

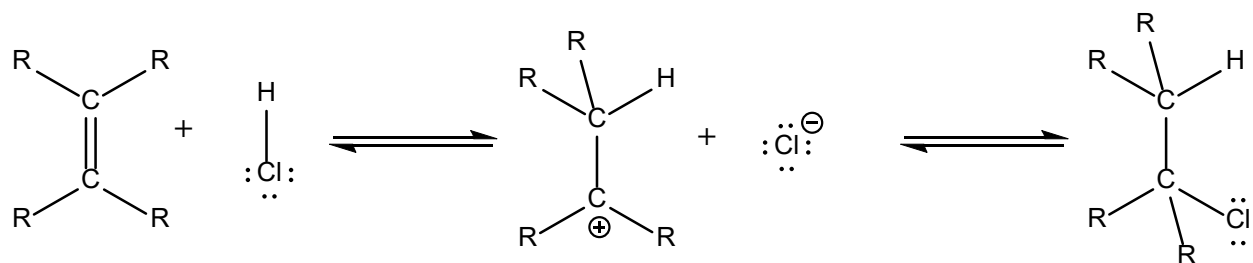


CHEMISTRY 2600

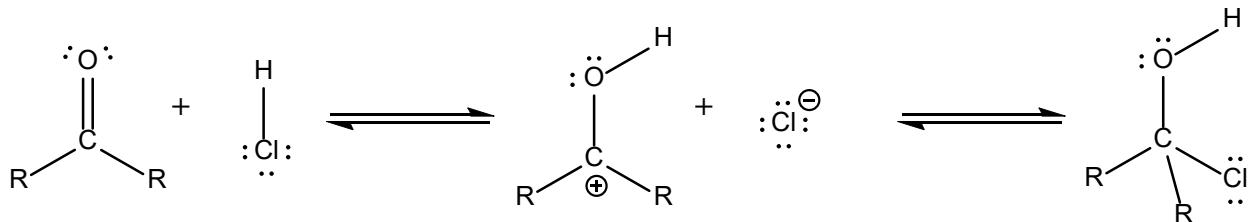
Topic #7: Acetals, Imines, etc.
Spring 2021
Dr. Susan Findlay

Electrophilic Addition to Carbonyl Groups

- In Chapter 8, you saw that water, HCl, HBr and HI could be added across the C=C of an alkene. This is an equilibrium reaction for which the equilibrium favours the products.



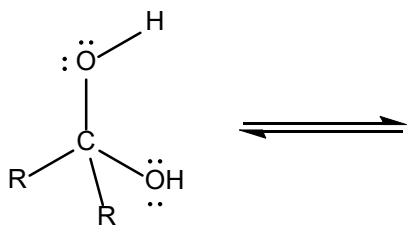
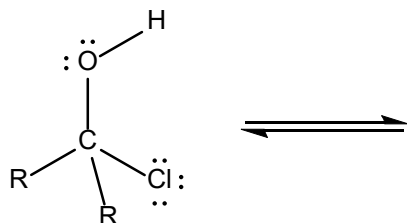
- These small molecules can be added across C=O via the same mechanism; however, this equilibrium favours the reactants.



- What causes this difference in reactivity?

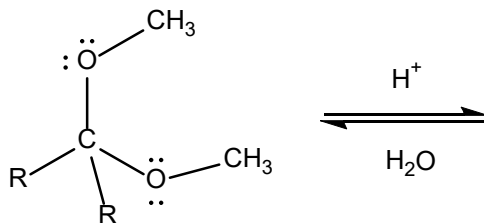
Electrophilic Addition to Carbonyl Groups

- Because electrophilic addition to a carbonyl group tends to be reactant-favoured, when we see a *gem*-diol (two –OH groups on one carbon) or a carbon atom with a –OH group and a halogen attached, we usually expect it to collapse to a carbonyl group:



Acetals and Ketals

- Similarly, a carbon atom with two alkoxy groups attached (an **acetal** or **ketal**) will collapse to a carbonyl group in the presence of aqueous acid:

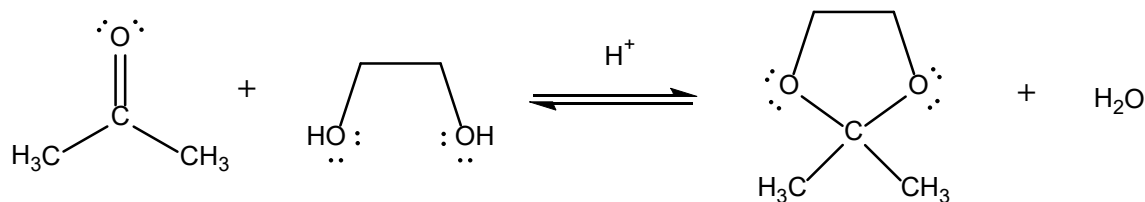
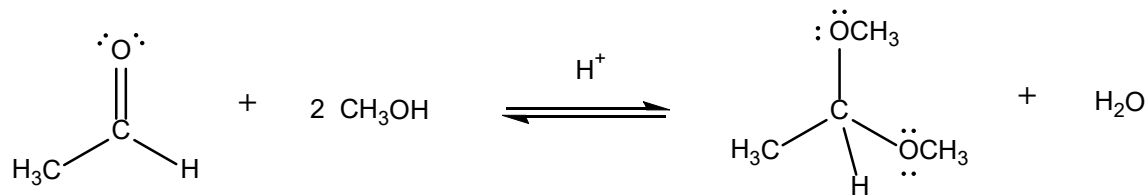


- Unlike the molecules on the previous page, acetals and ketals are stable in aqueous base. They won't collapse to carbonyl groups except in the presence of acid and water. This is very useful...

Acetals and Ketals

- By controlling the reaction conditions, we can favour formation of an acetal (from an aldehyde) or ketal (from a ketone):

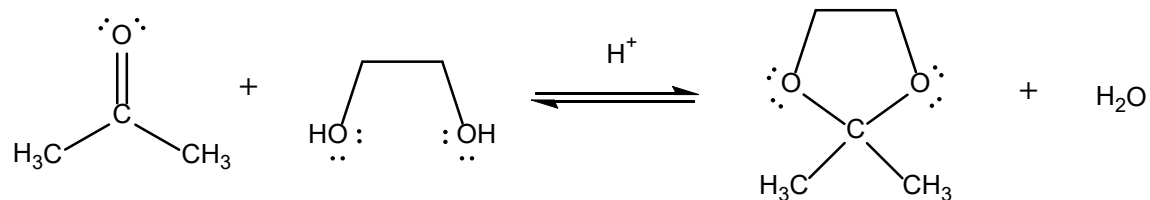
e.g.



How would you promote the forward reaction?

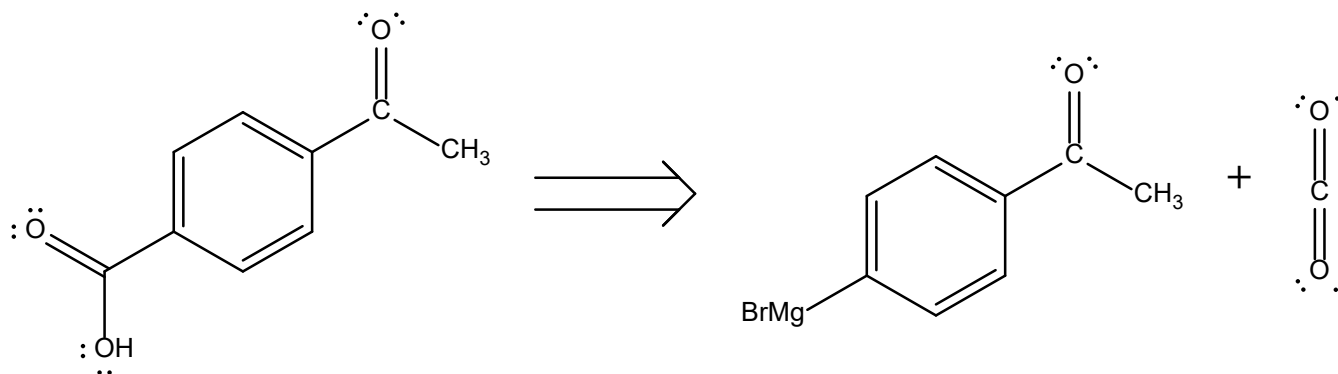
Acetals and Ketals

- Propose a reasonable mechanism for the following reaction:



Acetals and Ketals as Protecting Groups

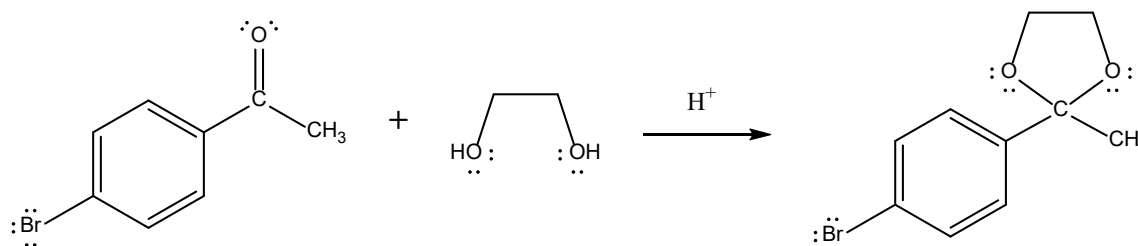
- So, what we have is a reaction that we can use to:
 - First, "protect" a carbonyl group as a less reactive species.
 - Second, do some reaction (*on another part of our molecule*) that would have been incompatible with the carbonyl group.
 - Third, remove the "protecting group" to recover the carbonyl group.
- e.g. Consider the following synthetic plan:



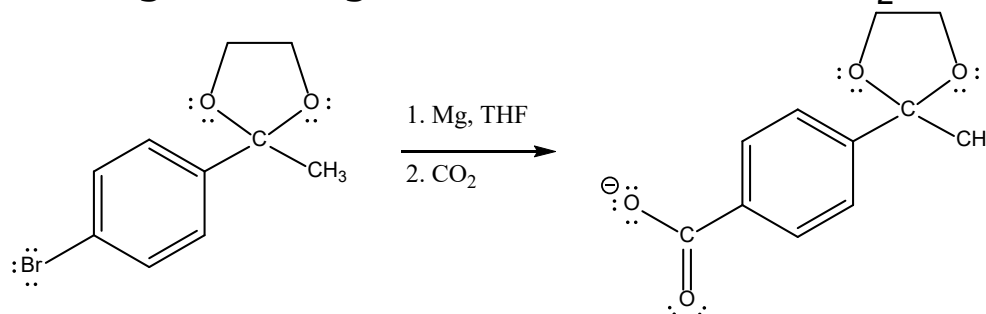
You can't just react the two proposed reactants. Why not?

Acetals and Ketals as Protecting Groups

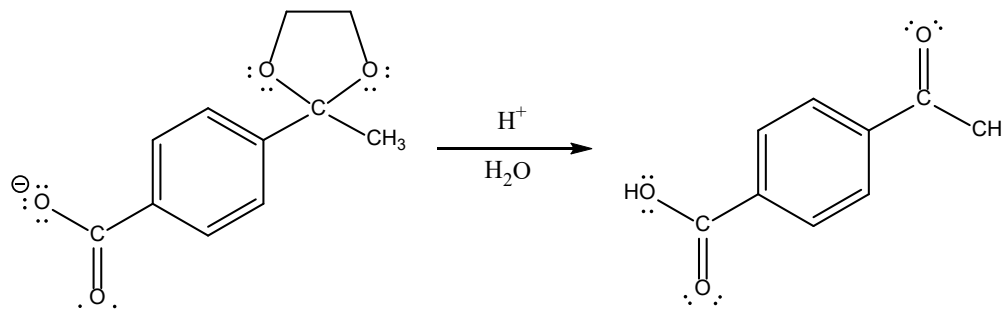
- Instead, what you could do would be:
 - Protect the ketone as a ketal:



- Make the Grignard reagent and react it with CO₂:

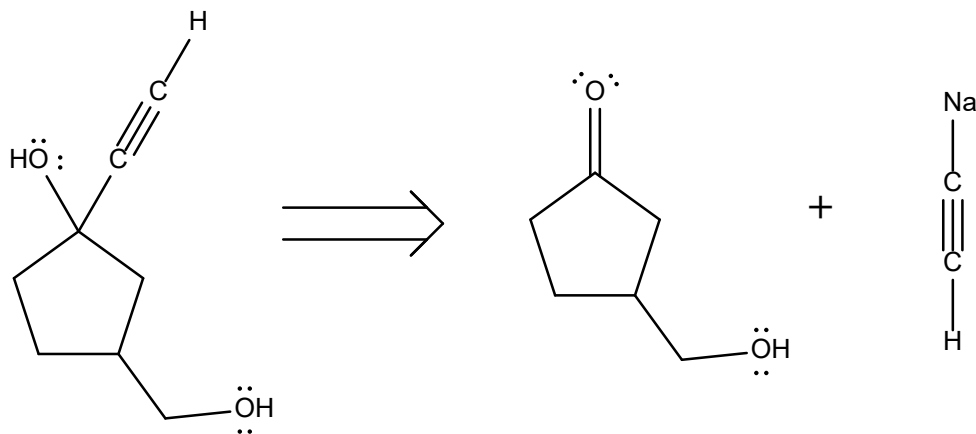


- Convert the ketal back into the ketone:



Acetals and Ketals as Protecting Groups

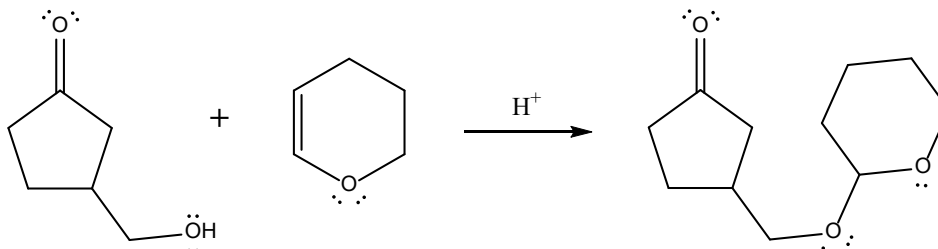
- e.g. Consider the following synthetic plan:



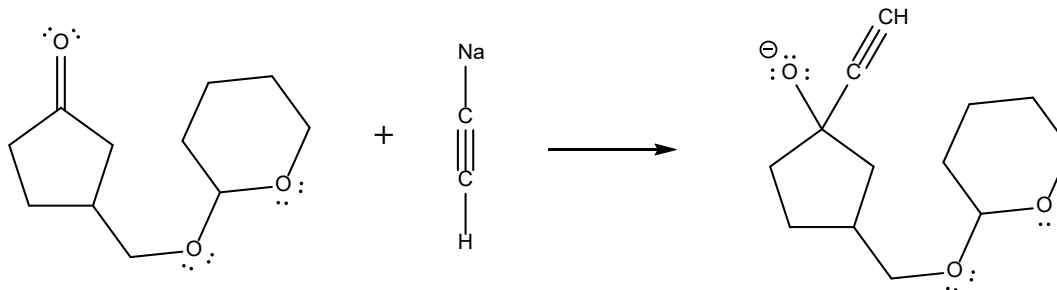
What is the problem with reacting these two proposed reactants?

Acetals and Ketals as Protecting Groups

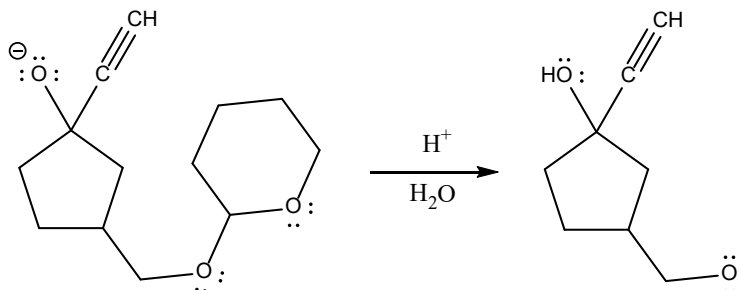
- This time, it's the alcohol that needs protecting:
 - Protect the alcohol as an acetal:



- React the ketone with the acetylide nucleophile:

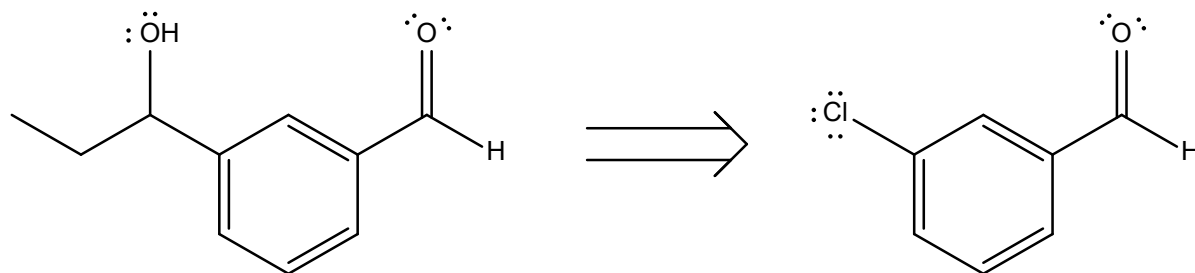


- Recover the alcohol from the acetal:



Acetals and Ketals as Protecting Groups

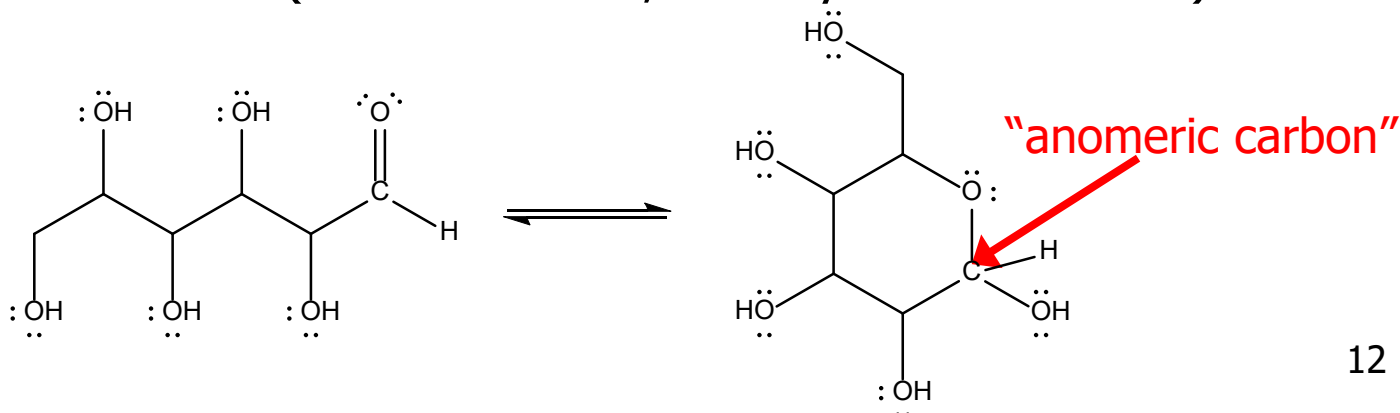
- Propose a series of reactions that would allow you to carry out the following synthetic plan:



Sugars as Hemiacetals and Hemiketals

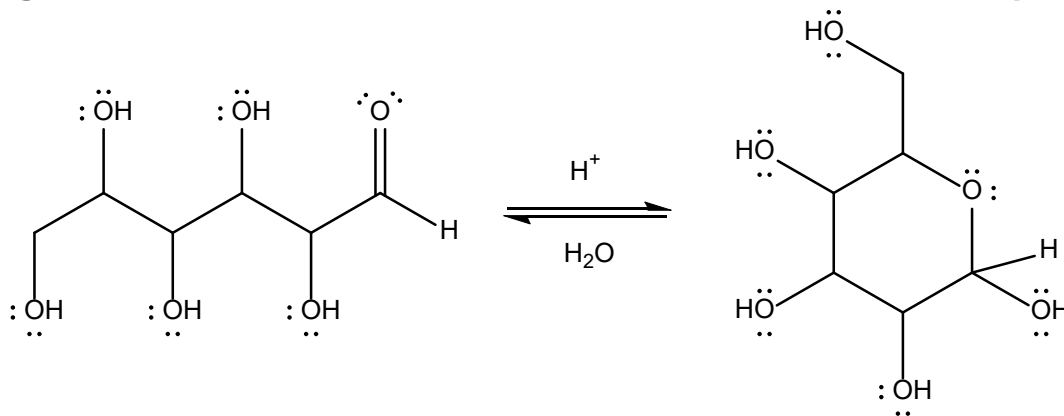
- While most electrophilic addition reactions to carbonyls aren't product-favoured (without careful consideration of the reaction conditions), there is a very important exception to this rule.
- Sugars are polyhydroxyketones or polyhydroxyaldehydes but the carbonyl group isn't immediately obvious because an electrophilic addition reaction occurs in the presence of aqueous acid, forming a stable 5- or 6-atom ring.

e.g. The polyhydroxyaldehyde below could be glucose (or galactose or any number of other sugars, depending on the stereochemistry). It exists primarily in the cyclic form shown (a **hemiacetal**, literally a "half acetal").



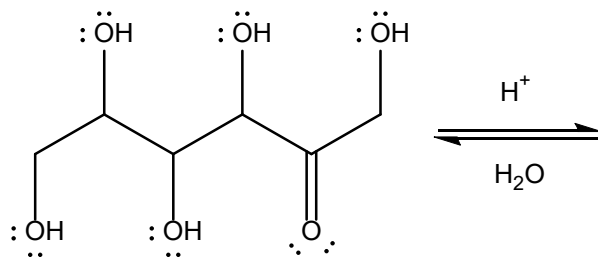
Sugars as Hemiacetals and Hemiketals

- Propose a mechanism for the equilibrium reaction converting linear glucose to the hemiacetal form in dilute aqueous acid.



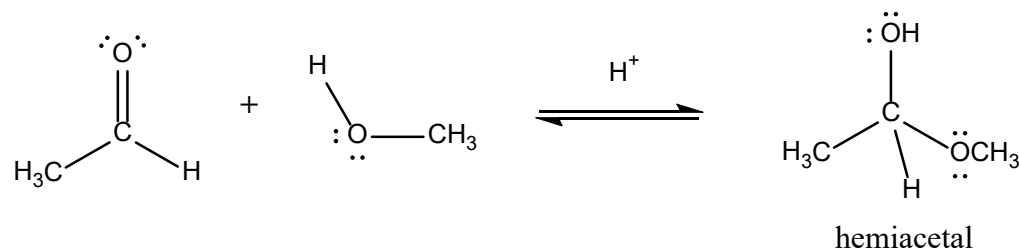
Sugars as Hemiacetals and Hemiketals

- Fructose occurs naturally as a mixture of two hemiacetals – one with a 5-atom ring (the “furanose” form) and one with a 6-atom ring (the “pyranose” form). The linear form of fructose is shown below – again, without the stereochemistry. Draw the structures of both hemiacetal forms of fructose.

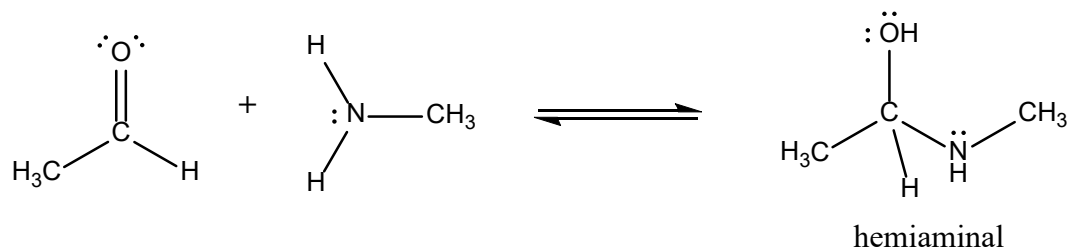


Hemiaminals, Imines and Enamines

- An aldehyde can react with an alcohol in the presence of catalytic acid to make a hemiacetal:



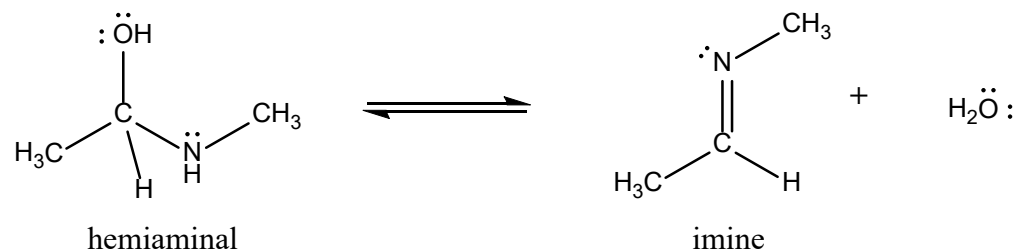
- Similarly, an aldehyde can react with an amine to make a hemiaminal:



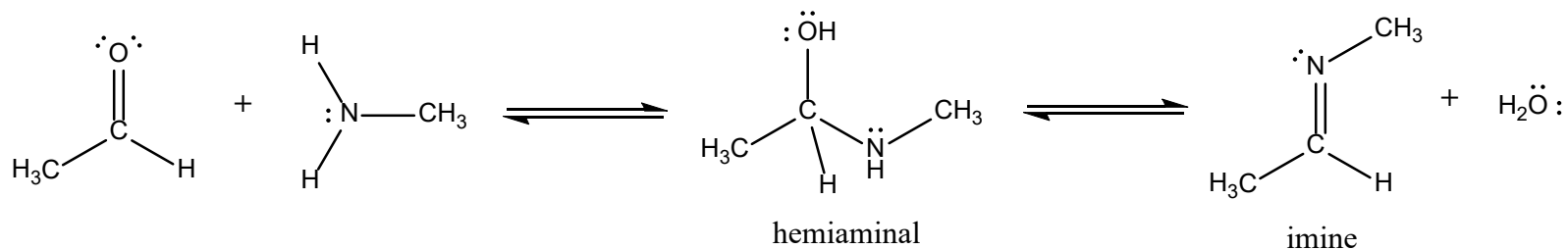
- These reactions are very similar, but there is one key difference. What is it?

Hemiaminals, Imines and Enamines

- Dehydration of a hemiaminal gives an imine:

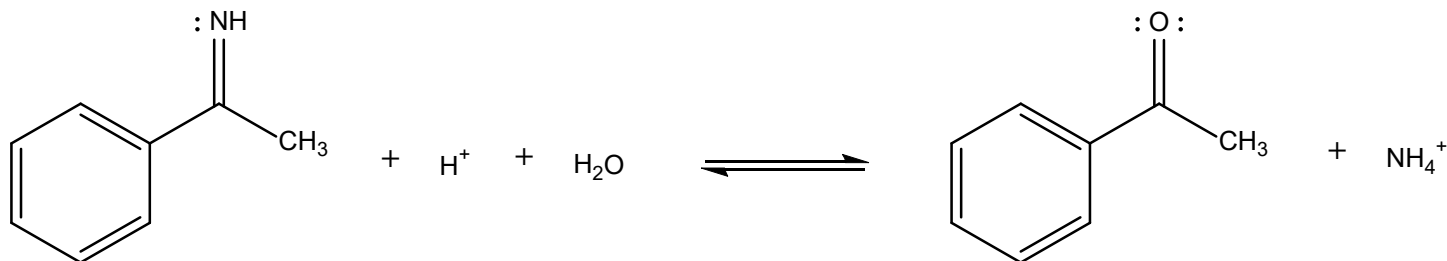


- Note that conversion of aldehyde or ketone to imine is reversible, and Le Châtelier's principle can be used to predict whether the reaction is favoured in the forward or reverse direction.



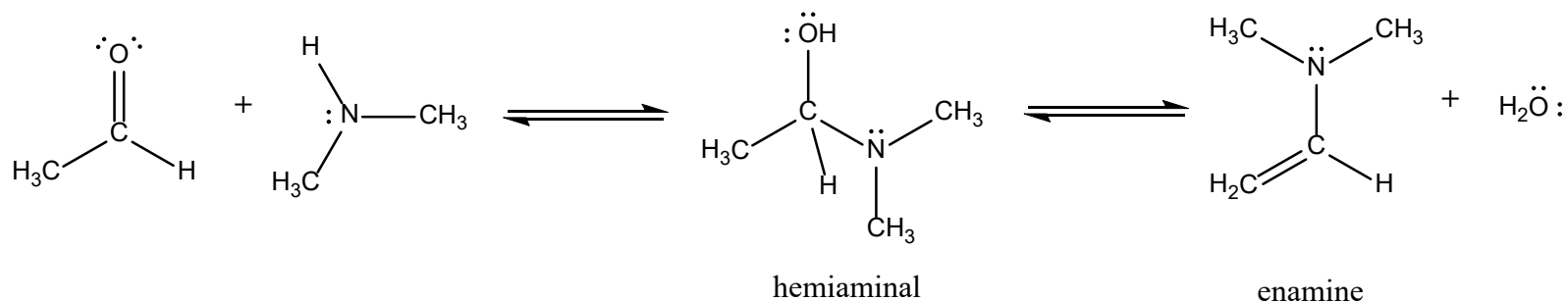
Hemiaminals, Imines and Enamines

- As such, imines are readily hydrolyzed to the corresponding aldehyde or ketone in the presence of aqueous acid. Propose a reasonable mechanism for the following reaction:



Hemiaminals, Imines and Enamines

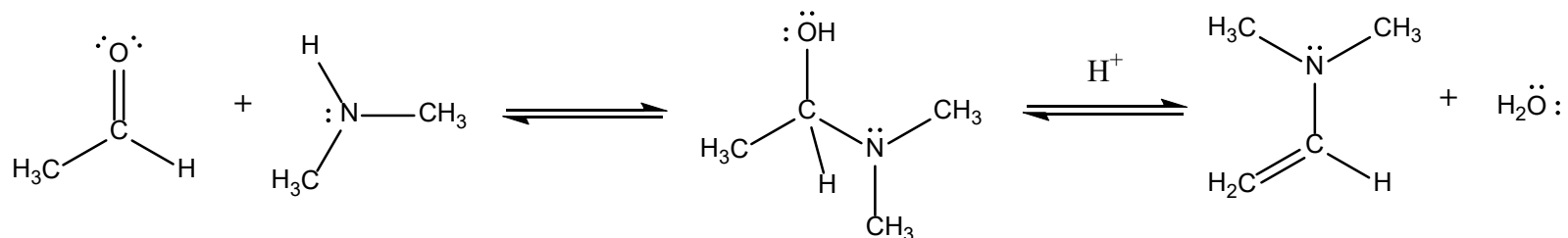
- In the examples on the past few slides, a primary amine (or NH_3) was reacted with a ketone or aldehyde. If a secondary amine is reacted with a ketone or aldehyde, a hemiaminal can also form – but it cannot be dehydrated to give an imine. Instead, an enamine forms:



- Why do we get an enamine instead of an imine in this case?
(If you're not sure, work through the mechanism on the next page first...)

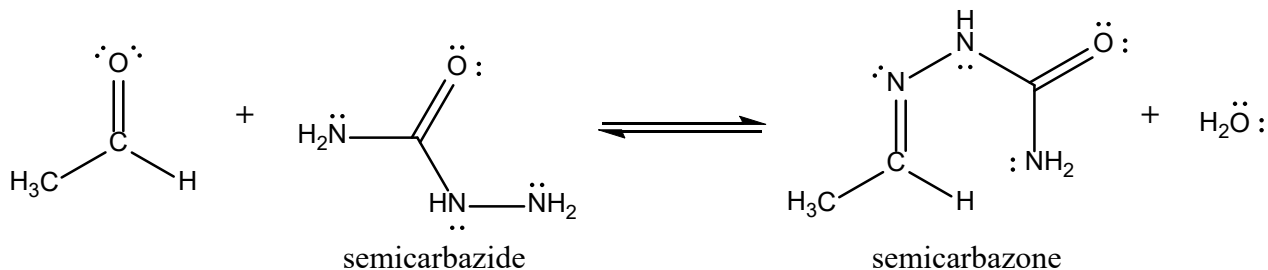
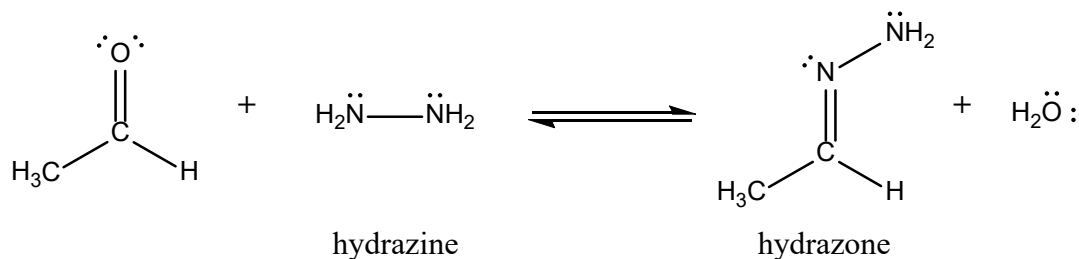
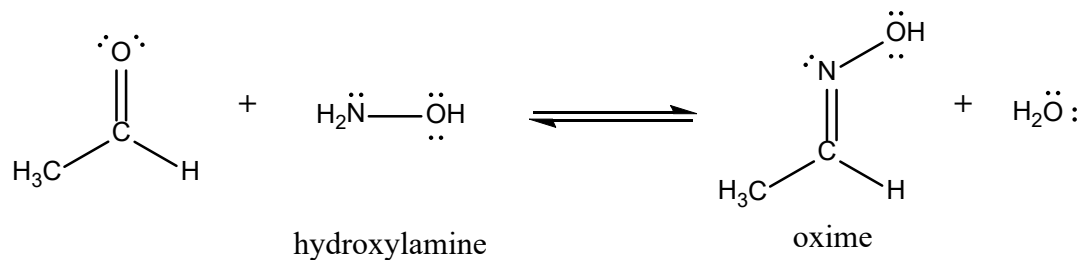
Hemiaminals, Imines and Enamines

- Propose a reasonable mechanism for this reaction:



Hemiaminals, Imines and Enamines

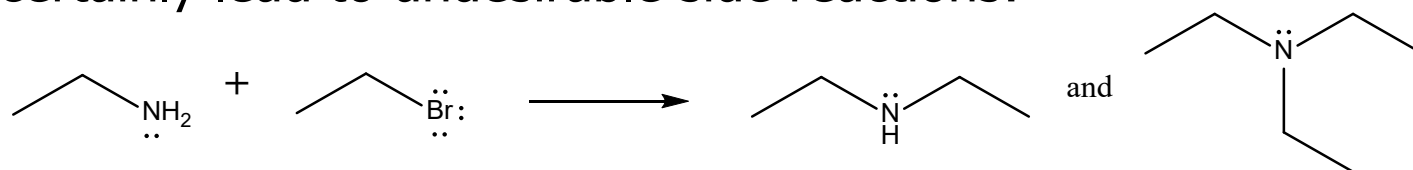
- Primary amines are not the only functional groups that can be reacted with ketones or aldehydes to make functional groups that resemble imines. Analogous reactions include:



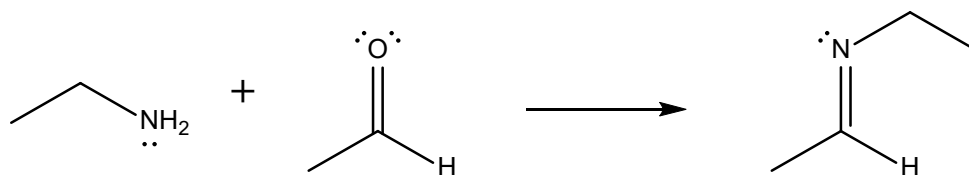
The products of these reactions are more stable than imines from primary amines.

Hemiaminals, Imines and Enamines

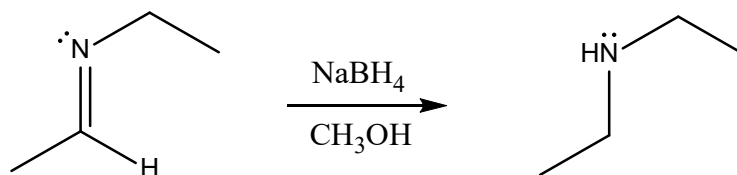
- Previously, we saw that preparing a secondary amine via an S_N2 reaction between a primary amine and alkyl halide would almost certainly lead to undesirable side reactions:



- On the other hand, a primary amine will only react once with an aldehyde:



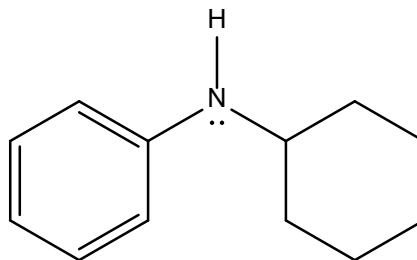
The imine can then be reduced with nucleophilic hydrogen to give the desired secondary amine.



This two-step process is called **reductive amination**.

Hemiaminals, Imines and Enamines

- How could you use reductive amination to prepare the following compound:





Wolff-Kischner Reaction

- Another use of nitrogen nucleophiles is to reduce a carbonyl group right down to a CH_2 (or CH_3 if it was an aldehyde). In the Wolff-Kischner reaction, a ketone or aldehyde is heated with hydrazine and aqueous potassium hydroxide:
 - First, the hydrazine reacts with the carbonyl group to make a hydrazone:



Wolff-Kischner Reaction

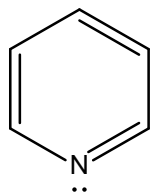
- Then the base deprotonates the terminal nitrogen, migrating the double bond from C=N to N=N:

- Finally, the base deprotonates the terminal nitrogen again, eliminating nitrogen gas (N₂) and giving a carbanion which is quickly protonated by water:

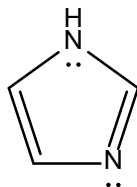
- This is one way to get rid of a carbonyl group that was useful to assemble a target molecule but is not wanted in the product.

Preparation of Heterocycles

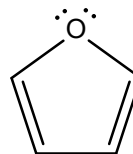
- A heterocycle is a ring containing at least one atom other than carbon (i.e. a ring containing at least one heteroatom). You have probably already encountered at least a few of them when discussing aromaticity and/or as common solvents:



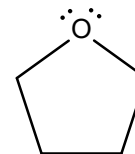
pyridine



imidazole



furan

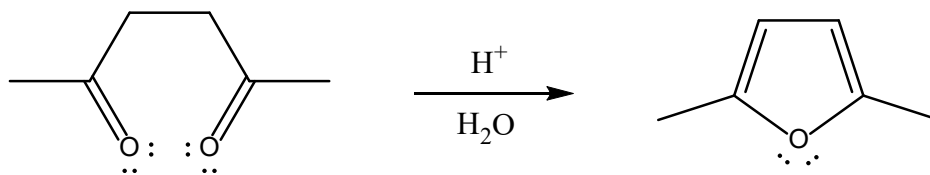


tetrahydrofuran (THF)

- Many heterocycles can be prepared via electrophilic addition to compounds containing two carbonyl groups separated by either one or two CH_2 groups (1,3-dicarbonyl compounds or 1,4-dicarbonyl compounds).

Preparation of Heterocycles

- Propose a mechanism for the formation of 2,5-dimethylfuran from hexane-2,5-dione in aqueous acid:



Preparation of Heterocycles

- Propose a mechanism for the formation of 3,5-dimethylpyrazole from pentane-2,4-dione and hydrazine:

