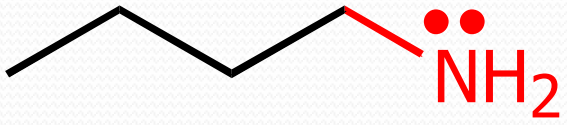
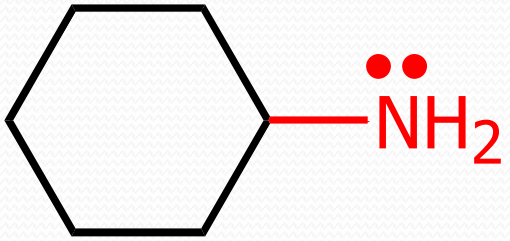
Amines

1. Nomenclature

- 1° Amines

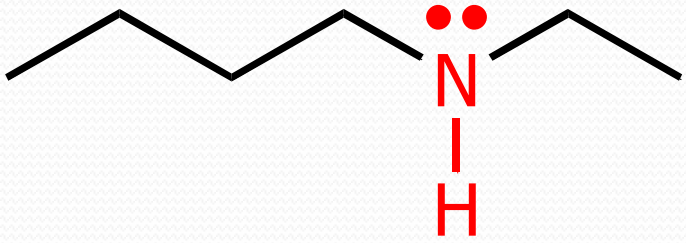


Butylamine

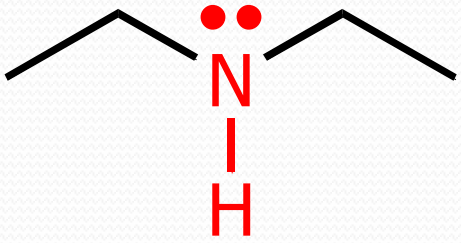


Cyclohexylamine

- 2° Amines

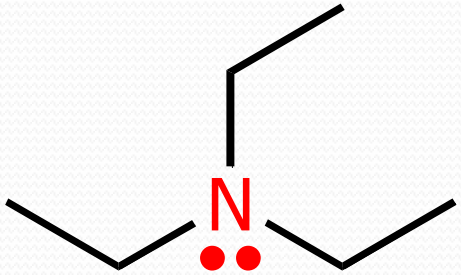


Butylethylamine

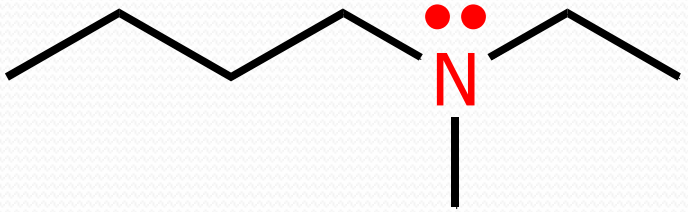


Diethylamine

- 3º Amines

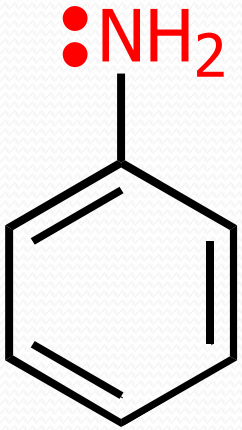


Triethylamine

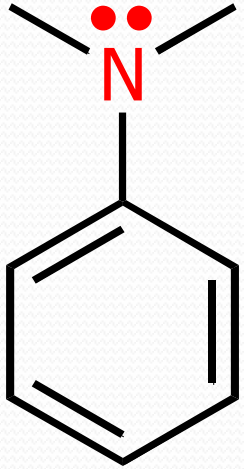


Butylethylmethylamine

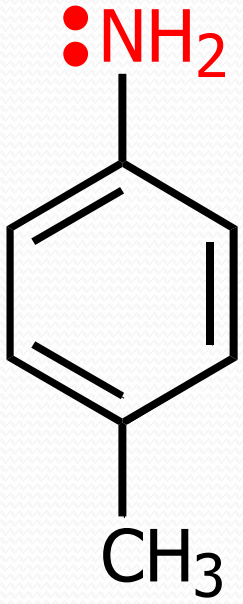
1A. Arylamines



Aniline

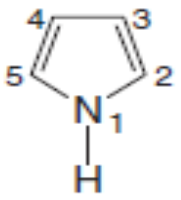


N,N-Dimethylaniline

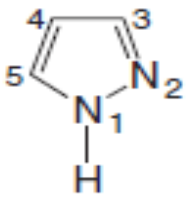


p-Toluidine
(4-Methylbenzeneamine)

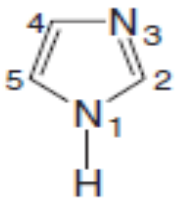
1B. Heterocyclic Amines



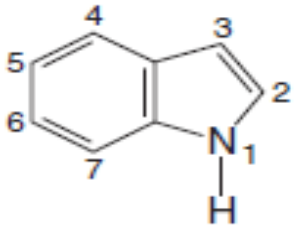
Pyrrole
(1-azacyclopenta-2,4-diene)



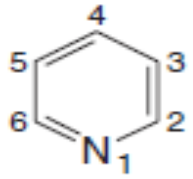
Pyrazole
(1,2-diazacyclopenta-2,4-diene)



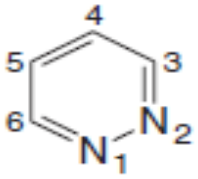
Imidazole
(1,3-diazacyclopenta-2,4-diene)



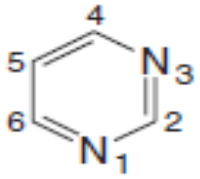
Indole
(1-azaindene)



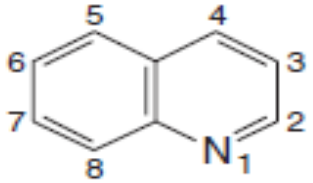
Pyridine
(azabenzene)



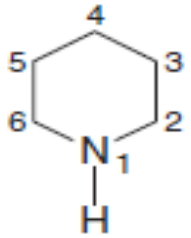
Pyridazine
(1,2-diazabenzene)



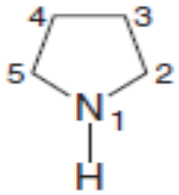
Pyrimidine
(1,3-diazabenzene)



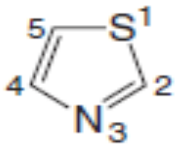
Quinoline
(1-azanaphthalene)



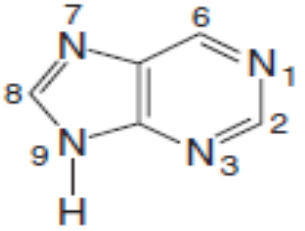
Piperidine
(azacyclohexane)



Pyrrolidine
(azacyclopentane)



Thiazole
(1-thia-3-azacyclopenta-2,4-diene)



Purine

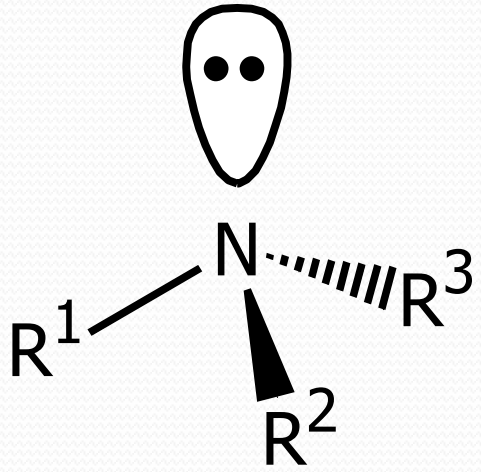
2. Physical Properties and Structure of Amines

2A. Physical Properties

TABLE 20.1 Physical Properties of Amines

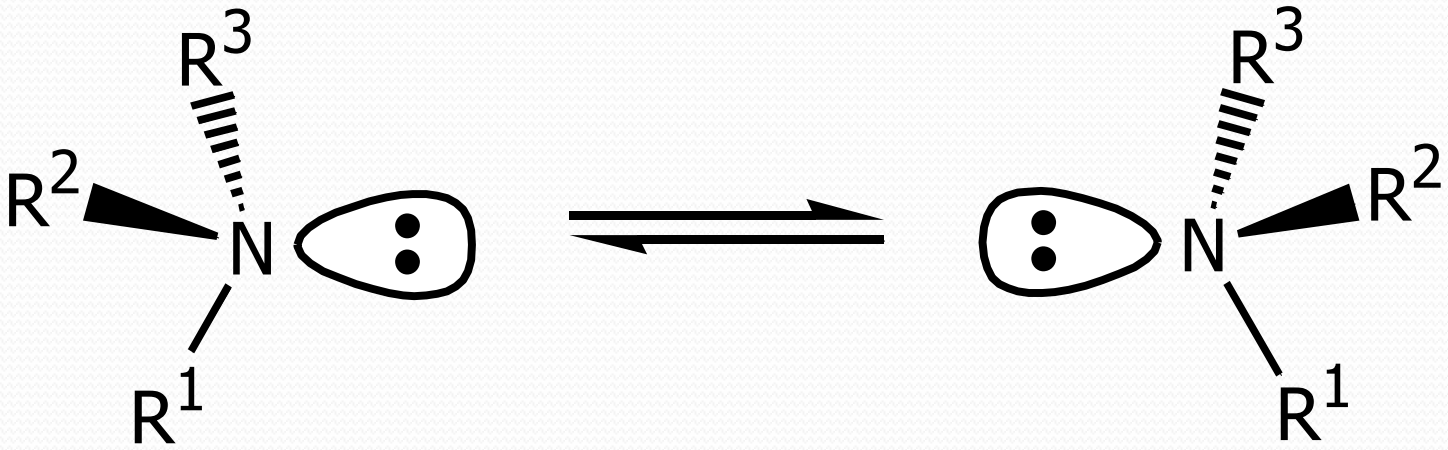
Name	Structure	mp (°C)	bp (°C)	Water Solubility (25°C) (g 100 mL^{-1})	pK_a (aminium ion)
Primary Amines					
Methylamine	CH_3NH_2	−94	−6	Very soluble	10.64
Ethylamine	$CH_3CH_2NH_2$	−81	17	Very soluble	10.75
Isopropylamine	$(CH_3)_2CHNH_2$	−101	33	Very soluble	10.73
Cyclohexylamine	Cyclo-$C_6H_{11}NH_2$	−18	134	Slightly soluble	10.64
Benzylamine	$C_6H_5CH_2NH_2$	10	185	Slightly soluble	9.30
Aniline	$C_6H_5NH_2$	−6	184	3.7	4.58
4-Methylaniline	4-$CH_3C_6H_4NH_2$	44	200	Slightly soluble	5.08
4-Nitroaniline	4-$NO_2C_6H_4NH_2$	148	332	Insoluble	1.00
Secondary Amines					
Dimethylamine	$(CH_3)_2NH$	−92	7	Very soluble	10.72
Diethylamine	$(CH_3CH_2)_2NH$	−48	56	Very soluble	10.98
Diphenylamine	$(C_6H_5)_2NH$	53	302	Insoluble	0.80
Tertiary Amines					
Trimethylamine	$(CH_3)_3N$	−117	2.9	Very soluble	9.70
Triethylamine	$(CH_3CH_2)_3N$	−115	90	14	10.76
N,N-Dimethylaniline	$C_6H_5N(CH_3)_2$	3	194	Slightly soluble	5.06

2B. Structure of Amines



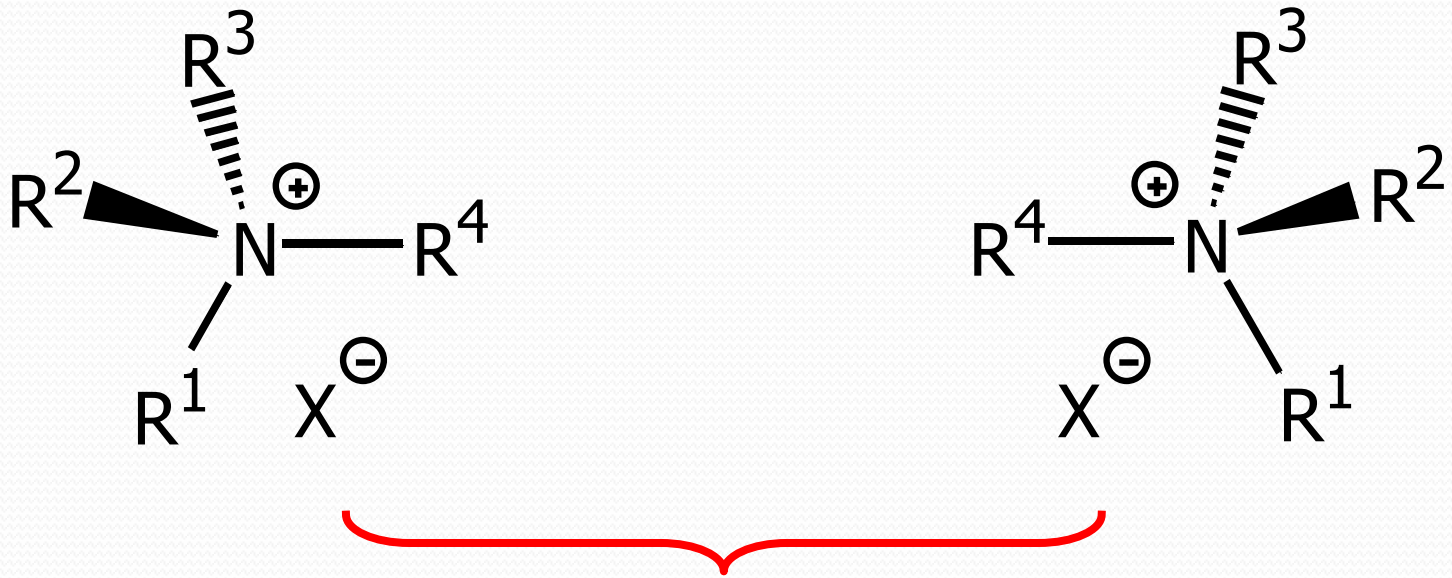
- N: sp^3 hybridized
- Trigonal pyramidal
- Bond angles close to 109.5^o

3° Amines with three different groups



- The two enantiomeric forms interconvert rapidly
  - Impossible to resolve enantiomers
- Pyramidal or nitrogen inversion
  - Barrier ~ 25 kJ/mol
  - Enough to occur rapidly at room temperature

Ammonium salts with four different groups



enantiomers
can be resolved

3. Basicity of Amines: Amine Salts

$$RNH_3^+ + H_2O \rightleftharpoons RNH_2 + H_3O^+$$

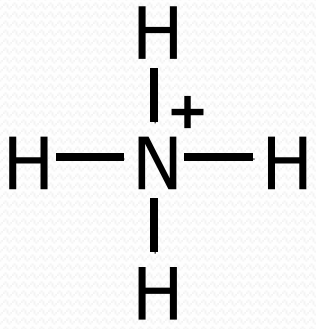
$$K_a = \frac{[RNH_2][H_3O^+]}{[RNH_3^+]}$$

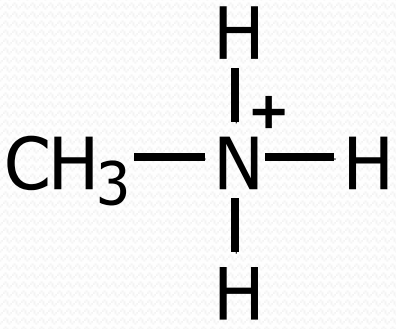
$$pK_a = -\log K_a$$

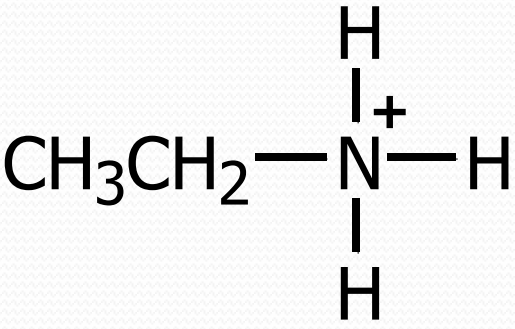
The equilibrium for an amine that is relatively more basic will lie more toward the left in the above chemical equation than for an amine that is less basic.

- The aminium ion of a more basic amine will have a larger pK_a than the aminium ion of a less basic amine.

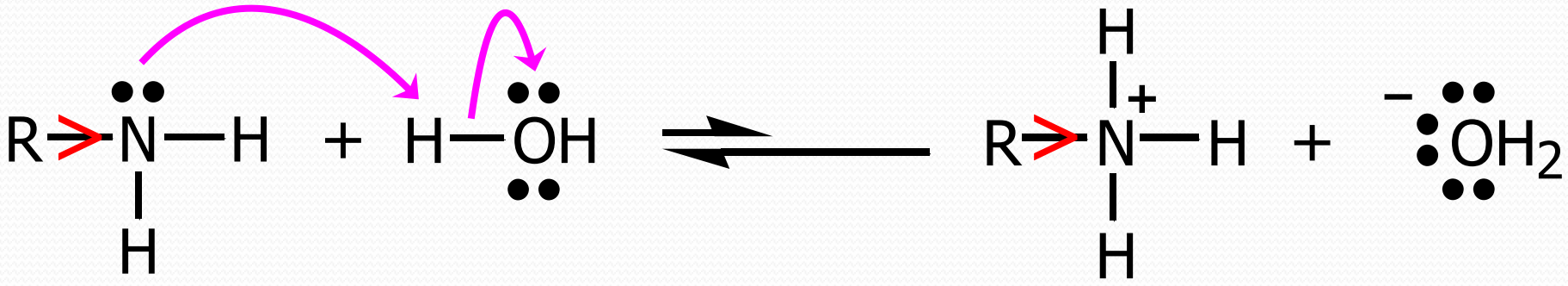
- The aminium ion of a more basic amine will have a larger pK_a than the aminium ion of a less basic amine







Aminium ion pK_a	9.26	10.64	10.75



By releasing electrons, R→ stabilizes the alkylaminium ion through dispersal of charge

This explanation is supported by measurements showing that in the *gas phase* the basicities of the following amines increase with increasing methyl substitution:

$(CH_3)_3N$ > $(CH_3)_2NH$ > CH_3NH_2 > NH_3

3^o 2^o 1^o

Gas phase

This is not the order of basicity of these amines in aqueous solution, however. In aqueous solution the order is

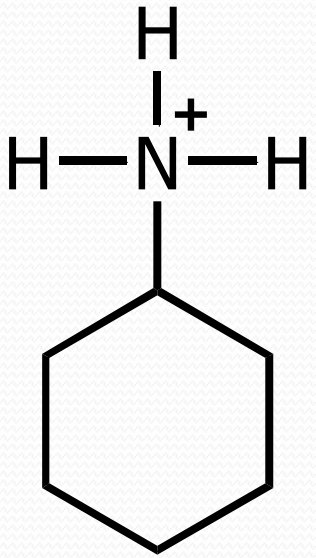
$(CH_3)_2NH$ > CH_3NH_2 > $(CH_3)_3N$ > NH_3

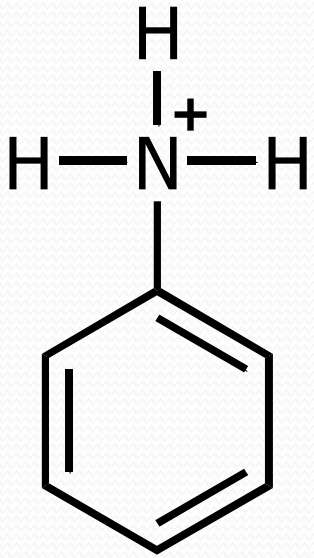
2^o 1^o 3^o

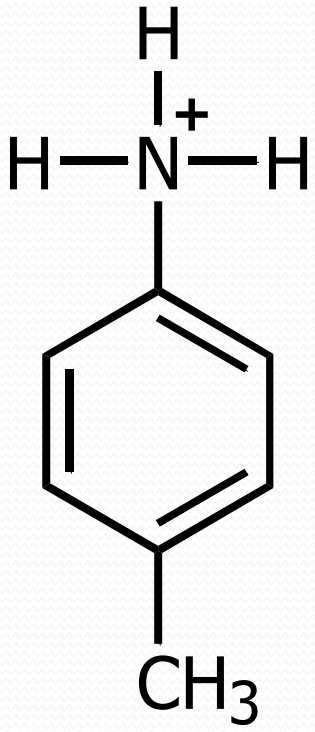
Aqueous solution

The reason for this apparent anomaly is now known. In aqueous solution the aminium ions formed from secondary and primary amines are stabilized by solvation through hydrogen bonding much more effectively than are the aminium ions formed from tertiary amines. The aminium ion formed from a tertiary amine such as $(CH_3)_3NH^+$ has only one hydrogen to use in hydrogen bonding to water molecules, whereas the aminium ions from secondary and primary amines have two and three hydrogens, respectively. Poorer solvation of the aminium ion formed from a tertiary amine more than counteracts the electron-releasing effect of the three methyl groups and makes the tertiary amine less basic than primary and secondary amines in aqueous solution. The electron-releasing effect does, however, make the tertiary amine more basic than ammonia.

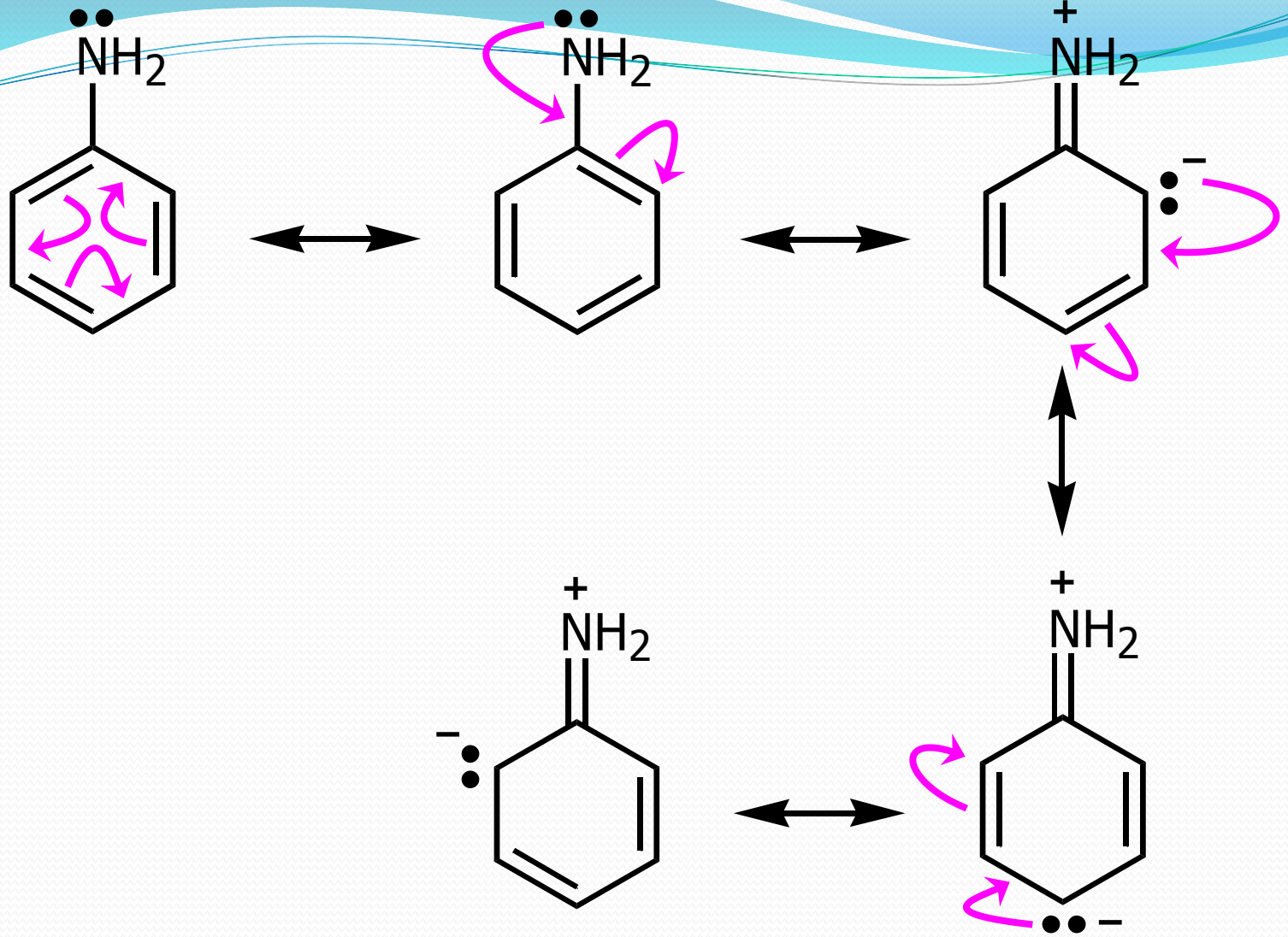
3A. Basicity of Arylamines



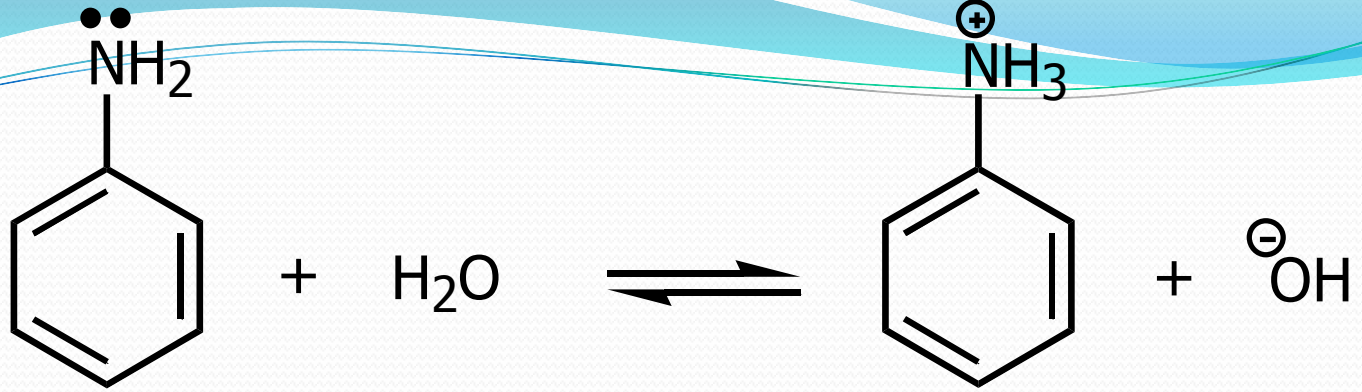




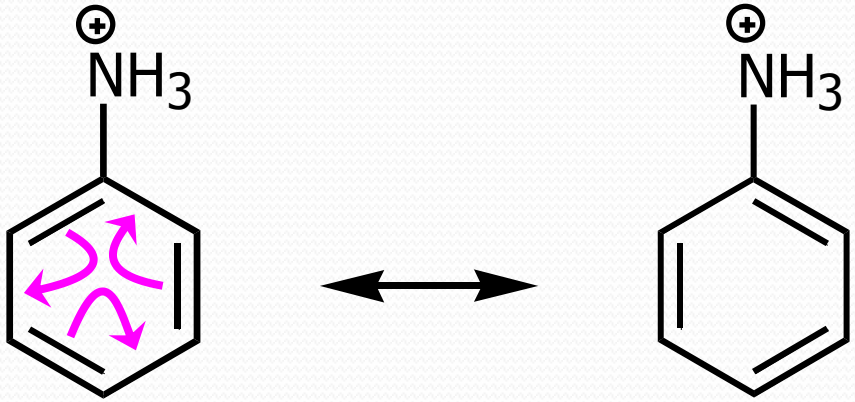
Aminium ion pK_a	10.64	4.58	5.08



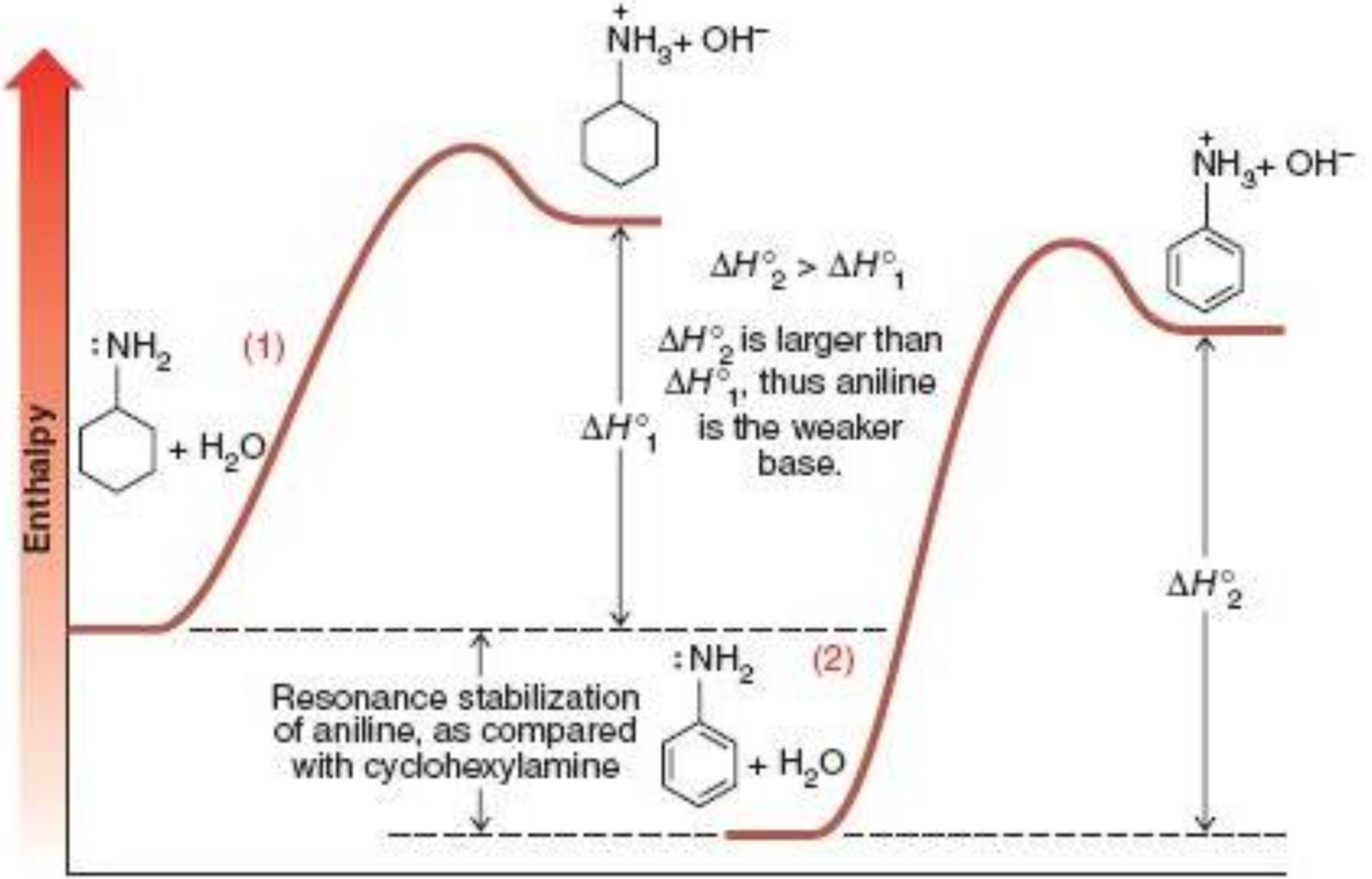
- Five resonance structures



Anilinium ion

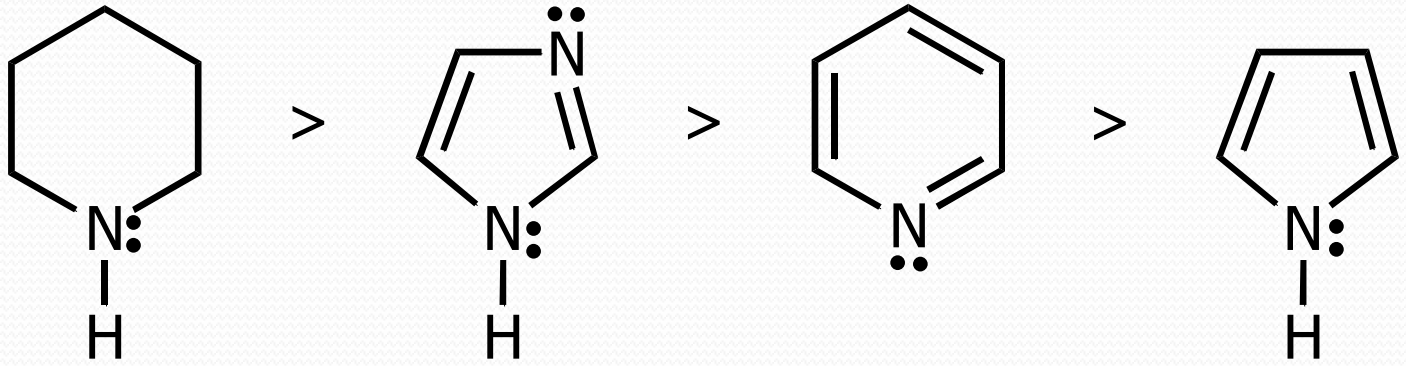


- Only two resonance structures


Enthalpy
$\overset{+}{N}H_3 + OH^-$
$\overset{+}{N}H_3 + OH^-$
$\Delta H^\circ_2 > \Delta H^\circ_1$
ΔH°_2 is larger than ΔH°_1, thus aniline is the weaker base.
:NH_2
(1)
+ H_2O
ΔH°_1
ΔH°_2
Resonance stabilization of aniline, as compared with cyclohexylamine
:NH_2
(2)
+ H_2O

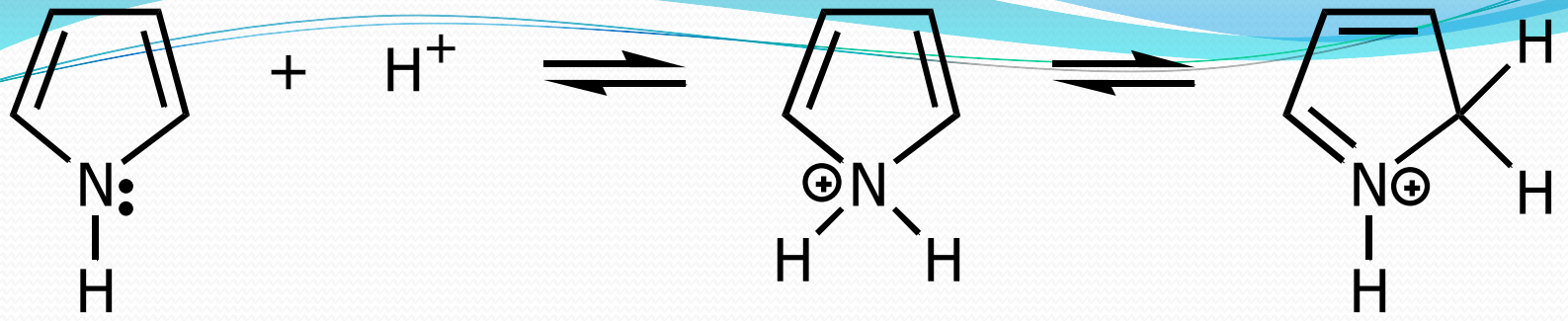
3B. Basicity of Heterocyclic Amines

Order of Basicity:

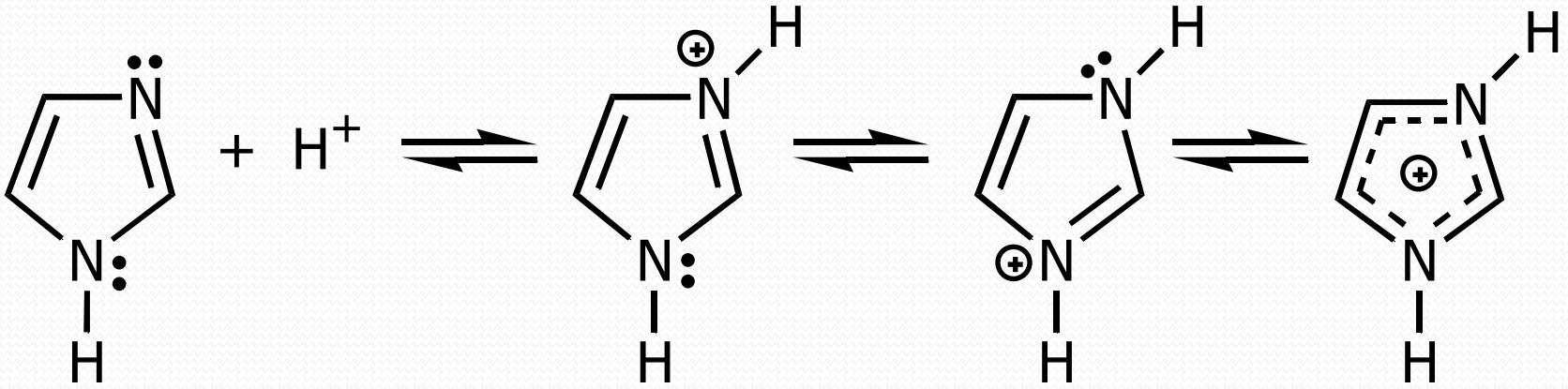


pK_a of the conjugate acid: 11.2 7 5.2 0.4

(c.f. Et_3N, pK_a of the conjugate acid = 9.7)

- 

(lost of aromaticity)

- 

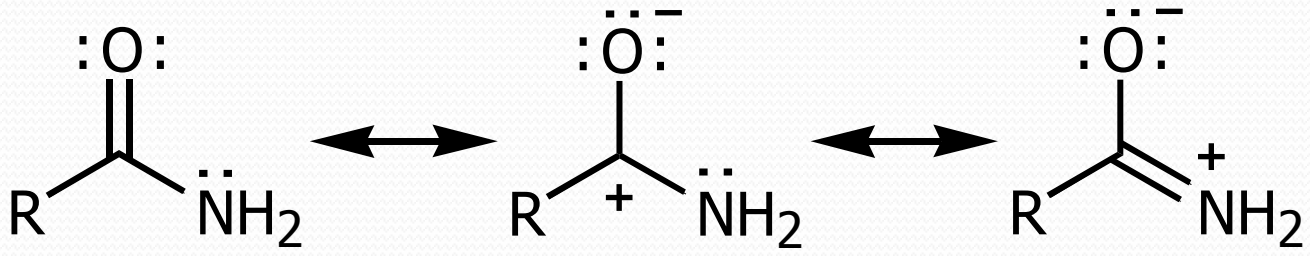
Imidazole
(a very common base in organic synthesis)

(still aromatic)

3C. Amines versus Amides

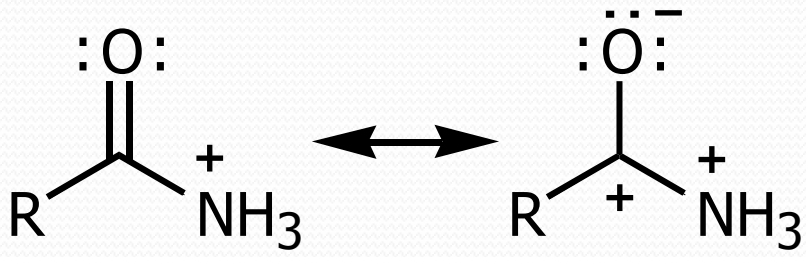
- Amides are far less basic than amines (even less basic than arylamines). The pK_a of the conjugate acid of a typical amide is about zero

Amide

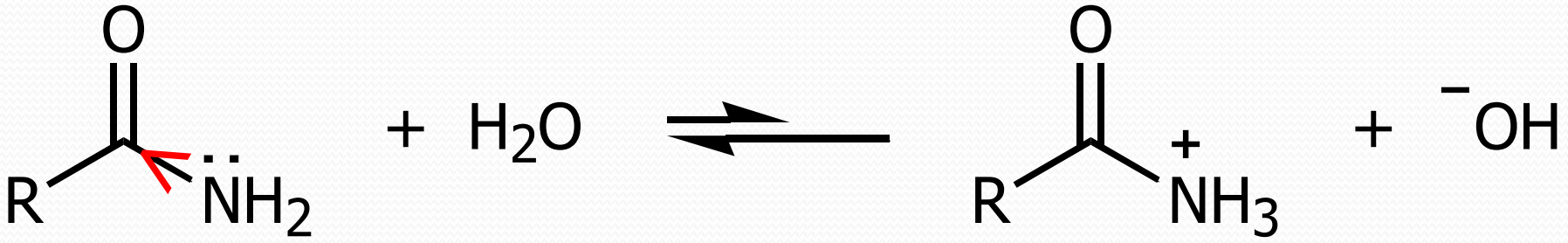


Larger resonance stabilization

N-Protonated Amide

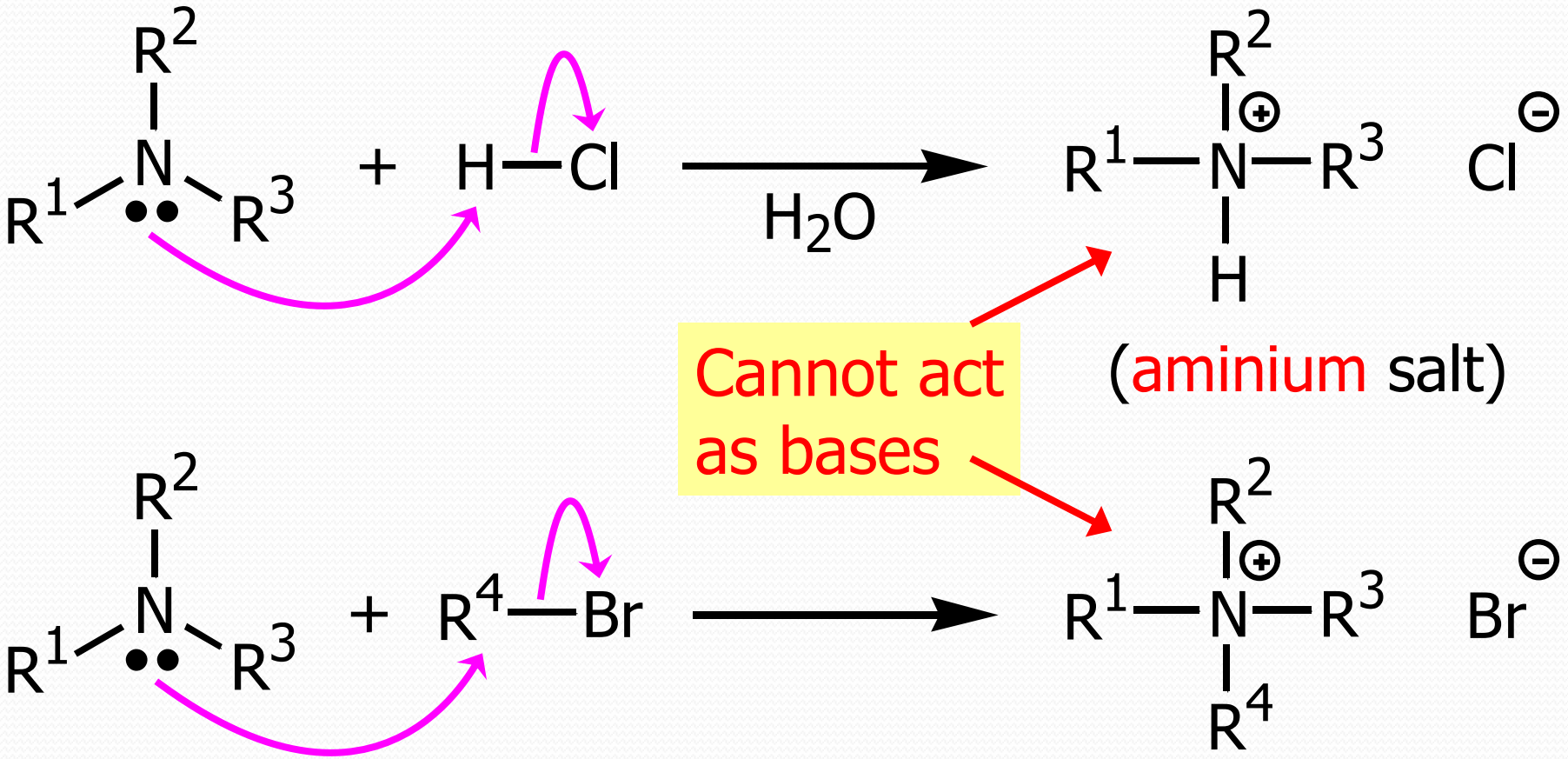


Smaller resonance stabilization


O
R
NH2
+ H2O
O
R
+
NH3
+ −OH


R
NH2
+ H2O
+
R
NH3
+ −OH

3D. Aminium Salts and Quaternary Ammonium Salts

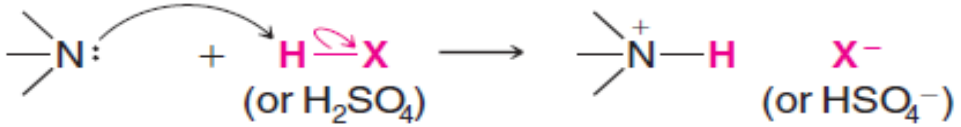


However, $R_4N^{\oplus}\ ^{\ominus}OH$ are strong bases (as strong as NaOH)

3E. Solubility of Amines in Aqueous Acids

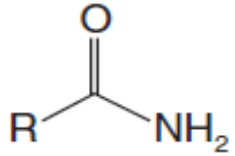
- Almost all alkylaminium chloride, bromide, iodide, and sulfate salts are soluble in water. Thus, primary, secondary, or tertiary amines that are not soluble in water will dissolve in dilute aqueous HCl, HBr, HI, and H_2SO_4.

Solubility in dilute acid provides a convenient chemical method for distinguishing amines from nonbasic compounds that are insoluble in water. Solubility in dilute acid also gives us a useful method for separating amines from nonbasic compounds that are insoluble in water. The amine can be extracted into aqueous acid (dilute HCl) and then recovered by making the aqueous solution basic and extracting the amine into ether or CH_2Cl_2.



Water-insoluble amine → **Water-soluble aminium salt**

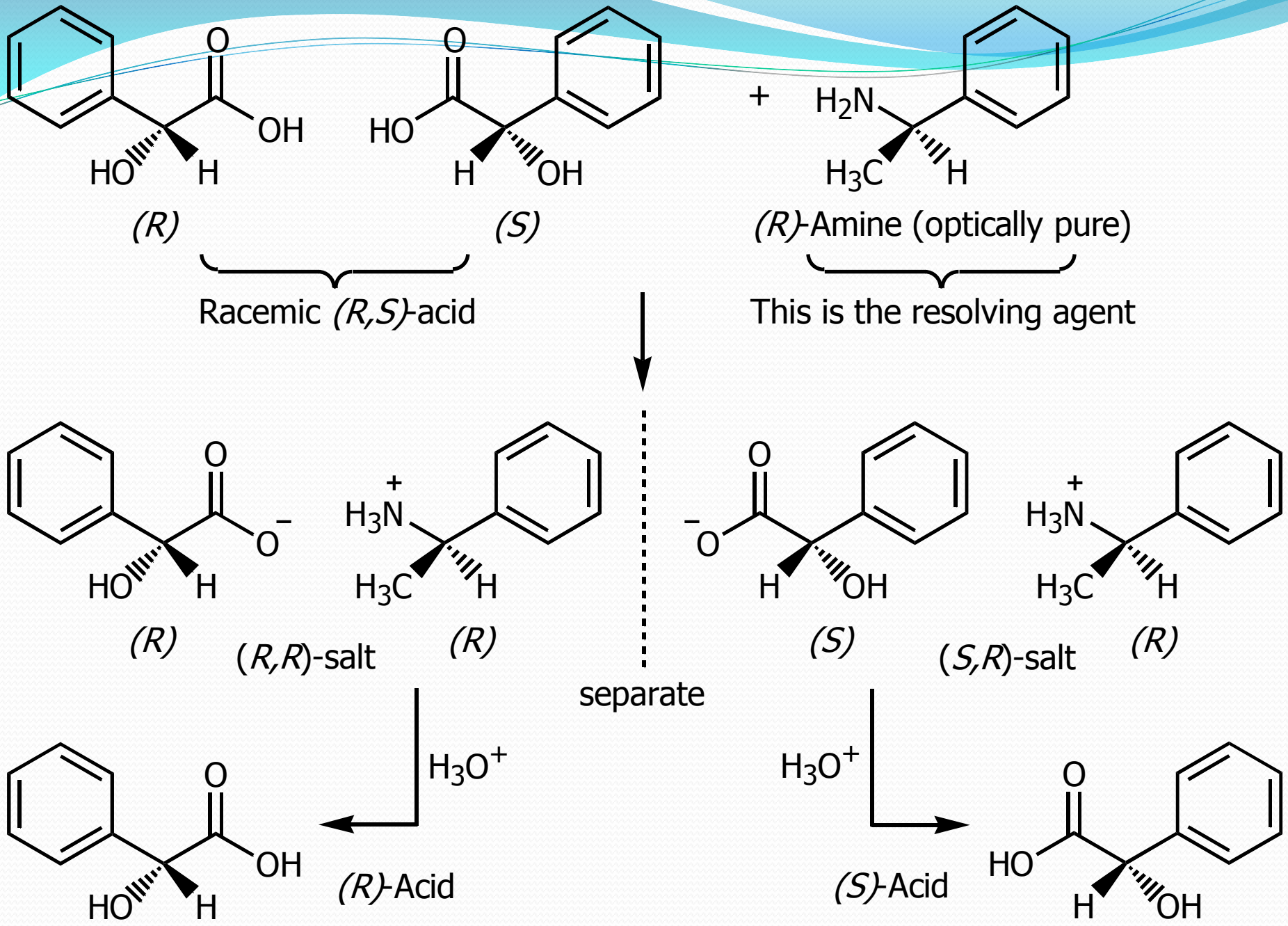
Because amides are far less basic than amines, water-insoluble amides *do not dissolve* in dilute aqueous HCl, HBr, HI, or H_2SO_4:



Water-insoluble amide (not soluble in aqueous acids)

3F. Amines as Resolving Agents

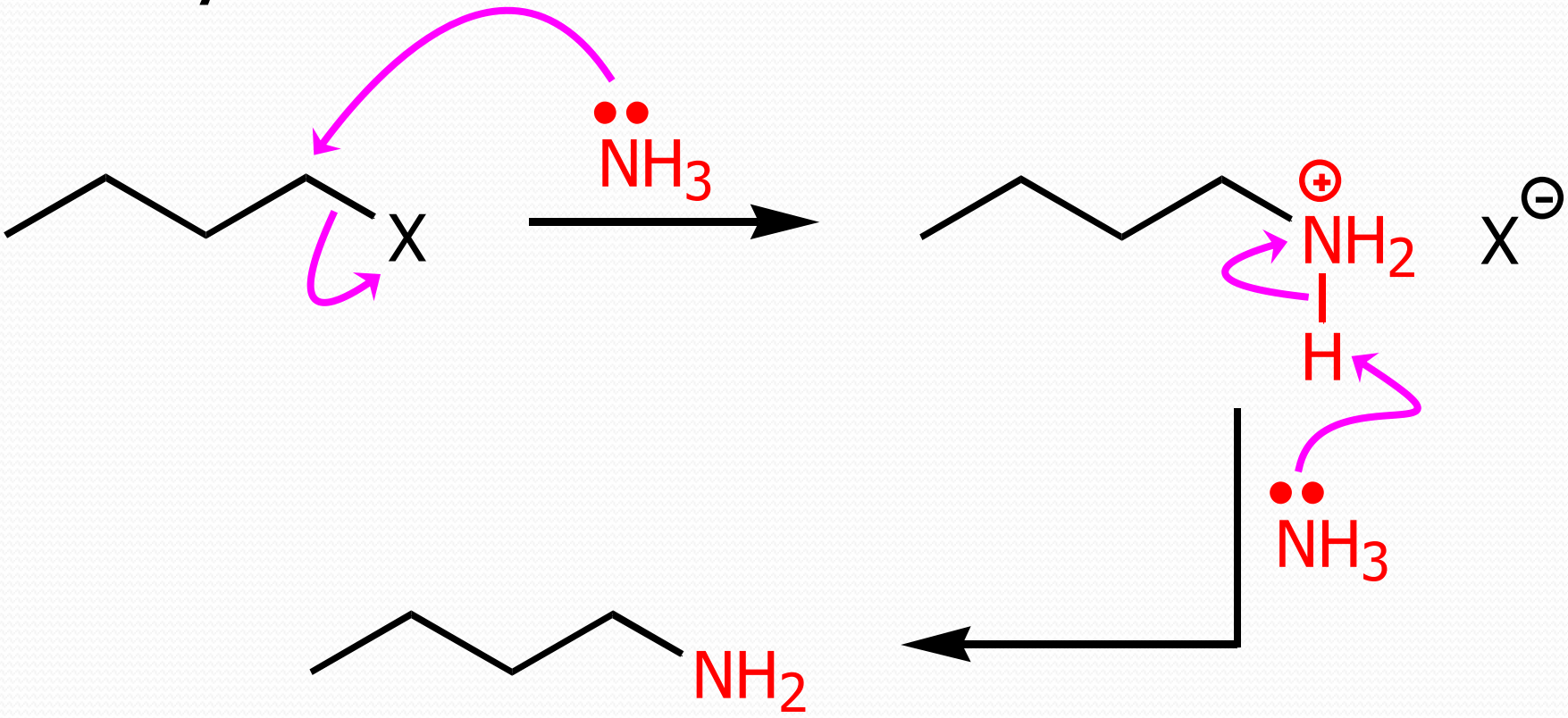
- Enantiomerically pure amines are often used to resolve racemic forms of acidic compounds by the formation of diastereomeric salts

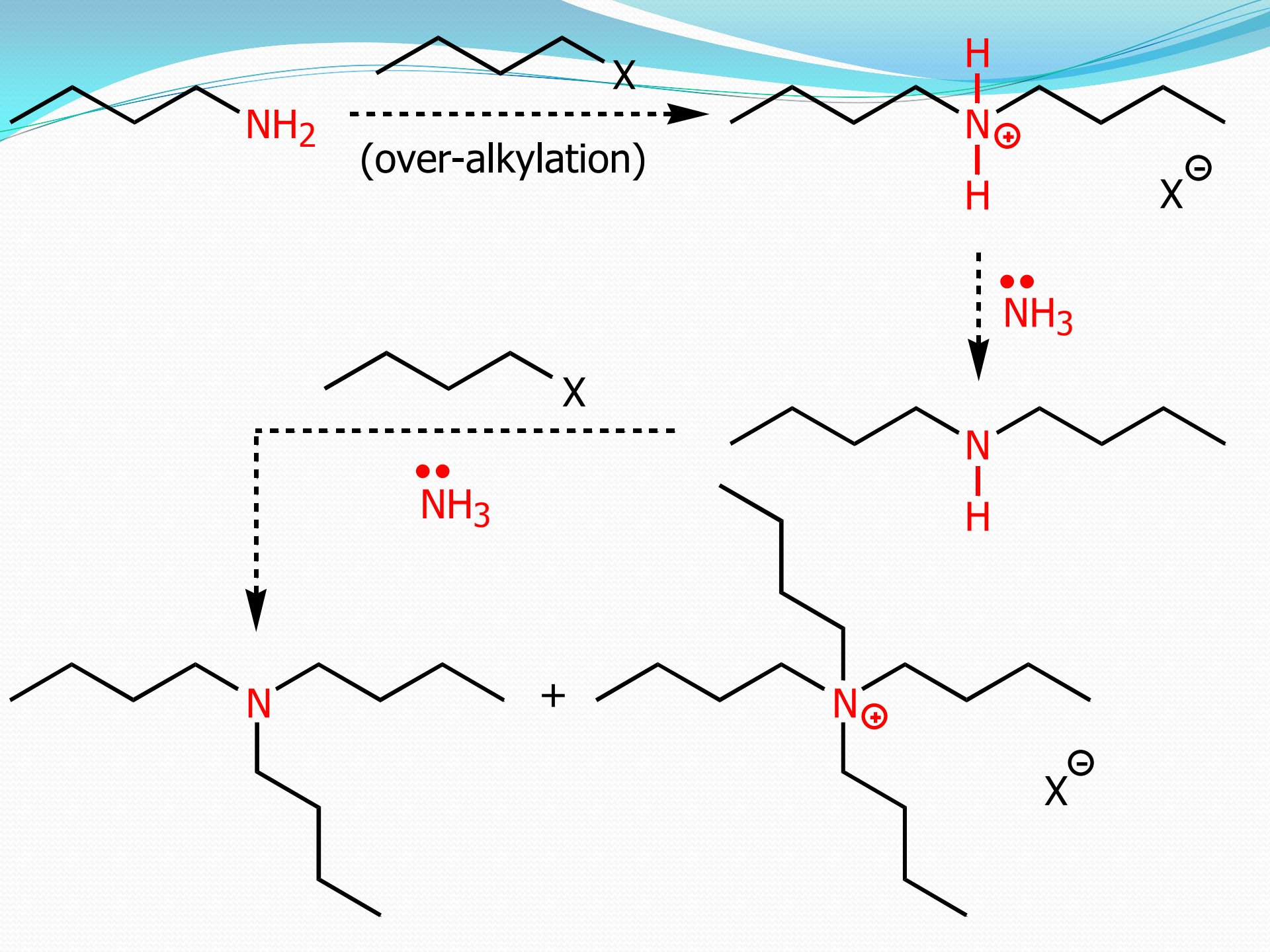

(R)
(S)
(R)-Amine (optically pure)
Racemic (R,S)-acid
This is the resolving agent
(R)
(R,R)-salt
(R)
separate
(S)
(S,R)-salt
(R)
H3O+
H3O+
(R)-Acid
(S)-Acid

4. Preparation of Amines

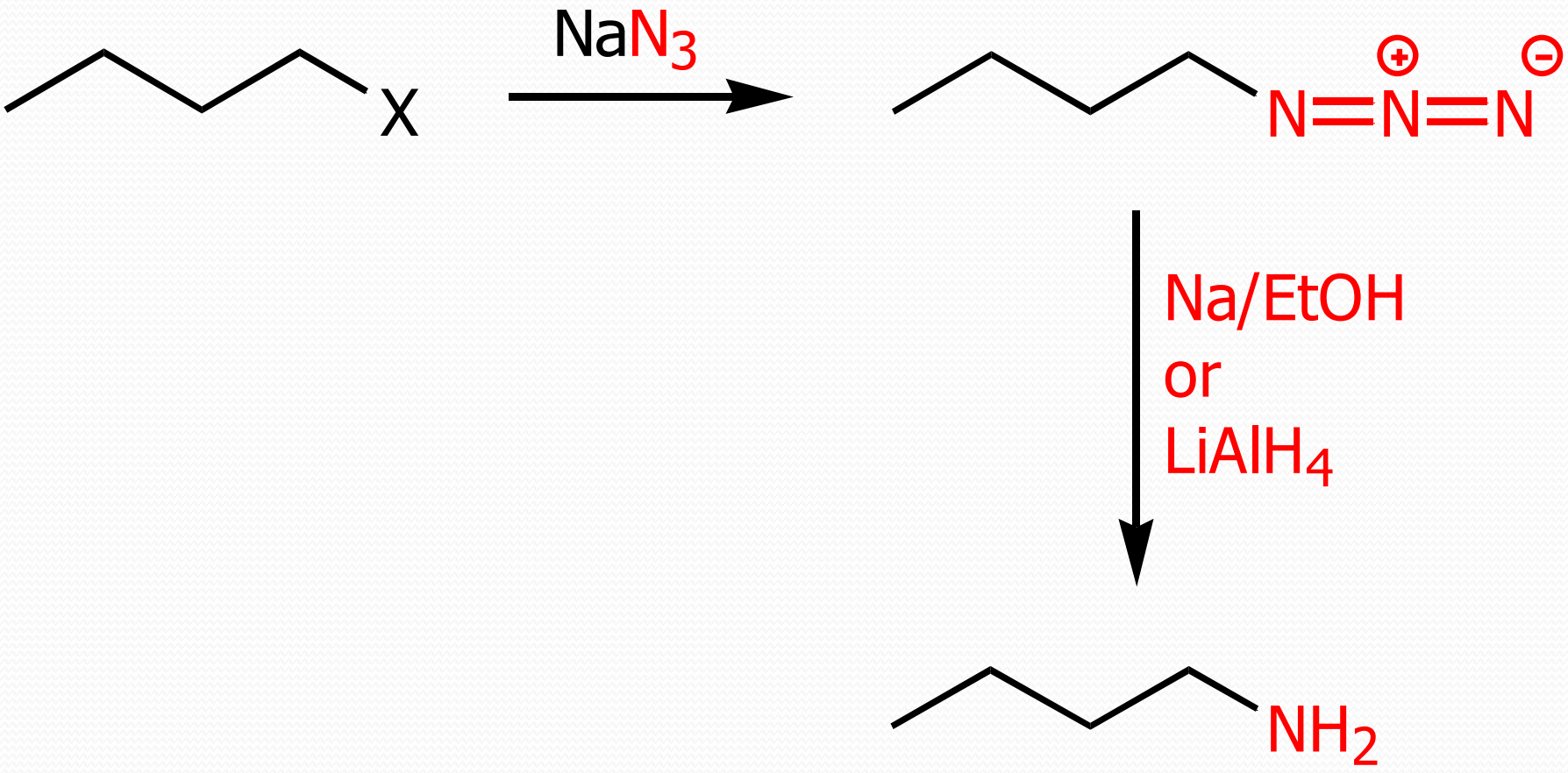
4A. Through Nucleophilic Substitution Reactions

- Alkylation of ammonia

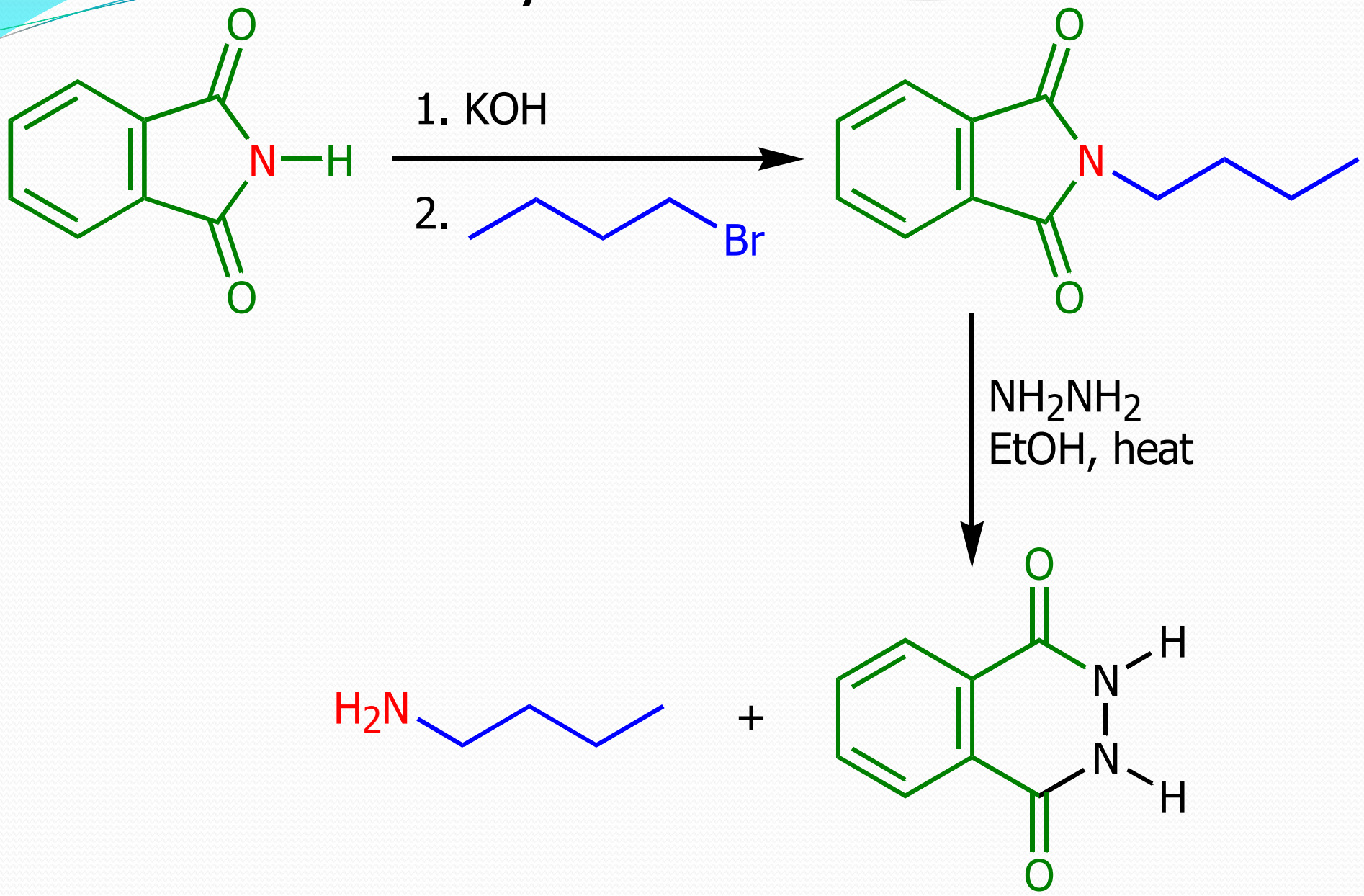


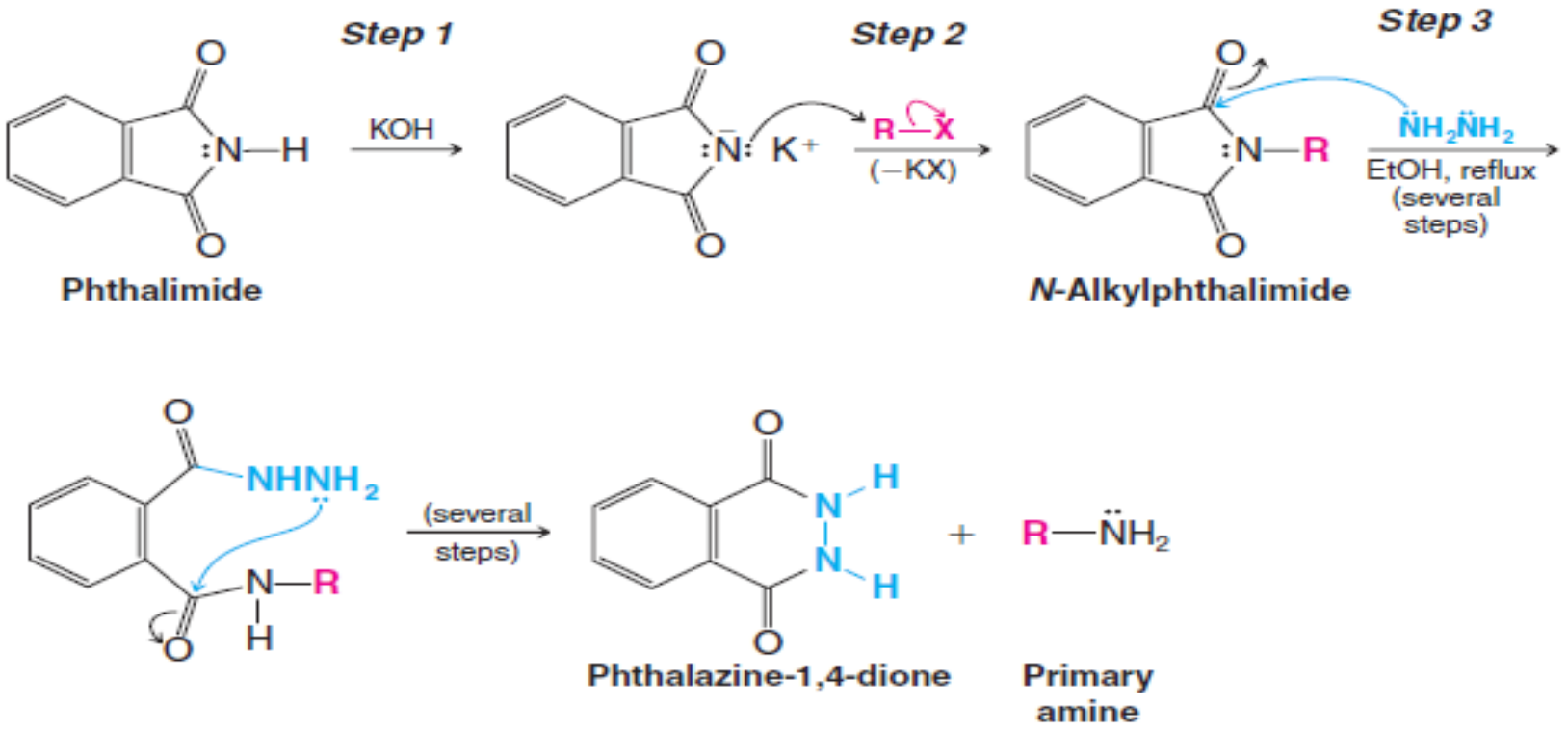

X
NH2
(over-alkylation)
H
N
H
X
NH3
X
NH3
N
H
N
+
N
X

Alkylation of azide ion and reduction



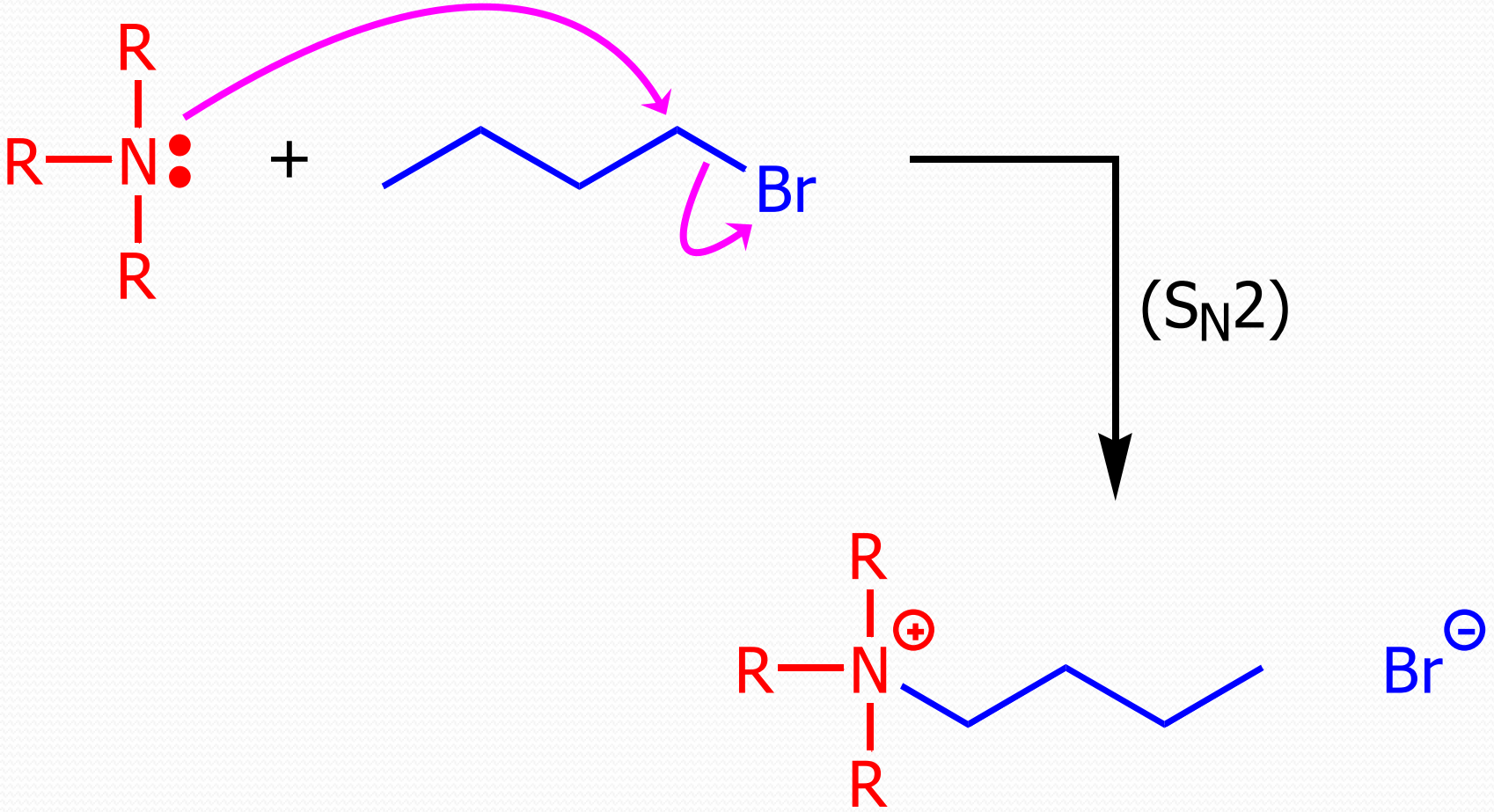
The Gabriel synthesis



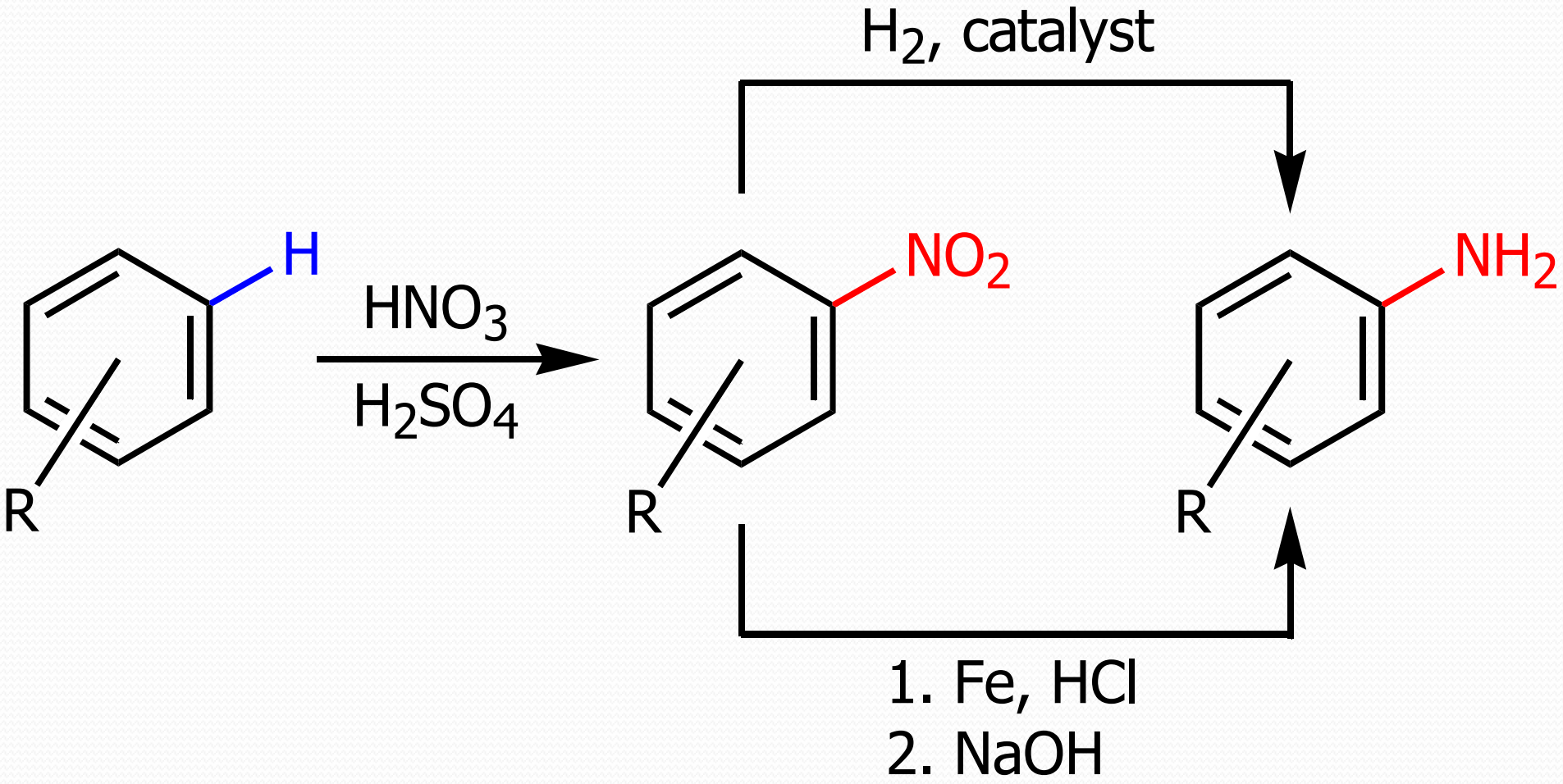


Phthalimide is quite acidic ($pK_a = 9$); it can be converted to potassium phthalimide by potassium hydroxide (step 1). The phthalimide anion is a strong nucleophile and (in step 2) it reacts with an alkyl halide by an S_N2 mechanism to give an *N*-alkylphthalimide. At this point, the *N*-alkylphthalimide can be hydrolyzed with aqueous acid or base, but the hydrolysis is often difficult. It is often more convenient to treat the *N*-alkylphthalimide with hydrazine (NH_2NH_2) in refluxing ethanol (step 3) to give a primary amine and phthalazine-1,4-dione.

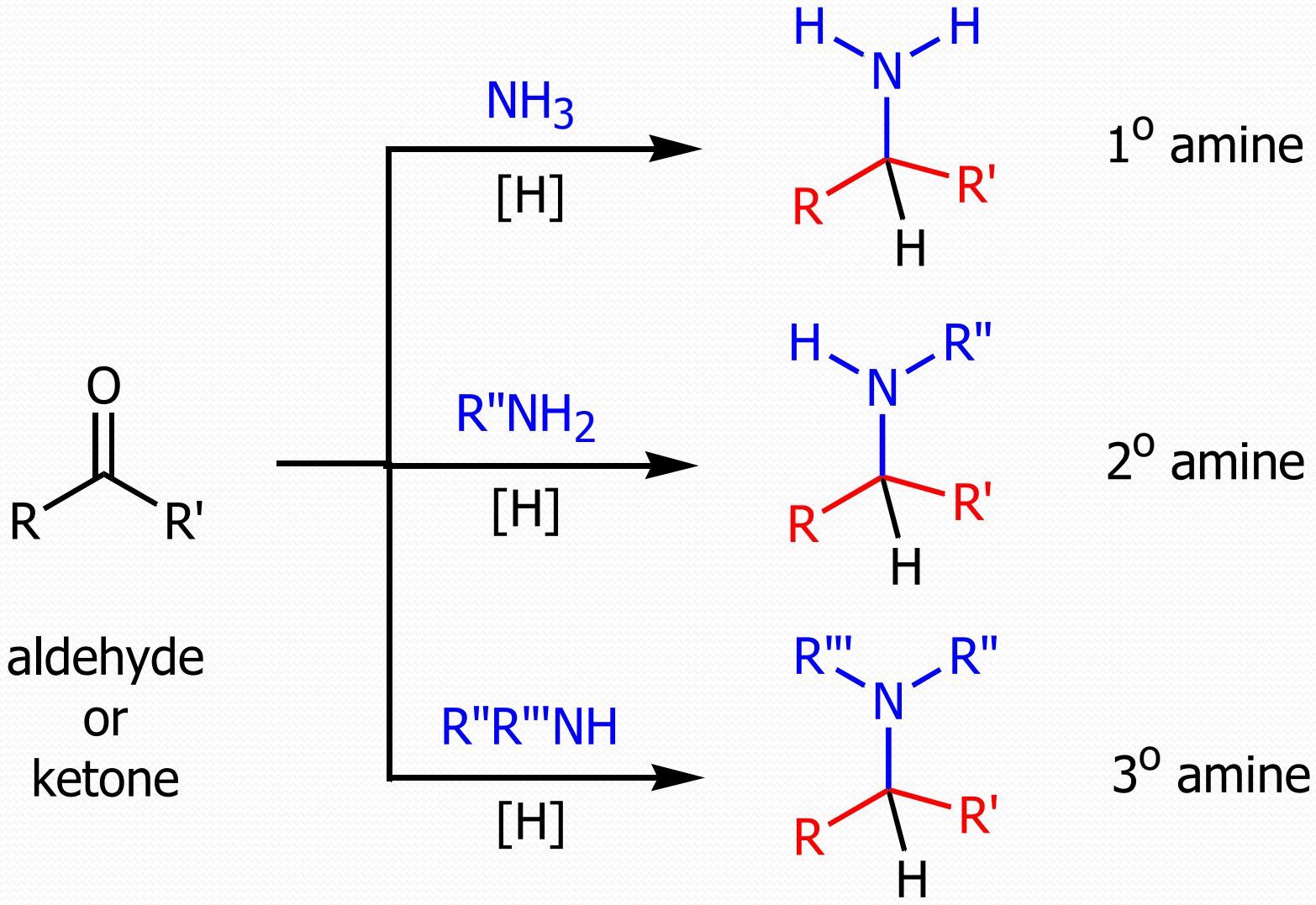
Alkylation of 3° amines



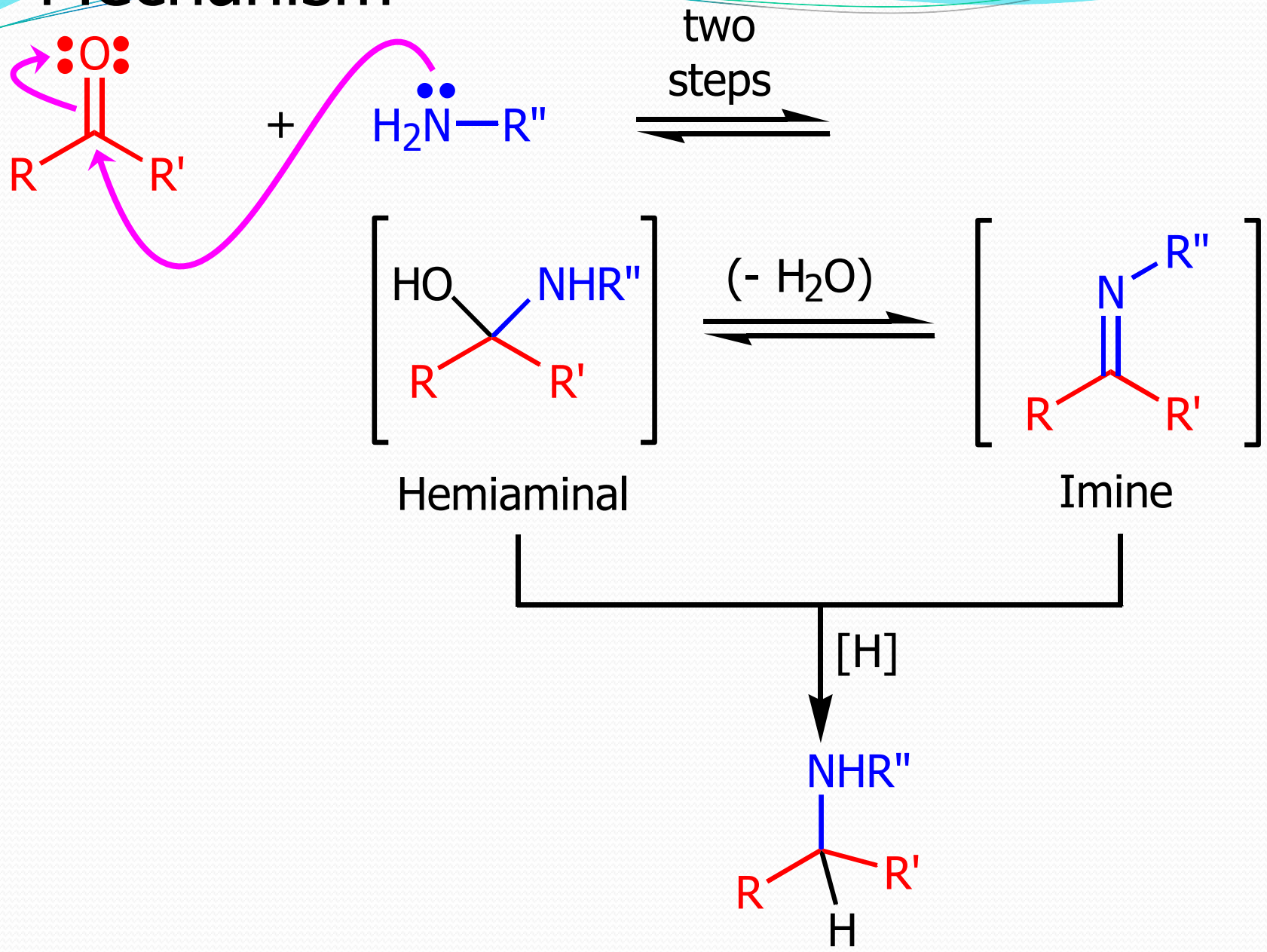
4B. Preparation of Aromatic Amines through Reduction of Nitro Compounds



4C. Preparation of Primary, Secondary, and Tertiary Amines through Reductive Amination

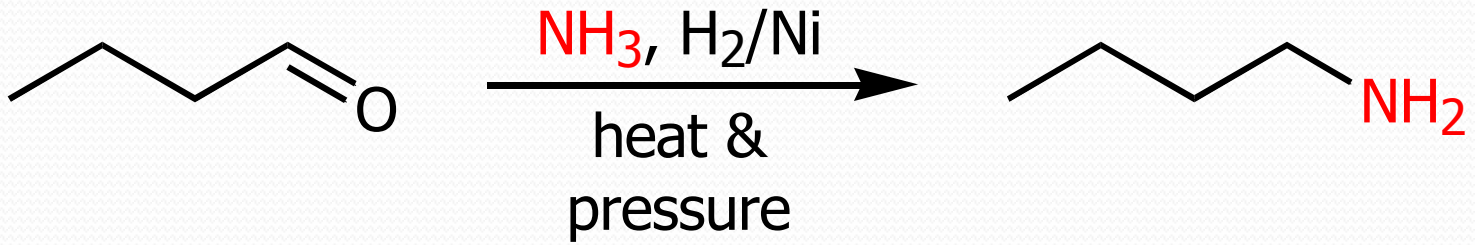


Mechanism

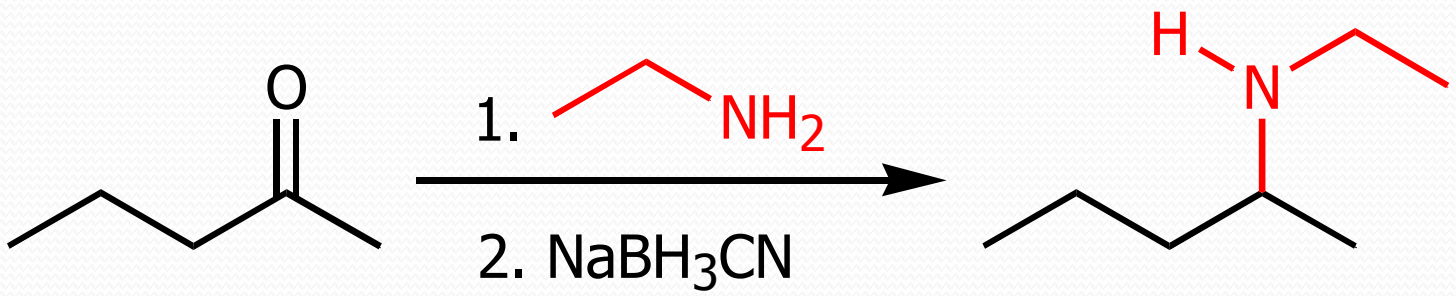


Examples

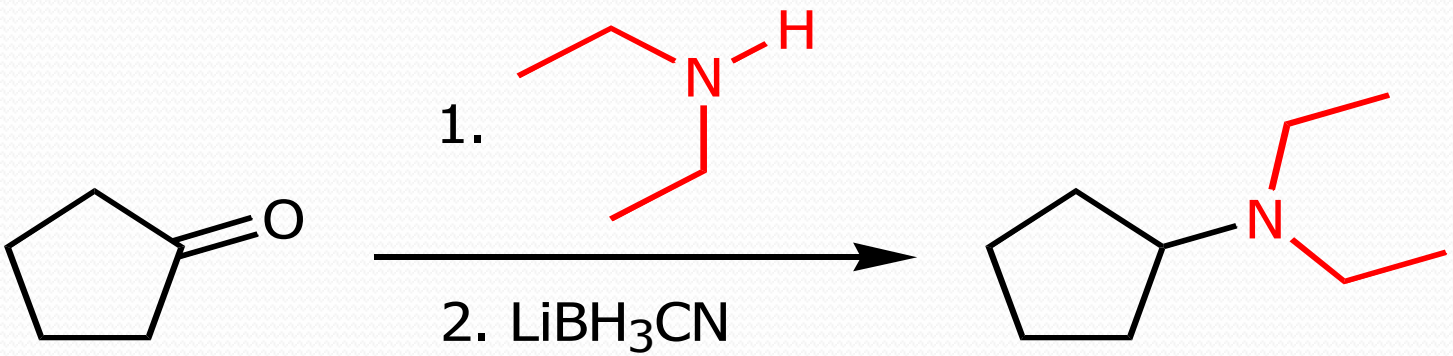
(1)



(2)

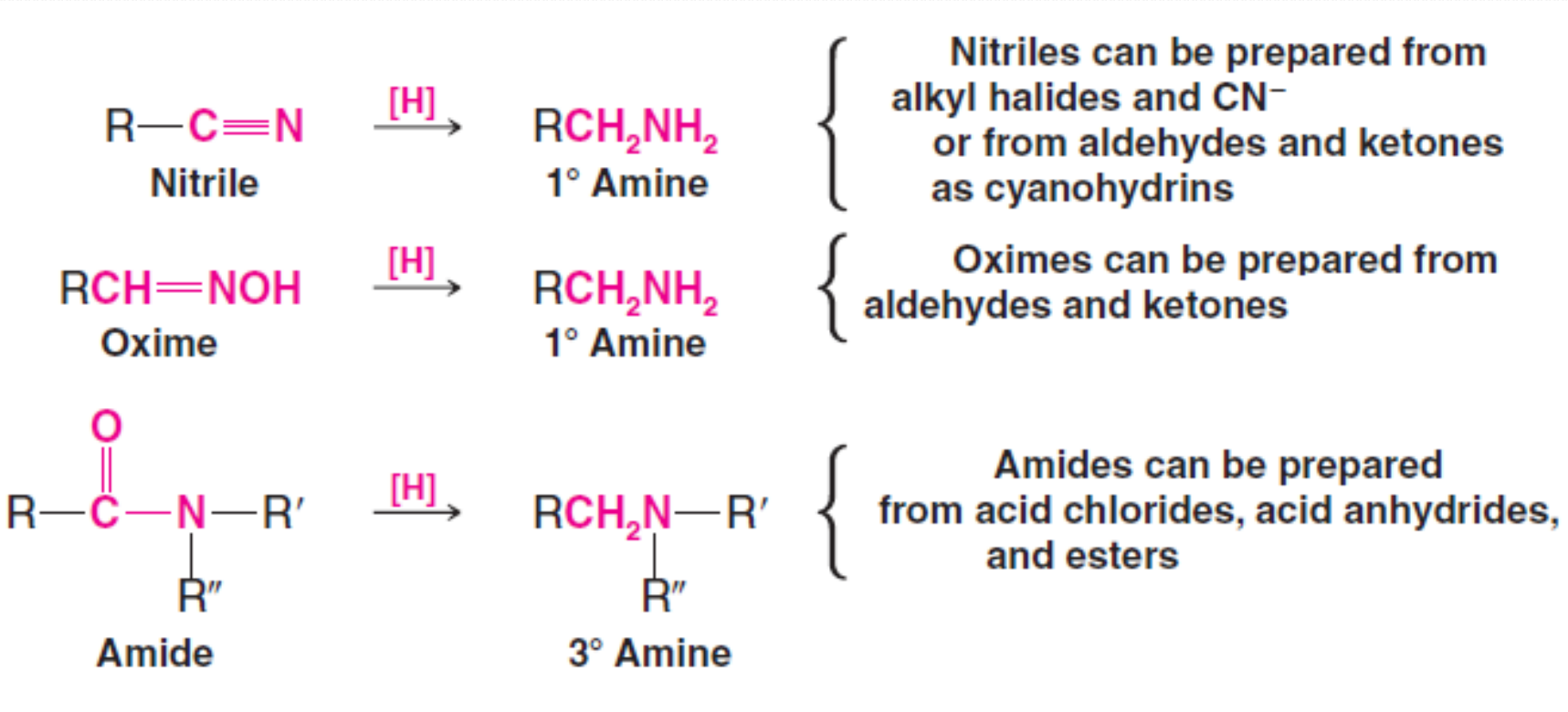


(3)



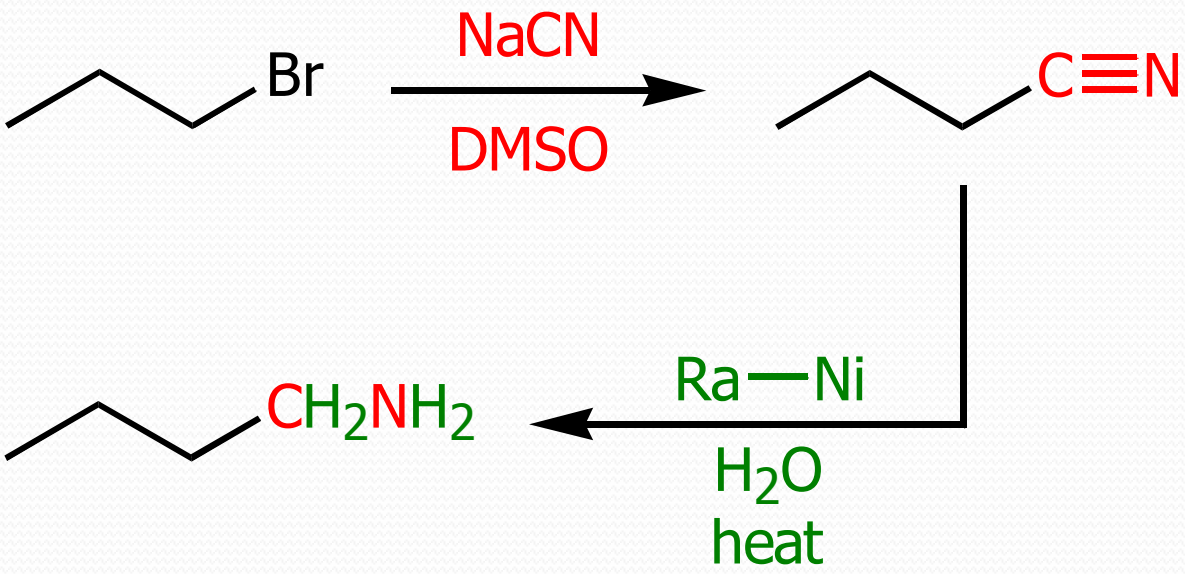
$NaBH_3CN$ or $LiBH_3CN$ (sodium or lithium cyanoborohydride).

4D. Preparation of Primary, Secondary, or Tertiary Amines through Reduction of Nitriles, Oximes, and Amides

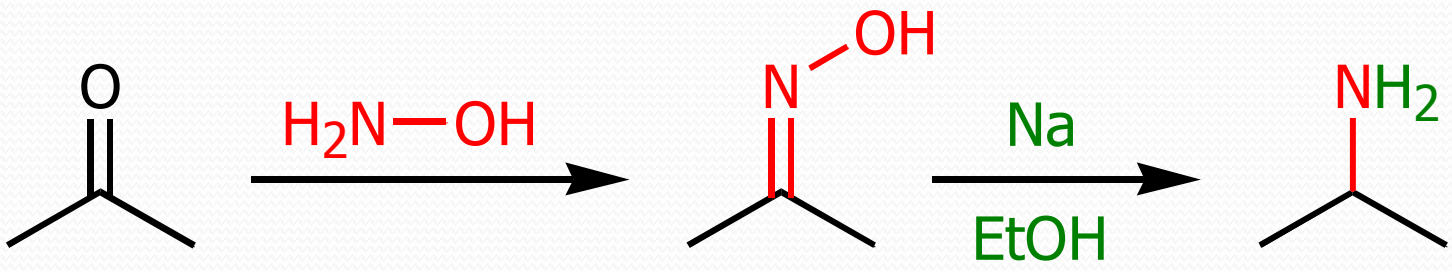


Examples

(1)

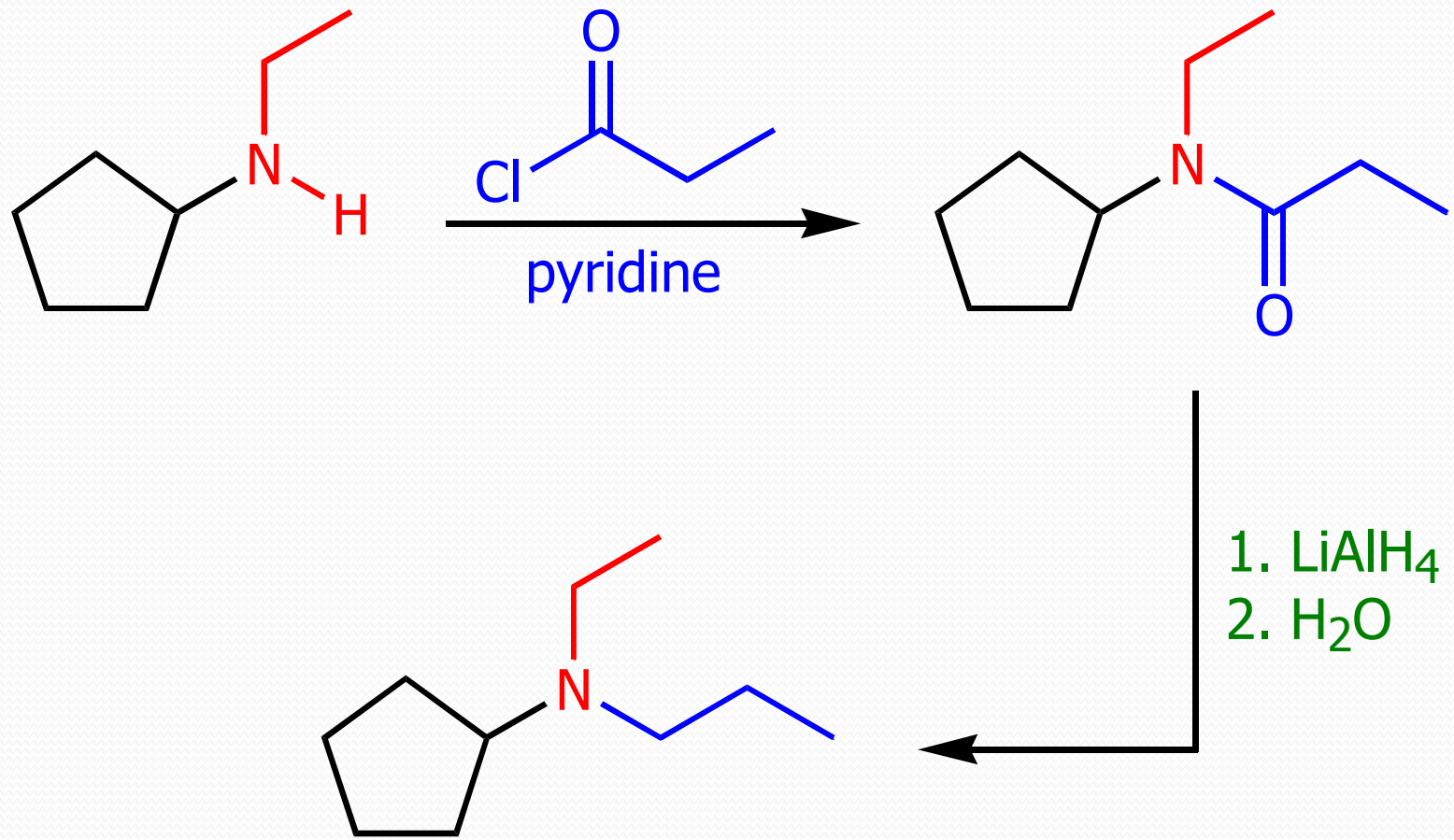


(2)



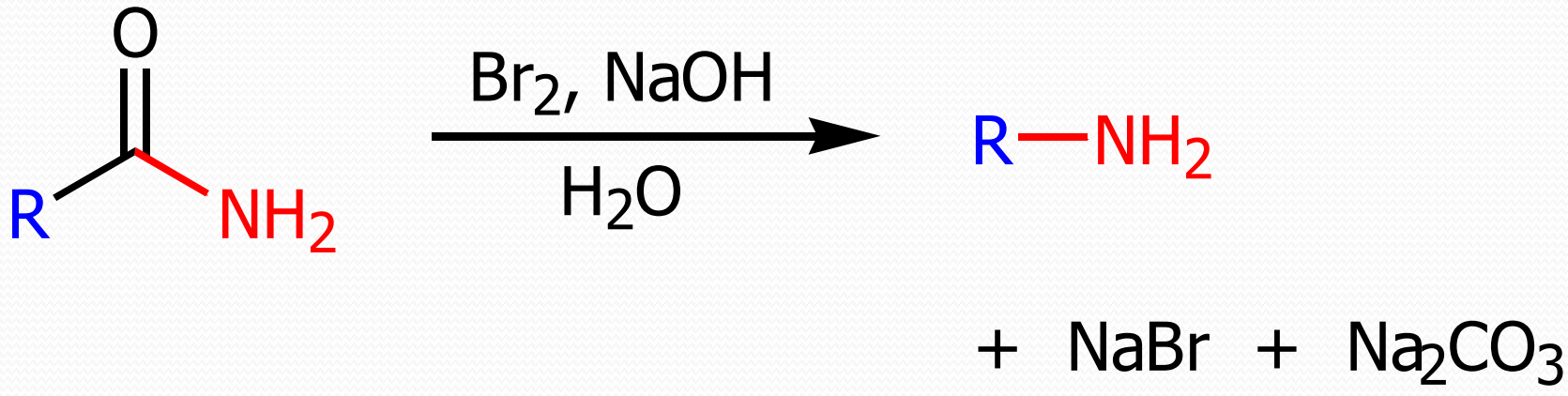
Examples

(3)



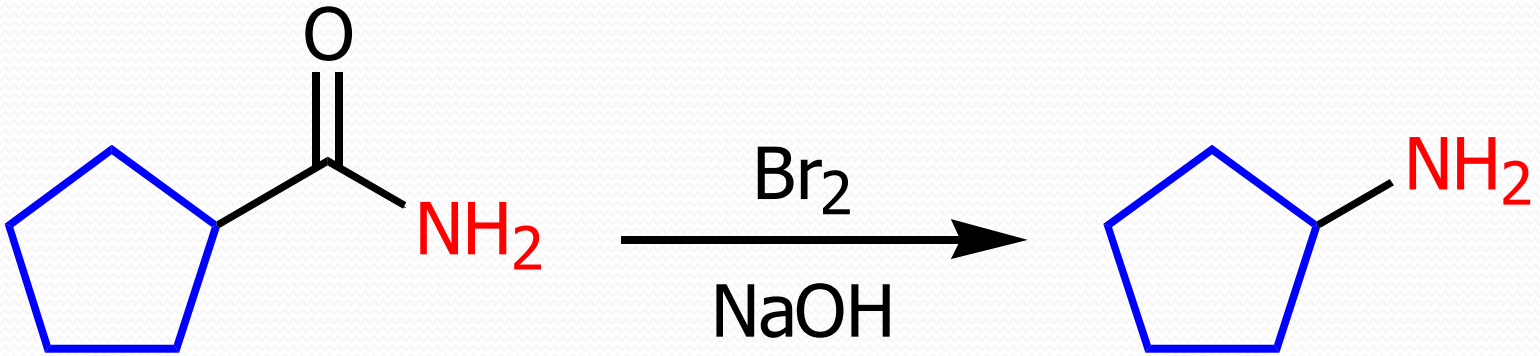
4D. Preparation of Primary Amines through the Hofmann and Curtius Rearrangements

- Hofmann rearrangement

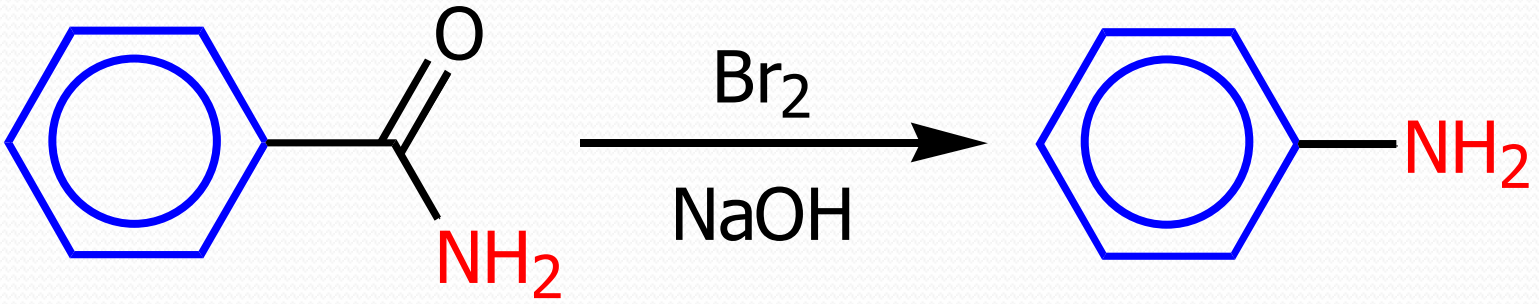


Examples

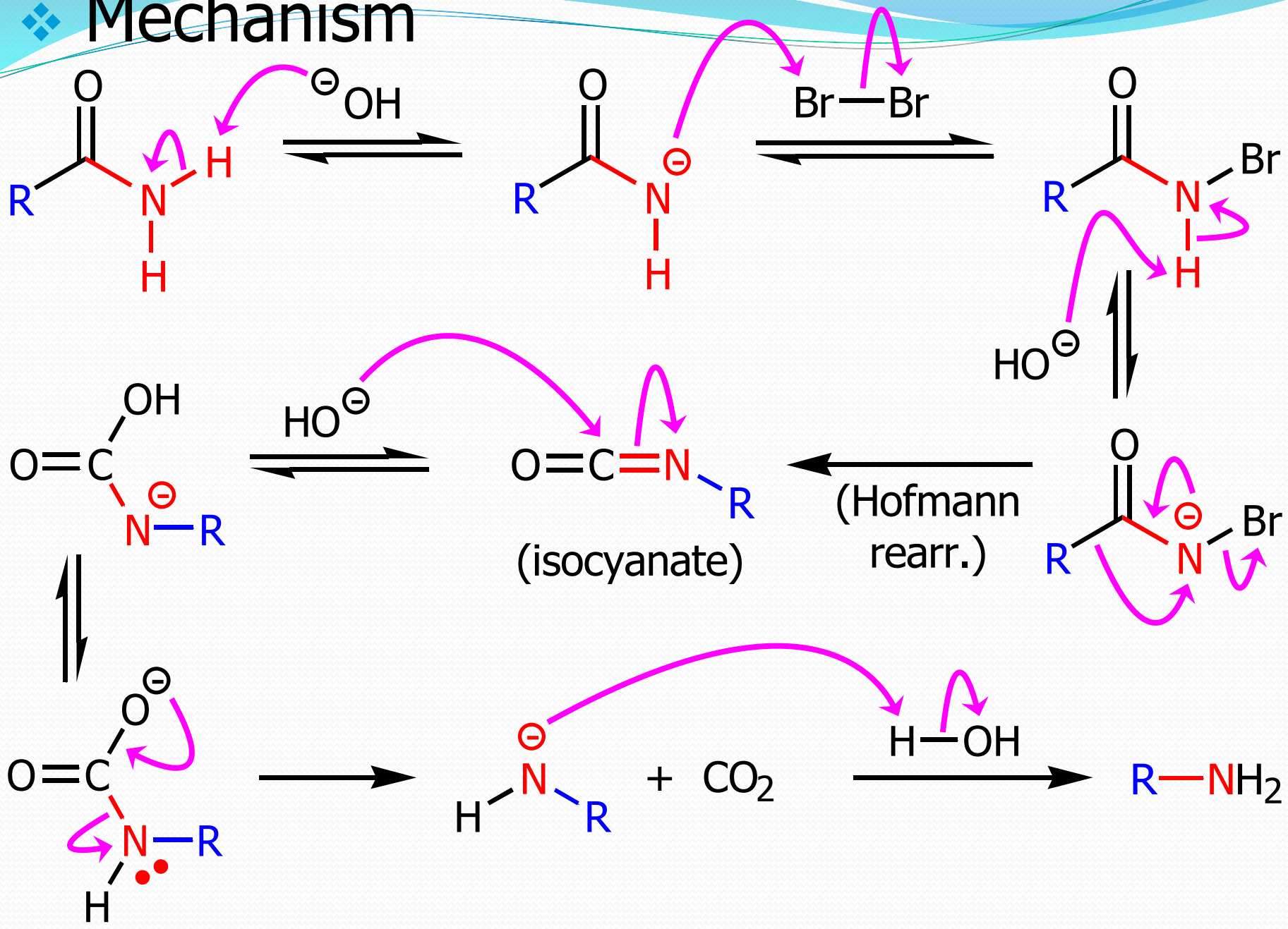
(1)



(2)



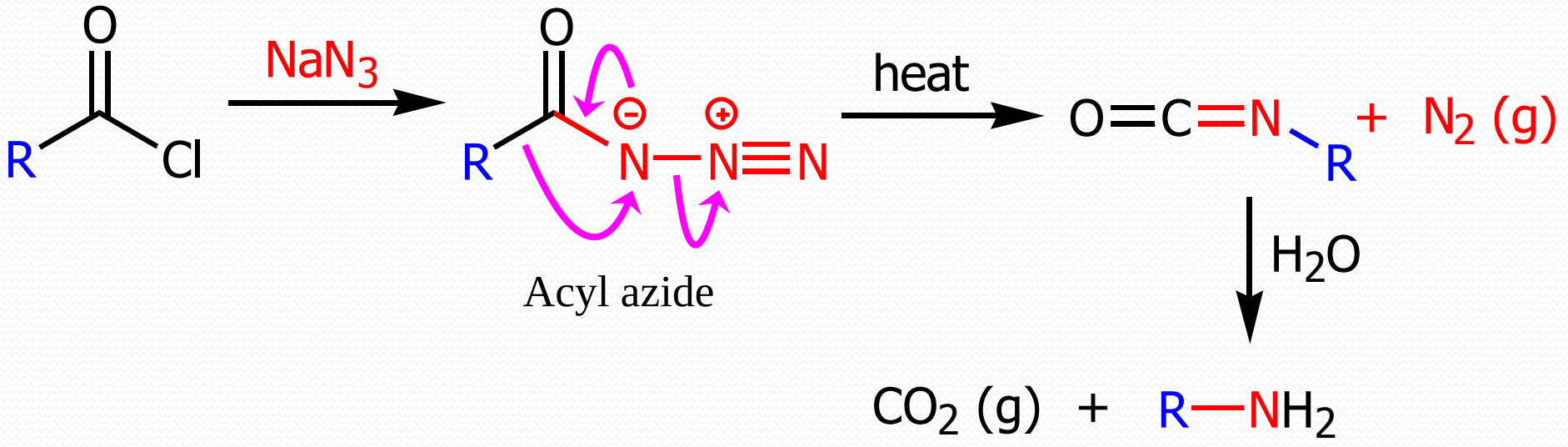
Mechanism



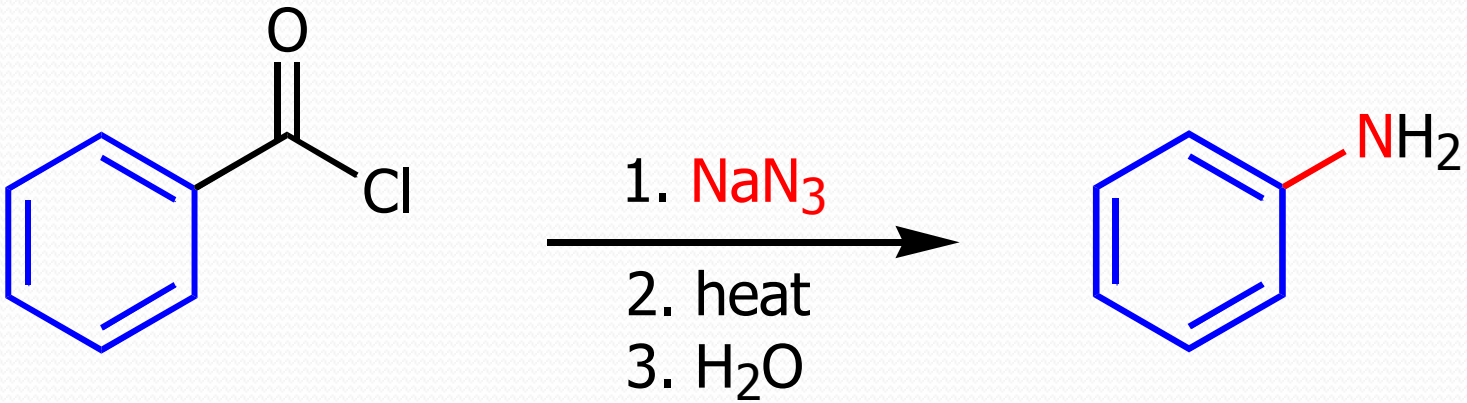
An examination of the first two steps of this mechanism shows that, initially, two hydrogen atoms must be present on the nitrogen of the amide for the reaction to occur. Consequently, the Hofmann rearrangement is limited to amides of the type $RCONH_2$.

Studies of the Hofmann rearrangement of optically active amides in which the chirality center is directly attached to the carbonyl group have shown that these reactions occur with *retention of configuration*. Thus, the R group migrates to nitrogen with its electrons, *but without inversion*.

Curtius rearrangement

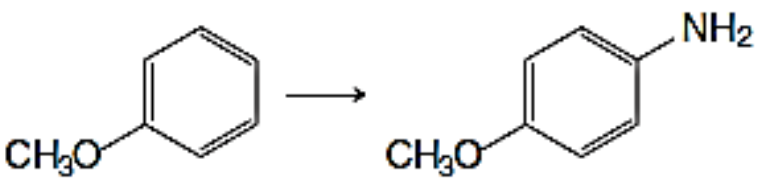


e.g.

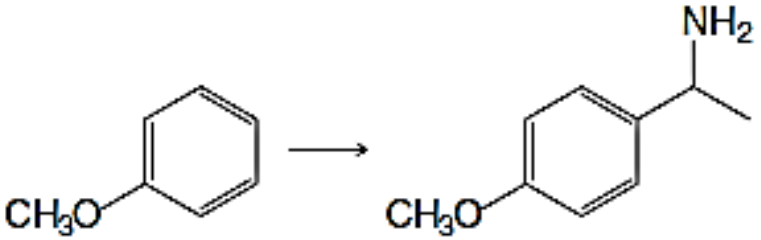


Using a different method for each part, but taking care in each case to select a *good* method, show how each of the following transformations might be accomplished:

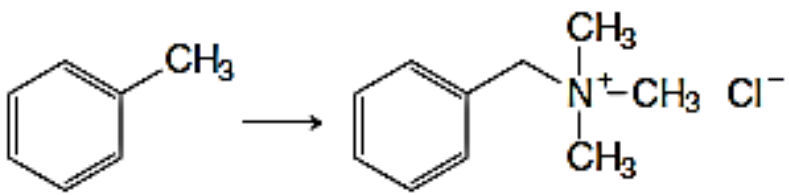
(a)



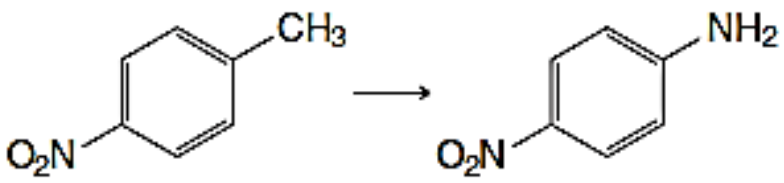
(b)



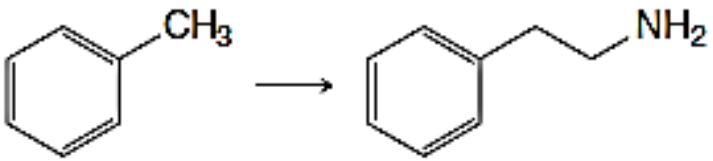
(c)



(d)

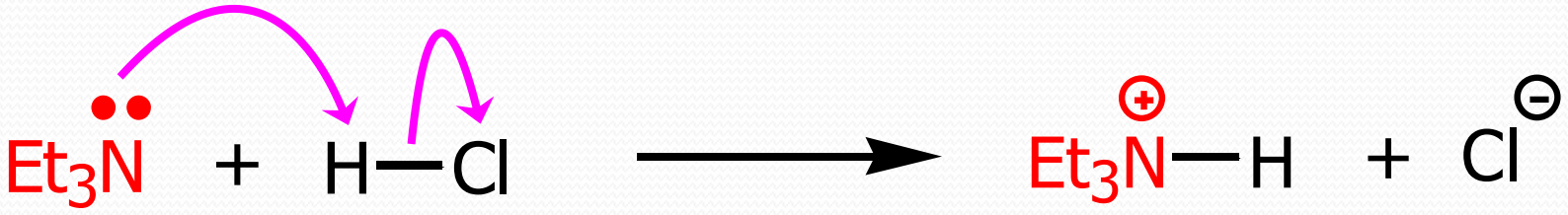


(e)

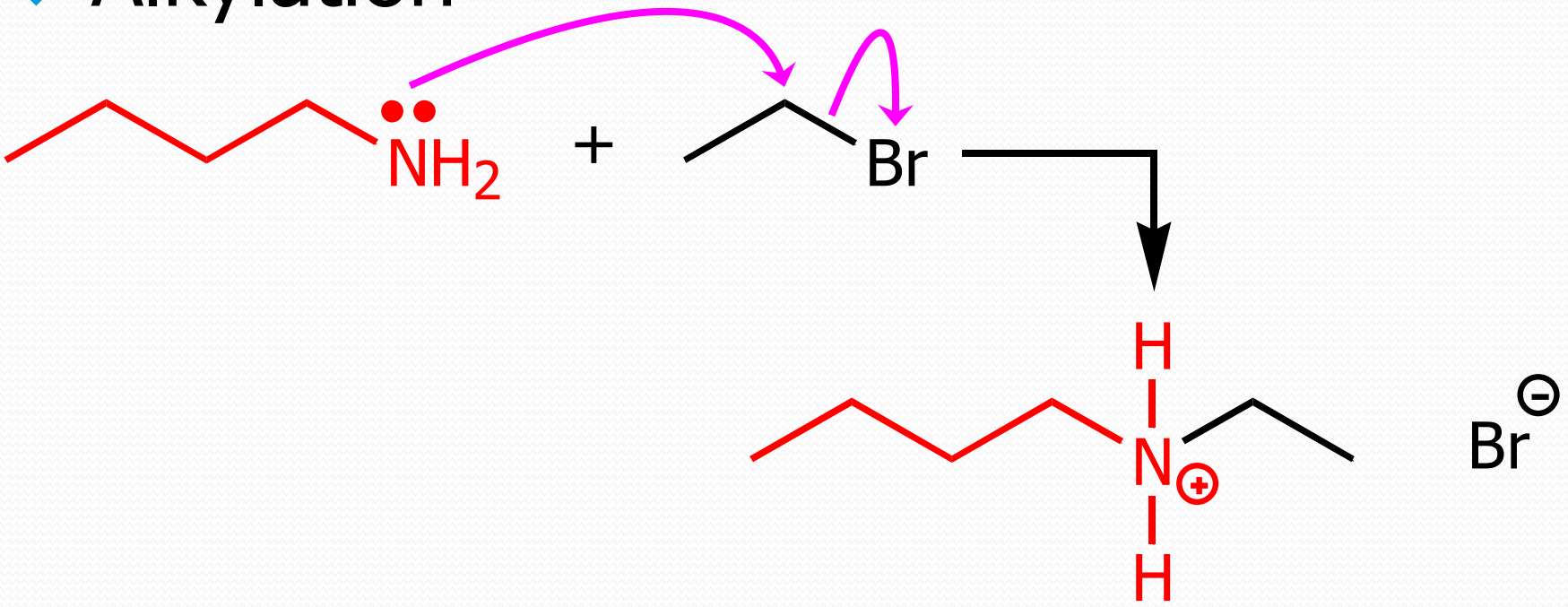


5. Reactions of Amines

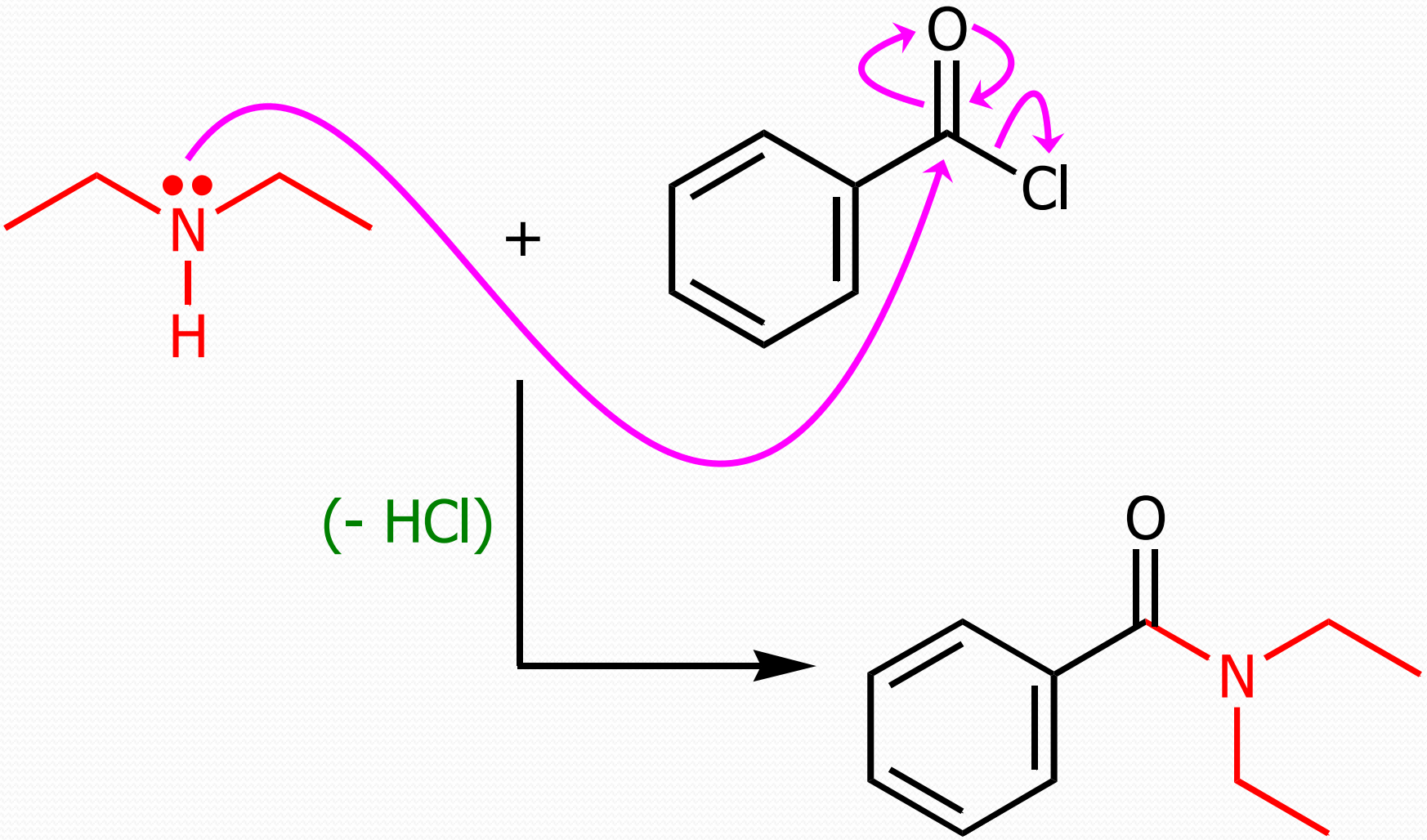
- Acid-base reactions



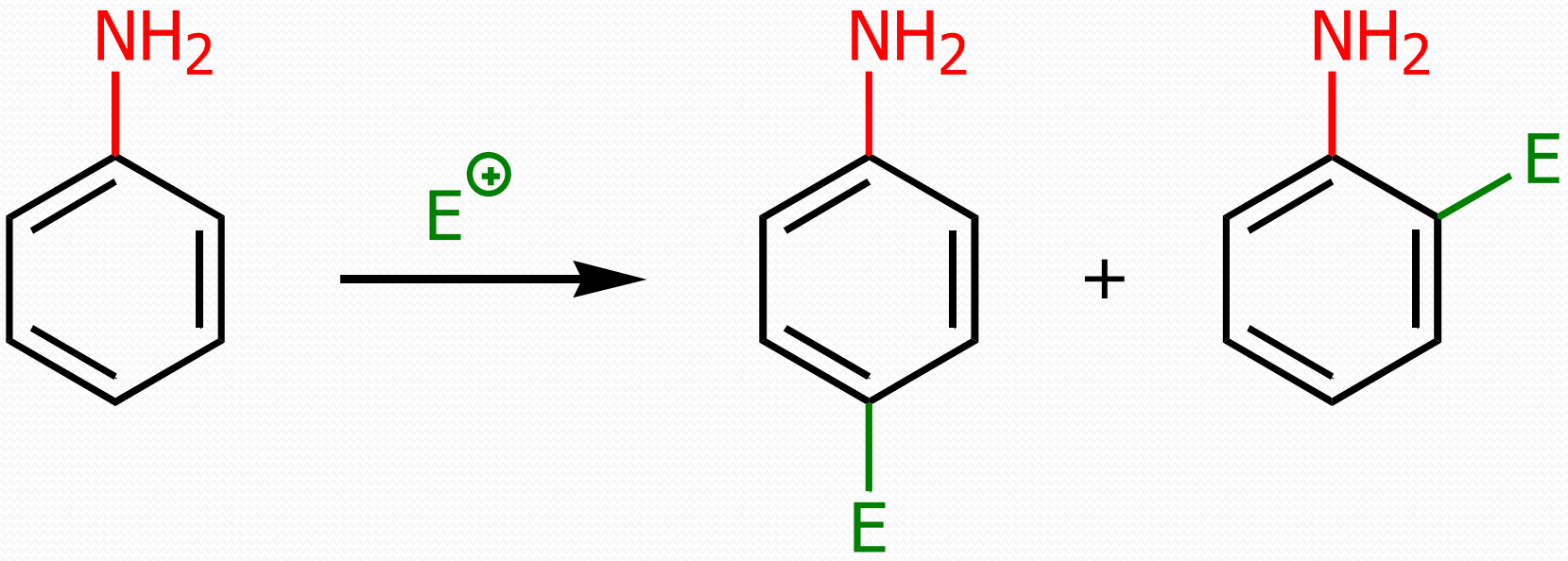
- Alkylation



Acylation

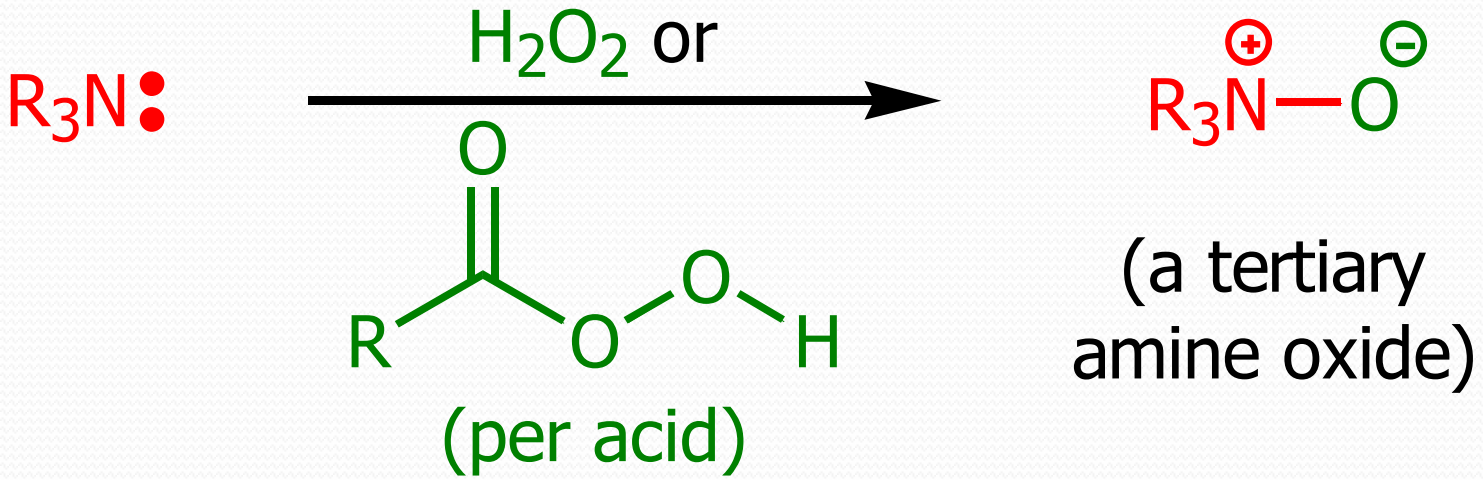


Electrophilic aromatic substitution



NH_2: powerful activating group, *ortho-para* director

5A. Oxidation of Amines



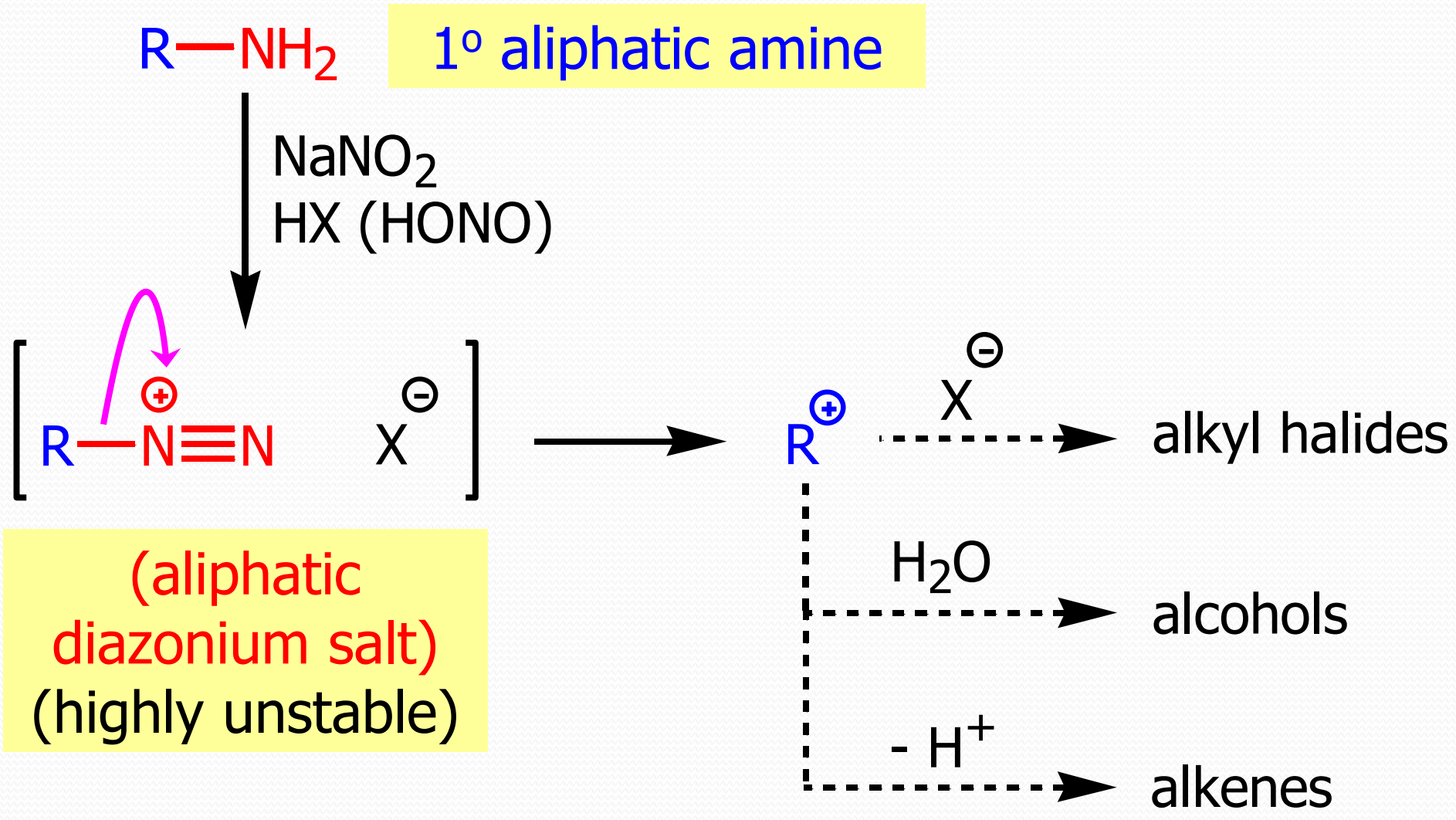
6. Reactions of Amines with Nitrous Acid

- Nitrous acid (HONO) is a weak, unstable acid

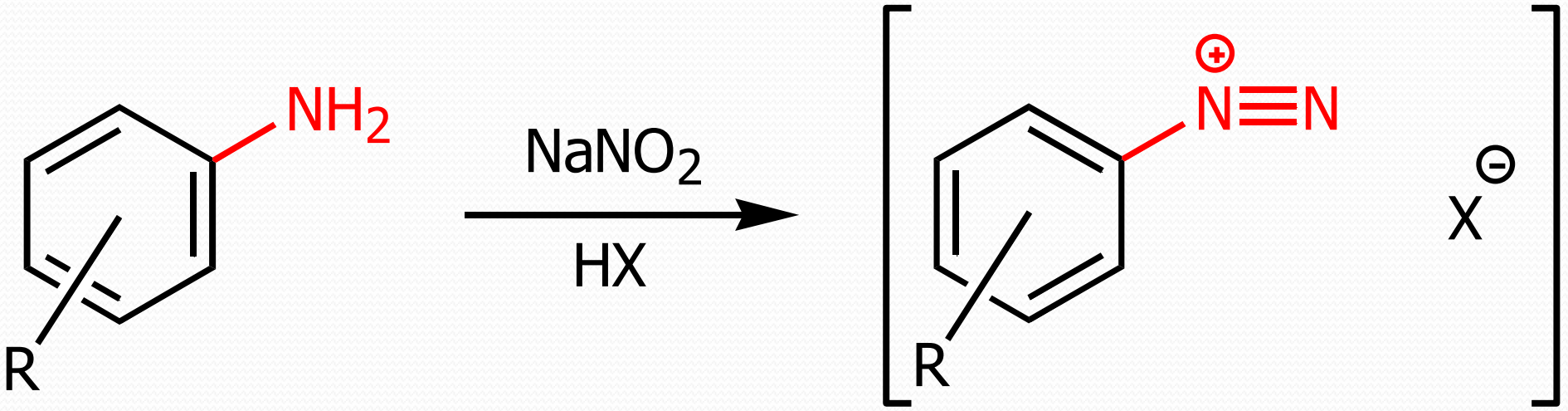
$$HCl_{(aq)} + NaNO_{2(aq)} \longrightarrow HONO_{(aq)} + NaCl_{(aq)}$$

$$H_2SO_{4(aq)} + 2\ NaNO_{2(aq)} \longrightarrow 2\ HONO_{(aq)} + Na_2SO_{4(aq)}$$

6A. Reactions of Primary Aliphatic Amines with Nitrous Acid

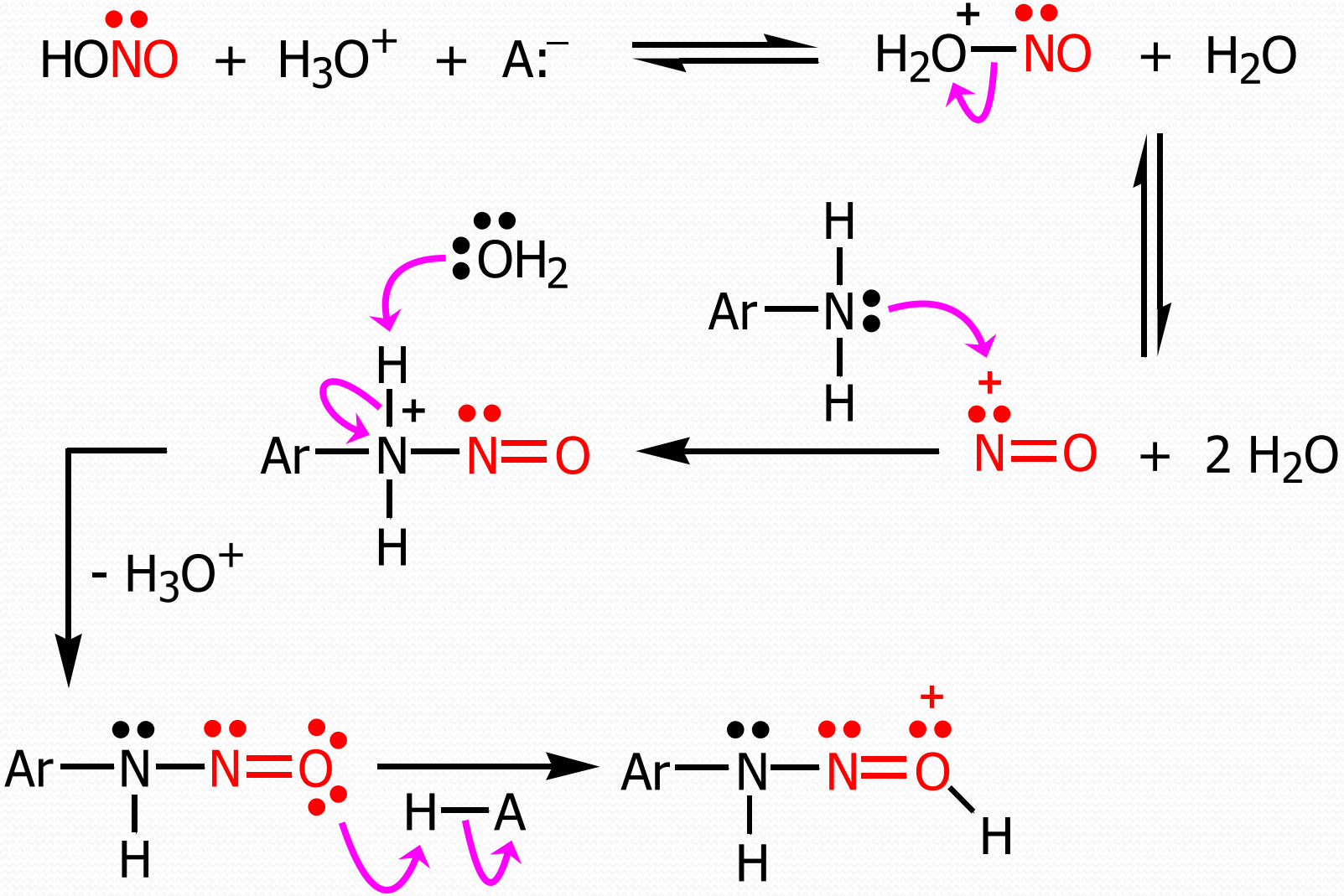


6B. Reactions of Primary Arylamines with Nitrous Acid

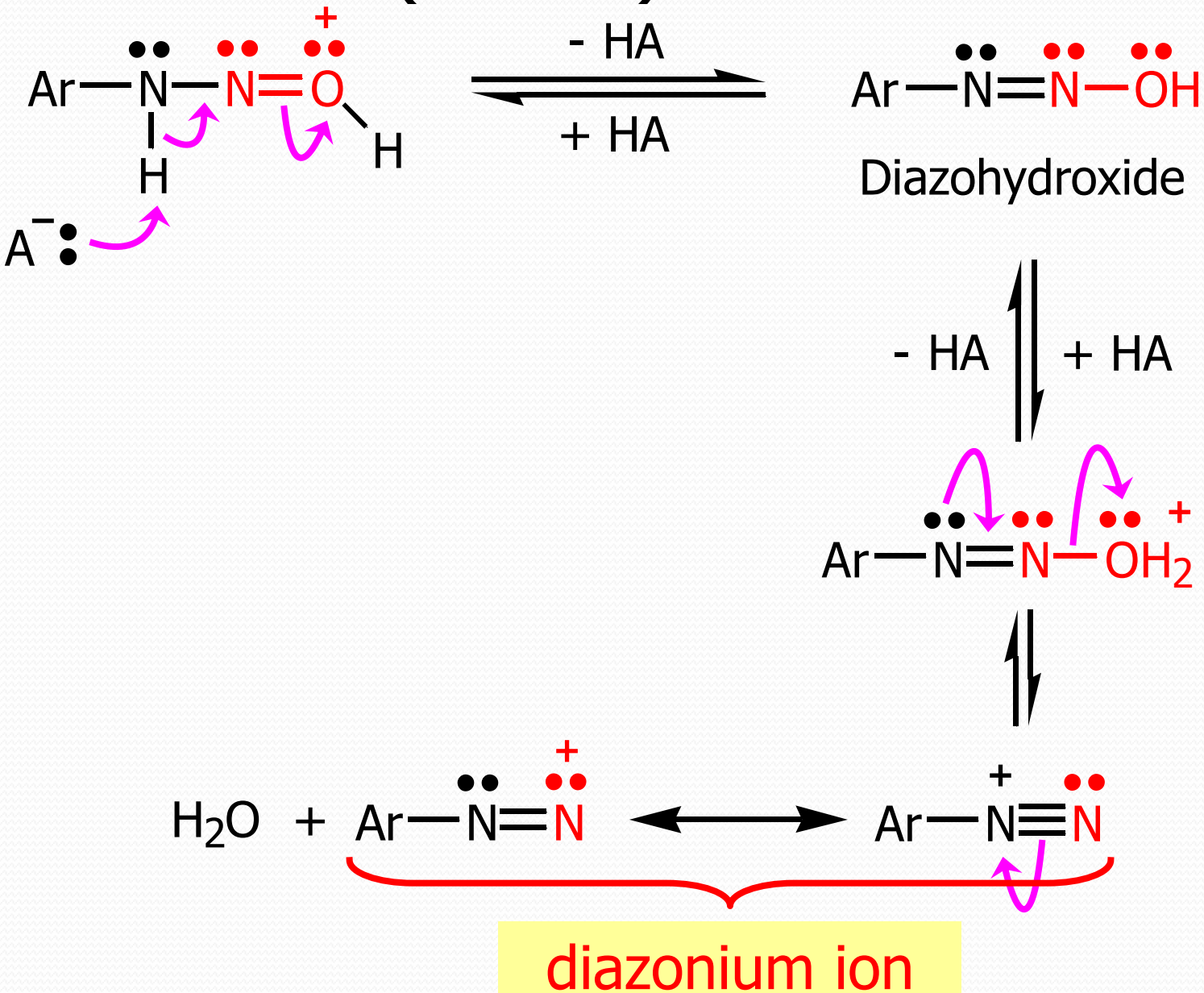


(arenediazonium salt)
(stable at <5°C)

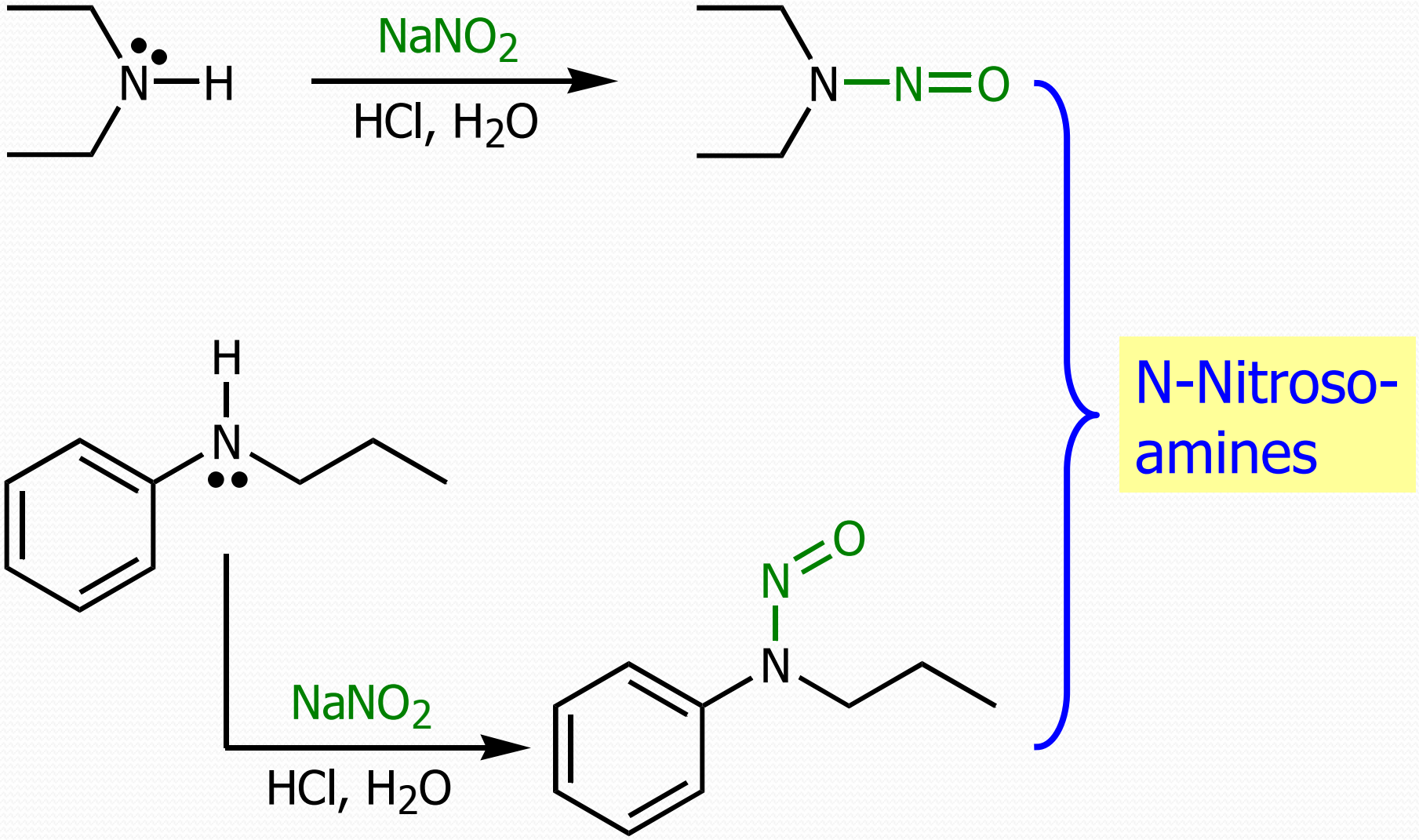
Mechanism


HONO + H3O+ + A:−
H2O NO + H2O
OH2
Ar N H
Ar N N O
N O + 2 H2O
- H3O+
Ar N N O
H A
Ar N N O H

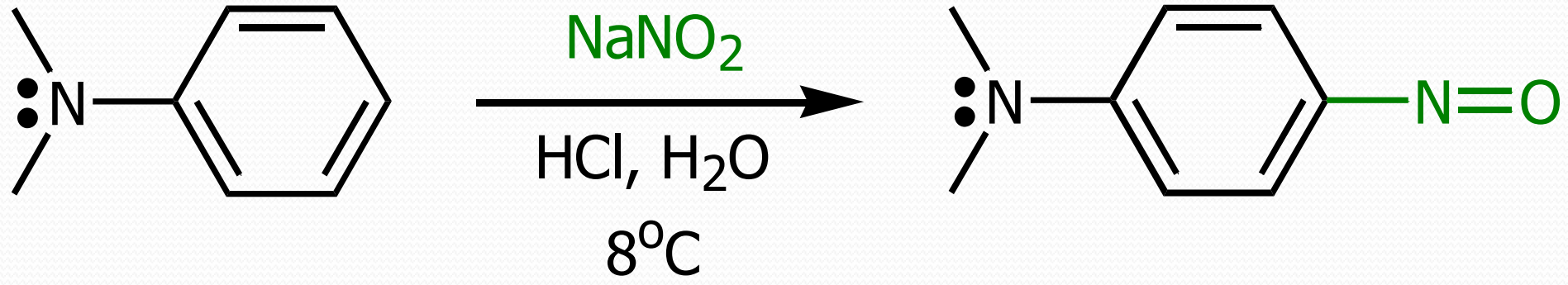
Mechanism (Cont'd)

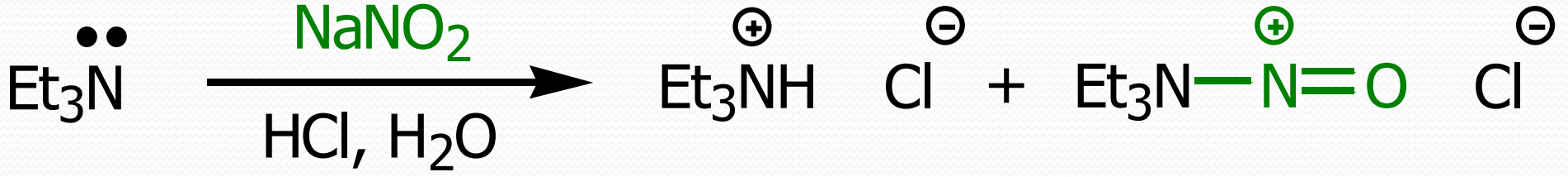


6C. Reactions of Secondary Amines with Nitrous Acid

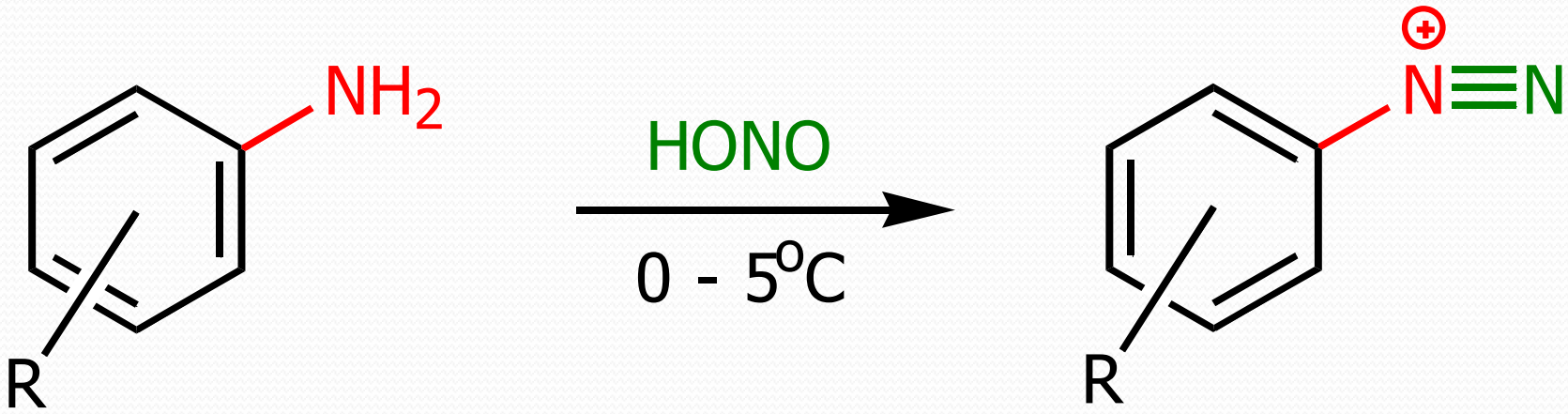


6D. Reactions of Tertiary Amines with Nitrous Acid

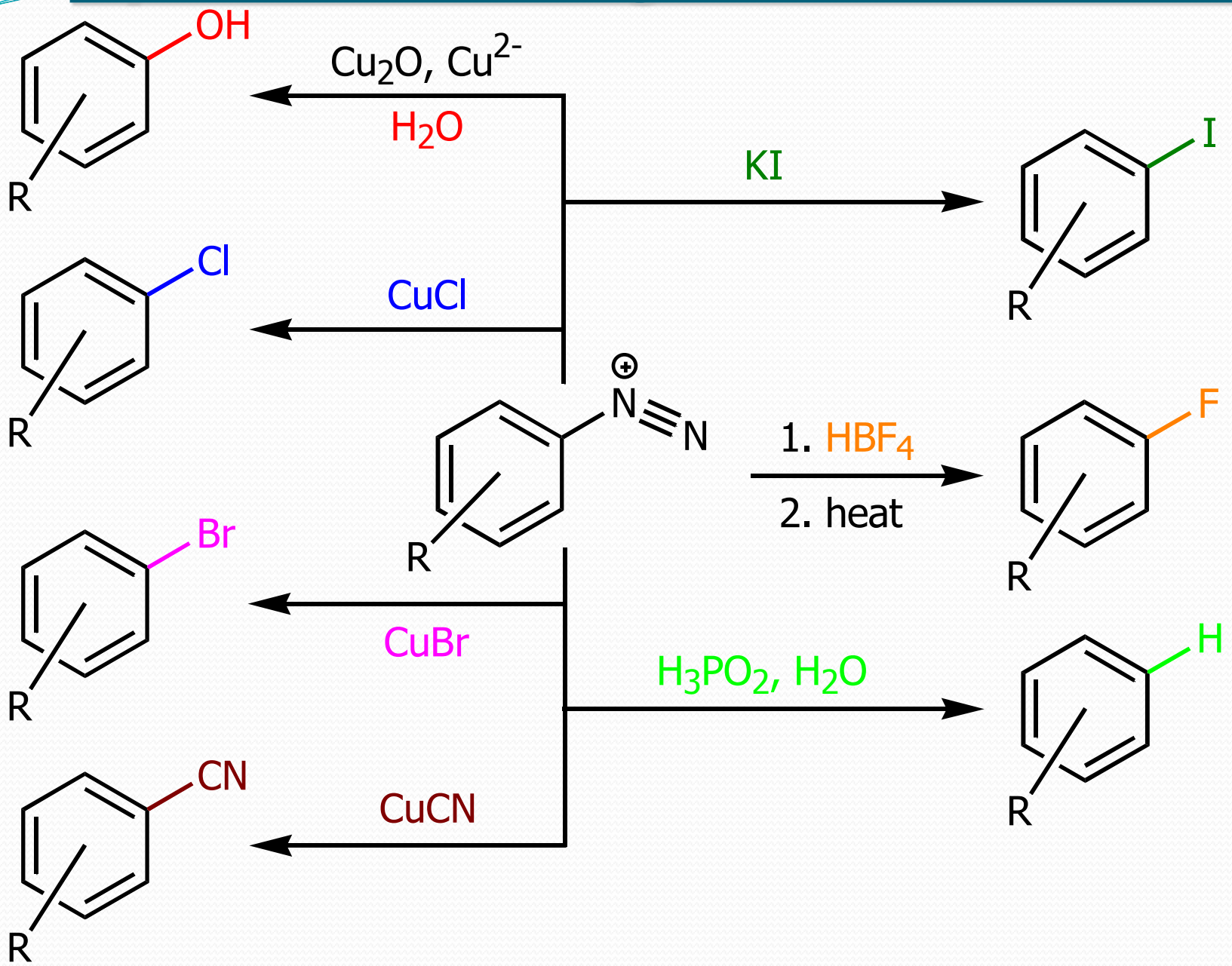




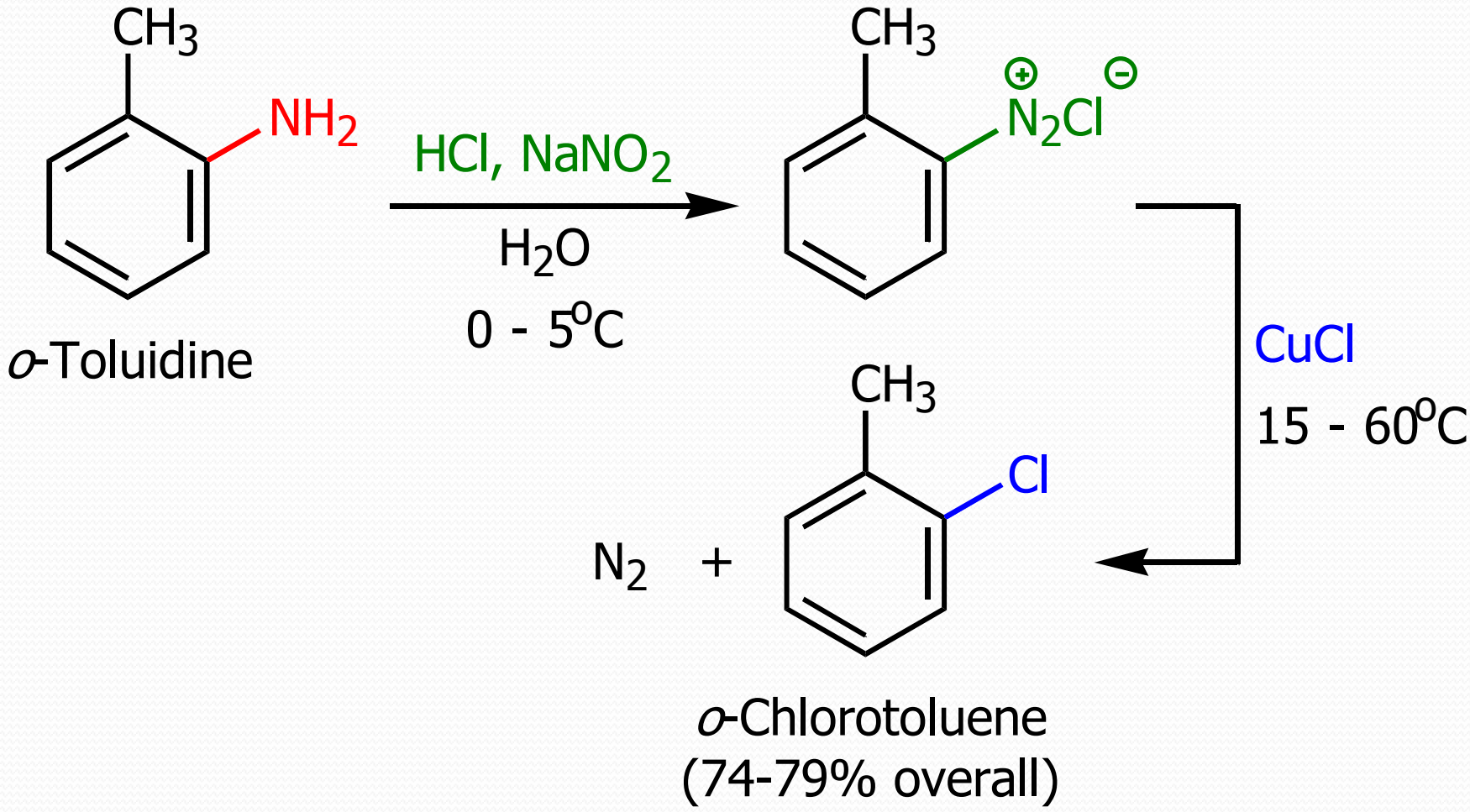
7. Replacement Reactions of Arenediazonium Salts



7A. Syntheses Using Diazonium Salts

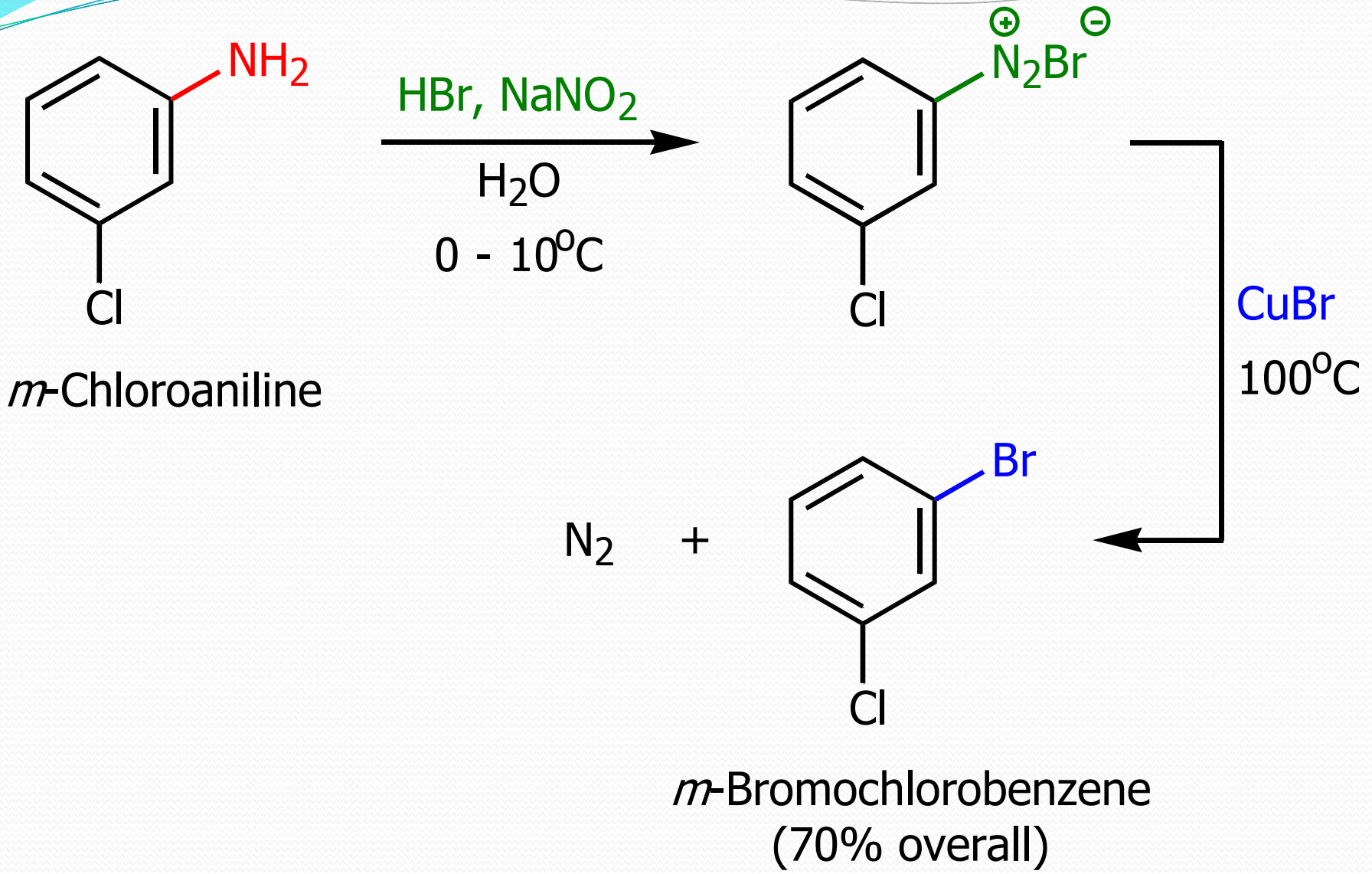


7B. The Sandmeyer Reaction: Replacement of the Diazonium Group by -Cl, -Br, or -CN



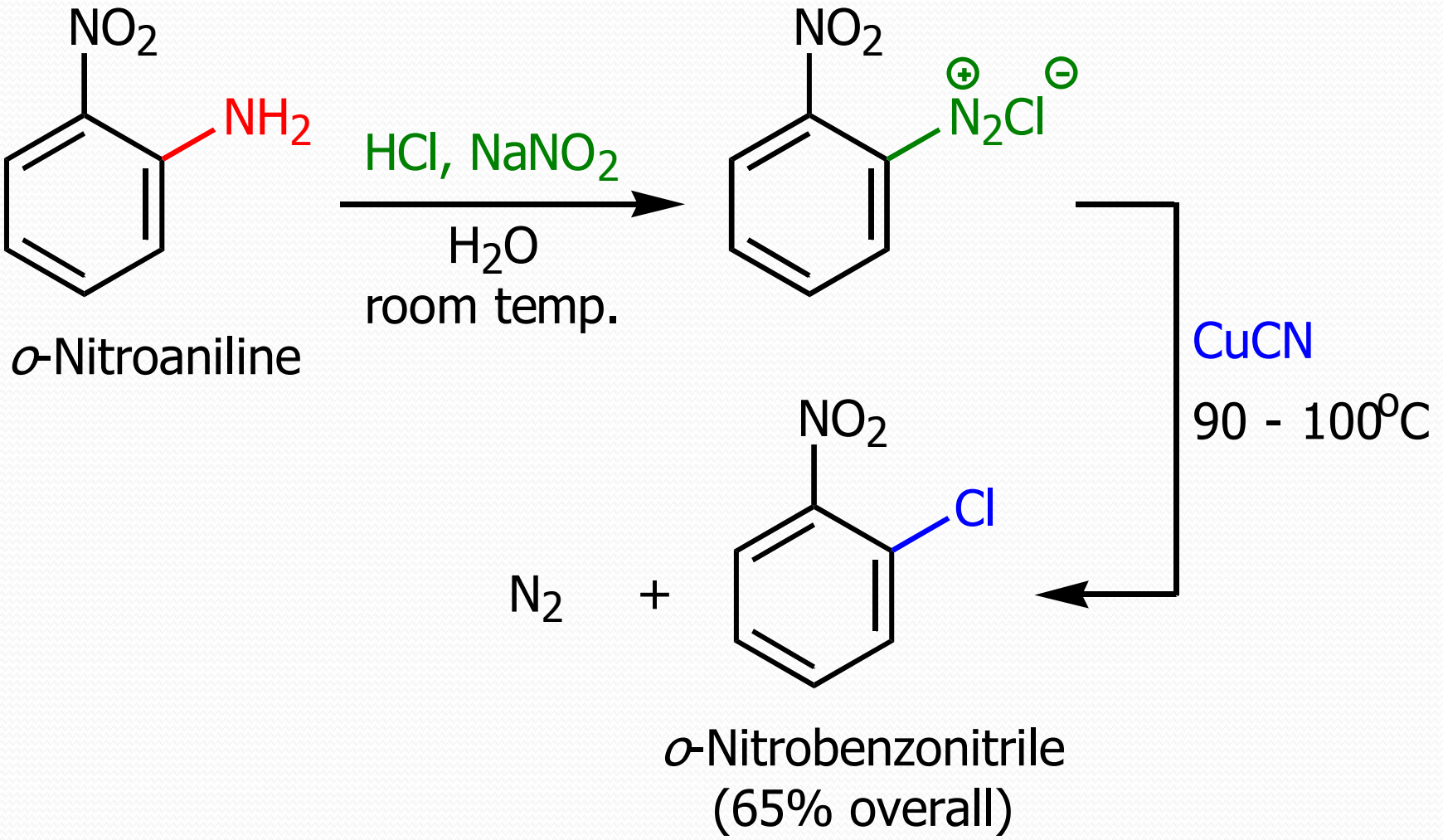
o-Toluidine

o-Chlorotoluene
(74-79% overall)

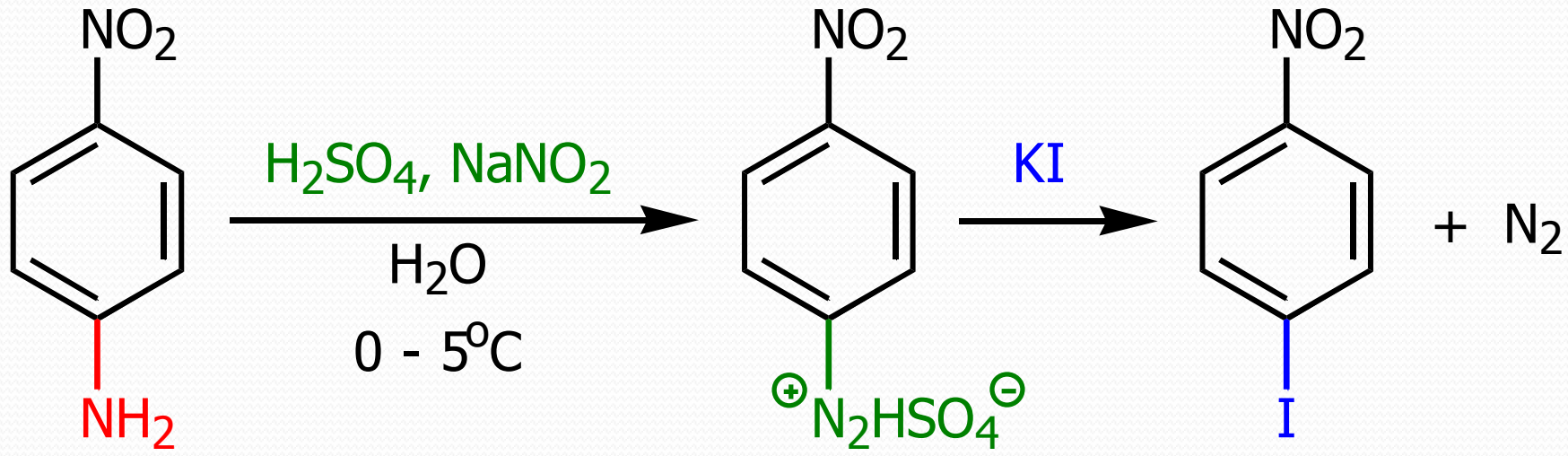


m-Chloroaniline

m-Bromochlorobenzene
(70% overall)


NO2
NH2
HCl, NaNO2
H2O
room temp.
NO2
N2Cl
CuCN
90 - 100°C
NO2
Cl
N2 +
o-Nitroaniline
o-Nitrobenzonitrile
(65% overall)

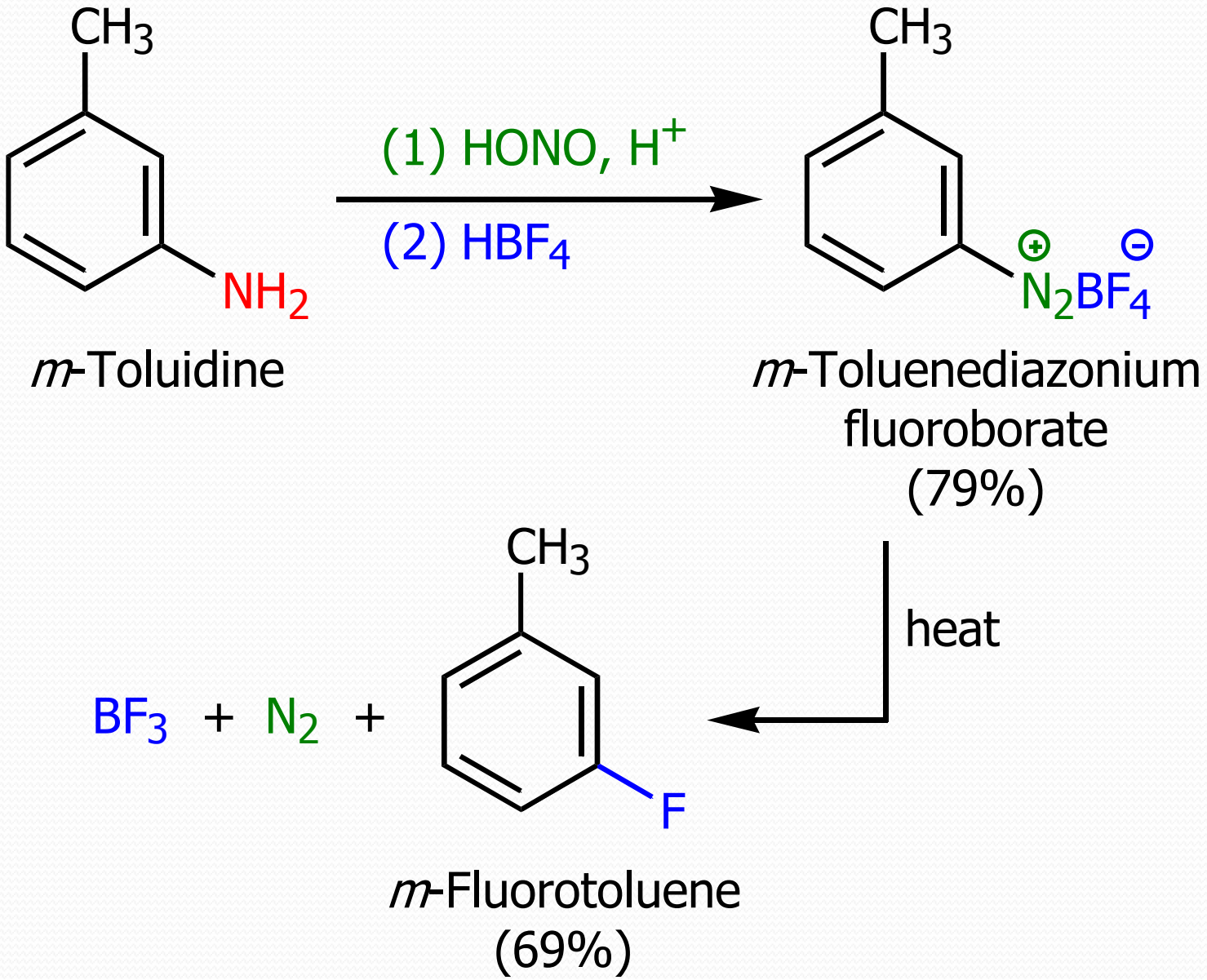
7C. Replacement by —I



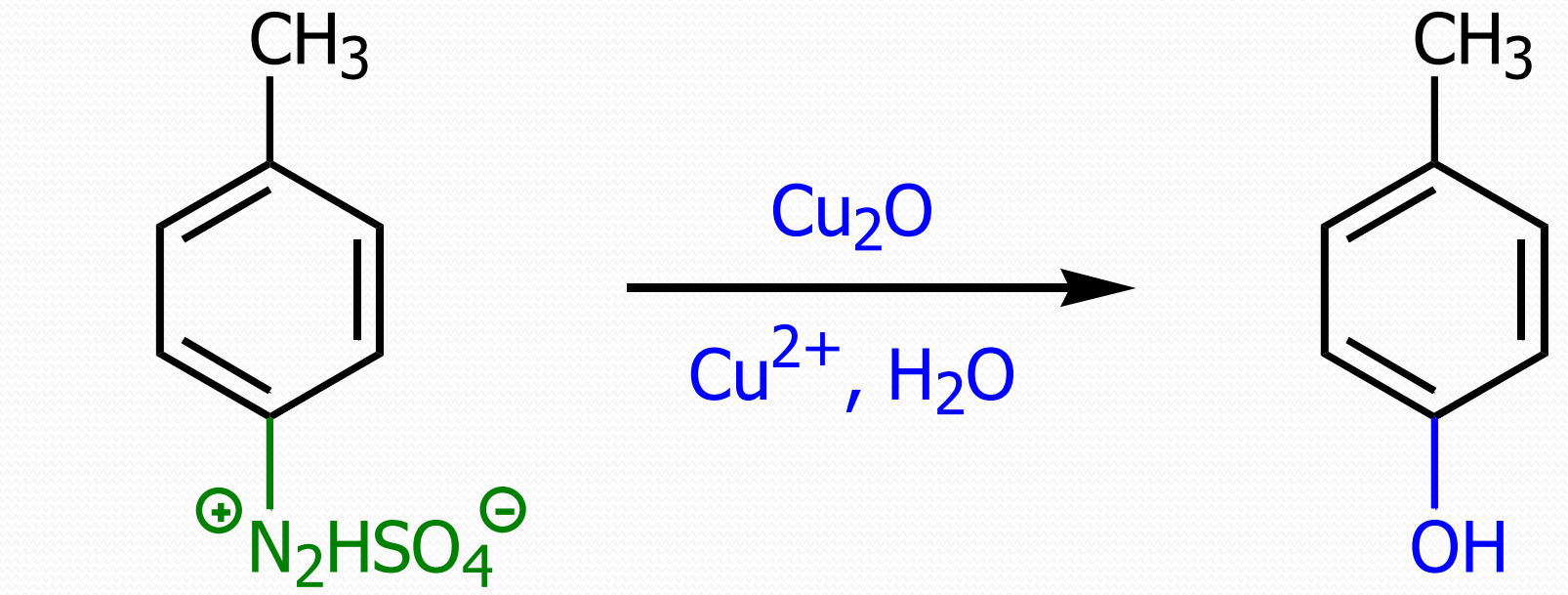
p-Nitroaniline

p-Iodonitrobenzene
(81% overall)

7D. Replacement by —F



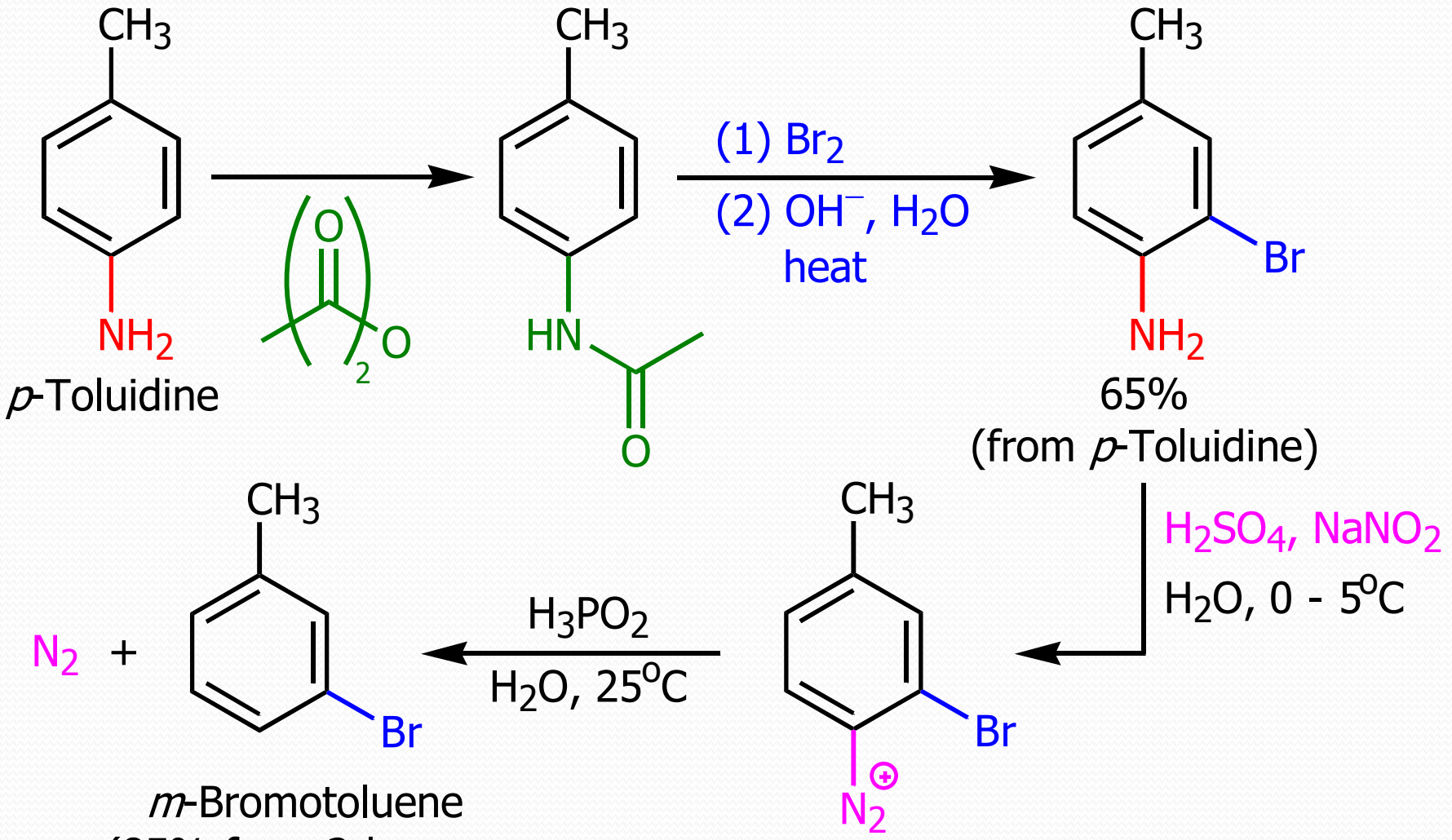
7E. Replacement by —OH



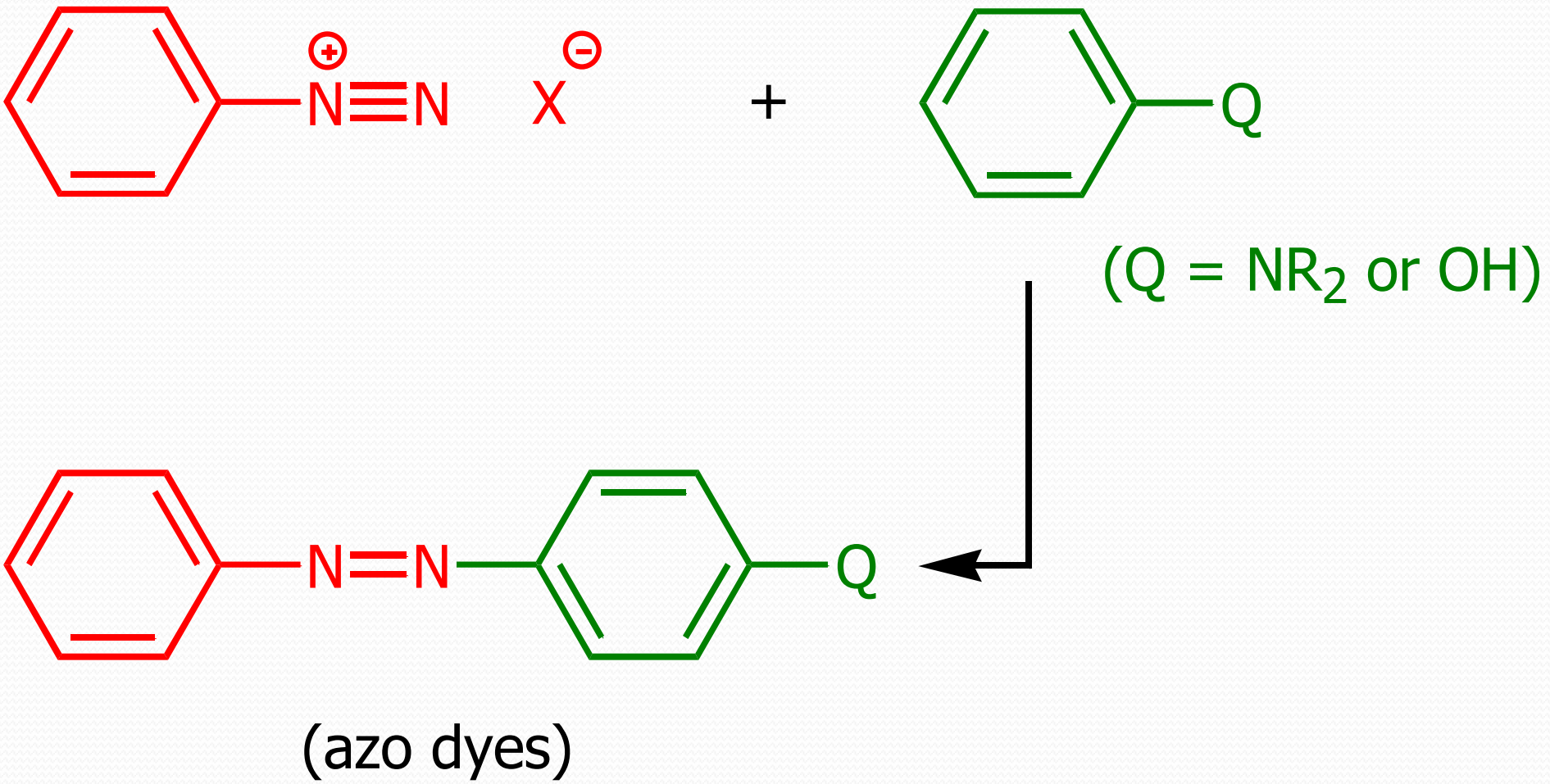
p-Toluenediazonium hydrogen sulfate

p-Cresol (93%)

7F. Replacement by Hydrogen: Deamination by Diazotization

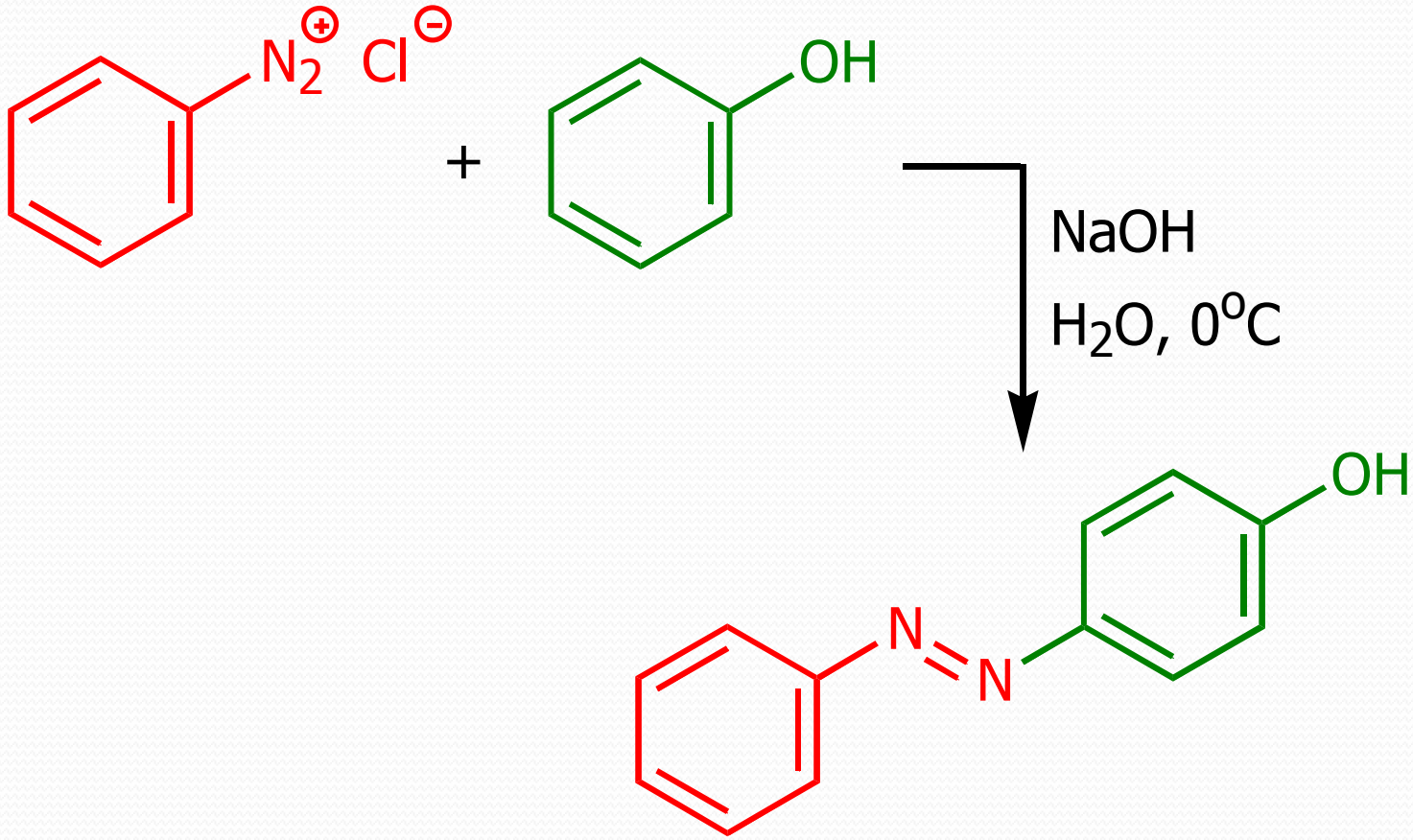


8. Coupling Reactions of Arenediazonium Salts



Examples

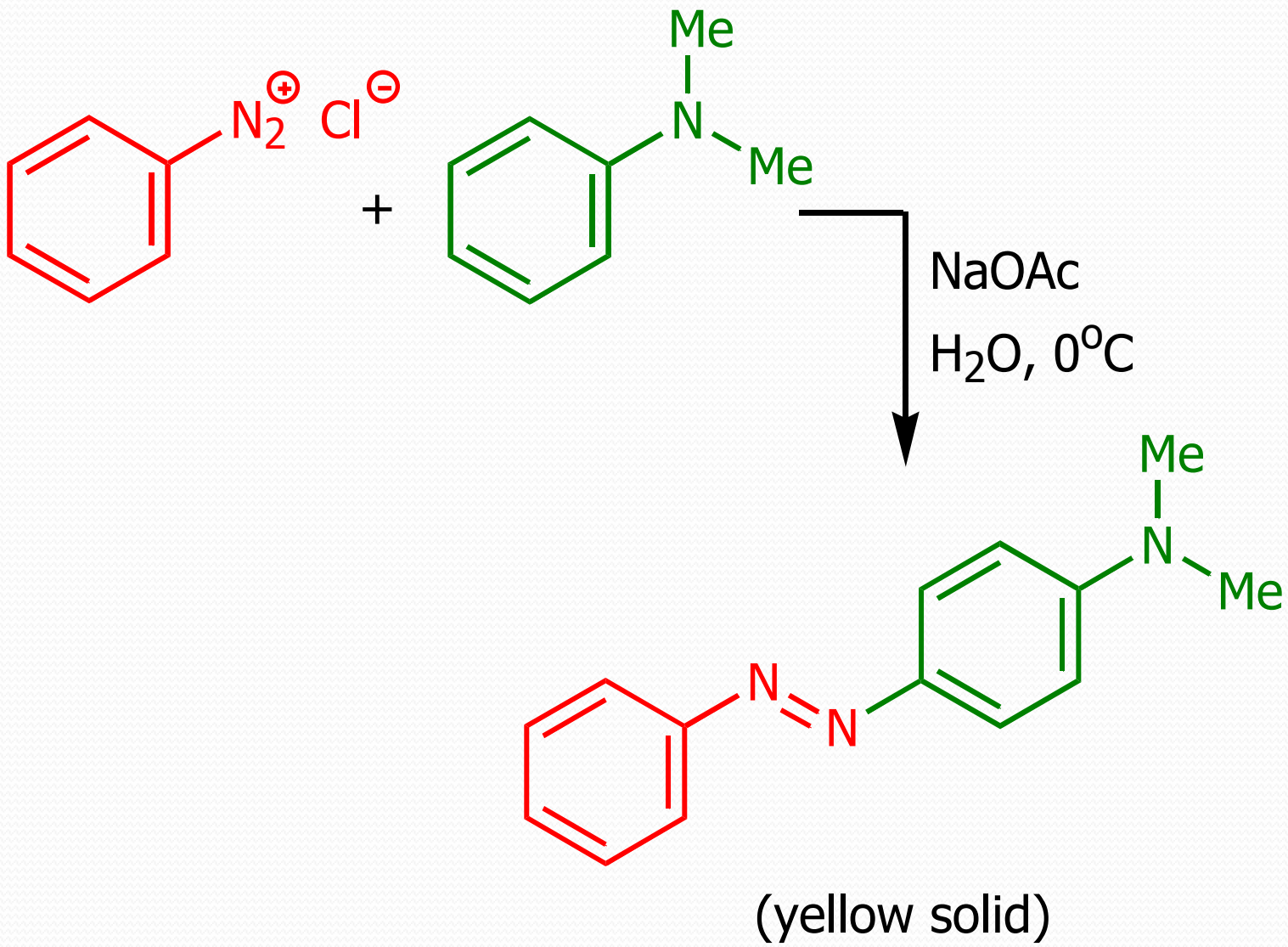
(1)



(orange solid)

Examples

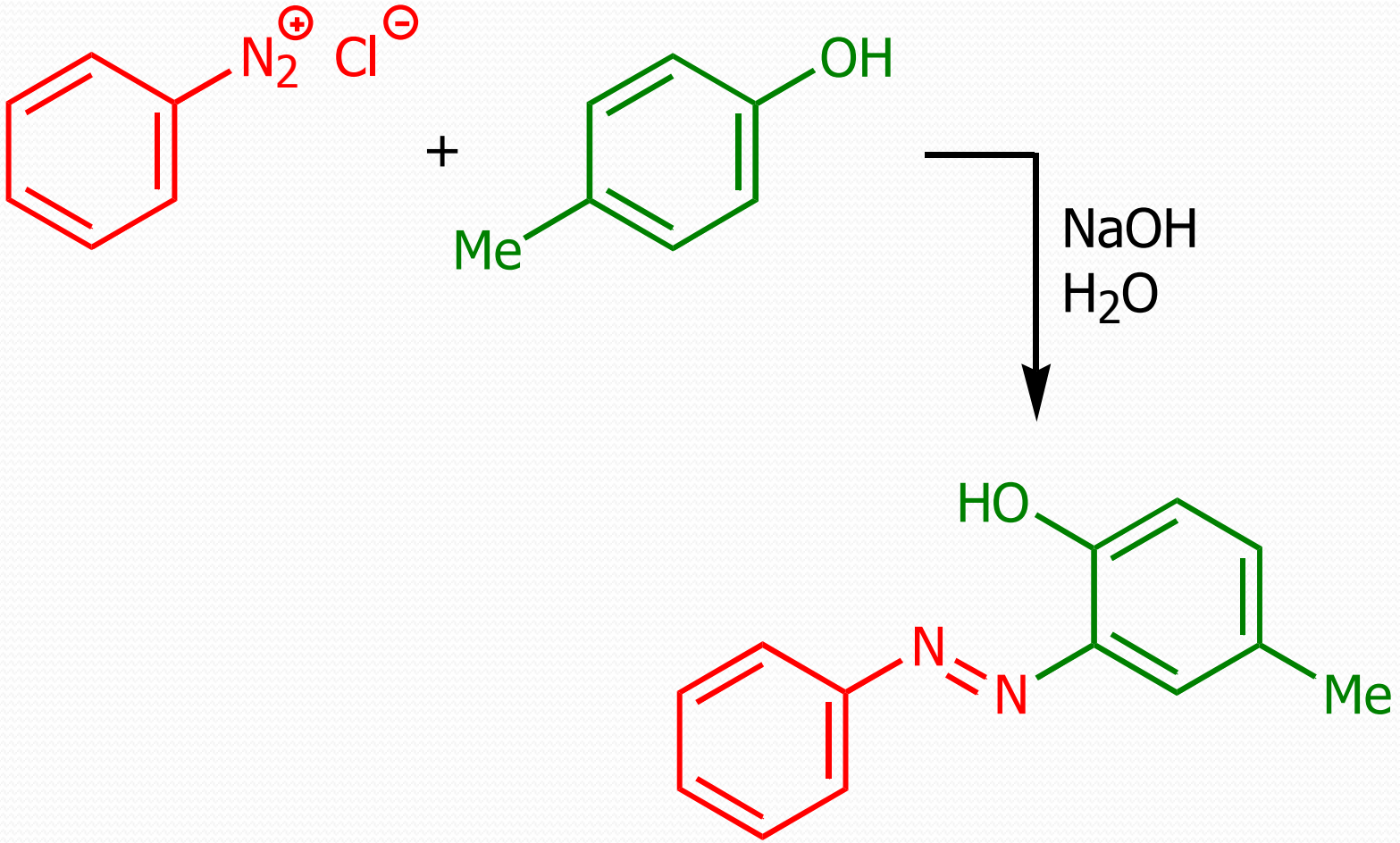
(2)



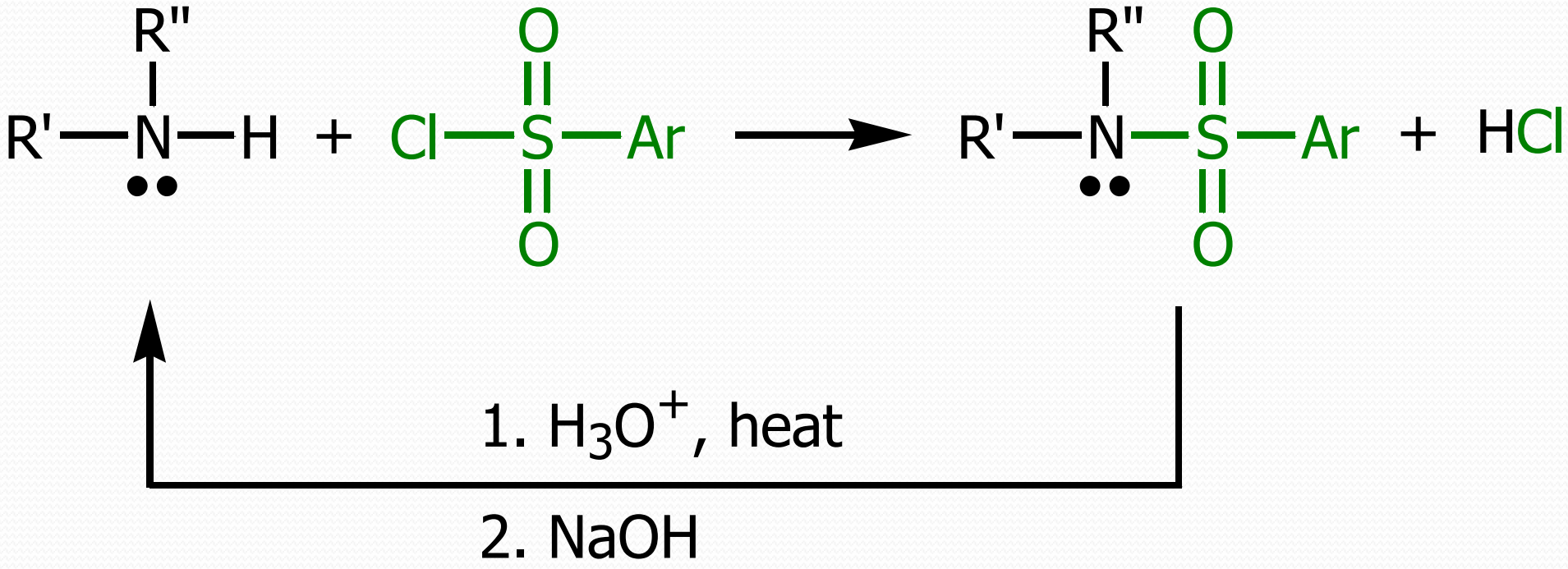
(yellow solid)

Examples

(3)



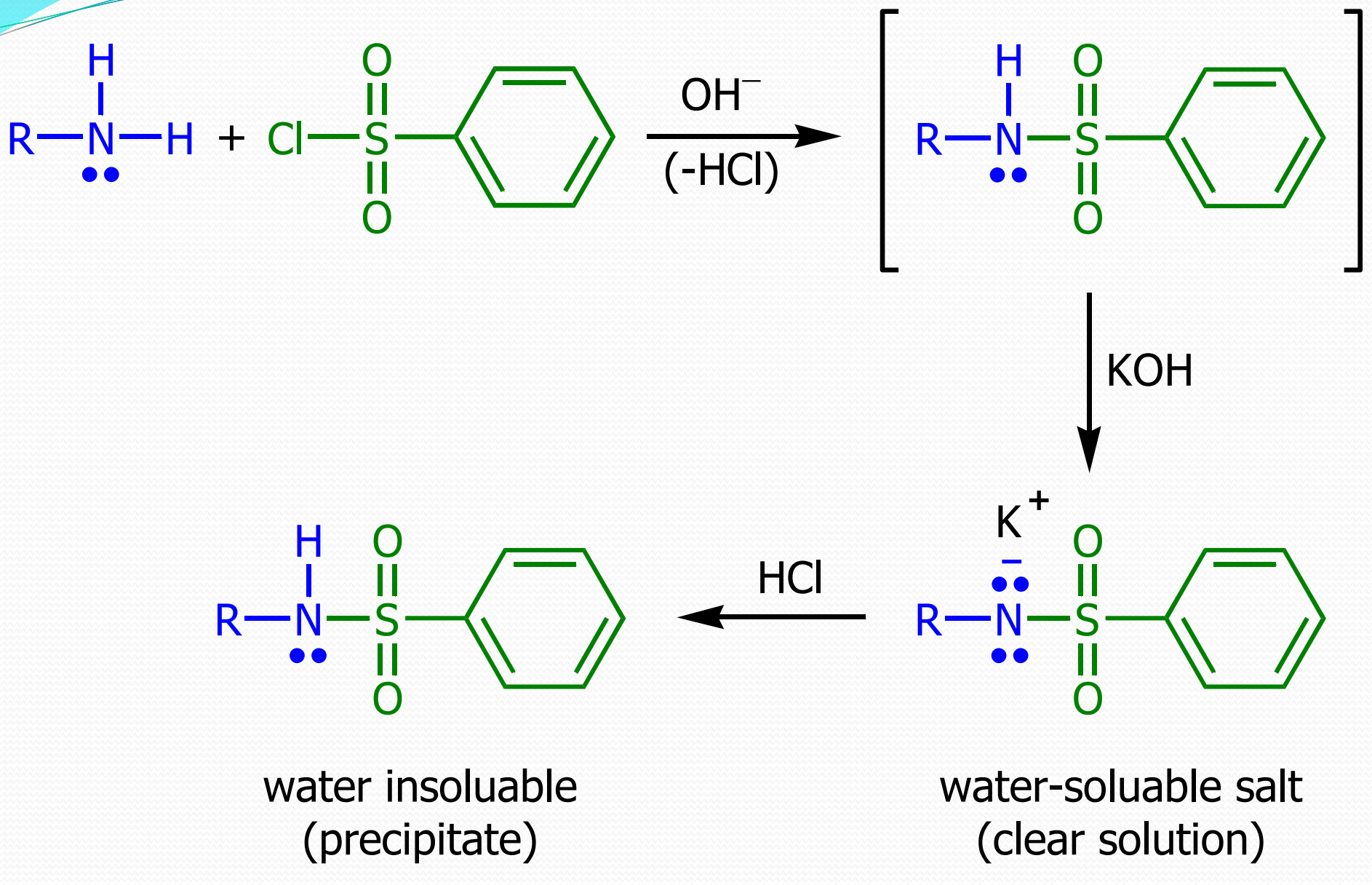
9. Reactions of Amines with Sulfonyl Chlorides



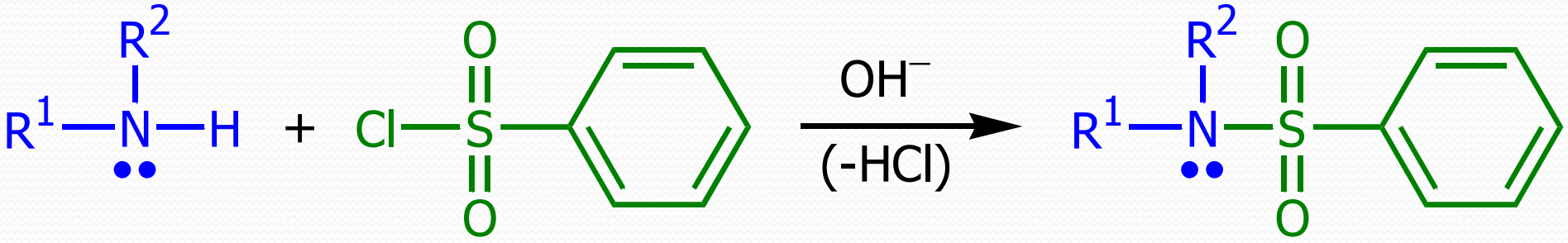
9A. The Hinsberg Test

- Sulfonamide formation is the basis for a chemical test, called the Hinsberg test, that can be used to demonstrate whether an amine is primary, secondary, or tertiary

1° Amine

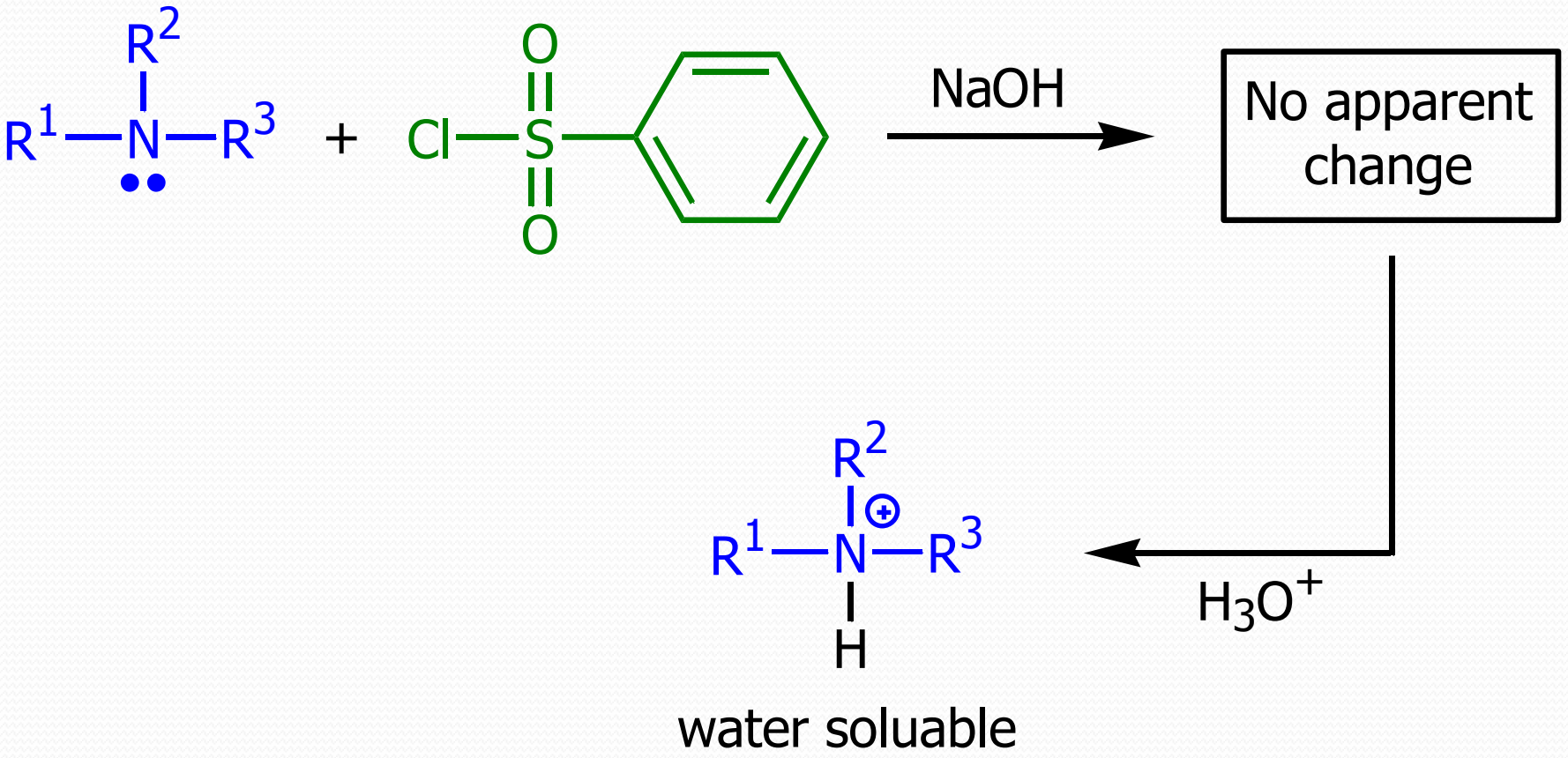

OH⁻
(-HCl)
KOH
HCl
water insoluable
(precipitate)
water-soluable salt
(clear solution)

2° Amine

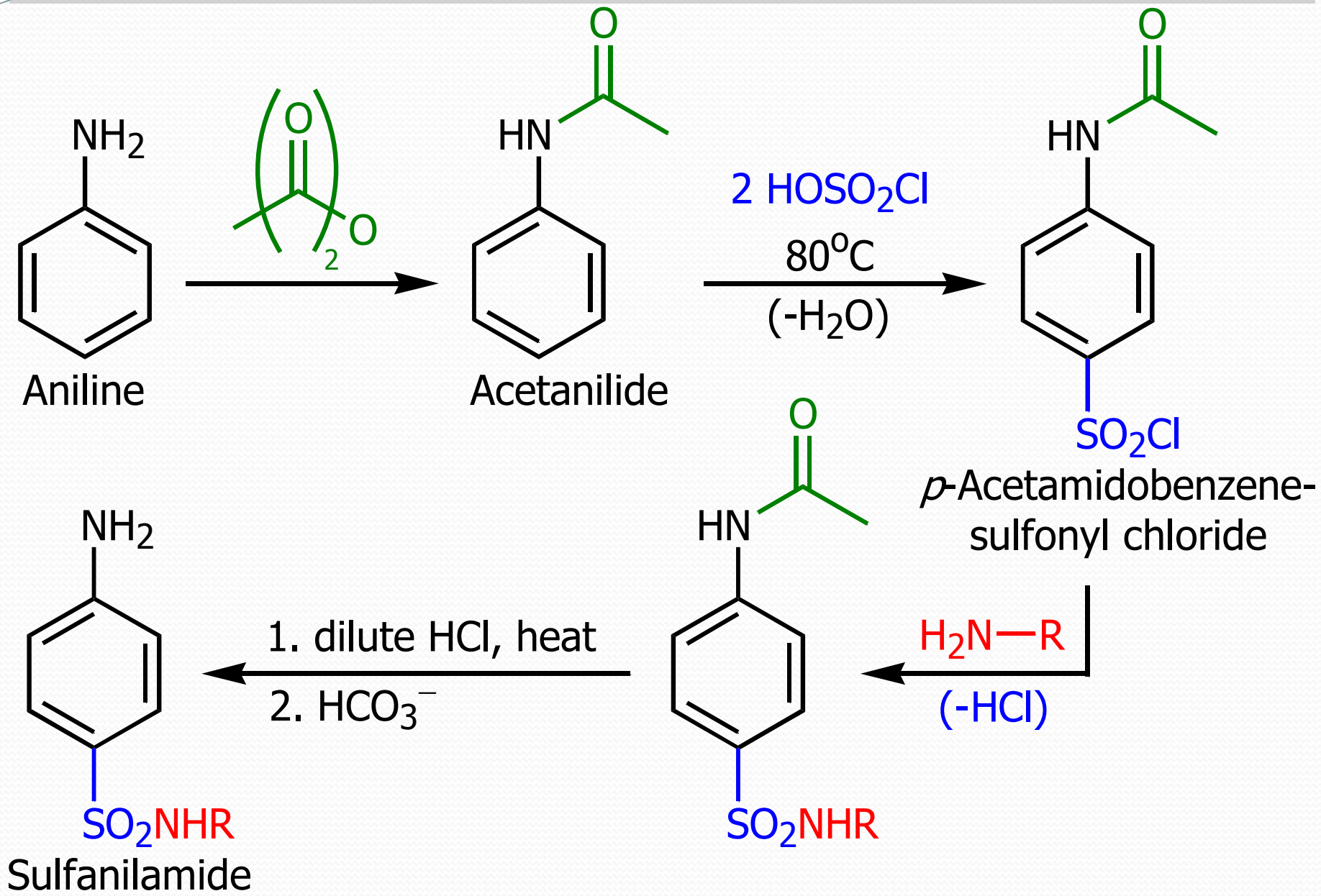


water insoluable
(precipitate)

3° Amine



10. Synthesis of Sulfa Drugs



11. Analysis of Amines

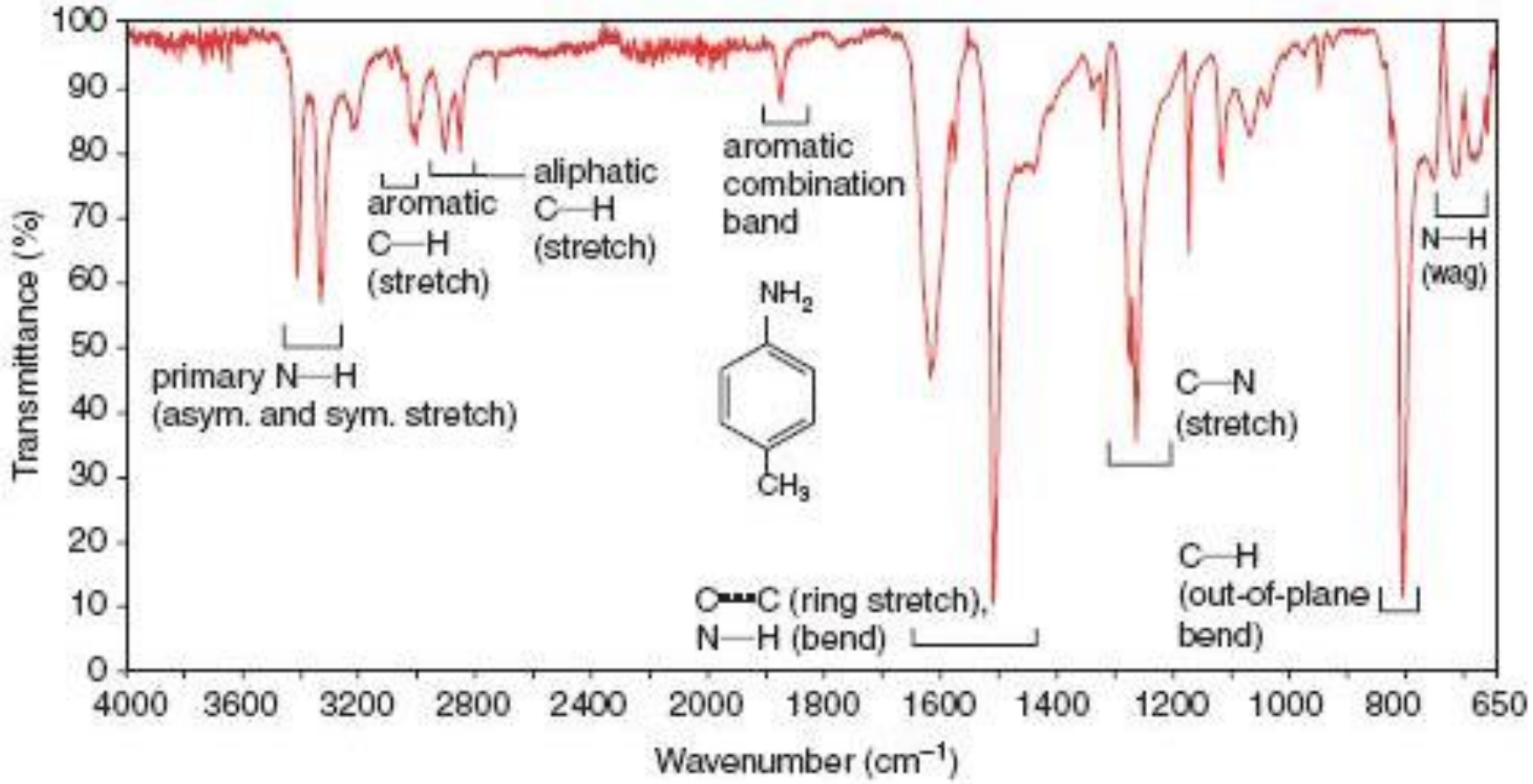
11A. Chemical Analysis

- Dissolve in dilute aqueous acid
- Moist pH paper
  $\Rightarrow$ basic
- Hinsberg test
- 1^{o} aromatic amines
  $\Rightarrow$ azo dye formation with 2-naphthol

11B. Spectroscopic Analysis

- IR
  - 1° amines
    - 3300 – 3555 cm^{-1} (N–H)
      $\Rightarrow$ two bands
  - 2° amines
    - 3300 – 3555 cm^{-1} (N–H)
      $\Rightarrow$ one band only
  - 3° amines
    - No bands at 3300 – 3555 cm^{-1} region

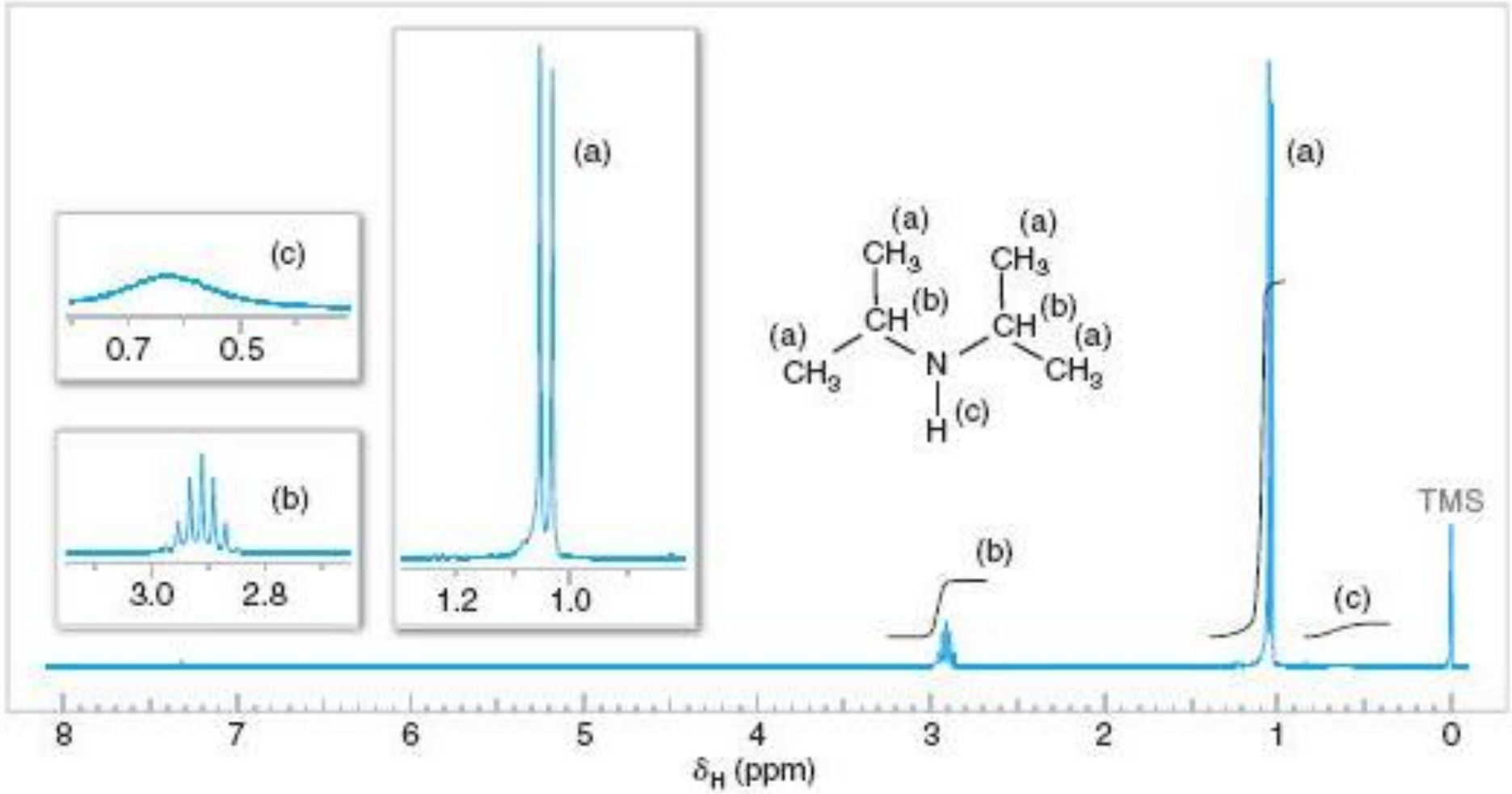
- Aliphatic amines
  - 1020 – 1220 cm^{-1} (C–N)
- Aromatic amines
  - 1250 – 1360 cm^{-1} (C–N)



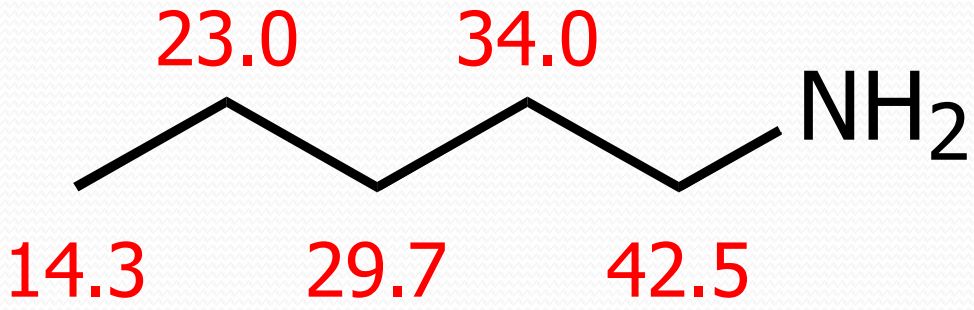
^{1}H NMR spectra

- 1° and 2° amines
  - N–H δ (0.5 – 5 ppm), usually broad, exact position depends on the solvent, concentration, purity and temperature
- N–H protons are not usually coupled to protons on adjacent carbons
- Protons on the α carbon of an aliphatic amine are deshielded by the electron-withdrawing effect of the nitrogen and absorb typically in the δ 2.2–2.9 region

- Protons on the β carbon are not deshielded as much and absorb in the range δ 1.0–1.7



^{13}C NMR spectra



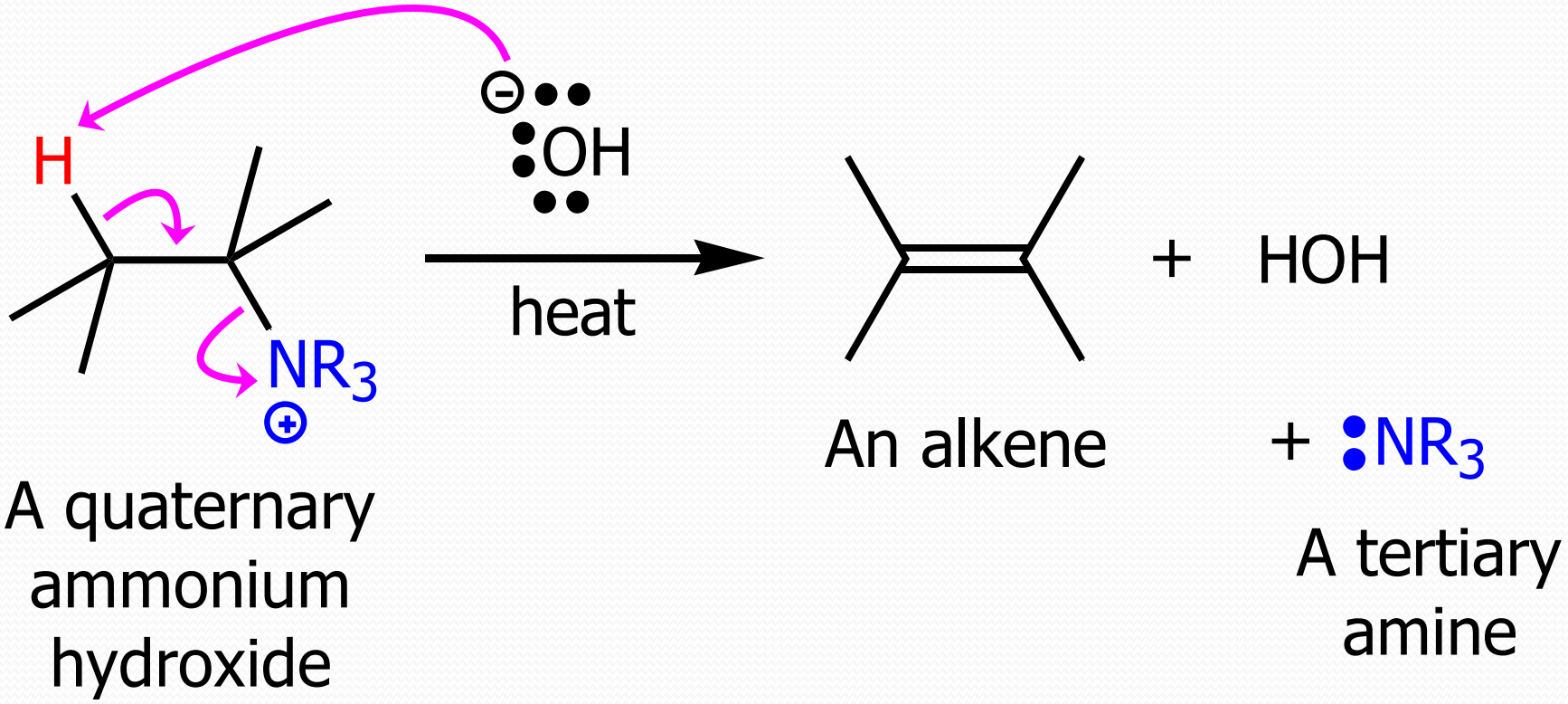
^{13}C NMR chemical shifts (δ)

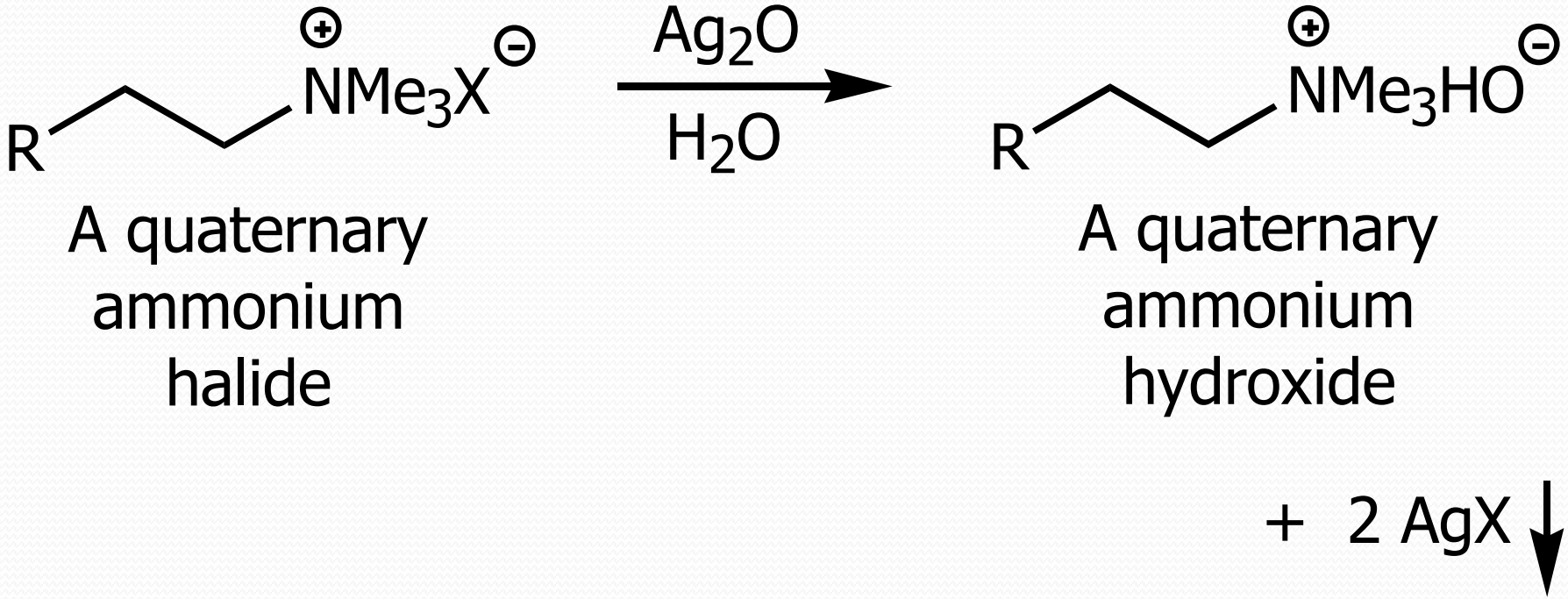
Mass spectra

- The molecular ion in the mass spectrum of an amine has an odd number mass (unless there is an even number of nitrogen atoms in the molecule)
- The peak for the molecular ion is usually strong for aromatic and cyclic aliphatic amines but weak for acyclic aliphatic amines
- Cleavage between the α and β carbons of aliphatic amines is a common mode of fragmentation

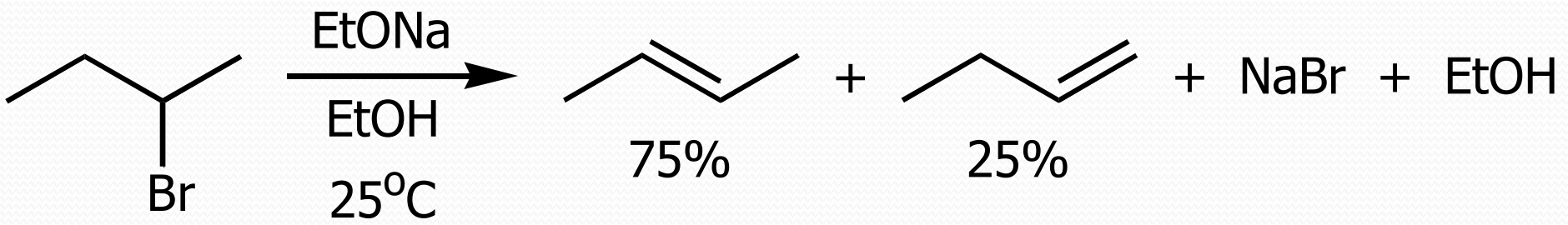
12. Eliminations Involving Ammonium Compounds

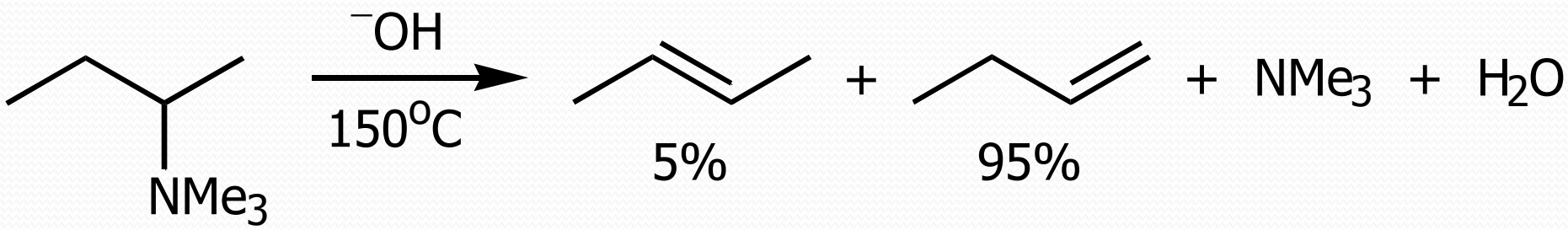
12A. The Hofmann Elimination

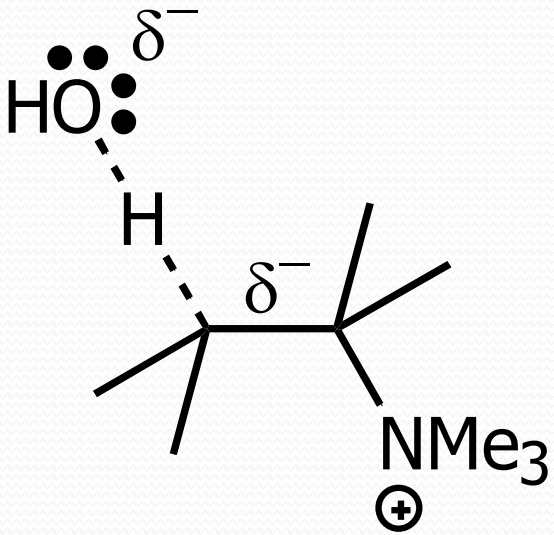



R
NMe3X
Ag2O
H2O
R
NMe3HO
A quaternary ammonium halide
A quaternary ammonium hydroxide
+ 2 AgX

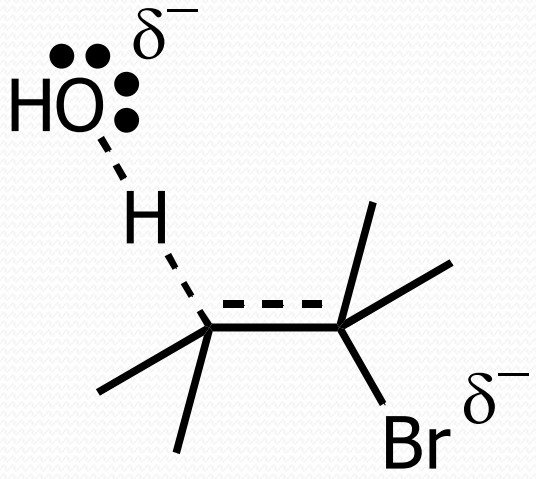
- Although most eliminations involving neutral substrates tend to follow the *Zaitsev rule*, eliminations with charged substrates tend to follow what is called the Hofmann rule and yield mainly the least substituted alkene





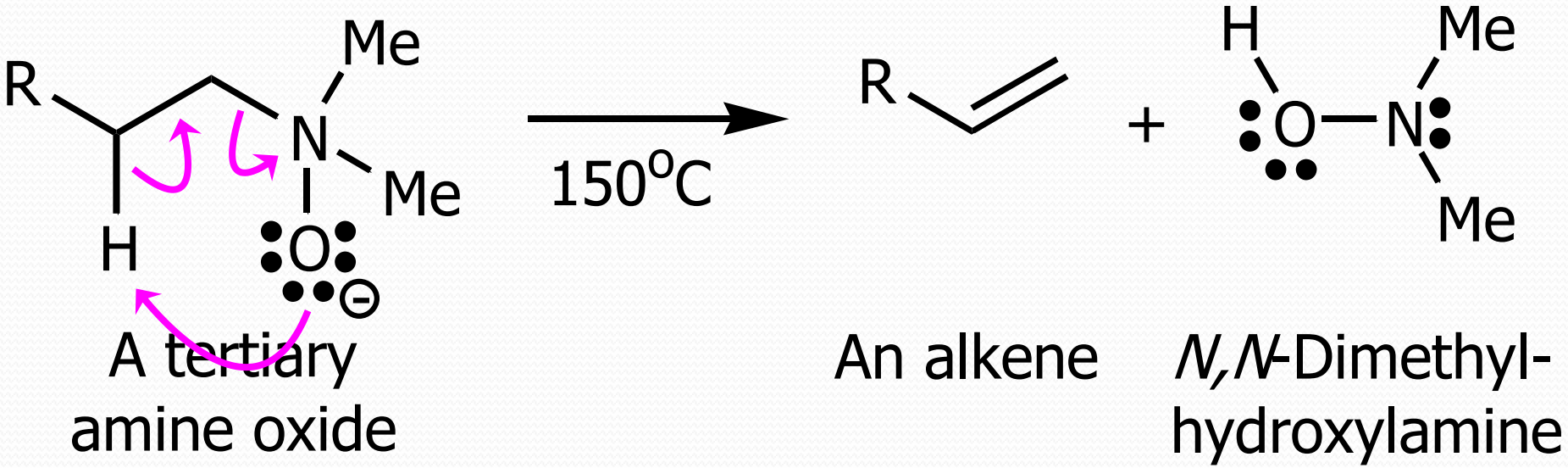


Carbanion-like
transition state
(gives Hofmann orientation)



Alkene-like
transition state
(gives Zaitsev orientation)

12B. The Cope Elimination

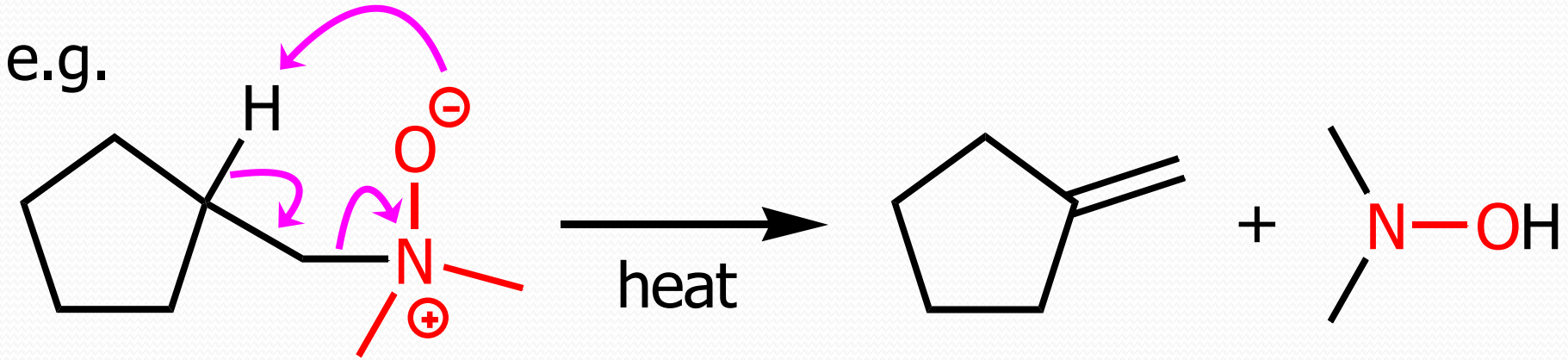


A tertiary amine oxide

An alkene

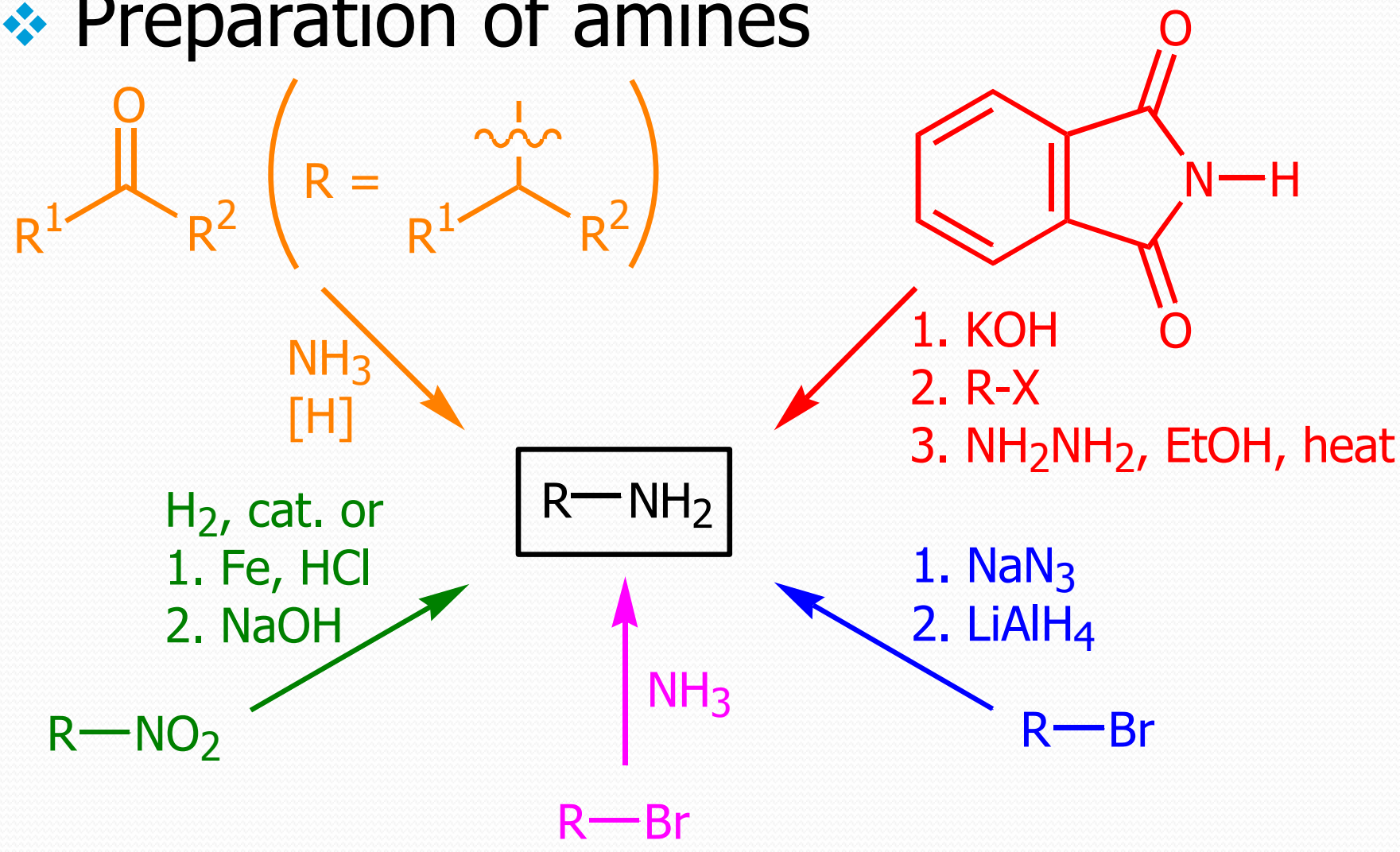
N,N-Dimethyl-hydroxylamine

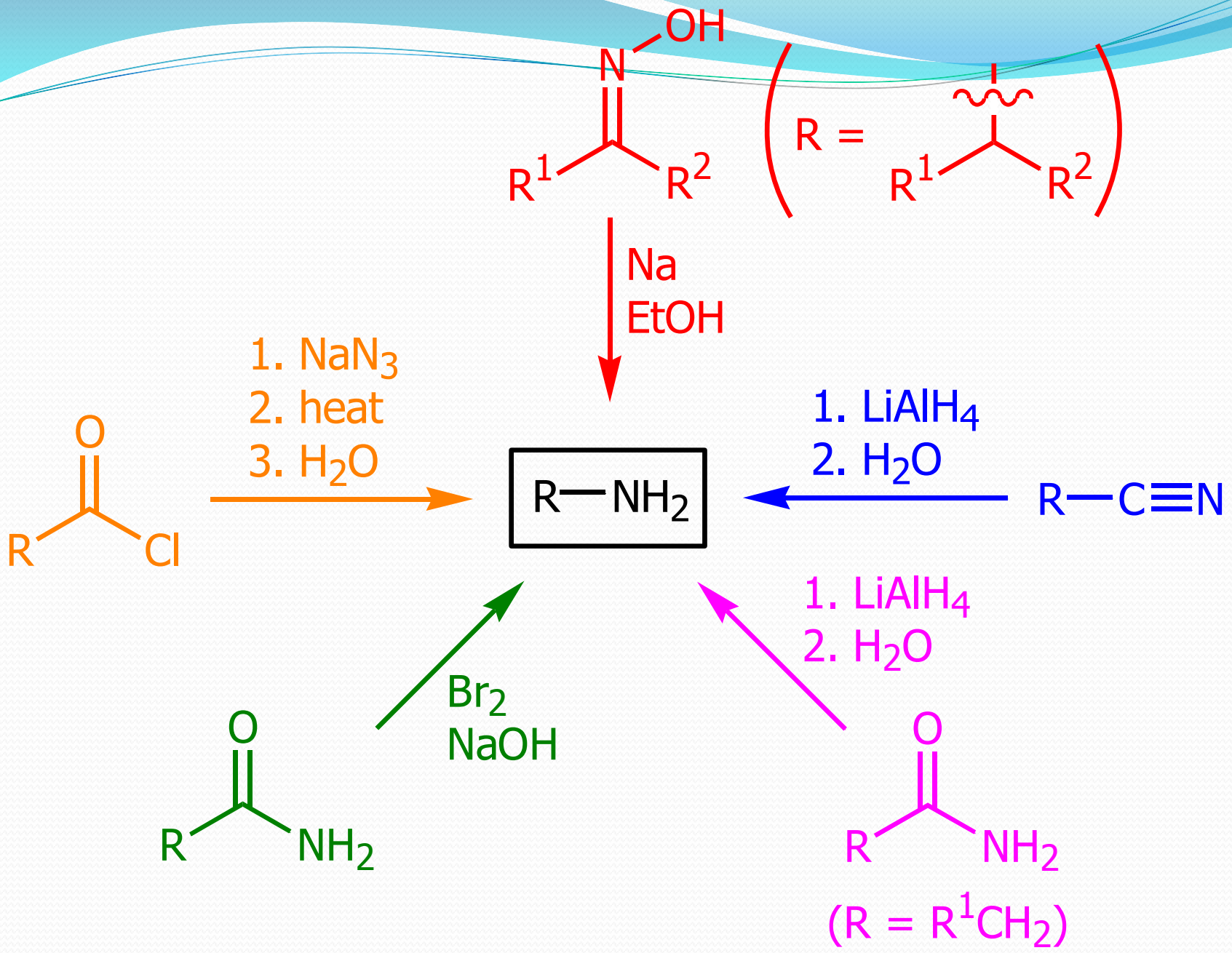
e.g.



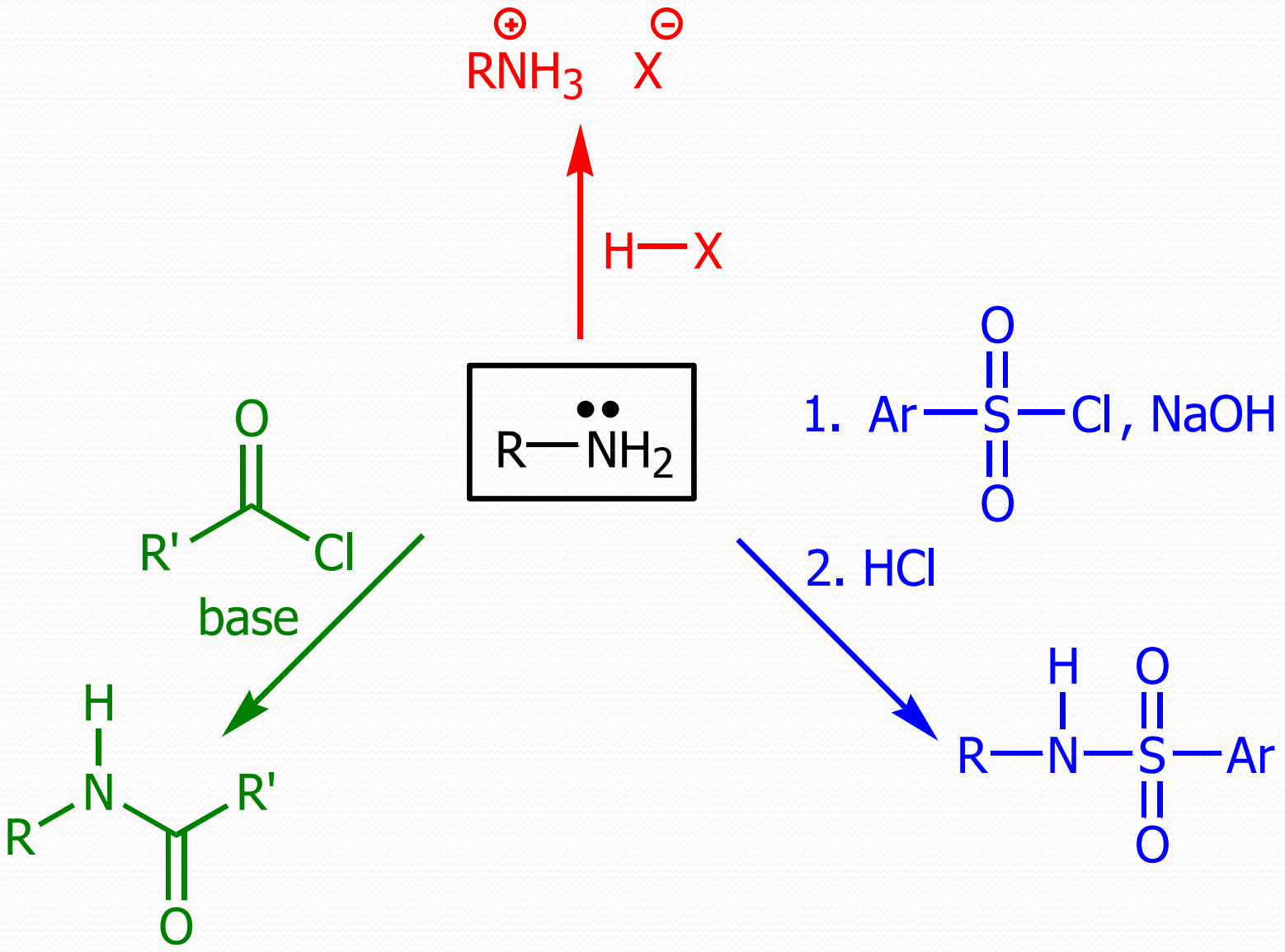
13. Summary of Preparations and Reactions of Amines

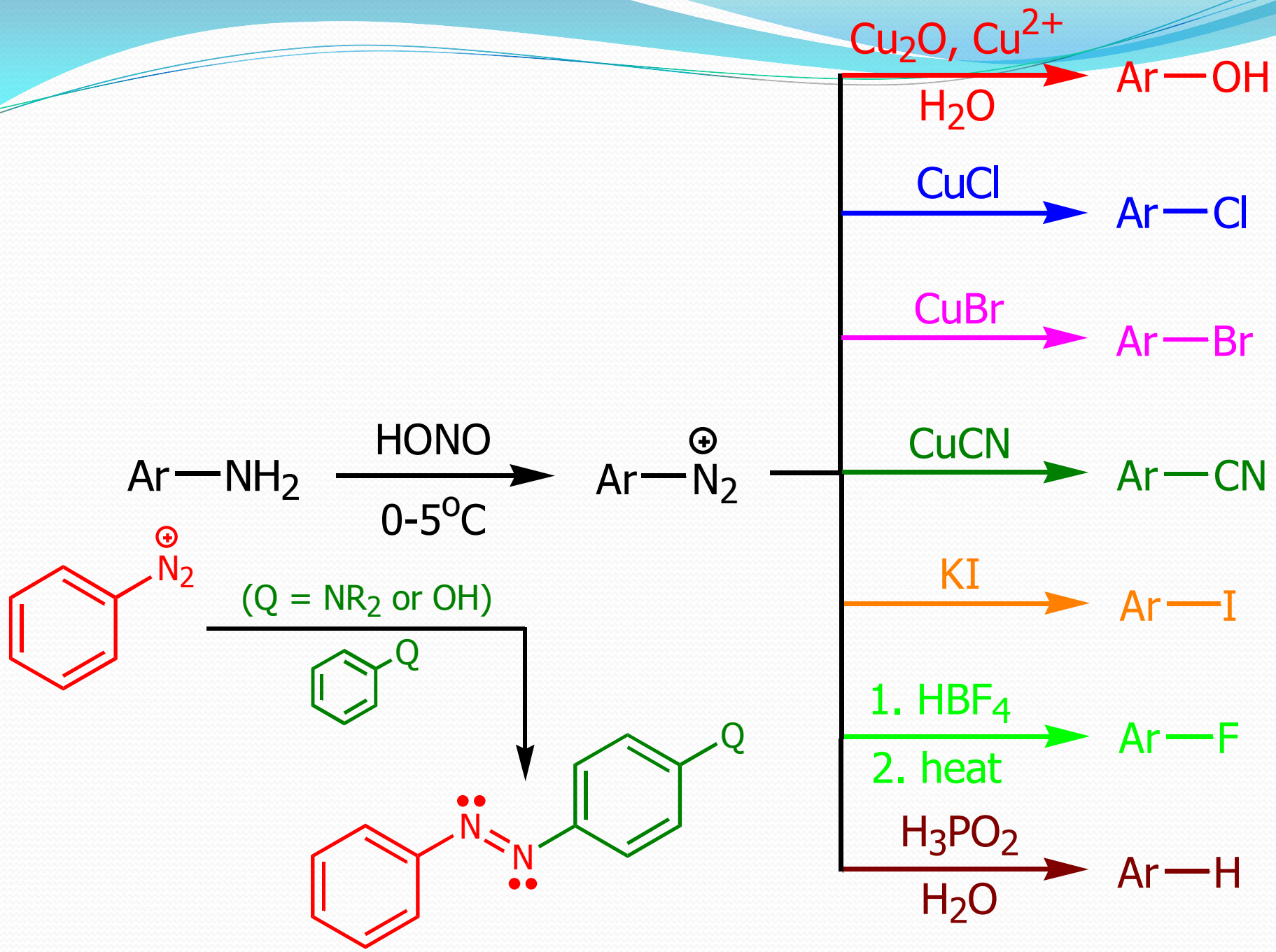
- Preparation of amines



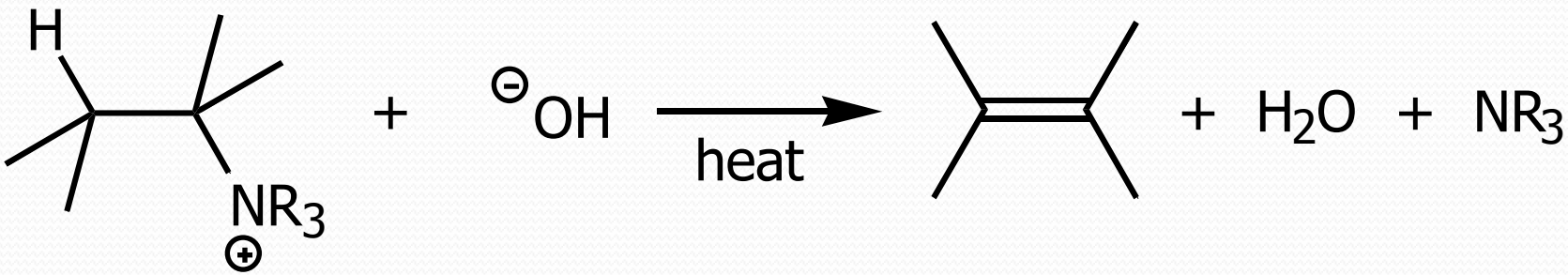

OH
N
R1
R2
R =
R1
R2
Na
EtOH
1. NaN3
2. heat
3. H2O
O
R
Cl
R—NH2
1. LiAlH4
2. H2O
R—C≡N
1. LiAlH4
2. H2O
Br2
NaOH
O
R
NH2
O
R
NH2
(R = R1CH2)

Reactions of amines

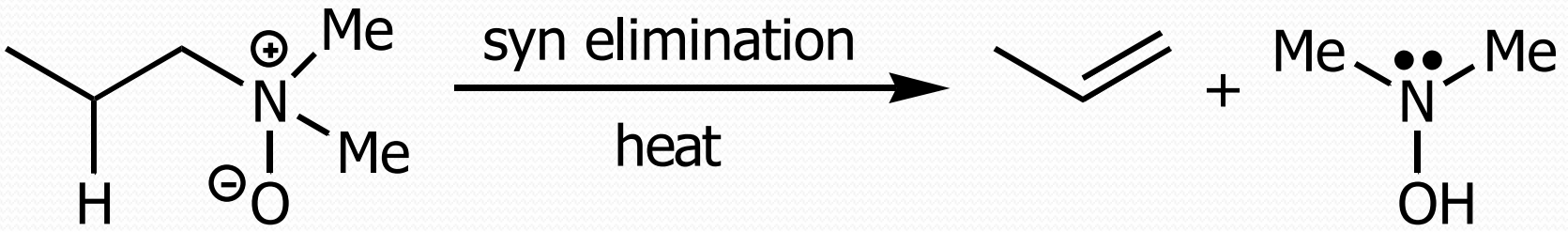



Cu2O, Cu2+
H2O
Ar—OH
CuCl
Ar—Cl
CuBr
Ar—Br
Ar—NH2
HONO
0-5°C
Ar—N2
CuCN
Ar—CN
KI
Ar—I
(Q = NR2 or OH)
Q
1. HBF4
2. heat
Ar—F
H3PO2
H2O
Ar—H

Hofmann Elimination



Cope Elimination



🔔 END OF CHAPTER 21 🔔