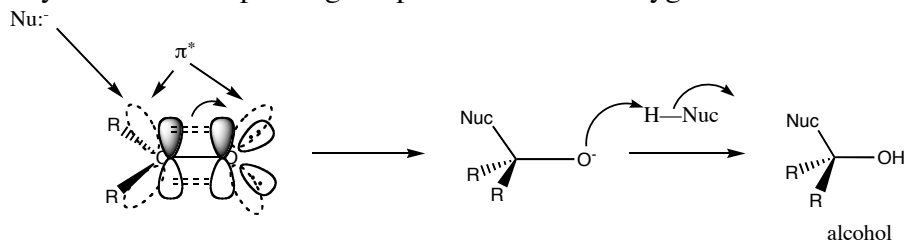


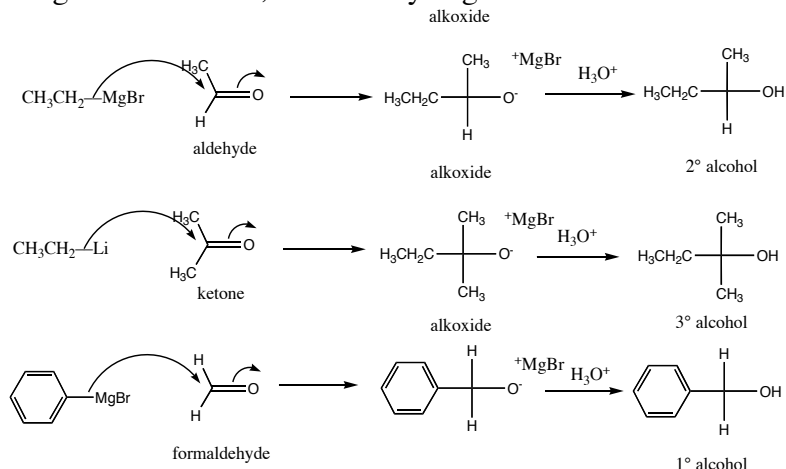
Reactions of Aldehydes and Ketones

- 1. Nucleophilic addition reactions:** nucleophile approaches electrophilic carbon atom and dumps electron density into π^* orbital, causing the pi bond of the carbonyl to break and pushing the pi electrons onto oxygen.

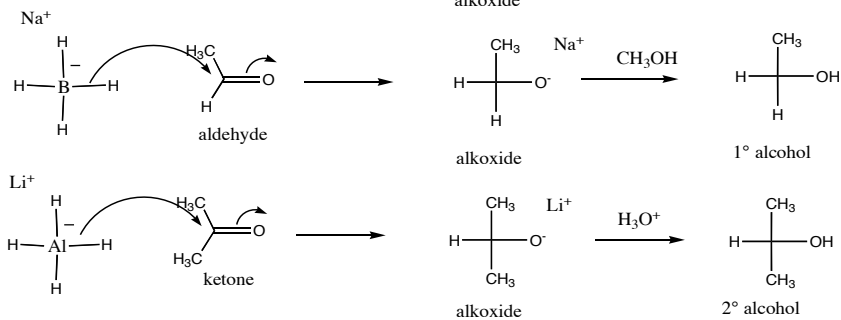


A. Irreversible additions to carbonyls: Strong Nucleophiles

- 1. Grignard and organolithium addition:** Highly basic grignard and organolithium reagents add to carbonyl irreversibly to give alcohols; aldehydes give 2° alcohols and ketones give 3° alcohols; formaldehyde gives a 1° alcohol:



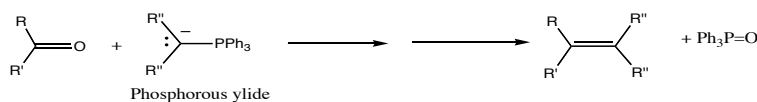
- 2. Hydride reduction:** NaBH_4 and LiAlH_4 are reducing agents which provide hydride as the nucleophile. Aldehydes are reduced to 1° alcohols, ketones to 2° alcohols:



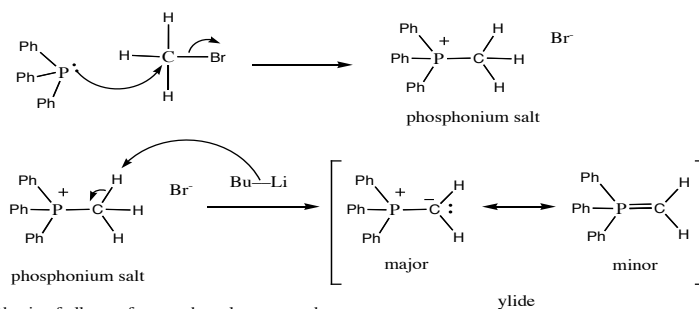
- 3. Wittig reaction:** A ketone or aldehyde reacts with a phosphorous ylide to produce an alkene. This is one of the most useful ways of preparing alkenes. The phosphorous ylide is generated by a two-step process: Triphenyl phosphine reacts with an alkyl halide in $\text{S}_\text{N}2$ fashion to generate a phosphonium salt, and then a strong base (like butyllithium) deprotonates the carbon next to the positively

charged phosphorous to generate the ylide, which is an internal salt. Note that the major resonance form of the ylide is the zwitterion and not the form containing the double bond (which contains a very weak pi bond due to poor P-C p-orbital overlap).

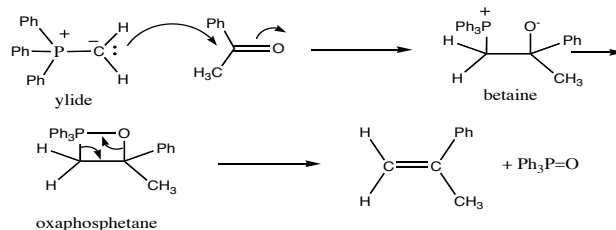
Wittig reaction:



Synthesis of ylides



Synthesis of alkenes from carbonyl compounds:



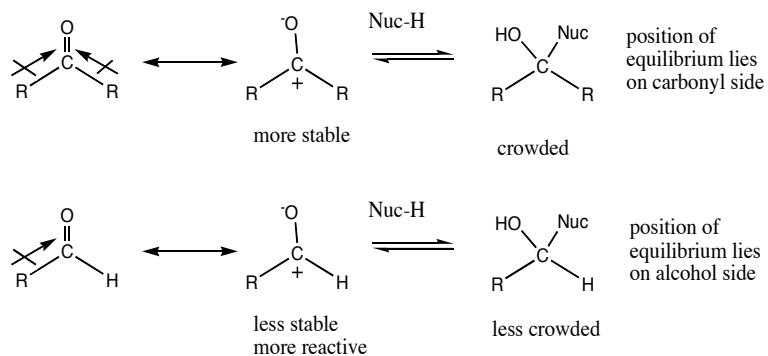
Addition of the ylide to a carbonyl yields a betaine intermediate, which rapidly becomes an oxaphosphetane. Elimination of phosphine oxide provides the alkene, with the driving force being creation of the strong phosphorous-oxygen double bond. This reaction is extremely useful for creating alkenes from a variety of carbonyl compounds

2. Reversible Additions to carbonyls: Weak Nucleophiles

Weak nucleophiles, such as water, alcohols, and amines, require acid or base catalysis to undergo addition to carbonyl compounds

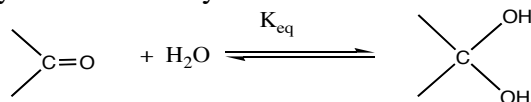
A. Relative Reactivity of carbonyls: Aldehydes are more reactive than ketones on steric and electronic grounds. The aldehyde carbonyl carbon is obviously more sterically accessible than the ketone carbonyl carbon because of the size of a hydrogen atom vs. an alkyl group. Two alkyl groups stabilize the partial positive charge on the ketone carbonyl carbon, whereas only one alkyl group stabilizes the aldehyde carbonyl carbon's partial positive charge. Thus, ketone carbonyl carbons are less electrophilic than aldehyde carbonyl carbons, and ketones in general are more stable and less reactive than aldehydes. Aldehydes are probably the best electrophiles in organic chemistry because of the accessibility (planarity, lack of steric hindrance) and electrophilicity of their carbonyl carbon. Thus, the position of equilibrium of weak nucleophiles adding to carbonyls lies on the reactant side for ketones and on the product side for aldehydes.

Addition of weak nucleophiles to carbonyls:



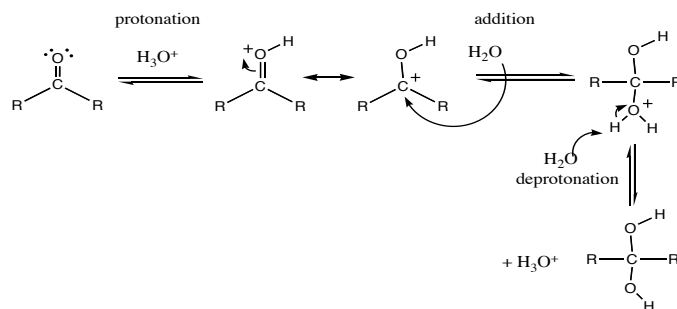
B. Hydration of Ketones and Aldehydes

Addition of water to carbonyls is both acid and base-catalyzed; the position of equilibrium favors the keto form of the carbonyl for ketones. Only formaldehyde and electron-deficient aldehydes favor the hydrate:

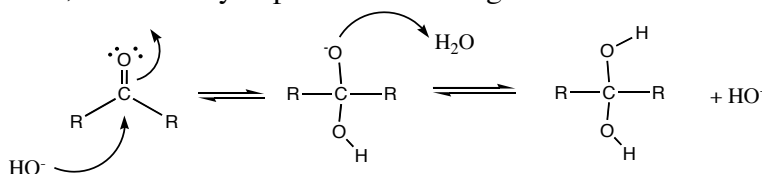


Ketones ($\text{R}_2\text{C}=\text{O}$)	$K_{\text{eq}}(\text{hydration}) = 10^{-4}-10^{-2}$
Aldehydes ($\text{RHC}=\text{O}$)	$K_{\text{eq}}(\text{hydration}) = 1$
formaldehyde ($\text{H}_2\text{C}=\text{O}$)	$K_{\text{eq}}(\text{hydration}) = 40$
chloral ($\text{CCl}_3\text{CH}=\text{O}$)	$K_{\text{eq}}(\text{hydration}) = 500$

The acid-catalyzed mechanism of hydration involves three steps: protonation of the carbonyl oxygen (to increase the electrophilicity of the carbonyl carbon—see resonance forms), addition of water, and deprotonation to yield the hydrate and regenerate the acid catalyst:

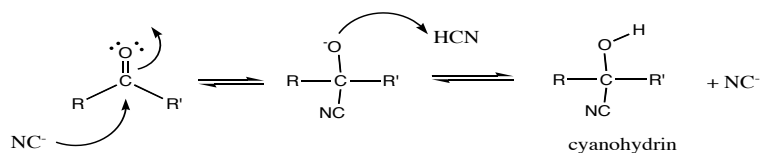


The base-catalyzed mechanism simply involves the addition of the strong base HO^- to the carbonyl carbon, followed by deprotonation to regenerate the base catalyst.



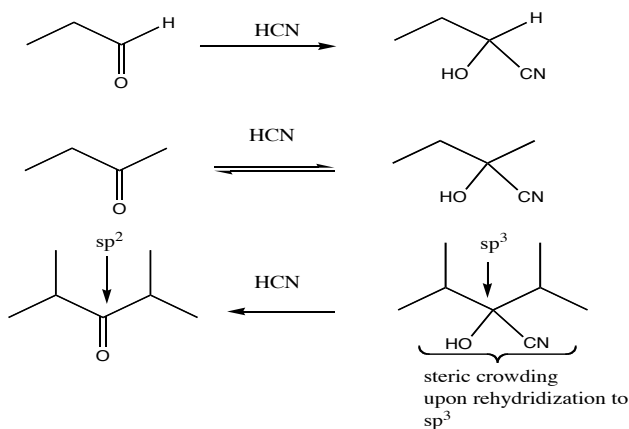
C. Formation of Cyanohydrins

HCN is a weak acid, and thus its conjugate base, NC^- , is strongly basic and nucleophilic. Cyanide ion undergoes nucleophilic addition to carbonyls in the same way as base-catalyzed hydration:

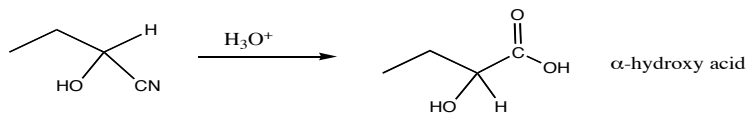


Equilibrium constants:
formaldehyde > aldehydes > ketones

Examples: Steric effect predominates in considerations of equilibrium

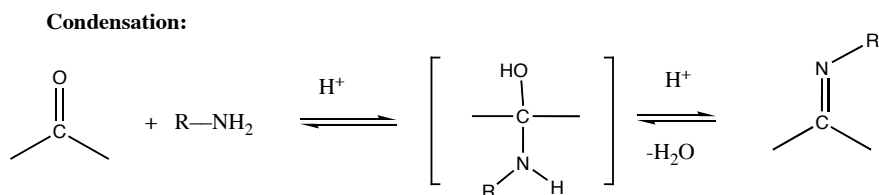


Utility of cyanohydrins: precursors to carboxylic acids via acidic hydrolysis:



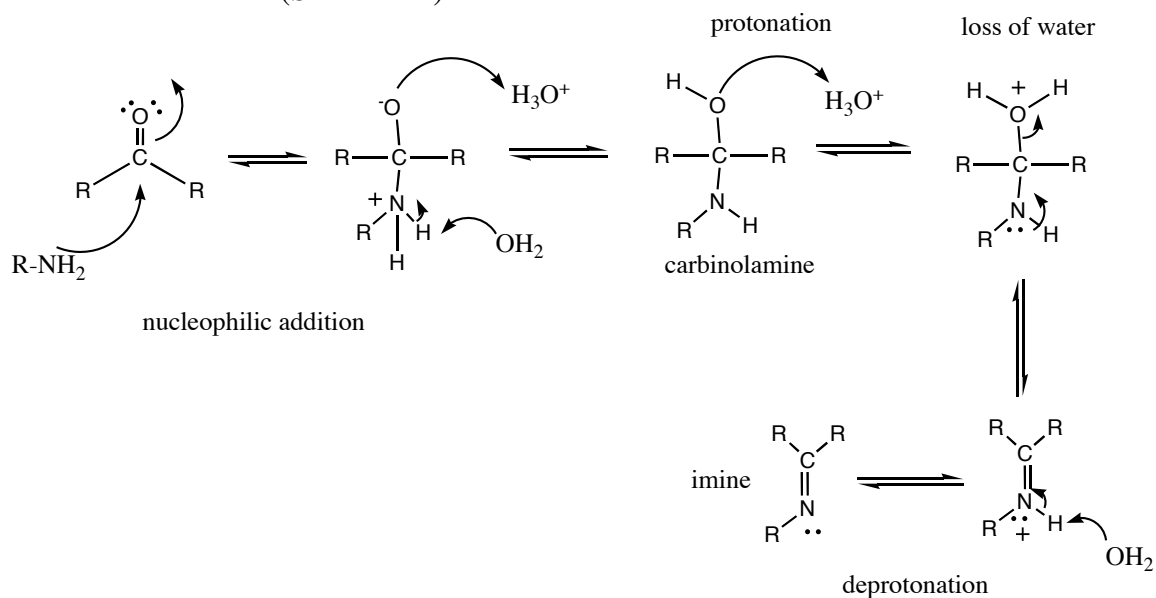
D. Amine Nucleophiles: Formation of imines

Ammonia or primary amines react with ketones and aldehydes to form imines; substituted imines are referred to as Schiff bases. The process of condensation refers to the joining of two molecules with loss of water:

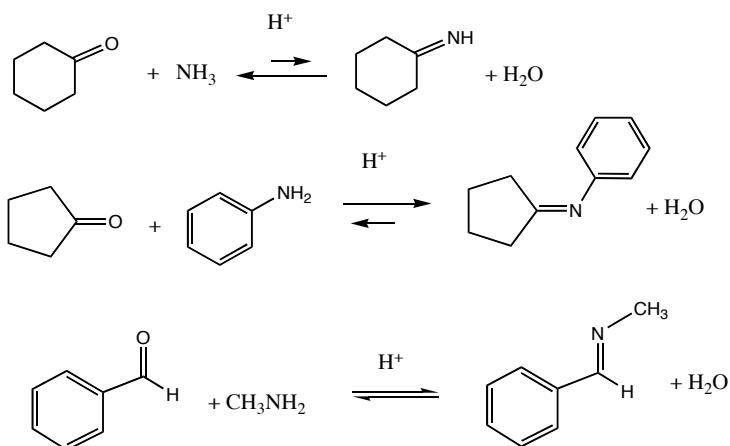


The pH for this reaction is crucial; the condensation proceeds fastest when the pH is 4.5. More acidic conditions lead to amine protonation, which destroys its nucleophilicity; higher pH's inhibit protonation of the intermediate and loss of water (see mechanism). Each step of the reaction is an equilibrium. Removal of water shifts the equilibrium toward the imine product.

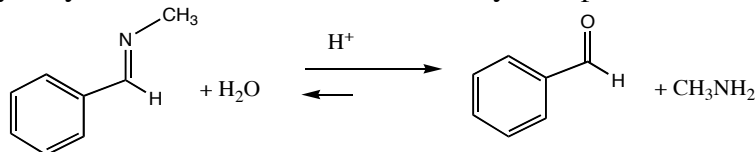
Mechanism of imine (Schiff base) formation



Examples:

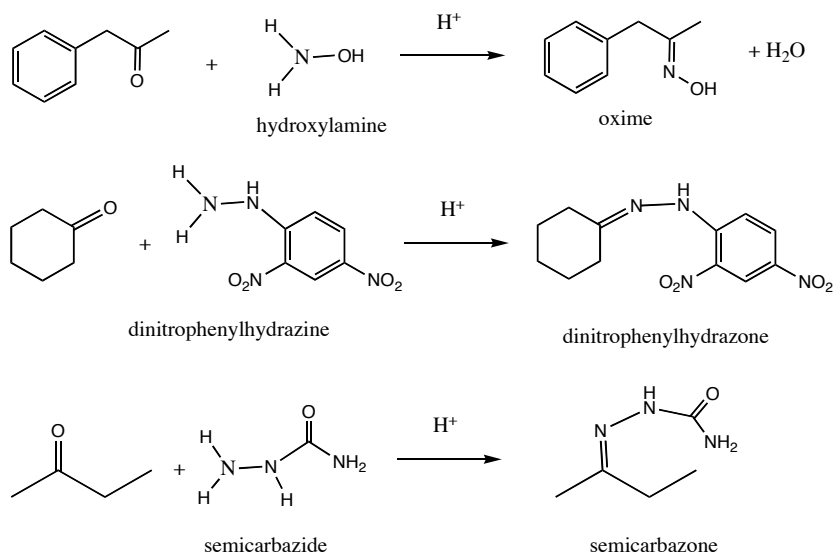


The reaction shown above is completely reversible, and thus adding the imine to excess aqueous acid hydrolyzes the imine back to the carbonyl compound:



note that the mechanism of this process is just the reverse of imine formation (principle of microscopic reversibility)!

F. Oximes, hydrazones, and semicarbazones are formed in a similar fashion, although equilibrium constants for these reactions are generally more favorable than for amines.

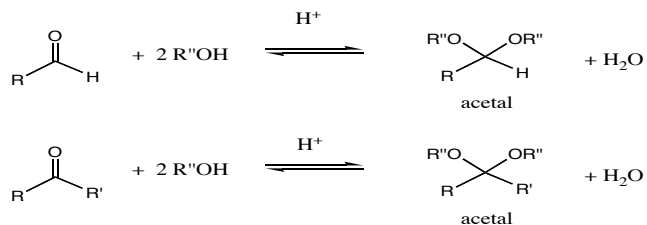


Oximes, hydrazones, semicarbazones are often solid compounds with characteristic melting points, and are useful for characterization and identification of carbonyl compounds, since there are standard tables of melting points compiled for these derivatives.

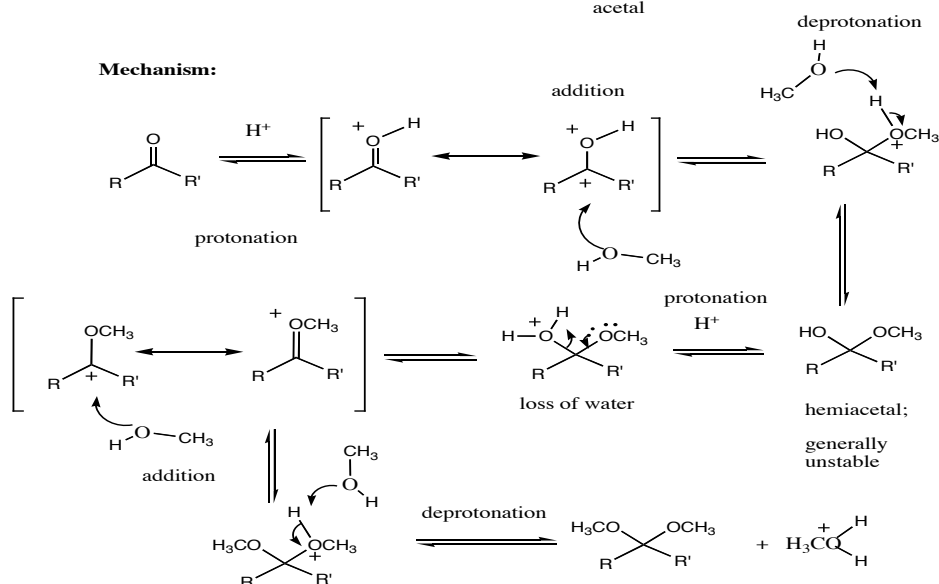
G. Acetal Formation

Acetals result from the acid-catalyzed reaction of ketones and aldehydes with alcohols. The intermediate is called a hemiacetal, and it must be protonated on oxygen for water to leave; a second molecule of alcohol may then attack to form the acetal product.

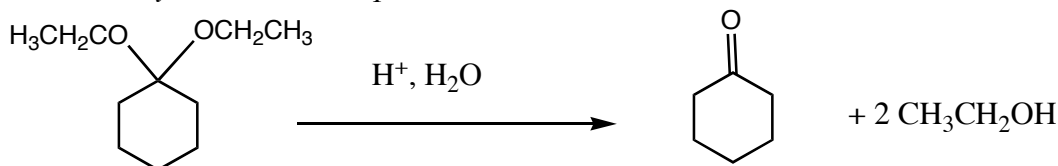
General:



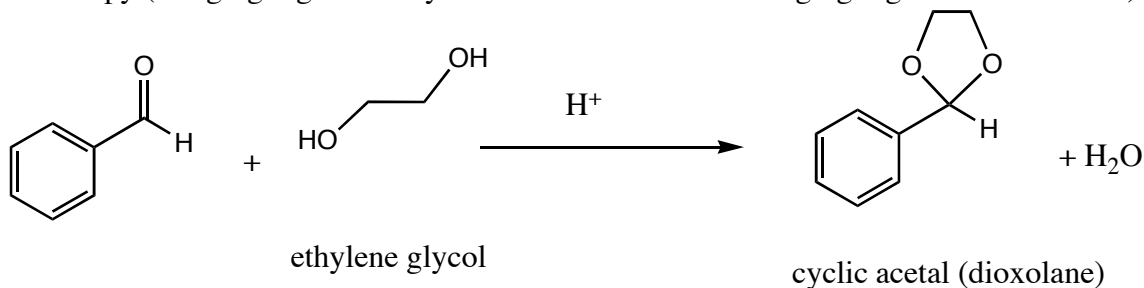
Mechanism:



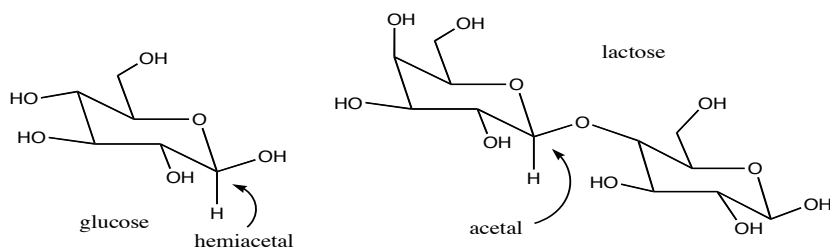
This reaction is completely reversible; for aldehydes, the equilibrium favors the acetal. With hindered aldehydes and ketones, the equilibrium favors the carbonyl. To drive the equilibrium toward acetal formation, the alcohol is used as solvent (Le Chatelier's principle) and water is removed from the reaction mixture as it is formed by distillation (Le Chatelier's principle). *Again, note that acid-catalyzed hydrolysis of acetals is simply the reverse of acetal formation. A large excess of water (solvent) is used in the presence of an acid catalyst to drive the equilibrium in reverse.*



Diols can form cyclic acetals (dioxanes or dioxolanes) with aldehydes and ketones; the equilibrium constants for cyclic acetal formation are more favorable due to less decrease of entropy (bringing together only 2 molecules instead of bringing together 3 molecules):

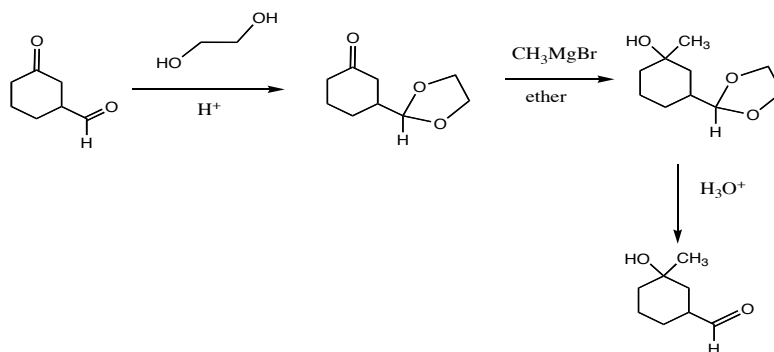
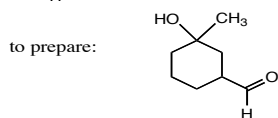
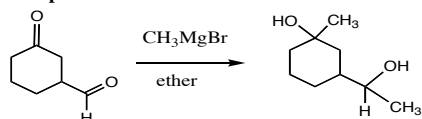


Carbohydrates are naturally occurring acetals and hemiacetals which are very stable:

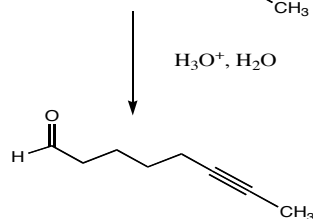
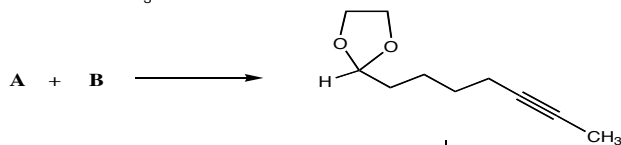
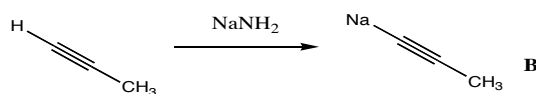
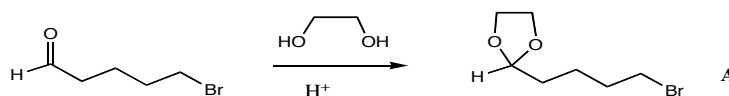
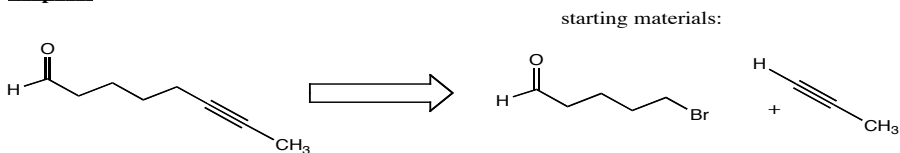


Acetals are protecting groups for carbonyl compounds. Acetals are stable to nucleophilic attack and are impervious to strong bases. Acidic hydrolysis gives the parent carbonyl compound.

Examples:

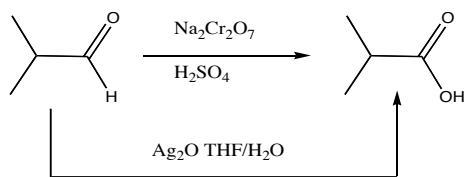


Prepare:

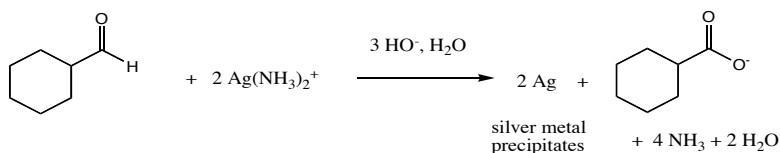


3. Oxidation Reactions

Aldehydes, not ketones, can be oxidized to carboxylic acids. Collins reagent or silver salts may accomplish this oxidation. The Tollens test for aldehydes is a redox process whereby an ammoniacal silver (I) solution is added to an aldehyde; oxidation occurs to generate the carboxylate and a characteristic precipitate of silver metal, which indicates a positive test.

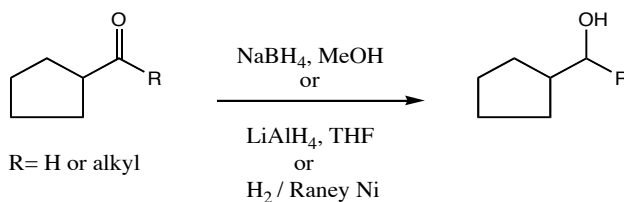


Tollens test for aldehydes:

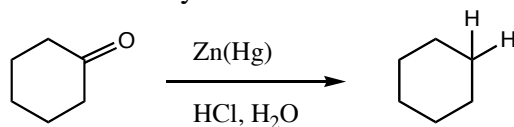


4. Reduction of Aldehydes and Ketones

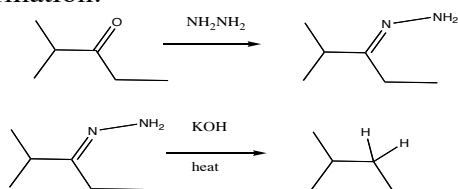
NaBH_4 , LiAlH_4 , and H_2 / Raney Nickel all reduce ketones and aldehydes to their corresponding alcohols:



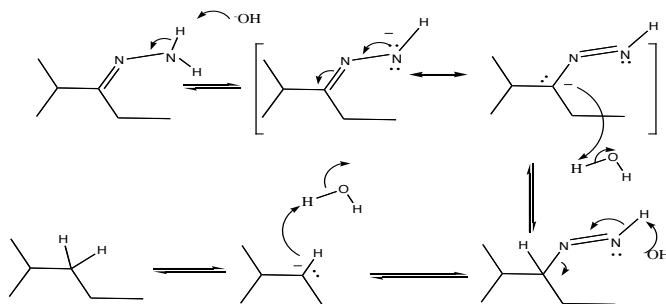
5. Deoxygenation of ketones and aldehydes can occur by three methods: Clemmenson reduction, Wolff-Kishner Reduction, and Raney-Nickel desulfurization of thioacetals. The Clemmenson reduction has already been encountered:



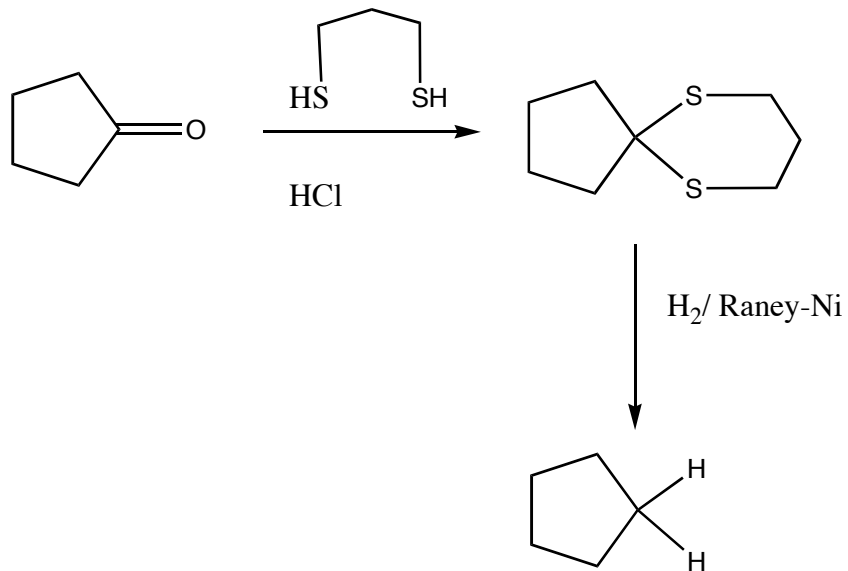
The Wolff-Kishner reduction involves treatment of a hydrazone with the strong base KOH under thermal conditions. The mechanism involves loss of nitrogen gas as a driving force for carbanion formation:



Mechanism:



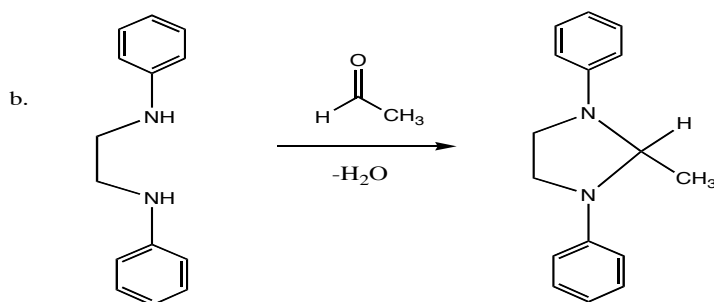
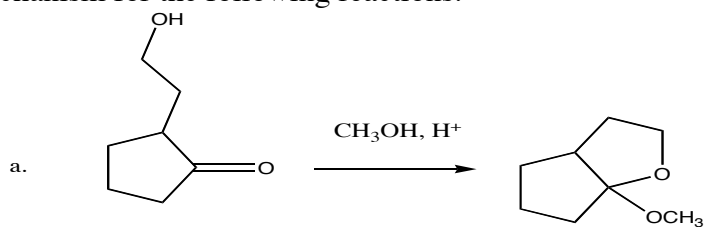
Raney-Nickel reduction of thioacetals leads to overall deoxygenation:



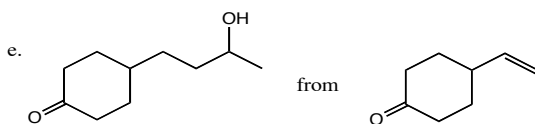
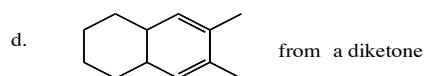
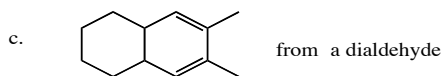
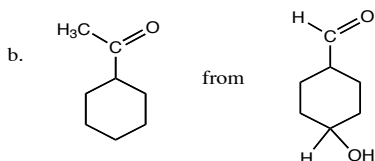
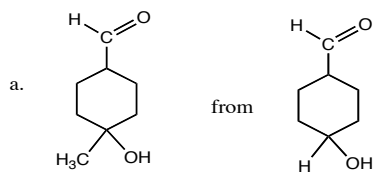
Thioacetals can be reduced in the presence of a Raney-nickel catalyst because of the high affinity of sulfur for nickel.

Additional Problems for Practice:

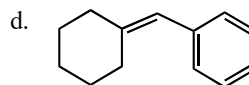
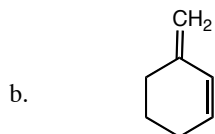
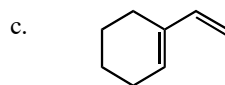
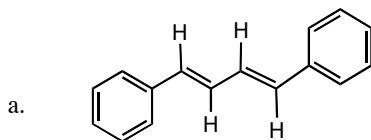
1. Show a mechanism for the following reactions:



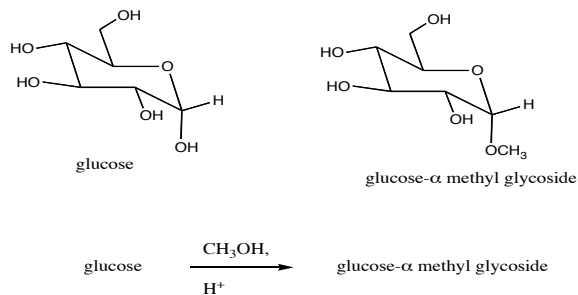
2. Propose efficient syntheses of each of the following molecules, beginning with the indicated starting materials:



3. Show how the Wittig reaction might be used to prepare these alkenes. Identify the alkyl halides and carbonyl components that would be used.



4. Why does glucose react with the Tollens reagent while glucose α -methyl glycoside does not? Draw a mechanism for the transformation of glucose into its α -methyl glycoside in acidic methanol.



5. 6-methyl-5-hepten-2-one is a common constituent of many essential oils, particularly the lemongrass species. How could you synthesize this natural product from 5-hydroxy pentan-2-one:

