Pericyclic Reactions

Introduction
Pericyclic reactions are one of the three major types organic reaction, wherein the transition state of the molecule has a cyclic geometry, and the reaction progresses in a concerted fashion, in a single step. Pericyclic reactions are usually rearrangement reactions.

There are three main types of pericyclic reactions:

1. **electroyclic reactions** (eg. 6π electrocyclisation)
   - ![Diagram](image1)
   - one more σ-bond
   - one less π-bond

2. **cycloaddition reactions** (eg. Diels-Alder reaction)
   - ![Diagram](image2)
   - two more σ-bonds
   - two less π-bonds

3. **sigmatropic reactions** (eg. Cope reaction)
   - ![Diagram](image3)
   - same number of σ-bonds and π-bonds, different connectivity

Note that each double pair of lines represents one pi bond, while each line segment, be it single or double, also indicates a sigma bond. So a double set of lines represents a pi bond and a sigma bond. Since there is no electrophilic or nucleophilic component, there is no beginning and ending for arrows. Arrow pushing can be either clockwise or anticlockwise.
Electrocyclic Reactions
A Reversible process in which a ring is formed by reorganisation of π-electrons of conjugated polyenes, promoted by either heat or light. The position of equilibrium (conjugated polyene or carbocycle) depends upon the relative stability of the compounds involved.

Molecular Orbital Theory
There are two possibilities for rearrangement to generate new σ-bond, depending upon the symmetry of HOMO for the π-system. Consider the possible alignments of the p-orbitals:

If we represent the possible phases of the nodes as positive and negative signs, we have:
Note that for a ground-state sigma bond to form, the orbitals must rotate so that constructive interference occurs between orbitals.
**Stereospecificity**

Electrocyclic reactions are stereospecific, in that the stereochemistry of the product is determined by the stereochemistry of the starting material. A quick method to determine the phase of the termini is that π-electron systems with \( n \) π-electrons have \( n/2 \) orbitals filled. If \( n \) is odd then the termini are in phase (disrotatory), while if it is even the termini are out of phase (conrotatory).

![Diagram of (2E,4Z,6E)-Octatriene leading to cis-5,6-Dimethyl-1,3-cyclohexadiene](image)

The relevant p-orbitals are seen as extending into and out of the plane of the ring, rotating inwards towards each other into order to form the new sigma bond.

*Different stereochemical outcome under photochemical conditions:* HOMO becomes \( \Psi_{\pm1} \); switch from conrotatory \( \iff \) disrotatory

![Diagram of (2E,4Z,6E)-Octatriene leading to trans-5,6-Dimethyl-1,3-cyclohexadiene](image)

**Electrocyclic Ring Opening**

This is the reverse of the electrocyclic reaction. Common for cyclobutenes to relieve ring strain. The method of ring opening must match that of ring closing, as the reactions are reversible.
cis-3,4-Dimethylcyclobutene $\xrightarrow{175^\circ C}$ (2E,4Z)-Hexadiene

trans-3,4-Dimethylcyclobutene $\xrightarrow{175^\circ C}$ (2E,4E)-Hexadiene

Excited-state HOMO

Ground-state HOMO

Excited-state HOMO

Ground-state HOMO

(2E,4E)-Hexadiene

cis-3,4-Dimethylcyclobutene

(2E,4Z,6E)-Octatriene

trans-5,6-Dimethyl-1,3-cyclohexadiene

Light

Heat

Light

Heat
**Cycloaddition Reactions**

A cycloaddition reaction involves two unsaturated systems combining to form a cyclic product with two new σ-bonds formed at the expense of two π-bonds. Such reactions are referred to as \([n+m]\), where \(n\) and \(m\) are the number of π-electrons involved in the reactant molecules.

![Diagram of [2 + 2] cycloaddition](image)

![Diagram of [4 + 2] cycloaddition](image) (Diels-Alder)

![Diagram of [4 + 4] cycloaddition](image)

**The Diels-Alder Reaction**

Arguably the most powerful reaction for the formation of C-C bonds.

The prototype reaction is very slow even at high temperatures:

![Diagram of Diels-Alder reaction](image) very slow

Incorporation of electron withdrawing groups increases the rate:

![Diagram of Diels-Alder reaction with electron withdrawing substituents](image) fast

![Diagram of Diels-Alder reaction with very fast rate](image) very fast

**Frontier Molecular Orbital Theory**

Cycloadditions occur by interaction of the HOMO of one reactant and the LUMO of the other. The smaller the HOMO-LUMO energy gap, the better the energy gain on bonding (better orbital overlap). Electron-donating substituents increase electron density and so raise the energy of MOs, while electron-withdrawing substituents lower the energy of MOs by removing electron density.
Cycloaddition reactions are symmetry allowed only when the lobes of the HOMO of one reactant and the LUMO of the other are of the same algebraic sign, in what is called the suprafacial reaction.

The alternative antarafacial docking mode is not geometrically possible in small π-systems.

Under thermal conditions, the diene HOMO interacts with the dienophile LUMO in a suprafacial reaction:

Diels-Alder reactions are thus said to be thermally allowed.
Stereochemistry of Diels-Alder

Diene and dienophile geometry are conserved in the cyclohexene product.

 cis-2-butene

 cis-product

 trans-2-butene

 trans-product

 E,E-geometry

 cis-product

 E,Z-geometry

 trans-product

For disubstituted dienophiles, two docking modes are possible, leading to two stereoisomers:

Two docking modes possible:

EXO

endo substituents on dienophile point away from diene

ENDO

endo substituents on dienophile lie directly underneath diene
The exo-stereoisomer is more stable (the thermodynamic product), but the endo-stereoisomer is formed faster (the kinetic product) and so is normally the predominant product, unless the reaction is run at high temperature for a long time.

**Regiochemistry of Diels-Alder Reaction**

With an unsymmetrical diene and dieneophile, two regioisomeric products are possible:

- For the diene and dieneophile indicated, the 'ortho' and 'para' products predominate over 'meta' products. This occurs because electron-donating groups on the diene increase the size of the HOMO coefficient at the β and δ positions. Likewise, for dienophiles, the LUMO coefficient is increased at the β position by the electron withdrawing group. More effective overlap occurs between nodes of similar size.
[2+2] Cycloadditions
These reactions are symmetry forbidden to occur via the suprafacial method, and geometrically implausible to occur via the antarafacial method.

As such, these reactions can only occur under photochemical conditions:

Sigmatropic Reactions
Introduction
Sigmatropic reactions occur when a σ-bonded substituent migrates across a π-system. The product has the same number of σ- and π-bonds, but in a different order. Reactions classified as [n,m]-sigmatropic rearrangements, which designates the positions where the new sigma-bond forms.
Cope Rearrangement

Cope rearrangements are reversible [3,3]-sigmatropic reactions of all-carbon systems. The starting material and product are both 1,5-dienes.
Stereochemistry is a result of a chair-like, six-membered transition state in which substituents prefer an equatorial-like position.

Claisen Rearrangement
Claisen rearrangements are related to the Cope rearrangement but involve an oxygen atom. These reactions often require high temperatures but are essentially irreversible as the product is more stable than the starting allyl vinyl ether. Overall a Claisen rearrangement transforms C−O bond into a C−C bond.

Aromatic Claisen rearrangement is a special case that involves migration of the allyl group of an aromatic allyl ether to the ortho-position of the aromatic ring.
alkyl aryl ethers → ortho-allyl phenols

HEAT

[3,3] sigmatropic rearrangement
(relatively slow)

keto-enol tautomerisation
(relatively fast)
Radical Reactions

Types of Reactions

**homolysis**

\[ \text{A-B} \rightarrow \text{A}^* + \text{B}^* \]

**coupling/recombination**

\[ \text{A}^* + \text{B}^* \rightarrow \text{A-B} \]

**substitution**

\[ \text{A}^* + \text{B-C} \rightarrow \text{A-B} + \text{C}^* \]

**addition**

\[ \text{A}^* + \text{B-C} \rightarrow \text{A-B-C}^* \]

**β-scission**

\[ \text{A-B-C} \rightarrow \text{A-B} + \text{C}^* \]

Mechanisms of Radical Reactions

**Radical Stability**

Bond-dissociation energy (BDE) is one measure of the strength in a chemical bond. It is defined as the standard enthalpy change when a bond is cleaved by homolysis - the amount of energy needed to break the bond.

The stability of radical \( R^* \) is estimated from Bond Dissociation Energy (BDE) of R-H. The weaker the bond, the less strong will be the tendency of the radical components to recombine, and thus the more stable will be the radical.

The smaller the BDE, the weaker the bond.

**Weakest C-H bond/**

Most stable C’ radical

- 361 kJ/mol

368

\( \text{H} \)

\( \text{H}_2\text{C-OH} \)

\( 390 \)

\( 401 \)

\( \text{H} \)

\( \text{H}_2\text{C-OH} \)

\( 368 \)

\( \text{H} \)

\( \text{H}_2\text{C-OH} \)

\( 390 \)

\( 401 \)

\( \text{H} \)

\( \text{H}_2\text{C-OH} \)

\( 390 \)

\( 401 \)

**Strongest C-H bond/**

Least stable C’ radical

- 420

438

444

464

552
Alkyl radical stabilities follow carbocation stabilities, so the most stable will be the most highly substituted carbon, as there is more space for electrons to 'spread out' over.

Radicals can also be stabilised through resonance stabilisation in π-systems, or by adjacent heteroatoms with lone pairs.

Free radicals are also stabilized by adjacent groups with lone pairs, such as oxygen and nitrogen. This occurs because the adjacent lone pair can donate electron density to the half-empty p orbital, which is a stabilizing interaction, lowering the energy of the SOMO orbital.
Radical Initiation

Usually occurs through homolysis of weak bonds through heating or irradiation with UV light:

**Halogens**

\[
\text{Br-Br} \rightarrow \text{Br}^\cdot + \text{Br}^\cdot
\]

**Alkyl peroxides**

\[
\text{O-O} \rightarrow \text{O}^\cdot\text{O}^\cdot
\]

**Acyl peroxides**

E.g. benzoyl peroxide

\[
\text{Ph-COO-O-Ph} \rightarrow \text{Ph-COO}^\cdot\text{O}^\cdot\text{Ph}
\]

**Azo compounds**

E.g. AIBN

2,2'-azobis(isobutyronitrile)

\[
\text{NC-N} \rightarrow \text{NC}^\cdot\text{N}^\cdot\text{CN}
\]

**Stages of Radial Reactions**

1. **Initiation**
   - \(\text{Ph-COO-O-Ph} \rightarrow \text{Ph-COO}^\cdot\text{O}^\cdot\text{Ph}\)

2. **Propagation**
   - \(\text{Ph-COO}^\cdot\text{O}^\cdot\text{Ph} \rightarrow \text{Ph-COOH} + \text{Br}^\cdot\text{Br}\)

3. **Termination**
   - \(\text{Br}^\cdot\text{Br} \rightarrow \text{Br}^\cdot\text{Br}\)
This can also be written in chain reaction form, ignoring the initiation and termination steps:

To determine which steps are the propagation steps, find the last radical product of a reaction (for the above it is Br), and trace back to the step where it was a reactant. Both those stages and all those in between are propagation steps.

Types of Radical Reactions

Addition Reactions
Radical addition reactions add a substituent across a double bond. They produce the anti-Markovnikov product (addition to the least substituted carbon), because that leaves the radical carbon to be the most substituted carbon, which yields the most stable intermediate.

Halogenation Reactions
These are bromination or chlorodation reactions which occur through free radicals. Unlike polar reactions, the halogen does not add over the double bond, but rather adds to a carbon one removed from the bond.
One problem with this reaction is in preventing the undesirable side ionic reaction of Br₂ or HBr with the alkene. The trick is to use a base to remove the HBr, and to keep [Br₂] low by adding it slowly. Another option is to use N-bromosuccinimide (NBS) in place of Br₂.

The N-bromosuccinimide does not actually react directly at all - the radical mechanism is the same. What it does rather is to remove HBr and convert it to Br₂ at the same rate as it is consumed, thus keeping Br₂ concentrations low. Basically it does the job of removing HBr and keeping low Br₂ automatically.
Radical Additions to form C-C Bonds

Tributyltinhydride (Bu₃SnH) is a very useful reagent in extracting a halogen from cyclohexane.

This is not particularly useful in itself, however. The real utility of this reaction is in generating a cyclohexane radical, which then can be used in further addition reactions. One advantage of tributyltin hydride chemistry is that a carbon-centred radical can be generated at a specific position through abstraction of a halogen placed at the desired position.
The difficulty with such reactions is in minimising the rate of potential side reactions, which include the following:

- Prevent the first reaction by adding excess alkene and adding BuSnH only slowly
- The second reaction is fairly slow so is not a big problem
- To prevent the third reaction, RX needs to react with the BuSn radical much more readily than the CN alkene. This occurs for X=I and often also X=Br but not X=Cl

**Intramolecular Radical Additions**

In contrast to most intermolecular radical reactions, intramolecular radical cyclisation reactions frequently proceed via the least stable (least substituted) radical. This is because such reactions are governed by stereoelectronic effects, relating to effects of geometry and orbital overlap.
These reactions proceed via a chair-like transition state, where the most stable form has substituents in equatorial positions.
5-Exo radical cyclisations are one of the most effective methods for generating 5-membered rings, and consequently have been used in many syntheses of cyclopentane-containing natural products. Of particular utility is the design of cascade or domino reactions, where the product of the first radical process is set up to undergo further processes, generating a polycyclic system in one step.
Carbon-Carbon Bond Formation

Enolate Chemistry

Introduction to Enolates
Aldehydes or ketones which have alpha-hydrogens can be formed into enolates by the addition of a strong base, which removes the weakly acidic alpha-proton. These enolates can then react in a number of ways to form carbon-carbon bonds.

The acidity of the alpha-proton is due to the presence of the carbonyl group, which enables the existence of stabilising resonance structures. Common bases that are used to form the enolate include:

Sodium and potassium bases can also be used to generate the corresponding enolate. The larger size of these alkali metals results in a larger separation of the cation, giving more reactive, but less stable ionic enolates. They are particularly useful for multiple substitution reactions:

Regioselectivity and Enolates
An unsymmetrical ketone can form two different enolates (different regioisomers) upon deprotonation. One is the kinetic product, and the other the thermodynamic product.
Kinetic reactions lead to the enolate that is formed the fastest, which is usually the least substituted enolate (fewest non-hydrogens on the new double bond). This occurs for two reasons:

1. The less substituted carbon will be quicker to deprotonate for steric reasons
2. The less substituted carbon has more hydrogens and so is simply statistically more likely to deprotonate

Just as alkenes are more stable when more highly substituted, enolates are also more stable the more substituents that they bear. In order to form the kinetic product, therefore, it is necessary to keep the reaction temperature low, and use excess base so that deprotonation is irreversible. Using a hindered base like LDA is also helpful, as it is less likely to protonate the more substituted site.

Aldol Addition Reaction
Aldehyde and/or ketone react with catalytic base to produce alpha-beta unsaturated aldehyde
The general structure of an aldol:

\[
\begin{align*}
\text{OH} & \quad \text{O} \\
R^1 & \quad R^2 \\
\text{R} & \quad \text{R}^3
\end{align*}
\]

**Crossed Aldol Reaction**

Crossed aldol reactions generally don't work so well, owing to the number of possible products:

\[
\begin{align*}
\text{CH}_3\text{CHO} + \text{CH}_3\text{COH} & \xrightarrow{\text{base}} \text{cross products} \\
& + \text{homocoupled}
\end{align*}
\]
Intramolecular Aldol Reaction

Bredt’s Rule
A double bond cannot be placed at the bridgehead of a bridged ring system, unless the rings are large enough.

Bredt’s rule is a consequence of the fact that having a double bond on a bridgehead would be equivalent to having a trans double bond on a ring, which is not possible for small rings due to a combination of ring strain, and angle strain. The p orbitals of the bridgehead atom and adjacent atoms are orthogonal and thus are not aligned properly for the formation of pi bonds.
Michael Reaction

An enolate reacts with an alpha,beta-unsaturated carbonyl compound (i.e. the product of an aldol addition) to give conjugate addition at the site of the double bond.
The Aldehyde Enolate problem
Aldehydes are so electrophilic that, even with LDA at −78°C, the freshly formed enolate reacts with unreacted aldehydes in a self-condensation reaction to form an aldol.

Direct addition of the base to the aldehyde can also pose a problem.

Stock Enamine Alkylation
Secondary amines react with aldehydes and ketones to form enamines, which are nucleophilic at carbon (like enols and enolates) and therefore can react with electrophiles such as alpha,beta-unsaturated carbonyl compounds to undergo an alpha-substitution. The overall process amounts to an enolate alkylation, but there is no strong base involved and so no danger of unwanted addition.
Any secondary amine can be used, but cyclic secondary amines are preferred as they are more nucleophilic. Examples include:

- pyrrolidine
- piperidine
- morpholine

Enamine reactions favour the less substituted enamine, owing to steric hindrance effects:

Enamines are more stable than enols, and are consequently less reactive and less nucleophilic. They typically do not react with aldehydes and ketones. Their reaction is typically limited to alkyl halides (alkylation) and alpha,beta-unsaturated carbonyls (Michael reactions).
Organometallic Chemistry

Grignard Reagents
Grignard reagents cause the carbon on the R group to become a nucleophile, making it suitable for nucleophilic attack:

\[
\delta^- \quad \delta^+ \quad \delta^- \\
R\text{-Mg}\text{-X} \quad \equiv \quad R: \quad \oplus \text{MgX}
\]

The standard method of preparation involves the reaction of an alkyl halide with magnesium metal in dry ether:

\[
R\text{-X} \quad + \quad \text{Mg} \quad \xrightarrow{\text{ether}} \quad R\text{MgX}
\]

The actual structure of Grignard reagents in solution has been a matter of considerable controversy. It has been proposed that they exist in an equilibrium of dimers called the Schlenck equilibrium:

\[
\text{RMgX} \quad \rightleftharpoons \quad \text{R}_2\text{Mg} \quad + \quad \text{MgX}_2 \quad \rightleftharpoons \quad \text{R}_2\text{Mg}\cdot\text{MgX}_2
\]

Organolithiums can be prepared from the corresponding halide and lithium metal:

\[
\begin{align*}
\text{CH}_2\text{CH}_2\text{Cl} & \quad + \quad 2\text{Li} \quad \rightarrow \quad \text{CH}_2\text{CH}_2\text{Li} \quad + \quad \text{LiCl} \\
\text{PhCH}_2\text{Br} & \quad \xrightarrow{\text{Mg}, \text{Et}_2\text{O}} \quad \text{PhCH}_2\text{MgBr} \quad + \quad \text{PhCH}_2\text{Br} \quad \xrightarrow{\text{Wurtz coupling}} \quad \text{PhCH}_2\text{C}(\text{Ph})\text{CH}_2\text{Ph}
\end{align*}
\]

To avoid this difficulty, an alternative approach is to use metal exchange with another organolithium:

\[
\begin{align*}
\text{PhCH}_2\text{Br} & \quad \xrightarrow{\text{nBuLi}} \quad \text{PhLi} \quad + \quad \text{nBuBr} \\
\text{Me}_2\text{C}(\text{Ph})\text{OBN} & \quad \xrightarrow{(t\text{-BuLi})} \quad \text{Me}_2\text{C}(\text{Ph})\text{OLi} \quad + \quad \text{OBn}
\end{align*}
\]
Grignard Reactions

The basic format for a grignard reaction is as follows:

\[
R-X + \text{alkyl or aryl halide} \xrightarrow{\text{Mg}^0} \text{Grignard reagent} \xrightarrow{\text{e.g. electrophile}} \text{product}
\]

**Note:** The example above shows a carbonyl group being converted to an alcohol. A variety of products are possible depending on the electrophile.

**Electrophile**
- Formaldehyde → 1° alcohol
- Aldehyde → 2° alcohol
- Ketone → 3° alcohol
- Carbon dioxide → Carboxylic acid
- Nitrile → Ketone

### Aldehydes and ketones

\[
\text{aldehyde or ketone} + R^*\text{MgX or R^*Li} \xrightarrow{\text{H}_2\text{O}^+} \text{1°, 2°, or 3° alcohol}
\]

### Strained ethers

\[
\text{MgBr or Li} \xrightarrow{\text{H}_2\text{O}^+} \text{OH}
\]
Nitriles

Organocuprates
Organocuprates can be formed by transmetallation of organolithiums or organomagnesiums with a copper(I) salt:

\[
RMgBr + Cul \rightarrow RCu + MgBrCl
\]

\[
RLi + Cul \rightarrow RCu + Lil
\]

This is useful because the addition of even a small amount of copper enables 1,4-addition to alpha,beta-unsaturated aldehydes and ketones, instead of the usual 1,2-addition.
Hard-SOft Acid Bases

Organolithiums and organomagnesiums are ‘hard’ nucleophiles/bases that have a high electronegativity difference $E(C-Mg) = 1.2$; $E(C-Li) = 1.5$, and the carbons therefore hold their valence electrons tightly. Organocopper is considered to be a ‘soft’ nucleophile/base that has a smaller electronegativity difference $E(C-Cu) = 0.6$ thus the carbon holds its valence electrons more loosely.

A carbonyl group is considered a ‘hard’ electrophile, with tightly bound electrons and thus high electronegativity and low polarizability across the 2 atoms of the carbonyl group. An $\alpha,\beta$-unsaturated carbonyl system is considered to be a ‘soft’ electrophile, with loosely bound electrons and high polarizability across the 4 atoms of the conjugated system.

The HSAB principle states that hard acids prefer to bond to hard bases, and soft acids prefer to bond to soft bases. Thus, lithium dialkylcuprates are highly selective for 1,4-addition.
The Wittig Reaction

Ylid Formation
An ylid is a neutral dipolar molecule containing a formally negatively charged atom directly attached to a heteroatom with a formal positive charge. Georg Wittig synthesized phosphorus ylids for the first time and found that these are stabilized by resonance because the P atom can become pentacoordinate.

Trialkyl- or triarylphosphorus(III) compounds are called phosphines and are the equivalent of amines. Reaction of a phosphine with an alkyl halide leads to a phosphonium salt. The positive charge on phosphorus increases the acidity of the neighboring protons, and they can be deprotonated to give an ylid.

\[
\text{Ph}_3\text{P}^- + \text{CH}_3\text{Br} \rightarrow \text{Ph}_3\text{P}^-\text{CH}_3\text{Br}^+ \rightarrow \text{BuLi} \rightarrow \text{Ph}_3\text{P}^-\text{CH}_2^- \rightarrow \text{Ph}_3\text{P}^-\text{CH}_2^- \rightarrow \text{Ph}_3\text{P}=\text{CH}_2
\]

triarylphosphine phosphonium salt an ylid

Use of Ylids
Ylids are nucleophilic species that attack the electrophilic carbon atom of aldehydes and ketones, forming first a betaine, and then eliminating to give an alkene and a phosphine oxide. Essentially, an alkyl group is added over the ketone group.

\[
\text{Ph}_3\text{P}^-\text{CH}_2^- + \text{PhC}=\text{O} \rightarrow \text{PhCH} = \text{C}=\text{O}^- + \text{Ph}_3\text{P}=\text{O}
\]

The mechanism for this reaction is given below:
**Vitamin A acetate synthesis**

The Wittig reaction is used for the industrial production of many important alkenes, particularly ones with very sensitive functional groups.

![Vitamin A acetate synthesis](image)

**Homologation**

A homologation reaction extends a chain by one methyl unit. It can be achieved through a Wittig reaction:

![Homologation](image)

**Stabilized and Unstabilized Ylids**

Ylids can be classified into two types: those with a conjugating or anion-stabilizing substituent adjacent to the negative charge, and those without. We call the first sort stabilized ylids because the negative charge is stabilized not only by the phosphorus atom, but also the adjacent functional group.

![Stabilized and Unstabilized Ylids](image)

Stabilized ylids are air stable and are frequently crystalline compounds that can be stored for extended periods. Stabilized ylids are less reactive and react effectively only with aldehydes and not ketones. Unstabilized ylids are highly reactive and react with both aldehydes and ketones.
Stereoselectivity
Unstabilized ylids usually give Z-stereochemistry, while stabilized ylids usually give E-stereochemistry.

Oxidation of Alkenes
Oxidation Reactions
In organic chemistry, oxidation refers to a reaction where C=O or C=O bonds are formed. Reduction refers to a reaction where C-O bonds are broken and/or C-H bonds are formed. This nomenclature arises because of how the oxidation state of carbon atoms is changed.

Hydroboration
Crucial to this reaction is borane (BH3), which itself is not a stable compound and dimerizes to diborane (B2H6). This in turn reacts to form complexes with electron donors such as ethers, amines and disulfides. It is these borane complexes that are used as reagents for this reaction.
The hydroboration reaction involves reaction a borane complex with alkenes, which add across the double bond, eliminating one hydrogen from boron to yield an organoborane.

Treatment of alkenes with borane, followed by oxidative hydrolysis of the alkylborane intermediate, leads to the formation of an alcohol through a formal hydration of the alkene.
Electrophilic Epoxidation

In this reaction, alkenes react with peroxyacids to yield an epoxide. A peroxyacid is basically like a carboxylic acid with an additional oxygen attached before the OH group:

\[
\begin{align*}
\text{CO}_2\text{H} & \quad \text{O}\quad \text{OH} \\
\text{R} & \quad \text{CO}\quad \text{OH}
\end{align*}
\]
H-bonding of the peracid leads to preferential oxidation of one face of the ring:

Protection of the alcohol by a silyl ether (silicon bonded to O-H) prevents H-bonding and leads to a reversal of stereoselectivity:

**Nucleophilic Epoxidation**

Alpha,beta-unsaturated ketones (conjugated) can be epoxidized by basic hydrogen peroxide.
Cis-Dihydroxylation
This reaction adds two OH groups over a double bond. Potassium permanganate is used as a catalyst in a basic environment.

Oxidation of alkenes with OsO₄ is usually a very high yielding reaction:

The addition on substituted cyclic compounds follows the syn-orientation:

The mechanism is as follows:
Trans-Dihydroxylation

Trans-Diols can be obtained in two steps by cleavage of an epoxide. One simple way to achieve this is by solvolysis (reaction with the solvent):

![Chemical structure](image1)

Alternatively, formation of the epoxide followed by its basic hydrolysis will afford the same outcome:

![Chemical structure](image2)

Oxidative cleavage of Alkenes and Diols

The OsO₄ reagent can be combined with periodate (IO₄) to cleave double-bonds:

![Chemical structure](image3)

The catalyst used can be OsO₄ or KMnO₄:

![Chemical structure](image4)

The mechanism is given below:
**Ozonolysis**
This reaction involves the cleavage of an alkene or alkyne with ozone to form organic compounds in which the multiple carbon–carbon bond has been replaced by a double bond to oxygen.

\[
\text{structure of ozone}
\]

The mechanism is as follows:

**Oxidation of Alcohols**

**Classes of Alcohols**
- Primary alcohols can be oxidized to aldehydes and carboxylic acids
- Secondary alcohols can be oxidized to ketones
- Tertiary alcohols cannot be oxidized without cleavage of C-C bonds and so are inert
**Chromium Oxidants**

Chromium(VI) is a useful oxidant, though unfortunately it is toxic and carcinogenic.

\[
\begin{align*}
\text{CH}_2\text{OH} & \quad \xrightarrow{\text{Cr}_2\text{O}_7^{2-}, \text{H}^+ \quad \text{(dichromate)}} \quad \text{CO}_2 \\
\text{or} & \\
\text{CrO}_3, \text{H}^+ \quad \text{(Jones' reagent)} & \quad \rightarrow \quad \text{HO-Cr-OH}
\end{align*}
\]

Primary alcohols can be further oxidized to carboxylic acids:

\[
\begin{align*}
\text{CH}_2\text{OH} & \quad \xrightarrow{\text{CrO}_3, \text{H}^+ \quad \text{(Jones' reagent)}} \quad \text{CHO} \\
& \quad \xrightarrow{\text{CrO}_3, \text{H}^+ \quad \text{(Jones' reagent)}} \quad \text{CO}_2
\end{align*}
\]

The mechanism is given below:

**Swern Oxidation of Alcohols**

This reaction converts primary alcohols to aldehydes using oxalyl chloride, dimethyl sulfoxide (DMSO) and an organic base, such as triethylamine. The reaction is known for its mild character and wide tolerance of functional groups. It does not over-oxidize to carboxylic acids, which is sometimes a problem with CrVI oxidants.

\[
\begin{align*}
\text{CH}_2\text{OH} & \quad \xrightarrow{1) \text{ Oxalyl chloride} \quad \text{DMSO}} \quad \text{CHO} \\
& \quad \xrightarrow{2) \text{ Et}_3\text{N}} \quad \text{R}_1\text{R}_2
\end{align*}
\]

The mechanism is given below:
Reductions

Hydride Reducing Agents
Hydride reducing agents function as sources of hydride ion (H−), which react readily with electrophilic carbonyl groups. Examples include LiAlH4, NaBH4, KBH4, LiAlH(OtBu)3, LiBH2Et3, BH3.

\[
\text{O} \quad \text{R} \quad \text{R} \quad \xrightarrow{\text{NaBH}_4 \text{ EtOH}} \quad \text{R}_2 \text{CHOH}
\]

The mechanism is given below:

Birch Reduction
A reaction with the unique ability to partially reduce an aromatic ring. The key to the method is the use of a solution of alkali metal in liquid ammonia. Aromatic rings are reduced to 1,4-cyclohexadienes.

**Electron-donating group:**

\[
\text{OMe} \quad \xrightarrow{\text{Li}} \quad \text{OMe}
\]

**Electron-withdrawing group:**

\[
\text{CO}_2 \text{H} \quad \xrightarrow{\text{Li}} \quad \text{CO}_2 \text{H}
\]
The mechanism is given below:

The regiochemistry of the reduction is dependent on the electronic nature of the substituents on the ring. EDGs typically give products with the double bond bearing the donating substituent, EWGs typically give products with the substituent not on a double bond:

**EDG**

- $\cdot\text{NR}_2$
- $\cdot\text{NH}_2$
- $\cdot\text{O}H$
- $\cdot\text{O}R$
- $\cdot\text{NH}\text{CR}$
- $\cdot\text{O}\text{CR}$
- $R$
- $H$
- $\text{CR}_2$

**Activating**

- Deactivating

- Strongly
- Moderately
- Weakly

**Most Activating**

**EWG**

- $\text{X}$
- $\text{CH}$
- $\text{CR}$
- $\text{CON}$
- $\text{CO}H$
- $\text{CCl}_2$
- $\text{CF}_3$
- $\text{C}N$
- $\text{SO}H$
- $\text{NI}_3$
- $\text{NR}_3$
- $\text{N}^+$

- Weakly
- Moderately
- Strongly

**Most Deactivating**