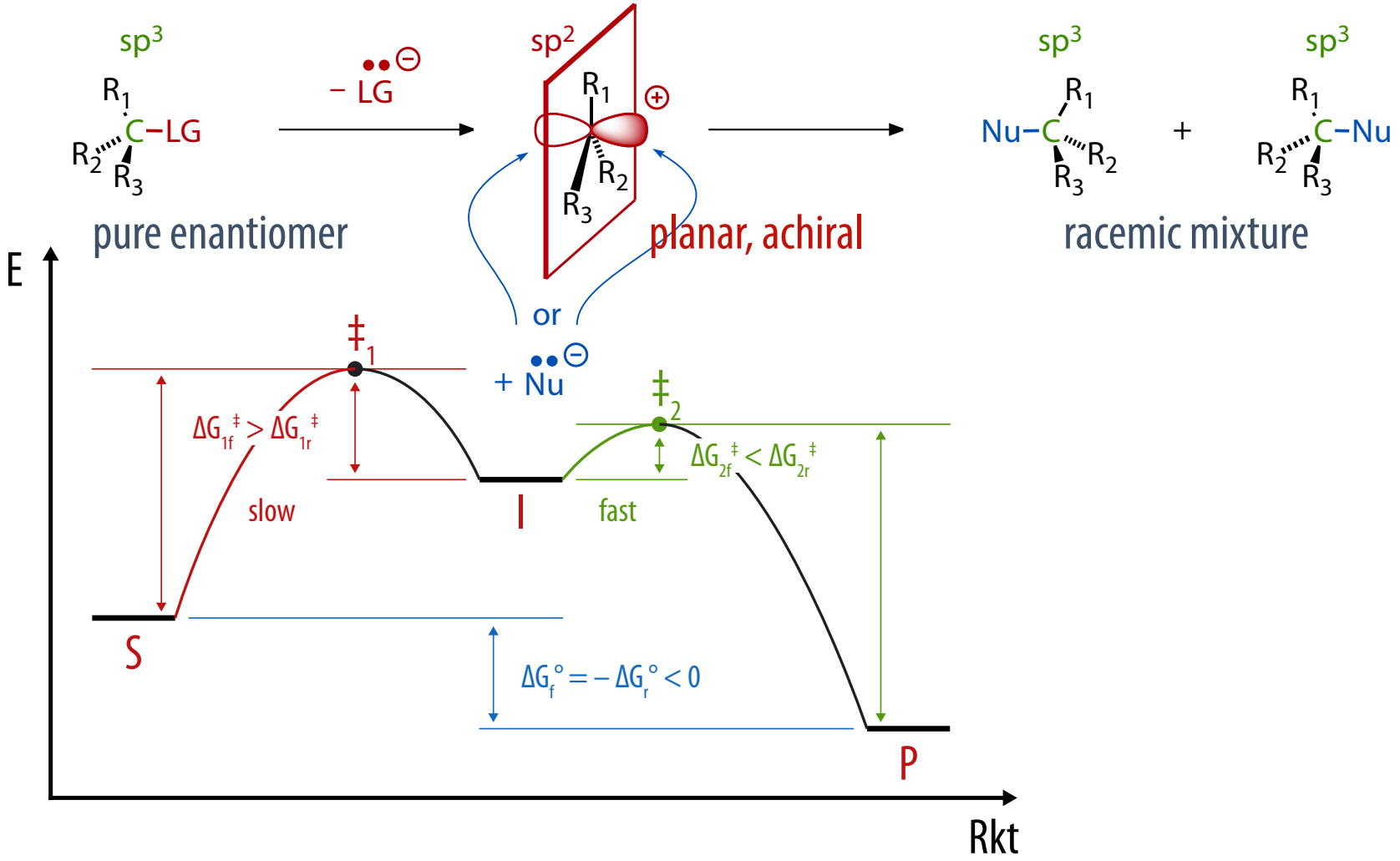
S_N1 Mechanism: leaving group leaves first (and allows nucleophile to come in subsequently



S_N2 Mechanism: nucleophile attacks (and forces leaving group to leave simultaneously)

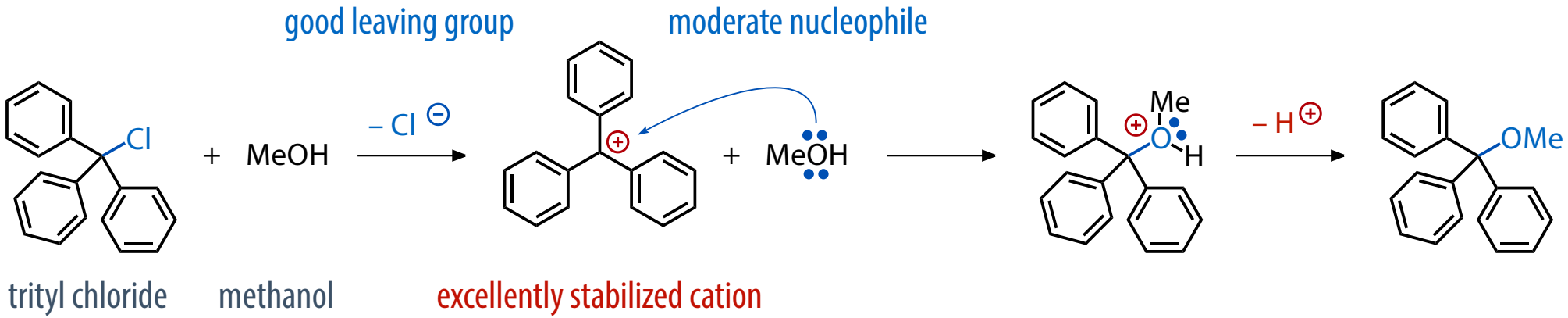
- a nucleophile is an electron pair donor, an electrophile is an electron pair acceptor

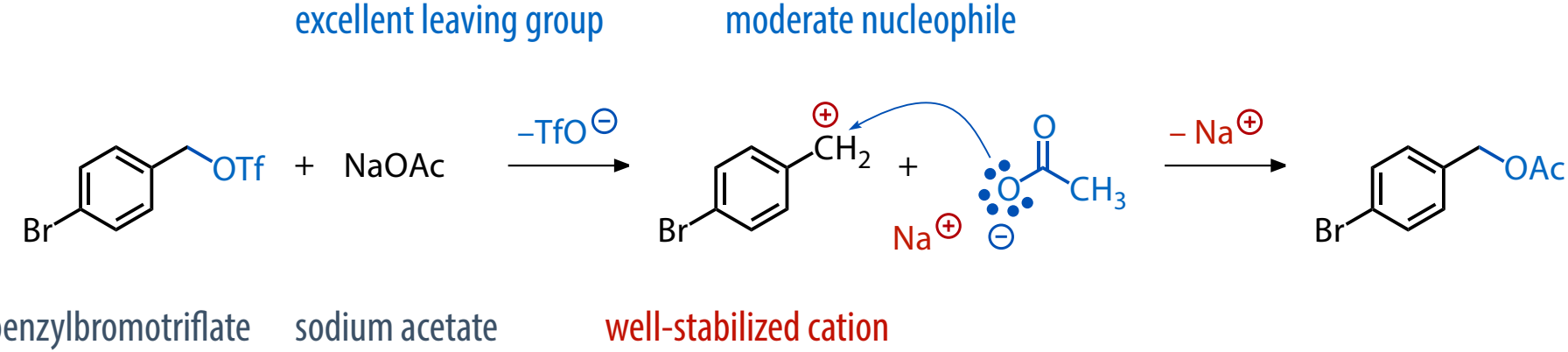
S_N1 Mechanism: Rate-Determining Step is Unimolecular



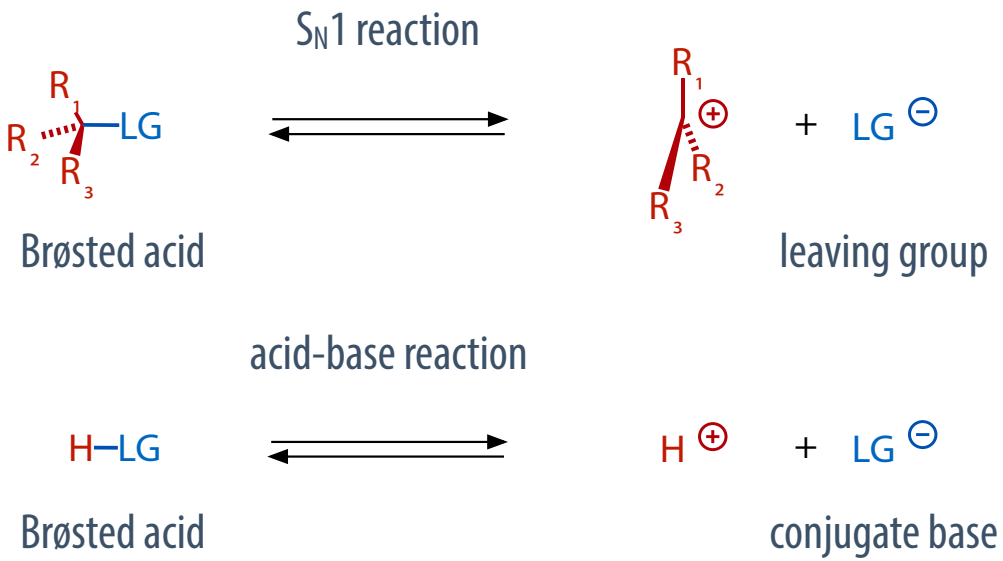
- the departure of the leaving group generates a carbocation as a true intermediate
- the formation of the intermediate is energetically disfavorable, rate-determining
- good leaving group, stabilized carbocation will decrease energy of the intermediate (favorable)

Examples of S_N1 Reactions





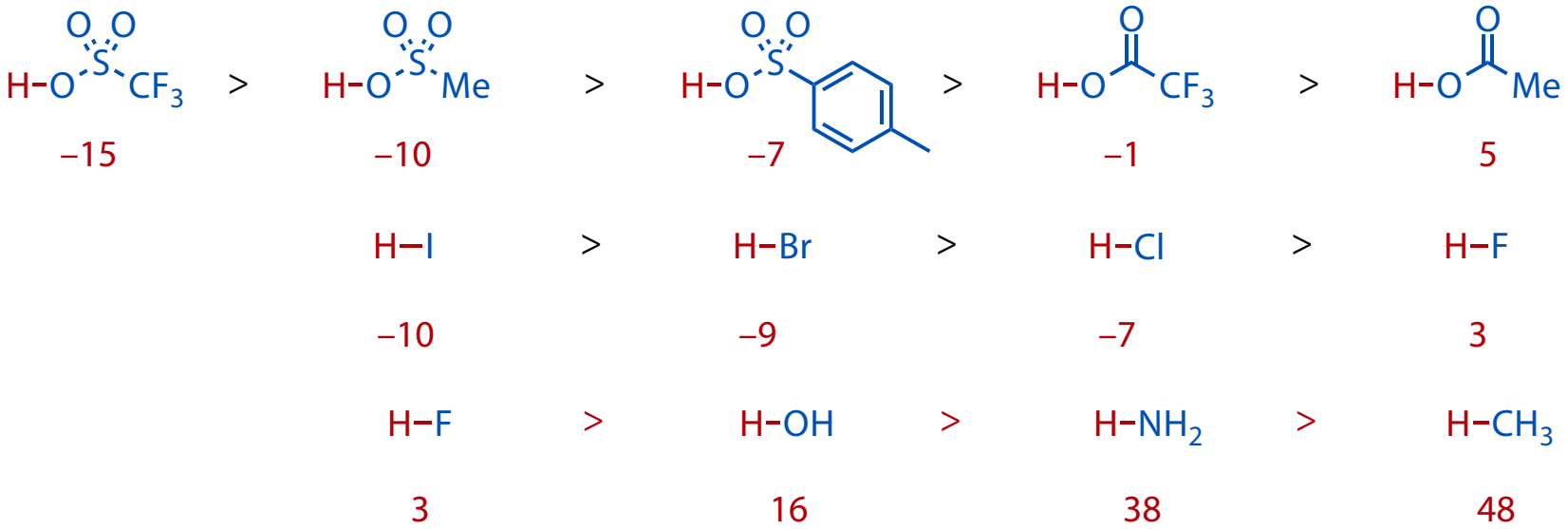
- S_N1 reactions are cation-anion dissociation reactions like acid-base reactions



$$pK_A = -\log K_A = -\log \frac{[H^+][LG^-]}{H\text{–}LG}$$

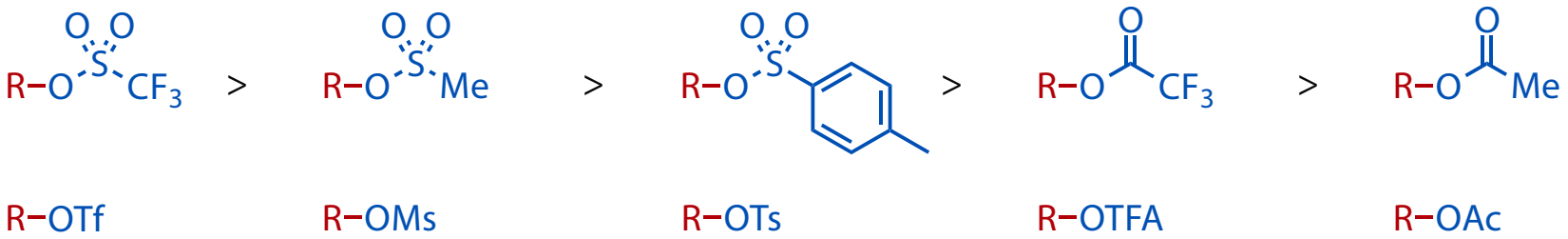
- pK_A values are a measure of the strength of a Brønsted acid
- the lower the pKA value, the more is the equilibrium on the side of the dissociated ions
- **pK_A values of the corresponding acids are a measure for leaving group quality (lower is better)**

- **leaving group** quality is approximately inverse to the basicity of the obtained anion
- scale by pK_A values of the corresponding acids



- residues that correspond to acids with $pK_A < 0$ are **good** leaving groups
- residues that correspond to acids with $pK_A < 10$ are **moderate** leaving groups
- residues that correspond to acids with $pK_A < 20$ are **poor** leaving groups
- residues that correspond to acids with $pK_A > 20$ are **not leaving groups** at all

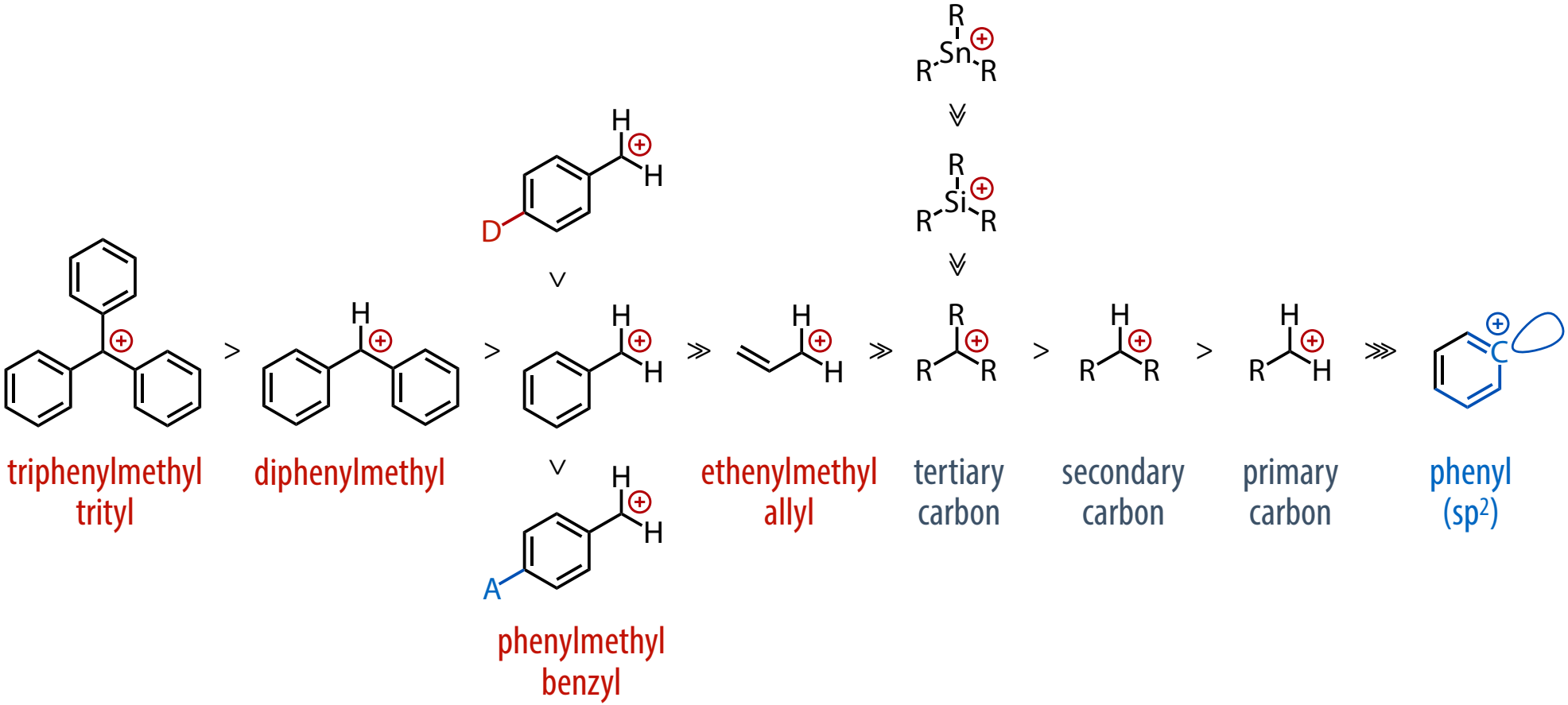
Trivial Names and Abbreviations of Important Leaving Groups



R–OTf	R–OMs	R–OTs	R–OTFA	R–OAc
trifluoromethanesulfonate triflate	methanesulfonate mesylate	4-toluenesulfonate tosylate	trifluoroacetate	acetate

Stabilization of the Carbocation Intermediate (1)

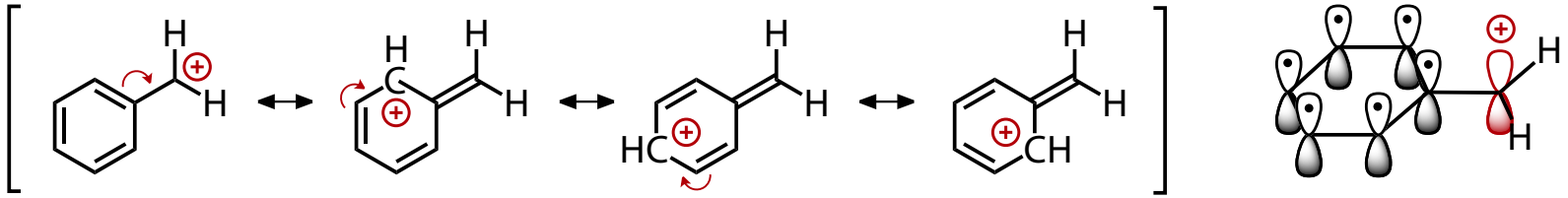
- **carbocations** are electron-deficient, must be stabilized by electron-donating groups



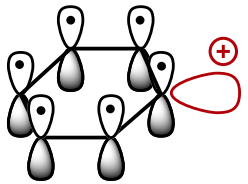
- S_N1 reactions very favorable in benzyl or allyl position (in particular with donor atoms)
- S_N1 reactions also observed on highly substituted sp^3 carbons
- S_N1 reactions never observed in phenyl position (or other sp^2 or sp hybridized carbons)

Stabilization of the Carbocation Intermediate (2)

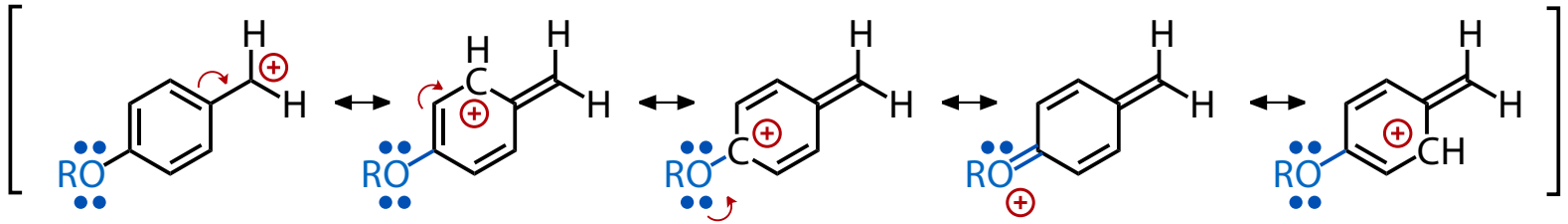
- stabilization by resonance (+M effect)



compare to phenyl cation

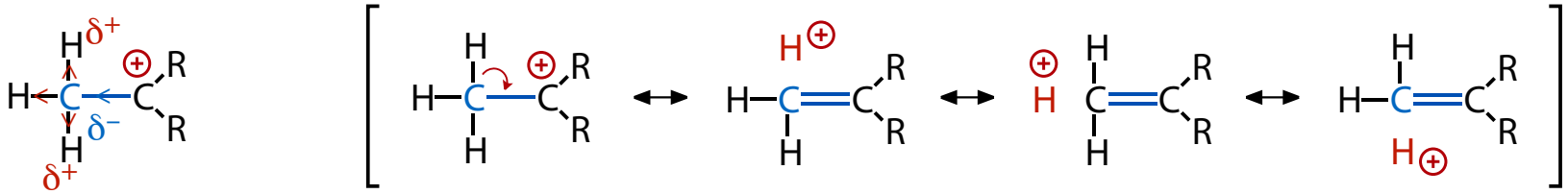


- the more delocalization (donor groups, larger aromatic systems), the better stabilization



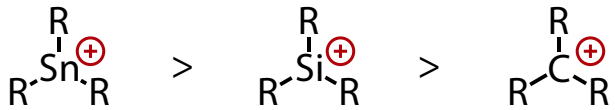
Stabilization of the Carbocation Intermediate (3)

- stabilization by inductive effects (+I effect); conceptual explanation by "hyperconjugation"

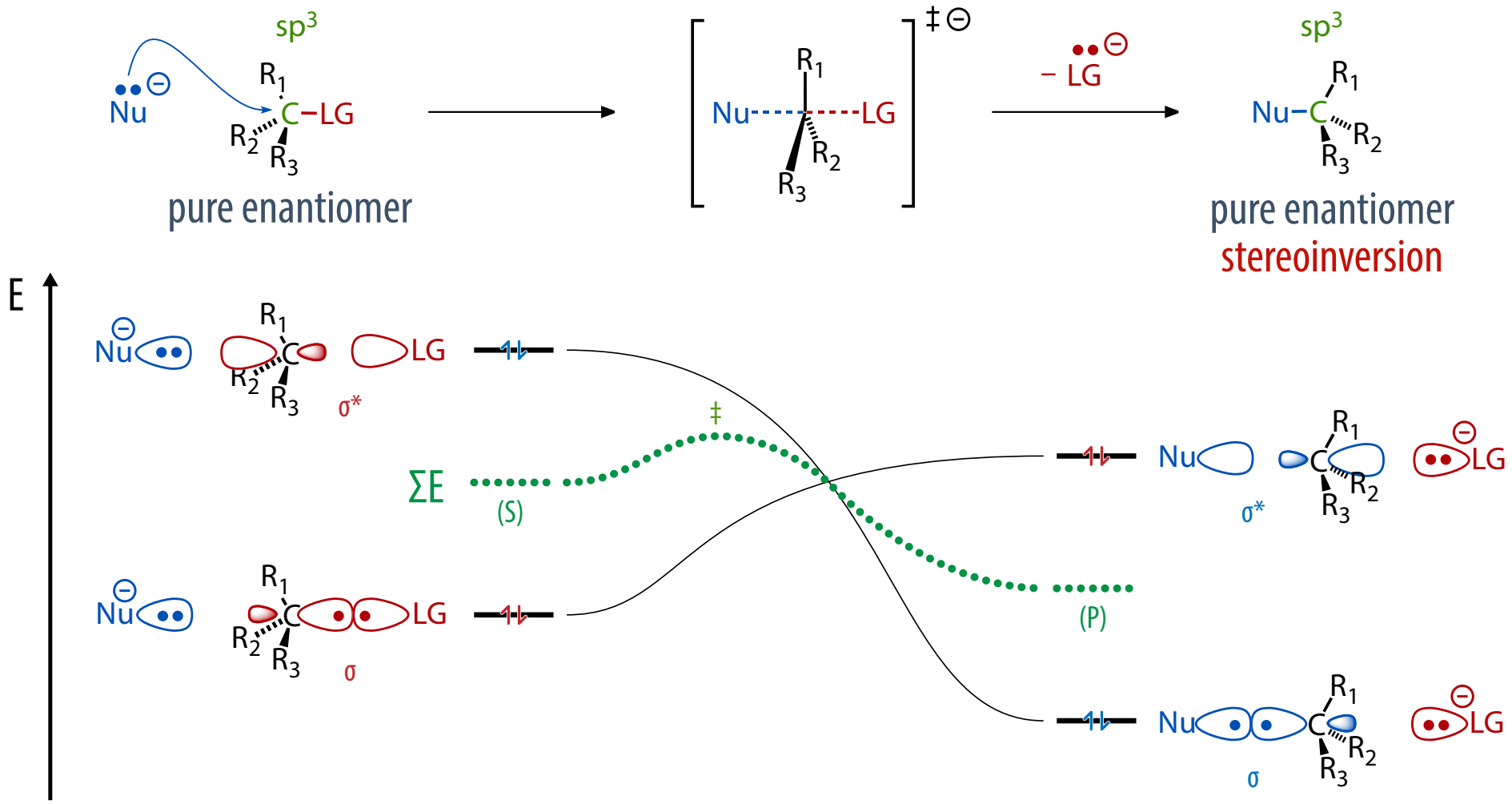


- the more alkyl groups (the higher substituted), the better stabilized is carbocation

- stabilization by decreasing electronegativity (and size) of cationic center



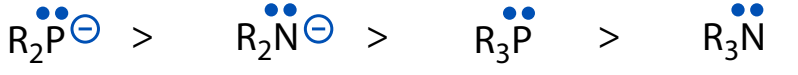
EN 1.9 EN 1.9 EN 2.5

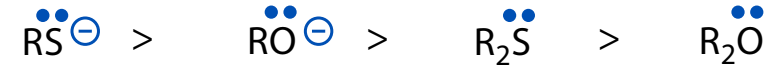


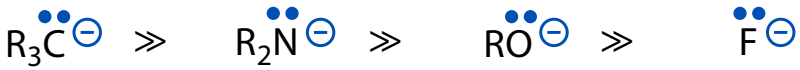
- nucleophile interacts with antibonding σ* orbital of the C–LG bond
- back-side attack and concerted departure of leaving group under stereoinversion
- good nucleophile (and good leaving group) will favor S_N2 reaction

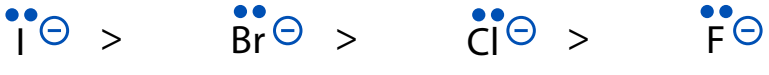
- **there is no simple, rational nucleophilicity scale! No relation to basicity!**
- **nucleophilicity is a kinetic parameter, basicity is a thermodynamic parameter**
- **determination of nucleophilicity *n* according to Pearson:**

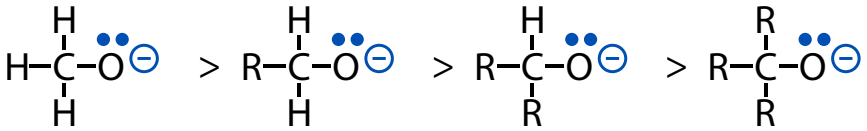
$$n = -\log \frac{k_{\mathrm{Nu}}}{k_{\mathrm{MeOH}}}$$



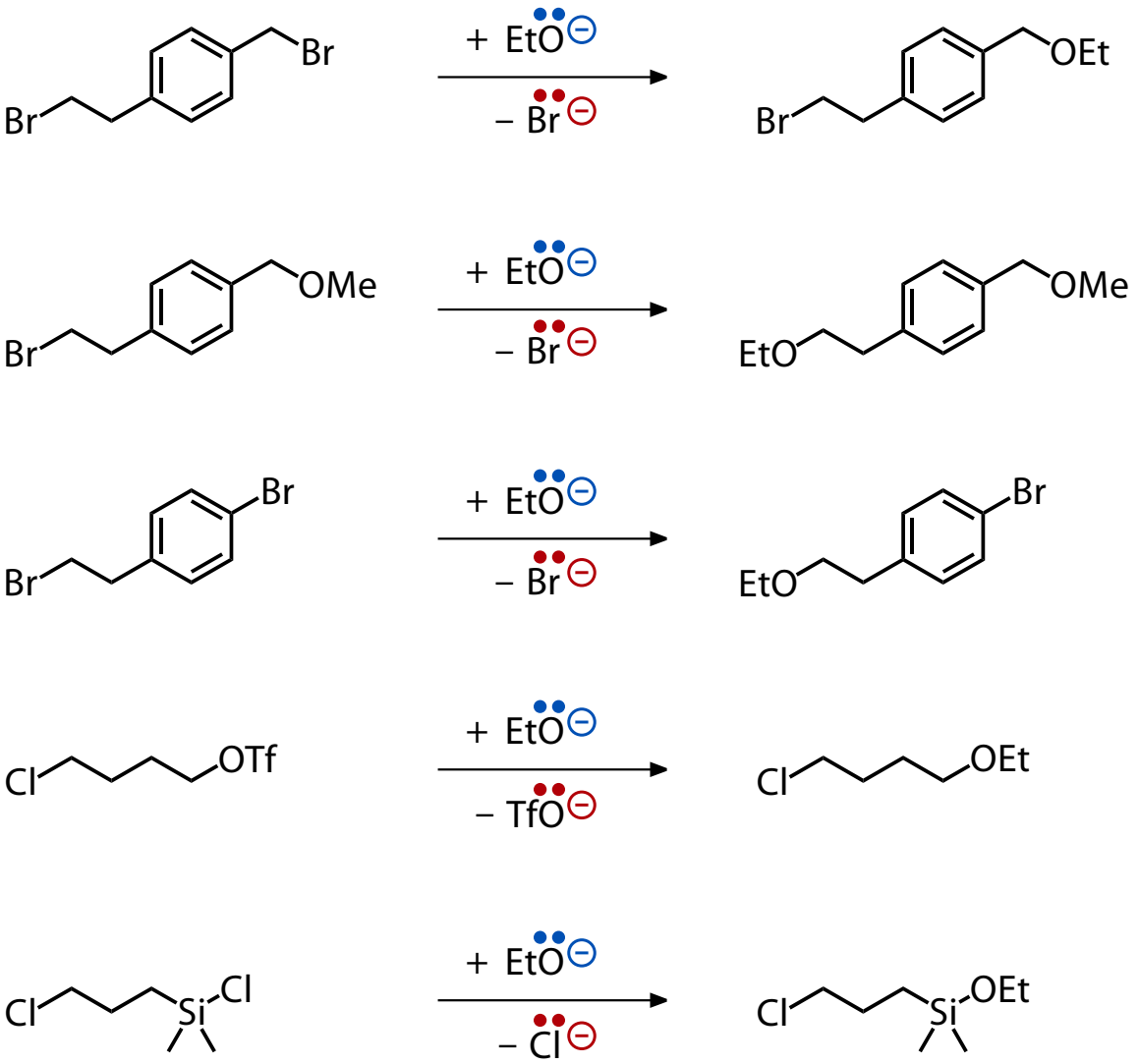






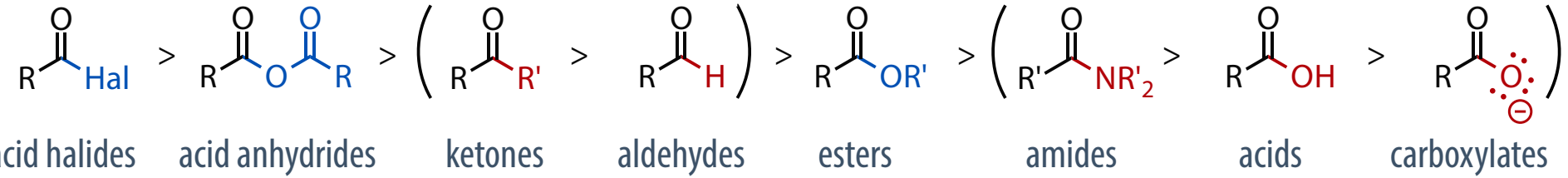


Examples for Nucleophilic Substitutions



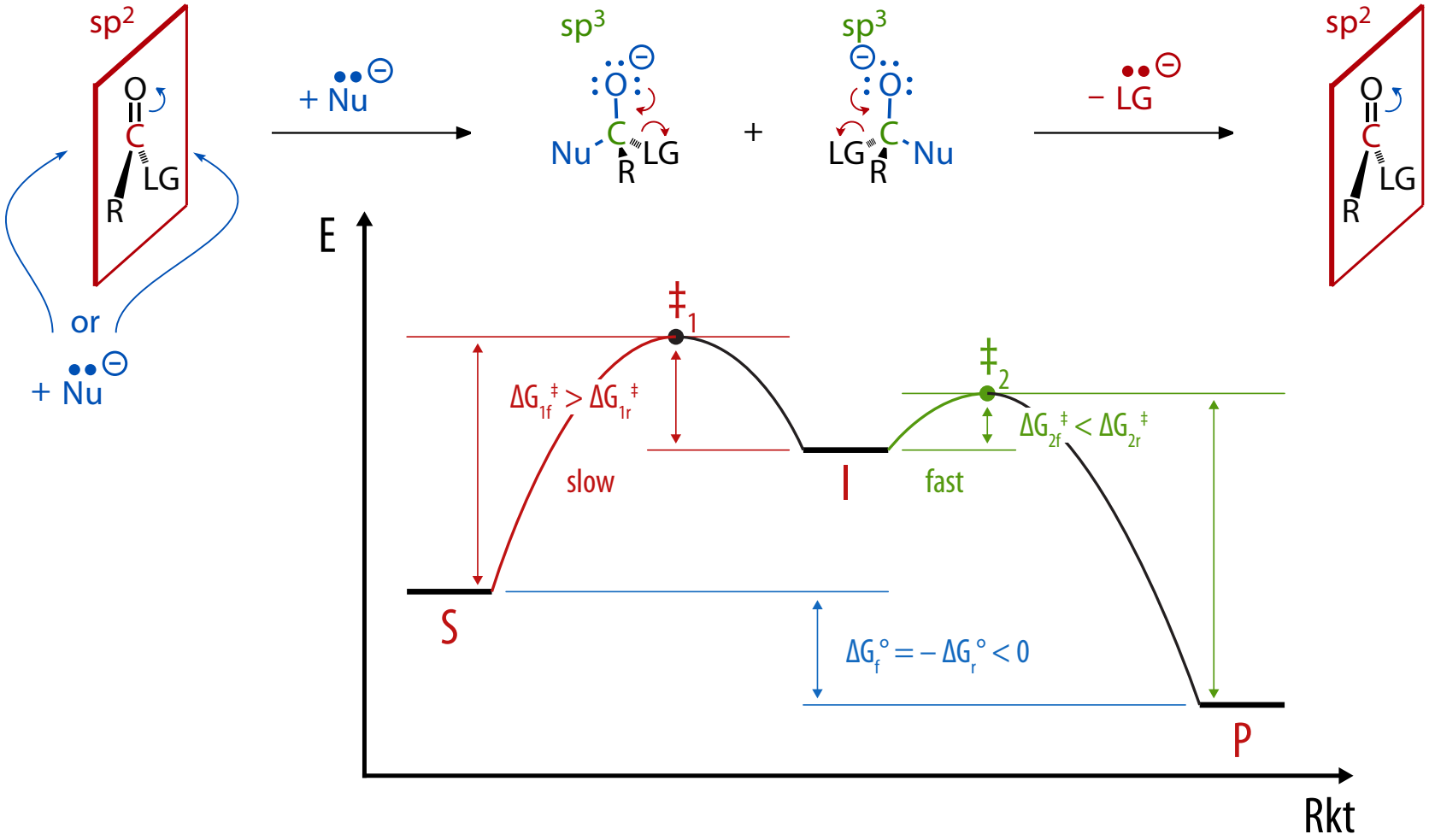
- carbonyl carbon atoms are inherently very reactive electrophilic centers

- electrophilicity controlled by ±M effect and ±I effect

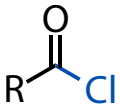


- aldehydes (H) and ketones (R') have no leaving groups
- amides (NR'_2), acids (OH), and carboxylates have very poor leaving groups
- acid halides, anhydrides (and some esters) have good (or at least moderate) leaving groups
- reminder: leaving group quality strictly controlled by basicity of the leaving group anion!

- carbonyl carbons are very reactive electrophilic centers
- carbonyl carbons are sp^2 hybridized, coordinatively unsaturated

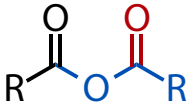


- addition of the nucleophile prior to cleavage of the leaving group is possible, advantageous!

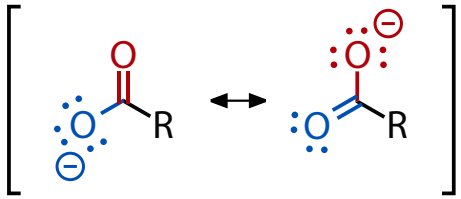


acid chlorides

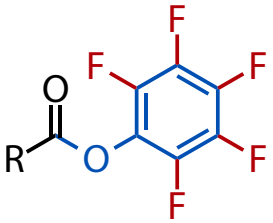
pK_A (HCl) = –7



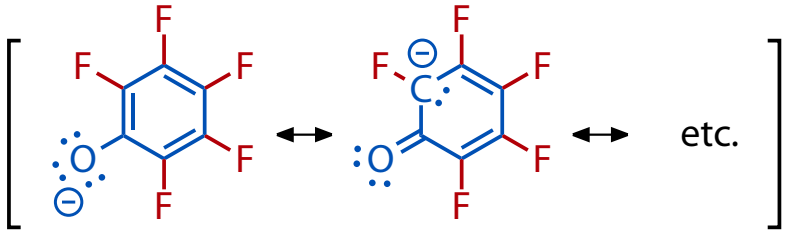
acid anhydrides



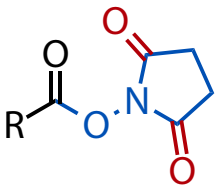
pK_A (RCOOH) ≈ 4



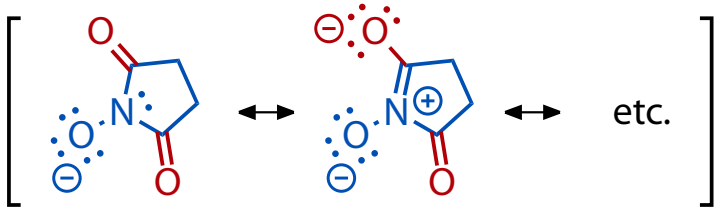
perfluorophenyl esters



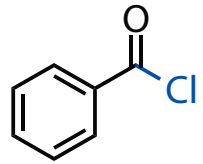
pK_A (PfpOH) ≈ 6 "active ester"



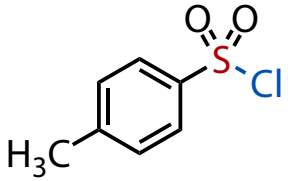
N-succinyl esters



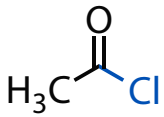
pK_A (SuOH) ≈ 10 "active ester"



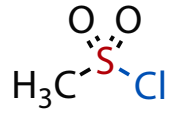
benzoyl chloride
(BzCl)



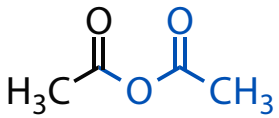
tosyl chloride
(TsCl)



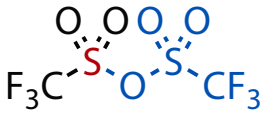
acetyl chloride
(AcCl)



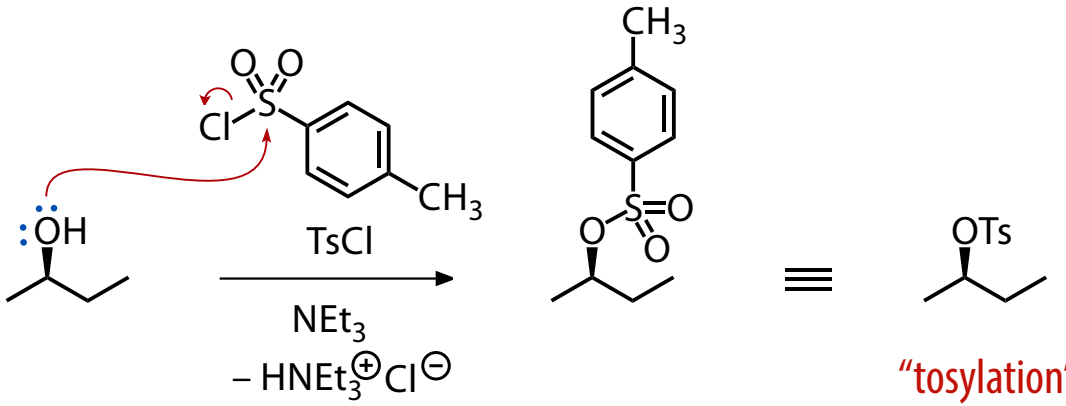
mesyl chloride
(MsCl)



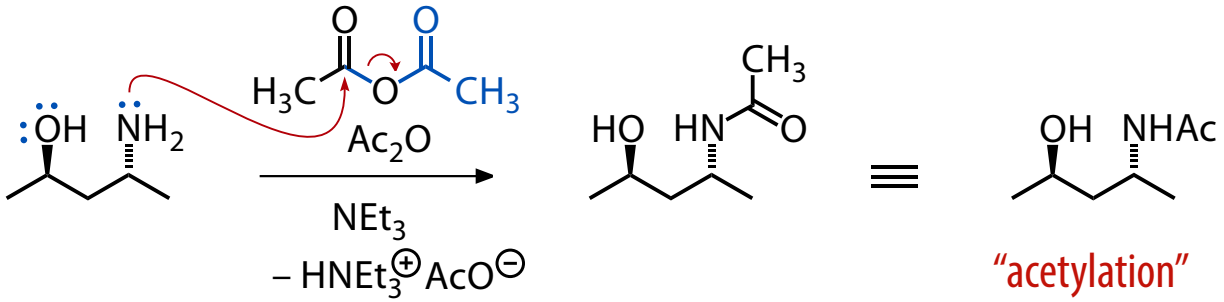
acetic anhydride
(AcOAc, Ac_2O)



Triflic anhydride
(TfOTf, Tf_2O)

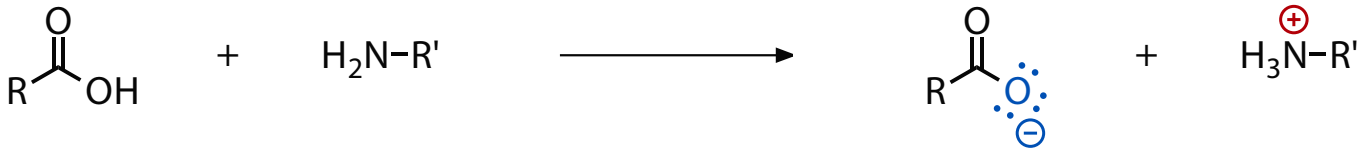


"tosylation"



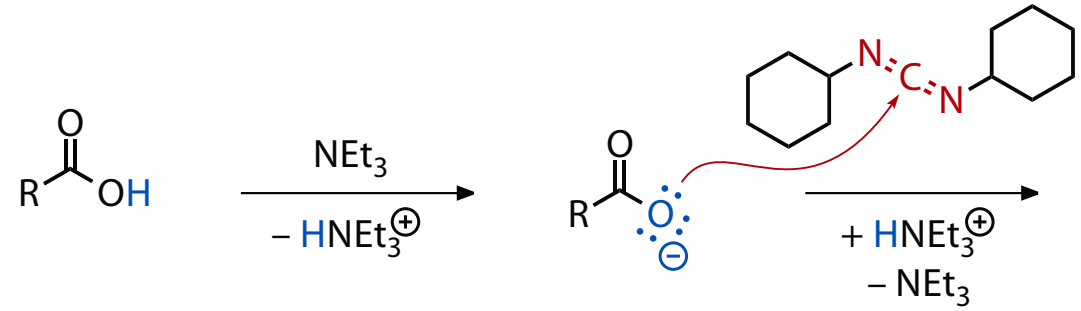
"acetylation"

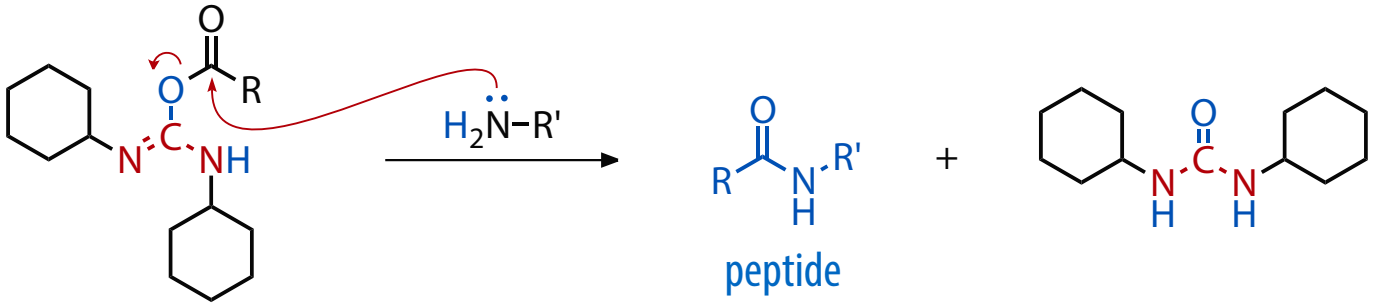
- no amide (peptide) formation between carboxylic acid and amine:



- solution: peptide coupling reagents

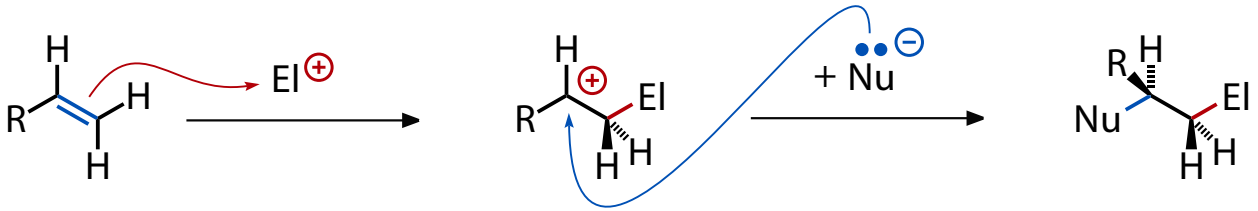
dicyclohexyl**carbodiimide** (DCC)



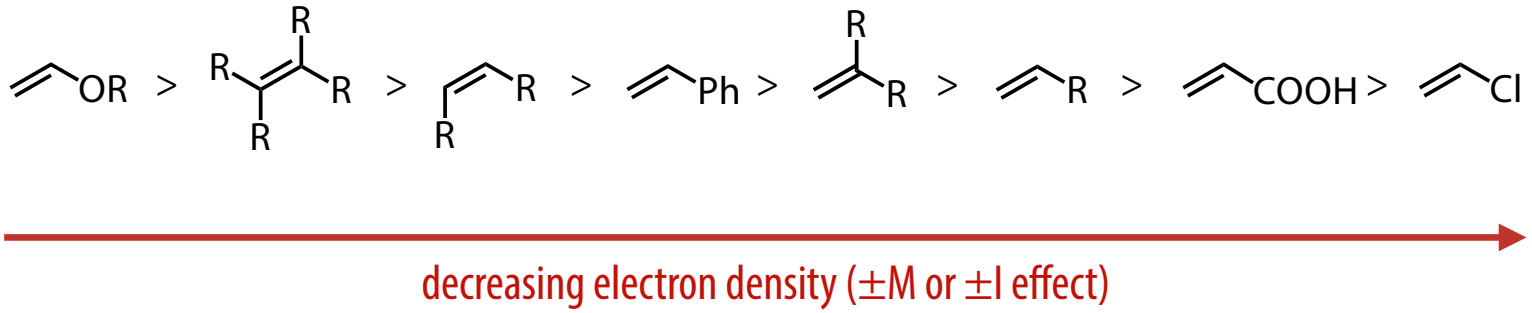


3.4
Electrophilic Additions to Olefins (A_E Reactions)

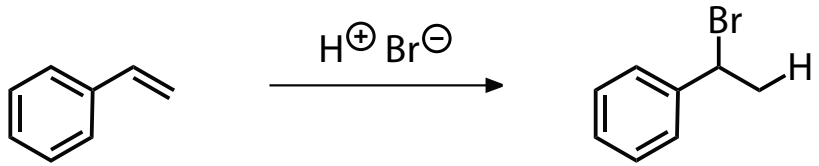
- olefins are (weak) nucleophiles and react with electrophiles to form carbocations



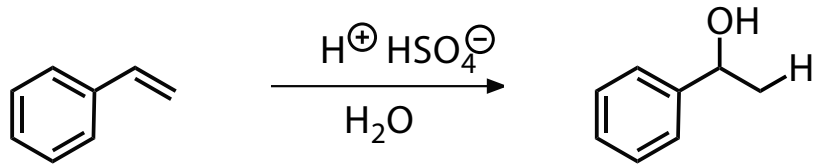
- reactivity order



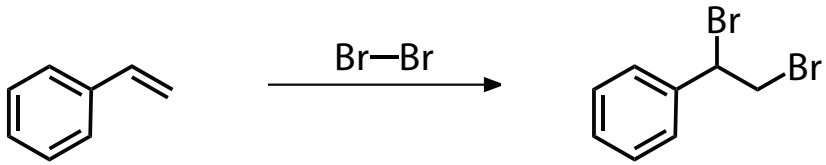
- hydrohalogenation of olefins

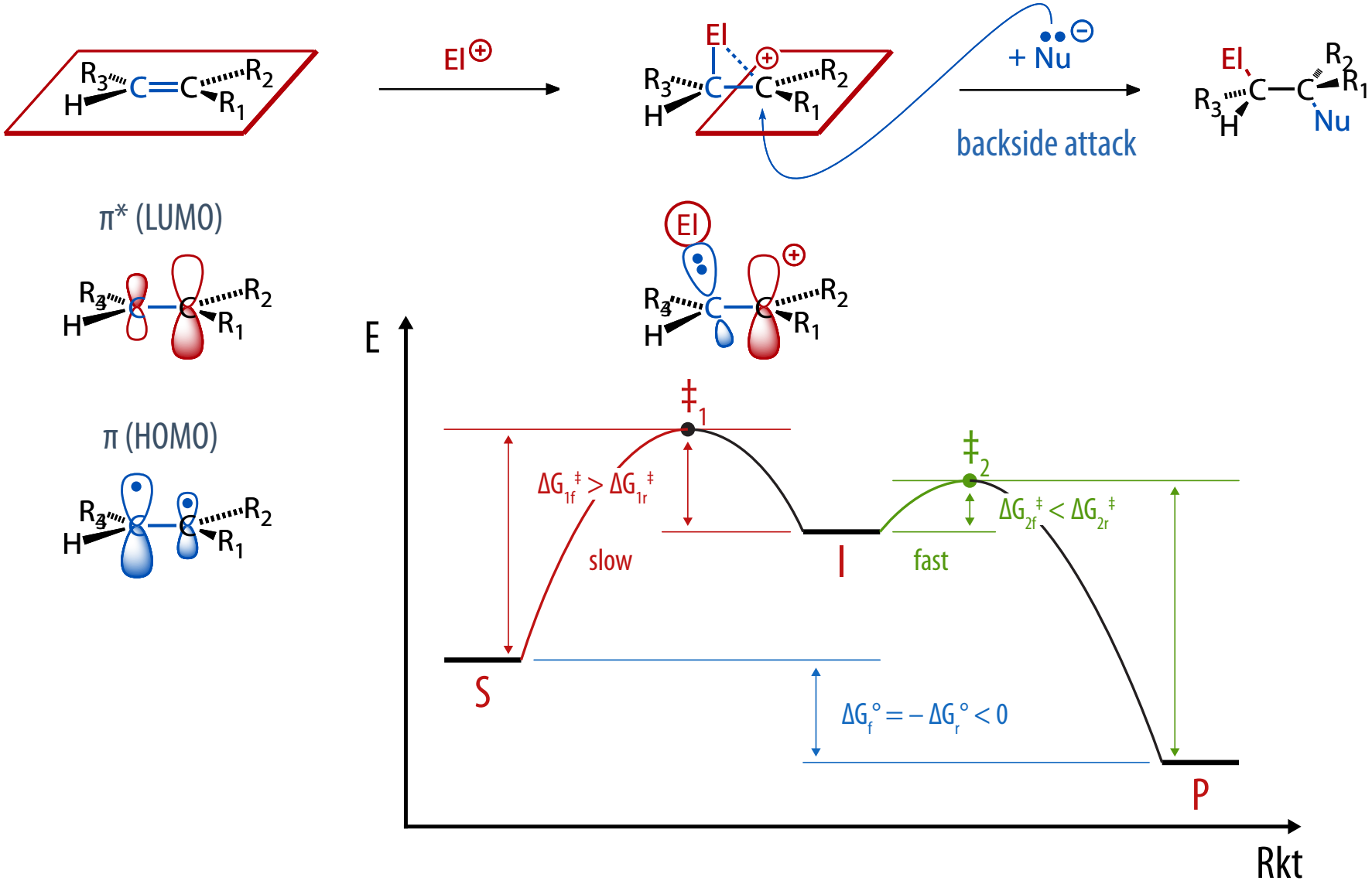


- hydration of olefins

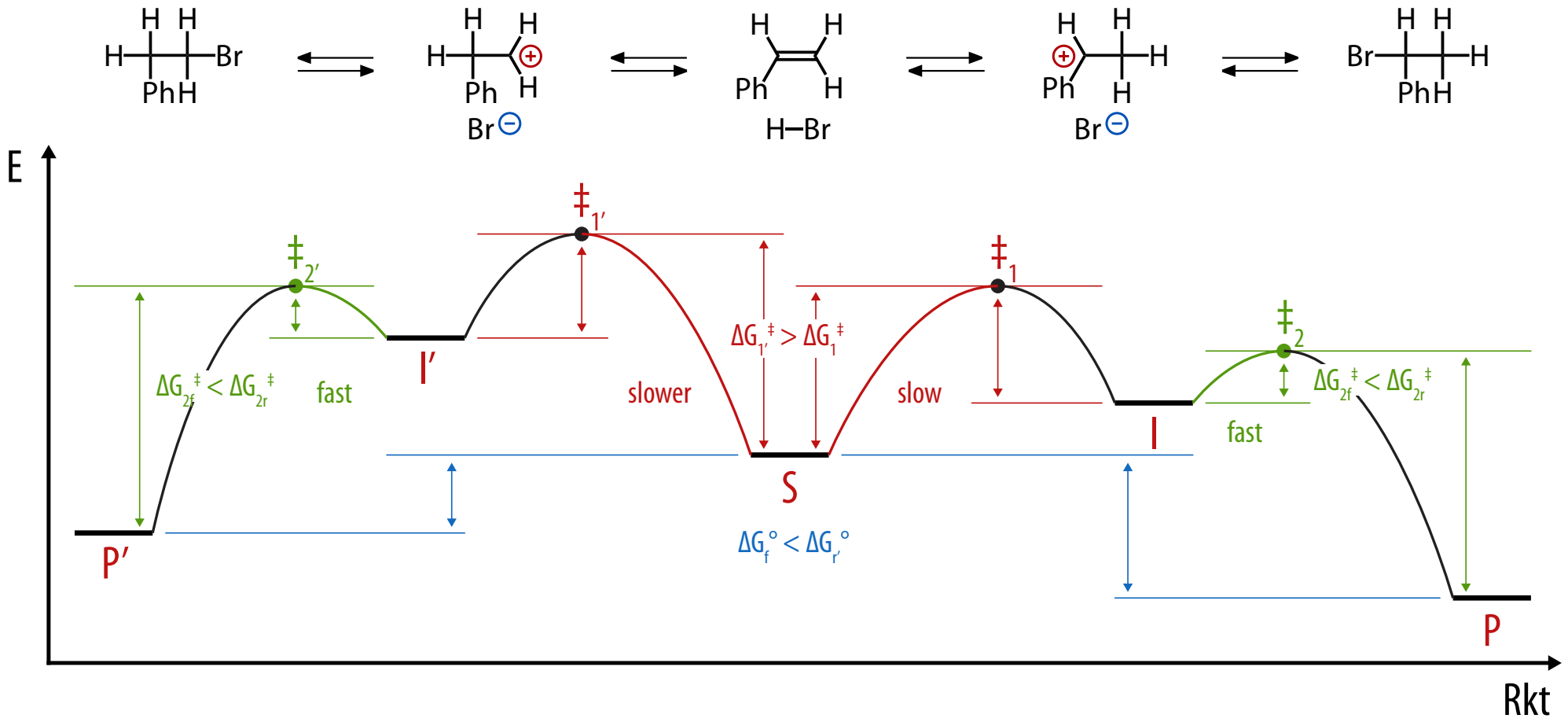


- halogen addition to olefins



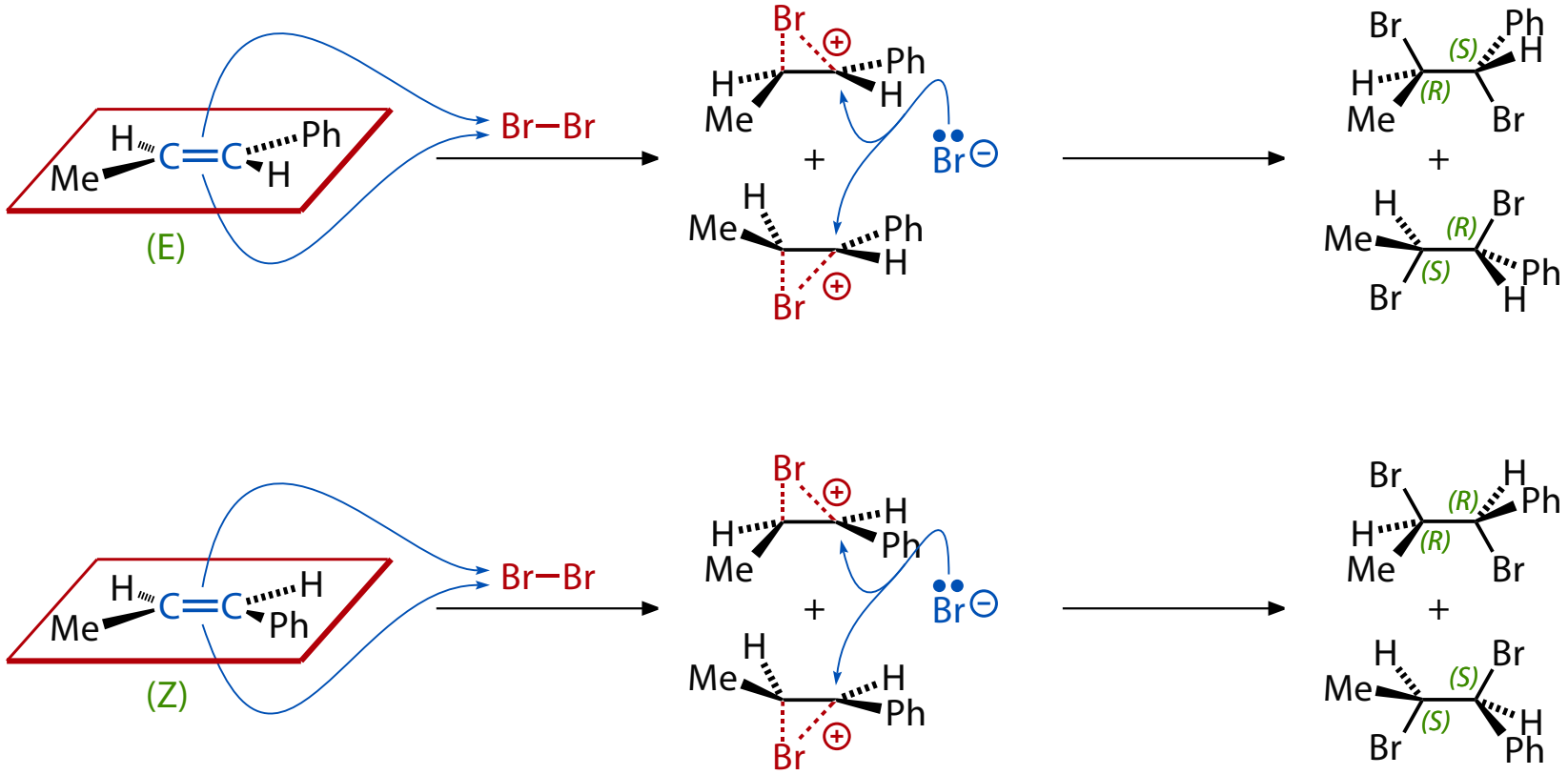


- electrophile adds to double bond so that more stable cation is formed
- nucleophile attacks from the other side



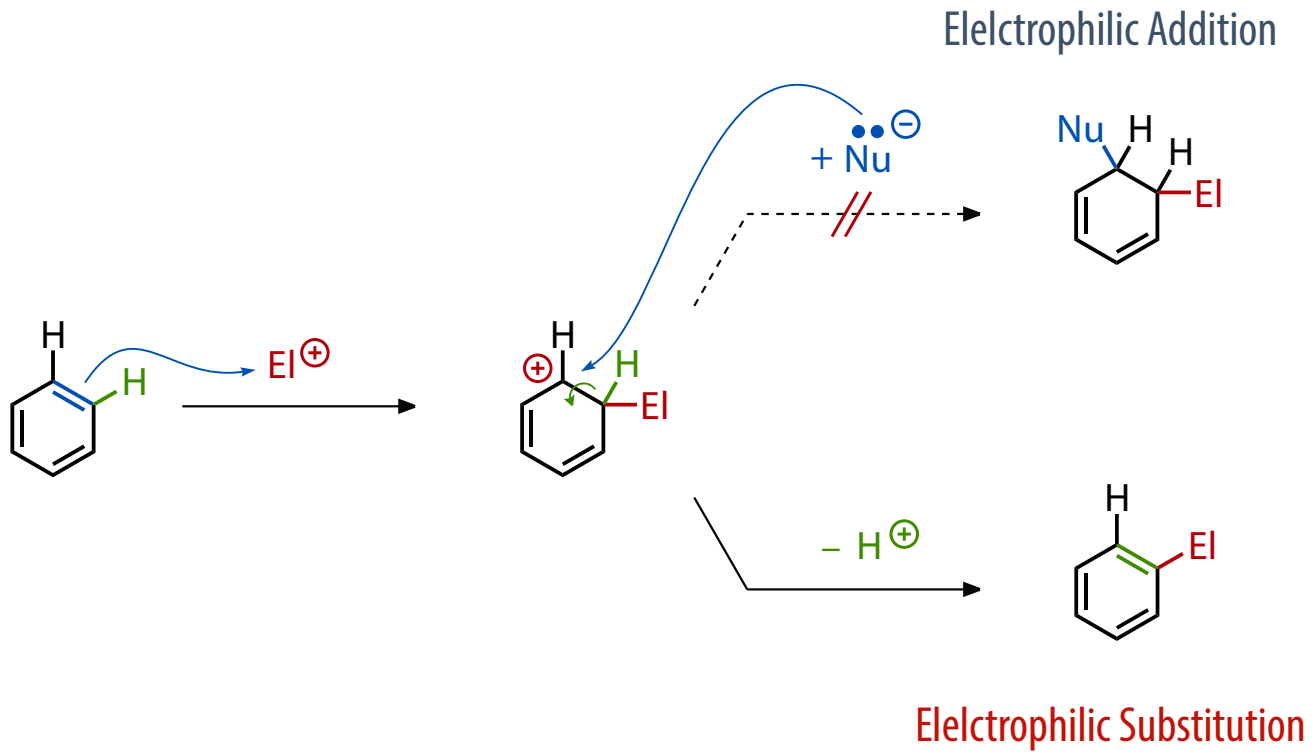
- electrophile adds to double bond so that more stable cation is formed
- IMarkovnikov rule: in HX addition, X is added to the higher substituted carbon (“the more you have, the more you get”)

- electrophilic additions are *trans*-additions



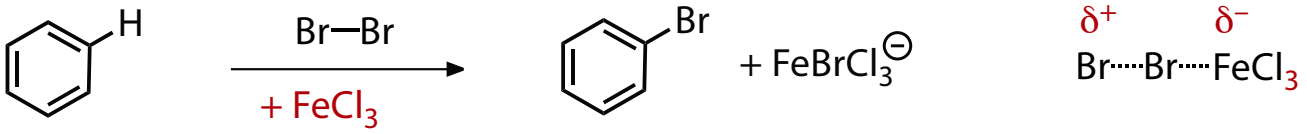
- electrophilic additions are diastereospecific, i.e., an olefin with a given configuration (*E* or *Z*) will specifically be transformed into one diastereomer of possible adducts (a pair of enantiomers)

3.5
Electrophilic Substitutions on Aromatic Compounds

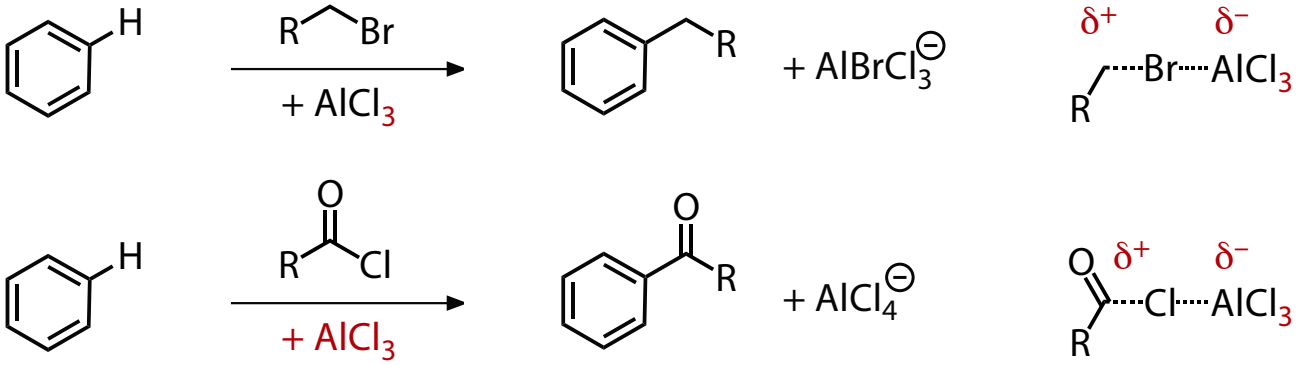


- electrophilic addition leads to loss of aromaticity, energetically disfavorable
- electrophilic Substitution re-establishes aromatic system

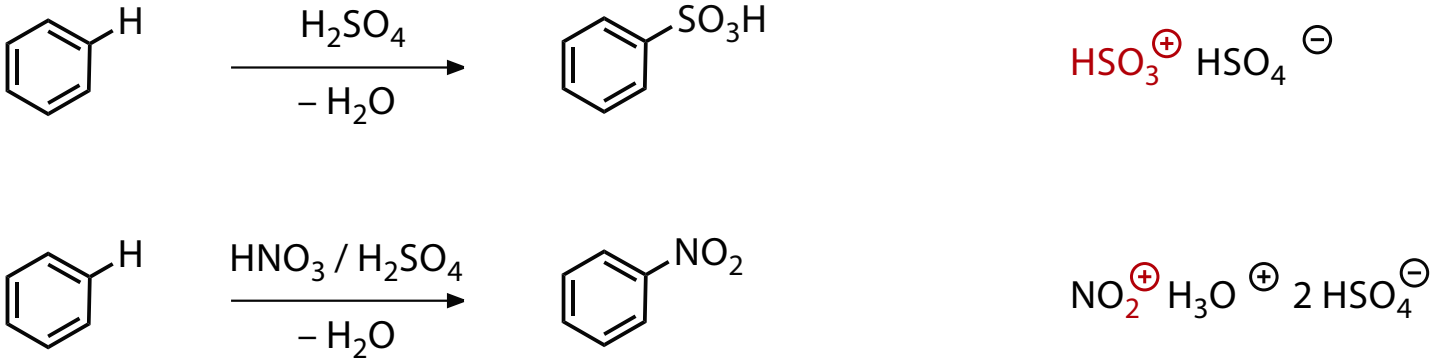
- **bromination**

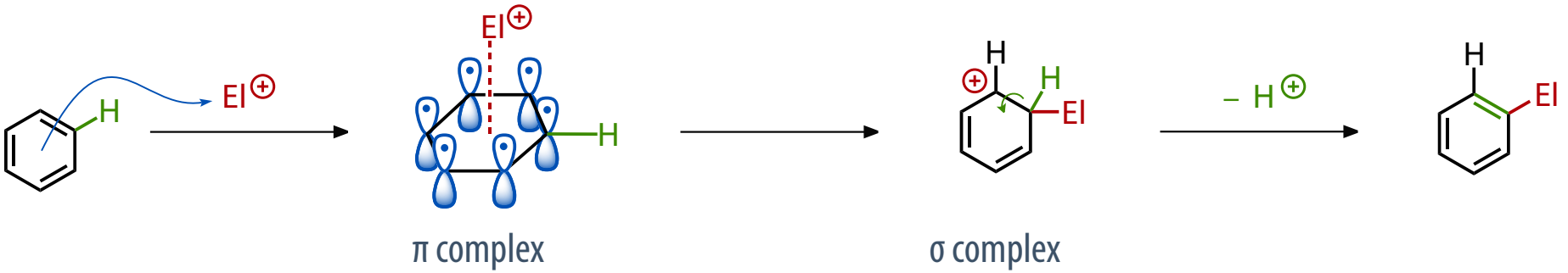


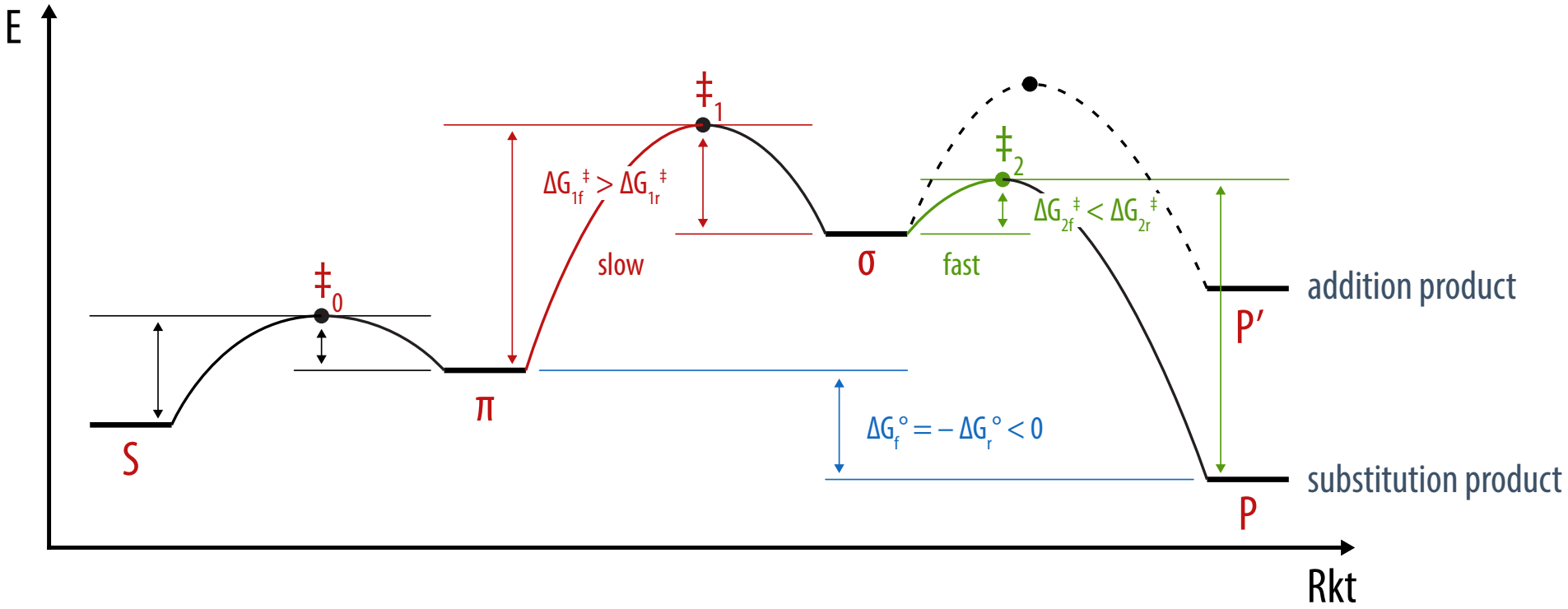
- **Friedl-Crafts alkylation and acylation**



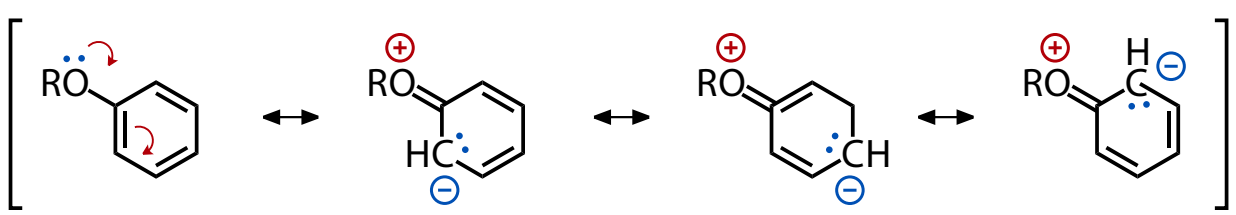
- **sulfonation and nitration**







- **in electrophilic aromatic substituions, the "most acidic" hydrogen is replaced with an electrophile**



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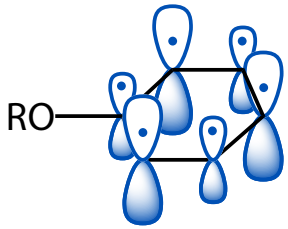
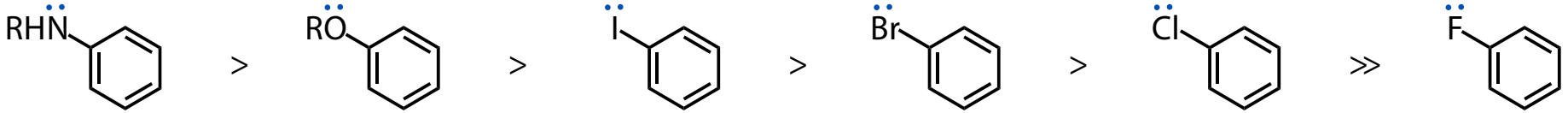
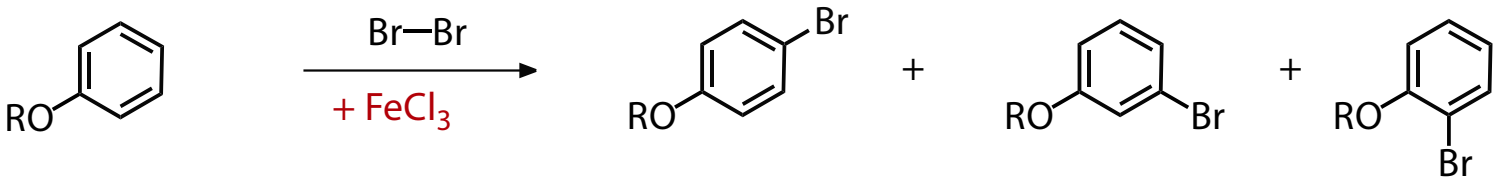
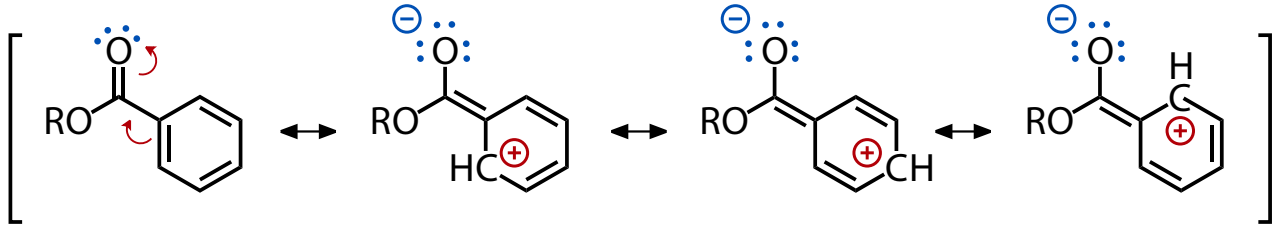


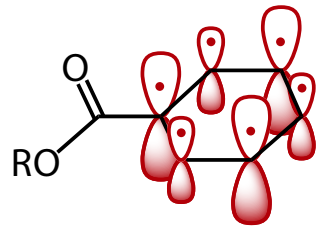


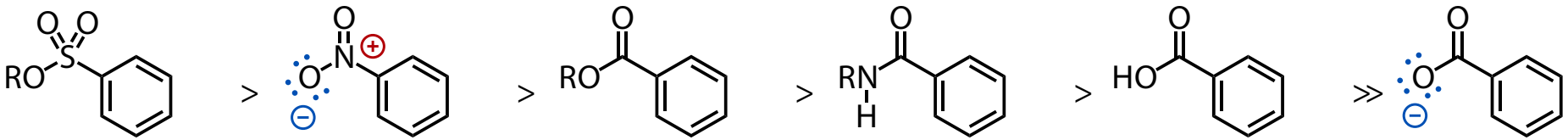


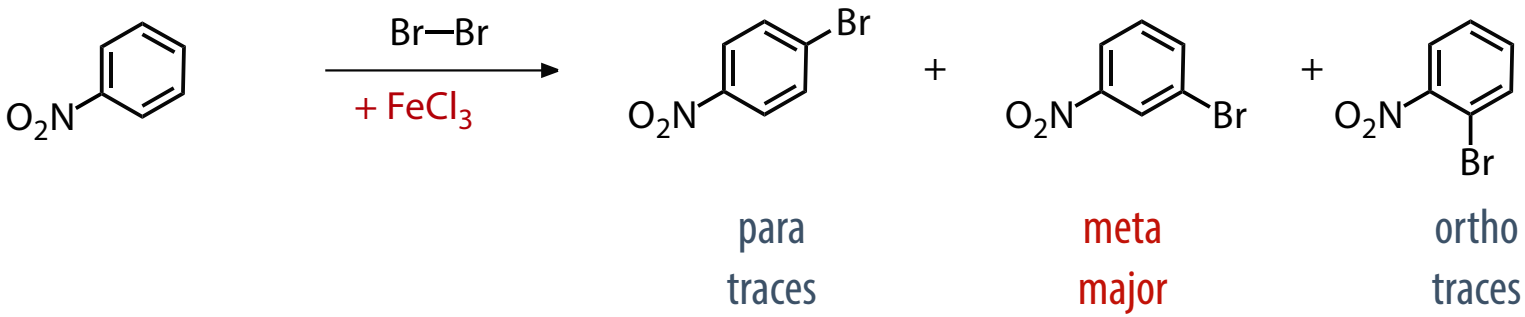
para	meta	ortho
major	none	minor

- substituents with +M effect direct the electrophile into *ortho* or *para*-positions
- substituents with +M effect increase electron density, nucleophilicity, reactivity







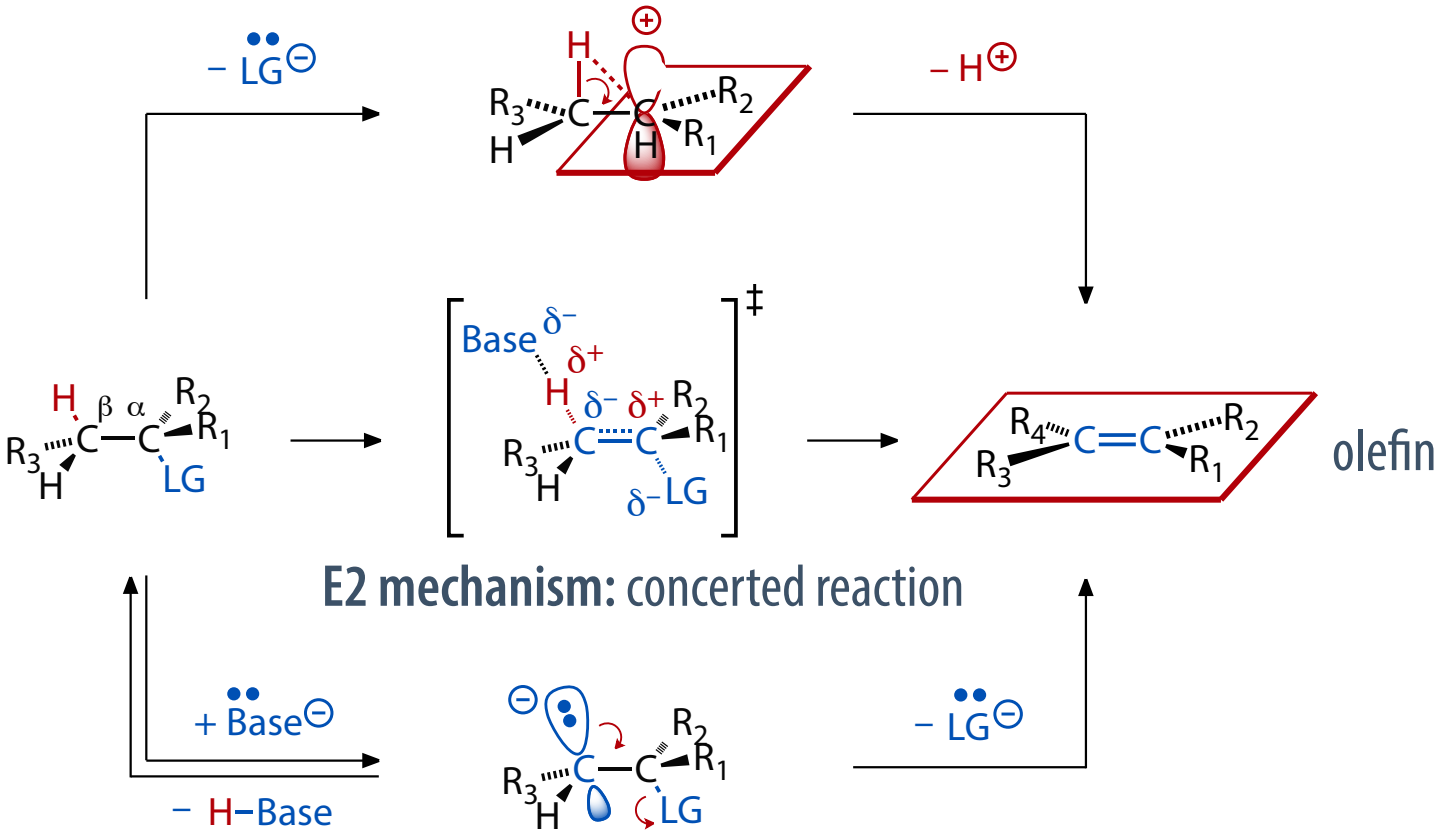


- **substituents with –M effect direct the electrophile into *meta*-positions**
- **substituents with –M effect decrease electron density, nucleophilicity, reactivity**

3.6
Elimination Reactions

- most common are eliminations of hydrogen (H) and leaving group (LG) on adjacent carbons

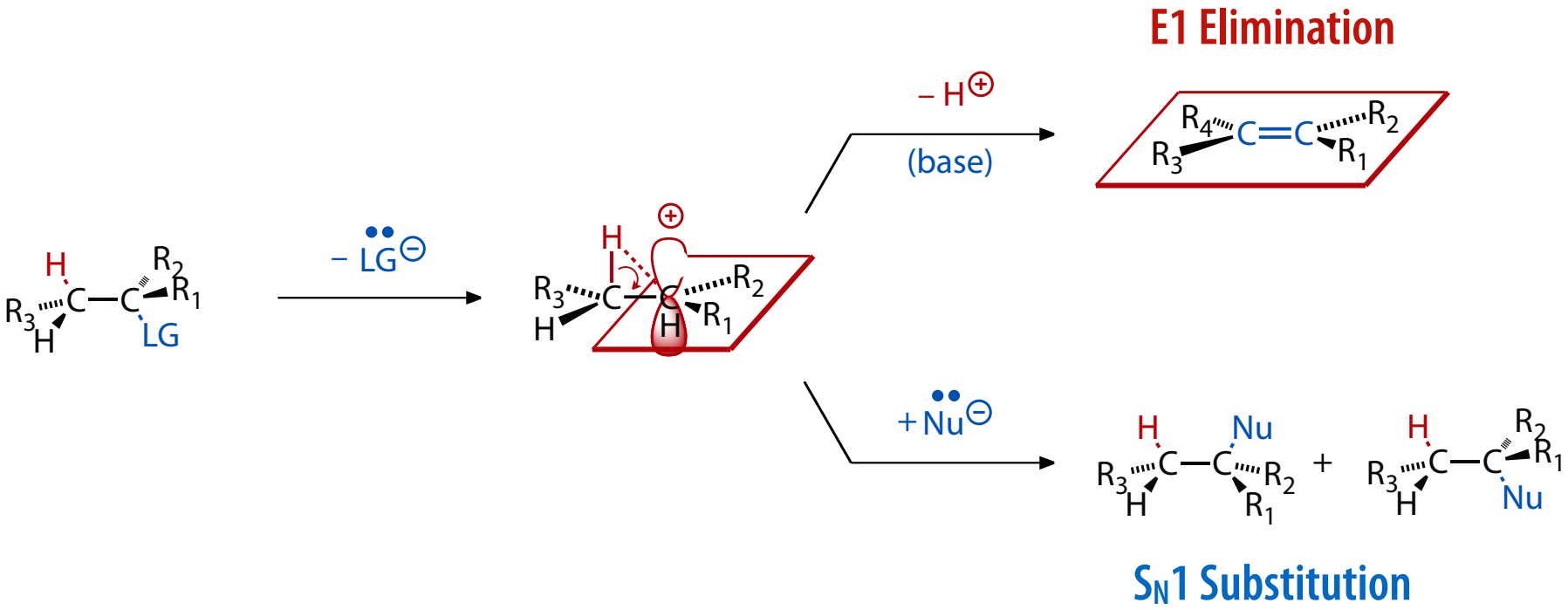
E1 mechanism: leaving group leaves first, hydrogen leaves subsequently



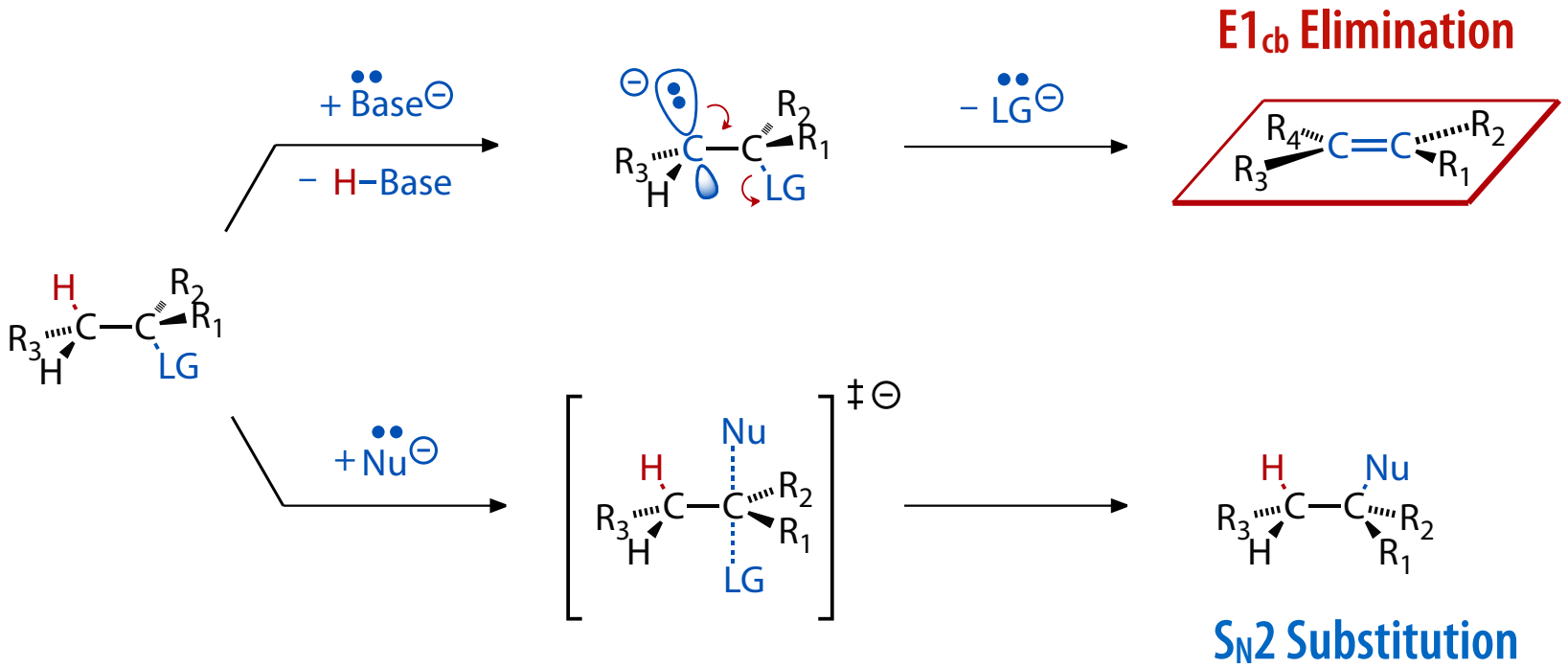
E2 mechanism: concerted reaction

E1$_{cb}$ mechanism: base first removes hydrogen and generates "conjugate base", then leaving group leaves

- **β-hydrogen eliminations are reverse reactions of electrophilic additions to olefins**

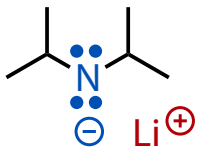


- E1 eliminations are inevitable side reactions of S_N1-type substitution reactions! Factors:
- both: good leaving group, stabilized carbocation (identical intermediate!)
- E1: absence of a nucleophile, non-nucleophilic base (if any), many or "acidic" β-hydrogens
- S_N1: presence of a (good, not too basic) nucleophile, few or non-acidic β-hydrogens

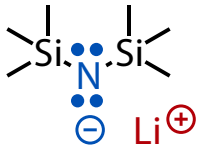


- eliminations are often-observed side reactions of S_N2-type substitution reactions!
- however, they do not share the same intermediate
- $E1_{cb}$/E2: moderate/poor leaving group, strong non-nucleophilic base, "acidic" β-hydrogens
- S_N2: good, non-basic nucleophile (e.g., I^-, RS^-, PR_3, H_2O), few or non-acidic β-hydrogens

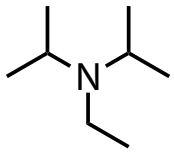
Non-Nucleophilic Bases



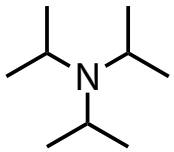
lithium diisopropylamide
LDA, $pK_A \approx 40$



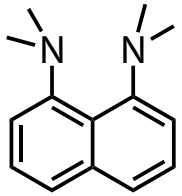
lithium hexamethyldisilazide
LHMDS, $pK_A \approx 40$



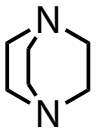
diisopropylethylamine
DIEA, $pK_A \approx 10$



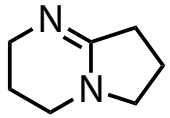
triisopropylamine
TIPA, $pK_A \approx 10$



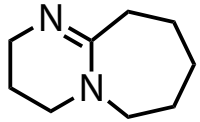
1,8-bis(dimethylamino)naphthalene
proton sponge, $pK_A \approx 12$



1,4-diazabicyclo[2.2.2]octane
DABCO, $pK_A \approx 12$



1,5-diazabicyclo[4.3.0]non-5-ene
DBN, $pK_A \approx 12$

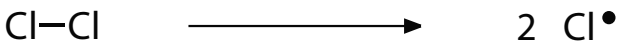


1,8-Diazabicyclo[5.4.0]undec-7-ene
DBU, $pK_A \approx 12$

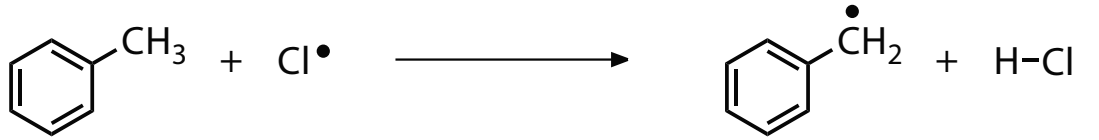
- **non-nucleophilic bases have a high pK_A (of BH) but are strongly sterically hindered!**

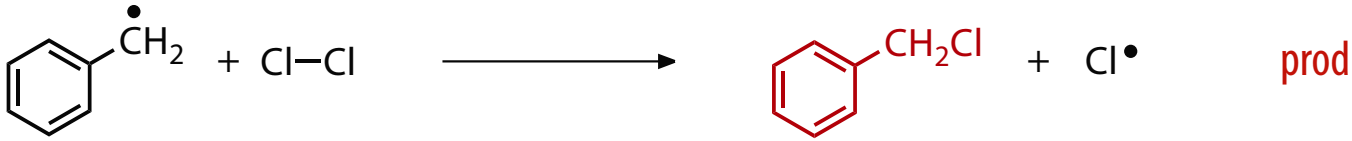
3.7
Radical Substitutions and Additions

initiation



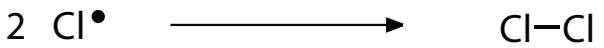
propagation

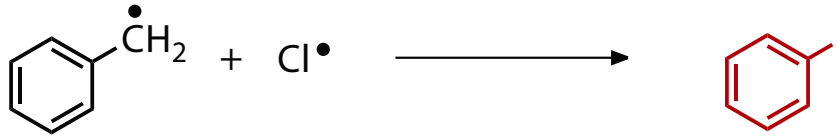




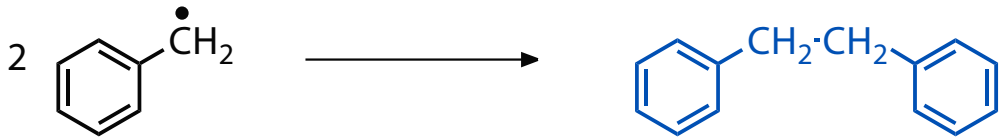
product

termination reactions



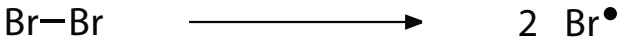


product

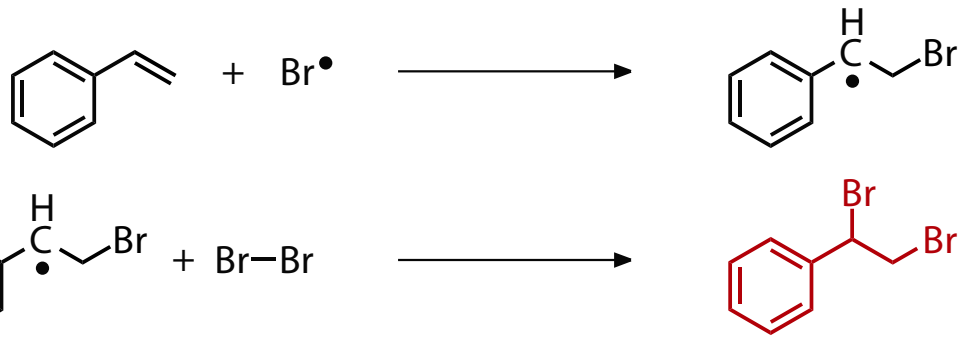


side product

initiation

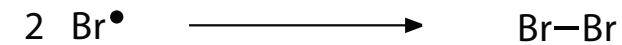


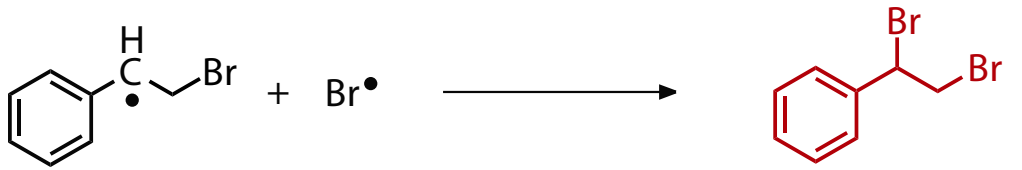
propagation



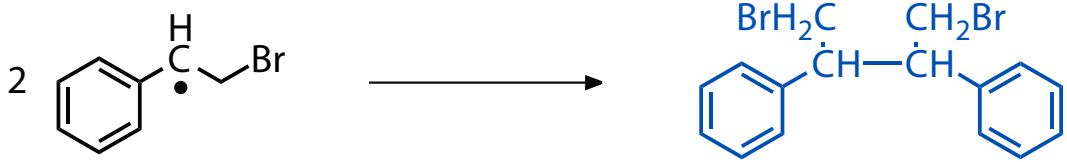
product

termination reactions





product



side product