### Summary of Alcohol Syntheses, Ch. 10 (and Review of Old Ones)

1. 
   - **R-OH** → **R-ONa**
   - Potassium (K) analogous.
   - Key way to convert alcohol to alkoxide, reactive as S_N2 nucleophile and E2 base.

2. 
   - **R-OH** → **R-O-R’**
   - Alkoxide formation-S_N2 route to ether
   - The electrophile R’-X must be S_N2 reactive, preferably 1° with a good leaving group

3. 
   - **R-Br** → **RMgBr**
   - Li is analogous for making RLi, which also act analogously.
   - MgBr is spectator: R O is key.

4. 
   - **H₂C=O** → **H₂C(OH)H**
   - 1 carbon chain extension

5. 
   - **RCHO** → **R-OH**
   - Mech

6. 
   - **R₂CO** → **R₂COH**
   - Mech

7. 
   - **R₂CO₂R** → **R₂CO₂R’**
   - All three R groups can be different.

8. 
   - **R₂O** → **R₂OH**
   - 2-Carbon chain extension
Review Routes to Alcohols

10. \( R = CH_3 \) or \( R = CH_2=CH_2 \)

11. \( R = CH_2CH=CH_2 \)

12. \( R = CH_3 \) or \( R = CH_2=CH_2 \)

13. \( R = CH_3 \) or \( R = CH_2=CH_2 \)
Summary of Mechanisms, Ch. 10

For Test:

1. \[ \text{RCO}_2 \text{H} \xrightarrow{1. \ \Theta} \text{HO}_2 \text{C} \xrightarrow{2. \ H_3O^+} \text{R} \\Theta \text{C} \]

   - aldehyde or ketone
   - \( \Theta \) may be \( \text{RMgBr} \)
   - or \( \text{NaBH}_4 \) or \( \text{LiAlH}_4 \)

   mech:

2. \[ \text{RCO}_2 \text{R'} \xrightarrow{1. \ \Theta} \text{HO}_2 \text{C} \xrightarrow{2. \ H_3O^+} \text{R} \\Theta \text{C} \]

   - esters or acid chlorides
   - \( \Theta \) may be \( \text{RMgBr} \)
   - or \( \text{LiAlH}_4 \)

   mech:

3. \[ \Theta \xrightarrow{1. \ R \Theta} \text{RCH} \xrightarrow{2. \ H_3O^+} \text{RCH}_2 \Theta \]

   mech:
10.1,2 Intro, Classification

“Alcohol”: OH attached to a saturated, sp³, “alkyl” carbon

1°, 2°, 3° Alcohols: based on whether the carbon with the OH is 1°, 2°, or 3°

“Phenol”: OH attached to an aromatic
-Note: phenol, not phenyl

“Enol” or “vinyl alcohol”: OH attached to an alkene

Problem: Classify each of the following either as a phenol, as a carboxylic acid, or as a 1°, 2°, 3°, or vinyl alcohol:

phenol vinyl alcohol 2° alcohol 3° alcohol 1° alcohol carboxylic acid

10.3 Nomenclature
A. IUPAC, when alcohol is priority functional group and is part of the core name: x-alkanol
• Choose longest carbon chain that has the OH attached
• Remember to number!
• The oxygen itself does not count as a number

4,4-dichloro-2-propyl-1-pentanol

4-ethyl-3-heptanol

B. Cycloalkanols: The OH-carbon is automatically Number 1

cis-2-allylcyclohexanol
C. **\textit{x-Alken-\textbf{-z-ol}}.** When an alkene is in the main carbon chain, you need two number descriptors, one for the alkene, the second for the alcohol.
- The OH still dictates the numbering
- The OH number gets moved right before the “ol”
- The alkene number goes in front, in front of the “alken” portion
- Note: you only put the OH number right in front of the “ol” when you have an alkenol (or alkynol)

\[ \text{OH} \quad \text{(E)-4-hexen-2-ol or trans-4-hexen-2-ol} \]

D. **Diols: \textit{x,y-alkanediol}**

\[ \text{OH} \quad \text{1,4-pentanediol} \]

E. Functional Group Priority: \textit{CO}_2\text{H} > \text{C}=\text{O} > \text{OH} > \text{amine} > \text{alkene} > \text{halide}
- When you have more than one functional group, the higher priority dictates the numbering
- **The higher priority is used in the “core name”**
- **The lower priority group may be forced to be named as a substituent**

F. OH as a Substituent: “\textit{Hydroxy}”

\[ \text{3-hydroxycyclohexanone} \]

G. **Common Names: Alkyl alcohol**

<table>
<thead>
<tr>
<th>CH\textsubscript{3}OH</th>
<th>Methyl alcohol</th>
</tr>
</thead>
<tbody>
<tr>
<td>OH</td>
<td>Isopropyl alcohol</td>
</tr>
<tr>
<td>t-butyl alcohol</td>
<td></td>
</tr>
</tbody>
</table>

H. **Substituted Phenols**
- **IUPAC:** use numbers, with OH carbon #1
- **Common:**
  - **Ortho:** 2-position, adjacent
  - **Meta:** 3-position, two carbons away
  - **Para:** 4 position
- **Skill:** be able to use or recognize either system

\[ \begin{array}{ccc}
\text{IUPAC:} & 2\text{-bromophenol} & 3\text{-vinylphenol} & 4\text{-isopropylphenol} \\
\text{Common} & \text{ortho-bromophenol or} & \text{meta-vinylphenol or} & \text{para-isopropylphenol} \\
& \text{o-bromophenol} & \text{m-vinylphenol} & \text{or p-isopropylphenol} \\
\end{array} \]
10.4 Physical Properties: Dominated by H-Bonding

BP: Match the boiling point for the following structures: 35°, 137°, 187°

\[
\begin{align*}
\text{35° (no H-bond)} & & \text{137° (H-bond)} & & \text{187° (more H-bond)} \\
\end{align*}
\]

Water solubility: water solubility decreases as hydrophobic R gets longer
- In general,
  - R ≤ 4 carbons, ROH substantially water soluble
  - R ≥ 5 carbons, ROH minimal water solubility

\[
\begin{align*}
\text{infinite} & & \text{infinite} & & \text{9.1g/100mL} & & \text{2.7g/100mL} & & \text{0.6g/100mL} & & \text{0.1g/100mL} \\
\end{align*}
\]

10.5 Commercially Important Alcohols
- Toxic: All alcohols are “toxic” if swallowed in sufficient quantities

<table>
<thead>
<tr>
<th>CH₃OH</th>
<th>OH</th>
<th>OH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cheap</td>
<td>200 mL (7 oz) (\rightarrow) death</td>
<td>Rubbing alcohol</td>
</tr>
<tr>
<td>Solvent</td>
<td>Least toxic alcohol</td>
<td>100 mL (\rightarrow) death</td>
</tr>
<tr>
<td>Fuel</td>
<td>Alcoholic beverages</td>
<td>Kills germs on skin, but not absorbed</td>
</tr>
<tr>
<td>100 mL (\rightarrow) death</td>
<td>Fermentation</td>
<td></td>
</tr>
<tr>
<td>15 mL (\rightarrow) blindness</td>
<td>Solvent</td>
<td></td>
</tr>
</tbody>
</table>

10.6 Acidity of Alcohols and Phenols
A. Alcohols are weak acids \(\rightarrow\) can be ionized by stronger bases

\[
\text{ROH} + \text{B}^- \rightarrow \text{RO}^- + \text{BH}
\]
- goes to the right (alkoxide) only if \(\text{RO}^-\) is more stable than \(\text{B}^-\)
- ex. \(\text{NH}_2^-\), \(\text{CH}_3^+\)
- ex. If a less stable oxygen anion can convert to a more stable oxygen anion
B. Acidity Table

<table>
<thead>
<tr>
<th>Class</th>
<th>Structure</th>
<th>$K_a$</th>
<th>Acid Strength</th>
<th>Anion</th>
<th>Base Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong Acids</td>
<td>H-Cl</td>
<td>$10^2$</td>
<td>Most</td>
<td>Cl$^-$</td>
<td>Least</td>
</tr>
<tr>
<td>Carboxylic Acid</td>
<td>R$_2$COOH</td>
<td>$10^{-5}$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenol</td>
<td>![苯酚结构式]</td>
<td>$10^{-10}$</td>
<td></td>
<td>![苯酚阴离子]</td>
<td></td>
</tr>
<tr>
<td>Water</td>
<td>H$_2$O</td>
<td>$10^{-16}$</td>
<td></td>
<td>HO$^-$</td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>ROH</td>
<td>$10^{-18}$</td>
<td></td>
<td>RO$^-$</td>
<td></td>
</tr>
<tr>
<td>Amine (N-H)</td>
<td>RNH$_2$</td>
<td>$10^{-33}$</td>
<td>Least</td>
<td>RNH$^-$</td>
<td></td>
</tr>
<tr>
<td>Alkane (C-H)</td>
<td>RCH$_3$</td>
<td>$10^{-50}$</td>
<td>Least</td>
<td>RCH$_2$$^-$</td>
<td>Most</td>
</tr>
</tbody>
</table>

Notes/skills:
1. Be able to rank acidity.
2. Memorize/understand neutral OH acidity ranking: $RCO_2H > H_2O > ROH$
   - Reason: resonance stabilization of the anion
3. Predict deprotonation (acid/base) reactions
   - Any weak acid **will be** deprotonated by a **stronger base (lower on table)**
   - Any weak acid **will not be** deprotonated by a **weaker base (higher on table)**
4. Predict ether/water extraction problems
   - If an organic chemical is neutral and stays neutral, it will stay in ether layer
   - If an organic chemical is ionized (by an acid-base reaction), it will extract into the aqueous layer

Problems
1. Draw arrow to show whether equilibrium favors products or reactants. (Why?)

   ![化学反应图](image)

   **Resonance Stability**

2. Which of the following will deprotonate methanol?

<table>
<thead>
<tr>
<th></th>
<th>H$_2$O</th>
<th>CH$_3$CO$_2$Na</th>
<th>PhONa</th>
<th>NaOH</th>
<th>NaNH$_2$</th>
<th>CH$_3$MgBr</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

An acid (left side) will only be deprotonated by an anion/base that is **lower** on the right side.
3. When the following are dissolved in ether and then treated with NaOH/water, which would extract out of the ether layer into the water layer?

![Chemical structures](image)

Yes, converts to anion, water soluble

Yes, converts to anion, water soluble

No, stays neutral, stays in ether

10.6B Formation of Sodium, Potassium Alkoxides; 2-Step Conversion of Alcohols into Ethers via the Alkoxides

<table>
<thead>
<tr>
<th></th>
<th>R-OH + Na→ R-ONa</th>
<th>R-O⁻</th>
<th>R-OH + K→ R-OK</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Potassium (K) analogous.
- Key way to convert alcohol to alkoxide, reactive as $S_N$2 nucleophile and E2 base.

<table>
<thead>
<tr>
<th></th>
<th>R-OH</th>
<th>1. Na→ R-O⁻-R'</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td></td>
<td>2. R'-X</td>
</tr>
</tbody>
</table>

- Alkoxide formation-$S_N$2 route to ether
- The electrophile R'-X must be $S_N$2 reactive, preferably 1° with a good leaving group

Reaction 1: Key source of nucleophilic/basic alkoxides

![Chemical structures](image)

10.7 Synthesis of Alcohols: Review: See p. 2, from Alkyl Halides ($S_N$2) and Alkenes
10.8 Organometallics: RM (M = Metal) = R $\ominus$ M $\oplus$

3. R−Br $\xrightarrow{\text{Mg}}$ R\text{Mg}Br  "Grignard Reagent"
\[\text{R−Br} \xrightarrow{2\text{Li}} \text{RLi + LiBr}\]
-Li is analogous for making RLi, which also act analogously.
-MgBr is spectator: R $\ominus$ is key.

1. We will focus on the magnesium reagents RMgBr
2. RMgBr = “Grignard Reagents” (Victor Grignard)
3. Key: This is the way to make R $\ominus$, strong nucleophiles/bases
4. RMgBr are formed via redox reaction.
   - Mg gives up two electrons, is oxidized
   - Bromine is reduced to bromide anion
   - Carbon is reduced to carbanion

5. The formation of Grignard Reagents is completely general for all R-Halides:
   - $3^\circ$, $2^\circ$, and $1^\circ$ alkyl halides all work well
   - Aryl and Vinyl halides as well as alkyl halides work well
   - RCl, RBr, and RI all work well
   - For class, we will normally use bromides, due to synthetic accessibility

6. **View as carbanions: RMgBr = R $\ominus$ Super Strong Bases and Nucleophiles**
   - The counterion metal is a spectator
   - Stability-reactivity principle: very unstable $\rightarrow$ very reactive
   - This great reactivity is very useful (as nucleophile)
   - This great reactivity (as base) has implication for proper technical use (see following)

7. Solvent and handling: Grignard reactants RMgBr must be made, stored, and handled in special solvents under special conditions:
   - No water allowed
     - R $\ominus$ + H$_2$O $\rightarrow$ R-H + HO $\ominus$ Destroys carbanion
   - No alcohol or amines or acids allowed either, or carbanion will just deprotonate them too
   - If any chemicals with carbonyls are present, they too will react with the carbanion by nucleophile/electrophile reaction

8. Two perspectives for dealing with organometallics in general and RMgBr in particular
   - Mechanistic Thinking: R $\ominus$
   - Predict-the-product thinking: R-MgBr: easier to see source and substitution product.
10.9 Addition of RMgBr to Carbonyl Compounds: Alcohols are Produced

Exothermic Addition of Carbon or Hydrogen Anions:
- σ bond (made) stronger than π bond (broken)
- oxygen anion more stable than carbanion

Carbonyl is strongly electrophile
- much stronger even than a 1° alkyl iodide!
  1. Breakable π bond
  2. Carbonyl polarity

Additions of Grignard Reagents to Carbonyl Compounds

From Carbonyl’s Perspective

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>R'OH</td>
</tr>
<tr>
<td>formaldehyde</td>
<td>R'OH</td>
</tr>
<tr>
<td>1. R'MgBr</td>
<td></td>
</tr>
<tr>
<td>2. H₂O⁺</td>
<td></td>
</tr>
</tbody>
</table>

From Grignard’s Perspective

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>R'(CHO)</td>
</tr>
<tr>
<td>R'MgBr</td>
<td></td>
</tr>
<tr>
<td>1. RCHO</td>
<td></td>
</tr>
<tr>
<td>2. H₂O⁺</td>
<td></td>
</tr>
</tbody>
</table>

Pattern:
1. After reaction, the original carbonyl carbon will have one and only one C-O single bond
2. For formaldehyde, aldehydes, and ketones, one R group adds (reactions 4-6)
3. For esters or carbonyl chlorides (“acid chlorides”), two R groups add
   - Replace not only the carbonyl p-bond, but also the “extra” C-O or C-Cl single bond
4. Product output:
   - Formaldehyde (2 H’s) → 1° alcohol
   - Aldehyde (1 H) → 2° alcohol
   - Ketone (0 H) → 3° alcohol. No need for all 3 attachments to be the same.
   - Ester (0 H) → 3° alcohol. At least two common attachments at end.
Predicting Grignard Reaction Products

1. From carbonyl perspective:
   - The carbanion R’ adds to the carbonyl carbon
   - The carbonyl =O gets replaced by –OH
   - For formaldehyde, aldehydes, and ketones: the two attachments on the original carbonyl carbon remain attached as spectators
   - For esters or acid chlorides: the one non-heteroatom attachment on the original carbonyl carbon remain attached as spectators.
     - The “extra” heteroatom gets replaced by a second carbanion R’

2. From Grignard perspective:
   - Where R-MgBr begins, R-C-OH ends.
     - In other words, the MgBr gets replaced by the carbonyl carbon

Note: Be sure that in the product, no carbon has more than one C-O bond

Draw products from the following reactions.

1. \( \text{PhMgBr} \rightarrow \text{PhOH} \)

2. \( \text{MgBr} \rightarrow \text{H}_3\text{O}^+ \)

3. \( \text{MgBr} \rightarrow \text{H}_3\text{O}^+ \)

4. \( \text{excess CH}_3\text{MgBr} \rightarrow \text{OH} \)

5. \( \text{Mg} \rightarrow \text{PhCH}_3 \)

6. \( \text{Br} \rightarrow \text{H}_2\text{C} = \text{O} \)
10.9E Grignard Reaction with Ethylene Oxide (Simplest Epoxide)

Notes
1. Results in a 1º Alcohol
2. **Predicting product:** Two carbons end up in between the carbanion R' and the OH
3. Ethylene oxide and formaldehyde are complementary Grignard acceptors leading to 1º alcohols
   - Ethylene oxide extends the carbon chain by two (relative to the original RMgBr)
   - Formaldehyde extends the carbon chain by one (relative to the original RMgBr)
4. 2-Carbon ethylene oxide and 2-carbon ethanal give different products
   - Ethylene oxide → the OH is 1º and the OH is two carbons removed from the carbanion R
   - Ethanal → the OH is 2º and the OH and carbanion R are both connected to the same carbon

Draw products from the following reactions.
Reaction Mechanisms for Grignard Reactions

Formaldehyde, Aldehyde, or Ketone as Carbonyl Compound (Reactions 4, 5, and 6)

1. Two simple steps:
   a. **Addition**
   b. **Protonation**

2. Timing:
   a. The carbanion is added first, at one step in time, under strongly anionic conditions
   b. Later acid is added, in a second laboratory step. This provides a cationic environment

3. \( \text{RMgBr} = \text{R-MgBr} = \text{R}^\ominus \) carbanion
   a. The \( \text{MgBr} \) stuff is spectator, doesn’t need to be drawn in
   b. Ignore in mechanisms
   c. In reality, it actually does play a nontrivial role, but we’ll save that for grad school!

Draw mechanisms for the following reactions:

1. [Mechanism 1]
   1. \( \text{PhMgBr} \)
   2. \( \text{H}_3\text{O}^+ \)

2. [Mechanism 2]
   1. \( \text{MgBr} \)
   2. \( \text{H}_3\text{O}^+ \)
Esters or Acid Chlorides: More Complex, Needs to Explain Two Additions and More Bond Breakings

1. Four Step Mechanism:
   a. Addition
   b. Elimination
   c. Addition
   d. Protonation

2. Timing:
   a. The carbanion is added first, at one point in time, under strongly anionic conditions
      - The first three steps all occur under these anionic conditions
   b. Acid is only added much later, in a second laboratory step. This gives a cationic environment.
   c. Why don’t you just protonate after the first step?
      - There is no proton source available, and the elimination proceeds instead!

3. What if I add only one RMgBr?

   After Grignard reaction, **never** show any products in which a carbon has more than one oxygen

Why? Kinetics and Reactivity. **MEMORIZE.**

- Large differences in reactivity, with ketone > ester
- Elimination step 2 is also very fast
- Thus, under the anionic conditions, the addition is the slow step
  - After it does happen, elimination and another addition happens bang-bang.
Draw Mechanism:

**Cyclic Ester:** The O-Carbonyl single bond breaks, but the other C-O single bond does **not** break - the result is formation of a dialcohol.

Draw product and mechanism for the following:

**Ethylene Oxide Mechanism**

Draw product and mechanism for the following:
More Grignard Practice. Including polyfunctional Molecules: (Know relative reactivity)

1. \( \text{PhMgBr (excess)} \)
   \( \rightarrow \)
   \( \text{Ph} \)
   \( \text{Ph} \)
   \( \text{OH} \)
   \( \text{OH} \)
   \( \text{H}_3\text{O}^+ \)

2. \( \text{PhMgBr (1.0 equivalent)} \)
   \( \rightarrow \)
   \( \text{H}_3\text{CO} \)
   \( \text{Ph} \)

3. \( \text{PhMgBr (1.0 equivalent)} \)
   \( \rightarrow \)
   \( \text{H}_3\text{CO} \)
   \( \text{OH} \)
   \( \text{via} \)
   \( \text{H}_3\text{CO} \)
   \( \text{O}^- \)

4. \( \text{PhMgBr} \)
   \( \rightarrow \)
   \( \text{Ph} \)
   \( \text{H} \)

5. \( \text{BrMg} \)
   \( \rightarrow \)
   \( \text{H}_3\text{O}^+ \)

6. \( \text{Br} \)
   \( \rightarrow \)
   \( \text{H}_2\text{C}=\text{O} \)
   \( \text{OH} \)

7. \( \text{CH}_3\text{MgBr (excess)} \)
   \( \rightarrow \)
   \( \text{OH} \)

8. \( \text{BrMg} \)
   \( \rightarrow \)
   \( \text{OH} \)
Grignards in Synthesis: Provide Precursors.

**Think backwards from Targets to Reactants.**
- Identify possible Grignards and Grignard acceptors
- **Pattern:**
  - 3° alcohol, all three attachments different \(\leftrightarrow\) Ketone Precursor
  - 3° alcohol, two (or more) of the attachments identical \(\leftrightarrow\) Ester
  - 2° alcohol \(\leftrightarrow\) Aldehyde
  - 1° alcohol \(\leftrightarrow\) Formaldehyde or ethylene oxide

\[
\text{MgBr}_2 + \text{CH}_3\text{CO}_2\text{H} \rightarrow \text{MgBr}_2 + \text{CH}_3\text{CO}_2\text{H}
\]

\[
\text{H}_3\text{C-MgBr} + \text{CH}_3\text{CO}_2\text{H} \rightarrow \text{H}_3\text{C-MgBr} + \text{CH}_3\text{CO}_2\text{H}
\]

\[
\text{Ph-MgBr} + \text{CH}_3\text{CO}_2\text{H} \rightarrow \text{Ph-MgBr} + \text{CH}_3\text{CO}_2\text{H}
\]

\[
\text{Ph-MgBr} + \text{CH}_3\text{CO}_2\text{H} \rightarrow \text{Ph-MgBr} + \text{CH}_3\text{CO}_2\text{H}
\]

\[
\text{Ph-MgBr} + \text{CH}_3\text{CO}_2\text{H} \rightarrow \text{Ph-MgBr} + \text{CH}_3\text{CO}_2\text{H}
\]

Oops. The carbonyl to the left should be formaldehyde, with two hydrogen, not acetone, with two methyls as shown.
Provide Reagents for the Following Transformations. You may use whatever reagents, including ketones or aldehydes or Grignards or esters, that you need.

- Key: Try to identify key C-C connection in the product that wasn’t present to start with
- Try to identify the where the reactant carbons are in the final product
- Numbering your carbon chains is very helpful.
- Usually best to work backwards from the product

a. 

\[
\text{Ph-Br} \xrightarrow{1. \text{ Mg}} \xrightarrow{2. \text{ H}} \xrightarrow{3. \text{ H}_3O^+} \text{Ph-CH(OH)}
\]

b. 

\[
\xrightarrow{1. \text{ HBr (no peroxides)}} \xrightarrow{2. \text{ Mg}} \xrightarrow{3. \text{ H}_2\text{C=O}} \xrightarrow{4. \text{ H}_3\text{O}^+} \text{CH(OH)CH(OH)}
\]

c. 

\[
\xrightarrow{1. \text{ HBr, peroxides}} \xrightarrow{2. \text{ Mg}} \xrightarrow{3. \text{ PhCO}_2\text{CH}_3} \xrightarrow{4. \text{ H}_3\text{O}^+} \text{Ph-CH(OH)}
\]

d. 

\[
\text{CH-Br} \xrightarrow{1. \text{ Mg}} \xrightarrow{2. \text{ ethylene oxide}} \xrightarrow{3. \text{ H}_3\text{O}^+} \text{CH(OH)}
\]

e. 

\[
\text{CH-Br} \xrightarrow{1. \text{ Mg}} \xrightarrow{2. \text{ H}} \xrightarrow{3. \text{ H}_3\text{O}^+} \text{CH(OH)}
\]


Combining Grignard Reactions with Other Reactions

\[
\text{HOCH}_2\text{CH}=\text{CH}_2 + \text{PhMgBr} \xrightarrow{1.\ H_2O^+} \text{HOCH}_2\text{CH}=(\text{CH}_2\text{Ph})
\]

b. 1. Mg
2. \(\text{H}_2\text{O}^+\)
3. \(\text{H}_2\text{SO}_4\)
4. \(\text{H}_2\text{SO}_4\)
5. \(\text{BH}_3\cdot\text{THF}\)
6. \(\text{NaOH}\cdot\text{H}_2\text{O}_2\)

10.10 Restrictions on Grignard Reactions

- \(\text{RMgBr} = \text{R} \bigodot\) carbanion, highly unstable, highly reactive.
- Unstable in the presence of:
  1. OH’s (get proton transfer reaction)
  2. Carbonyls (get Grignard-type nucleophilic addition)

1. Solvent limitations. \(\text{RMgBr}\) cannot be formed and used in the presence of:
   - \(\text{H}_2\text{O}\)
   - \(\text{ROH}\)
   - Any solvent with a C=O

   Which Solvents (if any)
   Would be \textbf{OK} for Handling \(\text{RMgBr}\)?:
   ![Solvents](image)

2. Substrate limitations. Any organohalide that also contains an OH or C=O bond can’t be converted into a useful \(\text{RMgBr}\), because it will self-destruct.

   Which substrates could be converted into \(\text{RMgBr}\), and subsequently reacted with \(\text{CH}_3\text{CHO}\)?
   ![Substrates](image)

3. Atmosphere/Glassware/Storage limitations. Make, store, and use in:
   - water-free dried glassware
   - moisture-free atmosphere. (Dried air, or else under nitrogen or argon atmosphere)
   - When stored for extended periods, must have very good seals so that no air can leak in.
10.11 Alcohols by Reduction of Carbonyls: $\text{H}^-$ Addition

9. Aldehyde

$\text{RCHO} \quad \text{NaBH}_4 \quad \text{CH}_3\text{OH} \quad 1. \text{LiAlH}_4 \quad \text{CH}_3\text{OH} \quad 2. \text{H}_3\text{O}^+$

Mech

10. Ketone

$\text{RC(OCR') \quad \text{NaBH}_4 \quad \text{CH}_3\text{OH} \quad 1. \text{LiAlH}_4 \quad \text{CH}_3\text{OH} \quad 2. \text{H}_3\text{O}^+$

Mech

11. Ester

$\text{RC(OCR') \quad 1. \text{LiAlH}_4 \quad \text{CH}_3\text{OH} \quad 2. \text{H}_3\text{O}^+$

Mech

$\text{NaBH}_4 \quad \text{will not react with esters}$

Mechanism

Aldehydes and Ketones

$$\text{O} \quad \text{NaBH}_4 \quad \text{or ketone} \quad \text{CH}_3\text{OH} \quad 1. \text{LiAlH}_4 \quad \text{CH}_3\text{OH} \quad 2. \text{H}_3\text{O}^+$$

NaBH$_4$ = $\text{H}^-$

LiAlH$_4$ = $\text{H}^-$

Esters

$$\text{O} \quad \text{Addition} \quad \text{OR'} \quad \text{fast} \quad \text{Elimination} \quad \text{OR'} \quad \text{Addition} \quad \text{Fast} \quad \text{OR''}$$

Cyclic Esters

$$\text{O} \quad \text{Addition} \quad \text{H}^-$

Elimination

Add

Double Protonation
Notes:
- Mechanisms are exactly like with Grignard reactions
- LiAlH₄ and NaBH₄ function as hydride anions H⁻
- For mechanisms, just draw H⁻ rather than trying to involve the Li and Al and Na and B...

\[
\text{NaBH}_4 = \text{Na}^+ \xrightarrow{\text{H}^\text{-}} \text{B}^{-} + \text{H}_2 \quad \text{LiAlH}_4 = \text{Li}^+ \xrightarrow{\text{H}^\text{-}} \text{Al}^{-} + \text{H}_2
\]

- Boron is one row higher than aluminum, and in keeping with normal periodic patterns is more electronegative
  - Because boron is more electronegative, the BH₄⁻ anion is more stable, and less reactive.
    - The boron holds the H⁻ more tightly.
  - Aluminum being less electronegative doesn’t attract and hold the H⁻ as well, and thus is considerably more reactive.

<table>
<thead>
<tr>
<th>LiAlH₄</th>
<th>Aldehydes</th>
<th>Ketones</th>
<th>Esters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
</tbody>
</table>

NaBH₄

| Yes    | Yes       | No       |

**LiAlH₄ is much stronger, NaBH₄ much weaker**

1. LiAlH₄ is strong enough to react with esters, NaBH₄ isn’t
2. **Selective reduction**: if both an ester and an aldehyde/ketone are present:
   - LiAlH₄ reduces both
   - NaBH₄ selectively reduces the aldehyde/ketone but leaves the ester untouched
3. **LiAlH₄ is strong enough to react with and be destroyed by water or alcohol; NaBH₄ isn’t**
   \[
   \text{LiAlH}_4 + \text{H}_2\text{O} \rightarrow \text{H}_2(\text{gas}) + \text{LiOH} + \text{AlH}_3 + \text{heat}
   \]
   a. As a result, LiAlH₄ is harder to use and store
   b. Acid has to be added in a subsequent step with the LiAlH₄; (thus, 2-step recipe)
   c. NaBH₄ can be run in alcohol solvent which serves as a proton source for protonating alkoxide
   d. Solvent restrictions, glassware must be dry, wet air must be excluded, etc.
   e. Because NaBH₄ is stable to water, it’s easier to handle in air, easier to store, much easier to work with
   f. **Default**: for a simple aldehyde or ketone reduction, normally use NaBH₄ because it’s so much easier
4. LiAlH₄ is strong enough to react with esters, NaBH₄ isn’t
Draw the products for the following reactions.

1. \( \text{CH}_3\text{COO} \xrightarrow{1. \text{LiAlH}_4} \text{OH} \xrightarrow{2. \text{H}_3\text{O}^+} \text{OH} \)

2. \( \text{CH}_3\text{COO} \xrightarrow{\text{NaBH}_4} \text{OH} \xrightarrow{\text{H}_2\text{O}} \text{CH}_3\text{CO}_2\text{H} \)

3. \( \text{C}_8\text{H}_8 \xrightarrow{1. \text{LiAlH}_4} \text{OH} \xrightarrow{2. \text{H}_3\text{O}^+} \text{H}_2\text{C}_8\text{H}_6\text{OH} \)

4. \( \text{PhCH} \xrightarrow{1. \text{LiAlH}_4} \text{OH} \xrightarrow{2. \text{H}_3\text{O}^+} \text{PhCH}_2\text{OH} \)

5. \( \text{C}_8\text{H}_8\text{O}_2 \xrightarrow{1. \text{LiAlH}_4} \text{OH} \xrightarrow{2. \text{H}_3\text{O}^+} \text{PhCH}_2\text{OH} \)

Draw the mechanism for the following reaction.

6. \( \text{PhCH} \xrightarrow{\text{NaBH}_4} \text{OH} \xrightarrow{\text{CH}_3\text{OH}} \text{PhCH}_2\text{OH} \)

7. \( \text{PhCH} \xrightarrow{1. \text{LiAlH}_4} \text{OH} \xrightarrow{2. \text{H}_3\text{O}^+} \text{H}_2\text{C}_8\text{H}_6\text{OH} \)