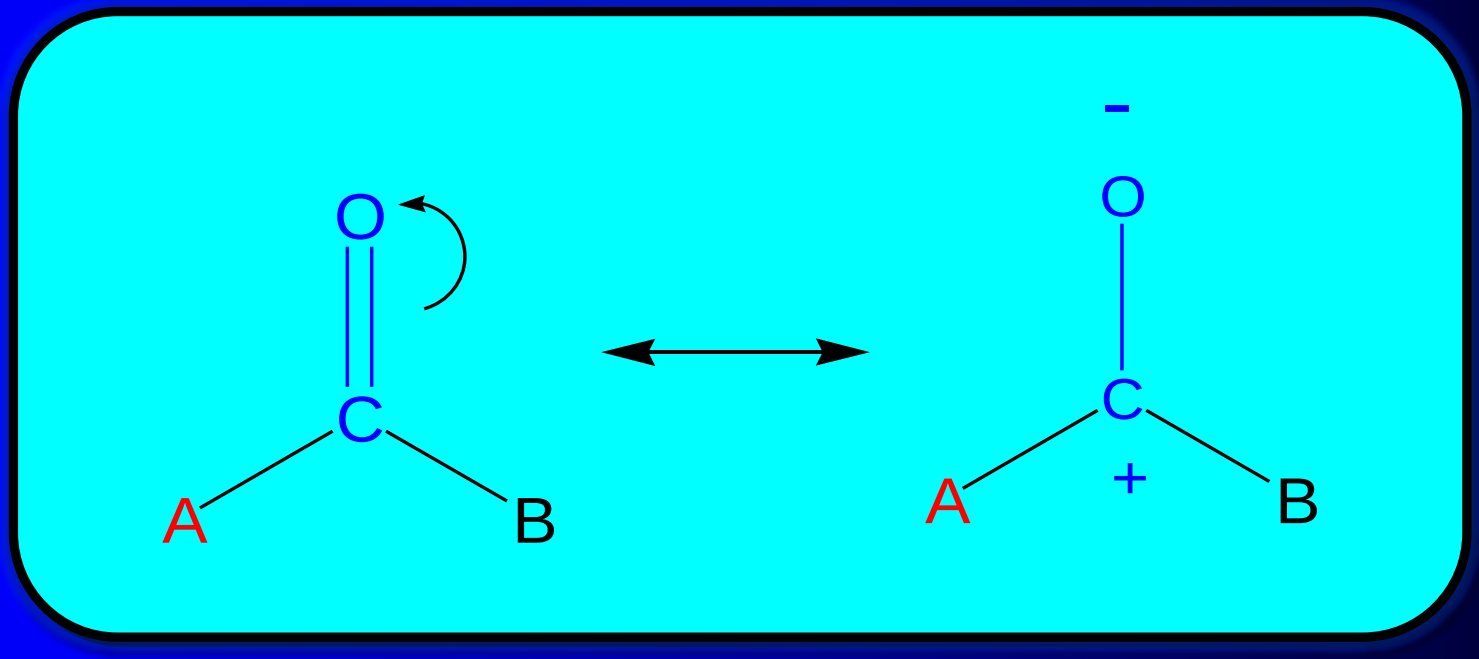
Lecture 14

Carbonyl Chemistry

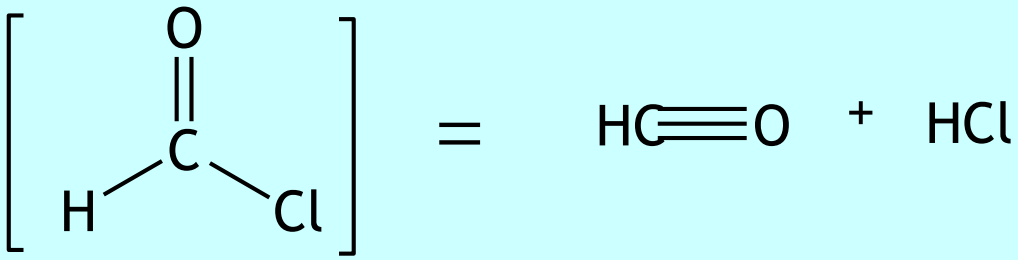


March 7, 2019

Chemistry 328N

A “loose end”

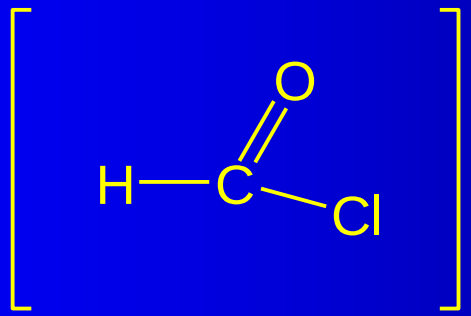
A word of caution regarding acylation reactions



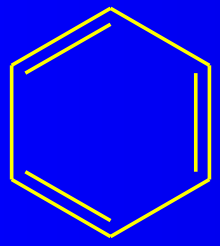
Does not exist!!

Please do not propose Friedel Crafts acylation with Formyl Chloride as a route to aryl aldehydes.

Gatterman-Koch Reaction



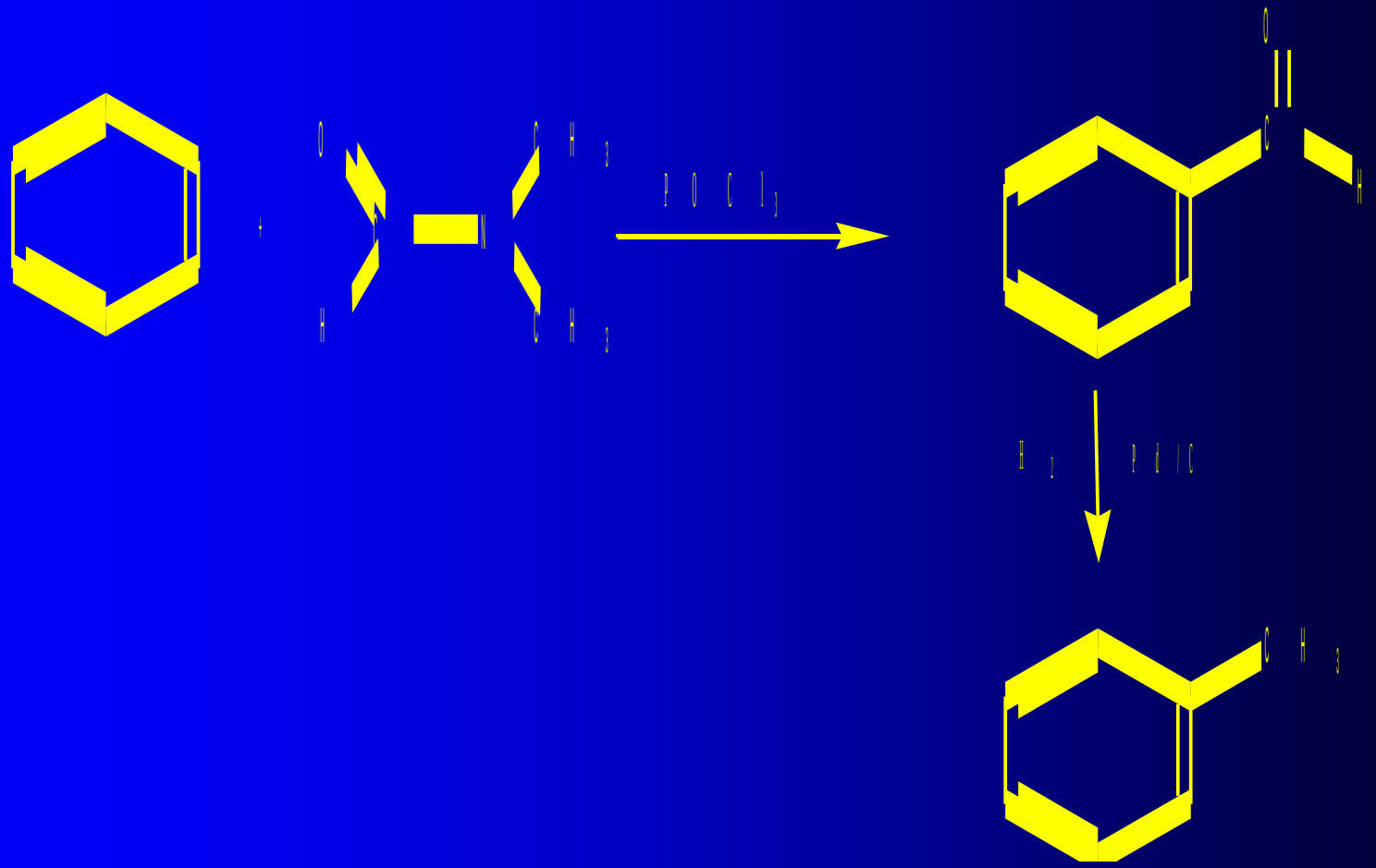
= HCl + C≡O



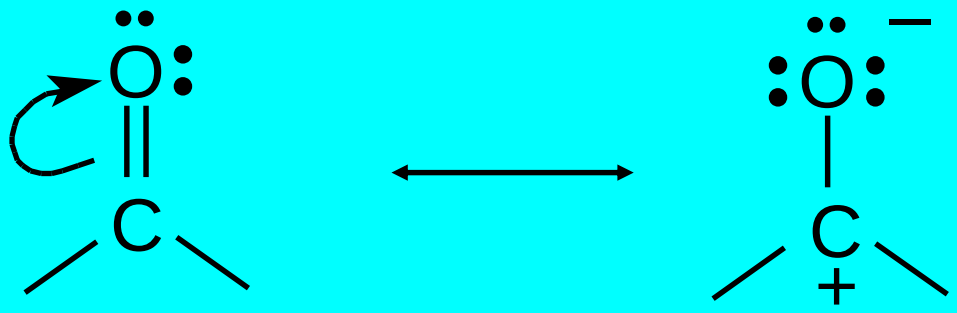
CO, HCl

$AlCl_3$, CuCl

Vilsmeier Reaction



Resonance Description of Carbonyl Group



nucleophiles attack carbon;

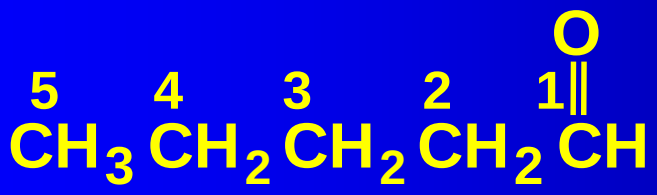
electrophiles attack oxygen

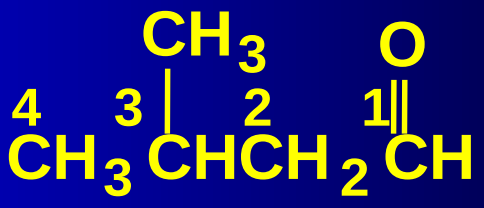
Nomenclature-Aldehydes

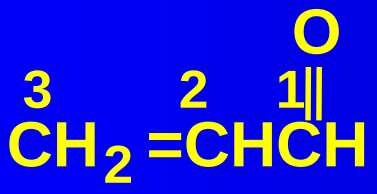
- IUPAC names: select as the parent alkane the longest chain of carbon atoms that contains the carbonyl group..subtract e and add al
  - because the carbonyl group of the aldehyde must be on carbon 1, there is no need to give it a number

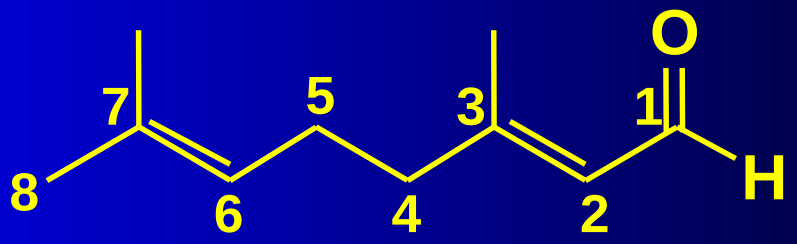
- For unsaturated aldehydes, show the presence of the C=C by changing -an- to -en-
  - the location of the suffix determines the numbering pattern

IUPAC Nomenclature-Aldehydes







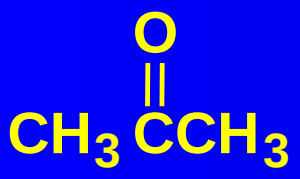


Formaldehyde

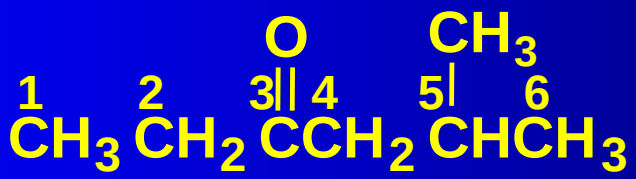
- "Formalin" is an aqueous solution of a mixture of formaledyde derived species
- Used for emblaming and preservation of tissue samples, bugs, etc.
- Widely used in melamine resins for plywood, flooring, etc…
- Naturally occuring at 0.1mm in blood derived from metbolism of amino acids
- Toxicity is an issue and level set at 0.016ppm in air. Thirty ml ogf

Nomenclature-Ketones

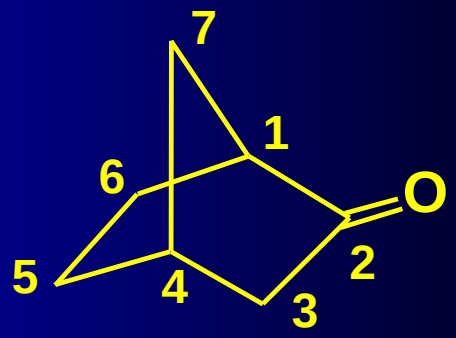
- **IUPAC names:**
  - select as the parent alkane the longest chain that contains the carbonyl group,
  - number to give C=O the smaller number and then subtract e and add one



Propanone (Acetone)

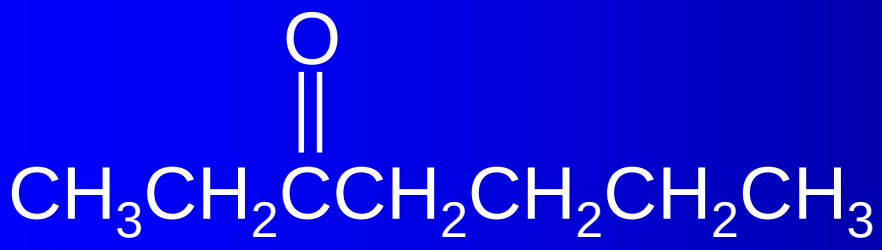


5-Methyl-3-hexanone

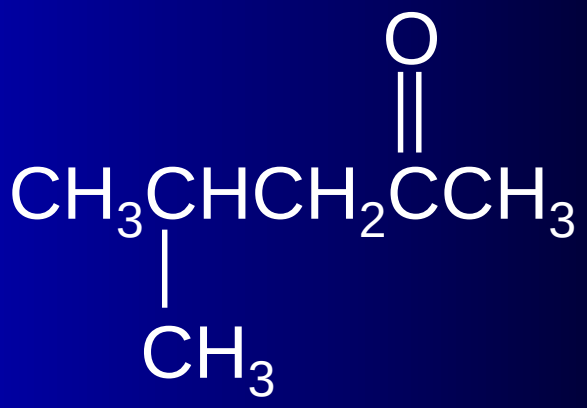


Bicyclo[2.2.1]-2-heptanone

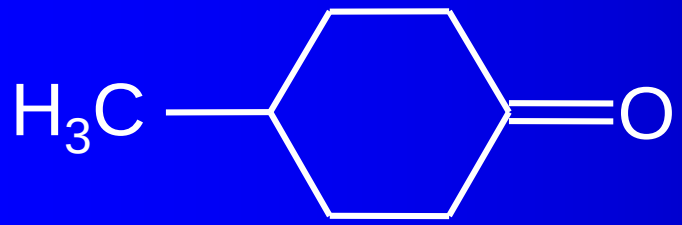
IUPAC Nomenclature of Ketones



3-heptanone

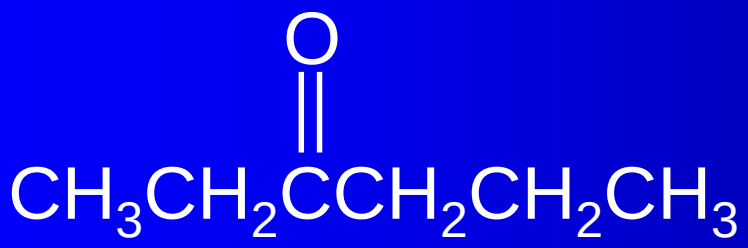


4-methyl-2-pentanone

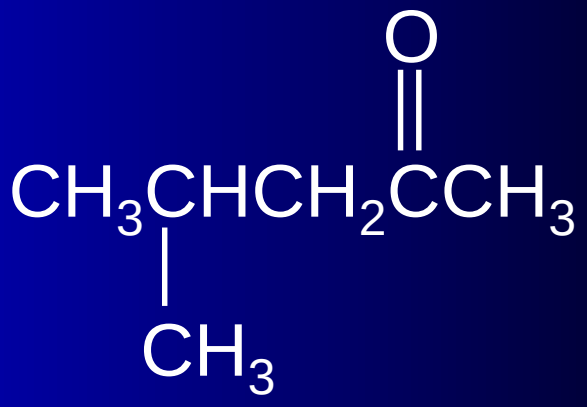


4-methylcyclohexanone

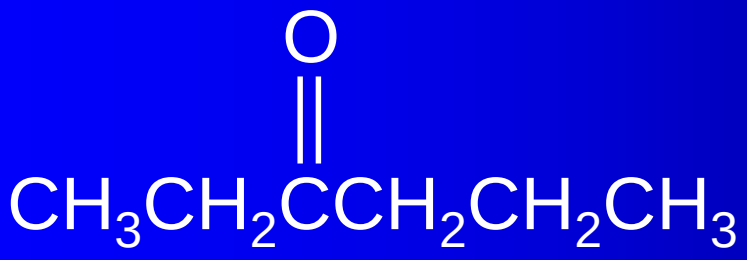
IUPAC Nomenclature of Ketones



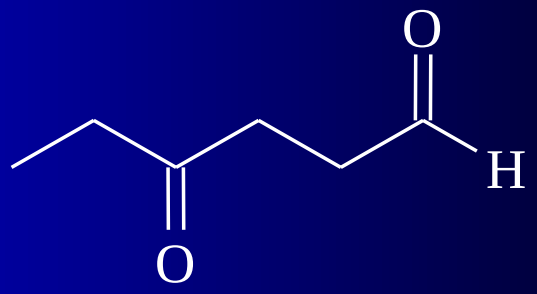
3-hexanone



4-methyl-2-pentanone

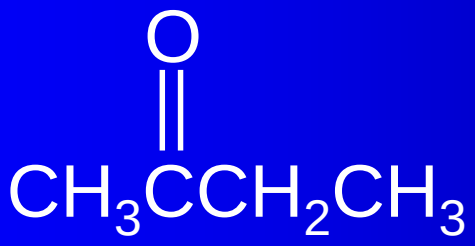


ethyl propyl ketone (trivial)

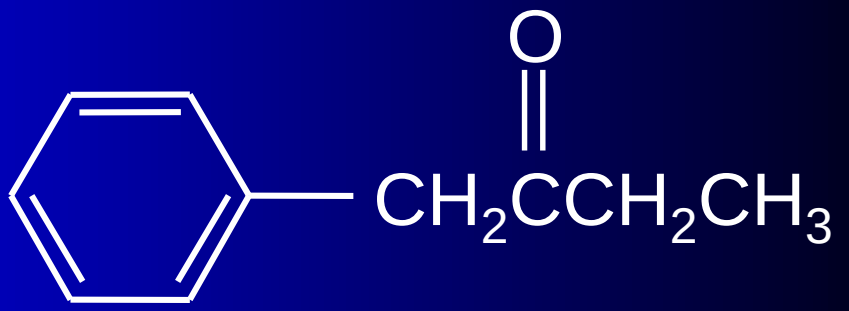


4-oxohexanal

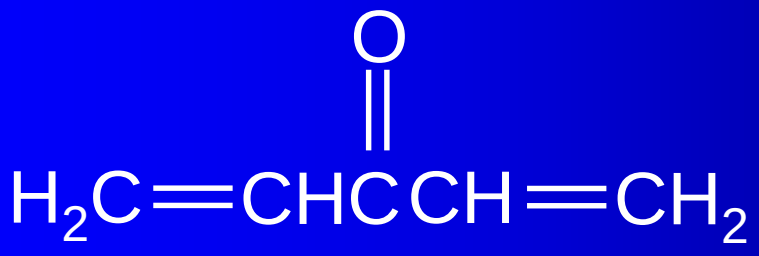
Trivial Nomenclature of Ketones



Methyl ethyl ketone



benzyl ethyl ketone



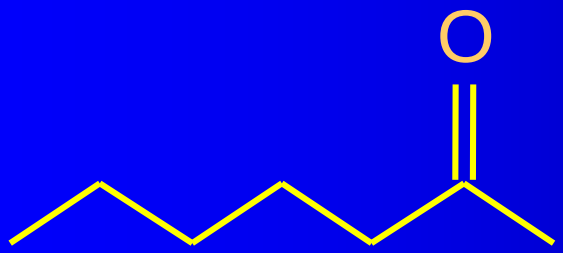
divinyl ketone

Order of Precedence (Pecking order)

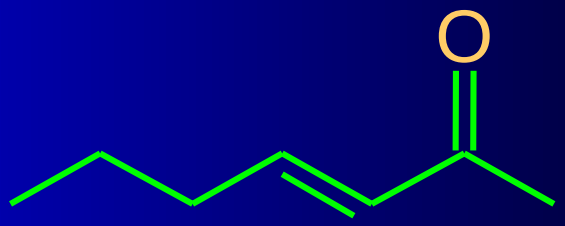
- For compounds that contain more than one functional group indicated by a suffix

Functional Group	Suffix if Higher in Precedence	Prefix if Lower in Precedence
Precedence ↑		
$-CO_2H$	-oic acid	———
-CHO	-al	oxo-
$>C=O$	-one	oxo-
-OH	-ol	hydroxy-
$-NH_2$	-amine	amino-
-SH	-thiol	mercapto-

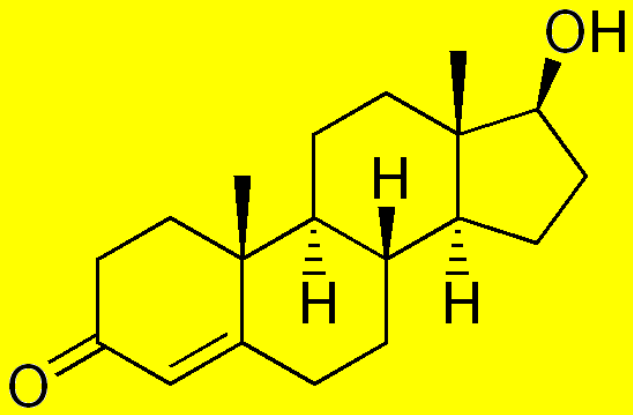
Many aldehydes and ketones occur naturally



2-heptanone
(component of alarm pheromone of bees)



trans-2-hexenal
(alarm pheromone of myrmicine ant)



Testosterone

Wild Kopi Luwak, the World's Most Exclusive Coffee

$416/pound on Amazon

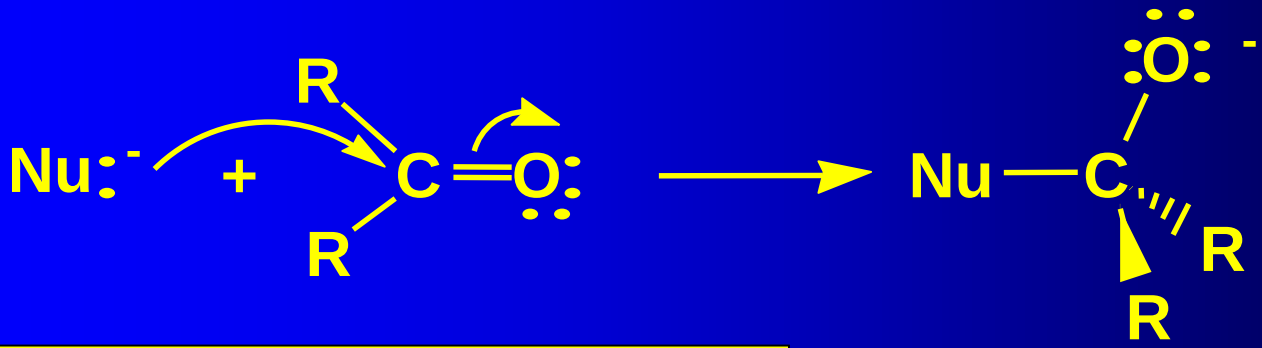
Synthesis of Aldehydes and Ketones

A number of reactions already studied provide efficient synthetic routes to aldehydes and ketones.

- from alkenes
  - by ozonolysis (p271)
- from alkynes
  - by hydration (via enol)
- from arenes
  - via Friedel-Crafts acylation

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

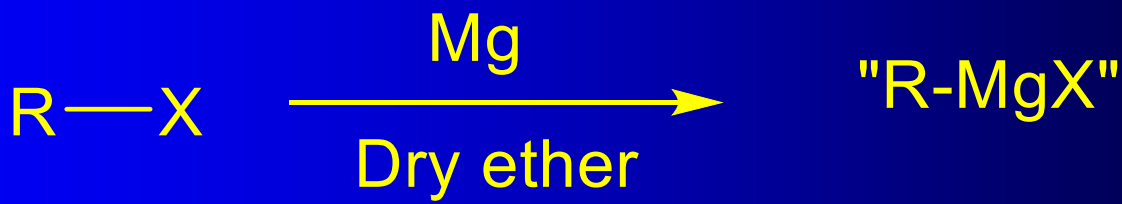
Shared Nobel Prize with Sabatier in 1912

“student” of Philippe Barbier

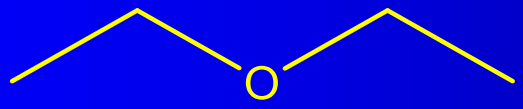
Grignard Reagents

- 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

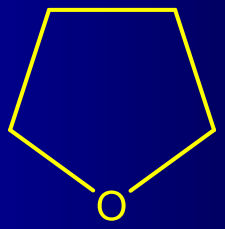
Grignard Reagents



X = Cl, Br, I



Diethyl ether
Et_2O



Tetrahydrofuran
THF

Crystal Structure of CH_3CH_2MgBr

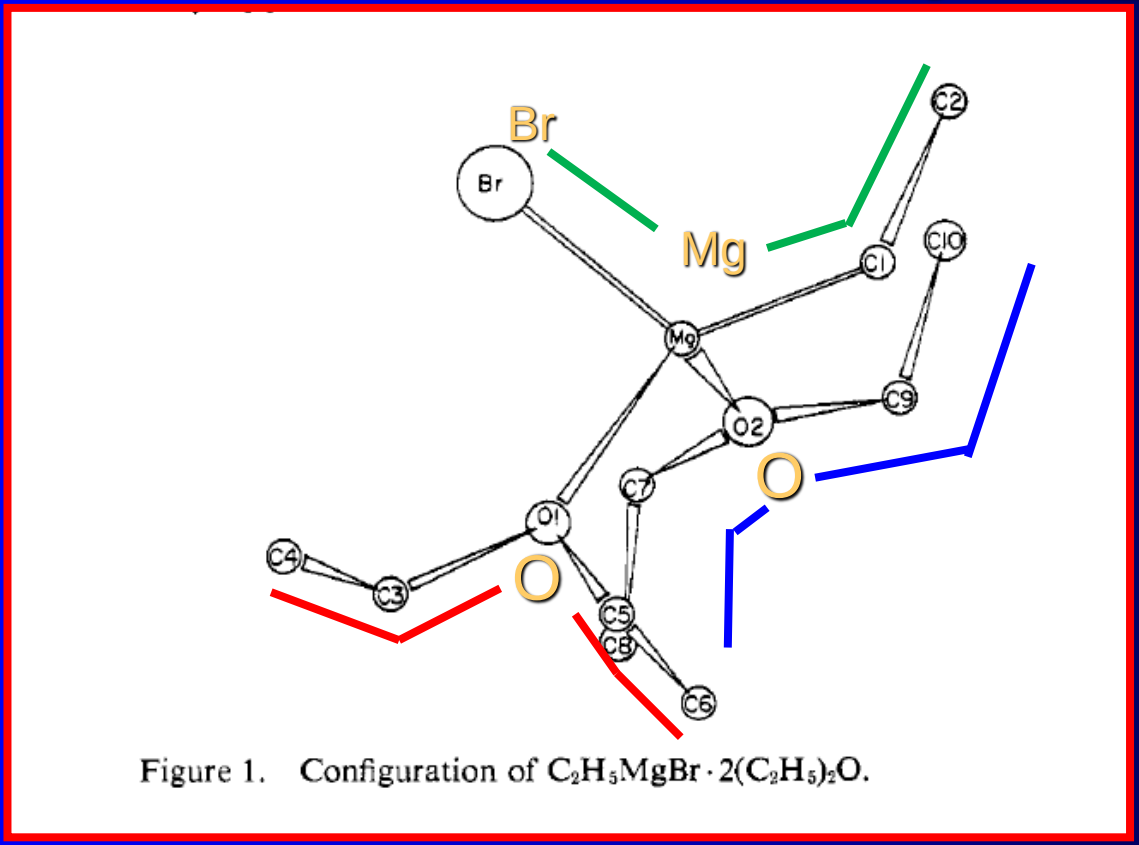
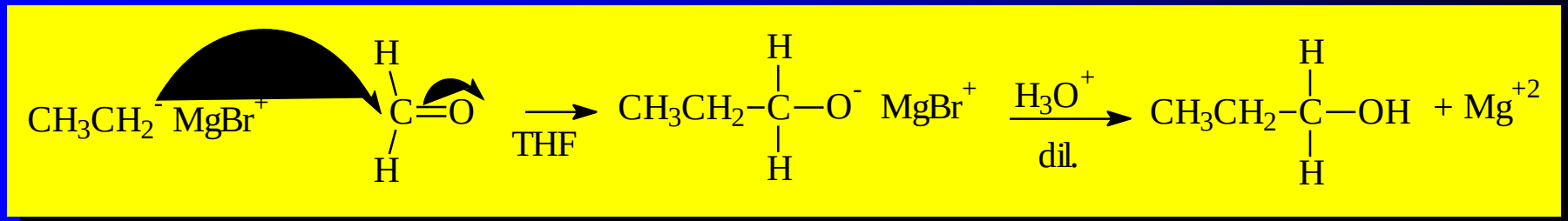


Figure 1. Configuration of $C_2H_5MgBr \cdot 2(C_2H_5)_2O$.

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

Grignard Reagents

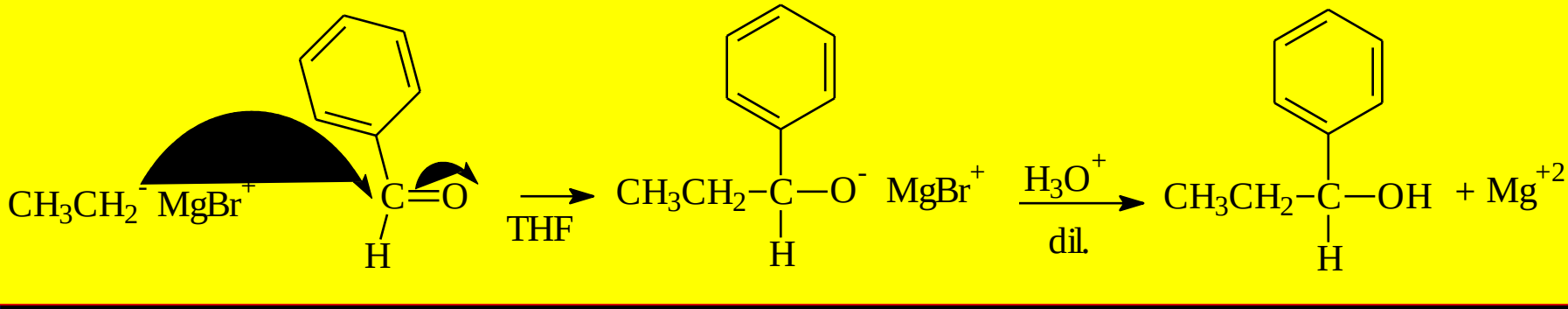
- Addition of a Grignard reagent to formaldehyde followed by H_3O^+ gives a 1° alcohol



- This sequence (mechanism) is general and important!

Grignard Reagents

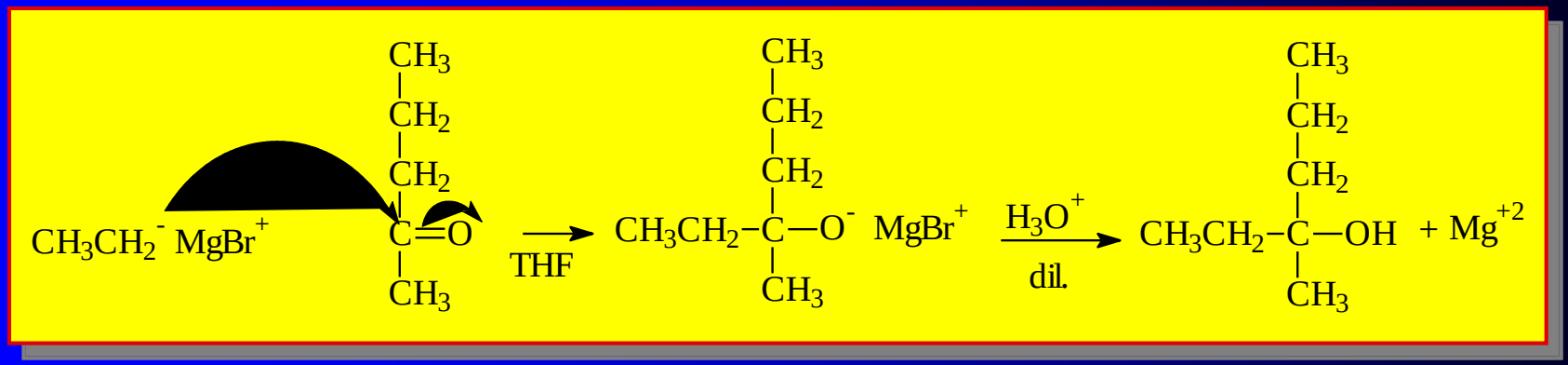
- **Addition to any other RCHO gives a 2° alcohol**



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

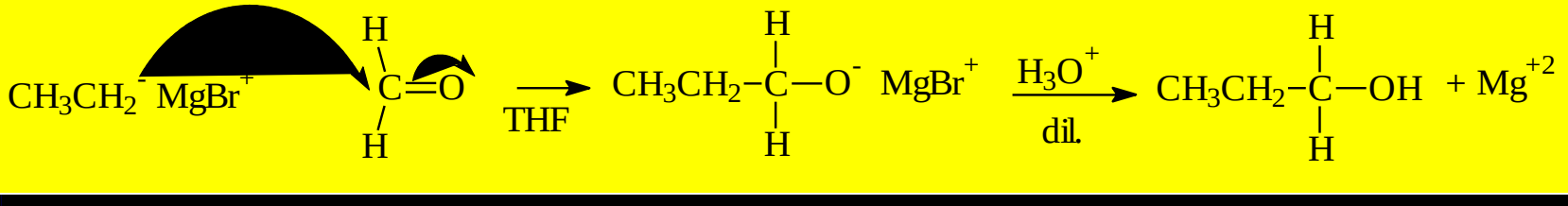
Grignard Reagents

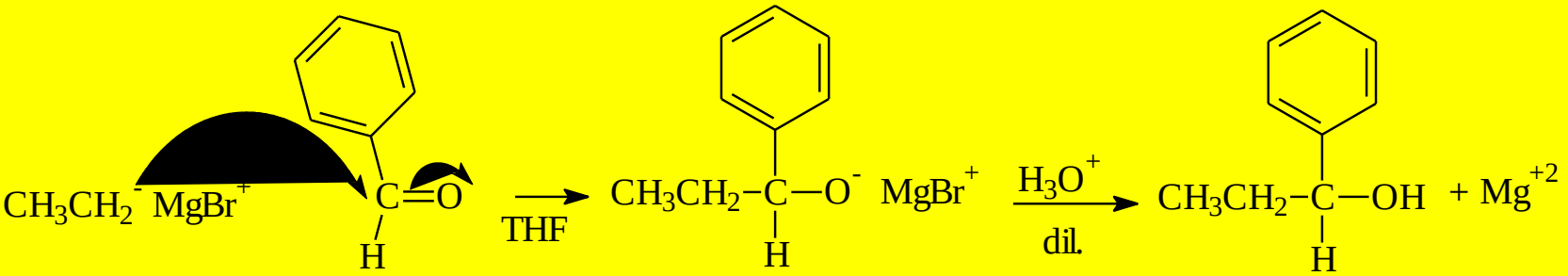
- Addition to a ketone gives a 3° alcohol

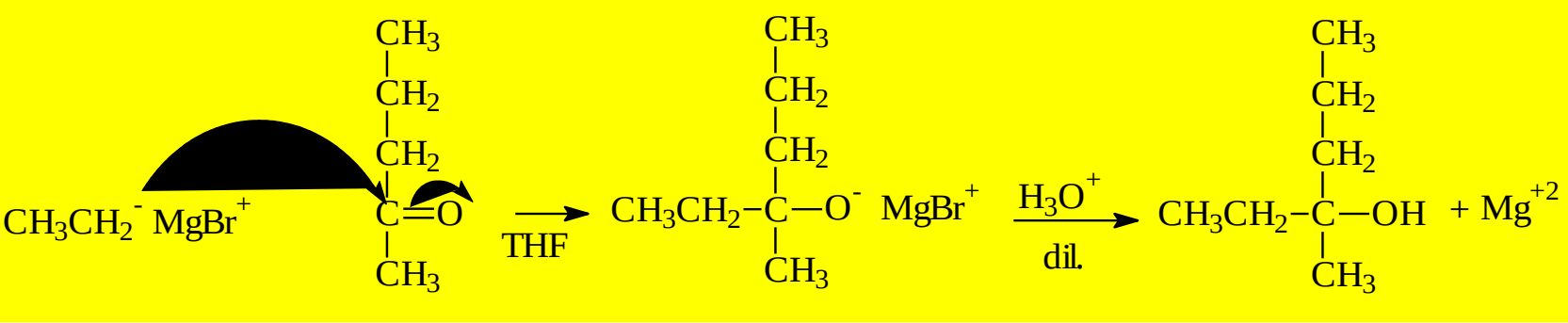


- Please try this with other Grignard reagents and other ketones

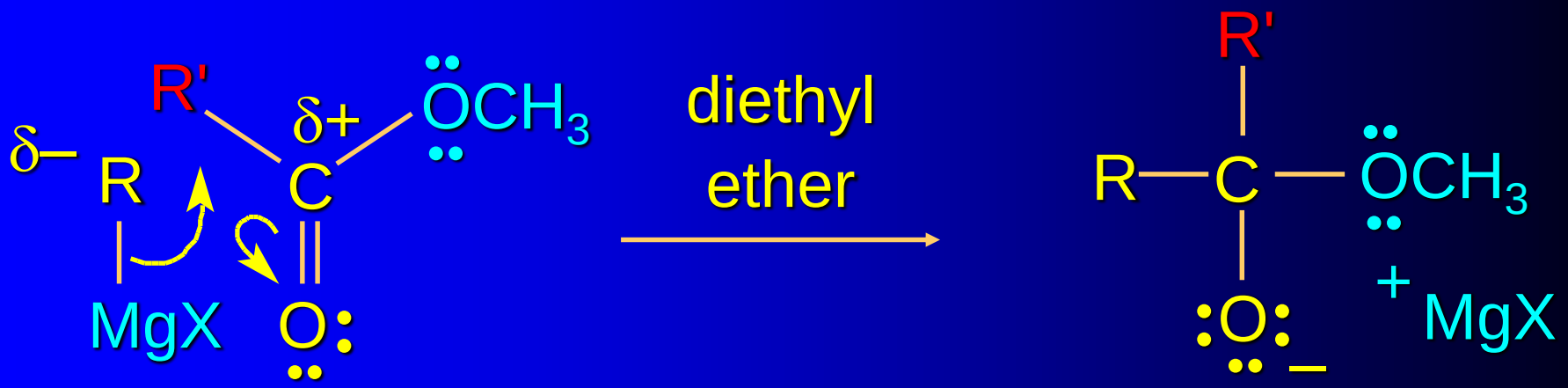
Grignard Reactions





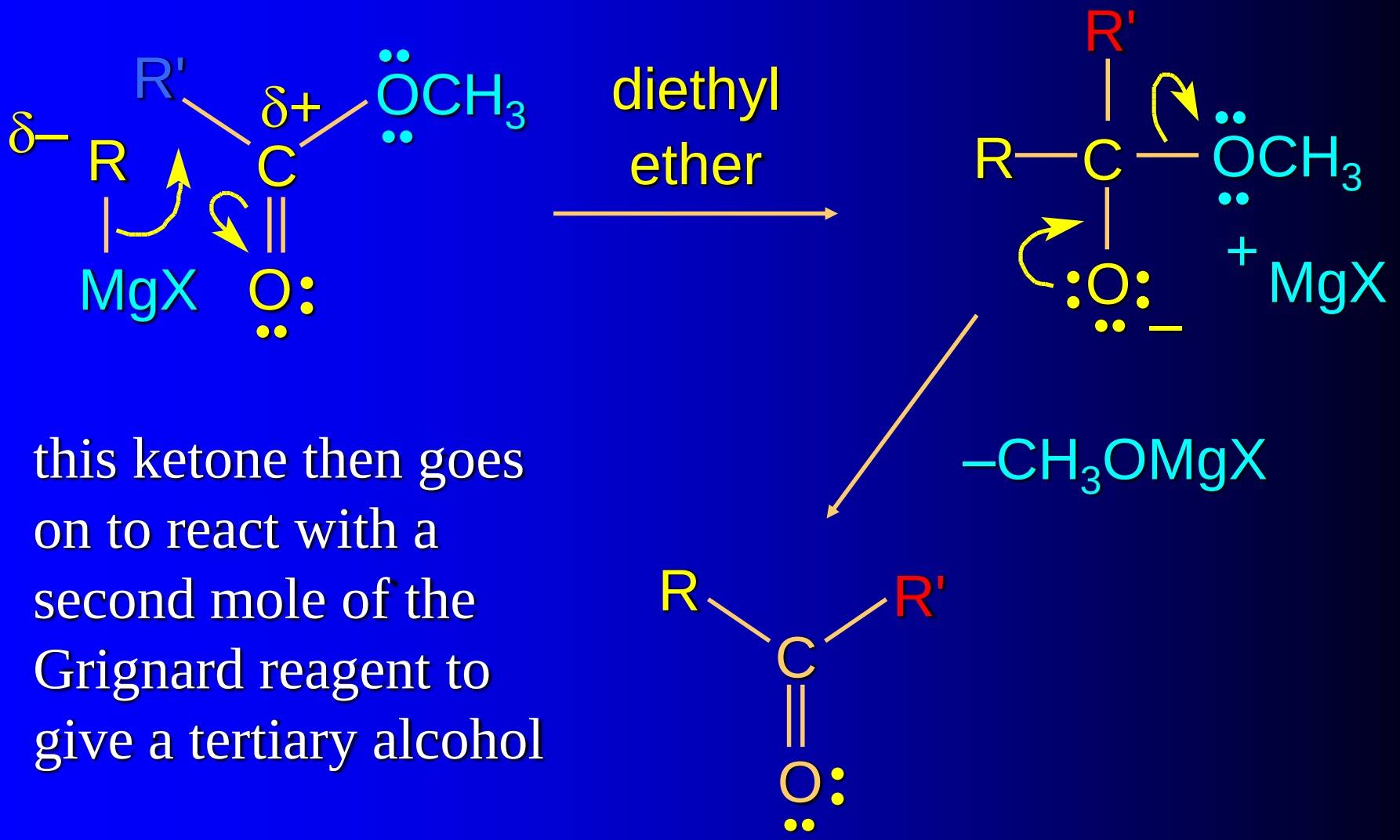


Grignard reagents also react with esters



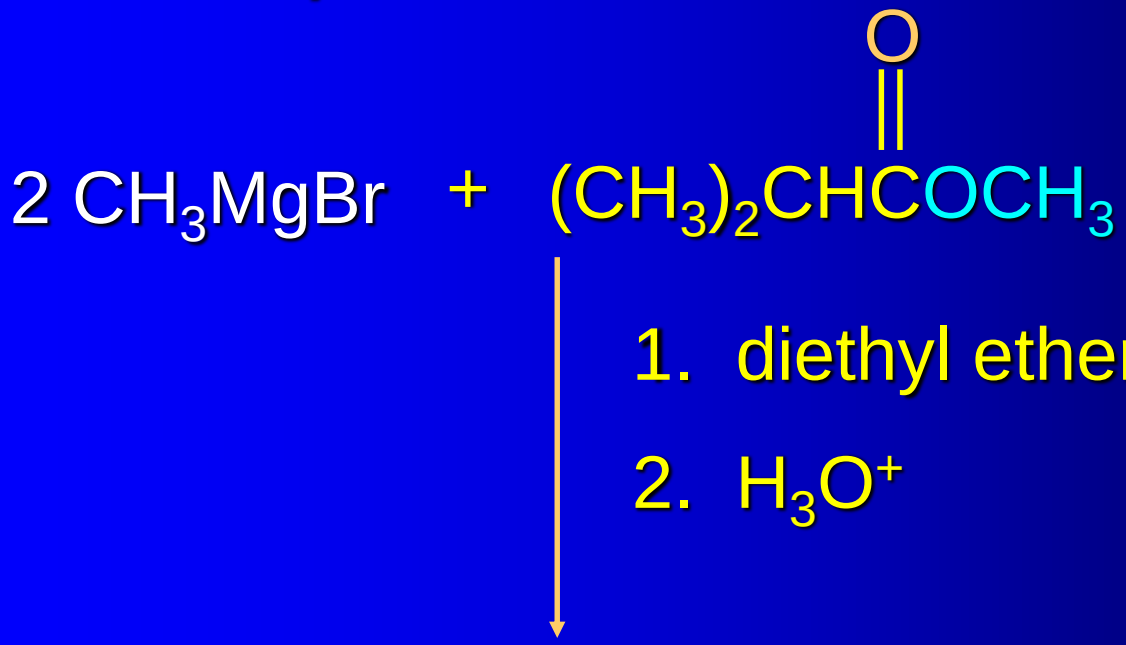
but species formed is unstable and dissociates under the reaction conditions to form a ketone

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

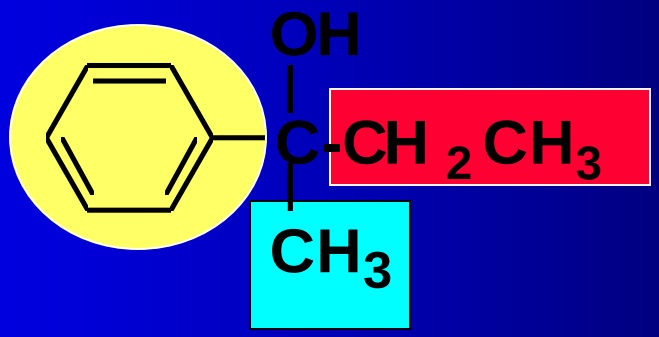
esters to give tertiary alcohols

CO_2 to give acids

 epoxides give primary alcohols

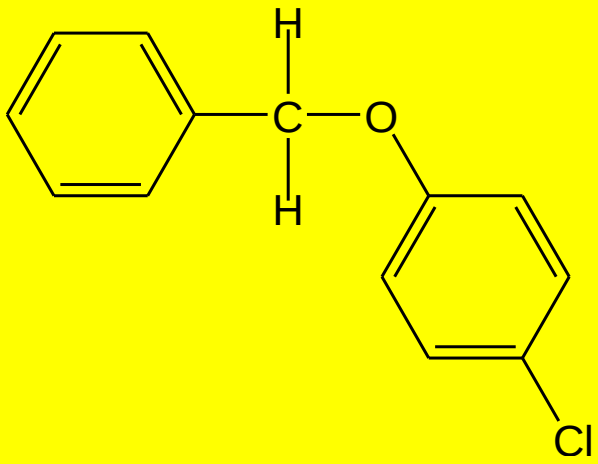
Grignard Reagents

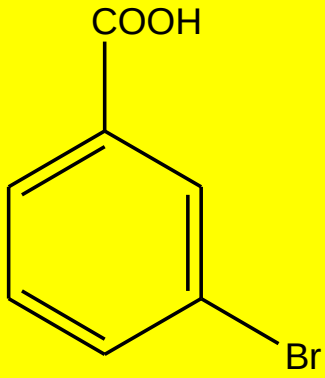
- **Problem:** 2-phenyl-2-butanol can be synthesized by three different combinations of a Grignard reagent and a ketone. Show each combination



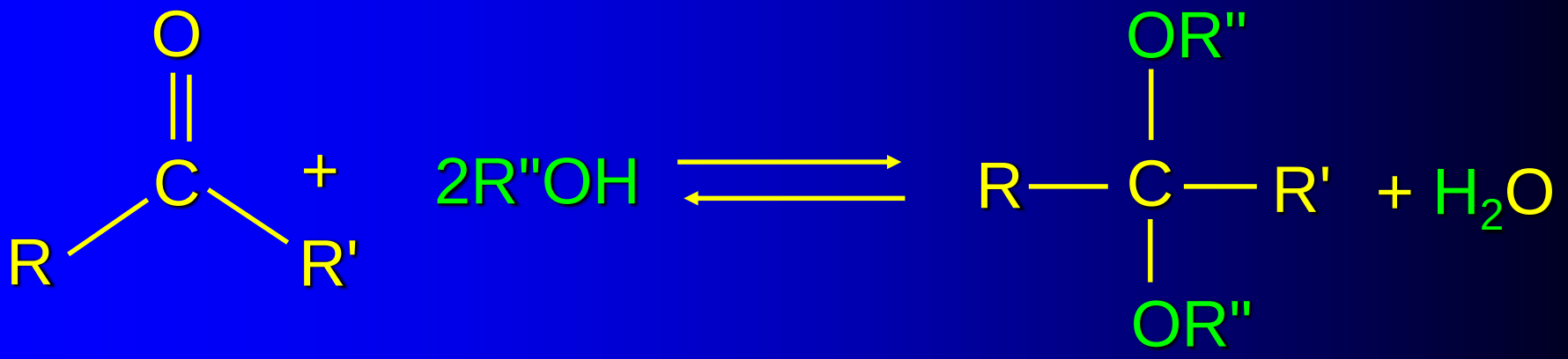
Practice Problem

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.

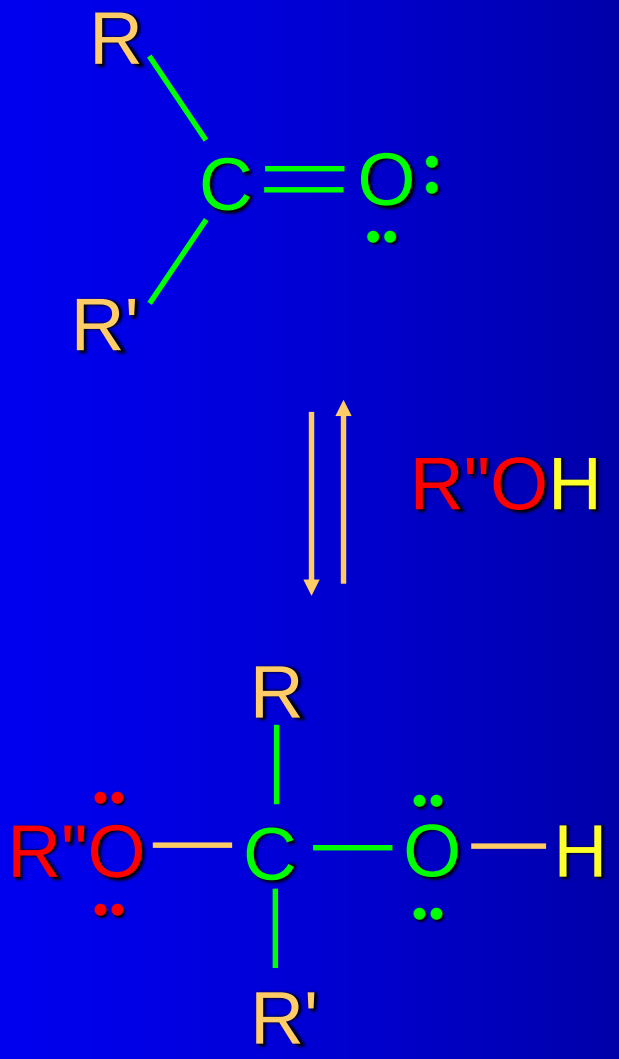




Oxygen Nucleophiles

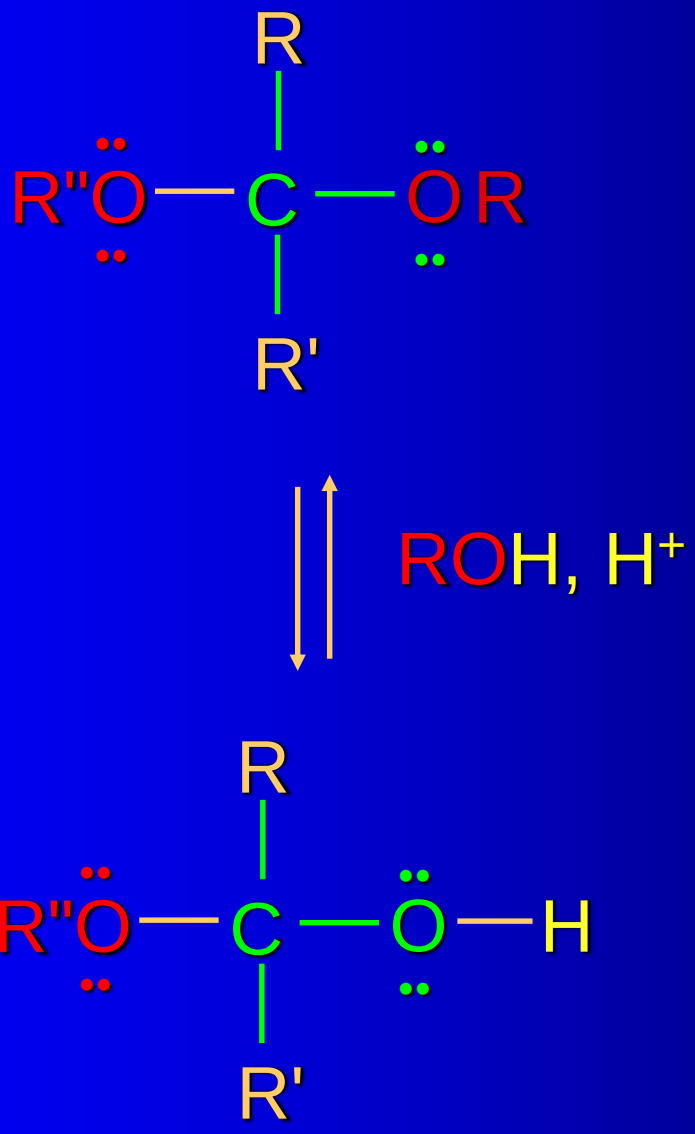


Alcohols React with Aldehydes and Ketones in two steps…first



Product is called a *hemiacetal*.

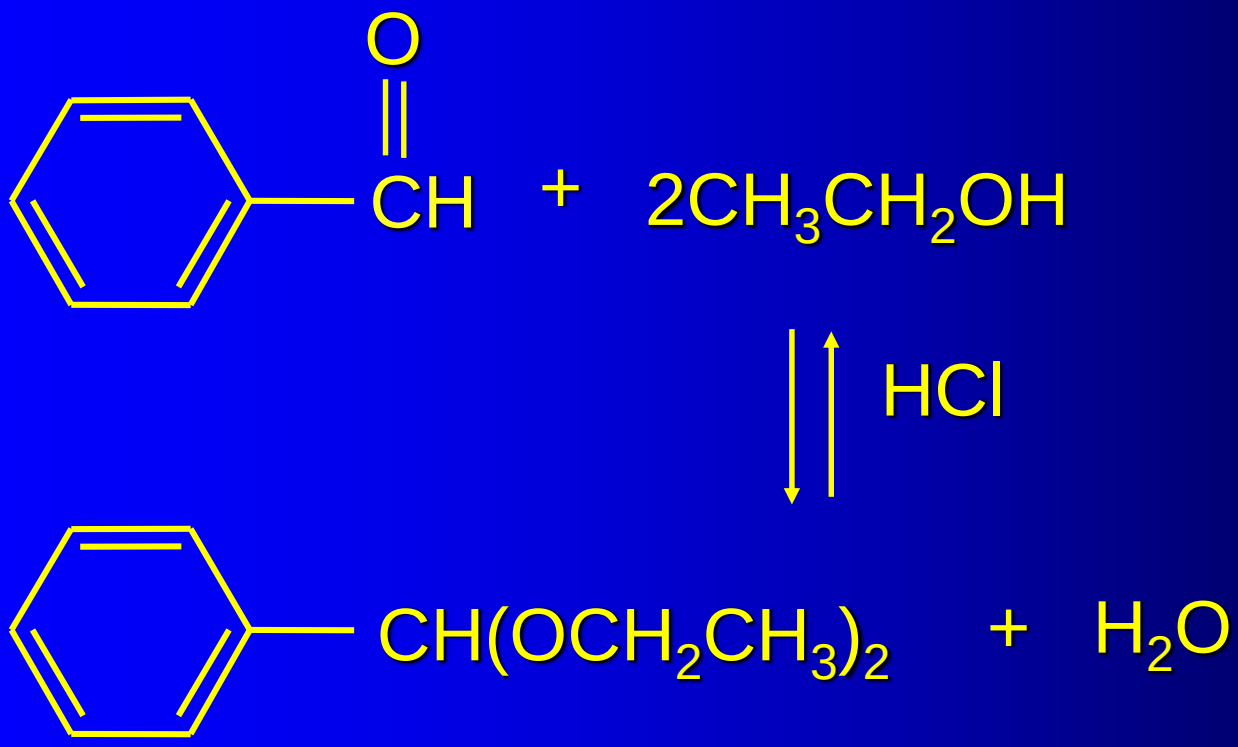
Hemiacetal reacts further in acid to yield an acetal



This product is called an *acetal*.

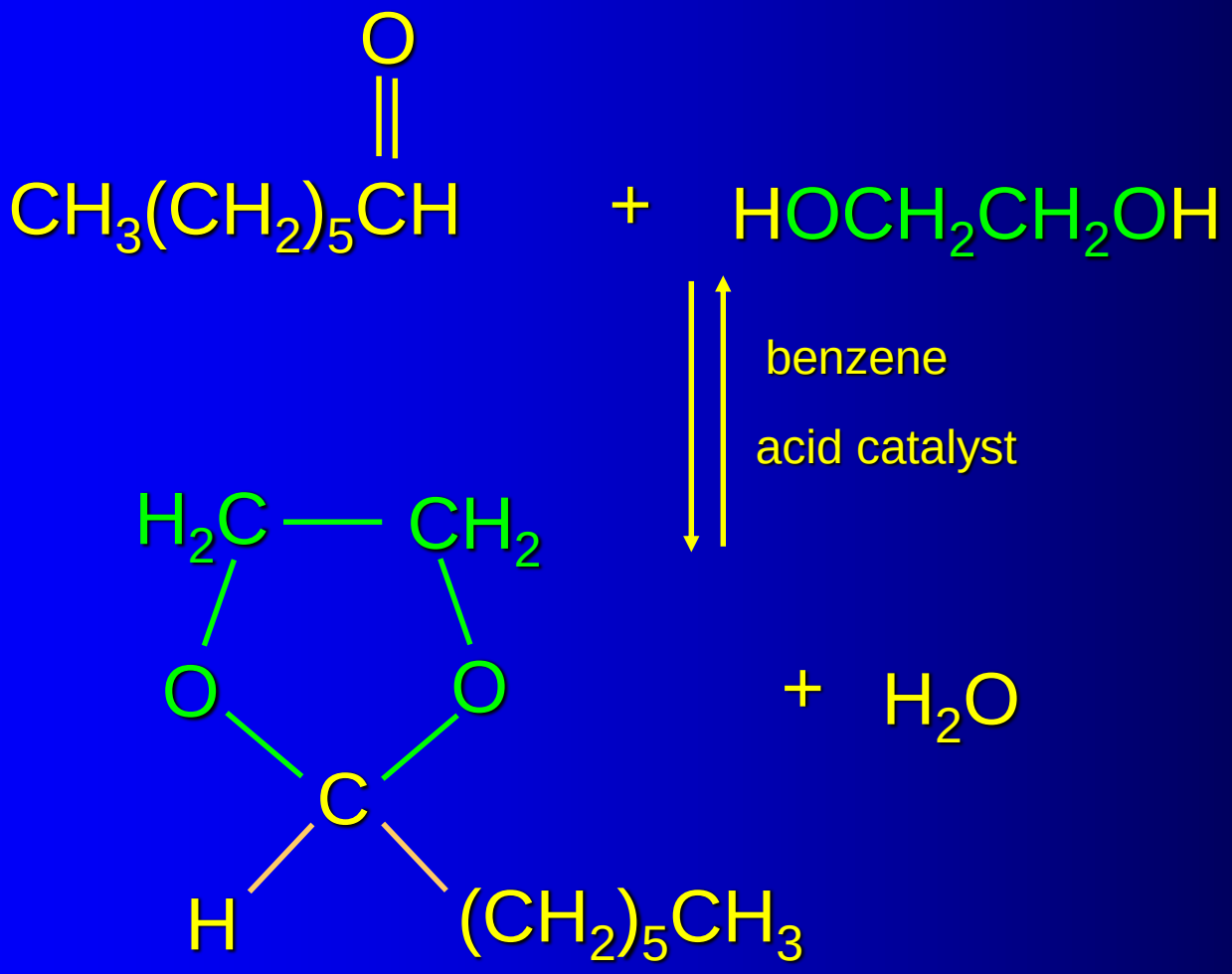
This *hemiacetal reacts further*.

Example

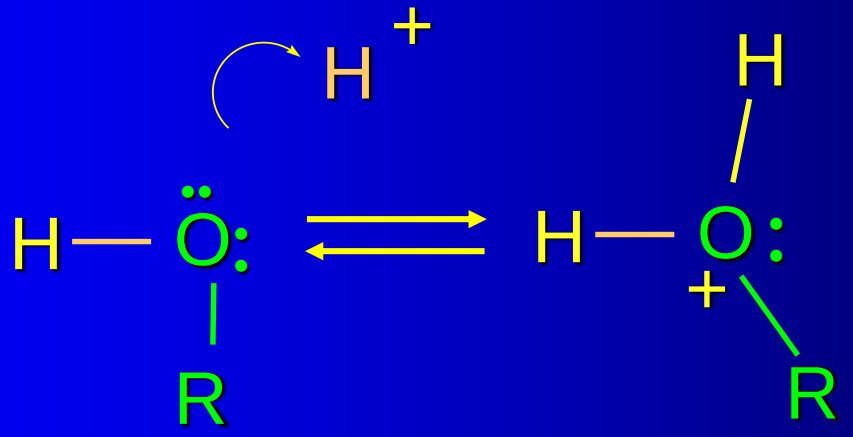


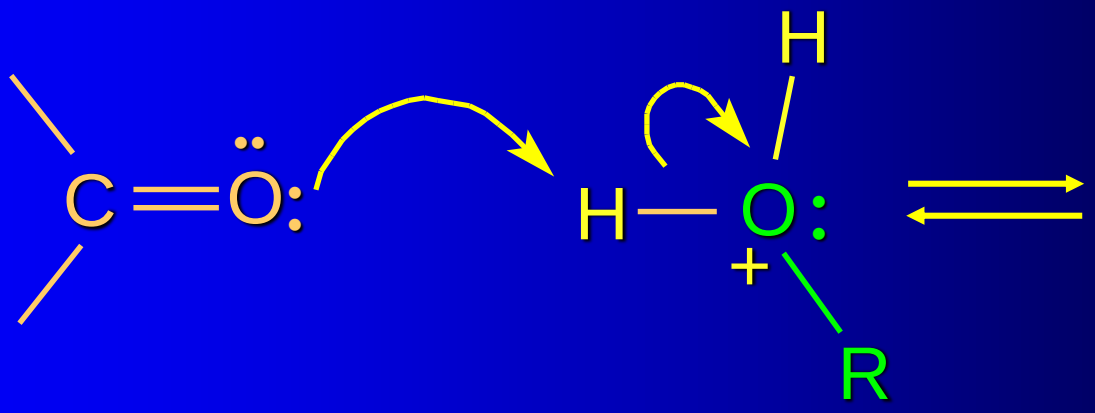
Benzaldehyde diethyl acetal

Diols Form Cyclic Acetals

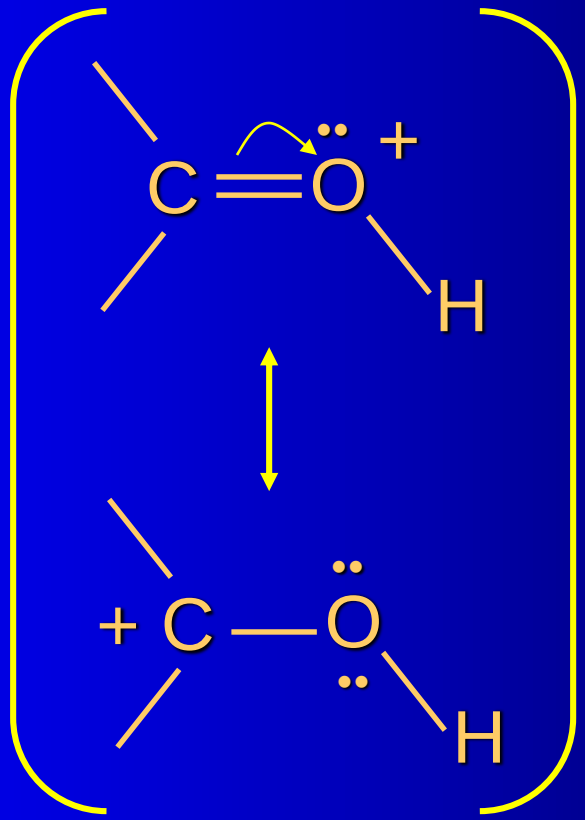


Mechanism of Acetal Formation



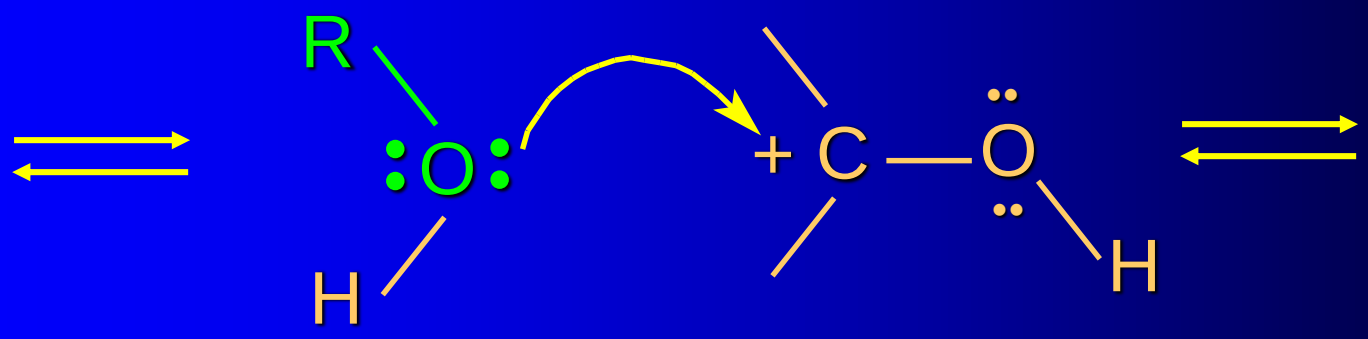


Mechanism

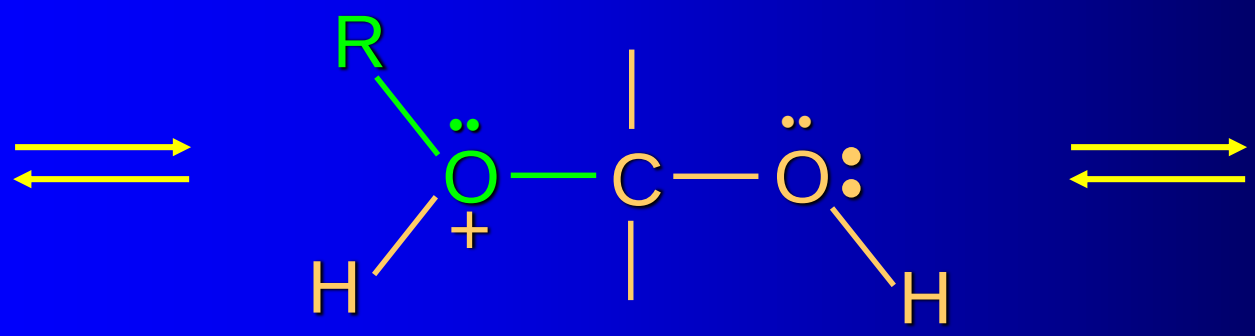


Resonance stabilized cation

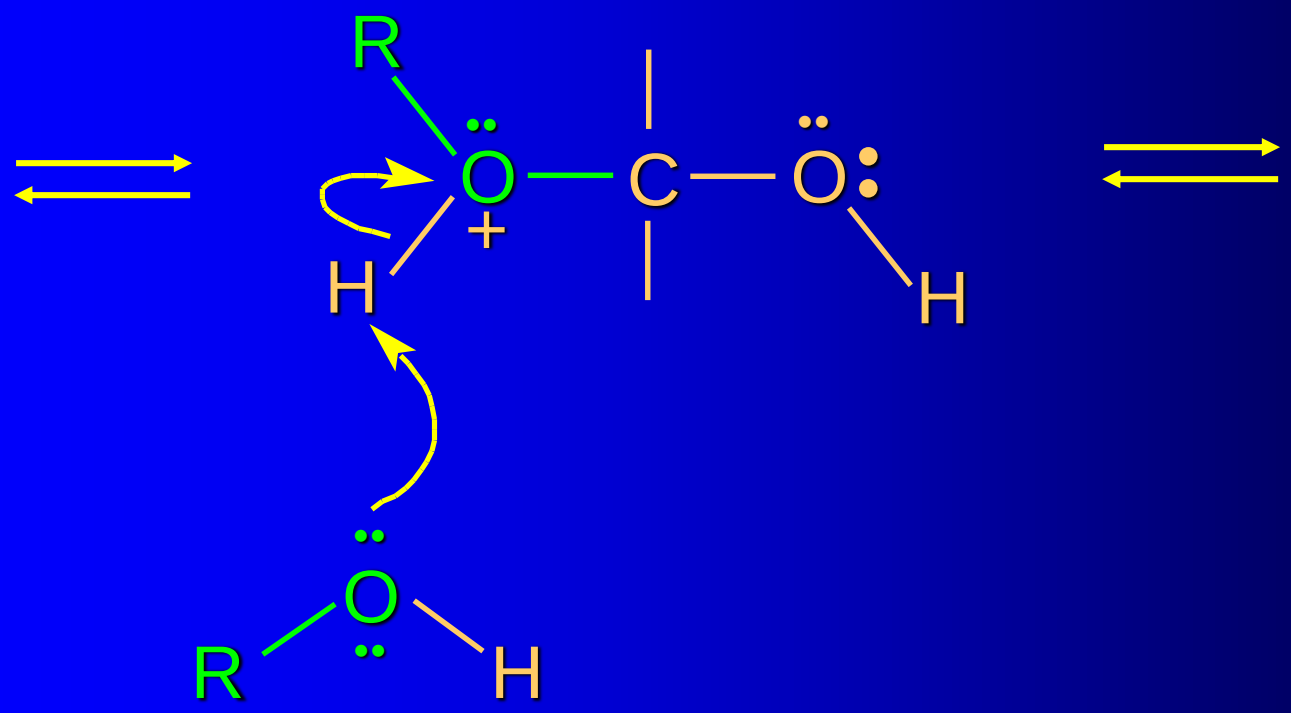
Mechanism



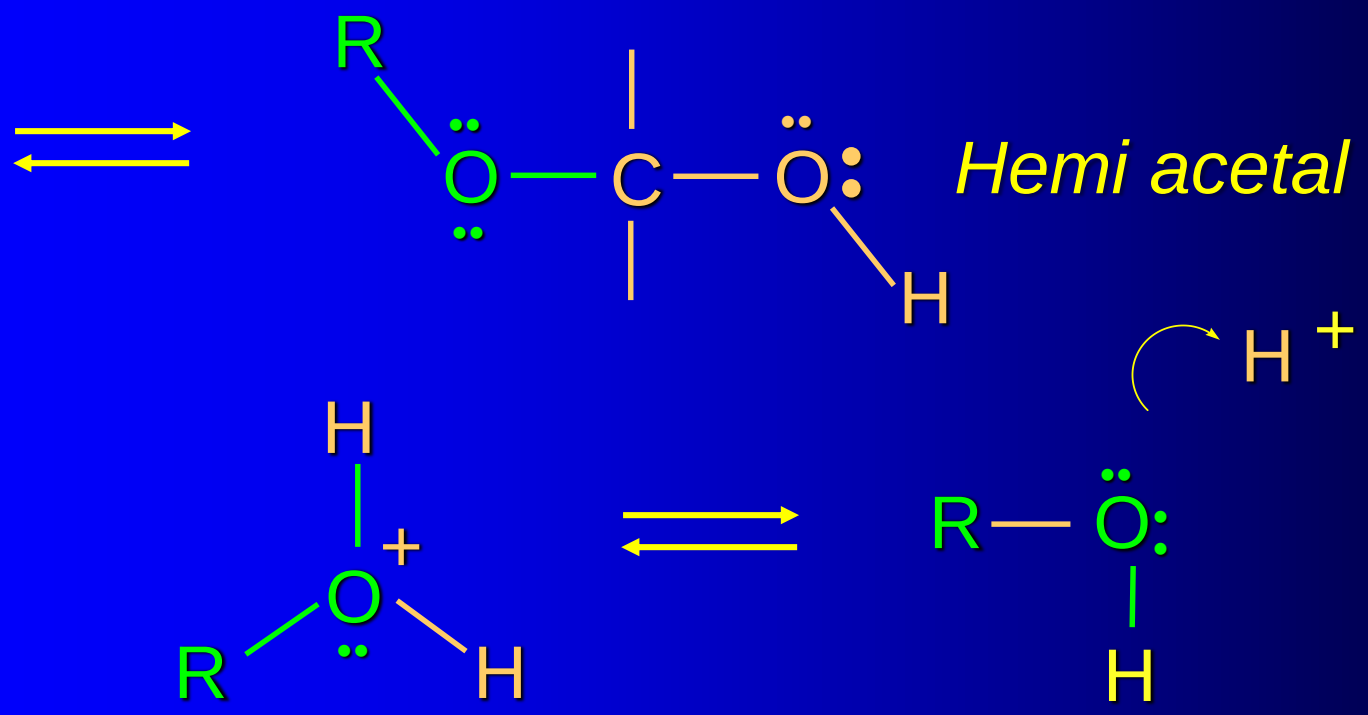
Mechanism



Mechanism



Mechanism

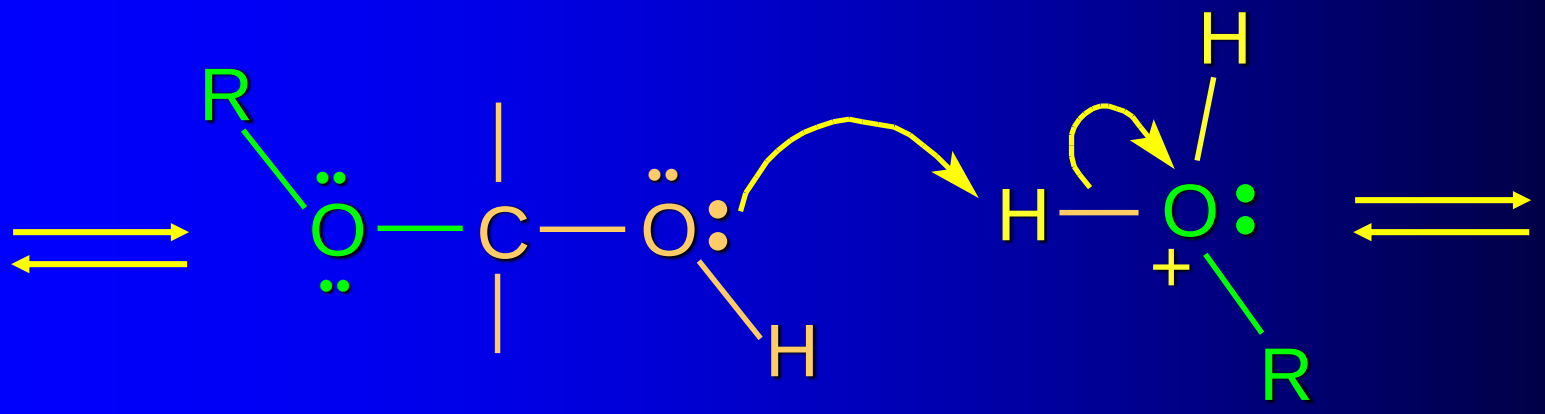


Mechanism of Acetal Formation

Second stage is hemiacetal-to-acetal conversion

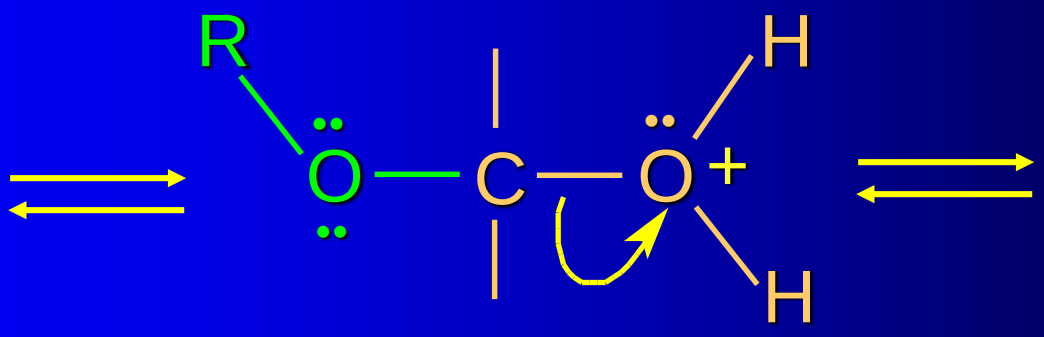
involves carbocation chemistry

Hemiacetal-to-acetal Stage

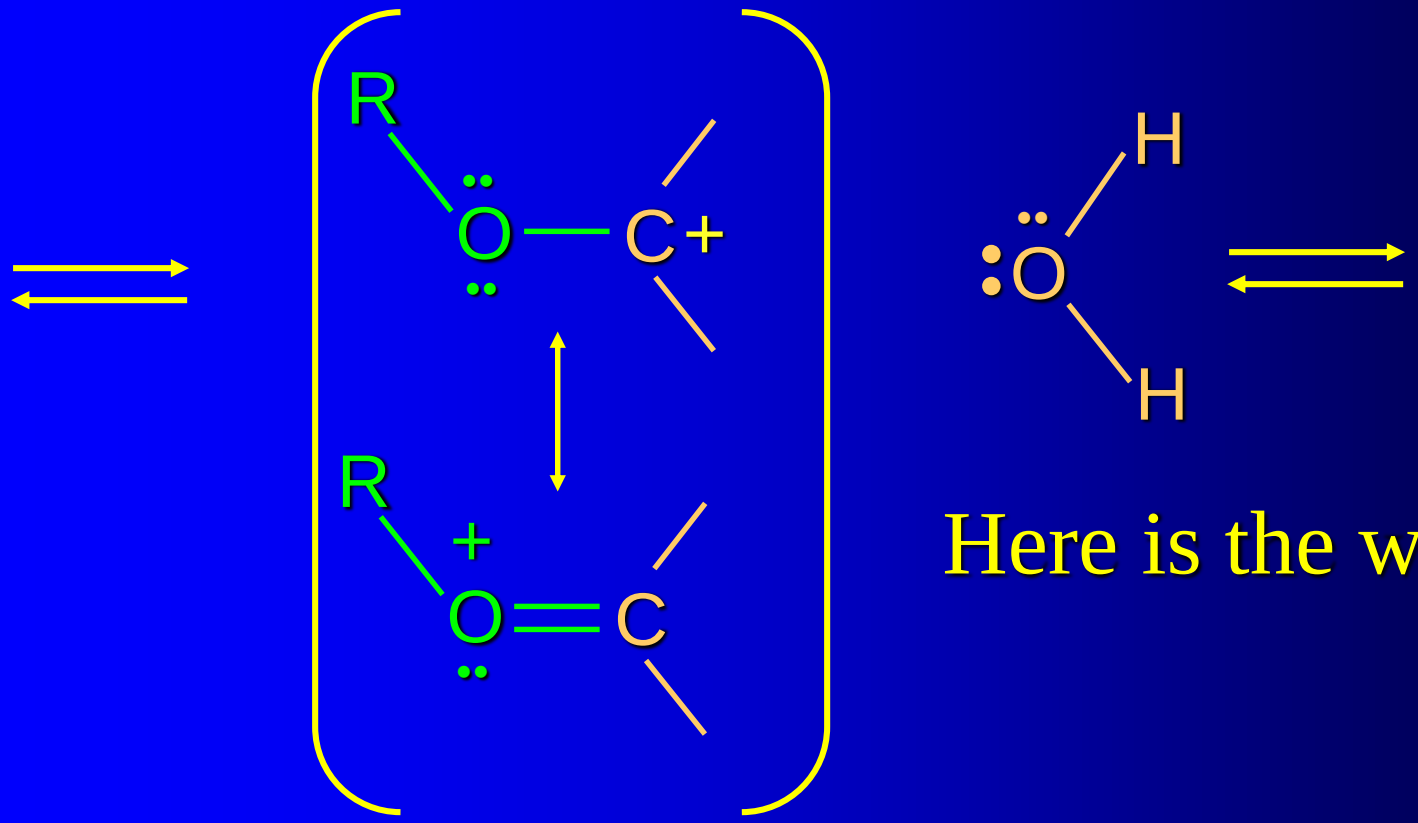


These are not separate reactions…
this is all one big equilibrium

Hemiacetal-to-acetal Stage

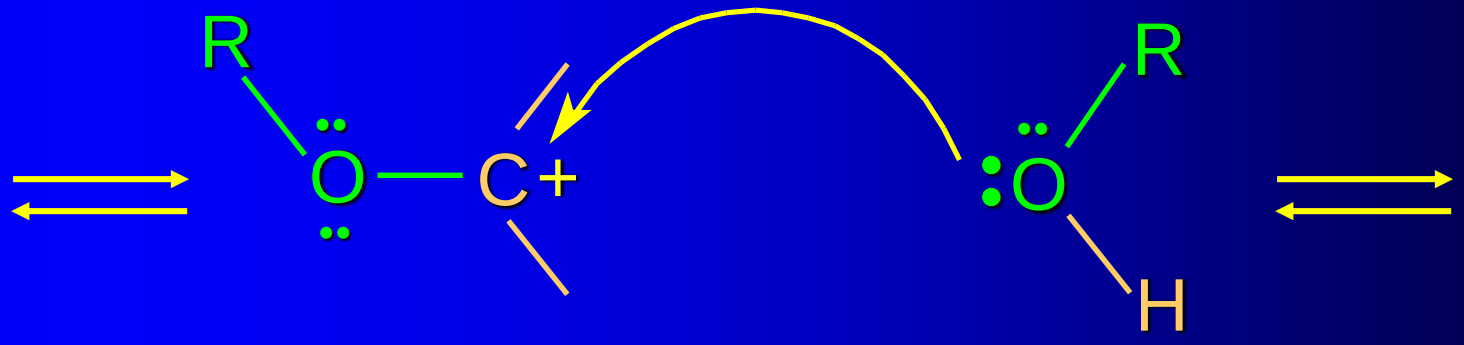


Hemiacetal-to-acetal Stage

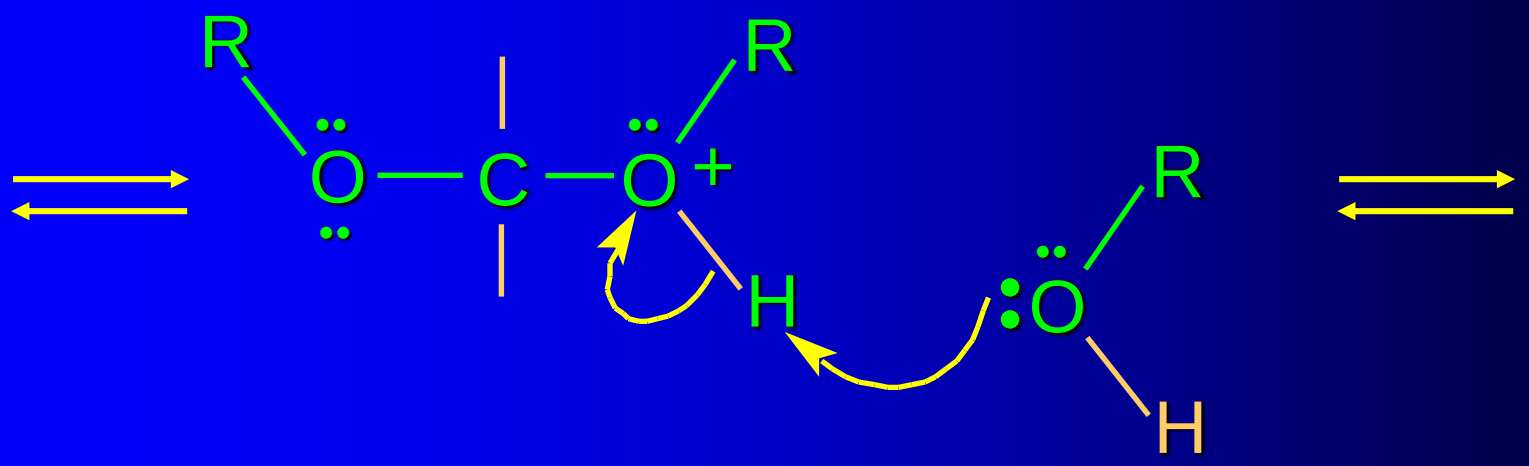


Here is the water!

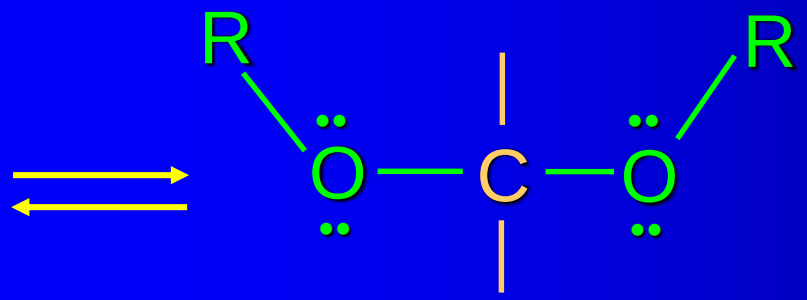
Hemiacetal-to-acetal Stage



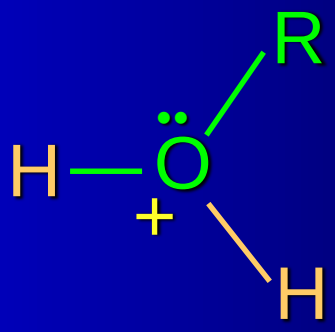
Hemiacetal-to-acetal Stage



Hemiacetal-to-acetal Stage



The acetal



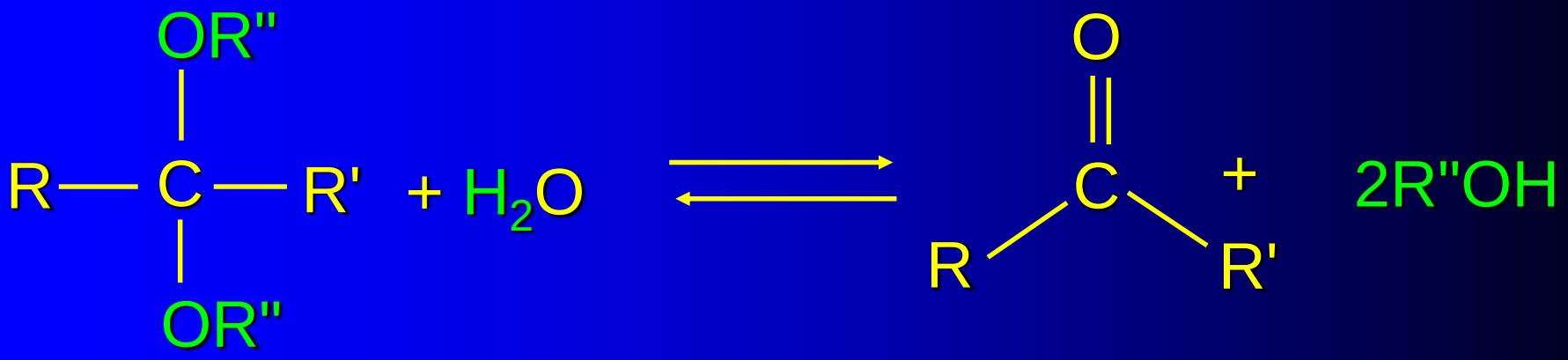
Regeneration of catalyst

Note that EVERY step is an equilibrium

Therefore, the reaction can be pushed forward or backward by appropriate choice of conditions

The forward reaction is synthesis
The backward reaction is hydrolysis

Hydrolysis of Acetals



mechanism:

reverse of acetal formation …hemiacetal is intermediate.

application:

aldehydes and ketones can be "protected" as acetals.