Advanced Organic Chemistry
روش‌های سنتز مواد آلی

Dr Morteza Mehrdad
University of Guilan, Department of Chemistry,
Rasht, Iran
m-mehrdad@guilan.ac.ir
Electrophilic Additions to Carbon-Carbon Multiple Bonds
4.1. Electrophilic Addition to Alkenes
   4.1.1. Addition of Hydrogen Halides
   4.1.2. Hydration and Other Acid-Catalyzed Additions of Oxygen Nucleophiles
   4.1.3. Oxymercuration-Reduction
   4.1.4. Addition of Halogens to Alkenes
   4.1.5. Addition of Other Electrophilic Reagents
   4.1.6. Addition Reactions with Electrophilic Sulfur and Selenium Reagents

4.2. Electrophilic Cyclization
   4.2.1. Halocyclization

4.3. Electrophilic Substitution $\alpha$ to Carbonyl Groups
   4.3.1. Halogenation $\alpha$ to Carbonyl Groups

4.4. Additions to Allenes and Alkynes

4.5. Addition at Double Bonds via Organoborane Intermediates
   4.5.1. Hydroboration
   4.5.2. Reactions of Organoboranes
   4.5.3. Enantioselective Hydroboration
   4.5.4. Hydroboration of Alkynes and Related Reactions
Addition of electrophilic reagents is one of the most general and useful reactions of alkenes and alkynes.

This chapter focuses on reactions that proceed through polar intermediates or transition structures.

This class of reactions, including:

Proton catalyzed additions of:

- Water
- Alcohols

the addition of:

- Hydrogen halides
- Halogens
- Positive halogen compounds
- Electrophilic sulfur and selenium reagents
- Mercuric salts
- Hydroboration
Synthetic application of these reactions:

- introduce functionality at double and triple bonds
- A new heterocyclic ring is formed (When the nucleophile addition step is intramolecular)
4.1. Electrophilic Addition to Alkenes

4.1.1. Addition of Hydrogen Halides

Hydrogen chloride and hydrogen bromide react with alkenes to give addition products.

Markovnikov’s rule  regioselective

Major (because of hyperconjugation); provides best stabilized carbocation

Hyperconjugation
increasing stability:

\[ \text{+CH}_2\text{CH}_2\text{R} < \text{CH}_3\text{+CH-R} < \text{CH}_3\text{CH+Ar} < \text{CH}_3\text{C+R}_2 < \text{CH}_3\text{C+Ar}_2 \]

1°  2°  2°/benzyl  3°  3°/benzyl

mechanism of addition of hydrogen halides:

In nonpolar solvents:
Terminal and disubstituted internal alkenes react rather slowly with HCl

In noncoordinating solvents (CH\_2Cl\_2 or CHCl\_3)
The rate is greatly accelerated in the presence of silica or alumina

The mechanism is thought to involve an interaction of the silica or alumina surface with HCl that facilitates proton transfer
Another convenient procedure for hydrochlorination involves adding trimethylsilyl chloride to a mixture of an alkene and water.

(Markovnikov orientation)

In nucleophilic solvents, products that arise from reaction of the solvent with the cationic intermediate may be formed.

acetic acid acts as a nucleophile in competition with the bromide ion.
The stereochemistry of addition depends on the details of the mechanism. An ion pair intermediate formed by an initial protonation step.

Most alkenes react via a complex that involves the alkene, hydrogen halide, and a third species that delivers the nucleophilic halide.

This **termolecular mechanism** is generally pictured as a nucleophilic attack on an alkene-hydrogen halide complex.

This mechanism bypasses a discrete carbocation and exhibits a preference for **anti** addition.
The major factor in two mechanisms = stability of carbocation
Alkenes that can give rise to a particularly stable carbocation are likely to react via the ion pair mechanism,
which is not necessarily stereospecific (carbocation intermediate permits loss of stereochemistry relative to the reactant alkene).

\[
\begin{align*}
\text{H}^+ & \text{X}^- \\
\text{R} & \text{C=CR} & \rightarrow & \text{R} & \text{C-RC}^+ \text{X}^- \\
\text{R} & \text{R} & & \text{R} & \text{R}
\end{align*}
\]

It might be expected that the ion pair mechanism would lead to a preference for *syn* addition, since at the instant of formation of the ion pair, the halide is on the same side of the alkene as the proton being added.
Syn addition is particularly common with alkenes having an aryl substituent.

<table>
<thead>
<tr>
<th>Alkene</th>
<th>Hydrogen halide</th>
<th>Stereochemistry</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,2-Dimethylcyclohexene&lt;sup&gt;a&lt;/sup&gt;</td>
<td>HBr</td>
<td>anti</td>
</tr>
<tr>
<td>1,2-Dimethylcyclohexene&lt;sup&gt;a&lt;/sup&gt;</td>
<td>HCl</td>
<td>Solvent and temperature dependent</td>
</tr>
<tr>
<td>Cyclohexene&lt;sup&gt;b&lt;/sup&gt;</td>
<td>HBr</td>
<td>anti</td>
</tr>
<tr>
<td>Z-2-Butene&lt;sup&gt;c&lt;/sup&gt;</td>
<td>DBr</td>
<td>anti</td>
</tr>
<tr>
<td>E-2-Butene&lt;sup&gt;c&lt;/sup&gt;</td>
<td>DBr</td>
<td>anti</td>
</tr>
<tr>
<td>1-Methylcyclopentene&lt;sup&gt;d&lt;/sup&gt;</td>
<td>HCl</td>
<td>anti</td>
</tr>
<tr>
<td>1,2-Dimethylcyclopentene&lt;sup&gt;e&lt;/sup&gt;</td>
<td>HBr</td>
<td>anti</td>
</tr>
<tr>
<td>Norbornene&lt;sup&gt;f&lt;/sup&gt;</td>
<td>HBr</td>
<td>syn and rearrangement</td>
</tr>
<tr>
<td>Norbornene&lt;sup&gt;g&lt;/sup&gt;</td>
<td>HCl</td>
<td>syn and rearrangement</td>
</tr>
<tr>
<td>E-1-Phenylpropene&lt;sup&gt;h&lt;/sup&gt;</td>
<td>HBr</td>
<td>syn (9:1)</td>
</tr>
<tr>
<td>Z-1-Phenylpropene&lt;sup&gt;h&lt;/sup&gt;</td>
<td>HBr</td>
<td>syn (8:1)</td>
</tr>
<tr>
<td>Bicyclo[3.1.0]hex-2-ene&lt;sup&gt;i&lt;/sup&gt;</td>
<td>DCl</td>
<td>syn</td>
</tr>
<tr>
<td>1-Phenyl-4-(t-butyl)cyclohexene&lt;sup&gt;j&lt;/sup&gt;</td>
<td>DCl</td>
<td>syn</td>
</tr>
</tbody>
</table>
4.1.2. Hydration and Other Acid-Catalyzed Additions of Oxygen Nucleophiles

Oxygen nucleophiles can be added to double bonds under strongly acidic conditions.

- regioselective
- accord with Markovnikov’s rule

synthesis of tertiary alcohols:

Addition of nucleophilic solvents such as **alcohols** and **carboxylic acids** can be effected by using strong acids as catalysts.

**Trifluoroacetic acid (TFA)** is strong enough to react with alkenes under relatively mild conditions.
4.1.3. Oxymercuration-Reduction

Moreover, because of the involvement of cationic intermediates, rearrangements can occur in systems in which a more stable cation can result by aryl, alkyl, or hydrogen migration.

Oxymercuration-reduction, a much milder and more general procedure for alkene hydration
Metal cations (mercuric ion) is the electrophile in several synthetically valuable procedures:

- mercuric acetate,
- trifluoroacetate,
- trifluoromethanesulfonate,
- or nitrate salts

**mercurinium ion as an intermediate**

The nucleophiles that are used for synthetic purposes:

- $\text{Nu}^-$: $\text{H}_2\text{O}$, ROH, RCOO-, HOO-, R-NH$_2$, R-CN

The regioselectivity is excellent
The reductive replacement of mercury using sodium borohydride is a free radical chain reaction involving a mercuric hydride intermediate.

The evidence for the free radical mechanism:
The reaction can be diverted by oxygen, an efficient radical scavenger.

In the presence of oxygen, the mercury is replaced by a hydroxy group.
**Stereochemistry:** product of *anti add.* indicates *mercurium* ion (Hg +) mechanism:
reactivity: (such electrophilic add; steric / electronic factors)

Terminal double bonds are more reactive than internal ones. Disubstituted terminal alkenes, however, are more reactive than monosubstituted cases.

regioselectivity: Ex. selective add (otherwise Markovnikov)
Diastereoselectivity has been observed in oxymercuration of alkenes having nearby oxygen substituents.

Terminal allylic alcohols show a preference for formation of the \textit{anti} 2,3-diols.

This result can be explained in terms of a steric preference for conformation \textbf{A} over \textbf{B}.

The approach of the \textit{mercuric} ion is directed by the \textit{hydroxy} group.

The selectivity increases with the size of the substituent \(R\).
directing effect: (cont.)

**acetoxy derivatives**: With acetoxy derivatives, the 2,3-*syn isomer* is preferred as a result of direct nucleophilic participation by the carbonyl oxygen.

![Chemical structure](image)

*syn diol*

electron withdrawing groups (EWG):

The polar effects of EWGs favors mercuration at the carbon that is closer to the substituent, which is attributed to a favorable polar effect that stabilizes the negative charge on the mercurated carbon.

![Chemical structure](image)
Markovnikov orientation under typical reaction conditions
The high exo selectivity is consistent with steric approach control on a weakly bridged (or open) mercurinium ion.

There is no rearrangement, indicating that the intermediate is a localized cation.
B. Ethers

\[
\begin{align*}
\text{formation of ethers using alcohols as solvents} \\
\text{Trifluoroacetic acid (TFA) is strong} \\
\text{enough to react with alkenes under} \\
\text{relatively mild conditions}
\end{align*}
\]
Formation of amide in acetonitrile
use of other nucleophiles to capture the mercurinium ion

D. Peroxides

\[ \text{CH}_3(\text{CH}_2)_4\text{CH}=\text{CHCH}_3 \quad \xrightarrow{1) \text{Hg(OAc)}_2, \quad \text{t-BuOOH}} \quad \text{CH}_3(\text{CH}_2)_4\text{CHCH}_2\text{CH}_3 \quad \text{OOC(\text{CH}_3)_3} \quad 40\% \]

E. Amines

\[ \text{CH}_3\text{O} - \text{CH}_2\text{CH}=\text{CH}_2 \quad + \quad \text{PhCH}_2\text{NH}_2 \quad \xrightarrow{1) \text{Hg(ClO}_4)_2} \quad \text{CH}_3\text{O} - \text{CH}_2\text{CHCH}_3 \quad \text{HNCH}_2\text{Ph} \quad 70\% \]
4.1.4. Addition of Halogens to Alkenes

**Bromination** of simple alkenes is extremely fast.

Involves *electrophilic attack*, substituents on the double bond that increase electron density *increase the rate of reaction*, whereas EWG substituents have the opposite effect.

**Mechanism:** by cyclic bromonium ion; provides *anti* product.
mix syn/anti products can be formed from Ph-substituted substrates because benzylic stable carbocation can weaken "Br-bridge":

\[
\text{rotation; equilibrium}
\]

smaller size; less polarizable,

forming weaker bridge; more cation character of TS; therefore:

- Syn addition is often dominant for phenyl-substituted alkenes
- Elimination of a proton from a cationic intermediate, (Branched alkenes)

\[
\text{Cl}_2 \quad \text{CH}_3=\text{CH}_2 \quad \text{Cl}_2 \quad (\text{CH}_3)_2\text{C}--\text{CH}_2\text{Cl} \quad \rightarrow \quad \text{H}_2\text{C}==\text{C}--\text{CH}_2\text{Cl} \quad \text{- H}^+ \quad \text{CH}_3 \quad 80% 
\]
- Rearrangement (+ elim) for appropriate intermediates

-nucleophilic solvents may be added (to benzylic cation),

MeOH:

\[ \text{PhCH}=\text{CHCH}_3 + \text{Cl}_2 \xrightarrow{\text{i}} \text{PhCHCHCH}_3 \xrightarrow{\text{ii}} \text{PhCHCHCH}_3 \text{Cl} \]

82%

AcOH:

\[ \text{PhCH}=\text{CH}_2 + \text{Br}_2 \xrightarrow{\text{i}} \text{PhCHCH}_2\text{Br} \]

20%
**Halohydrin** is the most important example of nucleophilic capture of the intermediate by solvent

To favor introduction of water, it is desirable to keep the concentration of the bromide ion as low as possible.

Can use N-bromosuccinimide (NBS)

\[
\text{NBS} = \text{N-Br-succinimide:} \quad \equiv \quad \text{"low Conc. Br}_2\text{"} = \text{electrophile "Br}^+\text{"}
\]
High yields of bromohydrins are obtained by using NBS in aqueous DMSO. The reaction is a stereospecific anti addition.

Nucleophilic attack by the sulfoxide oxygen

alkoxysulfonium ion intermediate reacts with water to give the bromohydrin

The participation of sulfoxo groups can be used to control the stereochemistry in acyclic systems.

Internal sulfoxide captures the bromonium ion

undergoes inversion at sulfur in the hydrolytic step
A procedure that is useful for the preparation of both bromohydrins and iodohydrins involves *in situ* generation of the hypohalous acid from NaBrO$_3$ or NaIO$_4$ by reduction with bisulfite.
Because of its high reactivity, special precautions must be taken with reactions of fluorine and its use is somewhat specialized.

- Z- and E-1-propenylbenzene
- Benzylic cation intermediate provides flexibility and rotation: anti and syn
- Not stereospecific, but syn addition is somewhat favored

In methanol, the solvent incorporation product is formed, as would be expected for a cationic intermediate.
CF₃OF and CH₃CO₂F, that transfer an electrophilic fluorine to double bonds.

\[
\text{PhCH} = \text{CHPh} + \text{CF}_3\text{OF} \rightarrow \text{PhCHCHPh} \quad \text{gives F}^+ \text{ addition;} \\
\text{CH}_3(\text{CH}_2)_9\text{CH} = \text{CH}_2 + \text{CH}_3\text{CO}_2\text{F} \rightarrow \text{CH}_3(\text{CH}_2)_9\text{CHCH}_2\text{F}
\]

The stability of hypofluorites (2,2-dichloropropanoyl hypofluorite) is improved in derivatives having electron-withdrawing substituents.

Fluorinating agents: e.g N-fluoropyridinium salts

In nucleophilic solvents: (acetic acid or alcohols give addition products,

in nonnucleophilic solvents: give substitution products (deprotonation of a carbocation intermediate)
Addition of iodine to alkenes can be accomplished by a photo-chemically initiated reaction.

Elimination of iodine is catalyzed by excess iodine, but the diiodo compounds can be obtained if unreacted iodine is removed.