Aldehydes and **Ketones**

Part 3

B. Pharm. Semester-1
Course Code: 0510210; Session: 2022-2023

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Learning Outcomes

At the end of this lesson, students will be able to describe

Reactions of Aldehydes and Ketones

- **Nucleophilic Addition of Amines: Imine and Enamine Formation**
- **Nucleophilic Addition of Hydrazine: The Wolff-Kishner Reaction**
- **Nucleophilic Addition of Alcohols: Acetal Formation**
- **Nucleophilic Addition of Phosphorus Ylides: The Wittig Reaction**
- **Biological Reductions: Cannizzaro Reaction**
- **Conjugate Nucleophilic Addition to α,β-Unsaturated Aldehydes and Ketones**
- **Spectroscopy of Aldehydes and Ketones**

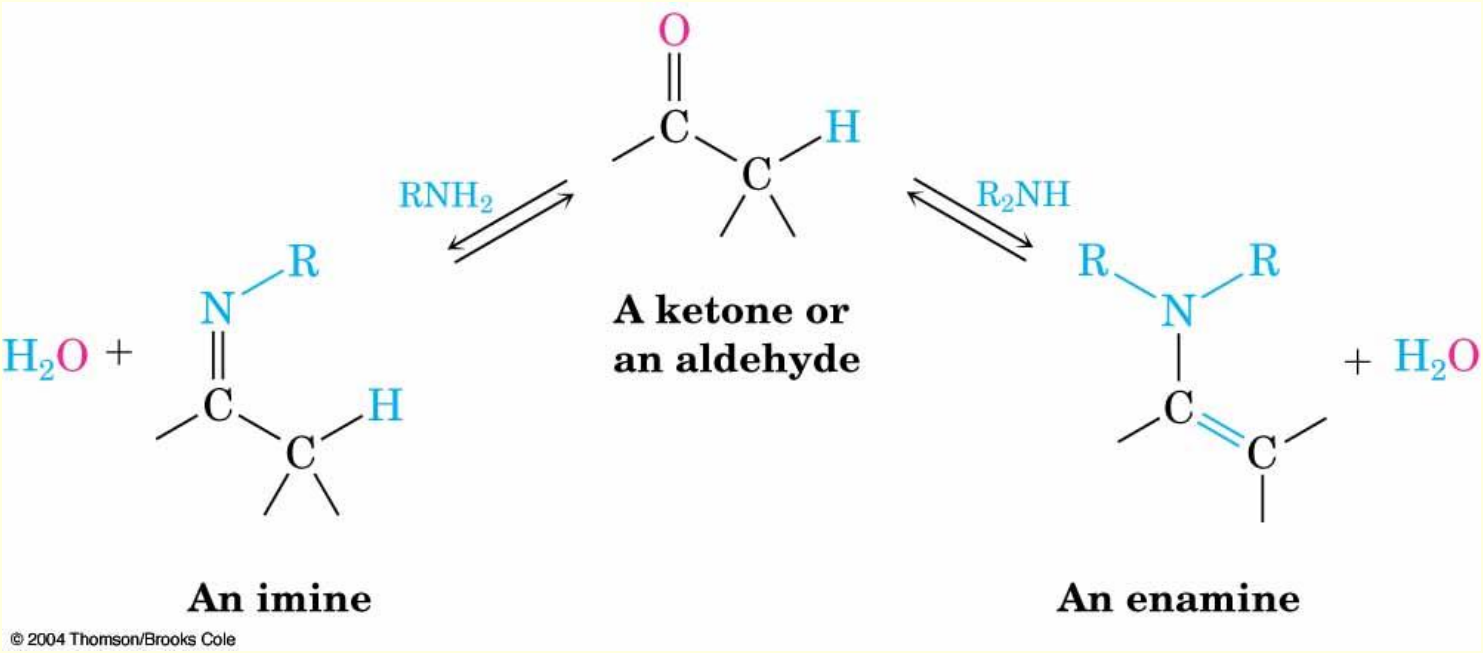
Objective

The objective of this course is to give to the students of pharmacy the basic knowledge about the organic chemistry.

Nucleophilic Addition of Amines: Imine and Enamine Formation

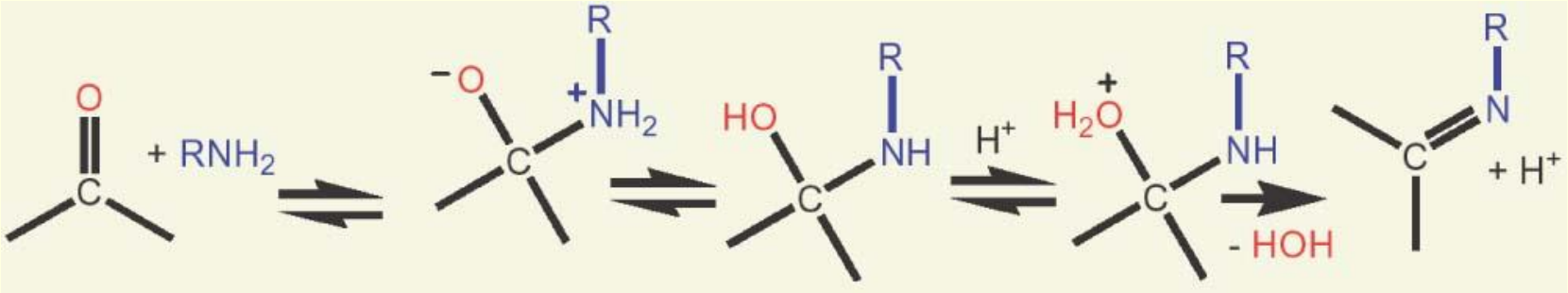
Primary amines, RNH_2, add to aldehydes and ketones to yield imines, $R_2C{=}NR$.

Secondary amines, R_2NH, add similarly to yield enamines $R_2N\text{-}CR{=}CR_2$ (ene + amine = unsaturated amine).



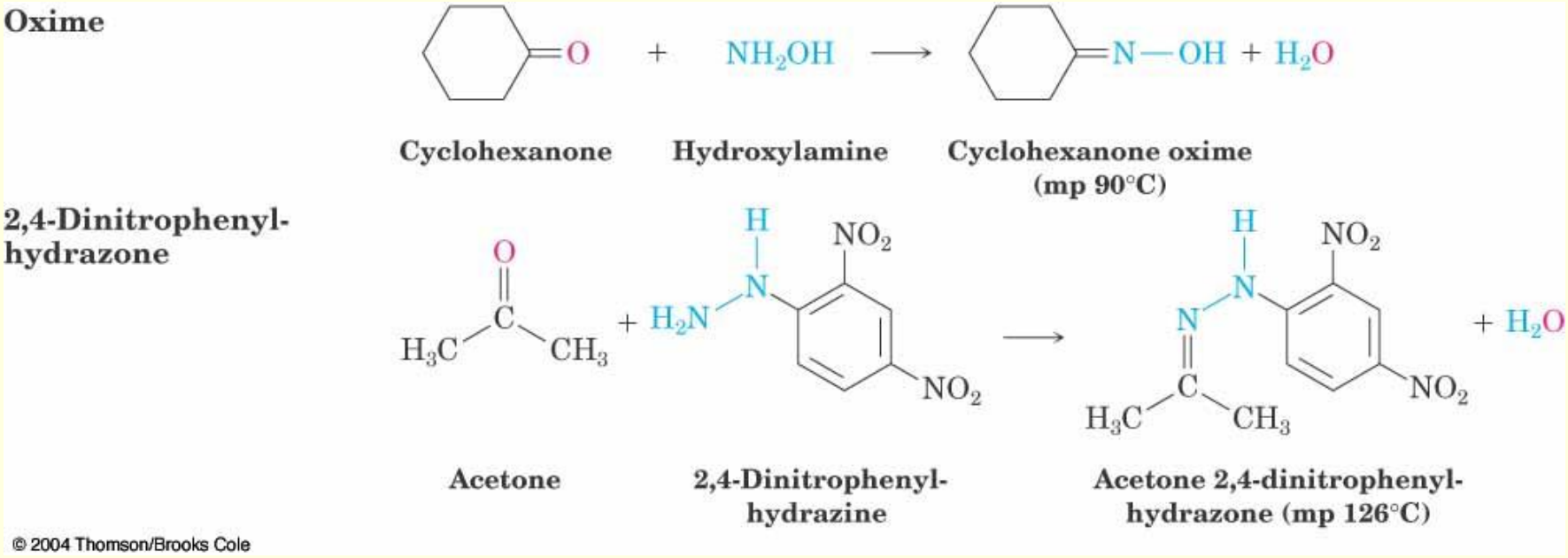
Nucleophilic Addition of Amines: Imine Formation: Mechanism

- Primary amine adds to C=O, proton is lost from ‘N’ and adds to ‘O’ to give a neutral amino alcohol (carbinolamine).
- Protonation of OH converts into water as the leaving group to give iminium ion, which loses proton.
- Acid is required as a catalyst – too much acid blocks RNH_2.



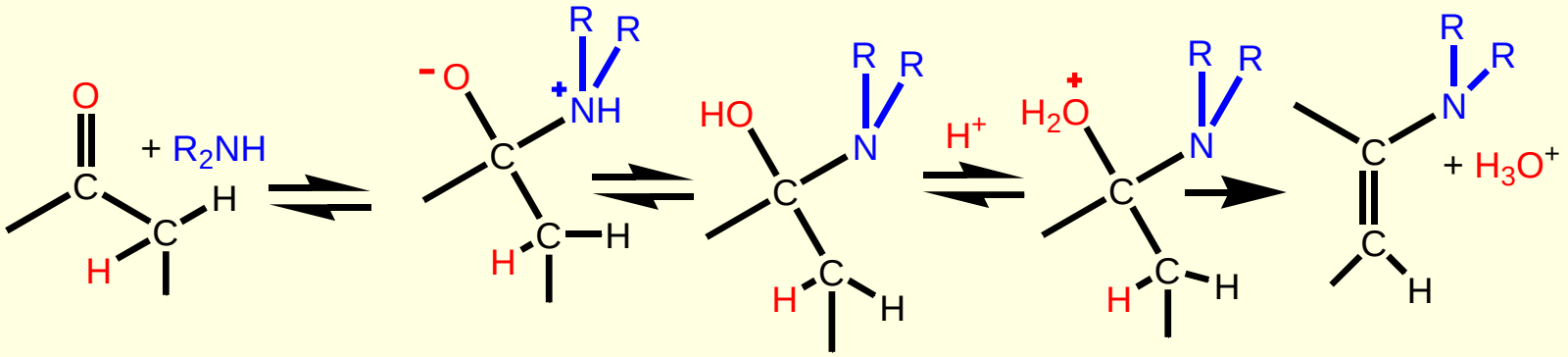
Imine Derivatives

Imine formation with such reagents as hydroxylamine and 2,4-dinitrophenylhydrazine gives oximes and 2,4-dinitrophenylhydrazones (2,4-DNPs).



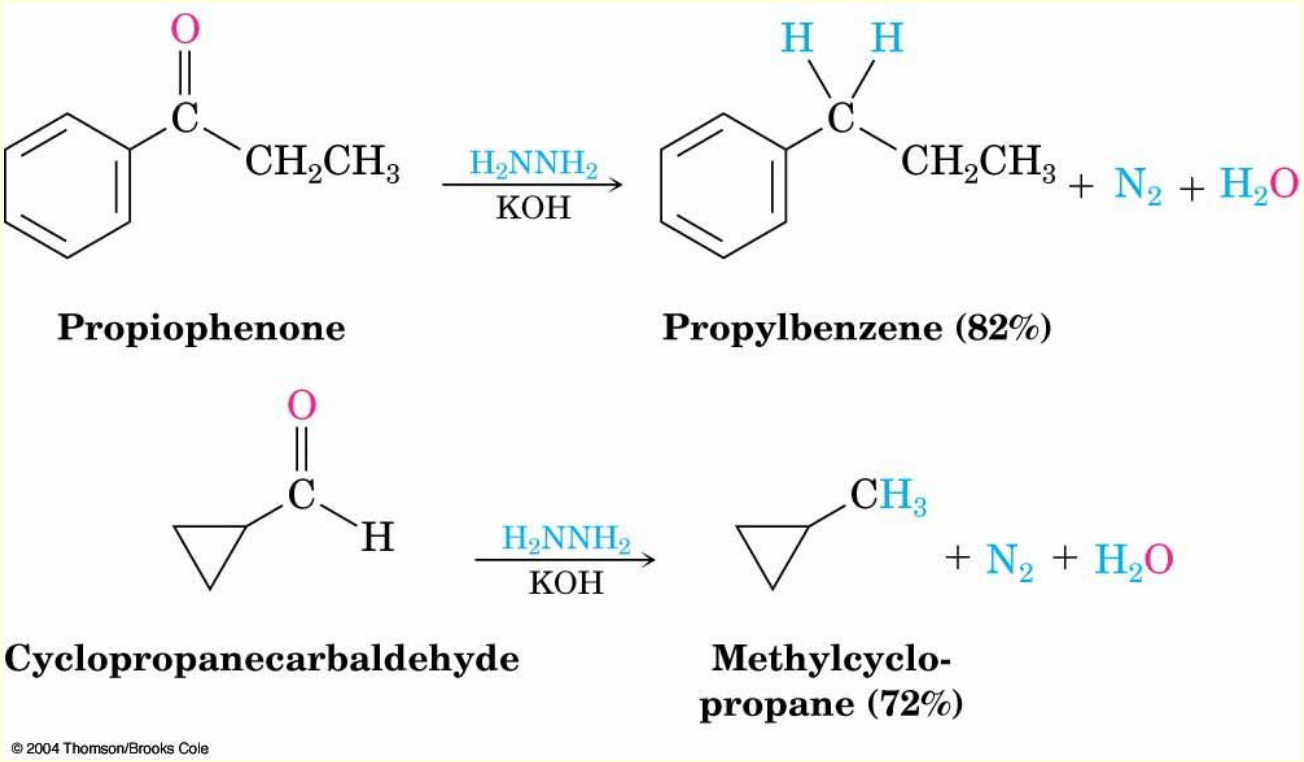
Enamine Formation

After addition of R_2NH, proton is lost from the adjacent carbon



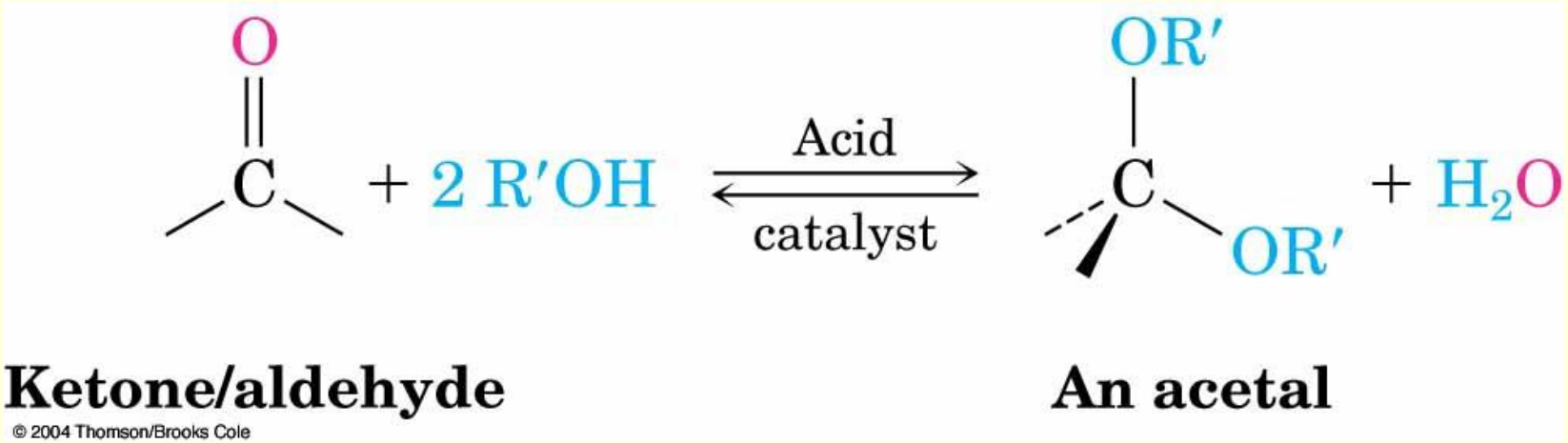
Nucleophilic Addition of Hydrazine: The Wolff–Kishner Reaction

Treatment of an aldehyde or ketone with hydrazine, $H_2N\text{-}NH_2$ and KOH gives an alkane.



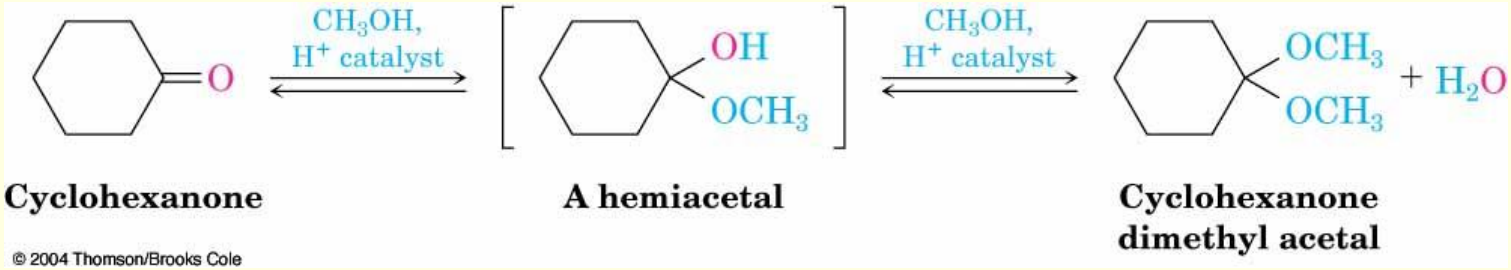
Nucleophilic Addition of Alcohols: Acetal Formation

Aldehydes and ketones react reversibly with 2 equivalents of an alcohol in the presence of an acid catalyst to yield acetals, $R_2C(OR')_2$, frequently called ketals, if derived from a ketone.



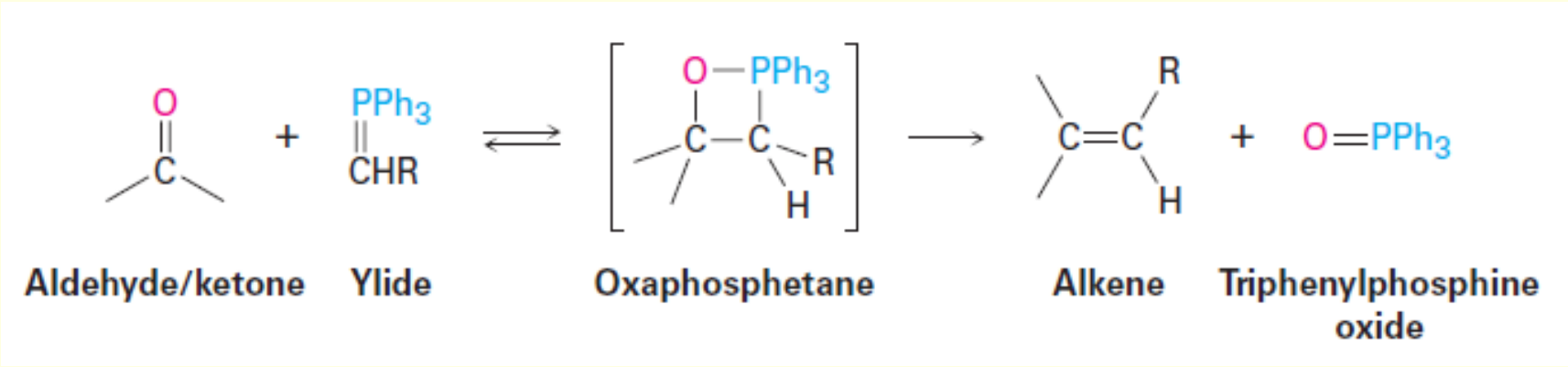
Nucleophilic Addition of Alcohols: Acetal Formation

- Alcohols are weak nucleophiles but acid promotes addition forming the conjugate acid of C=O.
- Addition yields a hydroxy ether, called a hemiacetal (reversible); 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.
- Cyclohexanone, reacts with methanol in the presence of HCl to give the corresponding dimethyl acetal.

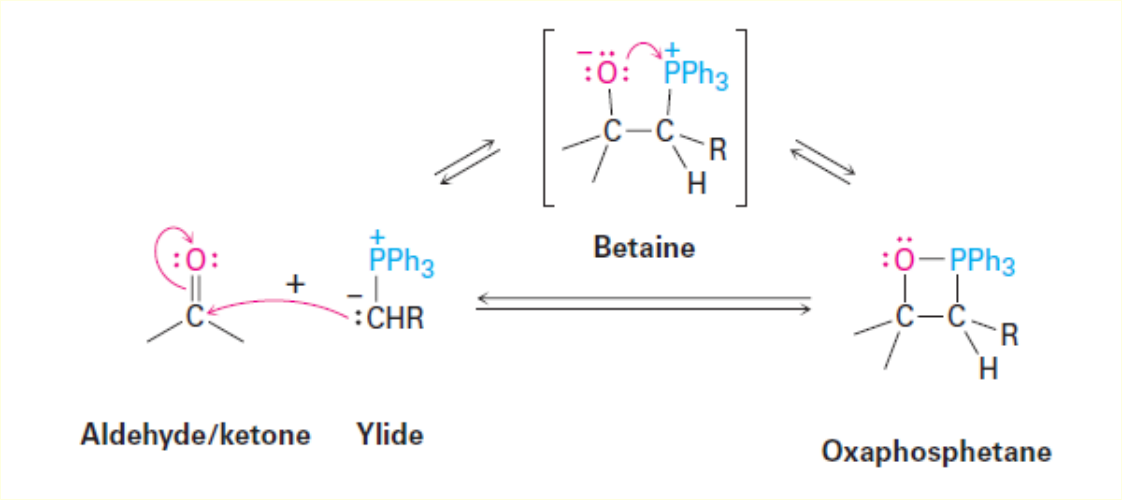


Nucleophilic Addition of Phosphorus Ylides: The Wittig Reaction

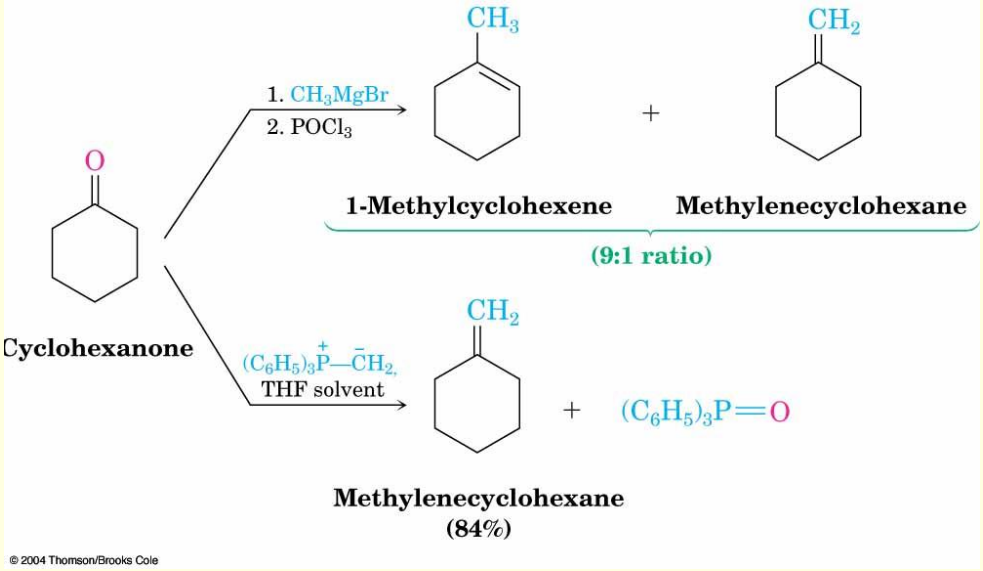
- Aldehydes and ketones are converted into alkenes by means of a nucleophilic addition is called the Wittig reaction.
- In the Wittig reaction, a triphenylphosphorus ylide, R_2-C=PPh_3, also called a phosphorane adds to an aldehyde or ketone to yield a four-membered cyclic intermediate called an oxaphosphetane.
- The oxaphosphetane spontaneously decomposes to give an alkene plus triphenylphosphine oxide, O=P-PPh_3.



The Wittig Reaction: Mechanism and uses



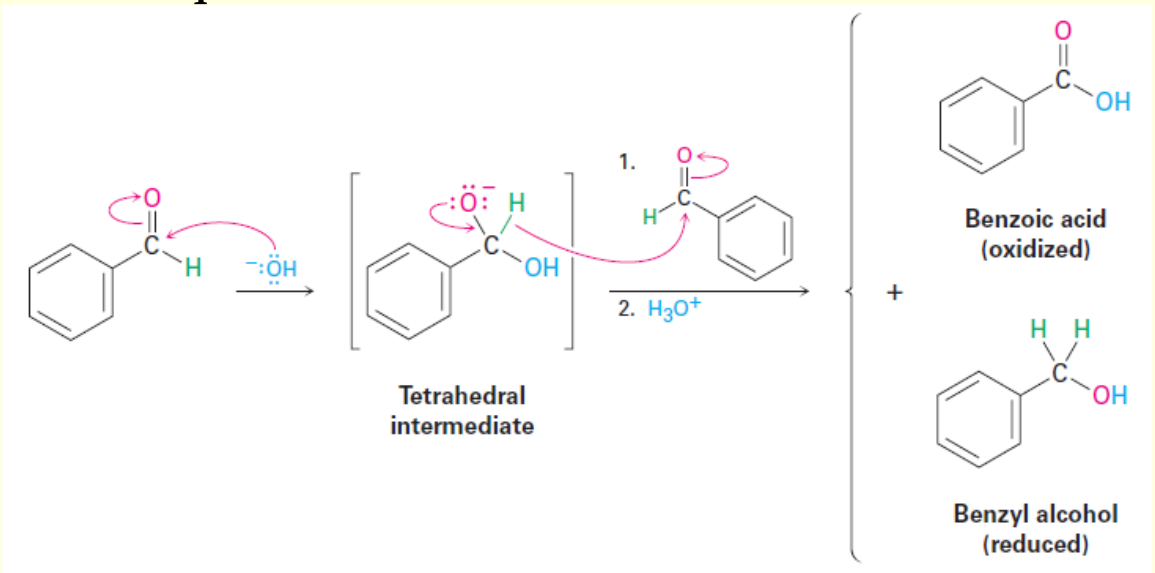
Mechanism



Uses: To prepare different alkenes.

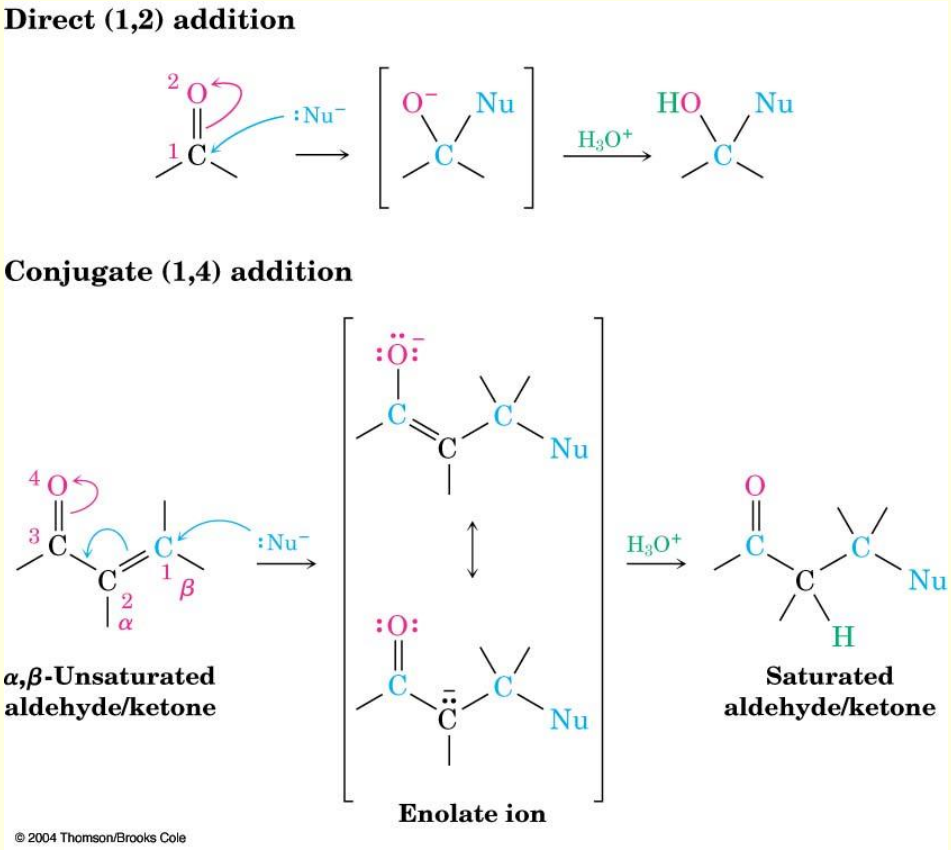
Biological Reductions: Cannizzaro Reaction

- Cannizzaro reaction takes place by nucleophilic addition of OH^- to an aldehyde to give a tetrahedral intermediate, which expels hydride ion as a leaving group and is thereby oxidized.
- A second aldehyde molecule accepts the hydride ion in another nucleophilic addition step and is thereby reduced.
- Benzaldehyde yields benzyl alcohol plus benzoic acid when heated with aqueous NaOH.



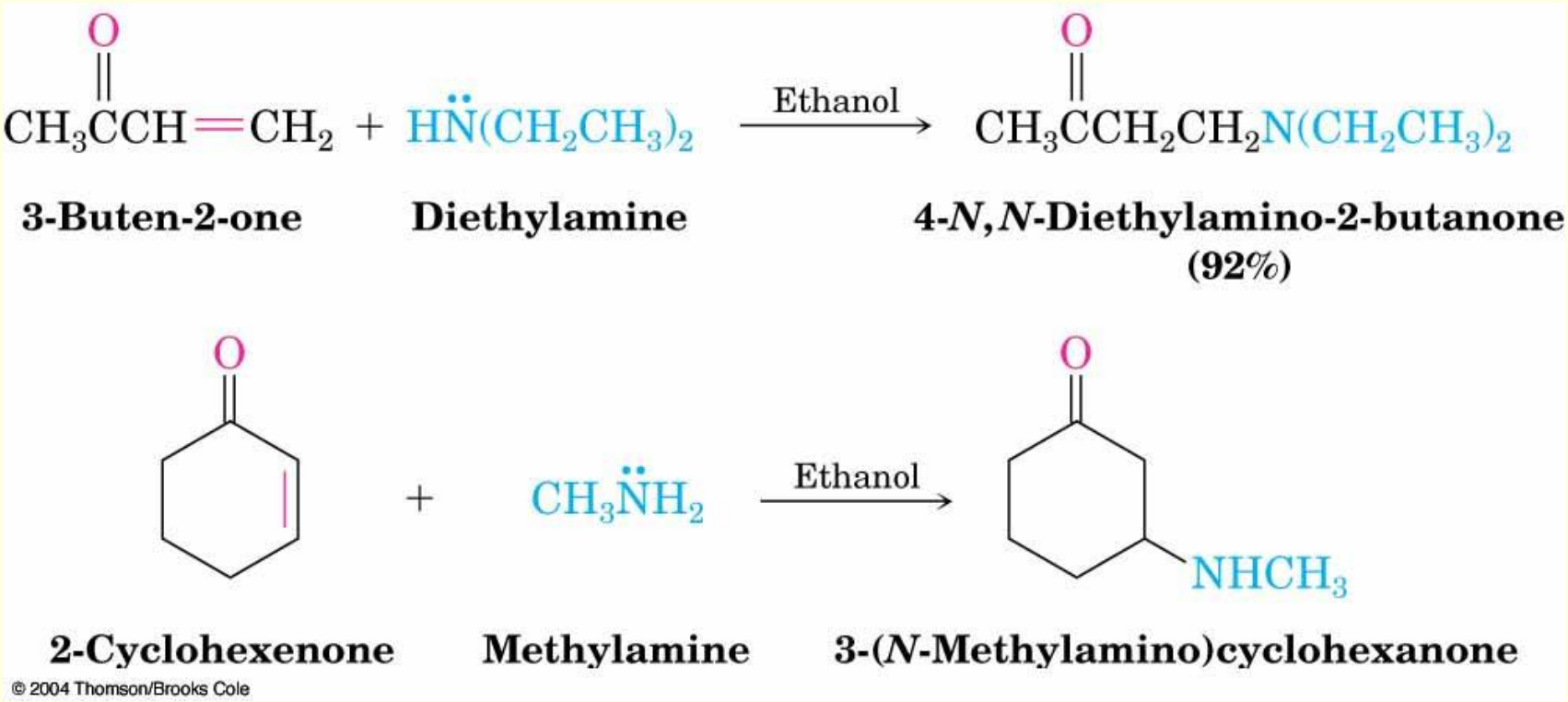
Conjugate Nucleophilic Addition to α,β-Unsaturated Aldehydes and Ketones

- 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 on the α–carbon to give a saturated aldehyde or ketone.



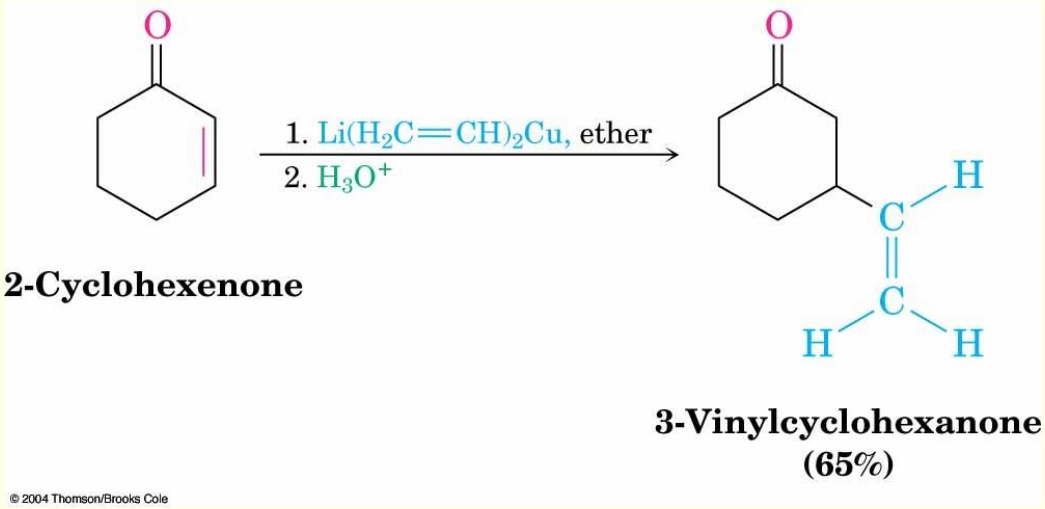
Conjugate Addition of Amines

Both primary and secondary amines add to α,β-unsaturated aldehydes and ketones to yield β-amino aldehydes and ketones.



Conjugate Addition of Alkyl Groups: Organocopper Reactions

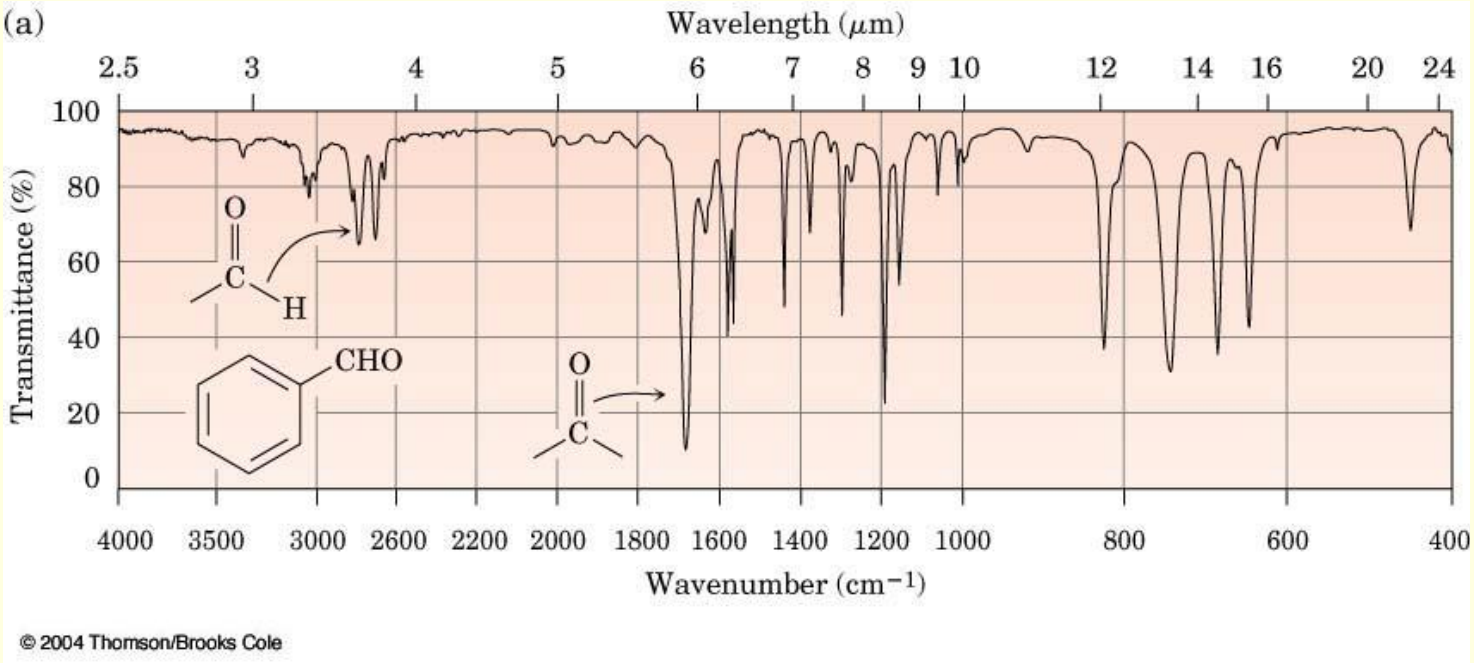
- Reaction of an α,β-unsaturated ketone with a lithium diorganocopper reagent, R_2CuLi.
- Lithium diorganocopper (Gilman) reagents formed by a reaction of 1 equivalent of copper (I) iodide and 2 equivalents of organolithium reagent, RLi.
- 1°, 2°, 3° alkyl, aryl and alkenyl groups undergo the conjugate addition reaction, as do aryl and alkenyl groups.



Spectroscopy of Aldehydes and Ketones

IR Spectroscopy

- Aldehydes and ketones show a strong C=O bond stretching peak 1660 cm^{-1} to 1770 cm^{-1}
- Aldehydes show two characteristic C–H absorptions in the 2720 cm^{-1} to 2820 cm^{-1}



IR Spectroscopy of C=O Peak Positions

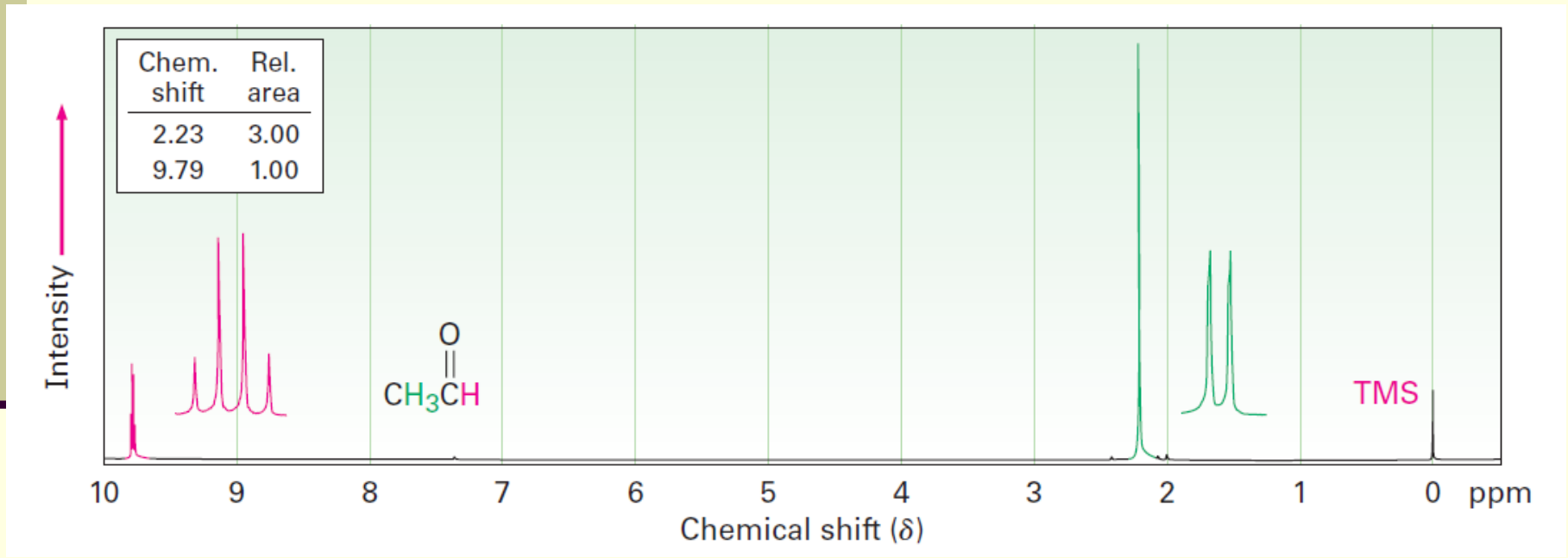
Carbonyl type	Example	Absorption (cm^{-1})
Saturated aldehyde	CH_3CHO	1730
Aromatic aldehyde	PhCHO	1705
α,β-Unsaturated aldehyde	$H_2C{=}CHCHO$	1705
Saturated ketone	CH_3COCH_3	1715
Cyclohexanone		1715
Cyclopentanone		1750
Cyclobutanone		1785
Aromatic ketone	$PhCOCH_3$	1690
α,β-Unsaturated ketone	$H_2C{=}CHCOCH_3$	1685

^{1}H-NMR Spectroscopy of Aldehyde

- Aldehyde proton (RC**H**O) signals are at δ 10 in ^{1}H NMR - distinctive spin–spin coupling with protons on the neighboring carbon, $J \approx 3$ Hz.
- Acetaldehyde shows a quartet at δ 9.8 for the aldehyde proton, indicating that there are three protons neighboring -CHO group.
- Hydrogens on the carbon next to a carbonyl group are slightly deshielded, absorb δ 2.0 to 2.3.
- In the acetaldehyde methyl group shows δ 2.20, while methyl ketones show δ 2.1.

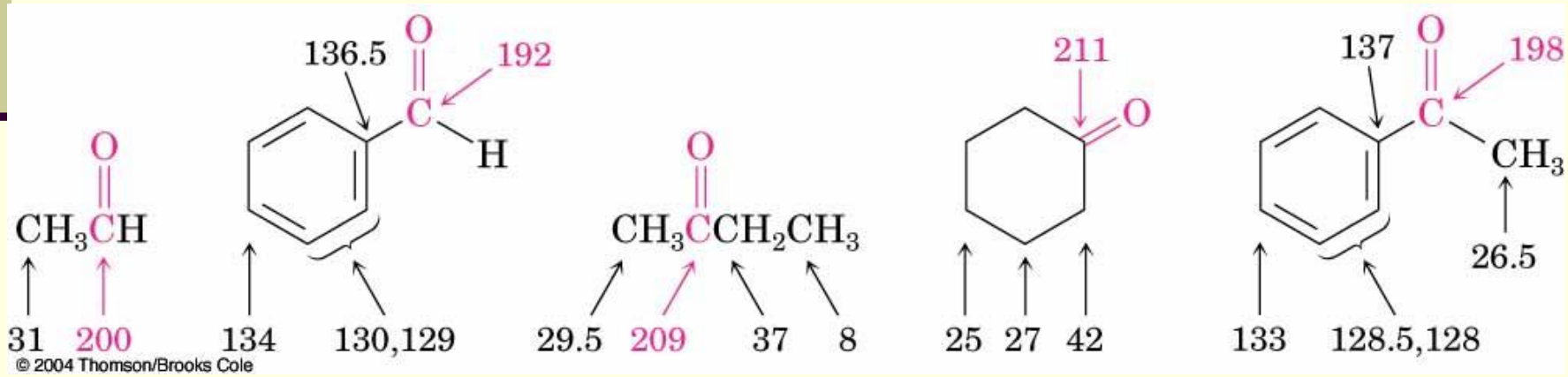
^{1}H-NMR Spectroscopy of Aldehyde

^{1}H-NMR Spectroscopy of Acetaldehyde



^{13}C-NMR Spectroscopy of C=O group

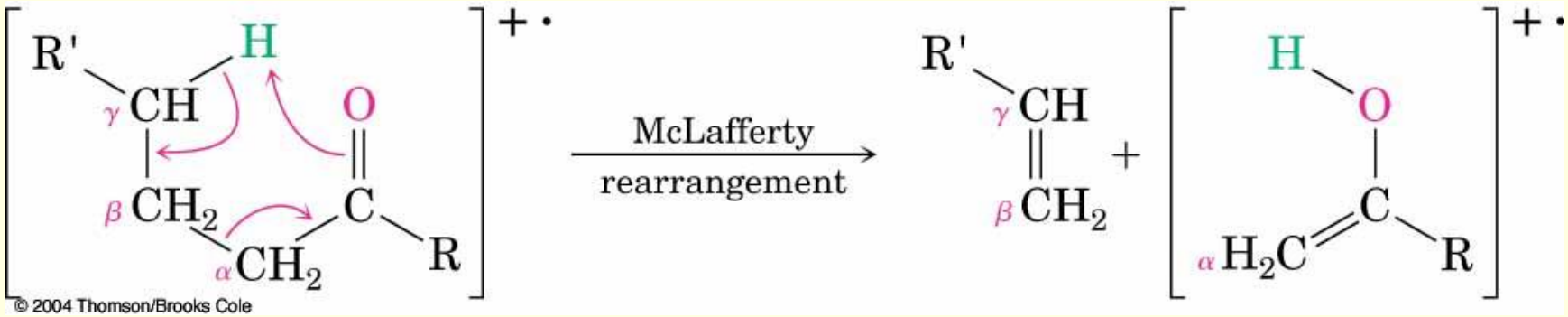
- The carbonyl-group carbon atoms of aldehydes and ketones will show the range δ 190 to 215.
- Saturated aldehyde or ketone carbons absorb in the region from δ 200 to 215, while aromatic and α,β-unsaturated carbonyl carbons absorb in the δ 190 to 200 region.



MASS Spectrometry-McLafferty Rearrangement

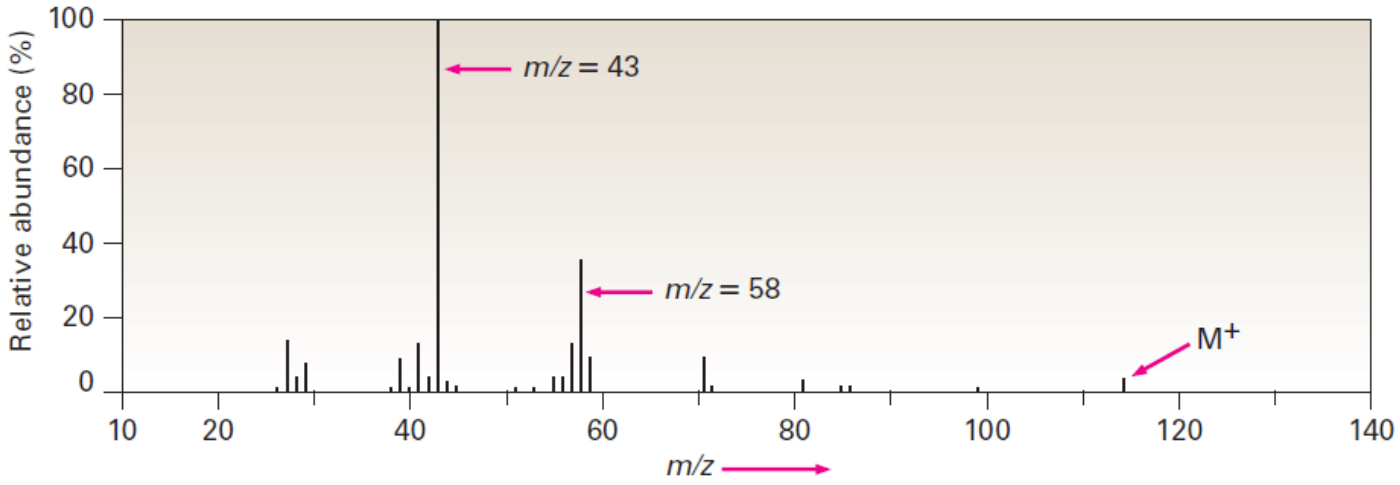
- Aliphatic aldehydes and ketones that have hydrogens on their gamma (γ) carbon atoms undergo a characteristic mass spectral cleavage called the McLafferty rearrangement.
- A hydrogen atom is transferred from the γ carbon to the carbonyl oxygen, the bond between the α and β carbons is broken, and a neutral alkene fragment is produced.
- The charge remains with the oxygen-containing fragment.

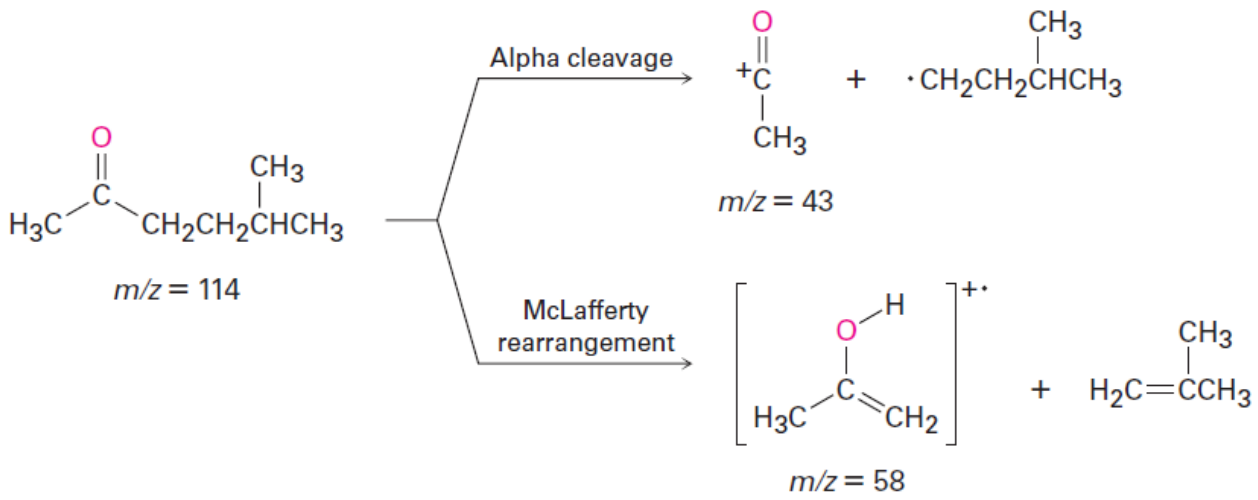
MASS Spectrometry-McLafferty Rearrangement



- In addition to fragmentation by the McLafferty rearrangement, aldehydes and ketones also undergo cleavage of the bond between the carbonyl group and the α carbon, called an α-cleavage.
- Alpha cleavage yields a neutral radical and a resonance-stabilized acyl cation.

Mass Spectrum of 5-methyl-2-hexanone





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3. **Textbook of Organic Chemistry, 22nd Edition, 2022, Authors: Arun Bahl & B S Bahl, Publisher: S Chand, ISBN: 978-9352531967.**

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