1) Synthetic utility: alkyl halide → alcohol → ether → thiol

2) Reagents: basic nucleophile
   ex: NaOH, NaOCH₃, NaCN

3) Conditions: polar aprotic solvent

4) Mechanism (above): anion, concerted

5) Stereochemistry: inversion of configuration

6) Regiochemistry: specific (at leaving group)

Substrate → target nucleophile → seeks + charge

In SN2 reaction, the nucleophile attacks by adding into the σ* bond to the leaving group. Since electrons are added into the antibonding orbital, the bond with the leaving group breaks. This allows for a new bond with the nucleophile to form, but in the exact opposite direction → inversion of configuration.
Factors that affect on S_n2 rxn

1) Substrate

\[ \text{CH}_3 - \text{Br} \quad \text{Br} \quad \text{OH} \quad + \text{Br} \]

relative rates

| 1200 | 40 | 0 |

(unreactive)

Since the S_n2 rxn depends on the nucleophile attacking the carbon bearing the leaving group, steric hindrance around that position will slow the rate of reaction.

\[ \text{NaOH} \quad \rightarrow \quad \text{no substitution} \]

(incredibly slow)

Phenyl halides do not undergo S_n2 because of too much steric hindrance (attack would have to occur through the ring).

2) Nucleophile

Nucleophilicity - how strongly does a compound seek + charge

Ex: H_2O vs OH -
hydroxide is much more nucleophilic because it has a - charge on it

Basicity - how able is a compound to remove H^+

R-O- alkoxide (alkyl + oxide)
OH⁻ VS SH⁻ | H₂O pKₐ = 15.74
Stronger base
H₂S pKₐ = 7
Stronger nucleophile

Polarizability — able to become polarized — larger ions are "squishier," meaning that electron density can more easily be displaced. Since sulfur is more polarizable than oxygen, the process of forming a bond occurs more easily — and therefore more quickly — for sulfur versus oxygen. Sulfur is a better nucleophile than oxygen (in similar molecules).

\[ \text{Br}⁻ + \overset{\text{O}}{\overset{\text{H}}{\text{O}}} \rightarrow \overset{\text{Br}}{\text{Br}} + \overset{\text{O}}{\text{H}} \]

(S₂ reaction requires strong nucleophiles (needs something able to attack), which are often, but not always, basic. Extremely basic or hindered nucleophiles can undergo elimination instead of substitution.

3) Leaving group

Good leaving groups are the conjugate bases of very strong acids:

\[ \text{Br}⁻ + \overset{\text{O}}{\overset{\text{H}}{\text{O}}} \rightarrow \overset{\text{Br}}{\text{Br}} + \overset{\text{O}}{\text{H}} \]

\[ \text{H}⁺ \overset{\text{O}}{\text{H}} \rightarrow \overset{\text{O}}{\text{H}} + \text{H}⁻ \ (\text{really basic}) \]
Examples:

\[ \text{Cl}^-, \text{Br}^-, \text{I}^- \quad (\text{not} \quad \text{F}^-) \]

\[ \downarrow \]

usually better than \( \text{Cl}^- \) since \( \text{HI} \) is a stronger acid than \( \text{HCl} \)

sulfonates

\[ \begin{array}{c}
\text{R} - \text{s} - \text{o} - \Theta \\
\text{O} \end{array} \]

Strongly resembles sulfuric acid