Lecture 15

More Carbonyl Chemistry

Shared Nobel Prize with Sabatier in 1912

"student" of Philippe Barbier

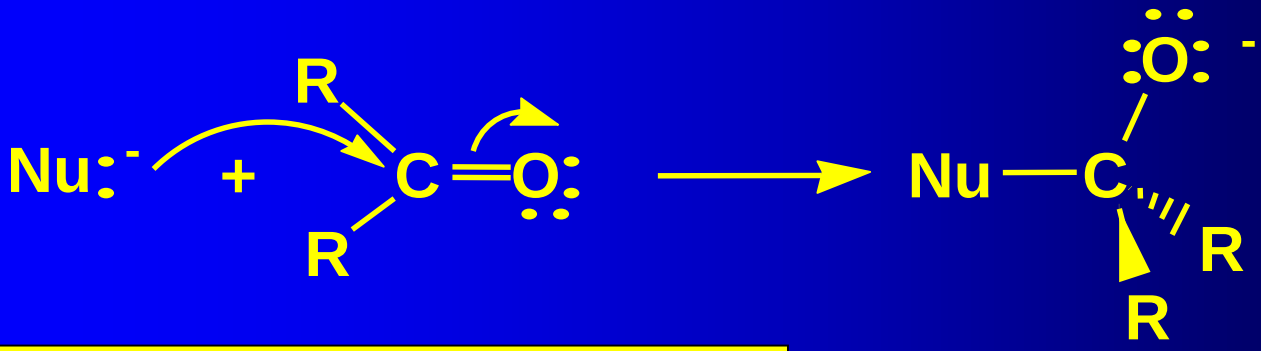
François Auguste Victor Grignard
1871-1935

March 3, 2016

Chemistry 328N

Reaction Theme

- The most common reaction of a carbonyl group is addition of a nucleophile to form a tetrahedral addition compound



Here it is an acid or electrophile

Tetrahedral carbonyl addition compound

Carbon Nucleophiles

- Addition of carbon nucleophiles is one of the most important types of nucleophilic additions to a C=O group; a new carbon-carbon bond is formed in the process!!!!

RMgX	RLi	$RC\equiv C:^-$	$^-:C\equiv N:$
A Grignard reagent	**An organolithium reagent**	**An anion of a terminal alkyne**	**Cyanide ion**

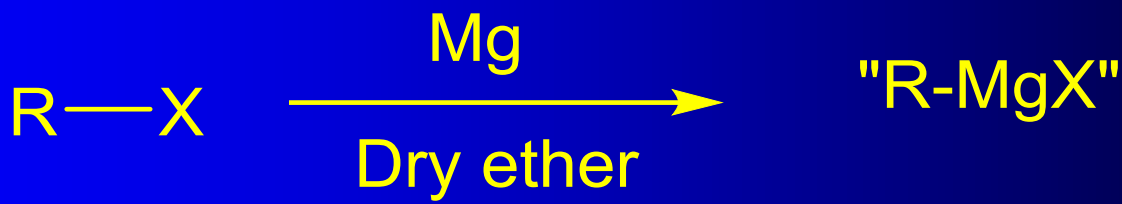
- We will study the addition of these carbon nucleophiles

Victor Grignard

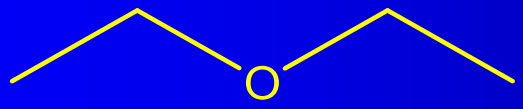
Shared Nobel Prize with Sabatier in 1912

“student” of Philippe Barbier

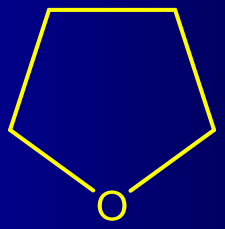
Grignard Reagents



X = Cl, Br, I



Diethyl ether
Et_2O



Tetrahydrofuran
THF

Crystal Structure of CH_3CH_2MgBr

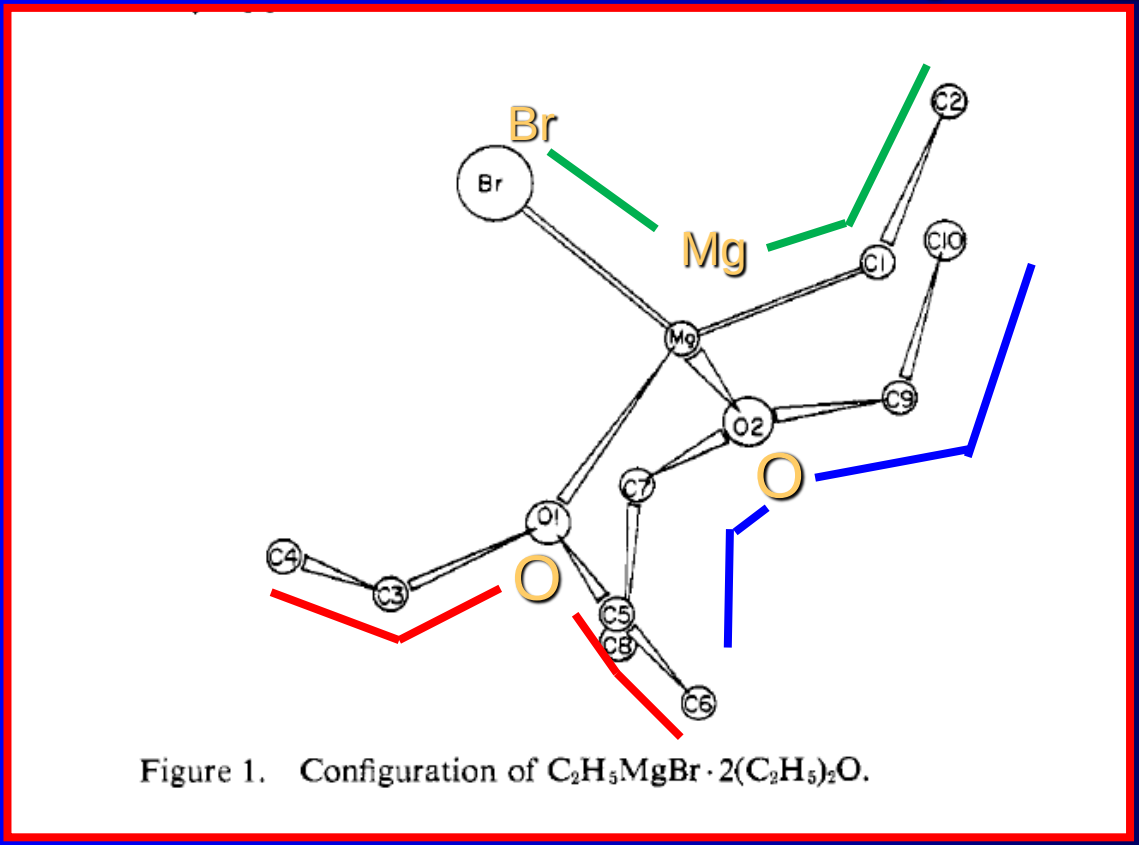


Figure 1. Configuration of $C_2H_5MgBr \cdot 2(C_2H_5)_2O$.

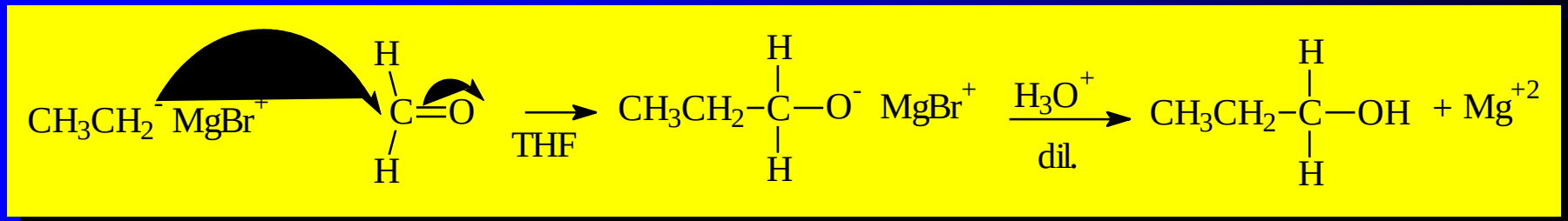
L.J. Guggenberger and R.E. Randle , J. Amer. Chem. Soc. 90(20) 5357 (1968)

Grignard Reagents

- Given the difference in electronegativity between carbon and magnesium, the C-Mg bond is polar covalent, with C δ- and Mg δ+
  - Grignard reagents behave like a carbanions
- Carbanion: an anion in which carbon has an unshared pair of electrons and bears a negative charge
  - a carbanions are good nucleophiles and add efficiently to the carbonyl group of aldehydes and ketones

Grignard Reagents

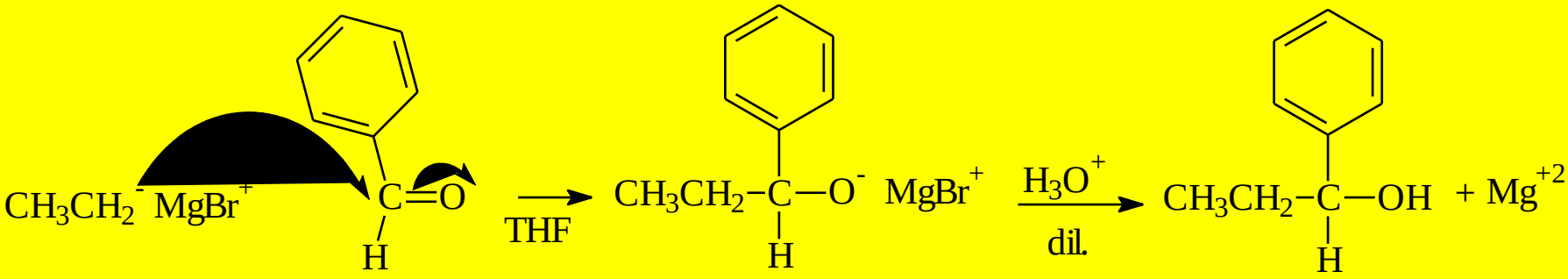
- Addition of a Grignard reagent to formaldehyde followed by H_3O^+ gives a 1° alcohol



- This sequence (mechanism) is general and important!

Grignard Reagents

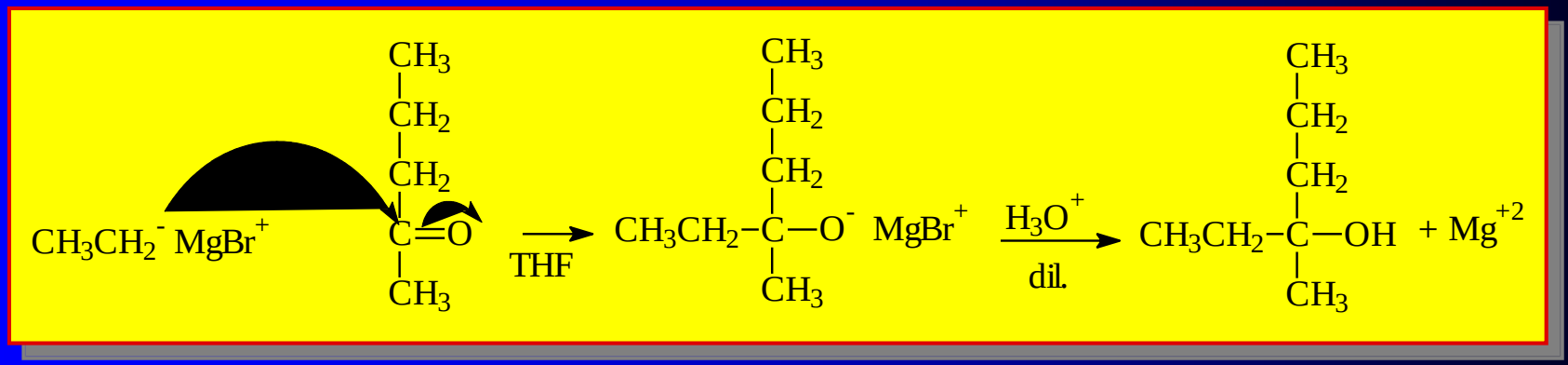
- **Addition to any other RCHO gives a 2° alcohol**



- You may change decorations at will…read pages 567-573
  - but, be careful of acidic functions like -OH

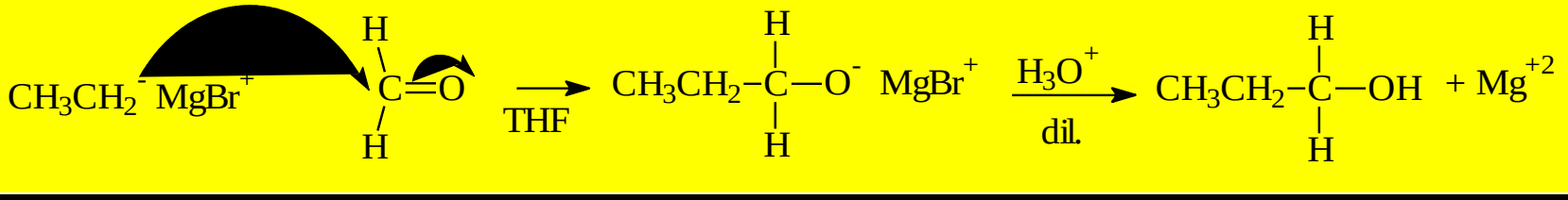
Grignard Reagents

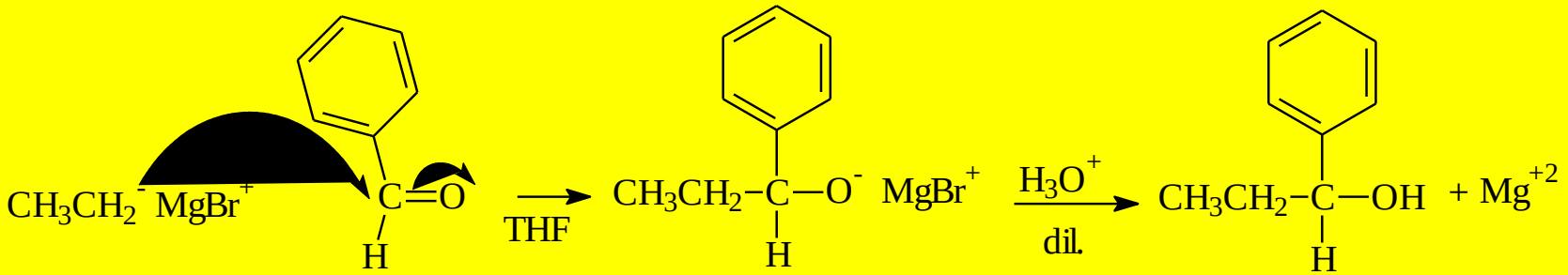
- Addition to a ketone gives a 3° alcohol

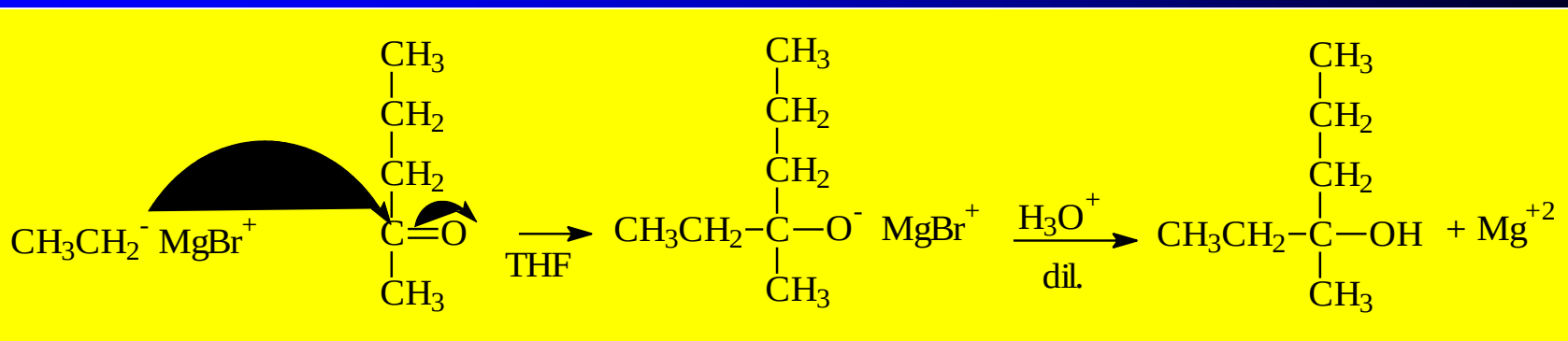


- Please try this with other Grignard reagents and other ketones

Grignard Reactions

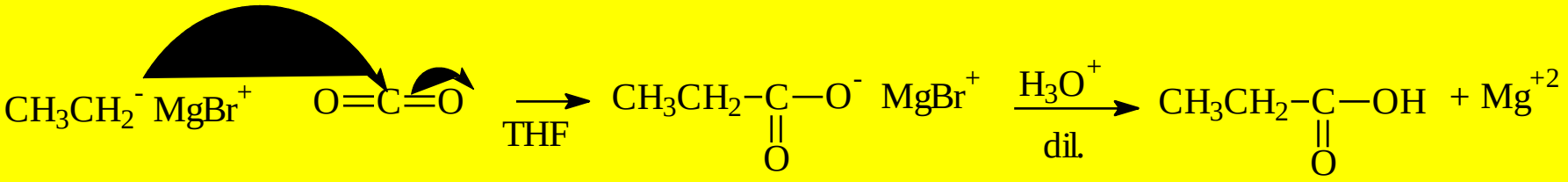






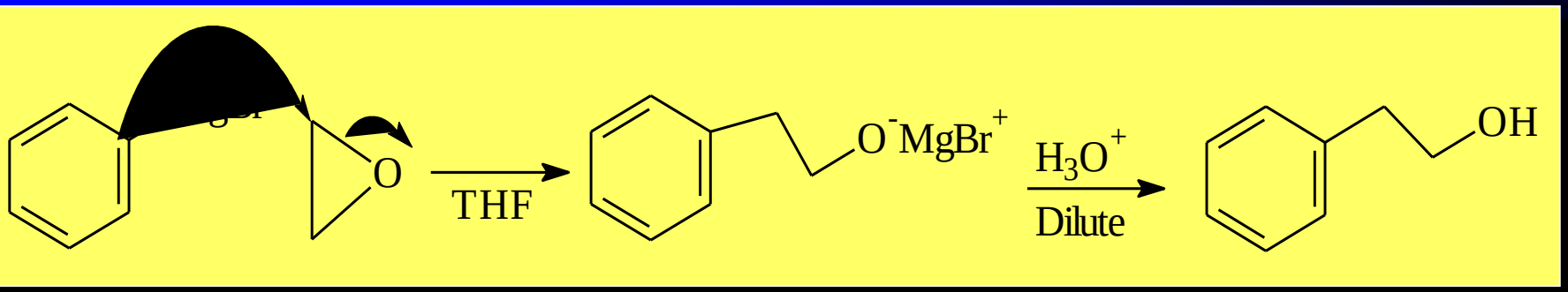
Grignard Reagents

- Addition to CO_2 gives a carboxylic acid



- This is a great way to add a carbon

Grignard Reactions

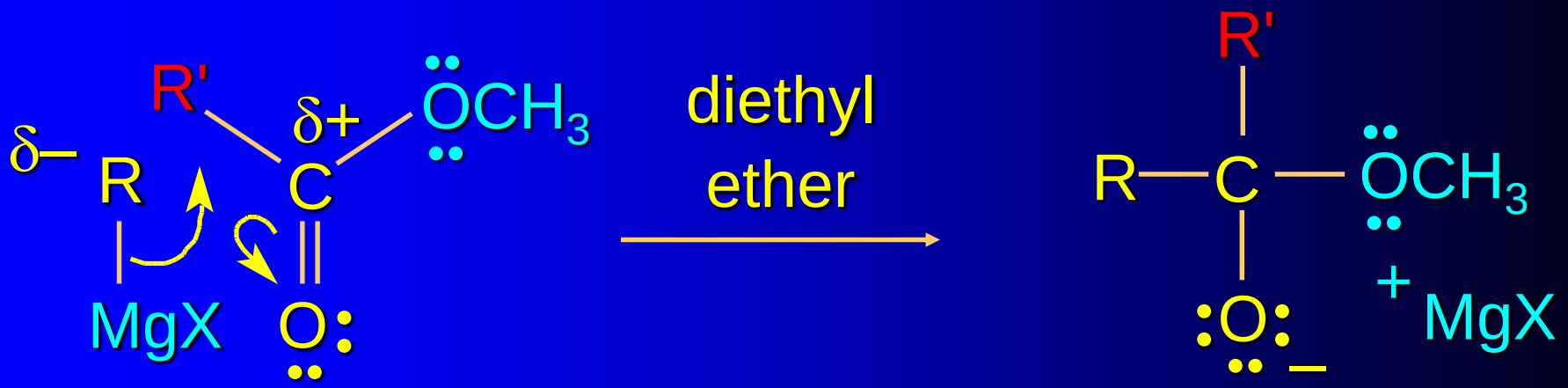


- This is a great way to add two carbons

These are very valuable and important reactions…

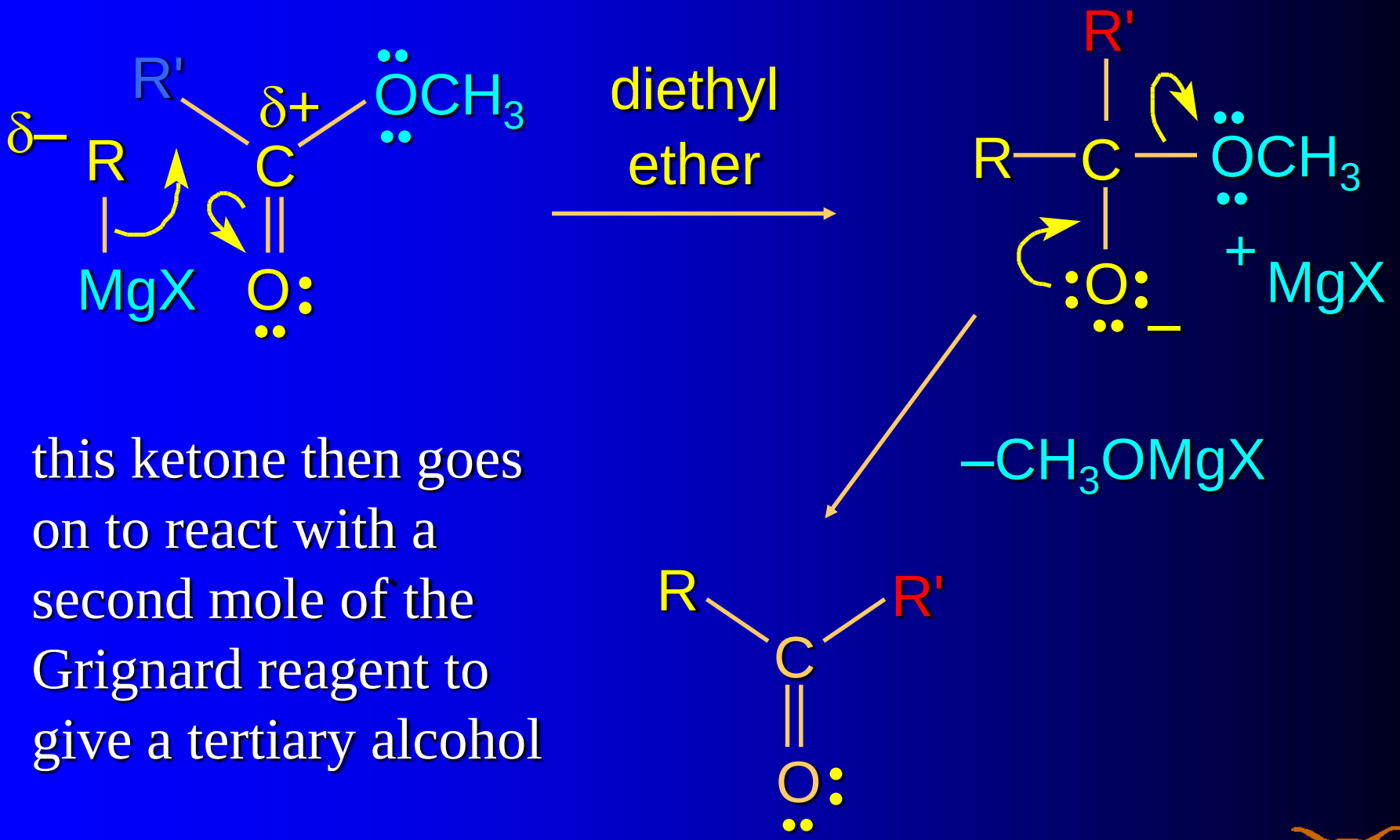
Please add to your card stock!

Grignard reagents react with esters



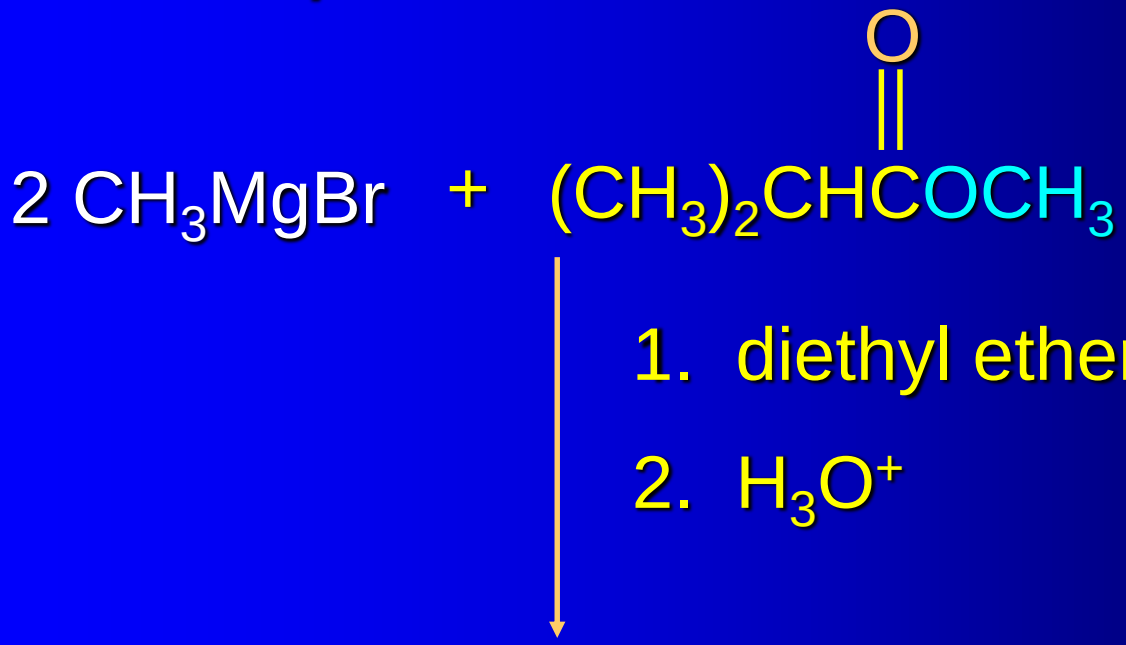
but species formed is unstable and dissociates under the reaction conditions to form a ketone

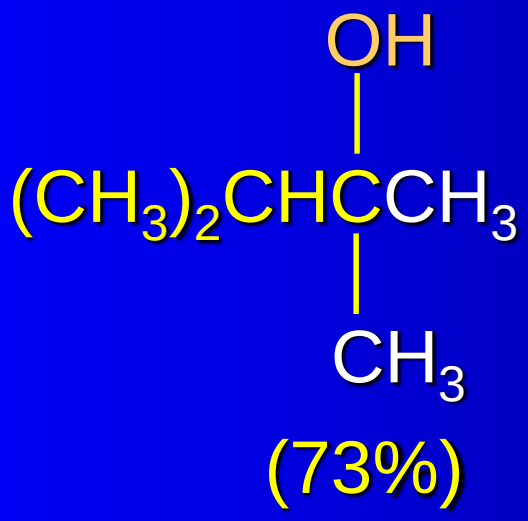
Grignard reagents react with esters



this ketone then goes on to react with a second mole of the Grignard reagent to give a tertiary alcohol

Example





Two of the groups attached to the tertiary carbon come from the Grignard reagent

Grignard reagents react with:

formaldehyde to give primary alcohols

aldehydes to give secondary alcohols

ketones to give tertiary alcohols

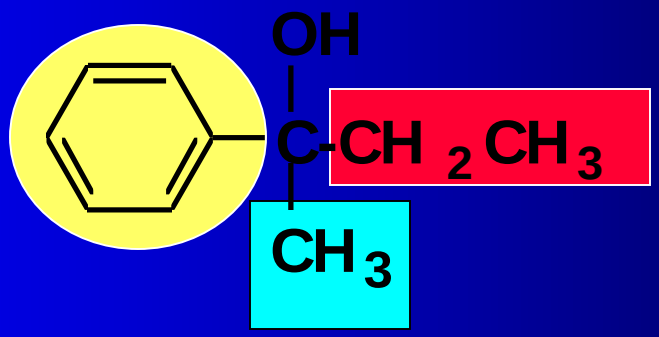
esters to give tertiary alcohols

CO_2 to give acids

 epoxides give primary alcohols

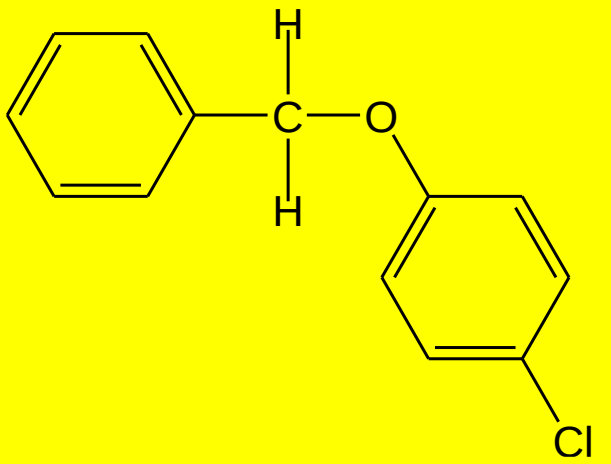
Grignard Reagents

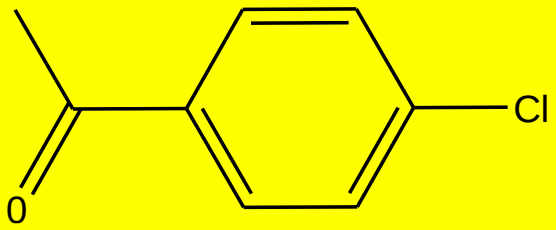
- **Problem:** 2-phenyl-2-butanol can be synthesized by three different combinations of a Grignard reagent and a ketone. Show each combination

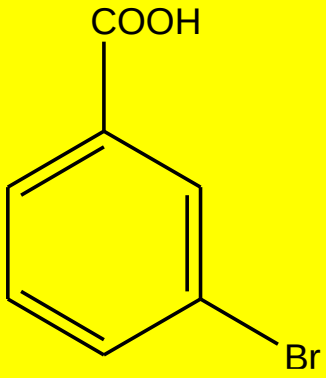


Practice Problem

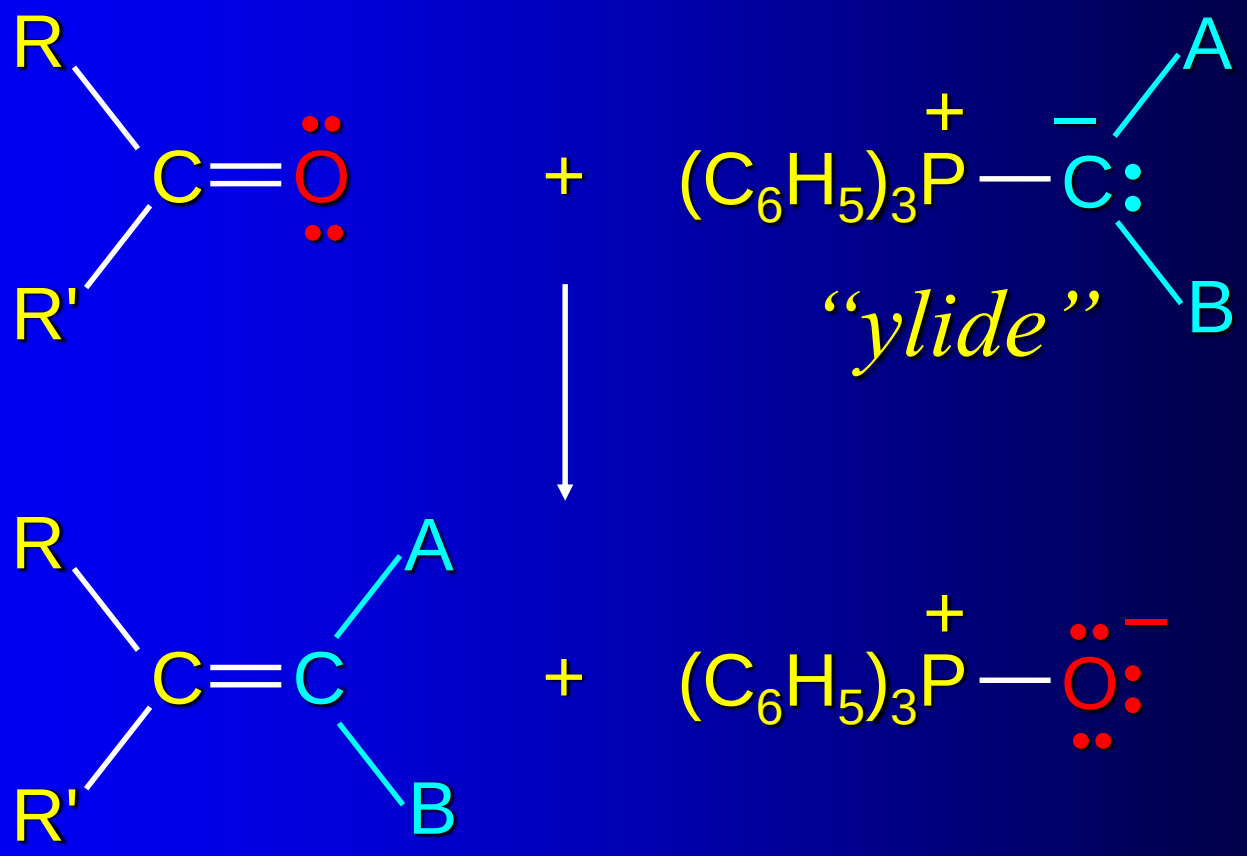
1. Starting from benzene, write a synthetic path to the structures below. You are free to use any reagents or reactants you choose, but you must start with benzene.







The Wittig Reaction



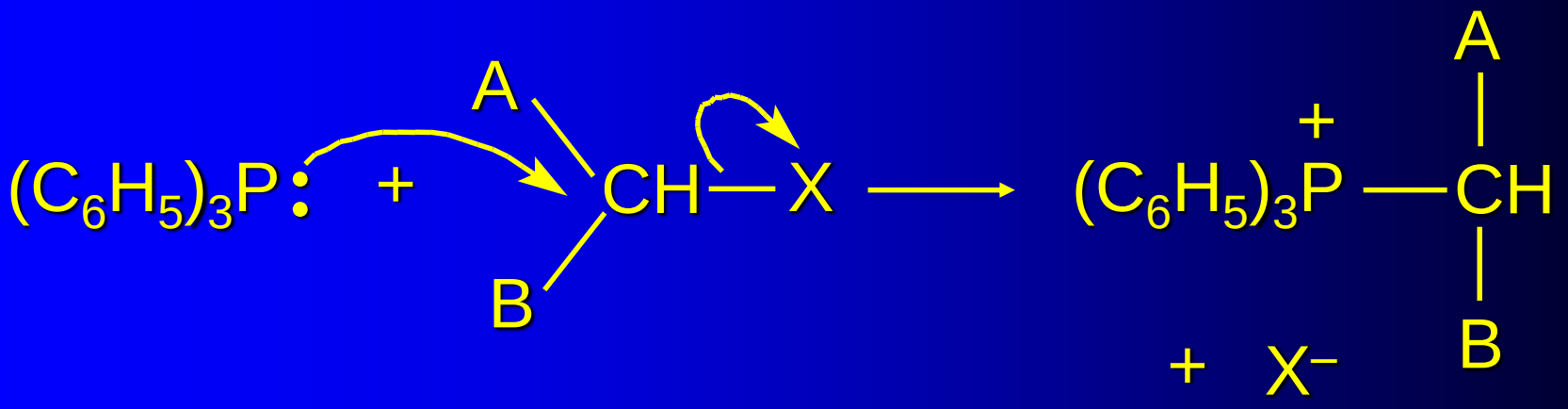
The Nobel Prize in Chemistry 1979

Georg Wittig 1897-1987

University of Heidelberg

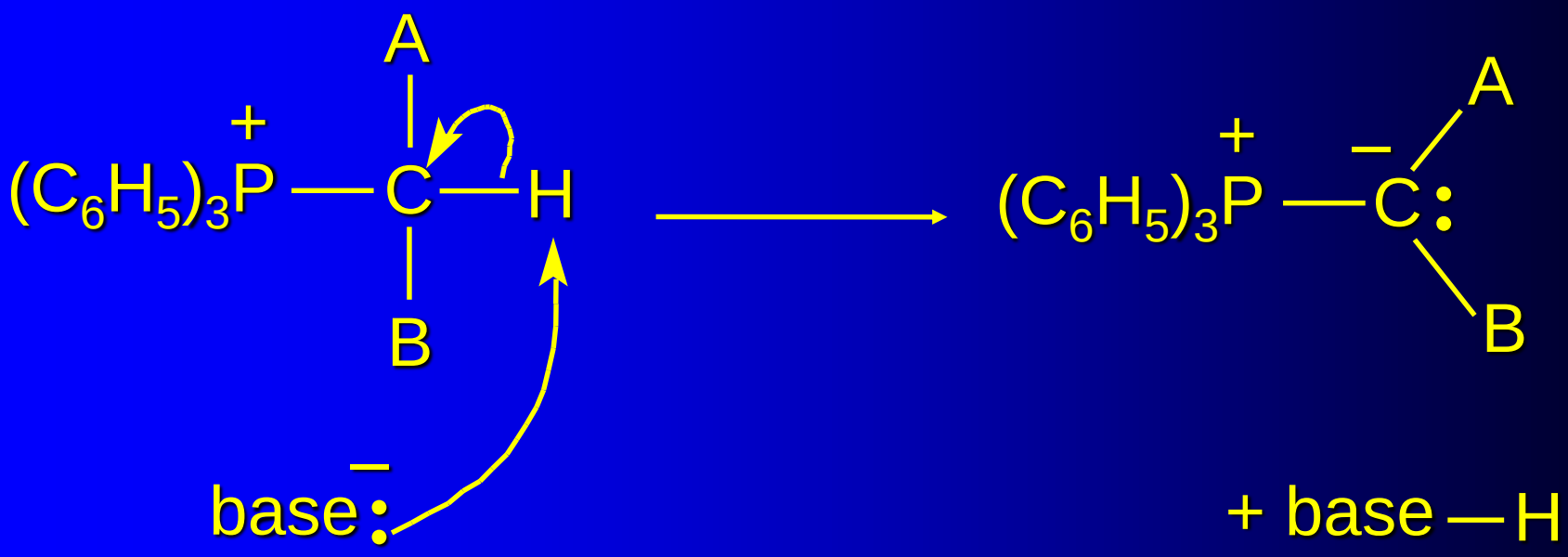
Preparation of Ylides

The ylid is made in a two step process. The first step is a nucleophilic substitution reaction that Forms a *phosphonium salt*



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.

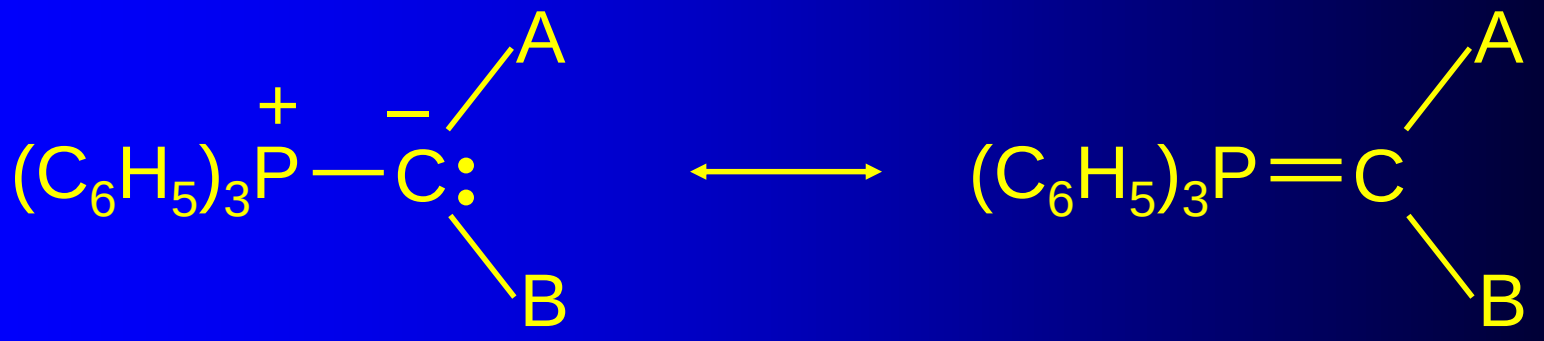


Phosphonium ylides

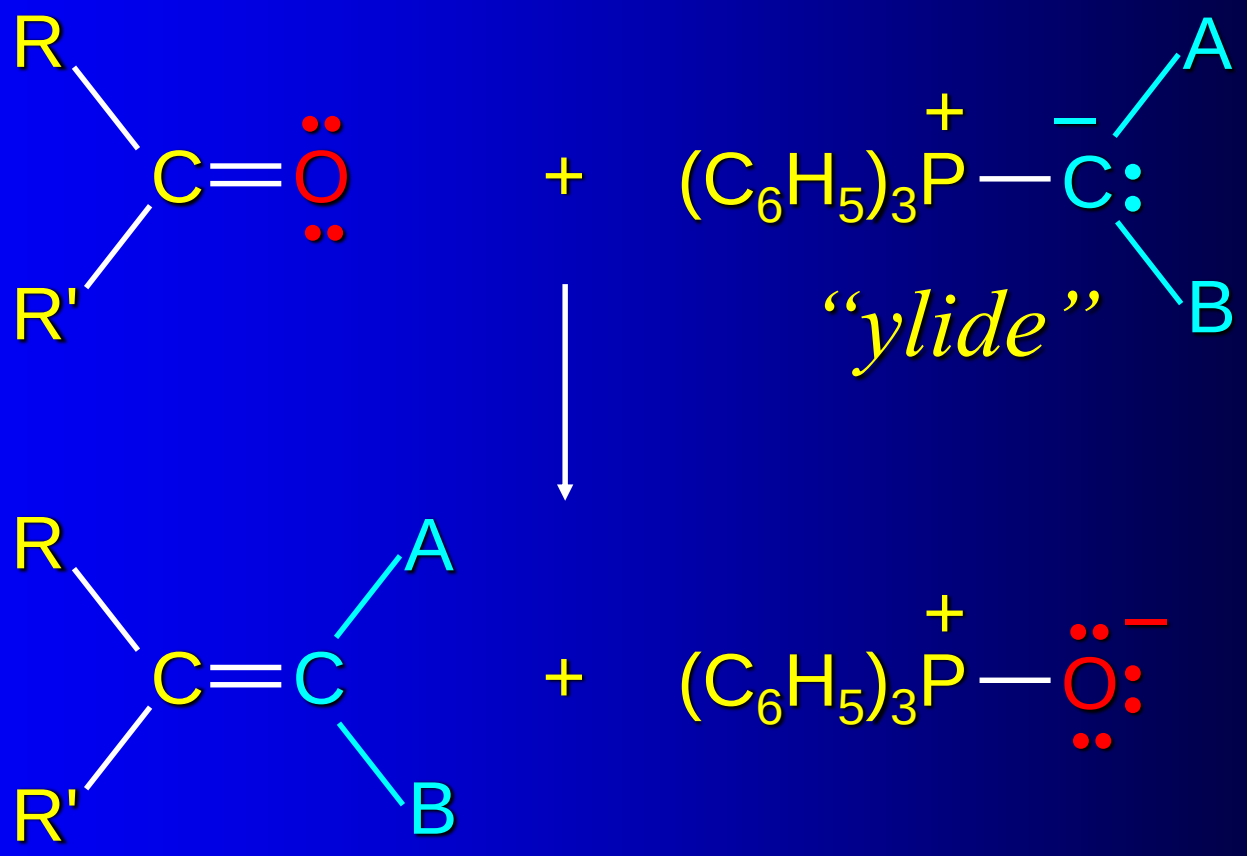
Resonance stabilized

R is usually C_6H_5 (phenyl)

Carbon is negatively polarized and nucleophilic

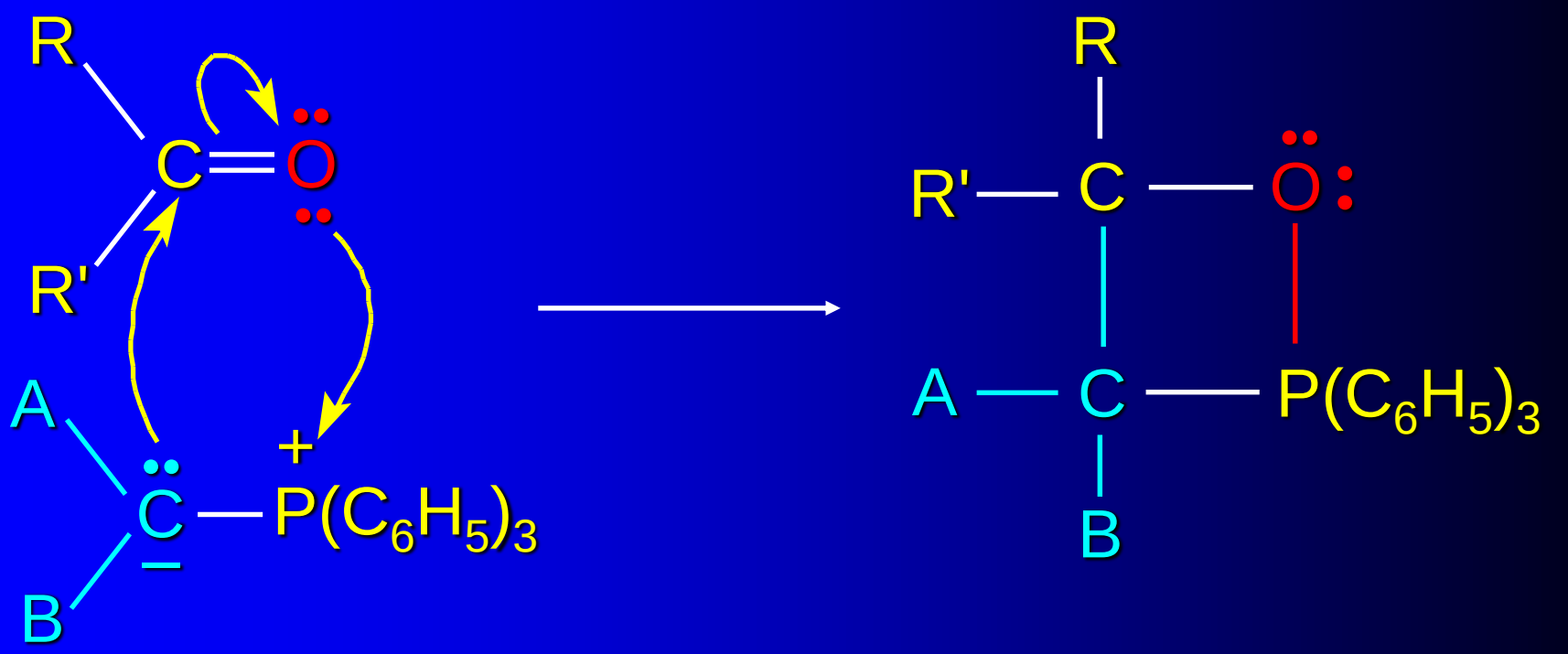


The Wittig Reaction



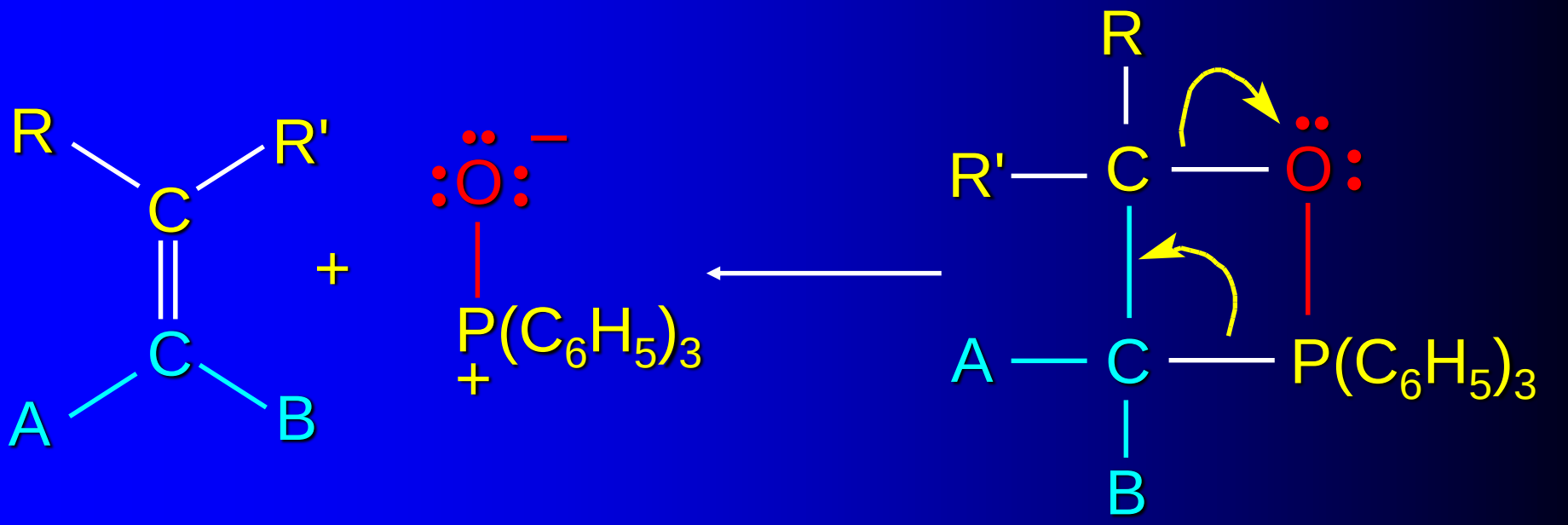
Mechanism

Step 1

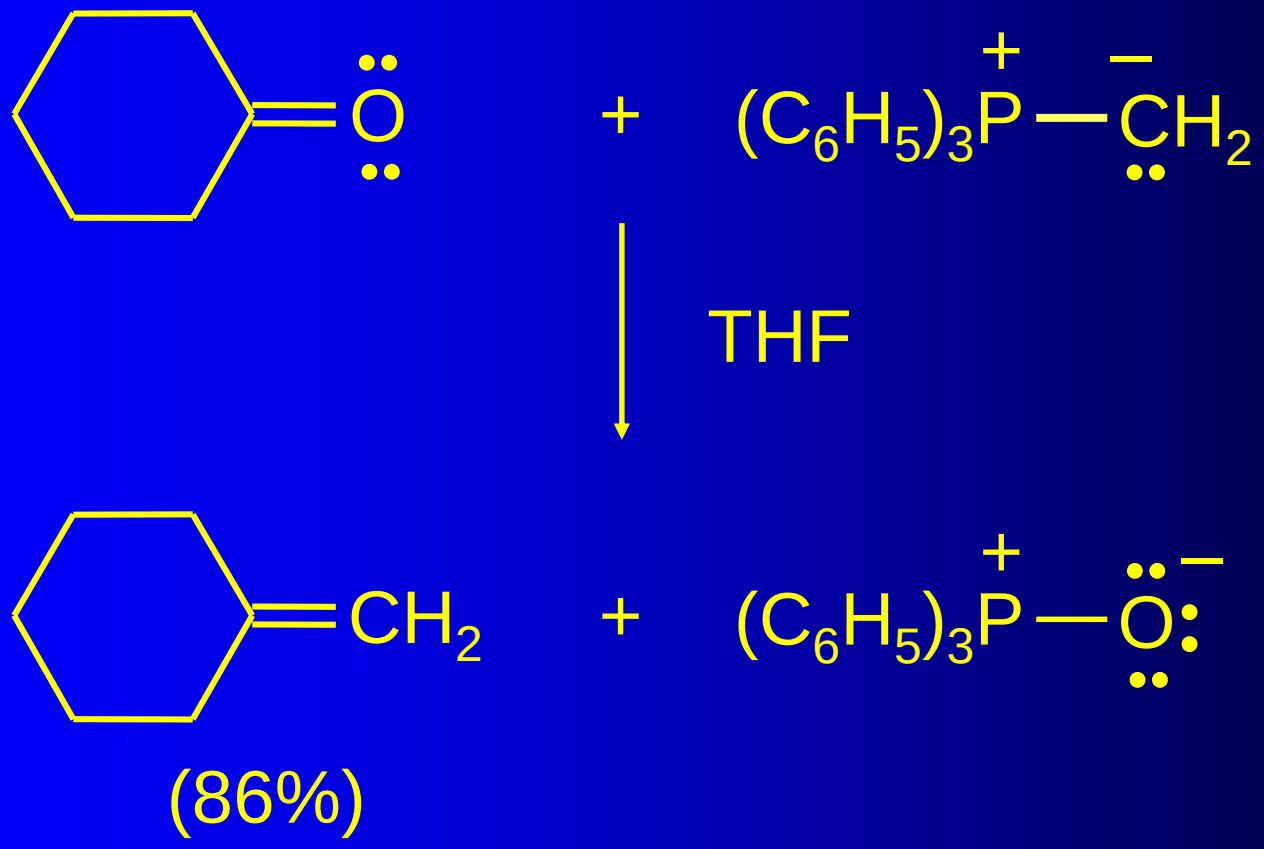


Mechanism

Step 2

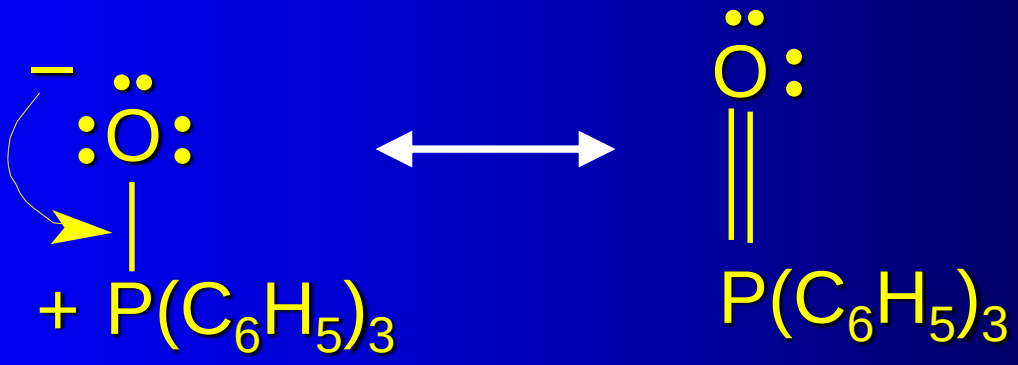


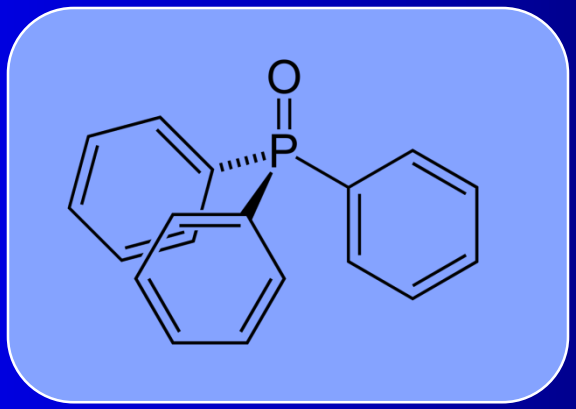
Example



(86%)

Triphenylphosphine oxide





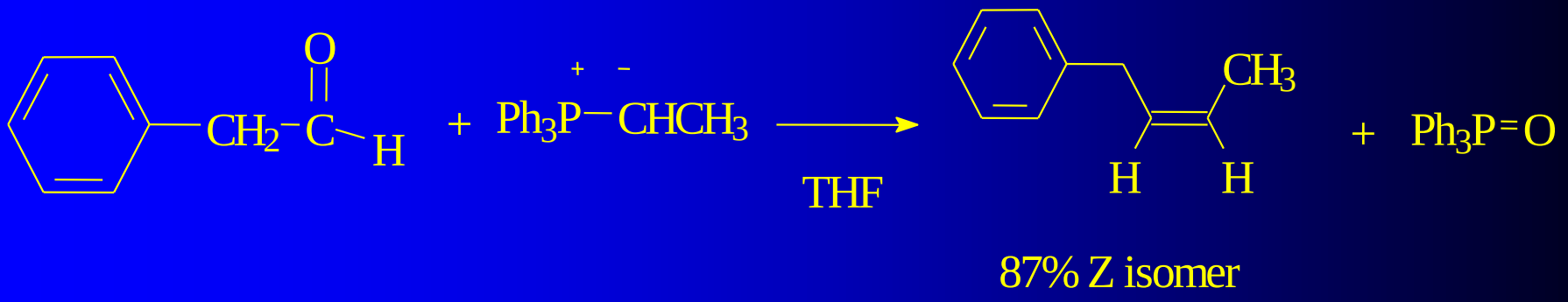
This substance is very stable

Nearly insoluble in many solvents, i.e. pentane

Oral, mouse: LD50 = 1380 mg/kg;

Wittig Reaction

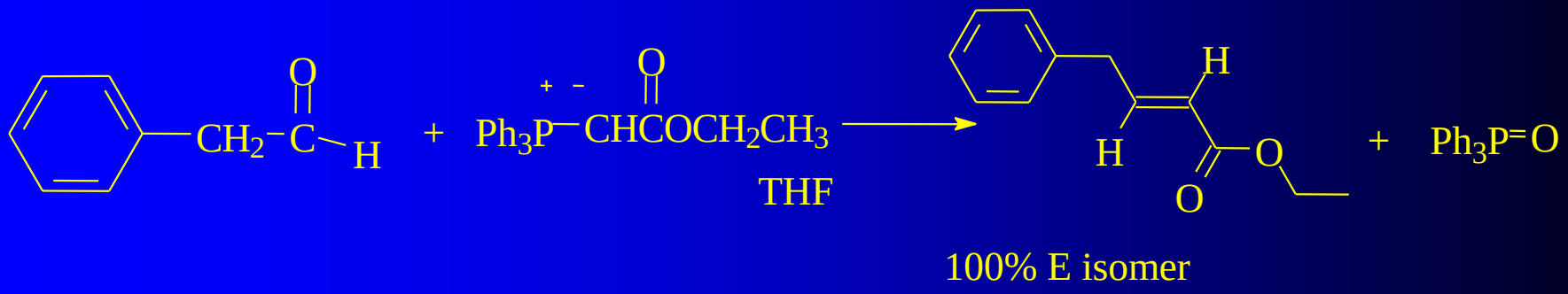
- **More examples**



Don’t plan to control the E/Z ratio…you get generally get a mixture

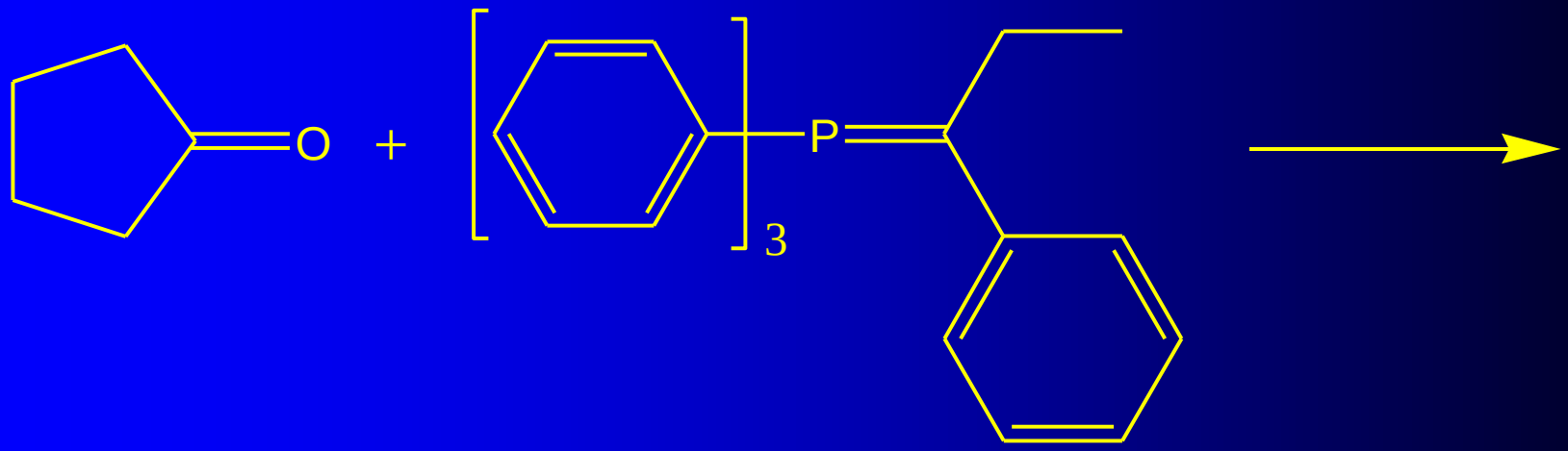
The Wittig Reaction

- **See... sometimes you can control it**
- **we won't try to do that in this class**
- **The reaction has broad "scope"**



100% E isomer

An Example: Write the structure of the products



To the 328N Band!!