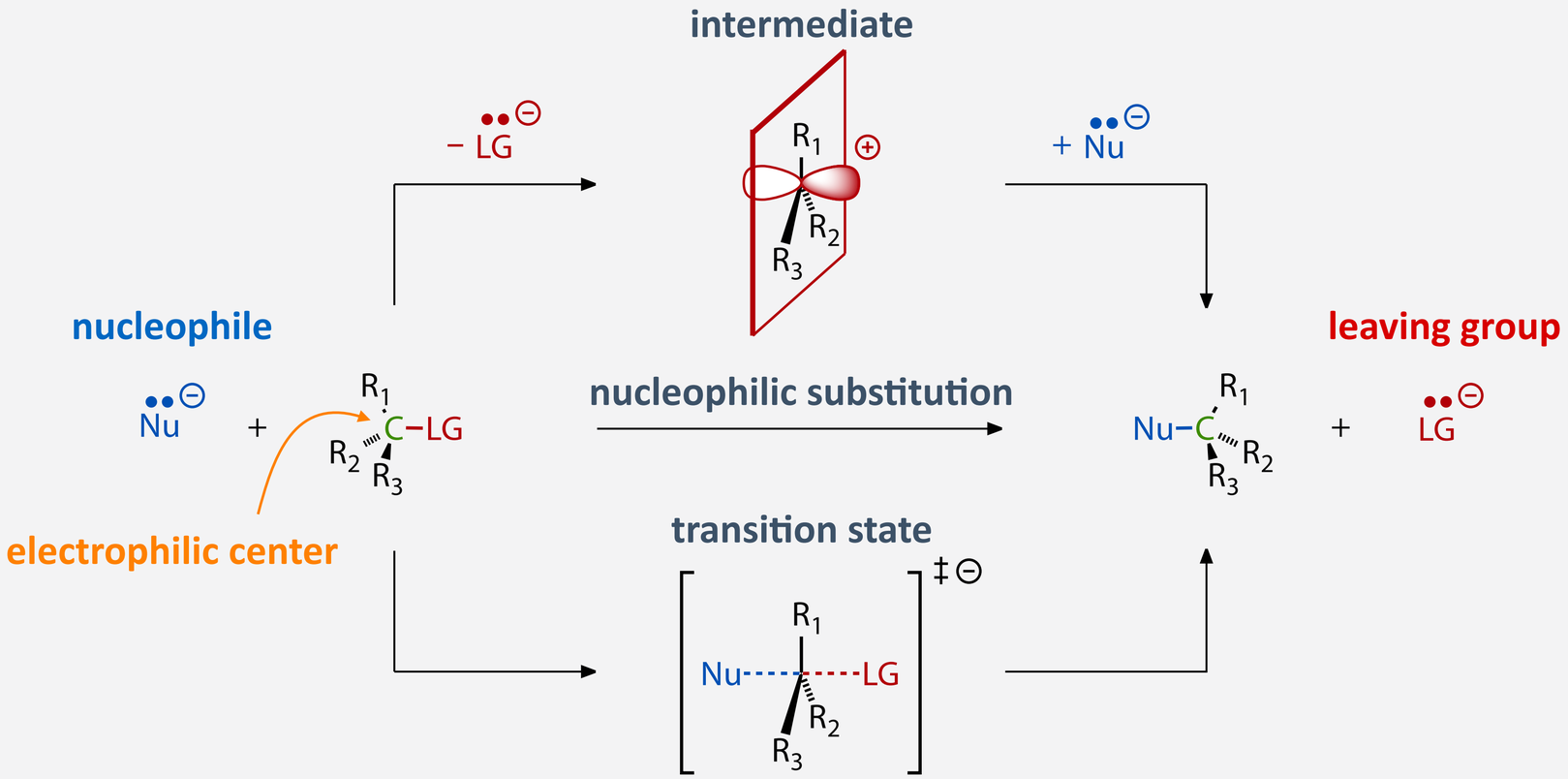
4.3 Nucleophilic Substitutions (S_N1, S_N2)

Nucleophilic Substitutions (S_N Reactions)

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

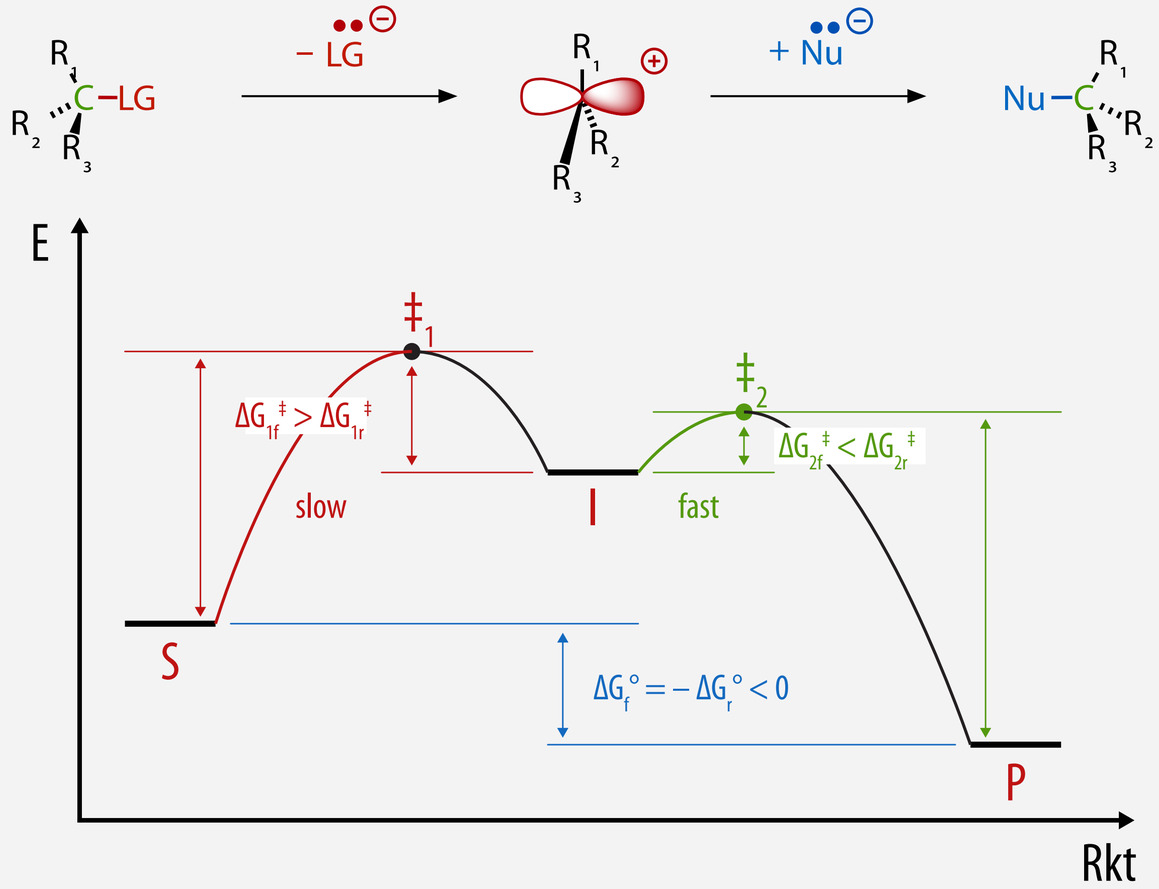


S_N2 Mechanism: nucleophile attacks (and forces leaving group to leave simultaneously)

- **nucleophile (electron pair donor)** reacts at an **electrophilic center (electron pair acceptor)**
- **nucleophile** replaces the **leaving group (which takes an electron pair with it)**

S_N1 Reactions

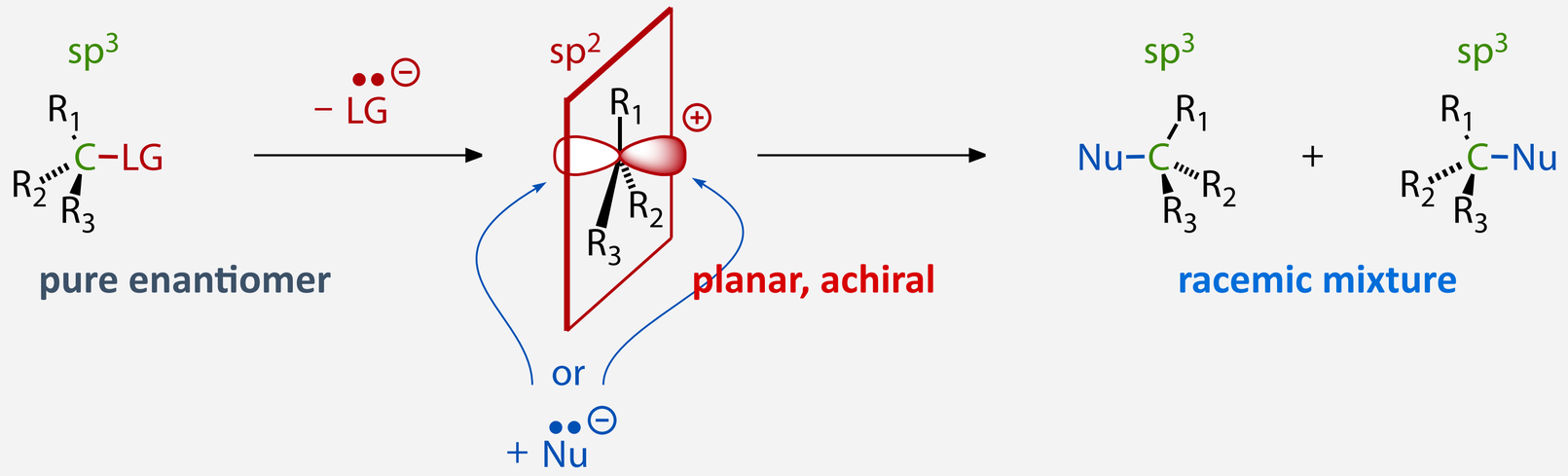
S_N1 Mechanism: Rate-Determining Step is Unimolecular



- departure of the leaving group generates a carbocation as a true intermediate
- first step is rate-determining, monomolecular, depends only on starting material
- good leaving group, stabilized carbocation accelerate reaction (Polanyi principle!)

S_N1 Mechanism: Loss of Stereochemical Information

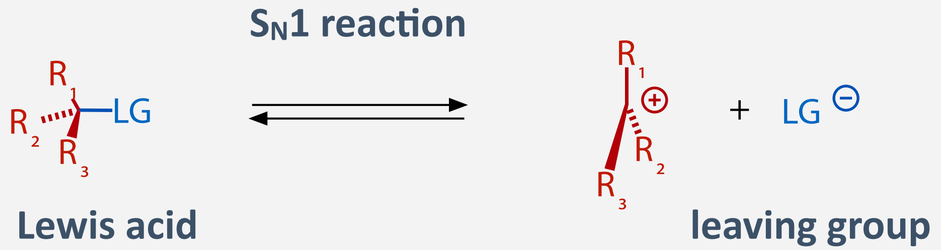
- if the electrophilic center is a stereocenter, and the starting material is a pure enantiomer:

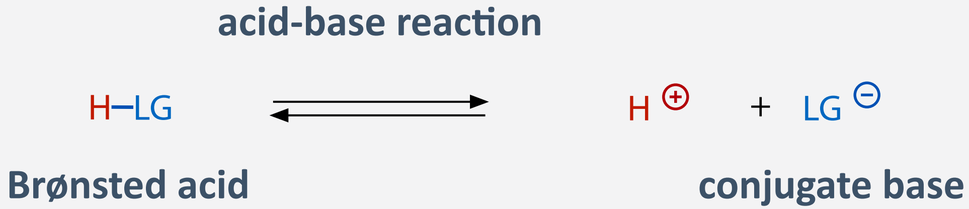


- **departure of the leaving group generates planar, achiral, sp^2-hybridized carbocation**
- **attack of the incoming nucleophile can occur from any side with equal probability**
- **product still contains a stereocenter, but is formed as a racemic mixture**

Analogy of S_N1 Reactions and Acid-Base Reactions

- S_N1 reactions are cation-anion dissociation reactions very similar to acid-base reactions



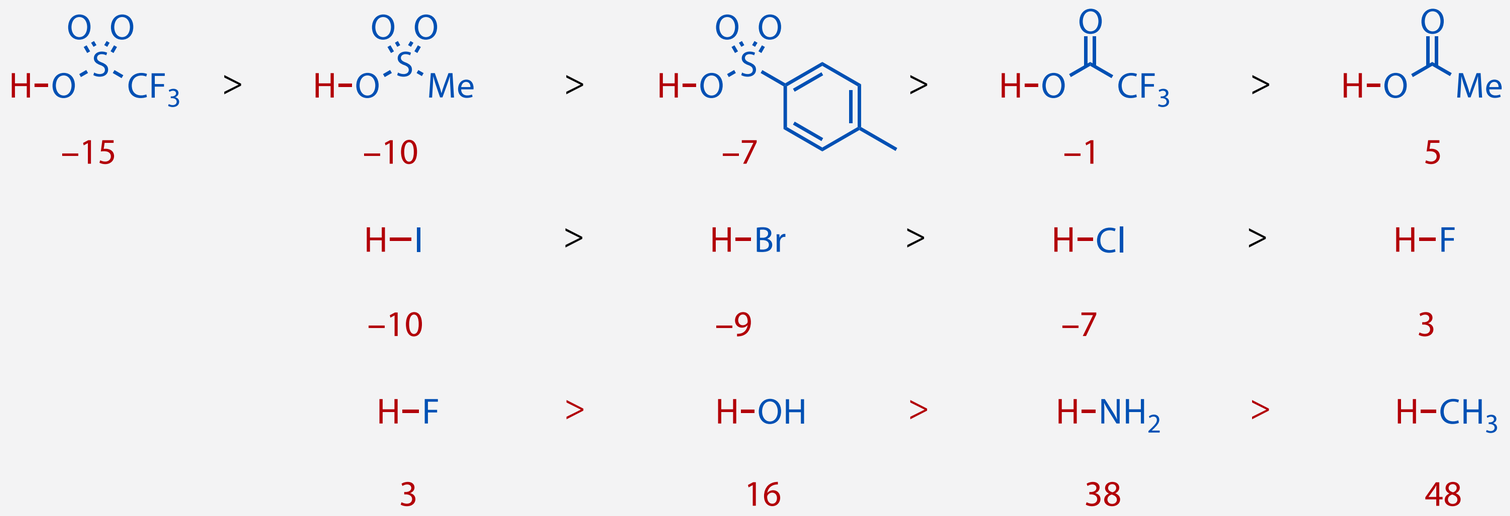


$$pK_A = -\log K_A = -\log \frac{[H^+][LG^-]}{[H\text{–}LG]}$$

- **pKA 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**
- **pKA values of corresponding acids are measure for leaving group quality (lower is better)**

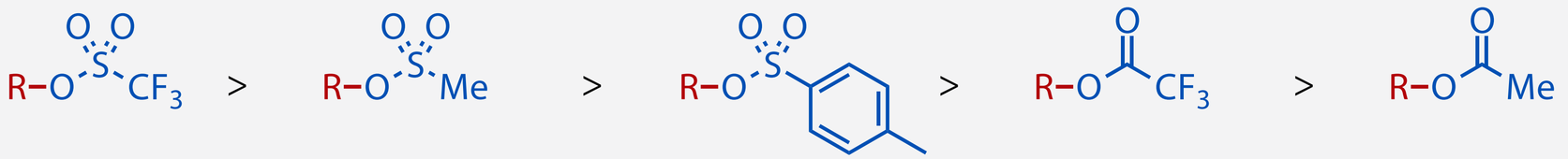
Leaving Group Quality

- leaving group quality is approximately inverse to the basicity of the corresponding anion



- **residues that correspond to acids with $pK_A < 0$ are excellent leaving groups**
- **residues that correspond to acids with $pK_A < 10$ are good 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 under any circumstance**

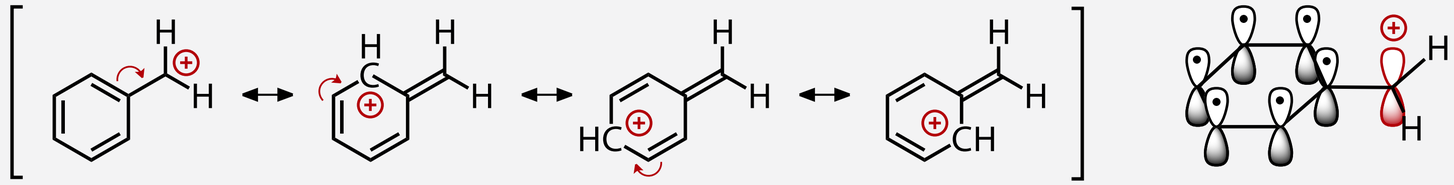
Trivial Names and Abbreviations of Important Leaving Groups



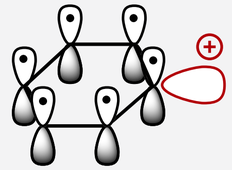
R–OTf	R–OMs	R–OTs	R–OTFA	R–OAc
trifluoromethanesulfonate triflate	methanesulfonate mesylate	4-toluenesulfonate tosylate	trifluoroacetate	acetate

Stabilization of the Carbocation Intermediate by Electron Delocalization

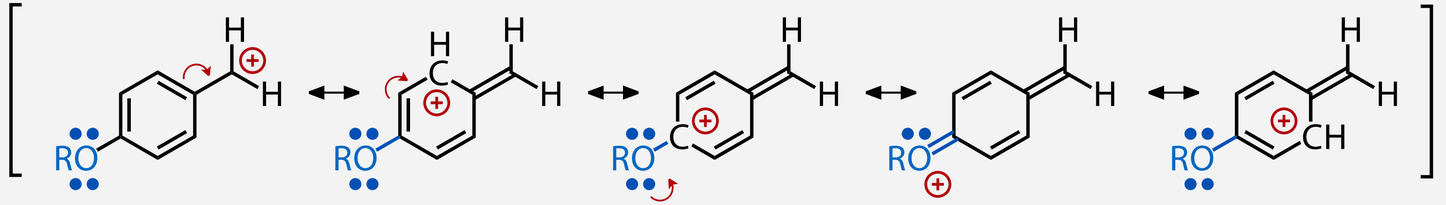
- stabilization of allyl / benzyl carbocations by electron delocalization by resonance (+M effect)



compare to phenyl cation:



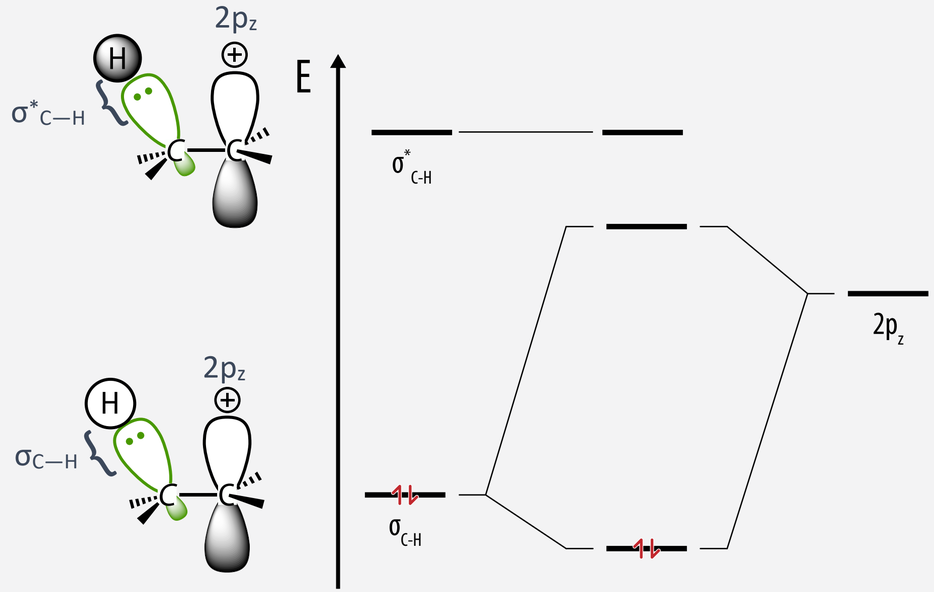
- the more delocalization (donor groups, larger aromatic systems), the better stabilization

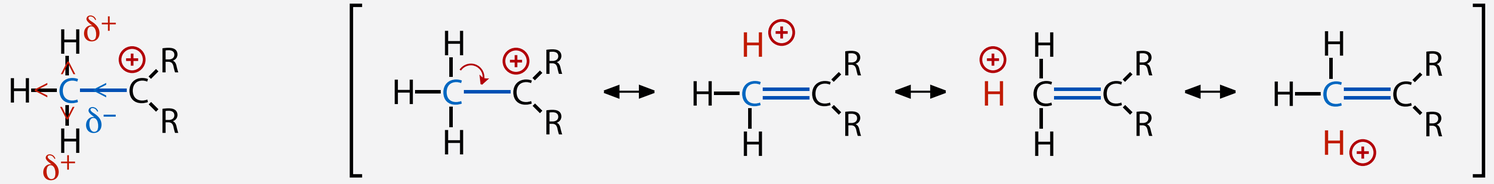


- **if leaving groups are in allyl / benzyl positions, S_N1 reactions are very likely**

Stabilization of the Carbocation Intermediate by Hyperconjugation

- stabilization by interaction of the carbocation $2p_z$ AO with neighboring $\sigma_{C–H}$ MO (matching symmetry)
- corresponding interaction with antibonding $\sigma^*_{C–H}$ MO negligible (non-matching symmetry)
- “three-center bond”, donation of electron density to electron-deficient carbocation

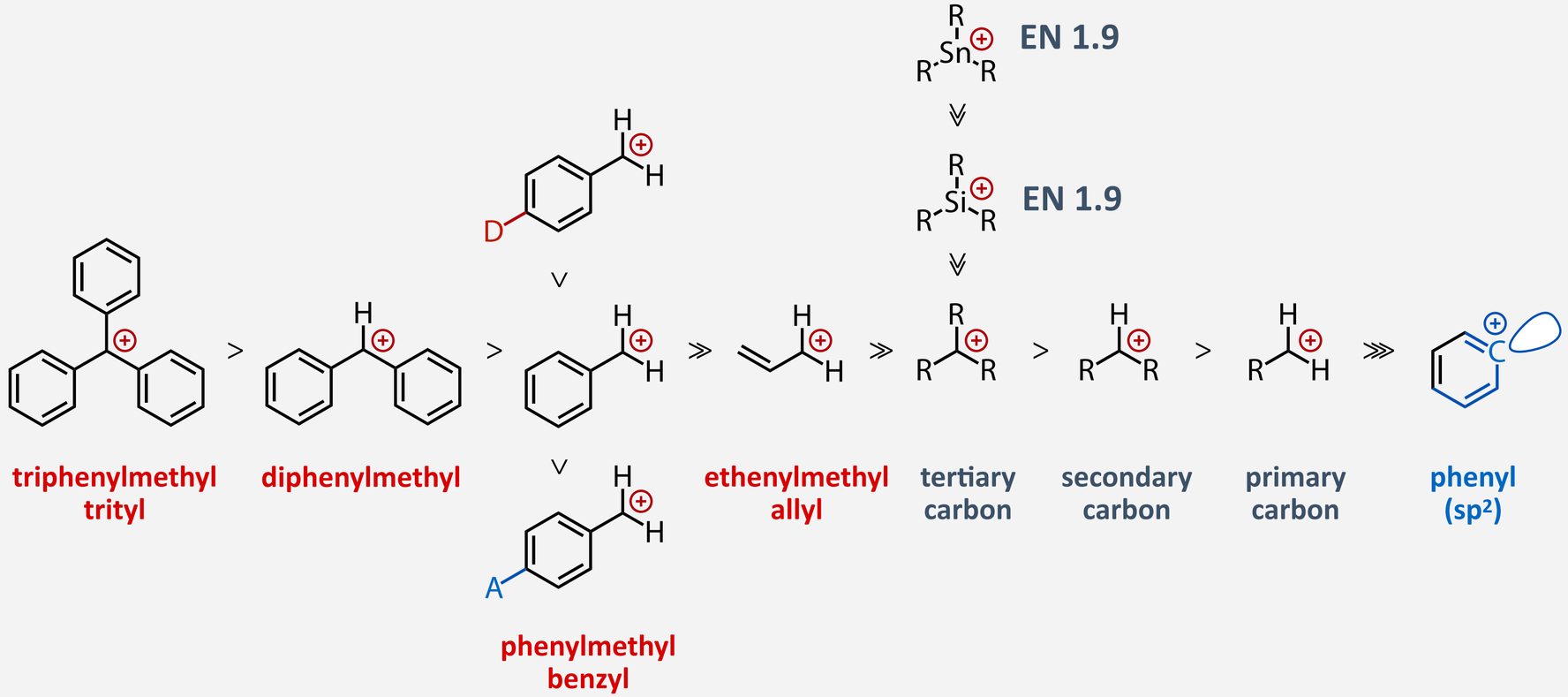




- **the higher substituted the electrophilic center, the better stabilized is carbocation**

Stabilization of the Carbocation Intermediate

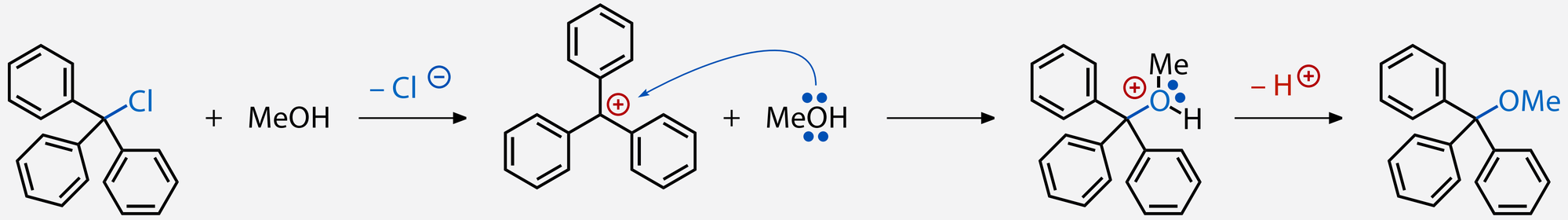
- carbocation intermediate is electron-deficient, stabilized by electron-donating groups (+M, +I)



- **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)**

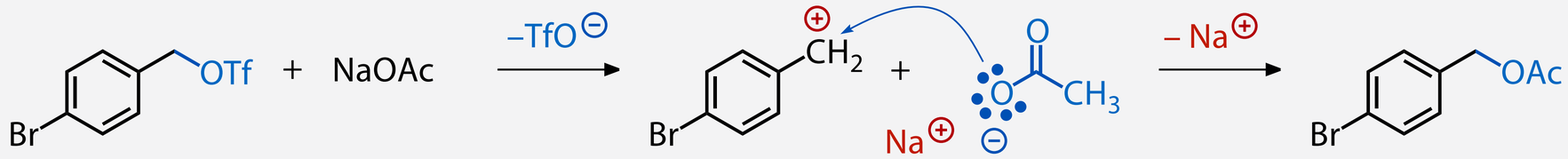
Examples of S_N1 Reactions

good leaving group **moderate nucleophile**



trityl chloride methanol **excellently stabilized cation**

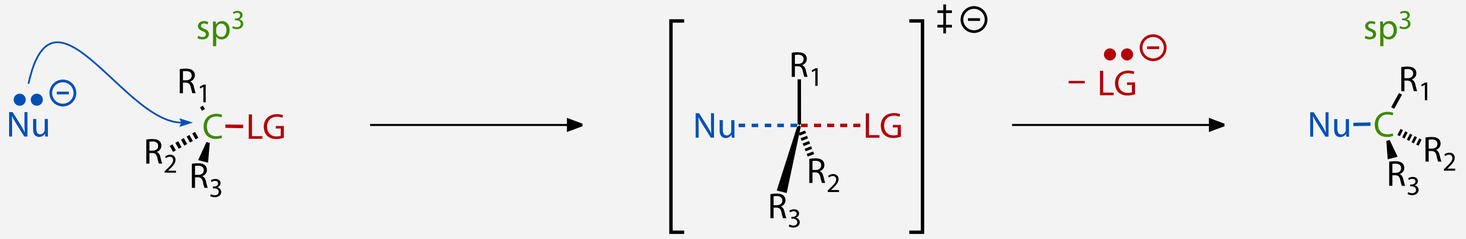
excellent leaving group **moderate nucleophile**

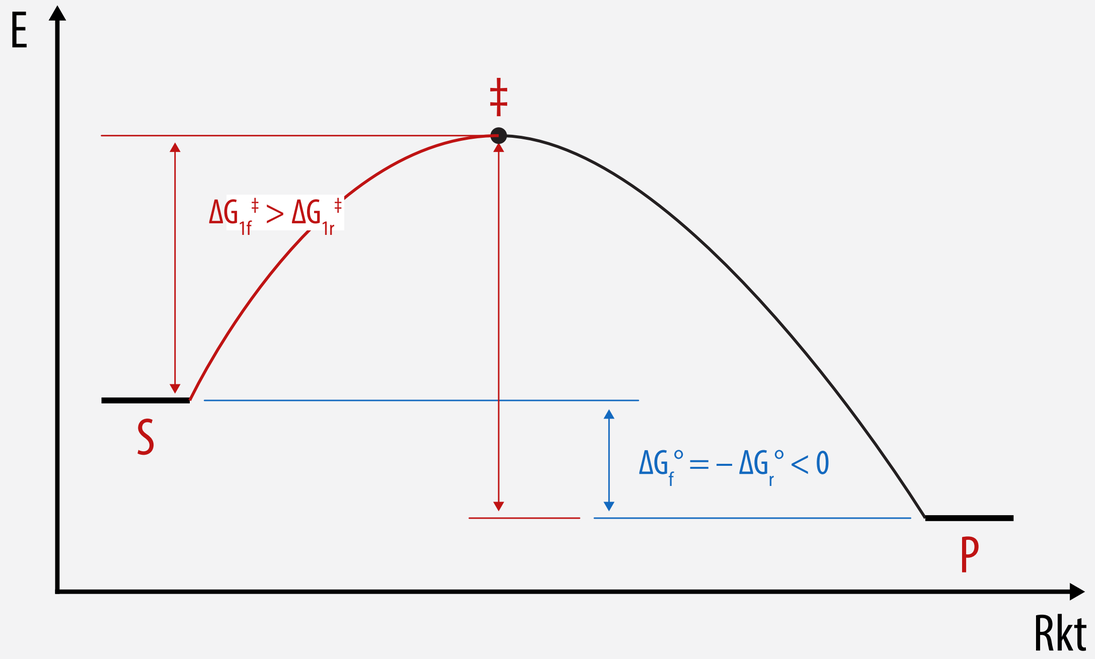


benzylbromotriflate sodium acetate **well-stabilized cation**

S_N2 Reactions

S_N2 Mechanism: Rate-Determining Step is Bimolecular

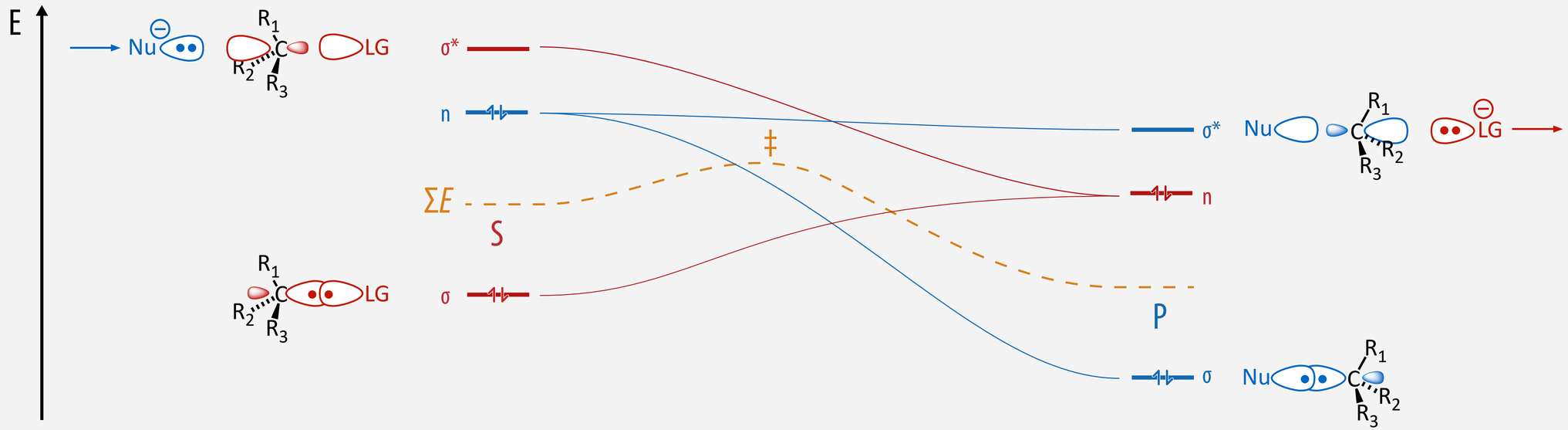




- attack of the nucleophile cannot result in a stable intermediate (pentavalent carbon!)
- S_N2 reactions are single-step reactions that pass through a “pentavalent” **transition state**
- rate-determining step is **bimolecular**, favored by good nucleophile and electrophilic center

Molecular Oribtal View of the Reaction and the Transition State

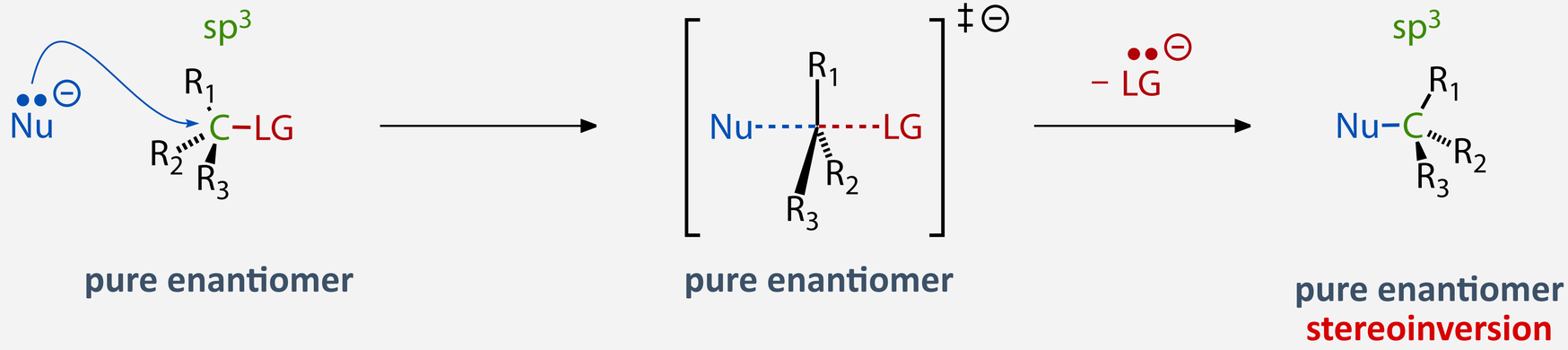
- “pentavalent” transition state possible because of simultaneous bond formation and cleavage



- **nucleophile electron pair** interacts with the **empty, antibonding σ* orbital of the C–LG bond**
- **back-side attack** required, and **concerted departure of leaving group inevitable**
- **“early” transition state** (similar to starting material; Hammond) avoids “pentavalent” state
- **good nucleophile (high energy electron pair)** and decent leaving group will favor S_N2 reaction

Stereochemical Inversion During the S_N2 Reaction

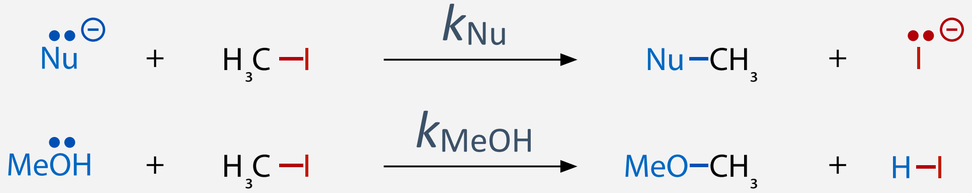
- if the electrophilic center is a stereocenter, and the starting material is a pure enantiomer, the stereochemical information is preserved during the S_N2 reaction



- **nucleophile & leaving group on opposite sides of the electrophilic center (back-side attack!)**
- **transition state has “trigonal-bipyramidal” geometry, R_1–R_3 in same plane, flip to other side**
- **stereochemical information preserved but stereoinversion (Walden Umkehr)**

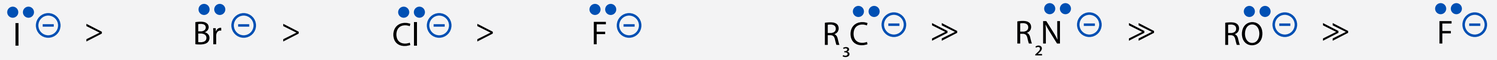
Nucleophilicity

- determination of relative nucleophilicity *n* according to Pearson:

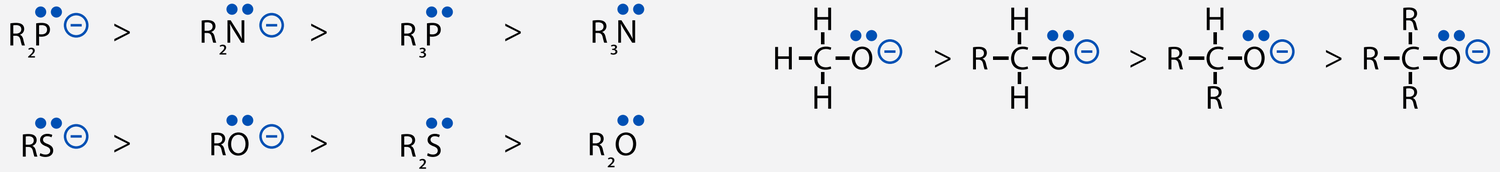


$$n = -\log \frac{k_{Nu}}{k_{MeOH}}$$

- nucleophilicity increases with polarizability, decreasing electronegativity (against basicity)



- anionic nucleophiles stronger than neutral ones; nucleophilicity decreases with steric hindrance

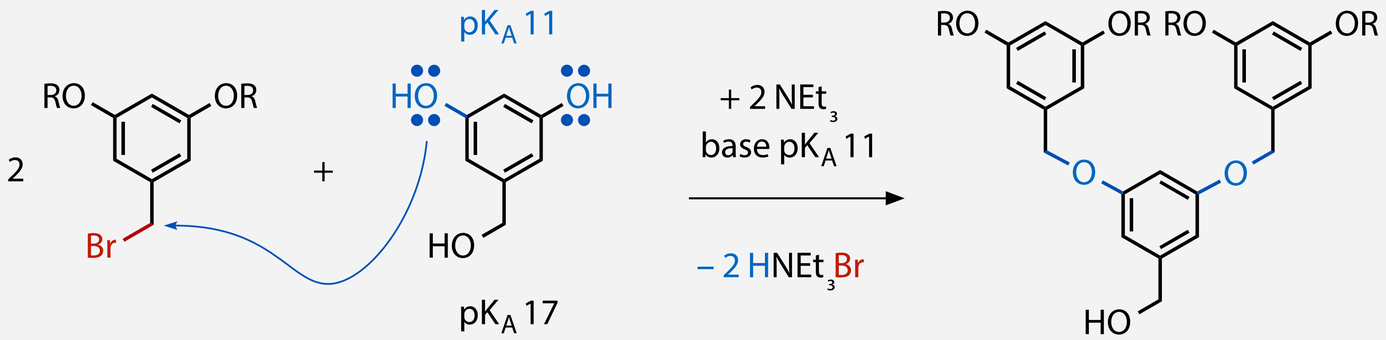


- **nucleophilicity is a kinetic parameter, while basicity is a thermodynamic concept**
- **all nucelophiles are bases, but not all bases are nucelophiles (“non-nucleophilic bases”)**
- **trends are clear but no simple nucleophilicity scale (different from leaving group quality)!**

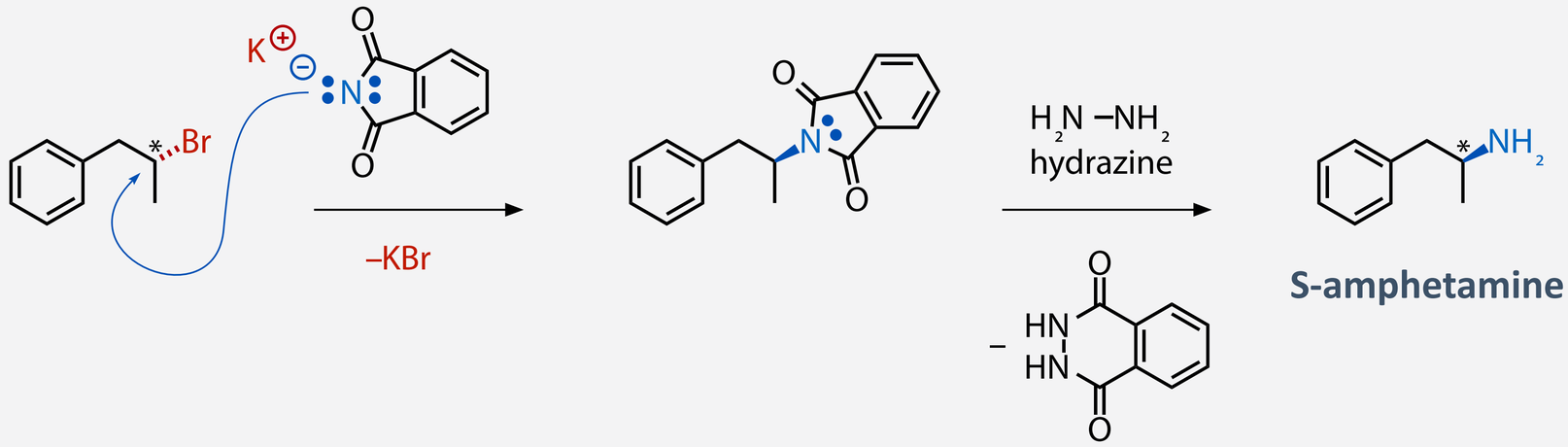
Pearson et al., *J. Am. Chem. Soc.* **1968**.

Examples for S_N2 Reactions

- Williamson synthesis of ethers



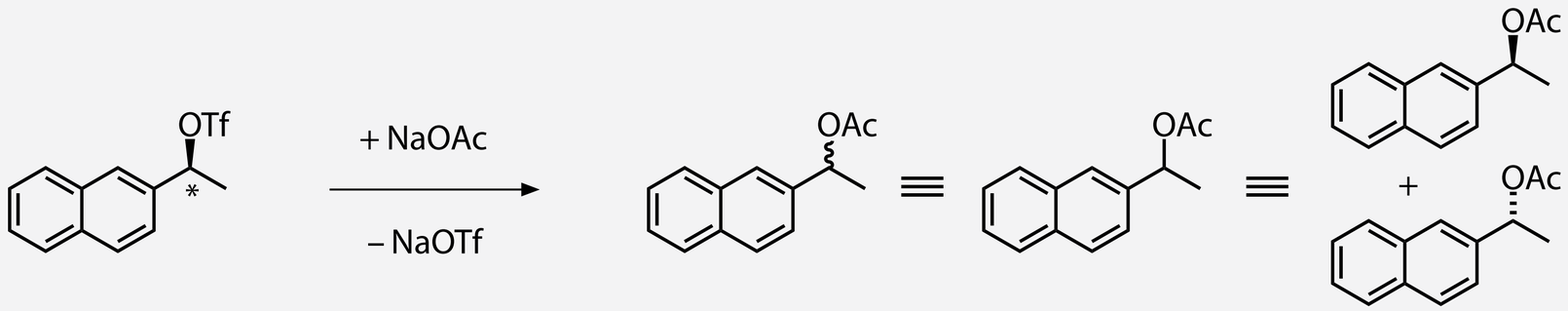
- Gabriel synthesis of primary amines



- **if reaction proceeds via an S_N2 mechanism, the stereochemistry must be respected!**

Does the Nucleophilic Substitution Follow the S_N1 or S_N2 Mechanism?

- consider leaving group quality, stabilization of the carbocation, and nucleophile

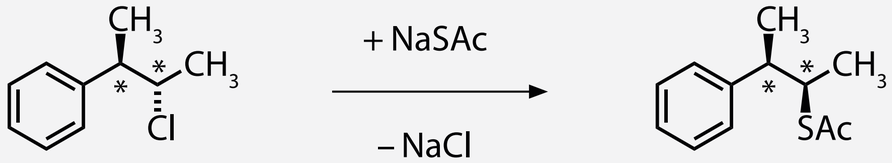


excellent leaving group
well-stabilized carbocation
moderate nucleophile

S_N1

loss of stereochemical information

racemic mixture



moderate leaving group
non-stabilized carbocation
good nucleophile

S_N2

inversion of stereoconfiguration

- **if you decide for a mechanism, give the arguments for your choice**
- **consider explicitly the stereochemical consequences (also in nomenclature of the products)**

Learning Outcome

- assign the roles of nucleophiles and electrophiles
- formulate nucleophilic substitution reactions
- estimate leaving group quality from pKa values of corresponding acids
- estimate carbocation stabilization
- compare nucleophilicity of different nucleophiles
- identify reactive centers and preferred reaction pathways (S_N1 or S_N2)