WILEY

Organic Chemistry

Third Edition

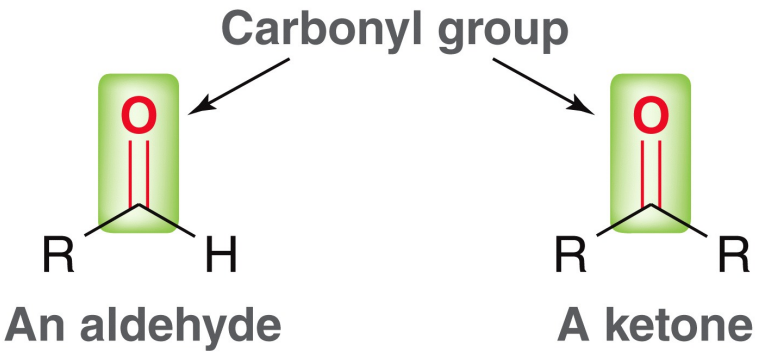
David Klein

Chapter 19

Aldehydes and Ketones

19.1 Ketones and Aldehydes

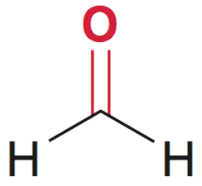
- Both functional groups possess the carbonyl group



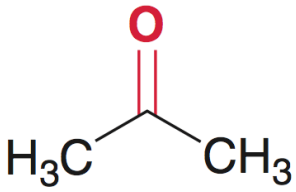
- Important in both biology and industry

Simplest aldehyde

used as a preservative



Formaldehyde

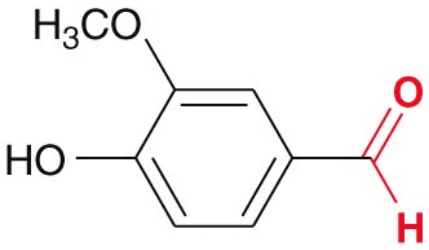


Acetone

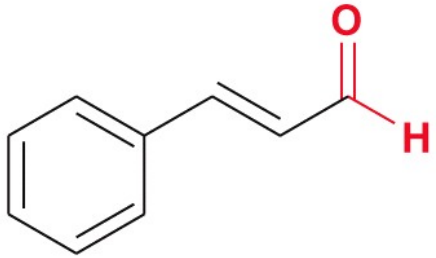
Simplest ketone

used mainly as a solvent

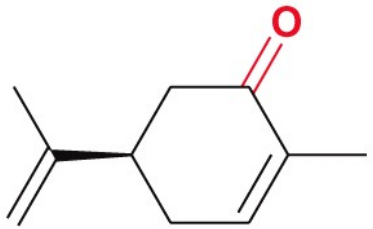
19.1 Ketones and Aldehydes



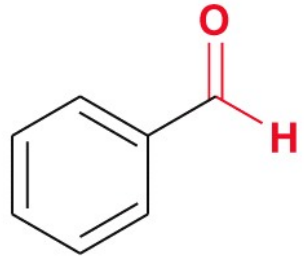
Vanillin
(Vanilla flavor)



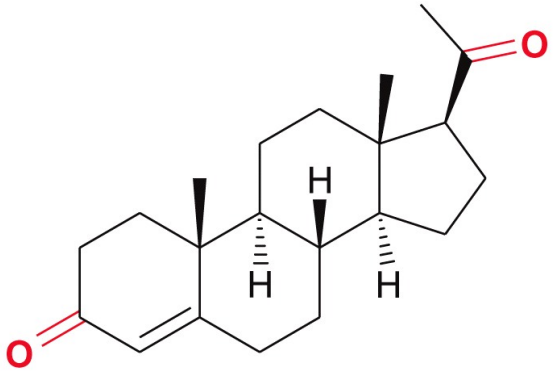
Cinnamaldehyde
(Cinnamon flavor)



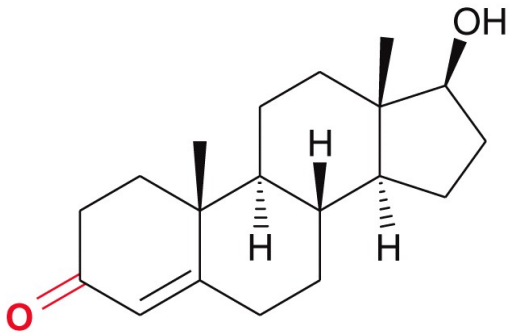
(*R*)-Carvone
(Spearmint flavor)



Benzaldehyde
(Almond flavor)



Progesterone



Testosterone

19.2 Nomenclature

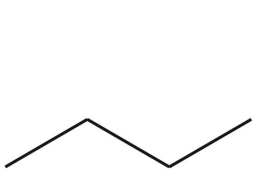
- Four discrete steps to naming an aldehyde or ketone
- Same procedure as with alkanes, alcohols, etc…

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

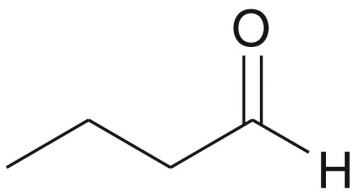
19.2 Nomenclature

1. Identify and name the parent chain

- For aldehydes, replace the "-**e**" ending with an "-**al**"

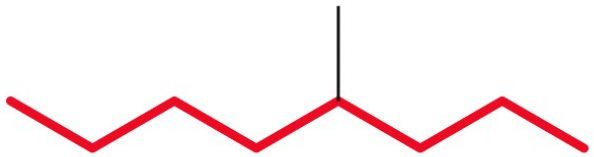


Butan**e**

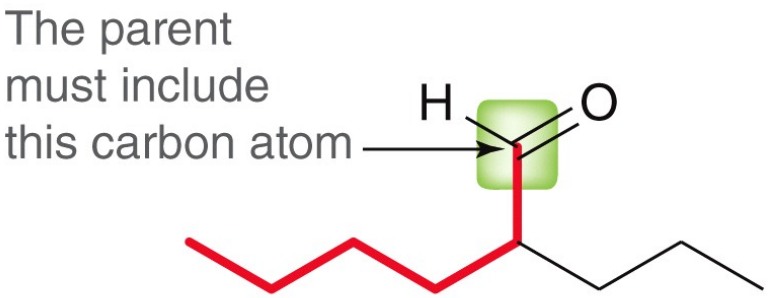


Butan**al**

- the parent chain must include the carbonyl carbon



Parent = Octane

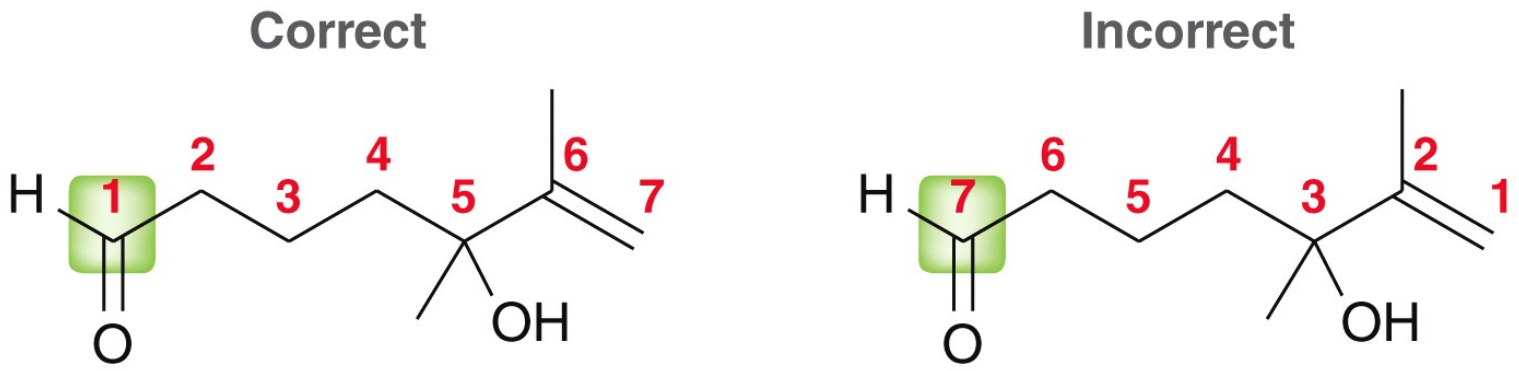


Parent = Hexanal

19.2 Nomenclature

1. Identify and name the parent chain

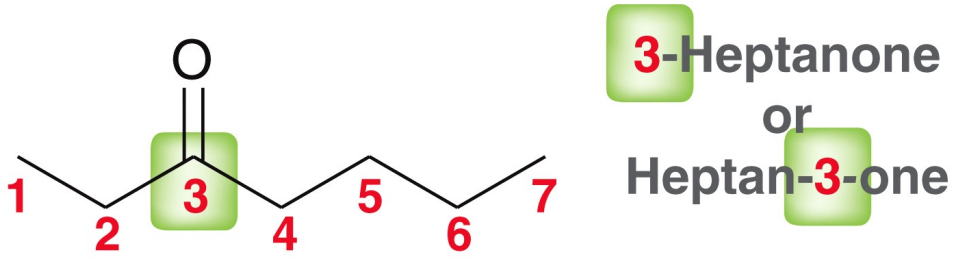
- The aldehydic carbon is assigned number 1:



19.2 Nomenclature

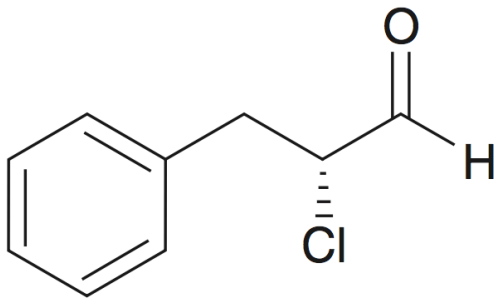
1. **Identify and name the parent chain**
   - For ketones, replace the "-**e**" ending with an "-**one**"

   - The parent chain must include the C=O group
   - the C=O carbon is given the lowest #, and can be expressed before the parent name or before the suffix



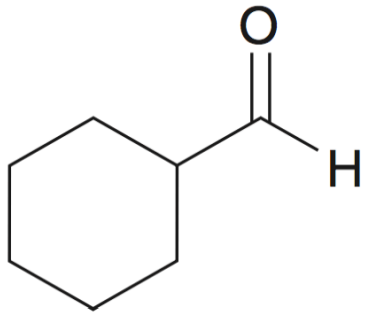
19.2 Nomenclature

- The configuration of a chiral center is indicated at the beginning of the name



(*R*)-2-Chloro-3-phenylpropanal

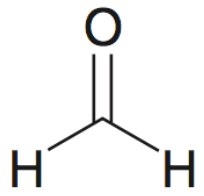
- Aldehyde next to a ring is named as a carbaldehyde



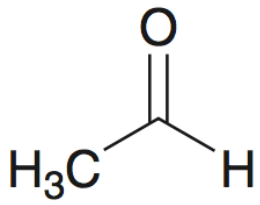
Cyclohexanecarbaldehyde

19.2 Nomenclature

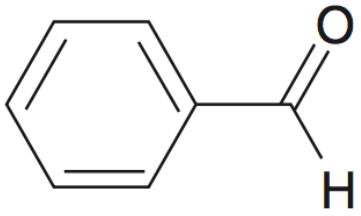
- IUPAC also recognizes the following common names as parent names:



Formaldehyde



Acetaldehyde



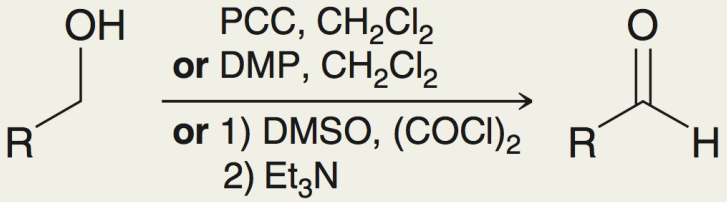
Benzaldehyde

- **Practice with SkillBuilder 19.1**

19.3 Preparing Aldehydes and Ketones

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

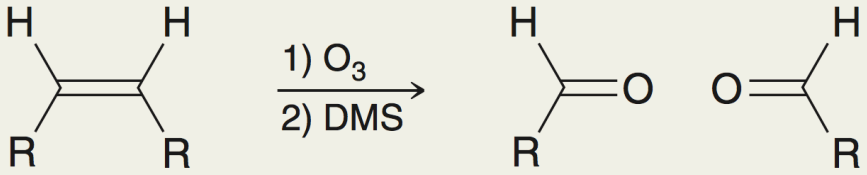
REACTION	SECTION
Oxidation of Primary Alcohols	12.10



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 and Ketones

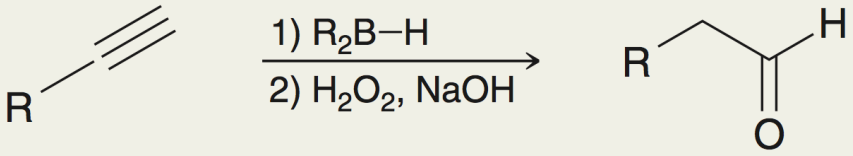
- Summary of **aldehyde preparation** (review)

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 Aldehydes and Ketones

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

REACTION	SECTION
Hydroboration-Oxidation of Terminal Alkynes	9.7

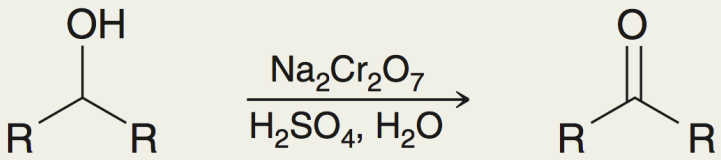


Hydroboration-oxidation results in an *anti*-Markovnikov addition of water across a π bond, followed by tautomerization of the resulting enol to form an aldehyde.

19.3 Preparing Aldehydes and Ketones

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

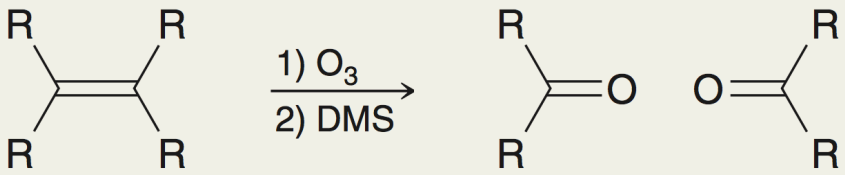
REACTION	SECTION
Oxidation of Secondary Alcohols	12.10



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

19.3 Preparing Aldehydes and Ketones

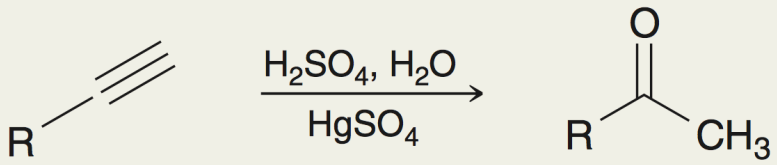
- Summary of **ketone preparation** (review)

REACTION	SECTION
Ozonolysis of Alkenes  Tetrasubstituted alkenes are cleaved to form ketones.	8.12

19.3 Preparing Aldehydes and Ketones

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

REACTION	SECTION
Acid-Catalyzed Hydration of Terminal Alkynes	9.7

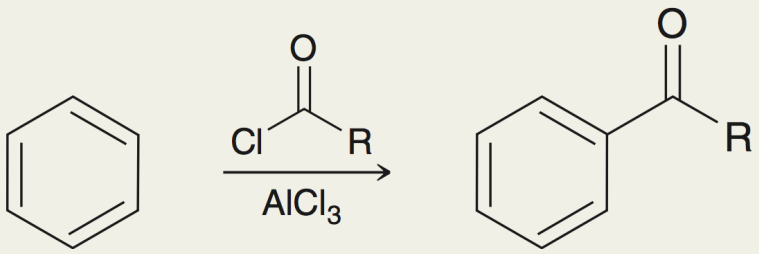


This procedure results in a Markovnikov addition of water across the π bond, followed by tautomerization to form a methyl ketone.

19.3 Preparing Aldehydes and Ketones

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

REACTION	SECTION
Friedel–Crafts Acylation	18.6

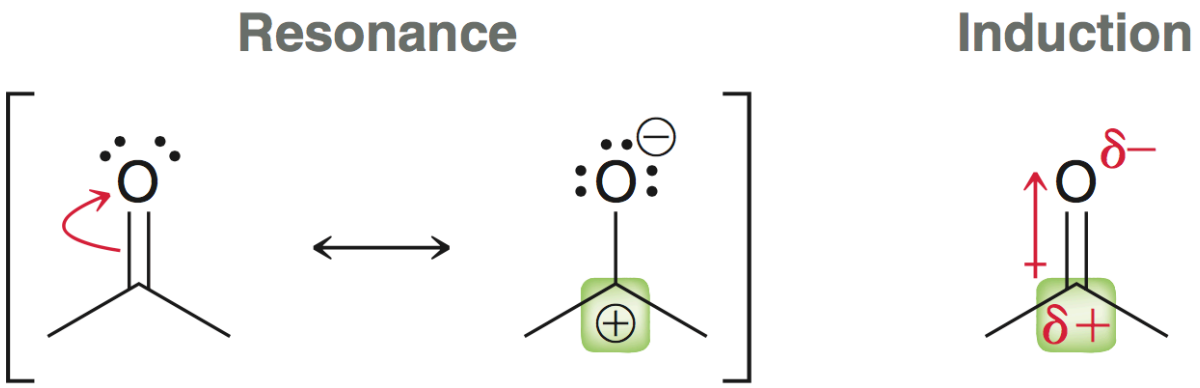


Aromatic rings that are not too strongly deactivated will react with an acyl halide in the presence of a Lewis acid to produce an aryl ketone.

- **Practice reviewing these rxns with Conceptual Checkpoint 19.5**

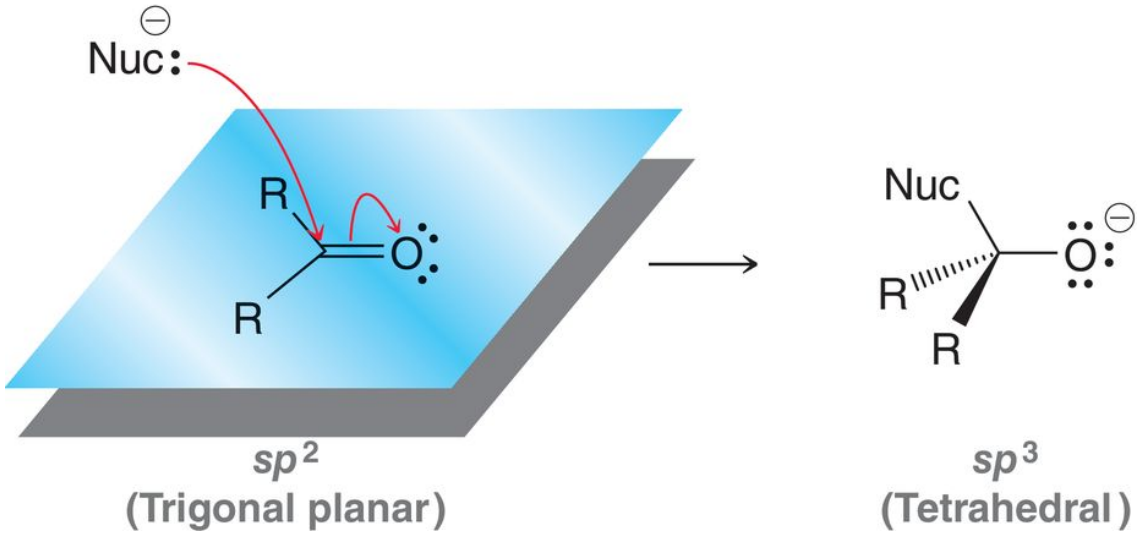
19.4 Nucleophilic Addition Reactions

- 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:

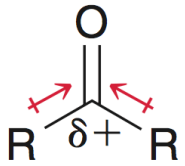


19.4 Nucleophilic Addition Reactions

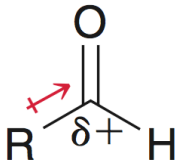
- **Aldehydes are generally more reactive towards nucleophiles than ketones**:

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

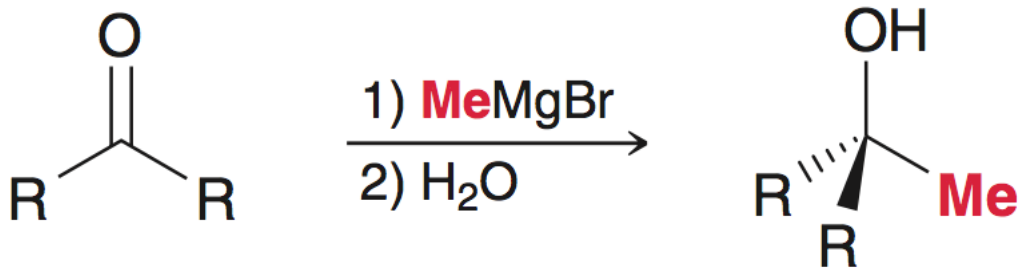


An aldehyde
has only one electron-donating alkyl group that stabilizes the partial positive charge

19.4 Nucleophilic Addition Reactions

- Some nucleophiles require **acidic conditions**, others require **basic conditions**

- Example: the **Grignard reaction = basic conditions**

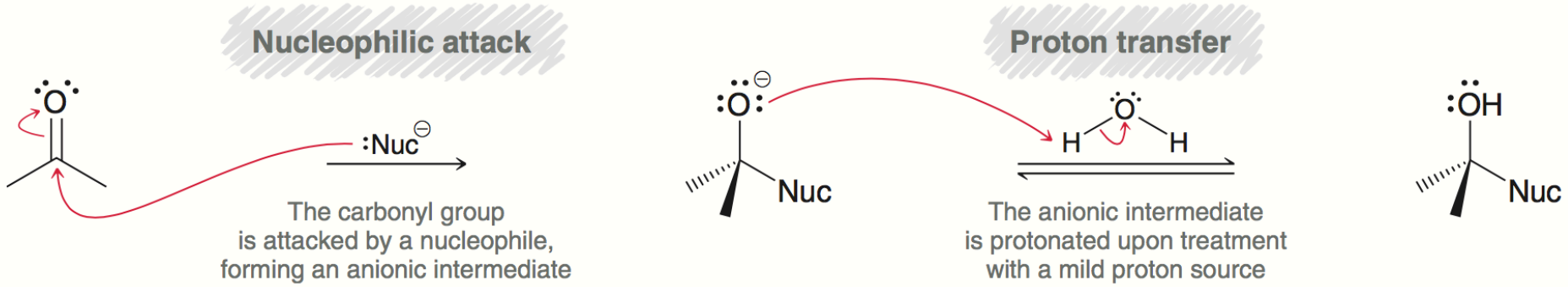


- Generally, a **strong nucleophile** means the reaction is under **basic conditions** (grignards, hydrides, etc)

19.4 Nucleophilic Addition Reactions

- Under **basic conditions**, all nucleophiles react with carbonyls by the **same general mechanism**:

MECHANISM 19.1 NUCLEOPHILIC ADDITION UNDER BASIC CONDITIONS

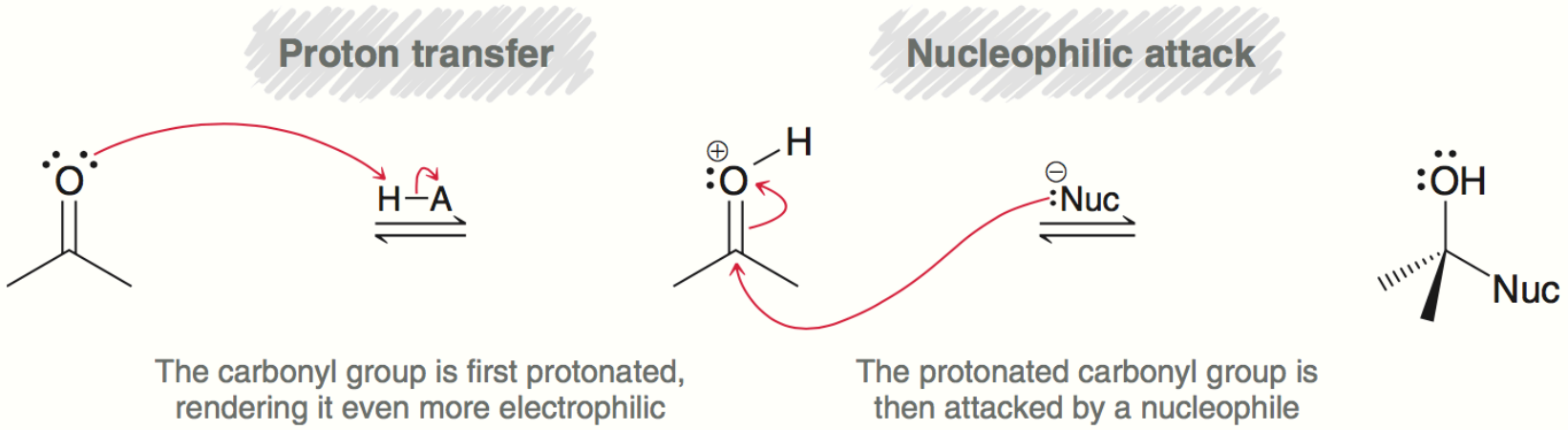


- Nucleophile attacks, forming a ***negatively*** **charged intermediate**, which is protonated upon acidic workup

19.4 Nucleophilic Addition Reactions

- Aldehydes/ketones react with a variety of weaker nucleophiles, under **acidic conditions**, by the same general mechanism:

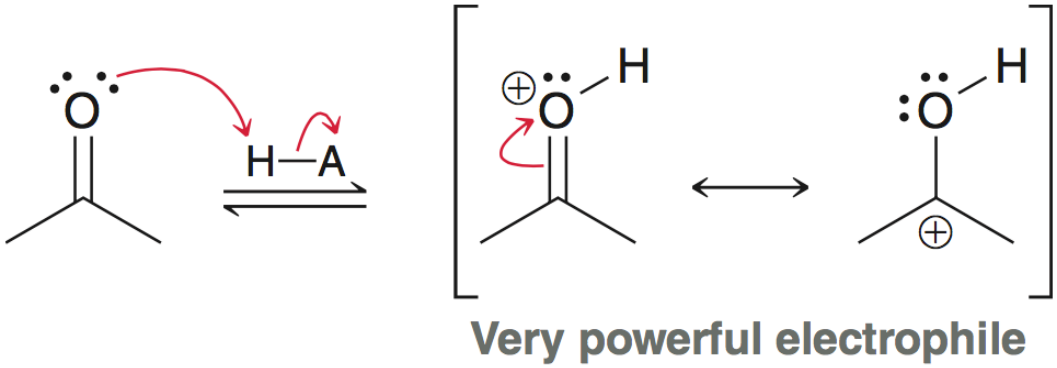
MECHANISM 19.2 NUCLEOPHILIC ADDITION UNDER ACIDIC CONDITIONS



- The carbonyl is protonated to form a ***positively*** **charged intermediate**, which can be attacked by a weak nucleophile

19.4 Nucleophilic Addition Reactions

- Acidic conditions are required in order for a weak nucleophile to attack a carbonyl carbon:

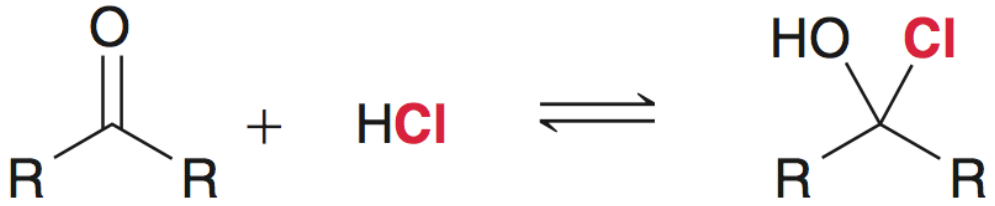


Very powerful electrophile

- Protonation of the carbonyl makes it a better electrophile

19.4 Nucleophilic Addition Reactions

- When a nucleophile attacks a carbonyl group, the equilibrium depends on the ability of the nucleophile to function as a leaving group.
- **Example:**

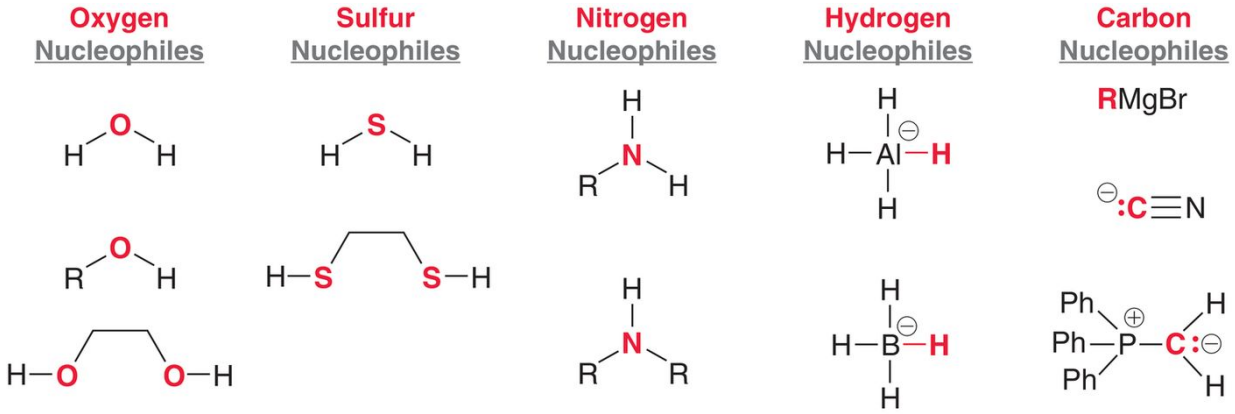


Favored at equilibrium

- Since the nucleophile, Cl^-, is also a good leaving group, equilibrium favors the starting ketone

19.4 Nucleophilic Addition Reactions

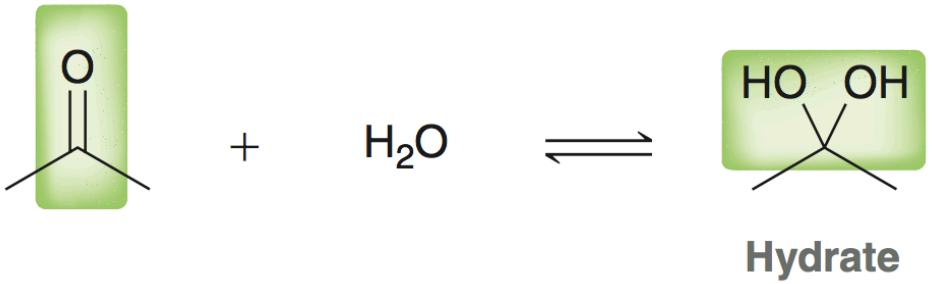
- We will cover the following nucleophiles and their reaction with ketones and aldehydes:



- **Practice with Conceptual Checkpoint 19.6**

19.5 Oxygen Nucleophiles

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



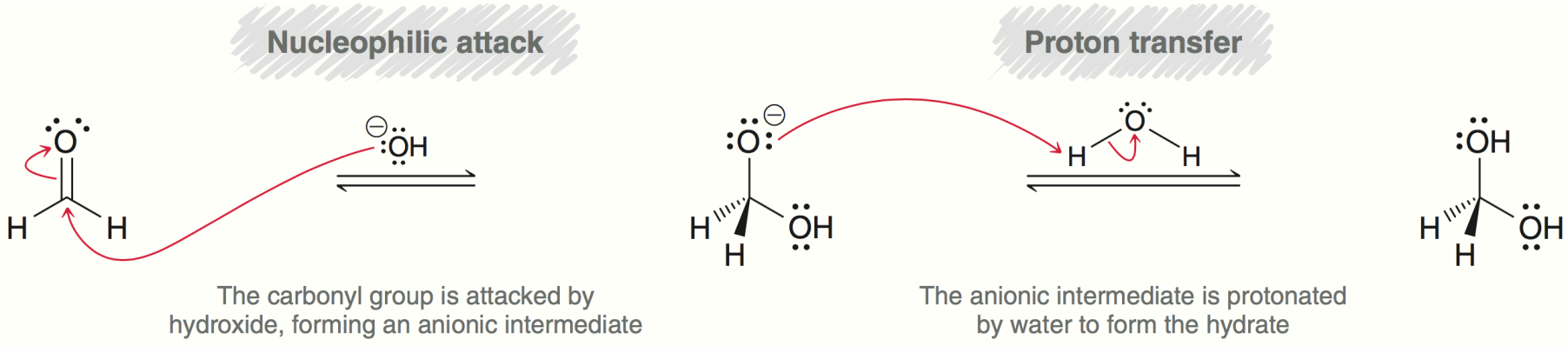
- **Equilibrium generally does not favor the formation of the hydrate (except for very simple aldehydes)**

- The rate of reaction is slow unless acidic or basic conditions are used

19.5 Oxygen Nucleophiles

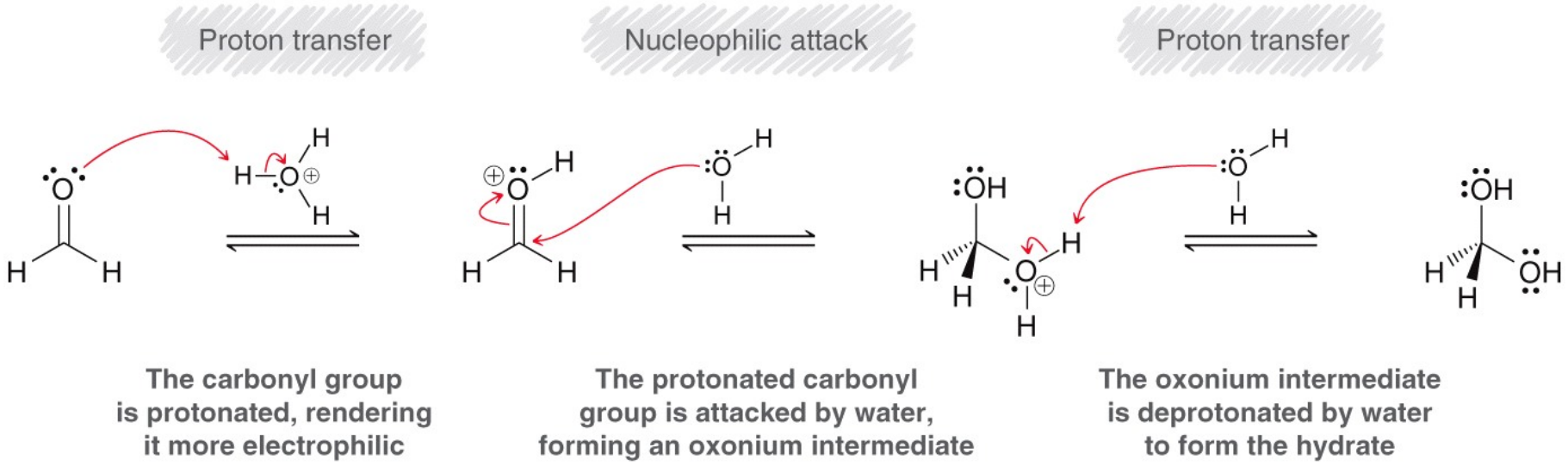
- Under basic conditions, OH^- is the nucleophile:

MECHANISM 19.3 BASE-CATALYZED HYDRATION



19.5 Oxygen Nucleophiles

- Under acidic conditions, the carbonyl is protonated, and H_2O is the nucleophile:



- **Practice with Conceptual Checkpoint 19.7**

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*

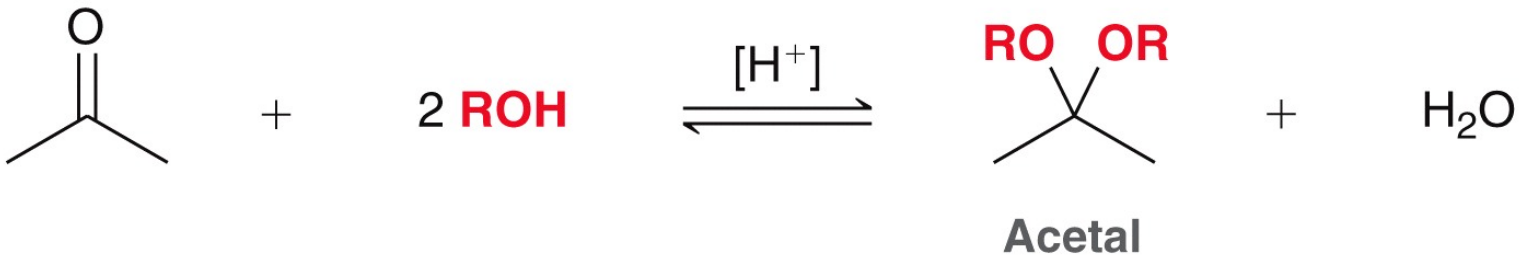
  - **A strong base cannot exist in an acidic environment.**

- *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**

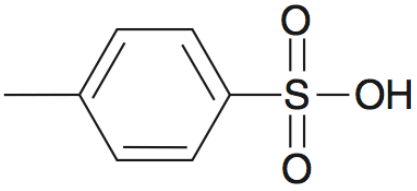
19.5 Oxygen Nucleophiles

- Alcohols can attack ketones/aldehydes:

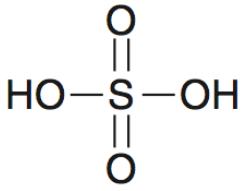


- Under acidic conditions, 1 ketone/aldehyde reacts with 2 alcohols to form an **acetal.**

Commonly used acid catalysts for acetal formation

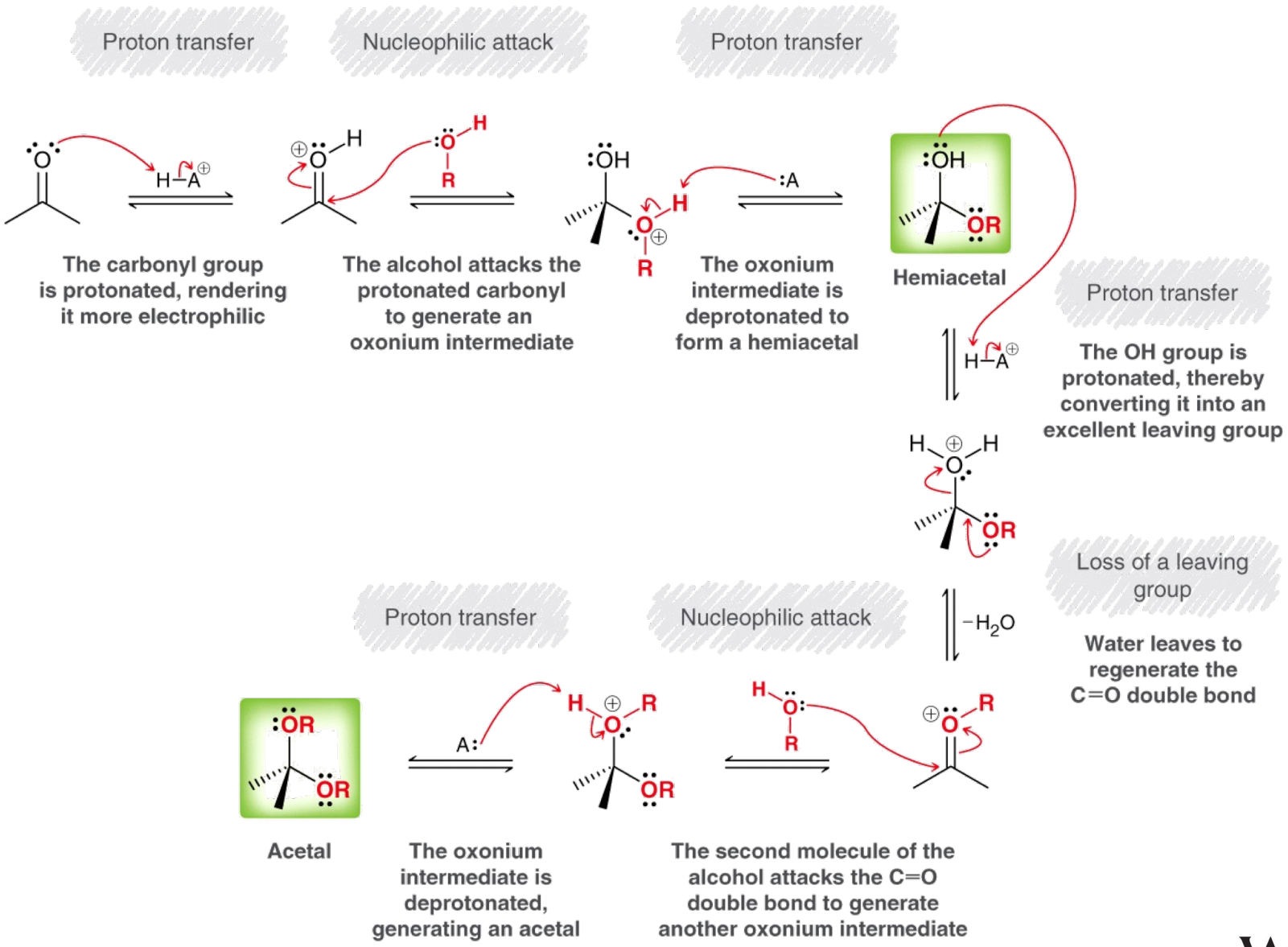


***p*-Toluenesulfonic acid**
(TsOH)



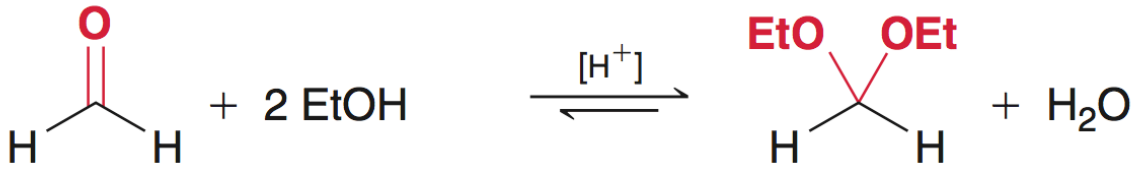
Sulfuric acid

19.5 Oxygen Nucleophiles



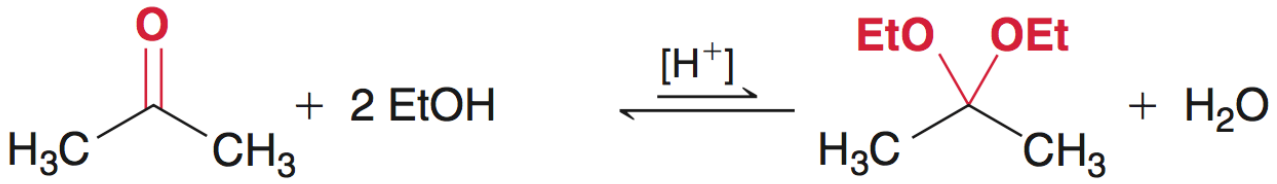
19.5 Oxygen Nucleophiles

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



Products are favored at equilibrium

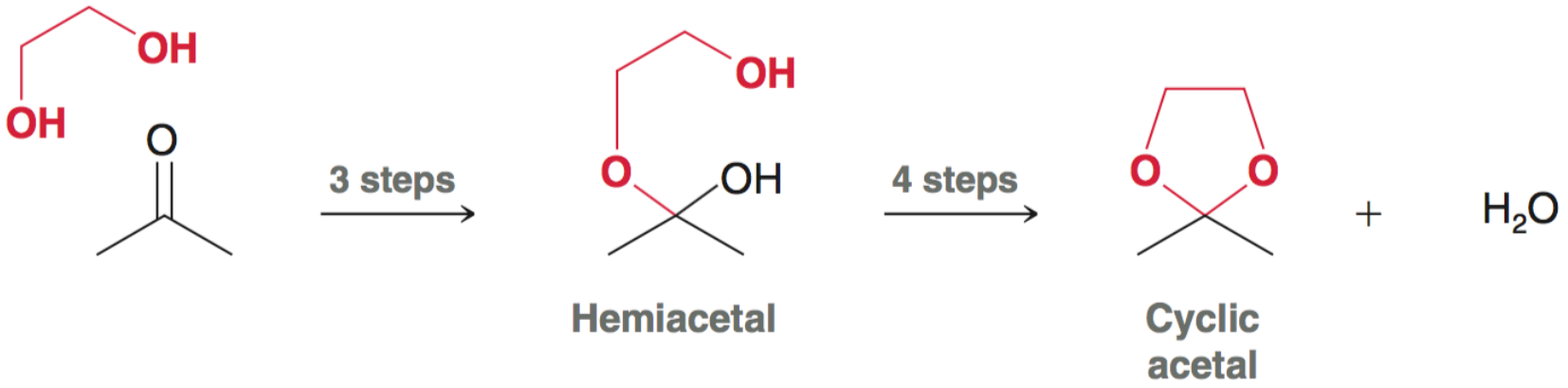
- For most ketones, the acetal is *not* favored at equilibrium



Reactants are favored at equilibrium

19.5 Oxygen Nucleophiles

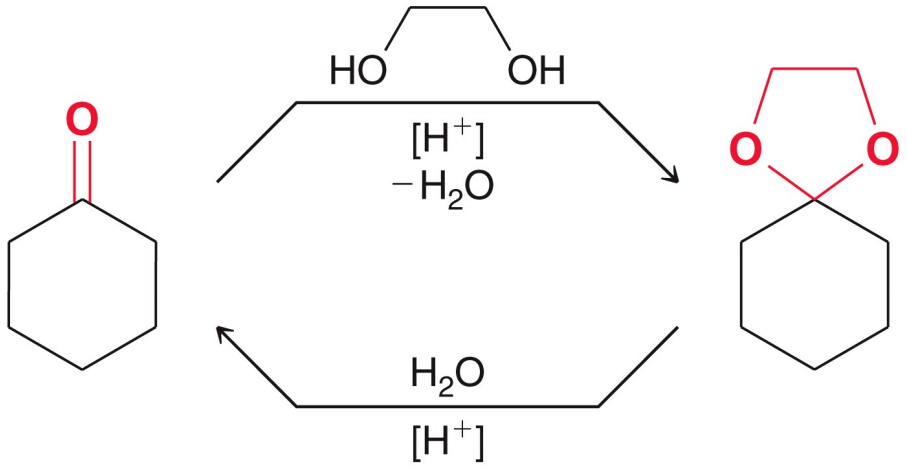
- If a diol is used, then both equivalents of alcohol come from the same compound, and a cyclic acetal is formed



- **Practice drawing the mechanism of acetal formation with SkillBuilder 19.2**

19.5 Oxygen Nucleophiles

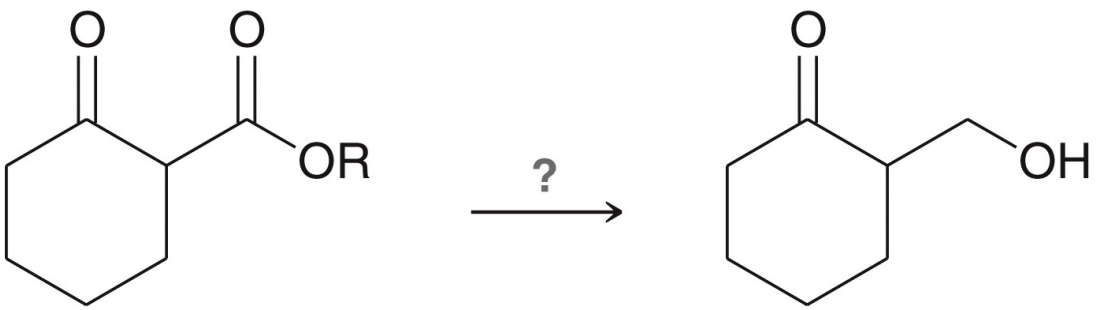
- Acetal formation is reversible, and can be controlled by adding/removing water:
- **To favor acetal formation**, **water is removed** from the reaction
- **To convert an acetal back into the ketone/aldehyde, water is added** to the acetal, with H+ catalyst:



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

19.5 Oxygen Nucleophiles

- Consider how the following synthesis could be accomplished:

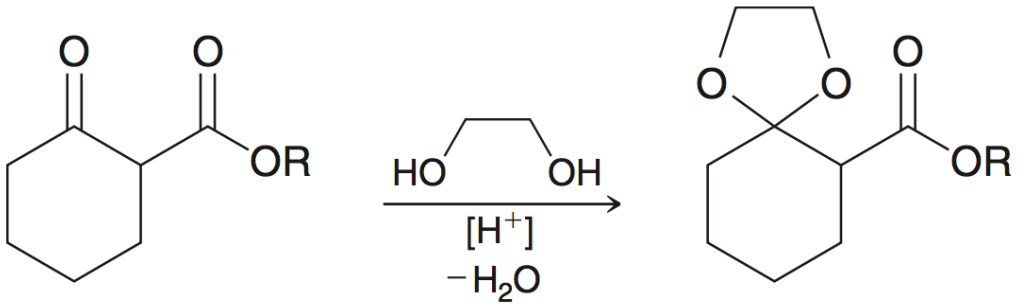


- We need to convert an ester to 1˚ alcohol, which requires LAH, while leaving the ketone unchanged.

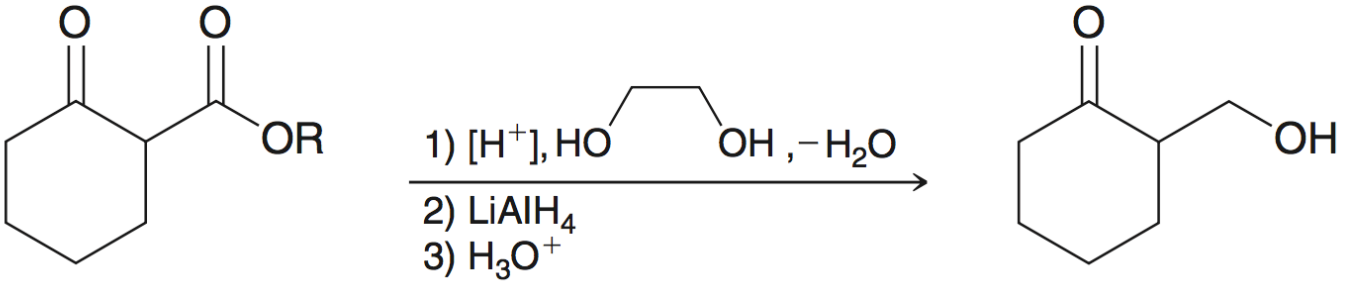
- **problem**: Using LAH would reduce the ketone as well
- **solution**: use a protecting group for the ketone

19.5 Oxygen Nucleophiles

- First, protect the ketone as a cyclic acetal:



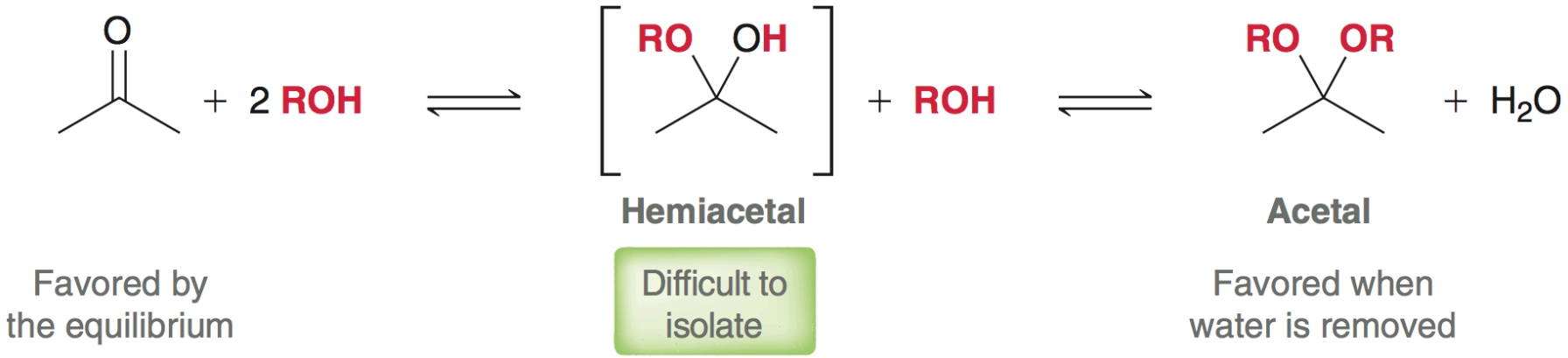
- Then we can reduce the ester, and deprotect the ketone
- **Overall**:



- **Practice with Conceptual Checkpoint 19.10-19.11**

19.5 Oxygen Nucleophiles

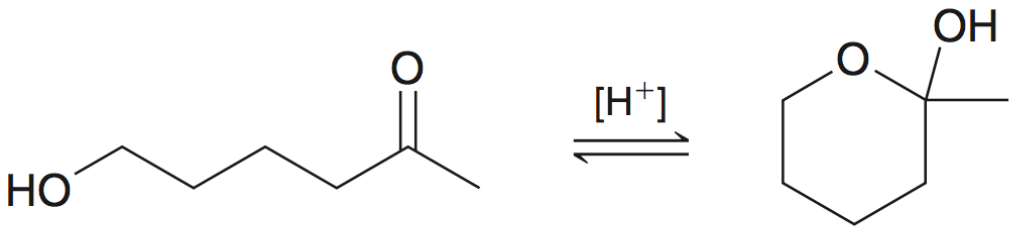
- A **hemiacetal** is the intermediate formed in the conversion of a ketone/aldehyde to an acetal
- The are generally difficult to isolate, as equilibrium either favors the aldehyde/ketone or the acetal, based on conditions used:



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

19.5 Oxygen Nucleophiles

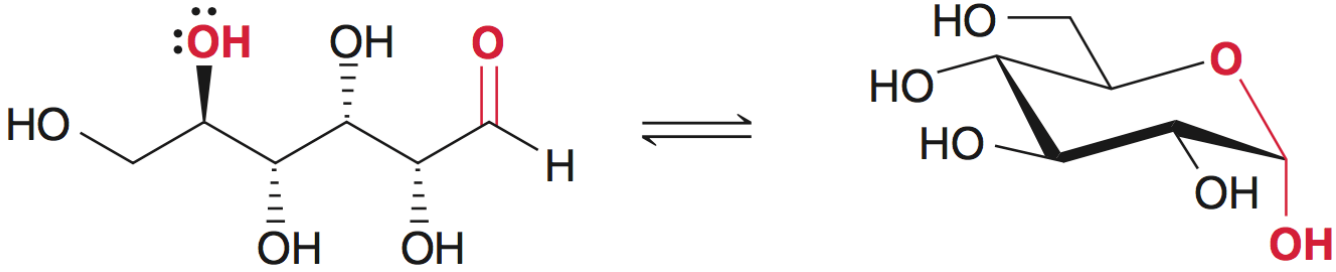
- A **cyclic hemiacetal** is possible when a compound contains both he carbonyl group and the hydroxy group:



favored at equilibrium

Cyclic hemiacetal

- Cyclic hemiacetals are important in carbohydrate chemistry:



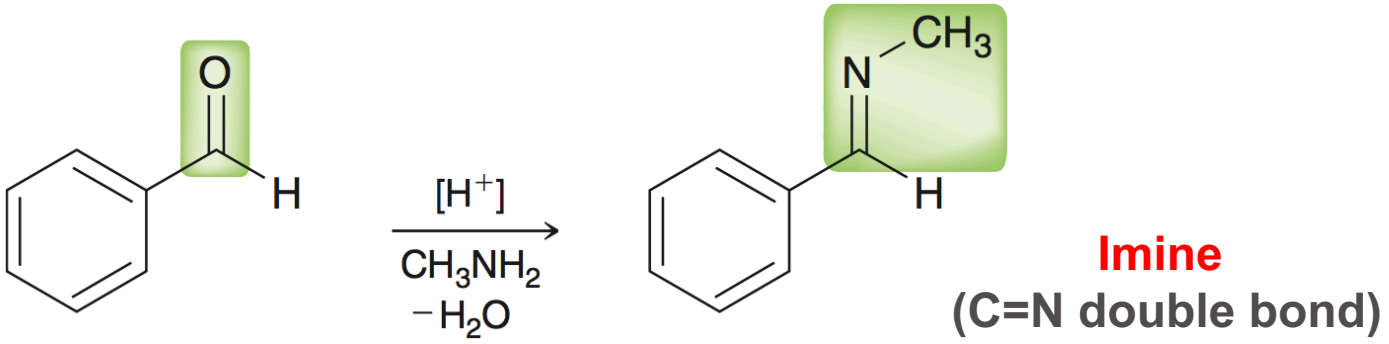
favored at equilibrium

Glucose
(Open-chain)

Glucose
(Cyclic hemiacetal)

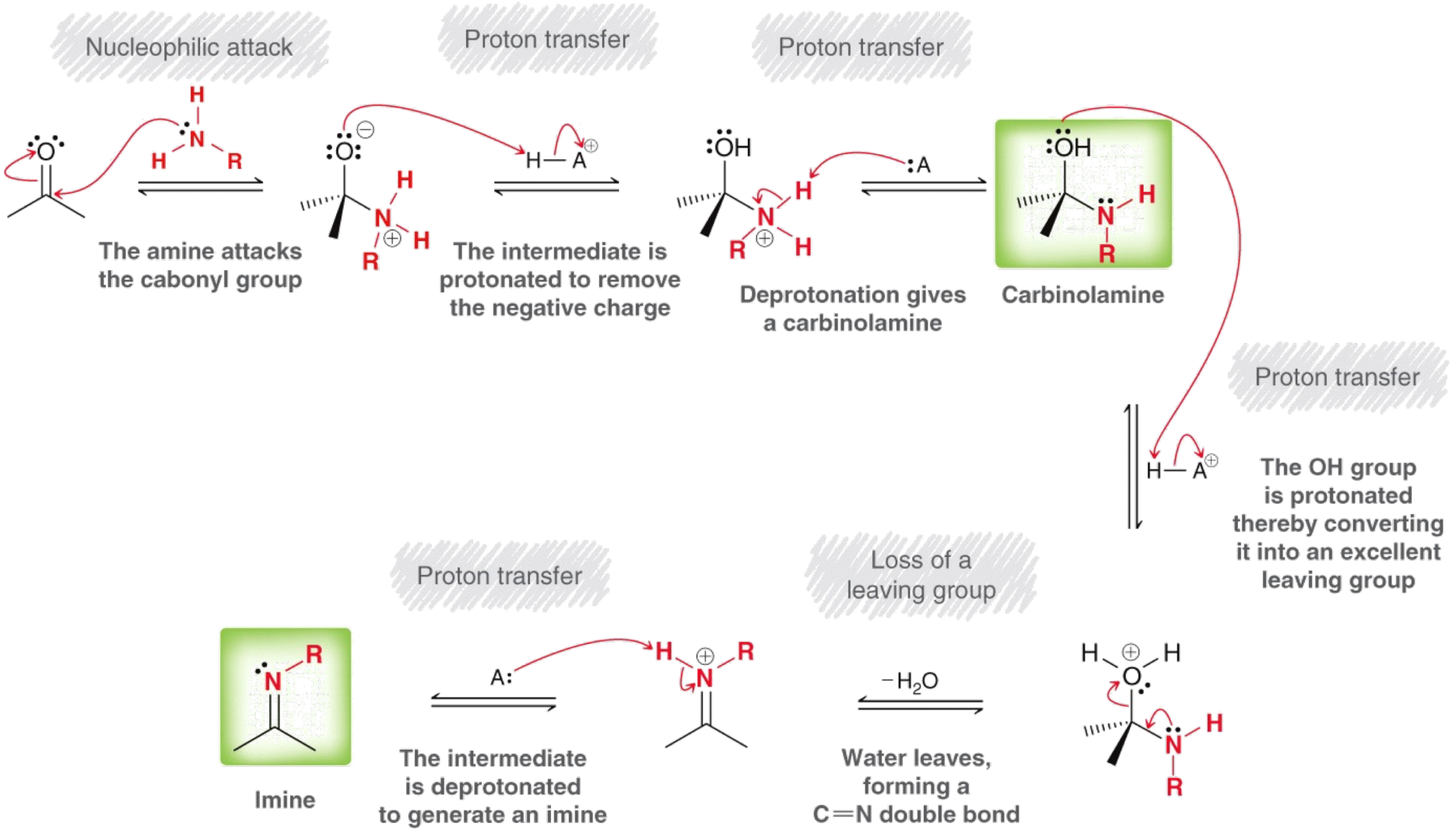
19.6 Nitrogen Nucleophiles

- Under acidic conditions, **aldehyde/ketone** reacts with a **1˚ amine** to form an **imine**:



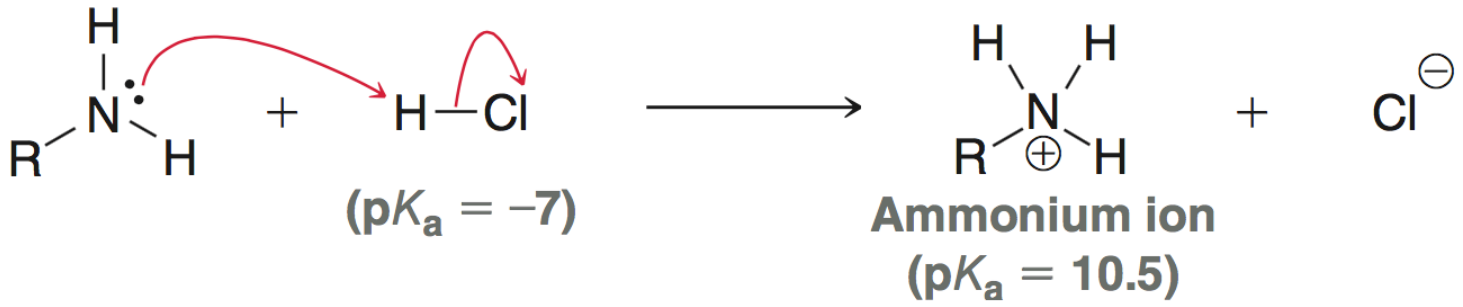
- The reaction requires acidic conditions to work;

19.6 Nitrogen Nucleophiles



19.6 Nitrogen Nucleophiles

- Even though it is under acidic conditions, protonation of the carbonyl is not the first step of imine formation mechanism



Amines are bases, and consume the H+ catalyst

The ammonium ion is the acid catalyst for the reaction

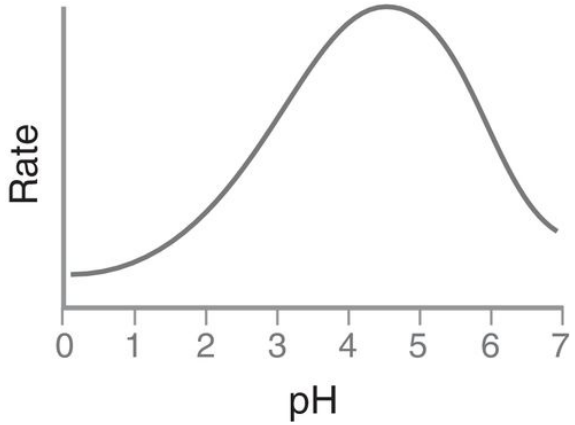
- The ammonium ion is not acidic enough to protonate an aldehyde or ketone, but it is acidic enough to transfer a proton to the negatively charged oxygen in the second step.

19.6 Nitrogen Nucleophiles

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

lower pH = all the amines are protonated, none Available to attack the carbonyl

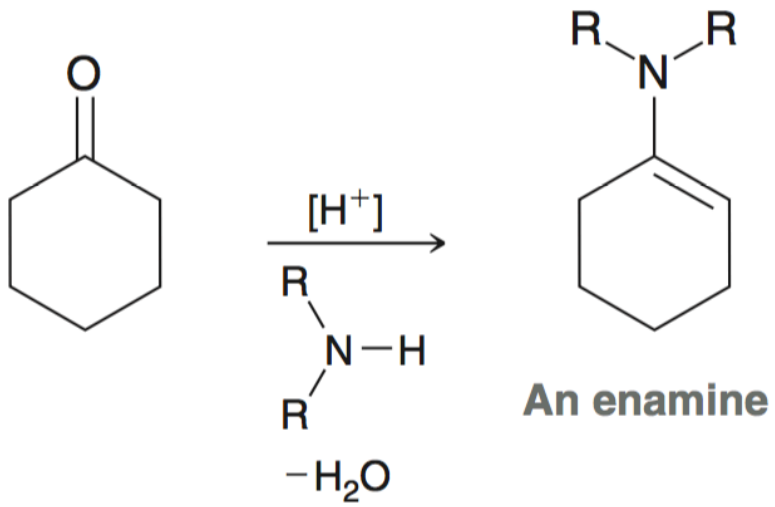
higher pH = not enough acid to catalyze the reaction effectively



- **Practice with SkillBuilder 19.3**

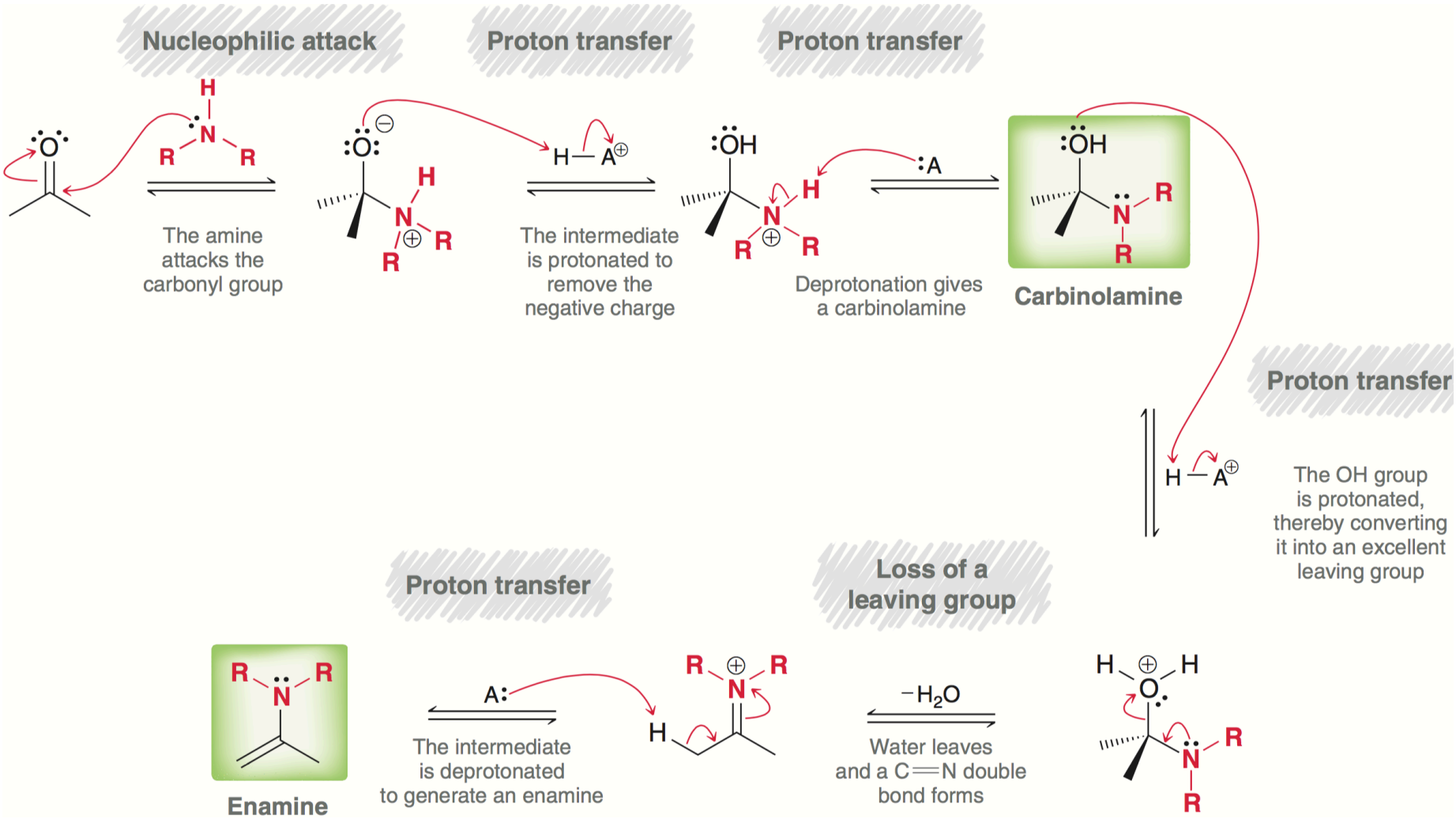
19.6 Nitrogen Nucleophiles

- Under acidic conditions, **aldehyde/ketone** reacts with a **2˚ amine** to form an **enamine**:



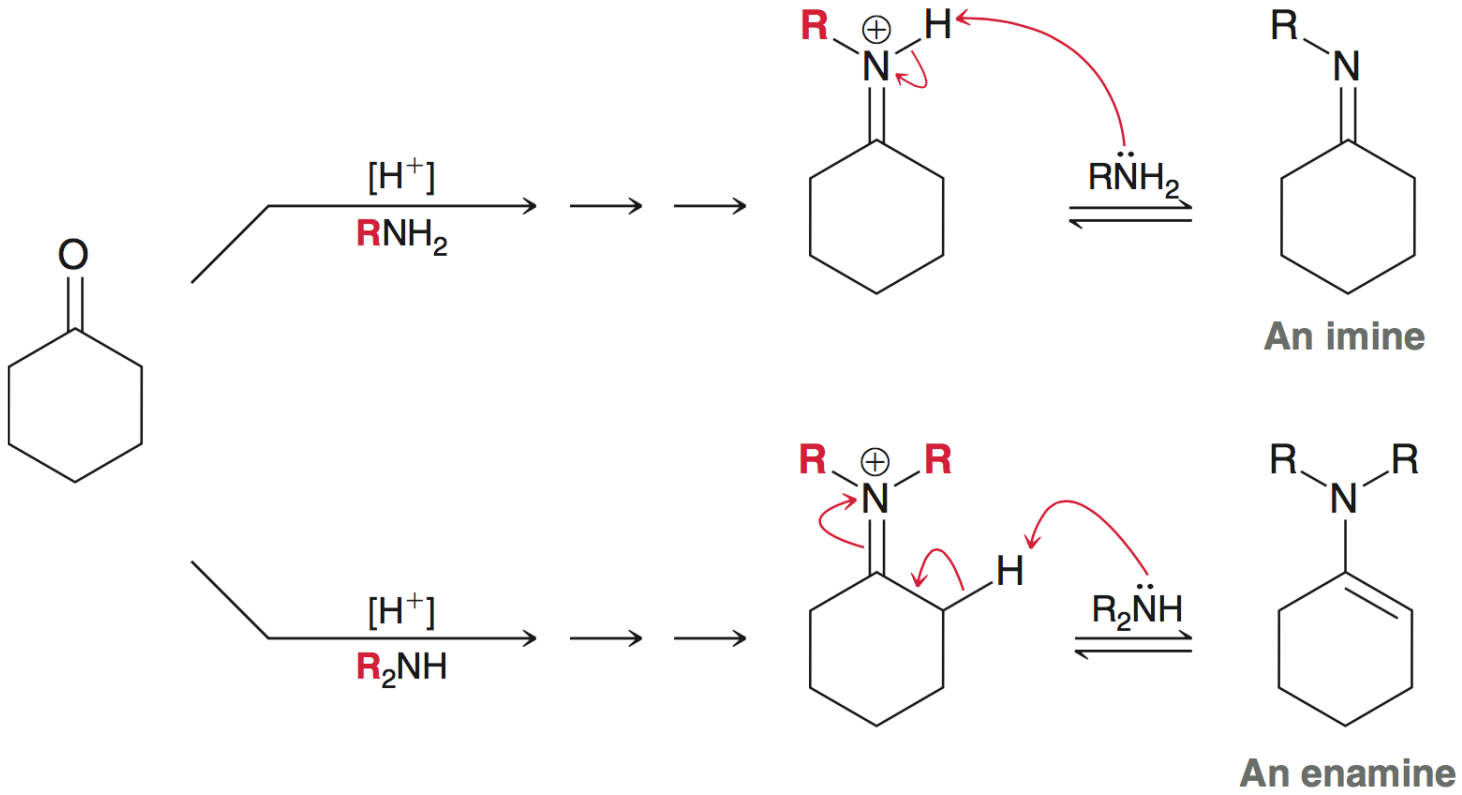
- The reaction requires acidic conditions to work; the mechanism is identical to imine formation, except for the last step

19.6 Nitrogen Nucleophiles



19.6 Nitrogen Nucleophiles

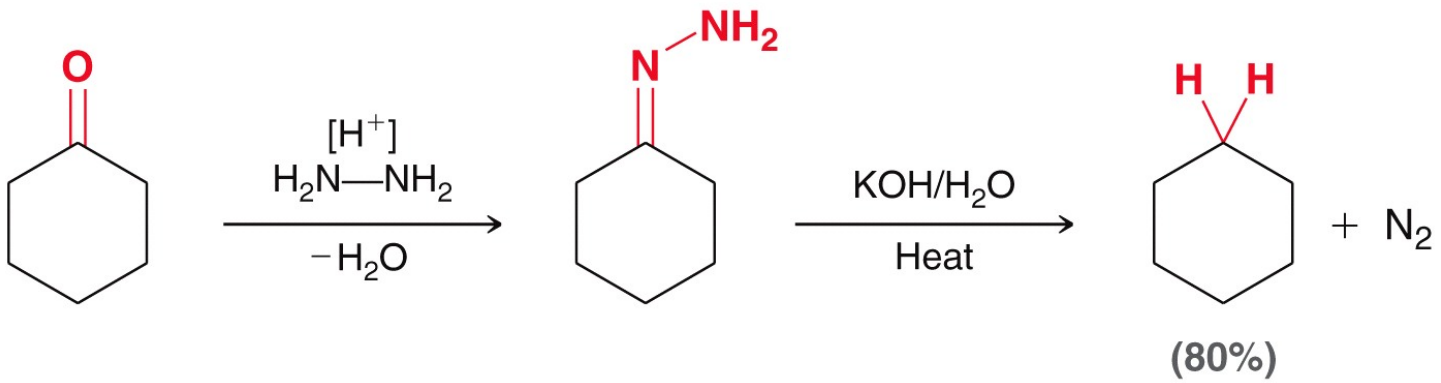
- The reaction requires acidic conditions to work; the mechanism is identical to imine formation, except for the last step



- **Practice with SkillBuilder 19.4**

19.6 Nitrogen Nucleophiles

- Wolff-Kishner reduction is a two-step synthesis, converting a ketone to an alkane:

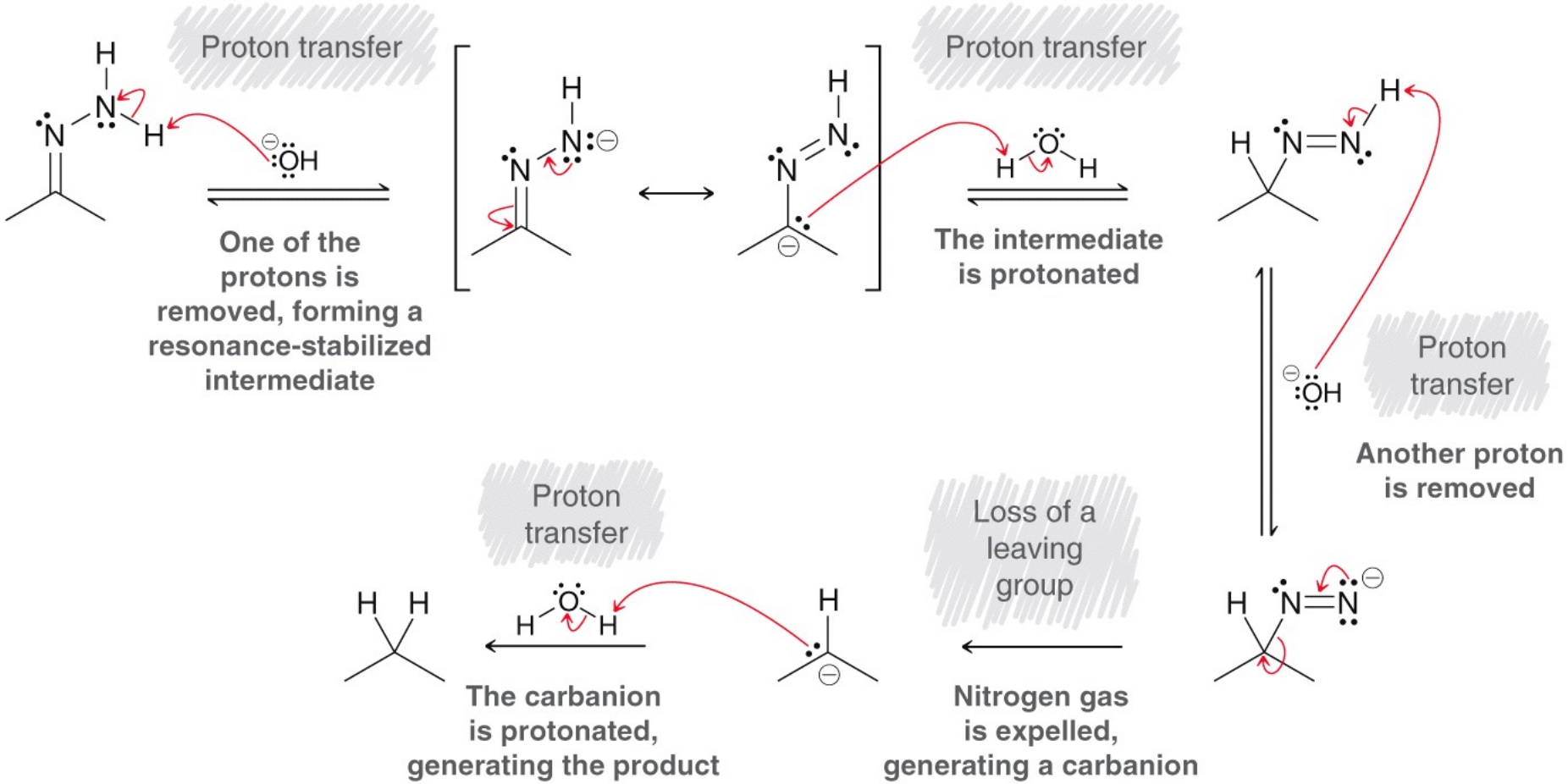


- First step is imine formation between the ketone and hydrazine (which is like a primary amine)

- Second reaction is like an elimination

19.6 Nitrogen Nucleophiles

- Mechanism of 2nd step of Wolff-Kishner reduction:



- **Practice with Conceptual Checkpoint 19.22**

19.6 Nitrogen Nucleophiles

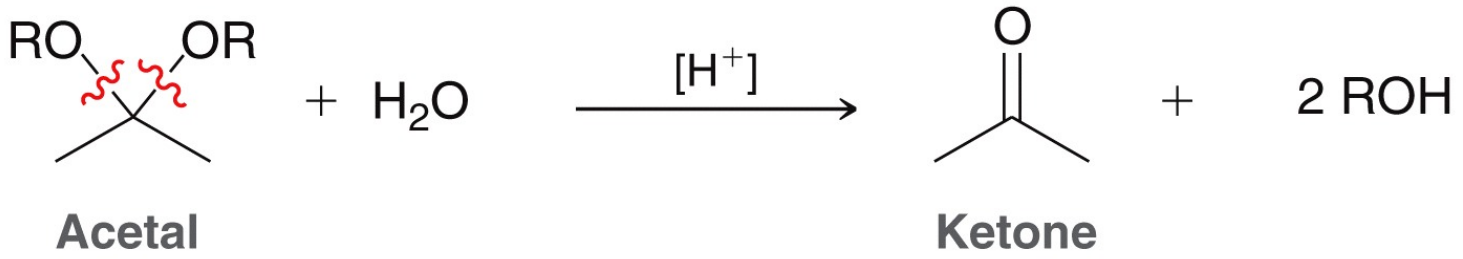
- Note the many similarities between the acid catalyzed mechanisms we have discussed

- One thing to always note:

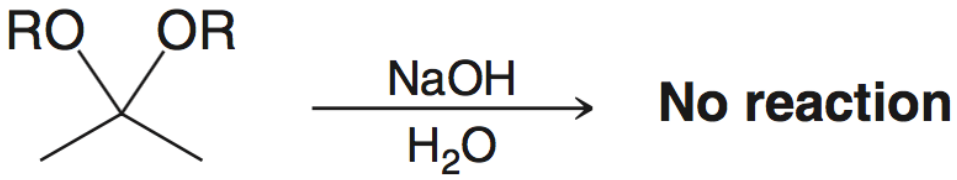
Under acidic conditions, reaction species should either be neutral or have a +1 formal charge

19.7 Hydrolysis of Acetals

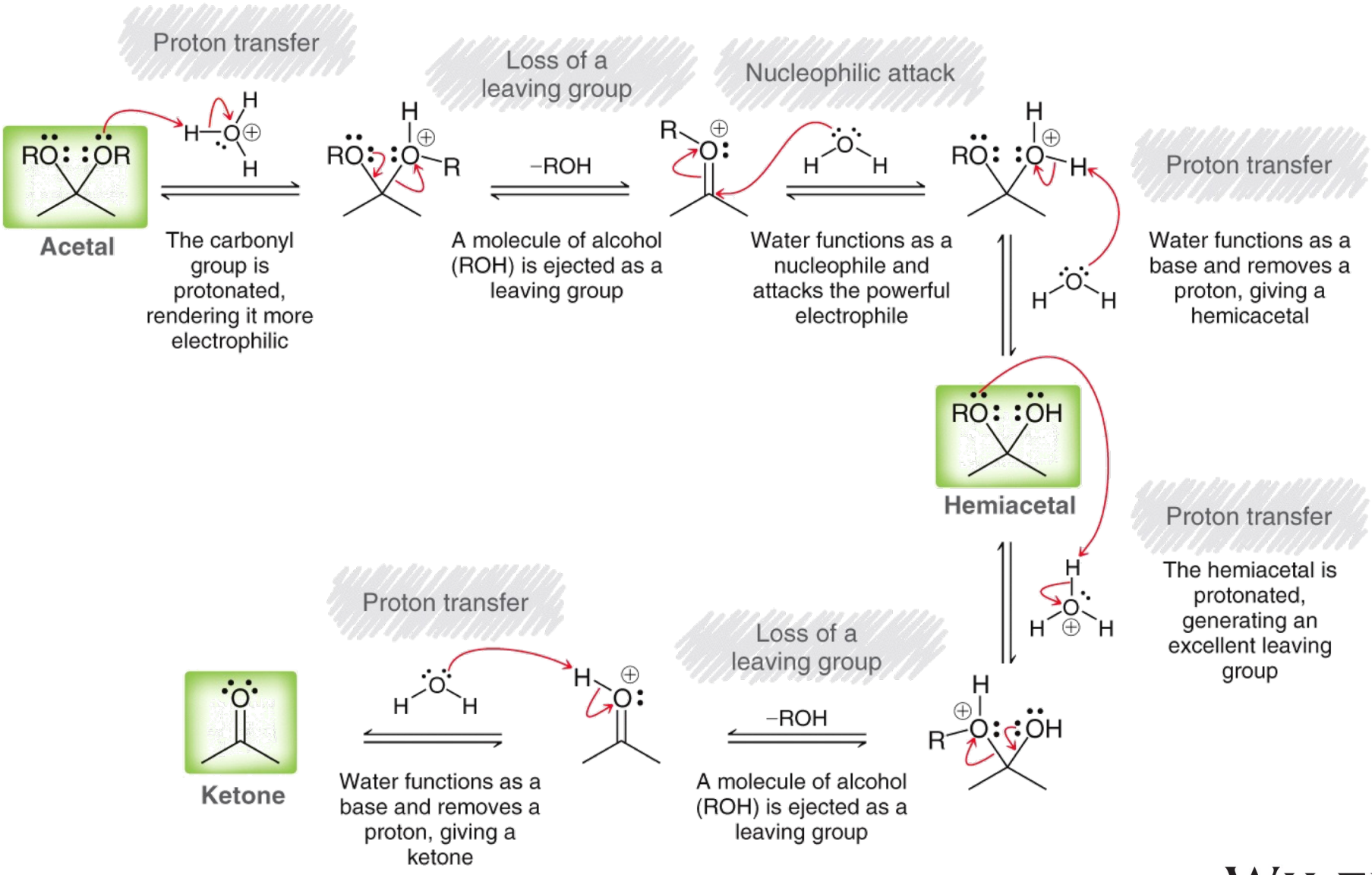
- Acetals are hydrolyzed with aqueous acid to yield a ketone (or aldehyde) and two equivalents of alcohol:
- Simply the reverse of acetal formation:



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

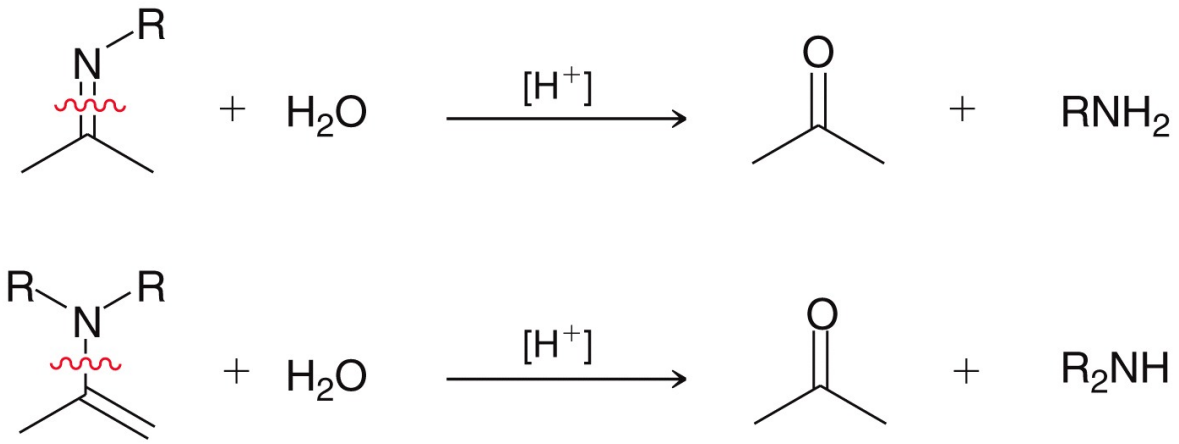


19.7 Hydrolysis of Acetals



19.7 Hydrolysis of Imines and Enamines

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

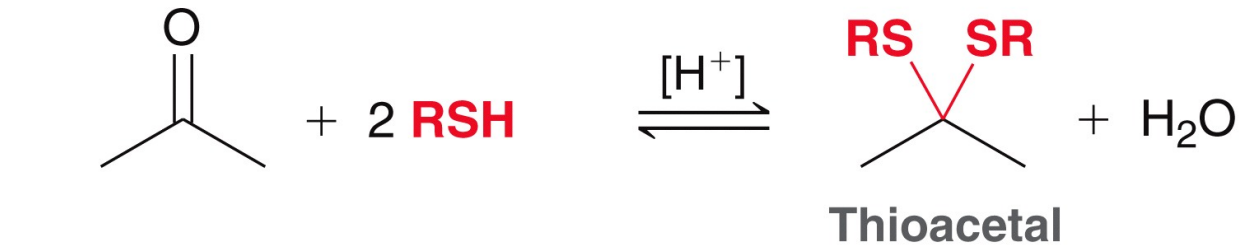


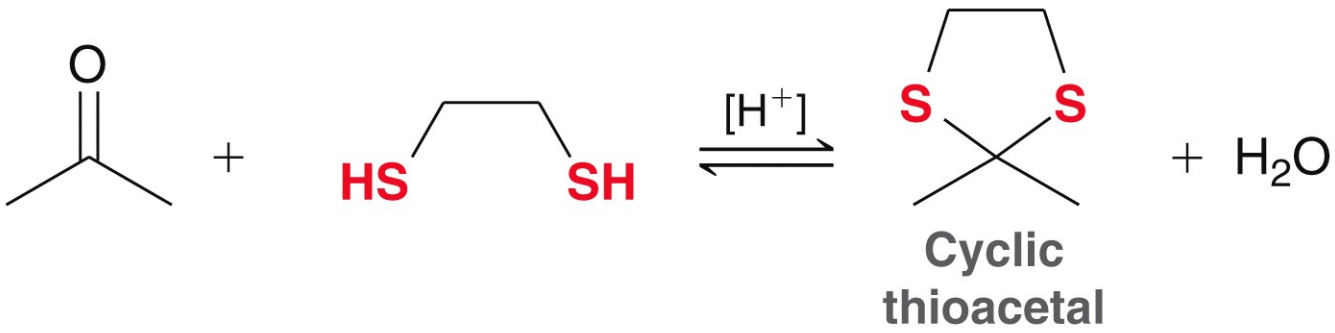
- The mechanism of hydrolysis for imines and enamines is simply the reverse of their mechanisms of formation

- **Practice with SkillBuilder 19.5**

19.8 Sulfur Nucleophiles

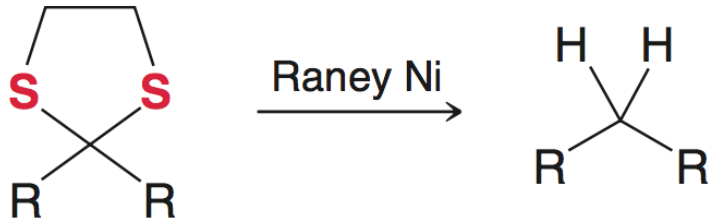
- Ketones/aldehydes reaction with thiols virtually the same way they react with alcohols:





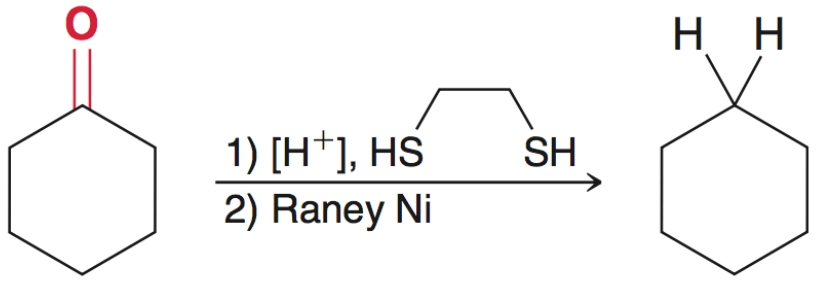
19.8 Sulfur Nucleophiles

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



thioacetal **alkane**

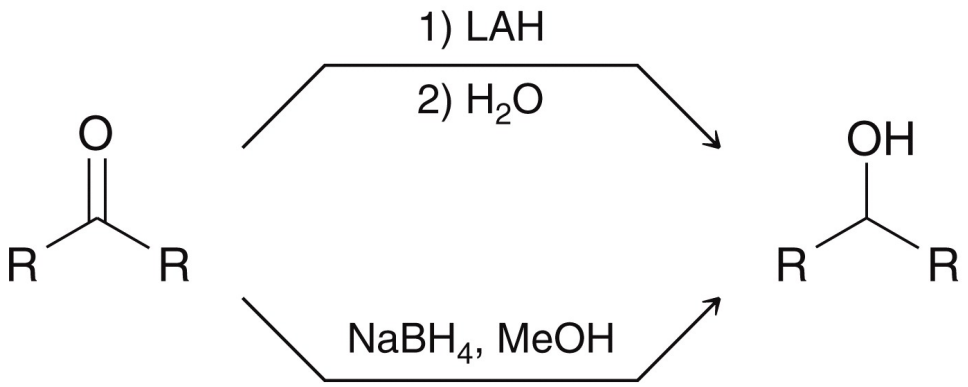
- This allows for another method for reducing a ketone/aldehyde to the corresponding alkane:



ketone **alkane**

19.9 Hydrogen Nucleophiles

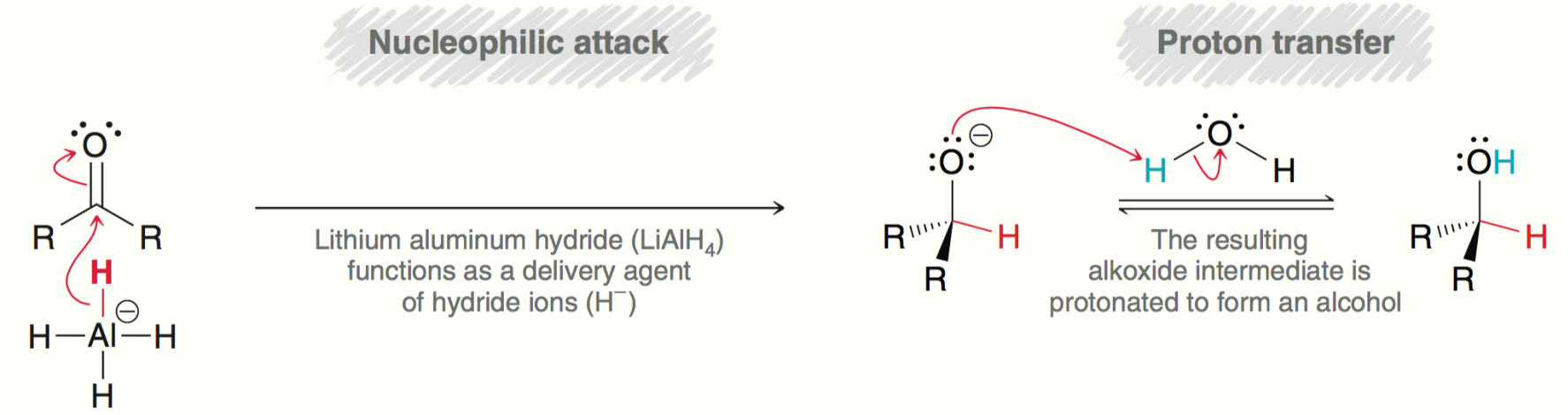
- Recall, aldehydes/ketones reduced to alcohols with a hydride reagent
- $LiAlH_4$ and $NaBH_4$ function as hydride delivery reagents:



- These reductions are **carried out under basic conditions** (hydrides are strong nucleophiles)

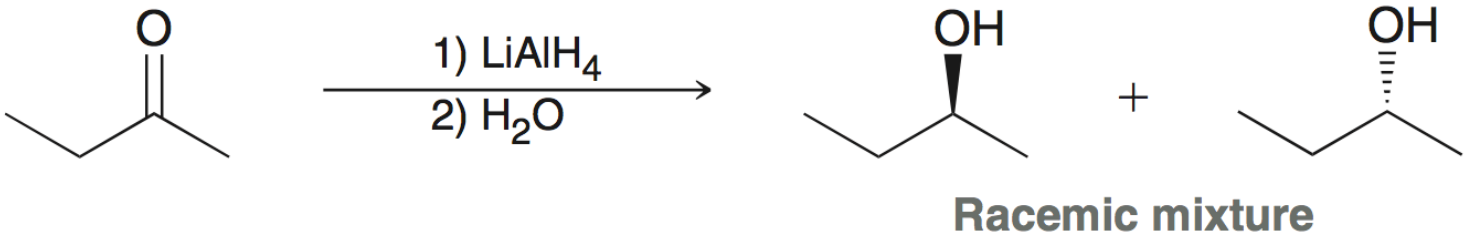
19.9 Hydrogen Nucleophiles

- **Basic conditions, so the first step of the mechanism is nucleophilic attack:**



19.9 Hydrogen Nucleophiles

- Recall, reduction of an **unsymmetrical ketone forms a new chiral center:**



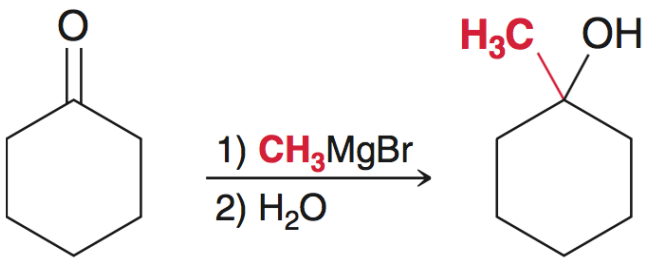
unsymmetrical ketone

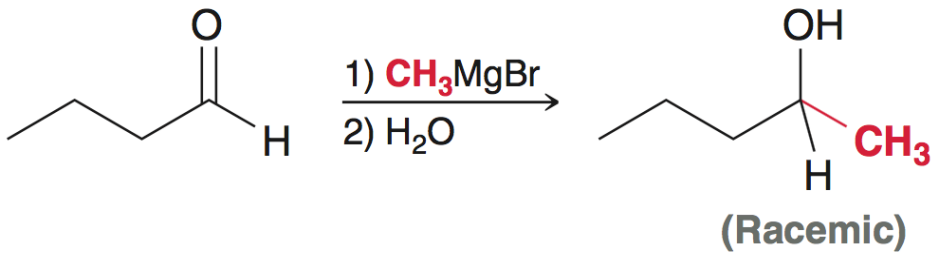
mixture of stereoisomers

- **Practice with Conceptual Checkpoint 19.28-19.29**

19.10 Carbon Nucleophiles

- Recall, grignard reagents attack ketones/aldehydes to make an alcohol, with a new C-C bond:

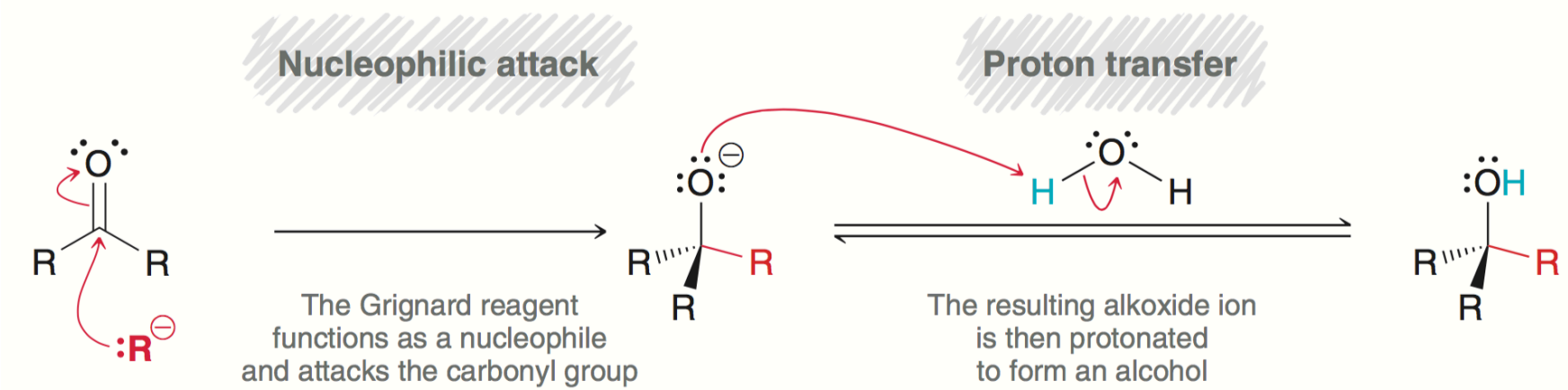




- **Note:** either face of the carbonyl is attacked by the nucleophile, and a new chiral center may result

19.10 Carbon Nucleophiles

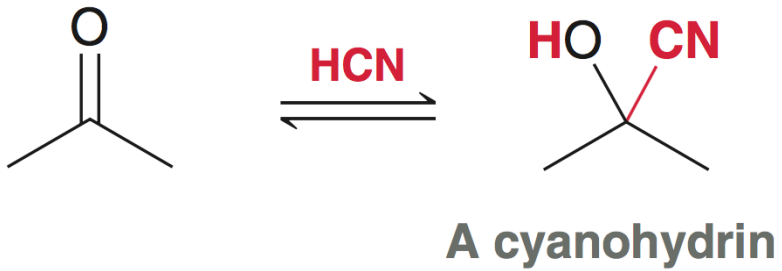
- Recall the mechanism of the Grignard reaction is consistent with **basic conditions** (Grignards are strong nucleophiles/strong bases)



- **Practice with Conceptual Checkpoint 19.30 – 19.31**

19.10 Cyanohydrin Formation

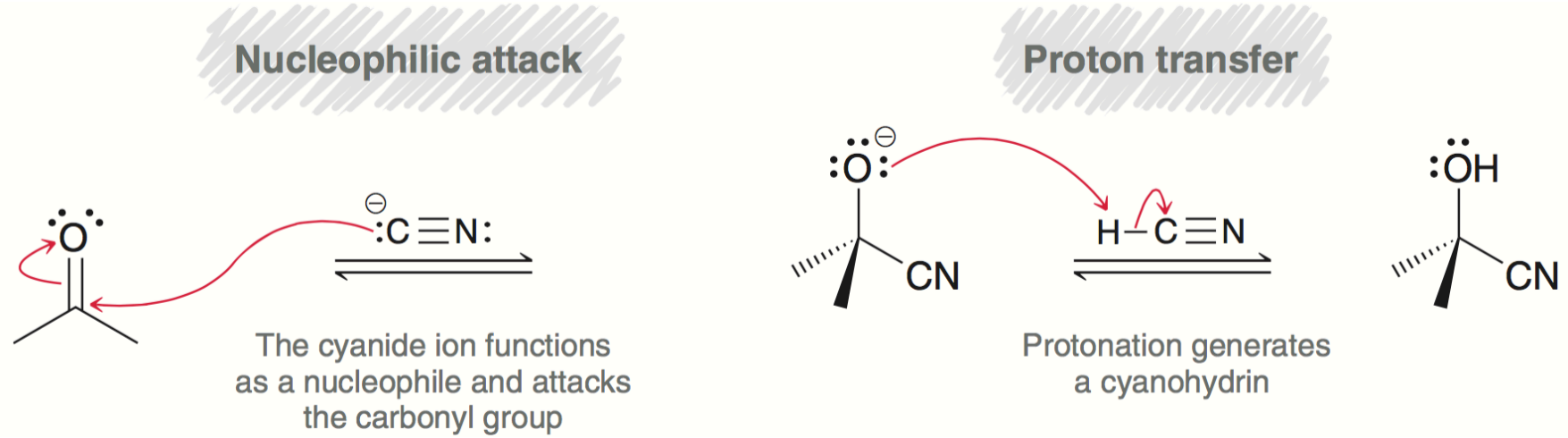
- The cyanide ion is also a carbon-based nucleophile, and reversibly adds to ketones/aldehydes to form a **cyanohydrin**



- This reaction works better under **basic conditions**, and so a catalytic amt of base is usually used

19.10 Cyanohydrin Formation

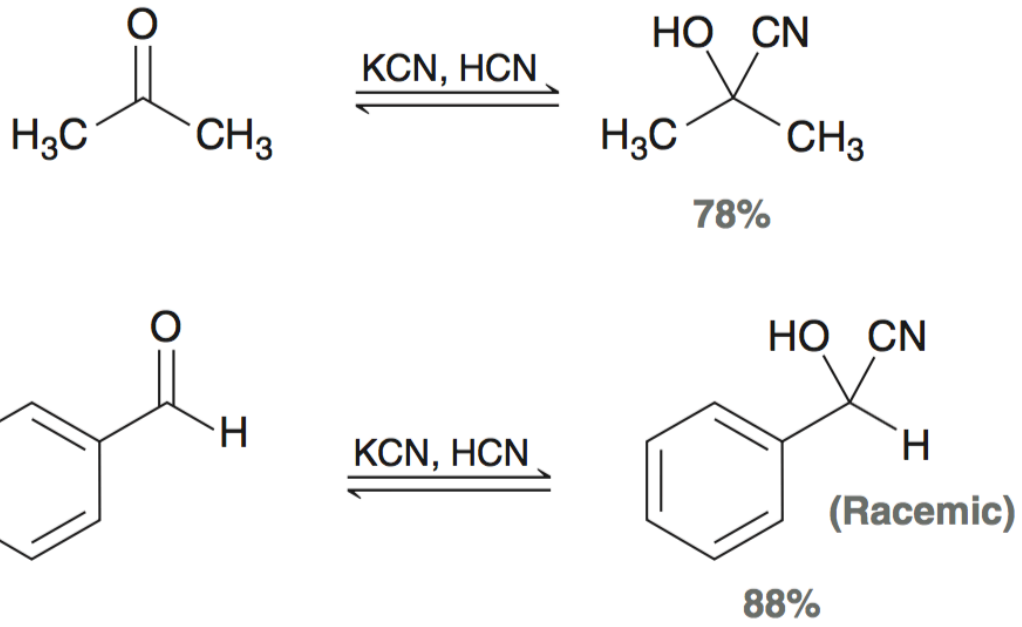
- Mechanism of cyanohydrin formation **under basic conditions**:



- Acidic workup is not necessary since HCN serves as a source of protons

19.10 Cyanohydrin Formation

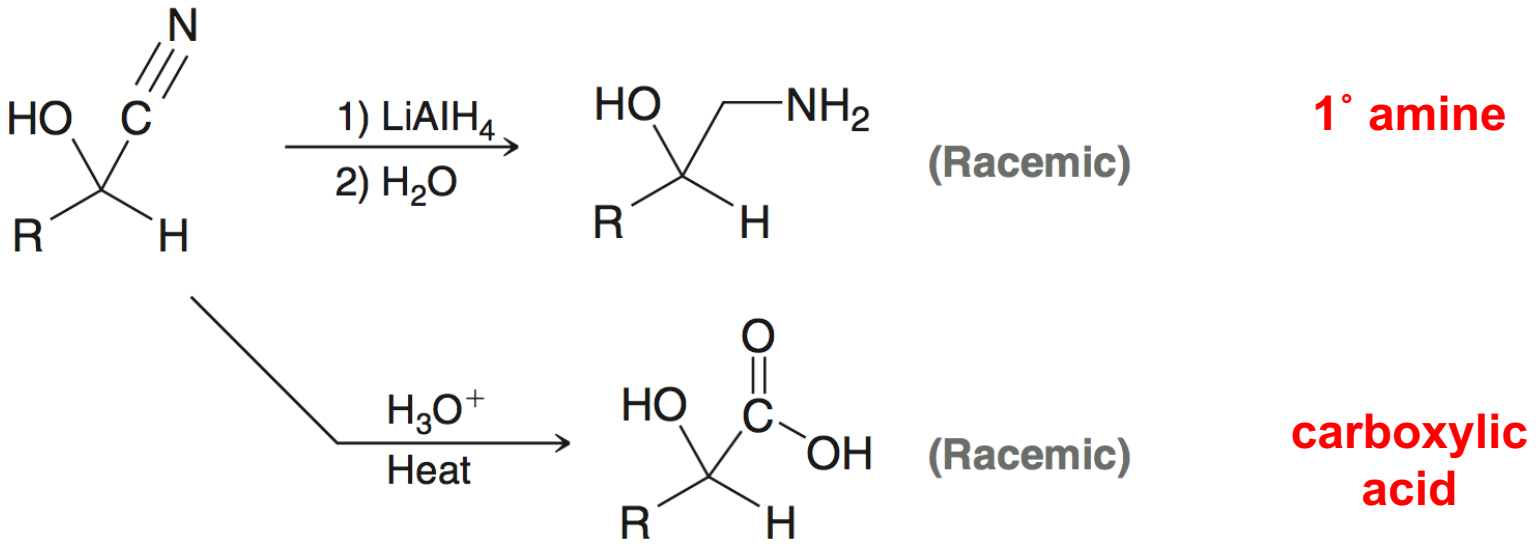
- To achieve basic conditions, KCN is usually added along with HCN.
- In this way, there is more CN^- than H^+



- A new chiral center is possible in this reaction as well

19.10 Cyanohydrin Formation

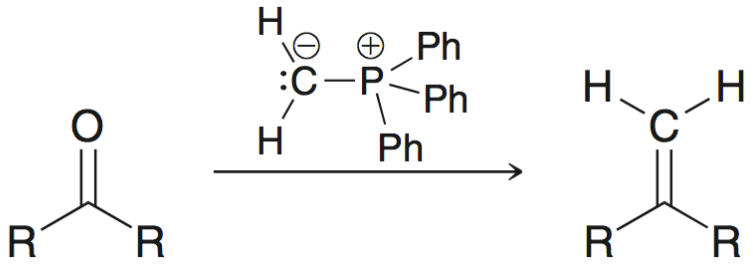
- Installation of a cyano group is advantageous because it can be converted to other functional groups:

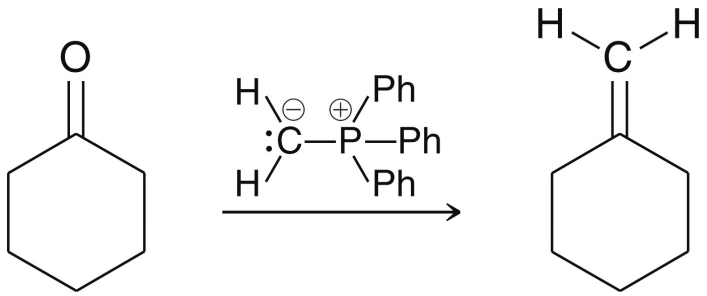


- **Practice with Conceptual Checkpoint 19.32 – 19.33**

19.10 Wittig Reactions

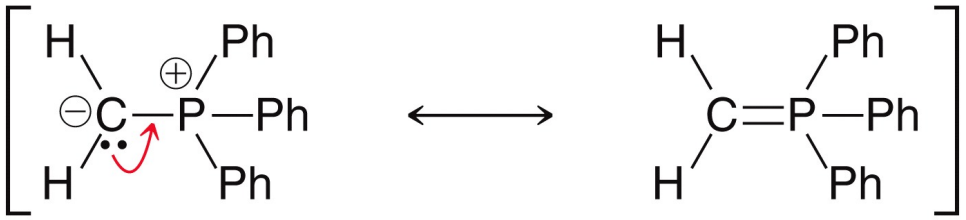
- **The Wittig Reaction is an extremely important reaction in organic chemistry, like Grignard reactions, in that carbon skeleton is modified**
- **Ketone/aldehyde is converted to an alkene**, with the formation of a *new* C=C double bond





19.10 Wittig Reactions

- The **Wittig reagent** is a **phosphorus ylide**, in which a carbon atom acts as the nucleophile

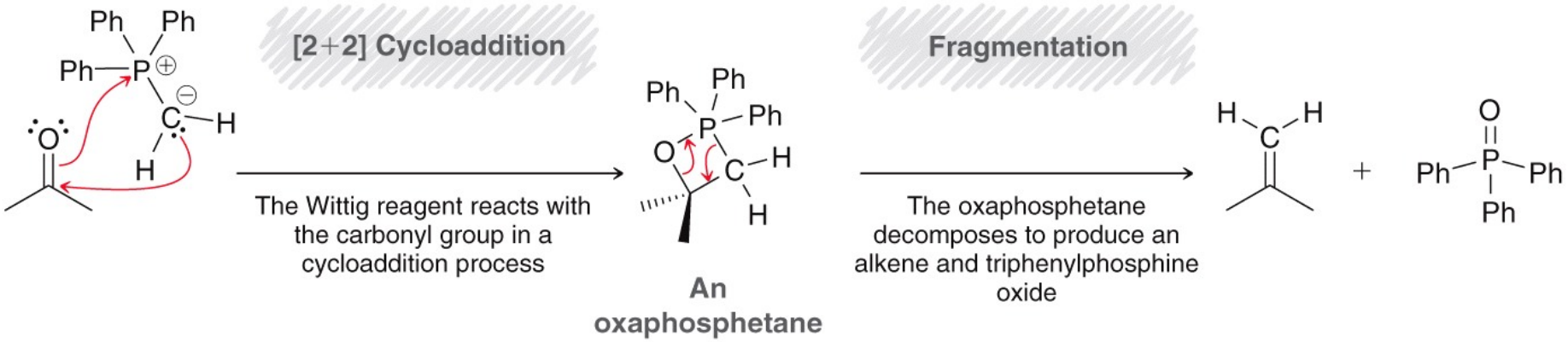


- **Ylide** – neutral compound that contains a negatively charged atom adjacent to a positively charged heteroatom

- The mechanism is likely a 2+2 cycloaddition between the Wittig reagent and the carbonyl group

19.10 Wittig Reactions

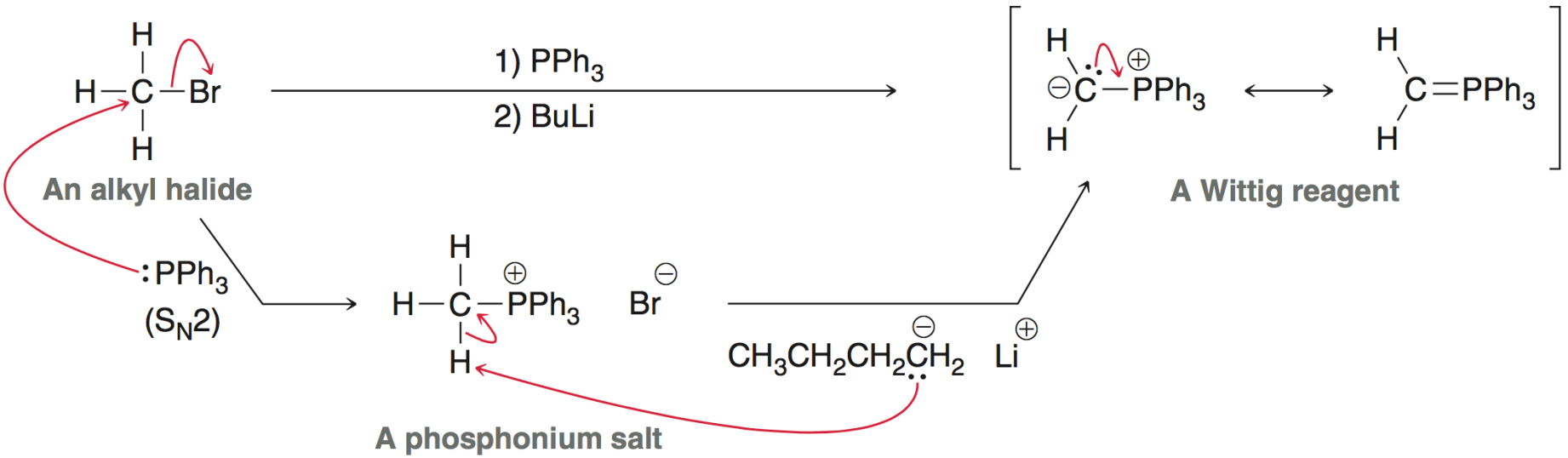
- Wittig reaction mechanism:



- The formation of the especially stable triphenylphoshine oxide byproduct drives the equilibrium to favor the formation of the desired alkene

19.10 Wittig Reactions

- A given Wittig reagent is synthesized in two steps from the corresponding alkyl halide:



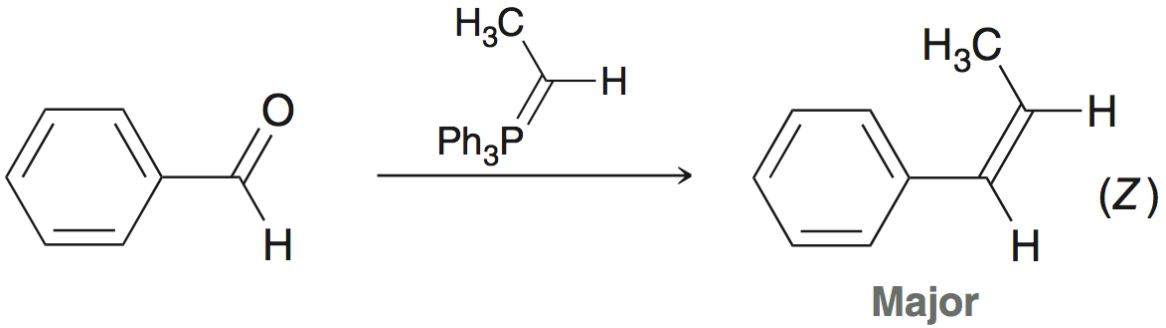
- The first step is SN2 substitution, so 1˚ halides are more easily made into Wittig reagents than 2˚ halides

19.10 Wittig Reactions

- Wittig reaction is particularly useful because it installs a C=C bond at a specific place (carbonyl carbon)

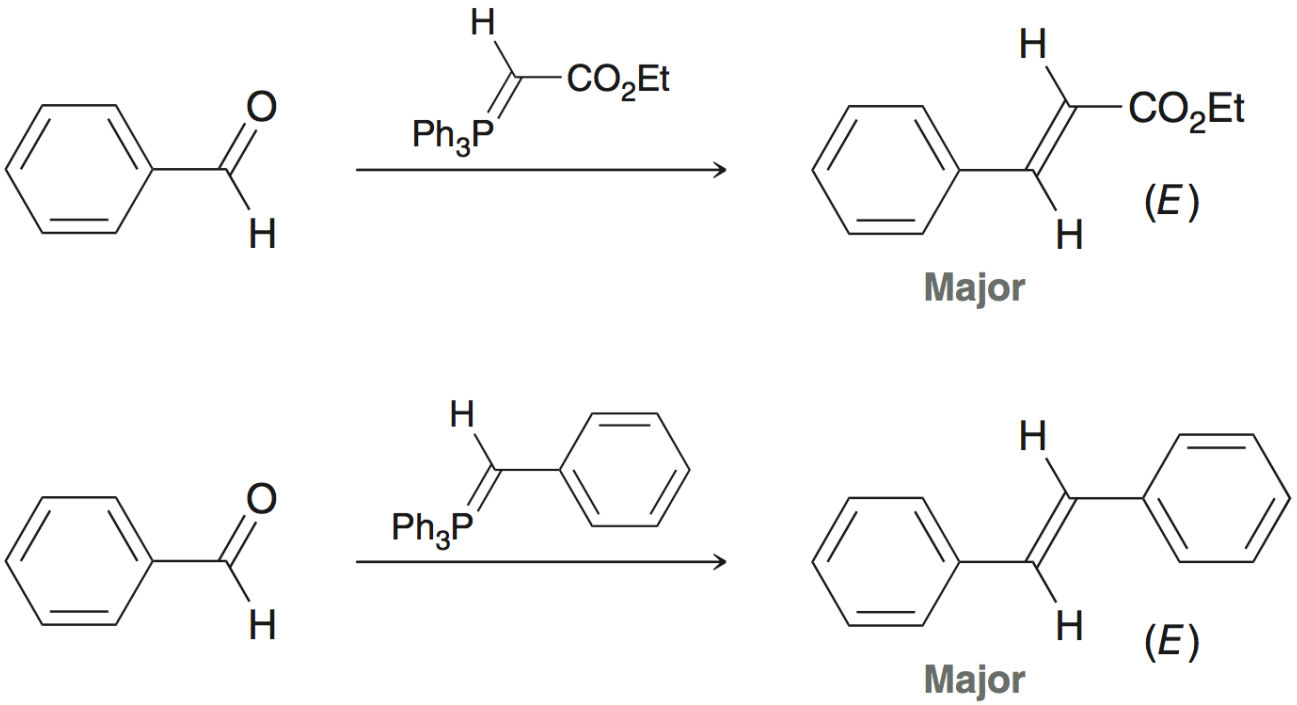
- AND, the **Wittig rxn is stereoselective:**

  - Using a Wittig derived from a simple alkyl halide, the **(Z) alkene is favored**



19.10 Wittig Reactions

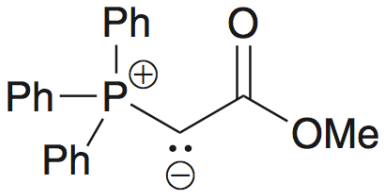
- AND, the **Wittig rxn is stereoselective:**
  - But if the Wittig rgt contains an electron-withdrawing group, the **(*E*) alkene is the major product:**



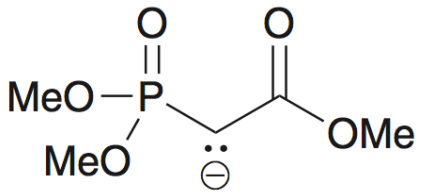
19.10 Wittig Reactions

- But if the Wittig rgt contains an electron-withdrawing group, the **(*E*) alkene is the major product:**
- An electron withdrawing group, or a phenyl ring, delocalizes the anionic charge of the Wittig rgt, stabilizing it.

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



A stabilized Wittig reagent
(resonance-stabilized by ester group)

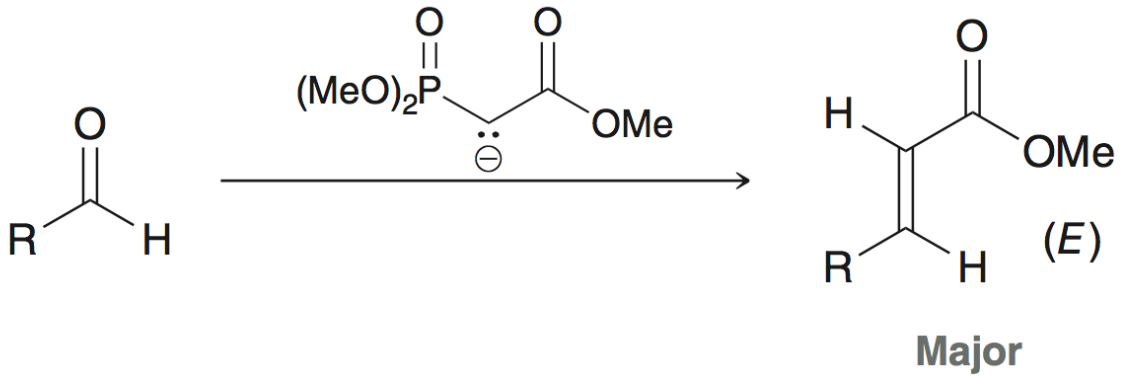


HWE reagent
(a resonance-stabilized phosphonate ester carbanion)

19.10 Wittig Reactions

- Example of an HWE reaction:

HWE reagent gives *E* alkene as major, like a stabilized Wittig rgt does

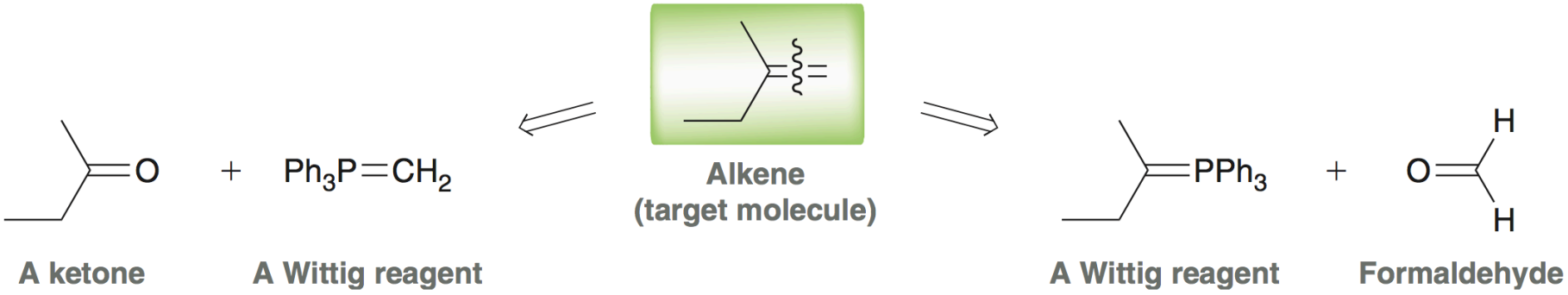


- Choice of solvent and use of Lewis acids can also effect stereoselectivity of Wittig and HWE reactions

- **Practice with SkillBuilder 19.6**

19.10 Wittig and HWE Reactions

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



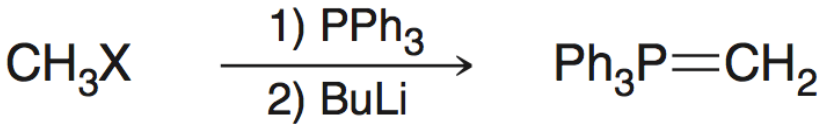
route #1 **route #2**

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

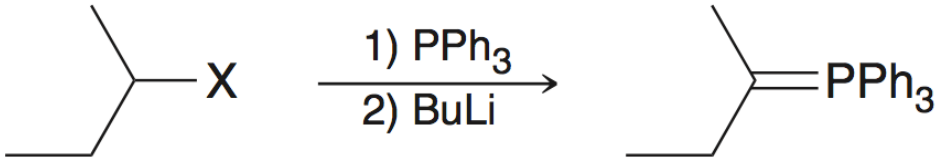
19.10 Wittig and HWE Reactions

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

route #1
methyl halide needed



route #2
2˚ halide needed

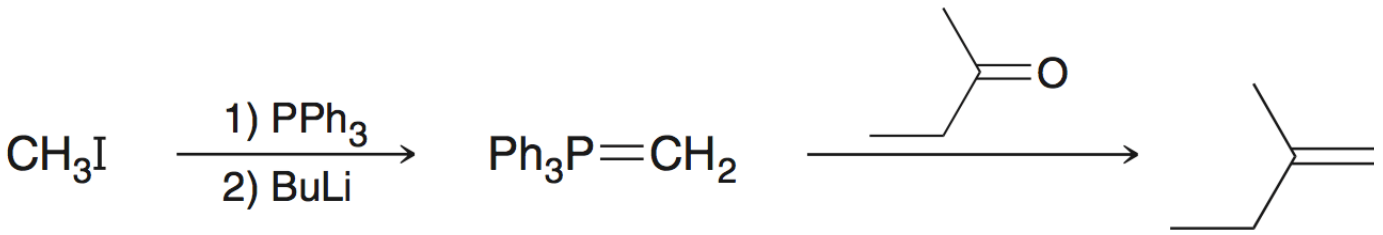


Route #1 is better, since S_N2 reaction with a methyl halide is better than a 2˚ halide

19.10 Wittig and HWE Reactions

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

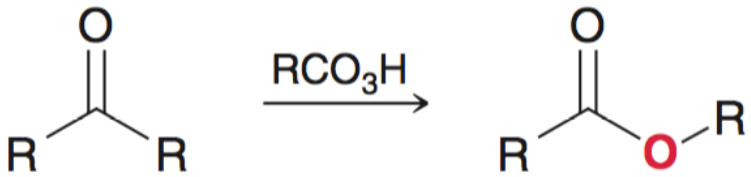
Overall synthesis of the alkene via Wittig reaction:



- **Practice with Conceptual Checkpoint 19.38**

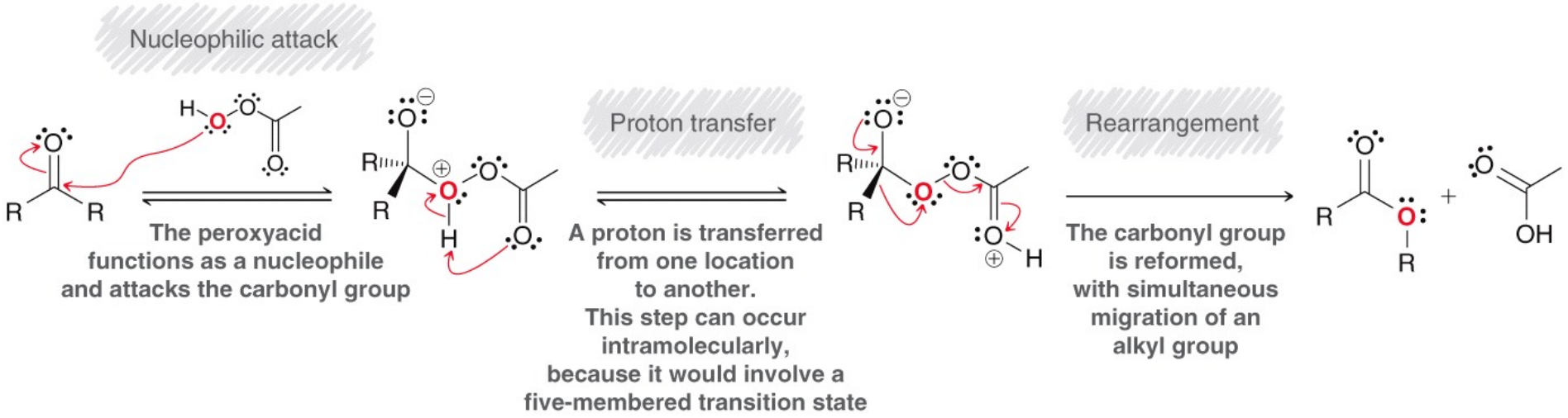
19.11 Baeyer-Villiger Oxidation

- **Baeyer Villiger Oxidation -** An oxygen is inserted into an aldehyde/ketone between a carbonyl carbon and neighboring alkyl group



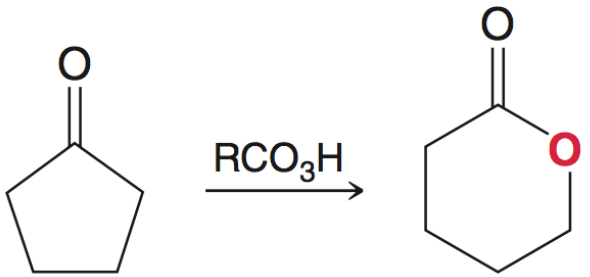
An aldehyde or ketone is converted to a carboxylic acid or ester, respectively

- Mechanism:



19.11 Baeyer-Villiger Oxidation

- Cyclic ketone produces a lactone (i.e. cyclic ester)



A lactone

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

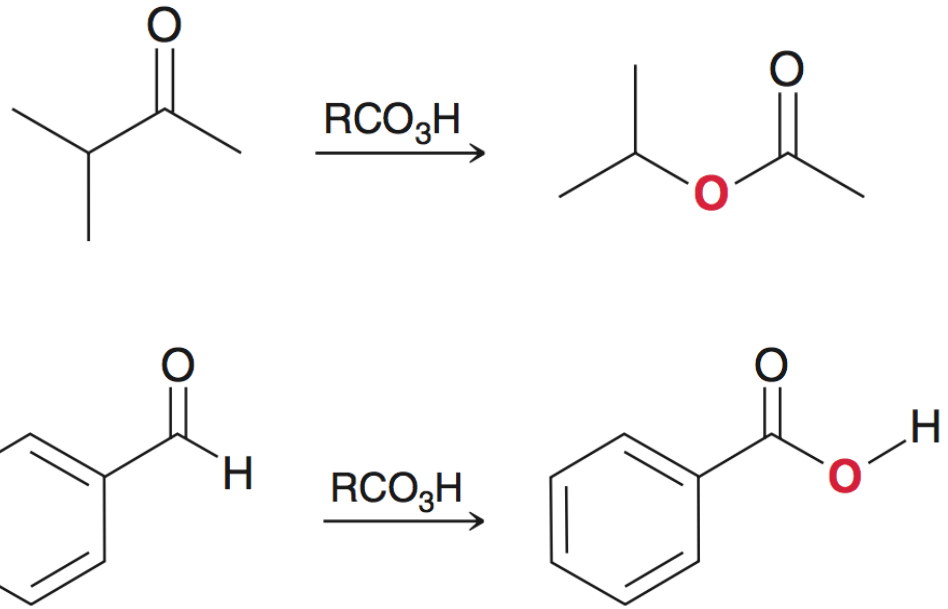
$$H > 3° > 2°, Ph > 1° > methyl$$

- **Use this trend to determine regioselectivity**

19.11 Baeyer-Villiger Oxidation

$$H > 3° > 2°, Ph > 1° > methyl$$

- Use this trend to determine regioselectivity

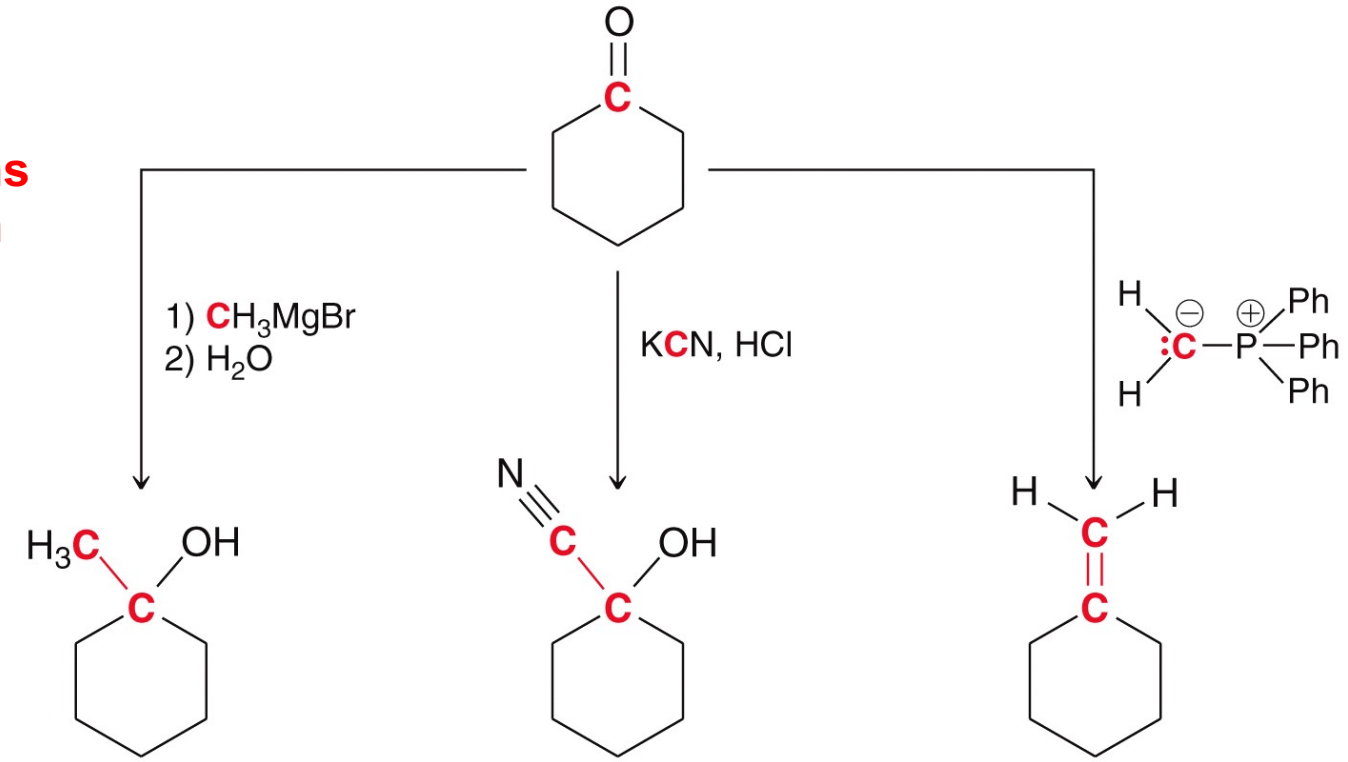


- **Practice with Conceptual Checkpoint 19.39**

19.12 Synthesis Strategies

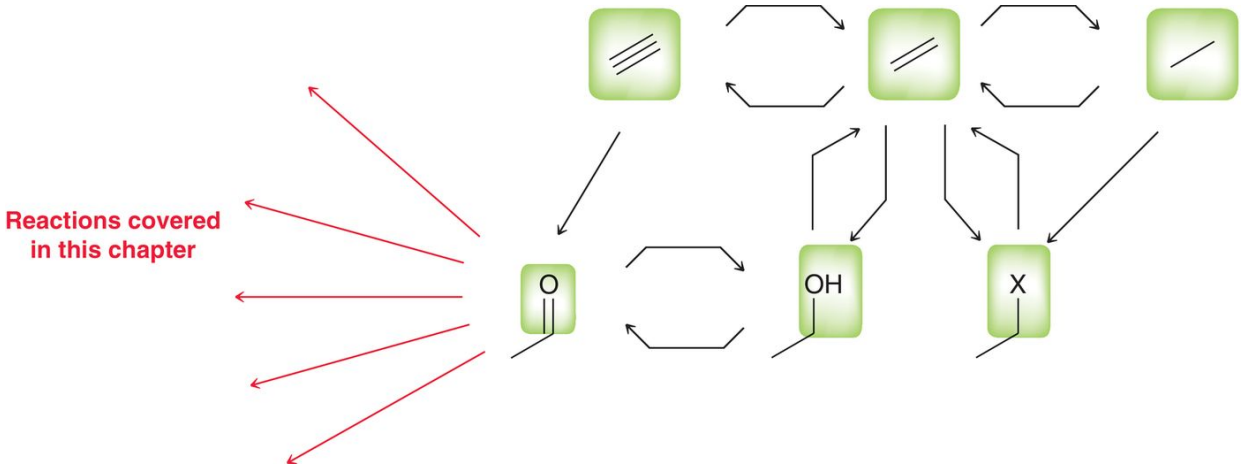
- **Recall the questions we ask when designing a synthesis:**
  1. Is there a change in the carbon skeleton?
  2. Is there a change in the functional group?

One of these reactions will be needed when the carbon skeleton is changed



19.12 Synthesis Strategies

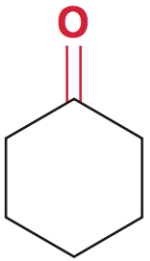
- Should be able to make a list of products that can be made from aldehydes/ketones, and identify the reagents needed:



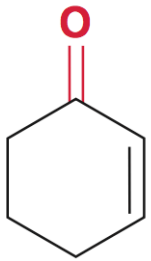
- **Practice with SkillBuilder 19.7**

19.13 Spectroscopic Analysis – IR Signals

- STRONG peak for the C=O stretch

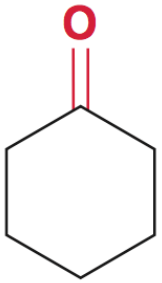


1715 cm^{-1}

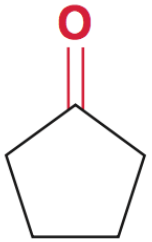


1680 cm^{-1}

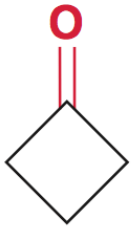
conjugated carbonyls stretch at a lower wavenumber



1715 cm^{-1}



1745 cm^{-1}



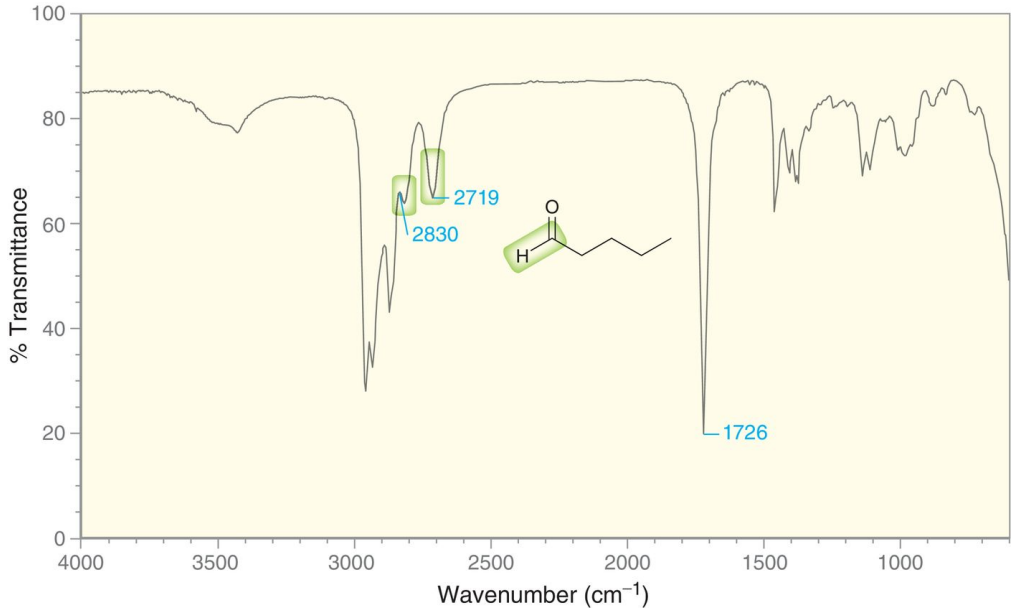
1780 cm^{-1}

increasing ring strain increases The wavenumber

- Aldehydes also give WEAK peaks around 2700-2800 cm^{-1} for the C-H stretch

19.13 Spectroscopic Analysis – IR Signals

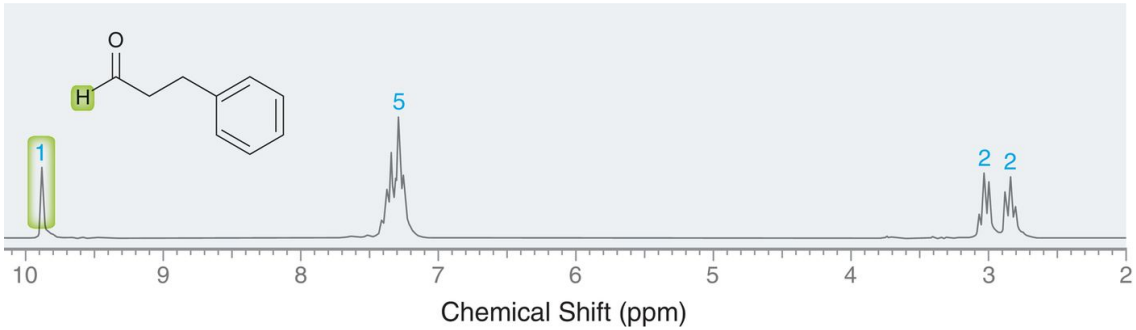
- Aldehydes give a weak absorbance around 2700-2800 cm^{-1} for the carbonyl C-H stretch



19.13 Spectroscopic Analysis – ^{1}H NMR

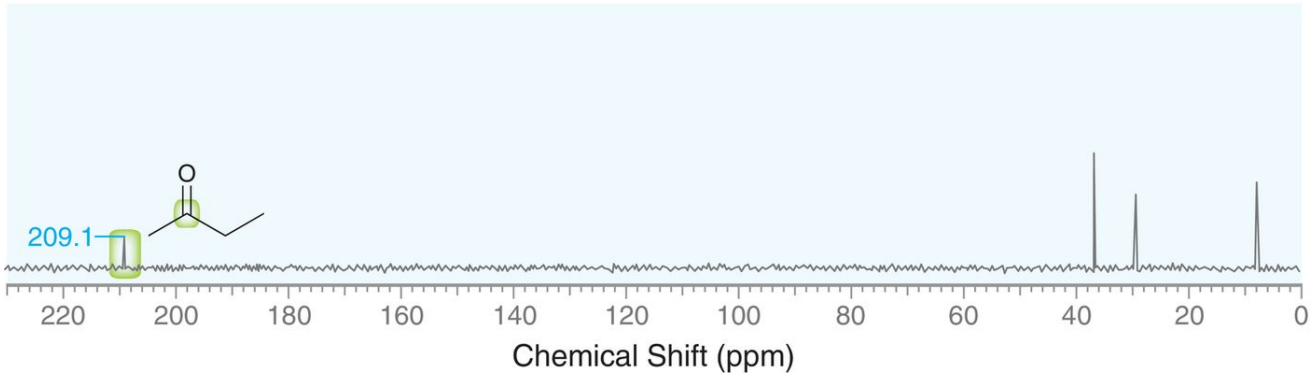
- Protons neighboring a carbonyl are weakly deshielded by the carbonyl group, and appear +1 ppm downfield (chapter 15.5)

- Aldehyde protons are strongly deshielded around 9 or 10 ppm.



19.13 Spectroscopic Analysis – ^{13}C NMR

- Carbonyl carbon produces a weak signal near 200 ppm



- **Practice with Conceptual Checkpoint 19.42**

19.13 Review of Reactions