Overview of Carbonyl Compounds.

1. Kinds of Carbonyl Compounds.
   a) Aldehydes and ketones. No leaving group attached to carbonyl C. Oxidation state +2.
   b) Carboxylic acids and their derivatives: esters, amides, acyl chlorides, acyl anhydrides. One leaving group attached to carbonyl C. Oxidation state +3. Nitriles are honorary members of the carboxylic acid family, and have much the same reactivity.
   c) Carbonates and their derivatives: urethanes (carbamates), ureas. Two leaving groups attached to carbonyl C. Oxidation state +4.
   d) CO_2.
2. Reactivity of carbonyl compounds.
   a) Basic at O. O reacts with H^+ or other Lewis acids such as BF_3, etc. Not much else.
   b) Electrophilic at carbonyl C. Under basic conditions, reacts as is. Under acidic conditions, O is protonated to give a compound even more electrophilic at C.
   c) Acidic at α-C. Acidic because of electrophilic nature of carbonyl C. Under basic conditions, bases deprotonate immediately to give enolate. Under acidic conditions, protonated on O first, then weak base deprotonates at C to give enol. Both enolate and enol are nucleophilic at C (and O).

Chapter 20. Addition of Hard Nucleophiles to Carbonyl Compounds.

1. Nucleophilic addition to aldehydes and ketones under basic conditions.
   a) Aldehydes and ketones are *electrophilic* at the carbonyl C. $\overset{+}{C}–\overset{-}{O}$ resonance structure.
   b) Nucleophiles (usually anionic, except for amines) add to neutral carbonyl compounds. After the addition, the former carbonyl O is protonated to give the product.
      i) Lone pair nucleophiles. HO^-, RO^-, $RC{\equiv}C^-$, $^-C{\equiv}N$, H_3N, RNH_2.
      ii) Sigma bond nucleophiles. $NaBH_4$ and $LiAlH_4$ (H^- sources), Grignard reagents such as EtMgBr or PhMgBr (R^- sources), organolithium reagents such as CH_3Li.
2. Nucleophilic addition to carboxylic acid derivatives under basic conditions.
   (a) Carboxylic acids and their analogs are electrophilic at the carbonyl C, just like aldehydes and ketones.
   (b) Nucleophiles add to carbonyl C under basic conditions (except for carboxylic acids under basic conditions) to give a *tetrahedral intermediate*.
   (c) After nucleophile adds, though, loss of a leaving group can occur to *re-form the carbonyl!* This is how carboxylic acid derivatives differ from ketones and aldehydes. Overall mechanism is called *addition–elimination.*
3. Reactions of carbonyls with reducing agents.
   a) Aldehyde + $NaBH_4$ or $LiAlH_4$ → 1° alcohol. Work-up necessary.
   b) Ketone + $NaBH_4$ or $LiAlH_4$ → 2° alcohol. Work-up necessary.
   c) Acids + $LiAlH_4$ → 1° alcohols, but hard to do; better to make ester or acyl chloride first.

d) Acyl chloride + $LiAlH_4$ or $NaBH_4$ or DIBAL → 1° alcohols.

e) Esters

i) + $LiAlH_4$ → 1° alcohols. Addition–elimination–addition.

ii) + DIBAL → aldehydes. Addition–elimination.

iii) $NaBH_4$ reacts only slowly with esters, so ketones can be reduced with $NaBH_4$ in presence of esters, but not vice versa

f) Nitriles

i) + DIBAL → aldehyde. Addition.

ii) + $LiAlH_4$ → 1° amines. Addition, then addition again.

iii) $NaBH_4$ does not react with nitriles

g) Amides

i) + $LiAlH_4$ or DIBAL → 1° amines. Addition–elimination–addition.

ii) $NaBH_4$ does not react with amides

4. Reactions of carbonyls with hard nucleophiles.

a) Kinds of hard nucleophiles.

i) Grignard and organolithium reagents made from halides.

ii) Acetylides made by deprotonating alkynes.

b) Aldehyde + RMgBr → 2° alcohol; ketone + RMgBr → 3° alcohol. Work-up necessary. **Another way to make C–C bond!**

c) Esters + RMgBr 3° alcohols. Addition–elimination–addition. **Makes a C–C bond!**

d) CO_2 + RMgBr → carboxylic acid. **Makes a C–C bond!**

e) Nitriles + RMgBr → ketone. Addition. **Makes a C–C bond!**

f) Amides + RMgBr not a useful reaction

g) Acids + RMgBr not a useful reaction

5. Oxidation of aldehydes and ketones.

a) 1° and 2° alcohols to aldehydes and ketones with PCC. RCH_2OH + PCC → RCHO; R_2CHOH + PCC → $R_2C{=}O$. Cr acts as electrophile toward OH, then acts as leaving group in elimination.

b) 1° alcohols and aldehydes to acids with Jones' reagent. RCHO + CrO_3/ H_2SO_4 → RCO_2H. Proceeds through hydrate.

6. Retrosynthetic analysis of alcohols, ketones, carboxylic acids.