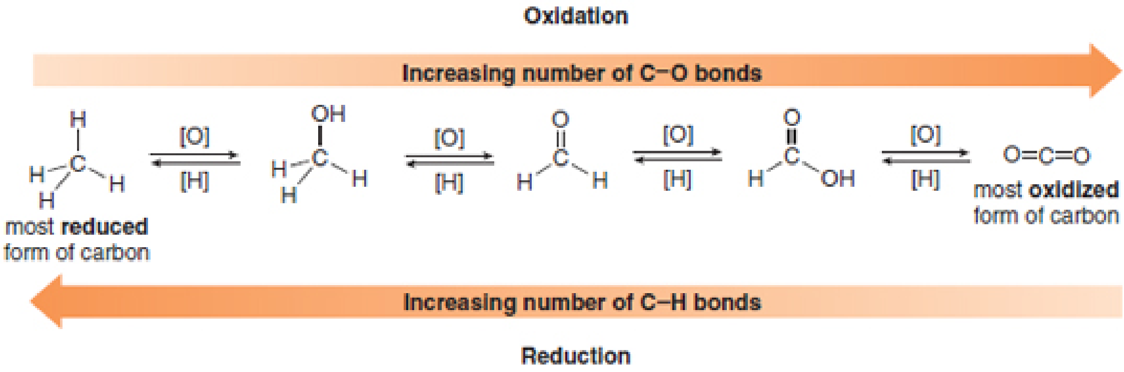
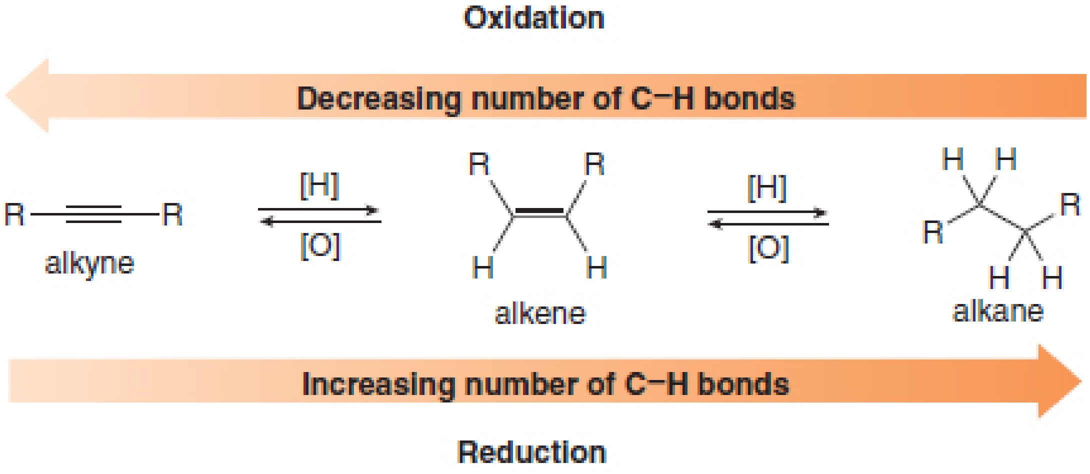
Organic Chemistry: Chapter 12 Notes

- ***Oxidation*** **results in an *increase* in the number of C — Z bonds (usually C — O bonds) *or a decrease* in the number of C — H bonds.**
- ***Reduction*** **results in a *decrease* in the number of C — Z bonds (usually C — O bonds) *or an increase* in the number of C — H bonds.**





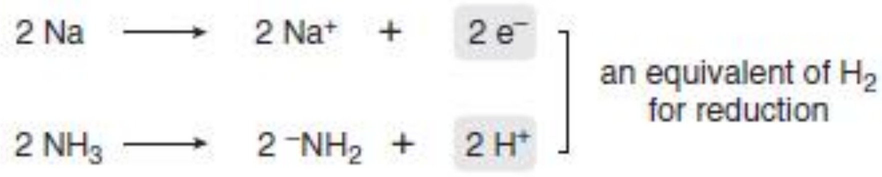
Reducing Agents

The Three Different Types of Reductions

1. **The simplest reducing agent is molecular H_2. Reductions of this sort are carried out in the presence of a metal catalyst that acts as a surface on which the reaction occurs.**

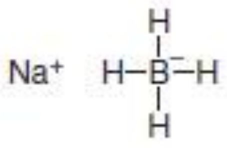
2. **The second way to deliver H_2 in a reduction is to add two protons and two electrons to a substrate—that is, $H_2 = 2\ H^+ + 2\ e^-$.**

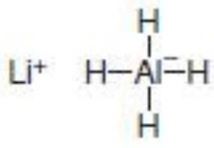
Reducing agents of this sort use alkali metals as a source of electrons and liquid ammonia (**NH_3**) as a source of protons. Reductions with **Na in NH_3** are called **dissolving metal reductions**.



3. **The third way to deliver the equivalent of two hydrogen atoms is to add hydride (H^-) and a proton (H^+).**

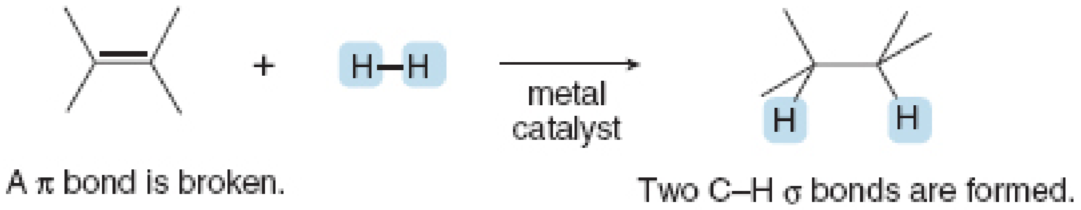
The most common hydride reducing agents contain a hydrogen atom bonded to boron or aluminum. Simple examples include **sodium borohydride ($NaBH_4$)** and **lithium aluminum hydride ($LiAlH_4$)**. These reagents deliver **H^-** to a substrate, and then a proton is added from H_2O or an alcohol.


sodium borohydride
$NaBH_4$

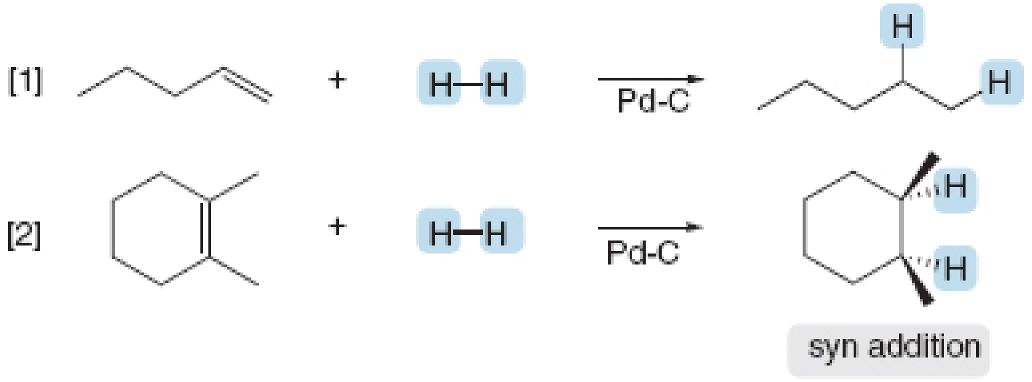

lithium aluminum hydride
$LiAlH_4$

- **Metal hydride reagents act as a source of H^- because they contain polar metal—hydrogen bonds that place a partial negative charge on hydrogen.**

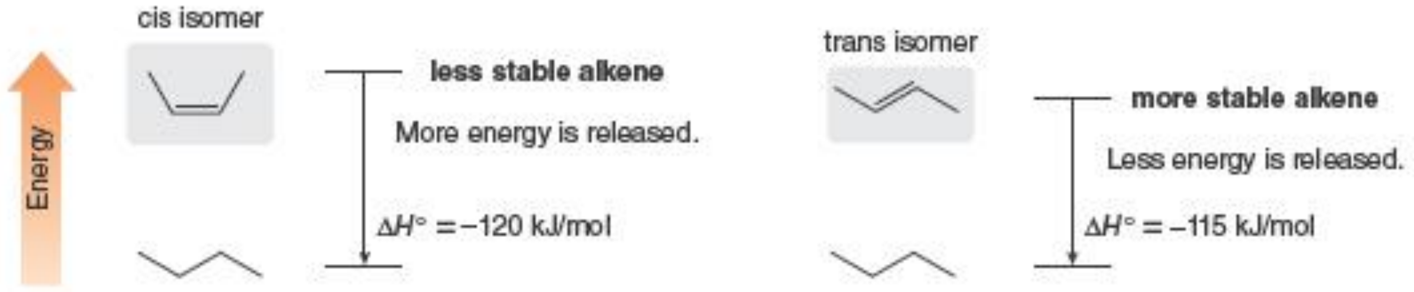
Reduction of Alkenes



The addition of H_2 occurs only in the presence of a **metal catalyst**, and thus, the reaction is called **catalytic hydrogenation**. The catalyst consists of a metal—usually Pd, Pt, or Ni



Hydrogenation and Alkene Stability

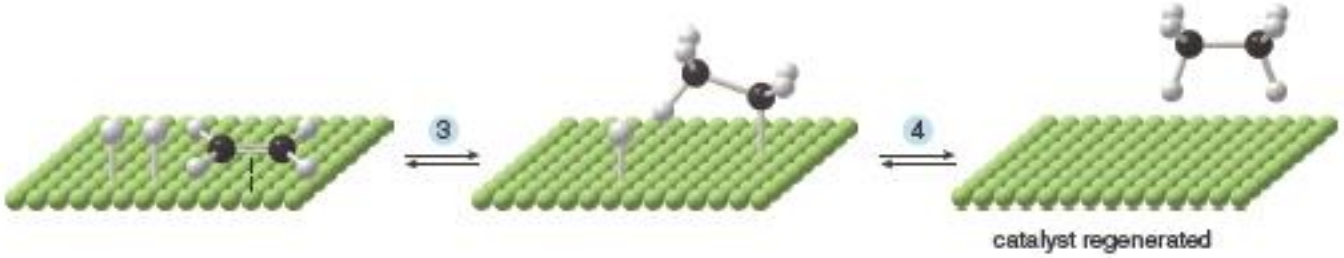


- **When hydrogenation of two alkenes gives the same alkane, the more stable alkene has the *smaller* heat of hydrogenation.**

The Mechanism of Catalytic Hydrogenation

Mechanism 12.1 Addition of H_2 to an Alkene—Hydrogenation

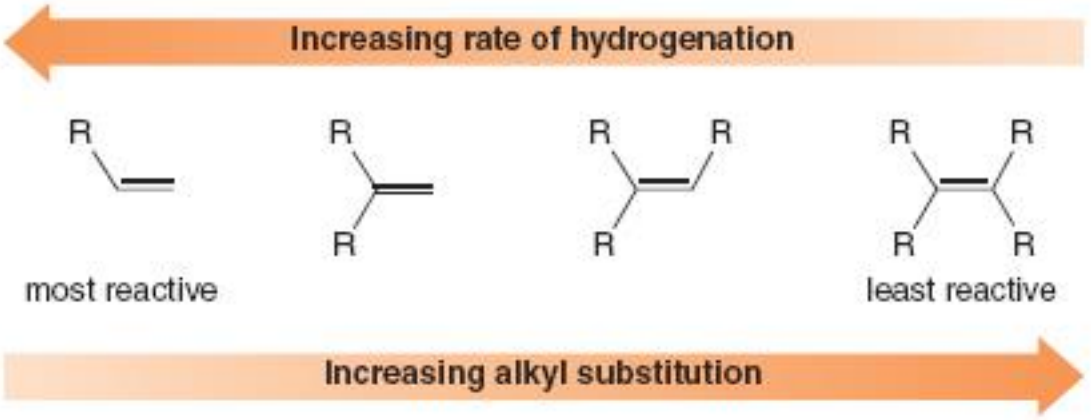
- ① **H_2 adsorbs to the catalyst surface** with partial or complete cleavage of the H—H bond.
- ② The π bond of the alkene complexes with the metal.



- ③ – ④ **Two H atoms are transferred sequentially** to the π bond in Steps [3] and [4], forming the alkane. Because the product alkane no longer has a π bond with which to complex to the metal, it is released from the catalyst surface.

The mechanism explains two facts about hydrogenation:

- **Rapid, sequential addition of H_2 occurs from the side of the alkene complexed to the metal surface, resulting in syn addition.**
- **Less crowded double bonds complex more readily to the catalyst surface, resulting in faster reaction.**



Hydrogenation Data and Degrees of Unsaturation

The **number of degrees of unsaturation gives the *total* number of rings and π bonds in a molecule**. Because H_2 adds to π bonds but does *not* add to the C—C σ bonds of rings, hydrogenation allows us to determine how many degrees of unsaturation are due to π bonds and how many are due to rings.

- This is done by comparing the number of degrees of unsaturation before and after a molecule is treated with H_2

+ **An acyclic alkene has the general molecular formula C_nH_{2n},** Cycloalkanes also have the general molecular formula C_nH_{2n}. Thus, **each π bond or ring removes two hydrogen atoms from a molecule, and this introduces one** *degree of unsaturation*.

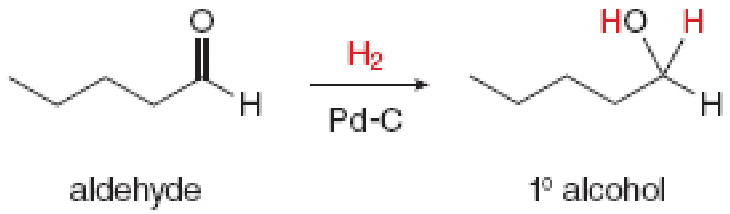
Calculate the maximum number of H's possible.

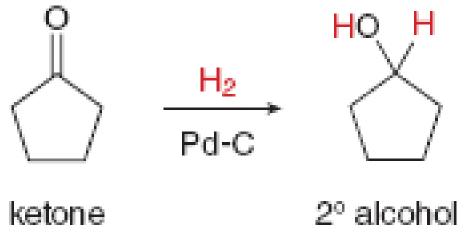
For *n* carbons, the maximum number of H's is 2*n* + 2

Subtract the actual number of H's from the maximum number and divide by two.

Hydrogenation of Other Double Bonds

Compounds that contain a carbonyl group also react with H_2 and a metal catalyst. For example, **aldehydes and ketones are reduced to 1° and 2° alcohols**

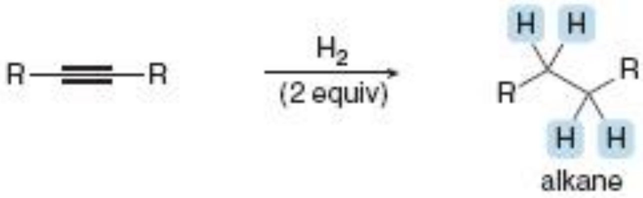




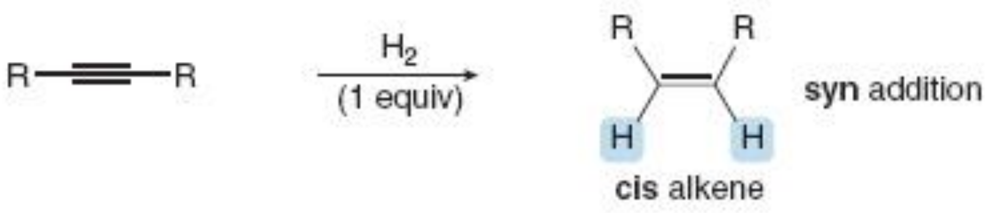
Reduction of Alkynes

Reduction of an alkyne adds H_2 to one or both of the π bonds. There are three different ways by which the elements of H_2 can be added to a triple bond.

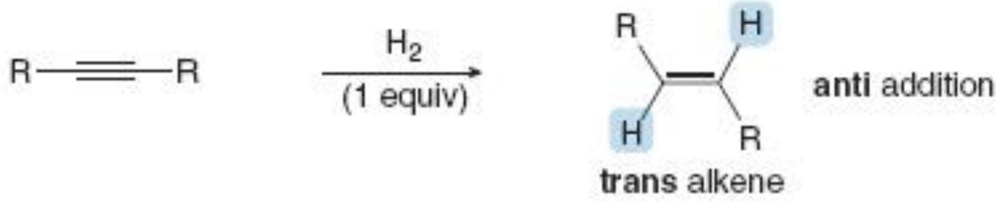
- **Adding two equivalents of H_2 forms an alkane.**



- **Adding one equivalent of H_2 in a syn fashion forms a cis alkene.**



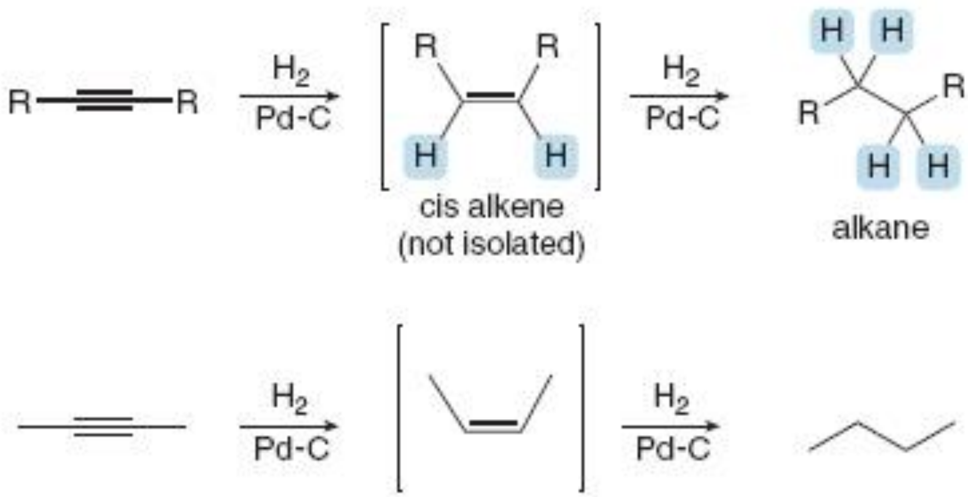
- **Adding one equivalent of H_2 in an anti fashion forms a trans alkene.**



Reduction of an Alkyne to an Alkane

- When an alkyne is treated with two or more equivalents of H_2 and a Pd catalyst, reduction of *both* π bonds occurs.
- **Syn addition** of one equivalent of H_2 forms a cis alkene, which adds a second equivalent of H_2 to form an **alkane.**

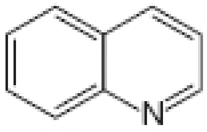
- **Four new C ─ H bonds are formed**. By using a Pd-C catalyst, it is not possible to stop the reaction after addition of only one equivalent of H_2.



Reduction of an Alkyne to a Cis Alkene

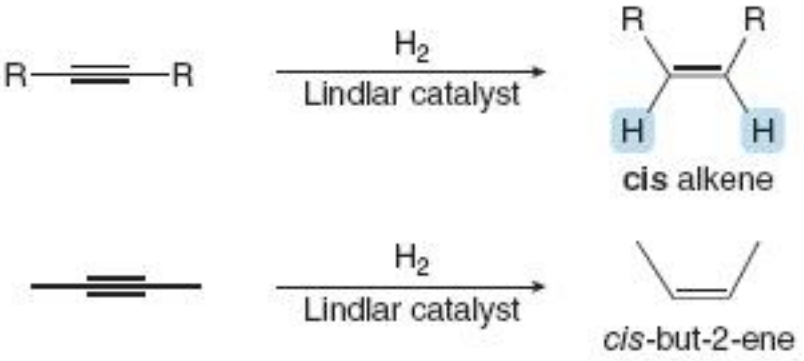
$$\text{Pd on } CaCO_3 + Pb(OCOCH_3)_2 + \text{quinoline}$$

Lindlar catalyst



quinoline

With the Lindlar catalyst, one equivalent of H_2 adds to an alkyne, and the cis alkene product is unreactive to further reduction.



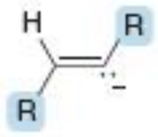
Reduction of an Alkyne to a Trans Alkene

Mechanism 12.2 Dissolving Metal Reduction of an Alkyne to a Trans Alkene

- ① Addition of an electron to the triple bond forms a **radical anion**, a species that contains *both* a negative charge *and* an unpaired electron.

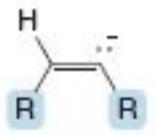
- ② Protonation of the anion with the solvent NH_3 yields a radical. The net result of the first two steps is the addition of a H atom.
- ③ Addition of a second electron forms a carbanion.
- ④ Protonation of the carbanion forms the trans alkene. Steps [3] and [4] add the second H atom to the triple bond.

Dissolving metal reduction of a triple bond with Na in NH_3 is a **stereoselective reaction** because it forms a trans product exclusively.



The larger R groups are farther away from each other.

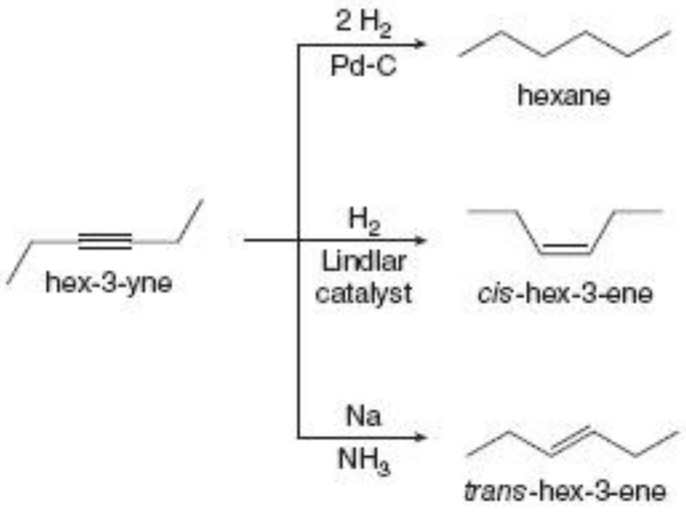
This more stable vinyl carbanion forms the trans alkene.



Steric interactions between closer R groups destabilize this carbanion.

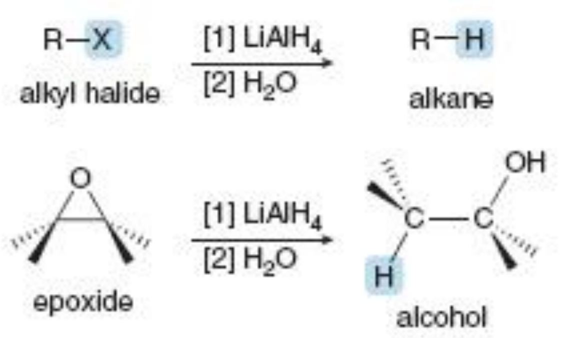
- **Dissolving metal reductions always form the more stable trans product preferentially.**

Summary: Three methods to reduce a triple bond

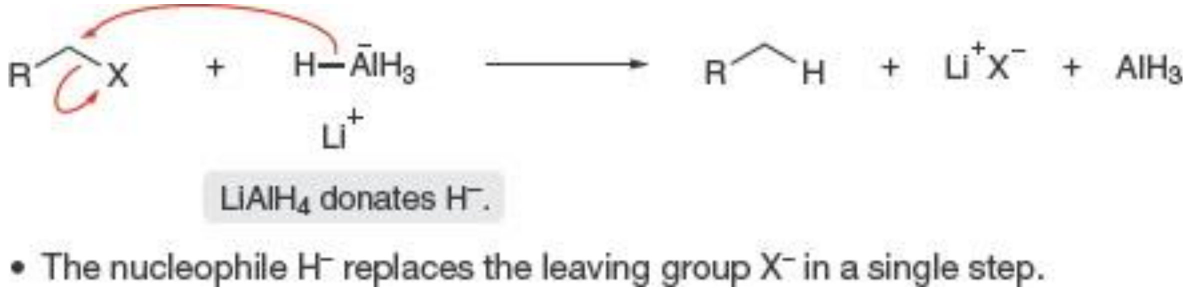


The Reduction of Polar C – X σ Bonds

- Compounds containing polar C ─ X σ bonds that react with strong nucleophiles are reduced with metal hydride reagents, most commonly lithium aluminum hydride.
- Two functional groups possessing both of these characteristics are **alkyl halides** and **epoxides**. Alkyl halides are reduced to alkanes with loss of X^- as the leaving group. Epoxide rings are opened to form alcohols.



Mechanism 12.3 Reduction of RX with LiAlH4

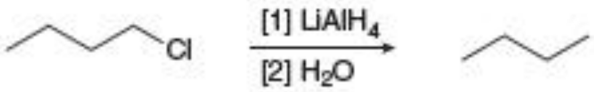


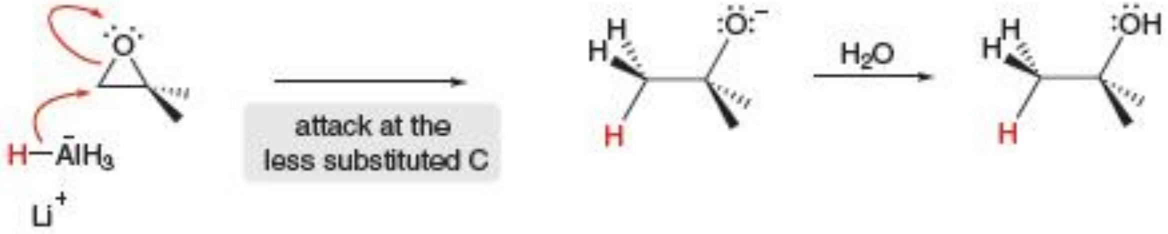
- The nucleophile H⁻ replaces the leaving group X⁻ in a single step.

Because the reaction follows an S_N2 mechanism:

- **Unhindered CH_3X and 1° alkyl halides are more easily reduced than more substituted 2° and 3° halides.**
- **In unsymmetrical epoxides, nucleophilic attack of H^- (from $LiAlH_4$) occurs at the less substituted carbon atom.**

Examples of reduction of C - X σ bonds with $LiAlH_4$

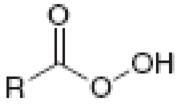




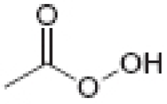
Oxidizing Agents

Oxidizing agents fall into two main categories:

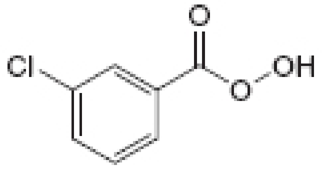
- **Reagents that contain an oxygen—oxygen bond**
- **Reagents that contain metal—oxygen bonds**
  - Oxidizing agents containing an O — O bond include…
    - **O_2, O_3** (ozone), **H_2O_2** (hydrogen peroxide)
    - **$(CH_3)_3COOH$** (*tert*-butyl hydroperoxide)
    - Peroxyacids.
  - **Peroxyacids**, a group of reagents with the general structure **RCO_3H,** have one more O atom than carboxylic acids (RCO_2H).



peroxyacid

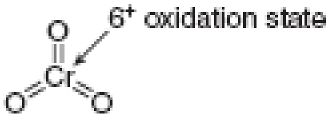


peroxyacetic acid



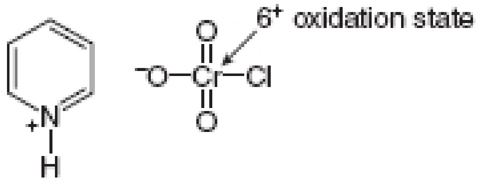
meta-chloroperoxybenzoic acid
mCPBA

- The most common oxidizing agents with metal—oxygen bonds contain either chromium in the +6 oxidation state (six Cr ─ O bonds) or manganese in the +7 oxidation state (seven Mn ─ O bonds).
  - Common Cr^{6+} reagents include chromium (VI) oxide **(CrO_3)** and sodium or potassium dichromate **($Na_2Cr_2O_7$** and **$K_2Cr_2O_7$)**.
  - **These reagents are strong oxidants** used in the presence of a strong aqueous acid such as H_2SO_4.
  - **Pyridinium chlorochromate (PCC),** a Cr^{6+} reagent that is soluble in halogenated organic solvents, can be used without strong acid present. This makes it a **more selective Cr^{6+} oxidant**
- The most common Mn^{7+} reagent is **$KMnO_4$** (potassium permanganate), a strong, water-soluble oxidant.
- Other oxidizing agents that contain metals include **OsO_4** (osmium tetroxide) and **Ag_2O** [silver(I) oxide].



chromium(VI) oxide

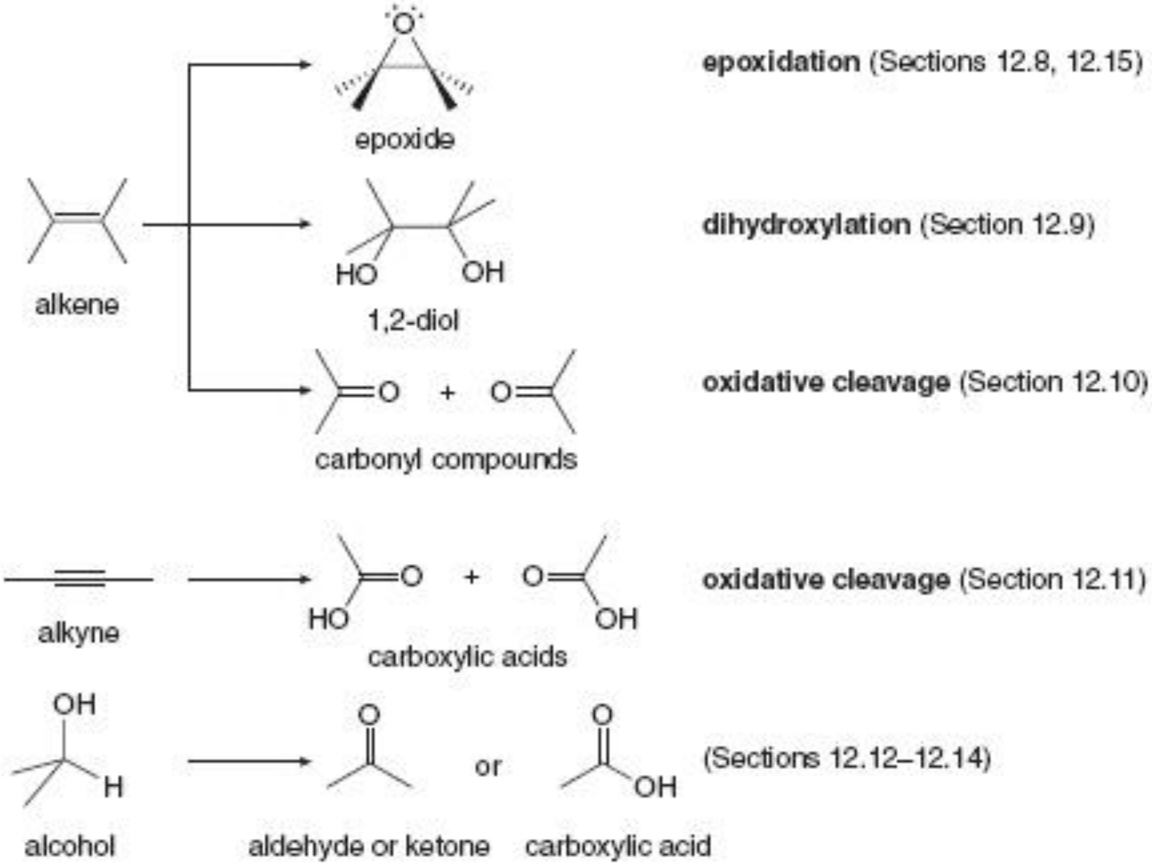
CrO_3



pyridinium chlorochromate

PCC

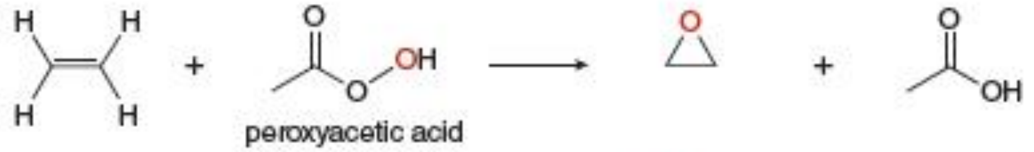
Oxidation reactions of alkenes, alkynes, and alcohols

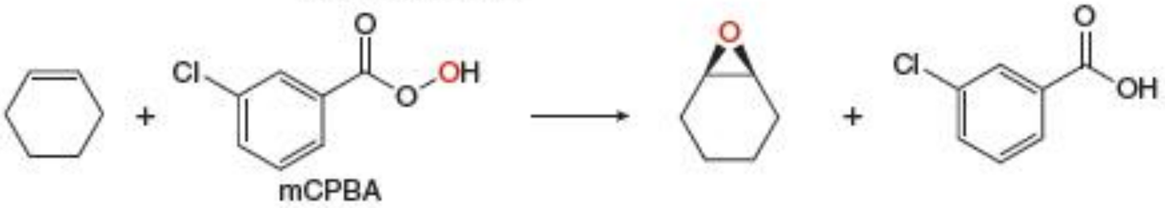


Epoxidation

Epoxidation is the addition of a single oxygen atom to an alkene to form an epoxide.

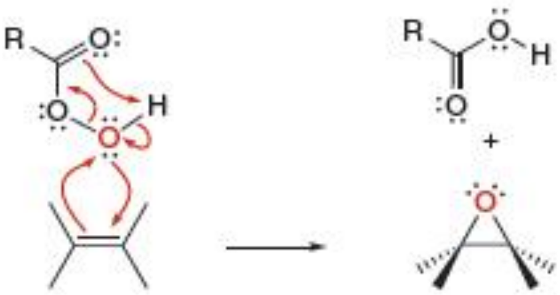
The weak π bond of the alkene is broken and two new C ─O σ bonds are formed. Epoxidation is typically carried out with a peroxyacid, resulting in cleavage of the weak O ─ O bond of the reagent.





Epoxidation occurs via the concerted addition of one oxygen atom of the peroxyacid to the π bond

Mechanism 12.4 Epoxidation of an Alkene with a Peroxyacid



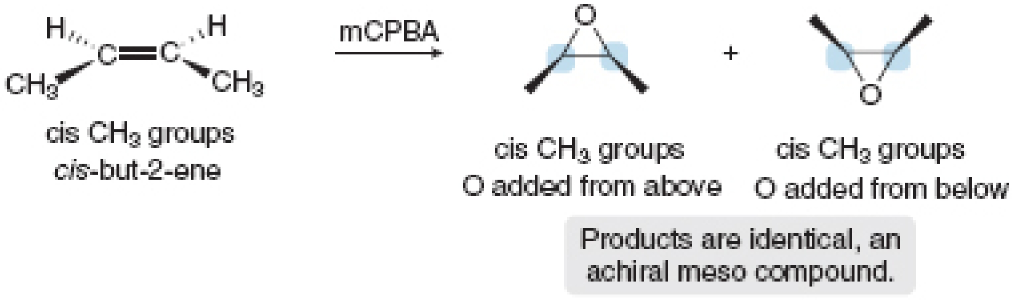
- All bonds are broken and formed in a single step. The two epoxide C—O bonds are formed from one electron pair of the π bond and one lone pair of the peroxyacid. The weak O—O bond is broken.

The Stereochemistry of Epoxidation

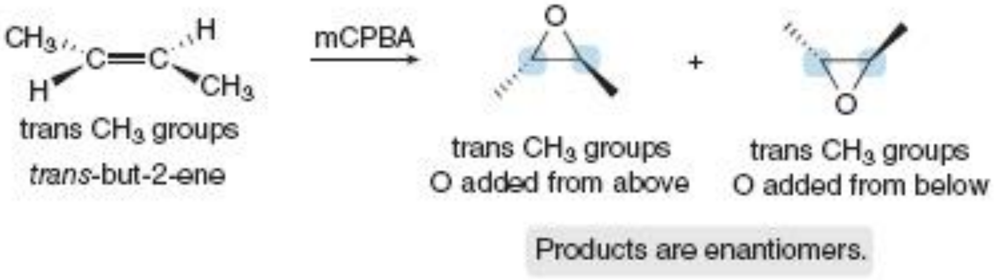
Epoxidation occurs via **syn addition** of an O atom from either side of the planar double bond, so that both C—O bonds are formed on the same side. The relative position of substituents in the alkene reactant is **retained** in the epoxide product.

- **A cis alkene gives an epoxide with cis substituents. A trans alkene gives an epoxide with trans substituents.**
- Epoxidation is a **stereospecific** reaction because cis and trans alkenes yield different stereoisomers as products
  - General rule about the stereochemistry of reactions: **an achiral starting material gives achiral or racemic products**.

Example

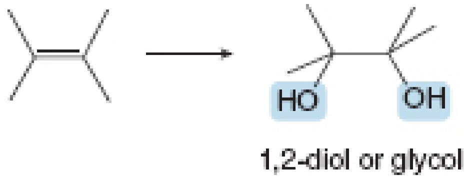


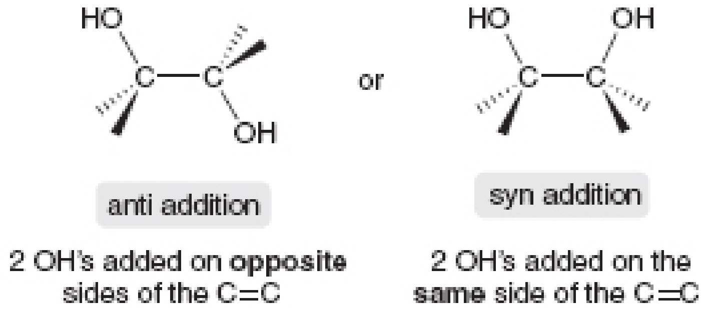
The **trans** methyl groups in *trans*-but-2-ene, become **trans** substituents in the epoxide. Addition of an O atom from either side of the trigonal planar alkene yields an equal mixture of two enantiomers—a **racemic mixture**—with two stereogenic centers labeled in blue.



Dihydroxylation

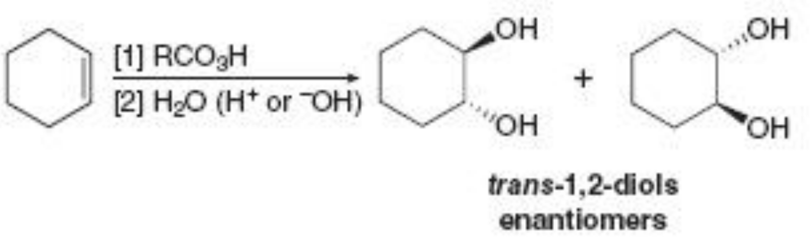
Dihydroxylation is the addition of two hydroxy groups to a double bond, forming a **1,2-diol** or **glycol.**



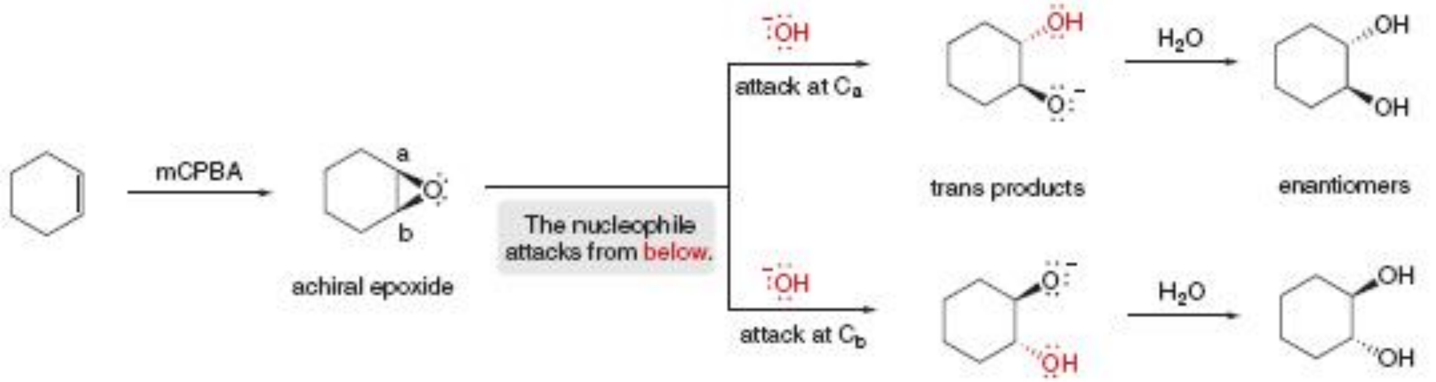


Anti Dihydroxylation

- **Anti dihydroxylation is achieved in two steps**—epoxidation followed by opening of the ring with ⁻OH or H_2O.
- Cyclohexene, for example, is converted to a racemic mixture of two *trans*-cyclohexane-1,2-diols by anti addition of two OH groups.



The stereochemistry of the products can be understood by examining the stereochemistry of each step.

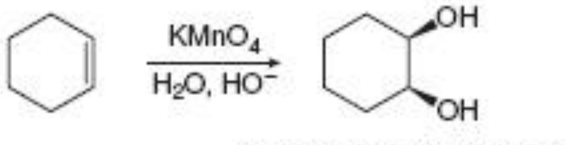


- Epoxidation of cyclohexene adds an O atom from either above or below the plane of the double bond to form a single **achiral epoxide**.
- Opening of the epoxide ring then occurs with **backside attack at either C — O bond**.
- Because the epoxide is drawn above the plane of the six-membered ring, nucleophilic attack occurs from **below** the plane.
- **This reaction is a specific example of the opening of epoxide rings with strong nucleophiles**

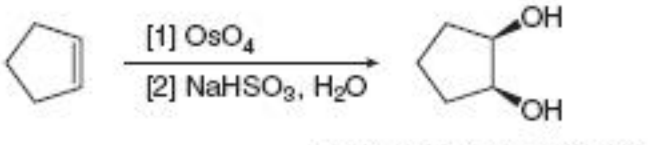
Overall result is **anti addition of two OH groups** to an alkene.

Syn Dihydroxylation

- **Syn dihydroxylation** results when an alkene is treated with either **$KMnO_4$** or **OsO_4**.

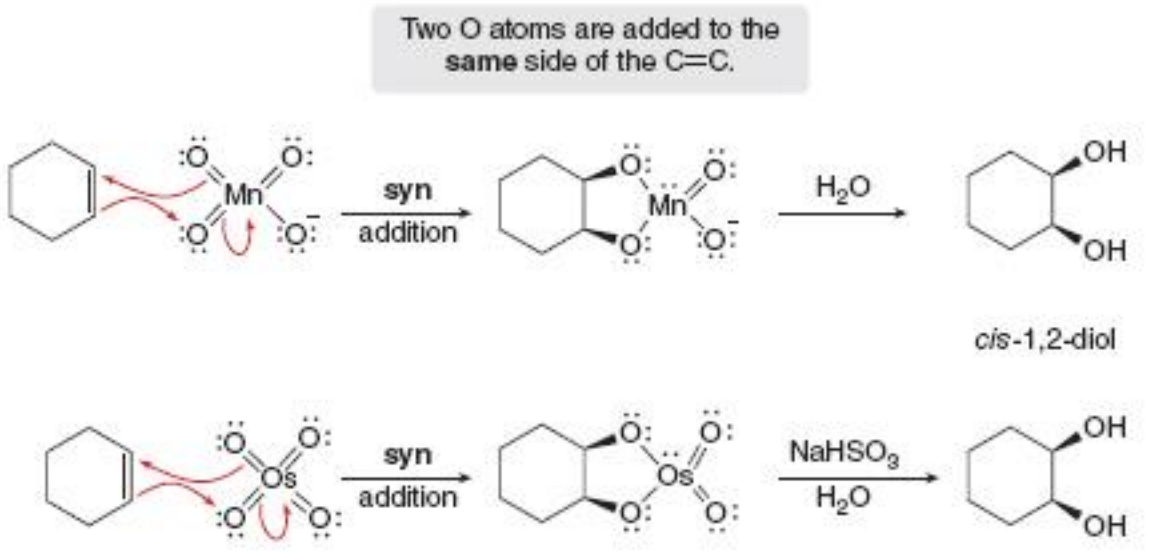


cis-cyclohexane-1,2-diol



cis-cyclopentane-1,2-diol

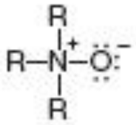
- **Each reagent adds two oxygen atoms to the same side** of the double bond—that is, in a **syn** fashion—to yield a cyclic intermediate.
- Hydrolysis of the cyclic intermediate cleaves the metal—oxygen bonds, forming the *cis*-1,2-diol. With OsO_4, sodium bisulfite ($NaHSO_3$) is also added in the hydrolysis step.


Two O atoms are added to the **same side** of the C=C.

cis-1,2-diol

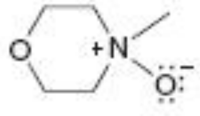
- Although $KMnO_4$ is inexpensive and readily available, its use is limited by its insolubility in organic solvents. To prevent further oxidation of the product 1,2-diol, the reaction mixture must be kept basic with added ^{-}OH.

- NMO is an **amine oxide**. It is not possible to draw a Lewis structure of an amine oxide having only neutral atoms.



amine oxide

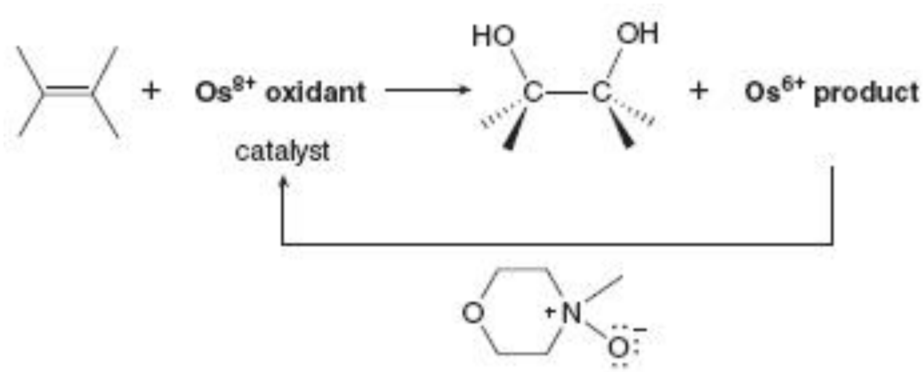
- Although OsO_4 is a more selective oxidant than $KMnO_4$ and is soluble in organic solvents, it is toxic and expensive. To overcome these limitations, dihydroxylation can be carried out by using a *catalytic* amount of OsO_4, if the oxidant ***N*-methylmorpholine *N*-oxide (NMO)** is also added.



N-methylmorpholine *N*-oxide

NMO

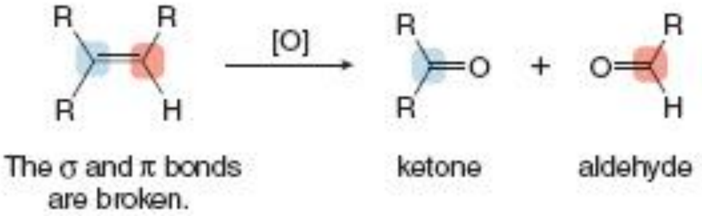
- In the catalytic process, dihydroxylation of the double bond converts the Os^{8+} oxidant into an Os^{6+}product, which is then re-oxidized by NMO to Os^{8+}. This Os^{8+} reagent can then be used for dihydroxylation once again, and the catalytic cycle continues.



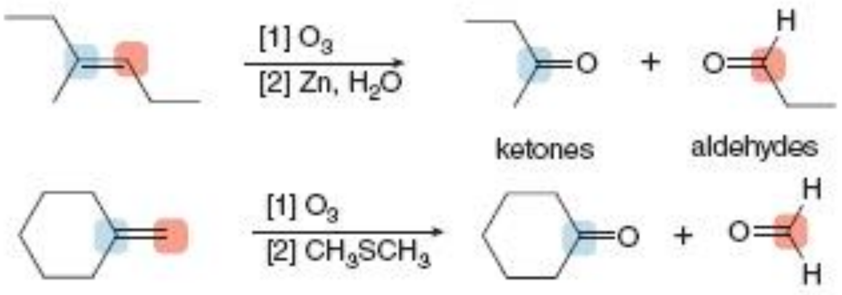
NMO oxidizes the Os^{6+} product back to Os^{8+} to begin the cycle again.

Oxidative Cleavage of Alkenes

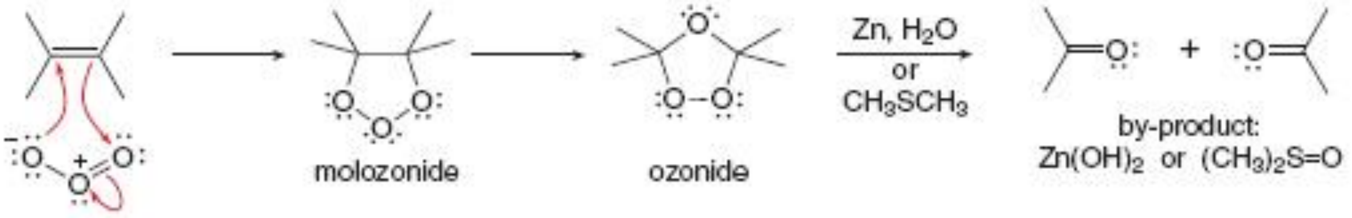
- **Oxidative cleavage of an alkene breaks both the σ and π bonds of the double bond to form two carbonyl groups**.
- Depending on the number of R groups bonded to the double bond, oxidative cleavage yields either**…ketones** or **aldehydes.**



- One method of oxidative cleavage relies on a two-step procedure using **ozone (O_3) as the oxidant** in the first step. Cleavage with ozone is called **ozonolysis.**



- Addition of ozone to the π bond of the alkene forms an unstable intermediate called a **molozonide**, which then rearranges to an **ozonide** by a stepwise process.
- The unstable ozonide is then reduced without isolation to afford carbonyl compounds.
- **Zn (in H_2O) or dimethyl sulfide (CH_3SCH_3)** are two common reagents used to convert the ozonide to carbonyl compounds.

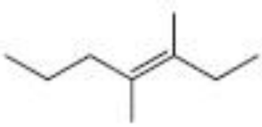


- **To draw the product of any oxidative cleavage:**
  1. **Locate all π bonds in the molecule.**
  2. **Replace each C=C by two C=O bonds.**

Sample Problem 12.3

Draw the products when each alkene is treated with O_3 followed by CH_3SCH_3.

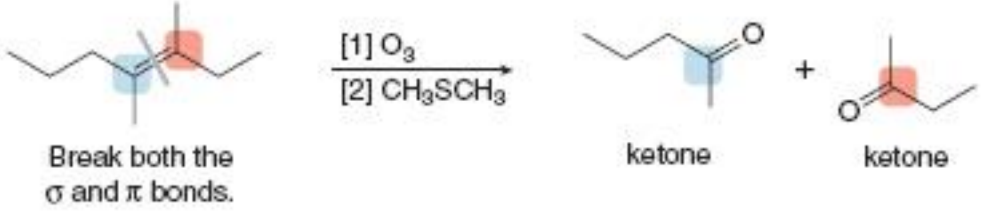
a.



b.

Solution

a. Cleave the double bond and replace it with two carbonyl groups.



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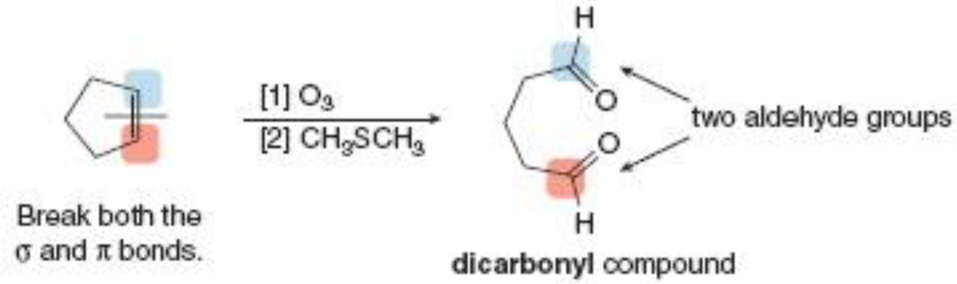
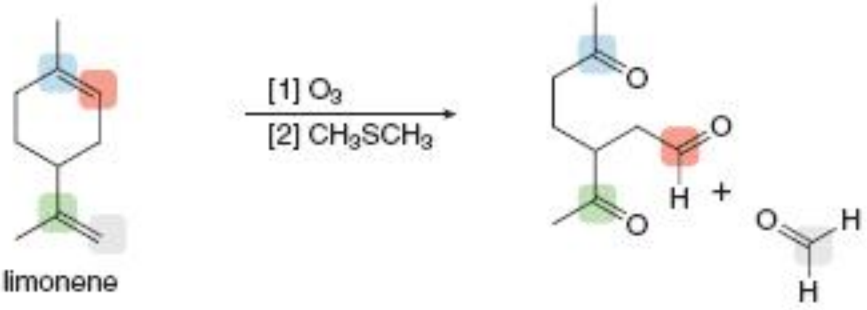
b. For a cycloalkene, oxidative cleavage results in a **single molecule with two carbonyl groups—a dicarbonyl compound.**

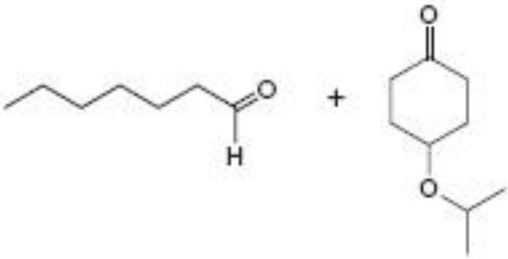


- **Ozonolysis of dienes (and other polyenes) results in oxidative cleavage of all C=C bonds**.
- The number of carbonyl groups formed in the products is *twice* the number of double bonds in the starting material.
- The *two* double bonds in limonene are converted to products containing *four* carbonyl groups.



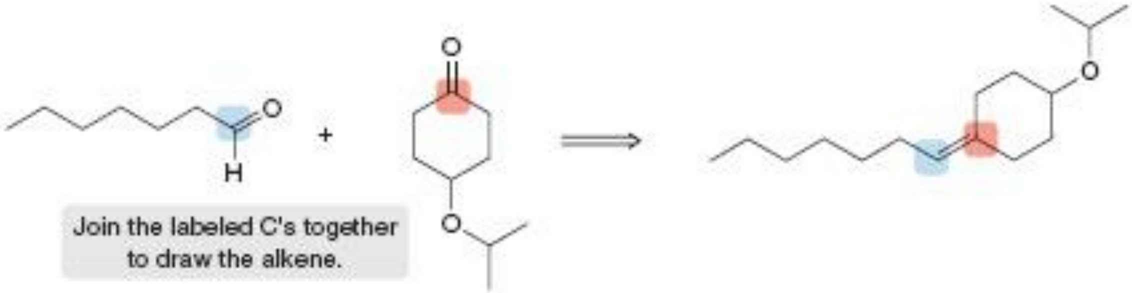
Sample Problem 12.4

What alkene forms the following products after reaction with O_3 followed by CH_3SCH_3?



Solution

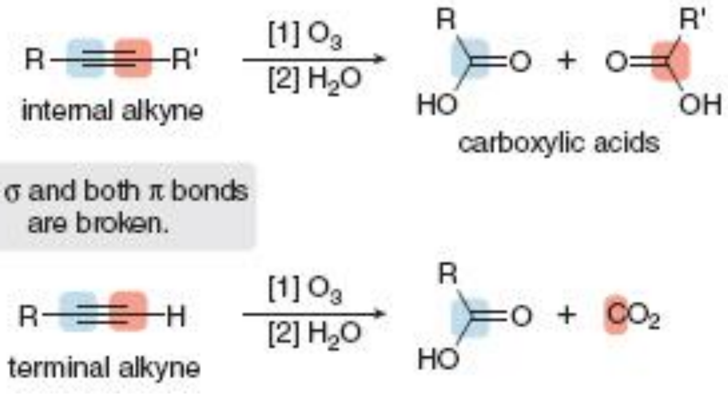
To draw the starting material, ignore the O atoms in the carbonyl groups and join the carbonyl carbons together by a C═C.



Join the labeled C's together to draw the alkene.

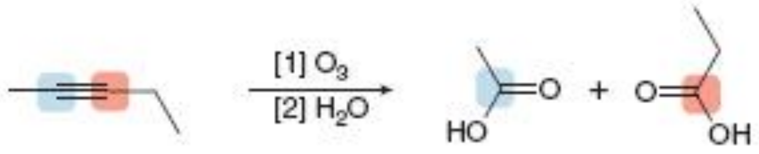
Oxidative Cleavage of Alkynes

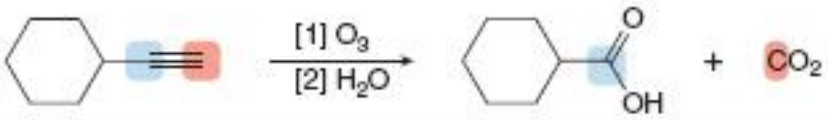
- **Alkynes also undergo oxidative cleavage** of the σ bond and both π bonds of the triple bond.
- Internal alkynes are oxidized to **carboxylic acids (RCOOH)**, whereas terminal alkynes afford carboxylic acids and **CO_2** from the *sp* hybridized C─H bond.



The σ and both π bonds are broken.

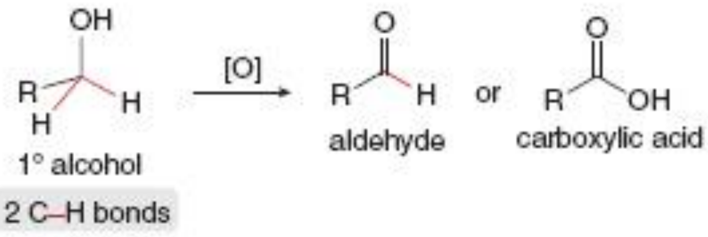
- Oxidative cleavage is commonly carried out with O_3, followed by cleavage of the intermediate ozonide with H_2O.



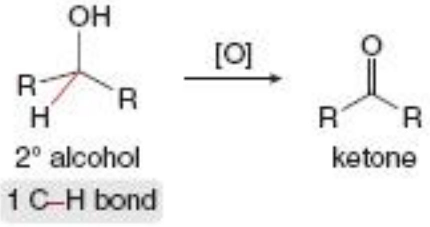


Oxidation of Alcohols

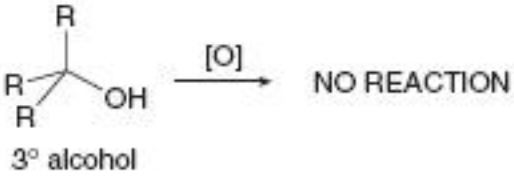
- **1° Alcohols are oxidized to either aldehydes or carboxylic acids by replacing either one or two C–H bonds by C–O bonds.**



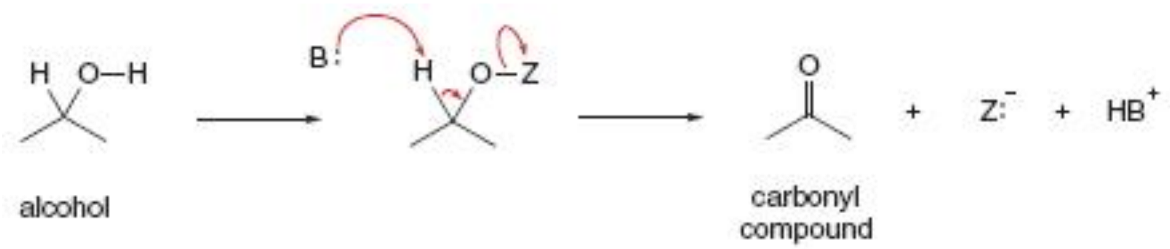
- **2° Alcohols are oxidized to ketones by replacing the one C–H bond by a C–O bond.**



- **3° Alcohols have no H atoms on the carbon with the OH group, so they are not easily oxidized.**



- **Alcohol oxidations often occur by a pathway that involves bonding a leaving group Z to the oxygen, where Z is typically a metal in a high oxidation state.**
- Elimination with a base then forms a C=O and a metal in a lower oxidation state.

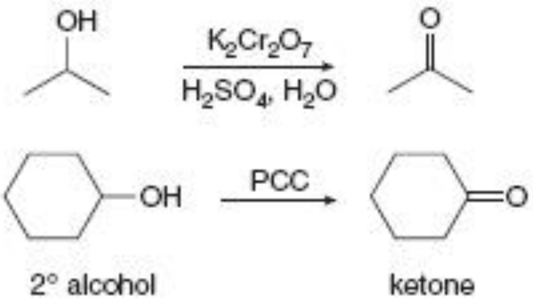


The oxidation of alcohols to carbonyl compounds is typically carried out with Cr^{6+} oxidants, which are reduced to Cr^{3+} products.

- **CrO_3, $Na_2Cr_2O_7$, and $K_2Cr_2O_7$ are strong, nonselective oxidants** used in aqueous acid (H_2SO_4+ H_2O).
- **PCC** (Section 12.7) is soluble in CH_2Cl_2 (dichloromethane), and can be used without strong acid present, making it a **more selective, milder oxidant.**

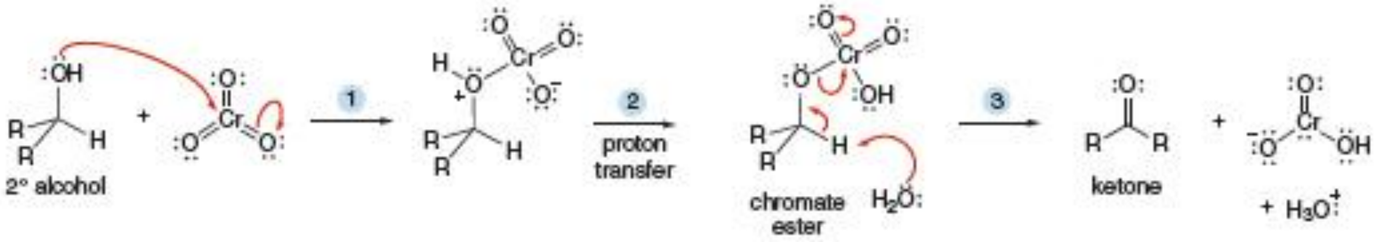
Oxidation of 2° Alcohols

Any of the Cr^{6+} oxidants effectively oxidizes 2° alcohols to ketones.



The mechanism for alcohol oxidation has two key parts: **formation of a chromate ester and loss of a proton.** Mechanism 12.5 is drawn for the oxidation of a general 2° alcohol with CrO_3.

Mechanism 12.5 Oxidation of an Alcohol with CrO_3



1 – 2 Nucleophilic attack of the alcohol on the electrophilic metal (Cr^{6+} oxidation state) followed by proton transfer forms a chromate ester.

3 A base removes a proton and the electron pair in the C – H bond forms the new π bond of the C=O. Carbon is oxidized because the number of C-O bonds increases, and Cr^{6+} is reduced to Cr^{4+}.

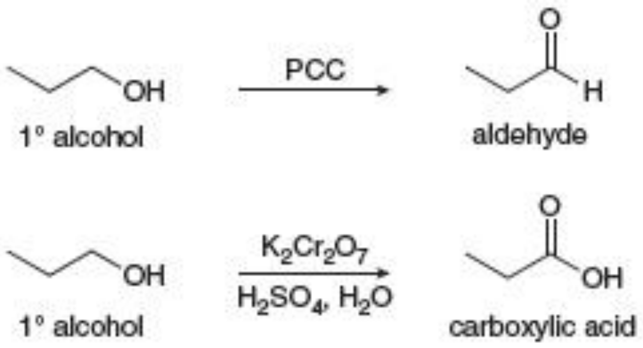
- These three steps convert the Cr^{6+} oxidant to a Cr^{4+} product, which is then further reduced to a Cr^{3+}product by a series of steps.

Oxidation of 1° Alcohols

1° Alcohols are oxidized to either aldehydes or carboxylic acids, depending on the reagent.

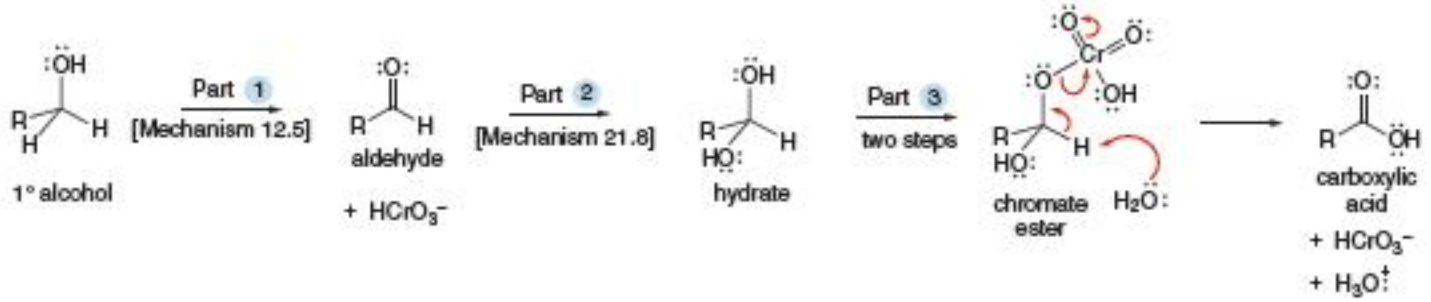
- **1° Alcohols are oxidized to aldehydes (RCHO) under mild reaction conditions—using PCC in CH_2Cl_2.**

- **1° Alcohols are oxidized to carboxylic acids (RCOOH) under harsher reaction conditions: $Na_2Cr_2O_7$, $K_2Cr_2O_7$, or CrO_3 in the presence of H_2O and H_2SO_4.**



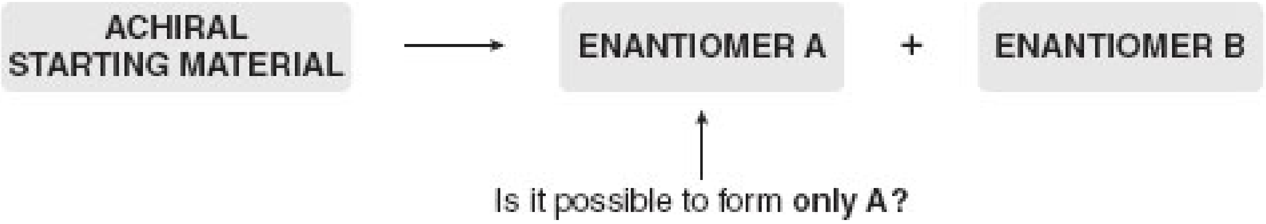
- **Oxidation of a 1º alcohol to a carboxylic acid requires three operations**
    1. **Oxidation first to the aldehyde**
    2. **Reaction with water**
    3. **Further Oxidation to the carboxylic acid**

Mechanism 12.6 Oxidation of a 1° Alcohol to a Carboxylic Acid



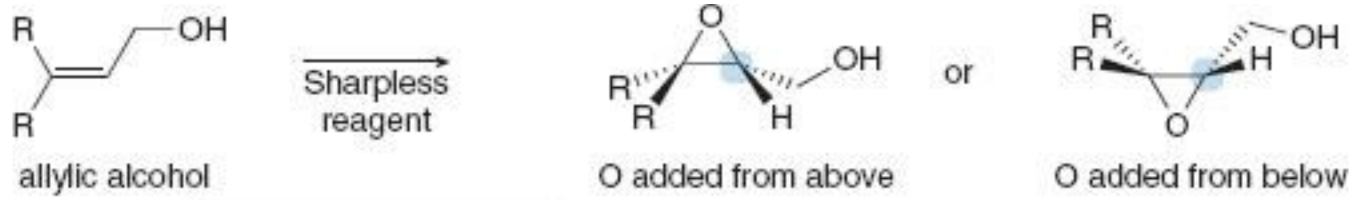
- Part ① The 1° alcohol is oxidized to an aldehyde by the three-step sequence in Mechanism 12.5.
- Part ② Water adds to the C=O to form a hydrate, a compound with two OH groups bonded to the same carbon, by a mechanism discussed in Section 21.13.
- Part ③ Oxidation of the C ─ H bond of the hydrate follows Mechanism 12.5–formation of a chromate ester and loss of a proton.

Sharpless Epoxidation



- **An *enantioselective* reaction affords predominantly or exclusively one enantiomer.**
- **A reaction that converts an achiral starting material into predominantly one enantiomer is also called an *asymmetric reaction.***

The Sharpless asymmetric epoxidation is an enantioselective reaction that oxidizes alkenes to epoxides. Only the double bonds of **allylic alcohols**—that is, alcohols having a hydroxy group on the carbon adjacent to a C═C—are oxidized in this reaction.



Sharpless reagent
$(CH_3)_3C\text{—}OOH$
$Ti[OCH(CH_3)_2]_4$
(+)- or (−)-diethyl tartrate

- With Sharpless reagent, one enantiomer is favored.
- The new stereogenic center is labeled in blue.

- **The Sharpless reagent consists of three components**
  1. *tert*-butyl hydroperoxide, **$(CH_3)_3COOH$;** a titanium catalyst—usually titanium(IV) isopropoxide,
  2. **$Ti[OCH(CH_3)_2]_4$**
  3. **Diethyl tartrate (DET)**

- There are two different chiral diethyl tartrate isomers, labeled as (+)-DET or (−)-DET to indicate the direction in which they rotate polarized light.

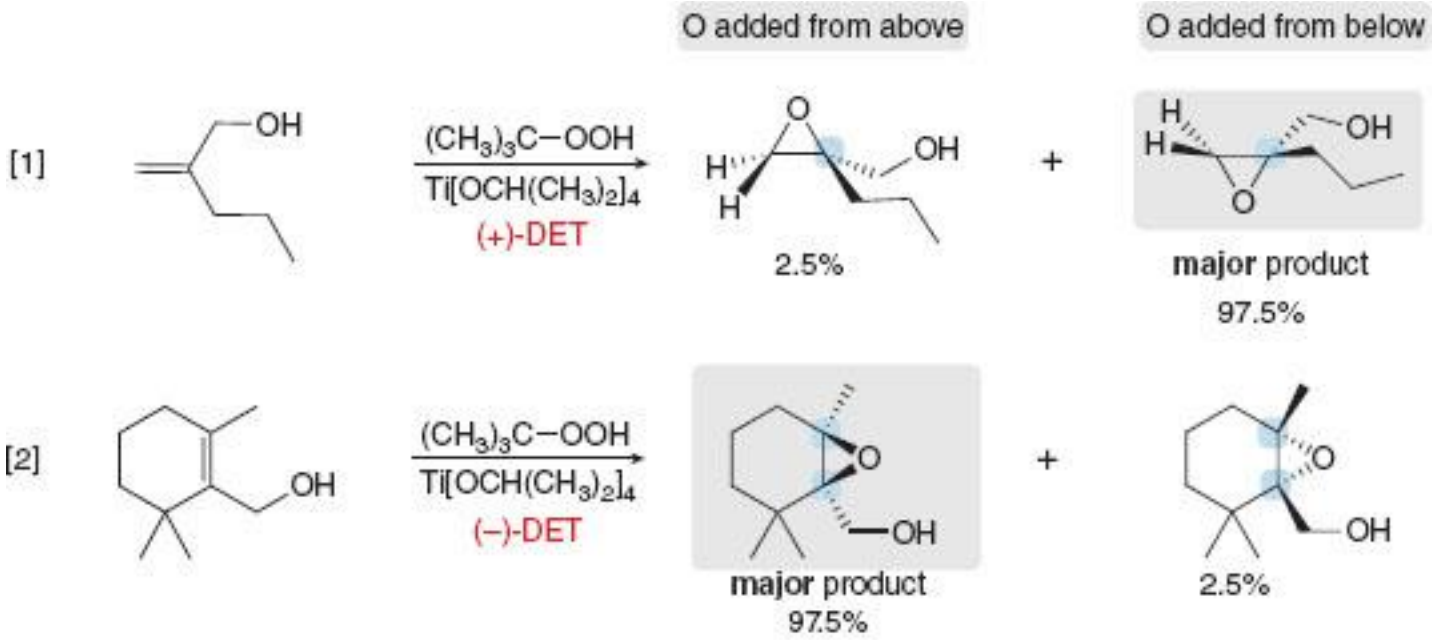
(+)-(*R*,*R*)-diethyl tartrate

(+)-DET

(−)-(*S*,*S*)-diethyl tartrate

(−)-DET

The identity of the DET isomer determines which enantiomer is the major product obtained in the epoxidation of an allylic alcohol with the Sharpless reagent.



Stereogenic centers are labeled in blue.

- The degree of enantioselectivity of a reaction is measured by its enantiomeric excess (***ee***)
- Reactions [1] and [2] are highly enantioselective because each has an enantiomeric excess of 95% (97.5% of the major enantiomer − 2.5% of the minor enantiomer).

To determine which enantiomer is formed for a given isomer of DET, draw the allylic alcohol in a plane, with the **C═C horizontal and the OH group in the upper right corner;** then:

Enantiomeric excess = *ee* = % of one enantiomer – % of the other enantiomer.

- **Epoxidation with (–)-DET adds an oxygen atom from above the plane.**
- **Epoxidation with (+)-DET adds an oxygen atom from below the plane.**