B.Sc. Semester-IV
Core Course-IX (CC-IX)
Organic Chemistry-III

I. Nitrogen Containing Functional Groups

1. Amines: Preparation of Amines

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I Nitrogen Containing Functional Groups

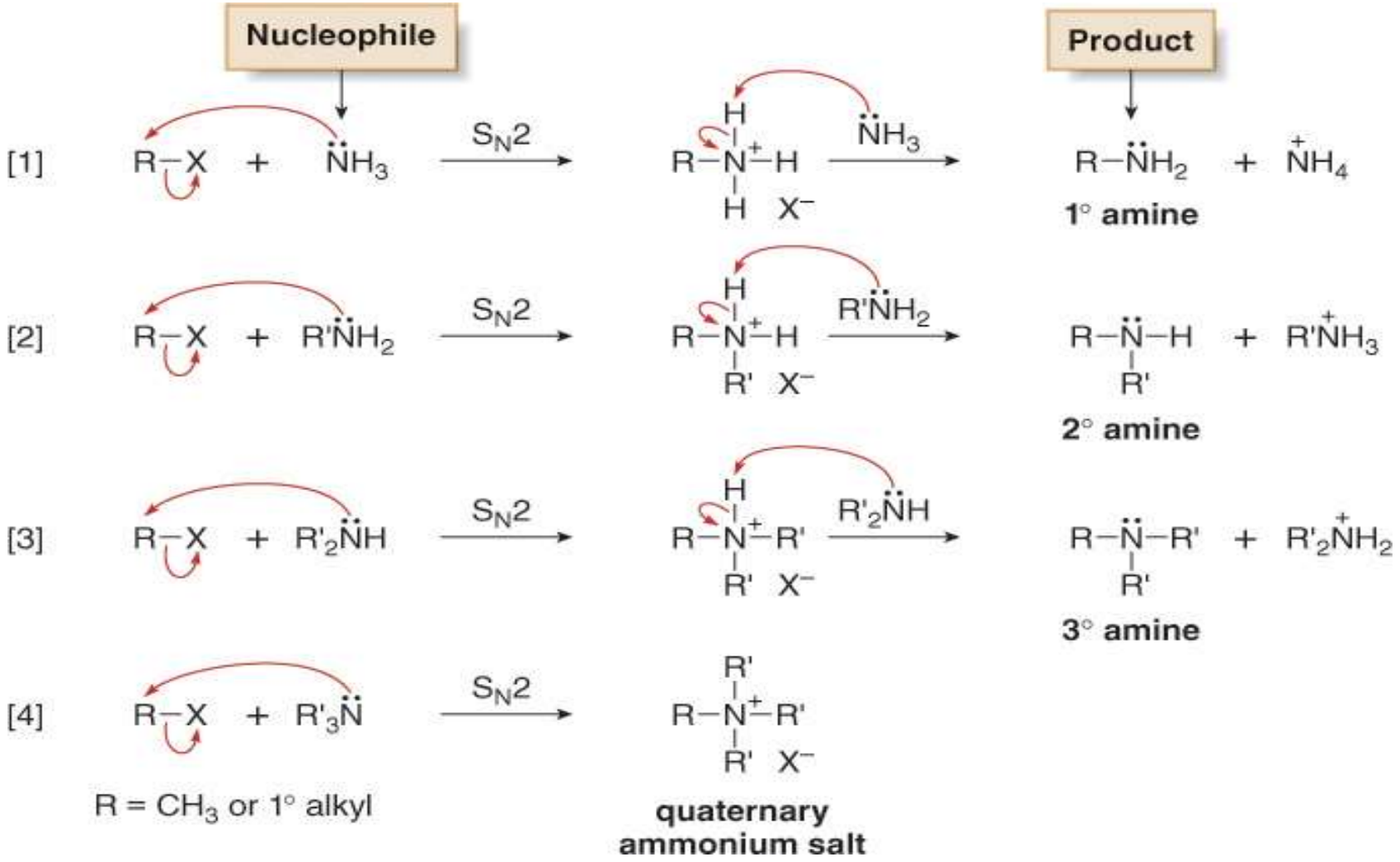
Preparation and important reactions of nitro and compounds, nitriles and isonitriles Amines: Effect of substituent and solvent on basicity; Preparation and properties: Gabriel phthalimide synthesis, Carbylamine reaction, Mannich reaction, Hoffmann's exhaustive methylation, Hofmann-elimination reaction; Distinction between 1°, 2° and 3° amines with Hinsberg reagent and nitrous acid.

Coverage:

1. Amines: Preparation of Amines

Amines

Preparation of Amines—Direct Nucleophilic Substitution

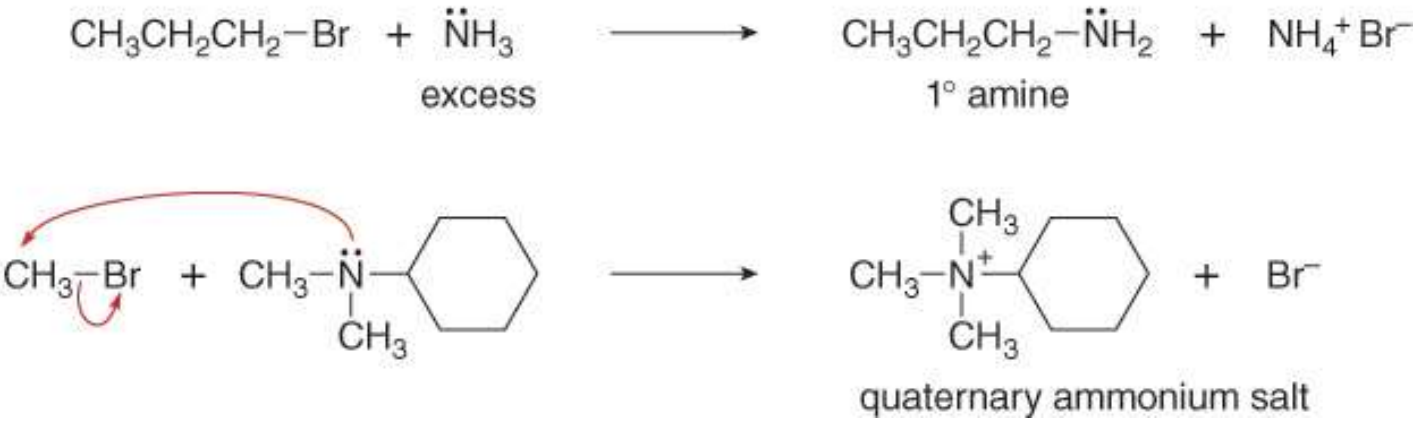


Amines

Preparation of Amines—Direct Nucleophilic Substitution

- **Although the process seems straightforward, polyalkylation of the nitrogen nucleophile limits its usefulness.**
- **Any amine formed by nucleophilic substitution still has a nonbonded electron pair, making it a nucleophile as well. It will react with remaining alkyl halide to form a more substituted amine, resulting in a mixture of 1^0, 2^0, and 3^0 amine products.**
- **Consequently, the reaction is most useful in preparing 1^0 amines by using a large excess of NH_3, and for preparing quaternary ammonium salts by alkylating any nitrogen nucleophile with one or more equivalents of alkyl halide.**

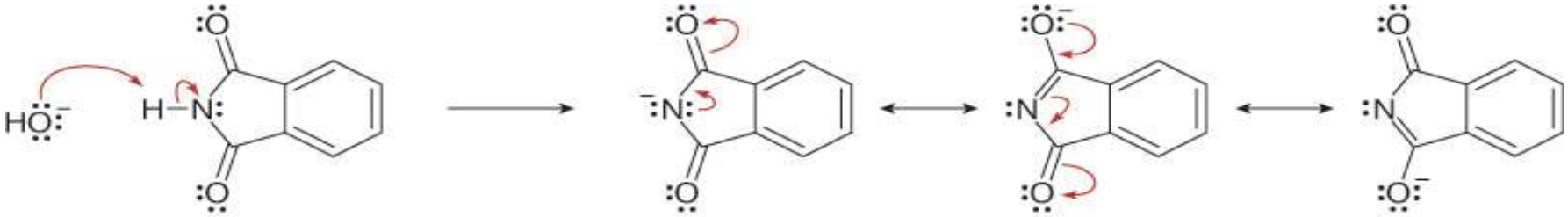
Useful S_N2 substitutions



Amines

Preparation of Amines—Gabriel Synthesis of 1^0 Amines

- **The Gabriel synthesis consists of two steps and uses a nucleophile derived from pthalimide to synthesize 1^0 amines via nucleophilic substitution.**
- **The N—H bond of a pthalimide is especially acidic because the resulting anion is resonance stabilized by the two flanking carbonyl groups.**



phthalimide
$pK_a = 10$

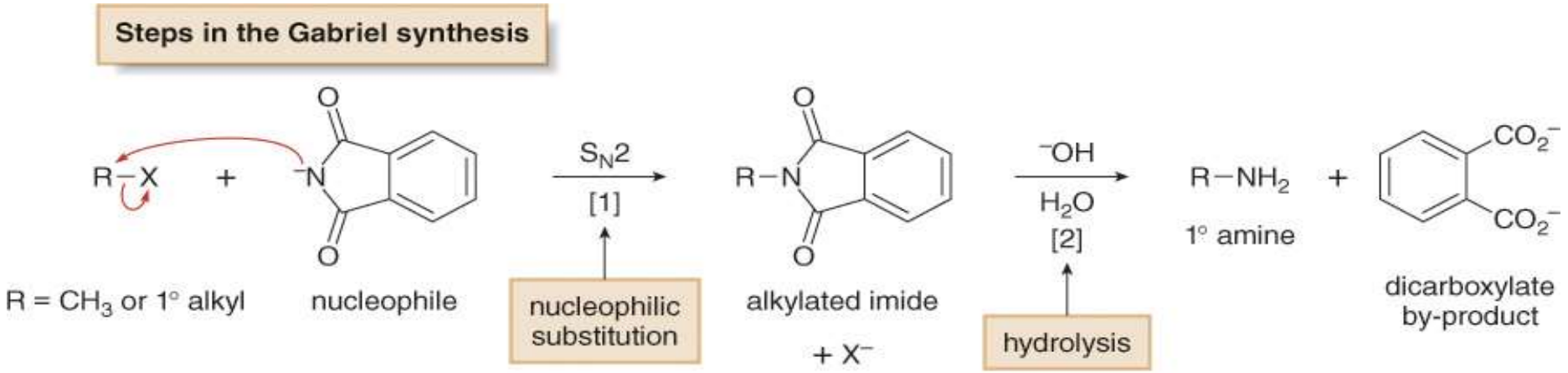
resonance-stabilized anion

- **An acid-base reaction forms a nucleophilic anion that can react with an unhindered alkyl halide in an S_N2 reaction to form a substituted product.**

Amines

Preparation of Amines—Gabriel Synthesis of 1^0 Amines

- **The alkylated imide is then hydrolyzed with aqueous base to give a 1^0 amine and a dicarboxylate.**



◆ The Gabriel synthesis converts an alkyl halide into a 1° amine by a two-step process: nucleophilic substitution followed by hydrolysis.

Amines

Preparation of Amines—Reduction of N-Containing Functional Groups

- **Recall that amines can be prepared by reduction of nitro compounds, nitriles and amides.**

[1] From nitro compounds (Section 18.14C)

Nitro groups are reduced to 1° amines using a variety of reducing agents.

$$R-NO_2 \xrightarrow[\text{or}\ \ Fe,\ HCl\ \ \text{or}\ \ Sn,\ HCl]{H_2,\ Pd\text{-}C} \underset{1^\circ\ \text{amine}}{R-NH_2}$$

[2] From nitriles (Section 22.18B)

Nitriles are reduced to 1° amines with $LiAlH_4$.

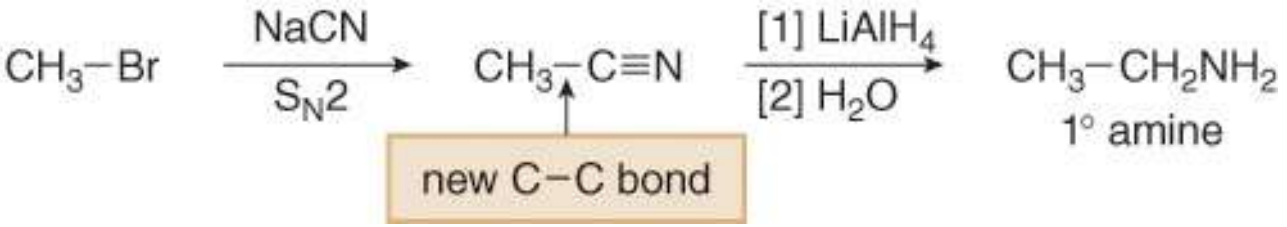
$$R-C\equiv N \xrightarrow[[2]\ H_2O]{[1]\ LiAlH_4} \underset{1^\circ\ \text{amine}}{R-CH_2NH_2}$$

Amines

Preparation of Amines—Reduction of N-Containing Functional Groups

- **Because the cyano group is readily introduced by S_N2 substitution of alkyl halides with ^-CN, this provides a two-step method to convert an alkyl halide to a 1^0 amine with one more carbon atom.**

Example

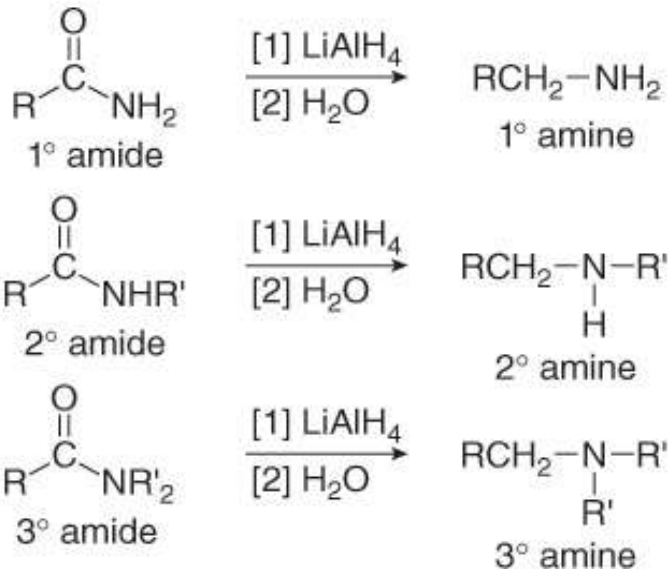


Amines

Preparation of Amines—Reduction of N-Containing Functional Groups

[3] From amides (Section 20.7B)

1°, 2°, and 3° amides are reduced to 1°, 2°, and 3° amines, respectively, by using $LiAlH_4$.



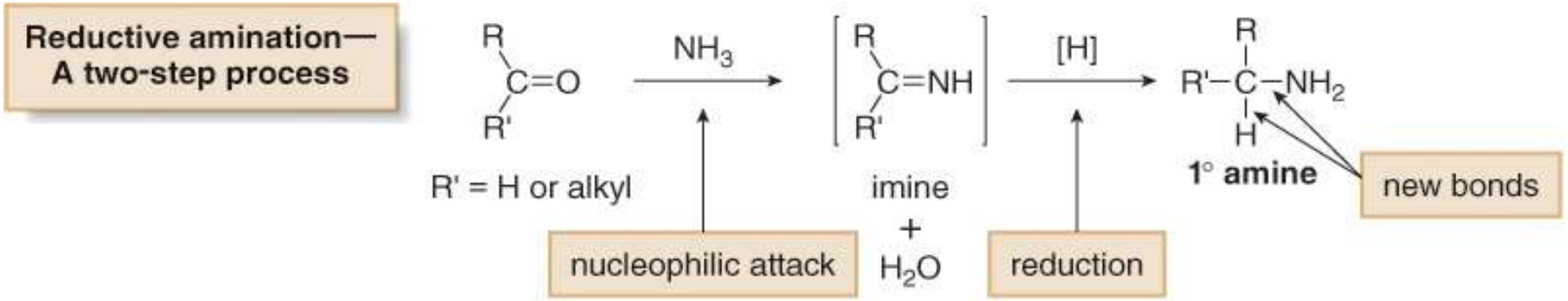
Amines

Preparation of Amines—Reductive Amination

- **Reductive amination is a two-step method that converts aldehydes and ketones into 1^0, 2^0, and 3^0 amines.**
- **Consider the reductive amination of an aldehyde or ketone using NH_3. There are two distinct parts to this reaction.**

[1] **Nucleophilic attack of NH_3 on the carbonyl group forms an imine.**

[2] **Reduction of the imine forms an amine.**

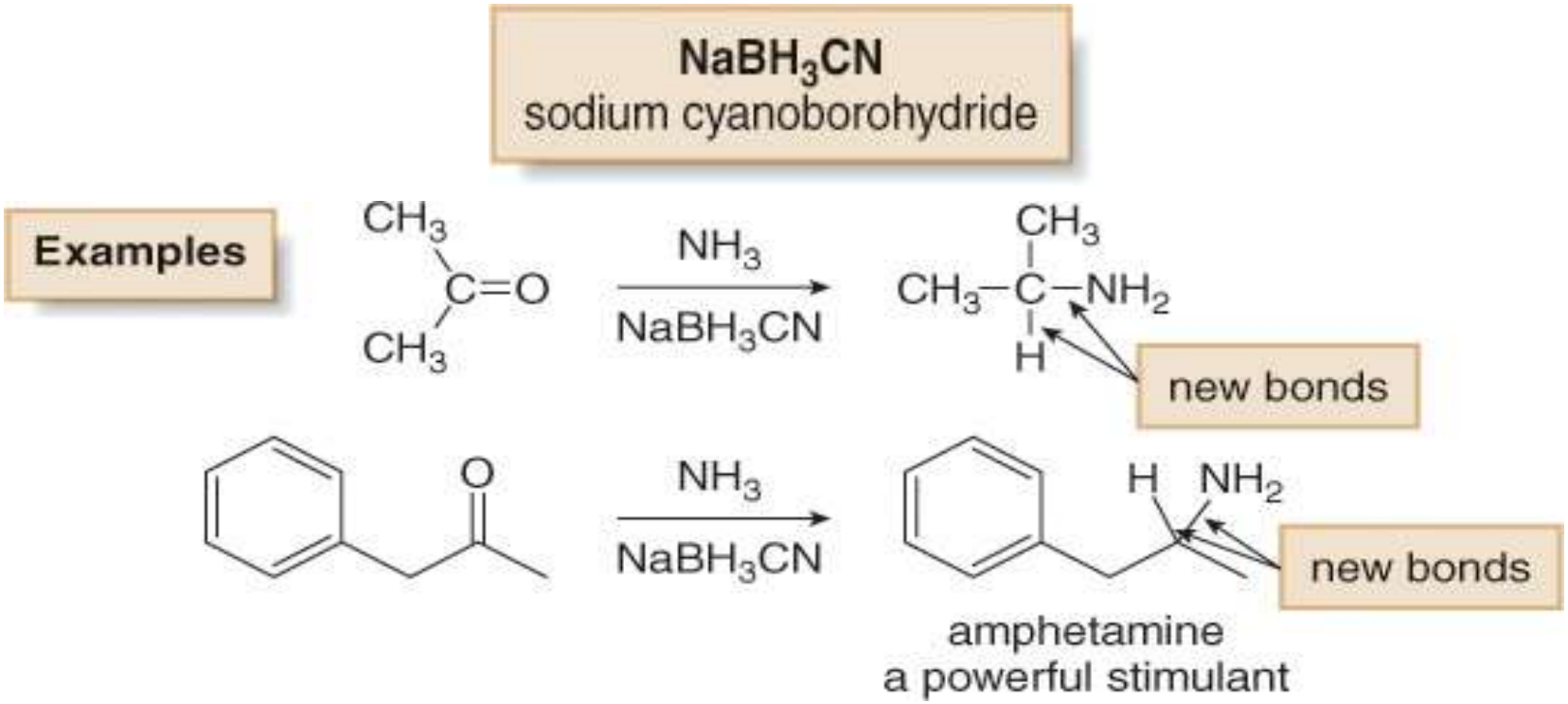


- Reductive amination replaces a C=O by a C–H and C–N bond.

Amines

Preparation of Amines—Reductive Amination

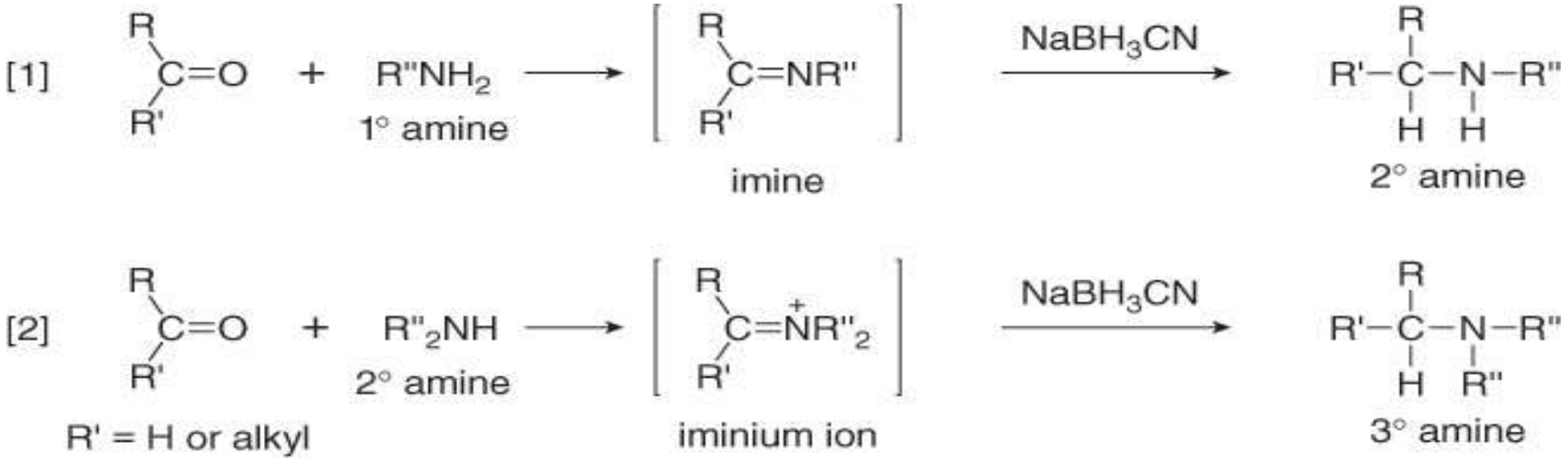
- **The most effective reducing agent for this reaction is sodium cyanoborohydride ($NaBH_3CN$).**



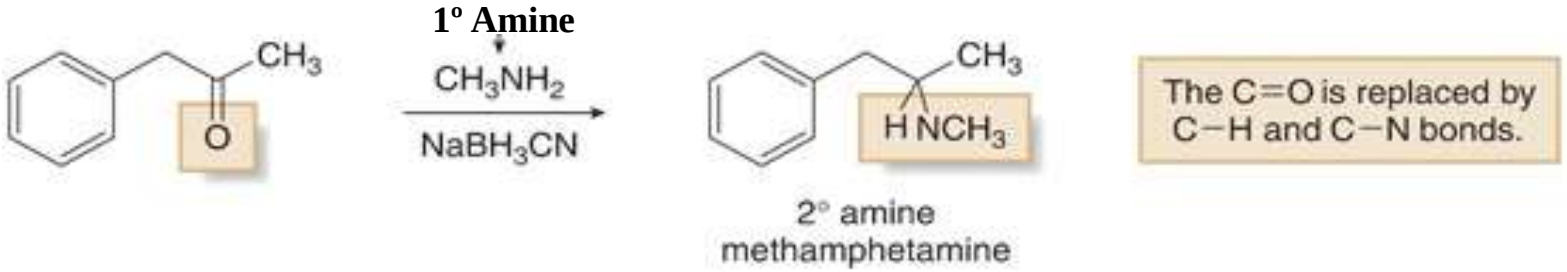
Amines

Preparation of Amines—Reductive Amination

- **With a 1^0 or 2^0 amine as starting material, reductive amination is used to prepare 2^0 and 3^0 amines respectively.**



- **Synthesis of methamphetamine by reductive amination**

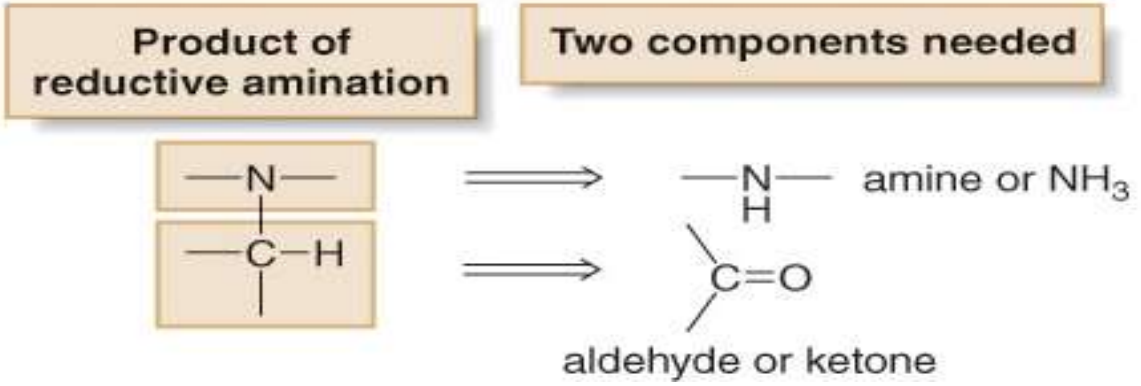


Amines

Preparation of Amines—Reductive Amination

- **To use reductive amination in synthesis, you must be able to determine what aldehyde or ketone and nitrogen compound are needed to prepare a given amine—that is, you must work backwards in the retrosynthetic direction. Keep in mind the following two points:**

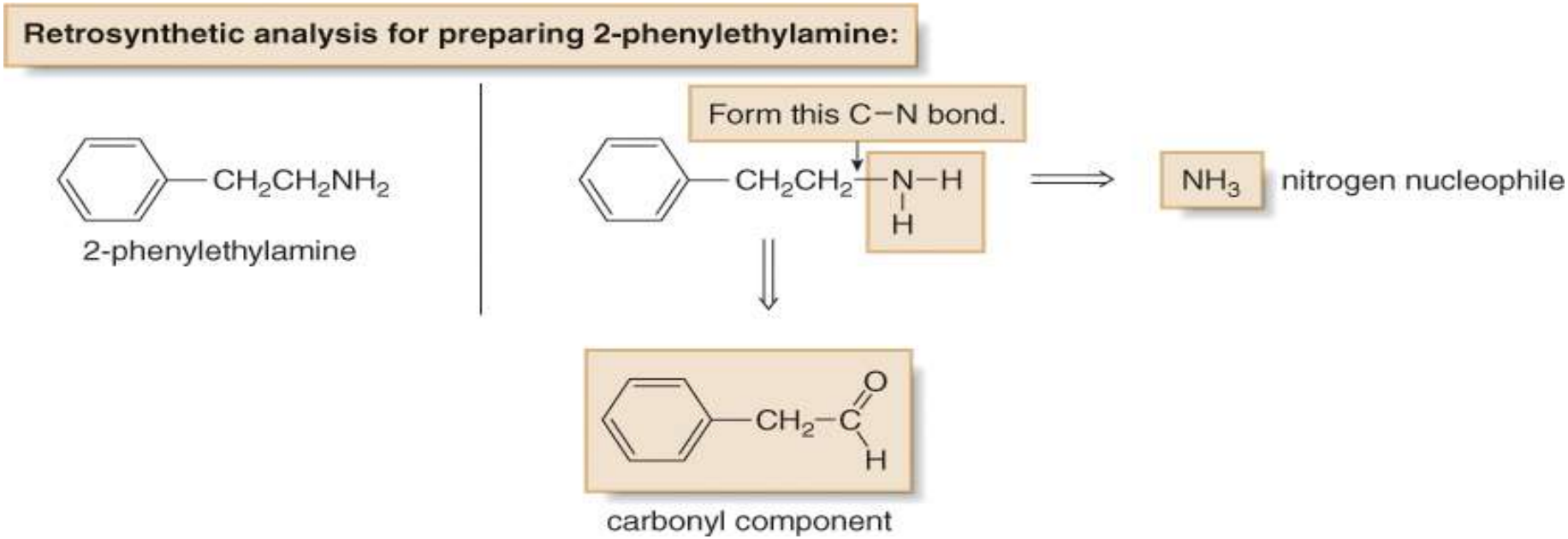
- One alkyl group on N comes from the carbonyl compound.
- The remainder of the molecule comes from NH_3 or an amine.



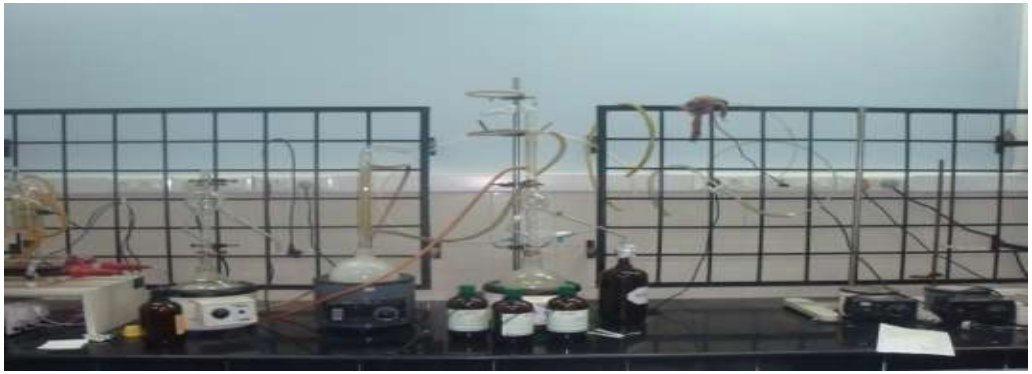
Amines

Preparation of Amines—Reductive Amination

- **For a 1^0 amine, the nitrogen component must be NH_3.**



Thank You



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