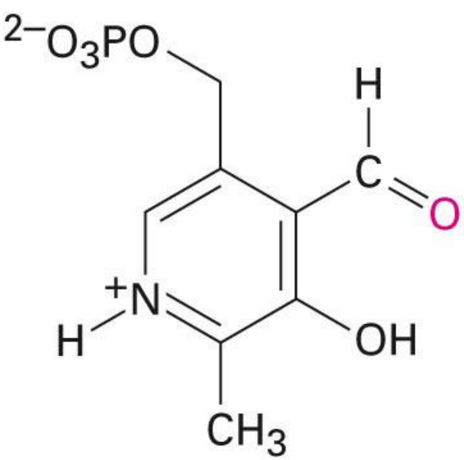
Aldehydes and Ketones: Nucleophilic Addition Reactions

McMurry, 'Fundamentals of Organic Chemistry', 7th Ed.

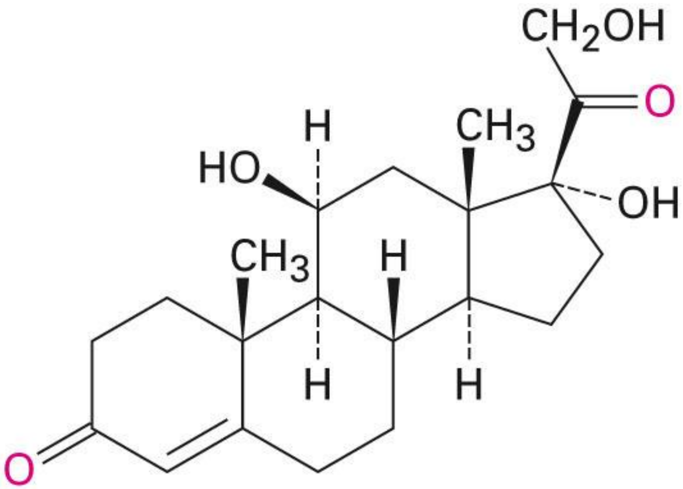
Chapter 9

Aldehydes and Ketones

- Aldehydes (RCHO) and ketones (R_2CO) are characterized by the the carbonyl functional group (C=O)
- The compounds occur widely in nature as intermediates in metabolism and biosynthesis



Pyridoxal phosphate (PLP)



Hydrocortisone

Why this Chapter?

- **Much of organic chemistry involves the chemistry of carbonyl compounds**

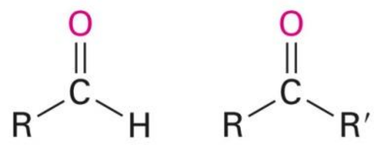
- **Aldehydes/ketones are intermediates in synthesis of pharmaceutical agents, biological pathways, numerous industrial processes**

- **An understanding of their properties is essential**

9.1 The Nature of Carbonyl Compounds

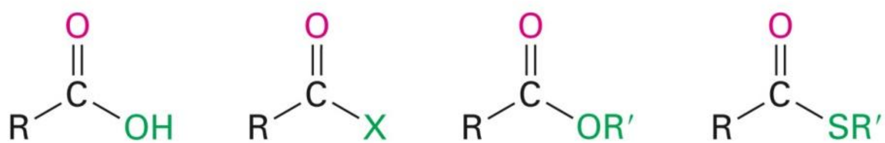
Carbonyl Compounds:

1. Aldehydes and Ketones
2. Carboxylic Acid and their Derivatives

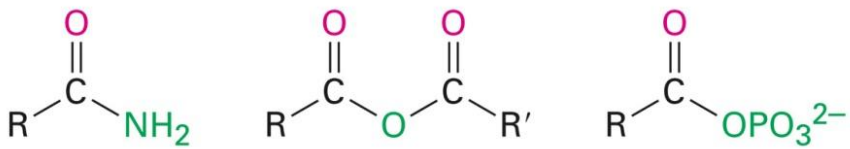


Aldehyde　Ketone

The –R′ and –H in these compounds *can't* act as leaving groups in nucleophilic substitution reactions.



Carboxylic acid　Acid halide　Ester　Thioester



Amide　Acid anhydride　Acyl phosphate

The –OH, –X, –OR′, –SR, $–NH_2$, –OCOR′, and $–OPO_3^{2-}$ in these compounds *can* act as leaving groups in nucleophilic substitution reactions.

Electronic Structure of the Carbonyl Group

- The carbonyl carbon atom is sp^2-hybridized and forms three σ bonds
- The fourth valence electron remains in a carbon *p* orbital and forms a π bond to oxygen by overlap with an oxygen *p* orbital
- Carbonyl compounds are planar about the double bond and have bond angles of approximately 120°

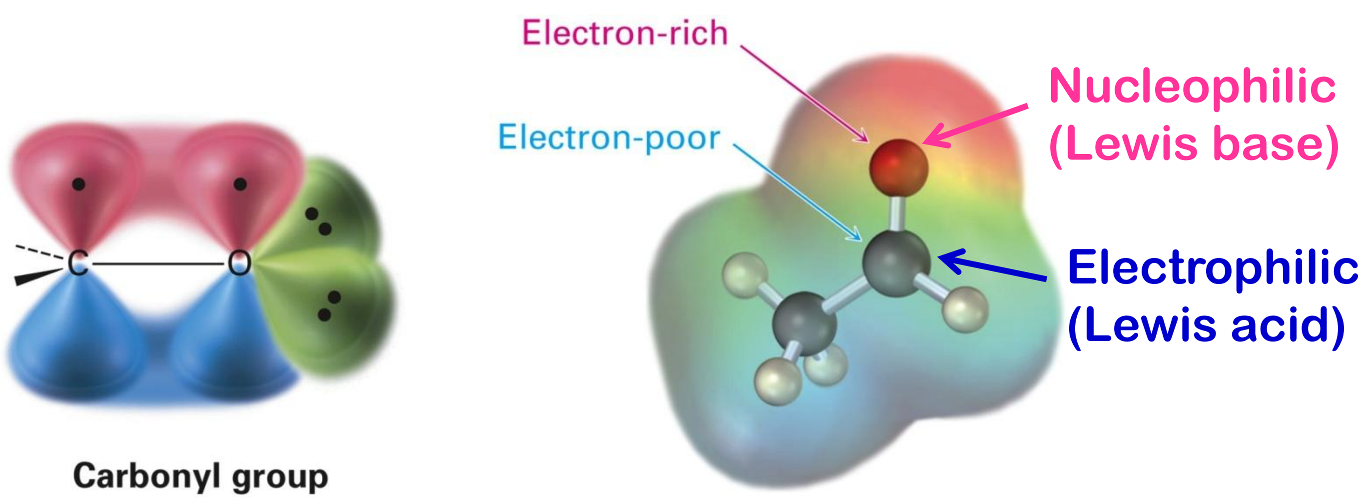
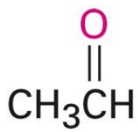


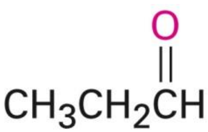
Figure 9.1 Electronic structure of the carbonyl group.

9.2 Naming Aldehydes and Ketones

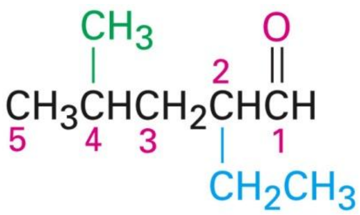
- **Aldehydes** are named by replacing the terminal -*e* of the corresponding alkane name with ***–al***
- The parent chain must contain the –CHO group
  - The –CHO carbon is numbered as C1



Ethanal
(acetaldehyde)

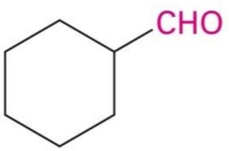


Propanal
(propionaldehyde)

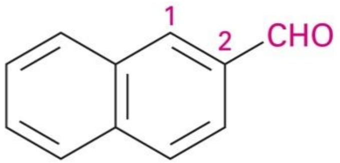


2-Ethyl-4-methylpentanal

- If the –CHO group is attached to a ring, use the suffix ***carbaldehyde***



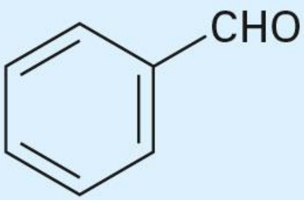
Cyclohexanecarbaldehyde



Naphthalene-2-carbaldehyde

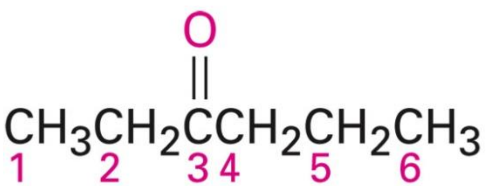
common names

Table 9.1 Common Names of Some Simple Aldehydes

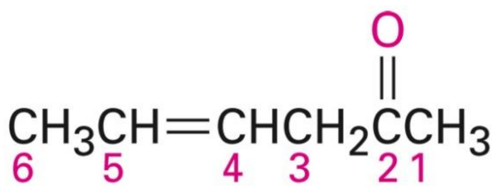
Formula	Common name	Systematic name
$HCHO$	Formaldehyde	Methanal
CH_3CHO	Acetaldehyde	Ethanal
$H_2C{=}CHCHO$	Acrolein	Propenal
$CH_3CH{=}CHCHO$	Crotonaldehyde	But-2-enal
	Benzaldehyde	Benzenecarbaldehyde

Naming Ketones

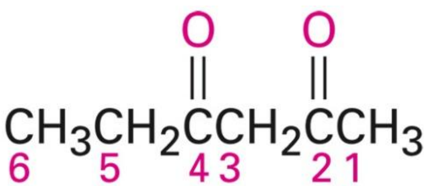
- Replace the terminal -*e* of the alkane name with –***one***
- Parent chain is the longest one that contains the ketone group
  - Numbering begins at the end nearer the carbonyl carbon



Hexan-3-one



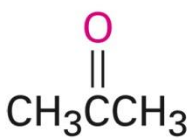
Hex-4-en-2-one



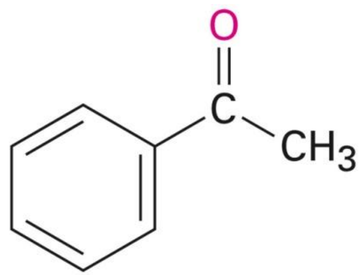
Hexane-2,4-dione

Ketones with Common Names

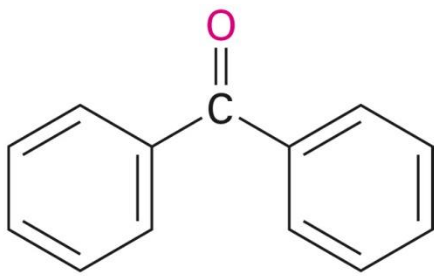
- **IUPAC retains well-used but unsystematic names for a few ketones**



Acetone



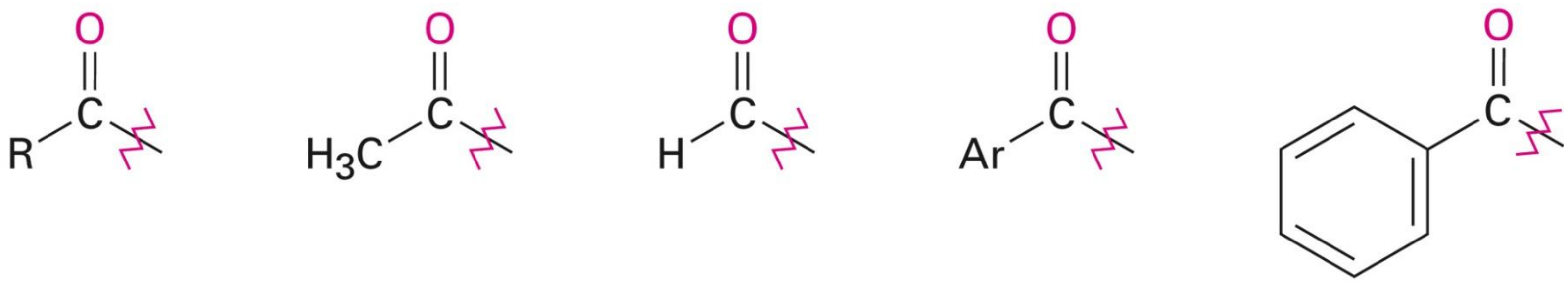
Acetophenone



Benzophenone

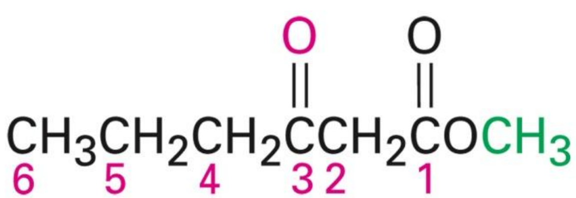
Ketones and Aldehydes as Substituents

- The R–C=O as a substituent is an **acyl group**, used with the suffix *-yl* from the root of the carboxylic acid



An acyl group (R = alkyl, alkenyl) | Acetyl | Formyl | Aroyl (Ar = aromatic) | Benzoyl

- The prefix *oxo-* is used if other functional groups are present and the doubly bonded oxygen is labeled as a substituent on a parent chain

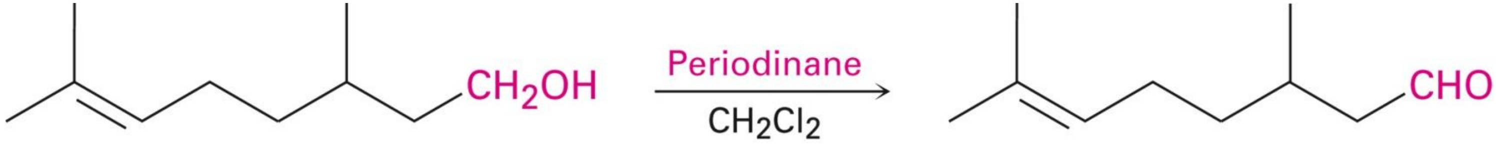


Methyl 3-oxohexanoate

9.3 Synthesis of Aldehydes and Ketones

Preparing Aldehydes

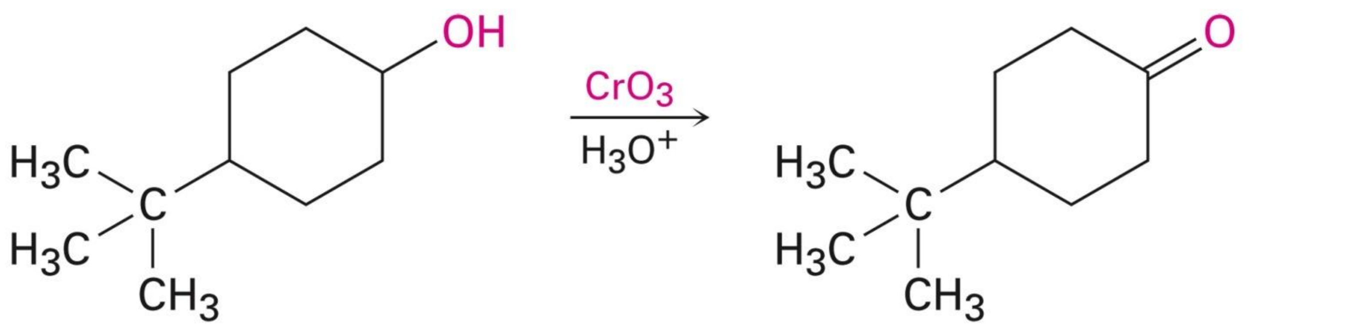
- **Oxidize primary alcohols using periodinane**



Citronellol **Citronellal (82%)**

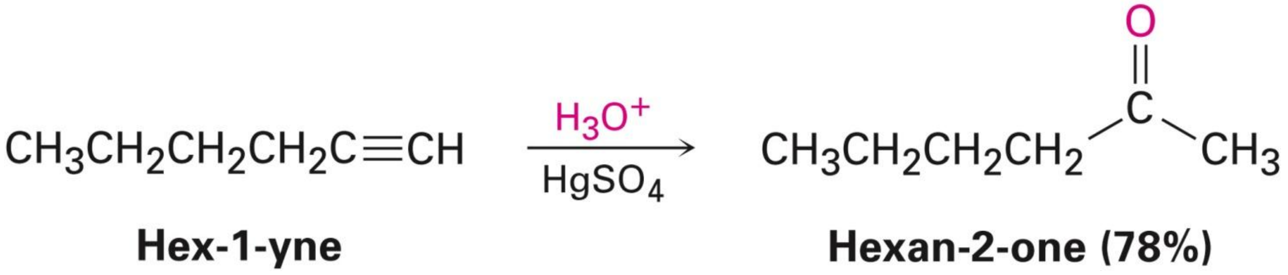
Preparing Ketones

- **Oxidize a 2° alcohol using CrO_3 or $Na_2Cr_2O_7$**

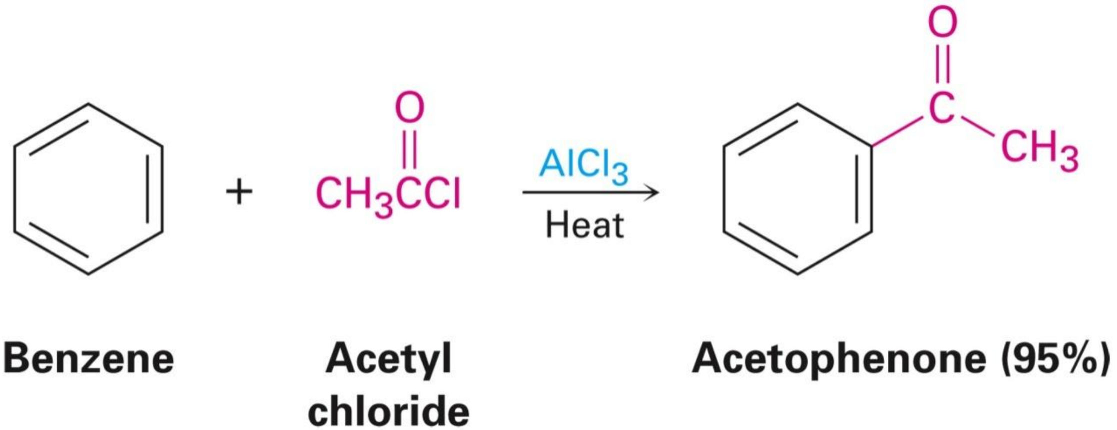


4-*tert*-Butylcyclohexanol **4-*tert*-Butylcyclohexanone (90%)**

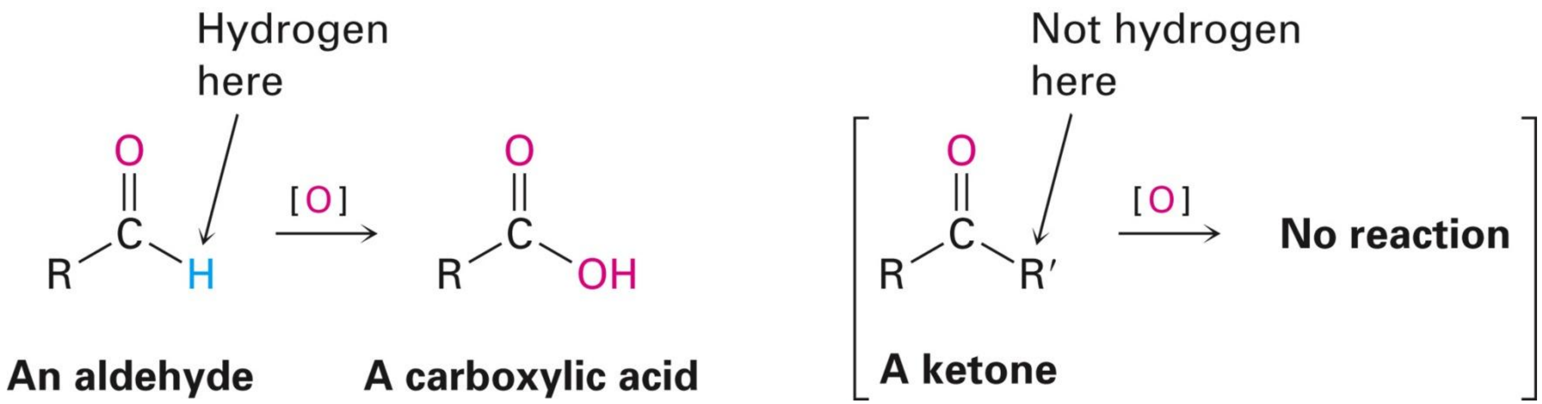
- **Hydration of terminal alkynes in the presence of Hg^{2+}**



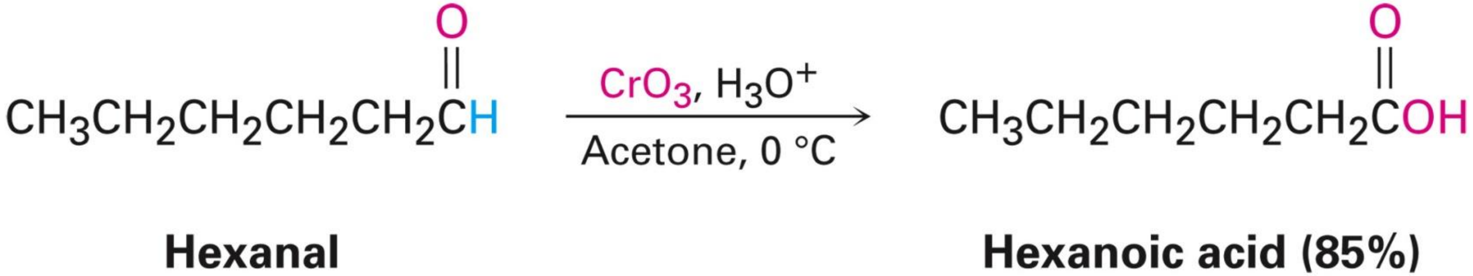
- **Friedel–Crafts acylation of an aromatic ring with an acid chloride in the presence of $AlCl_3$ catalyst**



9.4 Oxidation of Aldehydes

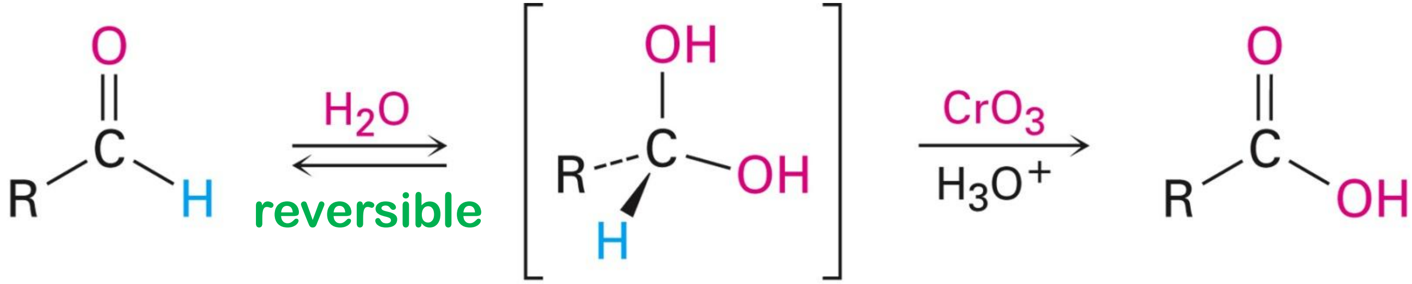


- **CrO_3 in aqueous acid oxidizes aldehydes to carboxylic acids efficiently**



Hydration of Aldehydes

- **Aldehyde oxidations occur through 1,1-diols ("*hydrates*")**
- **Reversible addition of water to the carbonyl group**
- **Aldehyde hydrate is oxidized to a carboxylic acid by usual reagents for alcohols**



An aldehyde **A hydrate** **A carboxylic acid**

9.5 Nucleophilic Addition Reactions

- **Nucleophile approaches to the plane of C=O and adds to C**
- **Nucleophiles can be negatively charged (:Nu⁻) or neutral (:Nu) at the reaction site**

Some negatively charged nucleophiles (basic conditions)		Some neutral nucleophiles (acidic conditions)	
$HO:^-$	(hydroxide ion)	HOH	(water)
$H:^-$	(hydride ion)	ROH	(alcohol)
$R_3C:^-$	(carbanion)	$:NH_3$	(ammonia)
$RO:^-$	(alkoxide ion)	RNH_2	(amine)
$N{\equiv}C:^-$	(cyanide ion)		

Mechanism

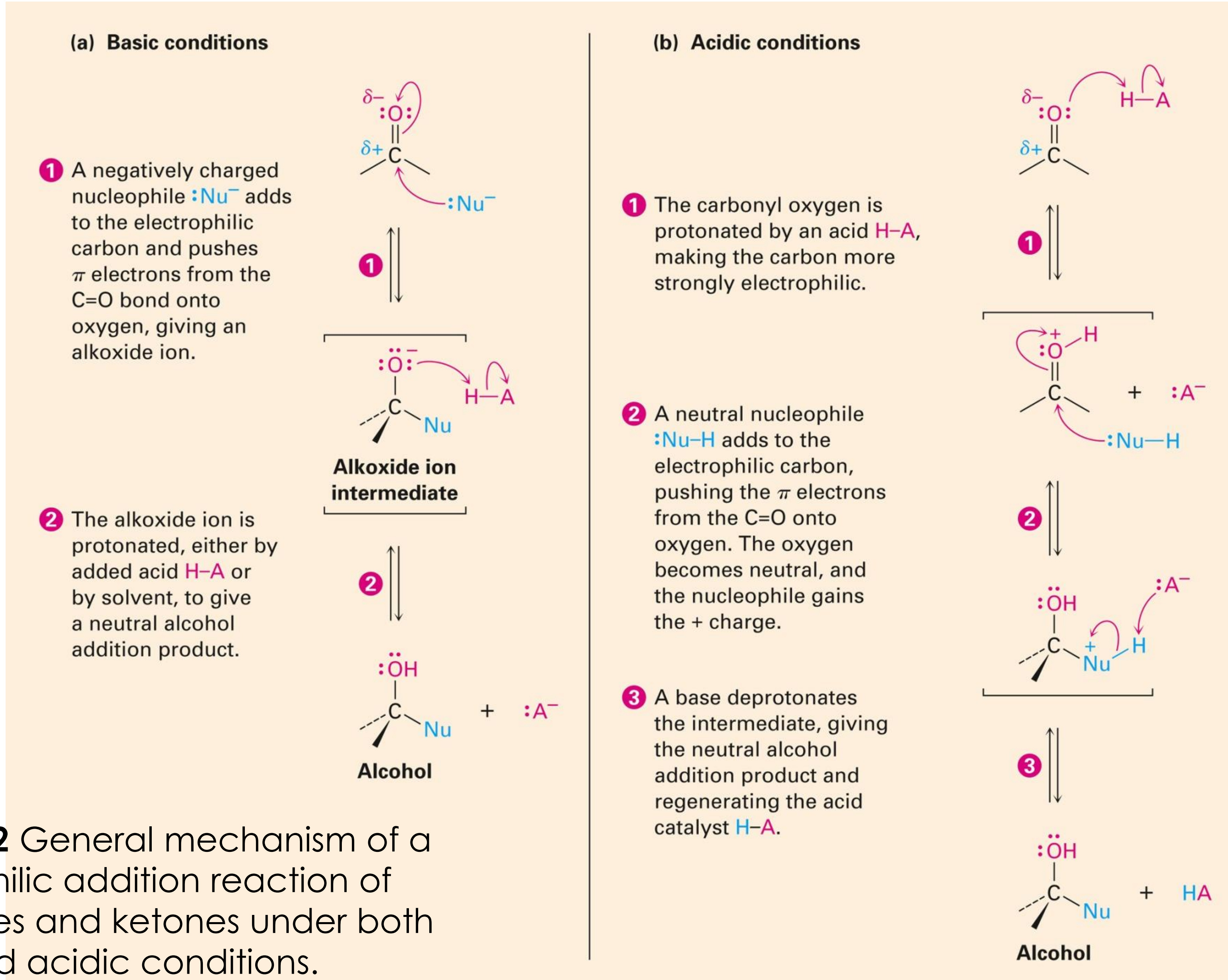
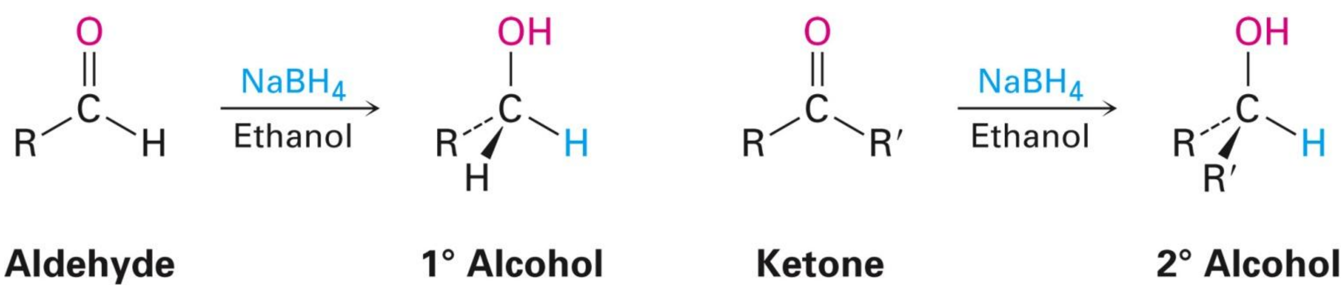


Figure 9.2 General mechanism of a nucleophilic addition reaction of aldehydes and ketones under both basic and acidic conditions.

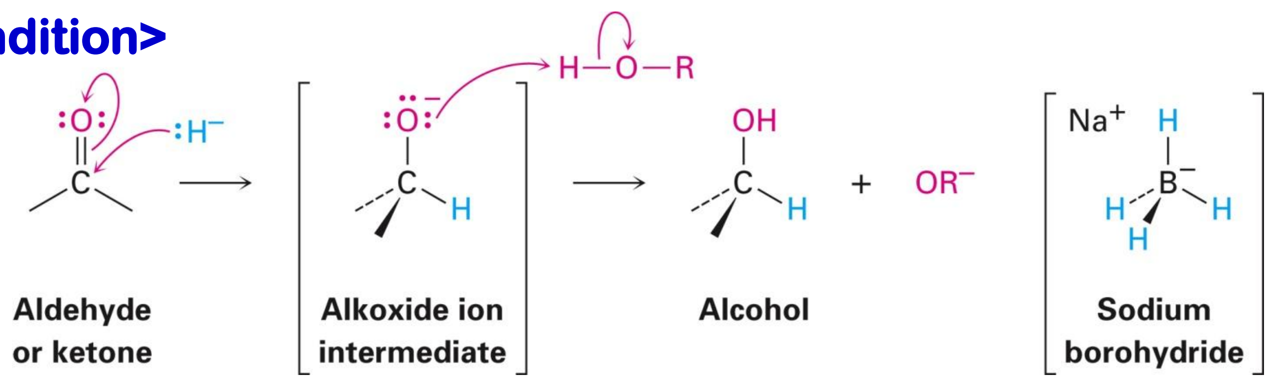
9.6 Nucleophilic Addition of Hydride and Grignard Reagents: Alcohol Formation

Addition of Hydride Reagents: Reduction

- Convert C=O to CH-OH
- $NaBH_4$ reacts as a donor of hydride ion
- Protonation after addition yields the alcohol



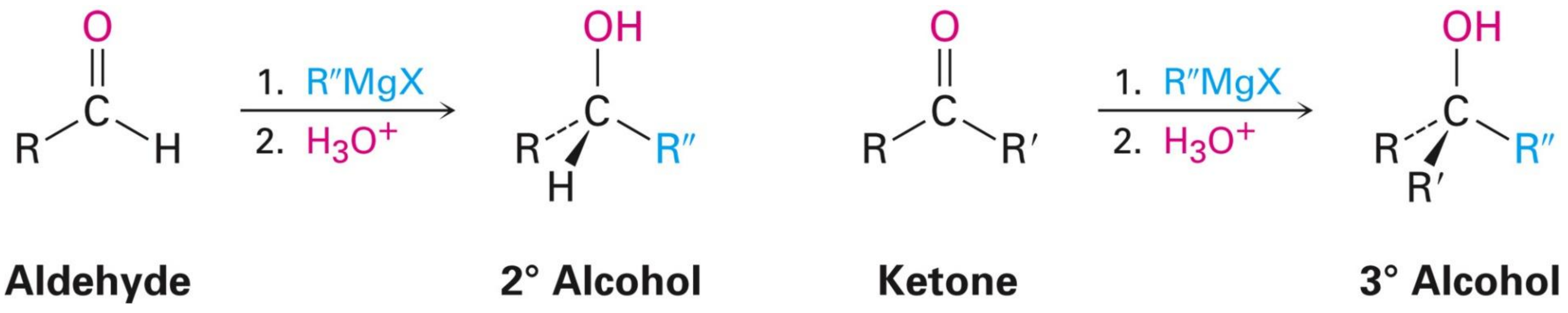
<Basic condition>



irreversible

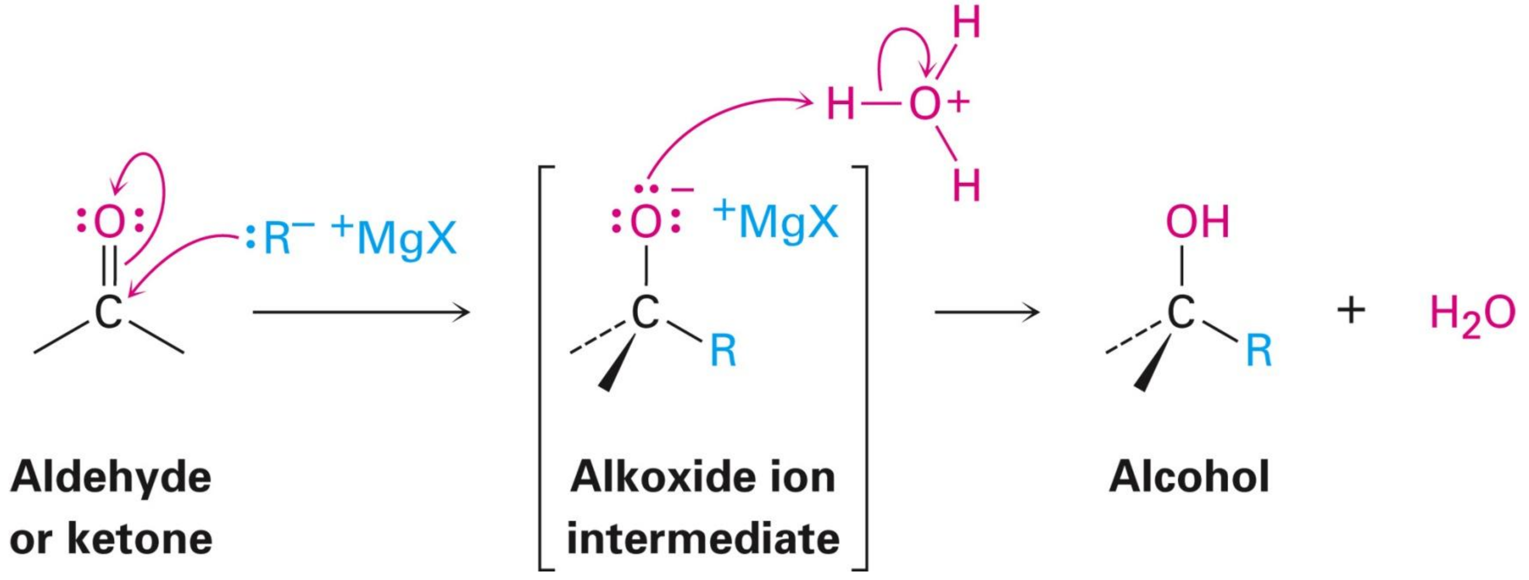
Addition of Grignard Reagents

- **Treatment of aldehydes or ketones with Grignard reagents yields an alcohol**
  - **Nucleophilic addition of the equivalent of a *carbon* anion, or carbanion. A carbon–magnesium bond is strongly polarized, so a Grignard reagent reacts for all practical purposes as $R{:}^{-}\ MgX^{+}$**



Mechanism of Addition of Grignard Reagents

- **Nucleophilic addition of R:⁻, protonation by dilute acid yields the neutral alcohol**
- **Grignard additions are irreversible because a carbanion is not a leaving group**



Limitations of Grignard Reagents

- **Grignard reagents can not be prepared from compounds that contain the following functional groups**

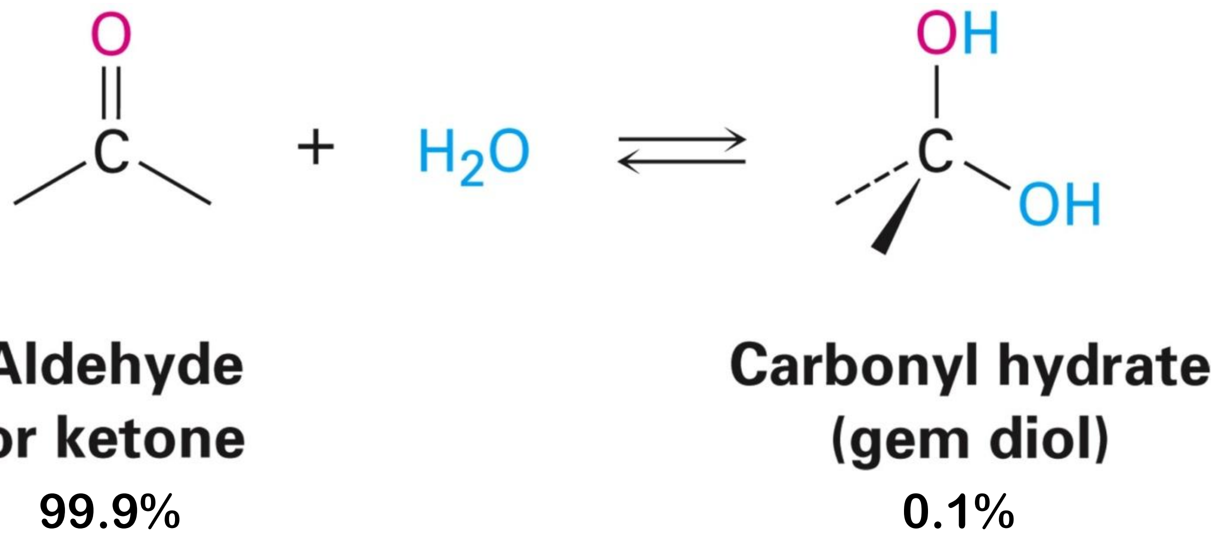
$-CHO$, $-COR$, $-CONR_2$, $-C{\equiv}N$, $-NO_2$, $-SO_2R$ } A Grignard reagent reacts with these groups.

$-OH$, $-NH_2$, $-NHR$, $-SH$, $-CO_2H$ } A Grignard reagent is protonated by these groups.

→ **Destroy the Grignard reagent by protonation**

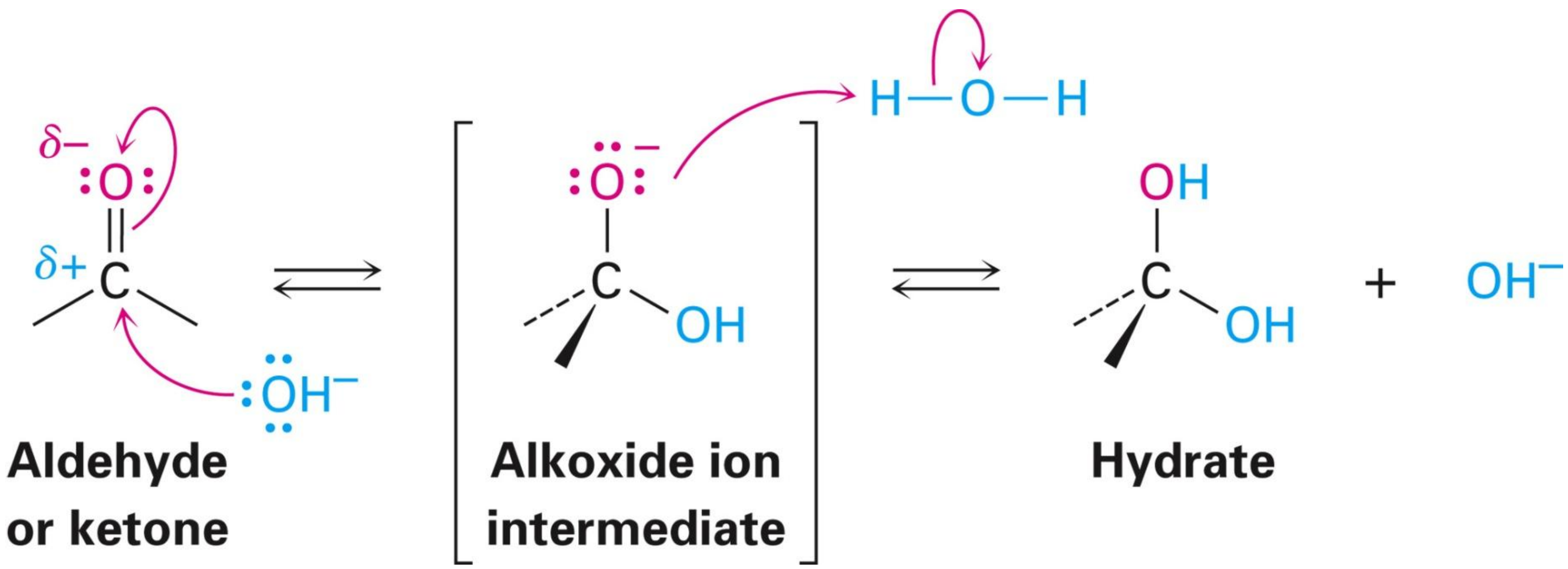
9.7 Nucleophilic Addition of H_2O: Hydrate Formation

- Aldehydes and ketones react with water to yield 1,1-diols (**geminal (gem) diols**)
- Hyrdation is reversible: a gem diol can eliminate water
- The position of the equilibrium depends on the structure of the carbonyl compound



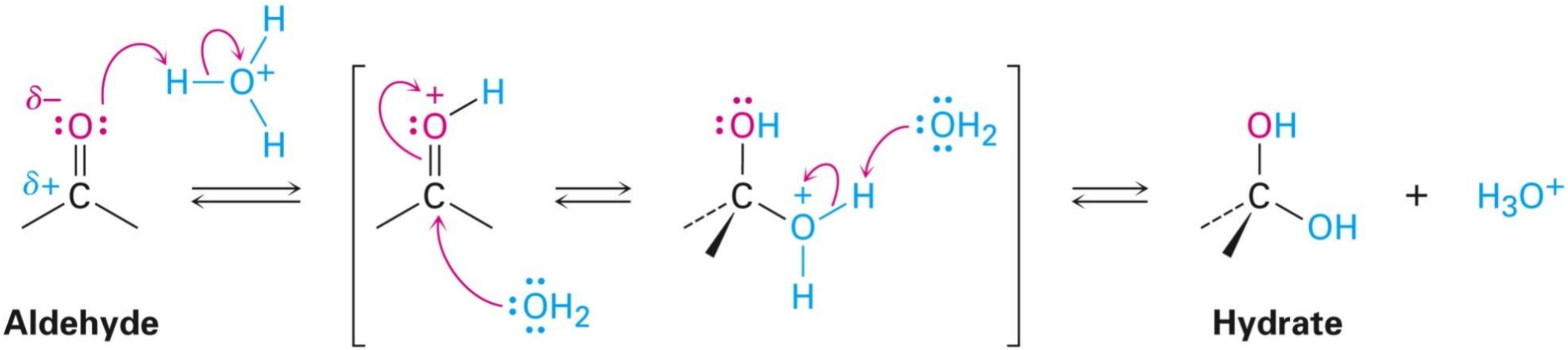
Base-Catalyzed Addition of Water

- Addition of water is catalyzed by both acid and base
- The base-catalyzed hydration nucleophile is the hydroxide ion, which is a much stronger nucleophile than water



Acid-Catalyzed Addition of Water

- **Protonation of C=O makes it more electrophilic**

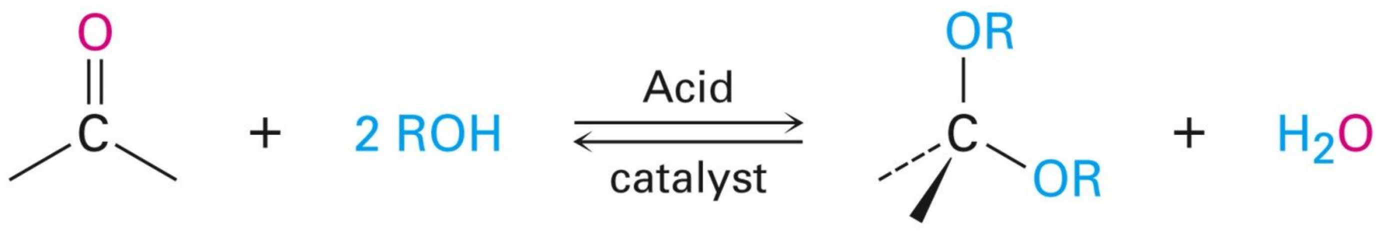


Aldehyde or ketone

Hydrate

9.8 Nucleophilic Addition of Alcohols: Acetal Formation

- Aldehydes and ketones undergo a reversible reaction with alcohols in the presence of an acid catalyst to yield **acetal, $R_2C(OR')_2$**, compounds that have two ether-like –OR groups bonded to the same carbon



Aldehyde or ketone **Acetal**

- Alcohols are weak nucleophiles but acid promotes addition forming the conjugate acid of C=O
- Addition yields a hydroxy ether, called a **hemiacetal**; further reaction can occur
- Protonation of the –OH and loss of water leads to an oxonium ion, $R_2C{=}OR^+$ to which a second alcohol adds to form the acetal
- All the steps during acetal formation are reversible

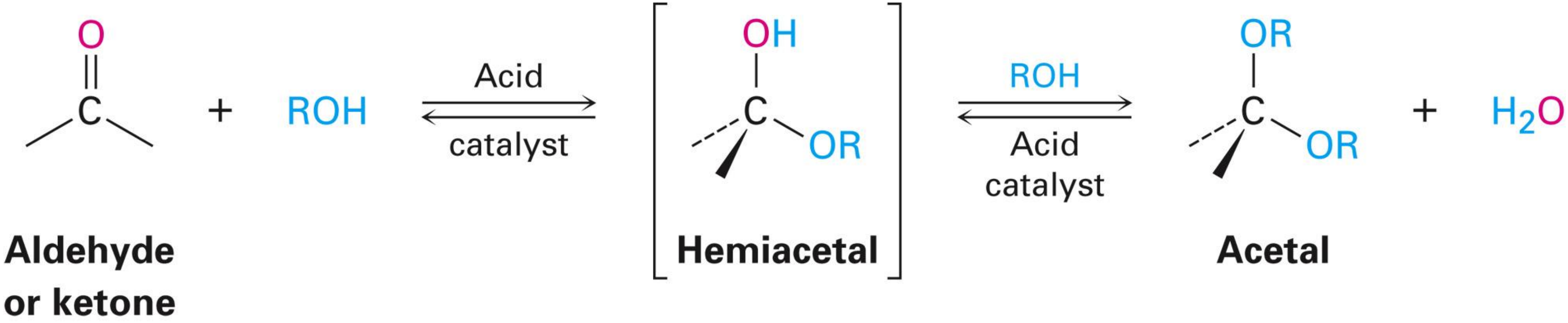
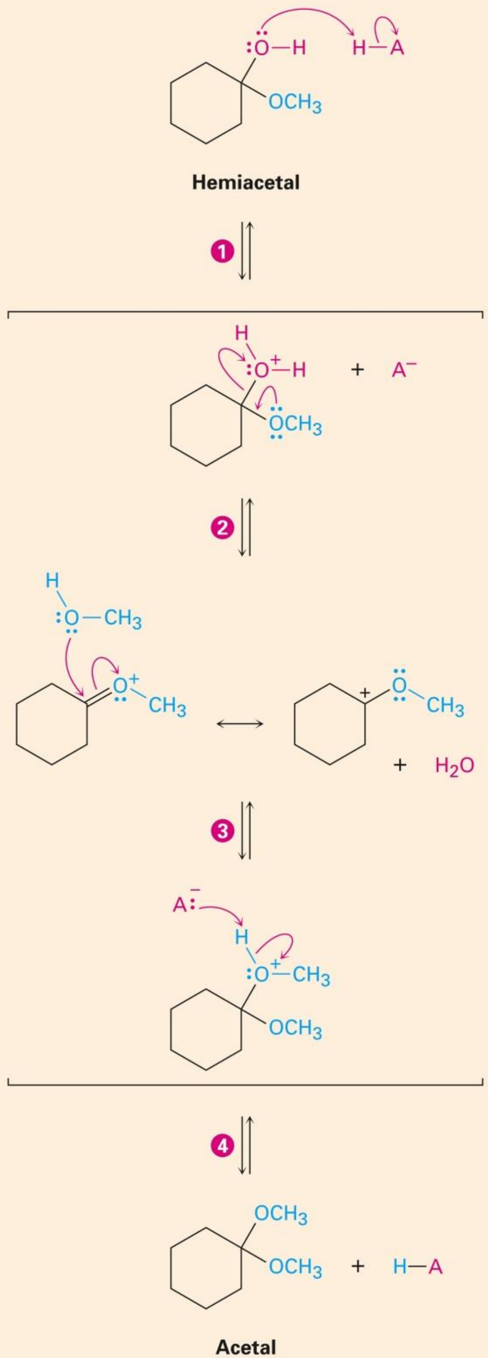


Figure 9.3 Mechanism of formation of an acetal from a hemiacetal.



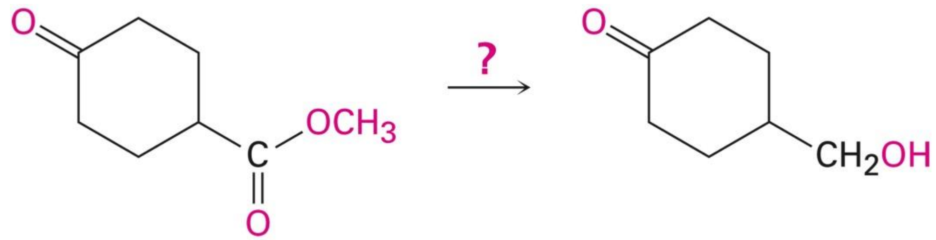
1. The –OH of the hemiacetal is protonated by an acid H–A, making it a good leaving group.

2. An electron pair on the $-OCH_3$ group moves toward carbon, expelling water and giving a $C{=}\overset{+}{O}CH_3$ bond with a positively charged, trivalent oxygen.

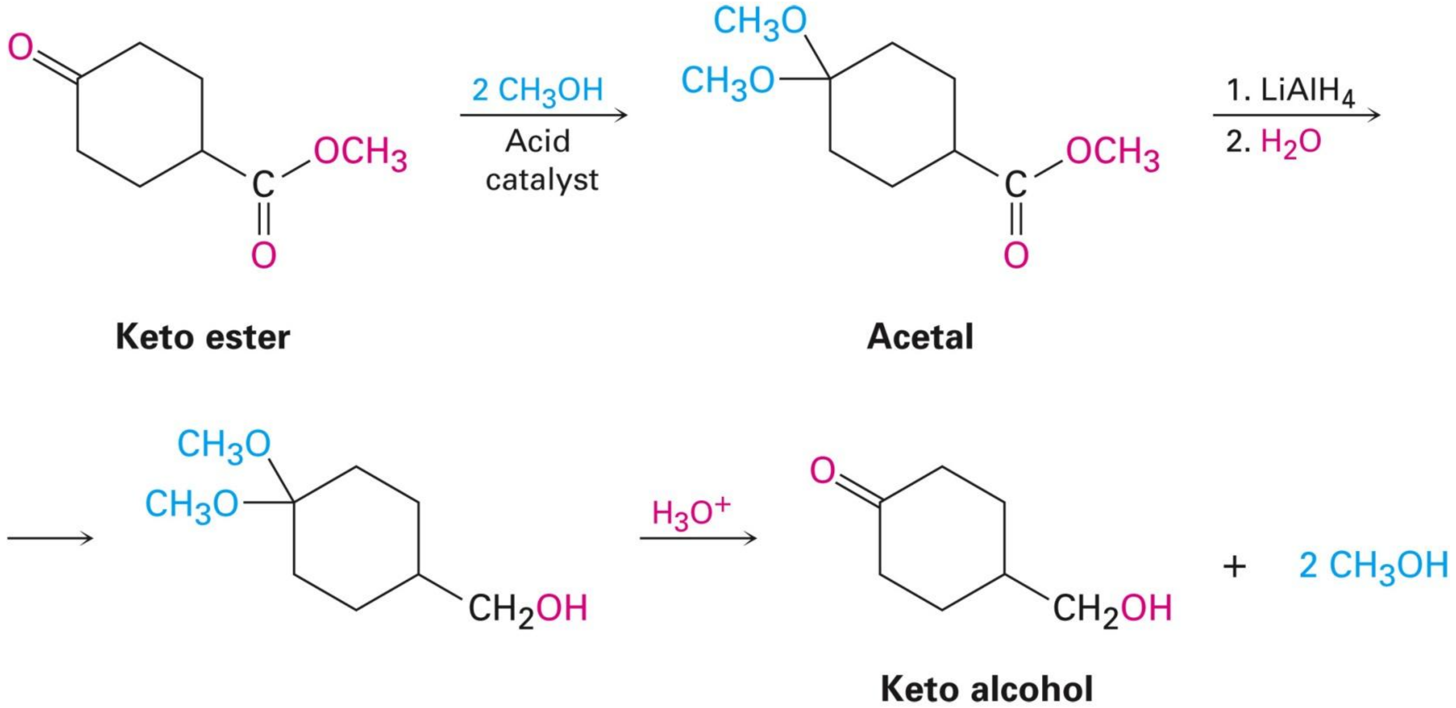
3. Nucleophilic addition of methanol to the C=O bond pushes the π electrons toward oxygen and neutralizes the positive charge.

4. Deprotonation by the base :A^- gives the neutral acetal and regenerates the acid catalyst.

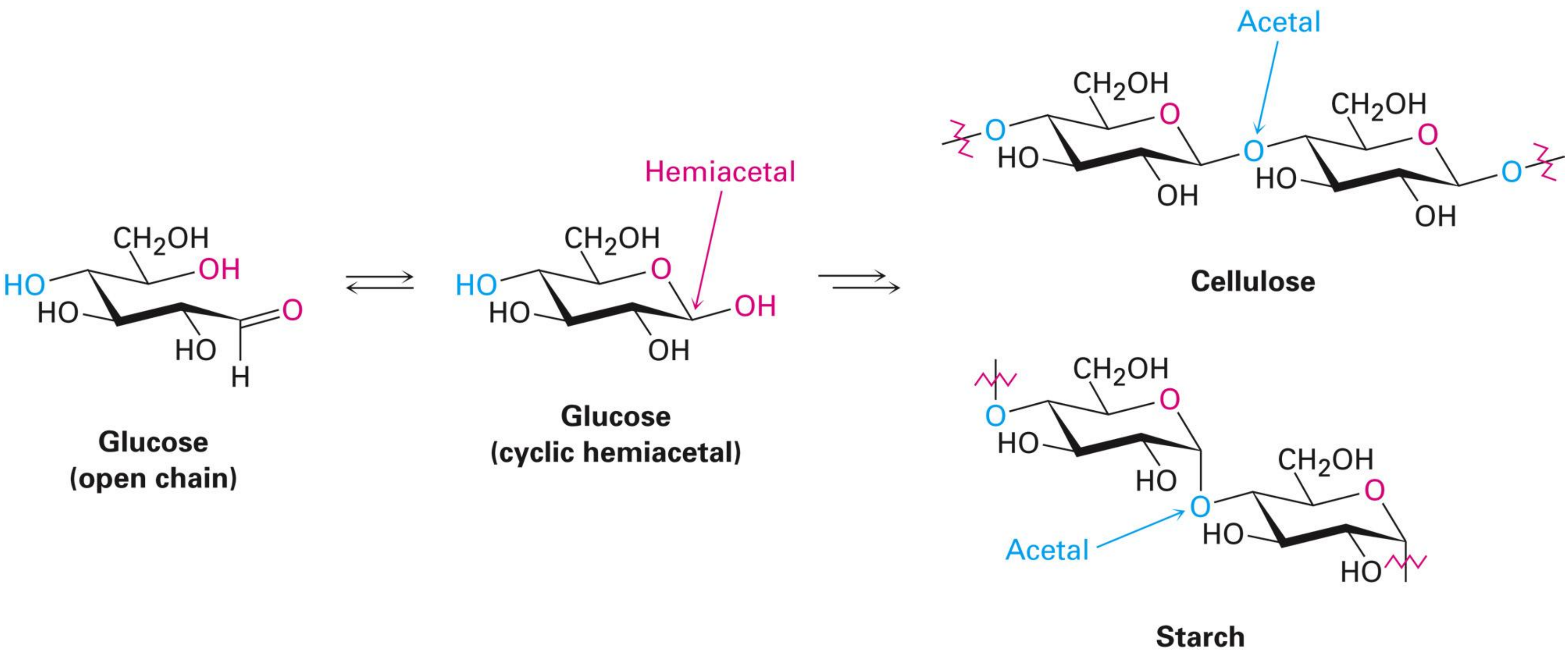
Uses of Acetals



- Acetals can serve as **protecting groups** for aldehydes and ketones

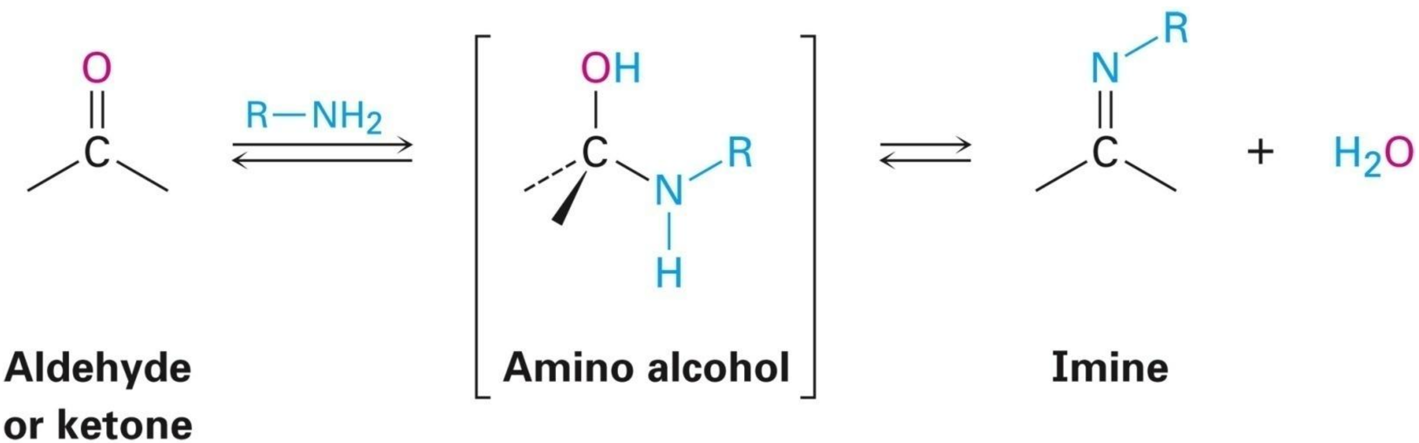


- **In nature, acetal and hemiacetal groups are particularly common in carbohydrate chemistry**

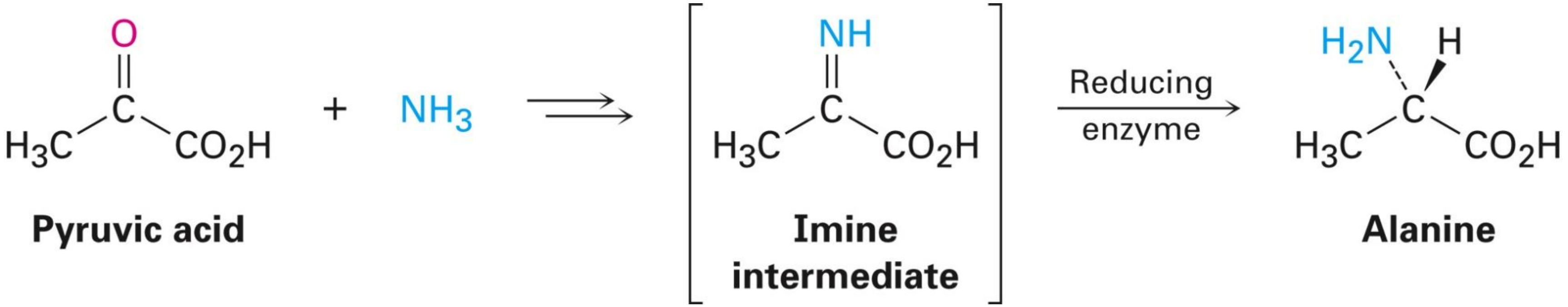


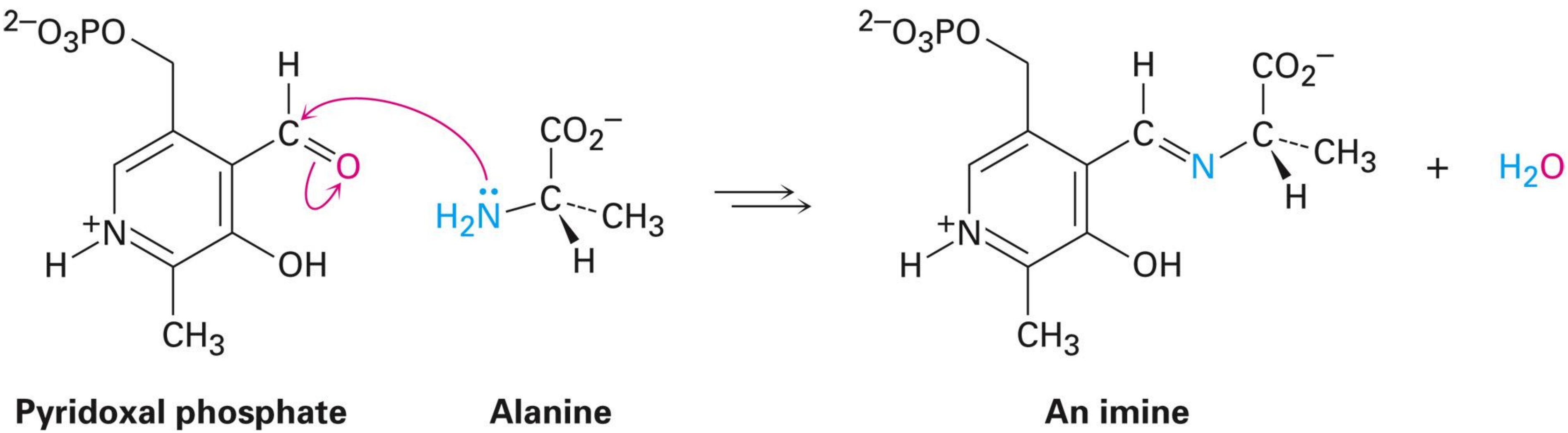
9.9 Nucleophilic Addition of Amines: Imine Formation

- **Ammonia and 1° amine, RNH_2, adds to C=O to form imines, $R_2C{=}NR'$ (after loss of HOH)**

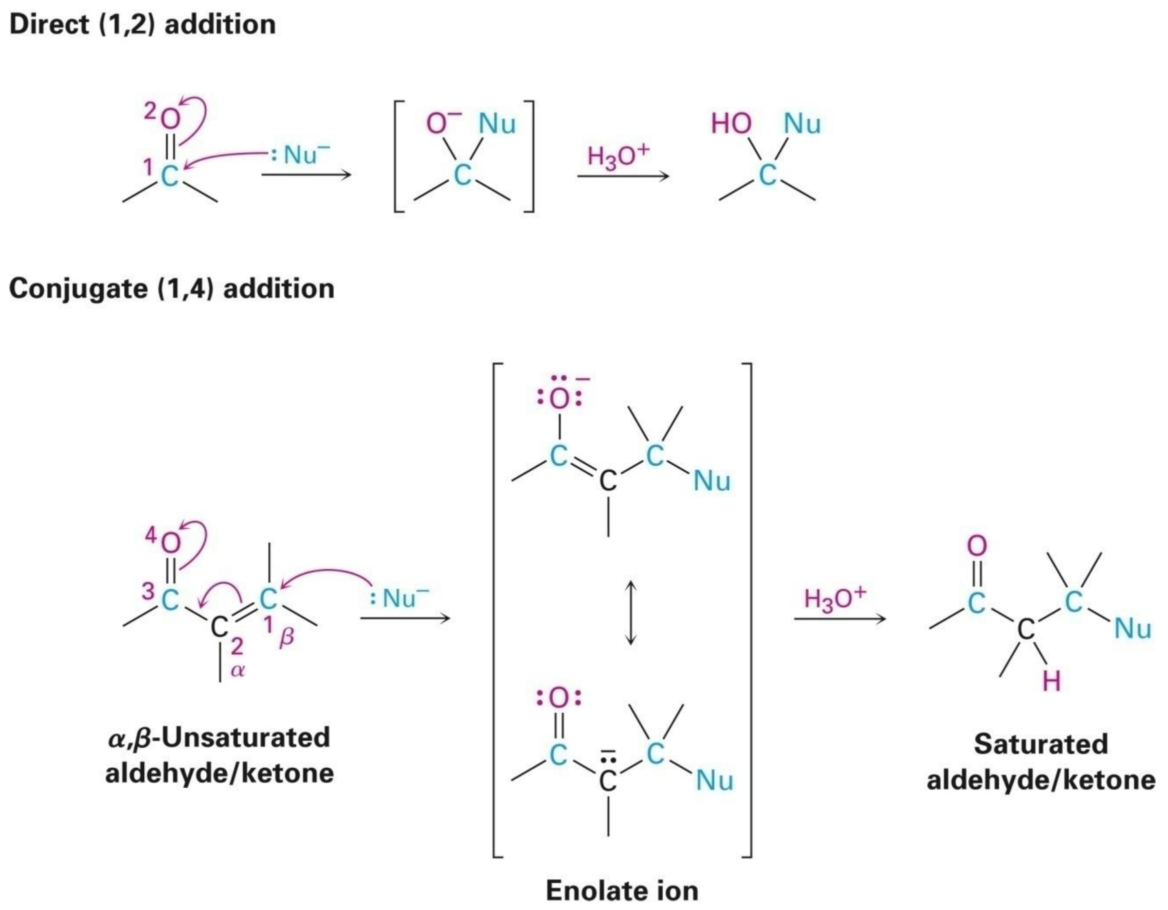


- **Imines are common intermediates in numerous biological pathway, including the route by which amino acids are synthesized and degraded in the body**





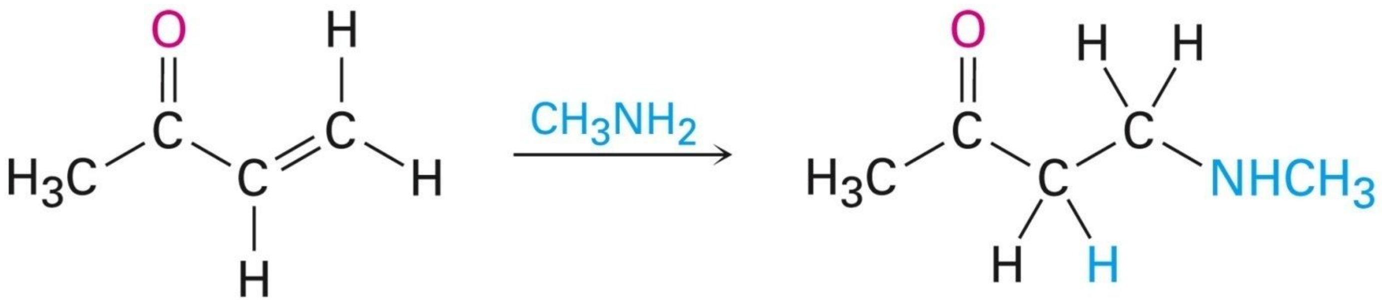
9.10 Conjugate Nucleophilic Reactions



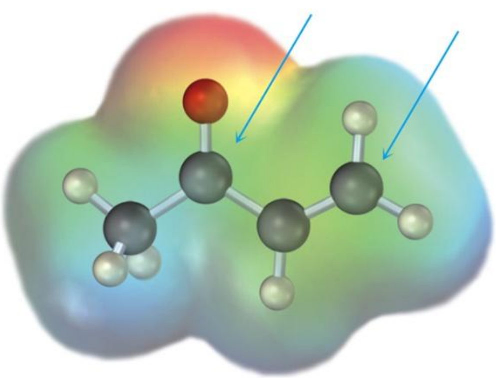
- **A nucleophile can add to the C=C double bond of an α,β-unsaturated aldehyde or ketone (conjugate addition, or 1,4 addition)**
- **The initial product is a resonance-stabilized enolate ion, which is then protonated**

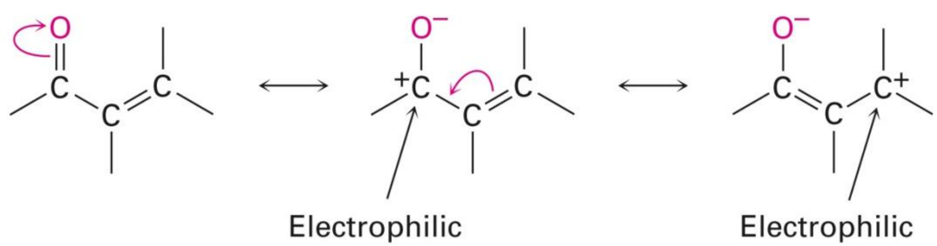
Conjugate Addition of Amines

- **Amines add to α, β-unsaturated aldehydes and ketones to yield β-amino aldehydes or ketones**

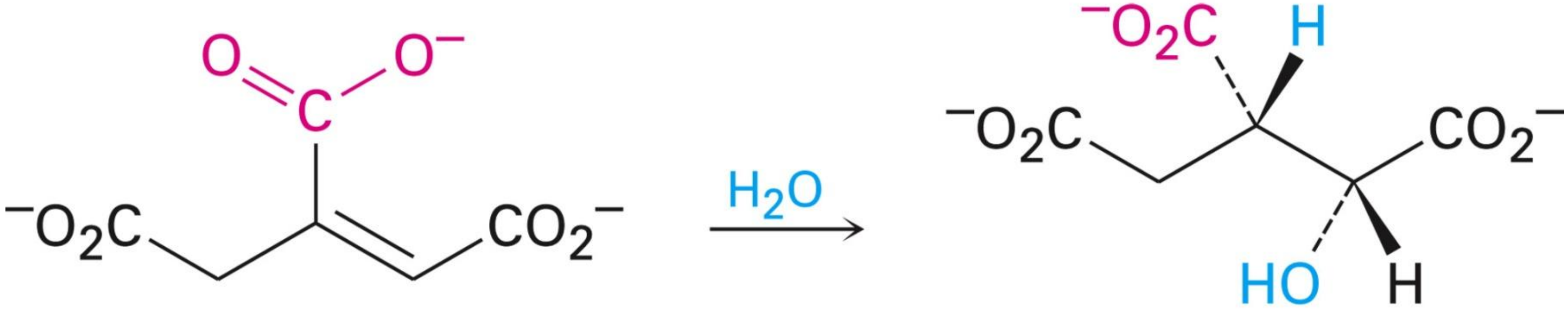


But-3-en-2-one **Conjugate addition product**





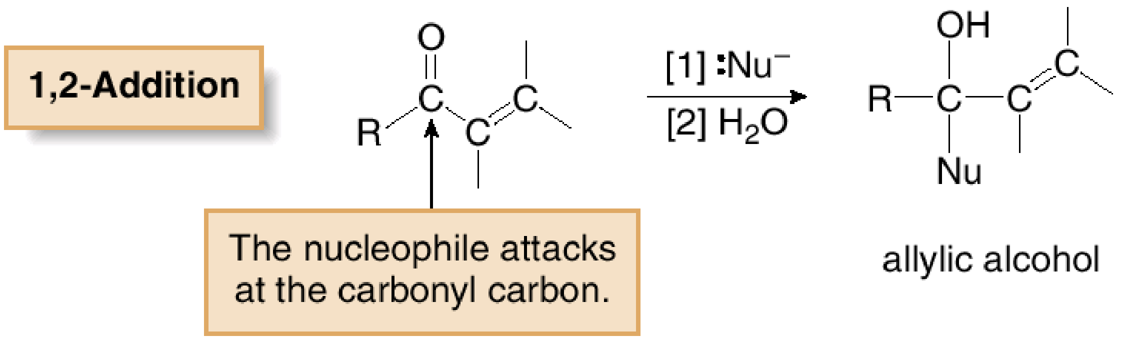
- **Conjugate additions are particularly common with amine nucleophiles and with water and occur in many biological pathways**



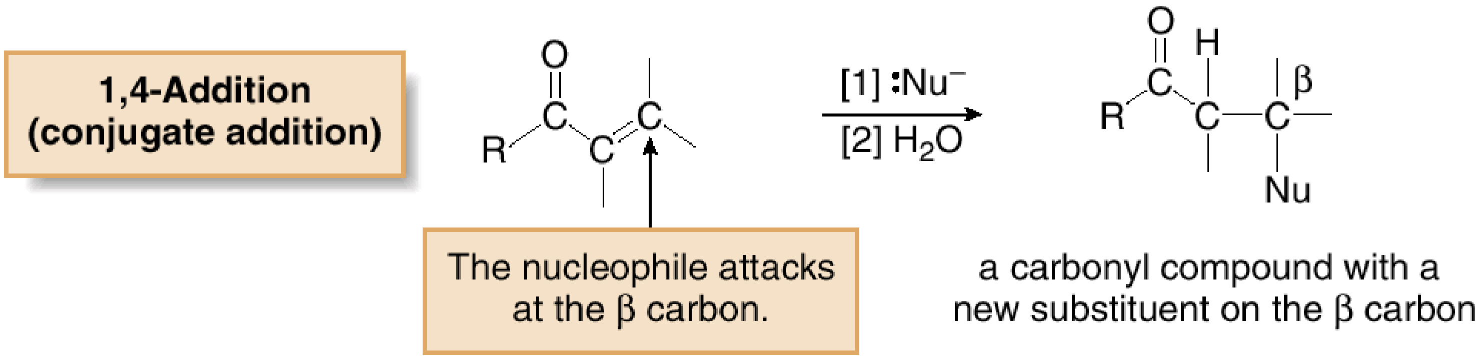
cis-Aconitate

Isocitrate

- **Addition of a nucleophile to the carbonyl carbon, called 1,2-addition, adds the elements of H and Nu across the C=O, forming an allylic alcohol.**

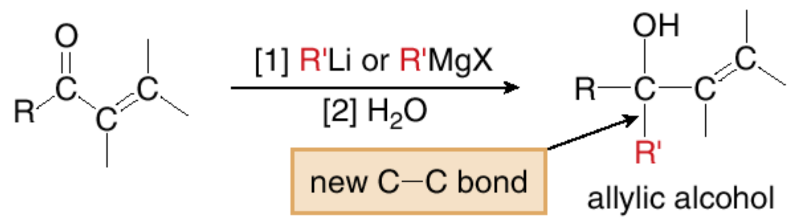


- **Addition of a nucleophile to the β carbon, called 1,4-addition or conjugate addition, forms a carbonyl compound.**

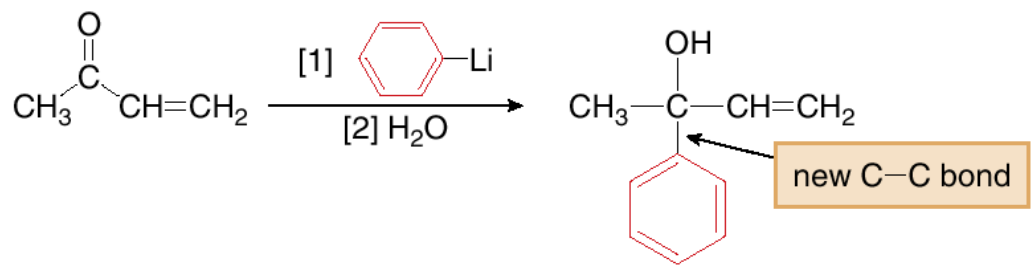


- **Organolithium and Grignard reagents form 1,2-addition products.**

1,2-Addition—General reaction

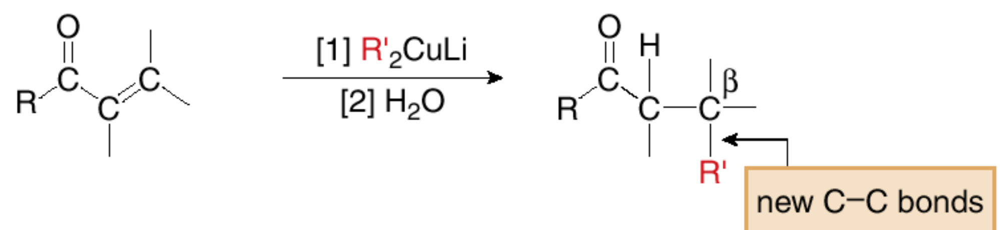


Example

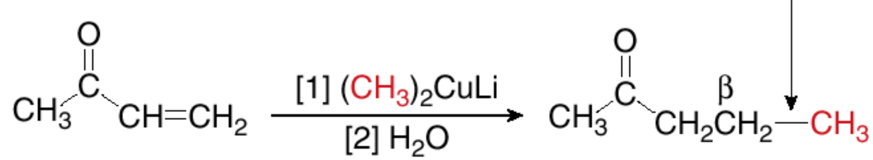


- **Organocuprate reagents form 1,4-addition products.**

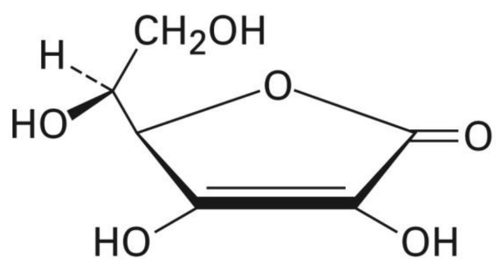
1,4-Addition—General reaction



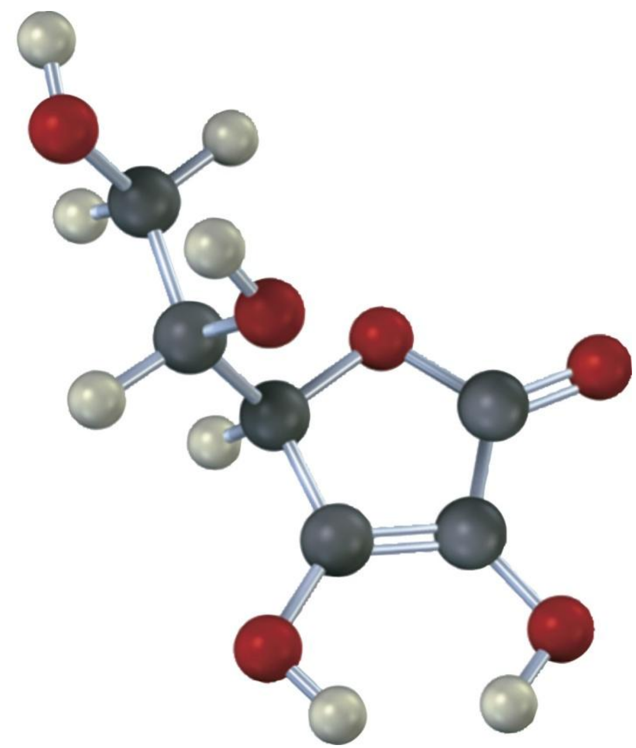
Example



Vitamin C



Vitamin C
(ascorbic acid)



- The industrial preparation of vitamin C involves an unusual blend of biological and laboratory organic chemistry