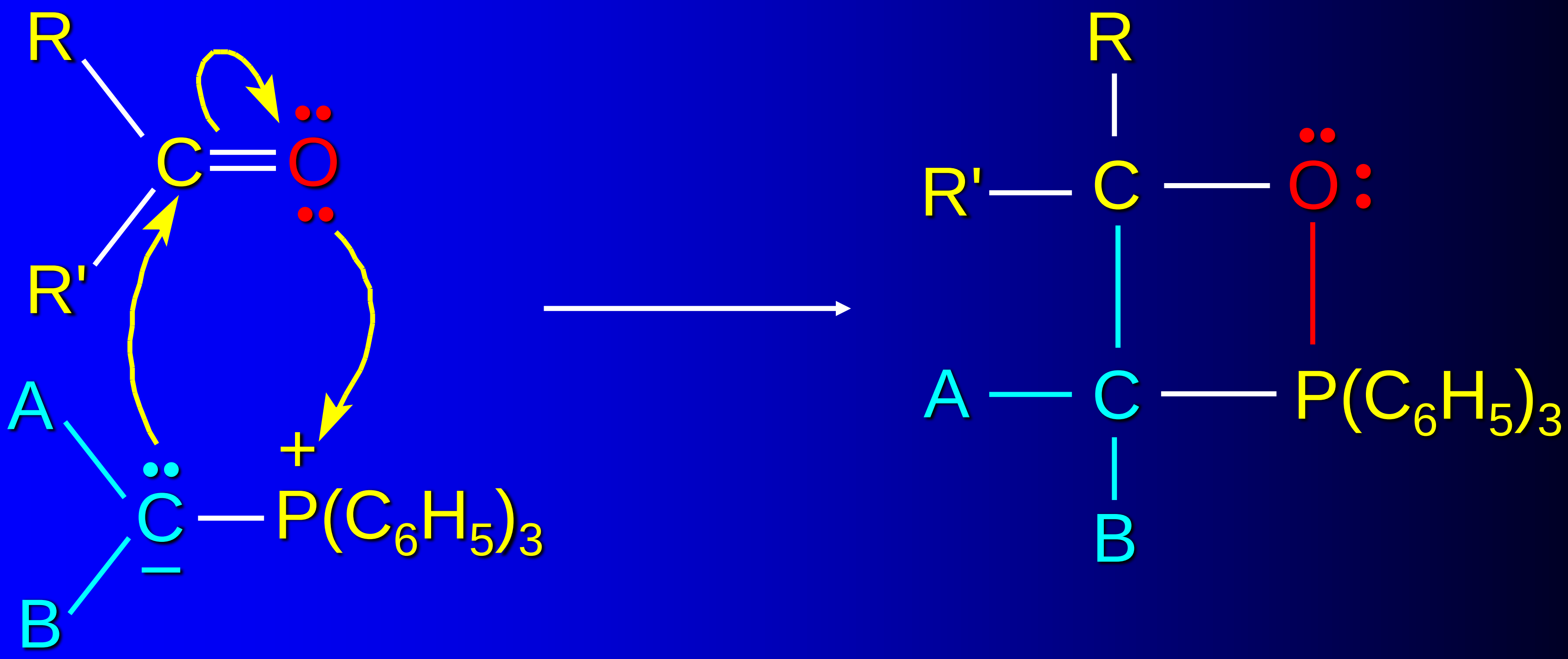
Lecture 16

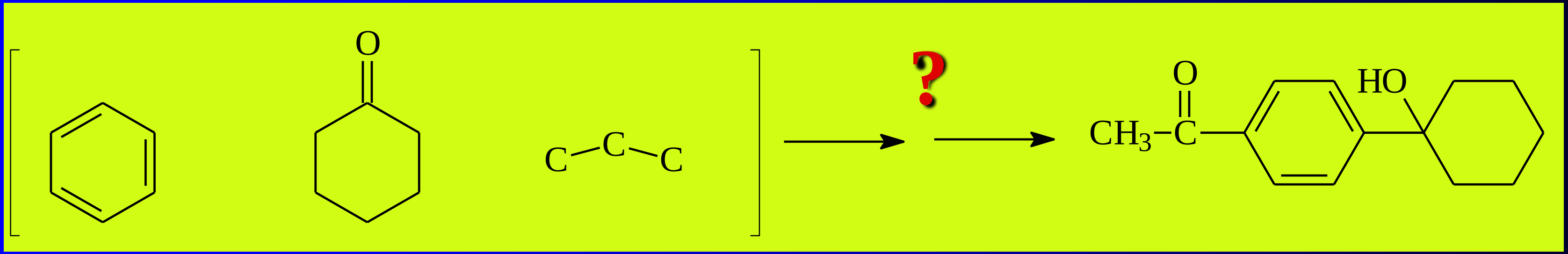
Still More Carbonyl Chemistry



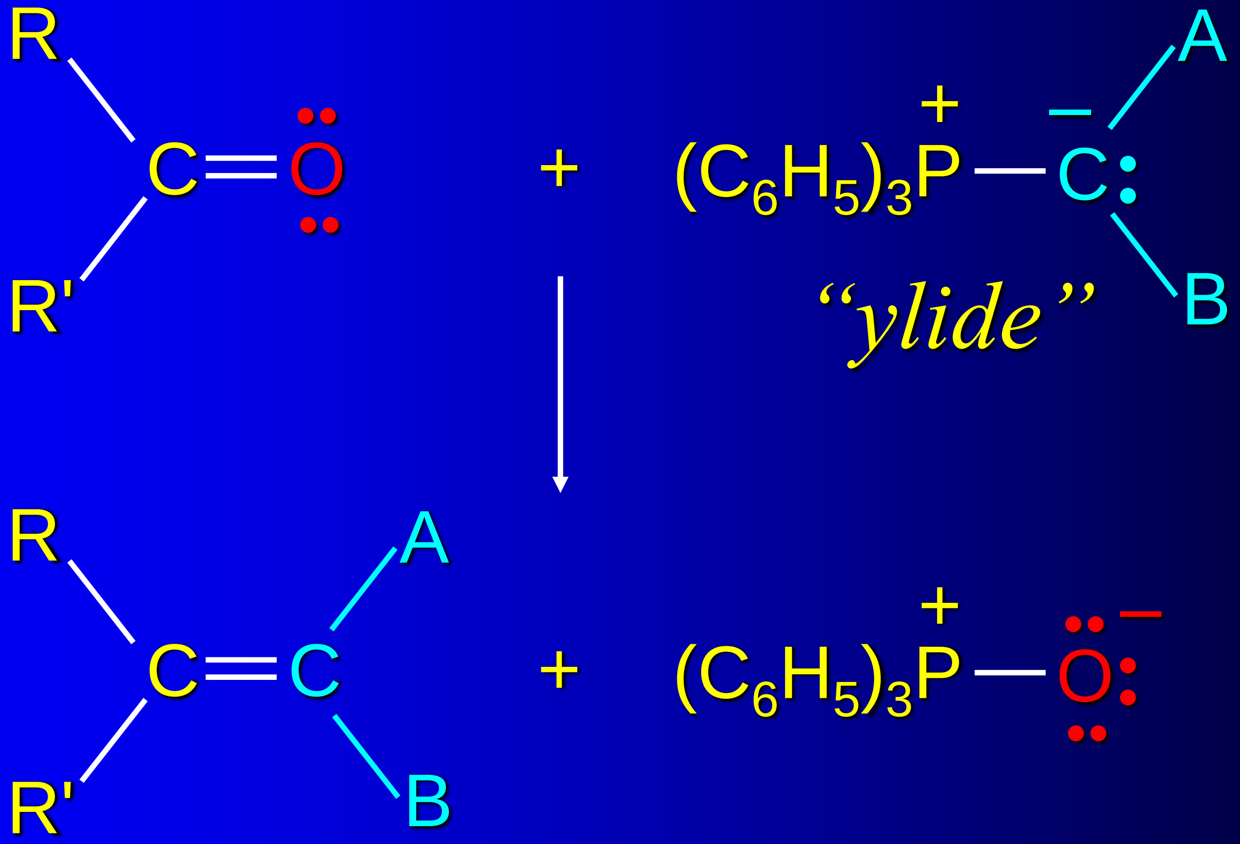
March 24, 2019

Thanks to the Orbitals

Ok…let's do some synthesis as a "warm up"

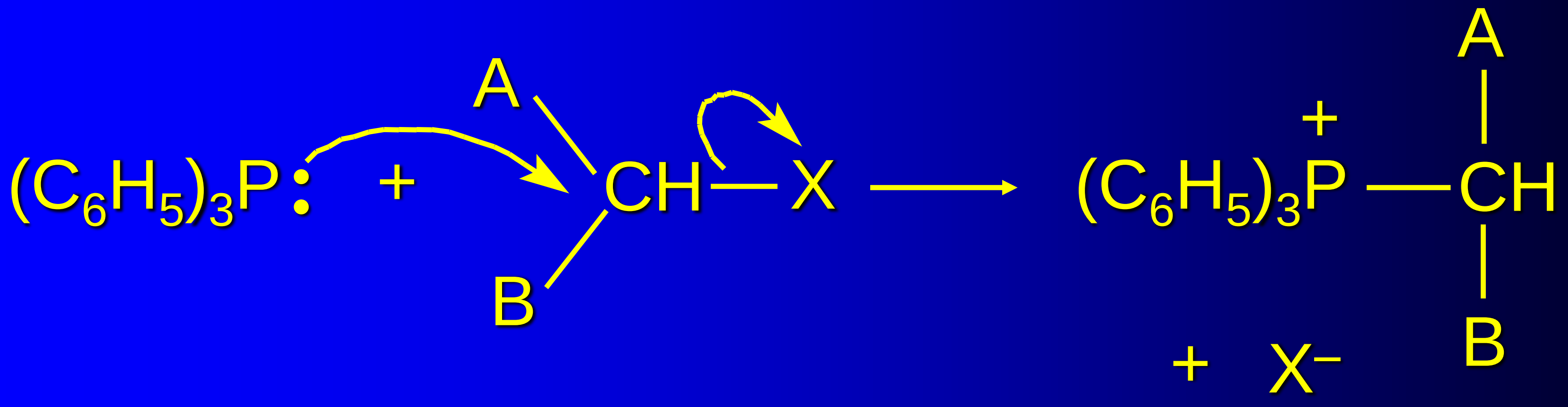


The Wittig Reaction



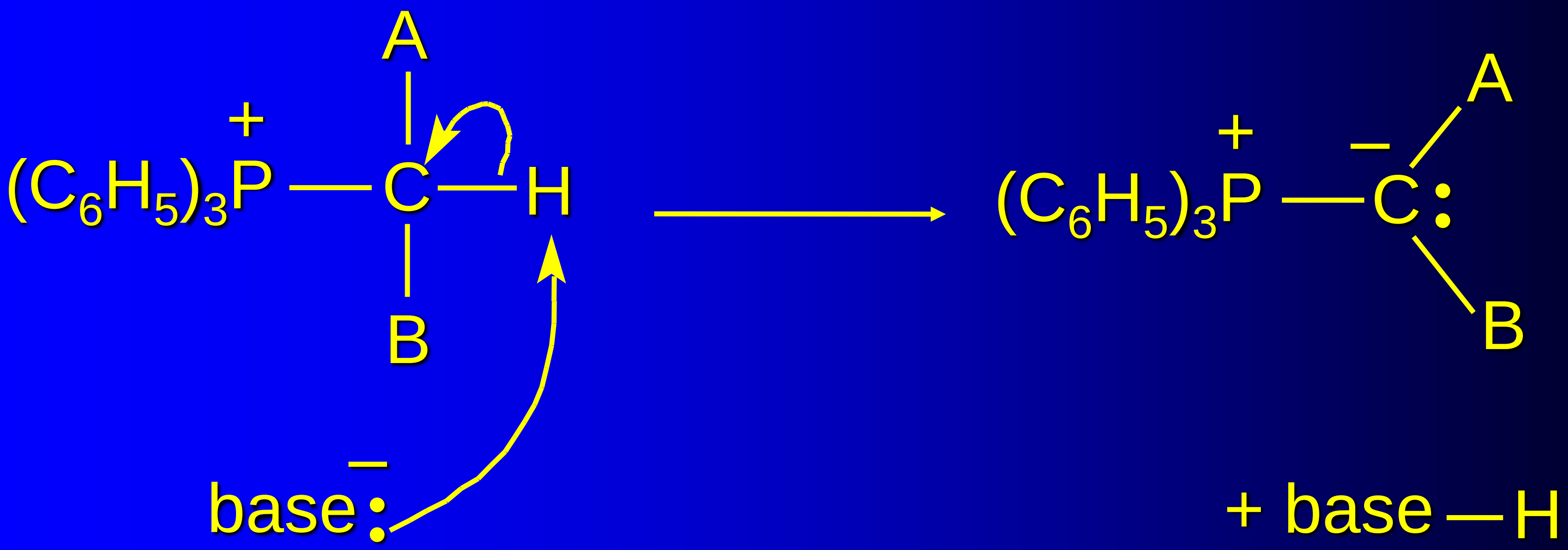
Preparation of Ylides

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



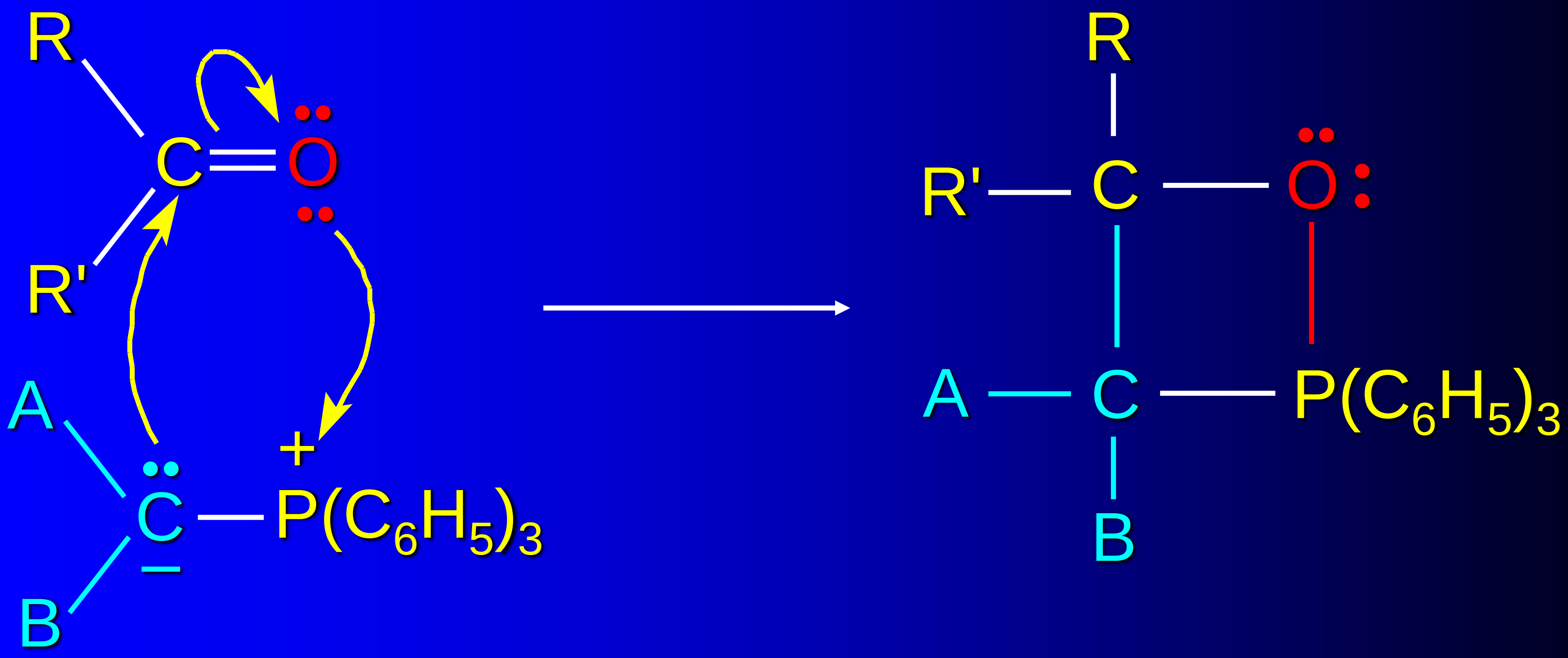
Preparation of Ylides

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.



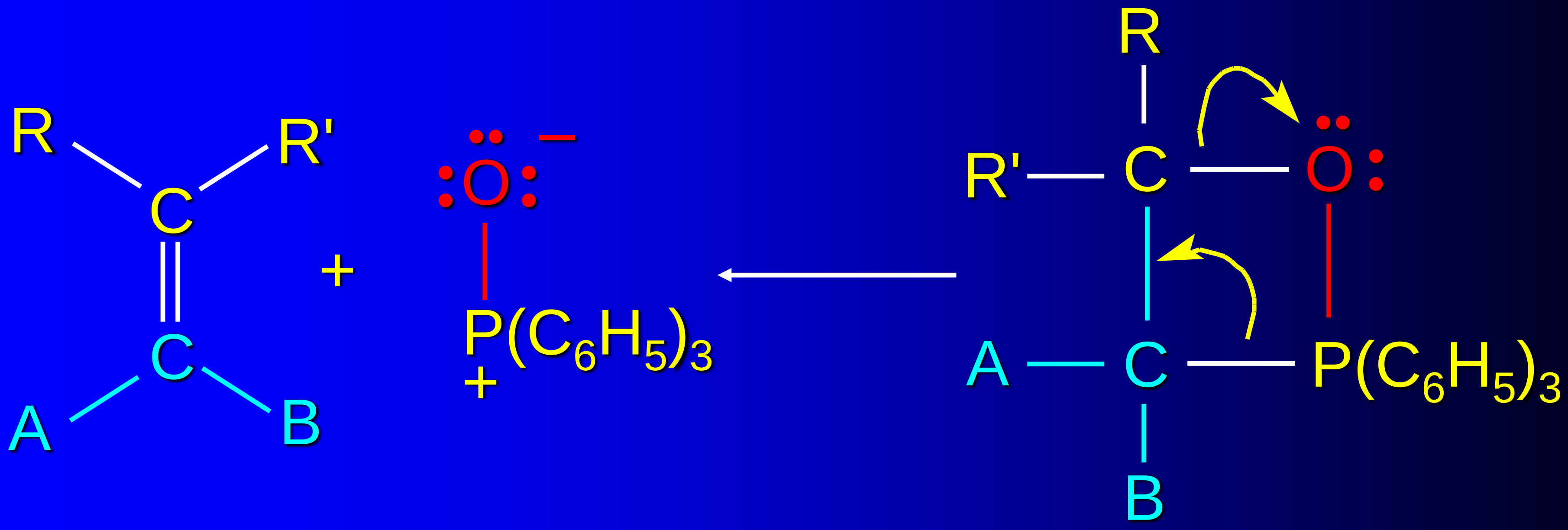
Mechanism

Step 1

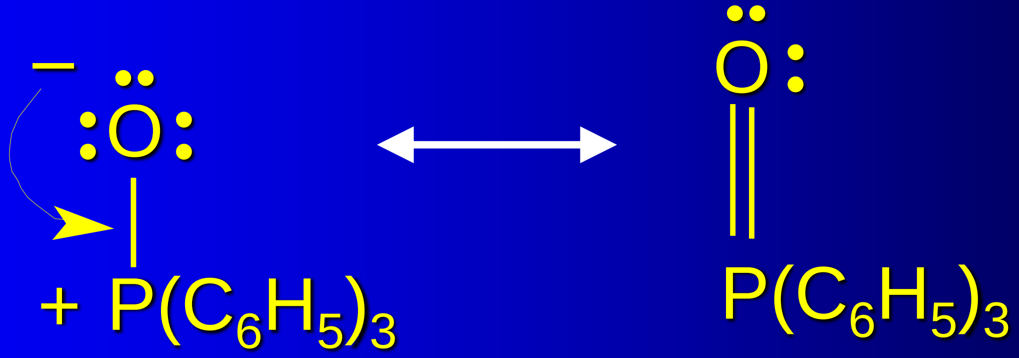


Mechanism

Step 2



Triphenylphosphine oxide

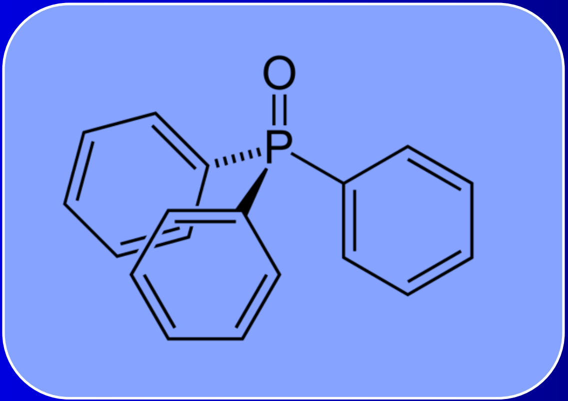


$^{-}:\ddot{O}:$

$+\ P(C_6H_5)_3$

$\ddot{O}:$

$P(C_6H_5)_3$



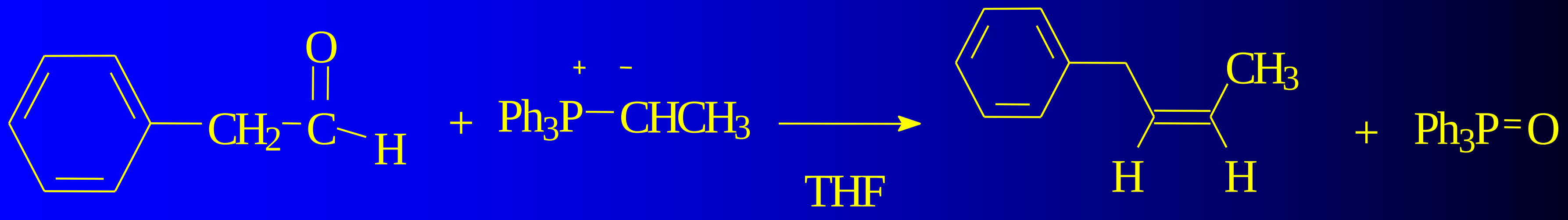
This substance is very stable

Nearly insoluble in many solvents, i.e. pentane

Oral, mouse: LD50 = 1380 mg/kg;

Wittig Reaction

- **More examples**

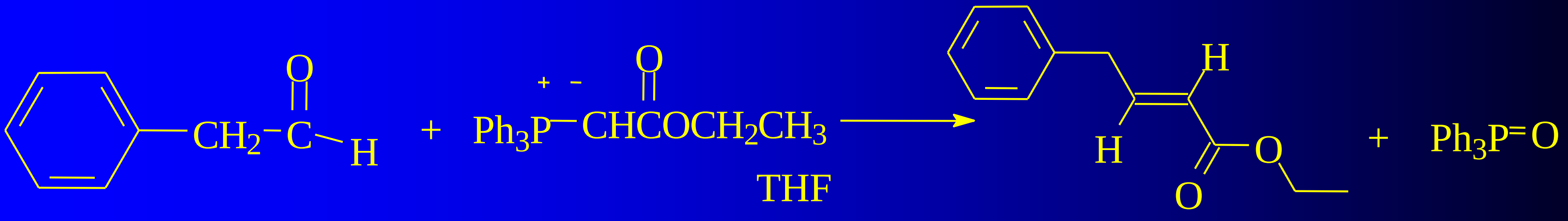


87% Z isomer

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

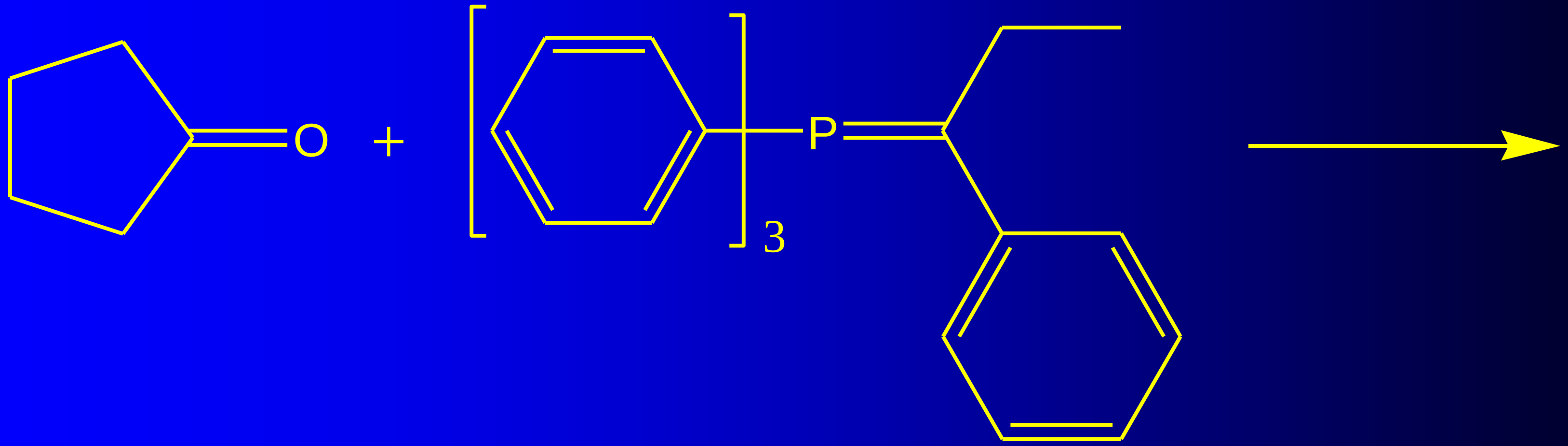
The Wittig Reaction

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



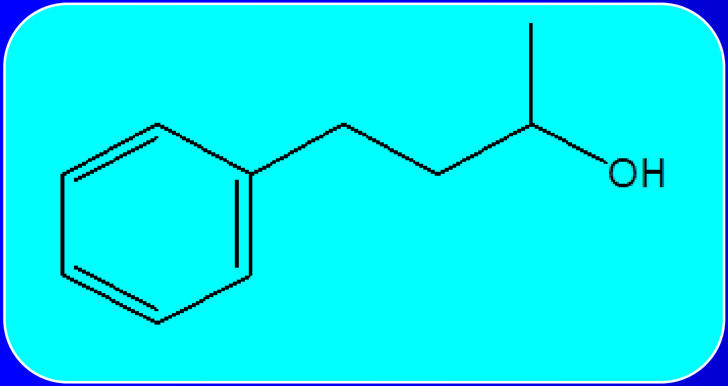
100% E isomer

An Example: Write the structure of the products

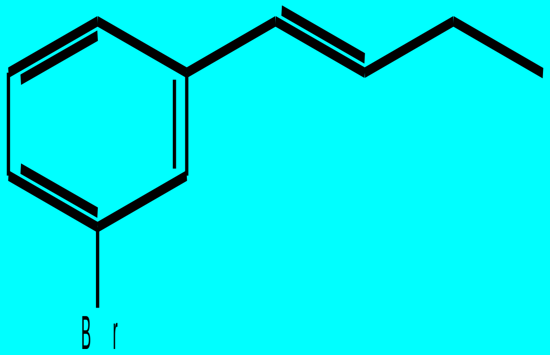


Synthesis..

benzene and 3 carbon starting materials

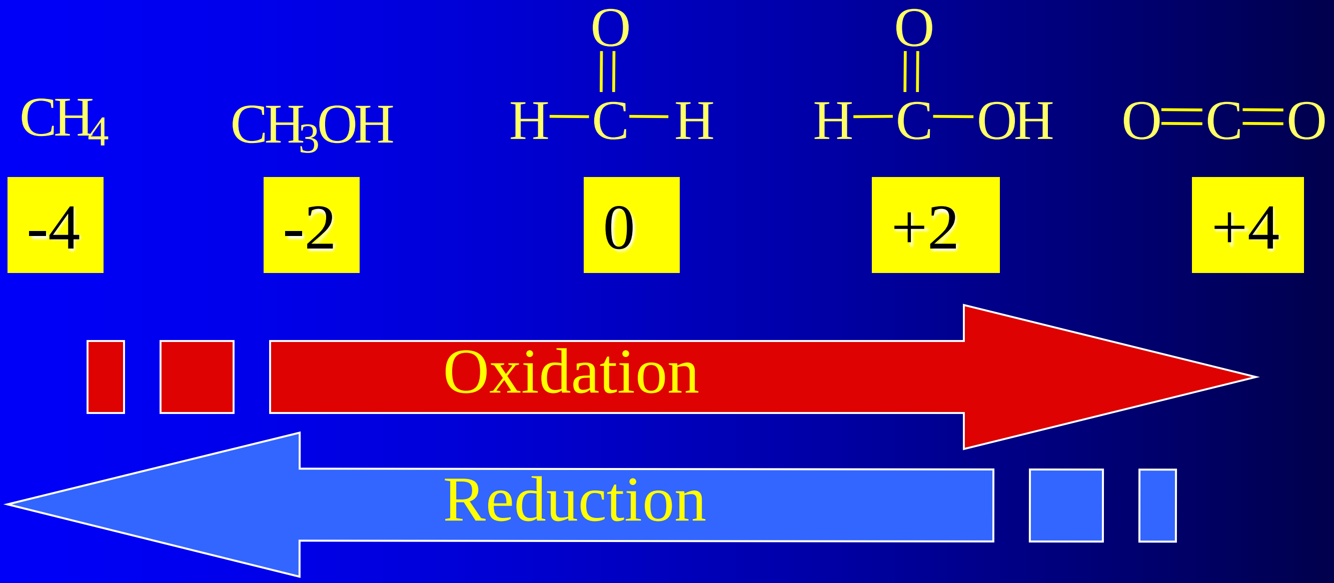


Synthesis



Oxidation and Reduction

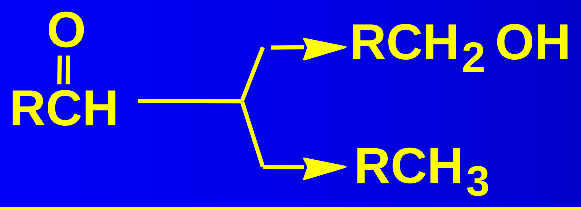
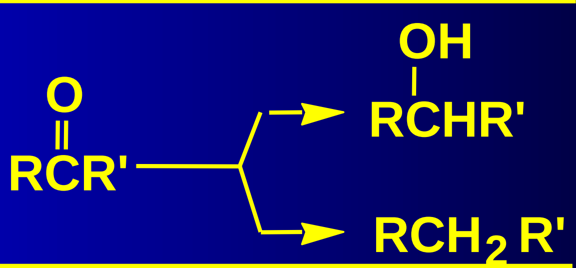
- Aldehydes are oxidized to carboxylic acids by a variety of oxidizing agents and it is possible to do some <u>selective</u> reduction reactions
- To calculate the oxidation state, assume that oxygen is “always” -2 and hydrogen is “always” +1



CH_4	CH_3OH	$H-\overset{\overset{\large O}{\|}}{C}-H$	$H-\overset{\overset{\large O}{\|}}{C}-OH$	$O=C=O$
-4	-2	0	+2	+4

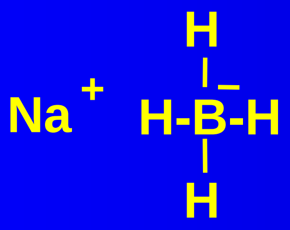
Reduction

- Aldehydes can be reduced to 1° alcohols and ketones to 2° alcohols. In addition, the C=O group can be reduced to a $-CH_2-$ group

Aldehydes	Can be Reduced to	Ketones	Can be Reduced to
 $R\overset{\overset{O}{\|}}{C}H$	RCH_2OH RCH_3	 $R\overset{\overset{O}{\|}}{C}R'$	$R\overset{\overset{OH}{\|}}{C}HR'$ RCH_2R'

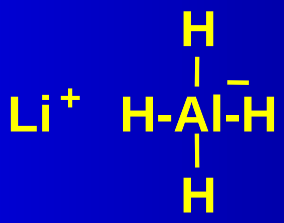
Metal Hydride Reduction

- The most selective reagents for the reduction of aldehydes and ketones are $NaBH_4$ and $LiAlH_4$
  - both are sources of hydride ion, $H:^-$, a very powerful nucleophile



$$Na^+ \quad H-\overset{\overset{\displaystyle H}{|}}{\underset{\underset{\displaystyle H}{|}}{B}}{}^{-}-H$$

Sodium borohydride



$$Li^+ \quad H-\overset{\overset{\displaystyle H}{|}}{\underset{\underset{\displaystyle H}{|}}{Al}}{}^{-}-H$$

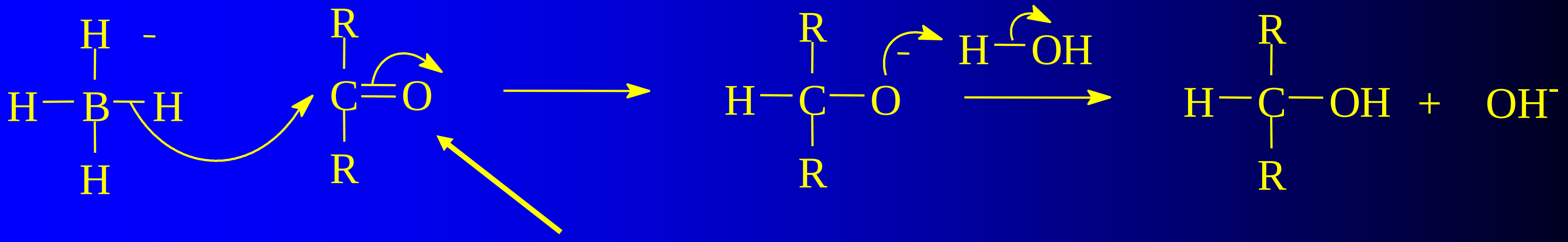
Lithium aluminum hydride (LAH)

$H:^-$

Hydride ion

$NaBH_4$ Reduction

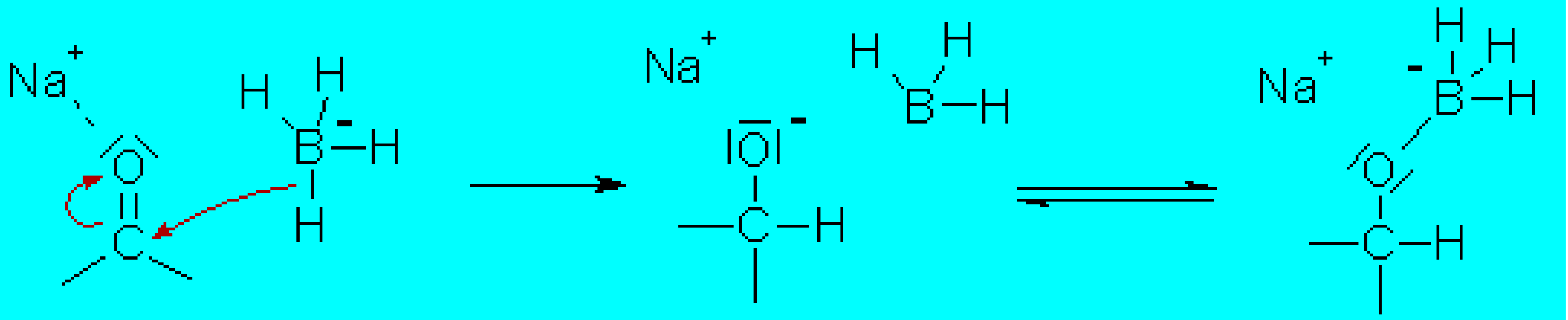
- The key step in metal hydride reduction is transfer of a hydride ion to the C=O group to form a tetrahedral carbonyl addition compound



$$\mathrm{H{-}BH_3^-} + \mathrm{R_2C{=}O} \longrightarrow \mathrm{H{-}CR_2{-}O^-} + \mathrm{H{-}OH} \longrightarrow \mathrm{H{-}CR_2{-}OH} + \mathrm{OH^-}$$

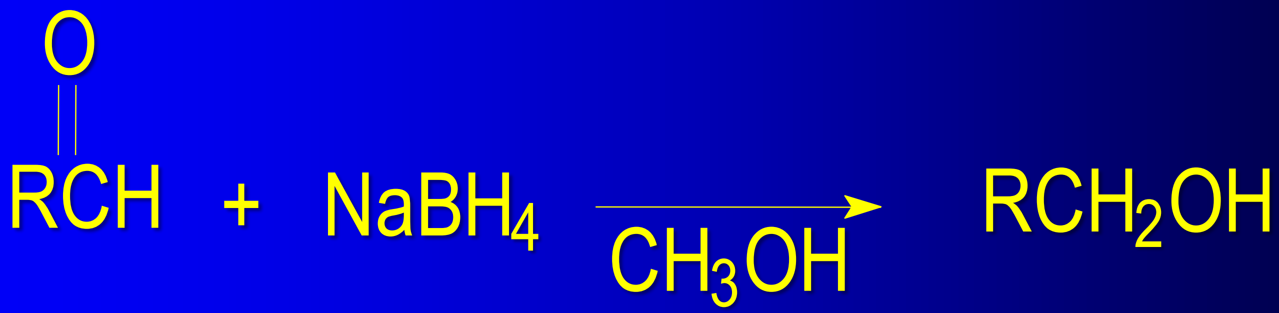
Closer look at borohydride reductions

B-O bond is much stronger than B – H bond
This is the driving force for the reaction…



$NaBH_4$ Reduction

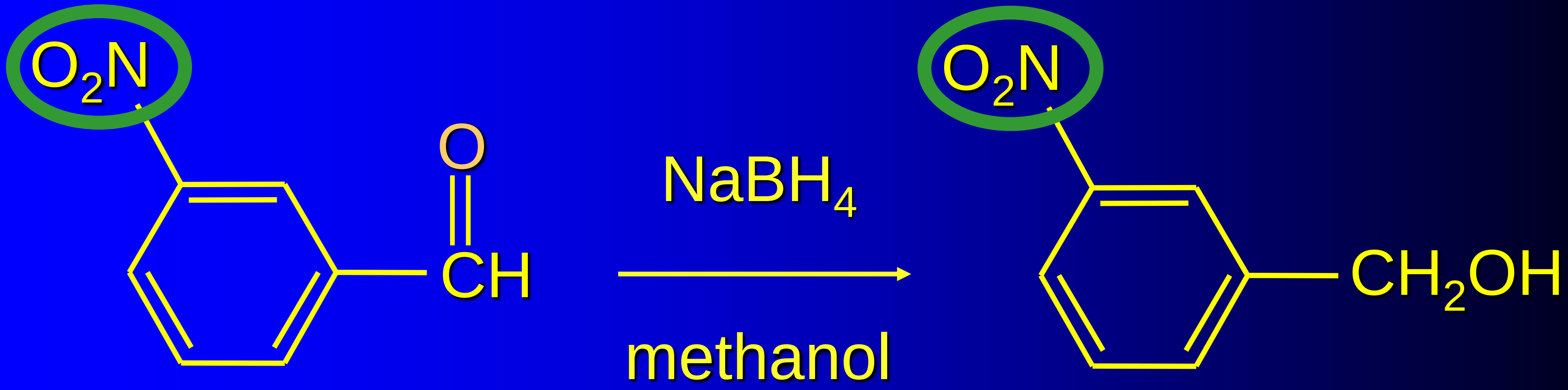
- Reductions with $NaBH_4$ are most commonly carried out in aqueous methanol, in pure methanol, or in ethanol



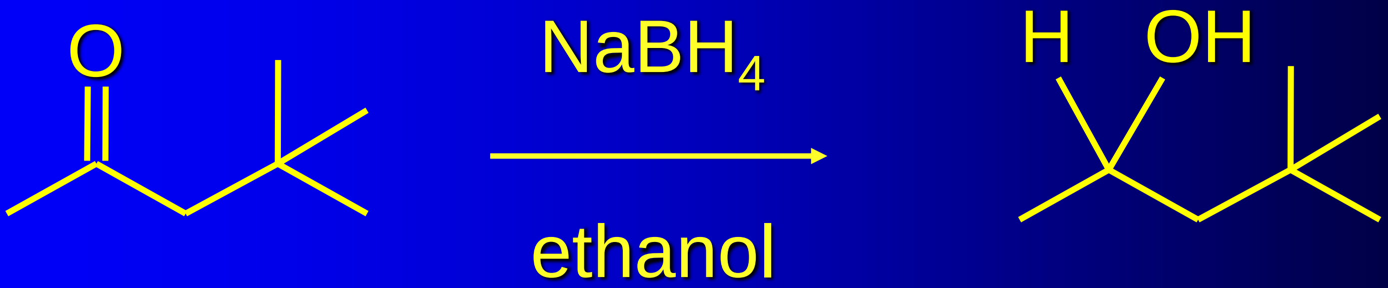
$$\overset{\displaystyle O}{\overset{\|}{RCH}} + NaBH_4 \xrightarrow[CH_3OH]{} RCH_2OH$$

Examples: Sodium Borohydride

Aldehyde



Ketone



Lithium aluminum hydride

$LiAlH_4$

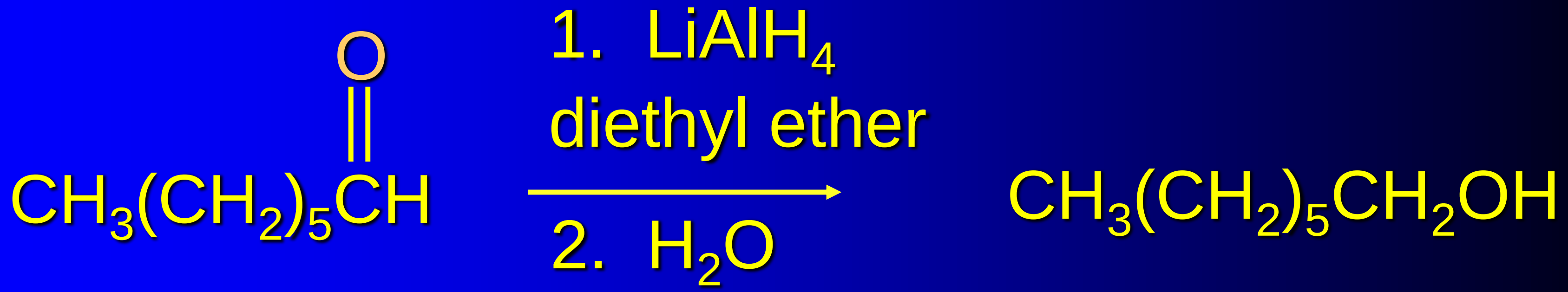
- More
- Can nts
- Diet ed solvent
- This

RC H_3

Examples: Lithium Aluminum Hydride

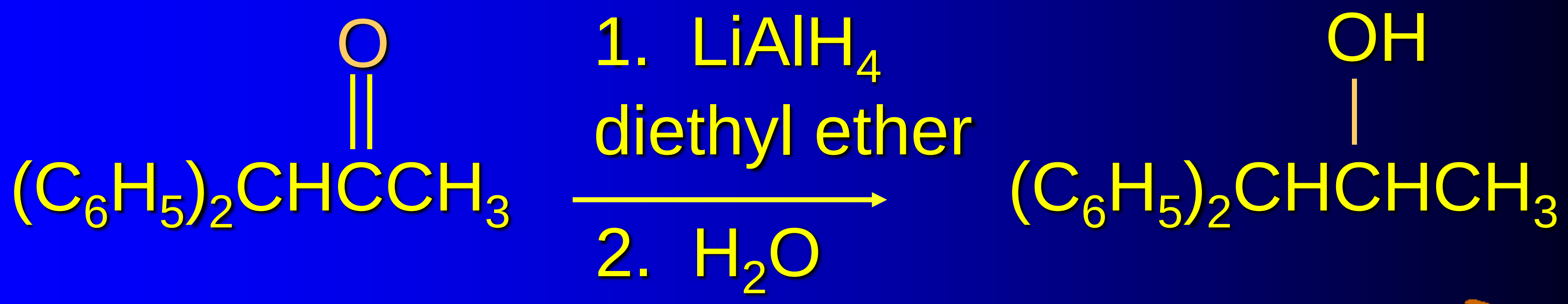
Aldehyde

This is "overkill"…just use safer $NaBH_4$



$$CH_3(CH_2)_5\overset{\overset{O}{\|}}{C}H \xrightarrow[\text{2. } H_2O]{\text{1. } LiAlH_4 \text{ diethyl ether}} CH_3(CH_2)_5CH_2OH$$

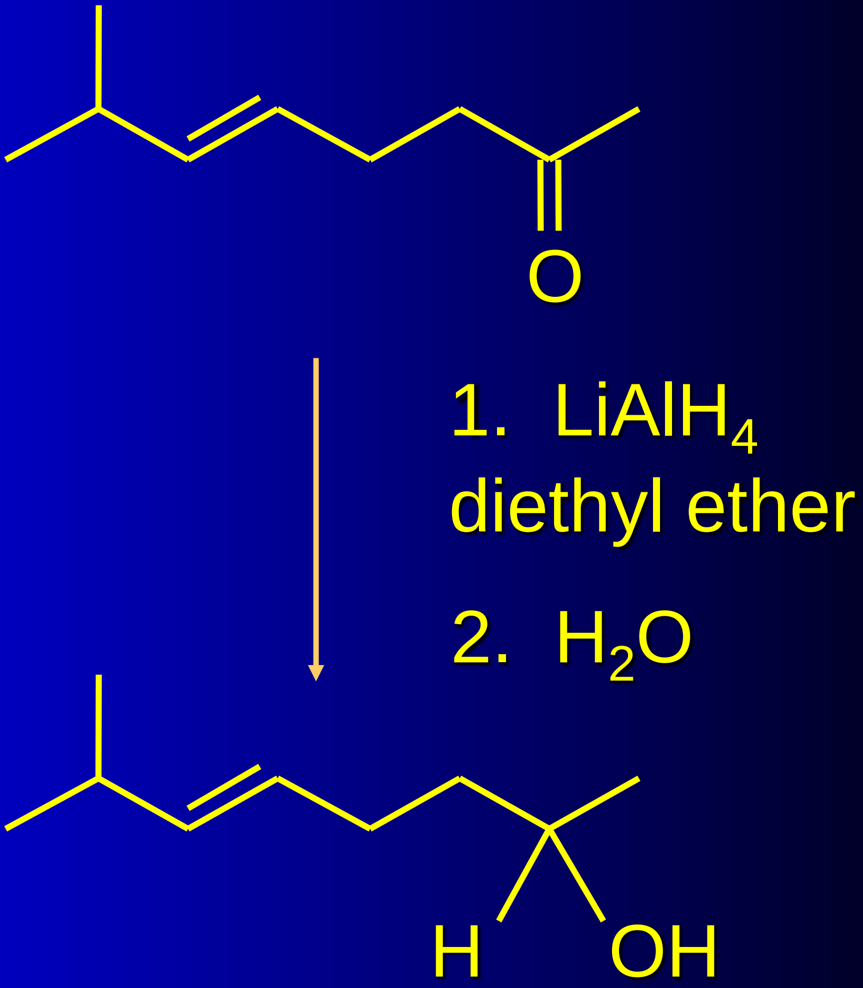
Ketone



$$(C_6H_5)_2CH\overset{\overset{O}{\|}}{C}CH_3 \xrightarrow[\text{2. } H_2O]{\text{1. } LiAlH_4 \text{ diethyl ether}} (C_6H_5)_2CH\overset{\overset{OH}{|}}{C}HCH_3$$

Selectivity

neither $NaBH_4$ or $LiAlH_4$ will reduce isolated double bonds



1. $LiAlH_4$ diethyl ether

2. H_2O

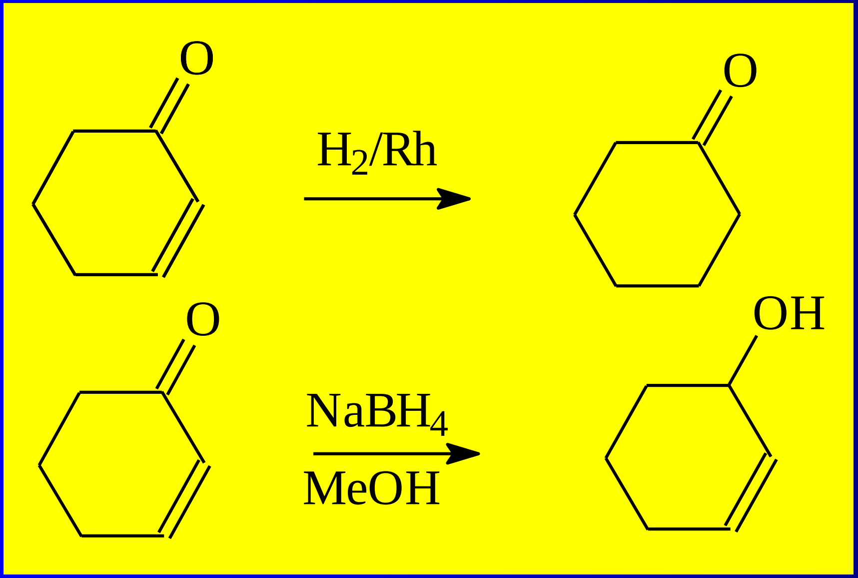
Selectivity in Reduction

- $LiAlH_4$ reduces *any* and all carbonyl compounds to the corresponding alcohols

- $NaBH_4$ *only* reduces aldehydes and ketone

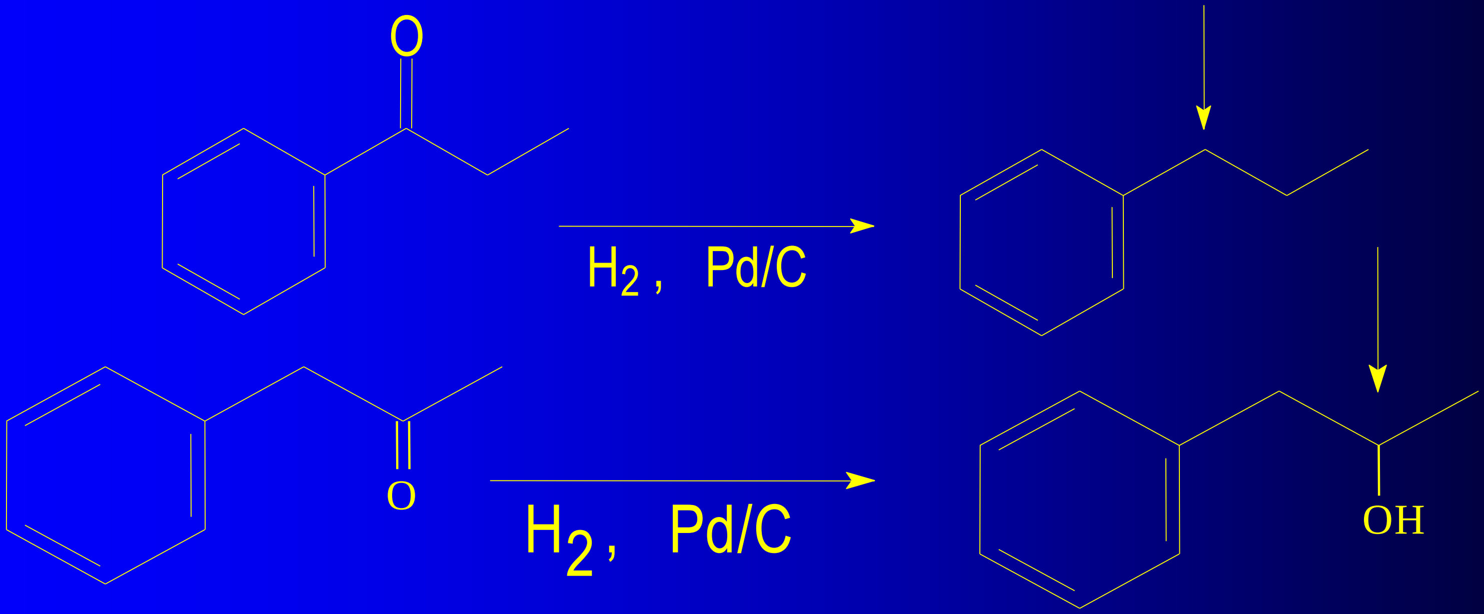
Catalytic Reduction

- Catalytic reductions are generally carried out from 25° to 100°C and from 1 to 5 atm H_2
- Carbon-carbon double bonds can be selectively reduced using Rhodium catalysts



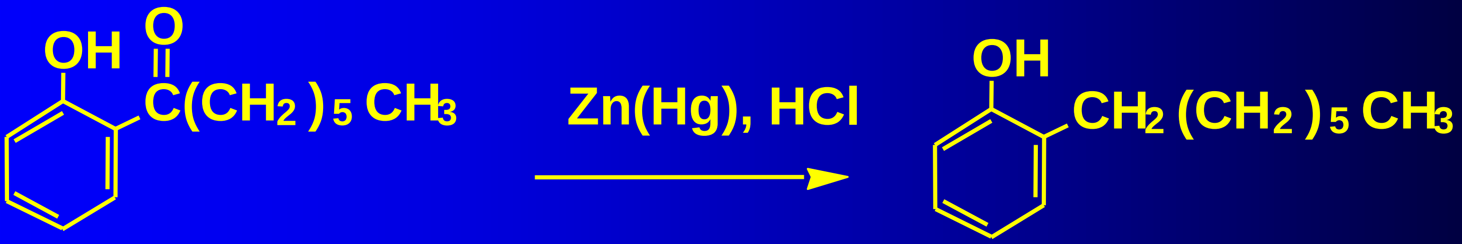
Hydrogenolysis of benzylic carbonyls

- Palladium catalysis of hydrogenation reduces *only* benzylic C-O bonds to methylene groups.
- Benzyl ethers, aldehydes and alcohols are also reduced to the corresponding methylene group



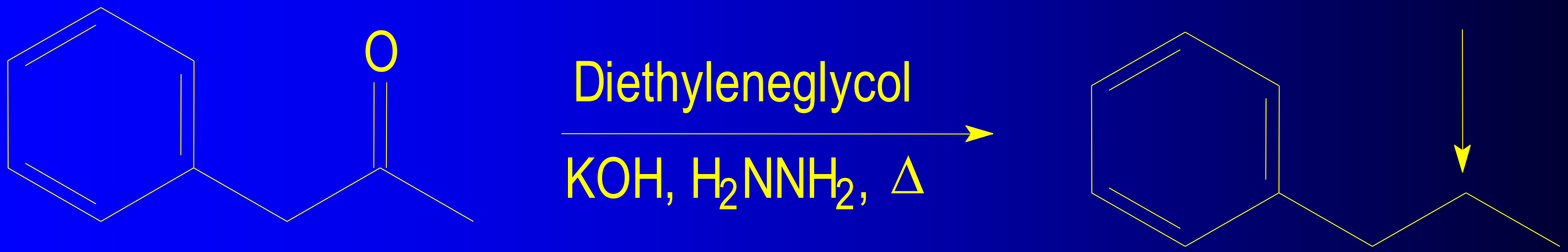
Clemmensen Reduction

- Refluxing an aldehyde or ketone with amalgamated zinc in concentrated HCl <u>converts the carbonyl group to a methylene group</u>
- Limitations…??

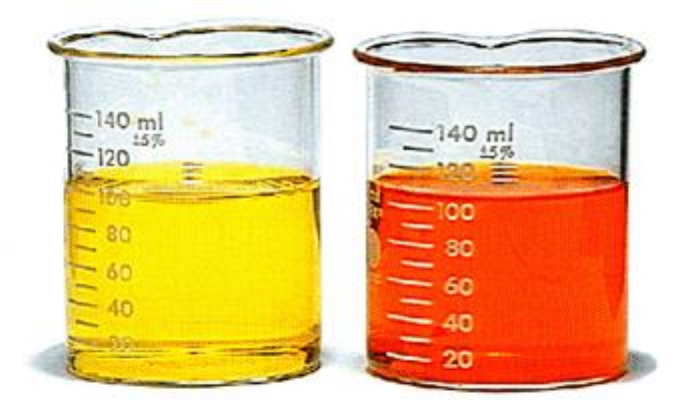


Wolff-Kishner Reduction

- If aldehydes or ketones are refluxed with hydrazine and KOH in a high-boiling solvent, the reaction converts carbonyls into methylenes….

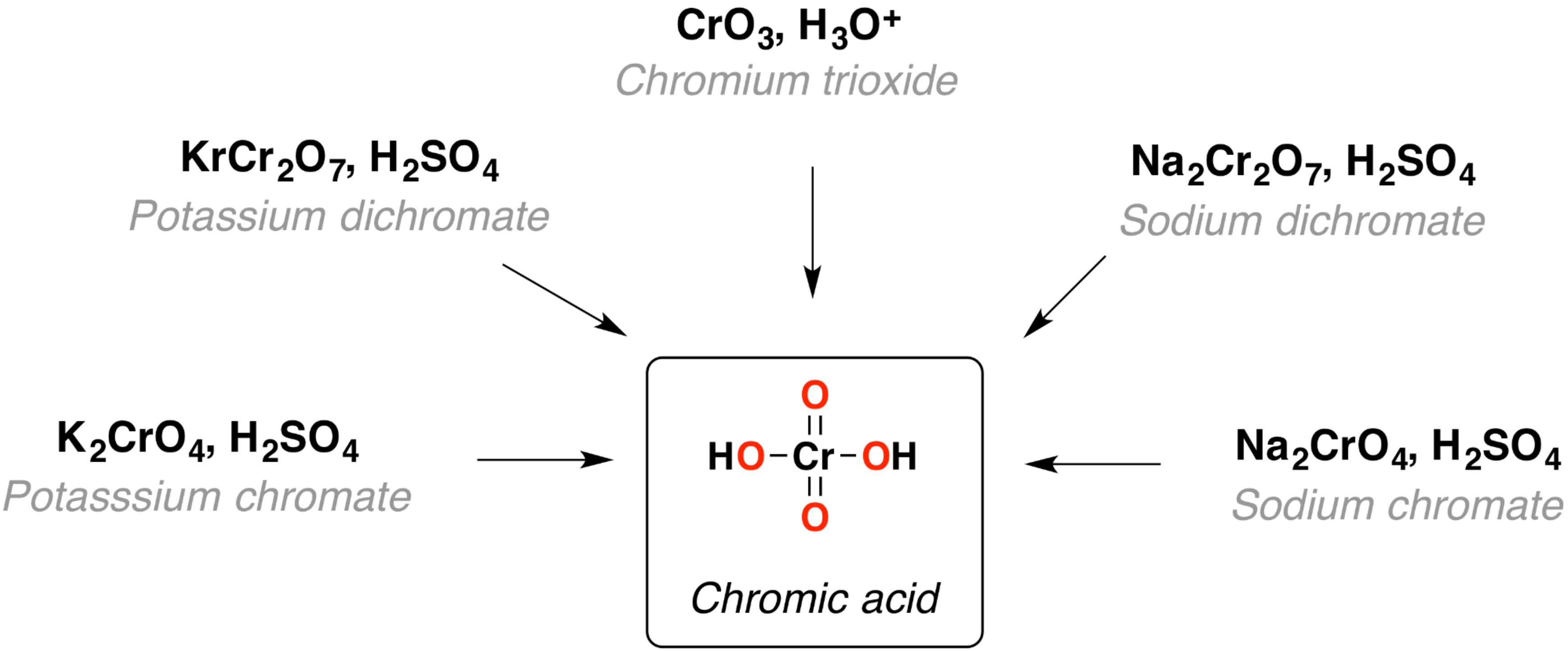


Chromic Acid Oxidations



$K_2Cr_2O_4$ **$K_2Cr_2O_7$**

- Hexavalent chromium compounds (including chromium trioxide, chromic acids, chromates, chlorochromates) are toxic and carcinogenic.



CrO_3, H_3O^+

Chromium trioxide

$KrCr_2O_7$, H_2SO_4

Potassium dichromate

$Na_2Cr_2O_7$, H_2SO_4

Sodium dichromate

K_2CrO_4, H_2SO_4

Potasssium chromate

Na_2CrO_4, H_2SO_4

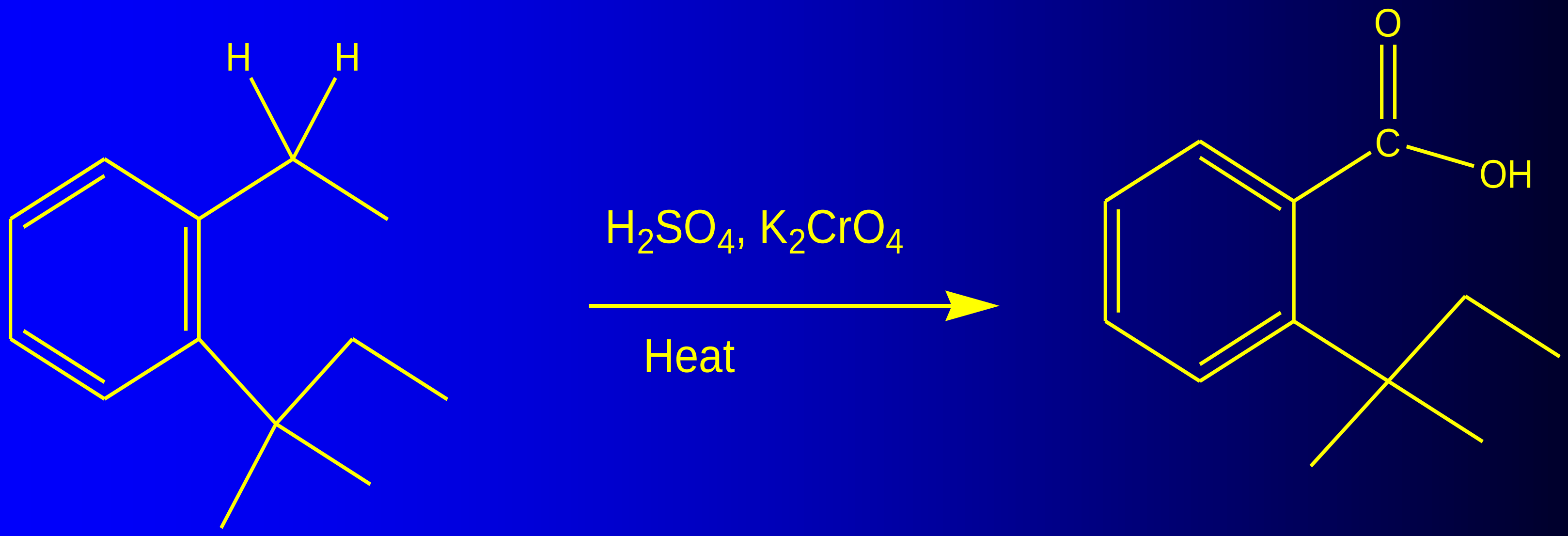
Sodium chromate

$HO-\overset{O}{\overset{\|}{\underset{\underset{O}{\|}}{Cr}}}-OH$

Chromic acid

Chromic acid is often made "in situ" (that is, in the reaction flask) through the addition of acid to sources of chromium (such as chromate salts). The large number of possible chromium sources (and acids!) can make this confusing, but it is chromic acid that is the active reagent.

Oxidation at Benzylic Positions



H_2SO_4, K_2CrO_4

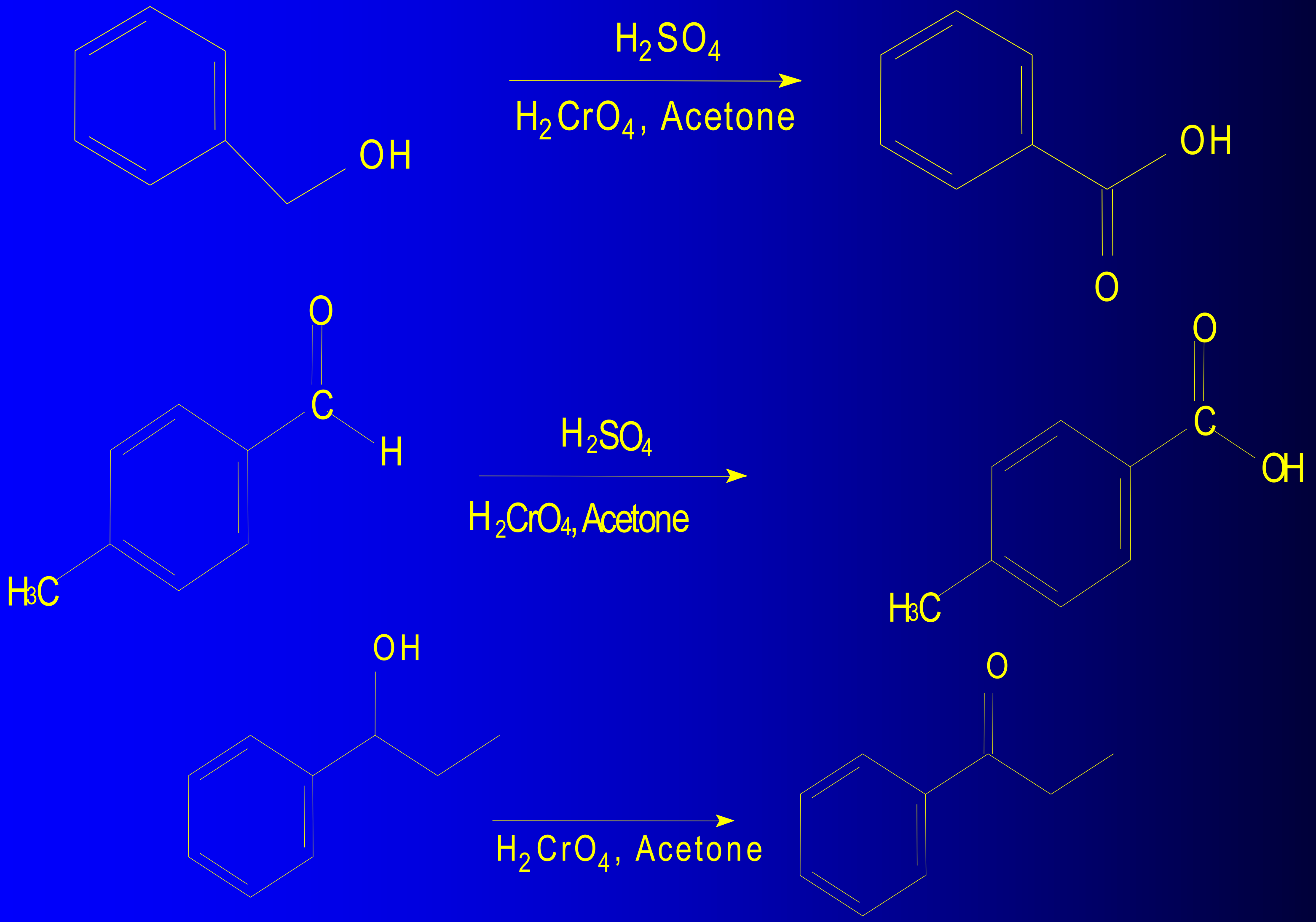
Heat

KMnO4 in Base also works

Selective Chromate Oxidations

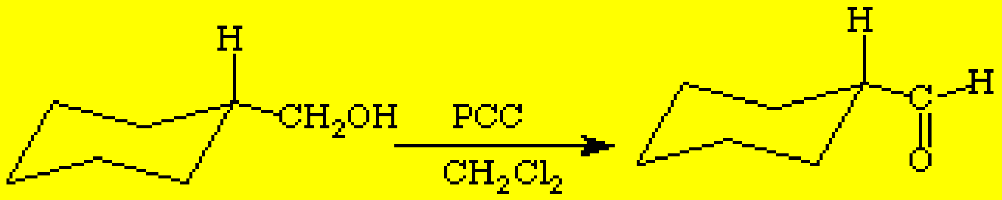
- **Chromic acid and heat** Oxidizes benzylic positions bearing at least one hydrogen to acids
- **Jones Reagent** (H_2CrO_4 in acetone) takes primary alcohols to acids and secondary alcohols to ketones…The acetone keeps the reaction cool. Jones oxidation does not oxidize benzylic positions even with a hydrogen.
- **PCC** (pyridinium chlorochromate) is weaker yet, it only oxidizes primary alcohols to aldehydes (!) and seconday alcohols to ketones.

The Jones Oxidation Examples

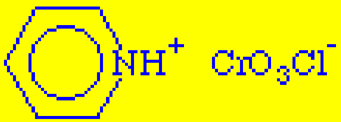


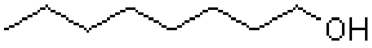
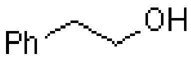
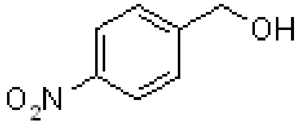
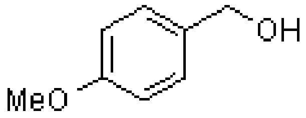
PCC Oxidations

$$C_5H_5N + HCl + CrO_3 \rightarrow [C_5H_5NH][CrO_3Cl]$$

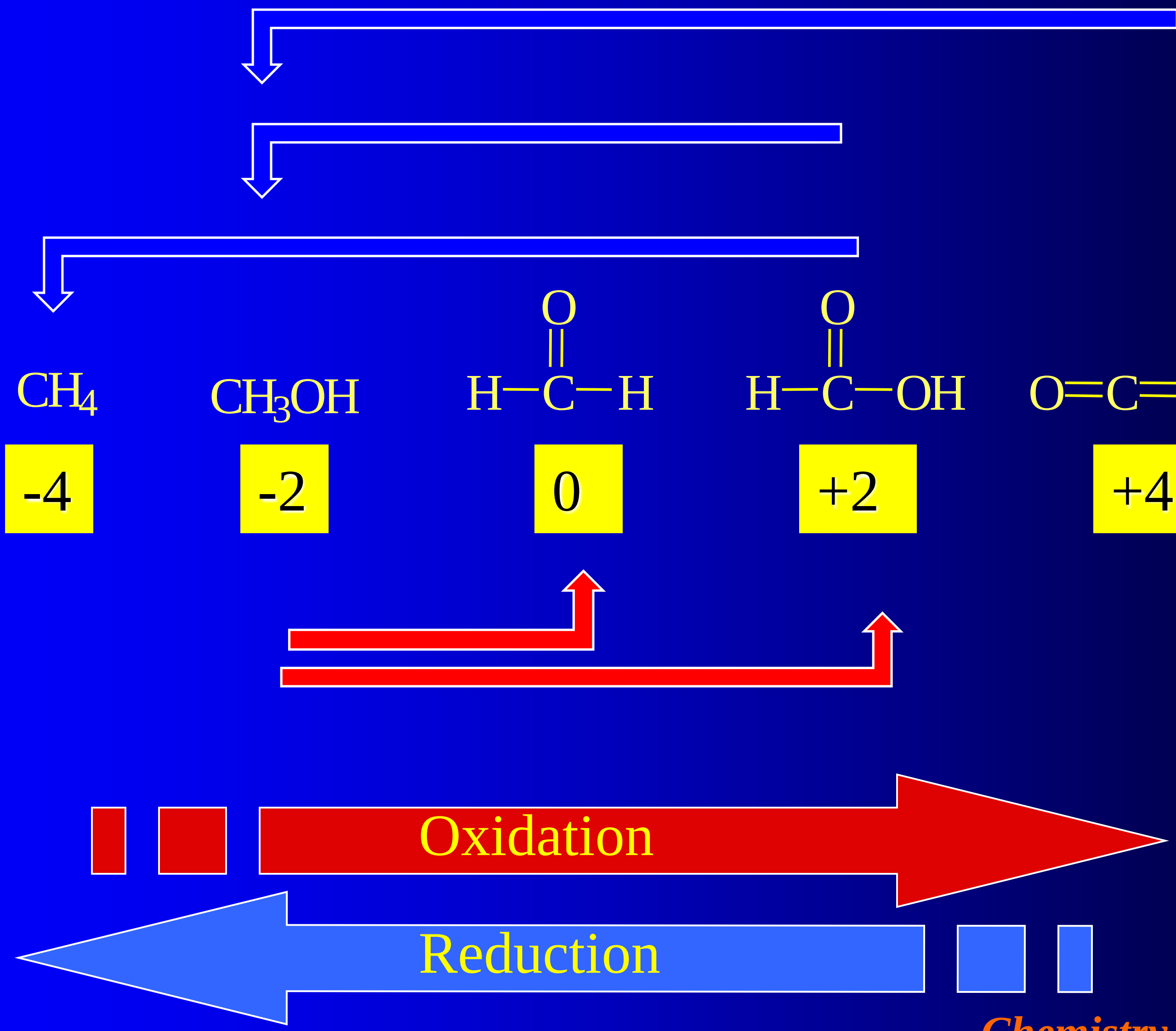


PCC: pyridinium chlorochromate



Substrate	Yield (%, isol.)
	99
	96
	99
	99
	97

Selectivity !! ?



CH_4 | CH_3OH | $H-\overset{O}{\overset{\|}{C}}-H$ | $H-\overset{O}{\overset{\|}{C}}-OH$ | $O=C=O$

-4 | -2 | 0 | +2 | +4

Oxidation

Reduction

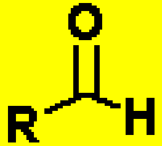
Selective Oxidation Reactions

- **Jones Reagent** (H_2CrO_4 in acetone) takes primary alcohols to acids and secondary alcohols to ketones
- **The Tollen's Test** $Ag(NH_3)_2OH$…the silver mirror reaction is a qualitative test for aldehydes and an efficient but expensive way to make acids form aldehydes

Tollens Test

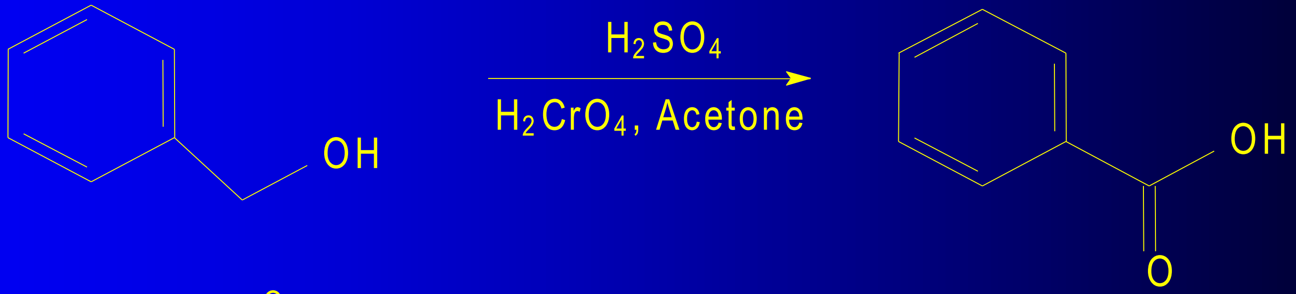
$2\ AgNO_3 + 2\ NaOH \longrightarrow Ag_2O(s) + H_2O + 2\ Na^{+1} + 2\ NO_3^{-1}$

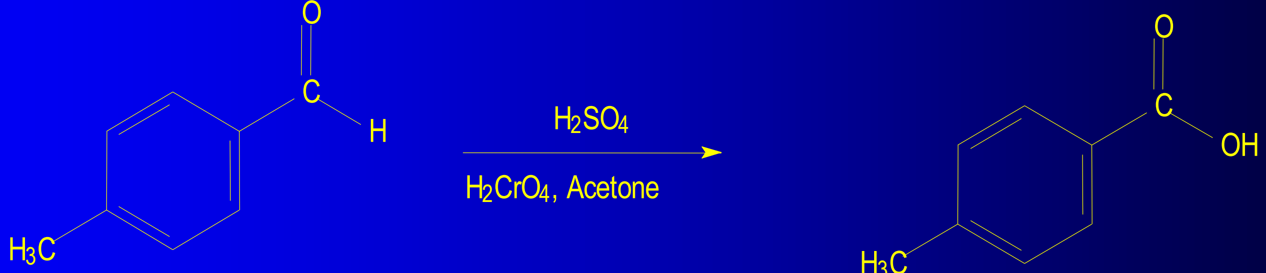
$Ag_2O(s) + 4NH_3 + H_2O \longrightarrow 2Ag(NH_3)_2^{+} + 2OH^{-}$ (Totally Dissolved)

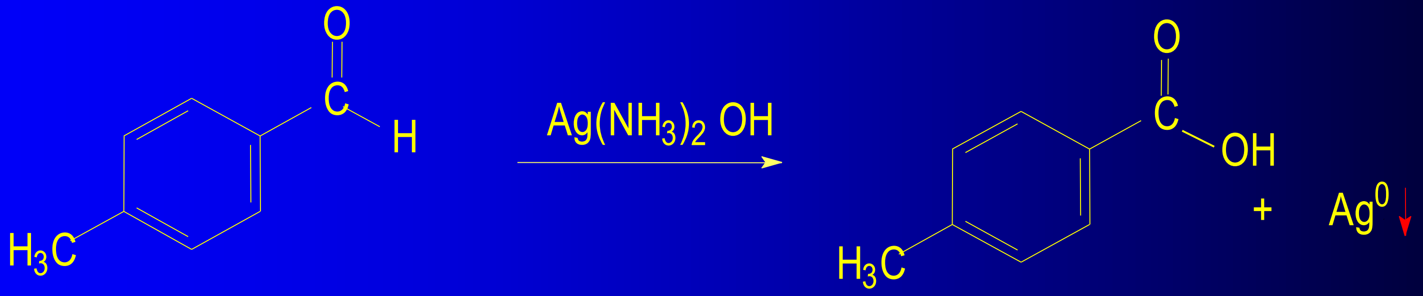
$2(Ag(NH_3)_2^{+}\ OH^{-}) +$  $RCHO \longrightarrow 2Ag + RCOO^{-}\ NH_4^{+} + H_2O + 3NH_3$

Examples


OH
H_2CrO_4, Acetone
O


OH
H_2SO_4
H_2CrO_4, Acetone
OH
O


O
C
H
H_3C
H_2SO_4
H_2CrO_4, Acetone
O
C
OH
H_3C


O
C
H
H_3C
$Ag(NH_3)_2 OH$
O
C
OH
H_3C
+
Ag^0

Ok…more synthesis

From benzene, any thing with less than 3 carbons, and any other reagents that do not become part of the structure.