Review Chapter 19
This chapter highlights solutions to synthetic problems with new reactions

Reduction of C=O to CH₂
Carbonyl compounds can be used to build (via carbonyl, α or β carbon) new carbon-carbon bonds. Once the framework is built, the C=O may no longer be needed.

Three reactions can be used to replace ketone or aldehyde C=O with -CH₂-. The choice depends on the tolerance of other functional groups in the molecule.

To draw a Wolff-Kishner, Clemmensen or Raney-Nickel product:

Simply erase the =O!

Practice:

a.

b.

c.
**Protection of alcohols**

Alcohols are a common organic functional group. The prevalence of this group is in no small part due to its myriad of reaction pathways. Alcohols are weak acids, weak bases, nucleophiles and electrophiles. Sometimes it is necessary to cover over this reactivity to react a group elsewhere in the molecule. Simply converting the alcohols to the far less reactive ethers may seem a reasonable solution, but to convert the ether back to the alcohol requires strongly acidic conditions.

The text reviews five methods for the protection of alcohols as ethers. In class we highlighted the two most useful. In each case the alcohol is converted to an ether, but the nature of the group allows a highly effective and selective reagent for removal.

**Protection with MOM-Cl**

Protection

\[
\begin{align*}
\text{Protection} & : OH & \xrightarrow{1) \text{NaH or NaNH}_2} & \text{Reaction} & \xrightarrow{} & \text{Deprotection} & \xrightarrow{\text{H}_2\text{O} \text{ dil. H}_3\text{O}^+} & \text{OH} \\
& & & & & & & + \text{formaldehyde} \\
& & & & & & & + \text{methanol}
\end{align*}
\]

**Protection with TBDMS-Cl**

Protection

\[
\begin{align*}
\text{Protection} & : OH & \xrightarrow{\text{TBDMS-Cl imidazole}} & \text{Reaction} & \xrightarrow{} & \text{Deprotection} & \xrightarrow{Bu_4\text{N}^+\text{F}^-} & \text{OH} \\
& & & & & & & + \text{TBDMS-F}
\end{align*}
\]

Practice:

a. Show the protection of the following alcohol with MOM, react the ketone with PhMgBr, and deprotect and to afford final product:

\[
\begin{align*}
\text{OH} & & \xrightarrow{\text{1) NaH or NaNH}_2} & \text{Reaction} & \xrightarrow{} & \text{Deprotection} & \xrightarrow{\text{H}_2\text{O} \text{ dil. H}_3\text{O}^+} & \text{OH} \\
& & & & & & & + \text{formaldehyde} \\
& & & & & & & + \text{methanol}
\end{align*}
\]

b. Show the protection of the following alcohol with TBDMS-Cl, react the nitrile with LiAlH4, and deprotect to afford the final product:

\[
\begin{align*}
\text{OH} & & \xrightarrow{\text{TBDMS-Cl imidazole}} & \text{Reaction} & \xrightarrow{} & \text{Deprotection} & \xrightarrow{Bu_4\text{N}^+\text{F}^-} & \text{OH} \\
& & & & & & & + \text{TBDMS-F}
\end{align*}
\]
**Catalytic Hydrogenation**

The conversion of π-bonds to σ-bonds is a highly useful synthetic procedure where H₂ is added across the π-bond. Although this conversion is exothermic, a catalyst is required to disrupt the di-hydrogen bond. By increasing hydrogen pressure, reaction temperature and the catalyst type, virtually all π-systems can be reduced.

Catalytic hydrogenation is stereospecific and occurs *syn*. In the case of chain compounds, this will not matter. In the case of substituted cycloalkanes, stereochemistry must be represented properly.

Alkynes under excess hydrogen and catalyst hydrogenate twice to give alkane. If a Lindlar catalyst is used, hydrogenation is stopped at the addition of one equivalent of H₂; a *cis*-alkene results. If a *trans*-alkene is desired, a non-catalytic addition of hydrogen can be used where the alkyne is treated with Na°/NH₃ [1].

To draw the product of catalytic hydrogenation

For alkenes, alkynes, carbonyls and nitriles simply erase π-bonds and replace with hydrogens

For cycloalkenes, add H₂ in a *syn* manner in place of π-bond

For alkenes with Lindlar, replace triple bond with *cis*-double bond. With Na°/NH₃ replace with *trans*-double bond.
Practice:

a. \[
\text{\begin{tikzpicture}
\node (m1) at (0,0) {\text{H}_2};
\node (m2) at (1,0) {Pt/C};
\end{tikzpicture}}
\]

b. \[
\text{\begin{tikzpicture}
\node (m1) at (0,0) {\text{H}_2};
\node (m2) at (1,0) {Pt/C};
\end{tikzpicture}}
\]

c. \[
\text{\begin{tikzpicture}
\node (m1) at (0,0) {3 \text{ atm H}_2};
\node (m2) at (1,0) {Rh};
\end{tikzpicture}}
\]

d. \[
\text{\begin{tikzpicture}
\node (m1) at (0,0) {75 \text{ atm H}_2};
\node (m2) at (1,0) {Ni, 80 \degree C};
\end{tikzpicture}}
\]

e. \[
\text{\begin{tikzpicture}
\node (m1) at (0,0) {160 \text{ atm H}_2};
\node (m2) at (1,0) {Pt, 135 \degree C};
\end{tikzpicture}}
\]

f. \[
\text{\begin{tikzpicture}
\node (m1) at (0,0) {\text{H}_2};
\node (m2) at (1,0) {Pt, 25 \degree C};
\end{tikzpicture}}
\]

g. \[
\text{\begin{tikzpicture}
\node (m1) at (0,0) {\text{H}_2};
\node (m2) at (1,0) {Pt, 25 \degree C};
\end{tikzpicture}}
\]

h. \[
\text{\begin{tikzpicture}
\node (m1) at (0,0) {\text{H}_2};
\node (m2) at (1,0) {\text{Lindlar}};
\end{tikzpicture}}
\]

i. \[
\text{\begin{tikzpicture}
\node (m1) at (0,0) {Na};
\node (m2) at (1,0) {\text{NH}_3, -33 \degree C};
\end{tikzpicture}}
\]
Oxidation of Alcohols to Carbonyl Compounds

The oxidation of alcohols to carbonyl compounds is the reverse of nucleophilic addition (below). Most oxidants accept the alcohol oxygen as a nucleophile followed by loss of the acidic hydrogen. The process is completed by an E2-like elimination of hydrogen from the proto-carbonyl carbon in concert with formation of the C=O π-bond and reductive loss of the leaving group.

**General Mechanism**

\[
\begin{align*}
\text{Ox} & \quad \text{B} : \quad \text{Ox}^- \quad \text{B} - \text{H} \\
\end{align*}
\]

**Chromic Acid**

Scope and Limitations

1. As a hydrogen atom is needed for the elimination step, 3° alcohols do not oxidize to carbonyl compounds.
2. Normally 1° alcohols are converted to aldehydes and 2° alcohols to ketones.
3. However, in the presence of water, aldehydes form hydrates that undergo more rapid oxidation than the starting 1° alcohols. Thus with \( \text{CrO}_3/\text{H}_2\text{SO}_4, \text{Na}_2\text{CrO}_7, \text{K}_2\text{CrO}_7, \text{H}_2\text{CrO}_4 \), 1° alcohols are converted to carboxylic acids.

4. This over-oxidation is avoided with the use of PCC.
5. Aldehydes treated with with \( \text{CrO}_3/\text{H}_2\text{SO}_4, \text{Na}_2\text{CrO}_7, \text{K}_2\text{CrO}_7, \text{H}_2\text{CrO}_4 \) are converted to carboxylic acids.
Practice:

a.  
\[
\begin{array}{c}
\text{OH} \\
\text{CrO}_3 \\
\text{H}_2\text{SO}_4, \text{H}_2\text{O}
\end{array}
\]

b.  
\[
\begin{array}{c}
\text{OH} \\
\text{Na}_2\text{Cr}_2\text{O}_7 \\
\text{H}_2\text{SO}_4, \text{H}_2\text{O}
\end{array}
\]

c.  
\[
\begin{array}{c}
\text{OH} \\
\text{H}_2\text{CrO}_4 \\
\text{H}_2\text{O}
\end{array}
\]

d.  
\[
\begin{array}{c}
\text{OH} \\
\text{H}_2\text{CrO}_4 \\
\text{H}_2\text{O}
\end{array}
\]

e.  
\[
\begin{array}{c}
\text{OH} \\
\text{PCC} \\
\text{CH}_2\text{Cl}_2
\end{array}
\]

f.  
\[
\begin{array}{c}
\text{OH} \\
\text{Na}_2\text{Cr}_2\text{O}_7 \\
\text{H}_2\text{SO}_4, \text{H}_2\text{O}
\end{array}
\]

g.  
\[
\begin{array}{c}
\text{OH} \\
\text{PCC} \\
\text{CH}_2\text{Cl}_2
\end{array}
\]
**Reduction of C=O to CH$_2$**

a. 
\[
\text{O} \quad \text{O} \\
\text{O} \quad \text{H}_2\text{NNH}_2 \\
\text{DMSO, KOH} \\
\text{O} \quad \text{O}
\]

b. 
\[
\begin{align*}
\text{O} & \quad \text{Zn(Hg)} \\
\text{aq. HCl} & \quad \text{O} \quad \text{H}_2 \\
\end{align*}
\]

c. 
\[
\begin{align*}
\text{O} & \quad \text{HS} \\
\text{SH} & \quad \text{O} \quad \text{H}_2, \text{Raney Ni}
\end{align*}
\]

**Protection of alcohols**

a. 
\[
\begin{align*}
\text{OH} & \quad \text{1)} \text{NaH or NaNH}_2 \\
\text{O} & \quad \text{2)} \text{ClO}_2 \\
\end{align*}
\]

\[
\text{MOMO} \quad \text{O} \\
\text{OH} \quad \text{Ph}
\]

\[
\text{OH} \quad \text{Ph}
\]

b. 
\[
\begin{align*}
\text{HO} & \quad \text{TBDMS-Cl} \\
\text{CN} & \quad \text{imidazole}
\end{align*}
\]

\[
\text{O} \\
\text{H}_2 \text{NNH}_2 \\
\text{DMSO, KOH}
\]

**TBDMS-Cl**
**Catalytic Hydrogenation**

a. 
\[
\text{H}_2 \xrightarrow{\text{Pt/C}} \quad \text{H}_2
\]

b. 
\[
\text{H}_2 \xrightarrow{\text{Pt/C}} \quad \text{H}_2
\]

c. 
\[
\text{H}_2 \xrightarrow{3 \text{ atm H}_2, \text{ Rh}} \quad \text{H}_2
\]

d. 
\[
\text{H}_2 \xrightarrow{75 \text{ atm H}_2, \text{ Ni, 80 } \circ \text{C}} \quad \text{H}_2
\]

e. 
\[
\text{H}_2 \xrightarrow{160 \text{ atm H}_2, \text{ Pt, 135 } \circ \text{C}} \quad \text{H}_2
\]

f. 
\[
\text{H}_2 \xrightarrow{\text{Pt, 25 } \circ \text{C}} \quad \text{H}_2
\]

g. 
\[
\text{H}_2 \xrightarrow{\text{Pt, 25 } \circ \text{C}} \quad \text{H}_2
\]

h. 
\[
\text{H}_2 \xrightarrow{\text{Lindlar}} \quad \text{H}_2
\]

i. 
\[
\text{H}_2 \xrightarrow{\text{Na, NH}_3, -33 \circ \text{C}} \quad \text{H}_2
\]
Oxidation of Alcohols to Carbonyl Compounds

a.

\[
\text{\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}} \xrightarrow{\text{CrO}_3, \text{H}_2\text{SO}_4, \text{H}_2\text{O}} \text{\text{CH}_3\text{CH}_2\text{CH}_2\text{CHO}}
\]

b.

\[
\text{\text{CH}_3\text{CH}_2\text{CH}_2\text{OH}} \xrightarrow{\text{Na}_2\text{Cr}_2\text{O}_7, \text{H}_2\text{SO}_4, \text{H}_2\text{O}} \text{\text{CH}_3\text{CH}_2\text{CH}_2\text{CO}_2\text{H}}
\]

c.

\[
\text{\text{CH}_2\text{CH}_2\text{OH}} \xrightarrow{\text{H}_2\text{CrO}_4, \text{H}_2\text{O}} \text{\text{CH}_2\text{CH}_2\text{CO}_2\text{H}}
\]

d.

\[
\text{\text{C}_6\text{H}_5\text{OH}} \xrightarrow{\text{H}_2\text{CrO}_4, \text{H}_2\text{O}} \text{\text{C}_6\text{H}_5\text{CO}_2\text{H}}
\]

e.

\[
\text{\text{C}_6\text{H}_5\text{OH}} \xrightarrow{\text{PCC, \text{CH}_2\text{Cl}_2}} \text{\text{C}_6\text{H}_5\text{CHO}}
\]

f.

\[
\text{\text{C}_5\text{H}_9\text{OH}} \xrightarrow{\text{Na}_2\text{Cr}_2\text{O}_7, \text{H}_2\text{SO}_4, \text{H}_2\text{O}} \text{\text{C}_5\text{H}_9\text{CO}_2\text{H}}
\]

g.

\[
\text{\text{C}_5\text{H}_9\text{OH}} \xrightarrow{\text{PCC, \text{CH}_2\text{Cl}_2}} \text{\text{C}_5\text{H}_9\text{CO}}
\]