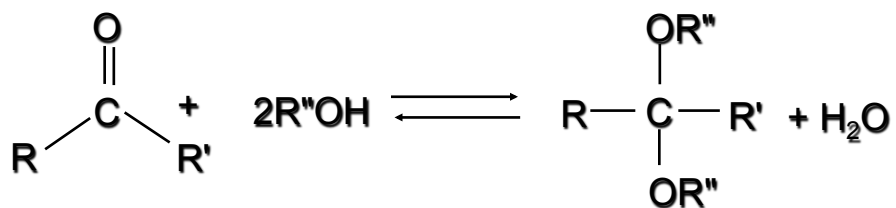


## Lecture 15

*More Carbonyl Chemistry*

March 8, 2016

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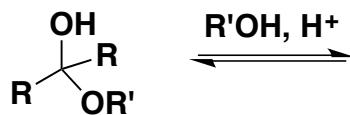
*Alcohols React with Aldehydes  
and Ketones in two steps...first*




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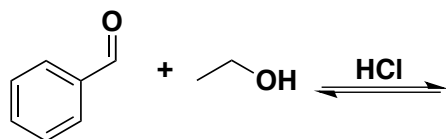



*Hemiacetal reacts further in acid to yield an acetal*



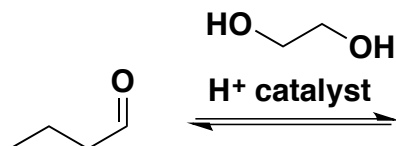
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*Example*



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Diols Form \_\_\_\_\_



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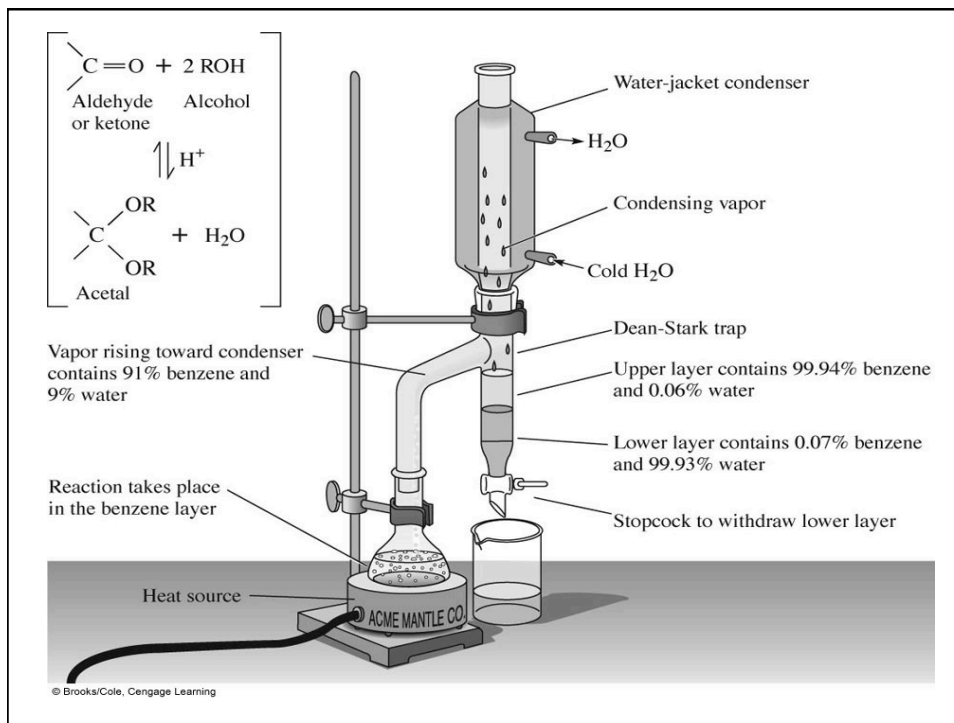
**Note that EVERY step is an equilibrium**

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

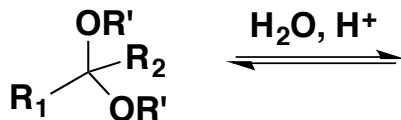
**The forward reaction is synthesis  
The backward reaction is hydrolysis**

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## Hydrolysis of Acetals



***mechanism:***

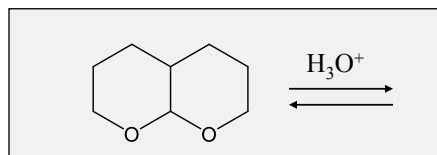
reverse of acetal formation ... hemiacetal is intermediate.

***application:***

aldehydes and ketones can be "protected" as acetals.



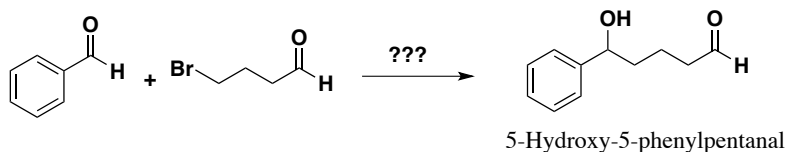
## Hydrolysis



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Suppose you want to make this compound?



It's an alcohol. Use the Grignard Reaction!!



*So...you got a problem with this plan ?????*

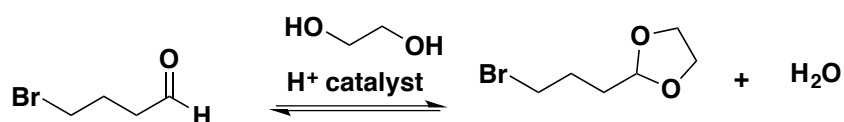
**Secret is....Acetals as protecting Groups**

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## Acetals as Protecting Groups

- If the Grignard reagent were prepared from 3-bromopropanal, it would self-destruct!
- First protect the -CHO group as an acetal

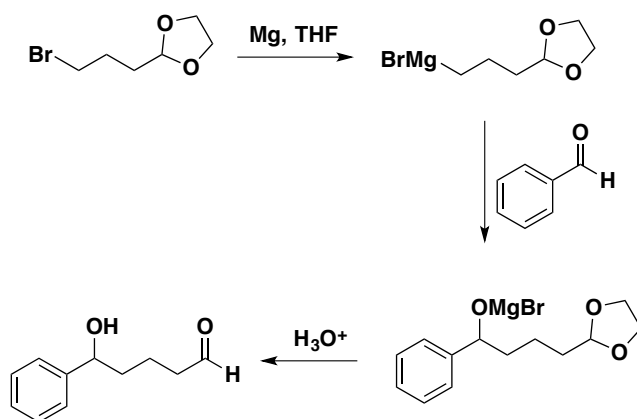


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## Acetals as Protecting Groups

- Then do the Grignard reaction

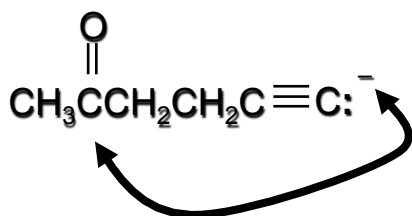
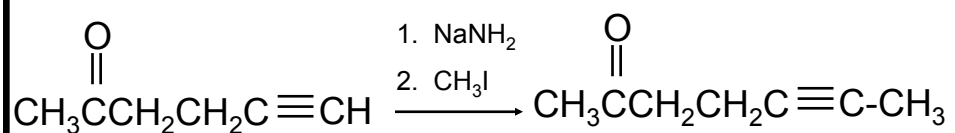


Hydrolysis in dilute acid gives the desired product

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For example, the conversion shown cannot be carried out directly.....why?



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

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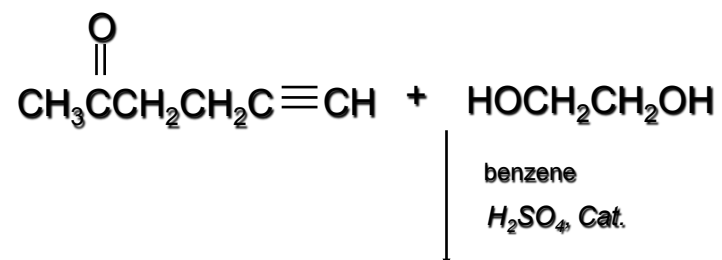


# Strategy

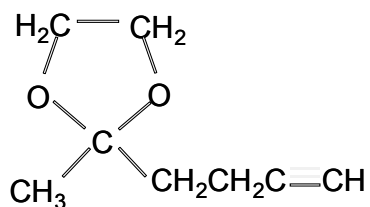
- 1) protect C=O
- 2) alkylate
- 3) restore C=O

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*Protect*

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*Alkylate*

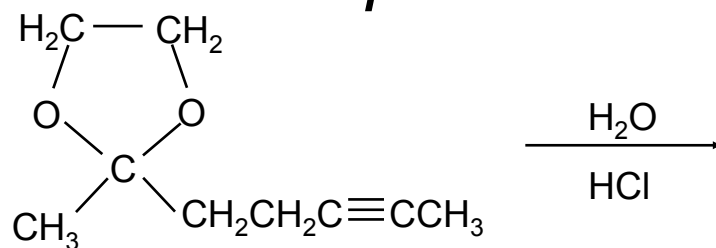
- $\downarrow$   
 1.  $\text{NaNH}_2$   
 2.  $\text{CH}_3\text{I}$

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## Deprotect

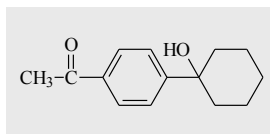


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## Synthesis!

Starting from benzene, cyclohexanone, and molecules with 3 carbons or less, synthesize the following molecule:

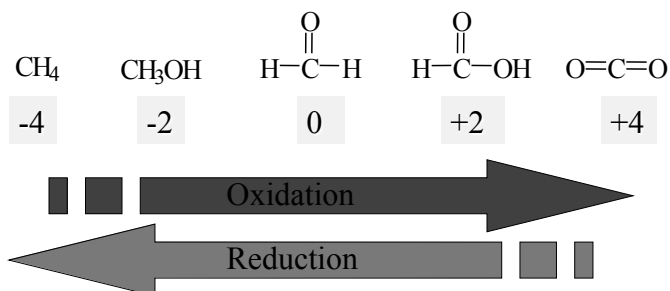


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## Oxidation and Reduction

- Aldehydes are oxidized to carboxylic acids by a variety of oxidizing agents and it is possible to do some selective reduction reactions

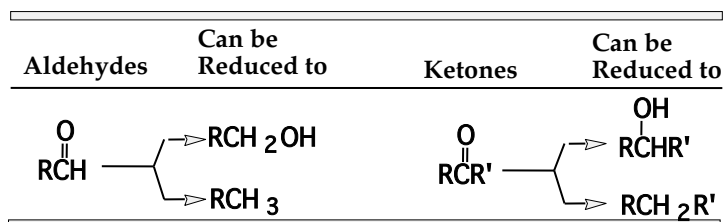


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## Reduction

- Aldehydes can be reduced to 1° alcohols and ketones to 2° alcohols. In addition, the C=O group can be reduced to a -CH<sub>2</sub>- group

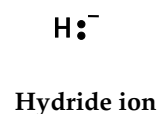
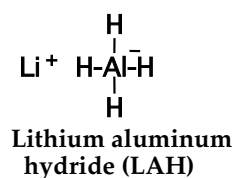
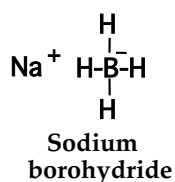


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## Metal Hydride Reduction

- The most selective reagents for the reduction of aldehydes and ketones are  $\text{NaBH}_4$  and  $\text{LiAlH}_4$ 
  - both are sources of hydride ion,  $\text{H}^-$ , a very powerful nucleophile

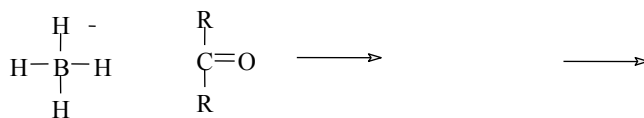


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## $\text{NaBH}_4$ Reduction

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

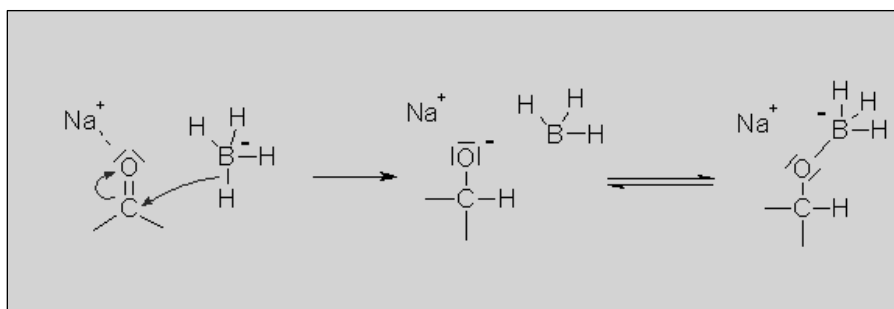


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## Closer look at borohydride reductions

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

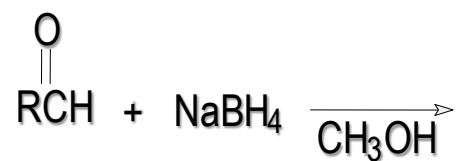


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## $\text{NaBH}_4$ Reduction

- Reductions with  $\text{NaBH}_4$  are most commonly carried out in aqueous methanol, in pure methanol, or in ethanol

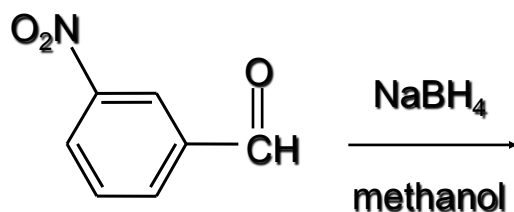


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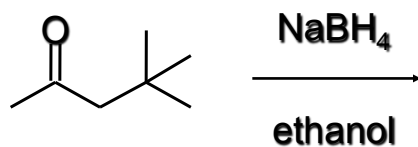


Examples: Sodium Borohydride

Aldehyde



Ketone



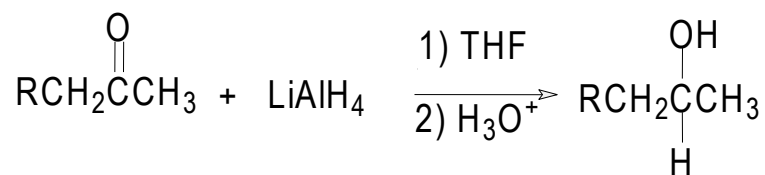
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*Lithium aluminum hydride*



- More reactive than sodium borohydride
- Cannot use water, ethanol, methanol etc., as solvents
- Diethyl ether and THF are the most commonly used solvent
- This is a dangerous but useful reagent

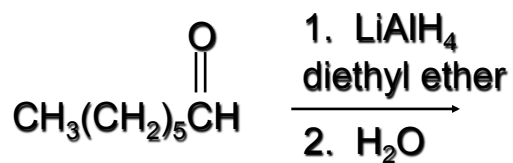


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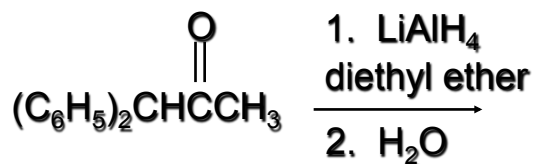


*Examples: Lithium Aluminum Hydride*

**Aldehyde**



**Ketone**

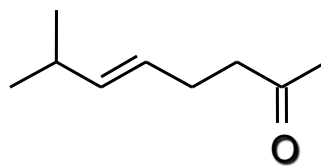


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*Selectivity*

neither  $\text{NaBH}_4$  or  $\text{LiAlH}_4$   
will reduce isolated  
double bonds



1.  $\text{LiAlH}_4$   
diethyl ether  
2.  $\text{H}_2\text{O}$

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## Selectivity in Reduction

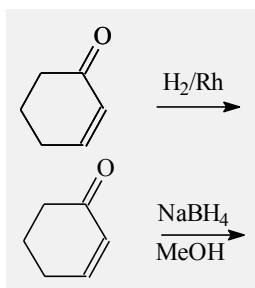
- $\text{LiAlH}_4$  reduces **any** and all carbonyl compounds to the corresponding alcohols
  
- $\text{NaBH}_4$  **only** reduces aldehydes and ketone

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## Catalytic Reduction

- Catalytic reductions are generally carried out from 25° to 100°C and from 1 to 5 atm  $\text{H}_2$
- Carbon-carbon double bonds can be selectively reduced using Rhodium catalysts



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## 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

