

CH 310N

T TH 2-3:30

LECTURE 9

Textbook Assignment: Chapter 15 Begin

Homework (for credit): POW 4 posted

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

Notice & Announcements:

Exam I: Grading in Progress

ORGANIC LECTURE SERIES

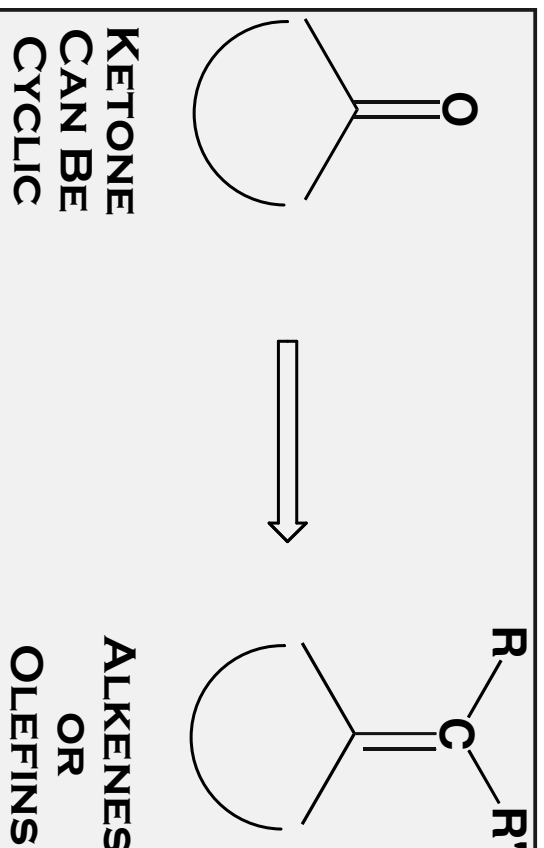
Aldehydes And Ketones

Drawing Mechanisms

- Use double-barbed arrows to indicate the flow of pairs of e^-
- Draw the arrow from higher e^- density to lower e^- density i.e. from the nucleophile to the electrophile
- Removing e^- density from an atom will create a formal + charge
- Adding e^- density to an atom will create a formal - charge
- Proton transfer is fast (kinetics) and usually reversible

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Overall Synthetic Transformation of Wittig Reagents & Its Variations

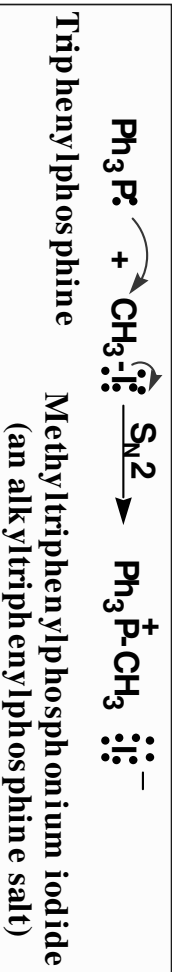


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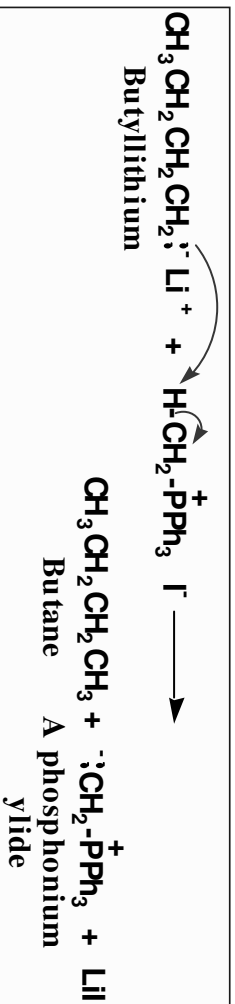
Phosphonium ylides

Phosphonium ylides are formed in two steps:

Step 1: nucleophilic displacement of iodine by triphenylphosphine



Step 2: treatment of the phosphonium salt with a very strong base, most commonly BuLi, NaH, or NaNH₂

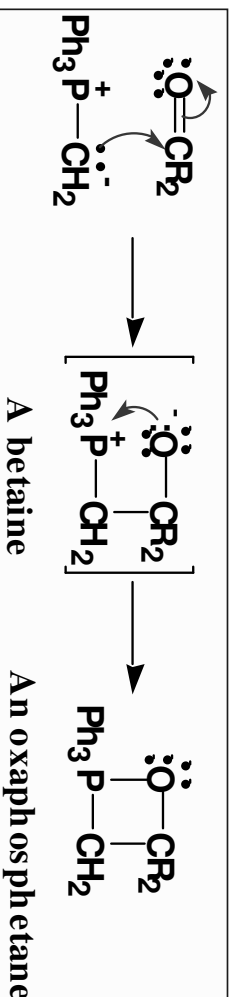


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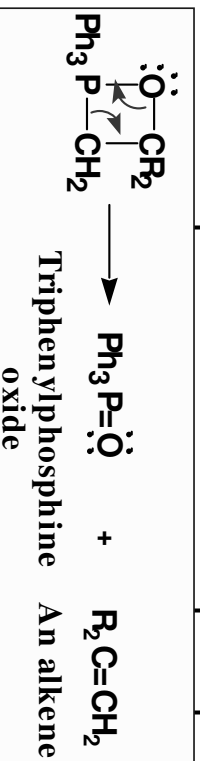
Wittig Reaction

Phosphonium ylides react with the C=O group of an aldehyde or ketone to give an alkene

Step 1: nucleophilic addition of the ylide to the electrophilic carbonyl carbon

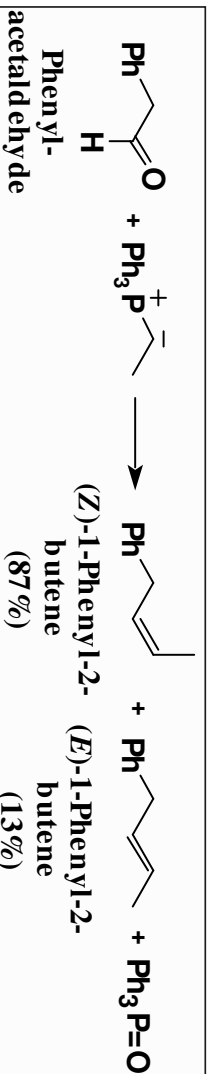
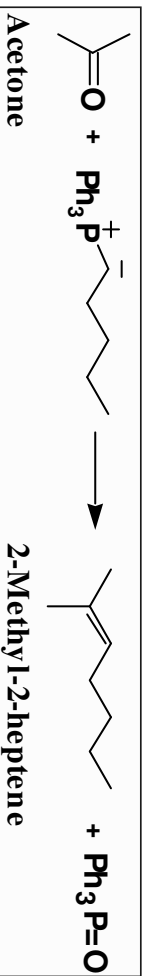


Step 2: decomposition of the oxaphosphetane

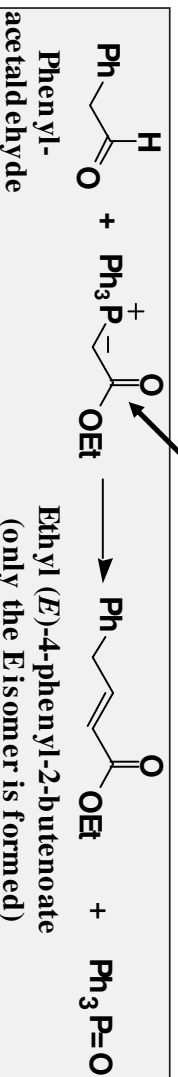


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Wittig Reaction



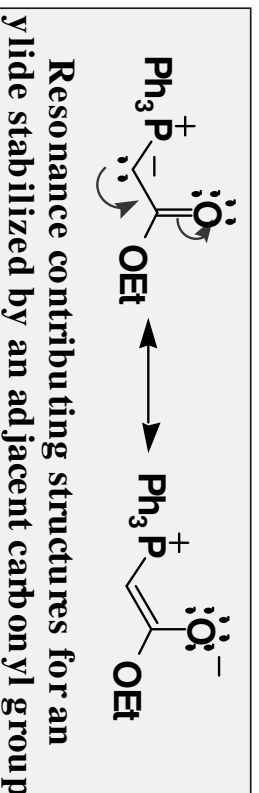
Resonance stabilized Wittig reagent:



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Wittig Reaction

- some Wittig reactions are Z selective, others are E selective
- Wittig reagents with an anion-stabilizing group, such as a carbonyl group, adjacent to the negative charge are generally E selective



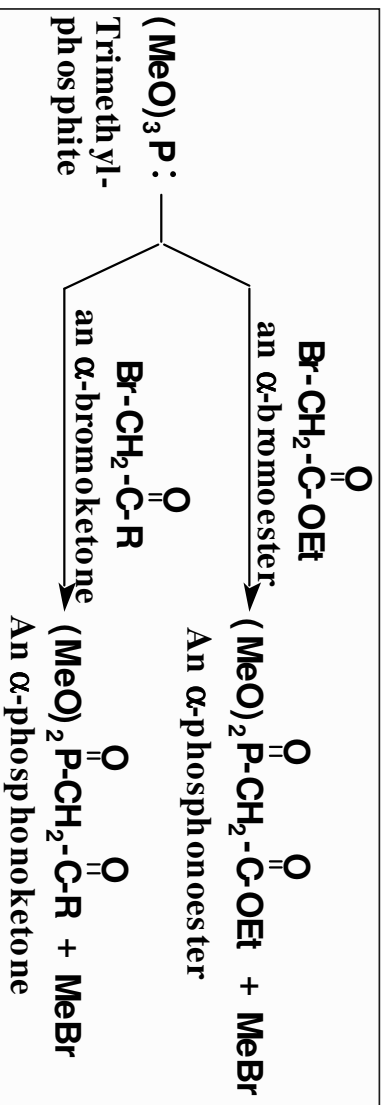
- Wittig reagents without an anion-stabilizing group are generally Z selective (cis)

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A Variant of the Wittig Reagent

Horner-Emmons-Wadsworth modification

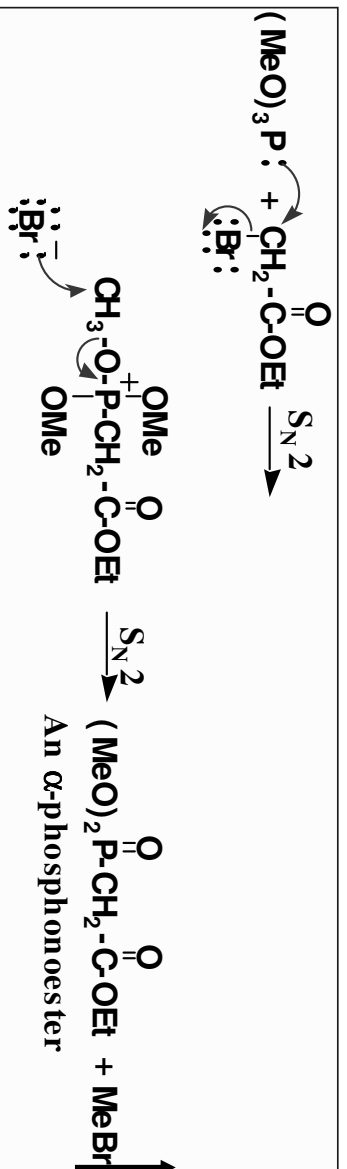
– uses a **phosphonoester**



These reagents are usually isolated.

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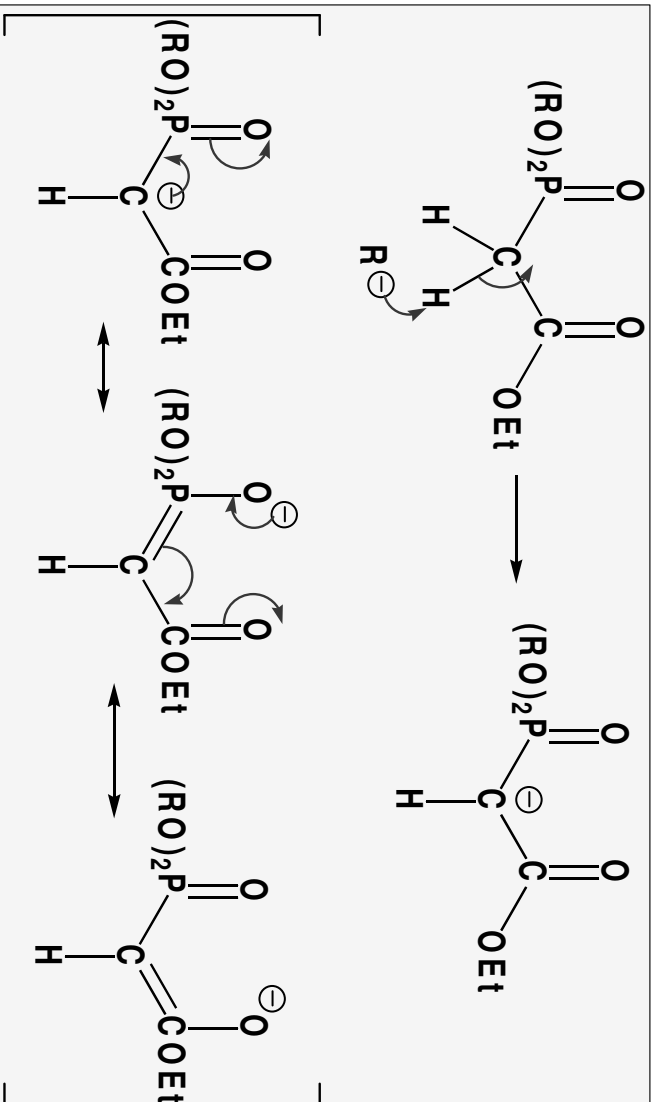
–phosphonoesters are prepared by successive $\text{S}_{\text{N}}2$ reactions



Very exothermic as MeBr is boiled from the reaction mixture

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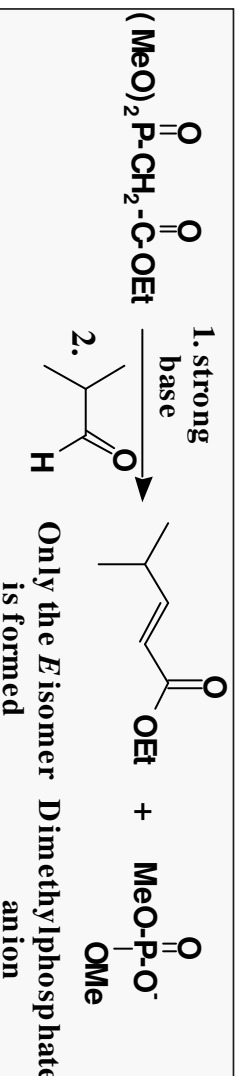
Resonance Stabilization:



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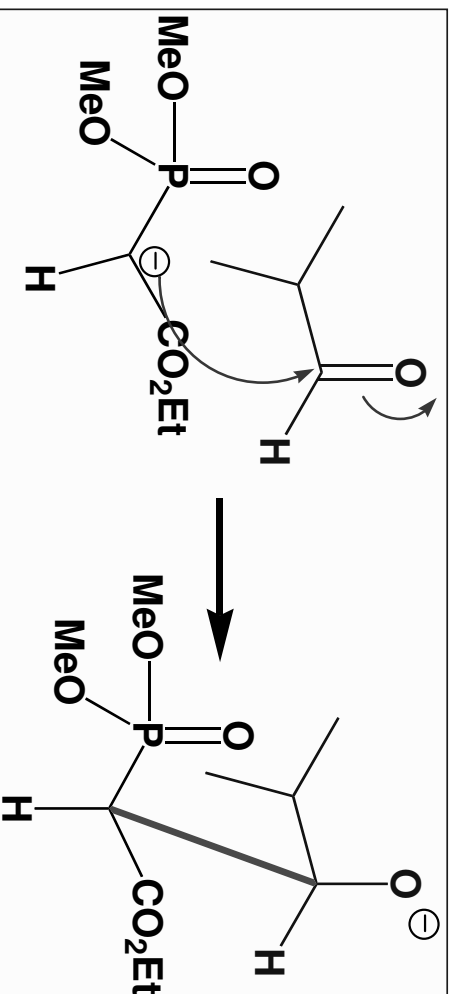
The Use of Phosphonoesters

1. treatment of a phosphonoester with a strong base followed by an aldehyde or ketone gives an alkene
2. a particular value of using a phosphonoester-stabilized anion is that they are almost exclusively *E* selective



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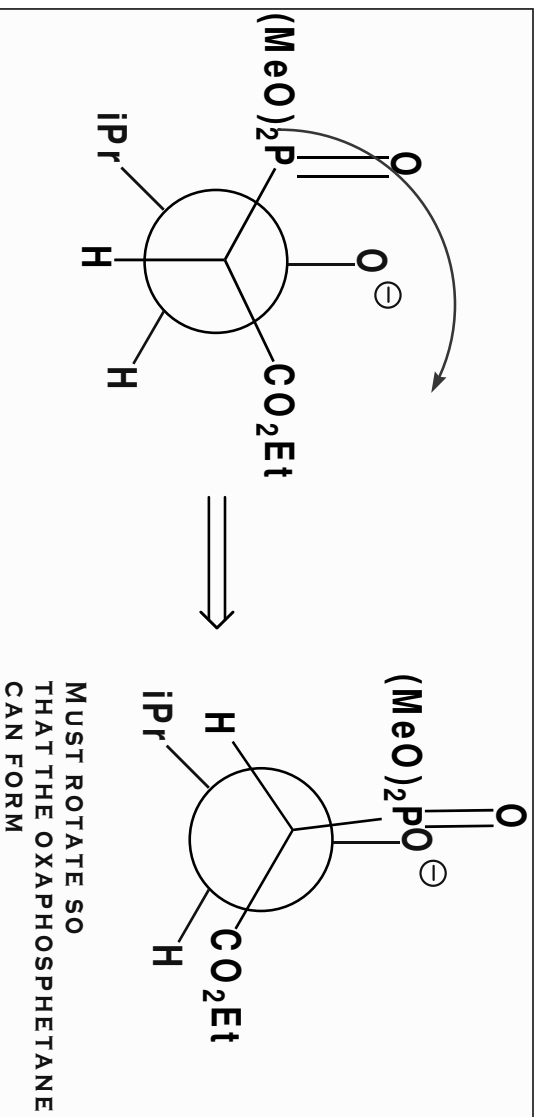
Why do Stabilized Horner-Emmons-Wadsworth Reagents give the E olefin?



Psst...
He will ask
this

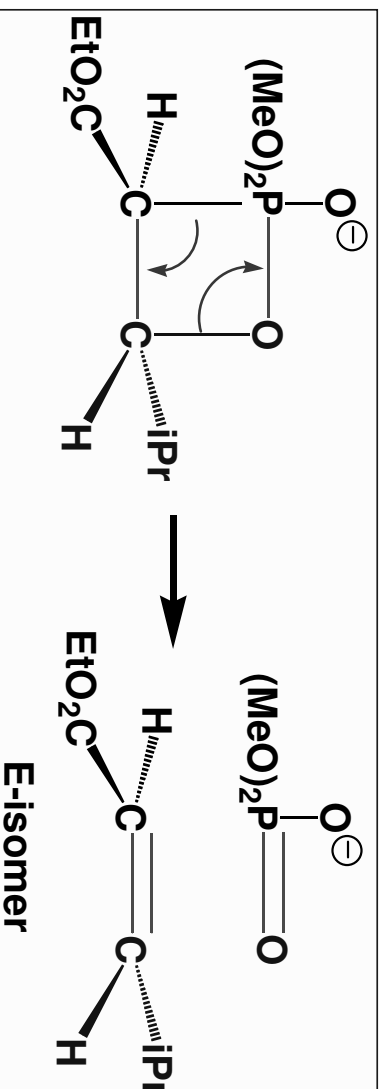
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Why do Stabilized Horner-Emmons-Wadsworth Reagents give the E olefin?



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Why do Stabilized Horner-Emmons-Wadsworth Reagents give the E olefin?

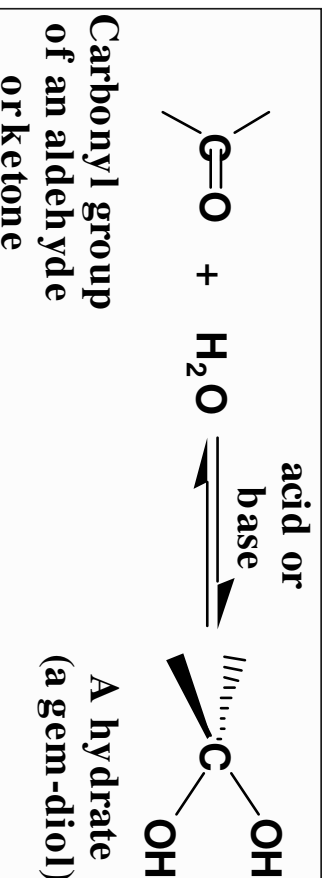


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Addition of H₂O to Carbonyls

Addition of water (**hydration**) to the carbonyl group of an aldehyde or ketone gives a geminal diol, commonly referred to a gem-diol

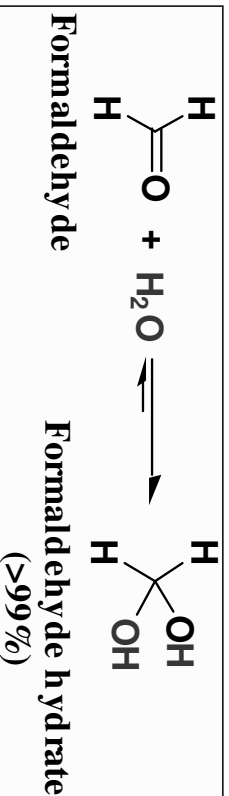
– gem-diols are also referred to as **hydrates**



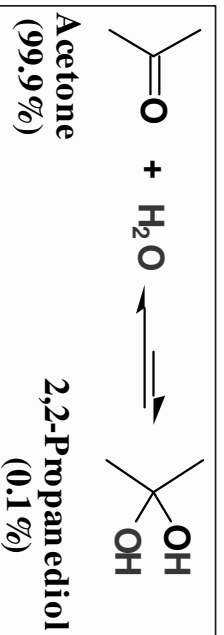
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Addition of H₂O to Carbonyls

– when formaldehyde (*g*) is dissolved in water at 20 °C, the carbonyl group is more than 99% hydrated



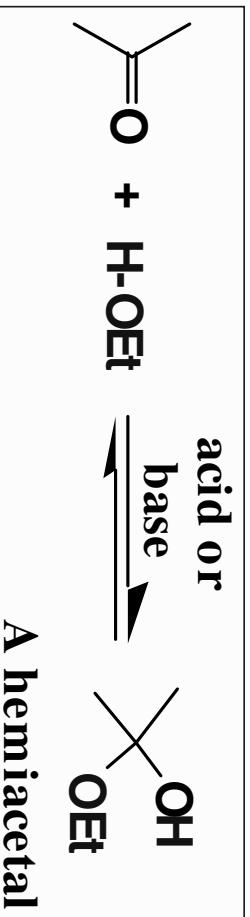
– the equilibrium concentration of a hydrated ketone is considerably smaller



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Addition of Alcohols to Carbonyls

- Addition of one molecule of alcohol to the C=O group of an aldehyde or ketone gives a hemiacetal
- **Hemiacetal:** a molecule containing an -OH and an -OR or -OAr bonded to the same carbon



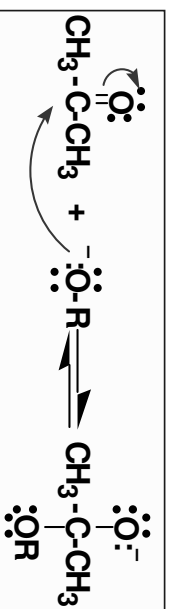
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Formation of a hemiacetal-- base catalyzed

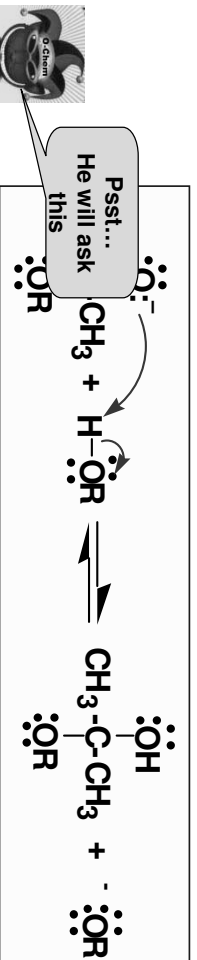
- Step 1: proton transfer from HOR gives an alkoxide



- Step 2: attack of RO⁻ on the carbonyl carbon



- Step 3: proton transfer from the alcohol to O⁻ gives the hemiacetal and generates a new base catalyst



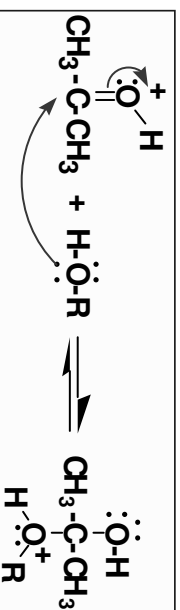
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Formation of a hemiacetal --acid catalyzed

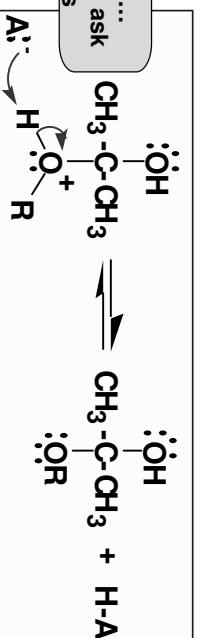
- Step 1: proton transfer to the carbonyl oxygen



- Step 2: attack of ROH on the carbonyl carbon



- Step 3: proton transfer from the oxonium ion to A⁻ gives the hemiacetal and generates a new acid catalyst



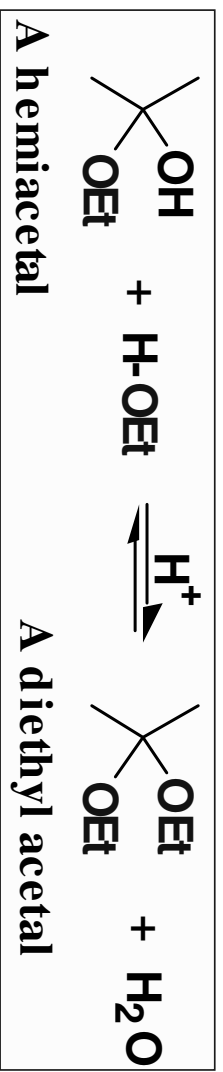
Psst...
He will ask
this

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Addition of Alcohols to Carbonyls

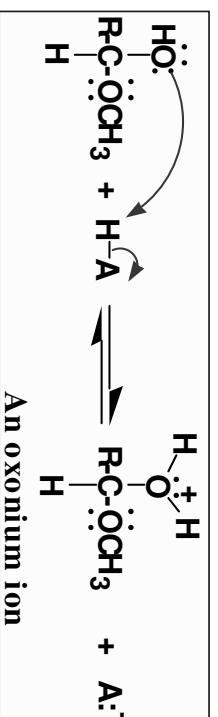
- Hemiacetals react with alcohols to form acetals

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

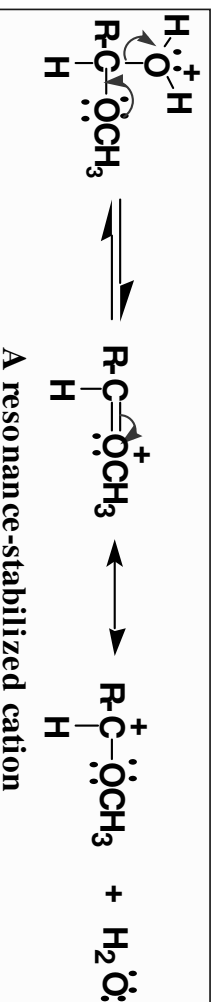


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Step 1: proton transfer from HA gives an oxonium ion

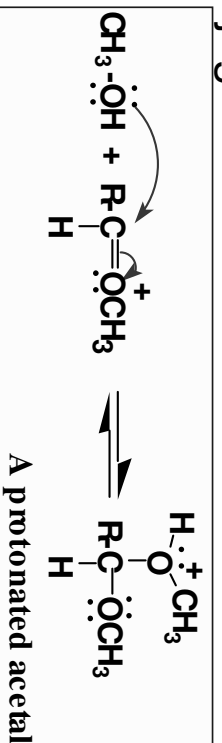


Step 2: loss of water gives a resonance-stabilized cation

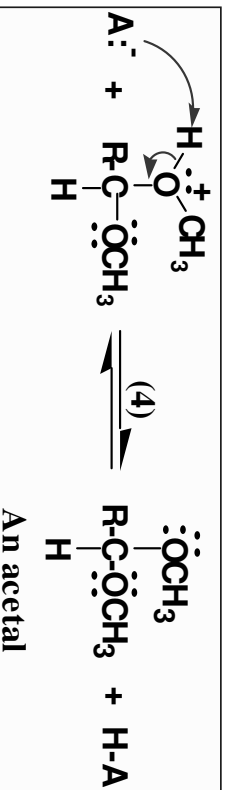


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Step 3: reaction of the cation (an electrophile) with methanol (a nucleophile) gives the conjugate acid of the acetal



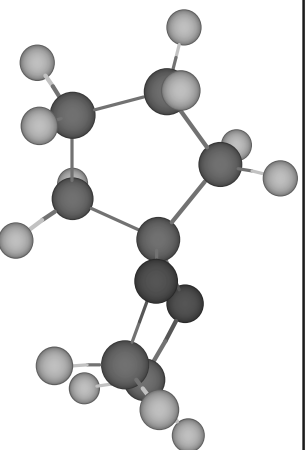
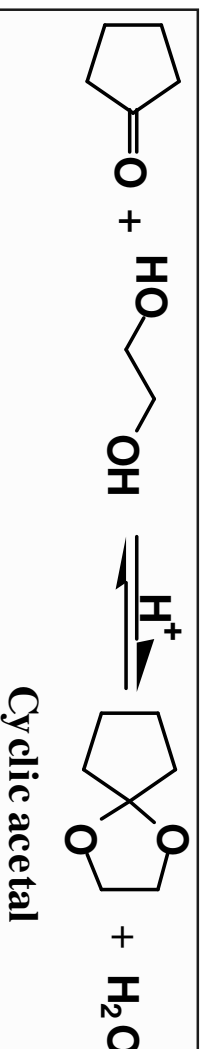
Step 4: proton transfer to A⁻ gives the acetal and generates a new acid catalyst



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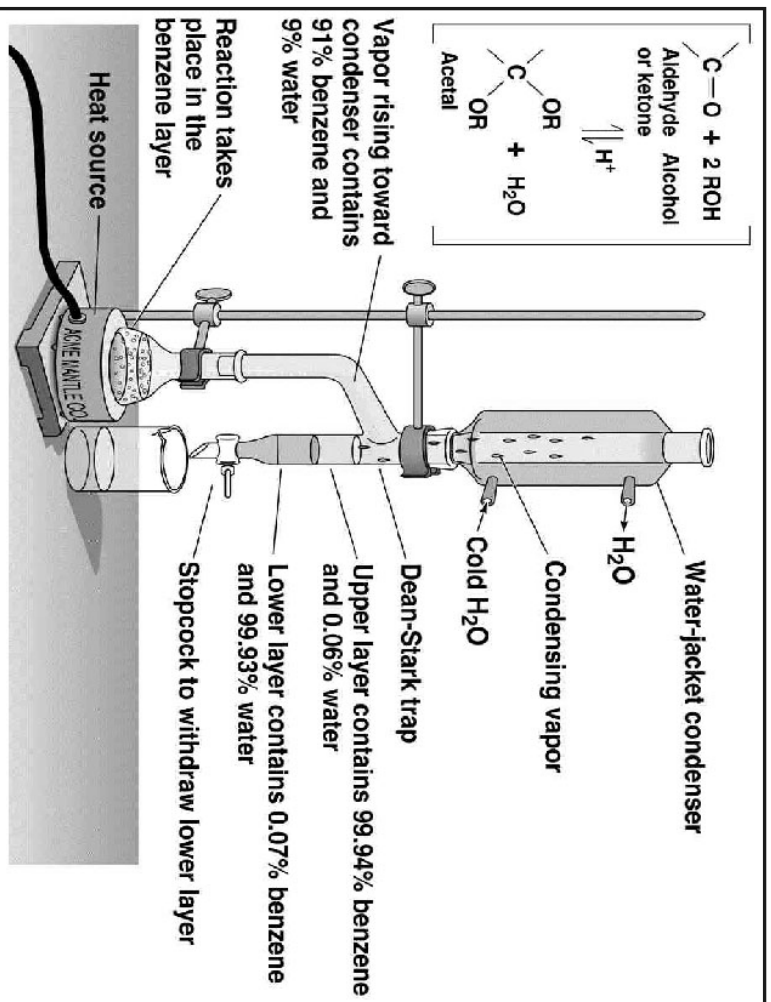
Addition of Alcohols to Carbonyls

- with ethylene glycol and other glycols, the product is a five-membered cyclic acetal
- this a method of “protecting” ketones



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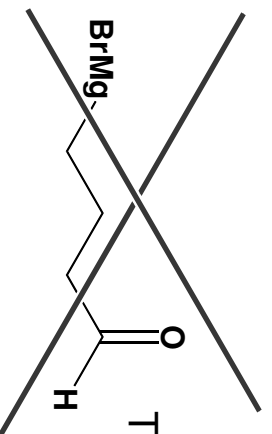
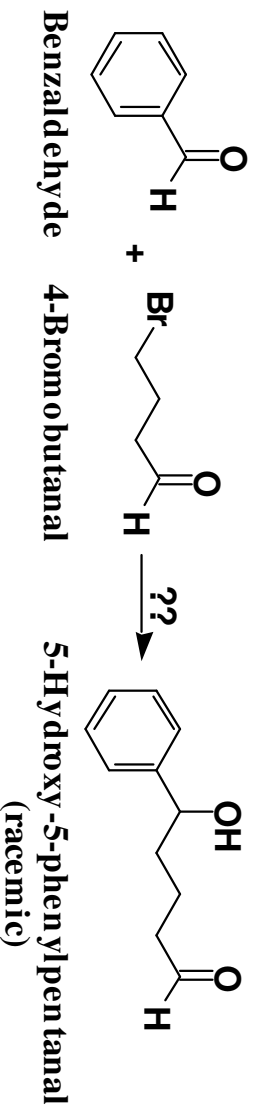
Dean-Stark Trap



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Acetals as Protecting Groups

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



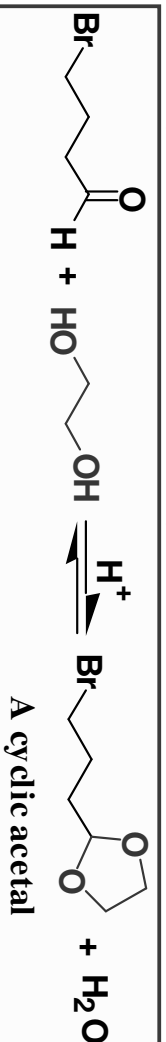
This Grignard cannot be made!!

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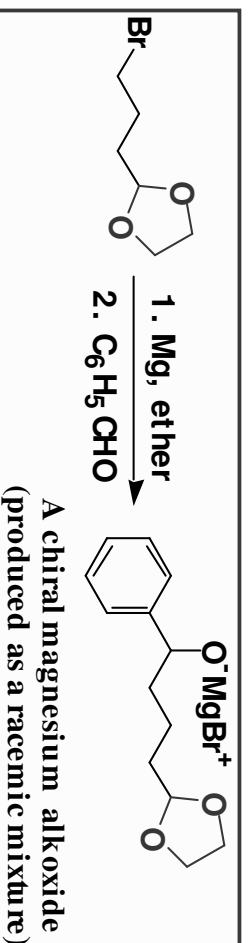
Acetals as Protecting Groups

- a Grignard reagent prepared from 4-bromobutanol will self-destruct (**decompose**).

– first protect the -CHO group as an acetal:



– then prepare the Grignard reagent:

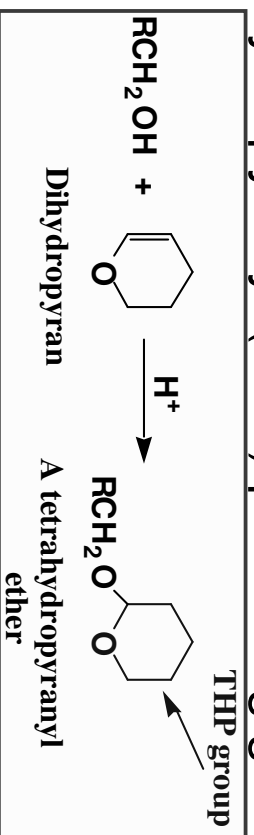


– hydrolysis (not shown) gives the target molecule

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Acetals as Protecting Groups

- Tetrahydropyranyl (THP) protecting group

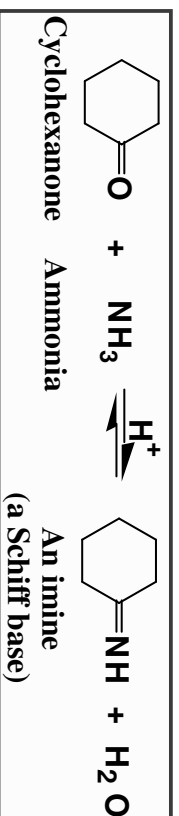
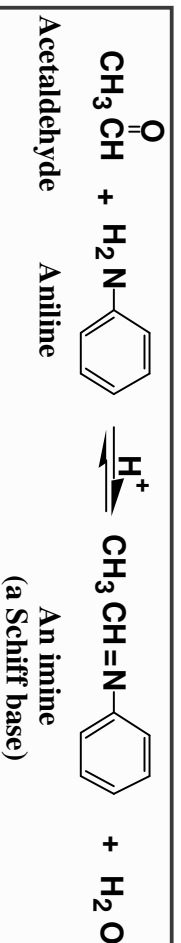


- the THP group is an acetal and, therefore, stable to neutral and basic solutions, and to most oxidizing and reducing agents
- it is removed by acid-catalyzed hydrolysis

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Addition of Nitrogen Nucleophiles

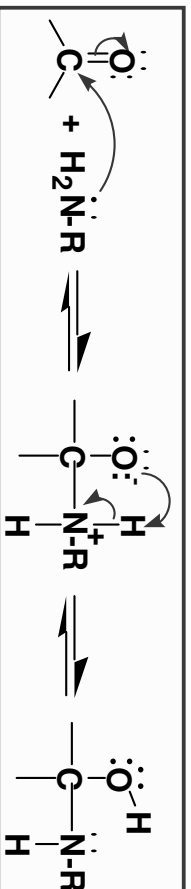
- Ammonia, 1° aliphatic amines, and 1° aromatic amines react with the C=O group of aldehydes and ketones to give **imines** (Schiff bases)
- Water is removed by Dean-Stark trap or chemical dehydration (e.g. molecular sieves)



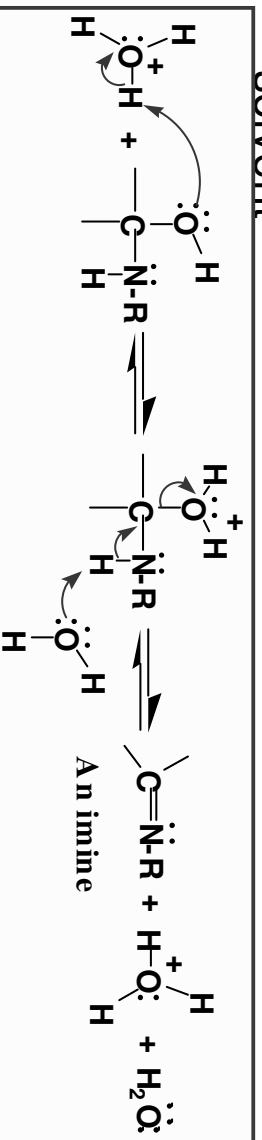
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Addition of Nitrogen Nucleophiles

- Formation of an imine occurs in two steps
- Step 1: carbonyl addition followed by proton transfer

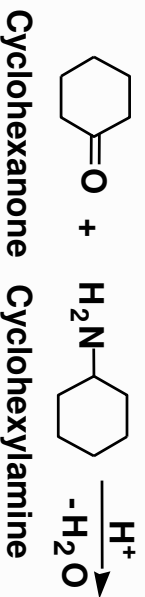


Step 2: loss of H_2O and proton transfer to solvent

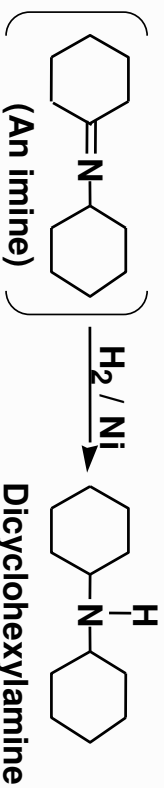


Addition of Nitrogen Nucleophiles

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



Cyclohexanone Cyclohexylamine



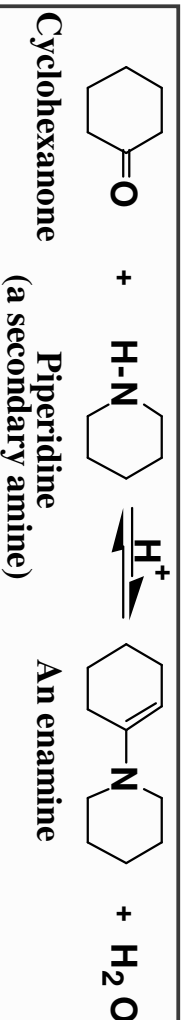
Dicyclohexylamine

Does not have to be isolated

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Addition of Nitrogen Nucleophiles

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



Cyclohexanone

Piperidine

(a secondary amine)

An enamine

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

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