Nitrogen Based
Carbonyl Reactions

*Some reactions of aldehydes and ketones progress beyond the nucleophilic addition stage*

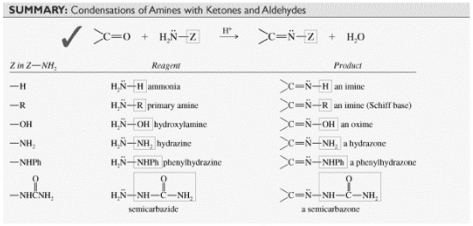
Acetal formation

Imines

Compounds related to imines

Enamines

The Wittig reaction




Enamine from 2° amines

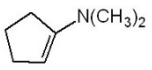
## Question

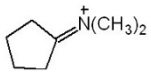
- The compound below is best classified as a(n)
  $(CH_3)_3CCH_2CH{=}NCH_3$

- A) carbinolamine.
- B) enamine.
- C) hydrazone.
- D) imine.

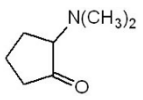
## Question

- Identify the product isolated when cyclopentanone reacts with dimethyl amine.

- A) 

B) 

- C) 

D) 


The Wittig Reaction

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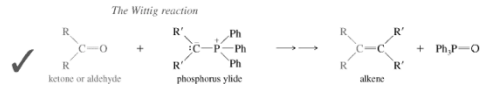
The Wittig reaction




*The Wittig Reaction*

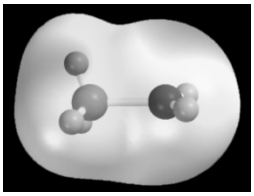
Synthetic method for preparing alkenes.

One of the reactants is an aldehyde or ketone.

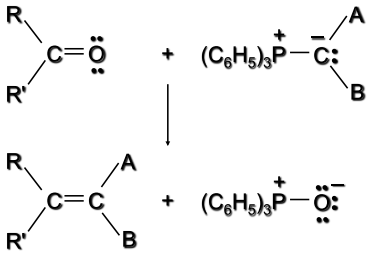
The other reactant is a phosphorus ylide.

A key property of ylides is that they have a negatively polarized carbon and are nucleophilic.

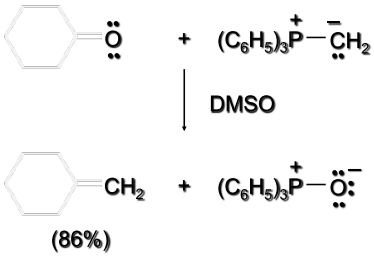
*Charge distribution in a ylide*



*The Wittig Reaction*



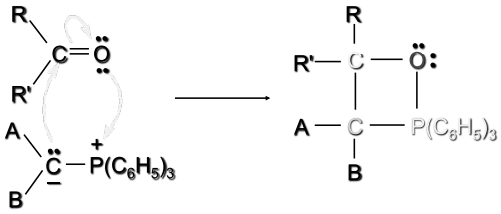
*Example*




dimethyl sulfoxide (DMSO) or tetrahydrofuran (THF) is the customary solvent

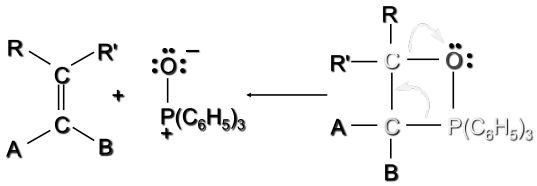
## Mechanism

Step 1



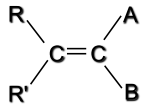
## Mechanism

Step 2



Alkene Synthesis via
the Wittig Reaction

## Retrosynthetic Analysis

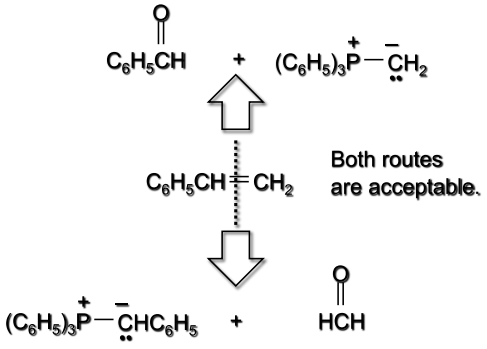


There will be two possible Wittig routes to an alkene.

Analyze the structure retrosynthetically.

Disconnect the doubly bonded carbons. One will come from the aldehyde or ketone, the other from the ylide.

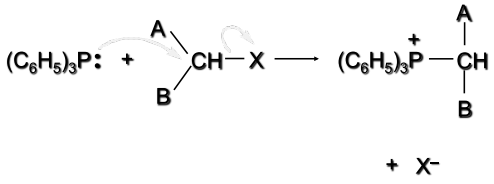
## Retrosynthetic Analysis of Styrene




## Preparation of Ylides

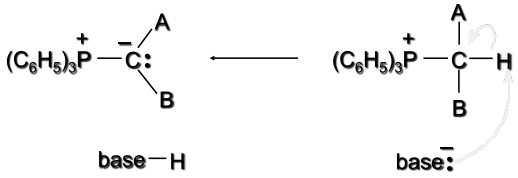
Ylides are prepared from alkyl halides by a two-stage process.

The first step is a nucleophilic substitution. Triphenylphosphine is the nucleophile.



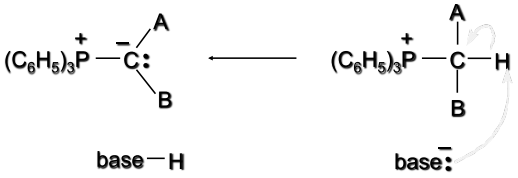
## *Preparation of Ylides*

In the second step, the phosphonium salt is treated with a strong base in order to remove a proton from the carbon bonded to phosphorus.

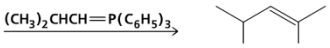



## *Preparation of Ylides*

Typical strong bases include organolithium reagents (RLi), and the conjugate base of dimethyl sulfoxide as its sodium salt [$NaCH_2S(O)CH_3$].




The object of this exercise is to recognize fragments in the product that imply particular starting materials. Click "Start" to begin.



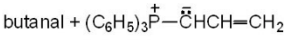


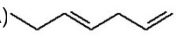
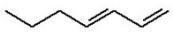
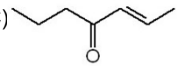
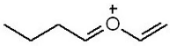

Start

http://chemconnections.org/organic/Movies%20Org%20Flash/flash-carbonyls-wade%2018%2622/wittig.swf

## Question

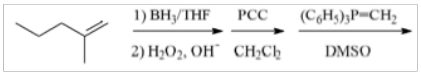
Select the product isolated when butanal reacts with the slide shown below.




- A)  B) 
- C)  D) 

## Question

What is the product of the reaction sequence below?

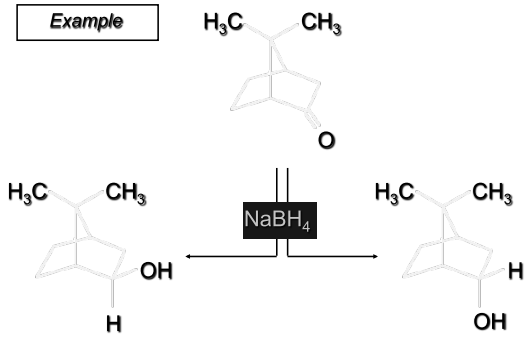



A. 2-methyl-1-hexene
B. 2,3-dimethyl-2-pentene
C. 2-methyl-2-hexene
D. 3-methyl-1-hexene

## Stereoselective Addition to Carbonyl Groups

Nucleophilic addition to carbonyl groups sometimes leads to a mixture of stereoisomeric products.

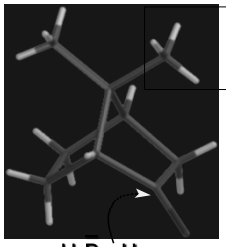
*Example*




80%

20%

*Steric Hindrance to Approach of Reagent*



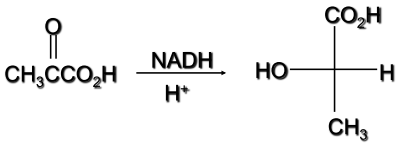
This methyl group hinders approach of nucleophile from top.

$H_3B—H^-$

Preferred direction of approach is to less hindered (bottom) face of carbonyl group.

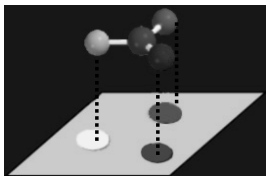
*Biological Reductions are Highly Stereoselective*

pyruvic acid → *S*-(+)-lactic acid



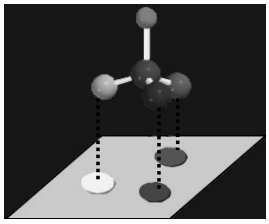

Enzyme is *lactate dehydrogenase*

*Figure 1*



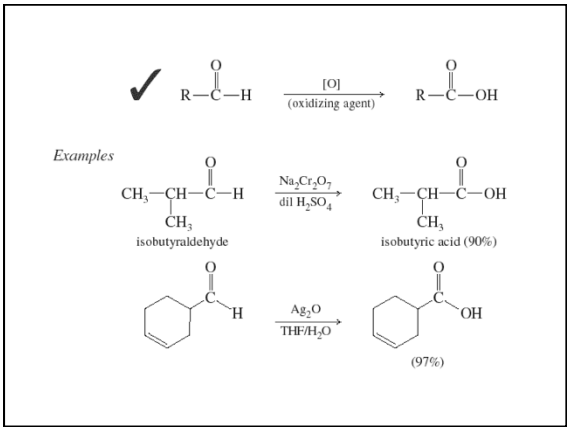
One face of the substrate can bind to the enzyme better than the other.

*Figure 2*

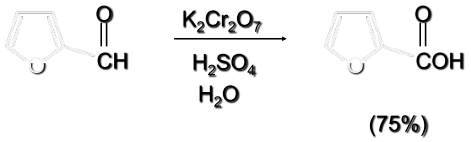


Change in geometry from trigonal to tetrahedral is stereoselective. Bond formation occurs preferentially from one side rather than the other.

Oxidation of Aldehydes



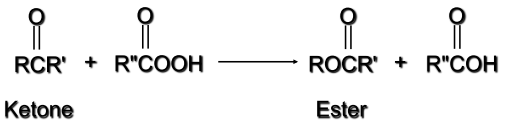

**Example**



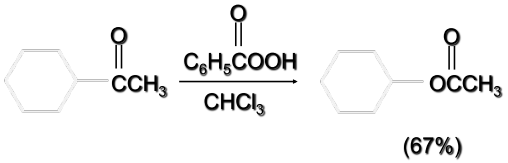

Baeyer-Villiger Oxidation
of Ketones

Oxidation of ketones with peroxy acids
gives esters by a novel rearrangement.

**General**



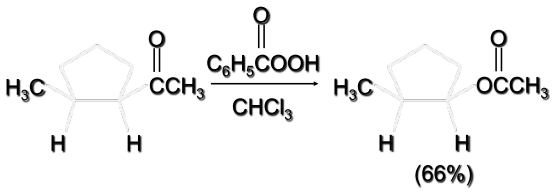

**Example**




Oxygen insertion occurs between carbonyl carbon and more substituted group.

Methyl ketones give acetate esters.

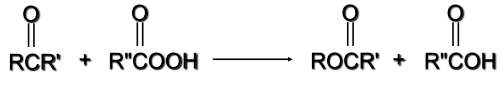
**Stereochemistry**



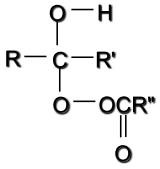

Reaction is stereospecific.

Oxygen insertion occurs with retention of configuration.

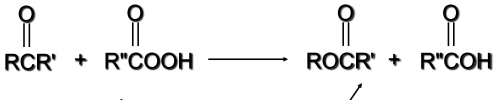
## *Mechanism*



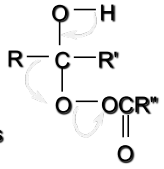
First step is nucleophilic addition of peroxy acid to the carbonyl group of the ketone.



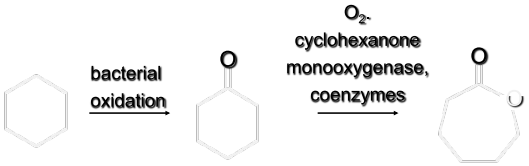
## *Mechanism*



Second step is migration of group R from carbon to oxygen. The weak O—O bond breaks in this step.



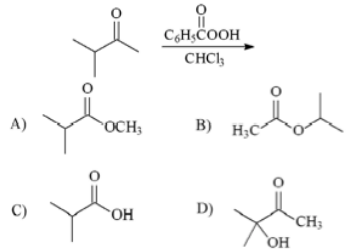
## *Biological Baeyer-Villiger Oxidation*




Certain bacteria use hydrocarbons as a source of carbon. Oxidation proceeds via ketones, which then undergo oxidation of the Baeyer-Villiger type.

## Question

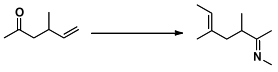
- What is the product of the following Baeyer-Villiger oxidation reaction?




## Question

What is the correct order of reagents to achieve the following synthesis.

HINT: If a reactant has two isolated C=C bonds, a mixture of products will form when hydrolyzed. The same problem occurs if there are two carbonyl groups when conducting a Wittig reaction.



a. $HOCH_2CH_2OH/H^+$
b. $HSCH_2CH_2SH/H^+$
c. $CH_3NH_2/H^+$
d. $(CH_3)_2NH/H^+$
e. 1) LAH 2) $H_2O$
f. 1) $CH_3MgBr$ 2) $H_2O$
g. PCC, $CH_2Cl_2$
h. 1) $KMnO_4$, NaOH, heat 2) $H_3O^+$
i. 1) HCN/KCN 2) LAH 3) $H_2O$
j. $CH_3CH{=}PPh_3$
k. Dilute $H_2SO_4$
l. $Hg(OAc)_2$, $H_2O$
m. MCPBA
n. TMSCl, $Et_3N$
o. TBAF

A. l, g, c
B. l, g, d
C. l, n, j, o, g, c
D. j, l, g, c
E. j, l, g, d