

21

Organic Chemistry

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21

Amines

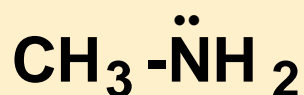
Chapter 21

21-2

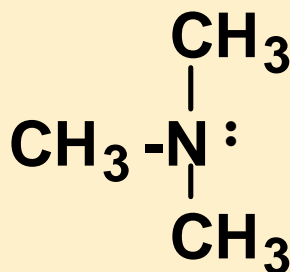
21 Structure & Classification

u Amines are classified as

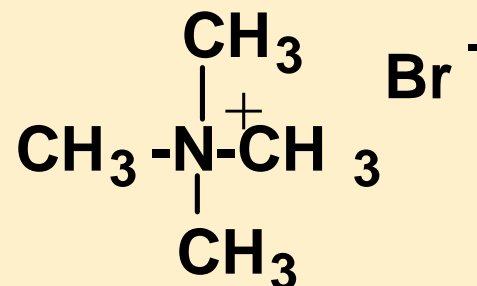
- **1°, 2°, or , 3° amines:** amines in which 1, 2, or 3 hydrogens of NH_3 are replaced by alkyl or aryl groups
- **4° amines:** ions in which nitrogen is bonded to four carbons and bears a positive charge



Methylamine
(a 1° amine)



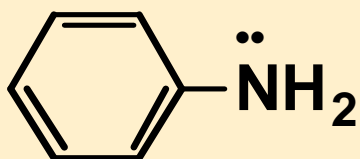
Trimethylamine
(a 3° amine)



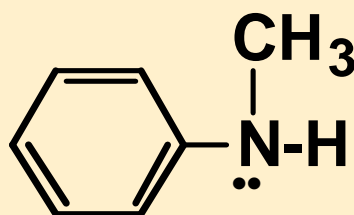
Tetramethylammonium
bromide
(a 4° ammonium salt)

21 Structure & Classification

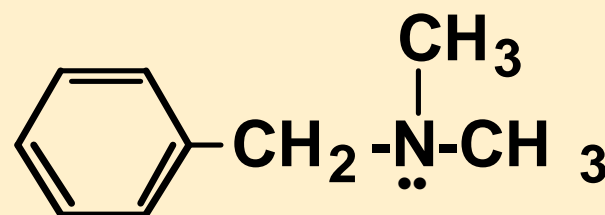
- u Amines are further divided into aliphatic, aromatic, and heterocyclic amines:
- **aliphatic amines:** amines in which nitrogen is bonded only to alkyl groups
 - **aromatic amines:** amines in which nitrogen is bonded to one or more aryl groups



Aniline
(a 1° aromatic amine)



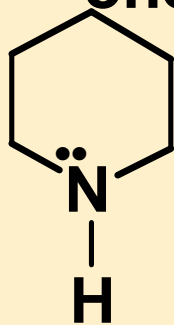
N-Methylaniline
(a 2° aromatic amine)



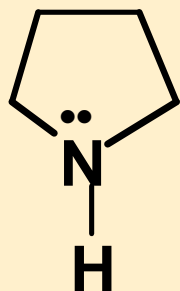
Benzyldimethylamine
(a 3° aliphatic amine)

21 Structure & Classification

- **heterocyclic amines:** amines in which nitrogen is one of the atoms of a ring

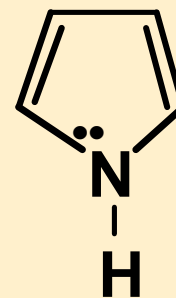


Piperidine

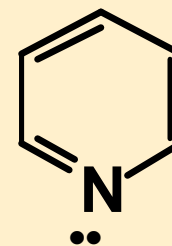


Pyrrolidine

(heterocyclic
aliphatic amines)



Pyrrole

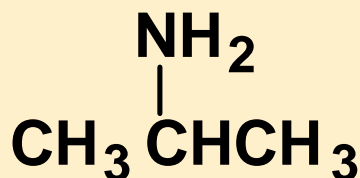


Pyridine

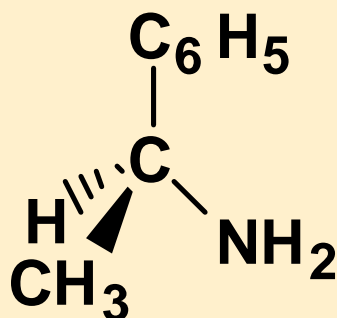
(heterocyclic
aromatic amines)

21 Nomenclature

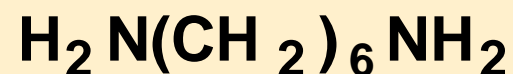
- u Aliphatic amines: replace the suffix **-e** of the parent alkane by **-amine**



2-Propanamine



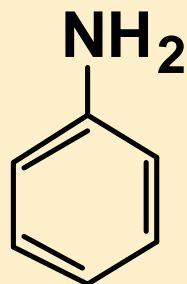
(S)-1-Phenylethan-
amine



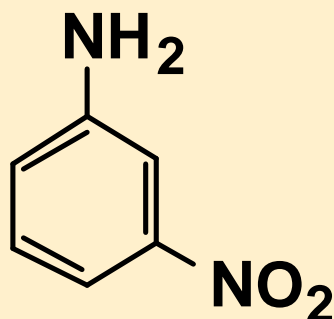
1,6-Hexanediamine

21 Nomenclature

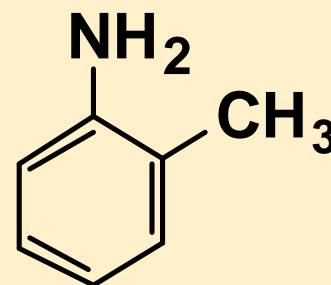
u The IUPAC system retains the name aniline



Aniline



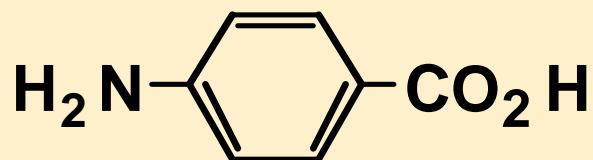
3-Nitroaniline
(m-Nitroaniline)



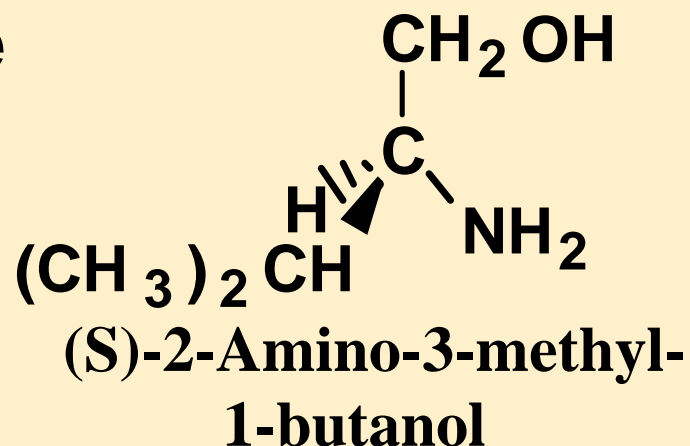
2-Methylaniline
(o-Toluidine)

21 Nomenclature

- u Among the various functional groups discussed in the text, -NH_2 is one of the lowest in order of precedence



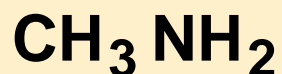
4-Aminobenzoic acid



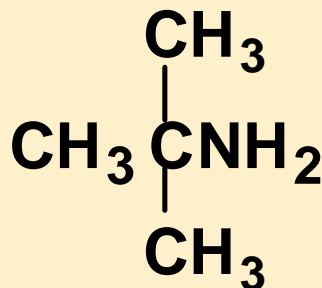
(S)-2-Amino-3-methyl-1-butanol

21 Nomenclature

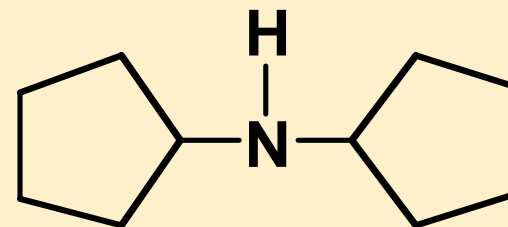
- Common names for most aliphatic amines are derived by listing the alkyl groups attached to nitrogen in one word ending with the suffix -amine



Methylamine



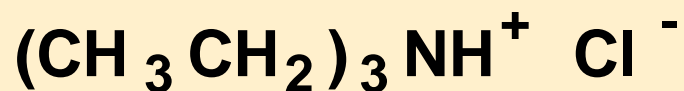
tert-Butylamine



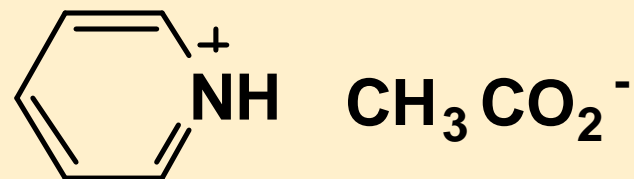
Dicyclopentylamine

21 Nomenclature

- u When four groups are bonded to nitrogen, the compound is named as a salt of the corresponding amine



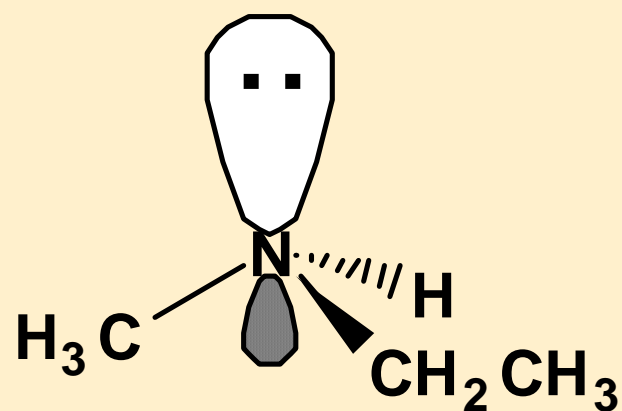
**Triethylammonium
chloride**



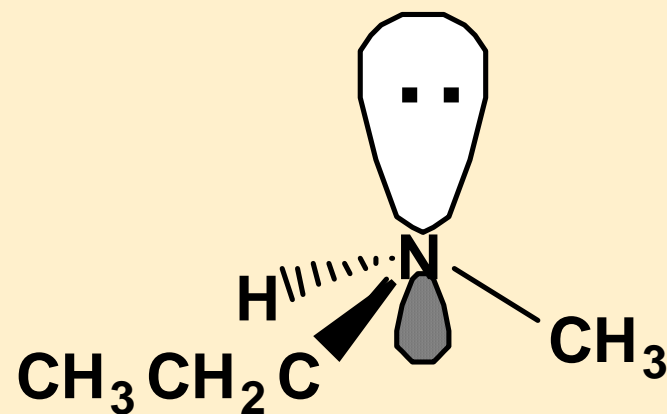
Pyridinium acetate

21 Chirality of Amines

- u If we consider the unshared pair of electrons on nitrogen as a fourth group, then the arrangement of groups around N is approximately tetrahedral
- u An amine with 3 different groups bonded to N is chiral and exists as a pair of enantiomers



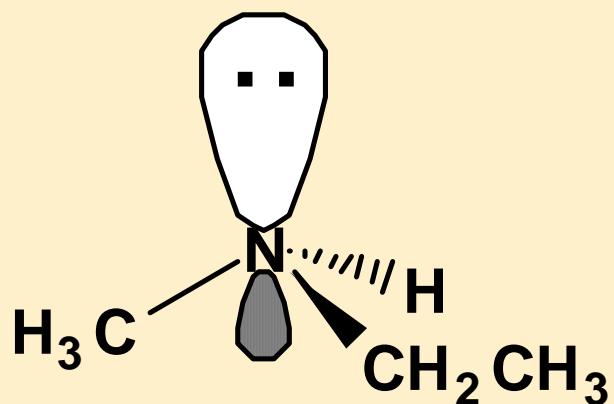
(S)-Ethylmethylamine



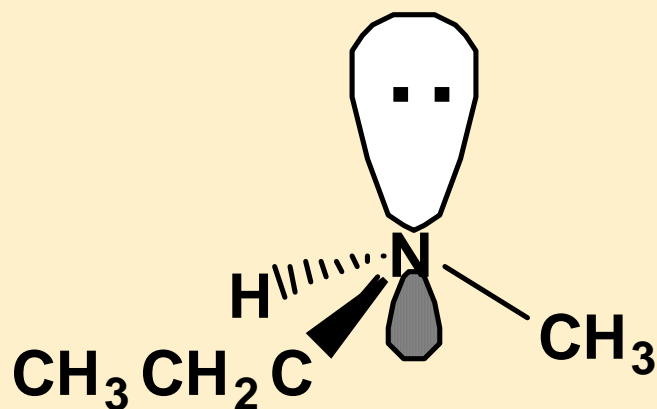
(R)-Ethylmethylamine

21 Chirality of Amines

u In principle a chiral amine can be resolved,



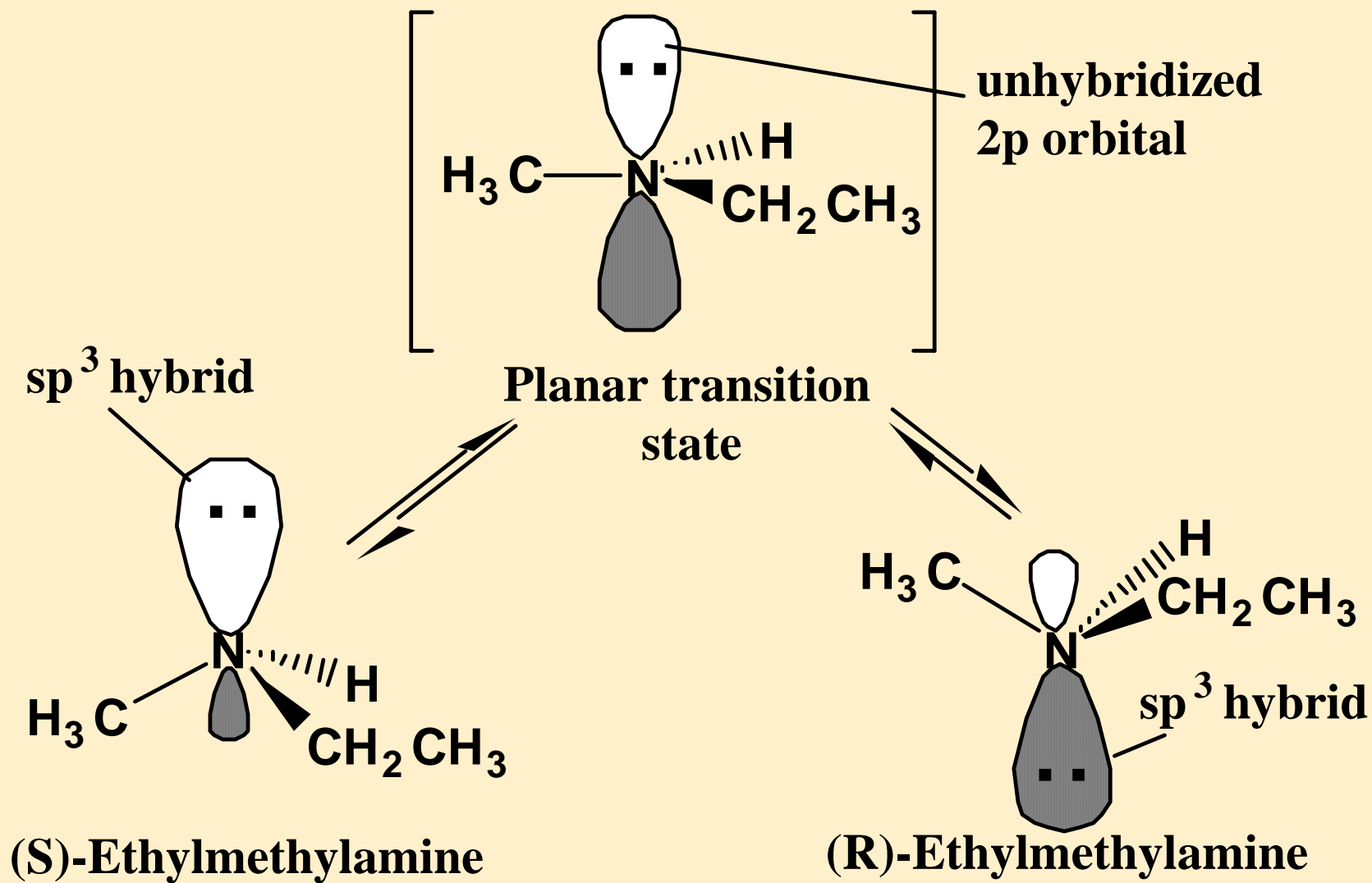
(S)-Ethylmethylamine



(R)-Ethylmethylamine

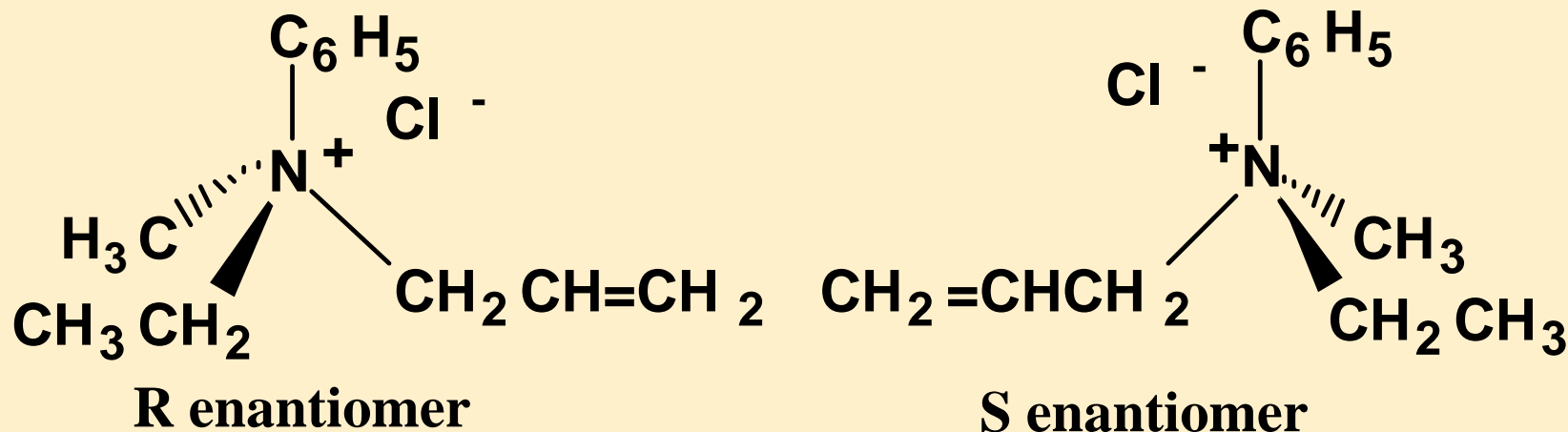
u but in practice they cannot be resolved because they undergo pyramidal inversion, which converts one enantiomer to the other

21



21 Chirality of Amines

- Pyramidal inversion is not possible with quaternary ammonium ions, and their salts can be resolved



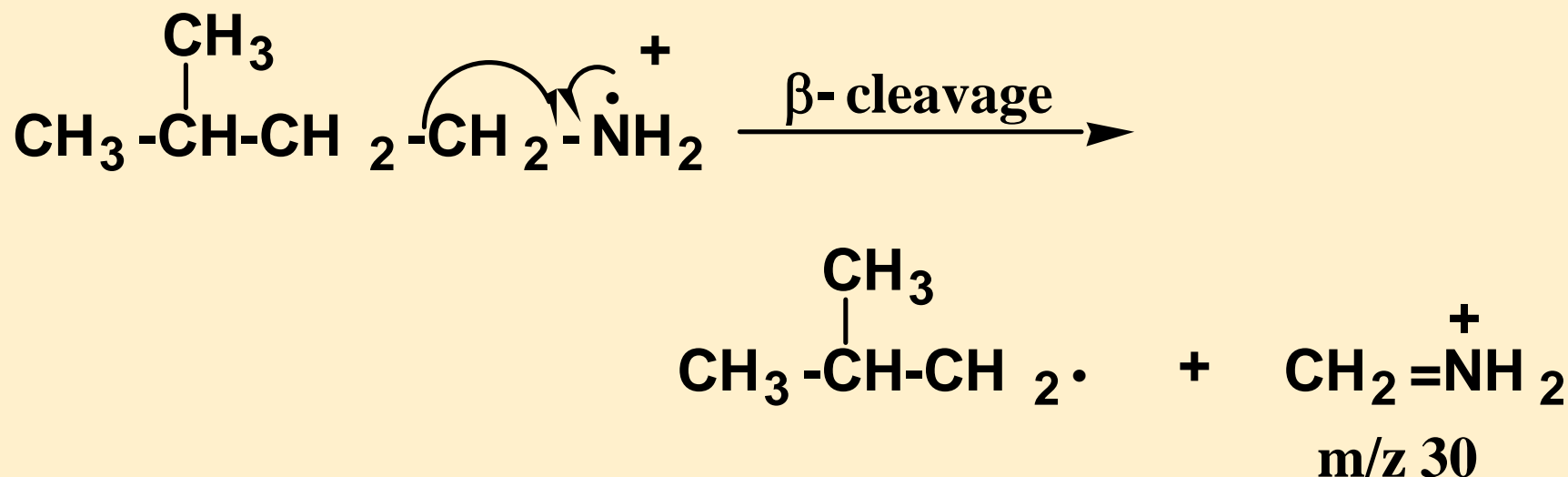
21 Physical Properties

- u Amines are polar compounds, and both 1° and 2° amines form intermolecular hydrogen bonds
- u N-H----N hydrogen bonds are not as strong as O-H---O hydrogen bonds, however, because the difference in electronegativity between N and H ($3.0 - 2.1 = 0.9$) is not as great as that between O and H ($3.5 - 2.1 = 1.4$)

	CH ₃ CH ₃	CH ₃ NH ₂	CH ₃ OH
MW (g/mol)	30.1	31.1	32.0
bp (°C)	-88.6	-6.3	65.0

21 Mass Spectrometry

- u The most characteristic fragmentation pattern of 1°, 2°, and 3° aliphatic amines is β -cleavage



21 NMR Spectroscopy

u ^1H -NMR

- the chemical shift of amine hydrogens is variable, a may be found in the region δ 0.5 to 5.0 depending on the solvent, concentration, and temperature
- they generally appear as singlets

u ^{13}C -NMR

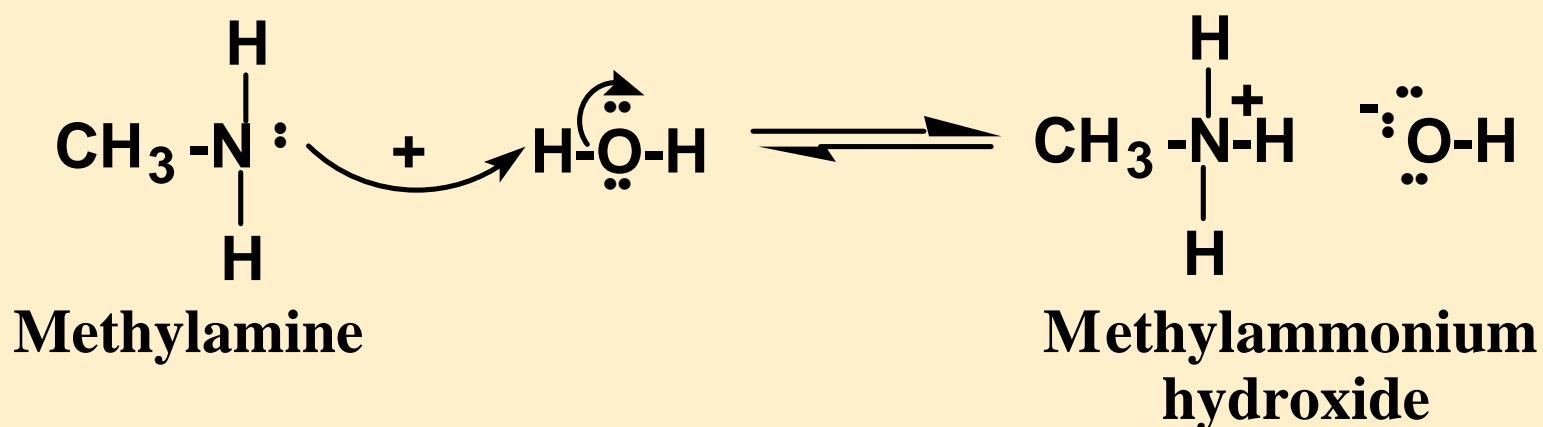
- carbons bonded to nitrogen are generally shifted approx. 20 ppm downfield relative to their signal in an alkane of comparable structure

21 IR Spectroscopy

- u **1° and 2° amines show N-H stretching absorption in the region 3300 - 3500 cm⁻¹**
 - **1° amines show two bands in this region**
 - **2° amines show only one band in this region**

21 Basicity

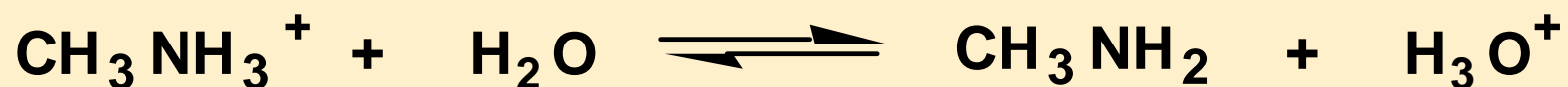
- u All amines are weak bases, and aqueous solutions of amines are basic



$$K_b = K_{\text{eq}} [\text{H}_2\text{O}] = \frac{[\text{CH}_3\text{NH}_3^+][\text{OH}^-]}{[\text{CH}_3\text{NH}_2]} = 4.37 \times 10^{-4}$$

21 Basicity

- u It is more common to discuss the basicity of amines by reference to the acid ionization constant of the corresponding conjugate acid



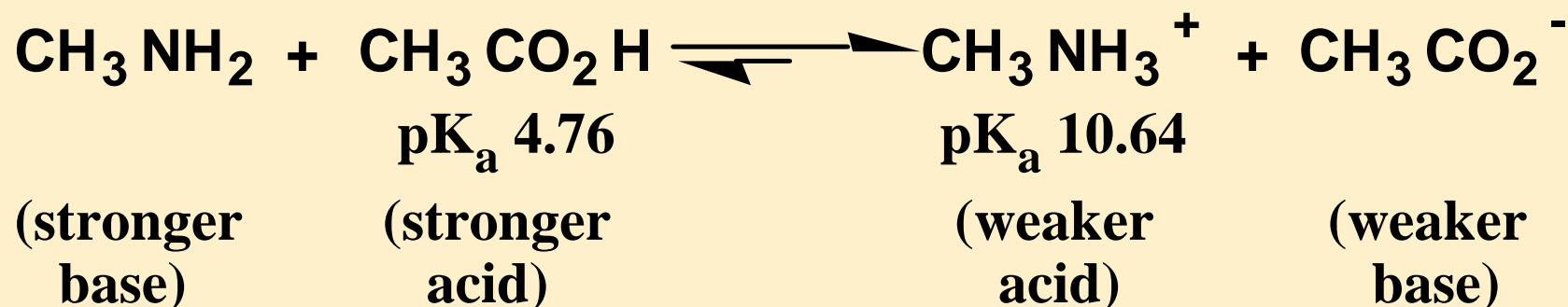
$$K_a = \frac{[\text{CH}_3\text{NH}_2][\text{H}_3\text{O}^+]}{[\text{CH}_3\text{NH}_3^+]} = 2.29 \times 10^{-11} \quad \text{p}K_a = 10.64$$

- u For any acid-conjugate base pair

$$\text{p}K_a + \text{p}K_b = 14.00$$

21 Basicity

- u Using values of pK_a , we can compare the acidities of amine conjugate acids with other acids



$$pK_{eq} = -5.88$$

$$K_{eq} = 7.6 \times 10^5$$

21 Basicity-Aliphatic Amines

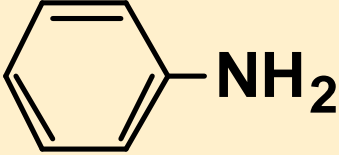
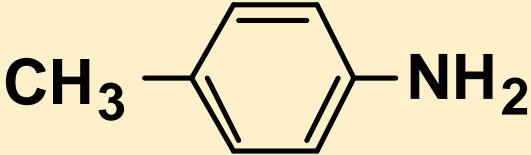
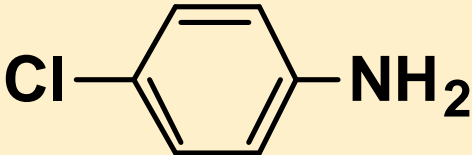
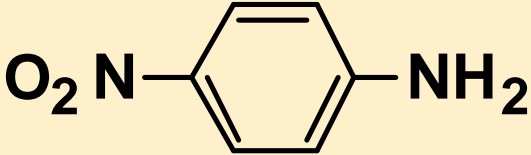
Amine	Structure	pK _b	pK _a
Ammonia	NH₃	4.74	9.26
Primary Amines			
methylamine	CH ₃ NH ₂	3.36	10.64
ethylamine	CH ₃ CH ₂ NH ₂	3.19	10.81
cyclohexylamine	C ₆ H ₁₁ NH ₂	3.34	10.66
Secondary Amines			
dimethylamine	(CH ₃) ₂ NH	3.27	10.73
diethylamine	(CH ₃ CH ₂) ₂ NH	3.02	10.98
Tertiary Amines			
trimethylamine	(CH ₃) ₃ N	4.19	9.81
triethylamine	(CH ₃ CH ₂) ₃ N	3.25	10.75

21 Basicity-Aliphatic Amines

- u All aliphatic amines have about the same base strength, pK_b 3.0 - 4.0, and are slightly stronger bases than ammonia

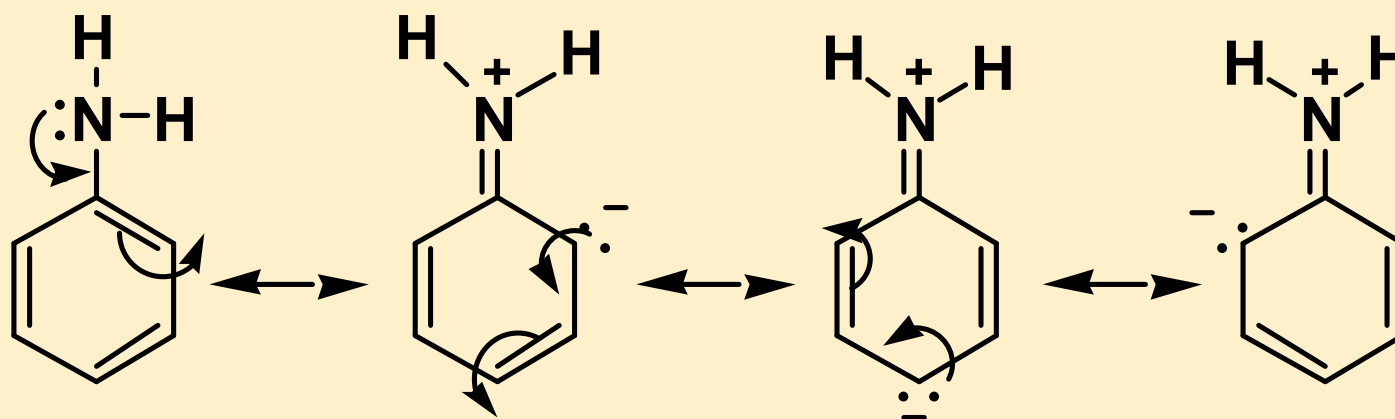
21 Basicity-Aromatic Amines

u Aromatic amines

Amine	Structure	pK _b	pK _a
aniline		9.37	4.63
4-methylaniline		8.92	5.08
4-chloroaniline		9.85	4.15
4-nitroaniline		13.0	1.0

21 Basicity-Aromatic Amines

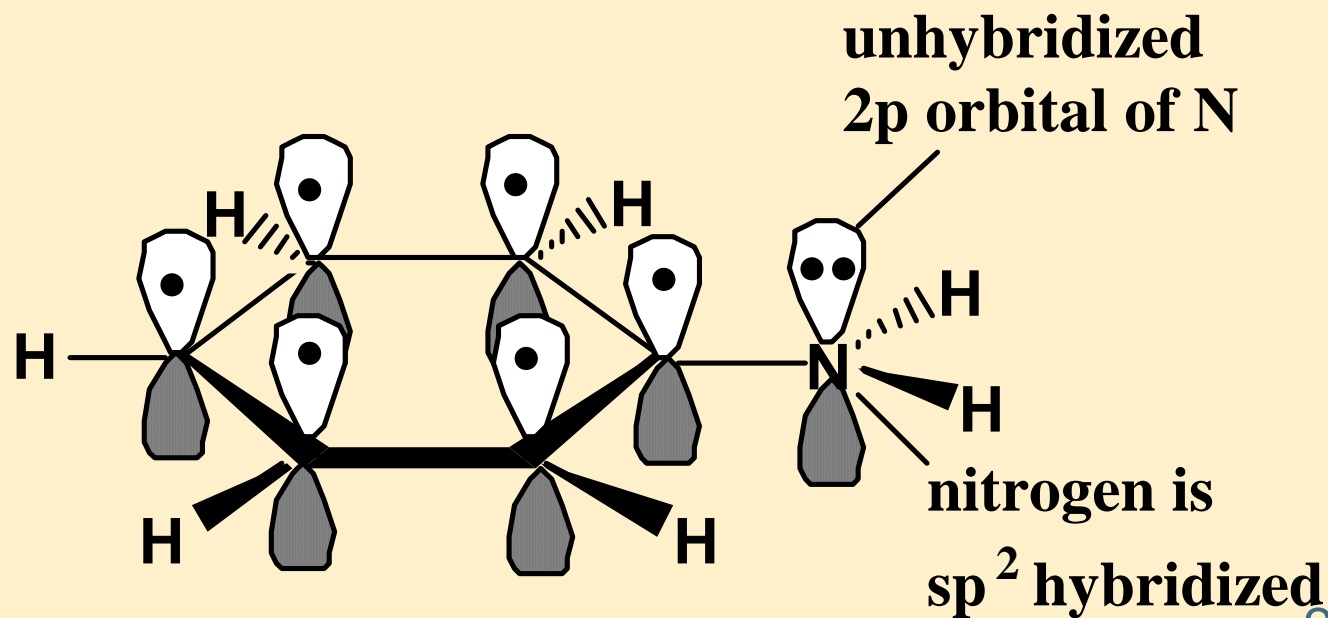
- u Aromatic amines are weaker bases than aliphatic amines because of two factors
 - resonance stabilization of the free base, which is lost on protonation



Interaction of the electron pair on nitrogen with the pi system of the aromatic ring

21 Basicity-Aromatic Amines

- u Resonance delocalization of the electron pair on nitrogen by interaction with the pi system of the aromatic ring

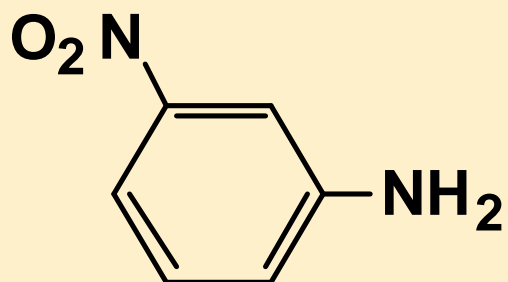


21-27

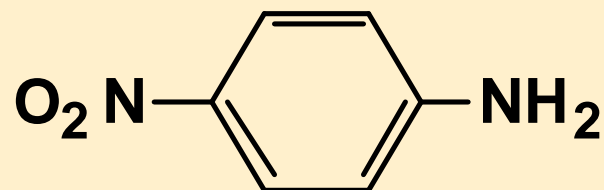
21 Basicity-Aromatic Amines

- and the greater electron-withdrawing inductive effect of the sp^2 carbon of an aromatic amine compared with the sp^3 carbon of an aliphatic amine
- u Electron-releasing, such as alkyl groups, increase the basicity of aromatic amines
- u Electron-withdrawing groups, such as halogens, the nitro group, and a carbonyl group decrease basicity by a combination of resonance and inductive effects

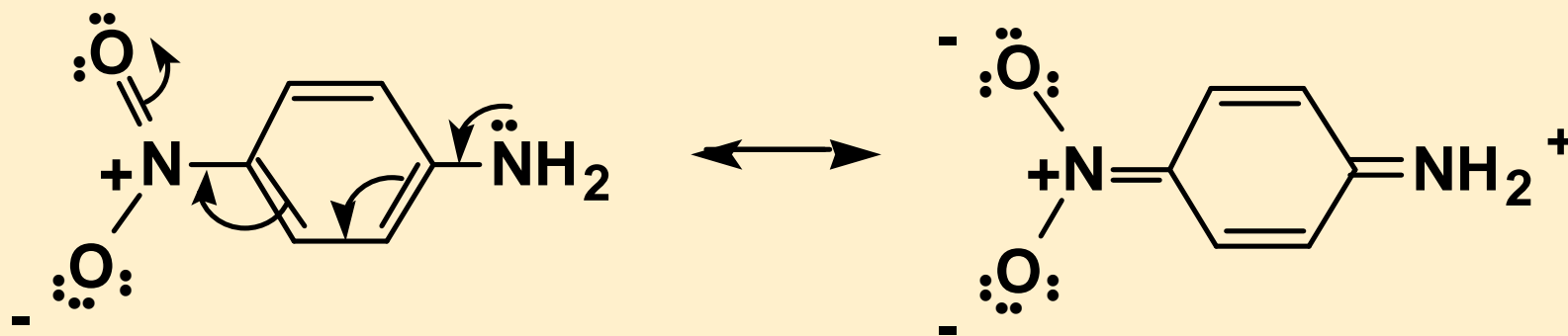
21 Basicity-Aromatic Amines



3-Nitroaniline
pK_b 11.53

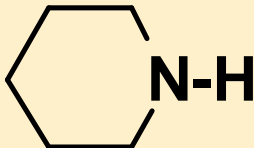
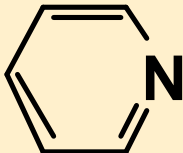
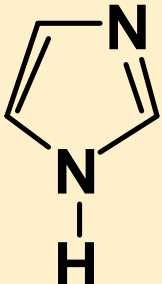


4-Nitroaniline
pK_b 13.0



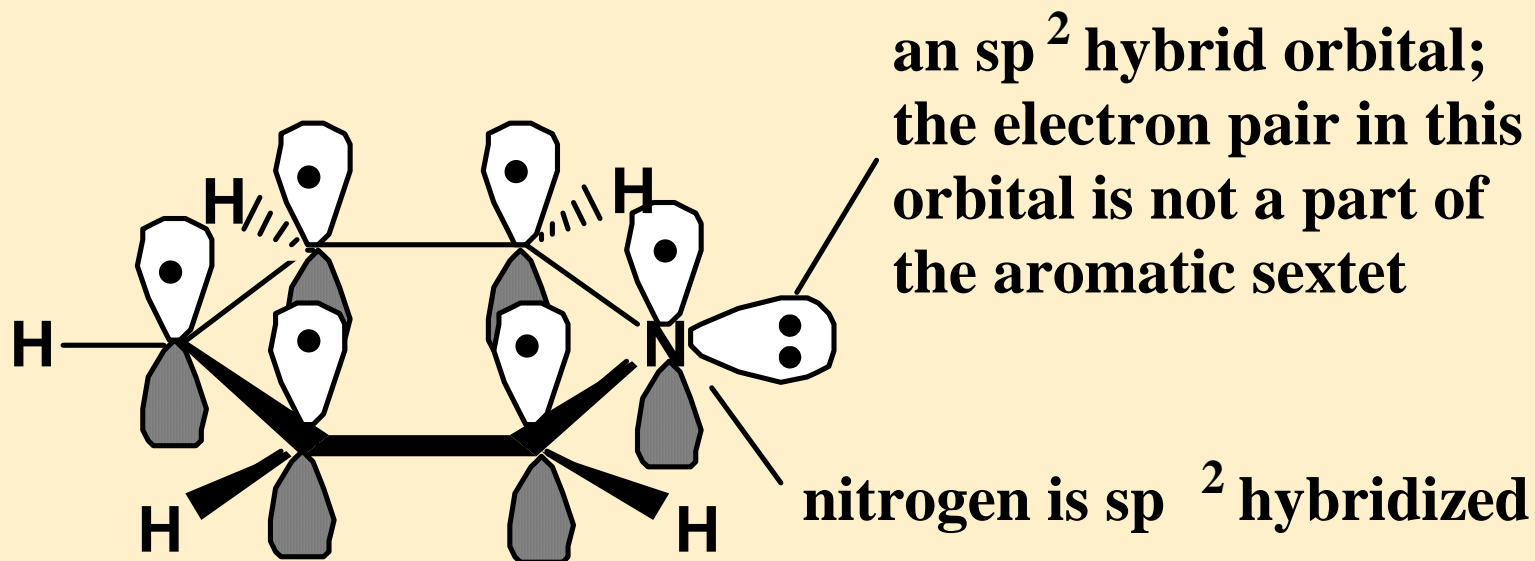
21 Basicity-Aromatic Amines

- u Heterocyclic aromatic amines are weaker bases than heterocyclic aliphatic amines

Amine	Structure	pK _b	pK _a
piperidine		3.25	10.75
pyridine		8.75	5.25
imidazole		7.05	6.95

21 Basicity-Aromatic Amines

- u In pyridine, the unshared pair of electrons on N lies in an sp^2 hybrid orbital in the plane of the ring and perpendicular to the six $2p$ orbitals containing the aromatic sextet

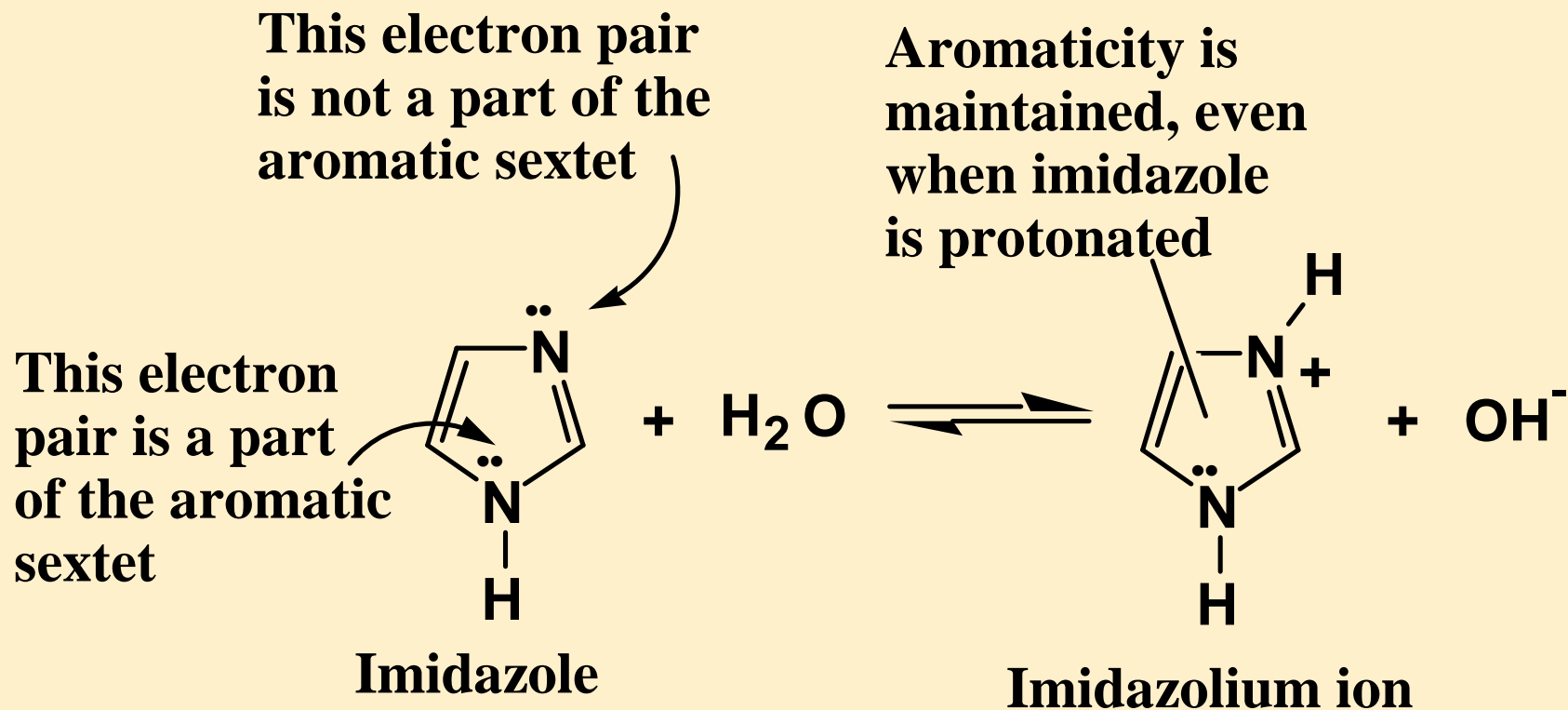


21 Basicity-Aromatic Amines

- u **Pyridine is a weaker base than heterocyclic aliphatic amines because the free electron pair on N lies in an sp^2 hybrid orbital (33% s character) and is held more tightly to the nucleus than the free electron pair on N in an sp^3 hybrid orbital (25% s character)**

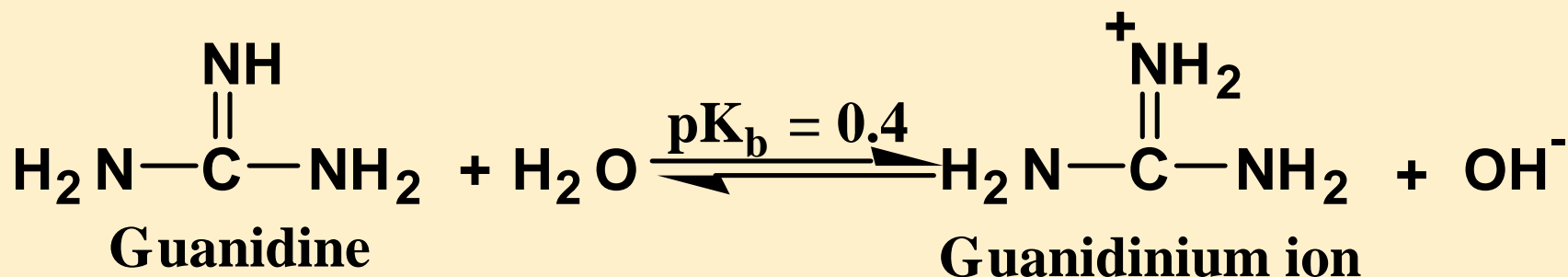
21 Basicity-Aromatic Amines

u Imidazole

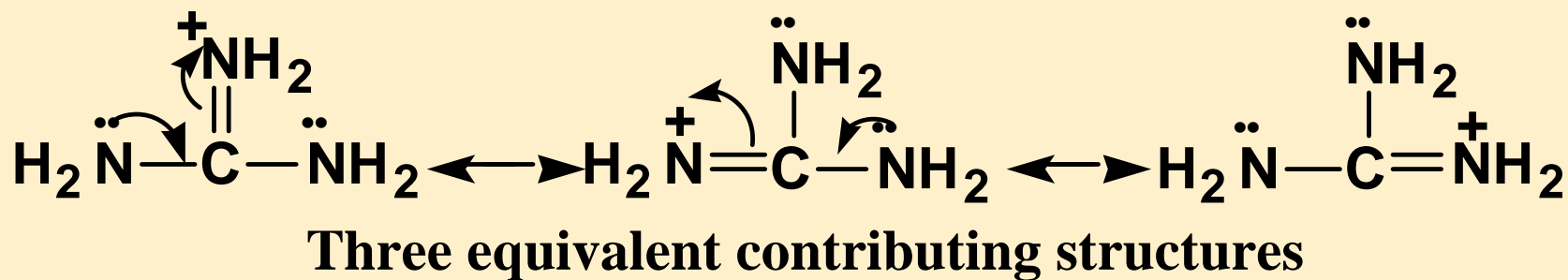


21 Basicity-Guanidine

- u Guanidine, pK_b 0.4, is the strongest base among neutral organic compounds

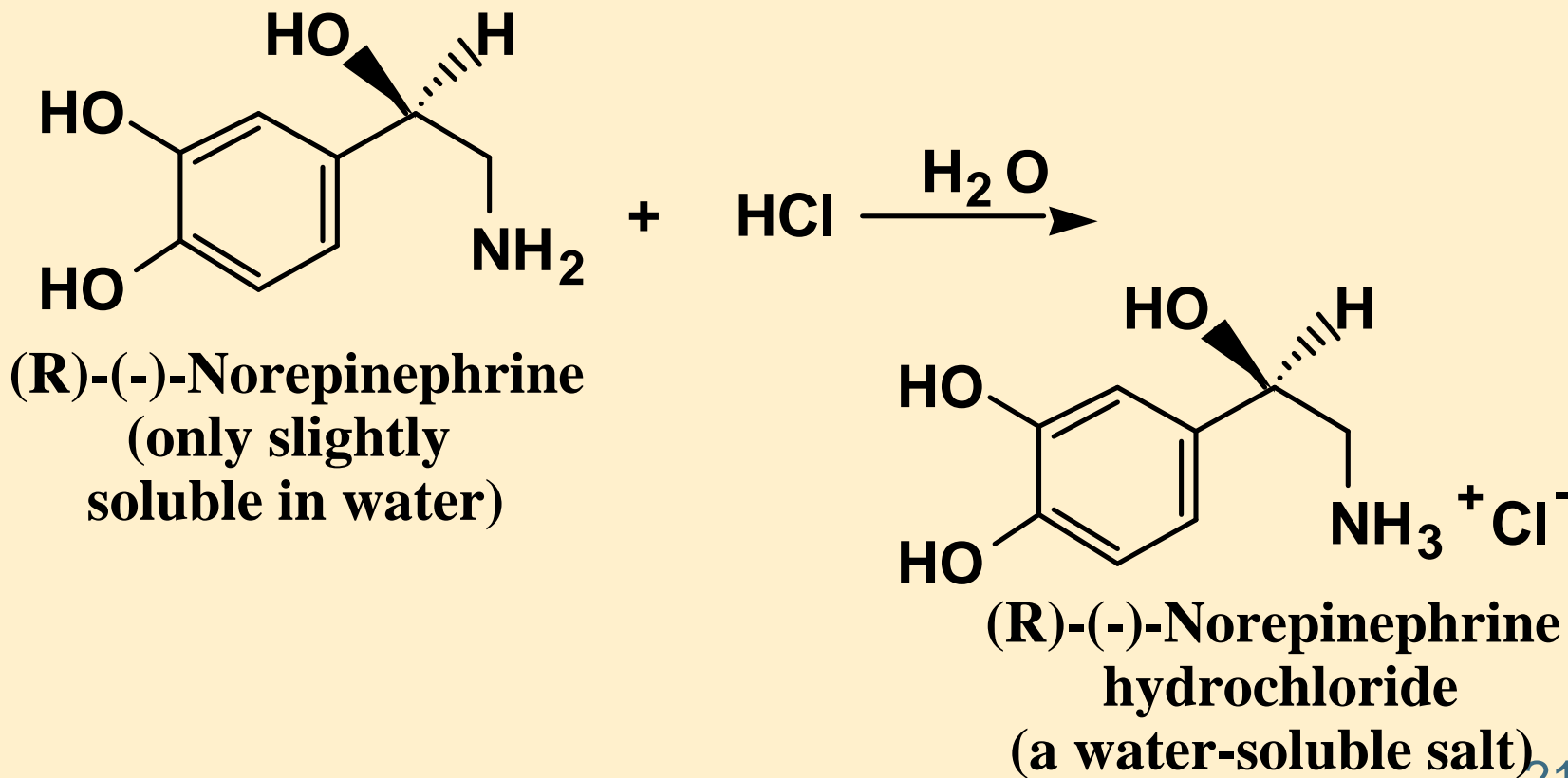


- its basicity is due to the delocalization of the positive charge over the three nitrogen atoms



21 Reaction with Acids

- u All amines, whether soluble or insoluble in water, react quantitatively with strong acids to form water-soluble salts

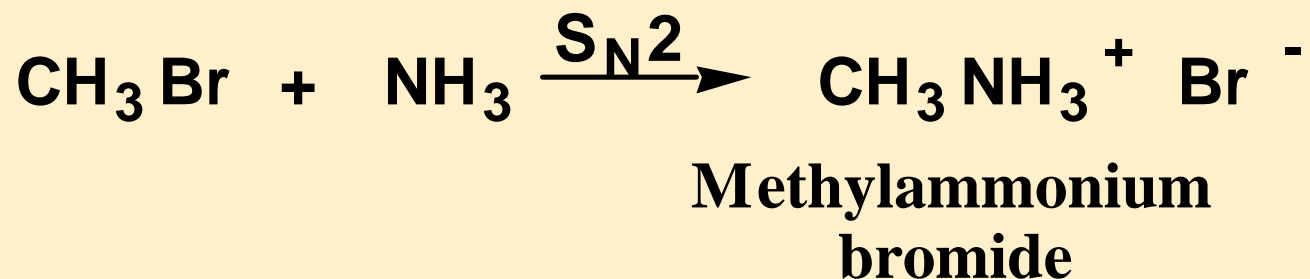


21 Preparation

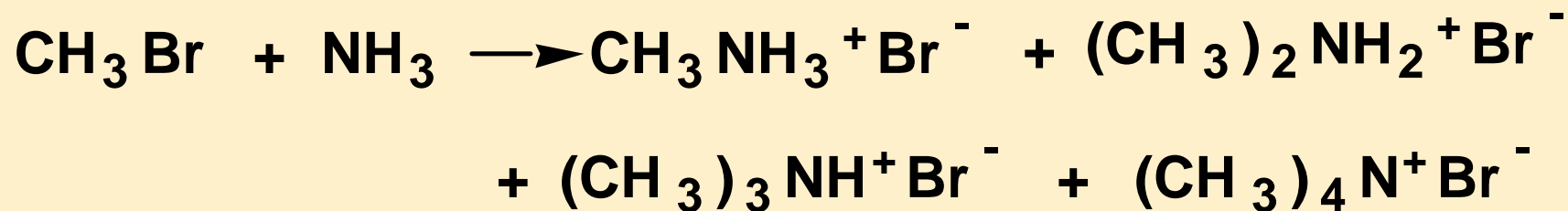
- u We have already covered these methods
 - nucleophilic ring opening of an epoxide by ammonia and amines (11.10B)
 - addition of ammonia and 1° and 2° amines to aldehydes and ketones to form imines followed by reduction of the imine to an amine (15.10)
 - reduction of an amide by LiAlH_4 (17.11B)
 - reduction of a cyano group to a 1° amine (17.11C)
 - Hofmann rearrangement of a 1° amide (17.12)
 - Nitration of an arene followed by reduction of the -NO_2 group to a 1° amine (20.1B)

21 Preparation

u Alkylation of ammonia and amines by S_N2

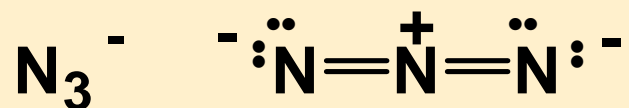


- unfortunately, such alkylations give a mixture of products through a series of proton transfer and nucleophilic substitution reactions

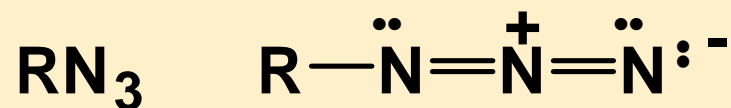


21 Preparation via Azides

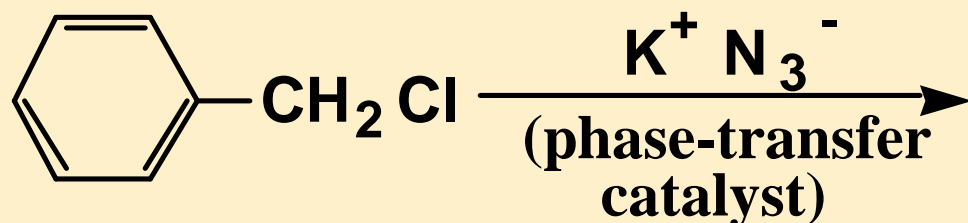
u Alkylation of azide ion



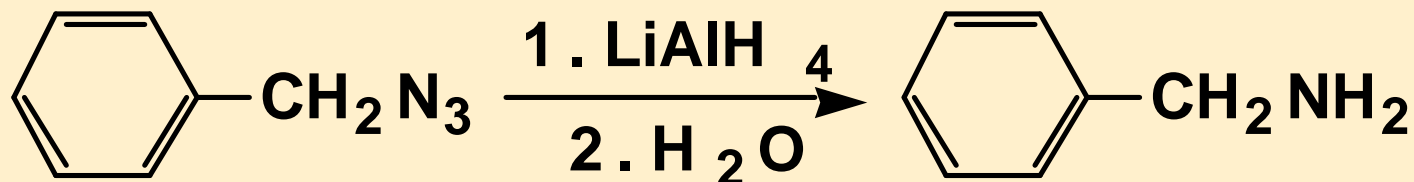
Azide ion
(a good nucleophile)



An alkyl azide



Benzyl chloride



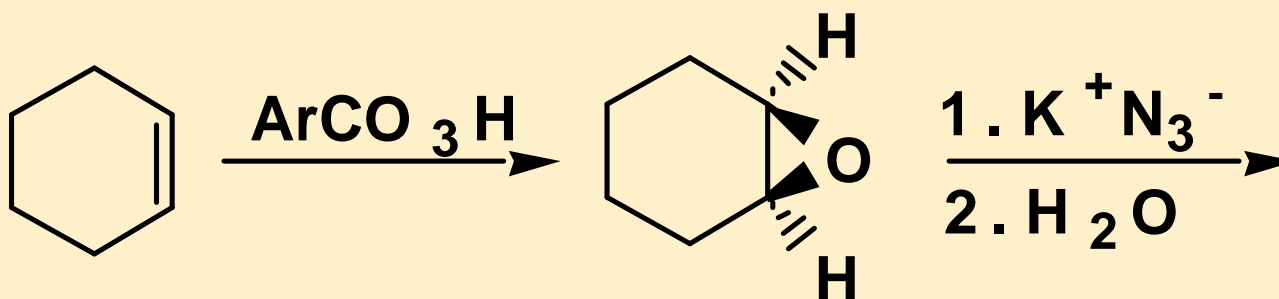
Benzyl azide

Benzylamine

21-38

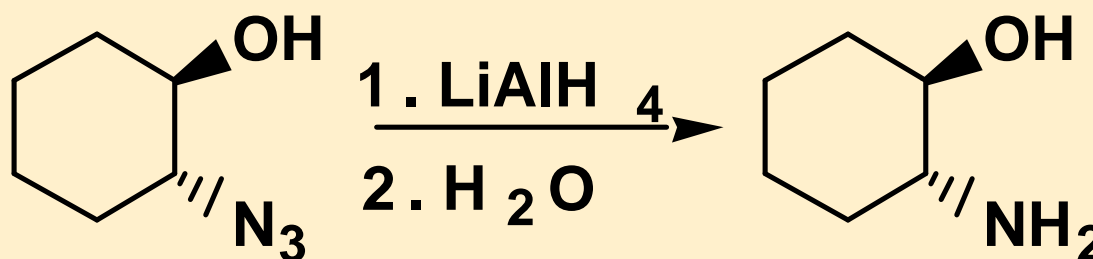
21 Preparation via Azides

u Alkylation of azide ion



Cyclohexene

1,2-Epoxycyclohexane

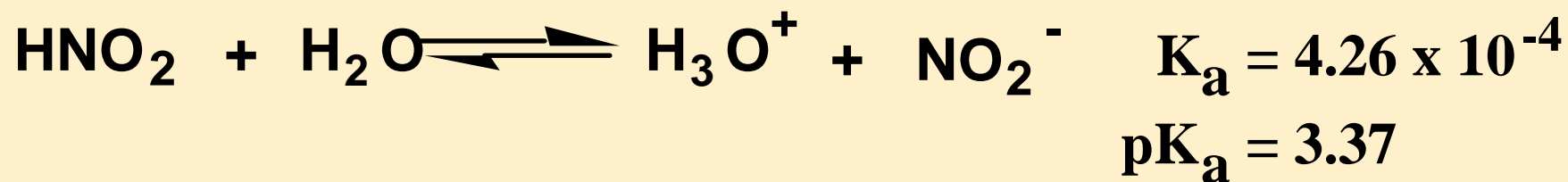


trans-2-Azidocyclohexanol

trans-2-Amino-
cyclohexanol

21 Reaction with HNO_2

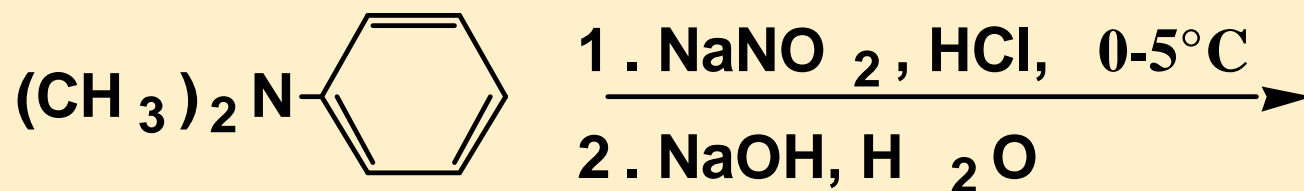
- u Nitrous acid is a weak acid, most commonly prepared by treating aqueous NaNO_2 aqueous H_2SO_4 or HCl



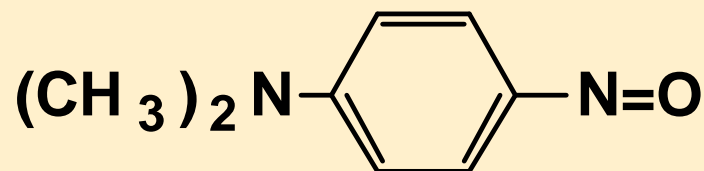
- u In its reactions with amines, it
 - participates in proton-transfer reactions
 - is a source of the nitrosyl cation, NO_2^+ , a weak electrophile

21 3° Amines with HNO₂

- u 3° aliphatic amines, whether water-soluble or water-insoluble, are protonated to form water-soluble salts
- u 3° aromatic amines: NO₂⁺ is a weak electrophile and, as such, participates in EAS



N,N-Dimethylaniline



N,N-Dimethyl-4-nitrosoaniline

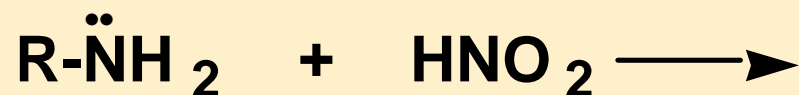
21 1° RNH₂ with HNO₂

- u 1° aliphatic amines give a mixture of unrearranged and rearranged substitution and elimination products, all of which are produced by way of a diazonium ion and its loss of N₂ to give a carbocation
- u **Diazonium ion:** an RN₂⁺ or ArN₂⁺ ion

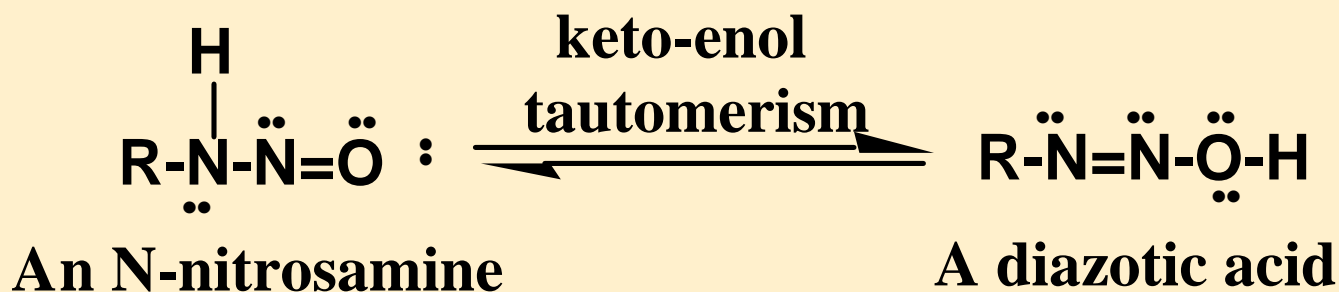
21 1° RNH₂ with HNO₂

u Formation of a diazonium ion

Step 1: reaction of a 1° amine with nitrous acid to form a diazotic acid



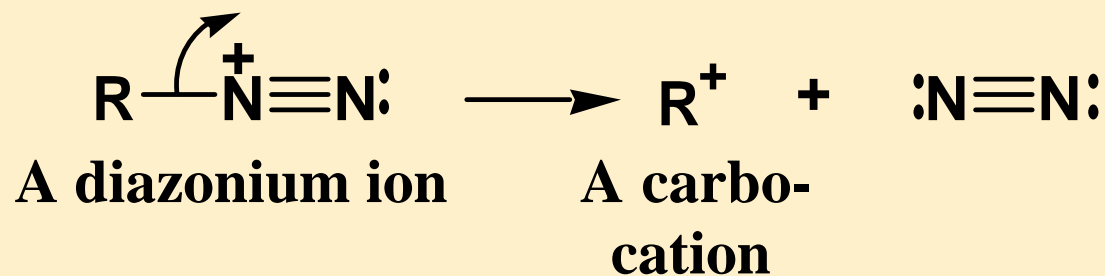
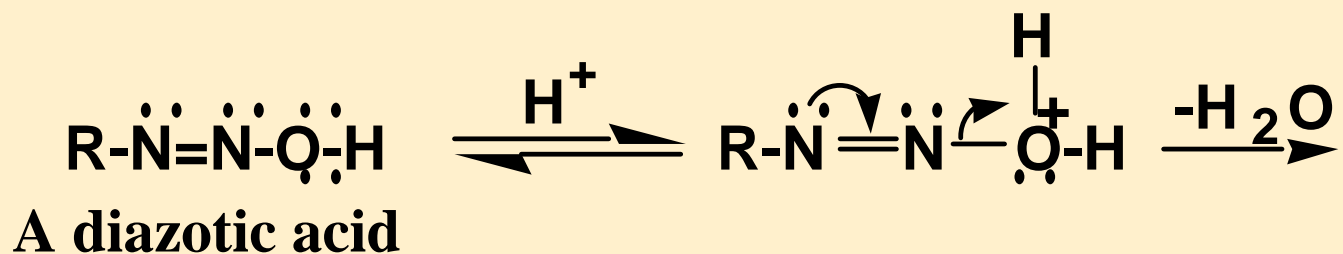
A 1° aliphatic
amine



21 1° RNH₂ with HNO₂

u Formation of a diazonium ion

Step 2: protonation of the diazotic acid followed by loss of H₂O and N₂ to give a carbocation

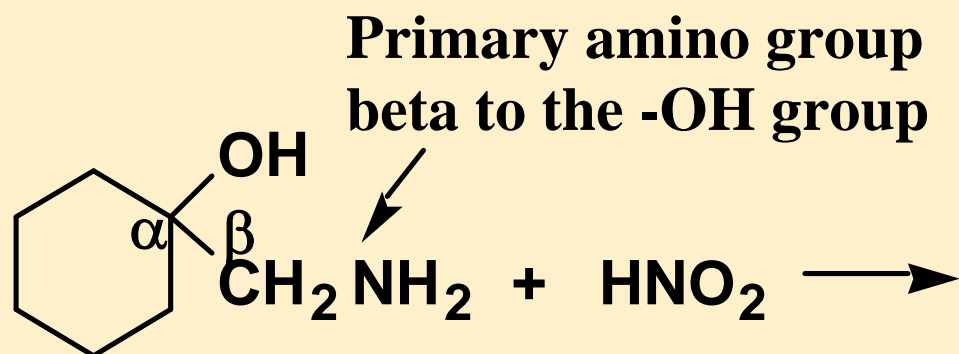


21 1° RNH₂ with HNO₂

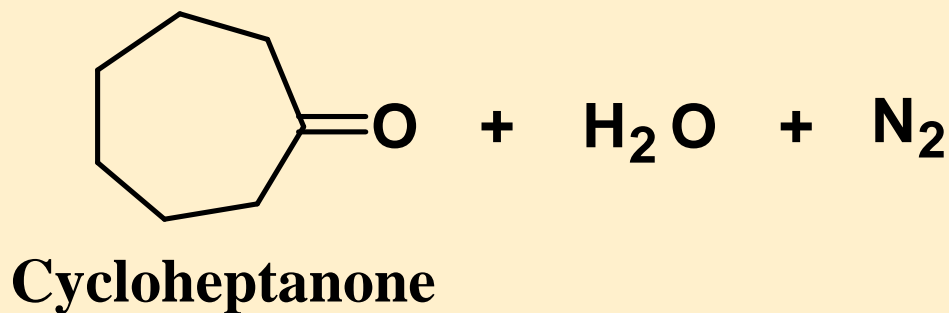
- u Aliphatic diazonium ions are unstable, even at 0°C and lose N₂ to give a carbocation which may
 1. lose a proton to form an alkene
 2. react with a nucleophile to give a substitution product
 3. rearrange and then react by 1 and/or 2
- because reaction of a 1° aliphatic amine with nitrous acid gives a mixture of products, it is not a generally useful synthetic reaction

21 1° RNH₂ with HNO₂

- u **Tiffeneau-Demjanov reaction:** treatment of a β -aminoalcohol with HNO₂ gives a ketone and N₂

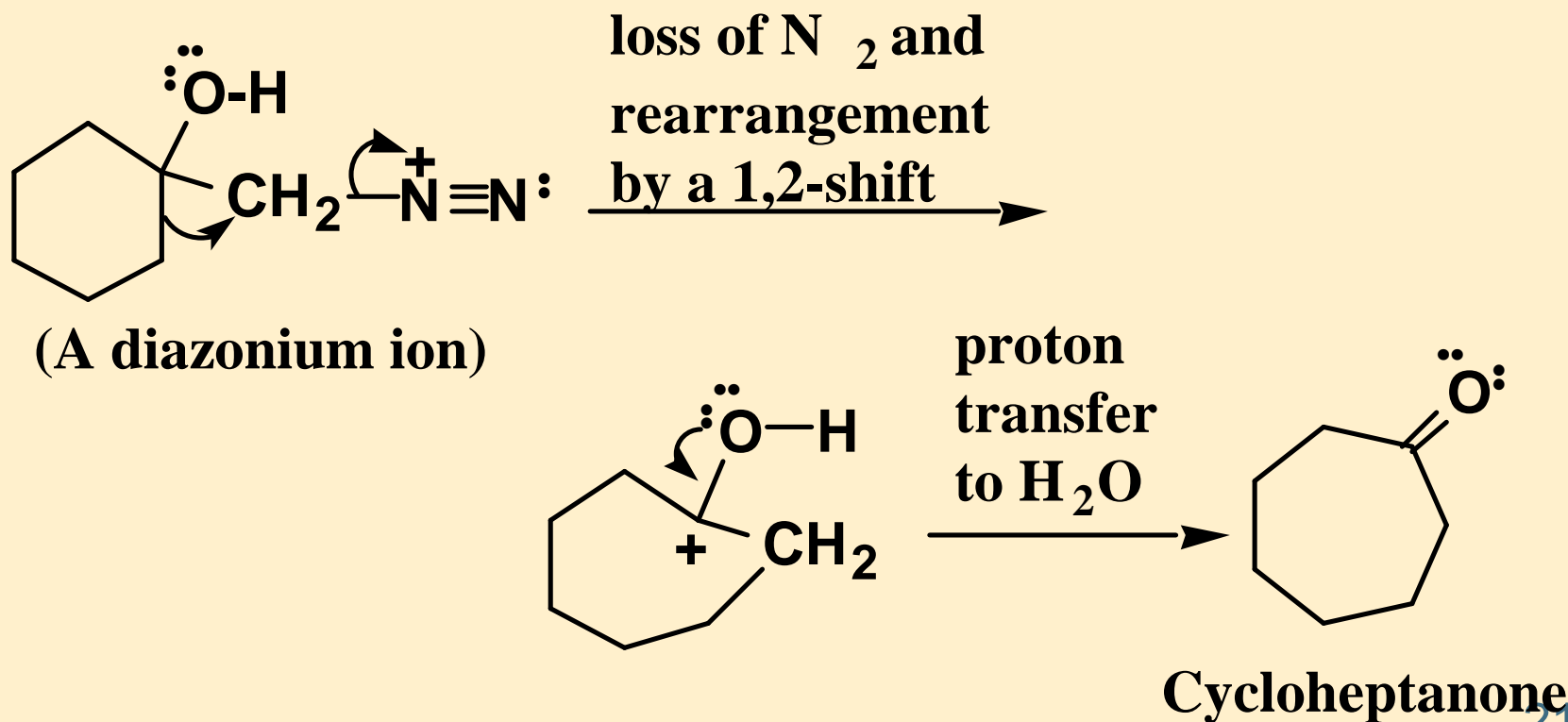


A β -aminoalcohol



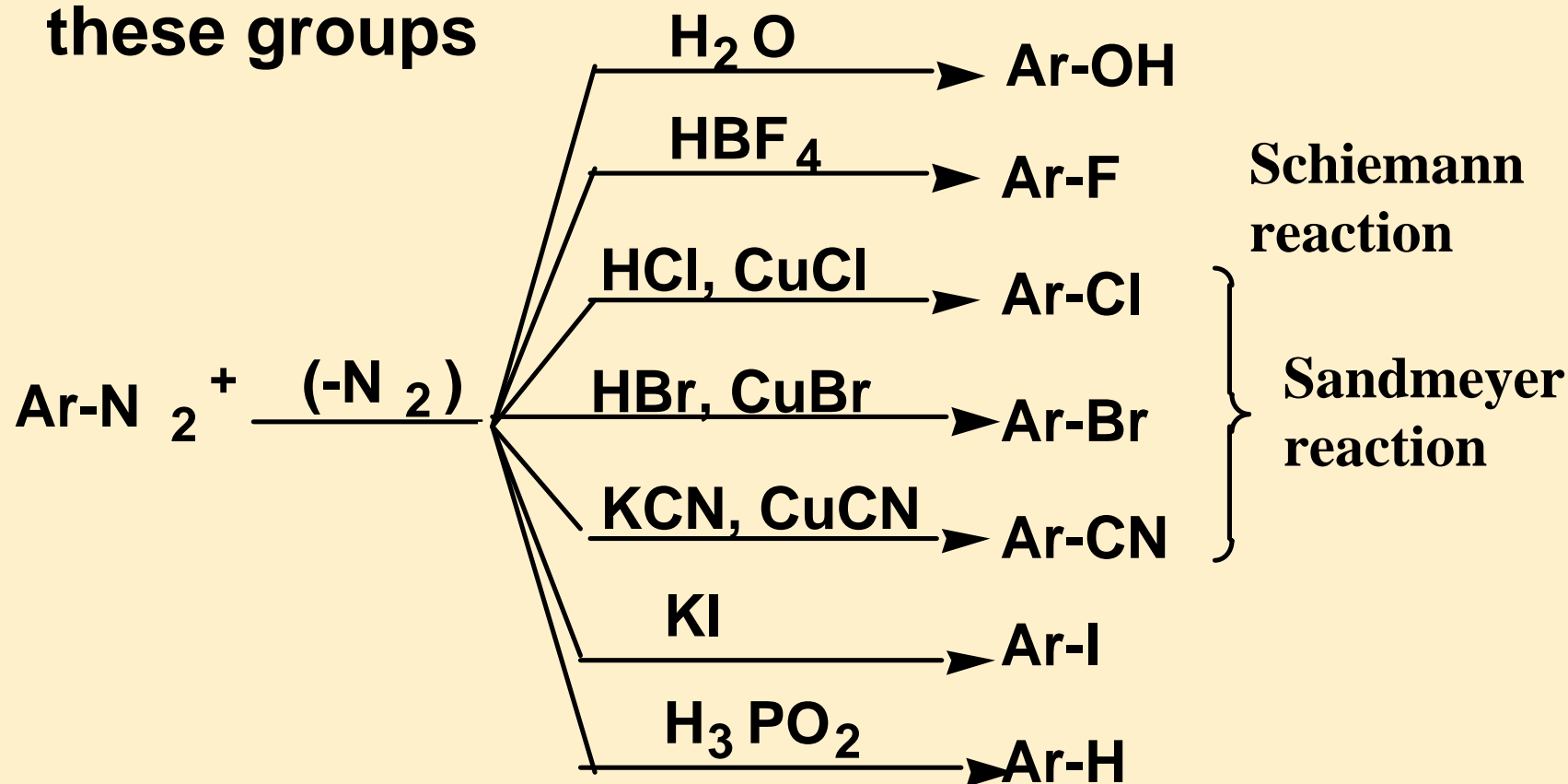
21 1° RNH₂ with HNO₂

- reaction of the 1° amino group with NO₂⁺ gives a diazonium ion
- concerted loss of N₂ and rearrangement followed by proton transfer gives the ketone



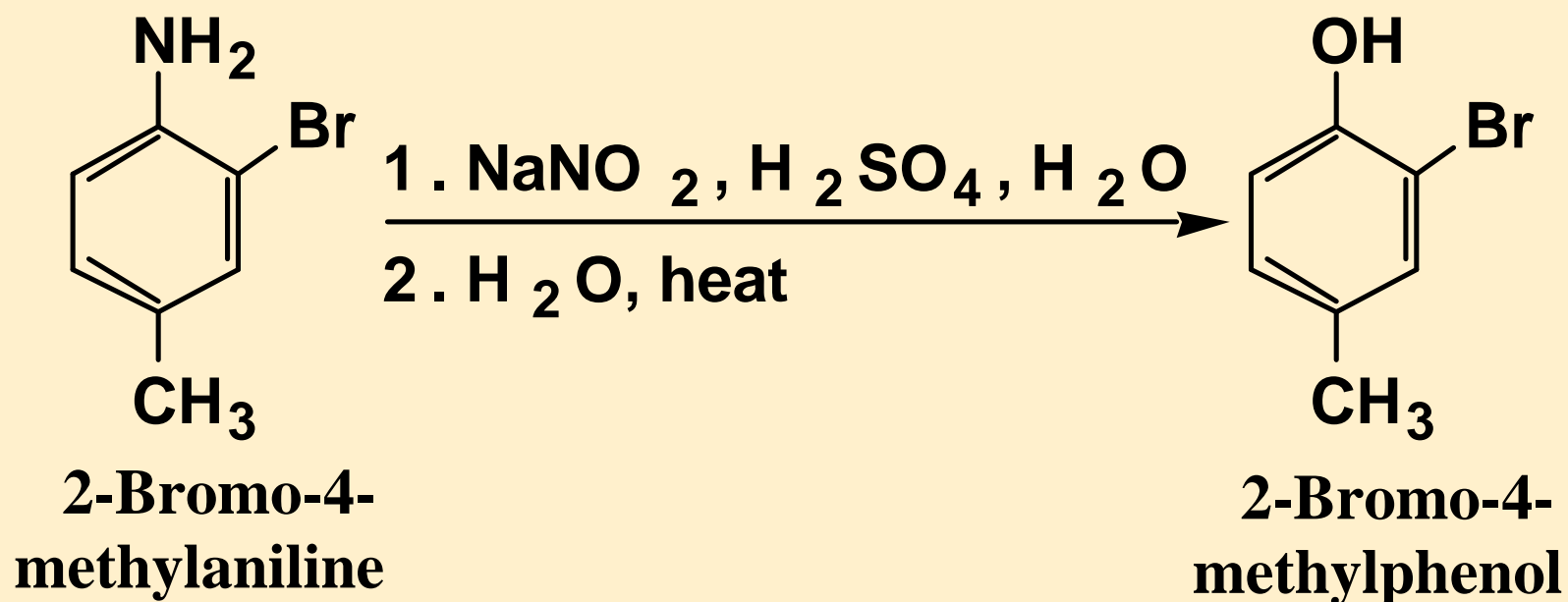
21 1° ArNH₂ with HNO₂

- The $-N_2^+$ group of an arenediazonium salt can be replaced in a regioselective manner by these groups



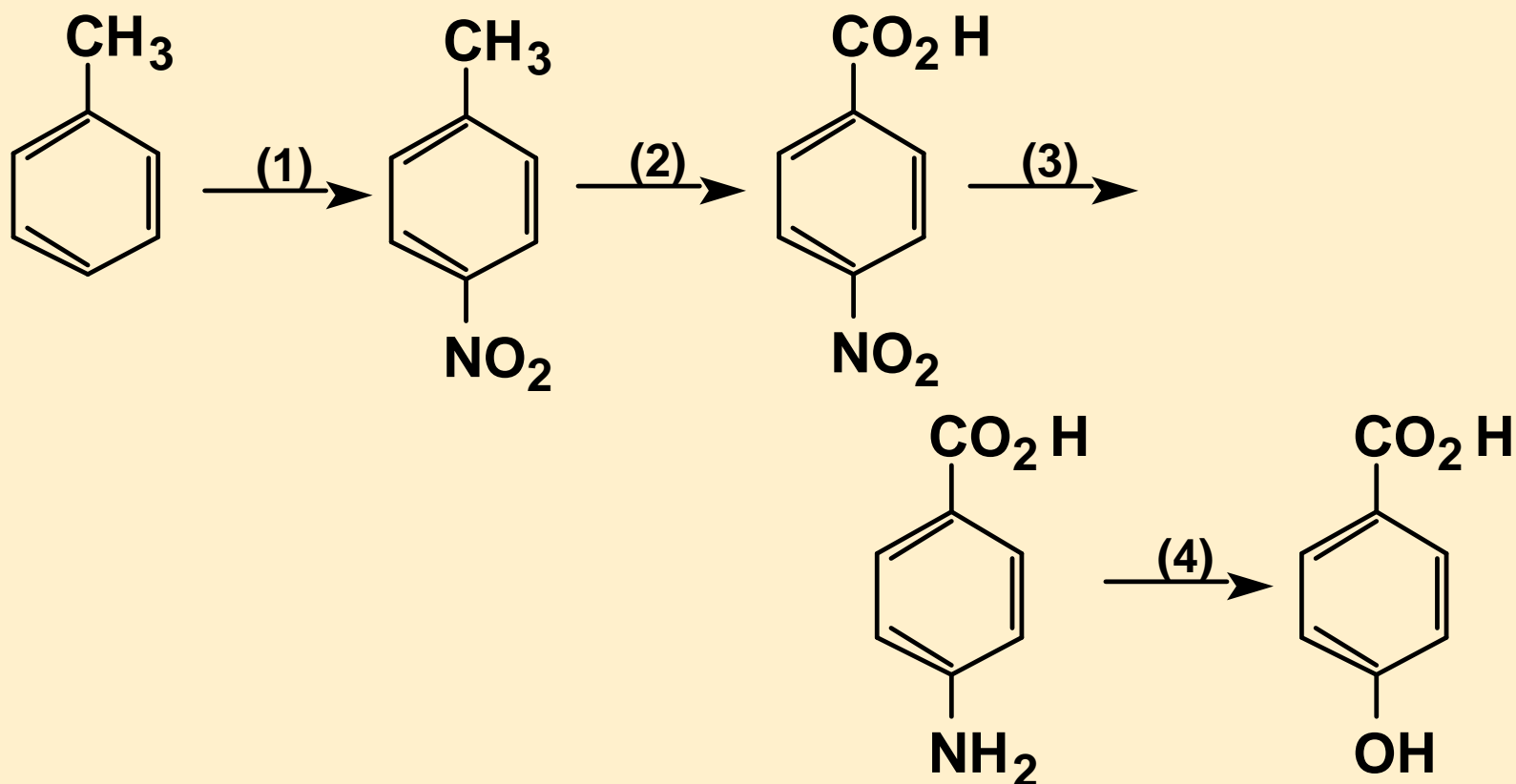
21 1° ArNH₂ with HNO₂

- u An 1° aromatic amine can be converted to a phenol



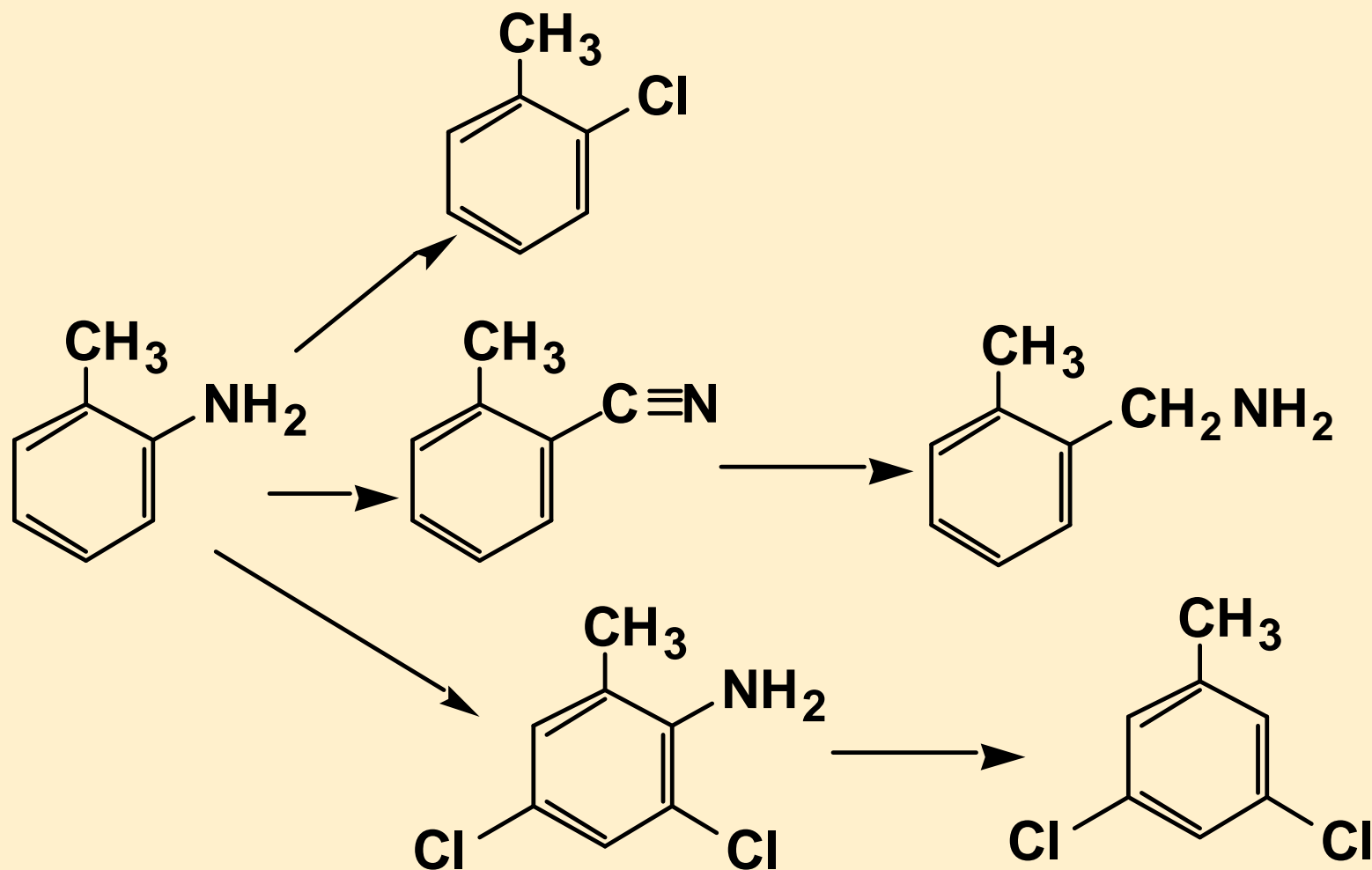
21 1° ArNH₂ with HNO₂

u **Problem:** what reagents and experimental conditions will bring about this conversion?



21 1° ArNH₂ with HNO₂

u Problems (contd.)



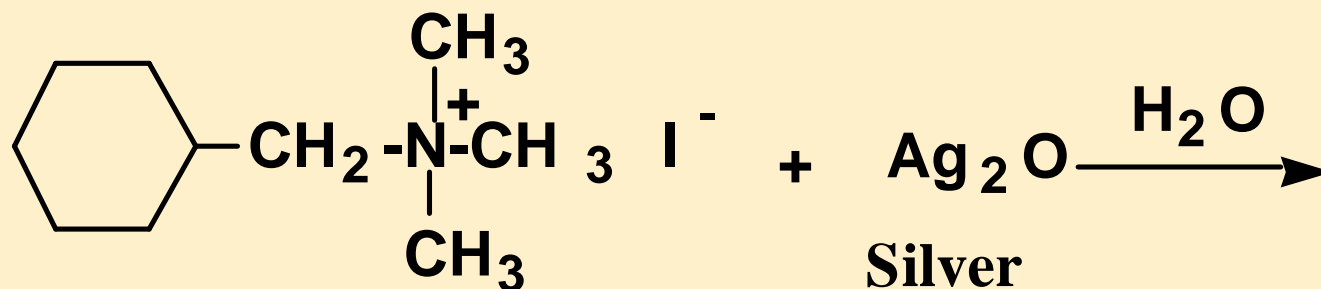
21 Hofmann Elimination

- u **Hofmann elimination:** thermal decomposition of a quaternary ammonium hydroxide to give an alkene

- u **We show this reaction in two steps**
 - **Step 1:** formation of the 4° ammonium hydroxide
 - **Step 2:** its thermal decomposition

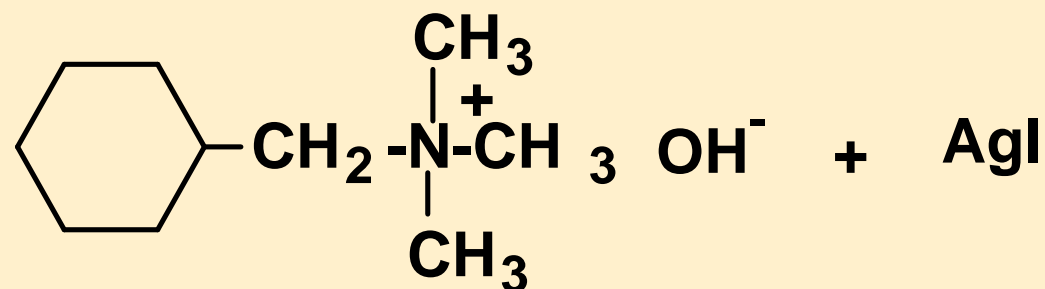
21 1° ArNH₂ with HNO₂

- Step 1: formation of a 4° ammonium hydroxide



A 4° ammonium salt

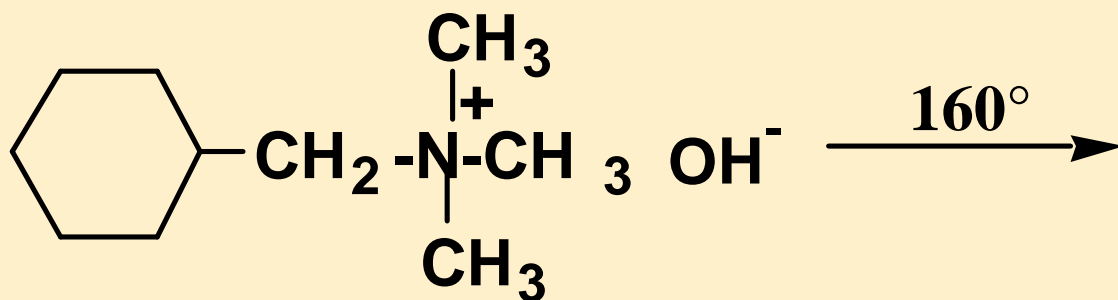
Silver
oxide



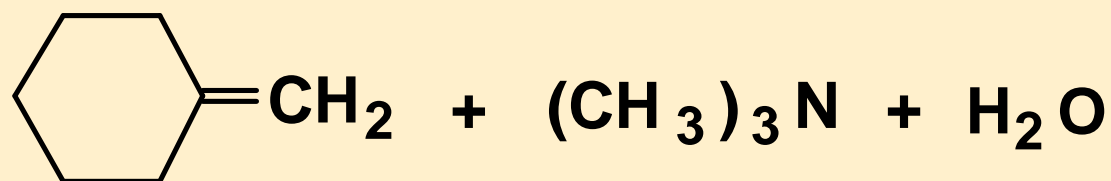
A 4° ammonium hydroxide

21 Hofmann Elimination

- Step 2: thermal decomposition of the 4° ammonium hydroxide



A 4° ammonium
hydroxide

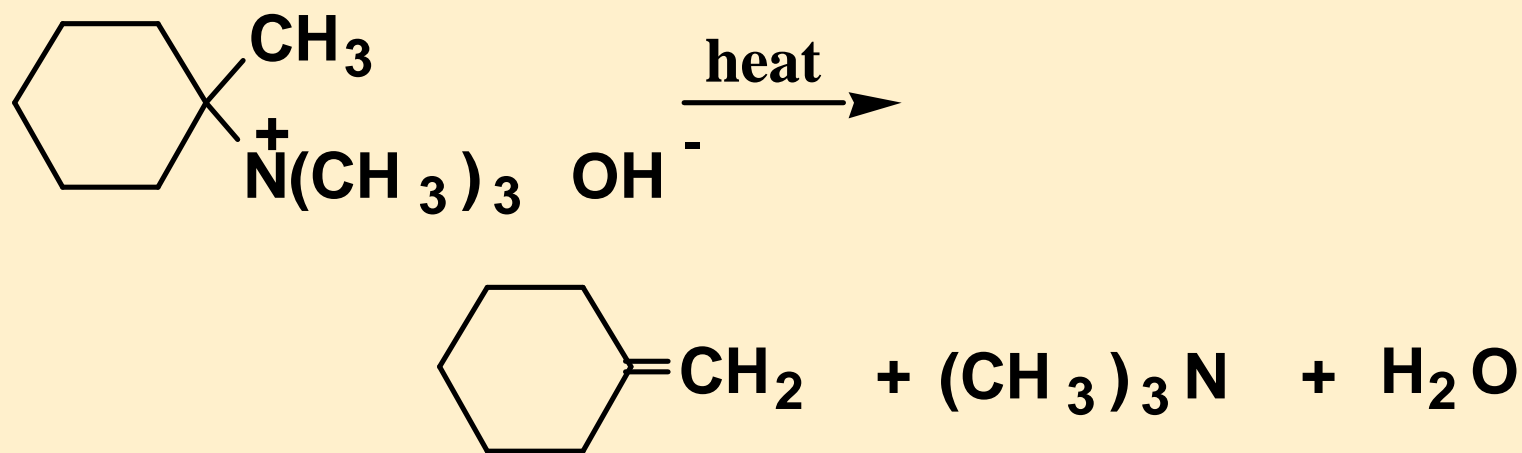


Methylene-
cyclohexane

Trimethylamine

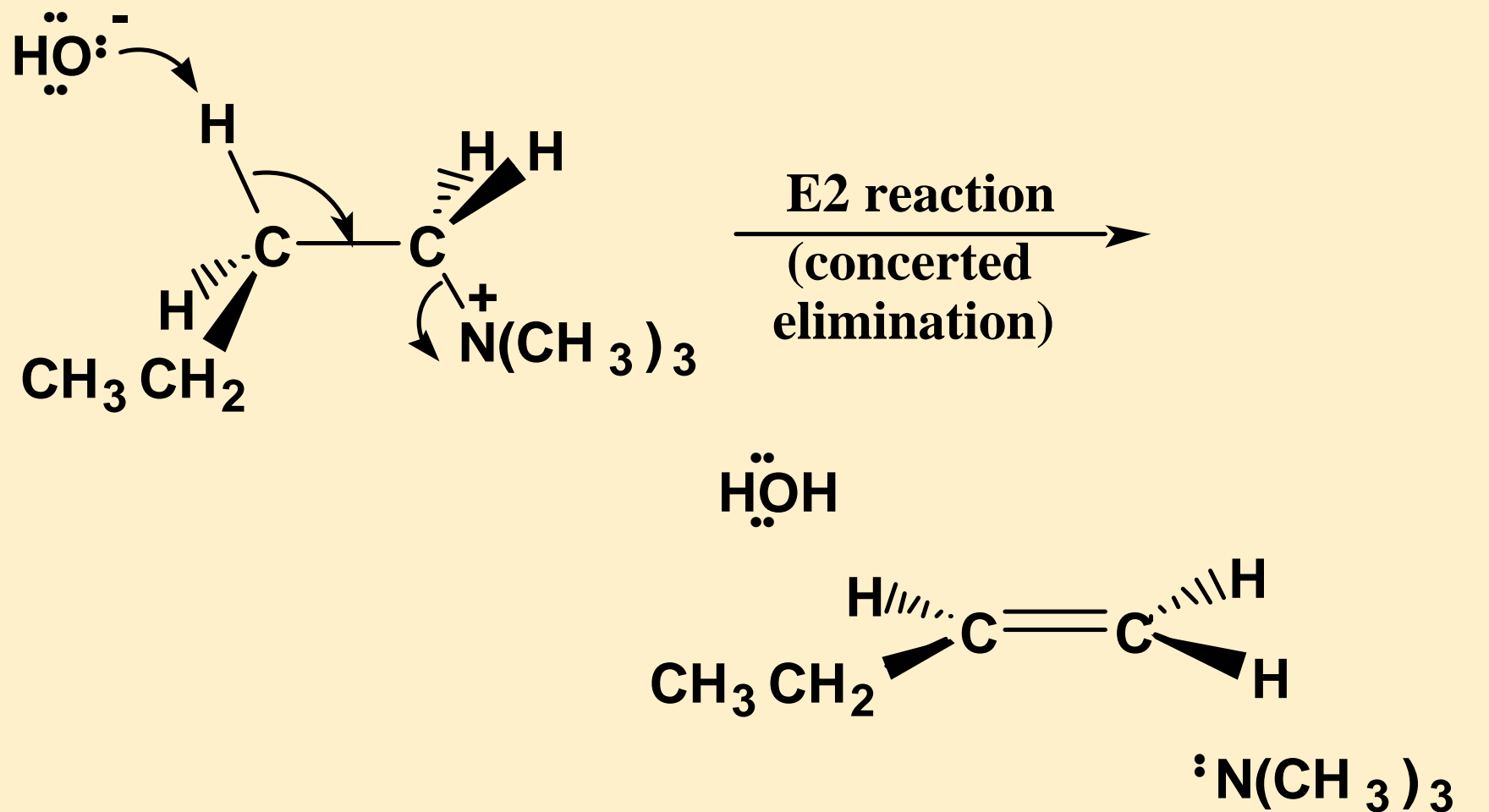
21 Hofmann Elimination

- u Hofmann elimination is regioselective - the major product is the least substituted alkene



- u **Hofmann's rule:** any β -elimination that occurs preferentially to give the least substituted double bond as the major product is said to follow Hofmann's rule

21 Hofmann Elimination



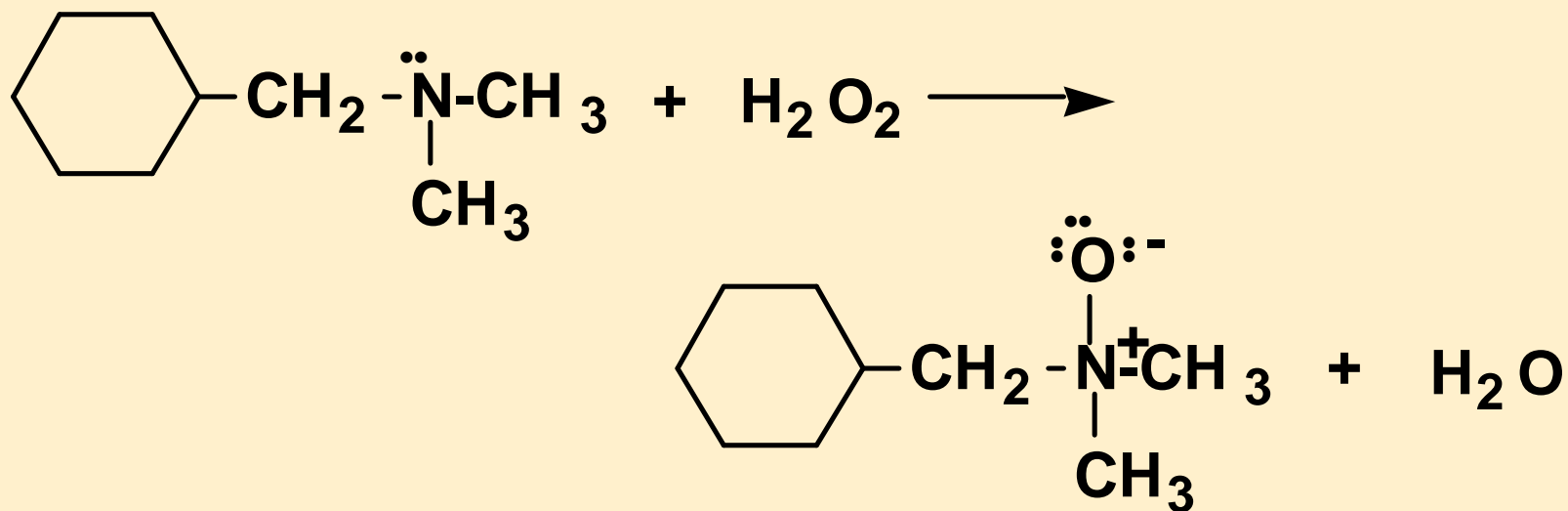
21 Hofmann Elimination

- u The regioselectivity of Hofmann elimination is determined largely by steric factors, namely the bulk of the $-NR_3^+$ group
 - the hydroxide ion preferentially approaches and removes the least hindered hydrogen and, thus, gives the least substituted double bond
- u For a similar reason, bulky bases such as $(CH_3)_3O^-K^+$ give largely Hofmann elimination with alkyl halides

21 Cope Elimination

u **Cope elimination:** thermal decomposition of an amine oxide

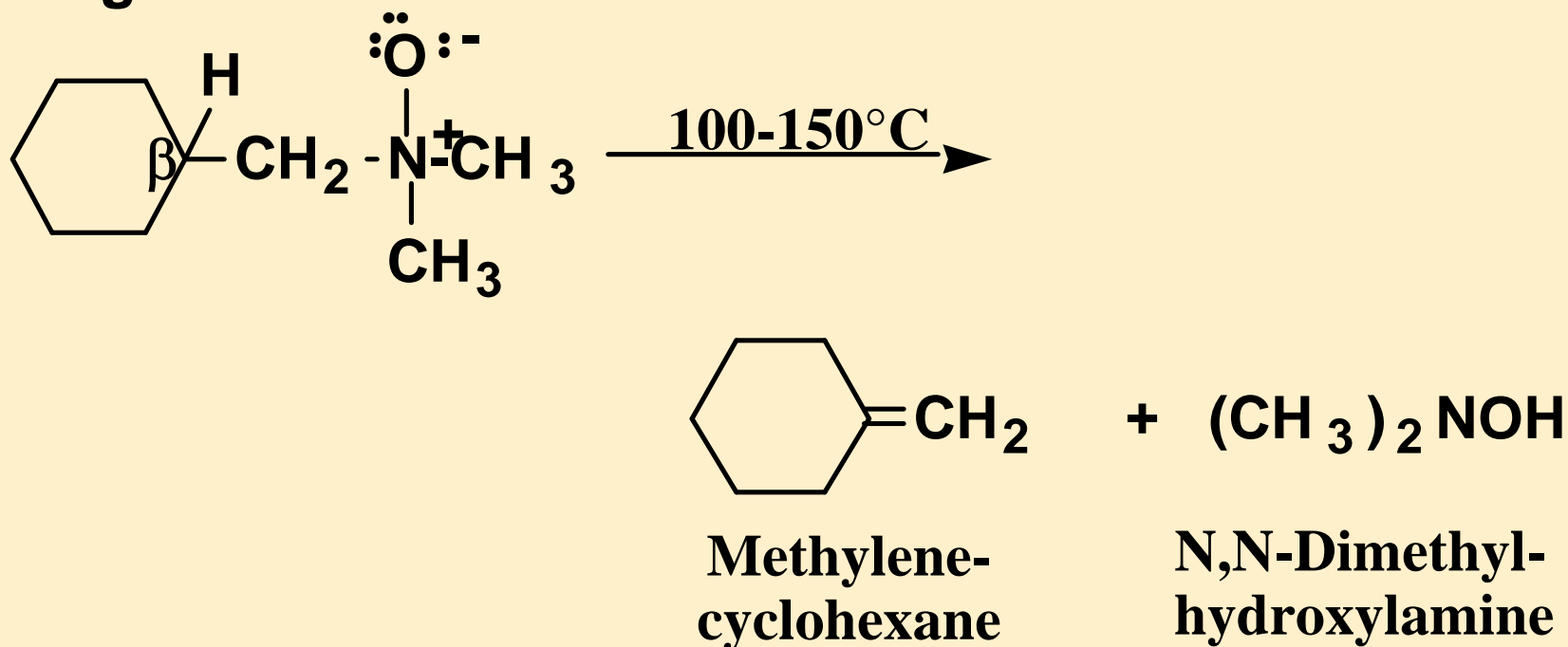
Step 1: oxidation of a 3° amine to form an amine oxide



An amine oxide

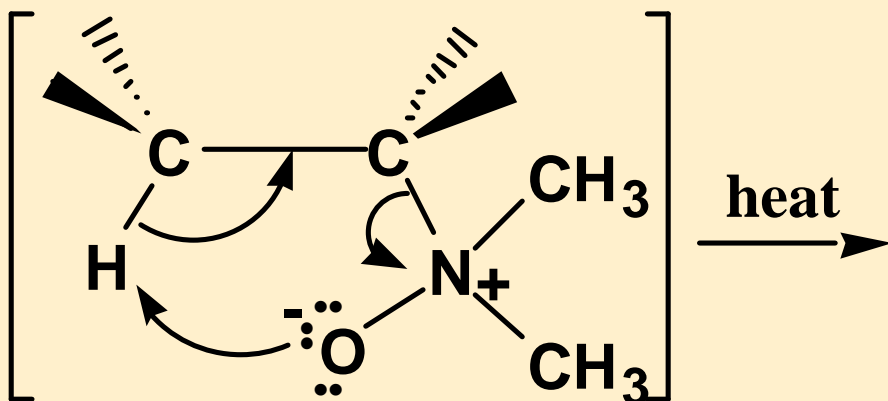
21 Cope Elimination

Step 2: if the amine oxide has at least one β -hydrogen, it undergoes thermal decomposition to give an alkene

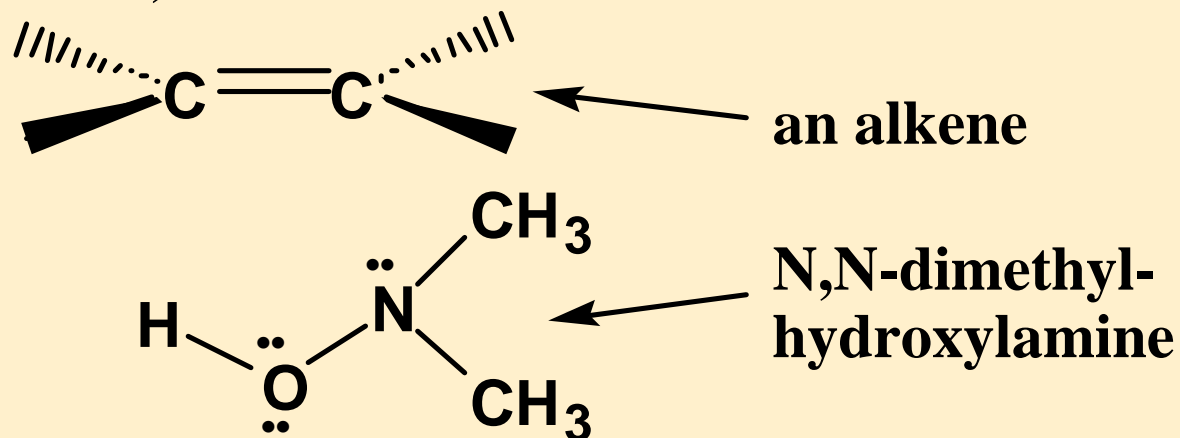


- Cope elimination shows syn stereoselectivity but little or no regioselectivity

21 Cope Elimination



Transition state
(cyclic flow of three
pairs of electrons)



21

Amines

End Chapter 21

21-63