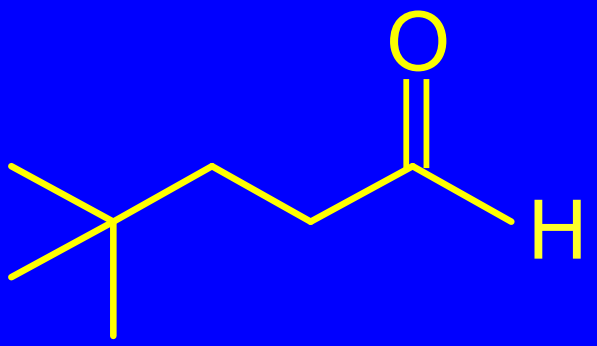
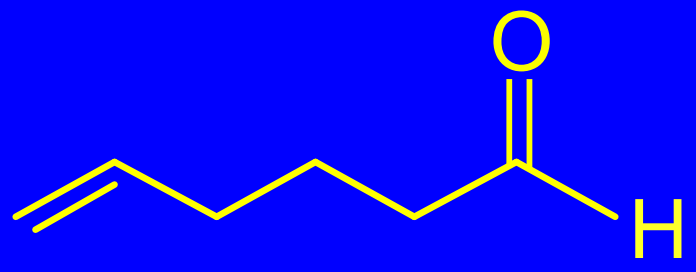
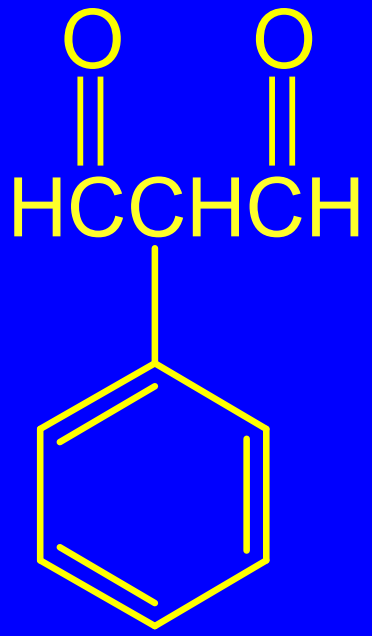
Aldehydes and Ketones. Nucleophilic Addition to the Carbonyl Group

Nomenclature

IUPAC Nomenclature of Aldehydes

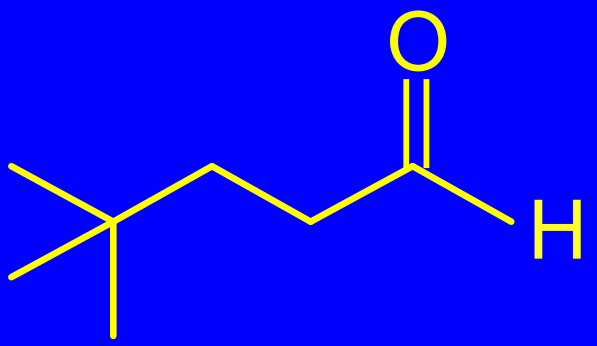




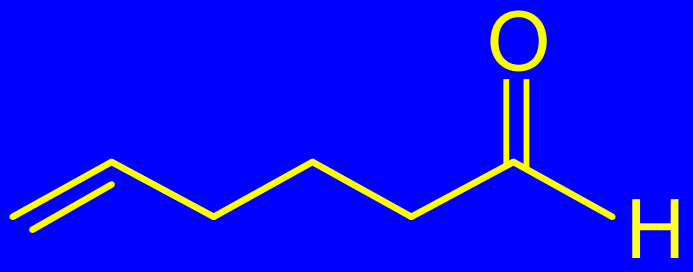


Base the name on the chain that contains the carbonyl group and replace the *-e* ending of the hydrocarbon by *-al*.

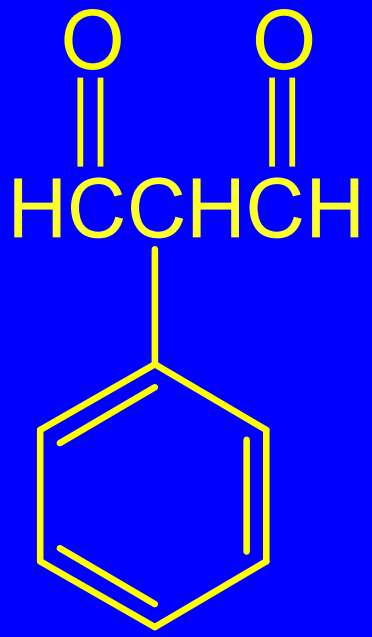
IUPAC Nomenclature of Aldehydes



4,4-dimethylpentanal

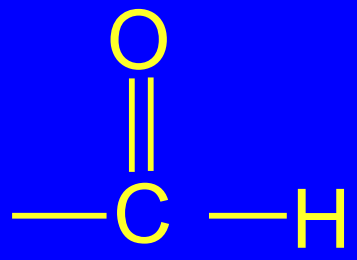


5-hexenal



2-phenylpropanedial
(keep the *-e* ending
before *-dial*)

IUPAC Nomenclature of Aldehydes



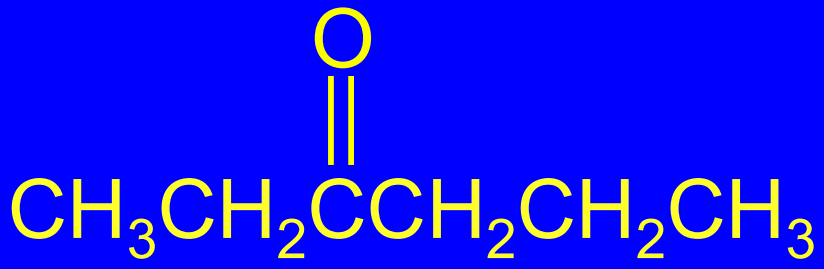
when named as a substituent

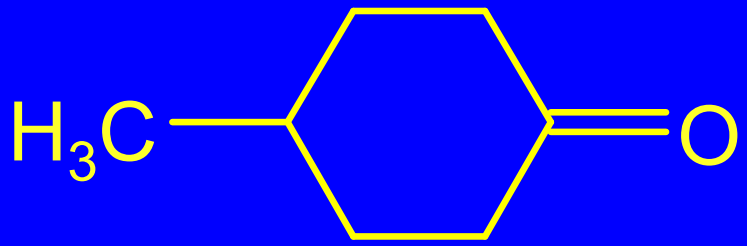
formyl group

when named as a suffix

carbaldehyde or carboxaldehyde

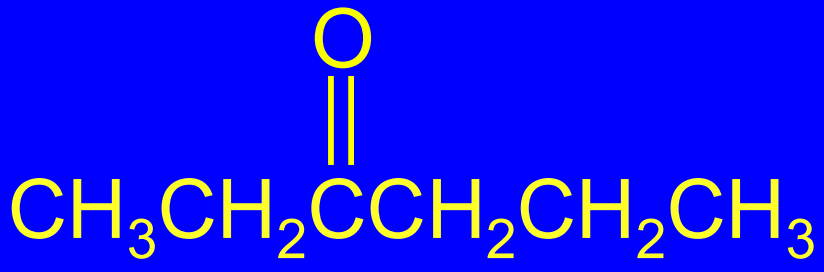
Substitutive IUPAC Nomenclature of Ketones





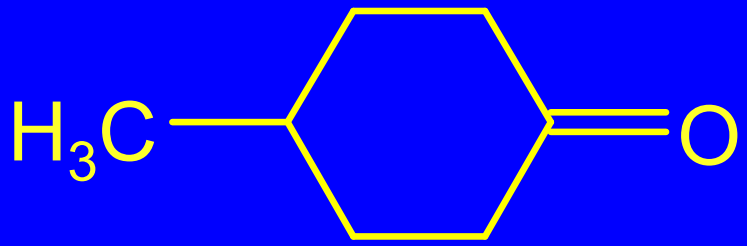
Base the name on the chain that contains the carbonyl group and replace *-e* by *-one*. Number the chain in the direction that gives the lowest number to the carbonyl carbon.

Substitutive IUPAC Nomenclature of Ketones



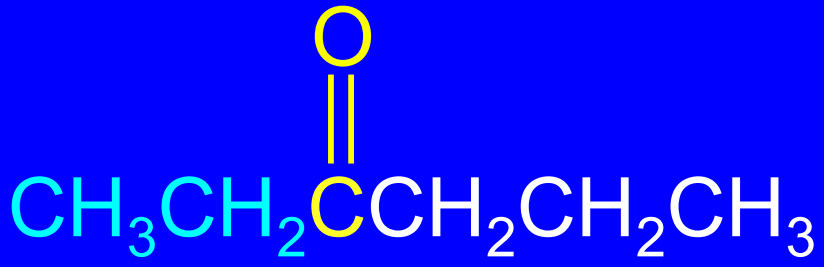
3-hexanone

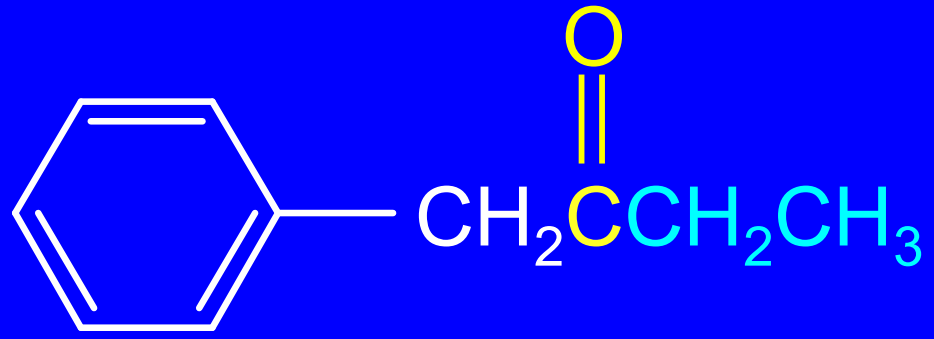
4-methyl-2-pentanone

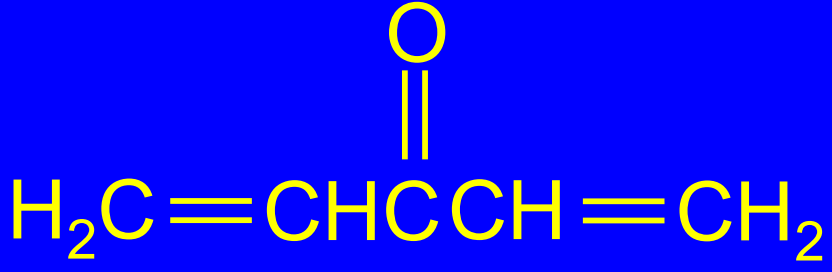


4-methylcyclohexanone

Functional Class IUPAC Nomenclature of Ketones

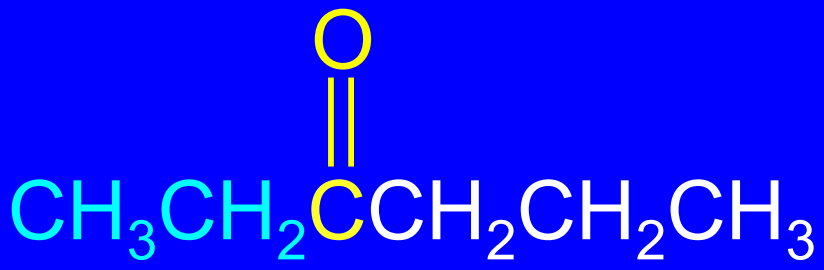




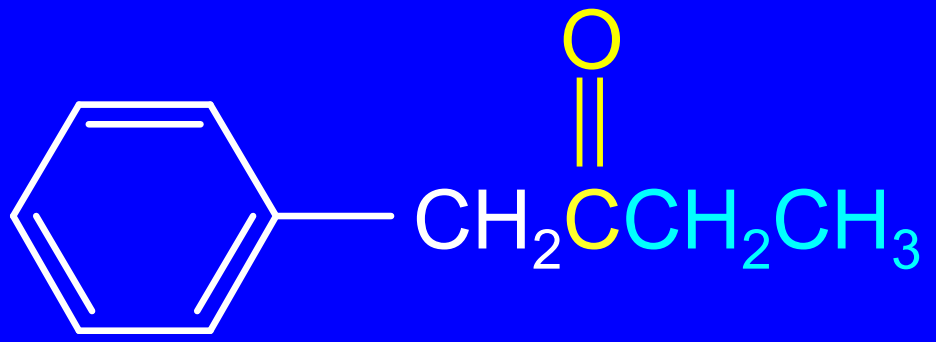


List the groups attached to the carbonyl separately in alphabetical order, and add the word *ketone*.

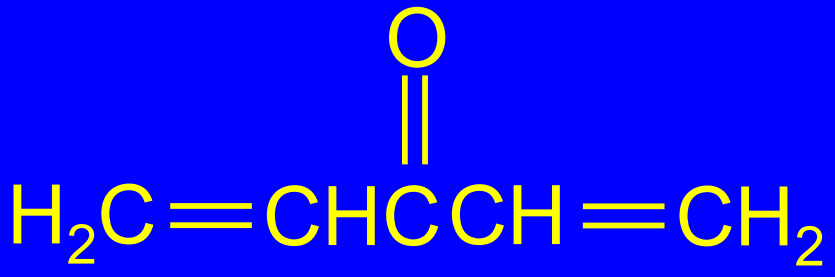
Functional Class IUPAC Nomenclature of Ketones



ethyl propyl ketone



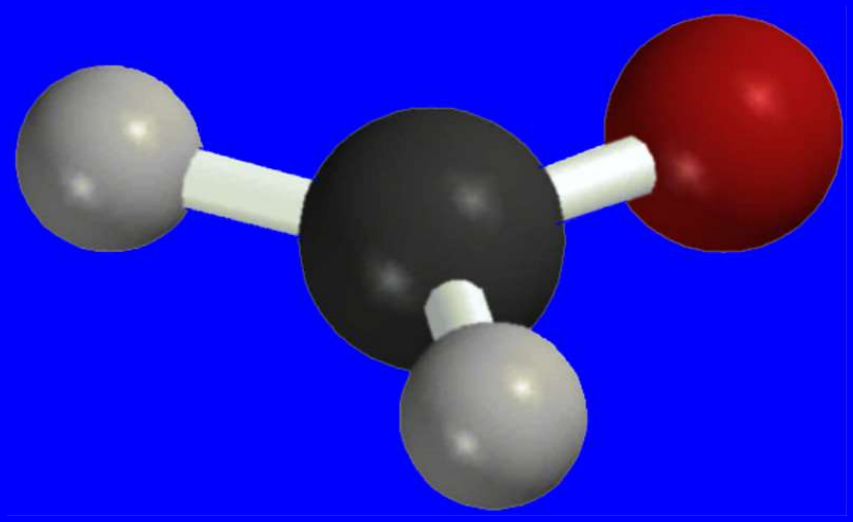
benzyl ethyl ketone



divinyl ketone

Structure and Bonding: The Carbonyl Group

Structure of Formaldehyde



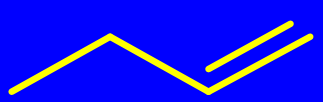
planar

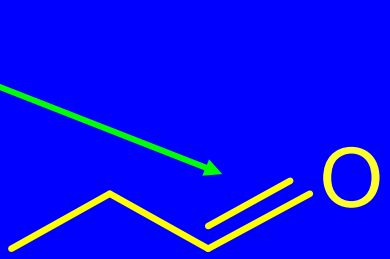
bond angles: close to 120°

C=O bond distance: 122 pm

The Carbonyl Group

very polar double bond





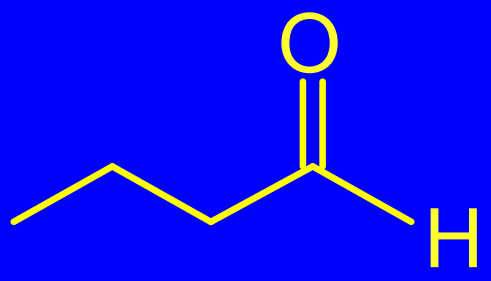
1-butene

propanal

dipole moment = 0.3D

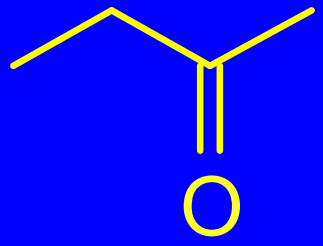
dipole moment = 2.5D

Carbonyl group of a ketone is more stable than that of an aldehyde



heat of combustion

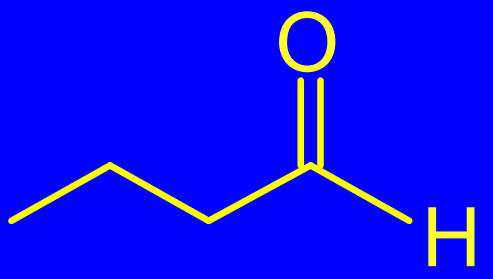
2475 kJ/mol



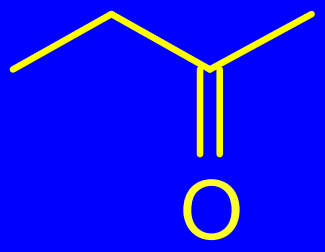
2442 kJ/mol

Alkyl groups stabilize carbonyl groups the same way they stabilize carbon-carbon double bonds, carbocations, and free radicals.

Spread is greater for aldehydes and ketones than for alkenes



2475 kJ/mol



2442 kJ/mol

Heats of combustion of C_4H_8 isomeric alkenes

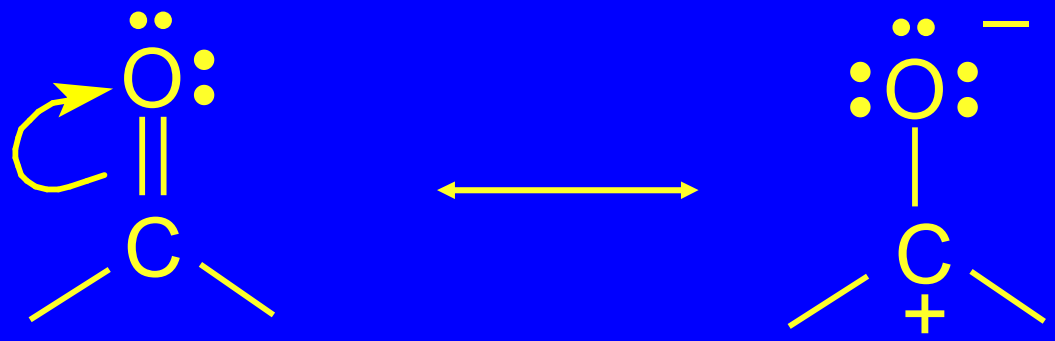
$CH_3CH_2CH=CH_2$
2717 kJ/mol

cis-$CH_3CH=CHCH_3$
2710 kJ/mol

trans-$CH_3CH=CHCH_3$
2707 kJ/mol

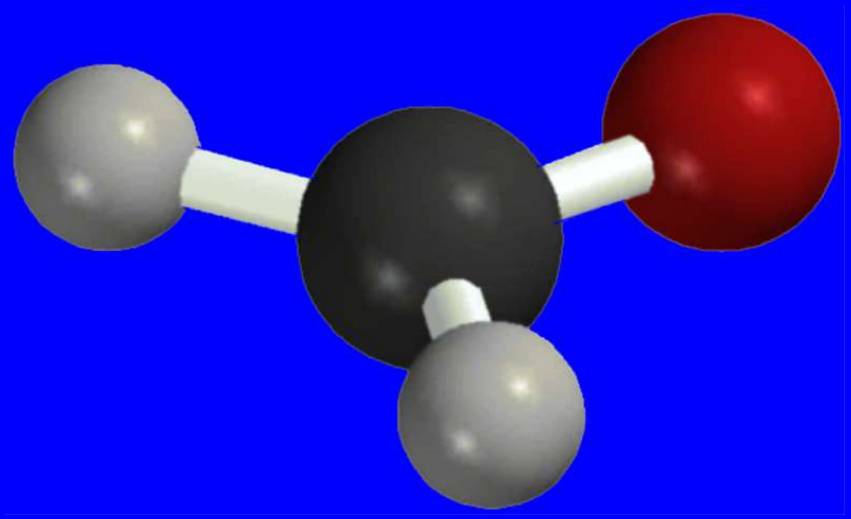
$(CH_3)_2C=CH_2$
2700 kJ/mol

Resonance Description of Carbonyl Group



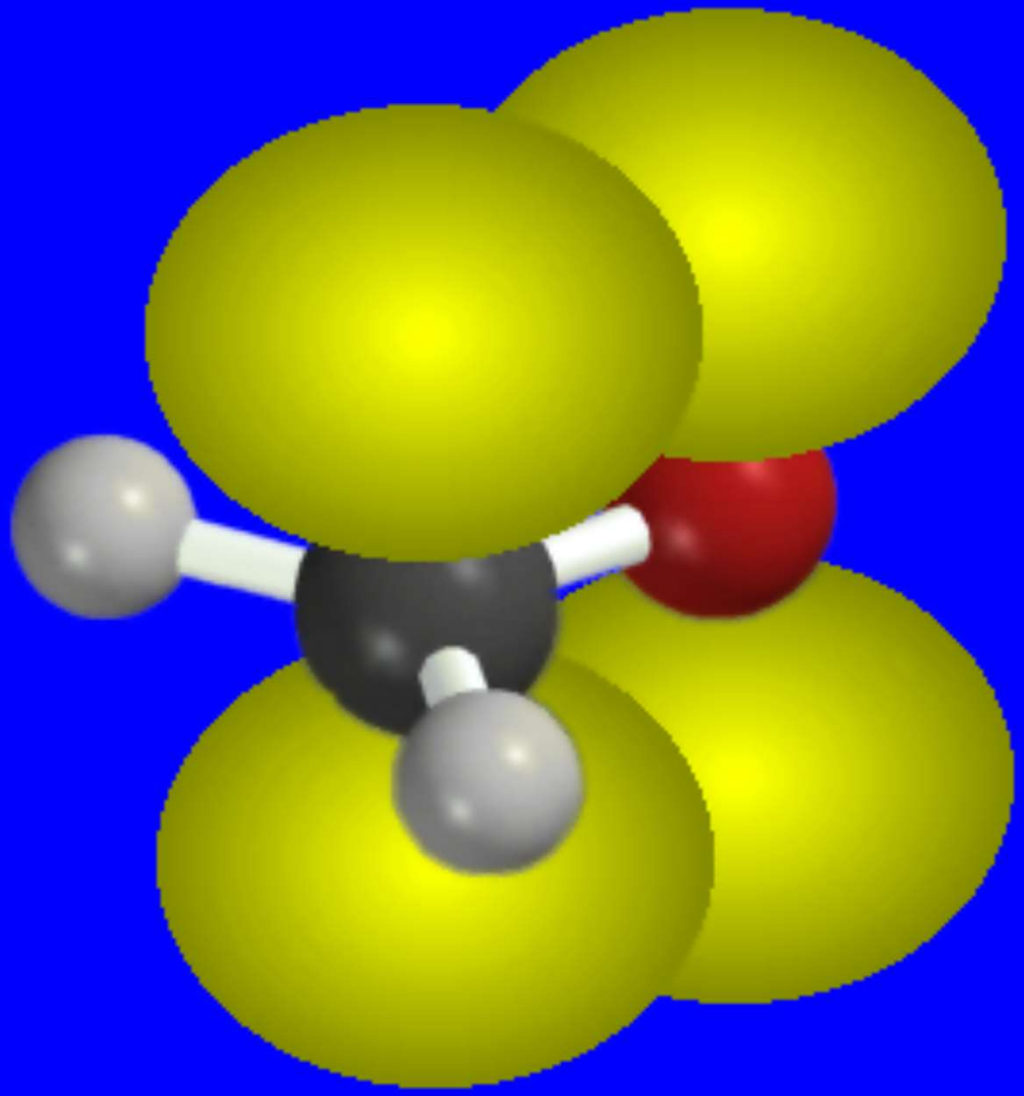
nucleophiles attack carbon;
electrophiles attack oxygen

Bonding in Formaldehyde



Carbon and oxygen are sp^2 hybridized

Bonding in Formaldehyde

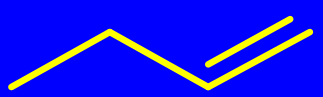


The half-filled *p* orbitals on carbon and oxygen overlap to form a π bond

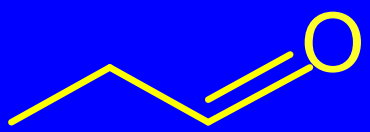
17.3
Physical Properties

Aldehydes and ketones have higher boiling than alkenes, but lower boiling points than alcohols.

boiling point



–6°C



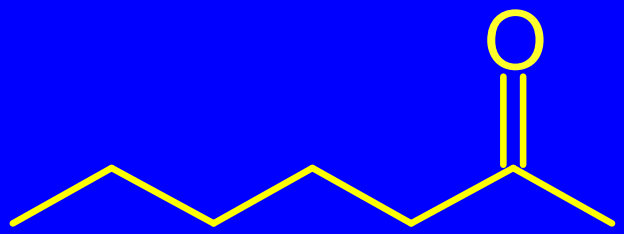
49°C

97°C

More polar than alkenes, but cannot form intermolecular hydrogen bonds to other carbonyl groups

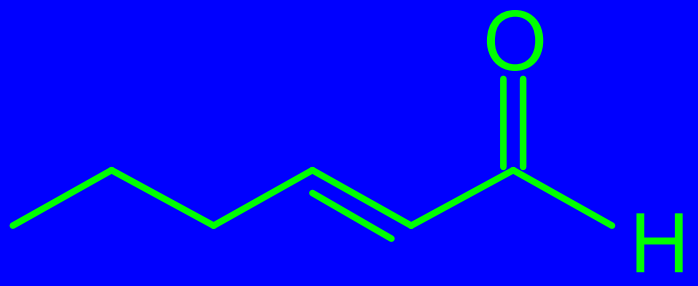
Sources of Aldehydes and Ketones

Many aldehydes and ketones occur naturally



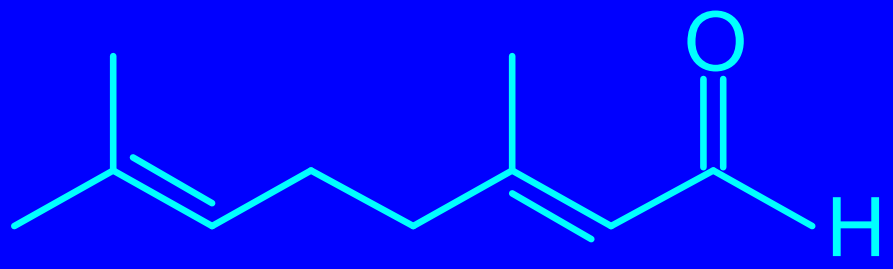
2-heptanone
(component of alarm pheromone of bees)

Many aldehydes and ketones occur naturally



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

Many aldehydes and ketones occur naturally



citral (from lemon grass oil)

Synthesis of Aldehydes and Ketones

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

from alkenes

ozonolysis

from alkynes

hydration (via enol)

from arenes

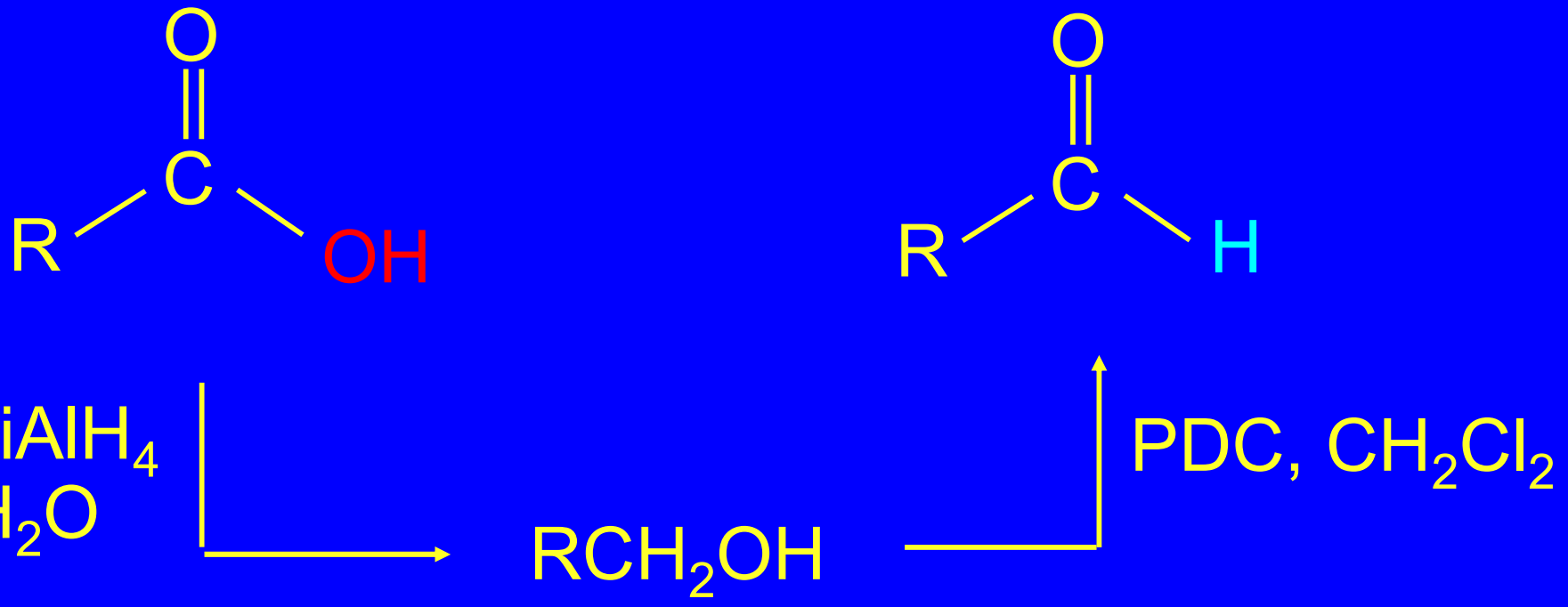
Friedel-Crafts acylation

from alcohols

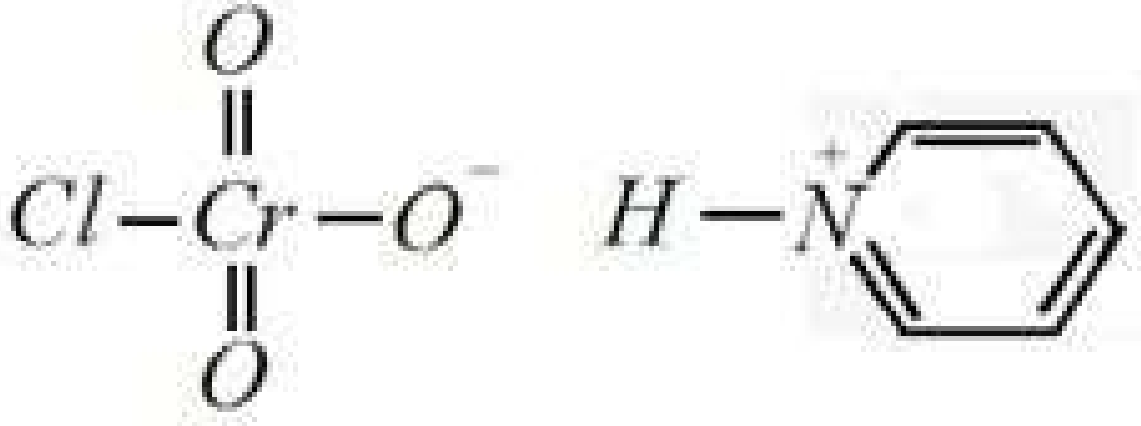
oxidation

What about..?

aldehydes from carboxylic acids



Oxidação de Álcoois em aldeídos e cetonas. o dicromato de piridínio (também conhecido como Reagente de Cornforth e citado em algumas literaturas como Piridínio Dicromato - PDC) é um reagente que é muito usado devido a sua eficiência na oxidação seletiva de álcoois em aldeídos e cetonas

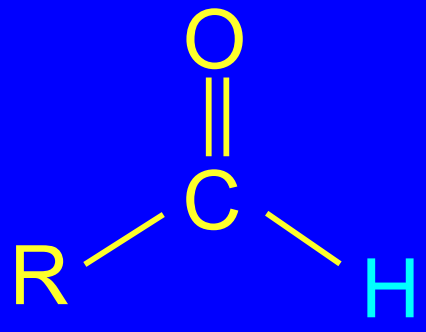


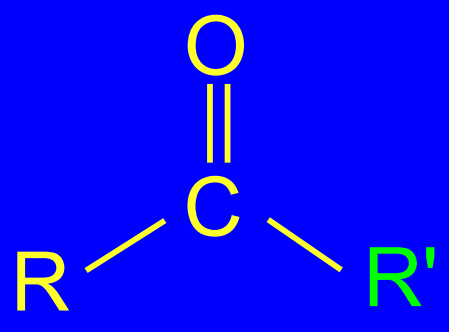
Example

benzaldehyde from benzoic acid

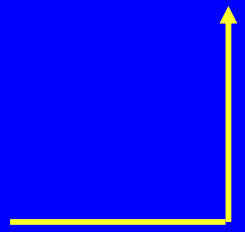
What about..?

ketones from aldehydes





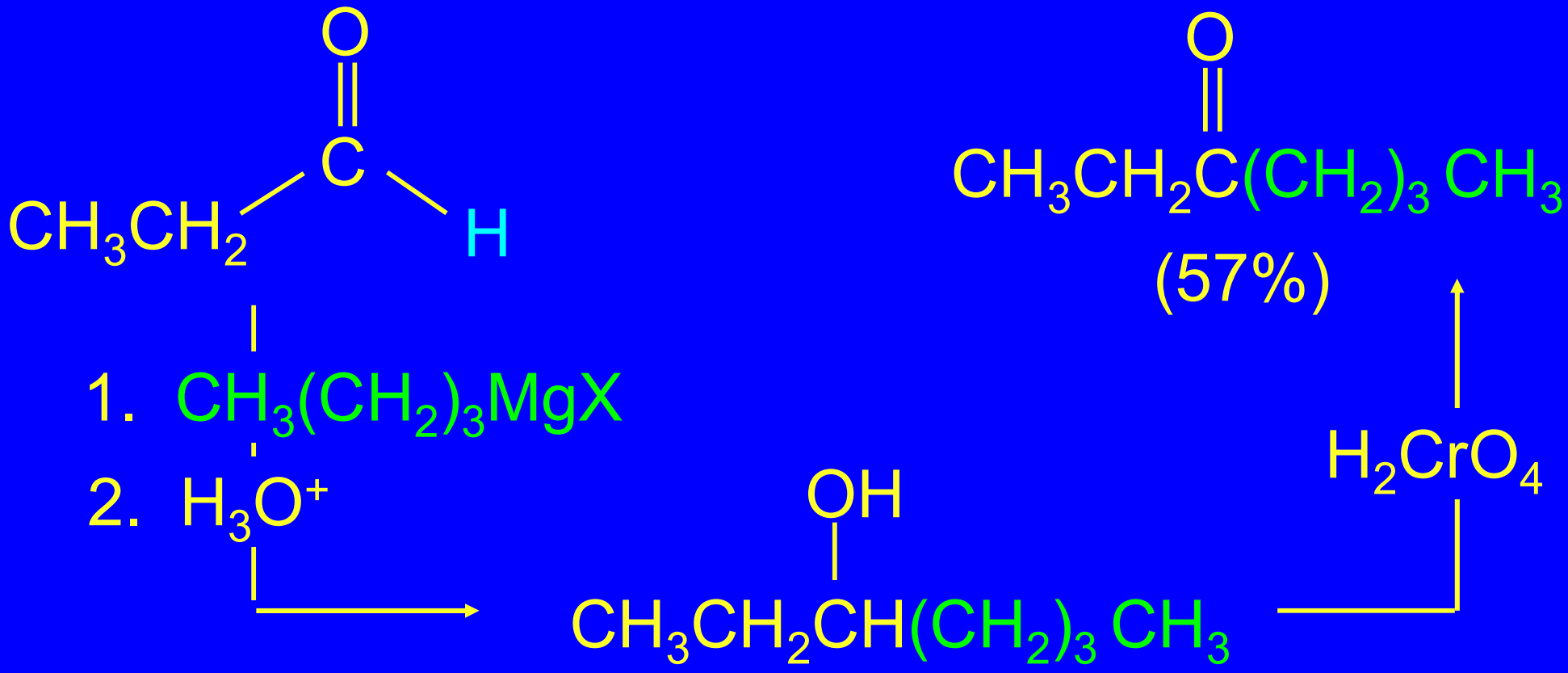
1. R'MgX
2. H_3O^+



PDC, CH_2Cl_2

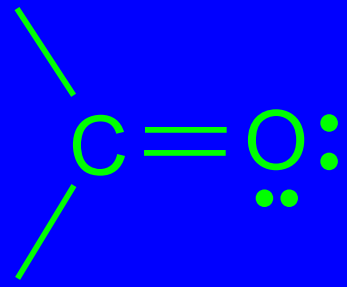
Example

3-heptanone from propanal

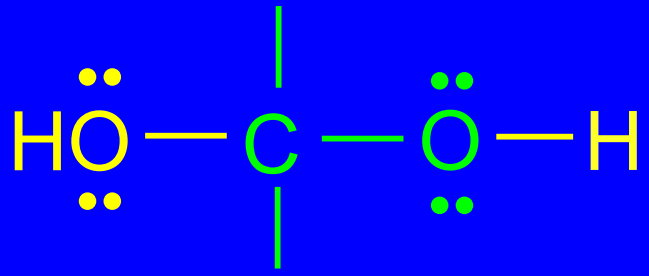


Principles of Nucleophilic Addition to Carbonyl Groups: Hydration of Aldehydes and Ketones

Hydration of Aldehydes and Ketones

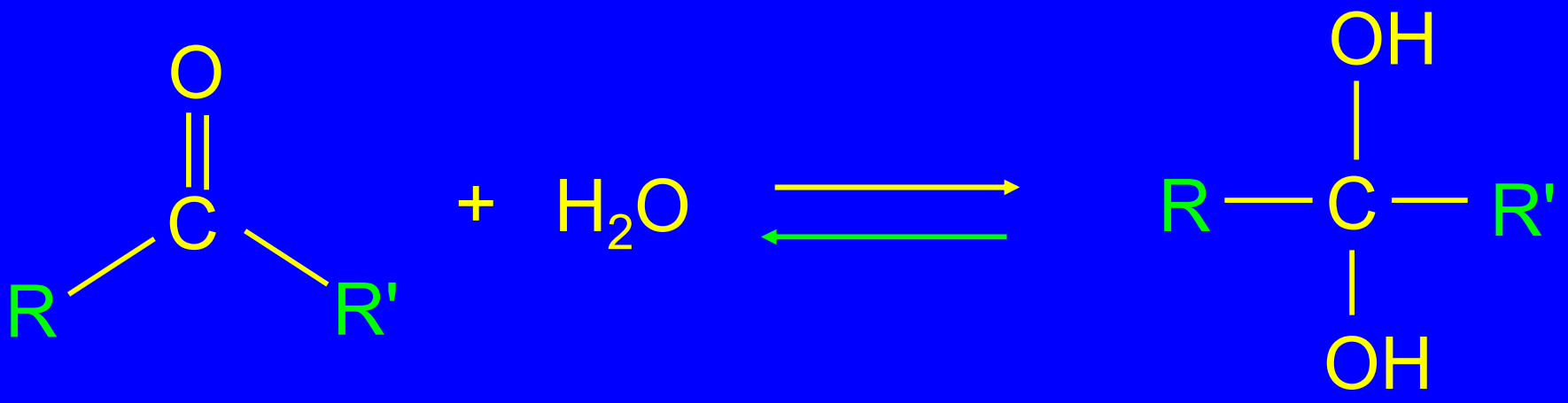


Elimination of Water → ⇌ H_2O ← Nucleophilic Addition



A Carbonyl Hydrate

Substituent Effects on Hydration Equilibria



compared to H

electronic: alkyl groups stabilize reactants

steric: alkyl groups crowd product

Equilibrium Constants and Relative Rates of Hydration

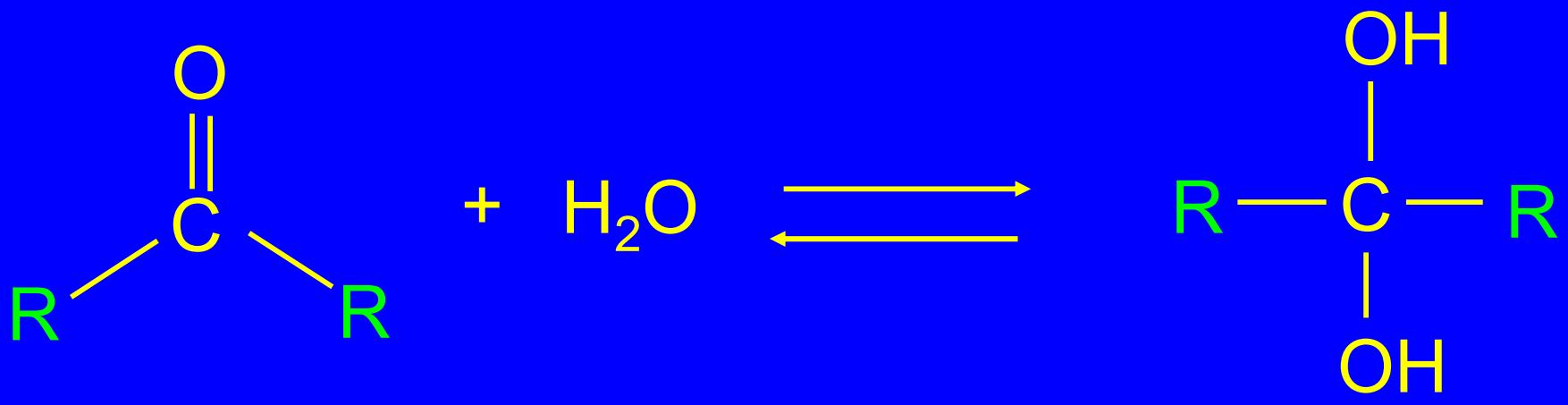
C=O	hydrate	*K*	%	Relative rate
$CH_2=O$	$CH_2(OH)_2$	2300	>99.9	2200
$CH_3CH=O$	$CH_3CH(OH)_2$	1.0	50	1.0
$(CH_3)_3CCH=O$	$(CH_3)_3CCH(OH)_2$	0.2	17	0.09
$(CH_3)_2C=O$	$(CH_3)_2C(OH)_2$	0.0014	0.14	0.0018

When does equilibrium favor hydrate?

when carbonyl group is destabilized

- alkyl groups stabilize C=O
- electron-withdrawing groups destabilize C=O

Substituent Effects on Hydration Equilibria

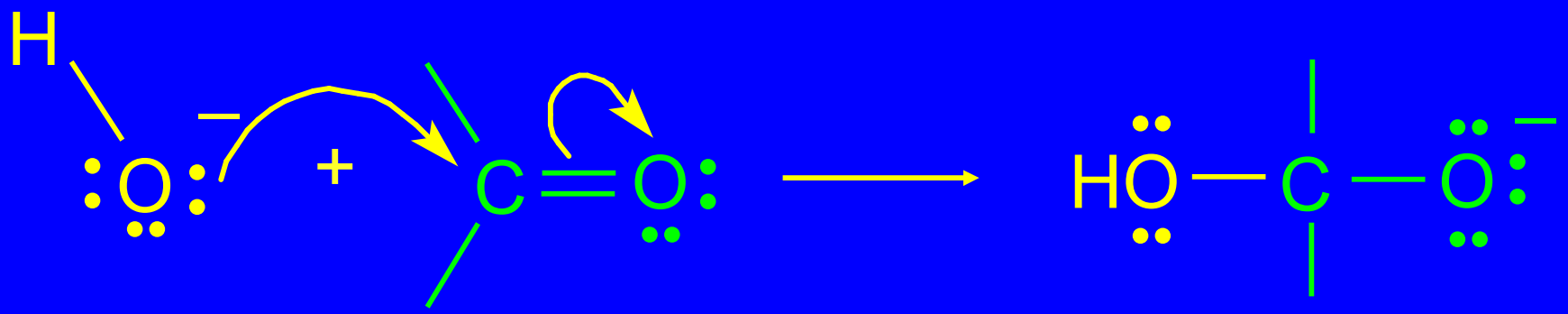


$R = CH_3$: $K = 0.000025$

$R = CF_3$: $K = 22{,}000$

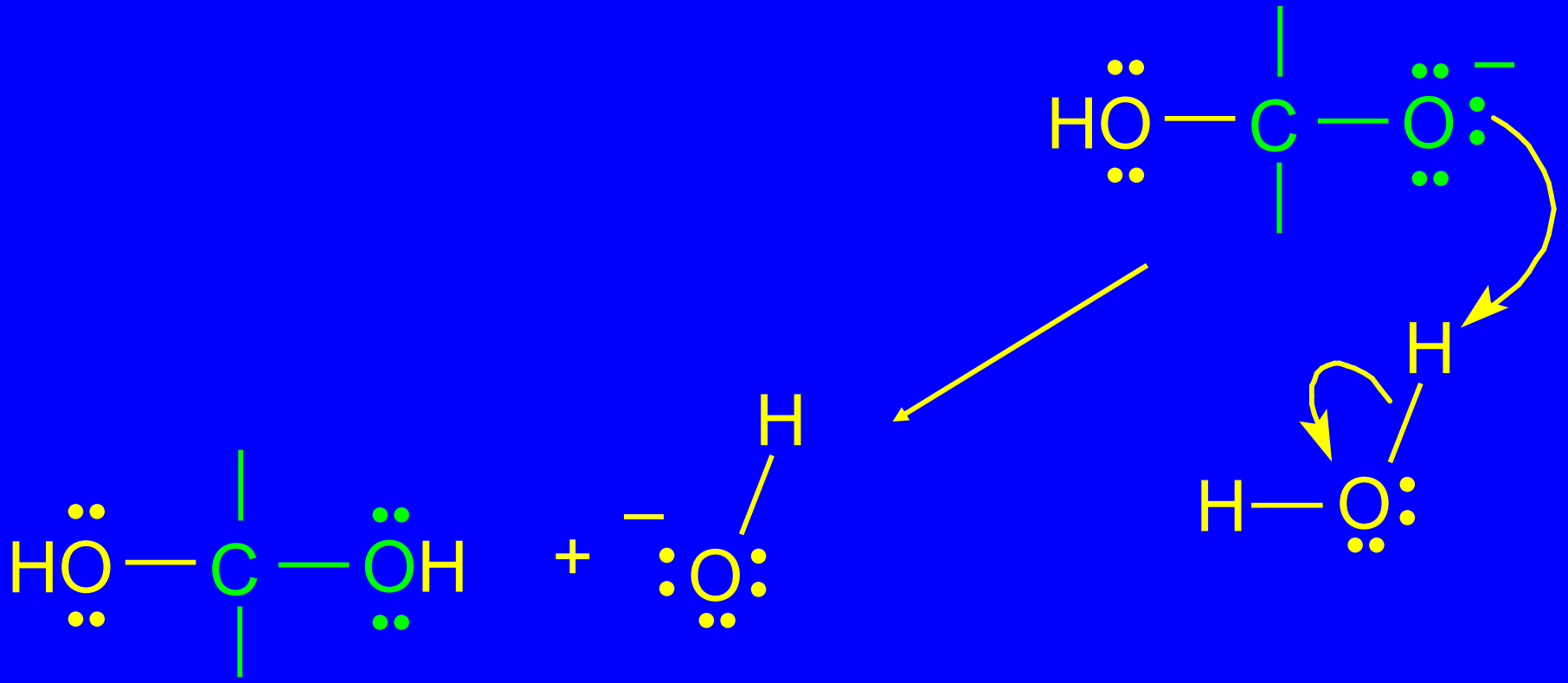
Mechanism of Hydration (base-catalyzed)

Step 1:



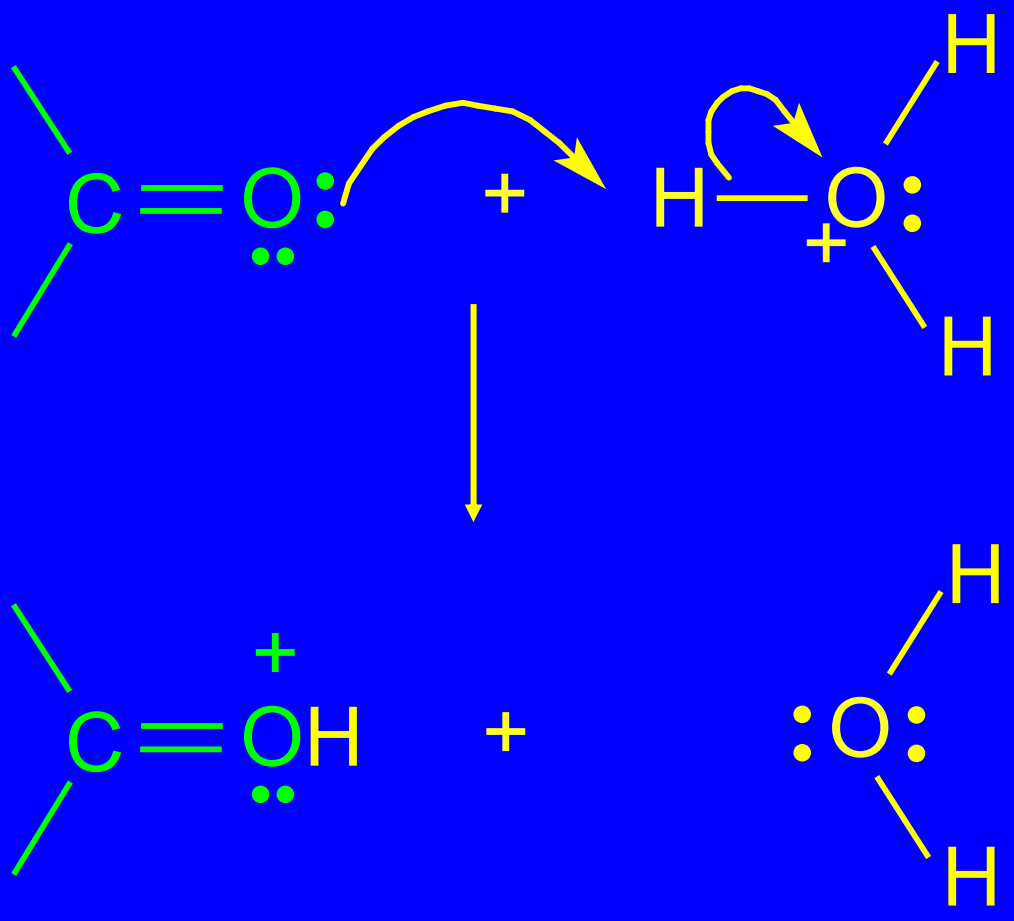
Mechanism of Hydration (base)

Step 2:



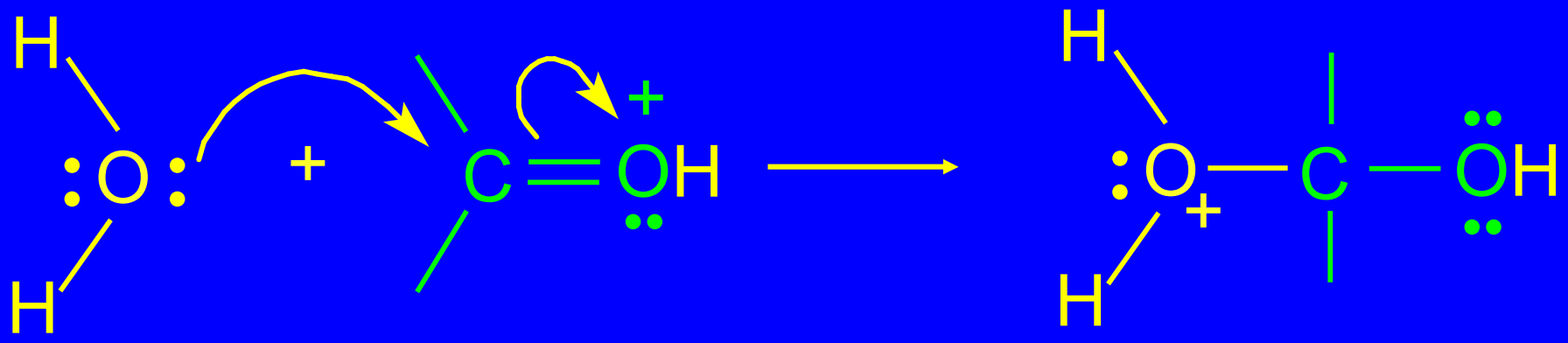
Mechanism of Hydration (acid-catalyzed)

Step 1:



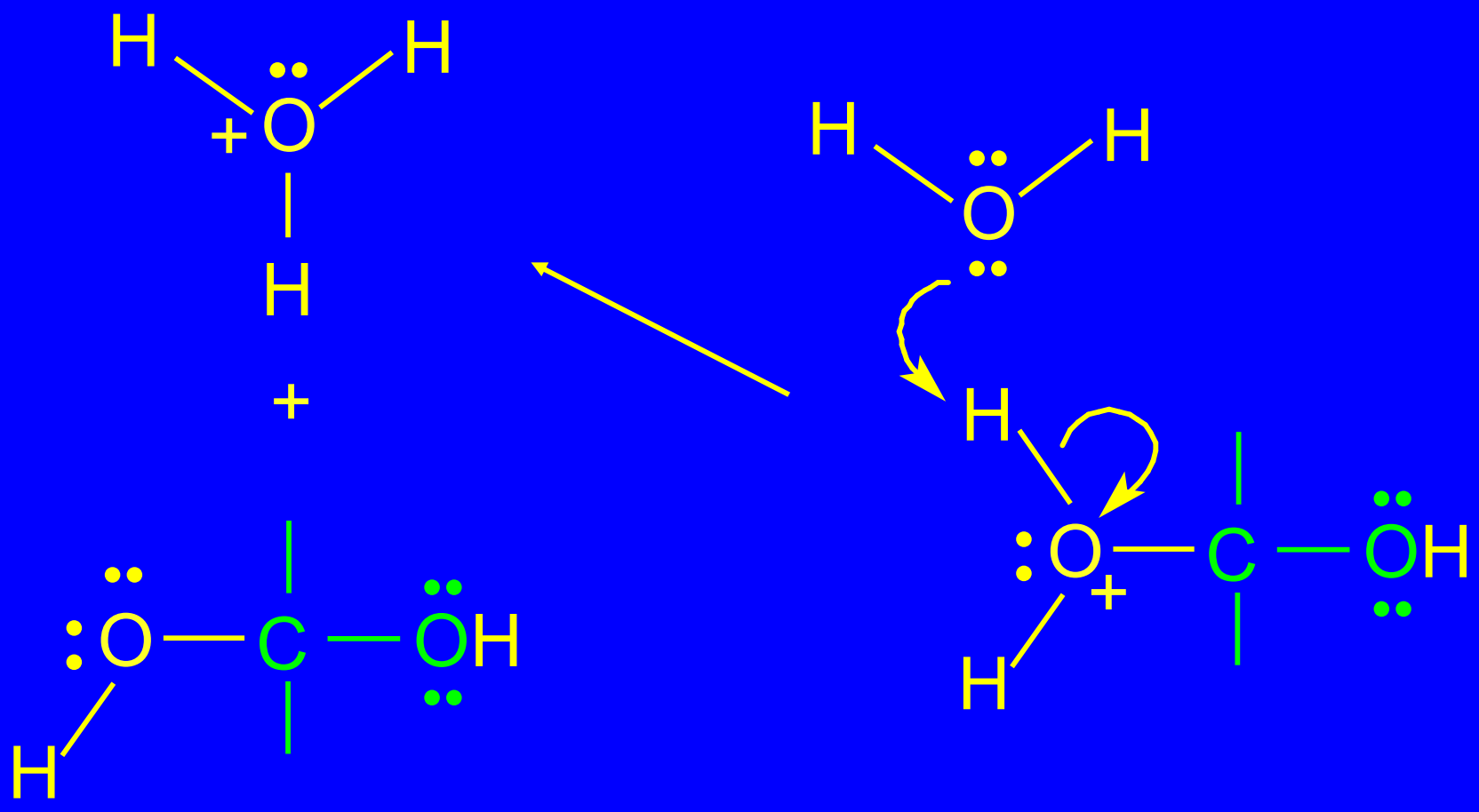
Mechanism of Hydration (acid-catalyzed)

Step 2:



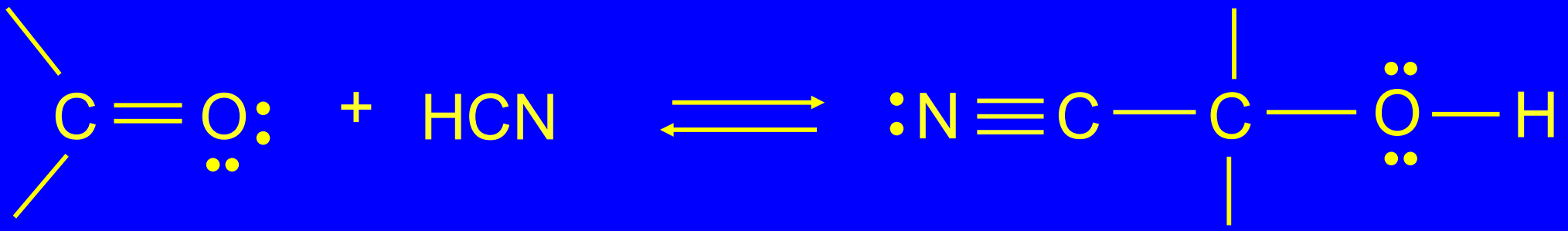
Mechanism of Hydration (acid-catalyzed)

Step 3:

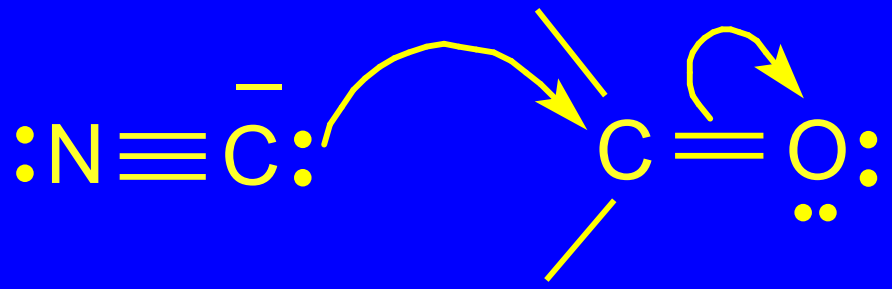


Cyanohydrin Formation

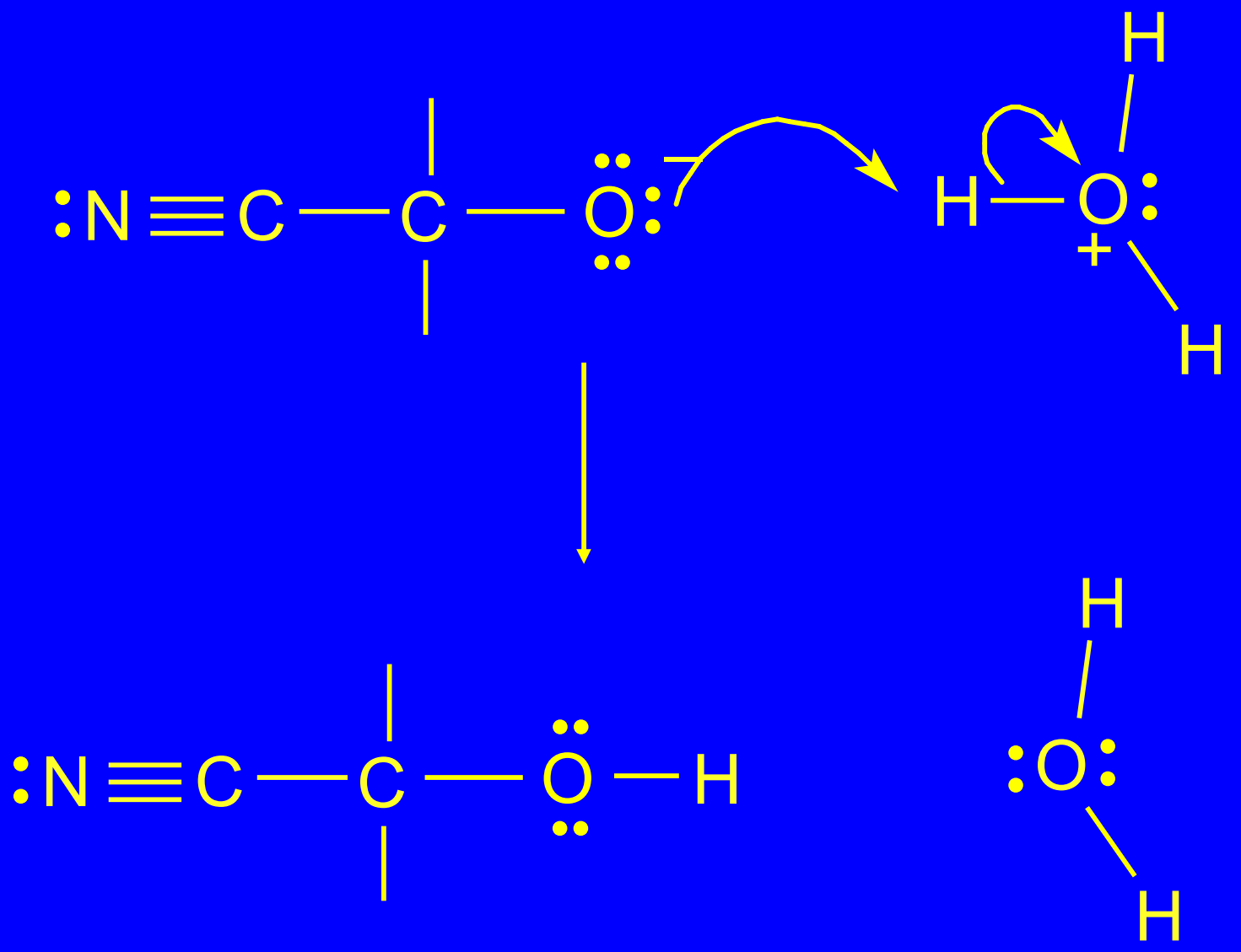
Cyanohydrin Formation



Cyanohydrin Formation



Cyanohydrin Formation



Example

2,4-Dichlorobenzaldehyde cyanohydrin (100%)

Example

(77-78%)

Acetone cyanohydrin is used in the synthesis of methacrylonitrile (see problem 17.7).

Acetal Formation

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

Acetal formation

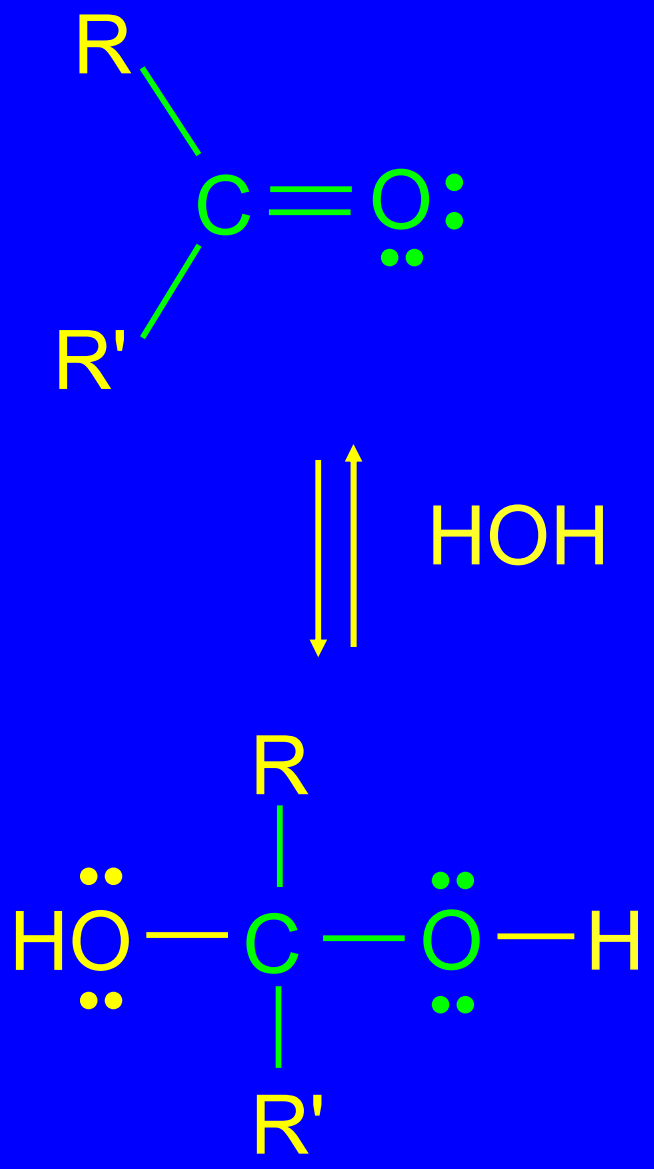
Imine formation

Enamine formation

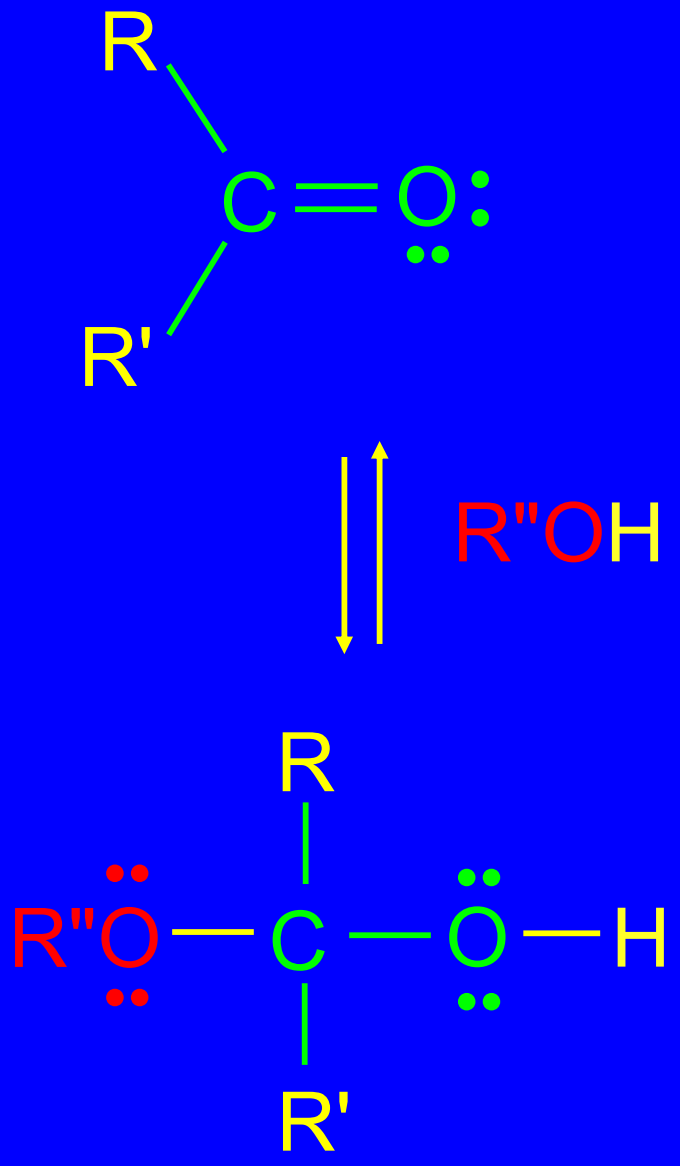
Compounds related to imines

The Wittig reaction

Recall Hydration of Aldehydes and Ketones

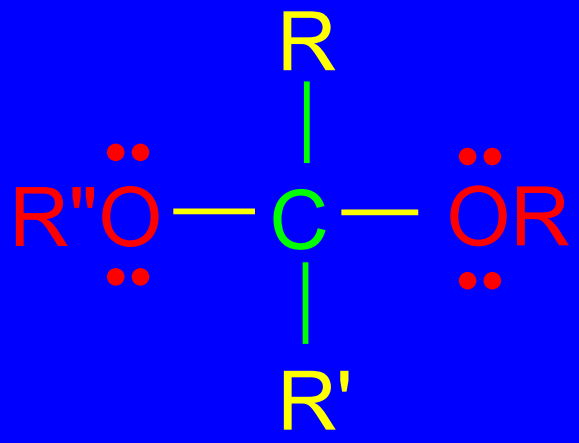


Alcohols Under Analogous Reaction with Aldehydes and Ketones

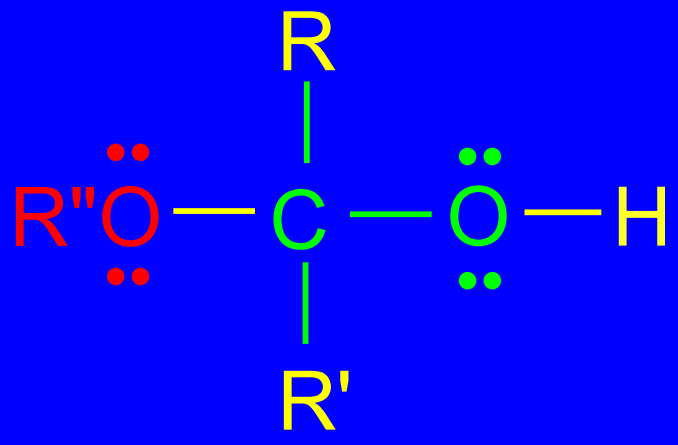


Product is called a *hemiacetal*.

Hemiacetal reacts further in acid to yield an acetal

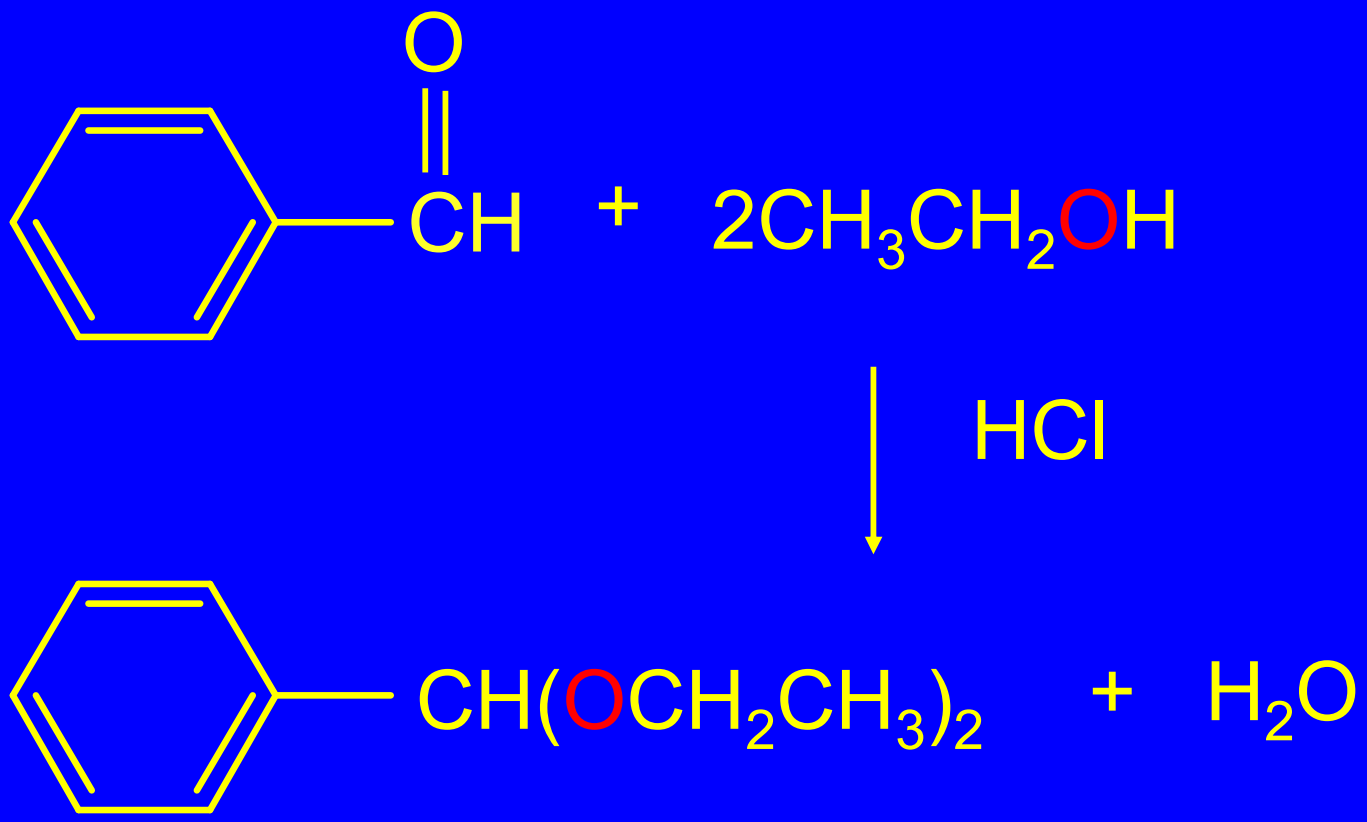


Product is called an *acetal*.



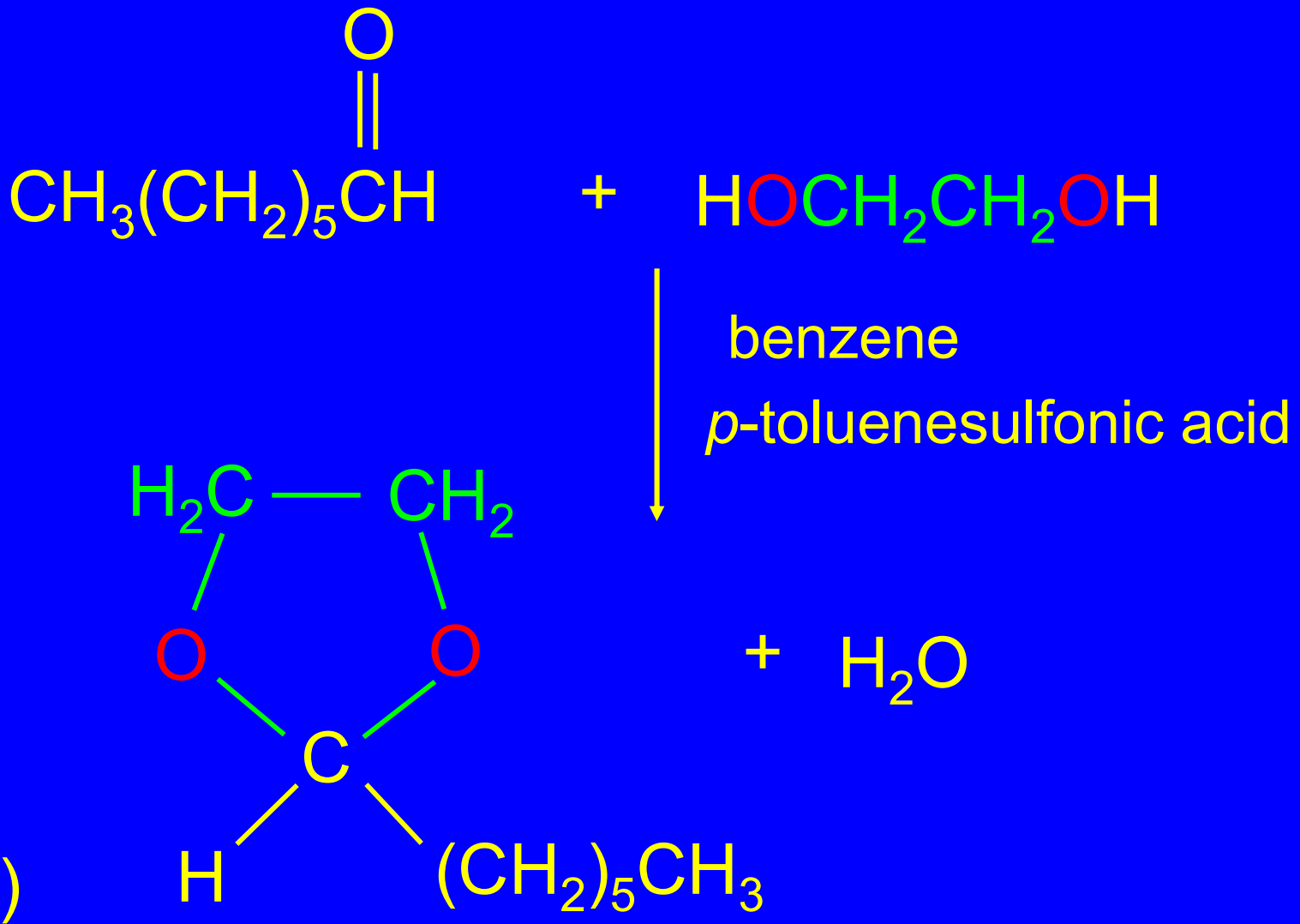
Product is called a *hemiacetal*.

Example



Benzaldehyde diethyl acetal (66%)

Diols Form Cyclic Acetals



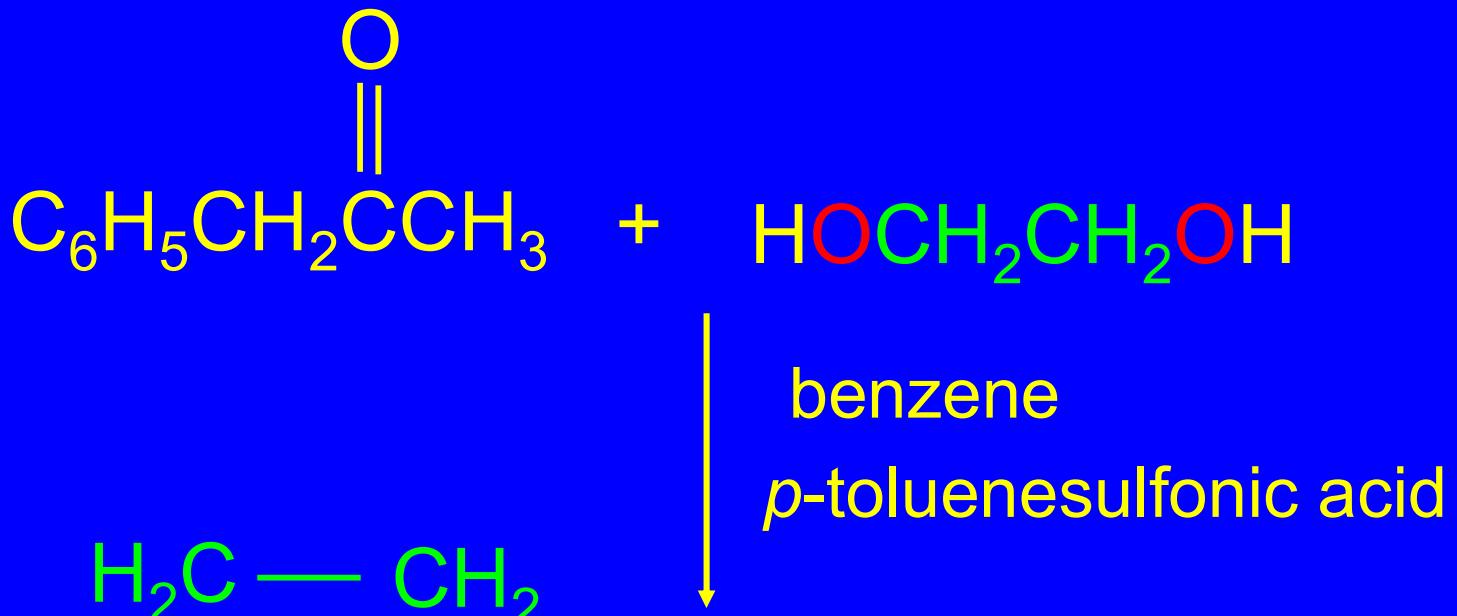
(81%)

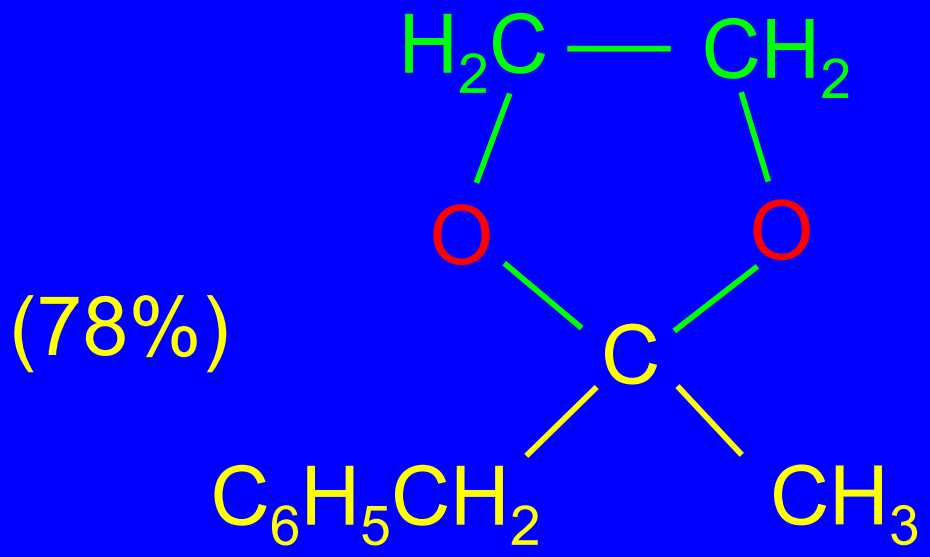
In general:

Position of equilibrium is usually unfavorable for acetal formation from ketones.

Important exception:
Cyclic acetals can be prepared from ketones.

Example


O
C6H5CH2CCH3
+
HOCH2CH2OH
benzene
p-toluenesulfonic acid
+ H2O


H2C
CH2
O
O
C
C6H5CH2
CH3

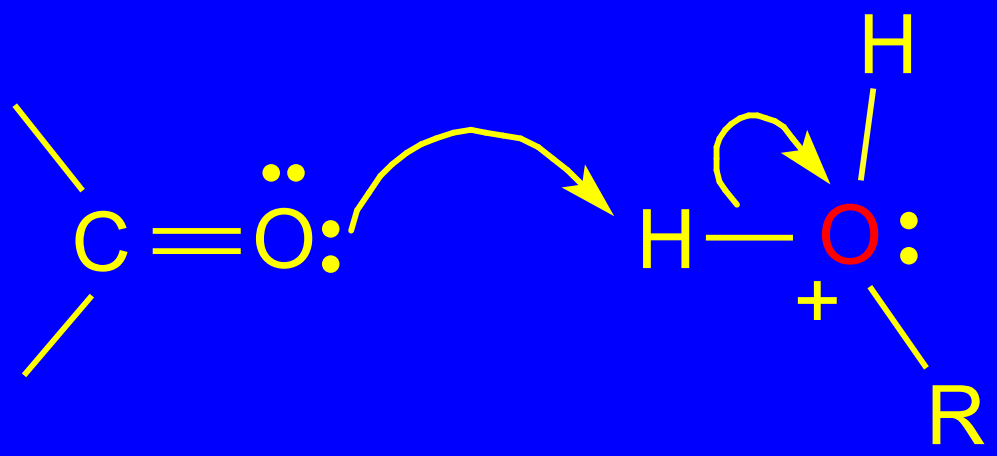
(78%)

Mechanism of Acetal Formation

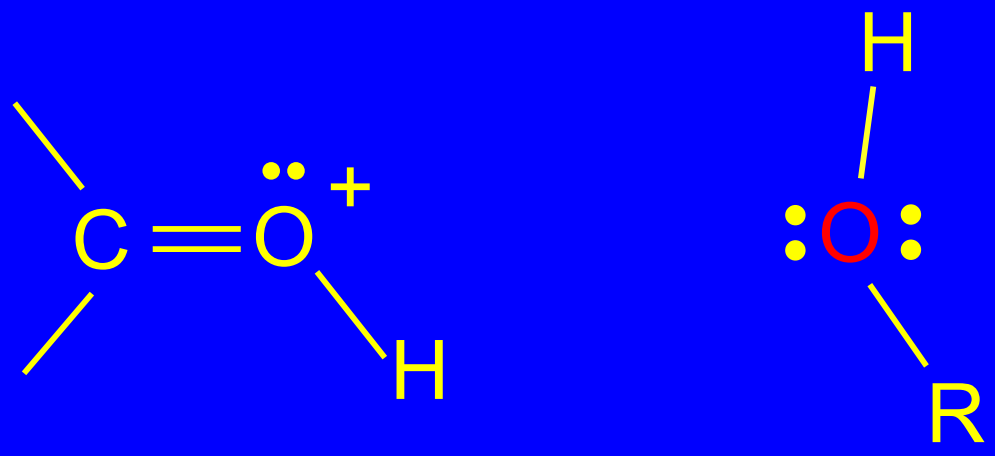
First stage is analogous to hydration and leads to hemiacetal

- acid-catalyzed nucleophilic addition of alcohol to C=O

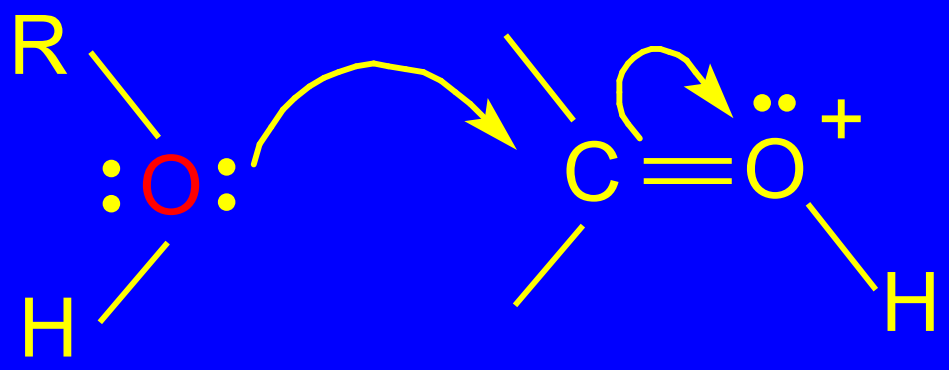
Mechanism



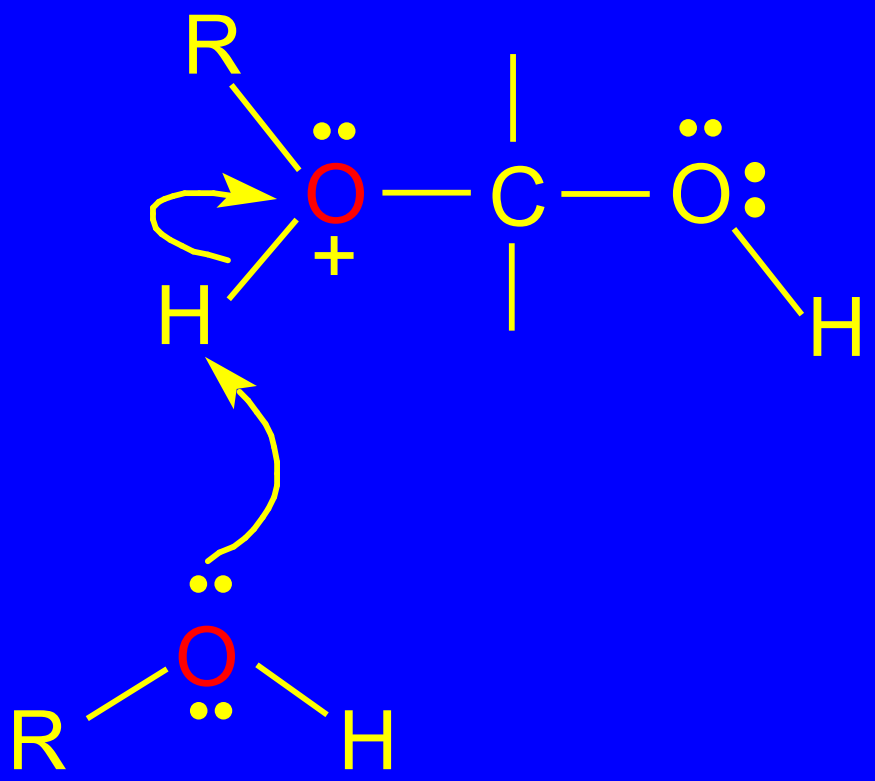
Mechanism



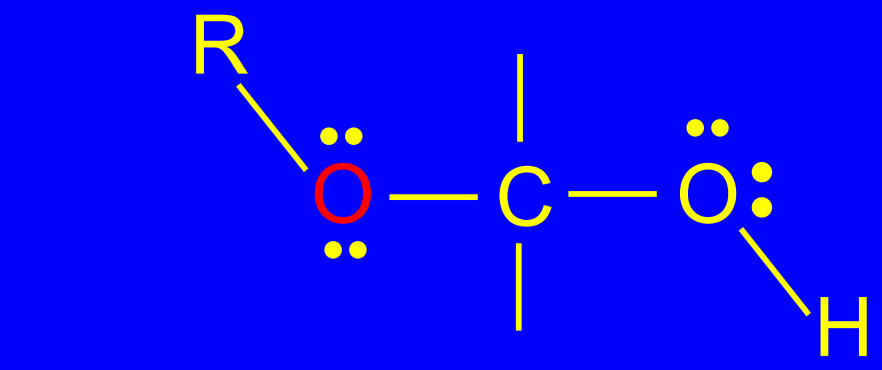
Mechanism

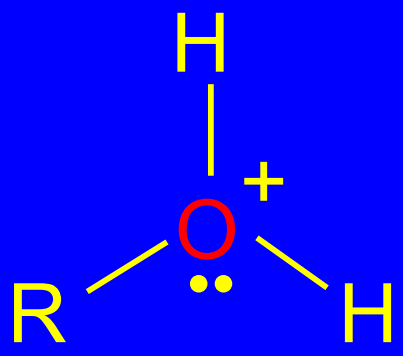


Mechanism



Mechanism



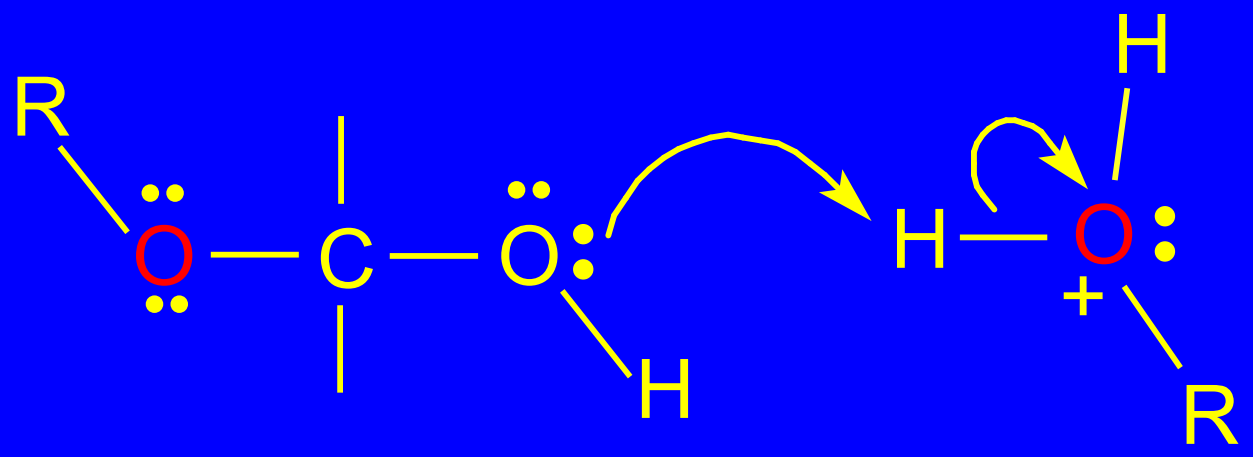


Mechanism of Acetal Formation

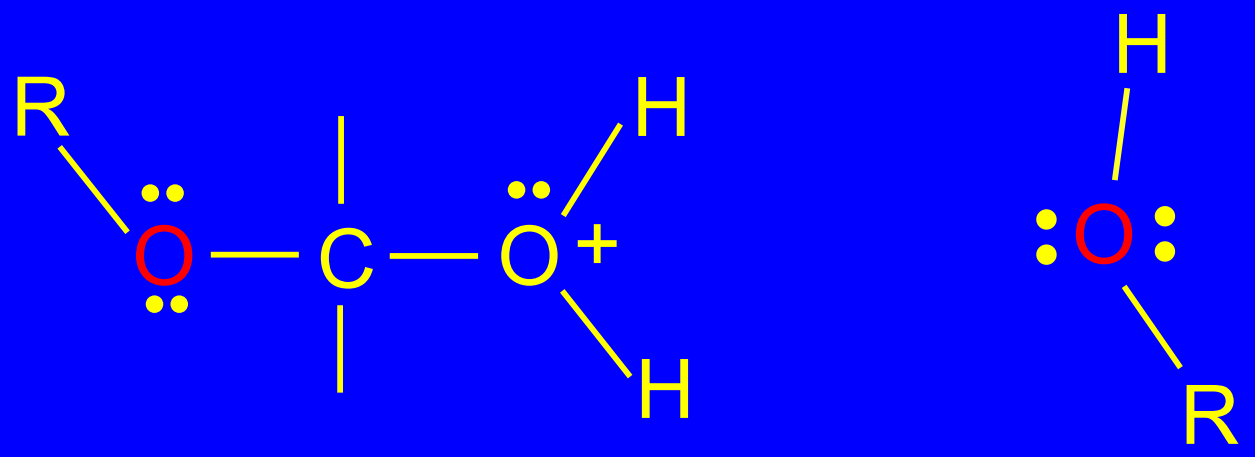
Second stage is hemiacetal-to-acetal conversion

involves carbocation chemistry

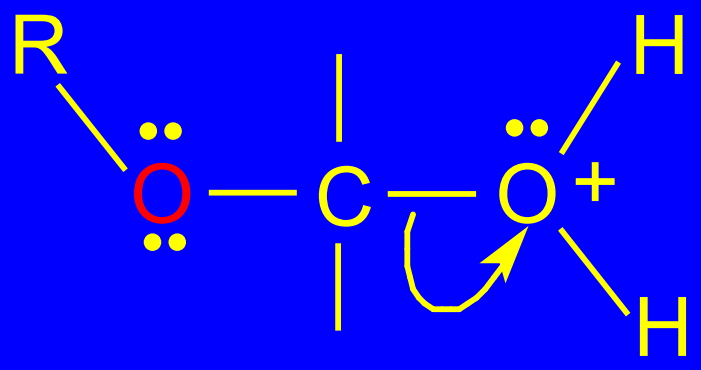
Hemiacetal-to-acetal Stage



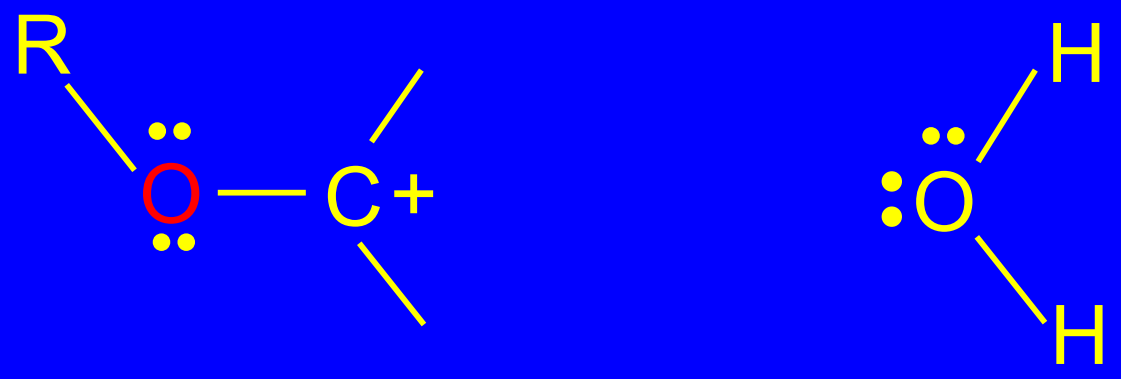
Hemiacetal-to-acetal Stage



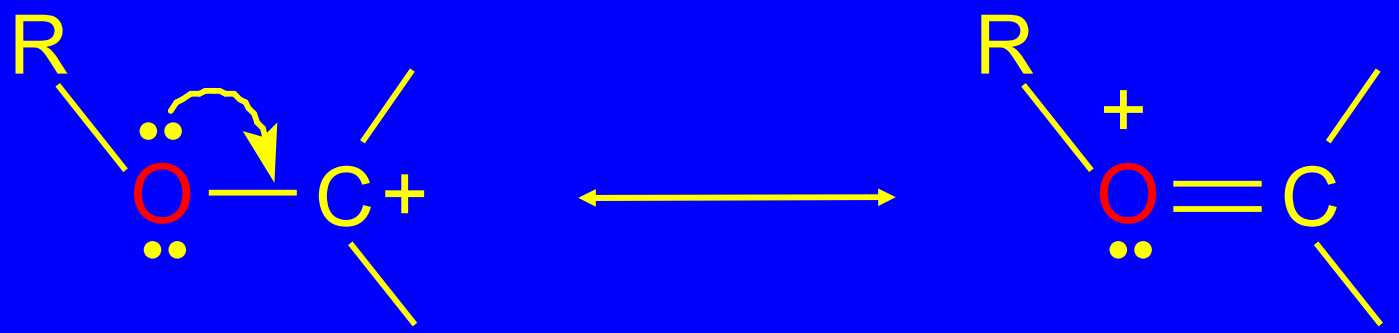
Hemiacetal-to-acetal Stage



Hemiacetal-to-acetal Stage

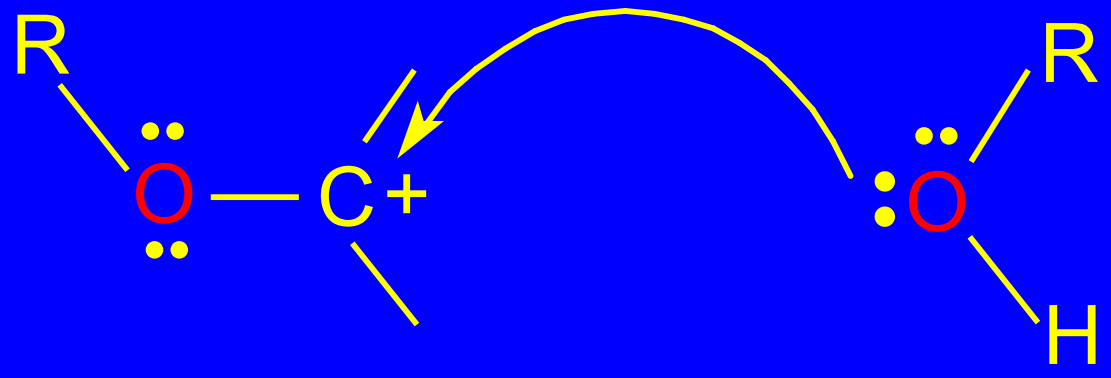


Hemiacetal-to-acetal Stage

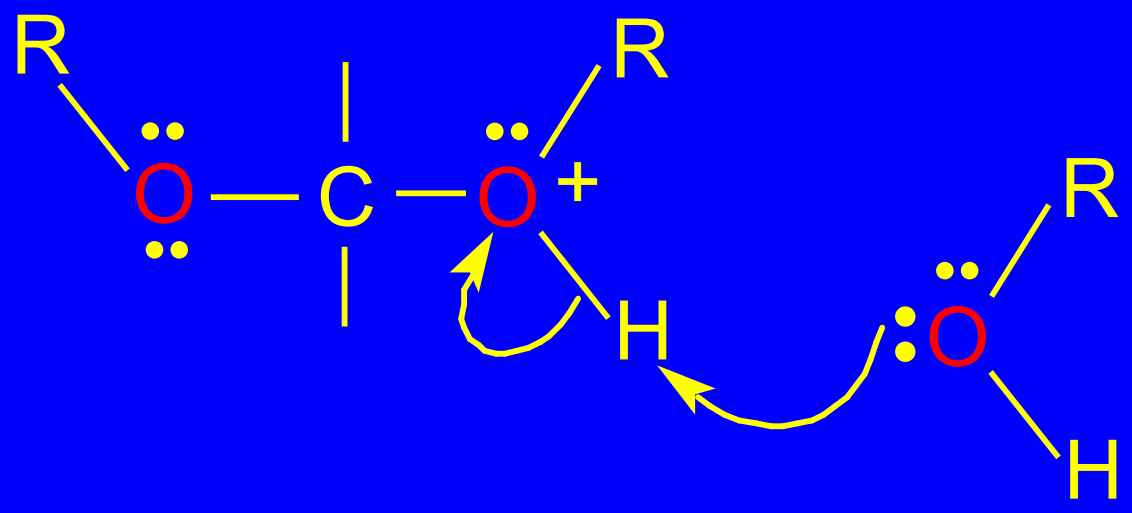


Carbocation is stabilized by delocalization of unshared electron pair of oxygen

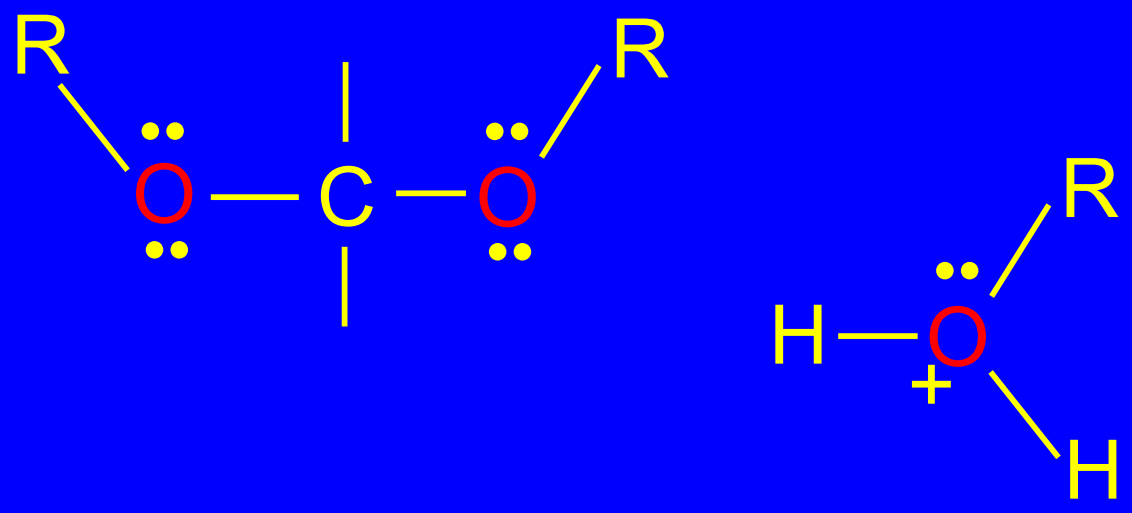
Hemiacetal-to-acetal Stage



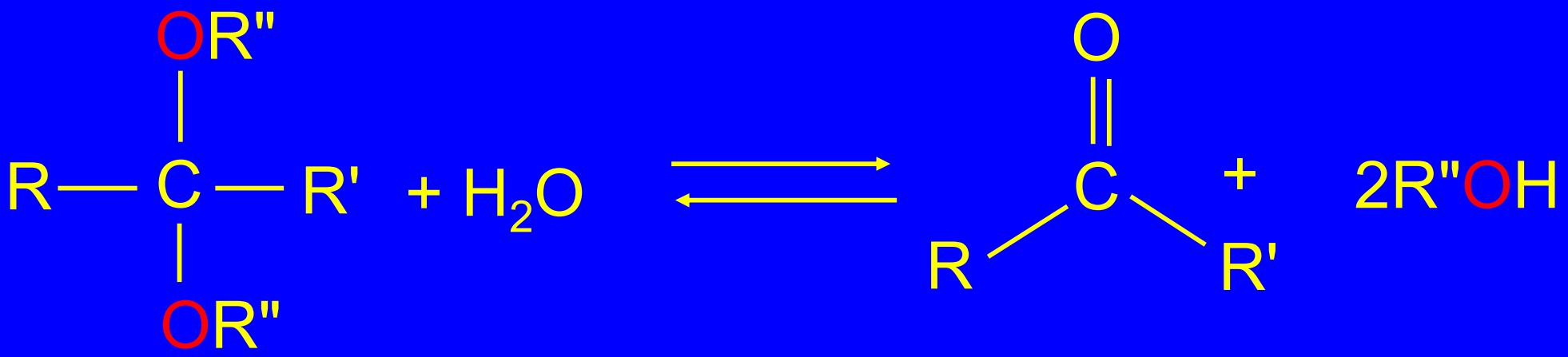
Hemiacetal-to-acetal Stage



Hemiacetal-to-acetal Stage



Hydrolysis of Acetals



mechanism:

reverse of acetal formation;
hemiacetal is intermediate

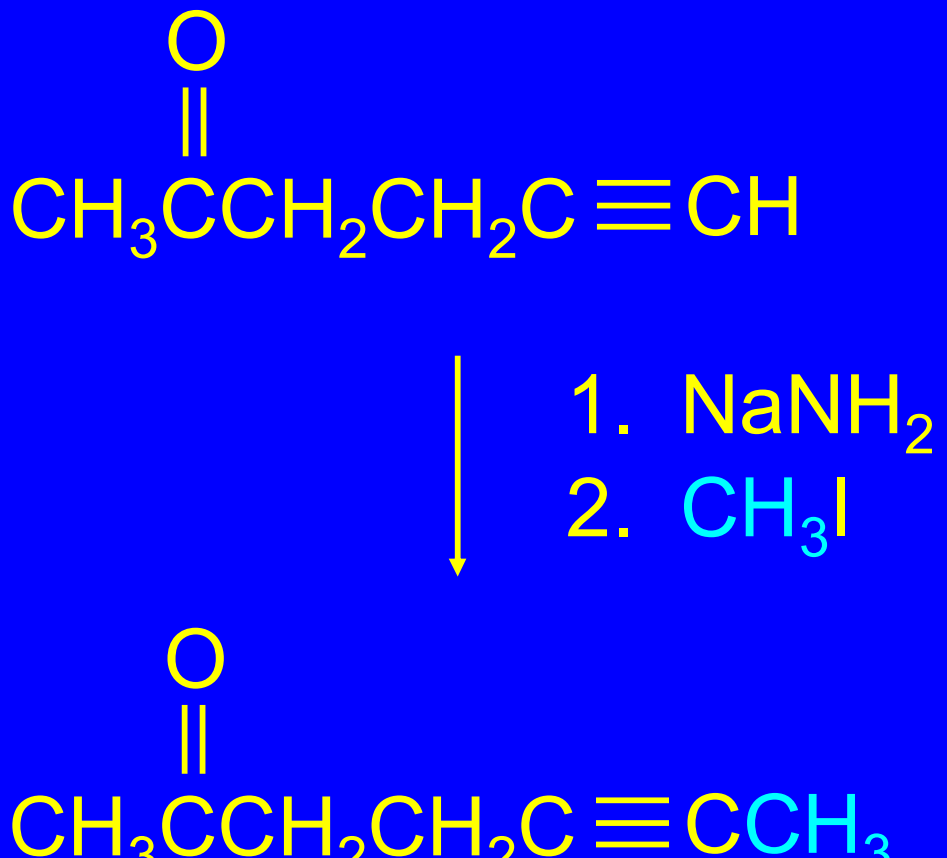
application:

aldehydes and ketones can be "protected" as acetals.

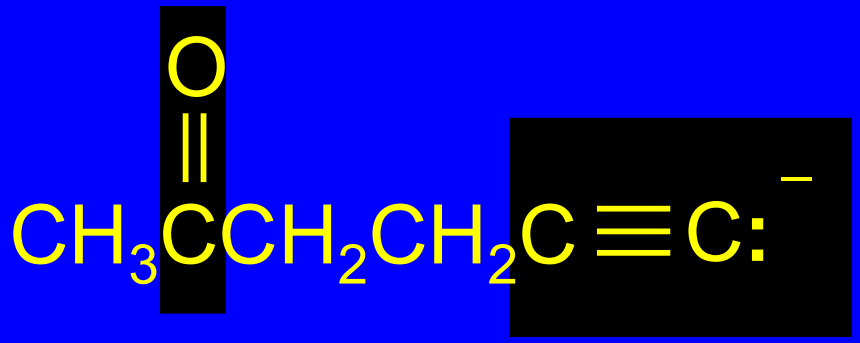
Acetals as Protecting Groups

Example

The conversion shown cannot be carried out directly...



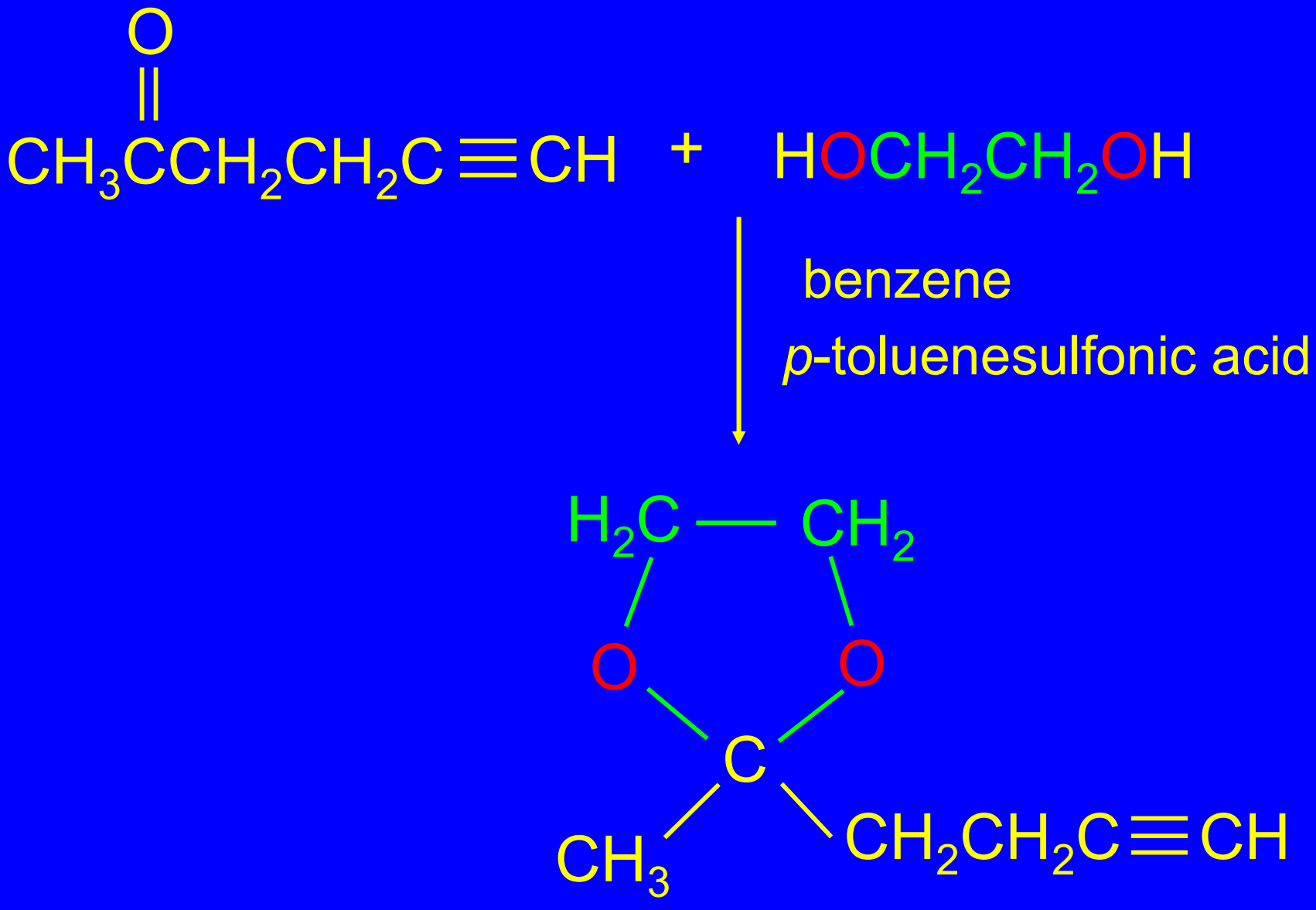
because the carbonyl group and the carbanion are incompatible functional groups.



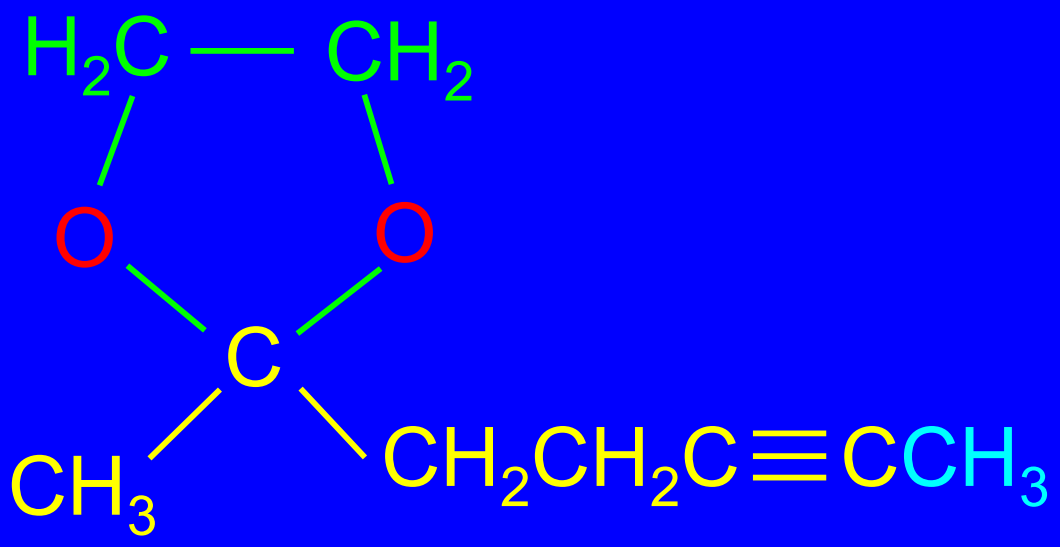
Strategy

1) protect C=O
2) alkylate
3) restore C=O

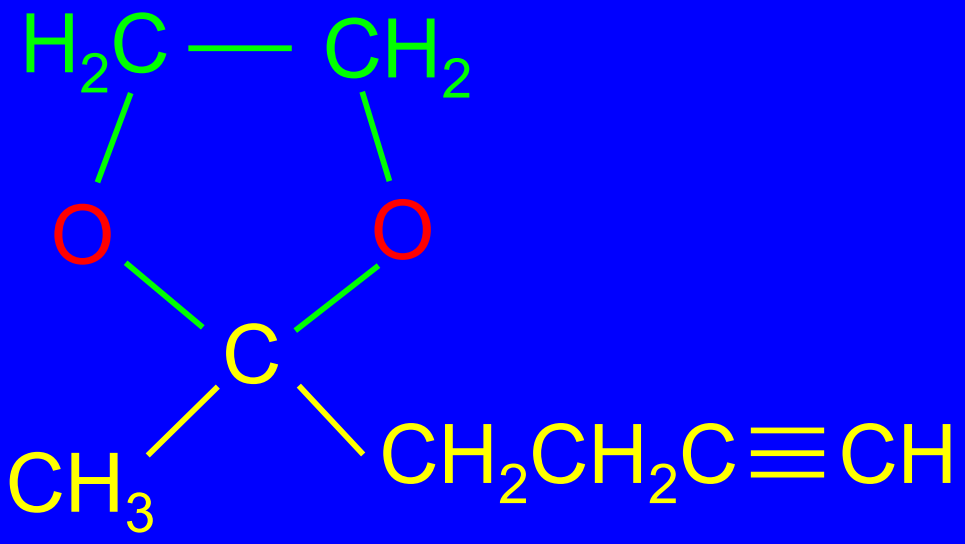
Example: Protect



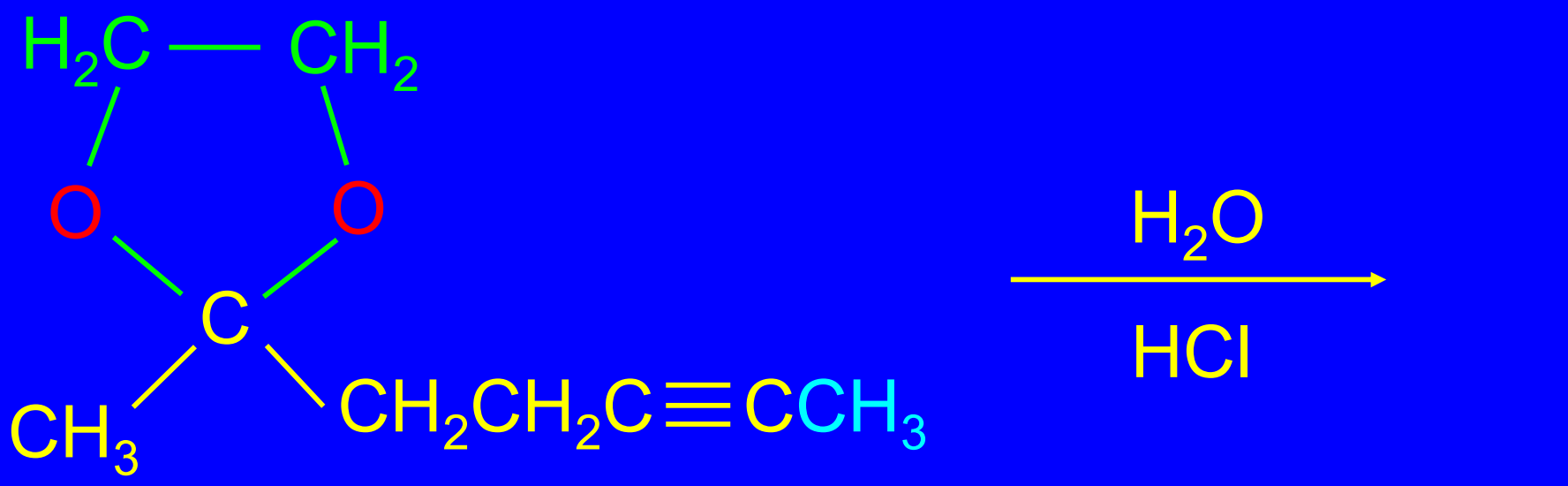
Example: Alkylate



1. $NaNH_2$
2. CH_3I



Example: Deprotect



Reaction with Primary Amines:

Imines

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

Acetal formation

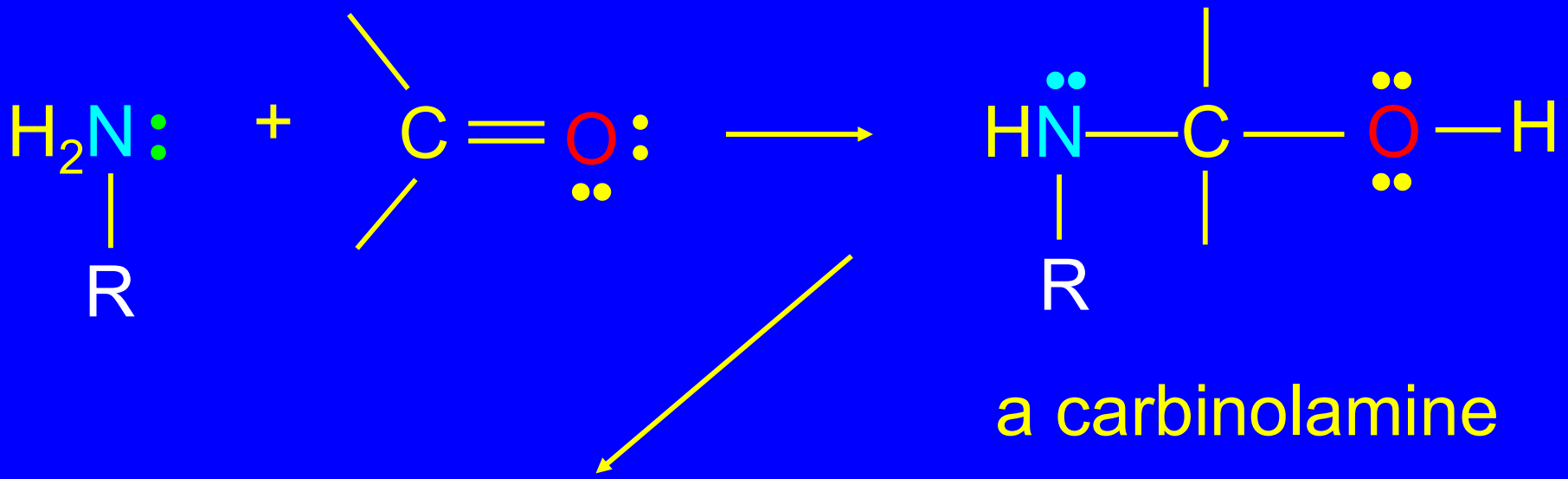
Imine formation

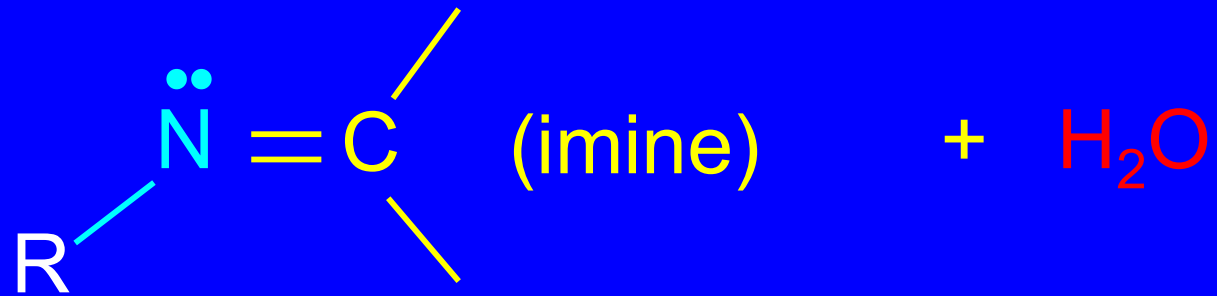
Compounds related to imines

Enamines

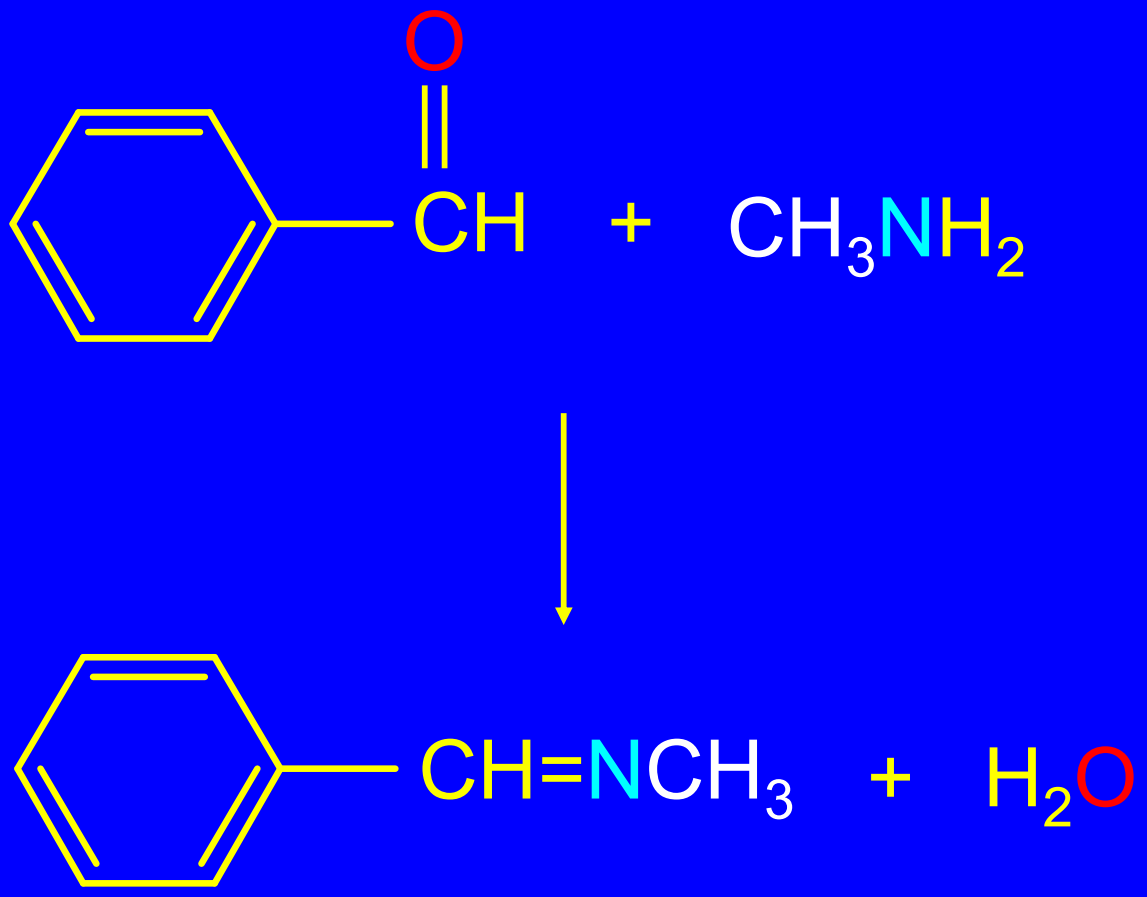
The Wittig reaction

Imine (Schiff's Base) Formation



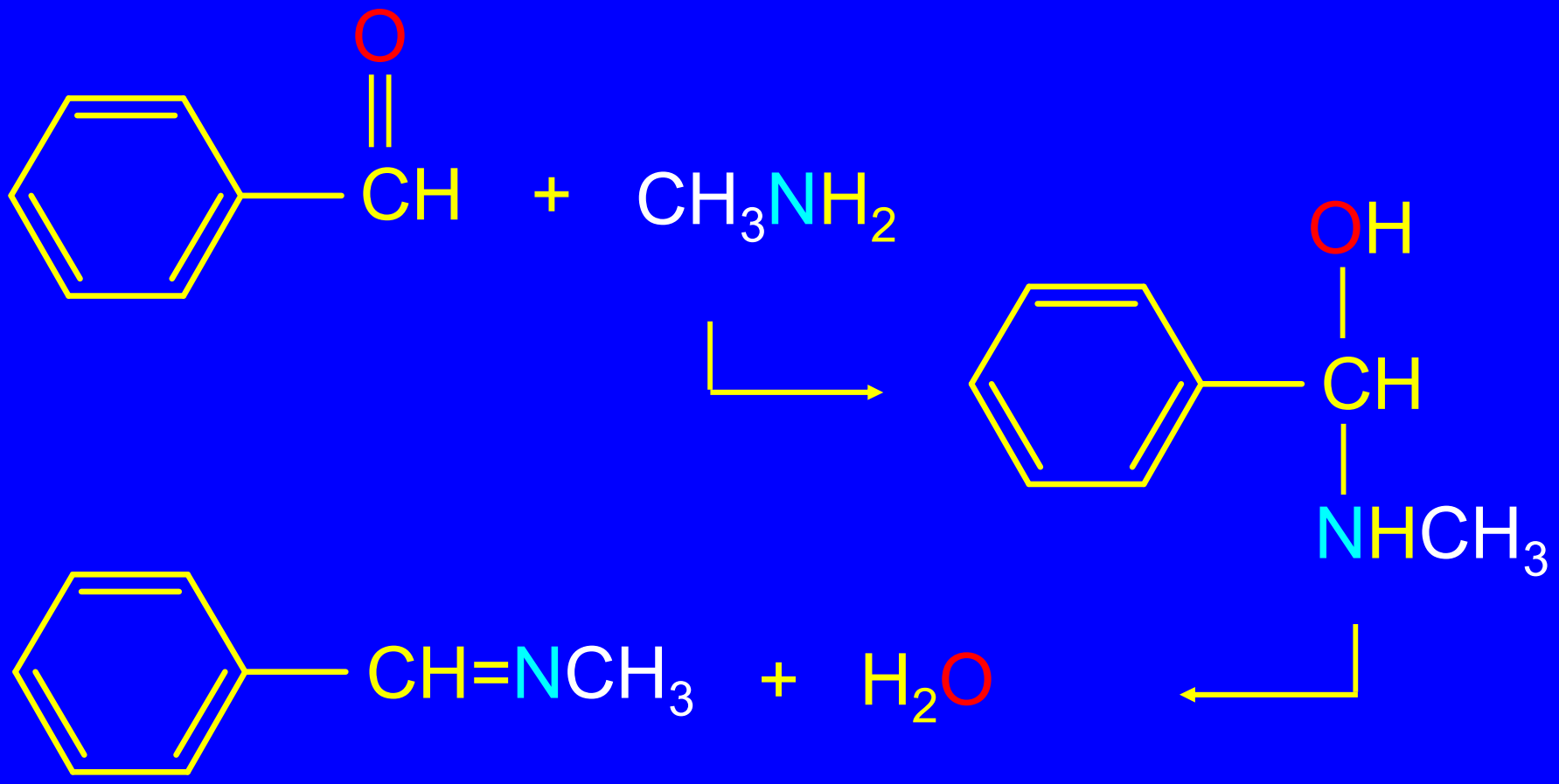


Example



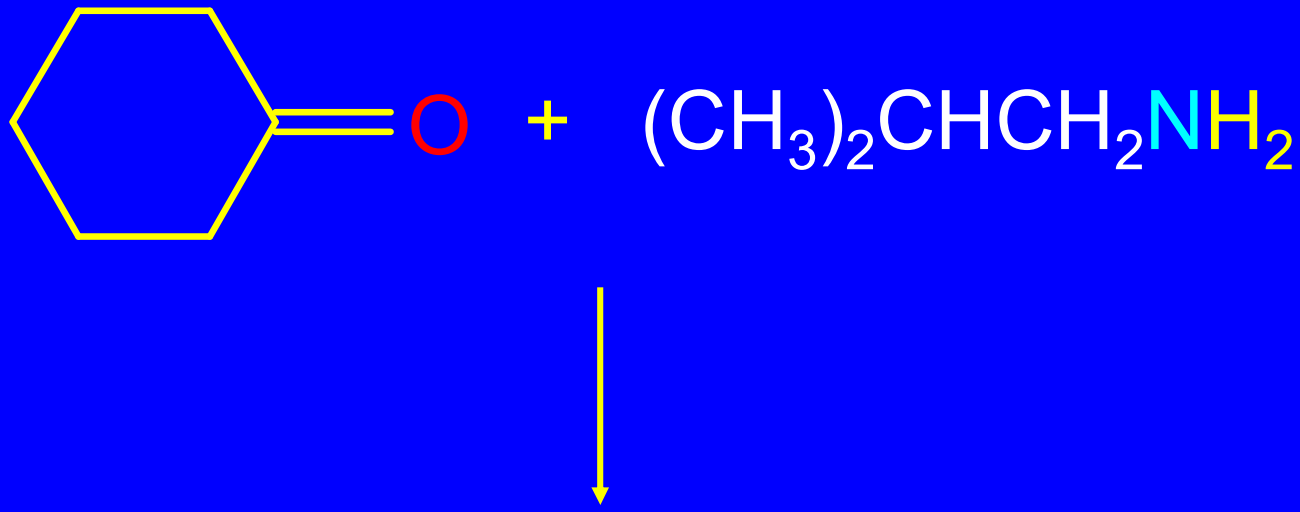
N-Benzylidenemethylamine (70%)

Example



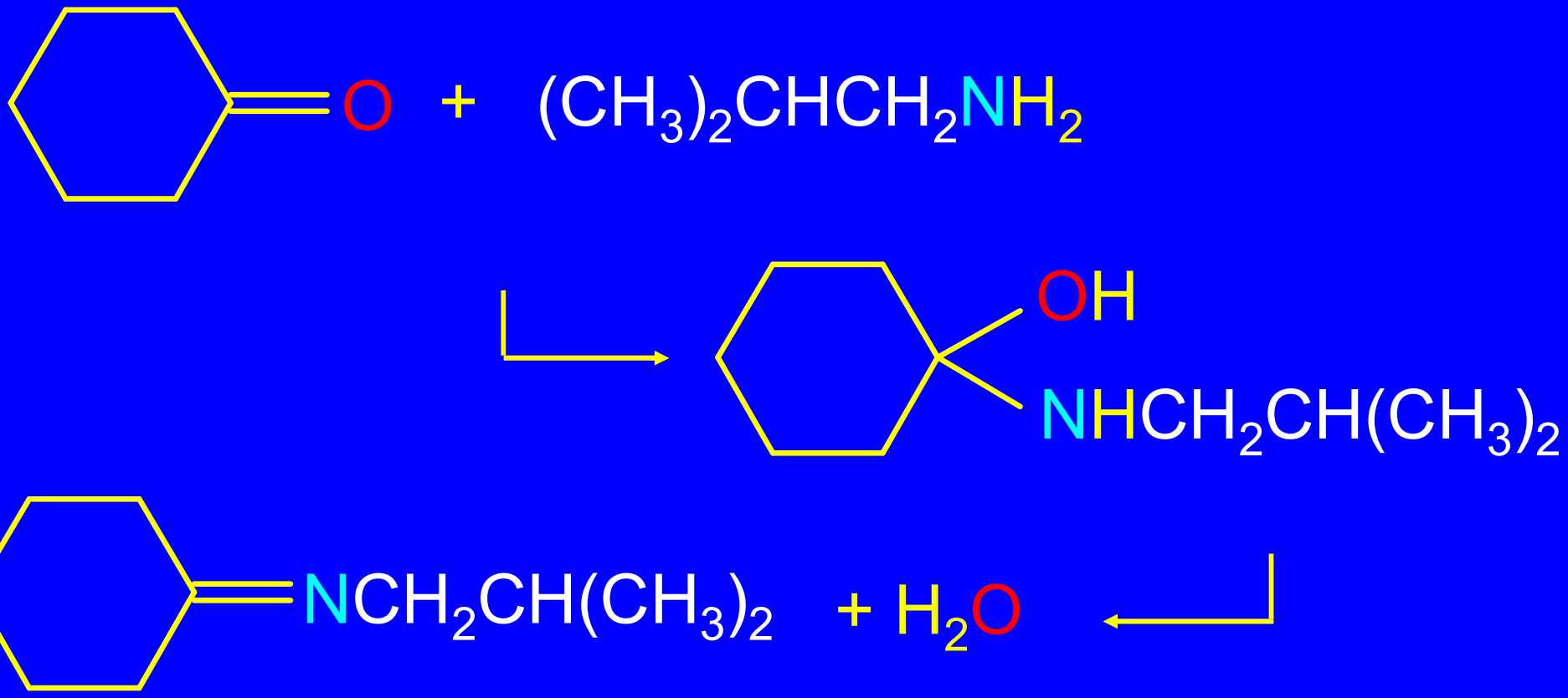
N-Benzylidenemethylamine (70%)

Example



N-Cyclohexylideneisobutylamine
(79%)

Example



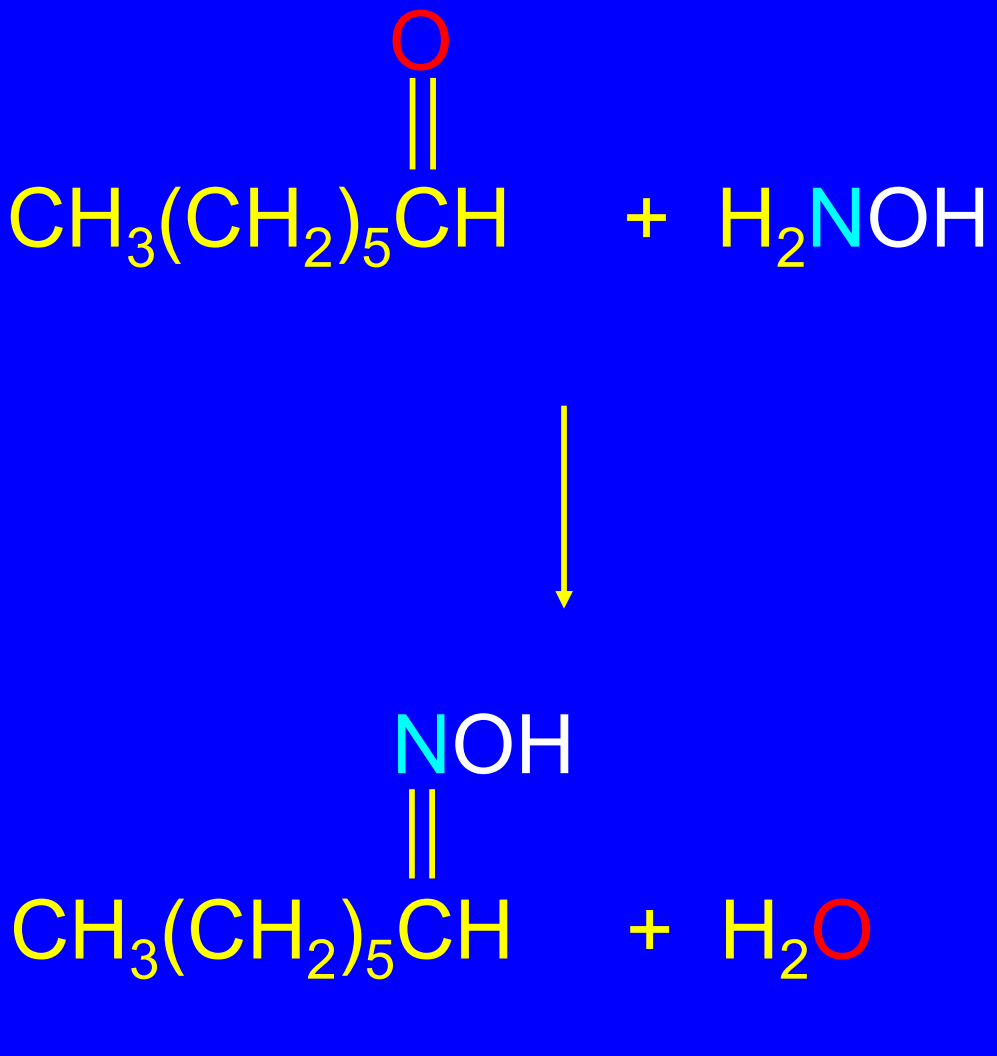
N-Cyclohexylideneisobutylamine
(79%)

Reaction with Derivatives of Ammonia

hydroxylamine

oxime

Example

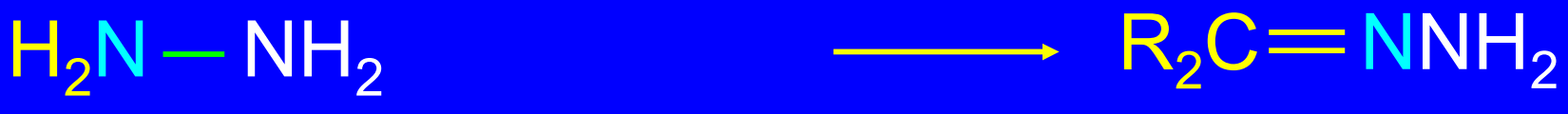


(81-93%)

Reaction with Derivatives of Ammonia

hydroxylamine

oxime

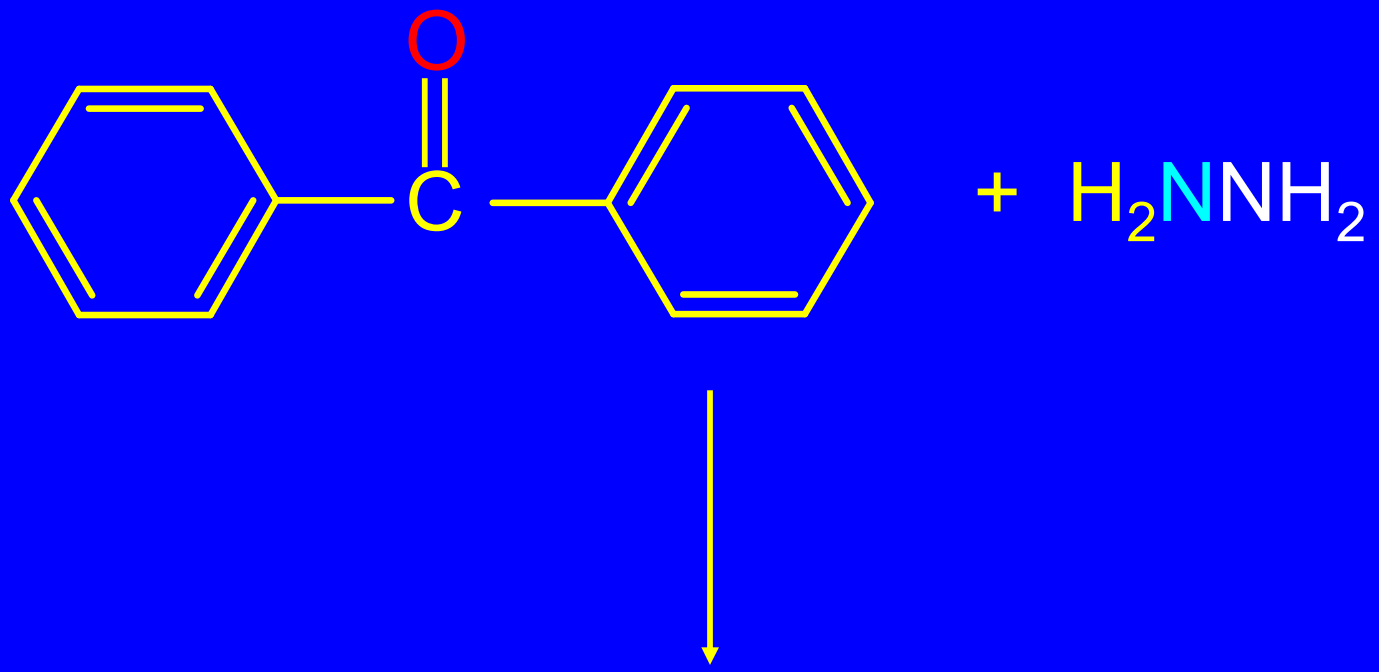


hydrazine

hydrazone

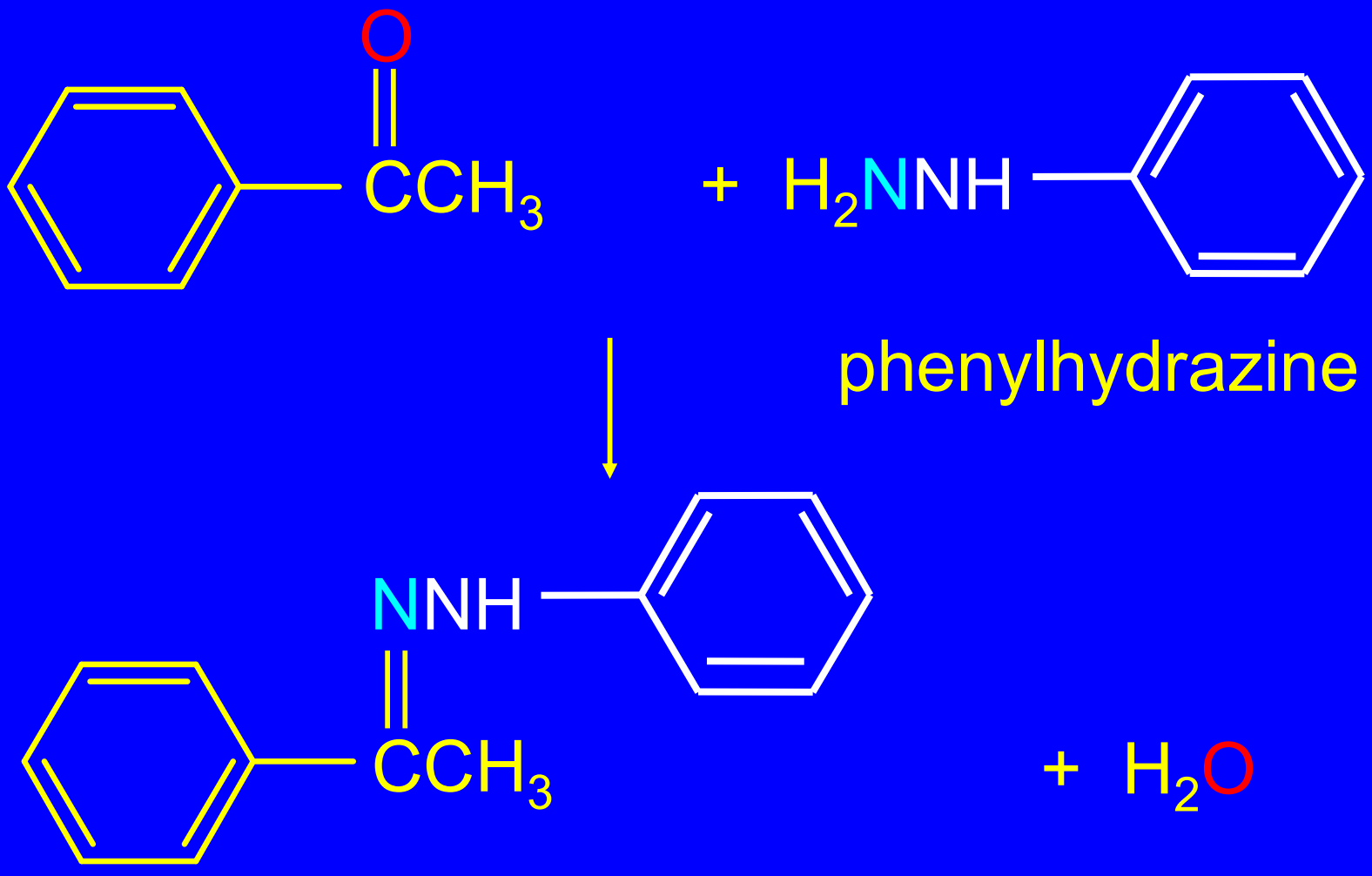
etc.

Example



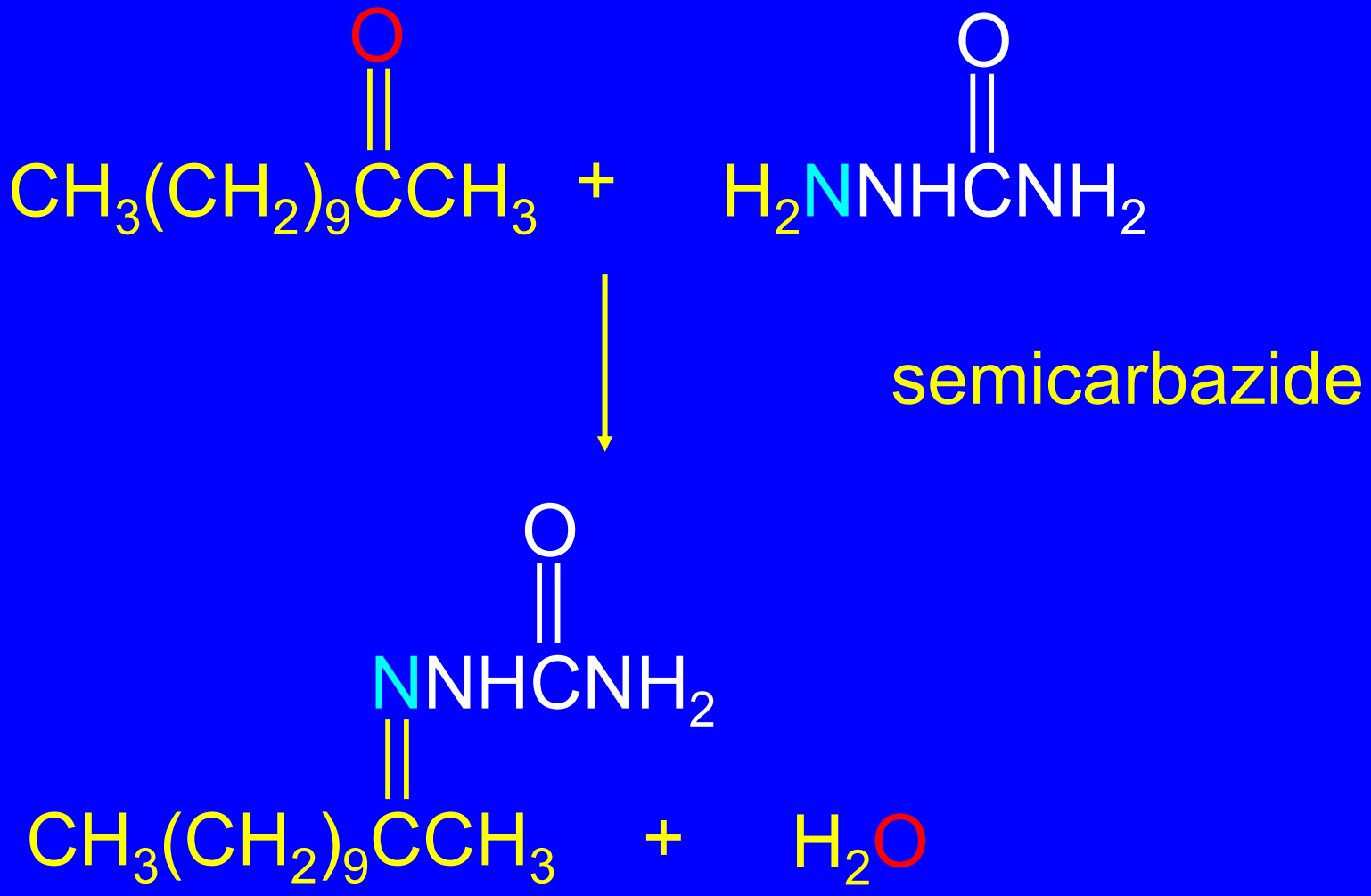
(73%)

Example



a phenylhydrazone (87-91%)

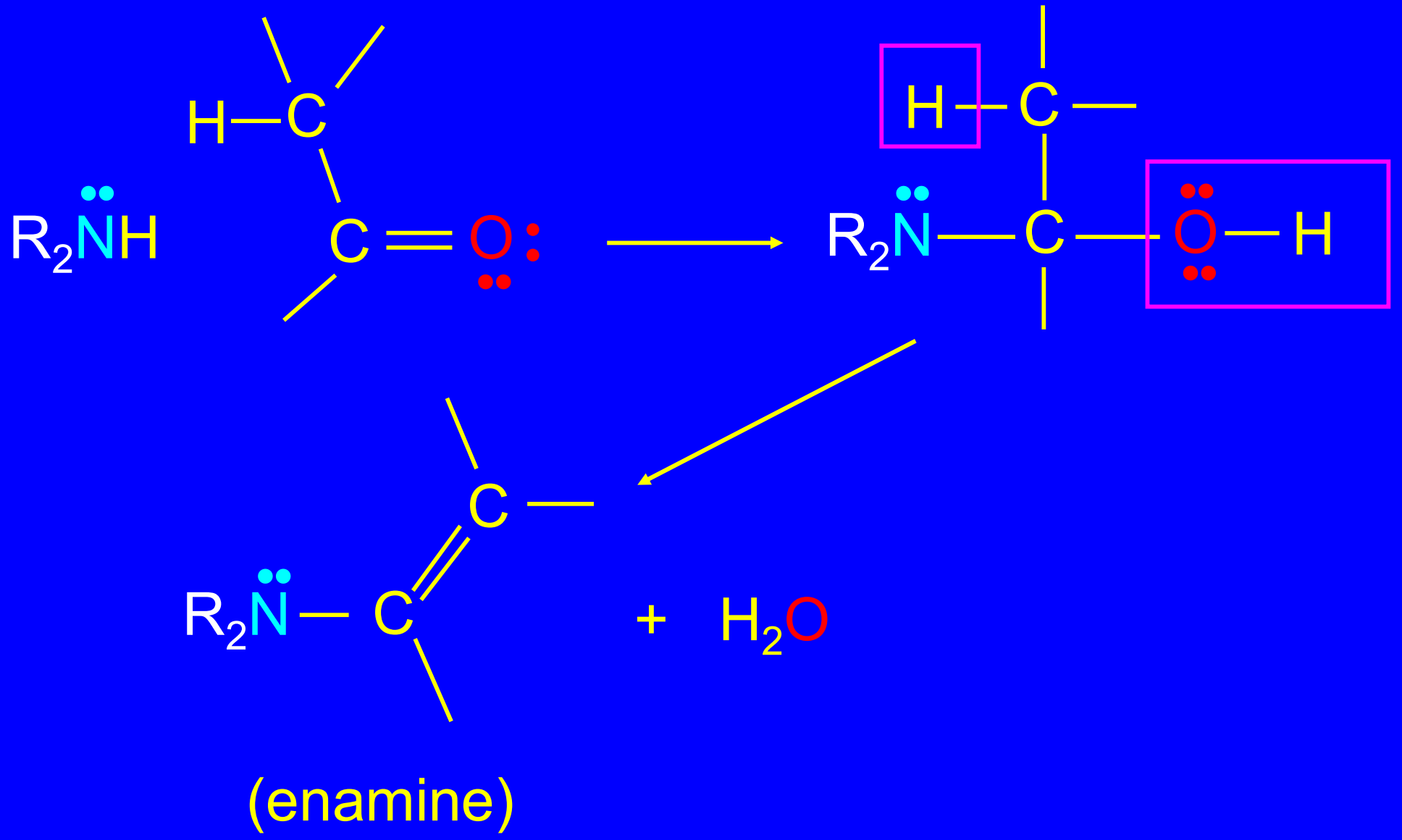
Example



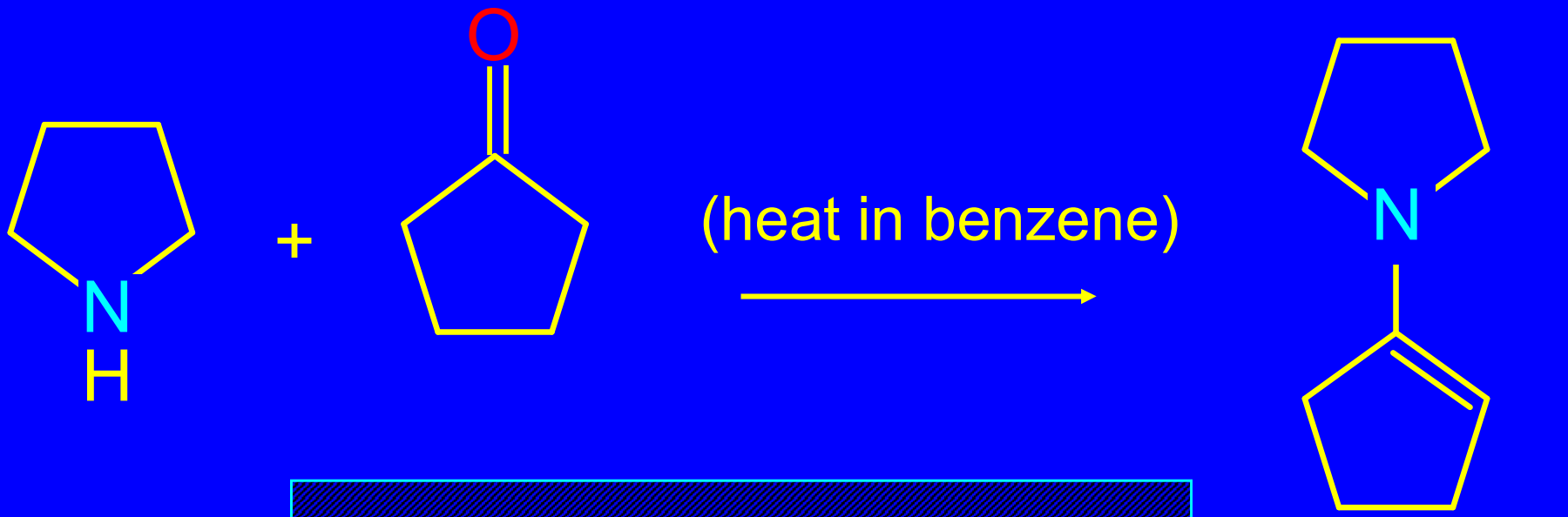
a semicarbazone (93%)

Reaction with Secondary Amines: Enamines

Enamine Formation



Example



(80-90%)

via

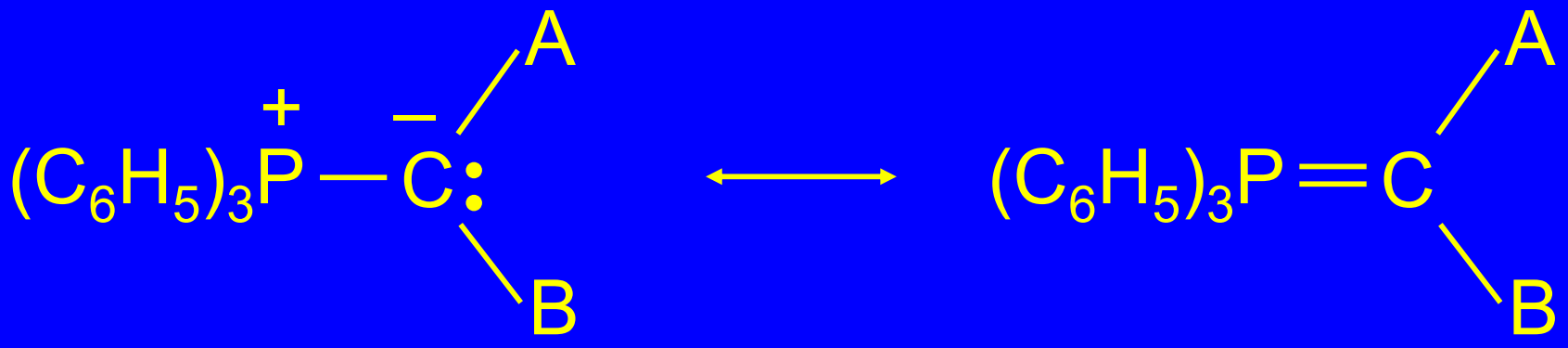
The Wittig Reaction

The Wittig Reaction

Synthetic method for preparing alkenes.

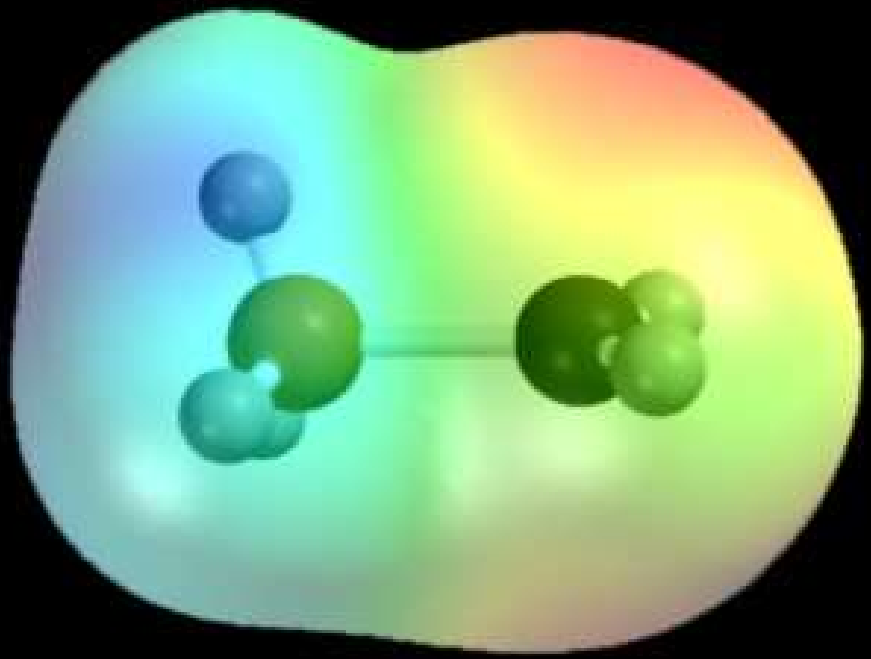
One of the reactants is an aldehyde or ketone.

The other reactant is a phosphorus ylide.

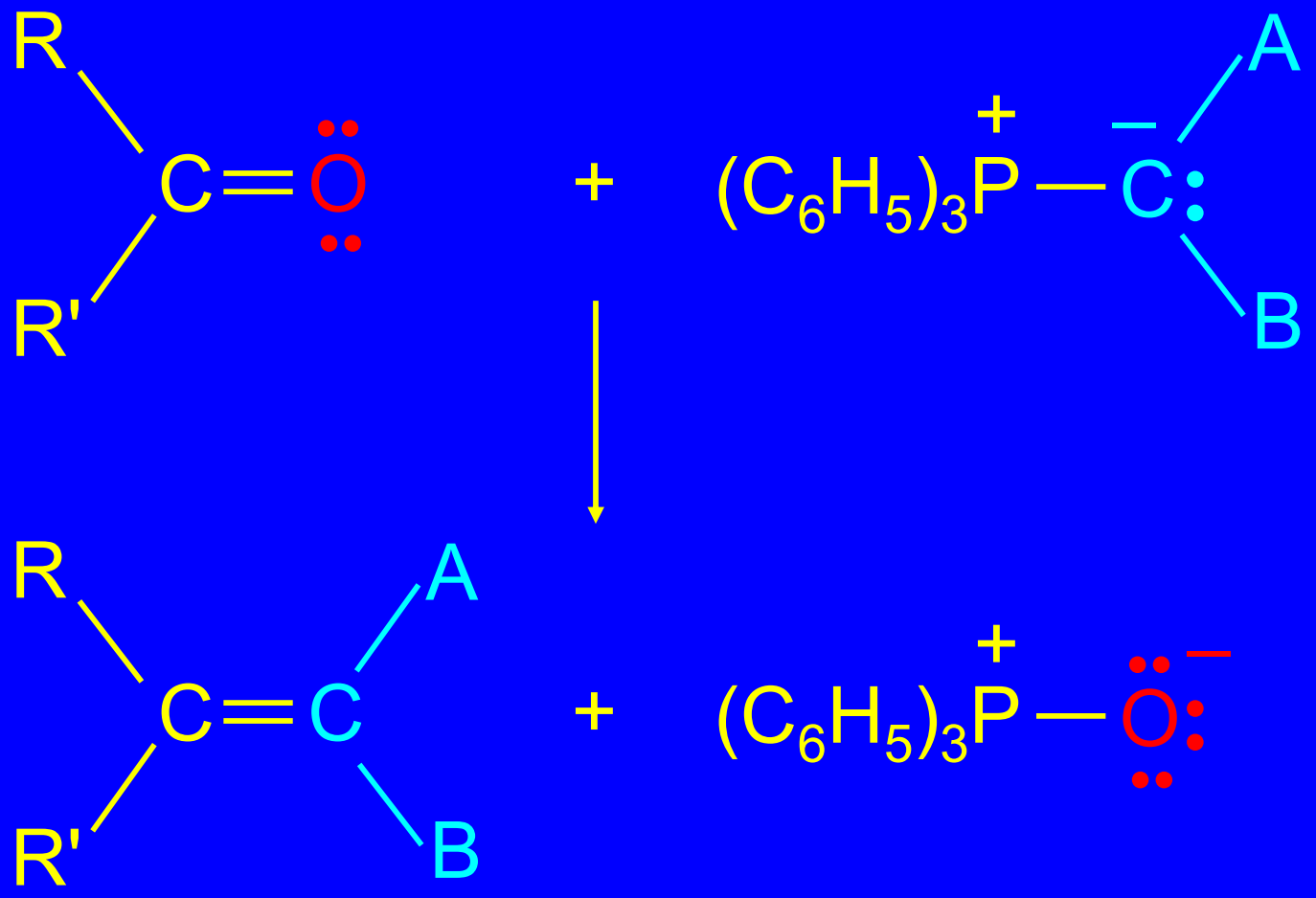


A key property of ylides is that they have a negatively polarized carbon and are nucleophilic.

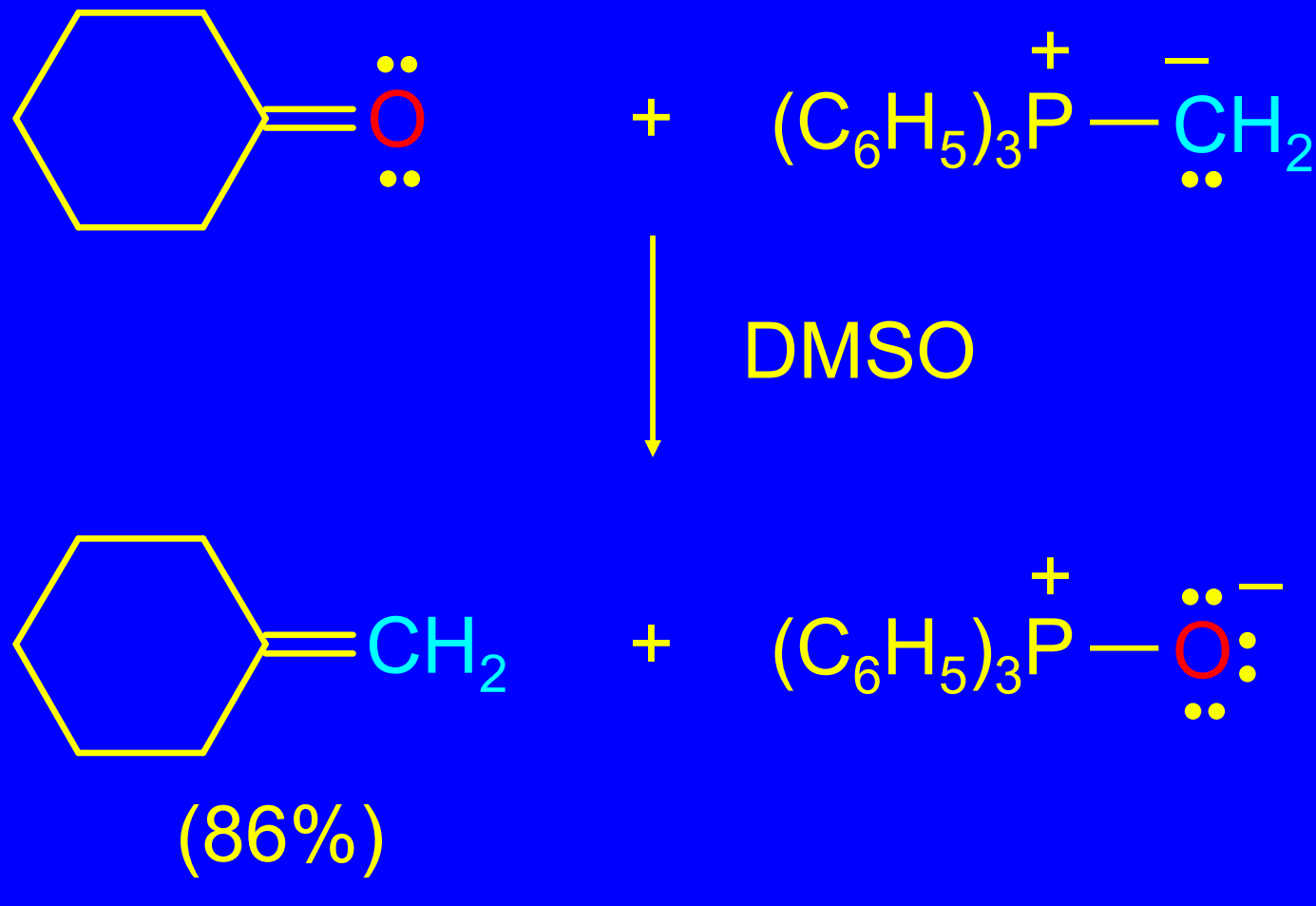
Figure 17.12 Charge distribution in a ylide



The Wittig Reaction



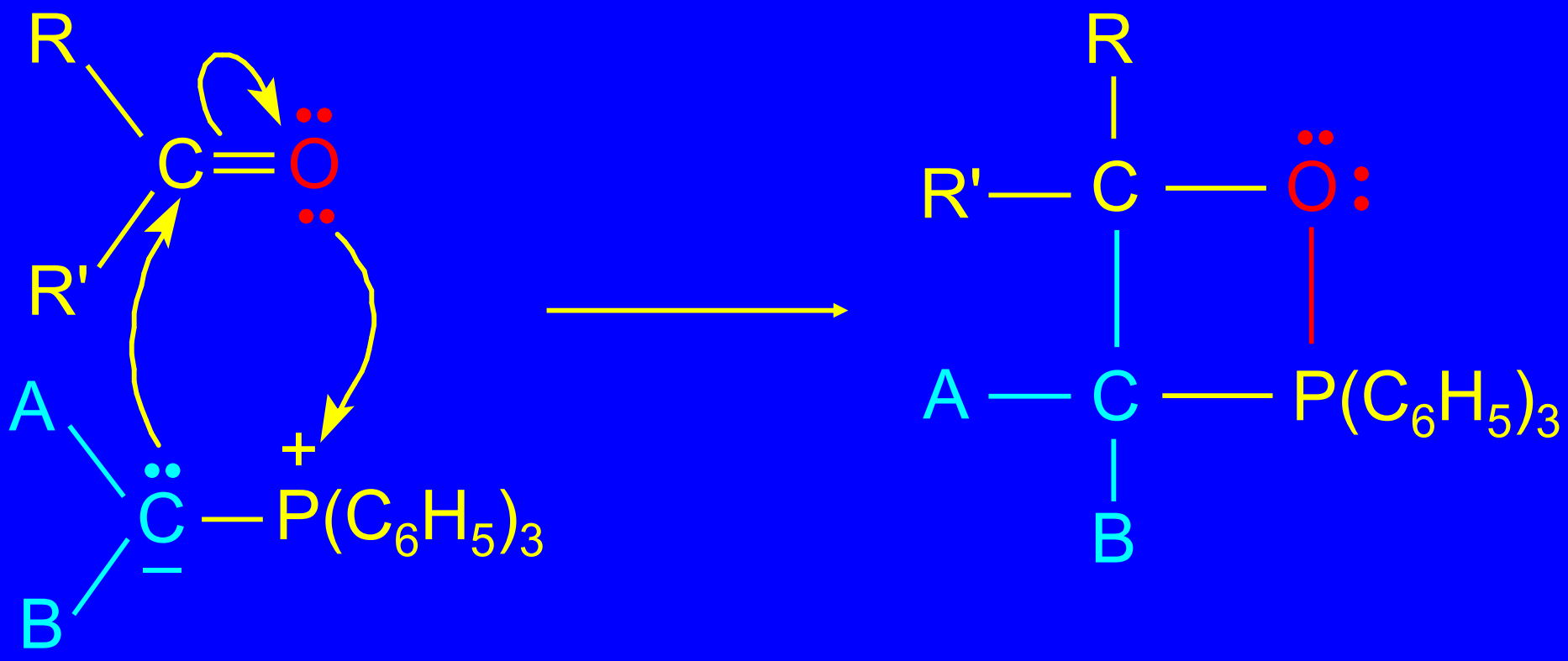
Example



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

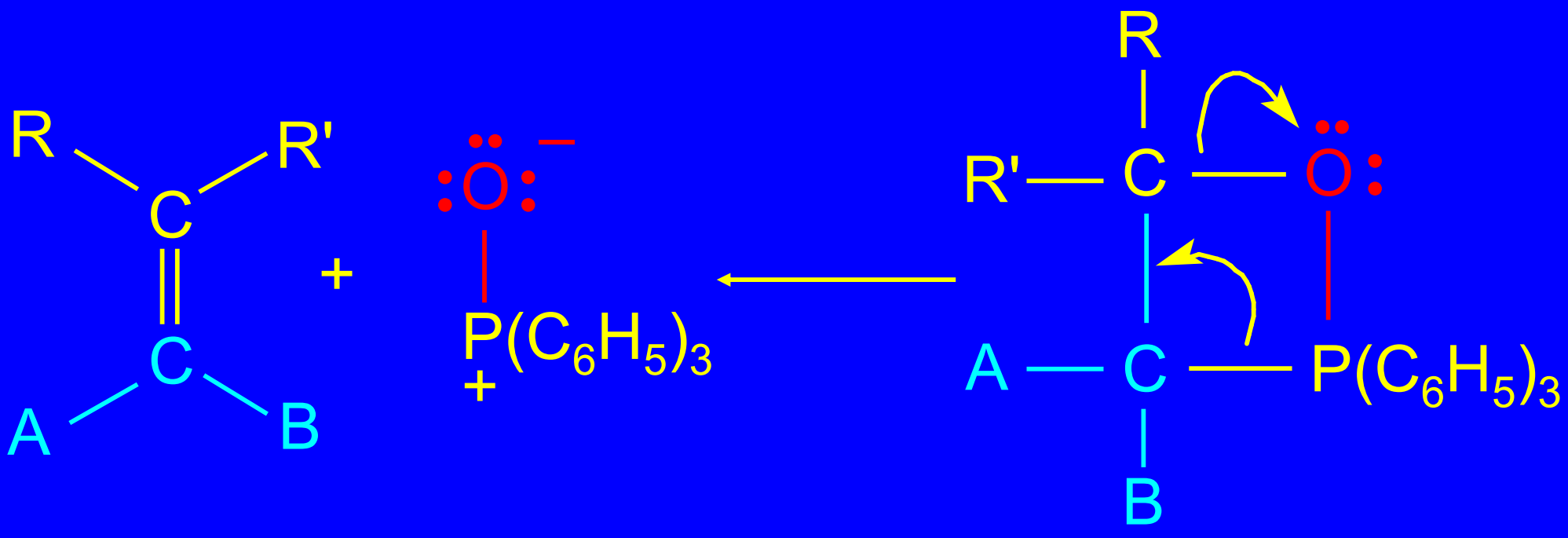
Mechanism

Step 1



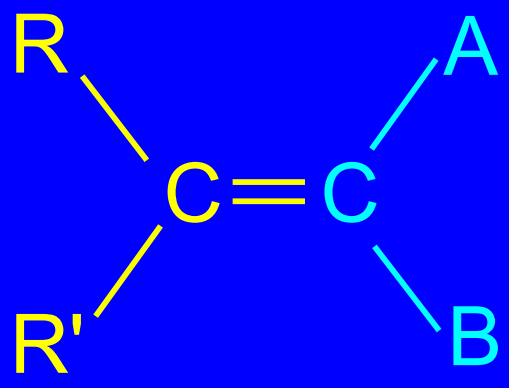
Mechanism

Step 2



Planning an Alkene Synthesis via the Wittig Reaction

Retrosynthetic Analysis

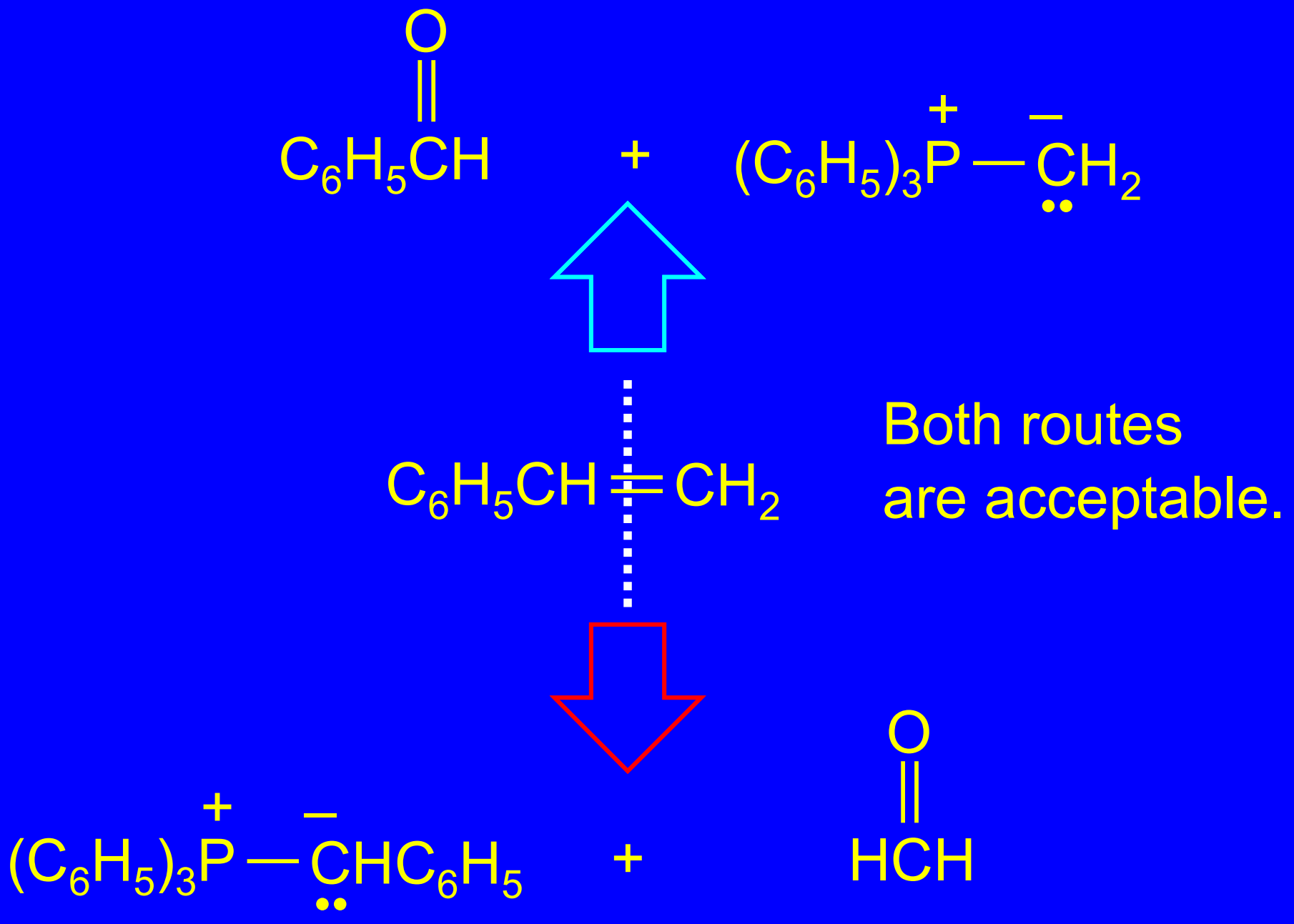


There will be two possible Wittig routes to an alkene.

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

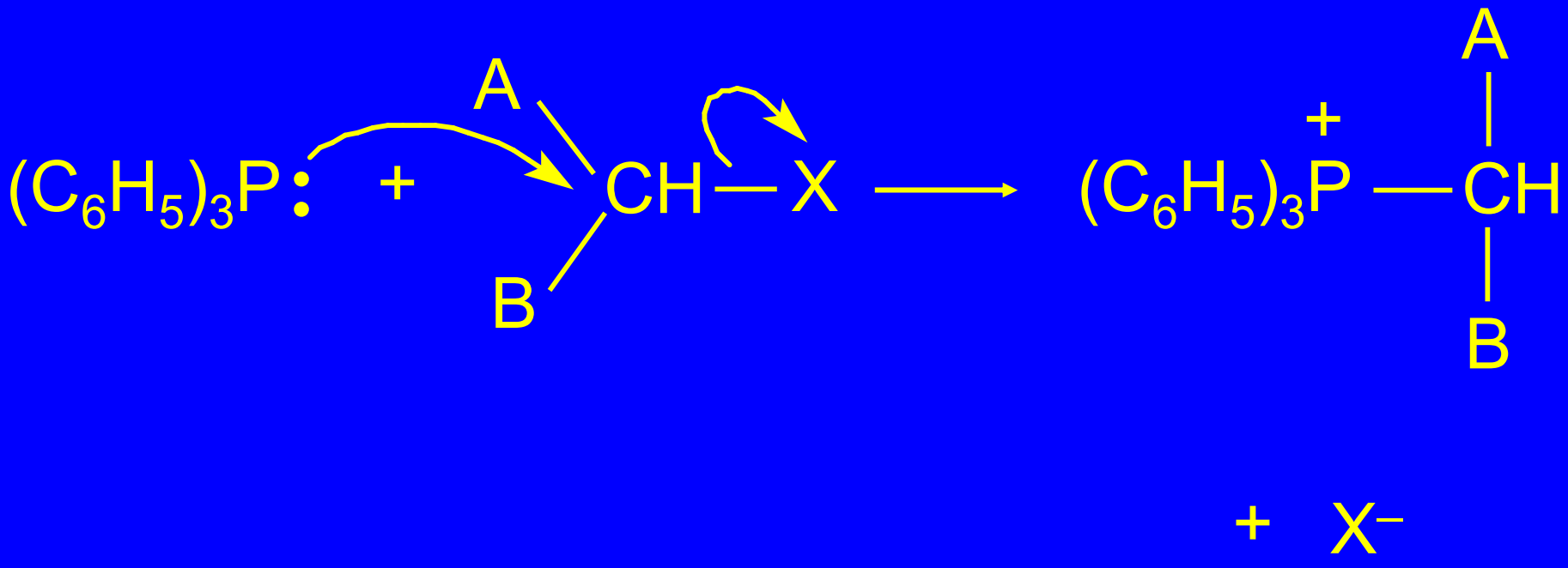


Both routes are acceptable.

Preparation of Ylides

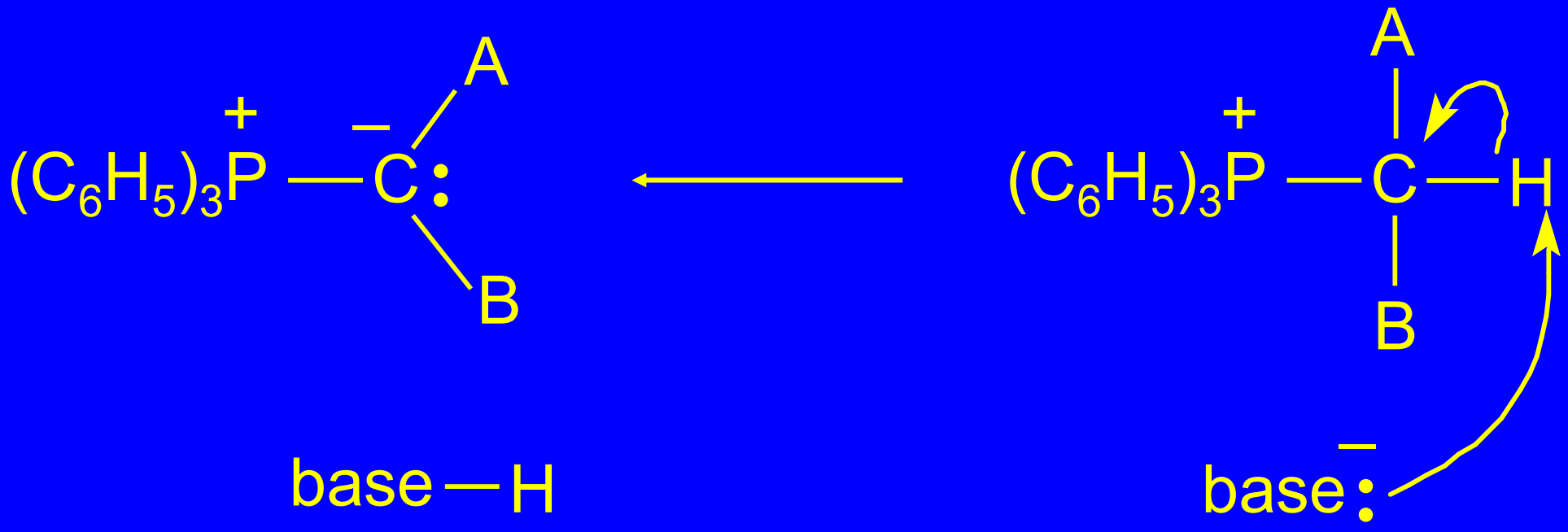
Ylides are prepared from alkyl halides by a two-stage process.

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

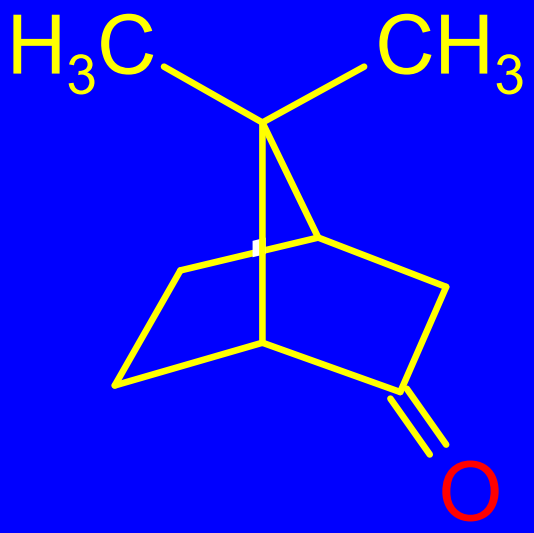
Typical strong bases include organolithium reagents (RLi), and the conjugate base of dimethyl sulfoxide as its sodium salt [$NaCH_2S(O)CH_3$].

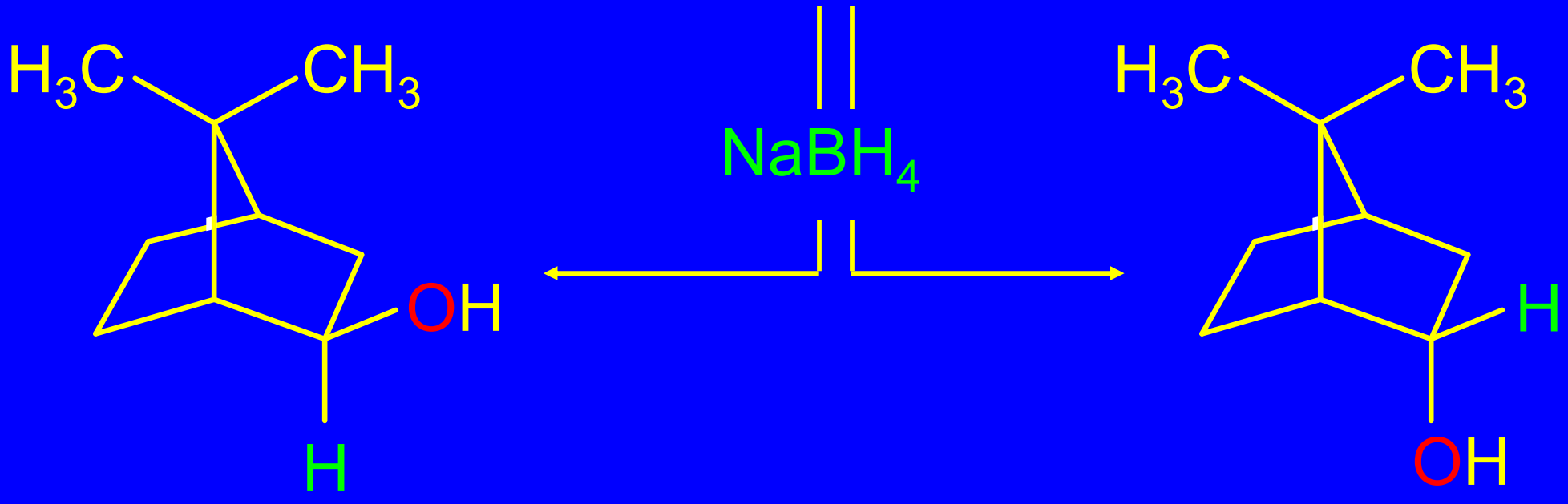
Stereoselective Addition to

Carbonyl Groups

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

Example

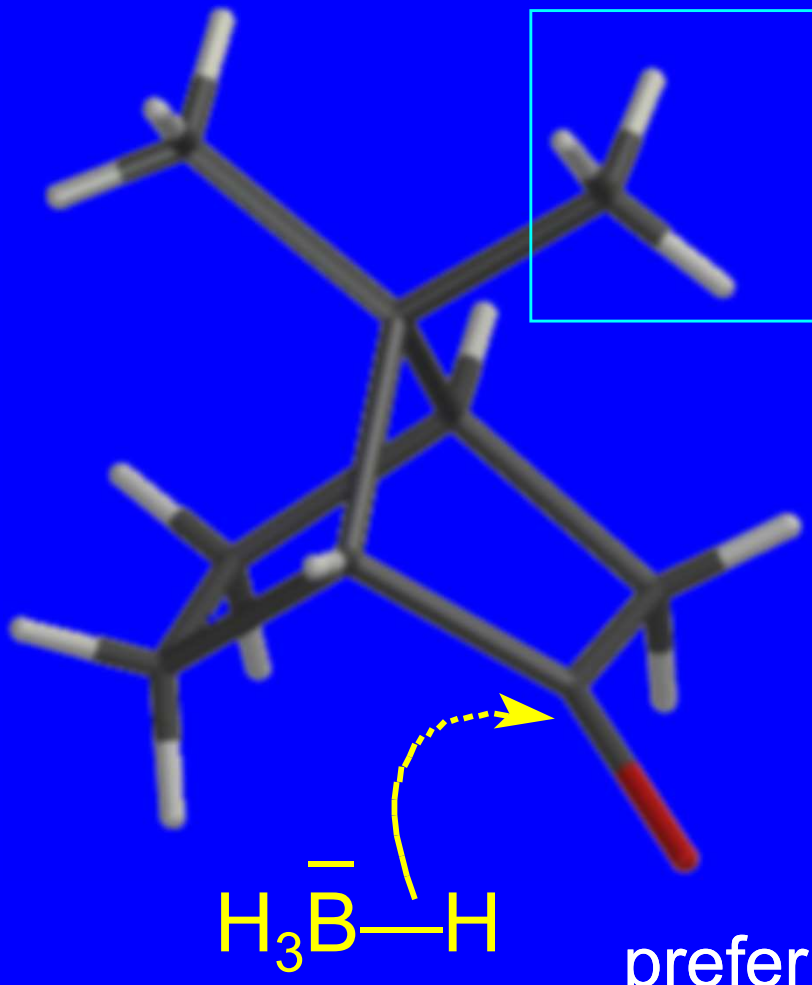




80%

20%

Steric Hindrance to Approach of Reagent

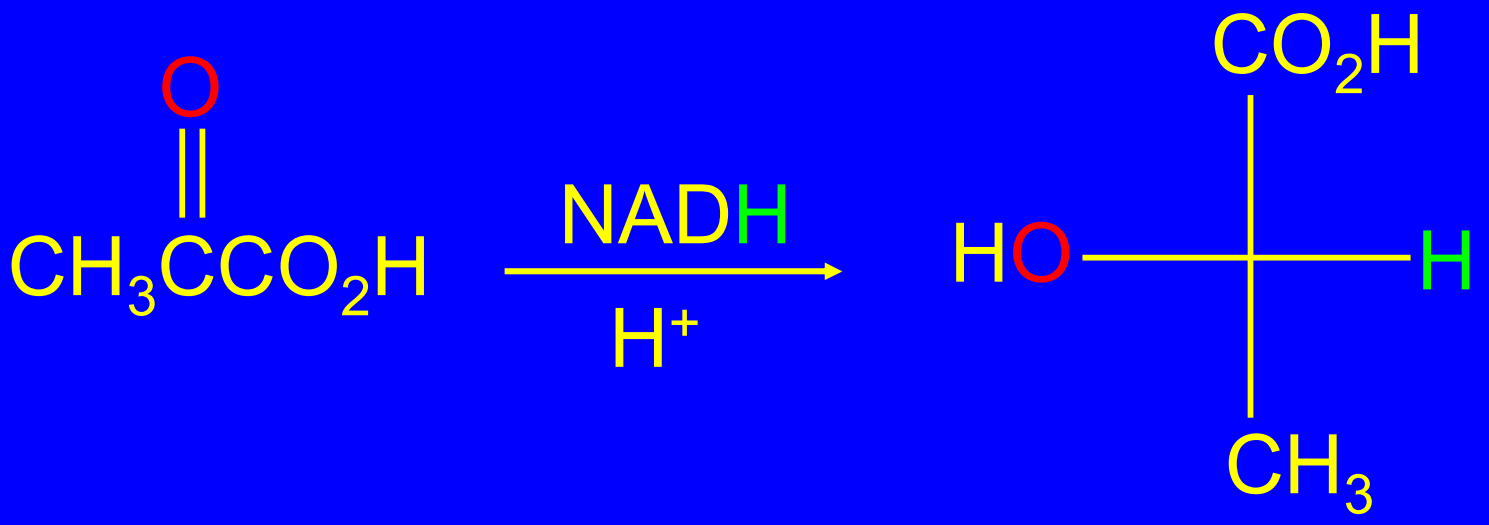


this methyl group hinders approach of nucleophile from top

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

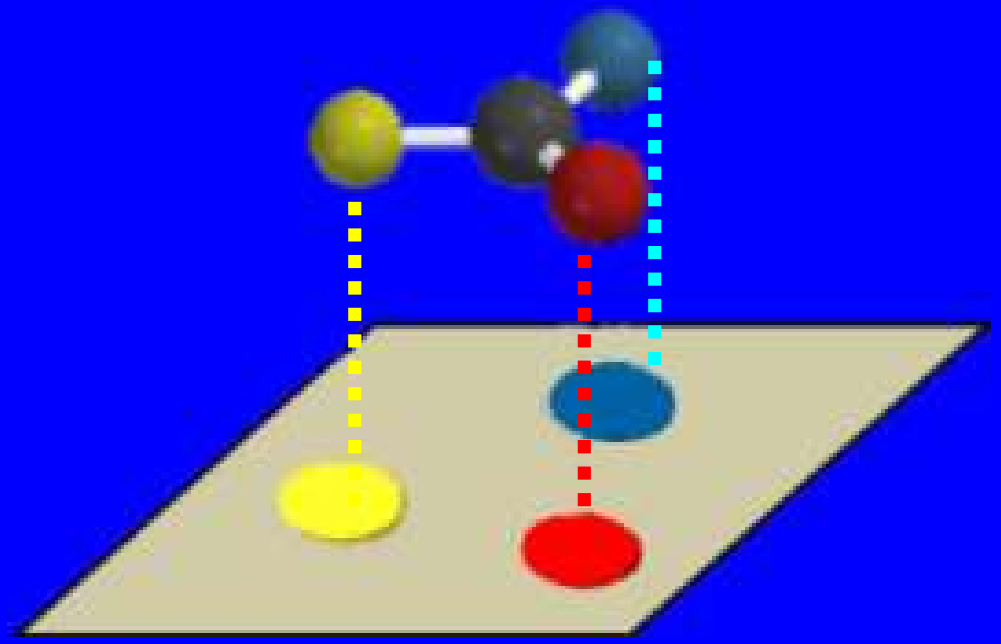
Biological reductions are highly stereoselective

pyruvic acid → *S*-(+)-lactic acid



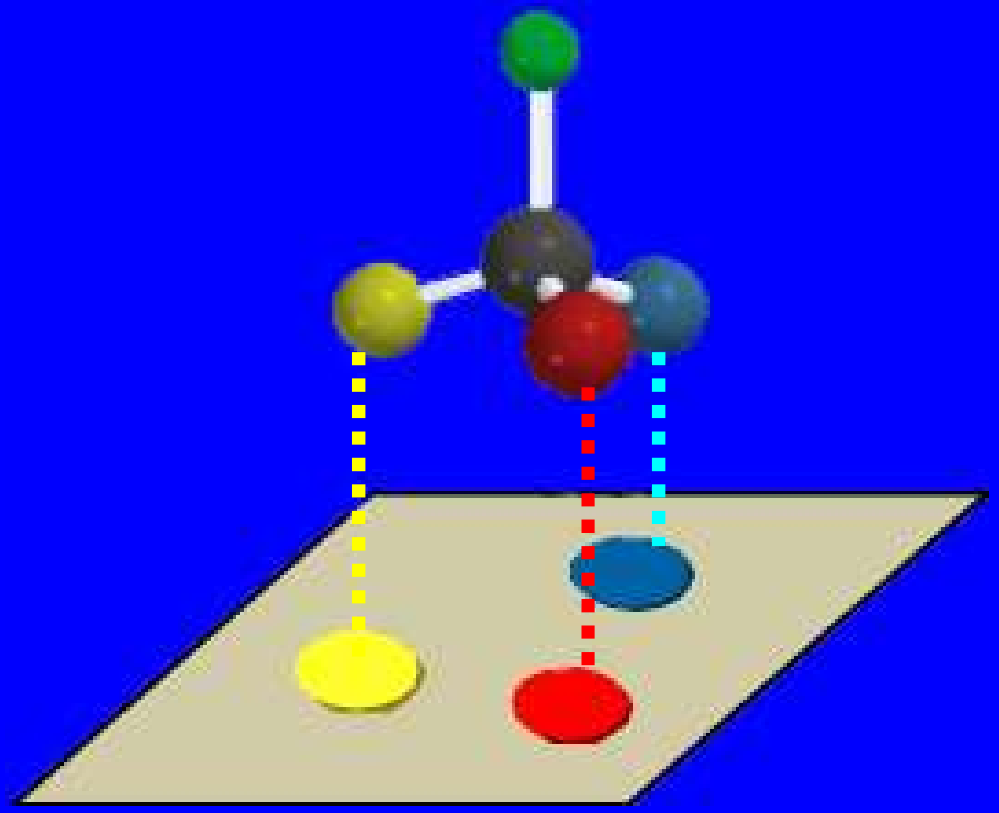
enzyme is *lactate dehydrogenase*

Figure 17.14



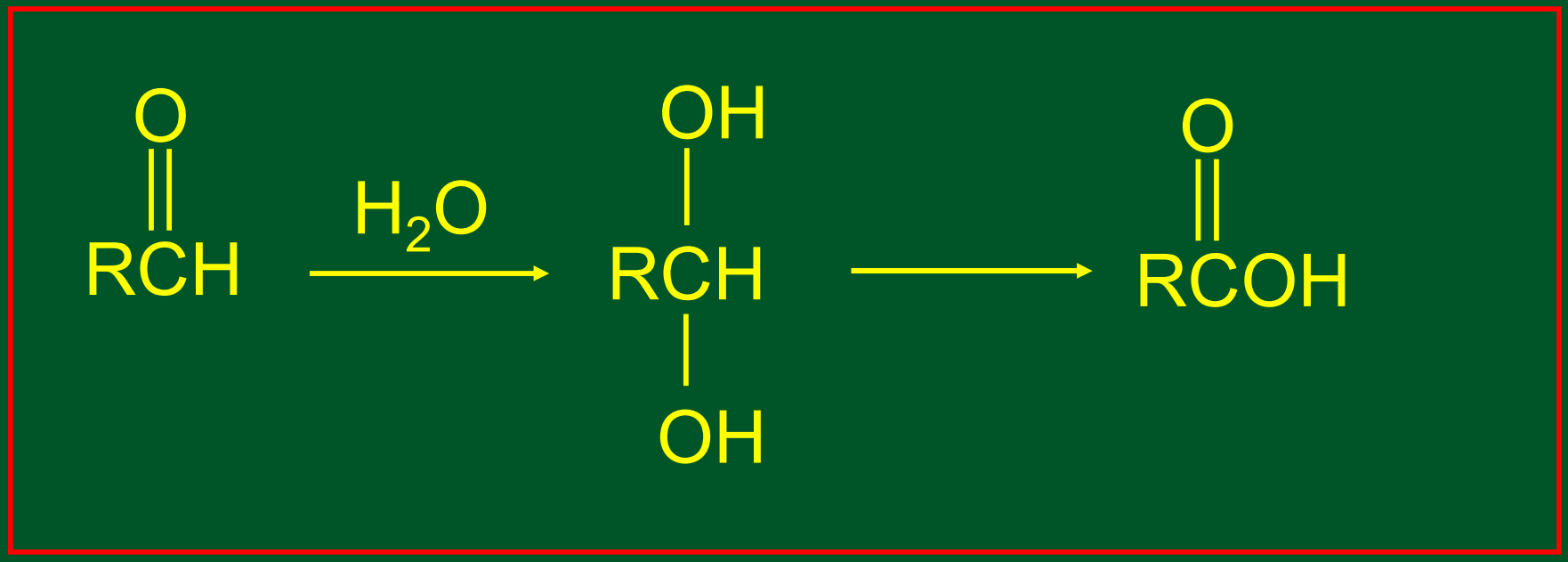
One face of the substrate can bind to the enzyme better than the other.

Figure 17.14



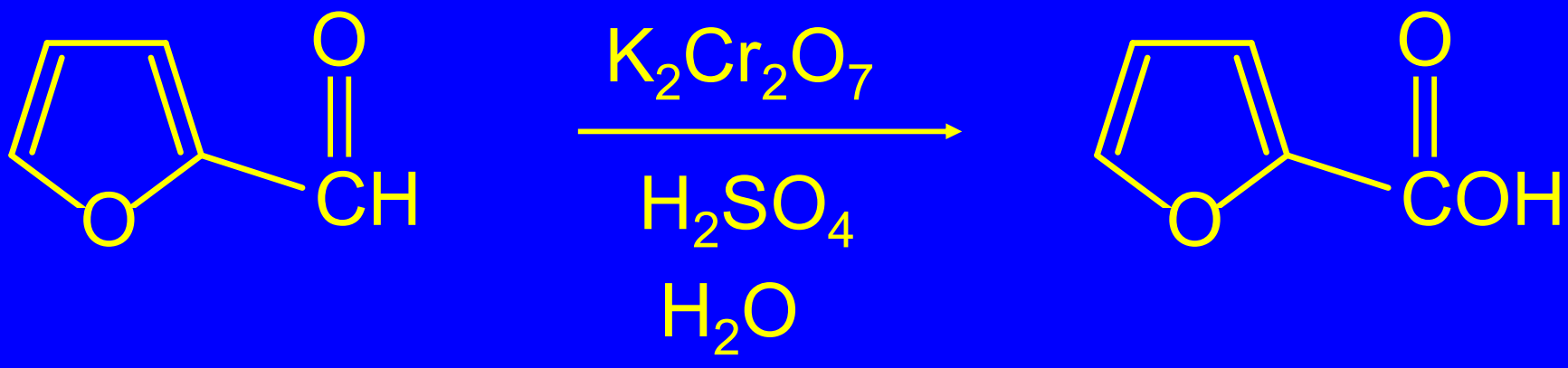
Change in geometry from trigonal to tetrahedral is stereoselective. Bond formation occurs preferentially from one side rather than the other.

Oxidation of Aldehydes



in aqueous solution

Example



(75%)

via

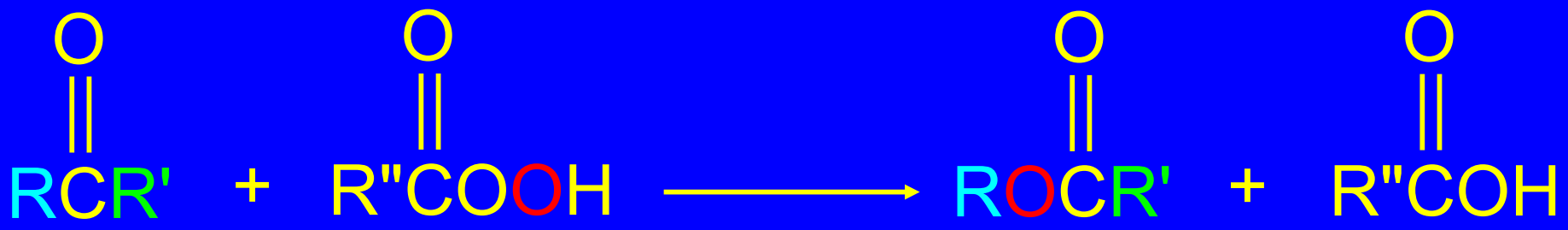
17.16

Baeyer-Villiger Oxidation

of Ketones

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

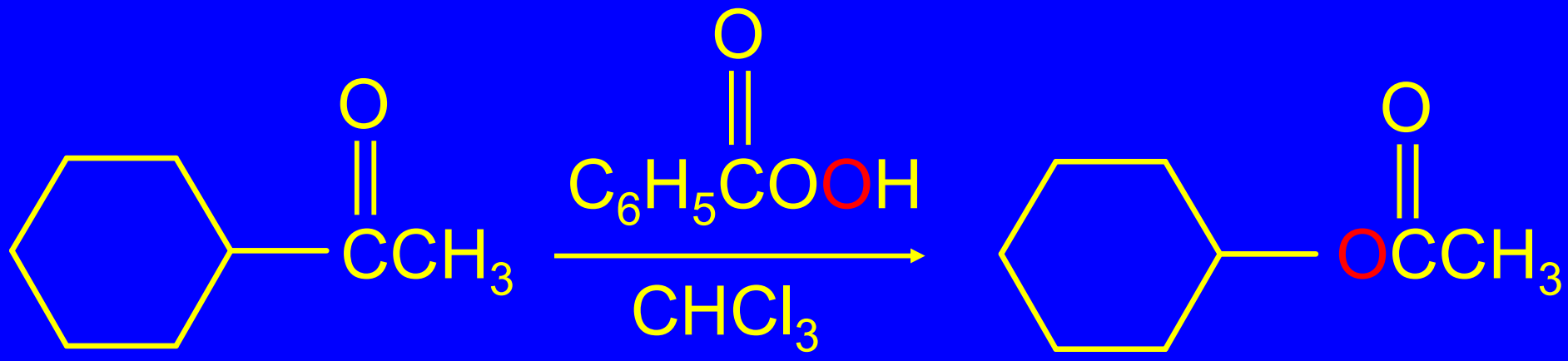
General



Ketone

Ester

Example

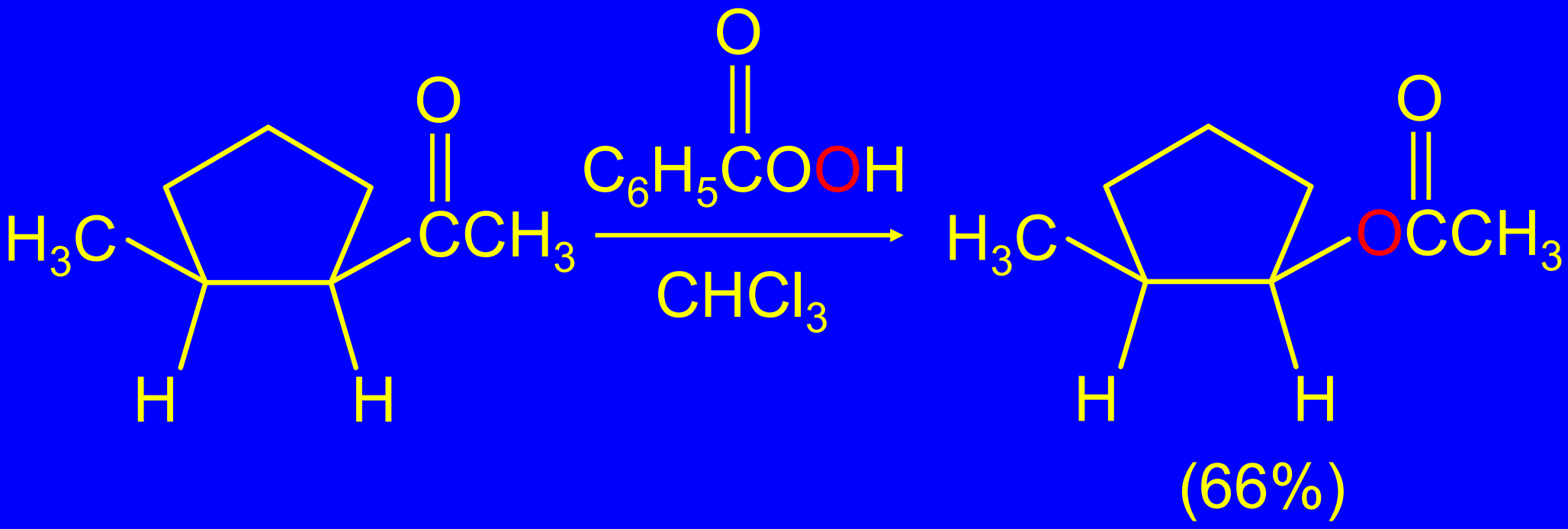


(67%)

Oxygen insertion occurs between carbonyl carbon and larger group.

Methyl ketones give acetate esters.

Stereochemistry

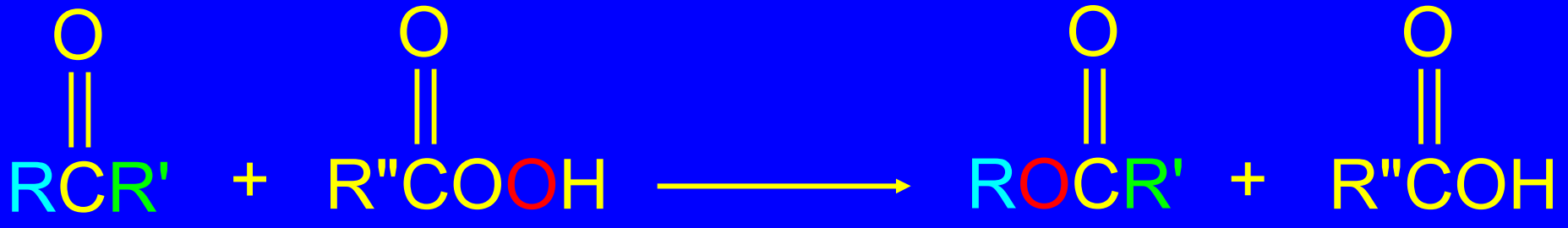


(66%)

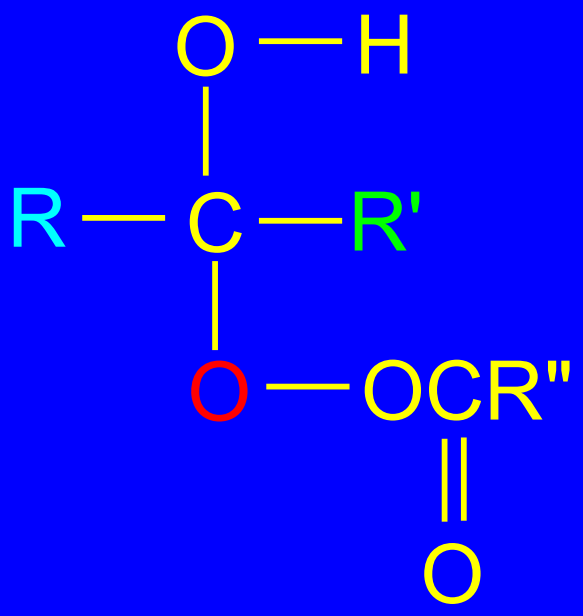
Reaction is stereospecific.

Oxygen insertion occurs with retention of configuration.

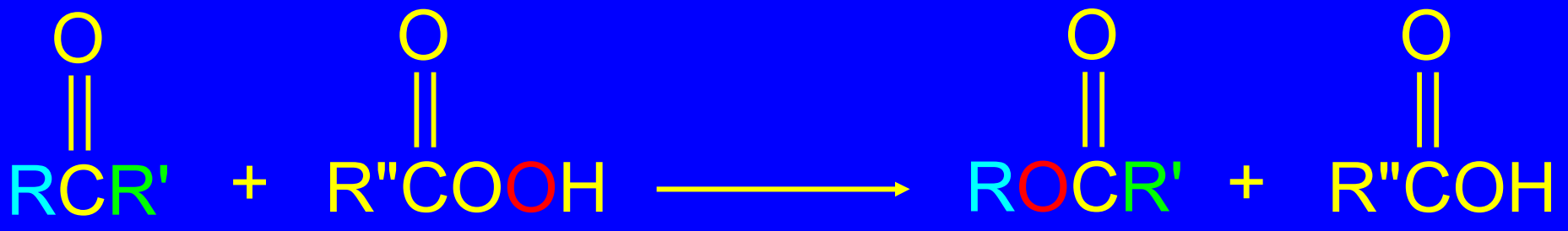
Mechanism

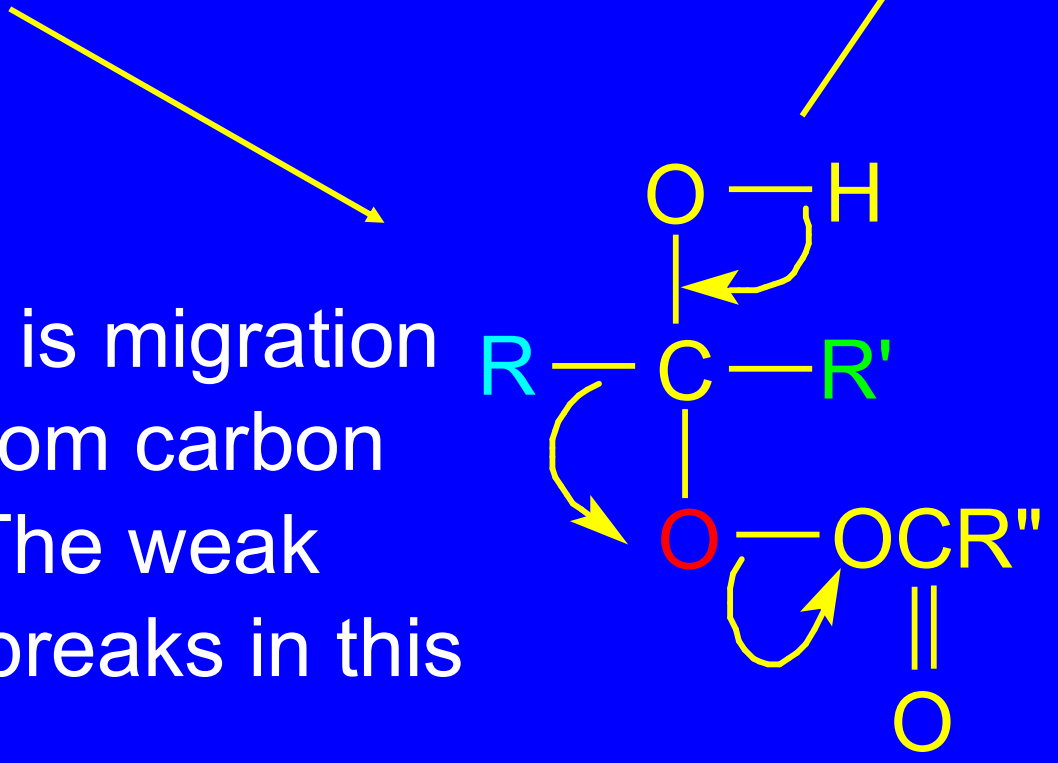


First step is nucleophilic addition of peroxy acid to the carbonyl group of the ketone.



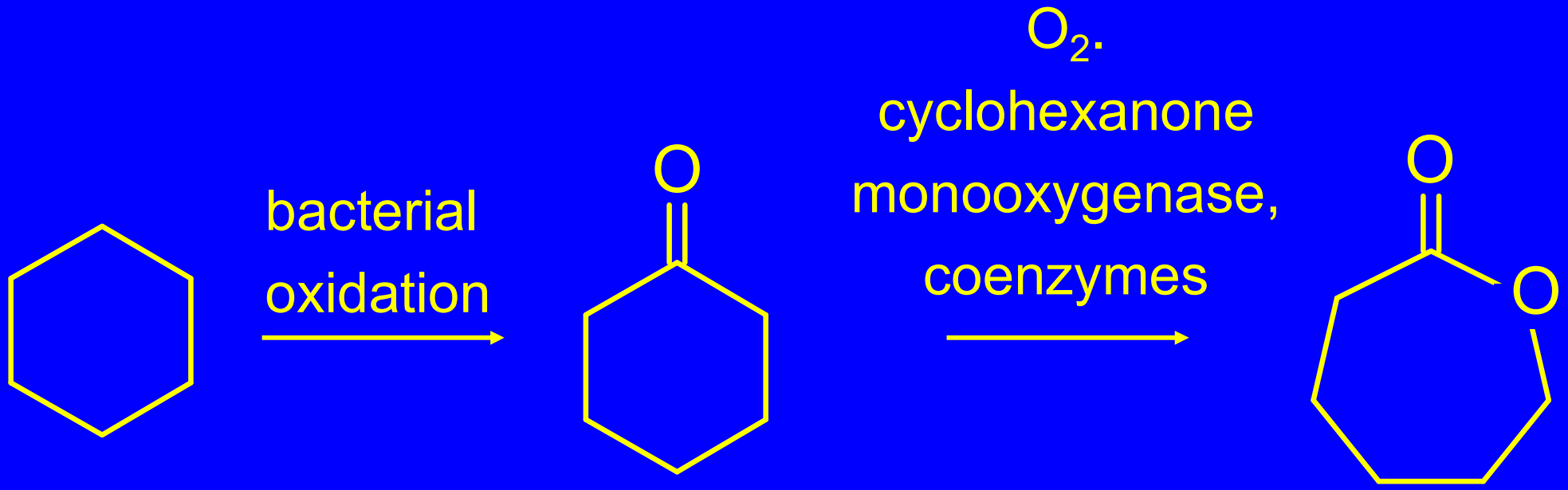
Mechanism





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

Biological Baeyer-Villliger Oxidation

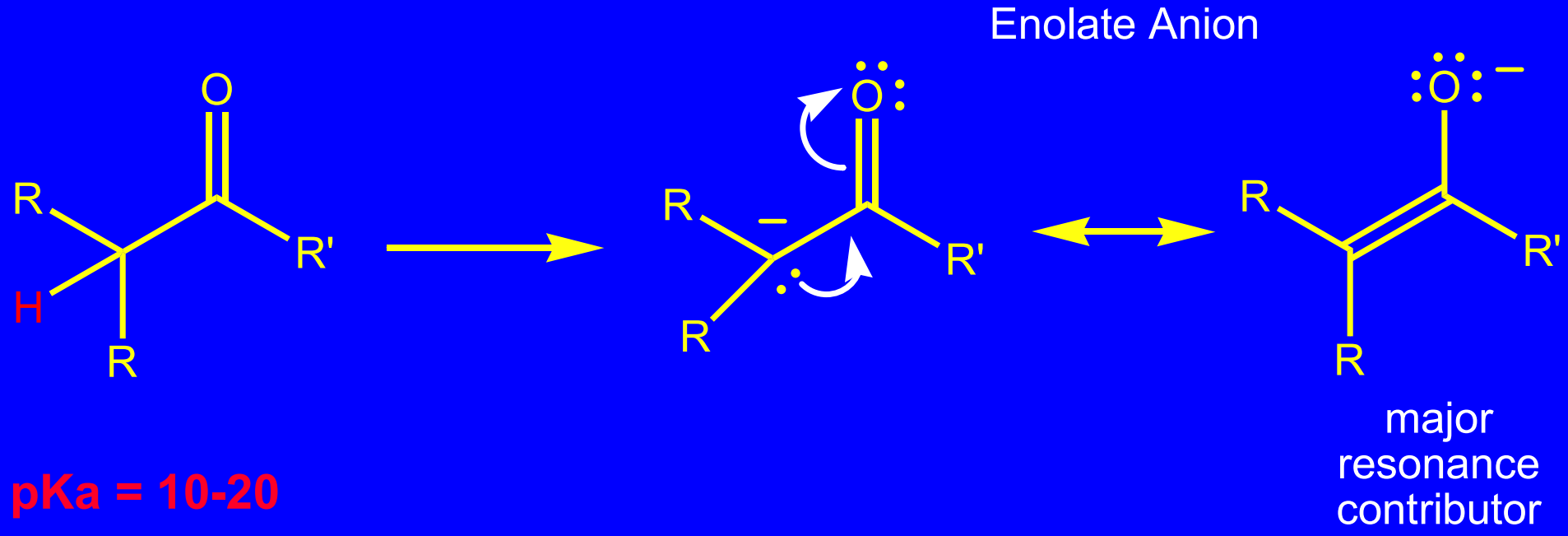


Certain bacteria use hydrocarbons as a source of carbon. Oxidation proceeds via ketones, which then undergo oxidation of the Baeyer-Villiger type.

Base-Catalyzed Enolization:
Enolate Anions and the Aldol Reaction

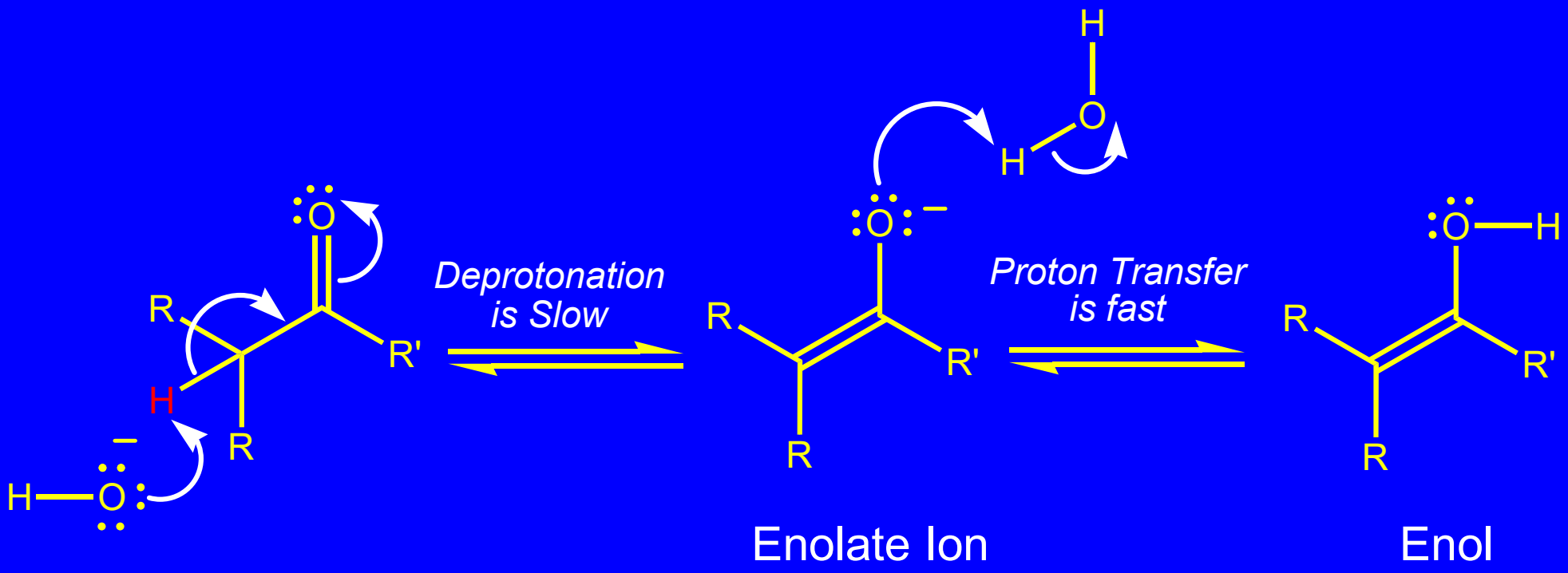
18.6
Base-Catalyzed Enolization: Enolate Anions

α-Hydrogens are Acidic

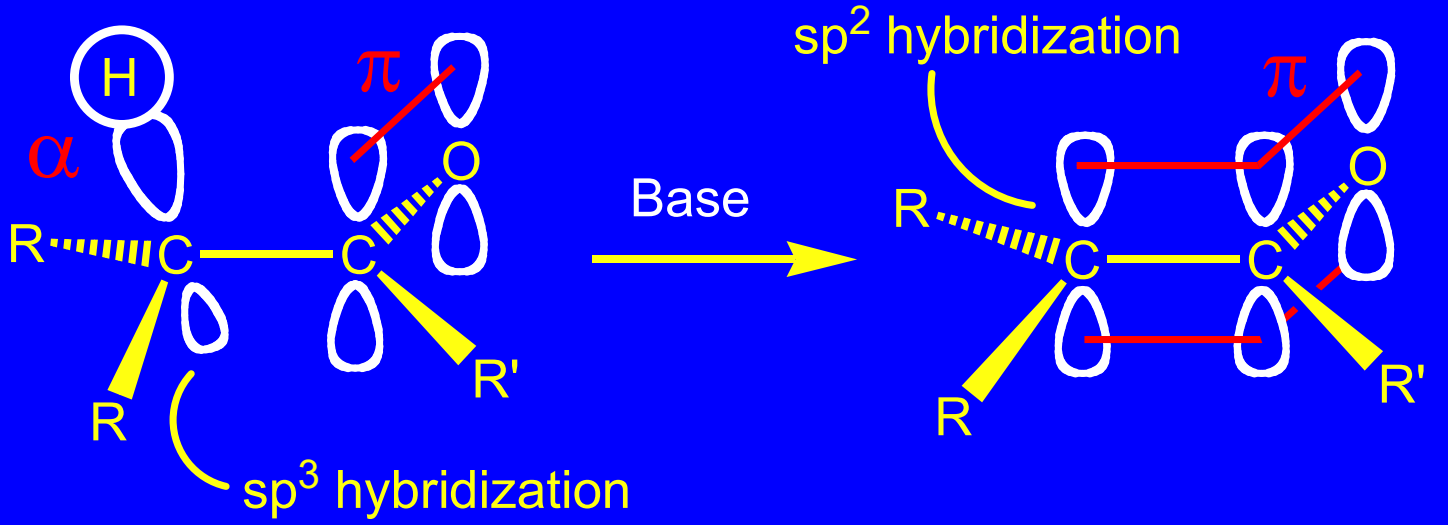


pKa = 10-20

Mechanism of Enolization (Base-catalyzed)



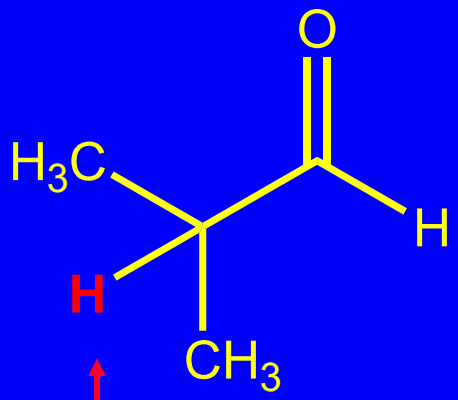
Orbitial Picture of Base-catalyzed Enolization



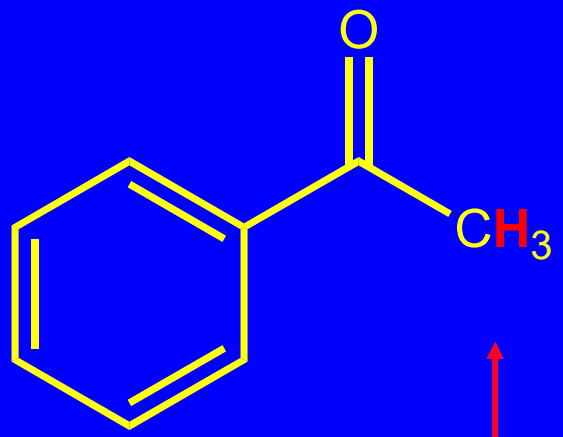
The more stable this ion, the more favorable this process becomes

What stablizes enolate ions?

Acidity of Typical Aldehydes and Ketones

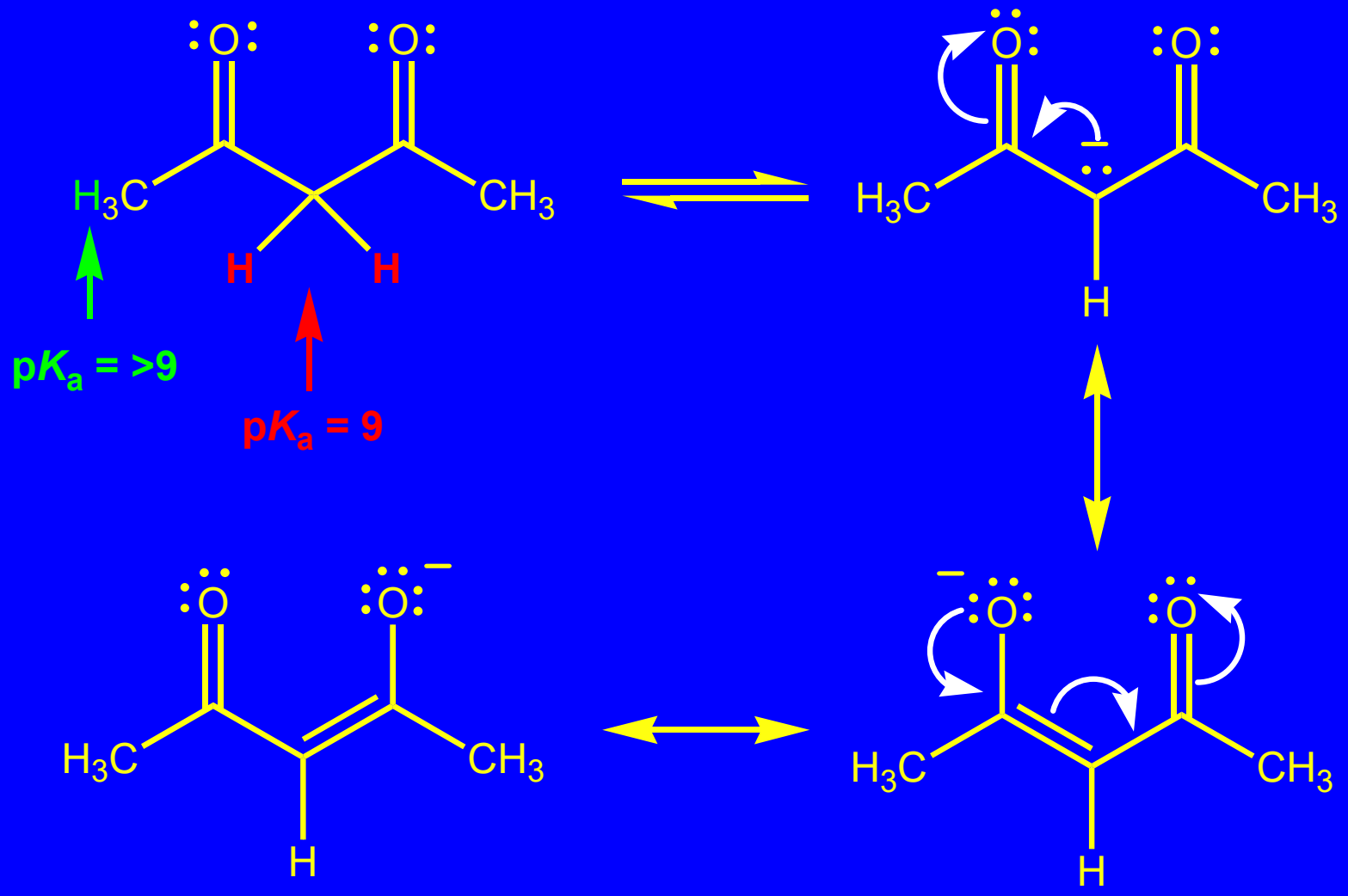


pK_a = 15.5



pK_a = 18.3

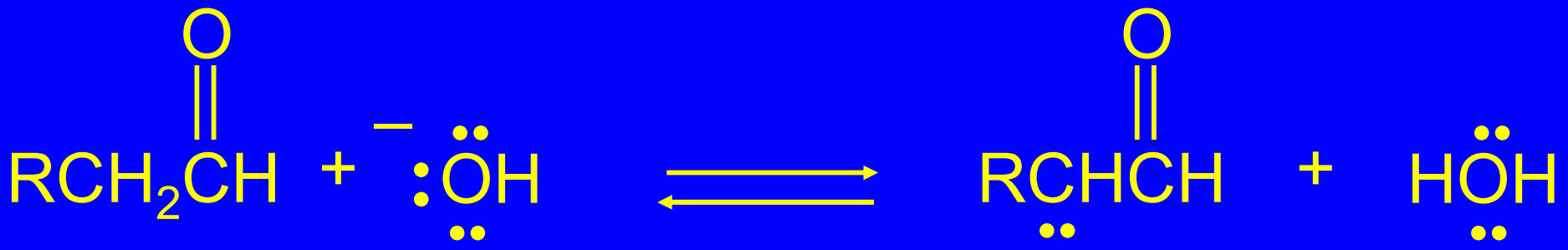
β-Diketones are much more acidic



The enolates of β-diketones are stabilized;
negative charge is shared by both oxygens

The Aldol Condensation

Some thoughts...



pK_a = 16-20

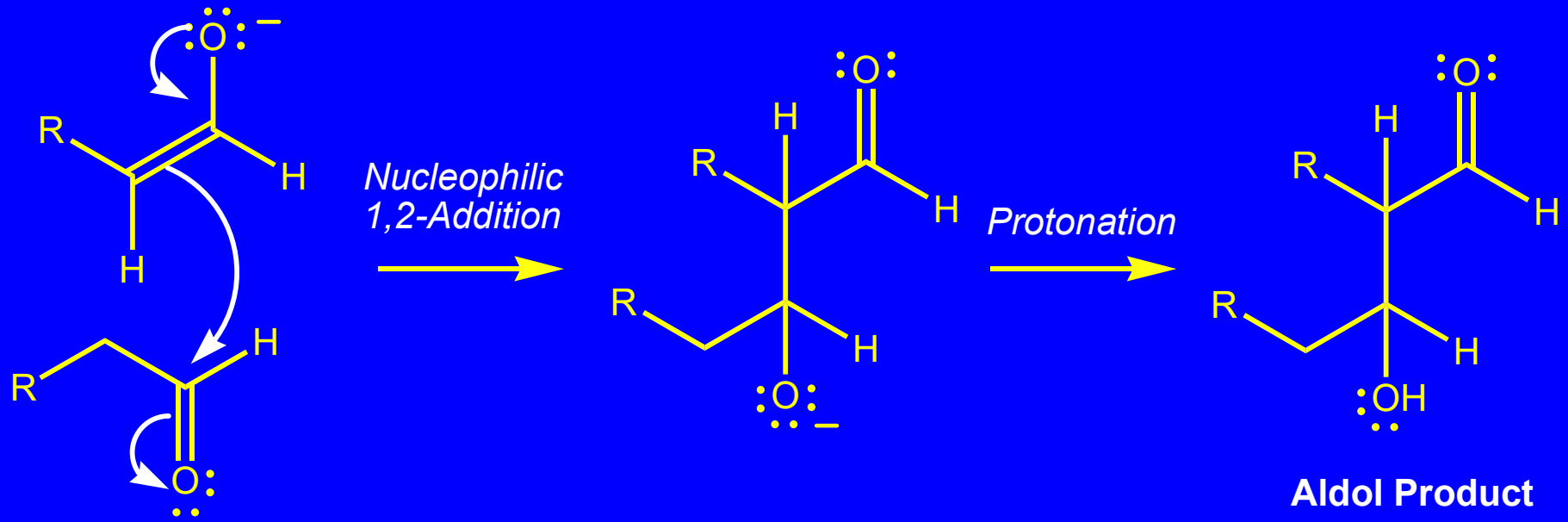
pK_a = 16

A basic solution contains comparable amounts of the aldehyde and its enolate.

Aldehydes undergo nucleophilic addition.

Enolate ions are nucleophiles.

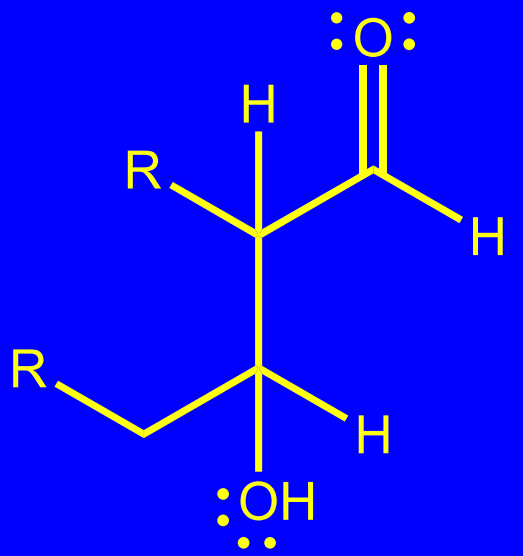
What about nucleophilic addition of enolate to aldehyde?



Aldol Product

(β–Hydroxy Carbonyl Compound)

Aldol Addition

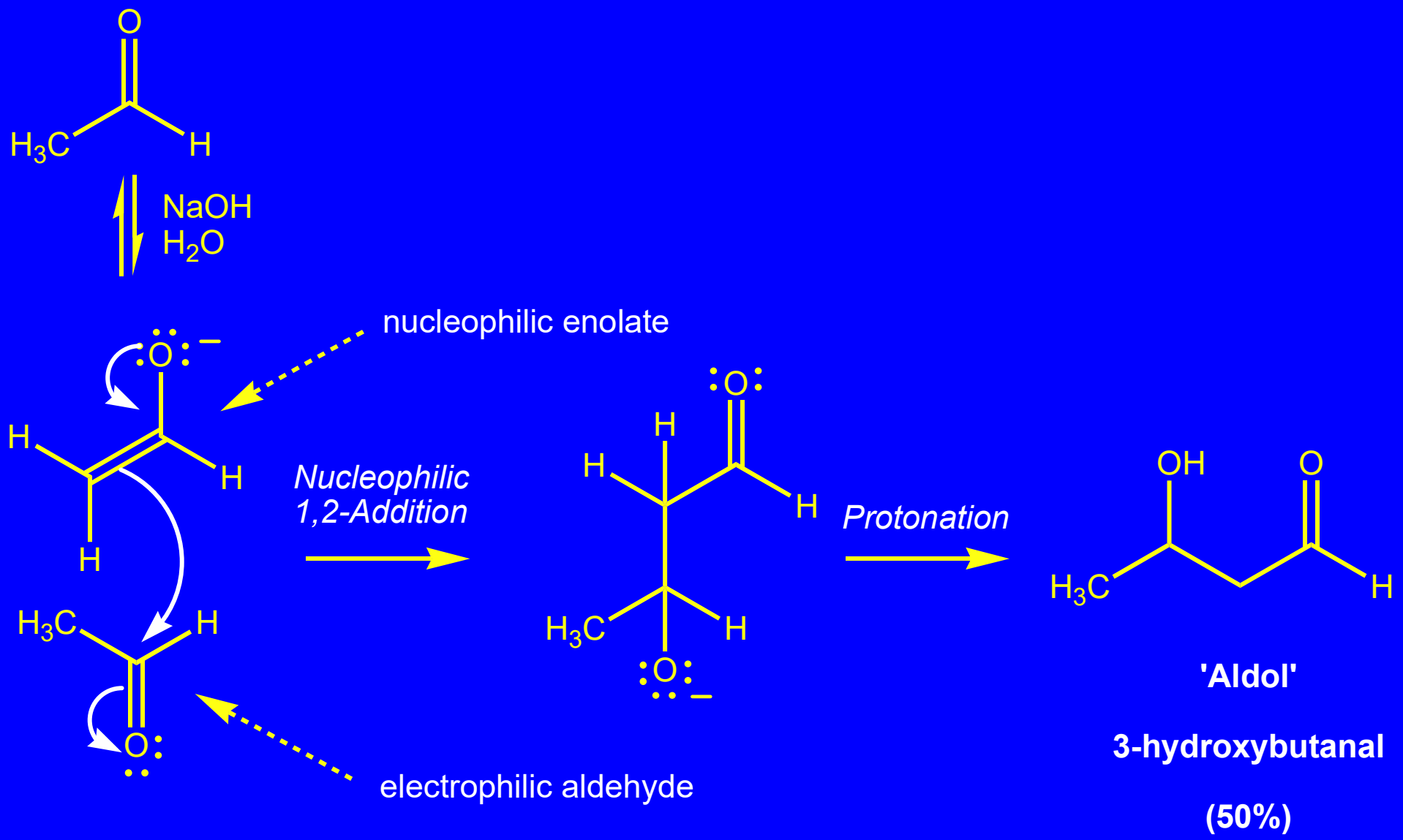


Aldol Product

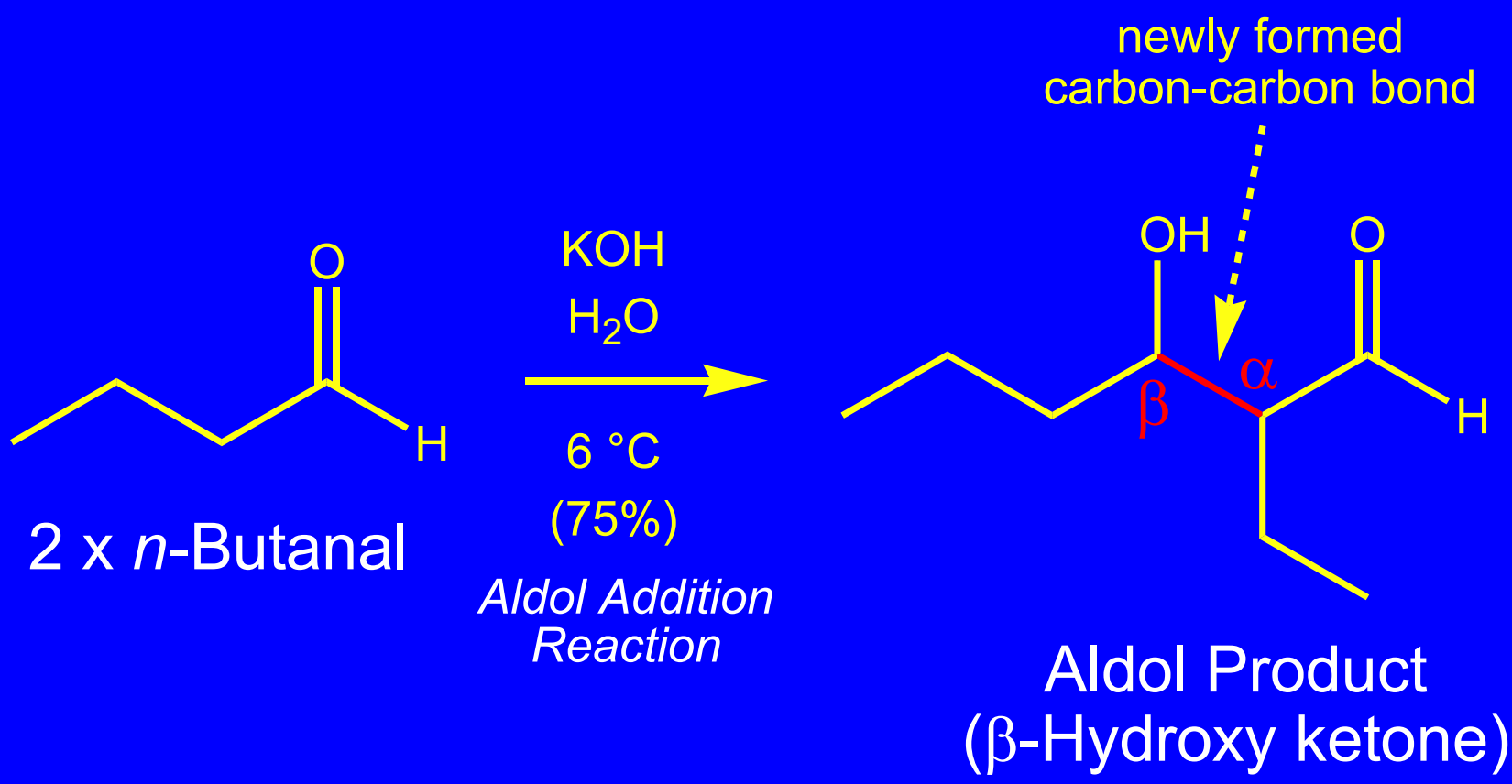
(β–Hydroxy Carbonyl Compound)

This product is called an "aldol" because it is both an aldehyde and an alcohol

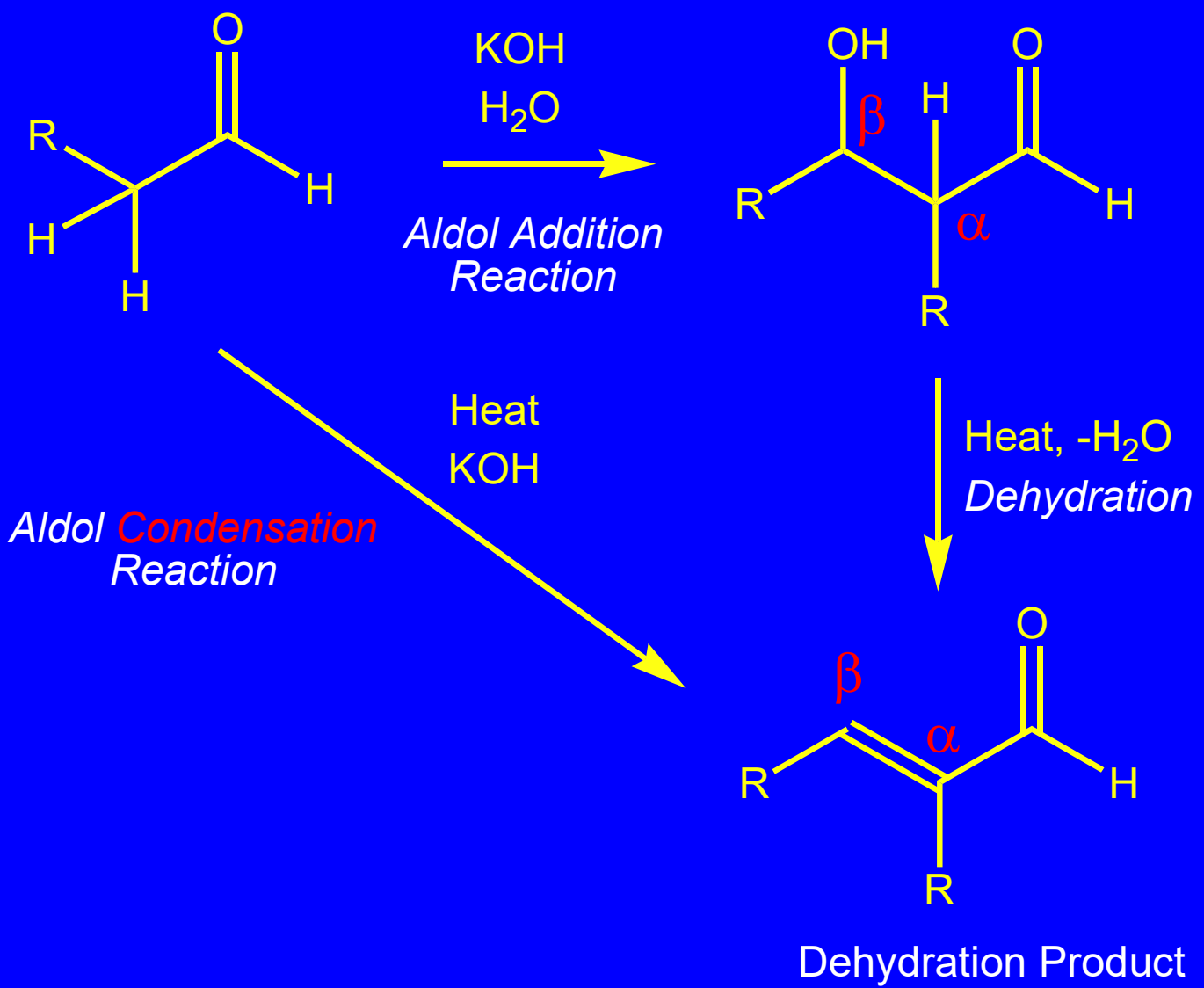
Aldol Addition of Acetaldehyde



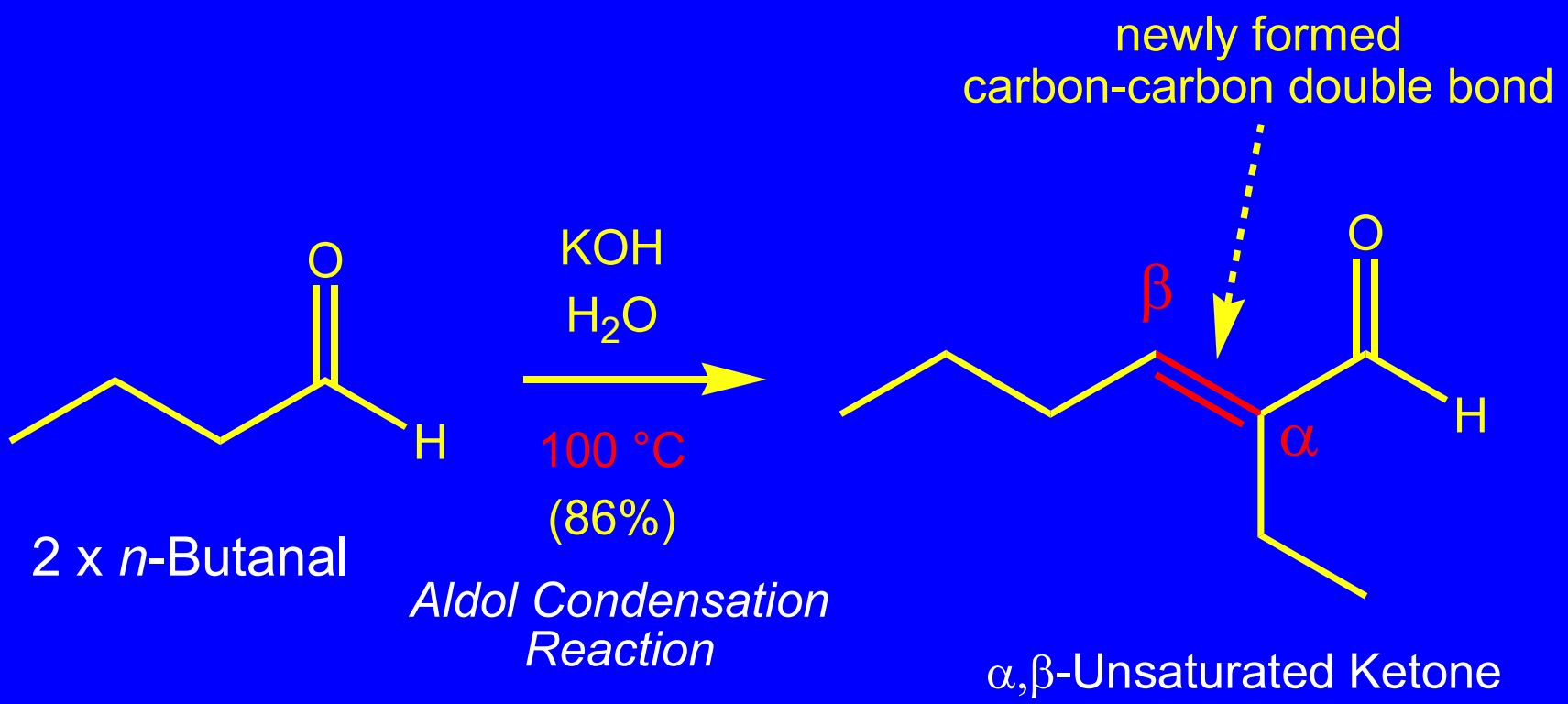
Aldol Addition of n-Butanal



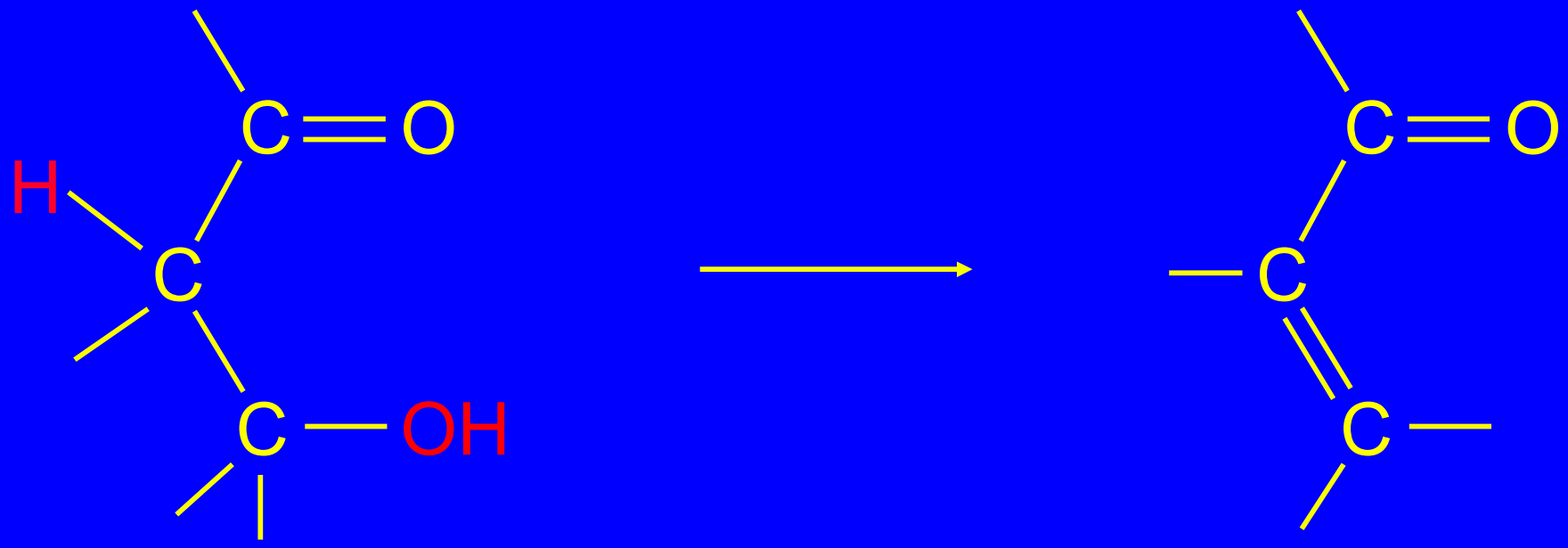
Aldol Condensation



Aldol Condensation of Butanal

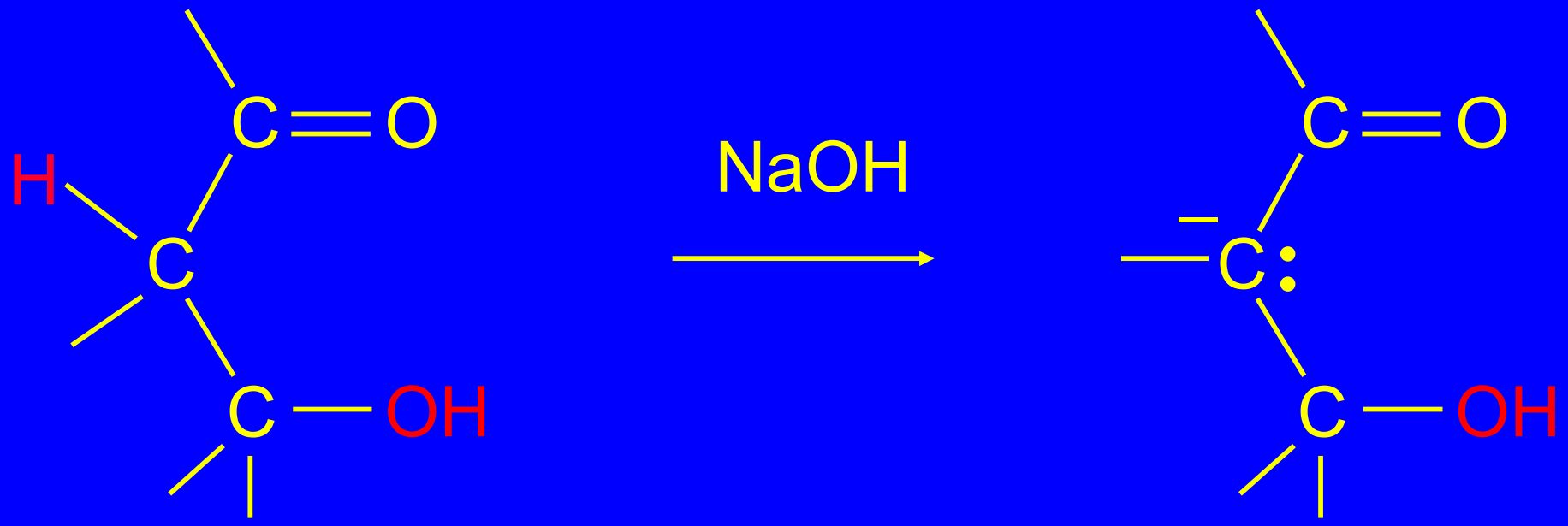


Dehydration of Aldol Addition Product



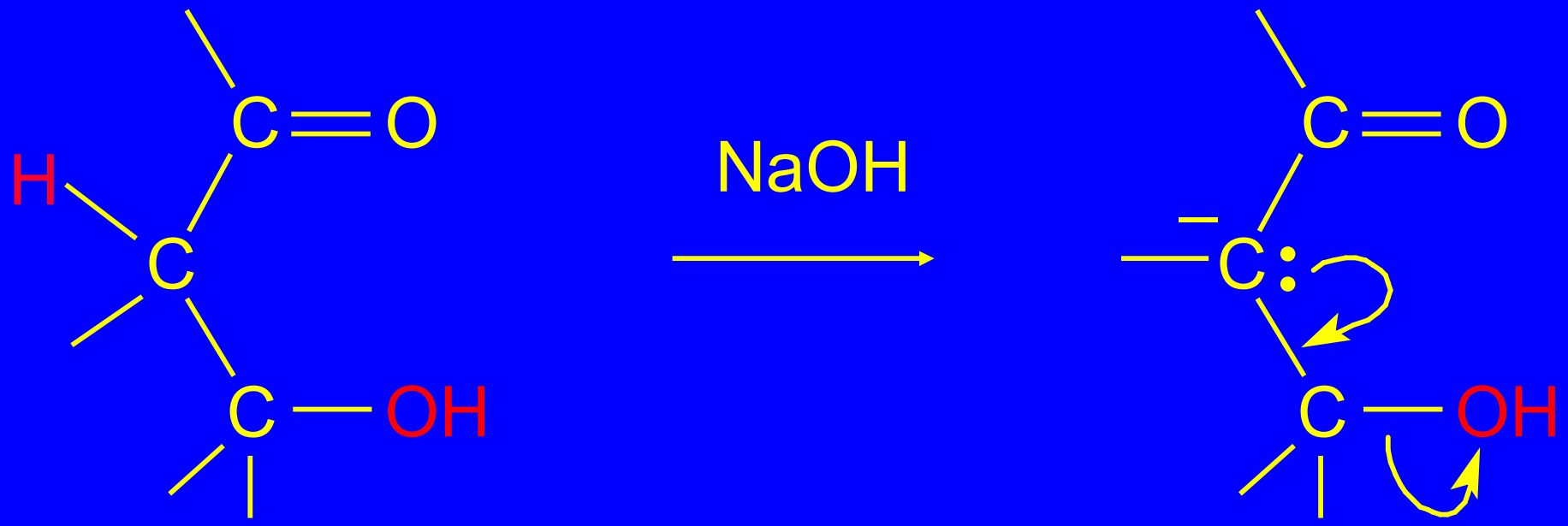
dehydration of β-hydroxy aldehyde can be catalyzed by either acids or bases

Dehydration of Aldol Addition Product



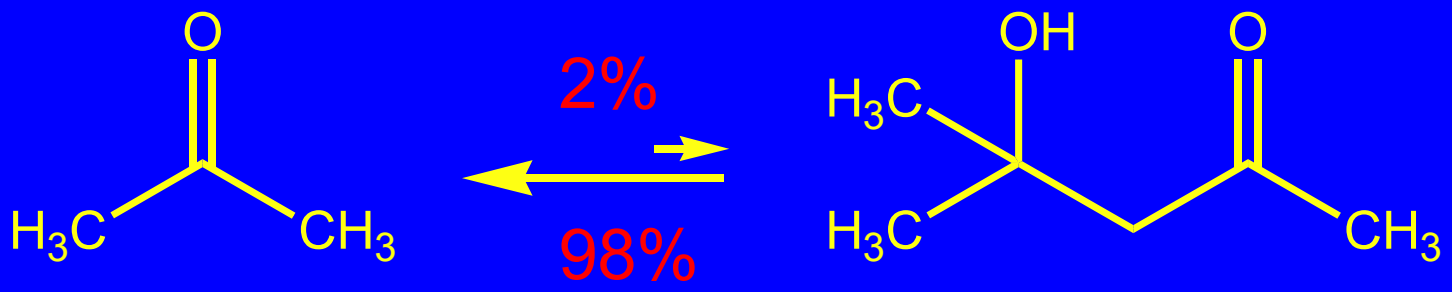
in base, the enolate is formed

Dehydration of Aldol Addition Product



the enolate loses hydroxide to form the α,β-unsaturated aldehyde

Aldol reactions of ketones

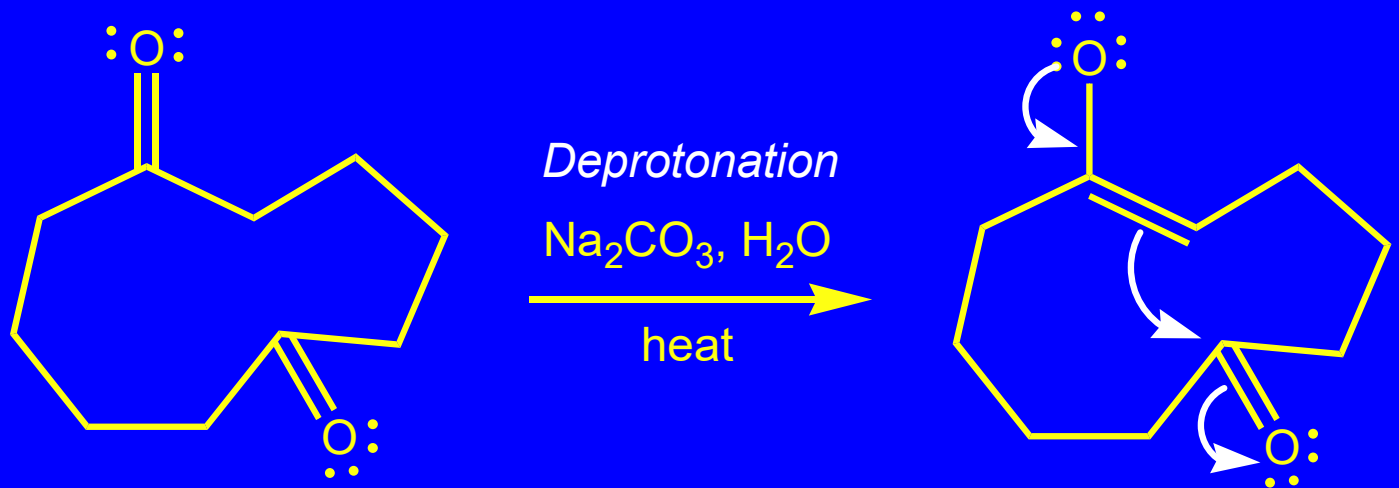


2 x Acetone

Formation of Aldol Product from Acetone is not thermodynamically favorable: *cf.* hydration of acetone [4-hydroxy-4-methylpentan-2-one]

the equilibrium constant for aldol addition reactions of ketones is usually unfavorable

Intramolecular Aldol Condensation



even ketones give good yields of aldol condensation products when the reaction is intramolecular