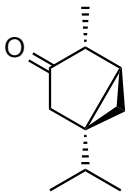


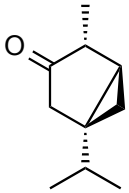
Chemistry 2600

Chapter 16

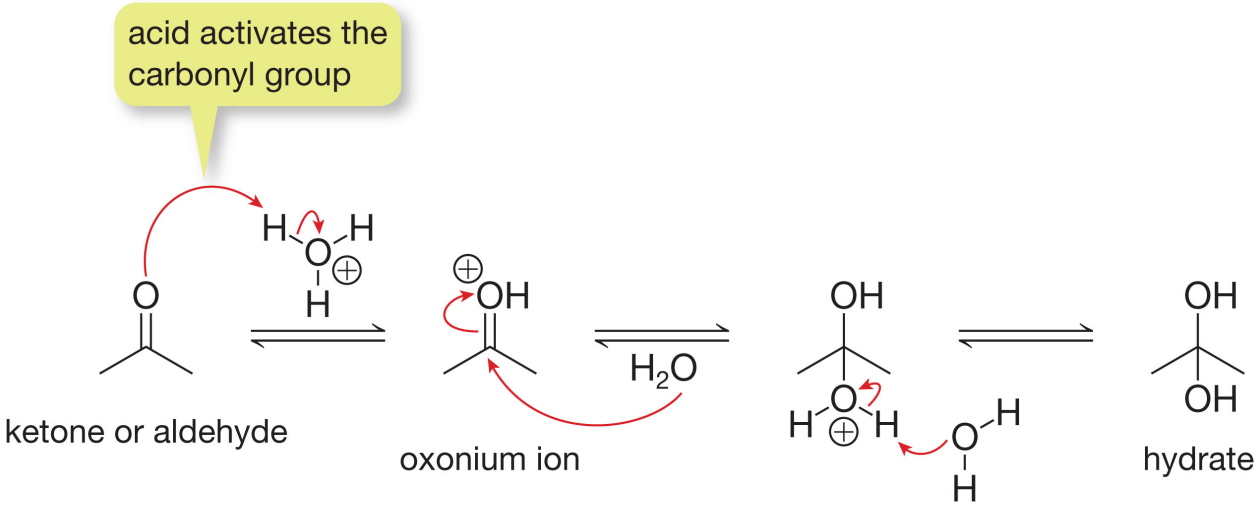
π Bonds With Hidden Leaving Groups

(sections 16.1-16.6 excluding 16.3.1 and 16.5.3)

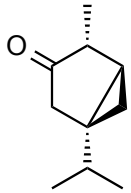
Formation and Reactivity of Acetals



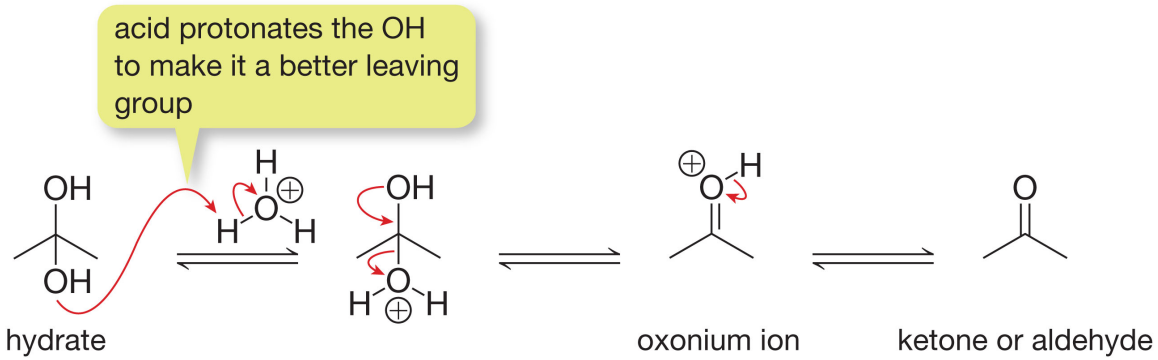
- In Chapters 7 and 15 we saw how carbonyl compounds undergo addition reactions with nucleophiles.
- We also saw how some of these reactions are reversible.
- For example, recall the formation of a hydrate when an aldehyde or ketone reacts with water under acidic condition:



Formation and Reactivity of Acetals

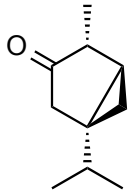


- This reaction is reversible and after the loss of a leaving group, the carbonyl group is reformed:

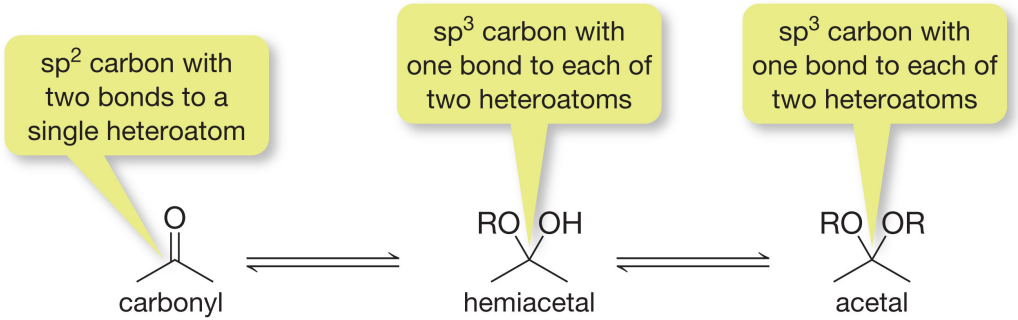


- Note that the oxygen that is lost could come from the initial carbonyl oxygen atom.
- We say these molecules have a ‘hidden leaving group’.
- This chapter explores the chemistry of the removal or replacement of these hidden leaving groups.

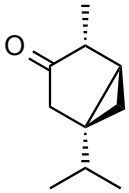
Formation and Reactivity of Acetals



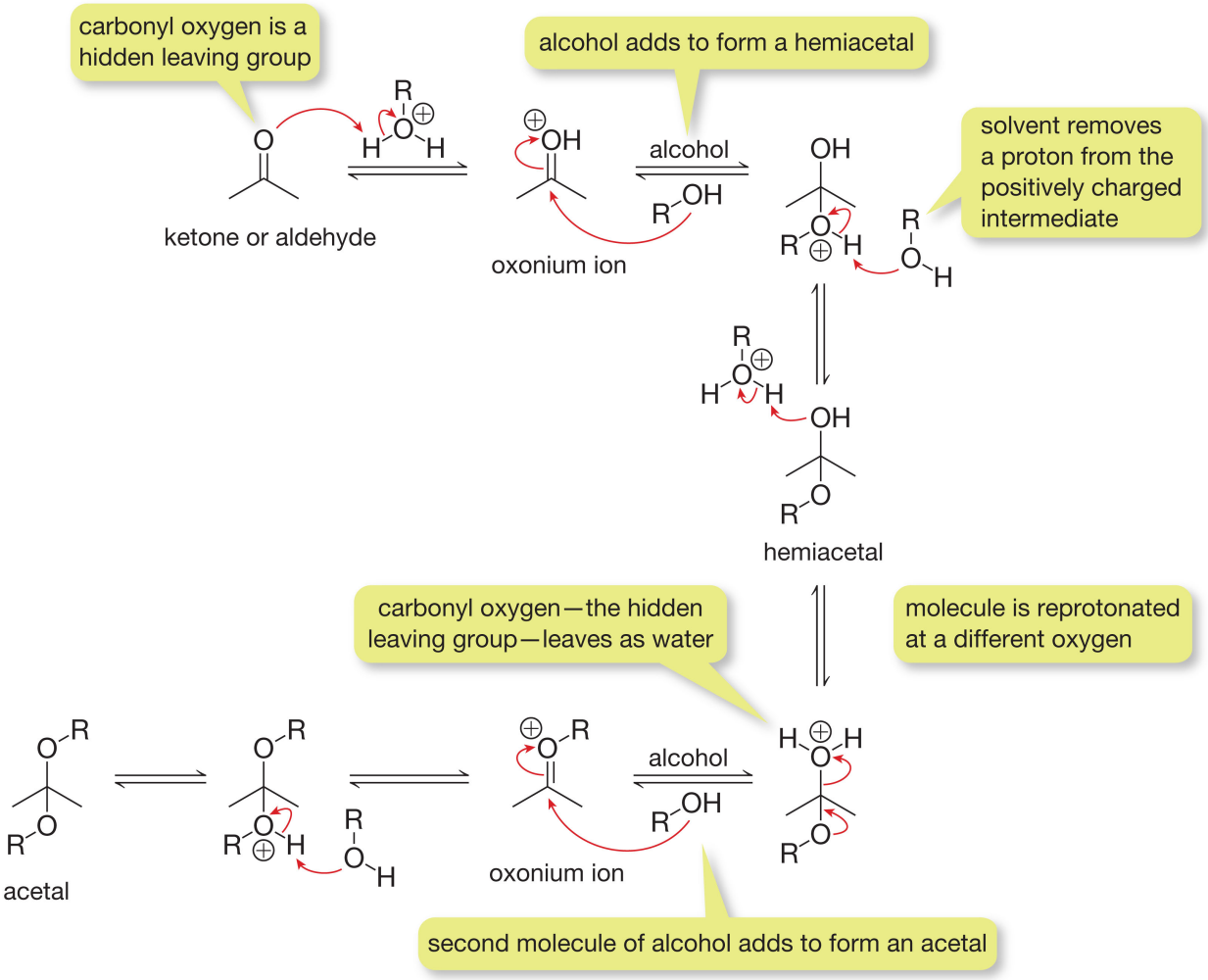
- When an aldehyde/ketone reacts with an alcohol in the presence of acid, a ***hemiacetal*** is formed.
- The only difference between hemiacetal formation and hydrate formation is the nucleophile (water vs alcohol).
- Hemiacetals have a hidden leaving group and in the presence of alcohol and acid, react quickly to form an ***acetal***.
  - Hemiacetal (tetrahedral carbon attached to –OH and –OR)
  - Acetal (tetrahedral carbon attached to two –OR groups)



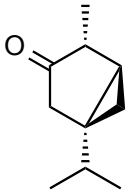
Formation and Reactivity of Acetals



- Acetal formation:

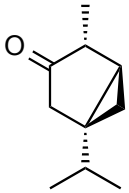


Formation and Reactivity of Acetals

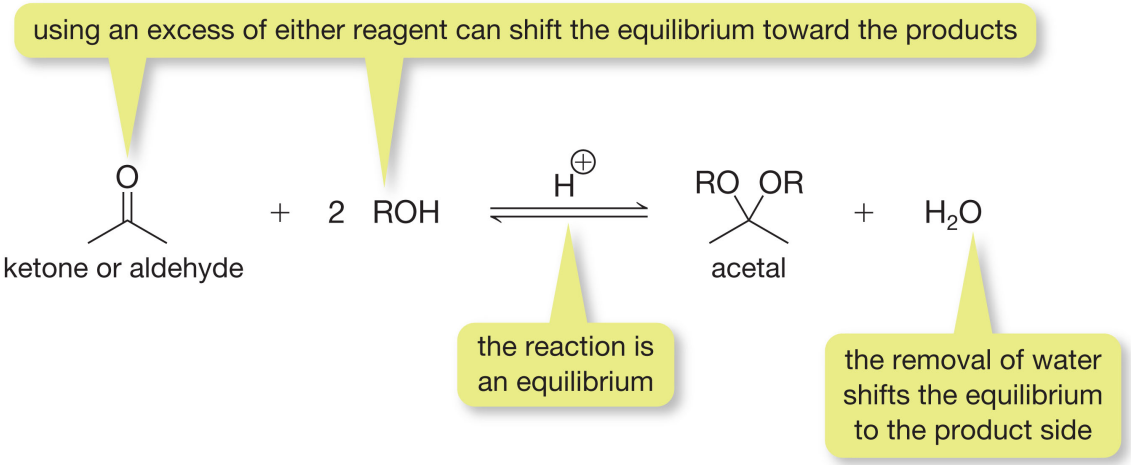


- Acetal formation is an equilibrium process, all the steps in the sequence can run in both directions.
- When an acetal is converted to a carbonyl compound, the reaction is called ***hydrolysis*** because water is being used to break (lyse) the acetal.
- Acetals are only be formed under acidic conditions. Acid is required to convert the –OH group of the hemiacetal into a good leaving group.
- Reversible reactions typically give poor yields and form a mixture of products.

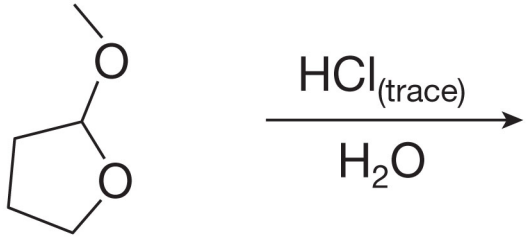
Formation and Reactivity of Acetals



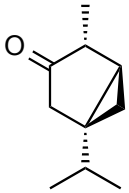
- We can use Le Chatelier's principle to control the equilibrium:



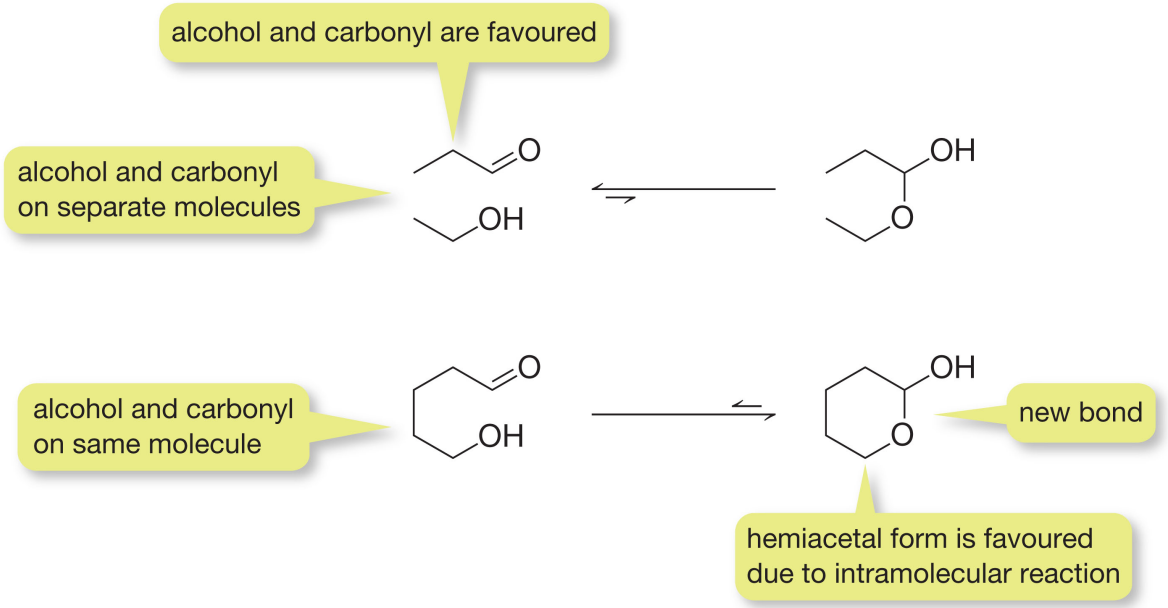
- Draw the product of the following reaction and the mechanism of formation:



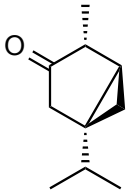
Hemiacetals in Sugars



- Acyclic hemiacetals are generally not very stable and the equilibrium favours the carbonyl group and the alcohol.
- Cyclic hemiacetals are more stable and the equilibrium favours their formation. This is especially true when 5- or 6-membered rings are formed.

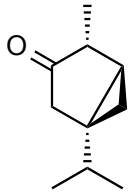


Hemiacetals in Sugars

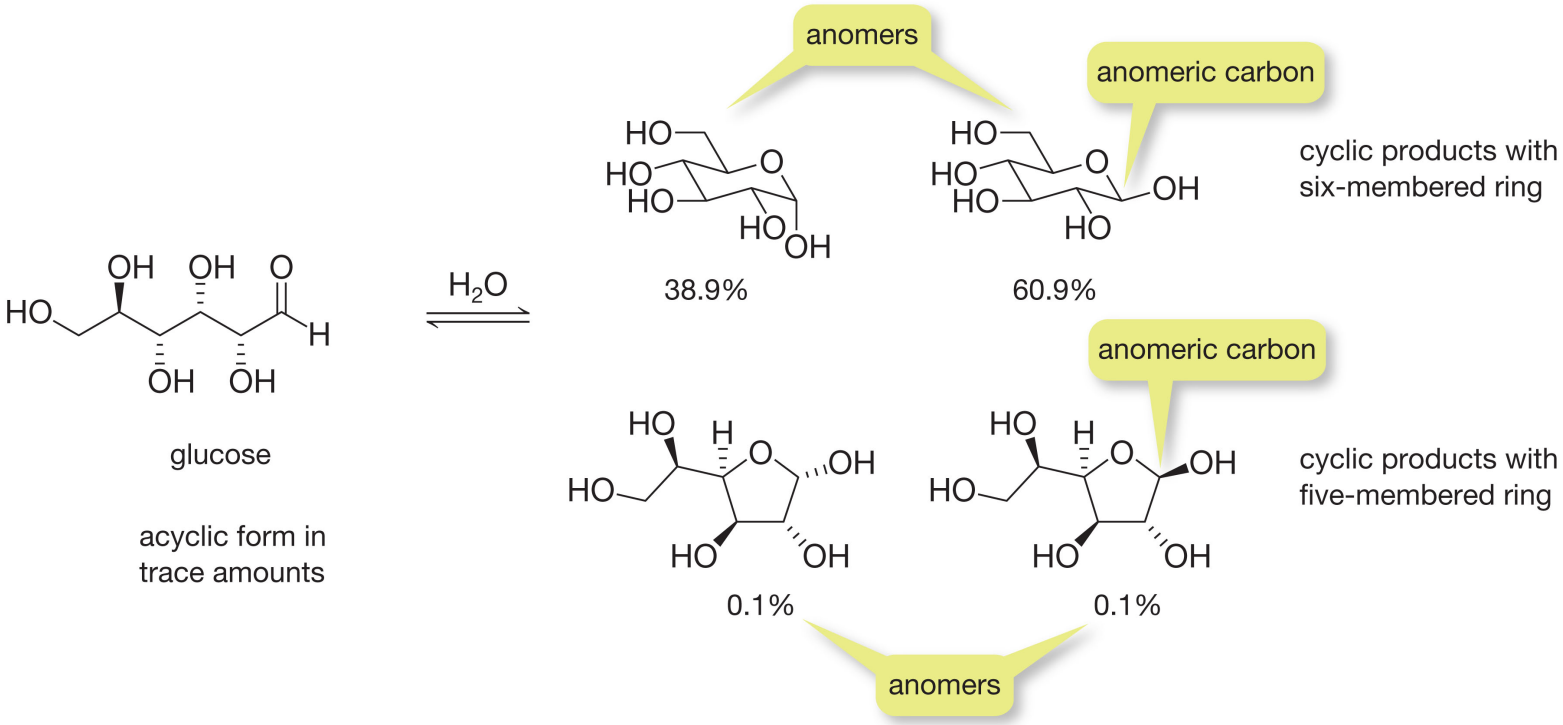


- Most sugars can exist in an open-chain form and several different cyclic hemiacetal forms.
- The hemiacetals of sugars are known as ***anomers***.
- Anomers are the different stereoisomers formed when the carbonyl carbon (the ***anomeric carbon***) of a sugar is converted to a cyclic hemiacetal.

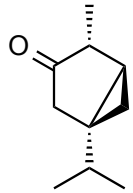
Hemiacetals in Sugars



- Most sugars exists in an open-chain form and several different cyclic hemiacetal forms.

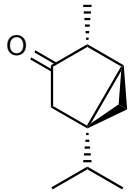


Acetals Used As Protecting Groups

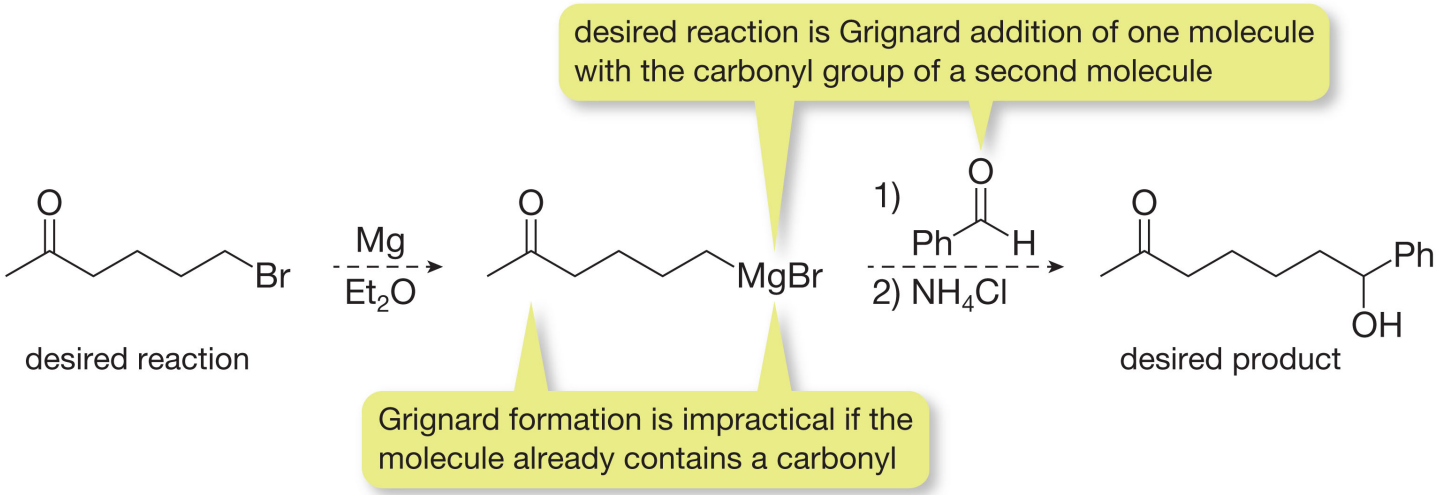


- Most organic molecules contain multiple functional groups. While functional groups give chemists 'handles' of reactivity, they can also interfere during other reactions.
- To ensure a reaction occurs at one particular functional group, the other functional groups may need to be temporarily inactivated.
- We can do this by using ***protecting groups***.
- Protecting groups change functional groups into a related functional group that will not react.
- Once the desired reaction has been completed, the protected functional group is then 'deprotected'.

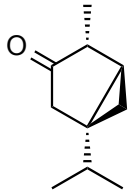
Acetals Used As Protecting Groups



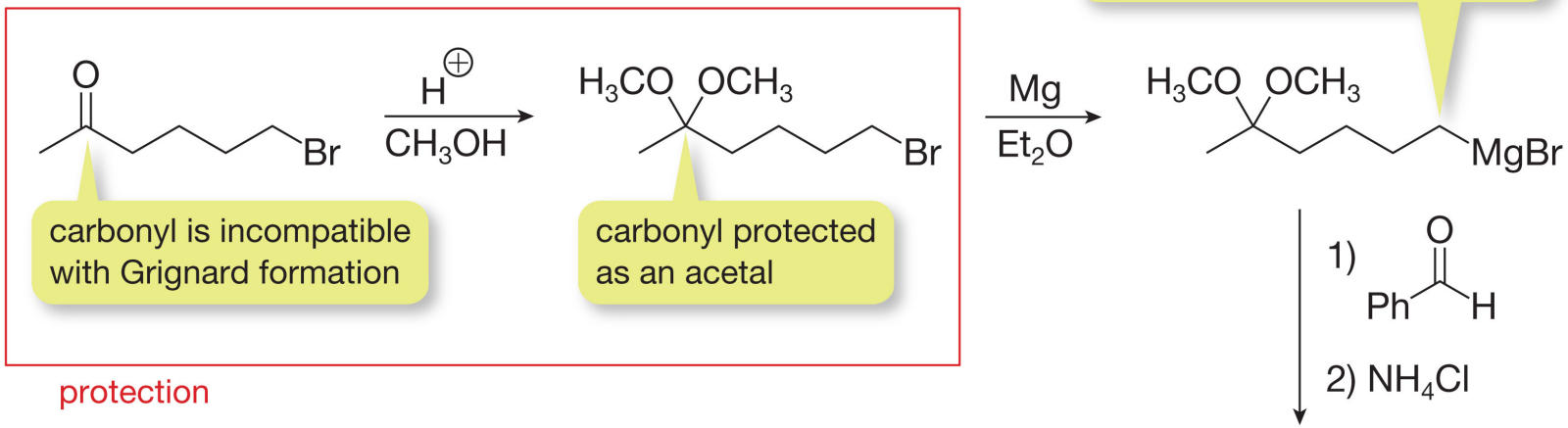
- The reactivity pattern of acetals make them useful as protecting groups.
  - They do not react easily with bases (no acidic protons)
  - They do not react with nucleophiles (no π bonds or good LGs)
  - They are easily installed to and removed from carbonyl groups.
- Consider the following reaction:



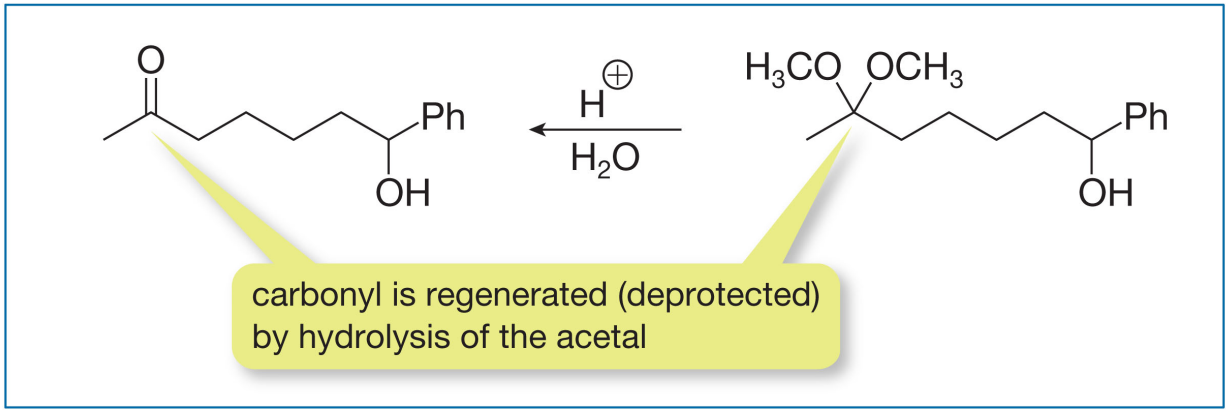
Acetals Used As Protecting Groups



Workable synthesis



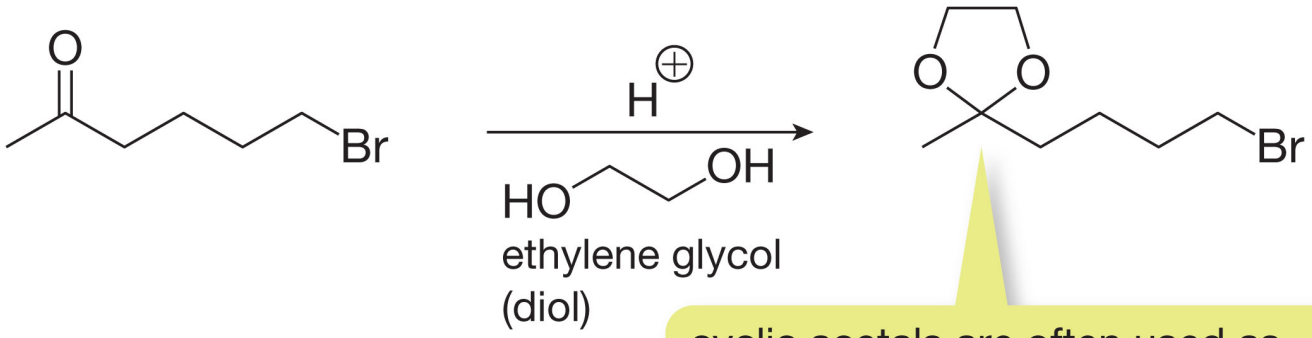
protection



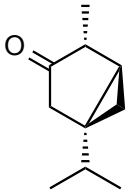
deprotection

Acetals Used As Protecting Groups

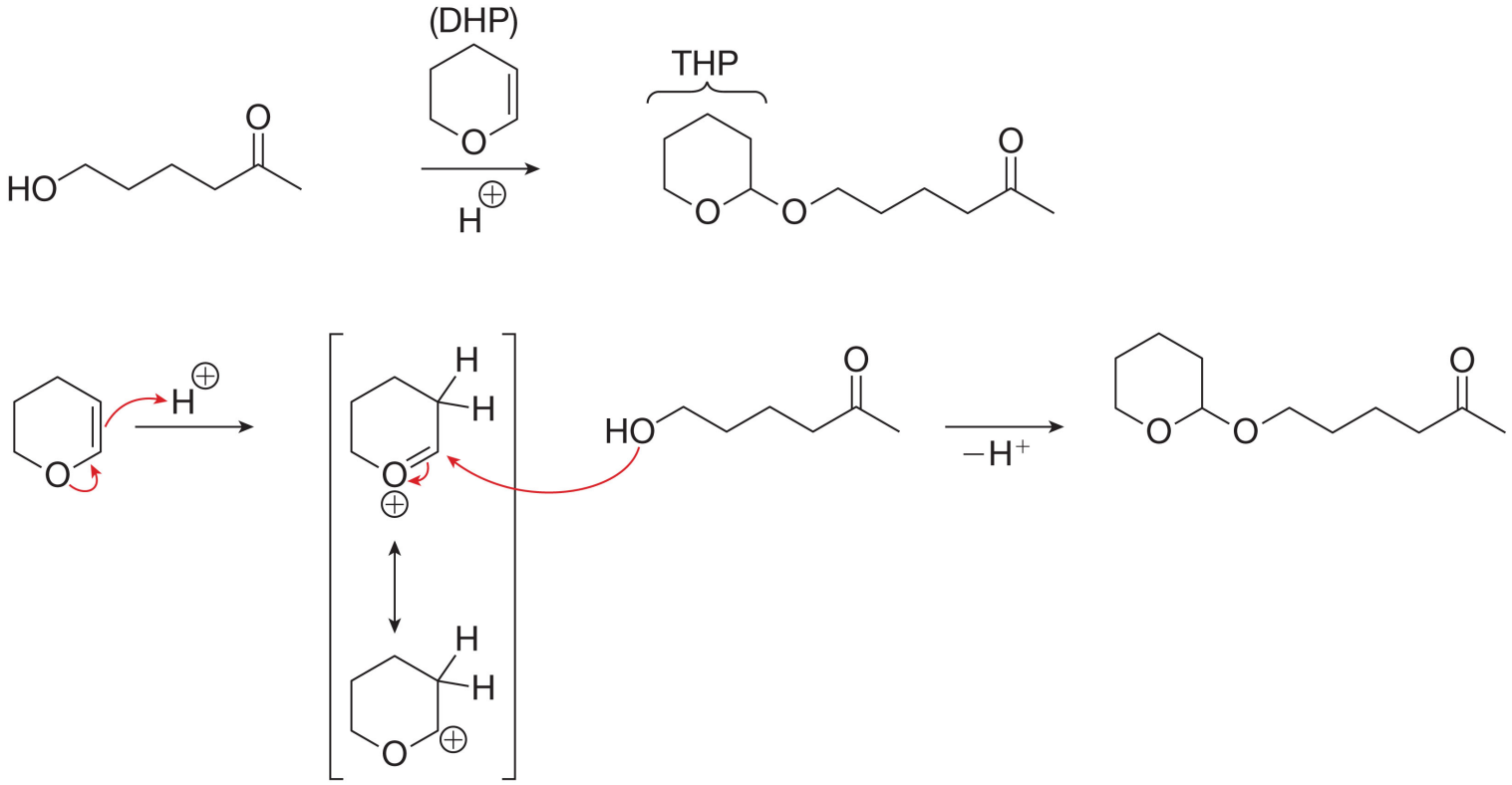
- Cyclic acetals are often used as they are more difficult to hydrolyze than acyclic ones.



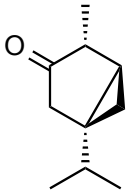
Acetals Used As Protecting Groups



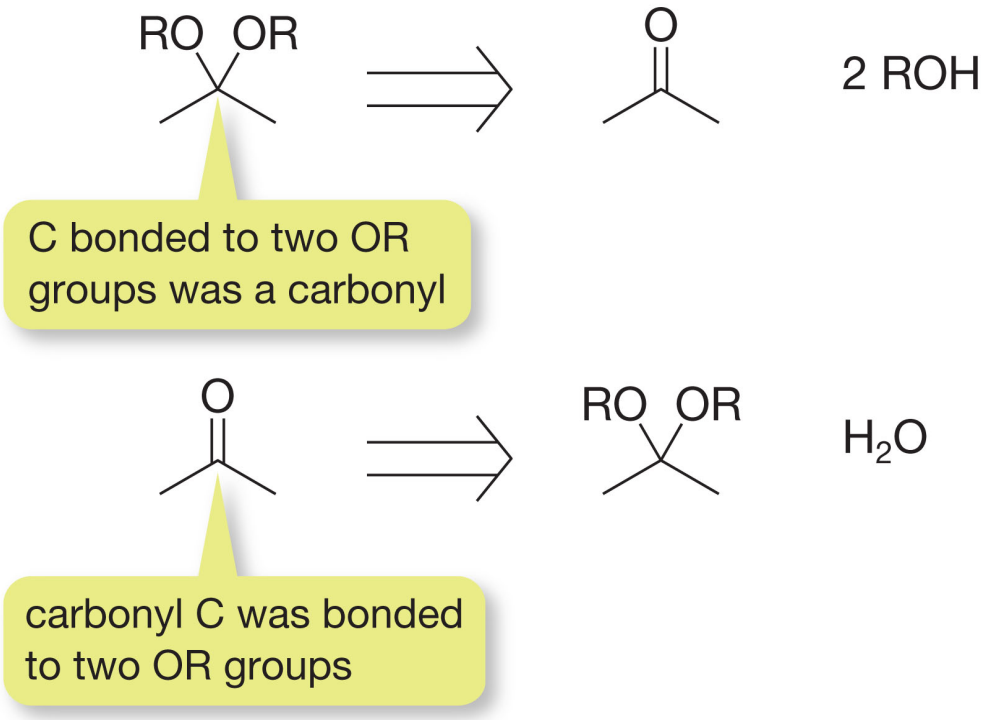
- Acetals can also be used to protect alcohols. In this case, the alcohol is reacted with dihydropyran (DHP) to give the tetrahydropyranyl (THP) acetal:



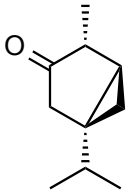
Retrosynthetic Analysis



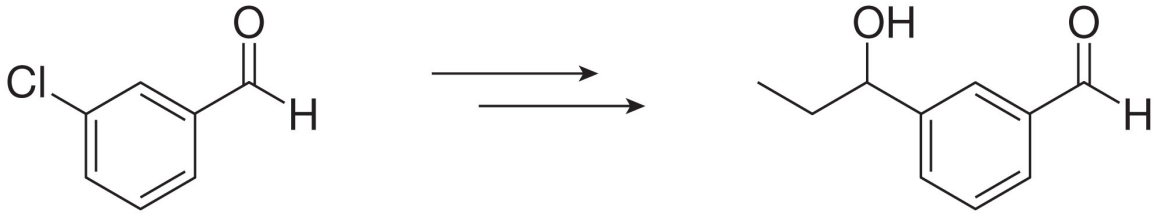
- Acetals, hemiacetals, and hydrates all disconnect to the corresponding carbonyl form. Similarly, carbonyls can be produced from the corresponding acetals.



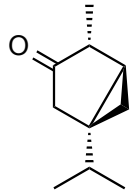
Retrosynthetic Analysis



- Suggest a series of reagents that could be used to carry out the following transformation:



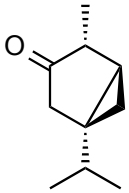
Aminals and Imines



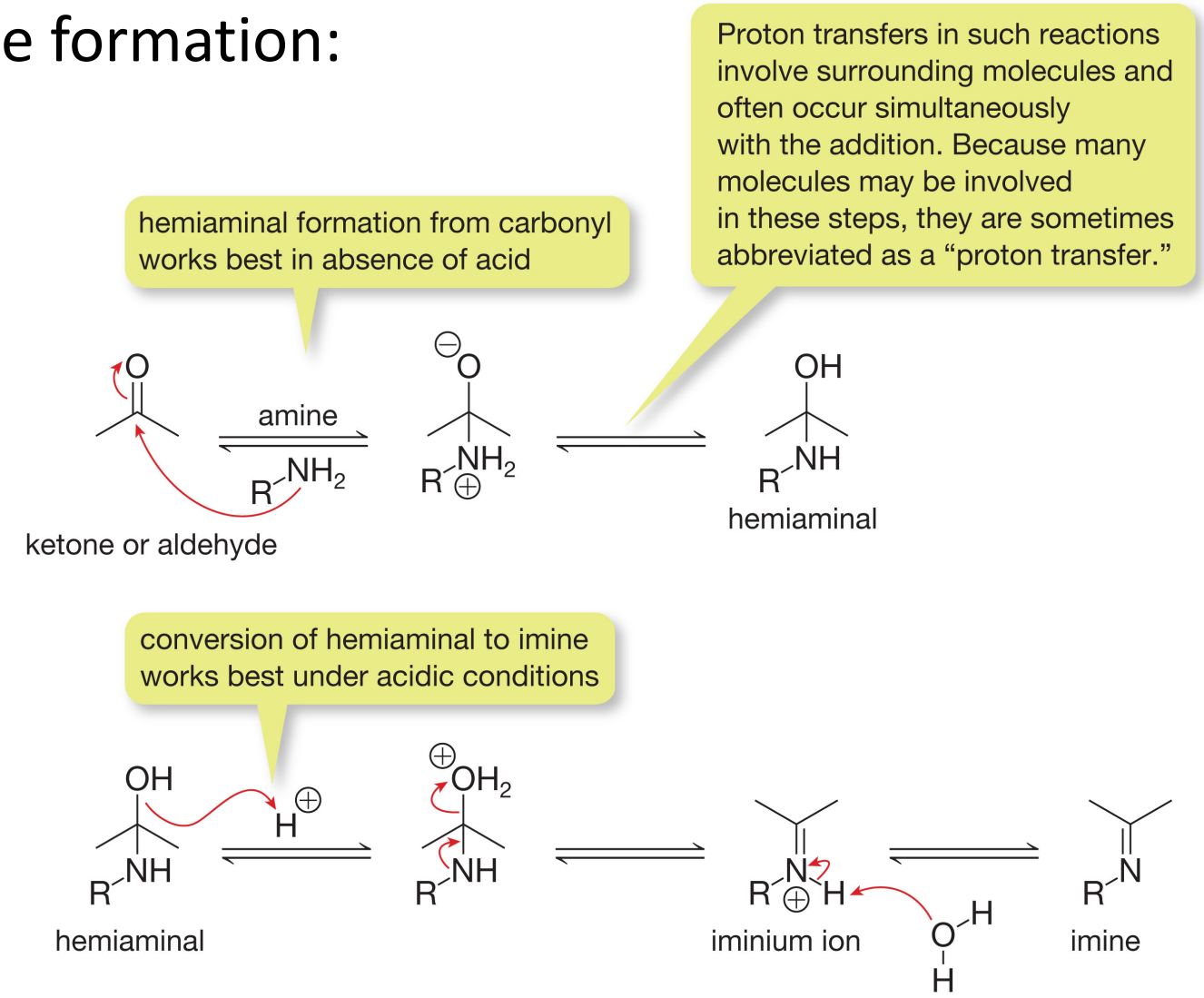
- Nitrogen can also form multiple bonds to carbon.
- Under the right conditions, nitrogen nucleophiles react with carbonyl groups to form an ***imine*** (C=N).
- Imines are formed in the same 2 step addition-elimination reaction as the CADs:
  - Nucleophilic attack of an amine onto a carbonyl carbon to form a ***hemiaminal***.
  - Elimination of water from the hemiaminal to form an iminium ion which give the imine.

- *These two steps have different pH requirements.*

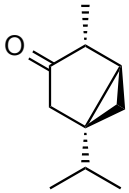
Aminals and Imines



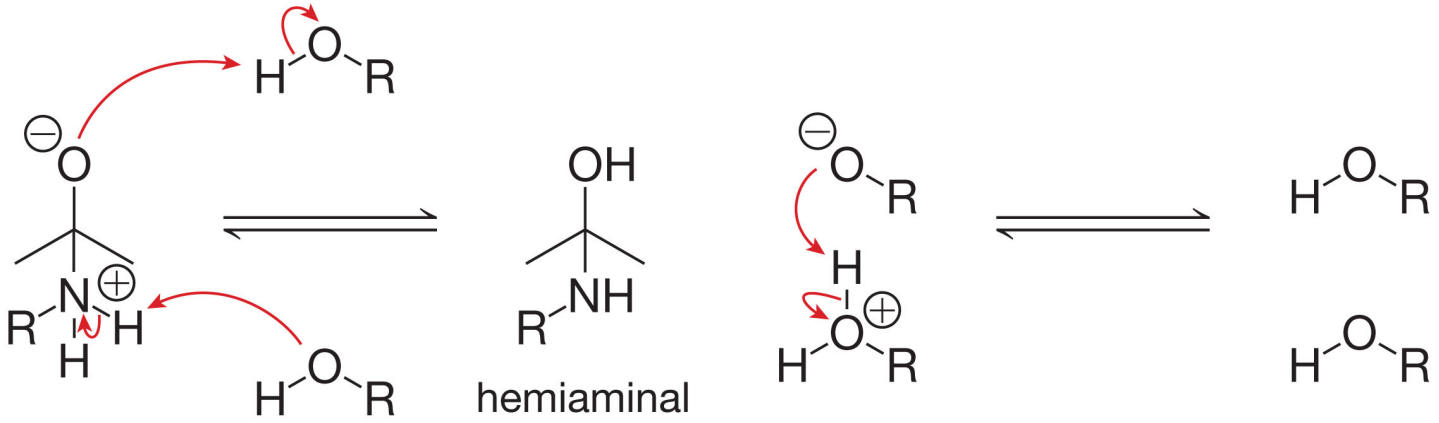
- Imine formation:



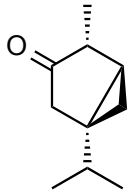
Aminals and Imines



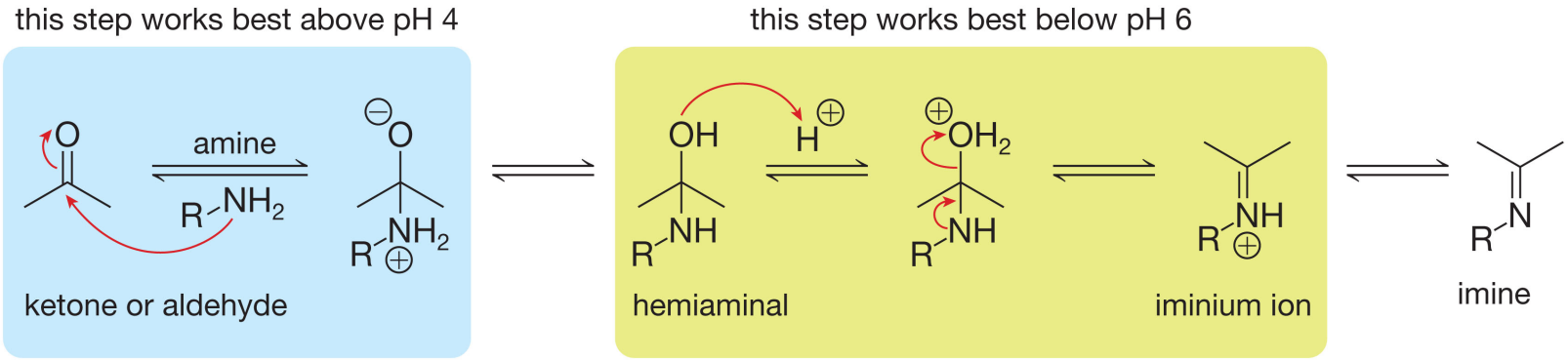
- Mechanistically, the steps of imine formation are the same as those of acetal formation.
- The proton transfer reactions occur between different protons. These steps occur rapidly and simultaneously in order to keep the charges balanced:



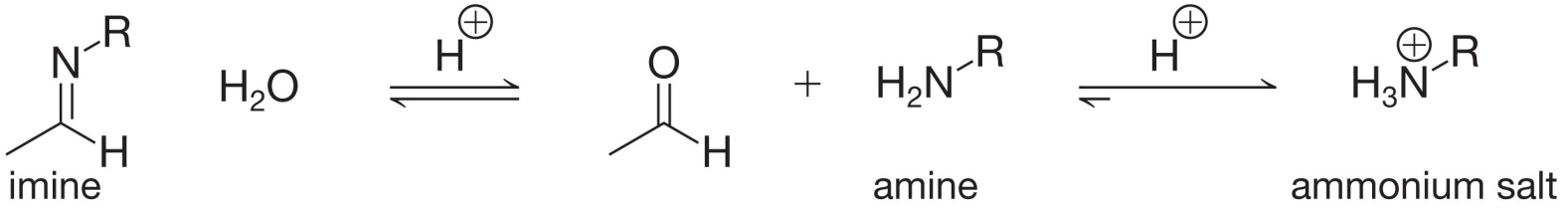
Aminals and Imines



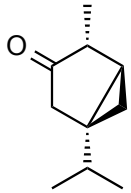
- Because of the different pH requirements of each step in imine formation, the pH of the reaction must be carefully controlled and kept between 4-6.



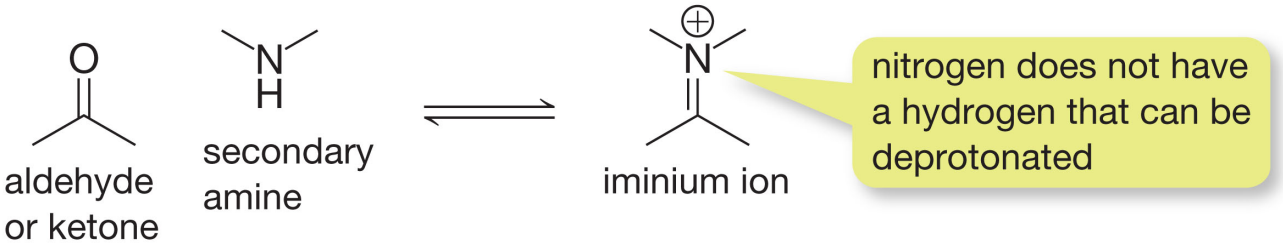
- Acylic imines typically unstable and rapidly hydrolyze.
- Cyclic imines are generally more stable.



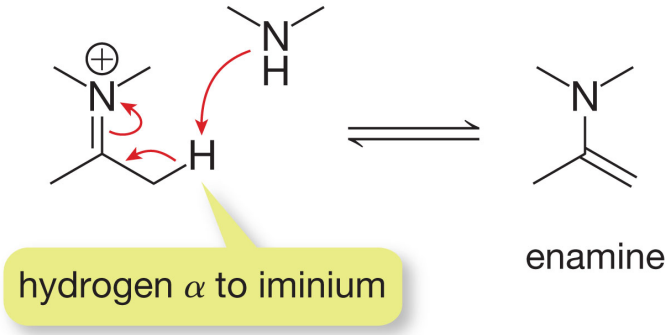
Enamines



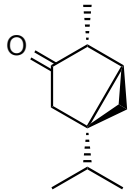
- Iminium ions form when 2° amines react with carbonyl compounds. These ions cannot convert to the imine because there is no proton on the nitrogen atom to remove.



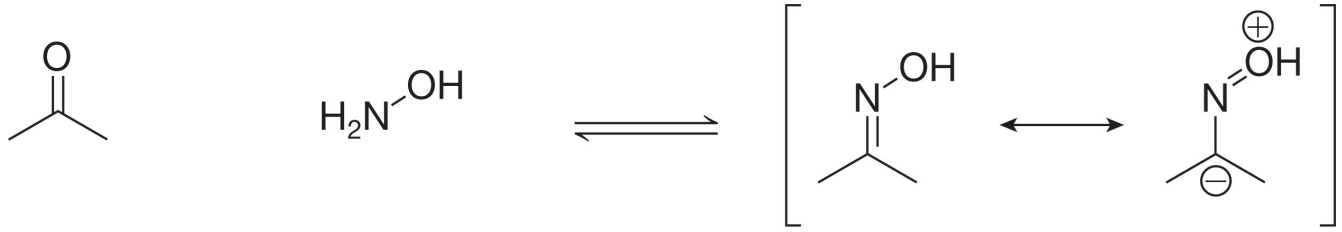
- Typically a proton is removed from an adjacent carbon atom to form an ***enamine***. Enamines are analogous to enols.



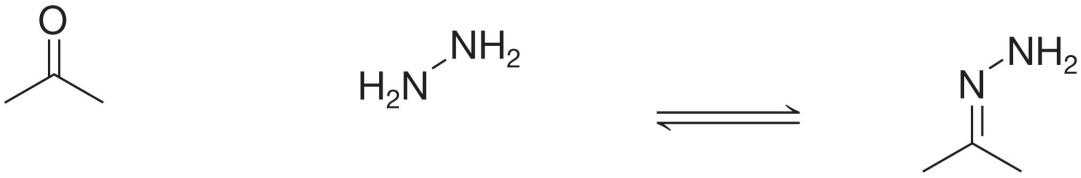
Stable Imines



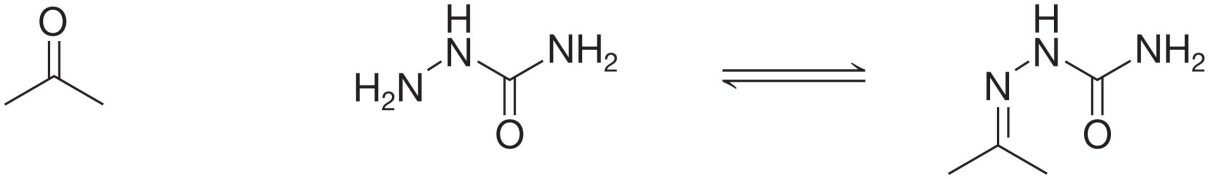
- Nitrogen nucleophiles attached to heteroatoms (N and O) can form especially stable imines.



ketone or aldehyde hydroxylamine oxime

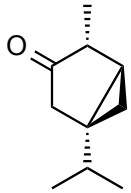


ketone or aldehyde hydrazine hydrazone

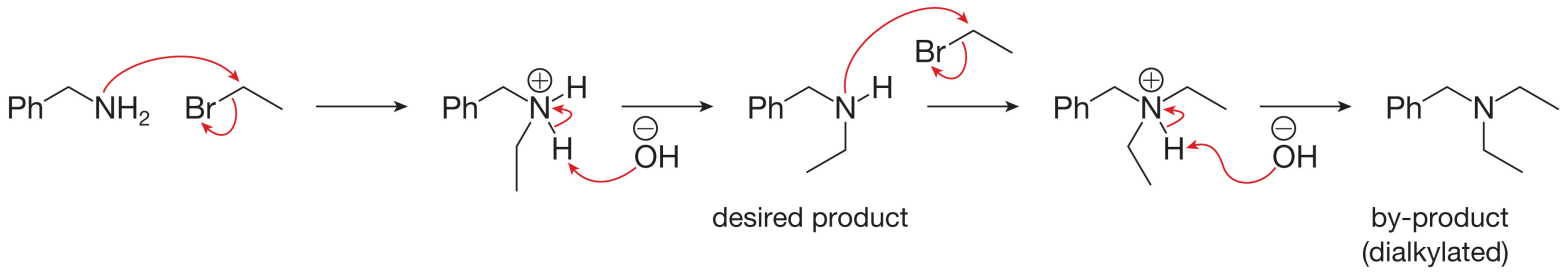


ketone or aldehyde semicarbazide semicarbazone

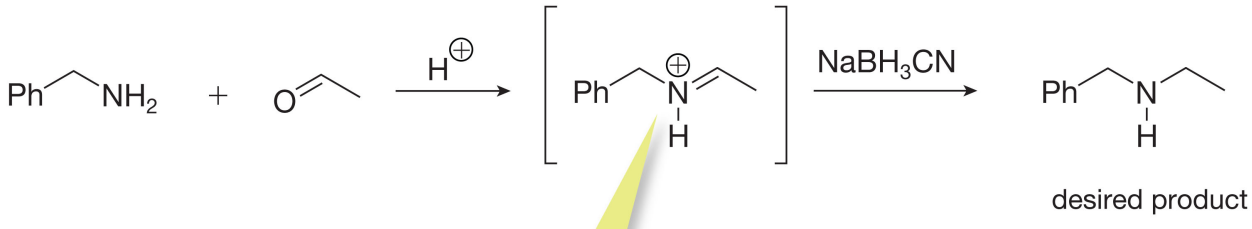
Reductive Amination



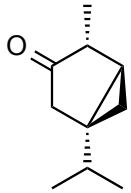
- Using amines in substitution reactions generally leads to complications because amines tend to over alkylate.



- One way to overcome this problem is a strategy called ***reductive amination:*** a reaction sequence that involves imine formation followed be immediate reduction.



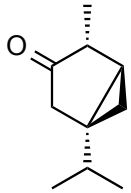
Wolff-Kishner Reduction



- The Wolff-Kishner reduction provides a method to reduce a hydrazone by eliminating nitrogen gas:

- Write a mechanism for the reduction of the hydrazone with base.

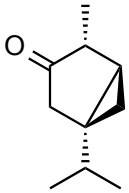
Heterocycle Formation



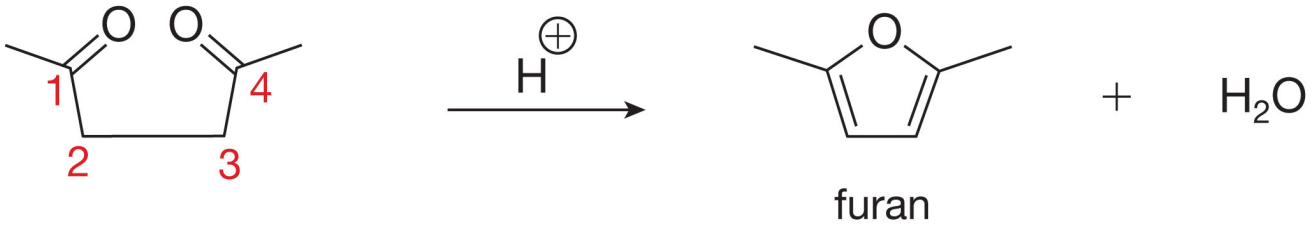
- Heterocycles are rings that contain one or more heteroatoms (atoms other than carbon).
  - e.g.

- Many aromatic heterocycles are prepared using 1,3- and 1,4-dicarbonyl reagents in reactions involving hidden leaving groups.

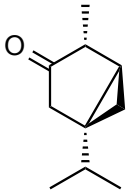
Heterocycle Formation



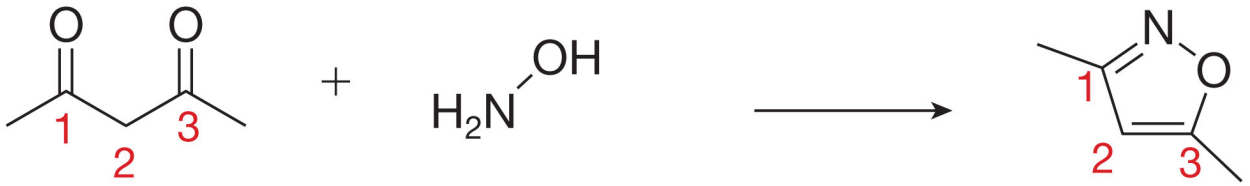
- Propose a mechanism for the following reaction:



Heterocycle Formation

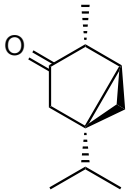


- Propose a mechanism for the following reaction:

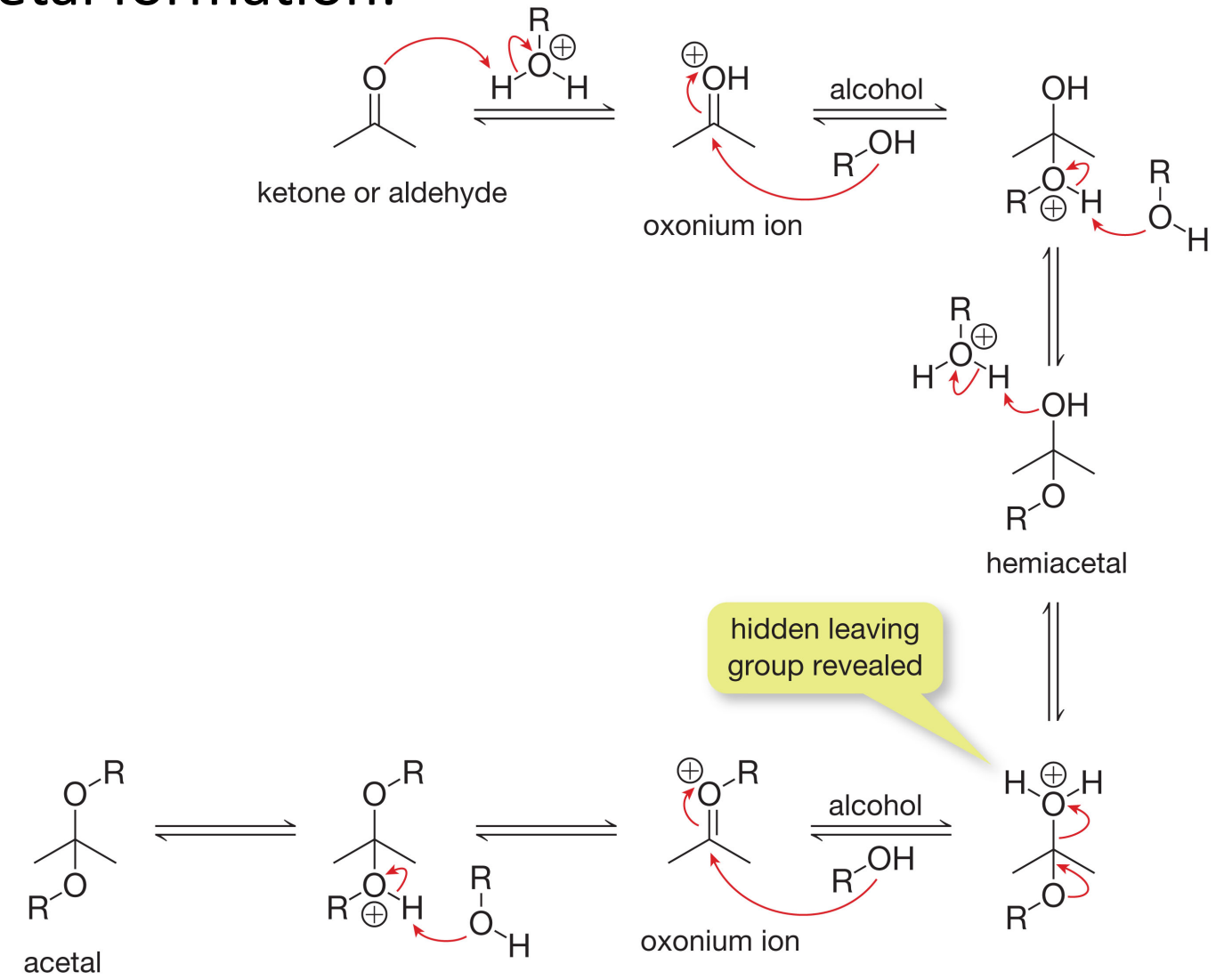


isoxazole

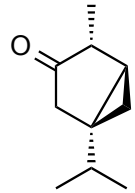
Patterns in Hidden Leaving Groups



- Acetal formation:



Patterns in Hidden Leaving Groups



- Imine formation: