#### Addition to carbonyl compounds (skip 8.25, Me3SiCN, 8.27, 8.4.5-7, 8.5, 8.7



1. general properties
   1. significant CO dipole attracts Lewis acids and bases
      1. lone pairs and partial charge at oxygen
      2. polarized  electrons readily displaced toward oxygen
      3. planar electrophile (3 sp2 hybridized orbitals), easy access
      4. addition results in rehybridization (4 sp3 orbitals), brings substituents closer together
   2. unactivated carbonyl reacts with good nucleophiles
      1. RS-, CN-, RLi, RMgBr, RO-, RNH2
      2. Acids activate carbonyl but deactivate basic nucleophile
   3. Lewis acid required for weak nucleophiles
      1. ROH, RSH, arene, PhNH2

 

* + 1. hydrogen bonding in protic solvent weakly activates
  1. Carbonyl is activated by electron withdrawing groups



* 1. deactivated by electron donating groups, bulky groups, resonance
  2. alkyl groups stabilize, and sterically inhibit attack, sp2 to sp3 (see hydration)

1. Hydration – water addition
   1. readily occurs for formaldehyde (reactive carbonyl) but not acetone
   2. steric and electronic effect



* 1. hydration unfavorable for most ketones
  2. hydration is reversible, 18O slow at pH 7, fast with trace acid or base



* 1. occurs in acid or base condition.
  2. RDS is water addition.
  3. GA, GB, SA and SB catalysis.
  4. What is mechanism with base-catalyzed water addition?



1. Alcohol addition is reversible as well: acetal and ketal formation
   1. acetals from aldehydes, ketals from ketones
   2. formation of hemiacetal fast when acid or base catalyzed even if not favorable
      1. hemiacetal is half alcohol, half ether from aldehyde, addition half done
      2. mechanism just like hydration
   3. protonation of OH leads to dehydration and to acetal
   4. geminal oxygen assists loss of water by concerted bond making with bond breaking



* 1. OH is poor leaving group, WHY? protonate first
  2. note interchange between 3 sp2 and 4 sp3 orbitals, preserves octet
  3. acid or base conditions forms hemiacetal, only acid forms the acetal. Why?
  4. drive reaction to completion with water or alcohol
  5. acetal is base stable, requires proton for loss of OR group
     1. ketals normally only form with diols



* 1. acetal and ketal formation good for protecting carbonyl from nucleophiles and strong bases
  2. thioacetals and thioketals also form, not as readily reversible



1. cyanohydrin
   1. quantitative for aldehydes and ketones but not aromatic ketones:
   2. HCN plus catalytic amount of base. show mechanism?



* 1. CN attack rate determining, rate = k[R2CO][CN-]



1. HCl addition
   1. equilibrium poor in water because Cl- is good leaving group
   2. addition works in alcohol where ether is stable, why?



1. metal hydrides
   1. aldehydes and ketone have single H- addition



* 1. esters have two H- addition, loss of OR has assistance from geminal oxygen and AlX3?



* 1. LiAlH4 reacts with aldehydes, ketones, esters, carboxylic acids and amides
  2. Cannot use protic solvent?
  3. NaBH4, reacts with aldehyde and ketones
  4. selectively reduce ketone in presence of amide? Amide in presence of ketone?

1. Meerwein-Pondorf – carbon to carbon H transfer



* 1. metal alkoxide transfer  H
  2. 6-member cyclic transition state
  3. Al is important in bringing together alkoxide and carbonyl
  4. equilibrium determined by reactivity of carbonyl
  5. driven by removal of propanone by distillation

1. Cannizzaro Reaction
   1. disproportionation, two aldehydes, one oxidized, the other reduced



* 1. Rate = k[PhCHO]2[HO-]
  2. Hydride transfer assisted by geminal oxygen
  3. does not work with ketones, alkyl does not migrate

1. amino group addition
   1. acid catalyzed, but not too much, Why?



* 1. low pH (RDS changes with pH)
     1. water elimination is fast (why?)
     2. amino group is protonated and amino addition is rate limiting
  2. high pH
     1. water elimination is slow (why?) and rate limiting
     2. amine addition is faster
  3. imine is more stable than enamine but tends to polymerize
  4. secondary amines can only form enamines (why?)
  5. enamine is formed like an enol
  6. powerful nucleophiles when R = OH, H, alkyl, NH2, NHCONH2, NHPh
     1. i.e. H2NOH, NH3, H2NNH2, etc.

1. Grignard addition



* 1. chelation by Mg important, impedes acid base reaction
  2. acid base reactions compete for carbonyl with -H
  3. reaction with esters?

 What is the product?

* 1. RLi
     1. tend not to undergo acid base reaction, or hydride transfer
     2. prefer 1,2 over 1,4 addition
  2. R2Cd react with ketones/aldehydes but not esters

1. acetylide addition



1. aldol condensation
   1. base catalyzed – enolate formation



* + 1. carbonyl activates -CH, stabilized anion
    2. equilibrium favorable for aldehydes
    3. not favorable for ketones
  1. acid catalyzed – enol formation add proton



* + 1. favorable for aldehydes and ketones
    2. tertiary alcohol products dehydrate, easy formation of tertiary carbocation
  1. crossed aldol
     1. mixed aldehydes gives four possible products if both aldehydes have -H
     2. synthetically useful if one does not have -H



1. Claisen Condensation add a lone pair



* 1. unfavorable leaving group assisted by geminal oxygen
  2. pKa of -keto ester?
  3. equilibrium favors -keto enolate
  4. neutralize to obtain product

1. Dieckmann - intramolecular Claisen condensation (in class)
2. Benzoin condensation
   1. Aromatic aldehydes used to avoid aldol condensation
   2. start with cyanohydrin formation



* 1. Rate = k[ArCHO]2[CN-], rate determining step? nucleophilic catalysis

1. Benzylic acid rearrangement



* 1. migration of Ph to electron deficient atom (carbon)
  2. similar to rearrangement of carbon cation
  3. in PhCOCHO, H instead of Ph migrates

1. Wittig reaction: phosphonium ylide



* 1. Phosphorus like amine, good nucleophile, not as good base (poor overlap)
  2. Phosphorus is polarizable, lone pair deformed by electrophile
  3. formation of strong P=O bond drives reaction
  4. does not react with esters or unconjugated C=C

1. Addition/elimination of acid derivatives: X = direct heteroatom attached: halogen, S, O, N?



* 1. trigonal-tetrahedral interchange, oxygen lone-pair assisted dissociation
  2. concerted SN2 never observed

1. AKA acyl transfer reactions (for example, from X to Y)



* 1. base “catalyzed” hydrolysis of esters follows this mechanism



* 1. no attack on R’, no label in carboxylate: Carbonyl 18O shows up in water. How?
  2. H\* = 112 kJ mol-1, S\* = -109 J K-1 mol-1
  3. OH-, OR-, RNH2 attack ester carbonyl without acid catalysis

1. acid catalyzed hydrolysis:



* 1. 18O in carbonyl, 30 min recover all starting material, missing some 18O, is in the water?
  2. H\* = 75 kJ mol-1, S\* = -105 J K-1 mol-1
  3. normally O-acyl not O-ether cleavage
  4. If R’ makes good carbon cation (tert-butyl or benzyl) carboyxlate leaves and ether oxygen cleaves



* 1. For t-butyl ester: H\* = 112 kJ mol-1, S\* = 55 J K-1 mol-1
  2. if acyl group is bulky, acylium is formed (strongly ionizing solvent required?)



* 1. acid esterification, same mechanism and restrictions



* 1. acid hydrolysis activation parameters indicate two different mechanisms

