CHEM 2OB3

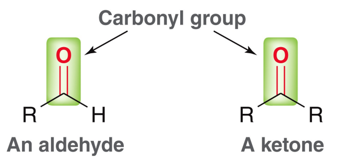
Chapter 19
Aldehydes and Ketones

Instructor: Dr. Kylie Luska

Based on Organic Chemistry (3rd edition) by David Klein

19.1 Ketones and Aldehydes

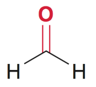
- Both functional groups possess the carbonyl group



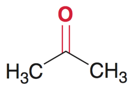
An aldehyde **A ketone**

- Important in both biology and industry

Simplest aldehyde
used as a preservative



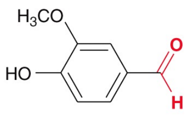
Formaldehyde



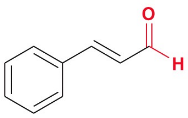
Acetone

Simplest ketone
used mainly as a solvent

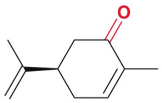
19.1 Ketones and Aldehydes



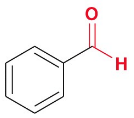
Vanillin
(Vanilla flavor)



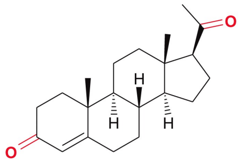
Cinnamaldehyde
(Cinnamon flavor)



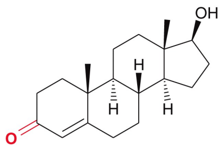
***(R)*-Carvone**
(Spearmint flavor)



Benzaldehyde
(Almond flavor)



Progesterone



Testosterone

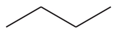
19.2 Nomenclature

- Four discrete steps to naming an aldehyde or ketone
- Same procedure as with alkanes, alcohols, etc…

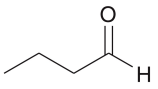
1. Identify and name the parent chain
2. Identify the name of the substituents (side groups)
3. Assign a locant (number) to each substituents
4. Assemble the name alphabetically

19.2 Nomenclature

1. **Identify and name the parent chain**
   - For aldehydes, replace the "-e" ending with an "-al"

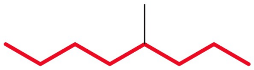


Butane

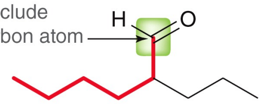


Butanal

   - the parent chain must include the carbonyl carbon



Parent=Octane



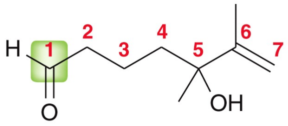
The parent must include this carbon atom

Parent=Hexanal

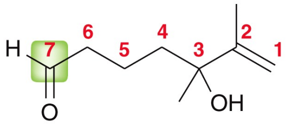
19.2 Nomenclature

1. Identify and name the parent chain
   - The aldehydic carbon is assigned number 1:

Correct

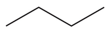


Incorrect

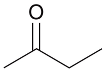


19.2 Nomenclature

1. Identify and name the parent chain
   - For ketones, replace the "-**e**" ending with an "-**one**"

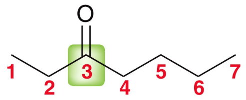


Butane



Butanone

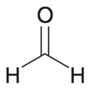
   - The parent chain must include the C=O group and is given the lowest number
   - Can be expressed before the parent name or before the suffix



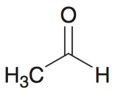
3-Heptanone
or
Heptan-3-one

19.2 Nomenclature

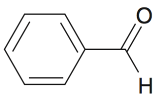
- IUPAC also recognizes the following common names as parent names:



Formaldehyde



Acetaldehyde

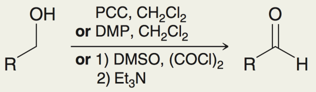


Benzaldehyde

19.3 Preparing Aldehydes

- Summary of **aldehyde preparation** (review)

REACTION	SECTION
Oxidation of Primary Alcohols	12.10

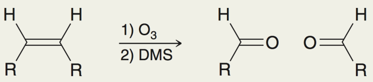


When treated with a strong oxidizing agent, primary alcohols are oxidized to carboxylic acids. Formation of an aldehyde requires a mild oxidizing agent, such as the oxidizing agents shown above, that will not further oxidize the resulting aldehyde.

19.3 Preparing Aldehydes

- Summary of **aldehyde preparation** (review)

REACTION	SECTION
Ozonolysis of Alkenes	8.12

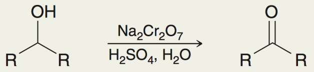


Ozonolysis will cleave a C═C double bond. If either carbon atom bears a hydrogen atom, an aldehyde will be formed.

19.3 Preparing Ketones

- Summary of **ketone preparation** (review)

REACTION	SECTION
Oxidation of Secondary Alcohols	12.10



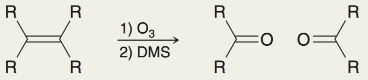
A variety of strong or mild oxidizing agents can be used to oxidize secondary alcohols. The resulting ketone does not undergo further oxidation.

- Other oxidizing agents: PCC or Swern or DMP or $KMnO_4$

19.3 Preparing Aldehydes and Ketones

- Summary of **ketone preparation** (review)

REACTION	SECTION
Ozonolysis of Alkenes	8.12

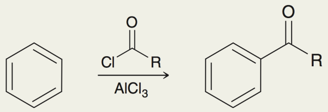


Tetrasubstituted alkenes are cleaved to form ketones.

19.3 Preparing Aldehydes and Ketones

- Summary of **ketone preparation** (review)

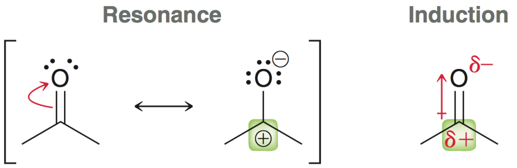
REACTION	SECTION
Friedel–Crafts Acylation	18.6



Aromatic rings that are not too strongly deactivated will react with an acyl halide in the presence of a Lewis acid to produce an aryl ketone.

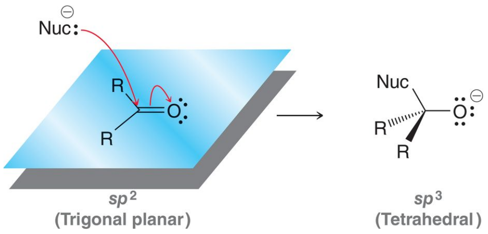
19.4 Nucleophilic Addition Reactions

- The carbonyl carbon is electrophilic; this is derived from resonance effects and inductive effects



19.4 Nucleophilic Addition Reactions

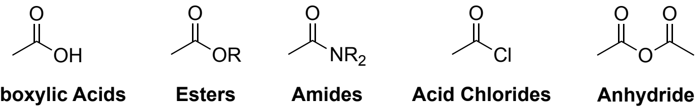
- The carbonyl carbon is attacked by nucleophiles, forming a new σ bond in exchange for the C=O π bond, and becoming a tetrahedral center:



19.4 Nucleophilic Addition Reactions

- Reminder that there are two different classes of carbonyl compounds

CLASS 1 - No Leaving Group

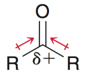


CLASS 2 - Contains Leaving Group
(Chapter 20)

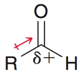
19.4 Nucleophilic Addition Reactions

- **Aldehydes are generally more reactive towards nucleophiles than ketones:**

1. **Steric effects** - aldehydes are less sterically hindered
2. **Electronic effects** - aldehyde has a larger δ$^+$ on the carbonyl carbon:



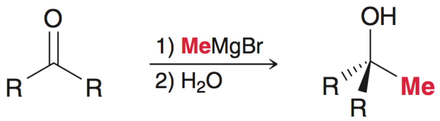
A ketone
has two electron-donating alkyl groups that stabilize the partial positive charge



An aldehyde
has only one electron-donating alkyl group that stabilizes the partial positive charge

19.4 Nucleophilic Addition Reactions

- Nucleophilic addition reactions can occur under either **acidic or basic conditions**
- **Strong nucleophiles** attack aldehydes and ketones under **basic conditions**
  - Nucleophiles that possess a negative charge (*i.e.*, Grignard reagents, hydrides, etc.)

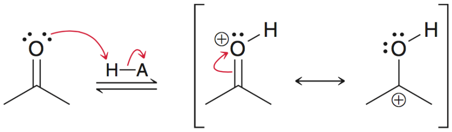


19.4 Nucleophilic Addition Reactions

- **Mechanism for Attack by a Strong Nucleophile:**

19.4 Nucleophilic Addition Reactions

- **Weak nucleophiles** attack aldehydes and ketones under **acidic conditions**
  - Nucleophiles that are neutral (*i.e.*, alcohols, amines, etc.)



Very powerful electrophile

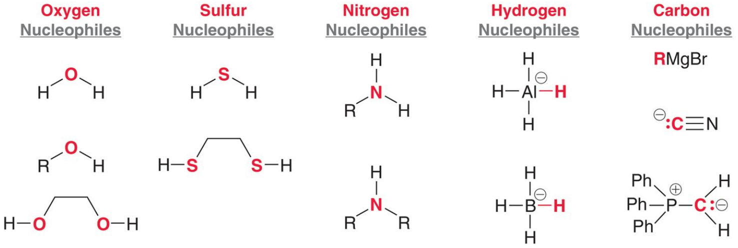
- Protonation of the C=O group makes the carbonyl carbon a better electrophile!

19.4 Nucleophilic Addition Reactions

- **Mechanism under Attack by a Weak Nucleophile:**

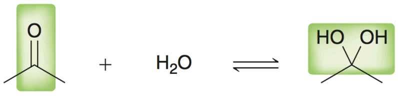
19.4 Nucleophilic Addition Reactions

- We will cover the following nucleophiles and their reaction with ketones and aldehydes:



19.5 Oxygen Nucleophiles

- In the presence of water, a ketone/aldehyde is in equilibrium with its **hydrate:**



Hydrate

- **Equilibrium generally does not favour the formation of the hydrate (except for very simple aldehydes)**
- The rate of reaction is slow unless acidic or basic conditions are used

19.5 Oxygen Nucleophiles

- **Hydration Mechanism (Basic Conditions):**

19.5 Oxygen Nucleophiles

- **Hydration Mechanism (Acidic Conditions):**

19.5 Oxygen Nucleophiles

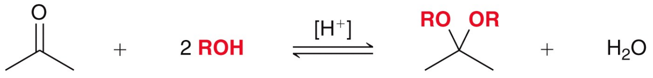
- **KEEP THE FOLLOWING IN MIND WHEN DRAWING MECHANISMS:**

- *Under acidic conditions, a mechanism will only be reasonable if it avoids the use or formation of strong bases*
  - **A strong base cannot exist in an acidic environment.**

- *Under basic conditions, a mechanism will only be reasonable if it avoids the use of formation of strong acids*
  - **A strong acid cannot exist in a basic environment**

19.5 Oxygen Nucleophiles

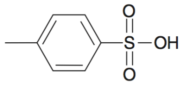
- Alcohols can attack ketones/aldehydes:



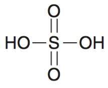
Acetal

- Under acidic conditions, 1 eq. of an aldehyde or ketone reacts with 2 eq. of alcohol to form an **acetal**

Commonly used acid catalysts for acetal formation



***p*-Toluenesulfonic acid** (TsOH)



Sulfuric acid

- **Note -** non-nucleophilic acids have to be used to avoid the introduction of a competing nucleophile

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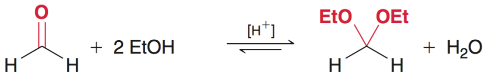
19.5 Oxygen Nucleophiles

- **Mechanism for Acetal Formation:**

19.5 Oxygen Nucleophiles

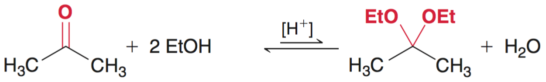
- **Acetal formation is an equilibrating process**
- For most simple aldehydes, the acetal is favoured at equilibrium



Products are favored at equilibrium

19.5 Oxygen Nucleophiles

- **Acetal formation is an equilibrating process**
- For most ketones, the acetal is *not* favoured at equilibrium

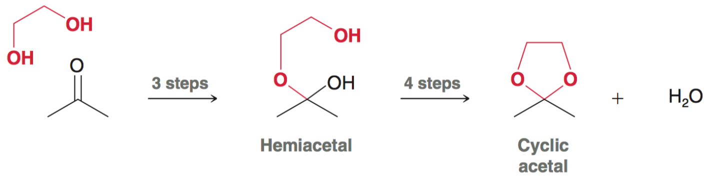


Reactants are favored at equilibrium

- Equilibrium can be pushed towards the acetal product by removing water throughout the reaction (e.g., Dean-Stark trap)

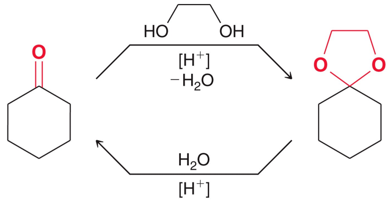
19.5 Oxygen Nucleophiles

- Formation of acetal product can also be achieved by using a diol starting material
- Cyclic acetals are more stable!



19.5 Oxygen Nucleophiles

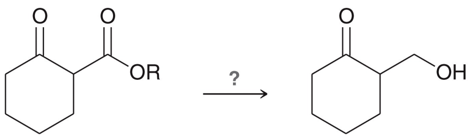
- Acetal formation is reversible
- **To favour acetal formation**, water is removed from the reaction
- **To convert back to an aldehyde or ketone,** water is added to the acetal with an acid catalyst



- In this way, acetals can be used as protecting groups for aldehydes and ketones

19.5 Oxygen Nucleophiles

- Consider how the following synthesis could be accomplished:

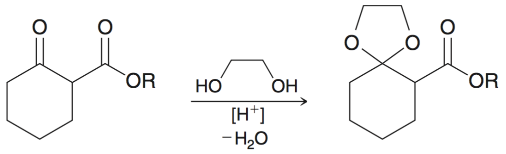


- We need to convert an ester to 1°alcohol, which requires LAH, while leaving the ketone unchanged

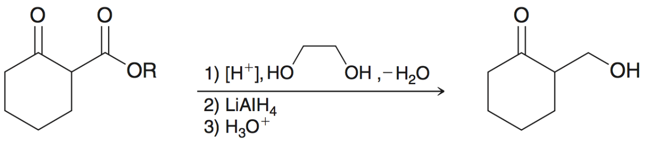
- **Problem**: use of LAH would reduce the ester and ketone
- **Solution**: use of protecting group for the ketone

19.5 Oxygen Nucleophiles

- First, protect the ketone as a cyclic acetal:

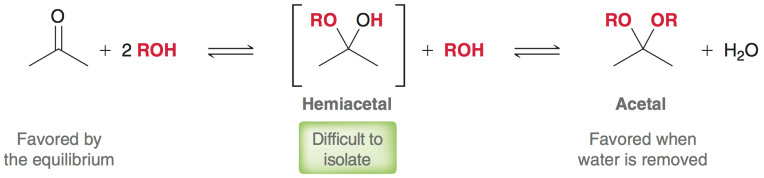


- Then we can reduce the ester and deprotect the ketone
- **Overall:**



19.5 Oxygen Nucleophiles

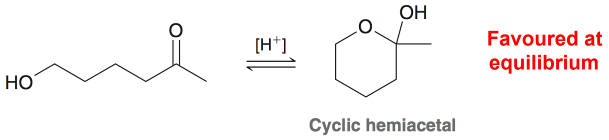
- A **hemiacetal** is the intermediate formed in the conversion of an aldehyde or ketone to an acetal
- Hemiacetals are difficult to isolate as the equilibrium either favours the aldehyde/ketone or the acetal



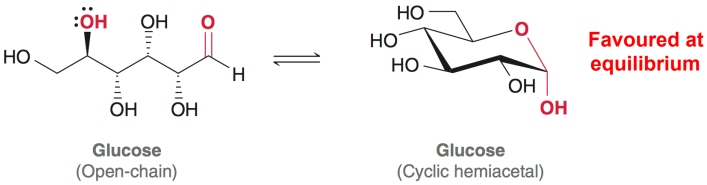
- However, **cyclic hemiacetals** can be usually be isolated

19.5 Oxygen Nucleophiles

- A **cyclic hemiacetal** is possible when a compound contains both a carbonyl group and a hydroxyl group:

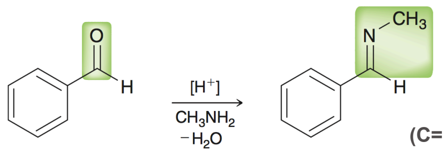


- Cyclic hemiacetals are important in carbohydrate chemistry



19.6 Nitrogen Nucleophiles

- Under acidic conditions, an aldehyde or ketones reacts with a **1°amine** to form an **imine**
- As amines are weak nucleophiles, this reaction must be performed under acidic conditions:



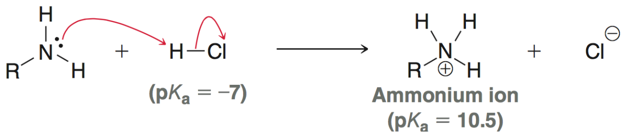
Imine
(C=N double bond)

19.6 Nitrogen Nucleophiles

- **Mechanism for Imine Formation:**

19.6 Nitrogen Nucleophiles

- Protonation of the carbonyl is NOT the first step in the formation imine formation mechanism
- Strong basicity of the amine causes the formation an ammonium salt
- Ammonium ion is not acidic enough to protonate an aldehyde or ketone, but it is acidic enough to protonate alkoxide or hydroxyl intermediates

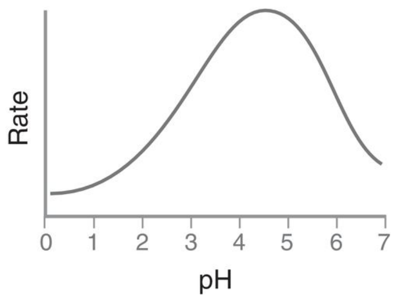


Amines are bases, and consume the H+ catalyst

The ammonium ion is the acid catalyst for the reaction

19.6 Nitrogen Nucleophiles

- For imine formation, the pH has to be ~5 or the reaction is too slow

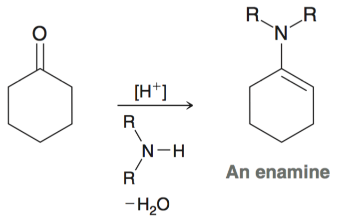


Low pH
complete formation of ammonium salt

High pH
no acid to catalyze removal of hydroxyl group

19.6 Nitrogen Nucleophiles

- Under acidic conditions, an aldehyde or ketones reacts with a **2°amine** to form an **enamine**:



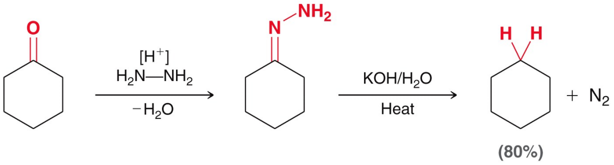
- Similar mechanism to 1°amines (except last step)

19.6 Nitrogen Nucleophiles

- **Mechanism for Enamine Formation:**

19.6 Nitrogen Nucleophiles

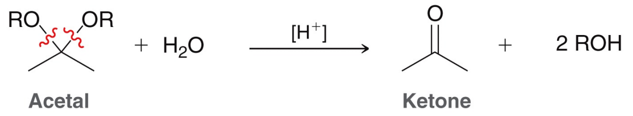
- **Wolff-Kishner reduction –** another method to convert an aldehyde or ketone to an alkane
- Same transformation as Clemmensen reduction



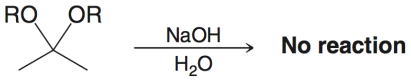
- First step is imine formation between the ketone and hydrazine (which is like a primary amine)
- Second reaction is like an elimination

19.7 Hydrolysis of Acetals

- Acetals are hydrolyzed with aqueous acid to yield an aldehyde or ketone and two equivalents of alcohol:
- Simply the reverse of acetal formation:



- **Acetals will only react with water under acidic conditions**

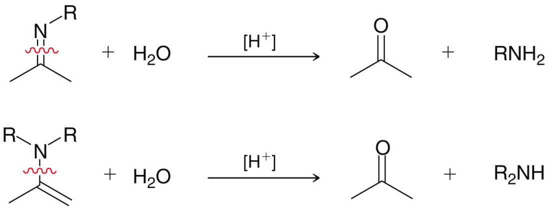


19.7 Hydrolysis of Acetals

- **Mechanism for the Hydrolysis of an Acetal:**

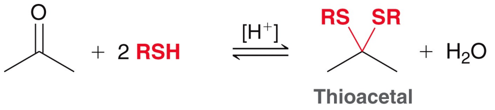
19.7 Hydrolysis of Imines and Enamines

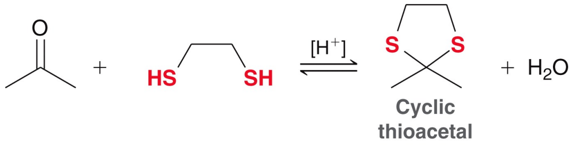
- Hydrolysis of imines and enamines undergoes a very similar mechanism under acidic conditions



19.8 Sulfur Nucleophiles

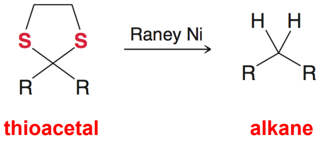
- Aldehydes and ketones reaction with thiols virtually the same way they react with alcohols:



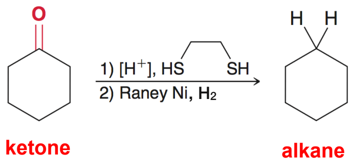


19.8 Sulfur Nucleophiles

- **Thioacetals can be converted to alkanes** when reacted with Raney nickel.

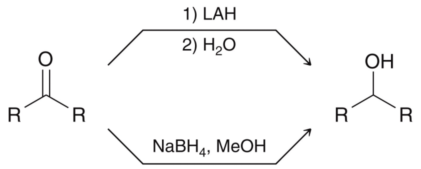


- Thioacetals provide another method for reducing an aldehyde or ketone to an alkane:



19.9 Hydrogen Nucleophiles

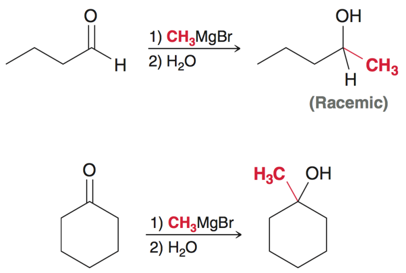
- Recall, aldehydes and ketones are reduced to alcohols using a hydride reagent



- Similar mechanism for a strong nucleophile (section 19.9)

19.10 Carbon Nucleophiles

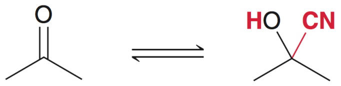
- Recall, Grignard reagents attack aldehydes and ketones to form an alcohol and a new C-C bond:



- Similar mechanism for a strong nucleophile (section 19.10)

19.10 Cyanohydrin Formation

- The cyanide ion is also a carbon-based nucleophile and reversibly adds to an aldehyde or ketone to form a **cyanohydrin**



A cyanohydrin

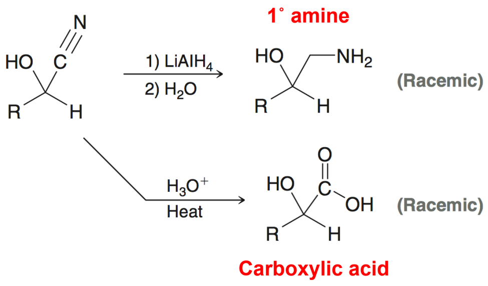
- **Reaction conditions:**
  - KCN and HCN
  - HCN and [Base]

19.10 Cyanohydrin Formation

- **Mechanism for Cyanohydrin Formation:**

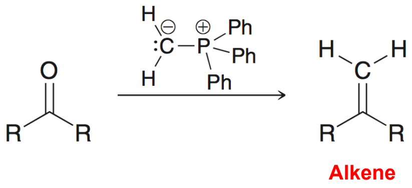
19.10 Cyanohydrin Formation

- Installation of a cyano group is advantageous because it can be converted to other functional groups:



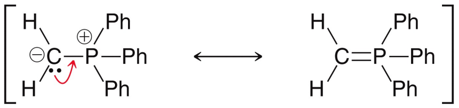
19.10 Wittig Reactions

- An aldehyde or ketone can be converted to an **alkene** using the **Wittig Reaction**
- An important transformation since it allows for the modification of the **carbon skeleton**



19.10 Wittig Reactions

- The **Wittig reagent** is a **phosphorus ylide**:



- **Ylide** – neutral compound that contains a negatively charged atom adjacent to a positively charged heteroatom
- The carbon atom acts as the nucleophile

19.10 Wittig Reactions

- A Wittig reagent is synthesized in two steps from an alkyl halide:

19.10 Wittig Reactions

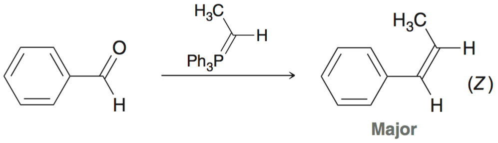
- **Mechanism for the Wittig reaction:**

- The formation of the highly stable triphenylphoshine oxide by-product drives the equilibrium to favour the formation of the alkene product

---

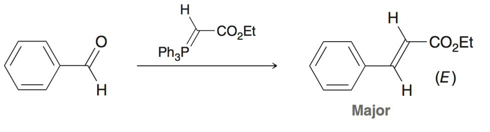
19.10 Wittig Reactions

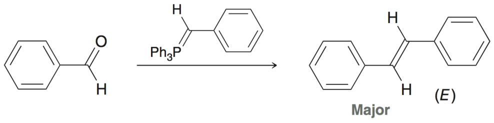
- Wittig reaction is particularly useful because it installs a C=C bond at a specific position in a molecule
- The Wittig reaction is also **stereoselective:**
  - Wittig reagents derived from simple alkyl halides favour the ***cis* or Z alkene**



19.10 Wittig Reactions

- Wittig reagents containing an electron-withdrawing group favour the ***trans* or *E* alkene**





- An electron withdrawing group stabilizes the negative charge within Wittig reagent via resonance

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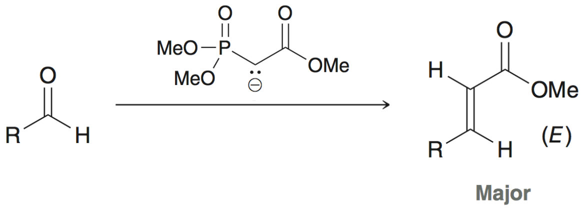
19.10 Wittig Reactions

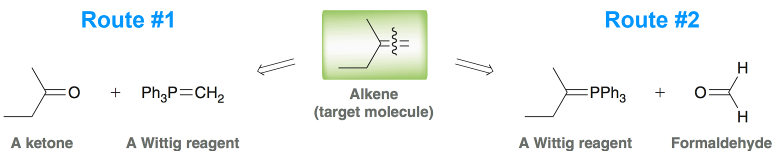
- **Horner-Wadsworth-Emmons (HWE) reaction** employs a reagent similar to a stabilized Wittig reagent to also **yield trans or *E* alkenes as the major product:**



- HWE reagent is a resonance-stabilized phosphonate ester carbanion

19.10 Wittig and HWE Reactions

- Retrosynthetic analysis reveals **two possible routes** to make a given alkene via a Wittig reaction:



To determine which route is better, consider the alkyl halide needed to make either of these Wittig reagents

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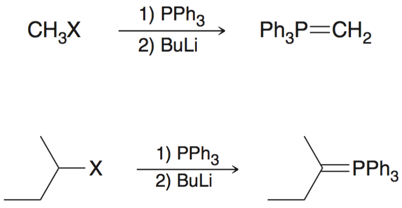
19.10 Wittig and HWE Reactions

- Retrosynthetic analysis reveals **two possible routes** to make a given alkene via a Wittig reaction:

Route #1
1° halide needed

Route #2
2° halide needed

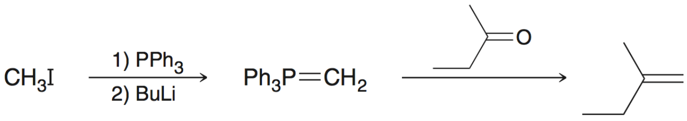


Route #1 is better since formation of the Wittig reagent is best for a 1° versus a 2° alkyl halide (S_N2 reaction)

19.10 Wittig and HWE Reactions

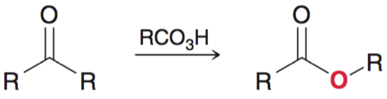
- Retrosynthetic analysis reveals **two possible routes** to make a given alkene via a Wittig reaction:

Overall Wittig reaction:



19.11 Baeyer-Villiger Oxidation

- **Baeyer Villiger Oxidation** - reaction of a peroxy acid with an aldehyde or ketone to form either a **carboxylic acid** or **ester**
- An oxygen is inserted between the carbonyl carbon and a neighbouring alkyl group

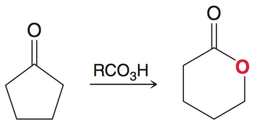


19.11 Baeyer-Villiger Oxidation

- **Mechanism for the Baeyer-Villiger Oxidation:**

19.11 Baeyer-Villiger Oxidation

- Cyclic ketone produces cyclic esters (known as lactones)



A lactone

- For an aldehyde or unsymmetrical ketone, the rate of migration is as follows:

H > 3° > 2°, Ph > 1° > methyl

- **Use this trend to determine regioselectivity**

19.11 Baeyer-Villiger Oxidation

- **Regioselectivity Examples:**