CH 310 N	T TH 2-3:30	LECTURE 10

Textbook Assignment: Chapter 16 Continue

Homework (for credit): POW 5 posted

Today's Topics: Aldehydes & Ketones (cont'd)

Notice & Announcements:

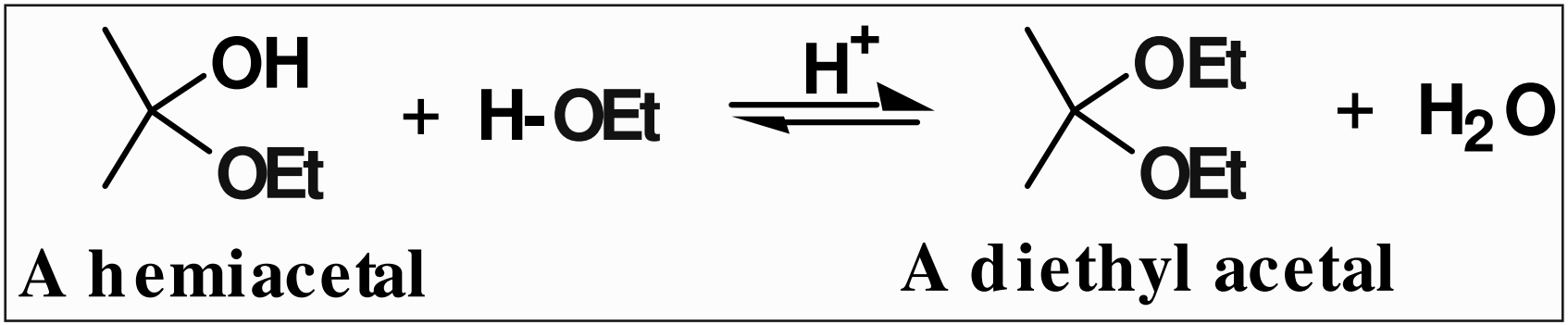
Papers in Undergrad office WEL 2.212

Aldehydes And Ketones

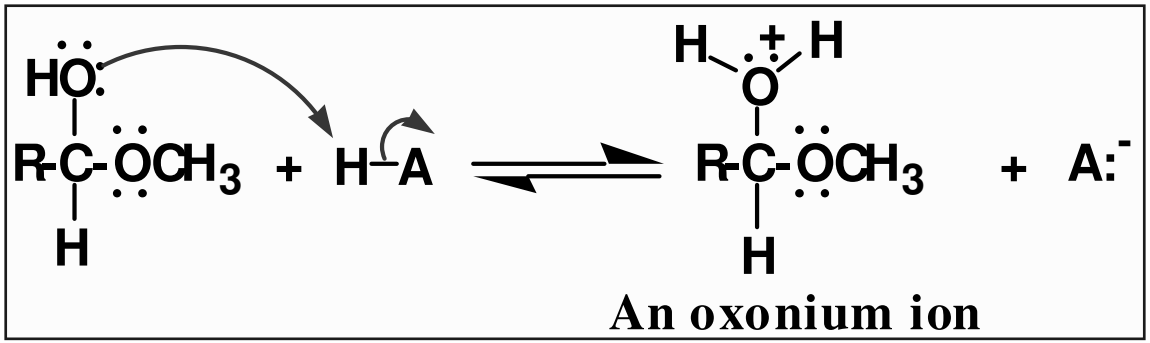
Addition of Alcohols to Carbonyls

- Hemiacetals react with alcohols to form acetals

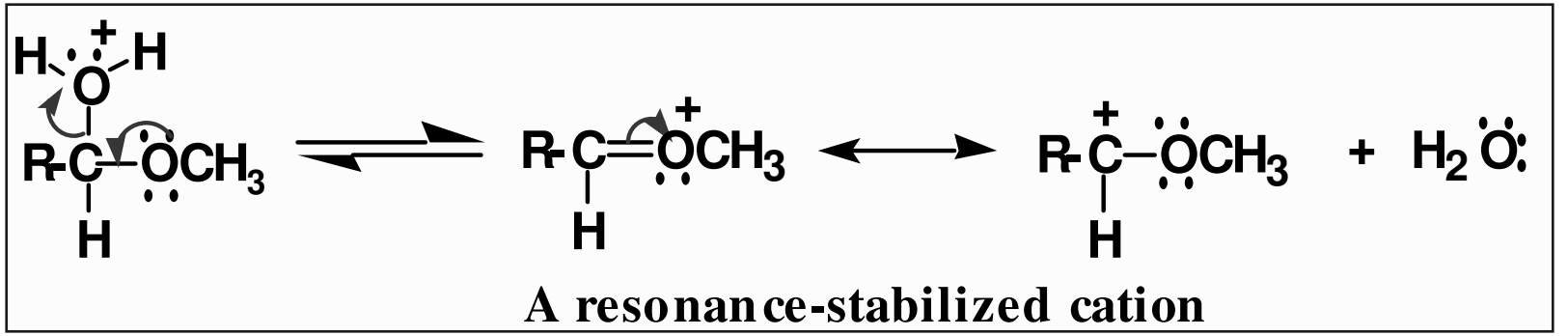
  Acetal: a molecule containing two -OR or -OAr groups bonded to the same carbon



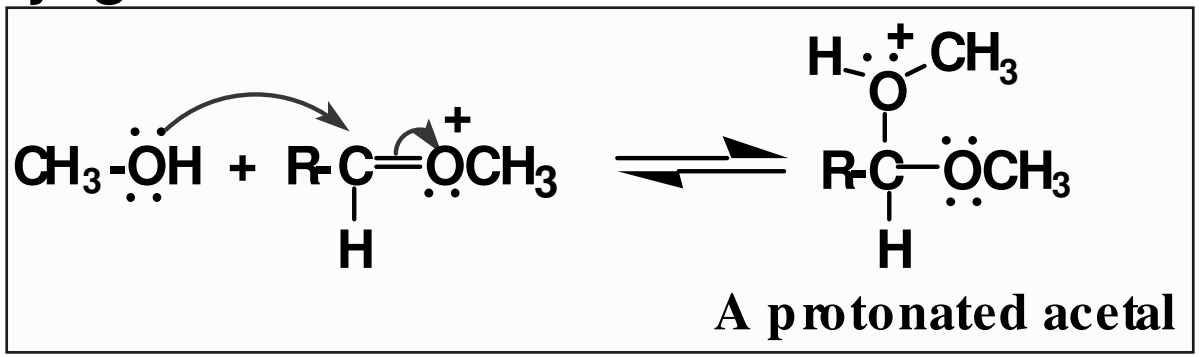
Step 1: proton transfer from HA gives an oxonium ion



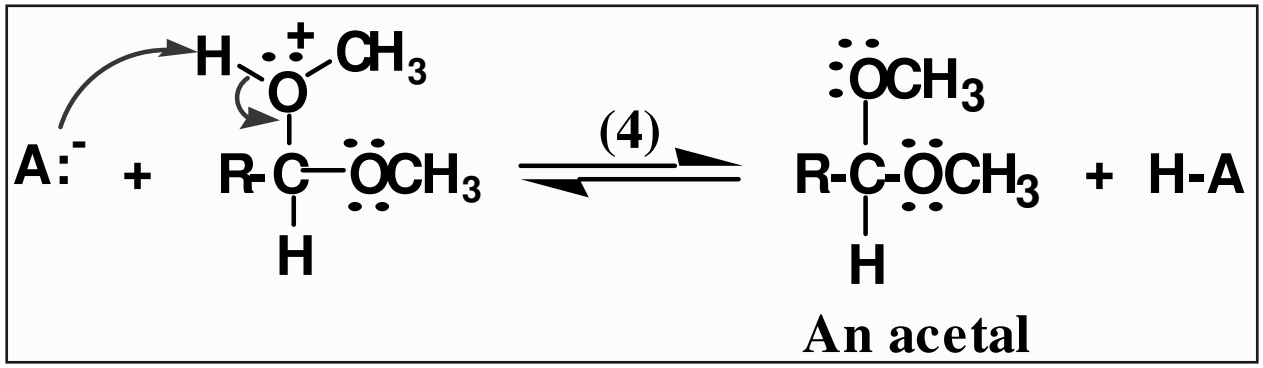
Step 2: loss of water gives a resonance-stabilized cation



Step 3: reaction of the cation (an electrophile) with methanol (a nucleophile) gives the conjugate acid of the acetal



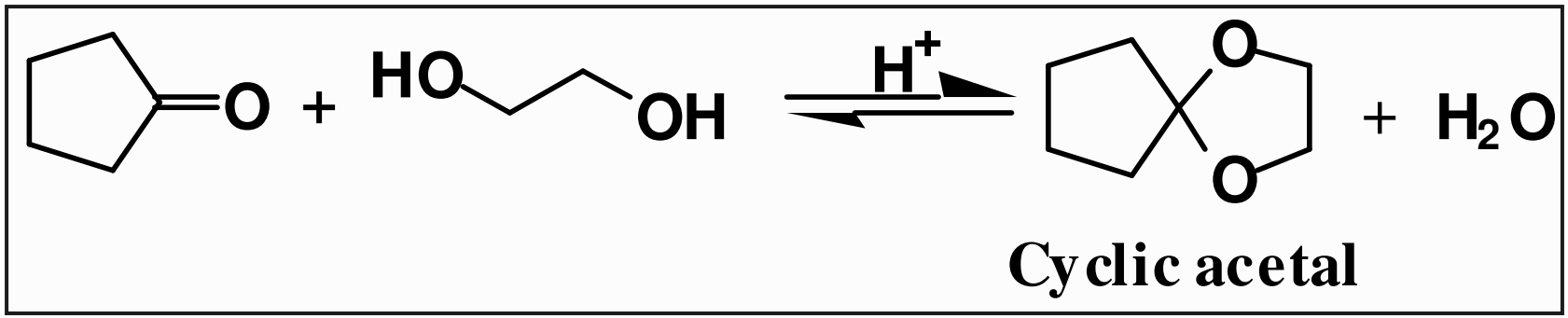
Step 4: proton transfer to A^- gives the acetal and generates a new acid catalyst

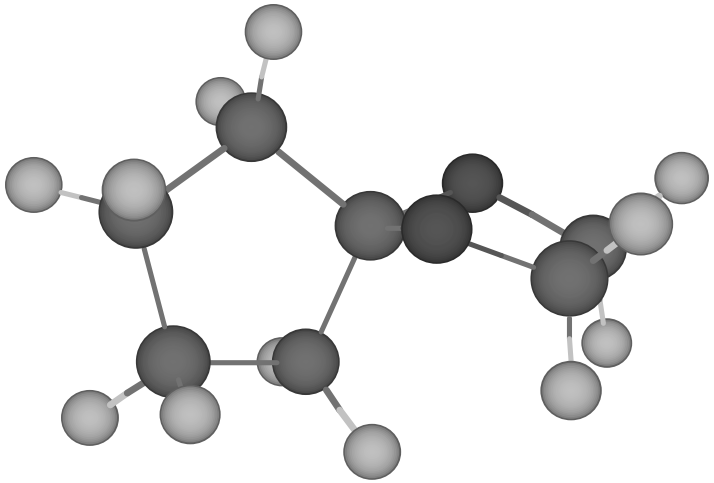


Addition of Alcohols to Carbonyls

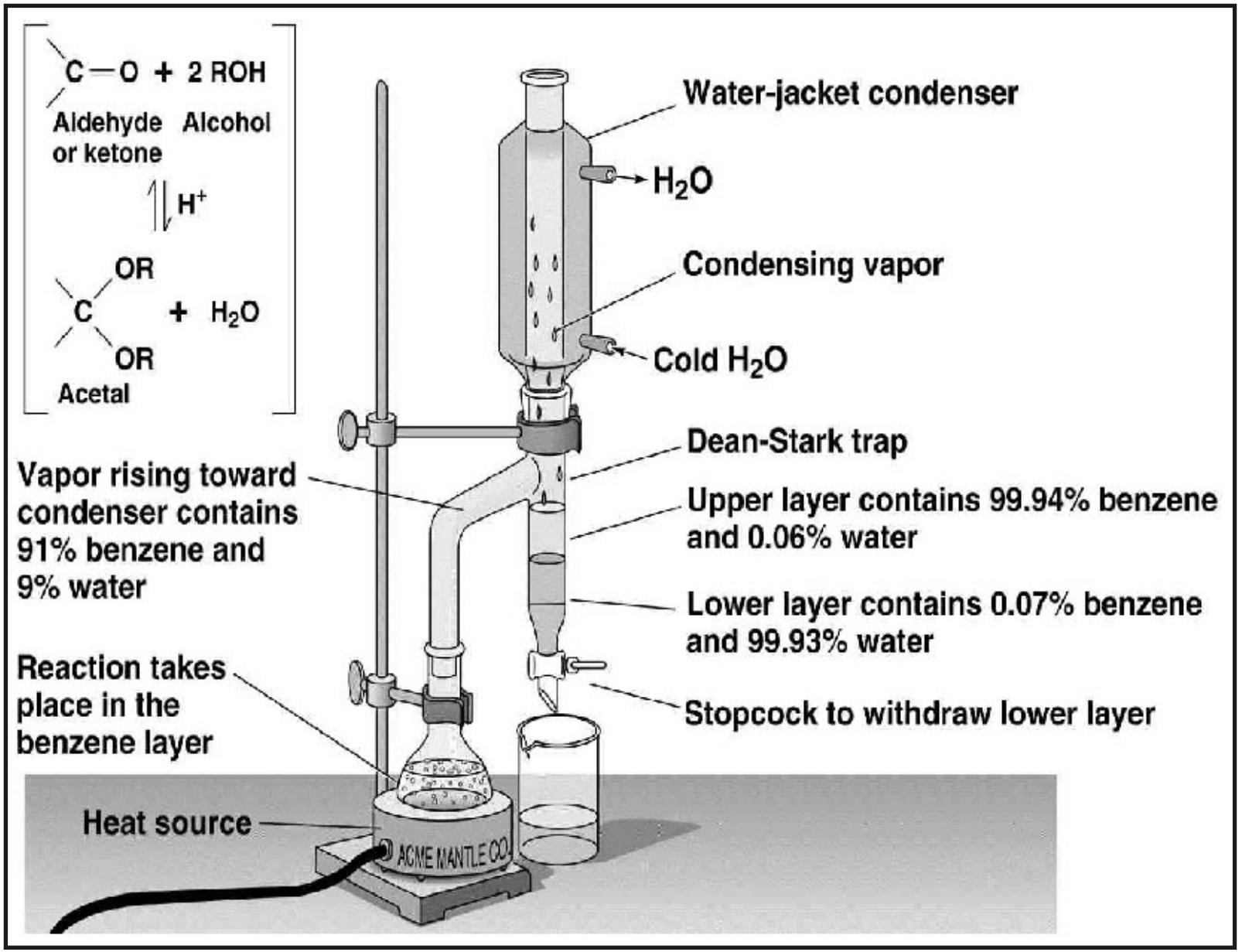
– with ethylene glycol and other glycols, the product is a five-membered cyclic acetal

– this a method of "protecting" ketones



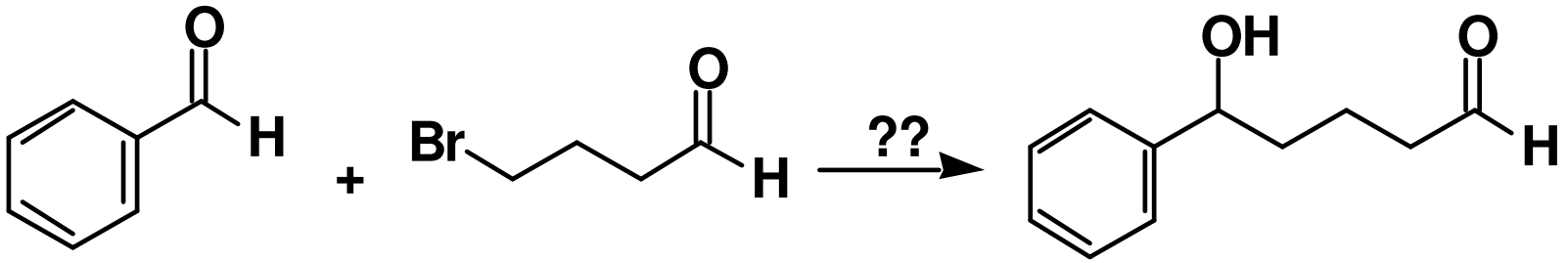


Dean-Stark Trap

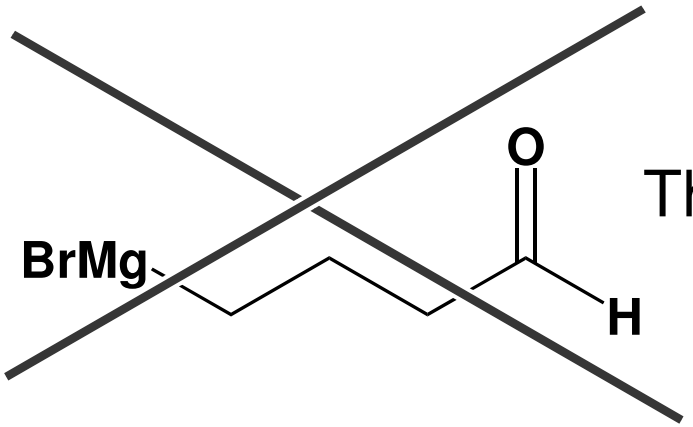


Acetals as Protecting Groups

- How to bring about a Grignard reaction between these compounds:



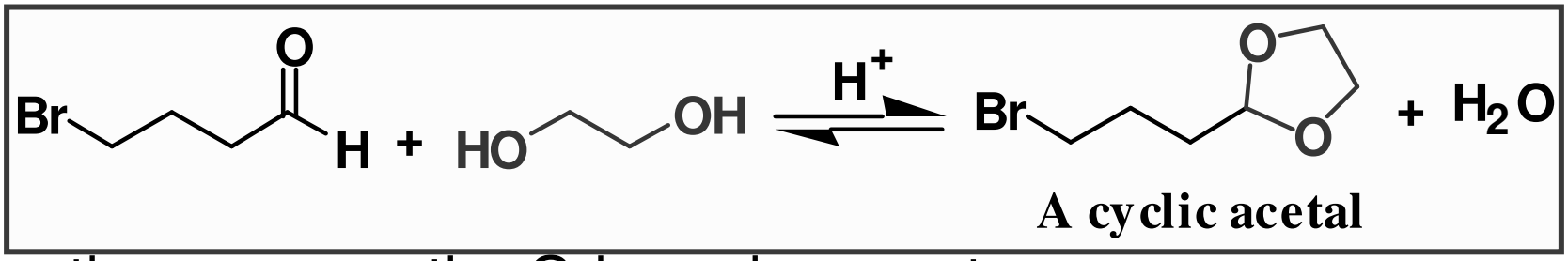
Benzaldehyde **4-Bromobutanal** **5-Hydroxy-5-phenylpentanal (racemic)**



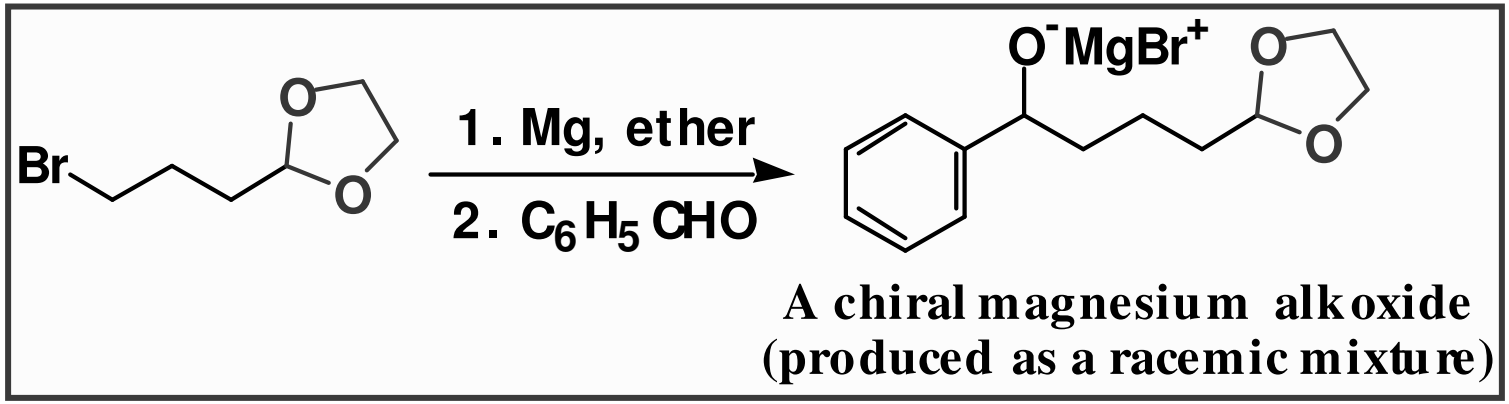
This Grignard cannot be made!!

Acetals as Protecting Groups

- a Grignard reagent prepared from 4-bromobutanal will self-destruct (**decompose**).
  - first protect the -CHO group as an acetal:



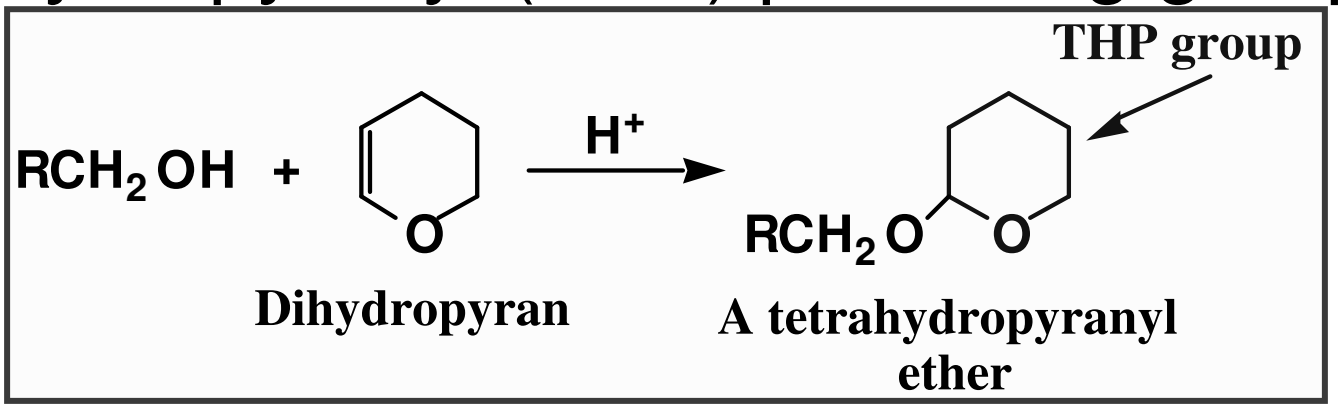
  - then prepare the Grignard reagent:



  - hydrolysis (not shown) gives the target molecule

Acetals as Protecting Groups

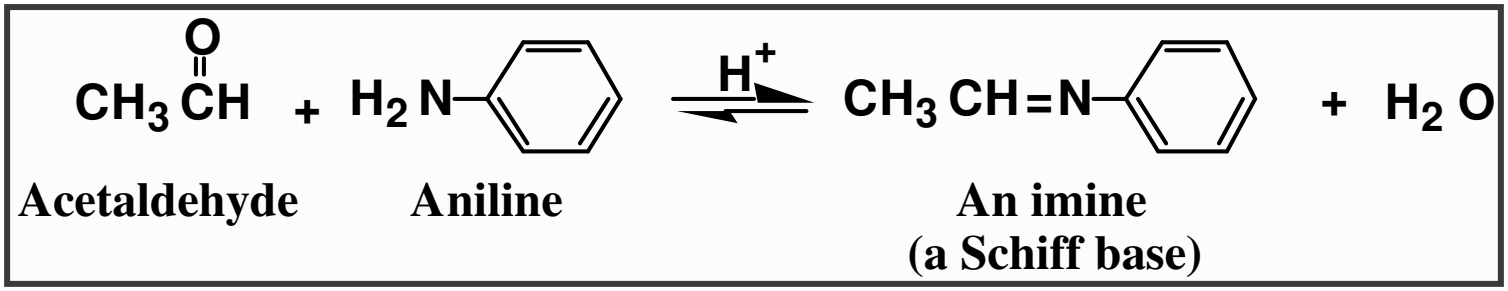
- Tetrahydropyranyl (THP) protecting group

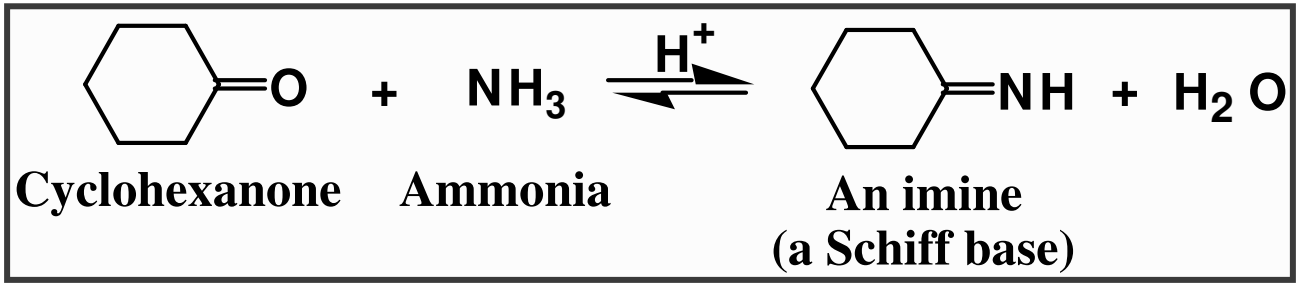


  - the THP group is an acetal and, therefore, stable to neutral and basic solutions, and to most oxidizing and reducing agents
  - it is removed by acid-catalyzed hydrolysis

Addition of Nitrogen Nucleophiles

- Ammonia, 1° aliphatic amines, and 1° aromatic amines react with the C=O group of aldehydes and ketones to give **imines** (Schiff bases)
- Water is removed by Dean-Stark trap or chemical dehydration (e.g. molecular sieves)

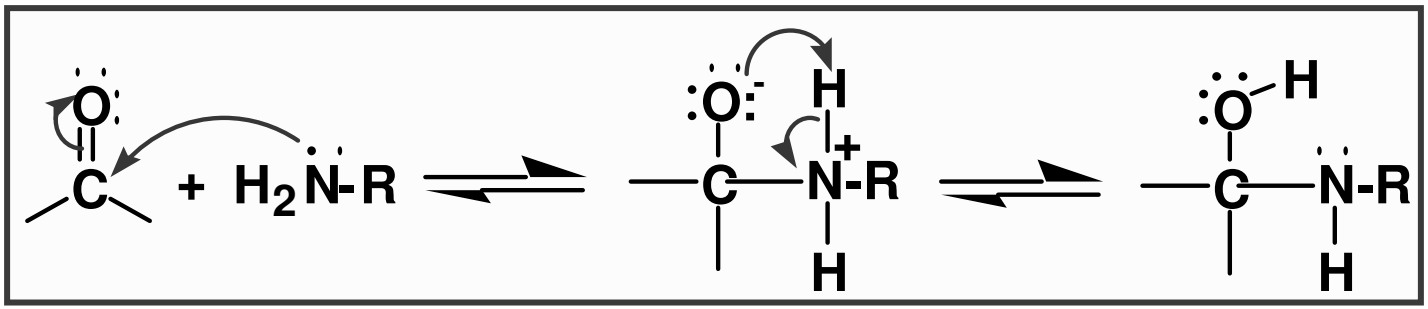




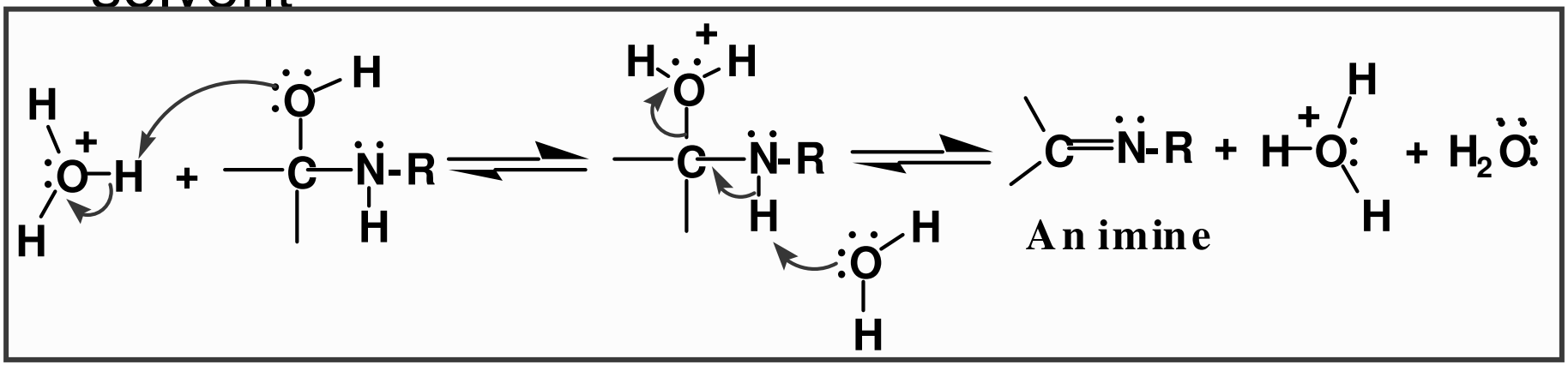
Addition of Nitrogen Nucleophiles

- Formation of an imine occurs in two steps

  Step 1: carbonyl addition followed by proton transfer

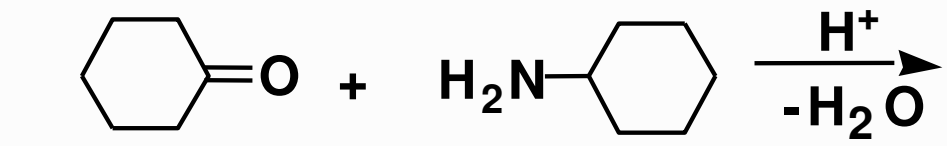


  Step 2: loss of H_2O and proton transfer to solvent

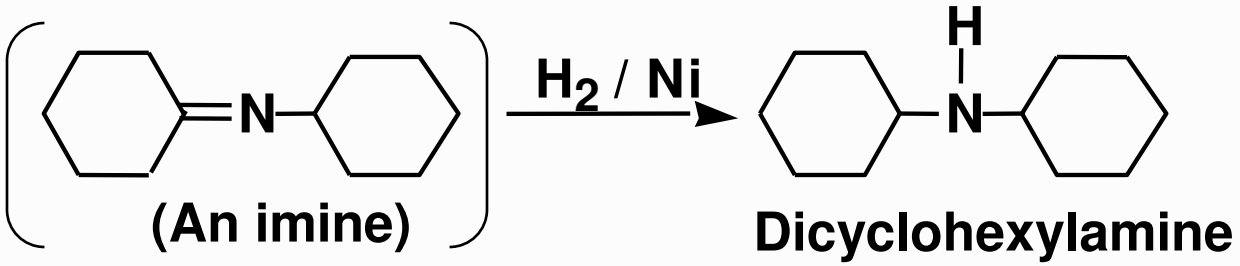


Addition of Nitrogen Nucleophiles

– a value of imines is that the carbon-nitrogen double bond can be reduced to a carbon-nitrogen single bond



Cyclohexanone **Cyclohexylamine**

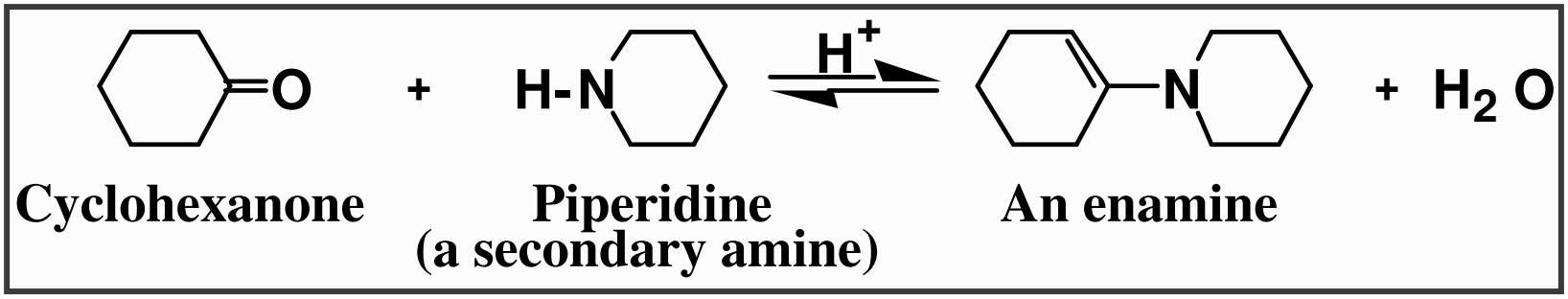


(An imine) **Dicyclohexylamine**

Does not have to isolated

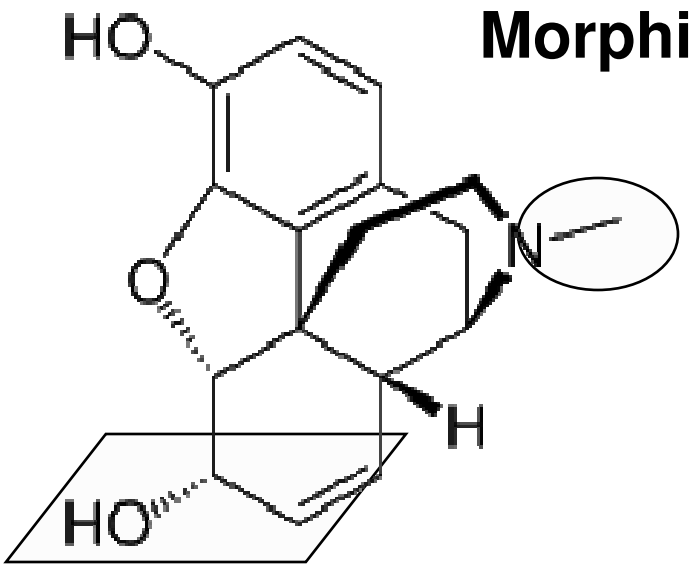
Addition of Nitrogen Nucleophiles

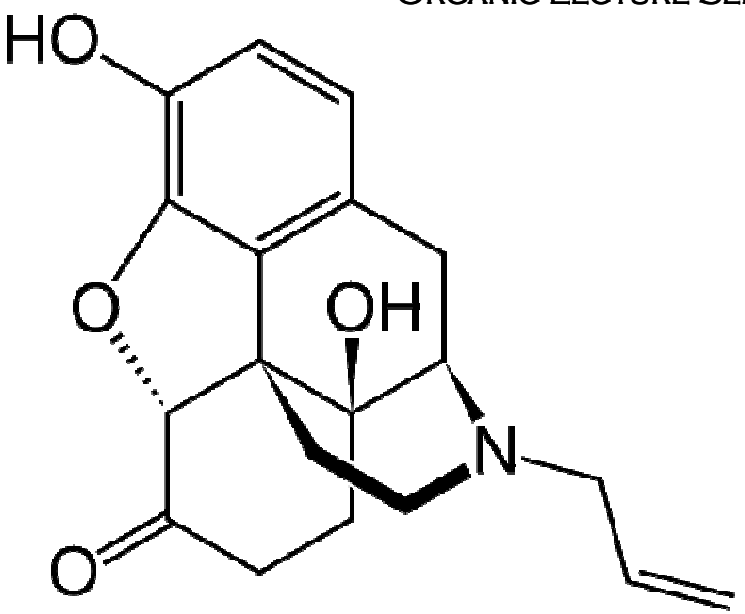
- Secondary amines react with the C=O group of aldehydes and ketones to form **enamines**



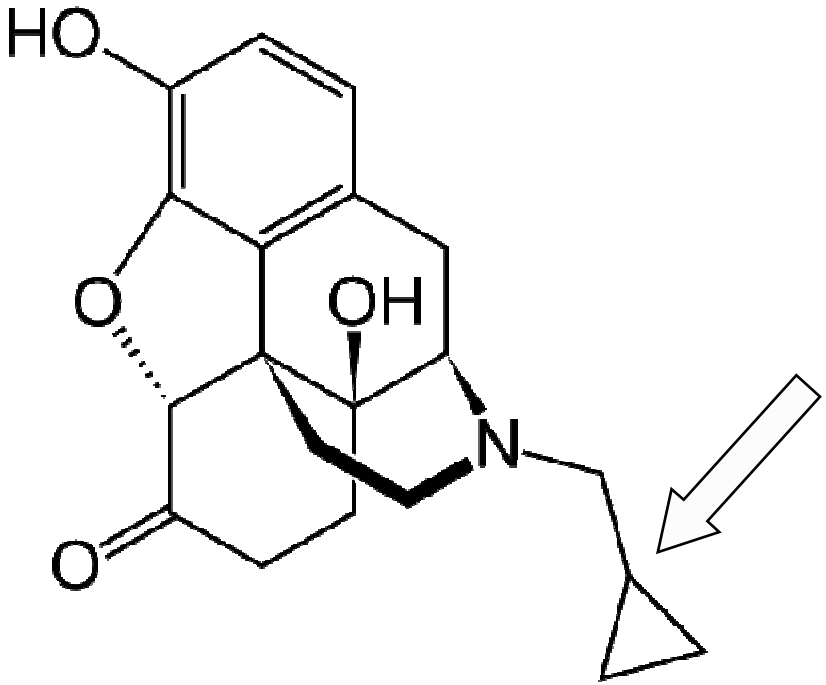
  - the mechanism of enamine formation involves formation of a tetrahedral carbonyl addition compound followed by its acid-catalyzed dehydration

Morphine





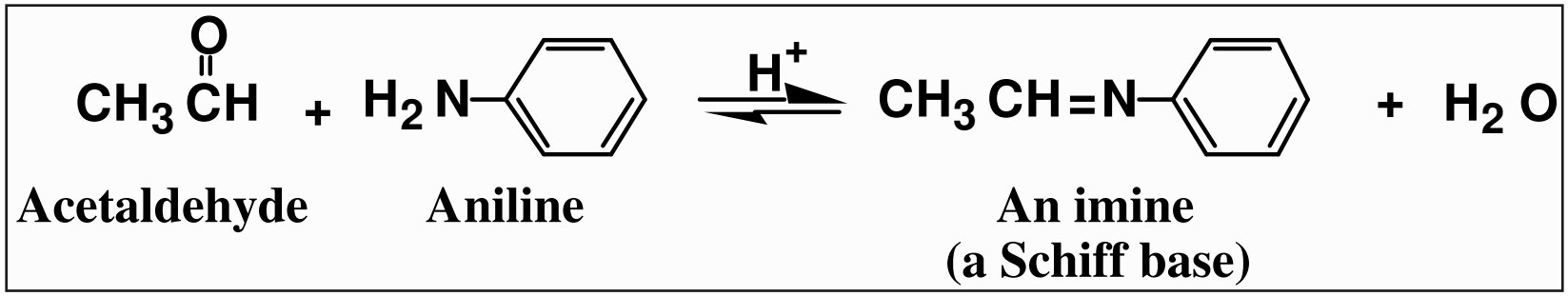
Naloxone-
Antagonist for acute opiate overdose

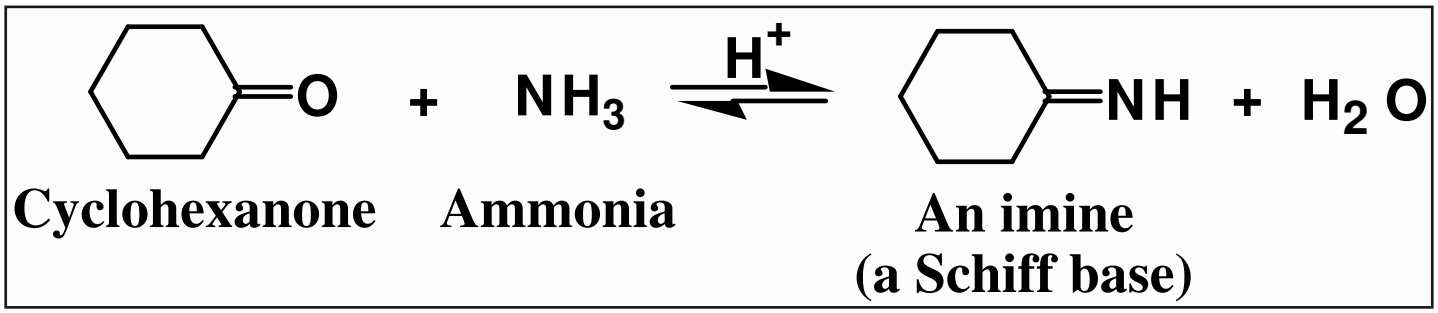


Natrexone-
Longer acting Antagonist
Used for opiate & alcohol dependence

Addition of Nitrogen Nucleophiles

- Ammonia, 1° aliphatic amines, and 1° aromatic amines react with the C=O group of aldehydes and ketones to give **imines** (Schiff bases)
- Water is removed by Dean-Stark trap or chemical dehydration (e.g. molecular sieves)

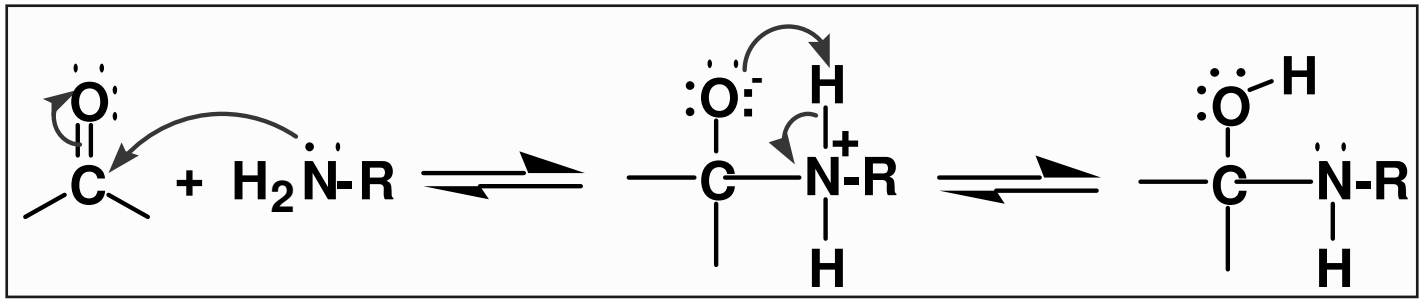




Addition of Nitrogen Nucleophiles

Formation of an imine occurs in two steps

Step 1: carbonyl addition followed by proton transfer



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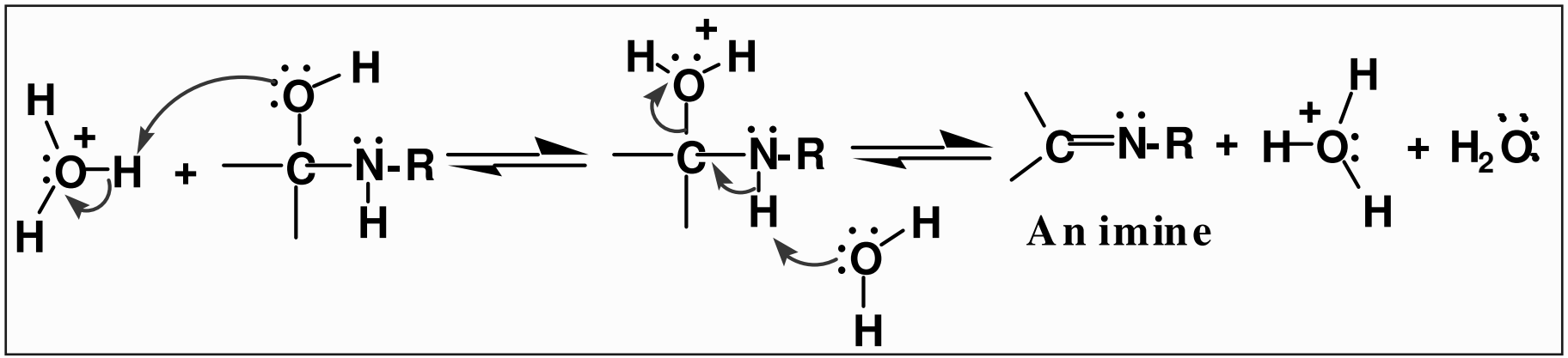

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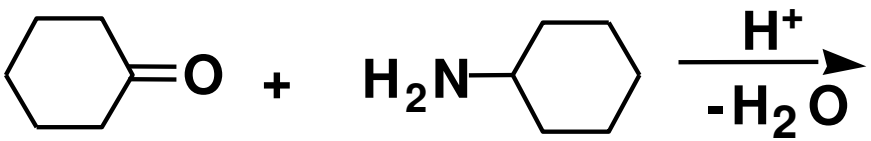
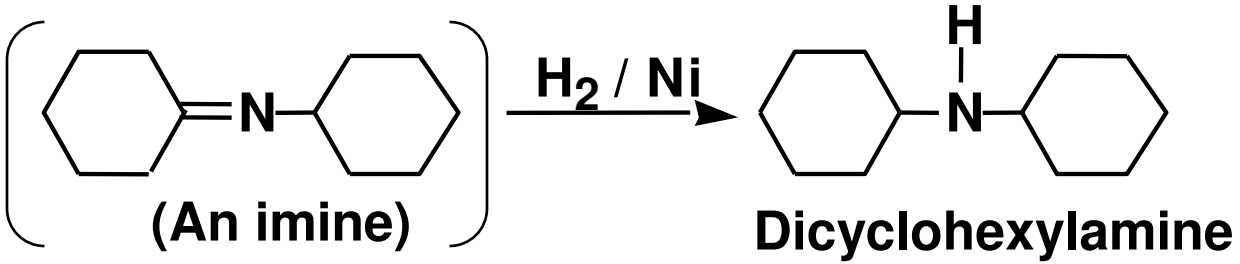


Cyclohexanone **Cyclohexylamine**

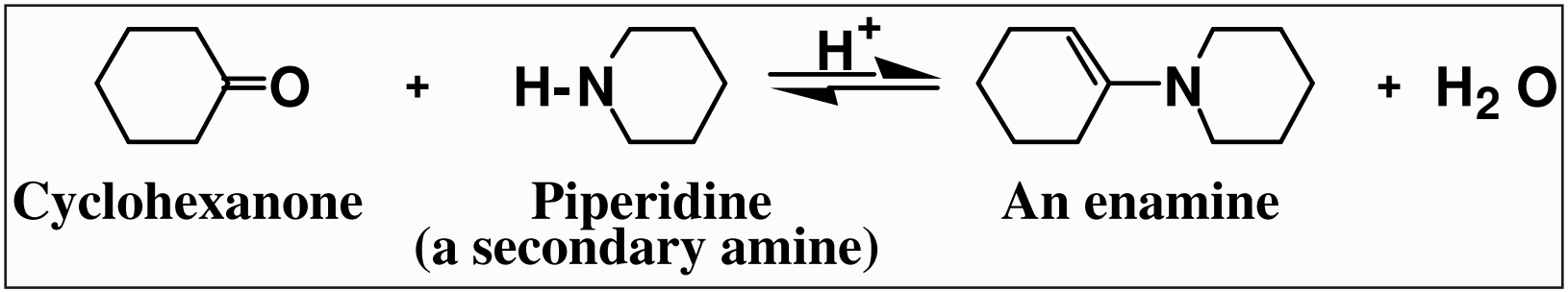


(An imine) **Dicyclohexylamine**

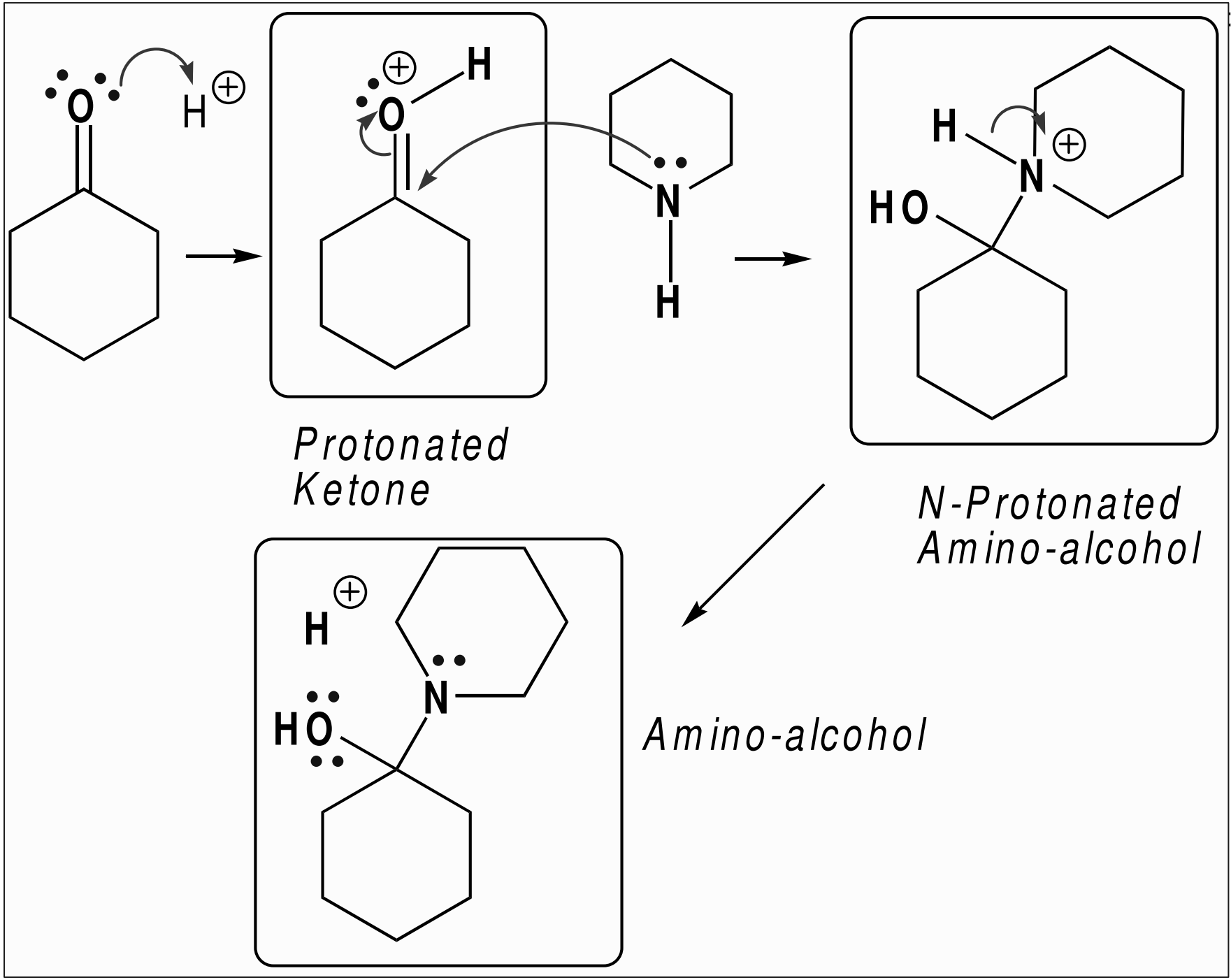
Does not have to isolated

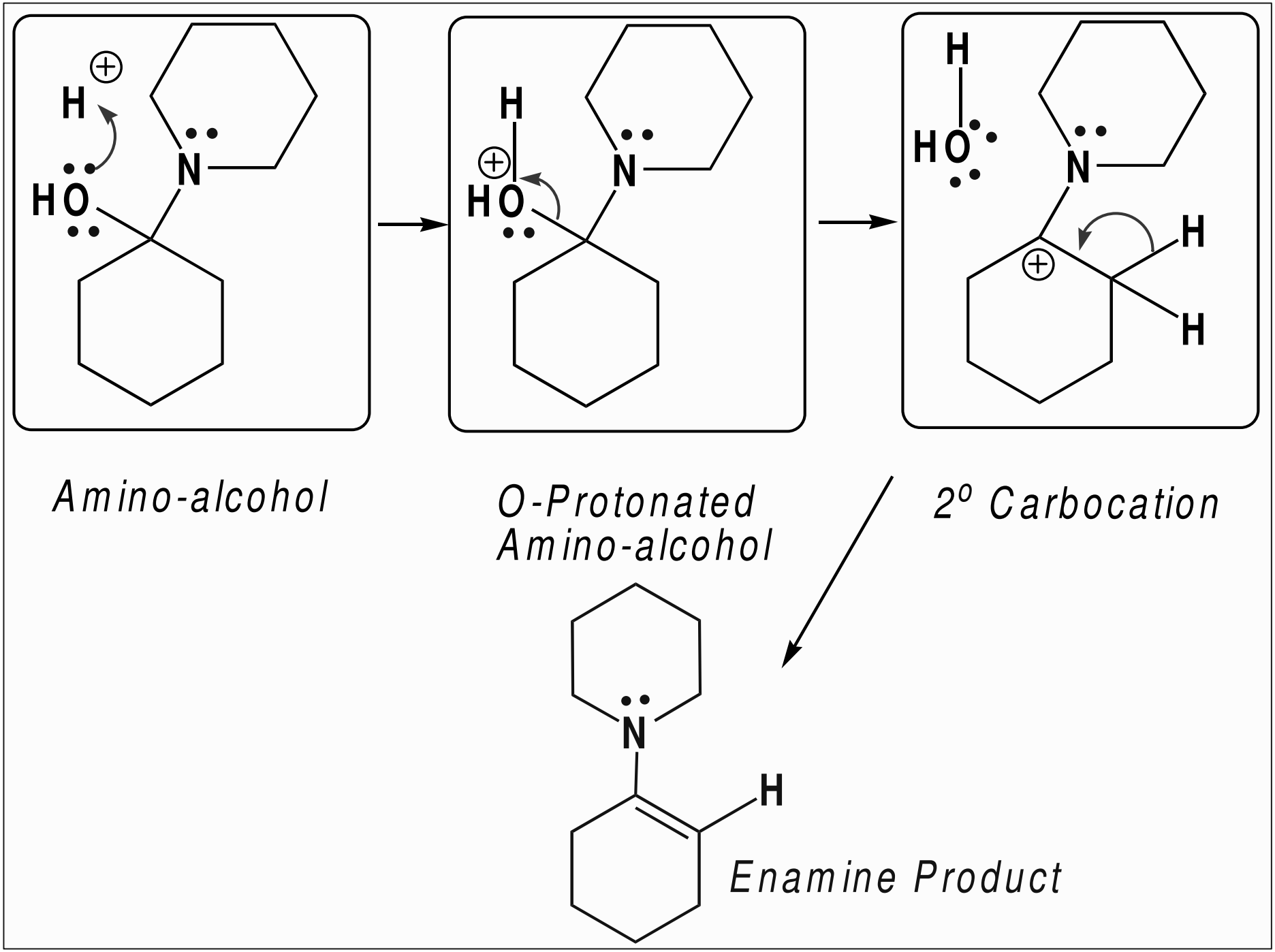
Addition of Nitrogen Nucleophiles

- Secondary amines react with the C=O group of aldehydes and ketones to form **enamines (alkene and amine)**



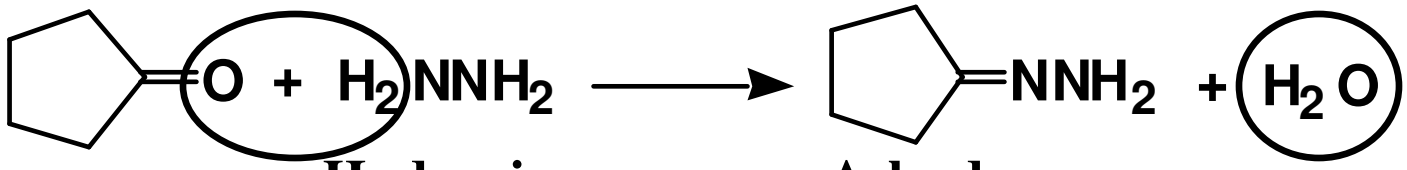
  - the mechanism of enamine formation involves formation of a tetrahedral carbonyl addition compound followed by its acid-catalyzed dehydration


O
H
O
H
N
H
H
N
HO
Protonated
Ketone
N-Protonated
Amino-alcohol
H
N
HO
Amino-alcohol


Amino-alcohol
O-Protonated
Amino-alcohol
2º Carbocation
Enamine Product

Addition of Nitrogen Nucleophiles

– the carbonyl group of aldehydes and ketones reacts with hydrazine and its derivatives in a manner similar to its reactions with 1° amines

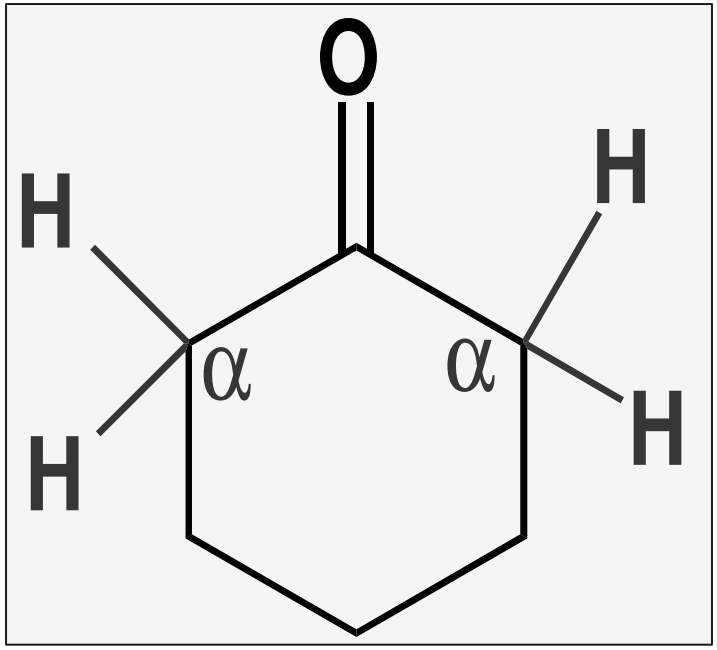


Hydrazine **A hydrazone**

Reagent, H_2N-R	Name of Reagent	Name of Derivative Formed
H_2N-OH	Hydroxylamine	Oxime
H_2N-NH-C$_6$H$_5$	Phenylhydrazine	Phenylhydrazone
H_2N-NH-C$_6$H$_3$(NO_2)(O_2N)	2,4-Dinitrophenyl-hydrazine	2,4-Dinitrophenylhydrazone
H_2N-NHC(=O)NH_2	Semicarbazide	Semicarbazone

Acidity of α-Hydrogens

Hydrogens alpha to a carbonyl group are more acidic than hydrogens of other hydrocarbons (e.g. alkanes, alkenes, aromatic). Acidity is measured as K_a



$$HA + H_2O \rightleftharpoons H_3O^+ + A^-$$

$$K_{eq} = \frac{[H_3O^+][A^-]}{[HA][H_2O]}$$

Note: ℓ and s are not used in K

$$[H_2O]\,K_{eq} = \frac{[H_3O^+][A^-]}{[HA]}$$

$$K_a = \frac{[H_3O^+][A^-]}{[HA]}$$

Acidity of α-Hydrogens

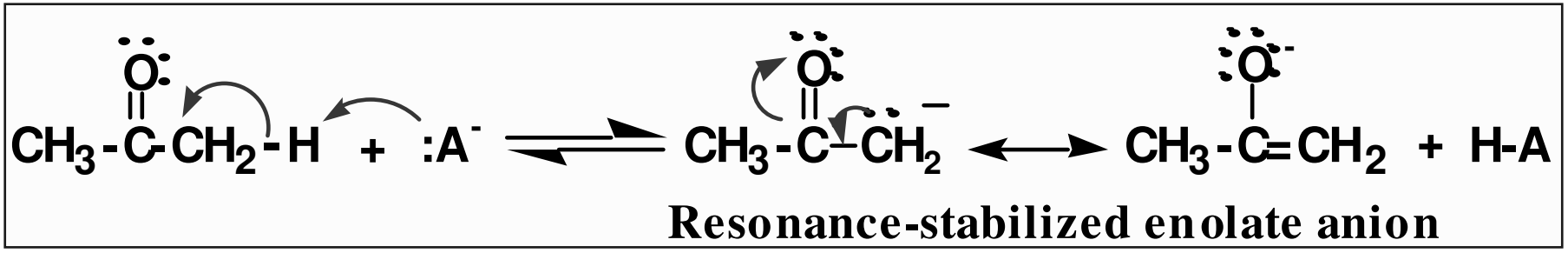
Hydrogens alpha to a carbonyl group are more acidic than hydrogens of alkanes, alkenes, and alkynes but less acidic than the hydroxyl hydrogen of alcohols

pKa = -log Ka

Type of Bond	pK_a
CH_3CH_2O-H	16
$CH_3C(=O)CH_2-H$	20
$CH_3C\equiv C-H$	25
$CH_2=CH-H$	44
CH_3CH_2-H	51

α-Hydrogens are more acidic because the enolate anion is stabilized by:

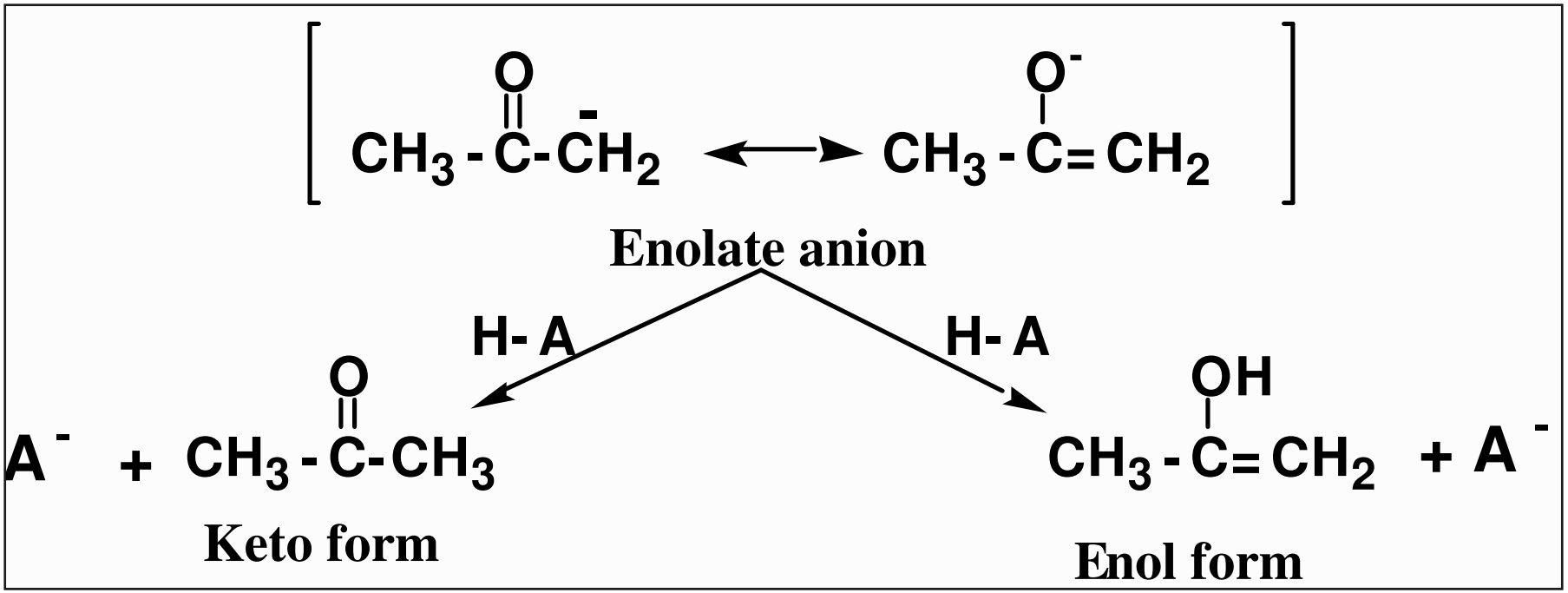
1. delocalization of its negative charge
2. the electron-withdrawing inductive effect of the adjacent electronegative oxygen



Note: α-hydrogens are not so acidic that they will destroy organometallic reagents

Keto-Enol Tautomerism

– protonation of the enolate anion on oxygen gives the **enol form***; protonation on carbon gives the **keto form**

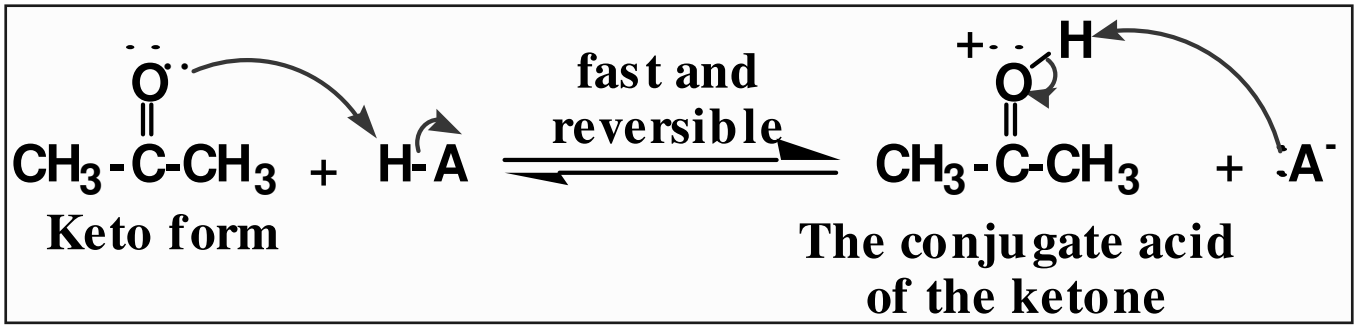


*Enol: made from 2 functional groups-alkene and alcohol

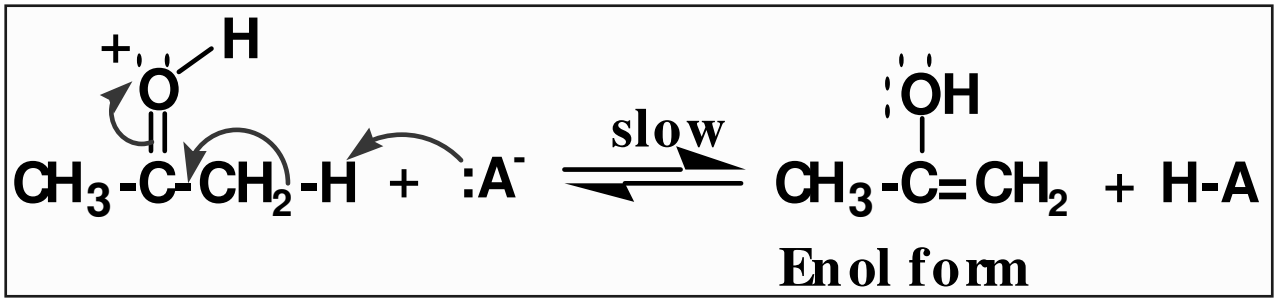
Keto-Enol Tautomerism

– **acid-catalyzed** equilibration of **keto** and **enol** tautomers occurs in two steps

Step 1: proton transfer to the carbonyl oxygen

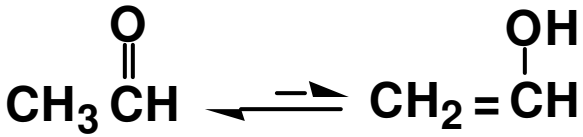
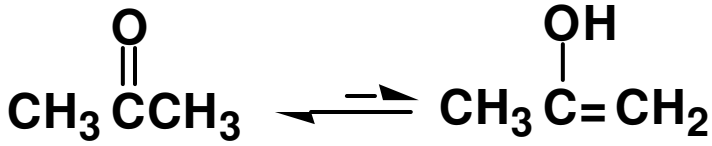
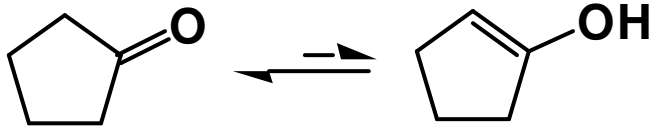
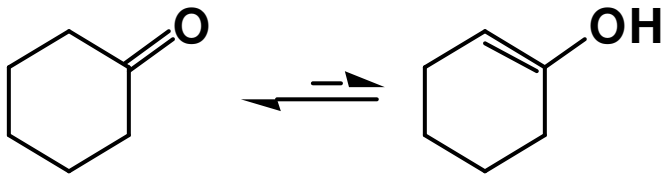


Step 2: proton transfer to the base A^-



Keto-Enol Tautomerism

Keto-enol equilibria for simple aldehydes and ketones lie far toward the keto form

Keto form	Enol form	% Enol at Equilibrium
		6×10^{-5}
		6×10^{-7}
		1×10^{-6}
		4×10^{-5}

Keto-Enol Tautomerism

For certain types of molecules, however, the enol is the major form present at equilibrium

- for β-diketones, the enol is stabilized by conjugation of the pi system of the carbon-carbon double bond and the carbonyl group
- for acyclic β-diketones, the enol is further stabilized by hydrogen bonding (i.e.1,3 diones)