

Week 9

Oxidation/Reduction and Organometallics

9.1 Reduction of Carbonyls

3/8:

- In general chemistry, oxidation and reduction referred to the loss and gain of electrons, respectively.
 - In organic chemistry, we think about it differently.
- **Organic oxidation:** Increasing the number of bonds to oxygen or decreasing the number of bonds to hydrogen.
- **Organic reduction:** Decreasing the bonds to oxygen or increasing the bonds to hydrogen.
- Example: Ethene to ethanol is neither an oxidation or reduction since the C–O bond formed is cancelled by the C–H bond formed.
- We now transition to carbonyl chemistry, which will also be really important next quarter.
- **Carbonyl:** Any carbon-oxygen double-bonded system.
 - Important derivatives include aldehydes, ketones, carboxylic acids, esters, and amides.
 - A defining character of carbonyls is their resonance, which we can formalize by representing them as an oxygen anion and a carbocation.
- General reactivity of carbonyls.
 1. Nucleophiles can add to the carbonyl carbon. A slightly acidic aqueous workup from here can form an alcohol.
 2. Oxidation/reduction. Alcohol to carbonyl and vice versa.
- Reduction of aldehydes and ketones.
- General form.
$$\text{RCOR}' \xrightarrow{\text{reagents}} \text{RC(OH)HR}'$$
 - This is a two-step process. We first need a source of H^- , and then an acidic workup.
 - Possible hydride sources are NaBH_4 (a weak source) and LiAlH_4 (a strong source).
 - The acidic workup reagents are always H_3O^+ , H_2O .
- Mechanism.
 - We use the hydride as a nucleophile to attack the carbonyl carbon, and then the acid to protonate the alkoxide intermediate.

- Varying types of carbonyls.
 - Aldehydes and ketones go through the full reaction with both reagents.
 - Esters do not react with NaBH_4 (not powerful enough), but do react with LiAlH_4 . However, they form a primary alcohol in this case.
- Reactivity of carbonyls.

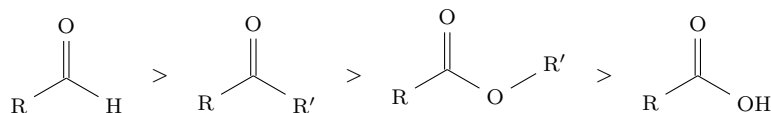
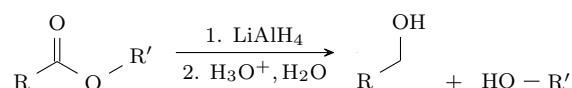


Figure 9.1: Reactivity of carbonyls.

- NaBH_4 stops working after ketones.
- Reduction of esters.
- General form.



- Mechanism.

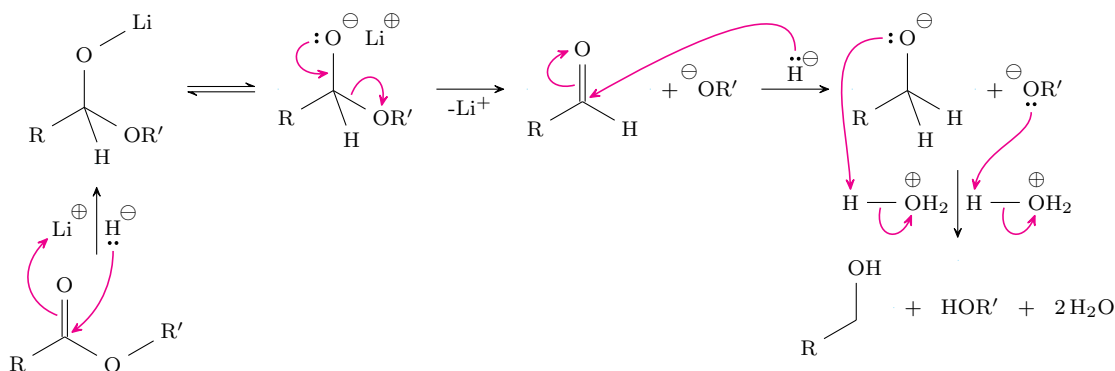
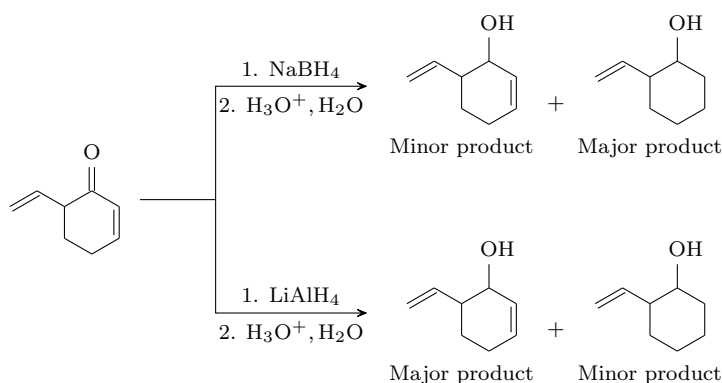


Figure 9.2: Reduction of esters mechanism.

- Positive lithium ions combine with the oxygen of the carbonyl in the first step. This activates the $\text{C}=\text{O}$ bond, making the carbon more electrophilic.
 - Thus, by using LiAlH_4 , we both make the electrophile stronger and introduce a stronger nucleophile.
- **Chemoselective** (reaction): React with one group in the presence of other “related” groups.
 - For example, if we have a ketone and ester in the same molecule, reacting with $\text{NaBH}_4 / \text{H}_3\text{O}^+, \text{H}_2\text{O}$ will yield a chemoselective reduction of the ketone in the presence of an ester. (Reacting with $\text{LiAlH}_4 / \text{H}_3\text{O}^+, \text{H}_2\text{O}$ will alter both groups in a non-chemoselective fashion.)
- Note that we can reduce alkyl halides to hydrocarbons with $\text{LiAlH}_4 / \text{H}_3\text{O}^+, \text{H}_2\text{O}$.
- Reactivity of an α - β unsaturated compound.

- General form.



- With NaBH₄, the major product has been reduced both at the ketone and the alkene.
- With LiAlH₄, the major product has been reduced at the ketone only.
- Note that the alkene that is not conjugated with the carbonyl is untouched.

- Mechanism.

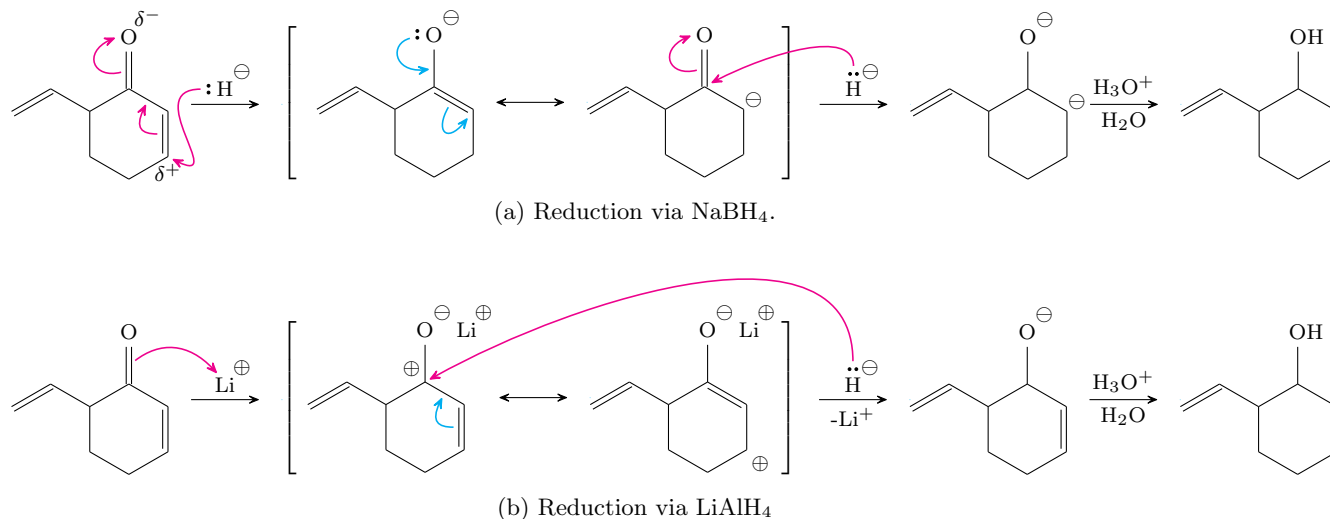


Figure 9.3: Reduction of an α-β unsaturated compound mechanism.

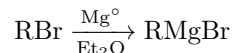
- On Figure 9.3a.

- In the leftmost molecule, resonance draws charge toward the electronegative oxygen, making the carbon at the end of the conjugated chain the most electrophilic site in the molecule. Thus, hydride attacks there.
- The resulting molecule has a ketone as one of its resonance structures, so since ketones are reactive to further hydride attacks, we take this to be the major contributor and react the molecule with hydride again.
- The 2⁻ product can now be reduced with acid and water.

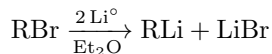
- On Figure 9.3b.

- When Li⁺ bonds to the oxygen, it creates a formal carbocation in the ring system that can be delocalized by resonance.
- However, the carbocation will preferentially exist as a 3° carbocation, so the α-carbon is the most electrophilic site in the molecule in this case, making hydride attack there.

- Grignard reagents provide a new way to form C–C bonds.
- **Grignard reagent:** An alkyl magnesium halide compound.
 - Creates carbanions that are both strong bases and strong nucleophiles.
- Forming Grignard reagents.



- We need an aprotic solvent such as diethyl ether to stabilize the positive Mg.
 - If there are acidic protons present, the Grignard will just deprotonate them.
- Common Grignard reagents.
 - To add phenyl groups to systems, use phenylmagnesium chloride.
 - To add alkenes to systems, use allylmagnesium bromide.
- Making a Grignard reagent basically inverts the reactivity of the precursor: While the precursor alkyl halide is electrophilic, Grignards are very nucleophilic.
- Grignards can be made out of iodides, bromides, and chlorides.
 - Iodides are more reactive than bromides, are more reactive than chlorides.
 - We commonly find them as bromides, though.
- We can use Grignards as nucleophiles in the reduction of formaldehyde.
 - Creates primary alcohols.
- Using an aldehyde makes a secondary alcohol.
- Using a ketone makes a tertiary alcohol.
- Using an ester adds the Grignard twice and kicks out an alcohol.
- Using a carboxylic acid protonates the alkyl part of the Grignard, releases a magnesium salt, and regenerates the carboxylic acid.
- Since Grignards deprotonate any acids present, we can't use them on molecules that contain alcohols, thiols, carboxylic acids, phenols, amines, and acetylenes.
- Organolithium reagents are conceptually identical to Grignards, but even more ionic/reactive.
- Forming organolithium reagents.



- Organolithium reagents are more ionic than Grignards.
 - They are 40% ionic; Grignards are much less.
- Very reactive (nucleophile and base), but very dangerous, too.

9.2 Chapter 12: Alcohols from Carbonyl Compounds

From Solomons et al. [1].

- 3/10:
- Together, reduction of carbonyls and modification by Grignards and organolithium reagents fall under the category of **nucleophilic addition**.
 - There exist lowest and highest oxidation states of an organic compound.

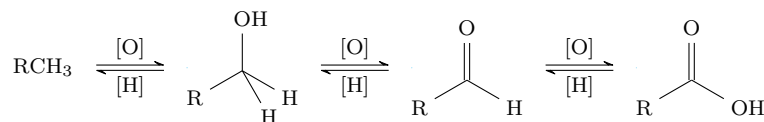
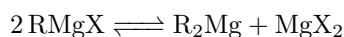


Figure 9.4: Oxidation state spectrum.

- Note that we use [H] to indicate in a general way that a molecule has been reduced and vice versa for [O].
- “Oxidation of an organic compound may be more broadly defined as a reaction that increases its content of any element more electronegative than carbon” [1, p 537].
- LiAlH_4 is also denoted by the acronym LAH.
- Since LAH reacts violently with proton donors to release hydrogen gas, NaBH_4 is a much safer (and therefore preferable) reagent for reducing aldehydes and ketones.
 - Importantly, it can be used along with protic solvents.
 - LAH is typically used in Et_2O . After the reaction is complete, EtAc is added cautiously to decompose remaining LAH and then water to decompose the alumina complex, rendering it inert.
- Aldehydes and ketones can also be reduced via $\text{H}_2 + \text{Pd/C}$ (hydrogen and a metal catalyst) and $\text{Na}^\circ + \text{ROH}$ (sodium metal in an alcohol solvent).
- Almost all types of alkyl halides can be reduced by LiAlH_4 in ether followed by sulfuric acid in water.
 - Note that the proton comes from LiAlH_4 , so we may use LiAlD_4 to replace the halide with deuterium.
- Primary and secondary alcohols can be reduced to carbonyl compounds, but tertiary ones cannot.
 - This is because we need a hydrogen on the α -carbon to lose along with the hydrogen from the alcohol group.
- Oxidation of alcohols.
- **Organometallic compound:** A compound that contains a carbon-metal bond.
- C–M bonds are largely ionic when $\text{M} = \text{Na}, \text{K}$, are largely covalent when $\text{M} = \text{Pb}, \text{Sn}, \text{Hg}, \text{Ti}$, and are in between when $\text{M} = \text{Mg}, \text{Li}$.
- Reactivity of organometallics increases with increasing ionic character.
 - Alkylsodium and alkylpotassium compounds are among the most powerful of bases, but also react explosively with water and burst into flame when exposed to air.
 - The more stable ones may only be volatile in air, but are still highly poisonous (e.g., Et_4Pb , the infamous antiknock compound formerly used in leaded gasoline).
- Most Grignards exist in equilibrium between an alkylmagnesium halide and a dialkyl magnesium.



- Grignards in their alkylmagnesium halide state also form a complex with their aprotic solvent, attracting electron pairs in two partial bonds to their positive magnesium.
- A Grignard reagent behaves like a strong base and reacts to form a weak conjugate acid (such as its protonated or otherwise alkylated form).
- Grignard reagents can even deprotonate terminal alkynes.
 - This serves as a method of production of alkynylmagnesium halides and alkynyllithiums, though.