Preparation of alkenes: two common elimination reactions

1. Dehydration of alcohols

Dehydration is a common biochemical reaction in carbohydrate and fatty acid metabolism and terpene biosynthesis – it’s catalyzed in vivo by specific enzymes.

In the lab, dehydration is an acid-catalyzed elimination reaction. The mechanism involves formation of a carbocation intermediate (more on eliminations in Ch. 11)

Example: Formation of 2-butene from 2-butanol

\[
\text{H}_3\text{C} \quad \text{H} \quad \text{C} \quad \text{C} \quad \text{H}_3\text{C} \quad \text{H} \quad \text{C} \quad \text{C} \quad \text{H}_3\text{C} \quad \text{H} \\
\text{OH} \quad \text{H}_2\text{SO}_4 \quad \text{heat} \quad \text{heat} \\
\rightarrow \quad \text{H}_3\text{C} \quad \text{C} \quad \text{C} \quad \text{C} \quad \text{H}_3\text{C} \quad \text{H} \\
\text{CH}_3 \quad \text{OH} \quad \rightarrow \quad \text{H}_2\text{O}
\]

The regiochemistry of elimination leads to the most substituted alkene possible = Zaitsev’s rule

2. Dehydrohalogenation of alkyl halides

Alkyl halides also undergo elimination to produce alkenes:

What’s the major alkene product of this elimination, based on Zaitsev’s rule?
Addition Reactions of Alkenes

A. Additions to produce alkyl halides and halohydrins

1. From Ch. 6, Alkene + HX \(\rightarrow\) alkyl halide

2. Halogenation: \(\text{Br}_2\) and \(\text{Cl}_2\) can add to alkenes just like \(\text{HBr}, \text{HCl}\) and \(\text{H}_2\text{O}\!\!\).  
   *Note: Similar reactions do not take place with \(\text{F}_2\) and \(\text{I}_2\)*

Where's the electrophile? \(\text{Br}_2\) makes both electrophile (\(\text{Br}^+\)) and nucleophile (\(\text{Br}^-\))

Mechanism is a little different: the intermediate is a cyclic cation

*Rearrangements do not occur with the cyclic cation mechanism!*

Solvent effects:
When planning a synthetic reaction in the lab, solvent should be chosen carefully
For halogenation reactions, solvents such as \(\text{CH}_2\text{Cl}_2\) & \(\text{CCl}_4\) do not interfere

3. Halohydrins: Use of a nucleophilic solvent like \(\text{H}_2\text{O}\) alters the outcome of the reaction, because both the halogen + water react with the alkene

How would the product change if an alcohol was the solvent?
Stereochemistry of halogenations:

Use of NBS to provide a bromine:

Some key points about this reaction:
1) Br$_2$ furnished by NBS is the electrophile, water is the nucleophile
2) The organic solvent used (DMSO) doesn’t take part in the reaction
3) The benzene double bonds don’t react:
   Aromatic C=C do NOT undergo electrophilic addition like alkene C=C!
B. More addition on the "Markovnikov" theme: Alcohol formation rxns

1. Acid-Catalyzed Hydration: Alkene → Alcohol

Mechanism: similar to addition of H - X:

Same rules apply as for addition of H - X:
1) The bond is attracted to an electrophile and a new σ bond forms
2) The intermediate is the most stable carbocation
3) The nucleophile reacts with the carbocation to form another new σ bond
4) Markovnikov's rule is obeyed and the OH group ends up on the most substituted C.

Another variation on this theme: alkenes → ethers when alcohols are present, they become the nucleophile and add a -OR group to the molecule:

In summary:

Alkenes + H - X → Alkyl halides
Alkenes + HX, H2O → Halohydrin
Alkenes + H2O, H+ → Alcohols
Alkenes + ROH, H+ → Ethers
2. Oxymercuration-Demercuration: Metal complexes in organic reactions

Some organic reactants are sensitive to harsh reagents (can cause decomposition!) How do we avoid this in the case of hydration?

A milder reagent for hydration: Mercuric acetate in THF & water

A two-step synthetic procedure:

\[
\begin{align*}
\text{H}_3\text{C} & \text{C} = \text{CH}_2 \\
\rightarrow & \text{Hg(OAc)}_2, \text{H}_2\text{O}, \text{THF} \\
\rightarrow & \text{NaBH}_4, \text{OH}^- \\
\text{H}_3\text{C} & \text{C} - \text{CH}_3 \\
\end{align*}
\]

THF (tetrahydrofuran) is a cyclic ether; a moderately polar solvent

“OAc” = CH₃COO-

No rearrangements occur with this process due to cyclic cation intermediate:

Demercuration step: NaBH₄ provides a hydride ion, H⁻

\[
\begin{align*}
\text{H}_3\text{C} & \text{C} = \text{CH}_2 \\
\rightarrow & \text{Hg(OAc)}_2 \\
\rightarrow & \text{NaBH}_4, \text{NaOH} \\
\text{H}_3\text{C} & \text{C} - \text{CH}_3 \\
\rightarrow & \text{H}_3\text{C} - \text{CH}_3 \\
\end{align*}
\]

A similar reaction, alkoxymercuration: Using ROH instead of H₂O produces ethers

Advantages of this procedure over hydration:

1) No rearrangements can occur
2) Conditions for reaction are less harsh
Electrophilic addition of mercuric acetate to an alkene produces an intermediate, three-membered mercurinium ion.

Water as nucleophile then displaces mercury by back-side attack at the more highly substituted carbon, breaking the C–Hg bond.

Loss of $\text{H}^+$ yields a neutral organo-mercury addition product.

Treatment with sodium borohydride replaces the –Hg by –H and reduces the mercury, yielding an alcohol product.

How would you prepare each of these alcohols?

(a) Syn, non-Markovnikov addition of $\text{H}_2\text{O}$

(b) Markovnikov addition of $\text{H}_2\text{O}$

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3. 1° alcohols by Hydroboration-Oxidation ("Anti-Markovnikov orientation")

\[
\begin{align*}
1) & \quad \text{BH}_3 \\
\text{CH}_3 - \text{CH} = \text{CH}_2 & \quad \text{CH}_3\text{CH}_2\text{CH}_2\text{OH} \\
2) & \quad \text{OH}^-, \text{H}_2\text{O}_2, \text{H}_2\text{O}
\end{align*}
\]

What’s new about this reaction:

1. The electrophile is a Lewis acid, BH$_3$
2. The nucleophile is a hydride (H-) from the borane…watch this:

\[
\begin{align*}
\text{CH}_3 - \text{HC} = \text{CH}_2 & \quad \text{CH}_3 - \text{CH}_2 - \text{CH}_2 - \text{BH}_2 \\
\text{H} - \text{BH}_2 & \quad \text{alkylborane}
\end{align*}
\]

3. It’s a concerted reaction (one step, no intermediate) and pericyclic
4. Cyclic transition state means no rearrangements
5. Product has “Anti-Markovnikov orientation” but…it only APPEARS to violate Markovnikov’s rule…the nucleophile (H-) still ends up on the most substituted C, because this gives the more stable transition state:

![Transition state diagram](image)

What happens next:
The alkylborane reacts with 2 more moles of alkene to produce a trialkylborane. Steric hindrance of alkyl groups promotes further addition to less-substituted C:

\[
\begin{align*}
\text{CH}_3\text{CH}_2\text{CH}_2\text{BH}_2 & \quad (\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{BH} \\
(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{BH} & \quad (\text{CH}_3\text{CH}_2\text{CH}_2)_3\text{B}
\end{align*}
\]

Trialkylborane

The trialkylborane reacts with peroxide and hydroxide ion to release 3 moles of alcohol:

\[
(\text{CH}_3\text{CH}_2\text{CH}_2)_3\text{B} \quad \text{H}_2\text{O}_2, \text{OH}^-, \text{H}_2\text{O} \quad 3 \quad \text{CH}_3\text{CH}_2\text{CH}_2\text{OH} + \text{BO}^{3-}
\]

Summary: Hydroboration is an effective route to 1° alcohols
C. Alkanes by Catalytic Hydrogenation (the "Crisco" reaction)

Suppose you want to prepare alkanes from alkenes? An example from real life:

Vegetable oil

Semi-solid “shortening”

Addition of $\text{H}_2$ is catalyzed by Pt or Pd on charcoal, PtO$_2$, or Ni (heterogeneous catalysts):

![Reaction diagram]

The H - H bond is particularly strong; requires a catalyst to help bond break. Addition occurs on one side of the molecule (syn addition)...see OWL tutorial

H$_2$ adsorbs on the catalyst surface and the reaction occurs there.

D. Cyclopropanation by using Carbenes: carbon adds to the C=C in a stereospecific way

Carbenes are an electron-deficient, sp$^2$-hybridized species with formula (R)$_2$C. These are reactive species generated “in situ” by deprotonation of chloroform:

\[
\text{CHCl}_3 + \text{KOH} \rightarrow \text{CCl}_3 - \text{CCl}_2 + \text{Cl}^{-}
\]

Or generated from similar reagents: Simmons-Smith reaction

\[
\text{CH}_2	ext{I}_2 \xrightarrow{\text{Zn/Cu/Ether}} \text{CH}_2
\]

As electrophiles, carbenes can react with C = C to form a cyclopropane ring:

![Cyclopropane reaction diagram]

Stereospecific: the original arrangement of groups around C = C bond is retained.
E. Oxidation of C = C bonds to produce oxygenated functional groups

Oxidation: Reaction resulting in an increased number of bonds from carbon to oxygen, and a decrease in bonds to hydrogen

Increasingly oxidized functional groups

<table>
<thead>
<tr>
<th>Alkanes</th>
<th>Alkenes</th>
<th>Alcohols</th>
<th>Ketones</th>
<th>Acids</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-CH&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;-R</td>
<td>R&lt;sub&gt;1&lt;/sub&gt;-CH&lt;sub&gt;2&lt;/sub&gt;-R&lt;sub&gt;2&lt;/sub&gt;</td>
<td>R&lt;sub&gt;1&lt;/sub&gt;-C&lt;sub&gt;2&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;</td>
<td>R&lt;sub&gt;1&lt;/sub&gt;-C&lt;sub&gt;2&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>R&lt;sub&gt;1&lt;/sub&gt;-C&lt;sub&gt;2&lt;/sub&gt;H&lt;sub&gt;3&lt;/sub&gt;</td>
</tr>
<tr>
<td>alkynes</td>
<td>aldehydes</td>
<td>esters</td>
<td></td>
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</tr>
</tbody>
</table>

Oxidation of C=C pi bonds is a versatile way to introduce new functional groups to molecules containing the alkene group.

1. Hydroxylation of alkenes: diol preparation

Alkenes can be oxidized by transition metal oxides with a high metal oxidation state

1. OsO<sub>4</sub>
2. H<sub>2</sub>O, NaHSO<sub>3</sub>

- Stereospecific syn addition occurs to produce vicinal diols
- The positive charge on the metal attracts electrons and sets a pericyclic reaction in motion; π electrons form σ bonds
- As the organic functional group gets oxidized, the inorganic reagent gets reduced (by products: MnO<sub>2</sub> or OsO<sub>3</sub>)
- KMnO<sub>4</sub> is cheaper but harsher (can completely oxidize C=C, see next page)
- OsO<sub>4</sub> is expensive, highly toxic
2. Oxidative Cleavage of alkenes: produces carbonyl compounds by breaking both $\sigma$ and $\pi$ bonds

The 1,2-diols produced by oxidation of alkenes can be further oxidized to carbonyl compounds by a second pericyclic reaction:

\[
\begin{align*}
\text{H}_3\text{C} & \text{C} - \text{C} - \text{CH}_3 & \text{H}_3\text{C} & \text{C}=\text{O} + \text{O}=\text{C} & \text{CH}_3 \\
\text{OH} & \text{OH} & \text{HIO}_4 \\
\end{align*}
\]

- Products may be aldehydes or ketones depending on structure at diol carbons
- Significant reaction because C - C bonds are not broken easily

A similar reaction occurs when KMnO$_4$ is used under acid conditions or heat:

\[
\begin{align*}
\text{R}_1 & \text{C}=\text{C} & \text{R}_3 & \text{KMnO}_4 & \text{R}_1 & \text{C}=\text{O} + \text{O}=\text{C} & \text{R}_3 \\
\text{R}_2 & & & \text{H}^+ \text{or heat} \\
\end{align*}
\]

- A disubstituted C= (two R groups attached) becomes a ketone carbon
- A monosubstituted C= (one H attached) becomes fully oxidized to a carboxylic acid (no aldehydes are produced under these conditions)
- $\text{=CH}_2$ from a terminal alkene becomes CO$_2$ instead of a carboxylic acid:

\[
\begin{align*}
\text{H}_3\text{C} & \text{C} - \text{C} & \text{H}_3\text{C} & \text{C}=\text{O} + \text{O}=\text{C} & \text{CO}_2 \\
\text{H} & \text{H} & \text{H}_3\text{C} & \text{CH}_2 \\
\end{align*}
\]

Oxidation of cyclic alkenes opens up the ring resulting in a diacid or a diketone:

\[
\begin{align*}
\text{KMnO}_4, \text{H}_3\text{O}^+ & \text{KMnO}_4, \text{H}_3\text{O}^+ \text{HOOC} & \text{COOH} \\
\hline
\end{align*}
\]
3. **Ozonolysis**: A milder, more efficient, "greener" (?) way to do oxidative cleavage!

Problems with transition metal-mediated oxidations:

- Reagents form toxic metal compounds as by-products (hazardous waste!)
- Conditions may be rather harsh, require heat, acids, bases
- Side reactions: KMnO₄ will oxidize any OH or C=O groups in the molecule too

The solution: **Ozone**!

**Cycloaddition** of ozone to C=C produces a molozonide which rearranges to an **ozonide**.

Cleavage under **oxidizing** or **reducing** conditions to yield different products as shown:

![Ozonolysis Reaction Diagram](image)

- A C bearing a single R group yields an aldehyde under reducing cond.
- Terminal alkenes form **formaldehyde** or **CO₂** as the second product
- Tetra-substituted alkenes form **only ketones** under any conditions
Ozonolysis is a useful way to determine the structure of an unknown alkene:

- React the unknown with ozone under controlled conditions
- Determine the identity of the oxidative cleavage products (the simpler the molecule, the easier it is to determine structure!)
- Figure out how the pieces would fit together

“Road map” problems!
Goal: Piece together information from reactions to figure out structures of unknown compounds. You are given some key pieces of information to help you figure out what is happening to the molecule in each step.

Example: Compound A has the formula C$_{10}$H$_{16}$. On catalytic hydrogenation over palladium (H$_2$, Pd) it reacts with only one molar equivalent of H$_2$. Compound A also undergoes reaction with ozone (O$_3$), followed by zinc treatment (Zn, H$_3$O$^+$) to yield a symmetrical diketone, B which has formula (C$_{10}$H$_{16}$O$_2$). Propose plausible structures for A and B.
What reagents would be best to carry out these reactions?

(a) \[\text{Cyclohexane} \xrightarrow{?} \text{Cyclohexanol} \]

(b) \[\text{Cyclohexene} \xrightarrow{?} \text{Cyclohexanol} \]

(c) \[\text{Cyclopentene} \xrightarrow{?} \text{Cyclopentane} \]

(d) \[\text{Cyclohexanol} \xrightarrow{?} \text{Cyclohexene} \]

(e) \[\text{2-Methylpentane} \xrightarrow{?} \text{2-Methylpropane + 2-Methylbutane} \]

(f) \[\text{Ethene} \xrightarrow{?} \text{Ethanol} \]

\[
\begin{align*}
\text{(a)} & \xrightarrow{\text{H}_2/\text{Pd}} \\
\text{(b)} & \xrightarrow{\text{Br}_2} \\
\text{(c)} & \xrightarrow{\text{HBr}} \\
\text{(d)} & \xrightarrow{1. \text{OsO}_4, 2. \text{NaHSO}_3} \\
\text{(e)} & \xrightarrow{\text{D}_2/\text{Pd}} \\
\text{(f)} & \xrightarrow{\text{KMnO}_4, \text{H}_3\text{O}^+}
\end{align*}
\]
Alkene + HX $\rightarrow$ Alkyl halide

Alkene + $X_2$ (Br$_2$, Cl$_2$) $\rightarrow$ Alkyl dihalide

Alkene + $X_2$, H$_2$O $\rightarrow$ Halohydrin

Alkene + H+, H$_2$O $\rightarrow$ Alcohol (Markovnikov)

Alkene + Hg(OAc)$_2$, NaBH$_4$ $\rightarrow$ Alcohol (Markovnikov)

Alkene + BH$_3$/THF, H$_2$O$_2$, OH- $\rightarrow$ Alcohol (Non-Markovnikov)

Alkene + H$_2$/ Pd, Pt or Ni catalyst $\rightarrow$ Alkane

Alkene + CH$_2$I$_2$, Zn/Cu $\rightarrow$ Cyclopropyl alkane

Alkene + OsO$_4$, H$_2$O, NaHSO$_3$ $\rightarrow$ diol + HIO$_4$ $\rightarrow$ aldehydes & ketones

Alkene + KMnO$_4$, H$_3$O$^+$, heat $\rightarrow$ carboxylic acids & ketones

Alkene + O$_3$, Zn, H$_3$O$^+$ $\rightarrow$ aldehydes & ketones