DIRECTORATE OF DISTANCE & CONTINUING EDUCATION

MANONMANIAM SUNDARANAR UNIVERSITY

TIRUNELVELI- 627 012

OPEN AND DISTANCE LEARNING (ODL) PROGRAMMES

(FOR THOSE WHO JOINED THE PROGRAMMES FROM THE ACADEMIC YEAR 2023–2024)

M. Sc. Chemistry

Course material

Core IV - Organic Reaction Mechanism – II

Course Code SCHM21

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Tirunelveli - 12

Semester - II

Course: CORE - IV **Course Code** SCHM21

ORGANIC REACTION MECHANISM - II

UNIT-I: Elimination and Free Radical Reactions:
Mechanisms: E2, E1, and E1cB mechanisms. Syn- and anti-eliminations. Orientation of the double bond: Hoffmann and Saytzeff rules. Reactivity: Effect of substrate, attacking bases, leaving group and medium. Stereochemistry of eliminations in acyclic and cyclic systems, pyrolytic elimination. Long lived and short-lived radicals – Production of radicals by thermal and photochemical reactions, Detection and stability of radicals, characteristics of free radical reactions and freeradical, reactions of radicals; polymerization, addition, halogenations, aromatic substitutions, rearrangements. Reactivity: Reactivity on aliphatic, aromatic substrates, reactivity in the attacking radical, effect of solvent.

UNIT-II: Oxidation and Reduction Reactions: Mechanisms:
Direct electron transfer, hydride transfer, hydrogen transfer, displacement, addition elimination, oxidative and reductive coupling reactions. Mechanism of oxidation reactions: Dehydrogenation by quinones, selenium dioxides, ferricyanide, mercuric acetate lead tetraacetate, permanganate, manganese dioxide, osmium tetroxide, oxidation of saturated hydrocarbons, alkyl groups, alcohols, halides and amines. Reactions involving cleavage of C-C bonds - cleavage of double bonds, oxidative decarboxylation, allylic oxidation, oxidation by chromium trioxide-pyridine, DMSO-Oxalyl chloride (Swern oxidation) and Corey-Kim oxidation, dimethyl sulphoxide dicyclo hexyl carbodiimide (DMSO-DCCD). Mechanism of reduction reactions: Wolff-Kishner, Clemmenson, Rosenmund, reduction with Trialkyl and triphenyltin hydrides, McFadyen-Steven's reduction, Homogeneous hydrogenation, Hydroboration with cyclic systems, MPV and Bouveault- Blanc reduction.

UNIT-III: Rearrangements:
Rearrangements to electron deficient carbon: Pinacol-pinacolone and semi-pinacolone rearrangements -applications and stereochemistry, Wagner-Meerwein, Demjanov, Dienone-phenol, Baker- Venkataraman, Benzilic acid and Wolff rearrangements. Rearrangements to electron deficient nitrogen: Hofmann, Curtius, Schmidt, Lossen, Beckmann and abnormal Beckmann rearrangements. Rearrangements to electron deficient oxygen: Baeyer-Villiger oxidation and Dakin rearrangements. Rearrangements to electron rich atom: Favorskii, Quasi-Favorskii, Stevens, [1,2]-Wittig and [2,3]-Wittig rearrangements. Fries and Photo Fries rearrangement. Intramolecular rearrangements – Claisen, abnormal Claisen, Cope, oxy-Cope Benzidine rearrangements.

UNIT-IV: Addition to Carbon Multiple Bonds: Mechanisms:
(a) Addition to carbon-carbon multiple bonds- Addition reactions involving electrophiles, nucleophiles, free radicals, carbenes and cyclic mechanisms-Orientation and reactivity, hydrogenation of double and triple bonds, Michael reaction, addition of oxygen and Nitrogen; (b) Addition to carbon-hetero atom multiple bonds: Mannich reaction, acids, esters, nitrites, addition of Grignard reagents, Wittig reaction, Prins reaction. Stereochemical aspects of addition reactions. Addition to Carbon-Hetero atom

Multiplebonds: Addition of Grignard reagents, organozinc and organolithium reagents to carbonyl and unsaturated carbonyl compounds. Mechanism of condensation reactions involving enolates –Stobbe reactions. Hydrolysis of esters and amides, ammonolysis of esters.

UNIT-V: Reagents and Modern Synthetic Reactions:

Lithium diisopropylamine (LDA), Azobisisobutyronitrile (AIBN), Sodium cyanoborohydride (NaBH3CN), meta-Chloroperbenzoic acid (m-CPBA), Dimethyl aminiopyridine (DMAP), n-Bu3SnD, Triethylamine (TEA), Diazobicyclo[5.4.0]undec-7-ene (DBU), Diisopropylazodicarboxylate (DIAD), Diethylazodicarboxylate (DEAD), N-bromosuccinimide (NBS), Trifluoroacetic acid (TFA), Tetramethyl piperiridin-1-oxyl (TEMPO), Phenyltrimethylammonium tribromide (PTAB). Diazomethane and Zn-Cu, Diethyl maleate (DEM), Copper diacetylacetonate (Cu(acac)2), TiCl3, NaIO4, Pyridinium chlorochromate (PCC), Pyridinium dichromate (PDC), Meisenheimer complex. Suzuki coupling, Heck reaction, Negishi reaction, Baylis-Hillman reaction.

Recommended Text

1. J. March and M. Smith, *Advanced Organic Chemistry*, 5th ed.,John-Wiley and Sons. 2001.
2. E. S. Gould, *Mechanism and Structure in Organic Chemistry,* Holt,Rinehart and Winston Inc., 1959.
3. P. S. Kalsi, *Stereochemistry of carbon compounds*, 8thedn, New Age International Publishers, 2015.
4. P. Y.Bruice, *Organic Chemistry*, 7thedn.,Prentice Hall, 2013.
5. R. T. Morrison, R. N. Boyd, S. K. Bhattacharjee*Organic Chemistry*, 7th edn., Pearson Education, 2010.

Reference Books

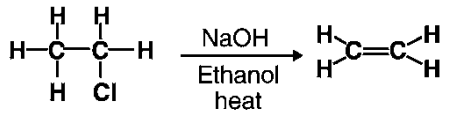
1. S. H. Pine, *Organic Chemistry*, 5thedn, McGraw Hill International Editionn, 1987.
2. L. F. Fieser and M. Fieser, *Organic Chemistry,* Asia Publishing House, Bombay, 2000.
3. E.S. Gould, *Mechanism and Structure in Organic Chemistry*, Holt,Rinehart and Winston Inc., 1959.
4. T. L. Gilchrist, *Heterocyclic Chemistry*, Longman Press, 1989.
5. J. A. Joule and K. Mills, *Heterocyclic Chemistry*, 4thed., John-Wiley,2010.

UNIT-I

ELIMINATION AND FREE RADICAL REACTIONS

Elimination Reactions:

Elimination reactions are exact reverse of addition reaction. It is defined as removal of atom or group of atom from the adjacent carbon of a molecule and this leads to the formation of multiple bonds depending on how many atoms are removed.



Alkyl halide Alkene

Classification :

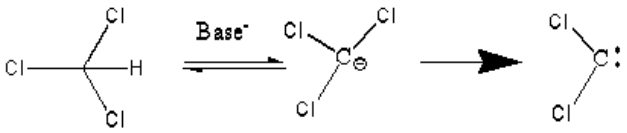
1.α-Elimination reaction

2. β-Elimination reaction

3. γ– Elimination reaction

α-Elimination reaction :

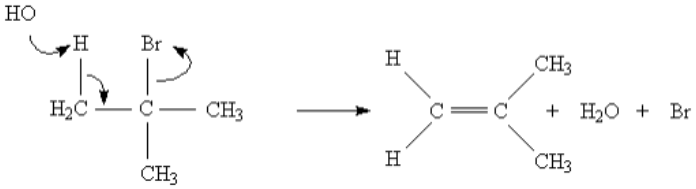
In α-elimination reaction, the leaving group and the proton are removed from the same α carbon which leads to formation of reactive carbene intermediate.It is also called 1,1-elimination.



chloroform Carbene

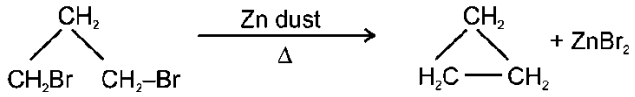
β-Elimination reaction :

In β-elimination reaction, the leaving group and the proton removed from the adjacent atoms leaving group from α-carbonand proton from β-carbon. It leads to theformation of alkene compounds. It is also called 1,2-elimination reaction.



γ-Elimination reaction :

In γ-elimination reactions, the atoms or group being removed are at alpha and gamma position. It results in the formation of a three membered ring . It is also called 1,3-elimination.

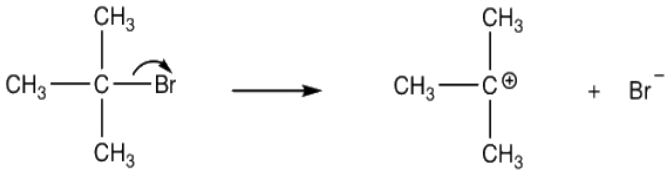


E1 Elimination Reaction:

- The E1 mechanism which is also known as unimolecular elimination.
- The are usually two steps involved- ionization and deprotonation .
- During ionization, there is a formation of carbocation as an intermediate.
- In deprotonation, a proton is lost by carbocation.
- This happens in the presence of a base which further leads to the formation of a pi-bond in the molecule.
- It exhibits first-order kinetics.

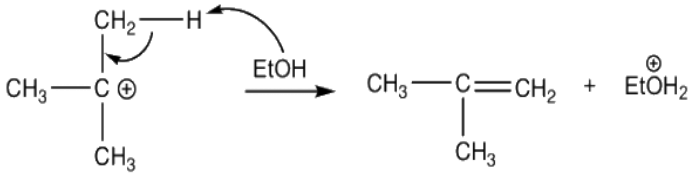
Mechanism:

Step 1: Cleavage of C-Br bond **slowly** to form the carbocation intermediate.



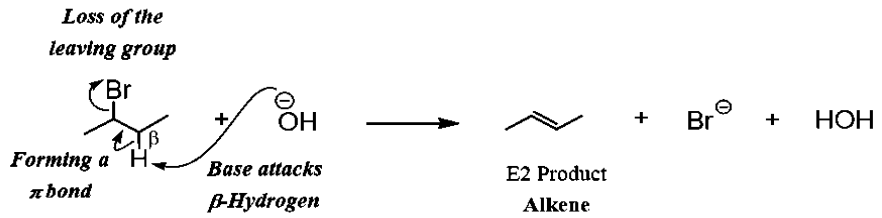
carbocation intermediate

Step 2: base (EtOH) removes H from a β-carbon, and double bond produced.

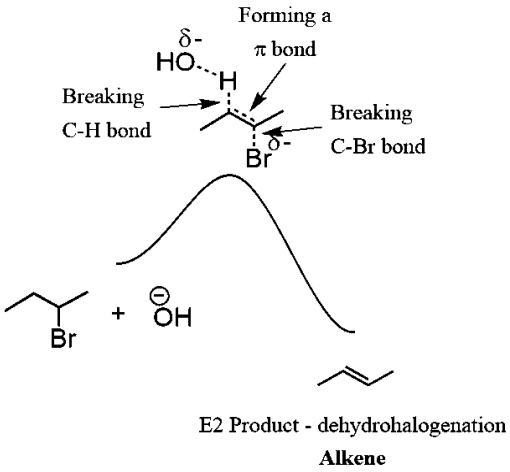


E2 – Elimination reaction:

- It refers to bimolecular elimination reaction.
- It is one step mechanism. Here,the carbon-hydrogen and carbon-halogen bonds mostly break off to form a new double bond.
- However, in the E2 mechanism, a base is part of the rate determining step and it has a huge influence on the mechanism.
- It exhibits second-order kinetics.
- It is concerted process.



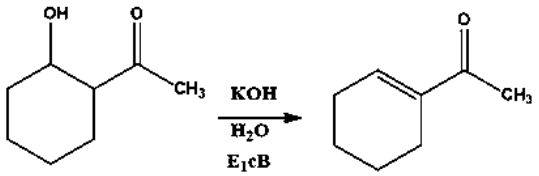
Mechanism:



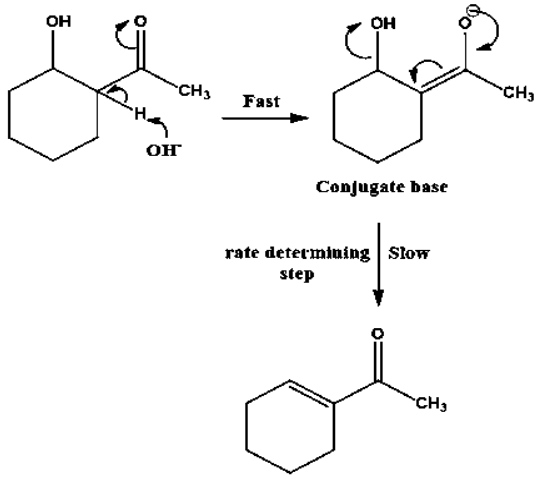
E1cb Mechanism :

- E1cb – Elimination unimolecular conjugative base.
- This is a third mechanism for β-eliminations.
- This mechanism involves the formation of carbanion by a rapid loss of proton to base as a transition state.

- The carbanion is then converted to an alkene, conversion of carbanion to an alkene is the rate determining step.
- This elimination, since it proceeds through the conjugate base of the starting material, is known as E1cb.



Mechanism:



Effect of the structure of substrate:

It has been found that branching at α and β carbons increase the rate of the E2 reaction. This is because as the number of substituents increases on the carbon atoms of the developing double bond, the stability of transition state increases. In primary non branched structure rate of the reaction is very slow and yield obtained is low.

Substrate	% yield	Rate of 25°C
CH_3CH_2Br	0.9	1.0×10^5
$CH_3-\overset{\alpha}{C}H(CH_3)-Br$ (branching at α-carbon)	80.3	2.3×10^5
$CH_3-C(CH_3)_2-Br$ (branching at α-carbon)	97	4.7×10^5
$CH_3\overset{\beta}{C}H_2CH_2-Br$ (branching at β-carbon)	8.9	5.3×10^5
$CH_3-\overset{\beta}{C}H(CH_3)-CH_2-Br$	59.5	8.5×10^5

This table shows that branching at α or β carbon increases the yield as well as rate of the E2 reaction. This table also shows that 30- halides are more reactive than secondary alkyl halides which are more than the primary alkyl halide.

$3^{\circ} > 2^{\circ} > 1^{\circ}$

Since the transition state of an S_N2 reaction involves high steric strain, the α and β branches slow down the S_N2 reaction rate while they speed up the E2 reaction rate. Thus, with increasing branching at α and β carbons, the E_2/S_N1 ratio increases.

It has also been found that the electron withdrawing groups on the β - carbon increase the rate of E2 reaction.

E1 Elimination Reaction:

E1 reaction takes place by the formation of carbocation as reaction intermediate. Thus, the rate of E1 reaction depends on the stability of the carbocation. Since +I effect, hyperconjugation and congujative effect stabilise carbocation, any structure which forms stable carbocation will be reactive. Steric strain around leaving group also favours the formation of carbocation thus, the order of reactivity in decreasing order is as follows:

$3^{\circ} > 2^{\circ} > 1^{\circ}$ alkyl halide.

Thus, alkyl and aryl substitutions on α and βcarbons with respect to the leaving group increase the rate of E1 reactions. As the strain increases the field of the E1 product increase.

Leaving Group:

Better leaving group, higher is the rate of E2 reaction.

Leaving group and its rate

Substrate	Rate at 25°C
$C_6H_5CH_2-CH_2-Cl$	0.007×10^3
$C_6H_5CH_2CH_2Br$	4.2×10^3
$C_6H_5CH_2-I$	27×10^3

It has also been found that with the increasing size of the halogen atom E2/SN2 ratio increases but to a minimum extent.

Reactivity of the substrate depends mainly on the nature of the leaving group. The best leaving group are those which are least basic and more polarisable. Thus, the decreasing order of the leaving group reactivity is :

$$I^- > Br^- > Cl^- > F^-$$

Attacking Base :

With the increasing basicity of the added base, the rates of the E2 reactions have been found to increase. The order of basicity: $NH_2^- > C_2H_5O^- > OH^-$

The rate of E2 reactions on a given substrate with the above bases under identical conditions is also found to be: $NH_2^- > C_2H_5O^- > OH^-$

Thus, the order of basicity is also the order of the rate.

When the base is weak but strongly nucleophilic toward carbon, E2/SN2 ratio is low but in the presence of a strong base the E2/SN2 ratio increases.

E_1 Elimination Reaction:

Since E1 reactions do not usually require any base the strength and concentration of the base have nothing to do with the rate of E1 reactions.

Medium:

The yield of the product in E2 reaction increases with the decrease in solvent polarity because this favours the

formation of the transition state of the reaction. Thus, the E2/SN2 ratio in the reaction of 2-bromo propane at 50°C with sodium hydroxide has been found to increase as the solvent polarity decreases.

Solvent	E2/SN2 ratio
60% C_2H_5OH and 40% HOH	1.17
80% C_2H_5OH and 20% HOH	1.44
100% C_2H_5OH	2.45

If the concentrated solvent is used the rate of the reaction increases.

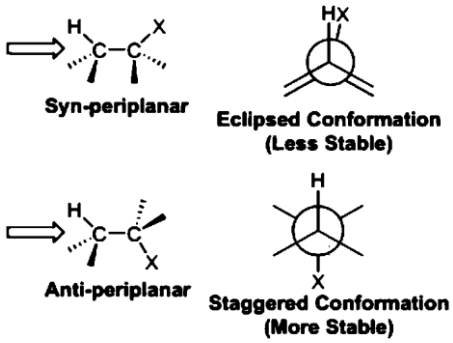
Syn and Anti Eliminations.

Anti-eliminations:

If the H and X (leaving group) are trans or anti to each other with a dihedral angle of 180°, the conformation is called anti-elimination. Therefore, the H and X depart (leave) in opposite directions. This type of elimination is called anti-elimination.

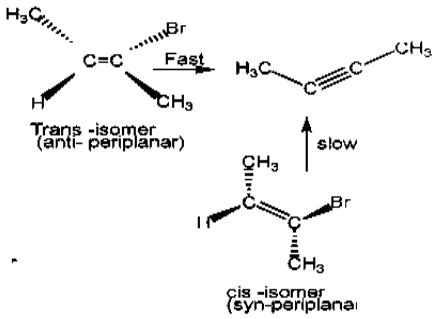
Syn-Eliminations:

If the H and X (leaving group) are cis or syn to each other with a dihedral angle of 0°, the conformation is called syn-elimination. Therefore, the H and X depart (leave) in same directions. This type of elimination is called anti-elimination.



Example 1:

Trans-2-bromo-2-butene undergoes E_2 reaction to give 2-butyne in a faster rate than in the cis-isomer. Here trans isomer fulfils the stereochemical requirements for E_2 elimination [anti-eliminations] but not is cis-isomer. Here trans-isomer, the stereochemical requirement for E_2 elimination [Anti-periplanar] but not in Cis-isomer. So trans-2-bromo-2-butyne undergoes E_2 Elimination in a faster rate than in cis-isomer.



Orientation in Eliminations of double bond:

1) Saytzeff rule
2) Hoffmann rule

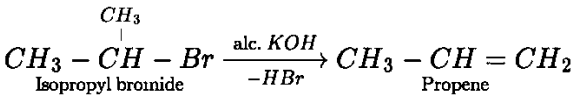
Orientation in Elimination reaction:

(Regioselectivity of elimination reaction)

This elimination reaction of symmetrical subtract which has only one type of β- hydrogen gives only one product (alkene).

The typical example is the dehydrohalogenation of isopropyl bromide.

Dehydrohalogenation of isopropyl bromide in presence of alc. KOH will give propene



The elimination reaction of unsymmetrical substrates which has more than one type of β- hydrogen usually yields mixture of possible product (alkene).

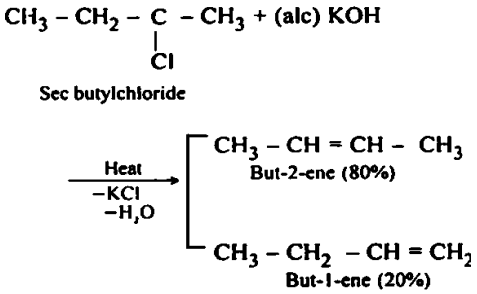
There are three empirical rules governing the orientation in the elimination reaction,

1) Saytzeff rule
2) Hoffmann rule

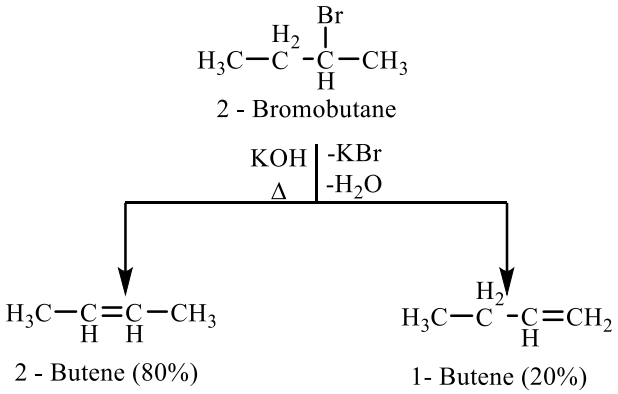
Saytzeff rule:

- Saytzeff rule states that the elimination reaction of unsymmetrical substrate yields highly substituted alkene one with large number of alkyl group attached to the double bond as the major product
- According to the saytzeff rule H atom is eliminated from the β-carbon having fewer (less) number of hydrogen atom. This elimination is called saytzeff type elimination.
- Saytzeff rule is applicable to all E_1 reaction and most of the E_2 reaction.
- When an alkyl halide undergoes dehydrohalogenation (-HX) the most substituted alkene will be the major product.
- Highly substituted alkene is the major product
- According to this rule H atom is preferentially removal from the C-atom with the fast H-atoms.

Example 1 :



Example 2:



Highly substituted alkene is the major product.

Hoffman Rule [Hoffmann Elimination]:

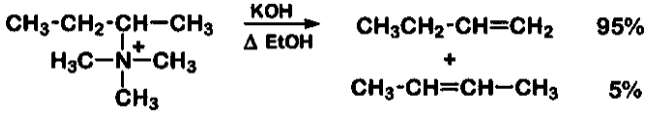
- Hoffmann rule states elimination reaction of charged substrates such on quaternary ammonium (or) sulfonium salts yields less substituted alkene is the major product.
- According to Hoffmann rule H-atom is eliminated from the β- Carbon having a greater number of H-atom. This elimination is called Hoffmann elimination.
- Hoffmann rule is usually applicable for all E_1 conjugated base reaction and some of E_2 elimination reaction.

Hoffmann elimination occurs:

- When the substrate molecule has bulky and for pour leaving group.
- When strong and bulky base is used KOH…etc.
- When the substrate has higher degree of branching.

Example 1:

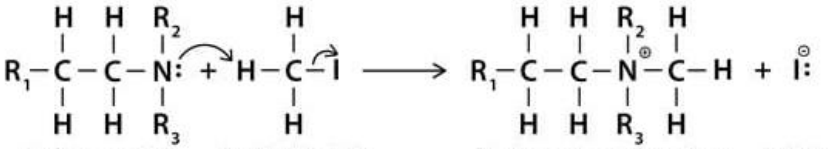
Elimination reaction of a quaternary ammonium hydroxide on heating this compound yield an alkene with tertiary amine.



- Least substituted alkene is the major Product.
- It is shown by Positive charged atom.

Mechanism of Hoffmann Elimination:

Step 1: Attack of the amine on methyl iodide to form an ammonium iodide salt

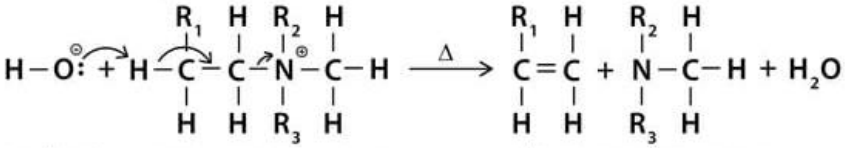


Tertiary amine Methyl iodide Quaternary ammonium Iodide

Step 2: Reaction between silver oxide and iodide to form silver oxide ion and silver iodide followed by deprotonation of water to form hydroxide

Silver oxide Water Iodide Hydroxide Silver iodide (insoluble)

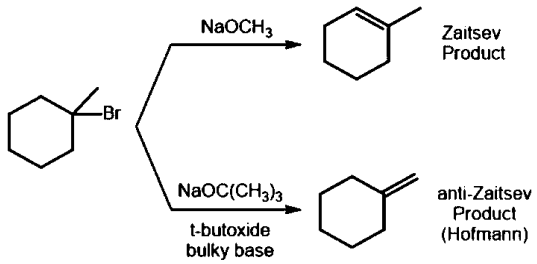
Step 3: Elimination of the β-hydrogen from the ammonium by the hydroxide after heating to form the final alkene



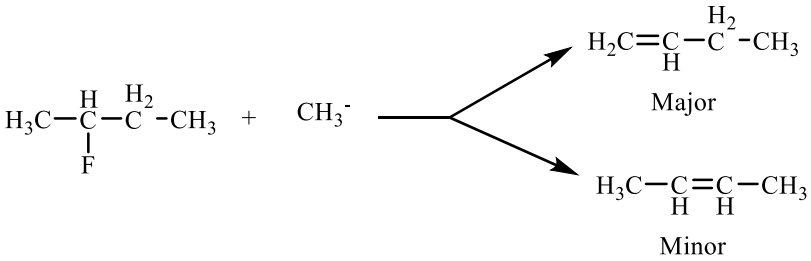
Hydroxyl Quaternary ammonium Alkene Tertiary amine

Hoffmann rule:

1. Base is bulky



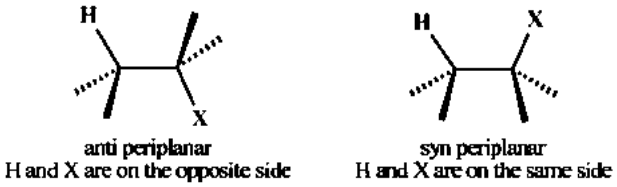
2. When leaving group is poor like F, N^+R_3, S^+R_2



Stereochemistry of Elimination in Acyclic and Cyclic System

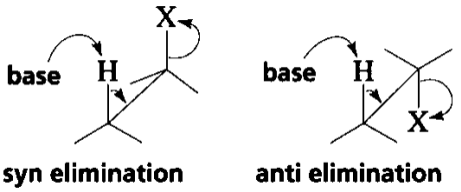
Stereochemistry of the E2 Reaction:(Acyclic system)

The transition state of an E2 reaction consists of four atoms from the substrate (one hydrogen atom, two carbon atoms and the leaving group x) aligned in a plane. There are two ways for the C-H and C-X bonds to be coplanar.



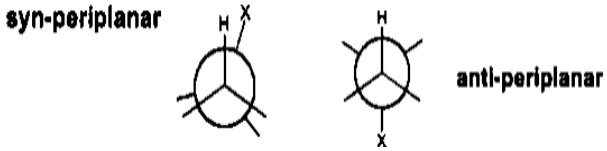
E2 elimination occurs most often in the antiperiplanar geometry. This arrangement allows the molecule to react in the lower energy staggered conformation and allows the incoming base and leaving group to be further away from each other.

The anti-periplanar geometry also allows direct interaction between the bonding electrons of C-H bond and the anti-bonding orbital of the C-X bond

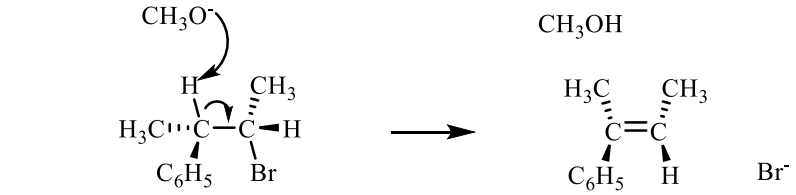


If the elimination reaction removes two substituents from the same side of the molecule it is syn-elimination. If the elimination reaction removes two substituents from opposite sides of the molecule it is anti-elimination.

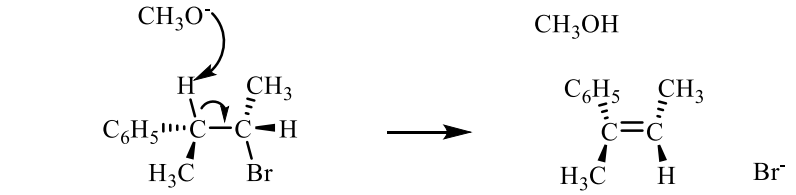
In this course E2 elimination will all go via anti periplanar conformation. Product analysis possible by drawing Newman projections if only one beta hydrogen is available.



When only one hydrogen is on the beta hydrogen predominantly anti elimination leads to high stereospecificity.



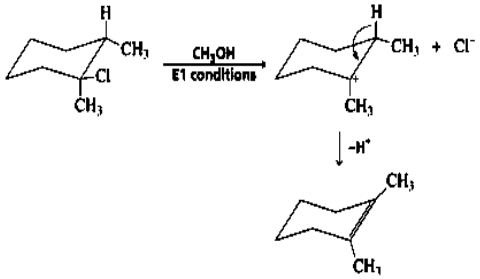
(2S, 3S)-2-bromo-3-phenylbutane (E)-2-phenyl-2-butene



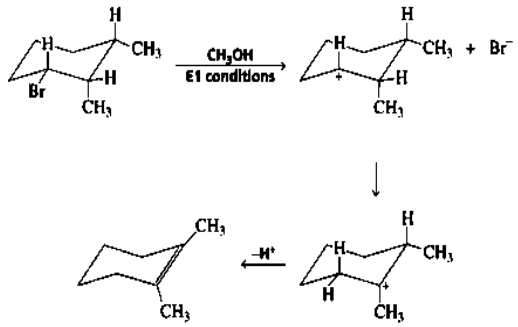
(2S, 3R)-2-bromo-3-phenylbutane (Z)-2-phenyl-2-butene

E1 Elimination from cyclic compounds

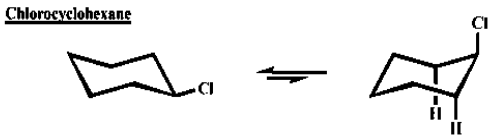
When a cyclohexyl chloride undergoes an E1 reaction. The two groups that are eliminated do not have to both be in axial position because the elimination reaction is not changed. In the following reaction a carbocation is formed in the first step.



Carbocation rearrangements must be considered for E1 reaction.



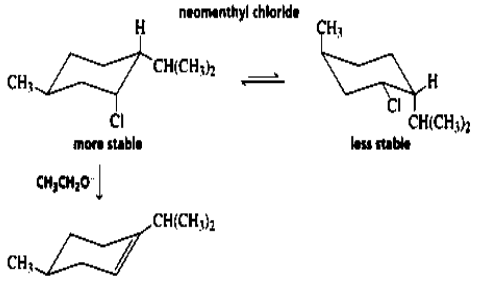
E2 Reaction of 6-membered rings



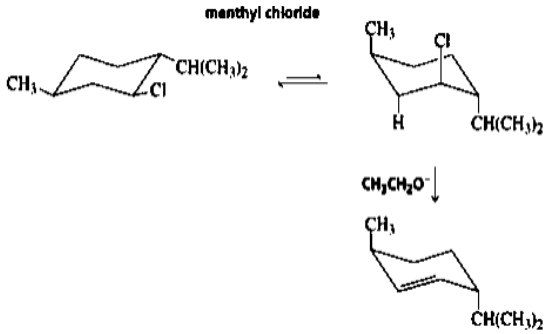
E2 elimination the C-Cl bond must be anti-periplanar to the C-H bond on a beta carbon and this occurs only when the H and Cl atoms are both in the axial position. The requirement for trans diaxial geometry means that elimination must occur from the less stable conformer. (Important consequences for compounds containing six membered rings)

E2 Reaction of cyclic compound

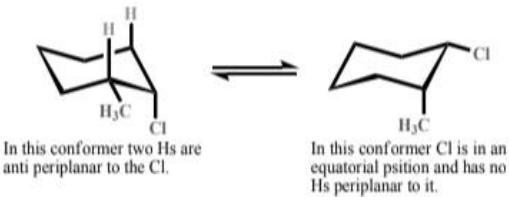
E2 reaction of cyclic compounds follows the same stereochemical rules as from open chain compounds.



The reaction of methyl chloride violates Zaitsev's rule.



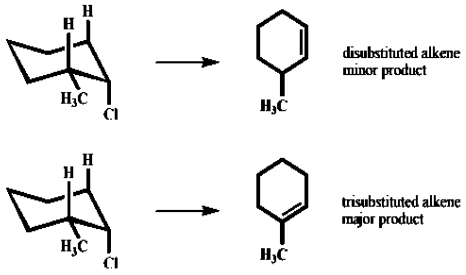
Dehydrohalogenation of cis-1- chloro-2 methylcyclohexane



In this conformer two Hs are anti periplanar to the Cl.

In this conformer Cl is in an equatorial psition and has no Hs periplanar to it.

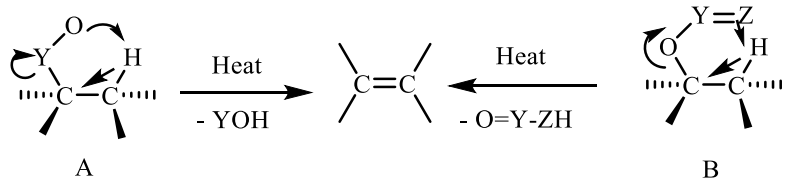
The conformer with Cl in an axial orientation reacts to give two alkenes. The alkene that is more substituted is the major product.



Pyrolytic elimination

The term pyrolytic elimination means an elimination reaction occurring in the organic substrate due to the application of heat or by the effect of heat in the absence of solvent or reagent and mostly carried out in the gaseous phase though can be performed in the inert solvent.

The pyrolytic elimination has a concerted mechanism reaction via cyclic transition state within which an intramolecular proton transfer is accompanied by syn- elimination to form a new Carbon-Carbon bond.



Reaction	Substituent	Type	Temperature Range
Cope Elimination	$Y - O = R_2N^+ - O^-$	A	110-170°C
Sulfoxide Pyrolysis	$Y - O = RS^+ - O^-$	A	100 - 150°C
Selenoxide Pyrolysis	$Y - O = RSe^+ - O^-$	A	0-25°C
Ester Pyrolysis	Y = Z = RC = O	B	430 - 480°C
Xanthate Pyrolysis	$Y = Z = CH_3SC = S$	B	180 - 210°C

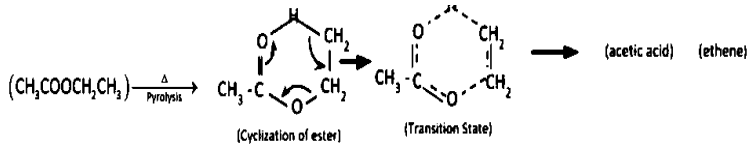
Pyrolysis of ester:

Ester having β-hydrogen atom in the alcohol, undergo elimination on pyrolysis to form alkene and carboxylic acid.

Example:

$$\underset{\text{Ethyl acetate}}{CH_3-COO-CH_2-CH_3} \xrightarrow{500^{\circ}C} \underset{\text{Acetic Acid}}{CH_3-COOH} + \underset{\text{Ethene}}{CH_2=CH_2}$$

Mechanism:



Ester pyrolysis reaction converting ester containing β-hydrogen atom into the corresponding carboxylic acid and the alkene. The reaction is an E_i elimination that is intramolecular elimination and operates in a Syn fashion.

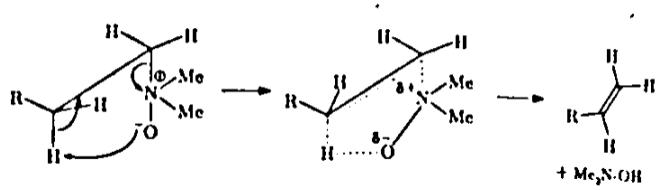
Cope elimination:

When tertiary amine oxides are heated undergo pyrolysis, alkene are formed via five membered cyclic transition state. This is also a Syn elimination.

Example:

$$R-CH_2-CH_2-\underset{\underset{O^-}{|}}{N^+Me_2} \xrightarrow[\Delta]{150^{o}C} R-\underset{H}{C}=CH_2 + Me_2NOH$$

Mechanism:



The Cope proceeds through a concerted Syn-elimination mechanism. The oxygen from N-oxides acts as a base, forming an O-H bond, while C-H and C-N bonds breaks to form the new C=C pi bond.

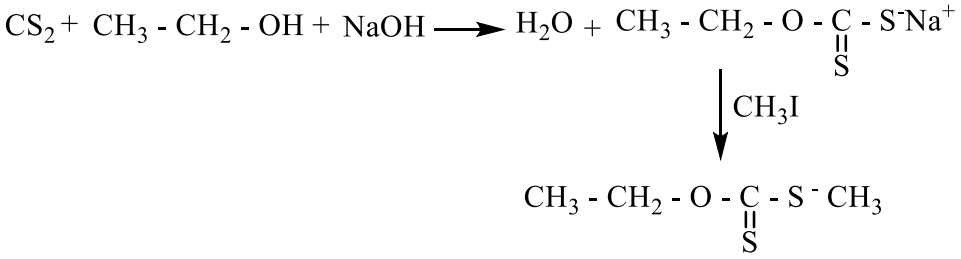
Pyrolsis of xanthates:

Chugaev Reaction:

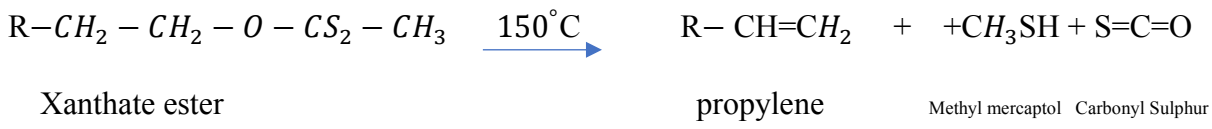
When Xanthates undergo Syn-elimination gives Alkene, Methyl mercaptol and Carbonyl Sulphur through a six membered cyclic transition state.

Preparation of Xanthate ester:

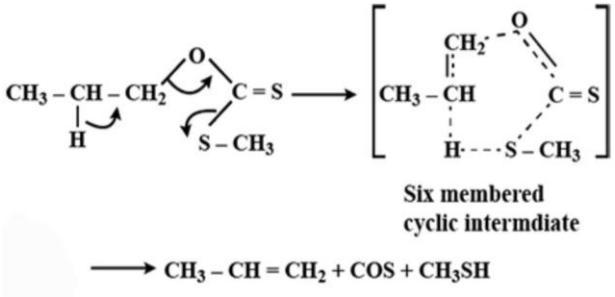
Xanthates are prepared by refluxing a mixture of alcohol and carbon disulphur with NaOH or NaH and the resulting sodium sulphonate is treated with an alkyl halide. The pyrolysis can be catalyzed by Lewis acid like BF_3 or carrying out the reaction in chlorosulphonic acid.



Example:



Mechanism:



Long lived and short-lived radicals

Rupture of covalent bond by homolytic cleavage in which both the atoms possess unpaired electron dur to the symmetrical rupture of the bond.

X-Y → X·+Y·

These fragments, which are neutral species. Are called free radicals.

Free radicals as an atom or group of atoms with an unpaired electron.

Characteristics of free radicals:

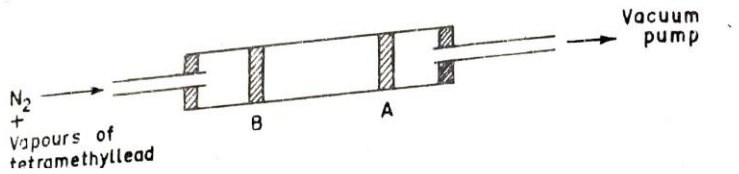
1. They are neutral molecule, highly stable.
2. They have electron deficient atom.
3. They seek electron to compete its octet, hence very reactive.
4. They are paramagnetic nature.
5. Free radicals combined to form neutral molecule.
6. Free radical can produced another free radical when react with neutral molecule.

Short lived radicals

Short lived free radicals are often produced when a molecule is supplied with sufficient energy – thermal or photochemical to cause homolysis of a covalent bond. In addition, oxidation – reduction reaction resulting in the gain or loss of a single electron can also be used for the generation of radicals.

A) Thermal reactions

Historically, the first work to demonstrate the formation and existence of free radicals was that of Paneth and Hofeditz in 1929-31. Their procedure often referred to as the Paneth technique, consists in passing a stream of nitrogen and the vapor of tetramethyl lead, through a quartz tube. The pressure in the quartz tube is held at about 2mm by the action of a vaccum pump.



On heating the tube strongly at any point (A), a lead mirror is deposited due to the decomposition was found to be ethane. Subsequent heating of the tube at another point (B) on the upstream side resulted on the simultaneous disappearance and formation of mirrors at points A and B respectively. Tetramethyllead was detected this time in the effluent gas. This unique experiment established that tetramethyllead decomposes to form lead and the methyl radical.

$$(CH_3)_4Pb \rightarrow 4CH_3^{\cdot} + Pb(\text{mirror})$$

Methyl radicals produced as a result of heating at point B react with the mirror at point A to regenerate the volatile tetramethyllead.

$$4CH_3{\cdot} + Pb \rightarrow (CH_3)_4Pb$$

In the absence of the lead mirror the free methyl radicals combine with each other to form ethane.

$$2CH_3{\cdot} \rightarrow CH_3\text{-}CH_3$$

Further the rate of the disappearance of the mirror at A was found to decrease with the increase in the distance between A and B there by suggesting that the methyl radicals react very rapidly to form ethane. Paneth estimated the half life of methyl radicals to be about 0.006sec under above experiment condition.

Thermal production of the radicals they are readily is not confined to the decomposition of tetramethyllead; rather they are readily generated whenever a compound having a weak covalent bond is heated. The O-O Bond of a peroxide or a peracid.

B) Photochemical reactions

Absorption of visible or ultraviolet light provides a molecule with sufficient energy to break covalent bonds, and thus photochemical dissociation to yield radicals may occur. Very frequently photochemical dissociation is preferred to thermolysis as the former results in the more selective reactions. Irradiations of gaseous acetone, for example yields ethane, biacetyl and carbon monoxide presumably via free radicals.

$$CH_3COCH_3 \rightarrow CH_3{\cdot} + COCH_3{\cdot}$$

$$2CH_3{\cdot} \rightarrow C_2H_6$$

$$CH_3CO{\cdot} \rightarrow CH_3{\cdot} + CO$$

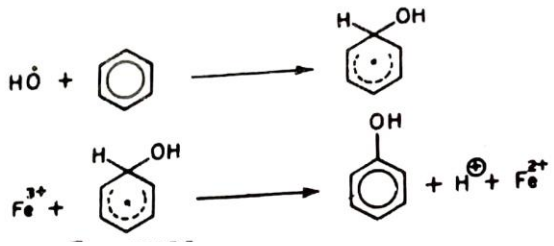
$$2CH_3CO{\cdot} \rightarrow CH_3COCOCH_3$$

C) Redox reactions

One electron oxidation reduction reaction are very often employed to produce radicals one such reactions that has considerably synthetic importance is the fenton's reagent produced by the reaction of hydrogen peroxide with ferrous ions.

$$Fe^{++} + H_2O_2 \rightarrow Fe^{+++} + HO^- + HO{\cdot}$$

The generated hydroxyl radicals then oxidise organic substances



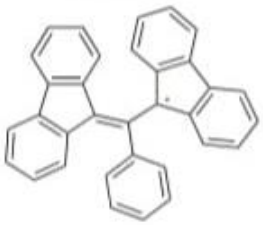
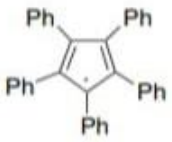
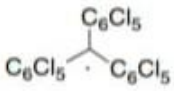
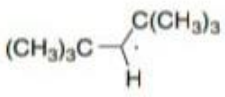
Long lived radicals

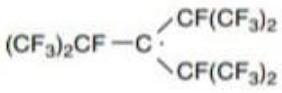
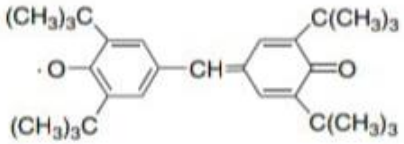
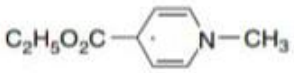
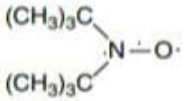
Gomberg 1900 discovered the first free radical i.e triarylmethyl. Actually he was trying to prepare hexaphenylethane by considering triphenylmethyl chloride with zinc dust in benzene as solvent in the absence of air.

$$2Ph_3CCl + 2Ag \rightarrow 2AgCl + Ph_3C\text{-}CPh_3$$

The product obtained by him was a colourless, crystalline solid.

Scheme 11.1. Properties of Some Long-Lived Free Radicals

	Structure	Stability
1[a]		Indefinitely stable as a solid, even in the presence of air
2[b]		Crystalline substance is not rapidly attacked by oxygen, although solutions are air-sensitive. The compound is stable to high temperature in the absence of air.
3[c]		Stable in solution for days, even in the presence of air. Indefinitely stable in the solid state. Thermally stable up to 300°C.
4[d]		Persistent in dilute solution (<10^{-5} *M*) below −30°C in the absence of oxygen; $t_{1/2}$ of 50 *s* at 25°C.

5[e]		Thermally stable to 70°C; stable to O_2.
6[f]		Stable to oxygen; stable to extended storage as a solid. Slowly decomposes in solution.
7[g]		Stable distillable liquid that is only moderately sensitive ot O_2.
8[h]		Stable to oxygen, even above 100°C

Production of radicals by thermal and photochemical reactions

Free Radicals

Free radicals are reactive intermediates with one or more unpaired electrons. They are generated by homolytic fission of a covalent bond.

Reactions involving free radicals take place in gaseous phase, but they also occur in solution, particularly if the reaction is carried out in non-polar solvents. Free radical reactions are catalyzed by light or by substances like peroxides which undergo decomposition easily to produce free radicals.

Generation of Free radicals

Free radicals are formed from molecules by breaking a covalent bond so that each fragment keeps one electron. There are a number of ways of radicals generation; the most important are:

a) Photolysis

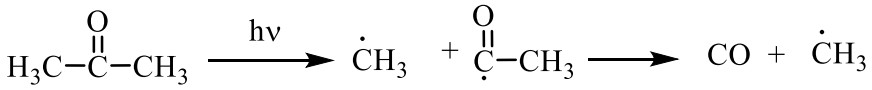
b) Thermolysis

c) Redox reactions

Photolysis

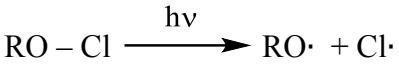
Photochemical dissociation or cleavage is an important method for the production of radicals. The prerequisite of this method is the ability of the molecule concerned to absorb radiation in the ultra-violet or visible range. The energy of radiation of wavelength 600 - 300 nm is 200-400 kJ $mole^{-1}$ which is of the order of magnitude of covalent bond energies. Radiation of wavelength corresponding to λ_{max} of a molecule can cause splitting of the latter into radicals.

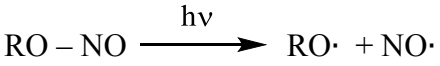
Many of these molecules also undergo homolysis on heating, but some do not. Chief among the latter group are aliphatic carbonyl compounds which have been studied most extensively in the vapour state. Thus propanone (acetone) in the vapour phase is decomposed by radiation of wavelength of 320 nm.



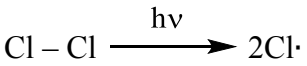
Initially, photochemical cleavage of one of the two methyl-carbonyl bonds occurs. This results in two radicals, the methyl and the acetyl. Acetyl radical then breaks down spontaneously to yield another methyl radical and a stable molecule of carbon monoxide.

Alkyl hypochlorites and nitrites are also an easy source of radicals. Alkoxyl radicals are obtained as products of their photolysis.





Photolysis of chlorine molecule has been mentioned above. This requires 244 kJ $mole^{-1}$ of energy which is supplied by irradiating chlorine at 487.5 nm or heating it to 525K.



Two major advantages of photolysis for generation of radicals are:

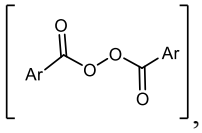
a) Bonds that are difficult to break or do not break at reasonable temperatures can be cleaved by photolysis, e.g. azoalkanes.

$$R - N = N - R \xrightarrow{h\nu} R\cdot + N{\equiv}N + R\cdot$$

b) The method is relatively more specific, in that radiation of only a particular wavelength is absorbed by a molecule leading to cleavage of specific bonds.

Thermolysis

Cleavage of organic molecules can occur in the gaseous phase at high temperatures to give free radicals. Cleavage can also occur in the liquid phase if a molecule contains bonds with dissociation energies of less than 165 kJ mole^{-1}.

Peroxides and azo compounds constitute a major source of radicals in solution, where O – O bond or C – N bond, respectively cleaves on heating. The O – O bond in peroxides is weak, with bond dissociation energy of about 120 kJ mole^{-1}. Diacyl peroxides are a source of alkyl radicals because the acyloxy radicals lose CO_2 very rapidly. In aroyl peroxides  , the products may be formed from aryloxy radicals.

A molecule like dibenzoyl peroxide can be considered as consisting of two dipoles joined at their negative ends. It, therefore, undergoes easy homolytic cleavage due to the repulsion between the two negative charges. Because it can generate radicals easily, dibenzoyl peroxide is used as an initiator in many reactions.

$$C_6H_5\overset{\delta+}{-}\underset{\|}{\overset{O}{C}}\overset{\delta-}{-}O\overset{\delta-}{-}O\overset{O}{\underset{\|}{C}}\overset{\delta+}{-}C_6H_5 \xrightarrow{\Delta} 2C_6H_5COO\cdot \longrightarrow 2C_6H_5\cdot + CO_2$$

Substituents affect the ease of cleavage of a substance. If a substance contains no substituents capable of promoting its decomposition or stabilising the product radical, then relatively rigorous conditions are required for cleavage.

The rate of decomposition generally follows first order kinetics, and is dependent on the solvent, temperature and structure of the compound. For Eg. $(C_6H_5CH_2CH_2COO)_2$ has a half life of 0.5h at 375K while the half life of $(CH_3)COO_2$ is as much as 200h at this temperature.

Aryl azo compounds undergo dissociation into radicals relatively more easily.

$$(C_6H_5)_3C - N = N - C_6H_5 \xrightarrow{325K} (C_6H_5)_3C\cdot + N_2 + \cdot C_6H_5$$

$$(C_6H_5)_3C - N = N - OH \xrightarrow{300K} (C_6H_5)_3\cdot + N_2 + \cdot OH$$

Detection and stability of free radicals

In addition to the classical methos based on the disappearance of lead mirror, there are now several other methods available for the detection of radicals.

One of the relatively simpler method to know whether a particular reaction proceeds via a radical intermediate or not is to introduce a small quantity of a radical inhibitor, such as hydraquinone. The kinetics of the reaction is then studied with and without inhibitor.

If the reaction proceeds via radical intermediate, its rate should be seriously affected by the presence of inhibitors. An alternate indication of a radical mechanism is the dependence of the reaction rate on a small amount of initiator such as organic peroxides.

There are many radical reactions that proceeds only on the addition of such initiator to the reaction mixture.

The direct evidence for the pressure of an odd electron is usually obtained from its magnetic properties. An earlier method made use of the magnetic susceptibility of the substance that depends on the paramagnetic contribution by the odd electron. However, this method of detecting radicals has been superceded by a technique which directly measures the paramagnetism due to an unpaired electron.

This method, known as electron spin resonance (or) electron paramagnetic resonance spectroscopy is applicable to study of radicals even in concentrations as low as 10^{-8}M.

The basic principle of this form of spectroscopy is that an unpaired electron like a proton. Has spin and this spin has an associated magnetic moment.

When a free radicals is placed in a magnetic field and subjected to electron magnetic radiation. The magnetic moment generated by the spinning electron can be lined up with or against the external magnetic field. These two orientations define two energy state which differ in energy contents, the aligned with the field obviously has less energy, and is therefore more stable than the other.

However, with the absorption of light energy in the microwave region, the spin state of the electron is changed from alignment with the field to against the field.

Transition between stable and less stable level produce a line in the ESR spectrum. The splitting of a line is due to the coupling of the odd electron most frequently with the protons situated on the same atoms that carry the odd electron. If the number of lines in the esr spectrum is always n+1.

Ex: cycloheptatrienyl radical

N+1 => 7+1=8 lines

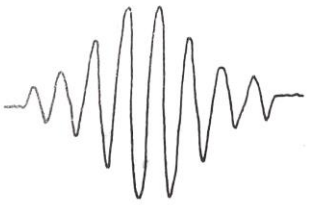


Fig. 12.4 Esr spectrum of cycloheptatrienyl radical

Methyl radicals

N+1 => 3+1=4 radicals

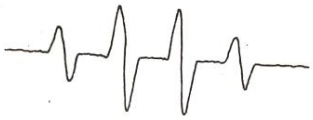


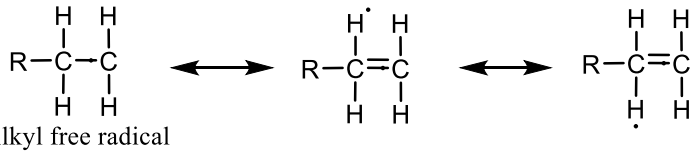
Fig. 12.3 Esr spectrum of methyl radical

Stability of free radicals

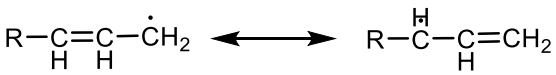
The stability of free radicals follows the same order of carbocations. Thus, $R_3C^{\cdot} > R_2CH^{\cdot} > RCH_2^{\cdot} > CH_3^{\cdot}$

Free radicals as a rule are stabilized both by conjugative and hyper conjugative interactions, but not so much like ions. Allylic and benzyl free radicals are stabilized due to delocalization where as hyperconjugation is responsible for the stability of alkyl radicals. Thus,

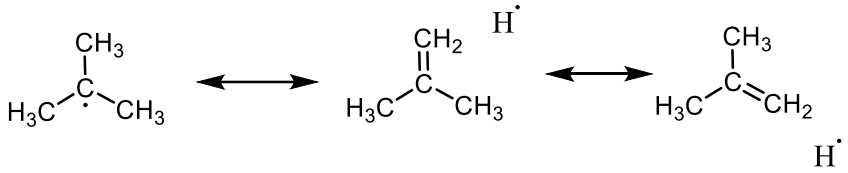
Hyperconjugation in tertiary butyl radical may be represented as follows,



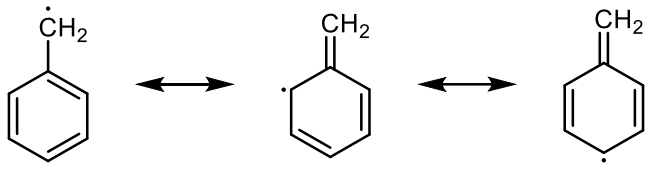
Alkyl free radical



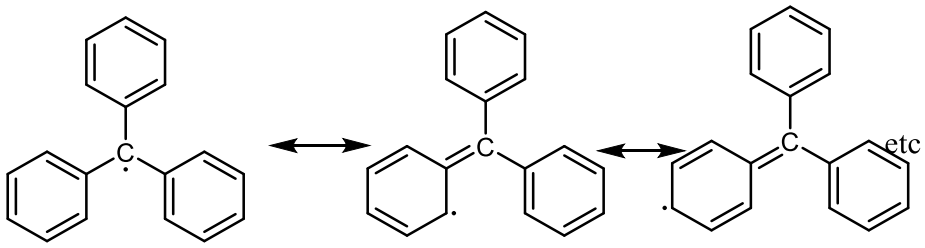
Allyl radical



Benzyl radical



Triphenyl methyl radical is much more stable because of delocalization.



Presence of a bulky p-substituted in each aromatic nucleus increases the stability of free radicals.

Polymerization:

- Polymerization is a process through which a large no. of monomer units reacts together to form a polymer.
- The polymer produced from a polymerization may have a linear or branched structure.
- It is of two types,

Addition polymerization:

- Polymers formed by the repeated addition of monomers by possessing double bond or triple bonds are called addition polymerisation.
- Example, Buna-N, Buna-S, Polythene.

Condensation polymerization:

- These polymers formed by repeated condensation of tri or bi- functional monomeric units. In this the elimination of small molecule like water, HCl etc…

- Example, Nylon 6,6.

➢ In both the polymerization mechanism it involves three steps: Initiation, Propagation, Termination.

➢ On the basis of chain initiation step it can be classified into two types,

➢ Ionic polymerization (cationic and anionic)

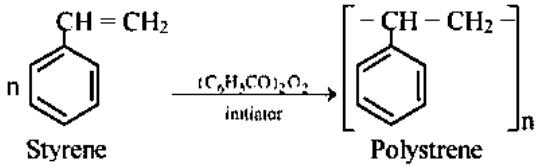
➢ Free radical polymerization.

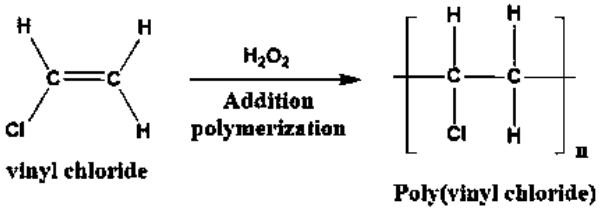
Free radical polymerization:

➢ Free radical polymerization is a method of polymerization by which a polymers forms by the successive addition of free radicals.

➢ Initiator used in free radical polymerization are benzoyl peroxide, acetyl peroxide, t- butyl peroxide, azo compounds like AIBN.

➢ Examples,

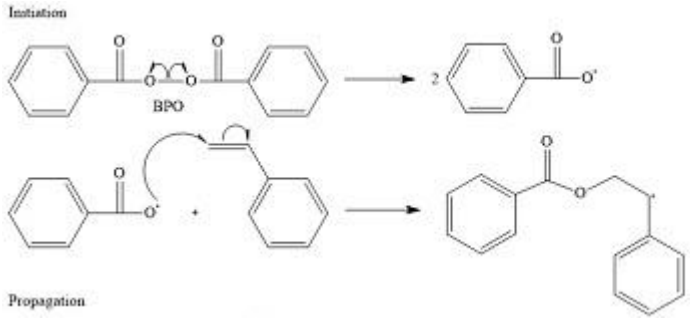




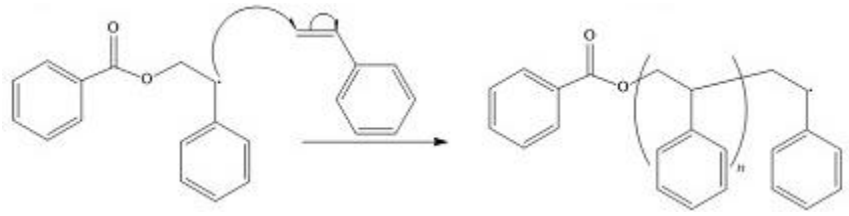
Mechanism:

Initiation:

Homolytic cleavage of benzoyl peroxide give phenyl free radical and it attack the monomer of styrene to form stabilised free radical.



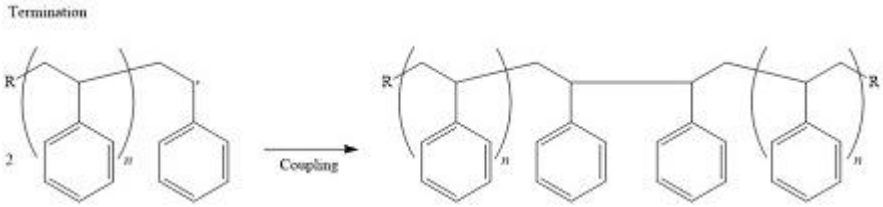
Propagation:



The stabilised radical further attacks another monomer of styrene and this process repeated until the thousands of monomers are connected.

Termination:

In this step, the chain is terminated by the combination of two radicals to form polystyrene.

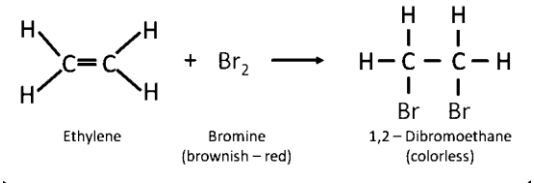


Halogenation reaction:

- Halogenation reaction is a chemical reaction that occurs with introduction of one or more halogens to a substance.
- It is of two types,

HALOGENATION ADDITION:

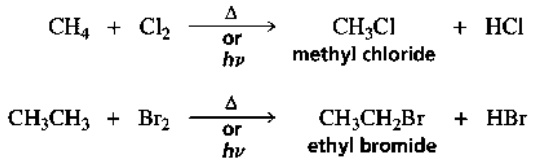
- This type of reaction common in unsaturated carbons like alkynes and alkenes follow this reaction where they add halogens.
- Example, addition of bromine to ethylene.



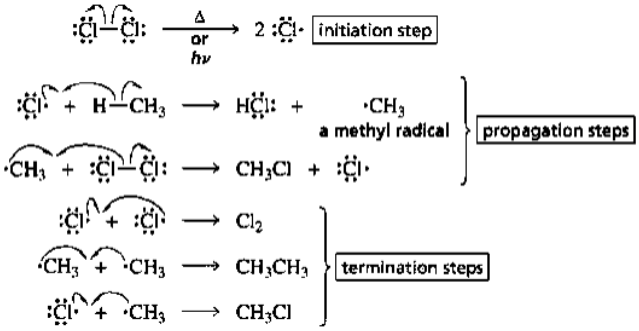
Halogenation substitution or free radical halogenation:

- In this reaction common in saturated carbons (alkane) where the hydrogen atom is usually replaced by halogens. The hydrocarbons basically undergo free radical halogenation.

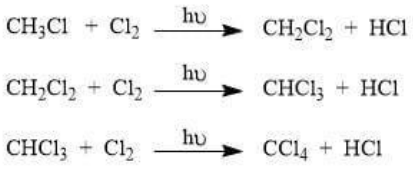
- This is a photochemical reaction and it only happens when the procedure carried out in the presence of UV light.
- In halogens, chlorine and bromine are widely used in halogenation reaction.
- While, fluorination generally proceeds too quickly and iodination proceeds too slowly.
- The order of reactivity among halogens, F>Cl>Br>I.
- The halogenation of alkanes through radical formation is extremely facile.
- Example, alkanes react with chlorine or bromine in the presence of light or heat to form alkyl halides.



Mechanism:



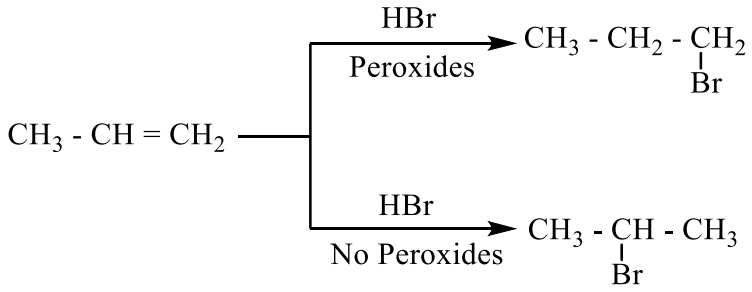
- In the initiation step, it involves the homolytic cleavage of Cl_2 bond to form two Cl free radicals.
- In the propagation step, the chlorine radical attacks the methane to form methyl radical and HCl.
- The newly formed methyl radical abstracts a Cl from a chlorine molecule, producing chloromethane and Cl radical.



- In this step the chloromethane is further chlorinated to dichloromethane and which in turn ultimately leads to formation of carbon tetrachloride due to high temperature of heat in the presence of light.
- In the termination step, the chain is terminated by the combination of two radicals.

Addition reaction:

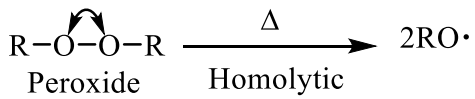
- Free radical addition is an addition reaction which involves free radicals.
- Radical additions are known for a variety of unsaturated substrates both olefinic or aromatic and with or without heteroatoms.
- The addition of halogen acid to unsymmetrical alkene in the presence of peroxide proceeds through radical intermediate giving anti-Markovnikov addition.
- This is generally referred to as peroxide effect.
- In the reaction halogen attack unsymmetrical alkene to generate a more stable secondary free radical.
- Example, propene reacts with HBr in the presence of hydrogen peroxide to form n-bromopropane.

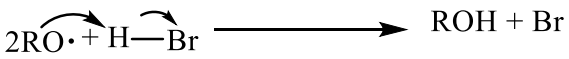


Mechanism:

STEP:1

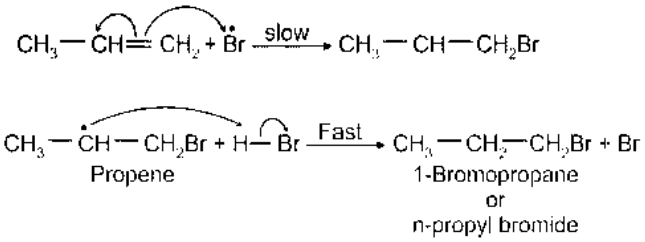
In the first step, it involves the homolytic cleavage of peroxide bond to form two RO free radicals and RO radical will go on attack HBr to form bromine radical.





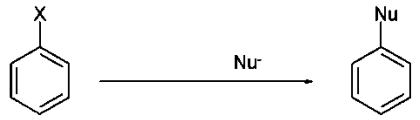
STEP:2

In the second step, the bromine radical attack the less substituted carbon of the alkene and forms a carbon radical and this radical attack the HBr by which the bromine radical will be re-formed.



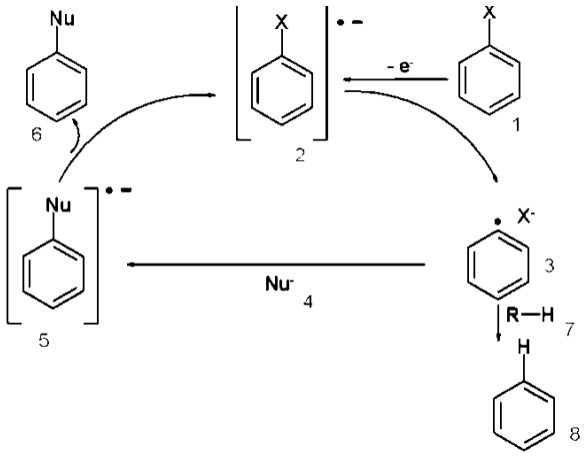
Radical – Nucleophilic aromatic Substitution

Radical-nucleophilic aromatic substitution or $S_{RN}1$ in organic chemistry is a type of substitution reaction in which a certain substitution on an aromatic compound is replaced by a nucleophile through an intermediary free radicals species:



The substituent X halide and nucleophiles can be sodium amide, an alkoxide or a carbon nucleophile such as an enolate. In contrast to regular nucleophilic aromatic substitution, deactivating groups on the arene are not required.

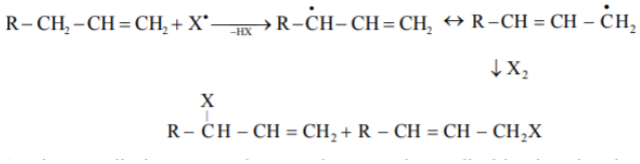
This reaction type was discovered in 1970 by Bunnett and Kim . As in the example of this reaction type is the Sandmeyer Reaction.



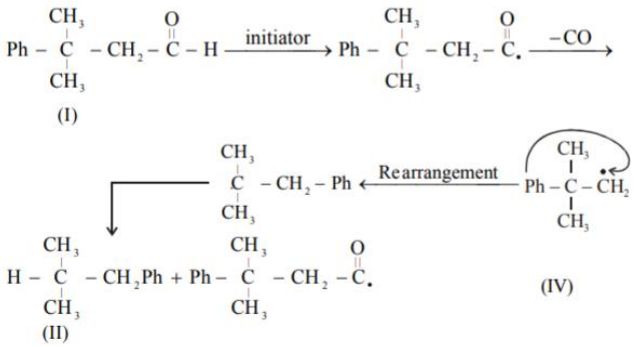
In this radical substitution the aryl halide accepts an electron from a radical initiator forming a radical anion. This intermediate collapses into an aryl radical and a halide anion. The aryl radical react with the nucleophile to a new radical anion. Which goes on to form the substituted product by transferring its electron to new aryl halide in the chain propagation. Alternatively the phenyl radical can abstract any loose proton from forming the arene in a chain termination reaction.

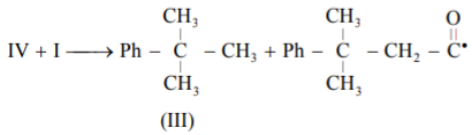
Free Radical Rearrangement

Allylic rearrangements are very common in free radical reactions on allylic substrates, for examples



A primary radical may be sometimes produce a tertiary radical by the migration of a substituent from the neighbouring carbon. However, such radical rearrangement are less common than carbocation rearrangements because the stability difference between a primary and tertiary radical is not as much as that between a primary and tertiary carbocation. Most of the reported rearrangements involve the shift of an aryl group from one atom to the adjacent atom. For example, the rearrangement of β-phenyl isovaleraldehyde I accompanying decarbonylation. The reaction is initiated by t-butyl peroxide and yields a mixture of almost equal amounts of isobutylbenzene II and t-butylbenzeneIII

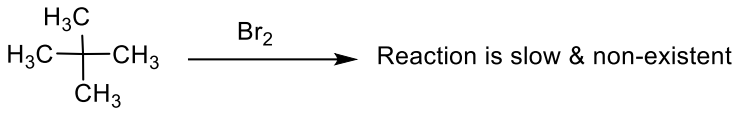




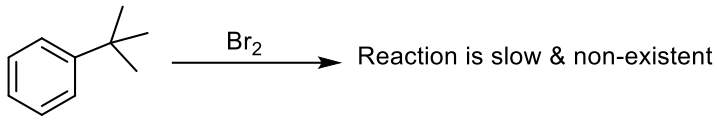
(III)

Reactivity in the attacking radicals

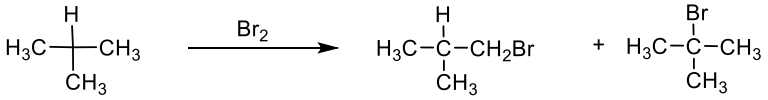
- Some radicals are much selective than other.
- The bromine is so selective that, when only primary hydrogens are available, as in neopentane (or) t-butyl benzene, the reaction is slow (or) non existent and isobutane can be selectively brominated to give t-butyl bromide in high yields.



neopentane



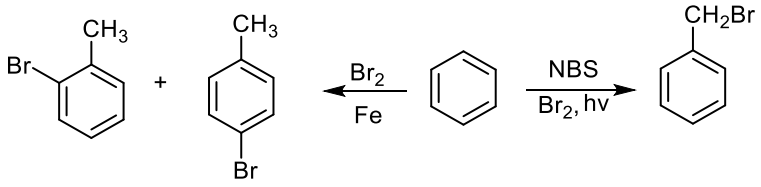
t-butyl benzene



isobutane 0% 100%

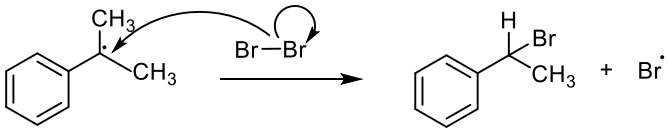
t-butyl bromide

- Bromination of other alkyl benzenes, for e.g. ethyl benzene and cumene take place exclusively at the position.



Ionic reaction Radical reaction

- The bond dissociation energy (C – H) bond is more important for radicals of low reactivity than highly reactive radicals.



Ethyl benzene Emphasizing the selective of bromine

- Some common free radical in decreasing order of activity

  $Br\cdot > Me\cdot > H\cdot > CF_3\cdot > MeO\cdot > Cl\cdot > F\cdot$

Radicals	E Value (kcal/mol^{-1})	kJ/mole^{-1}
F·	0.3	1.3
Cl·	1.0	4.2
MeO·	7.1	30
CF_3·	7.5	31
H·	9.0	38
Me·	11.8	49
Br·	13.2	55.2

The E value represent activation energies for the reaction

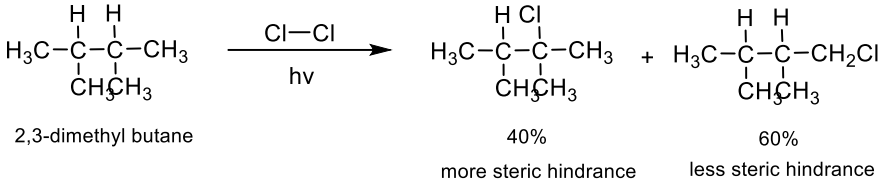
$X\cdot + C_2H_6 \rightarrow X\text{-}H + C_2H_5\cdot$

The effect of solvent of reactivity

The solvent usually has little effect on free radicals substitutions in contrast to ionic ones. But there are two types of solvent which different attack.

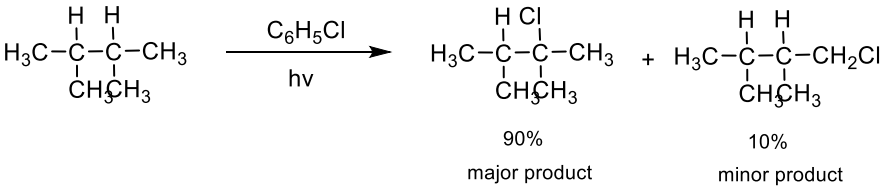
i) Aliphatic solvent

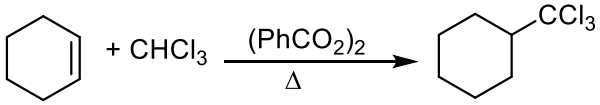
Chlorination of 2,3-dimethyl butane to major product is less steric hindrance and less product is more steric hindrance.



ii) Aromatic solvent

Chlorination of 2,3 dimethyl butane major product is more stable and less product is less stable and chlorine is more selective.





UNIT-II

OXIDATION AND REDUCTION REACTIONS

Hydride Transfer:

Hydride shift is a rearrangement of a hydrogen atom in a carbocation to make the intermediate structure more stable. It is generally observed in rearrangement reaction. After shifting a hydrogen atom from one carbon to another, structural isomers of compounds are formed. This rearrangement happens to make carbocation more stable.

When less stable carbocation is transformed to more stable carbocation, C-H bond in intermediate state is rearranged to proceed with the reaction.

Rearrangement Reaction:

A rearrangement reaction is a type of intermolecular substitution reaction in which the carbon skeleton of a molecule is rearranged to form a structural isomer of the original molecule.

The substituent moves from one atom to another atom within the same molecule.

Based on atom or group rearranging, rearrangement reactions are of two types.

1. Hydride Shift
2. Alkyl Shift

Based on the site of rearrangement, rearrangement reactions are of two types.

1. 1,2 Rearrangement Reaction
2. 1,3 Rearrangement Reaction

REACTION MECHANISM:

- Hydride shift is often initialised by forming a reactive intermediate carbocation.
- The driving force for the migration of hydrogen atoms in step of two of arrangement is the formation of more stable intermediate carbocation.
- A more substituted carbocation is found to be more stable.
- A tertiary carbocation is more stable than secondary carbocation followed by primary carbocation.

- Thus a rearrangement takes place to stabilise the intermediate transition state.
- The most crucial carbocation 1,2 hydride shift is the **Wagner-Meerwein rearrangement.**

Reaction is first reported by Wagner-1899 extended by Meerwein in 1914.It gives close relationship of carbocations as intermediate.

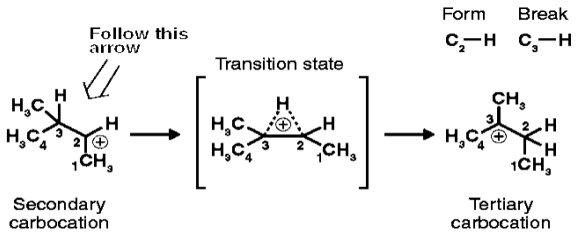
First discovered in bicyclic terpenes. For example: The conversion of isoborneol to camphene.

Wagner-Meerwein rearrangement:

Wagner- Meerwein rearrangement is a type of 1,2- rearrangement reaction in which hydrogen, an alkyl or an aryl migrates from one carbon to the adjacent carbon.

It is a cationic [1,2]-sigmatropic rearrangement.

- Rearrangement occurs because a tertiary carbocation is more stable than secondary carbocation, followed by primary carbocation.



This reaction is named after a Russian chemist Yegor Yegorovich Vagner. He was born in Germany and has also published German journals as Georg Wagner and Hans Meerwein.

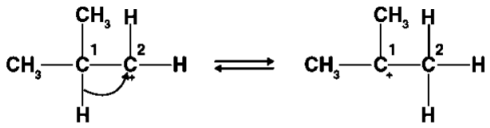
Conditions of Hydride Shift

A hydride shift will occur whenever we have a more substituted carbon around a cationic carbon. It would shift the positive charge over to carbon, stabilising it better, thus stabilising the intermediate state

1,2 Hydride Shift

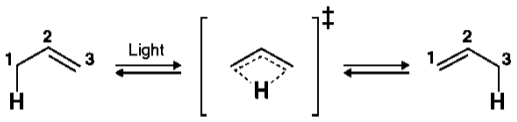
- Heinrich Otto Wieland reported the first 1,2 hydride shift in 1911.

- 1,2 Hydride Shift is a rearrangement reaction in which hydrogen moves from one carbon atom to another carbon in a chemical compound.
- In a 1,2hydride shift, the movement involves two adjacent atoms, but movement over more considerable distances is also possible.



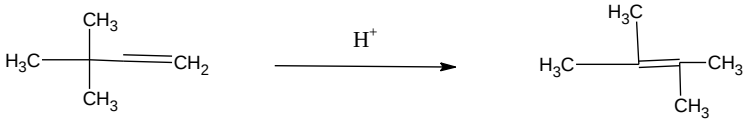
1,3 Hydride Shift

- 1,3 Hydride Shift is a rearrangement reaction in which hydrogen moves from **one carbon atom to the third carbon atom in a chemical compound.**

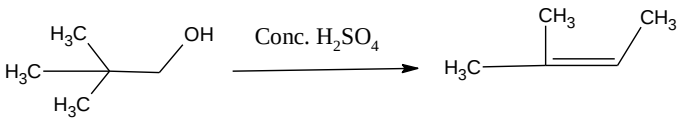


Applications:

In cracking of petroleum products.



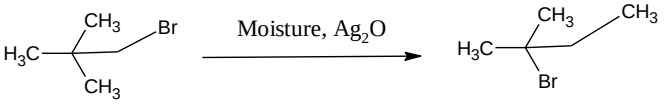
Dehydration of neopentyl alcohol.



2,2 dimethyl propanol

2 methyl but-2-ene

Hydrolysis of neopentyl bromide.

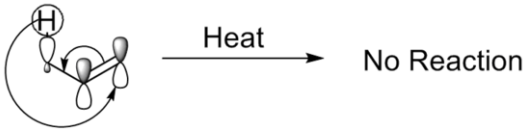


Neopentyl Brommide

Iso pentyl bromide

Thermal hydride shifts

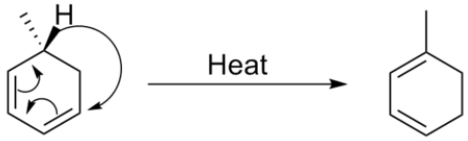
In a thermal [1,3] hydride shift, a hydride moves three atoms. The Woodward–Hoffmann rules dictate that it would proceed in an antarafacial shift. Although such a shift is symmetry allowed, the Mobius topology required in the transition state prohibits such a shift because it is geometrically impossible, which accounts for the fact that enols do not isomerize without an acid or base catalyst.



Geometrically impossible 1,3 shift

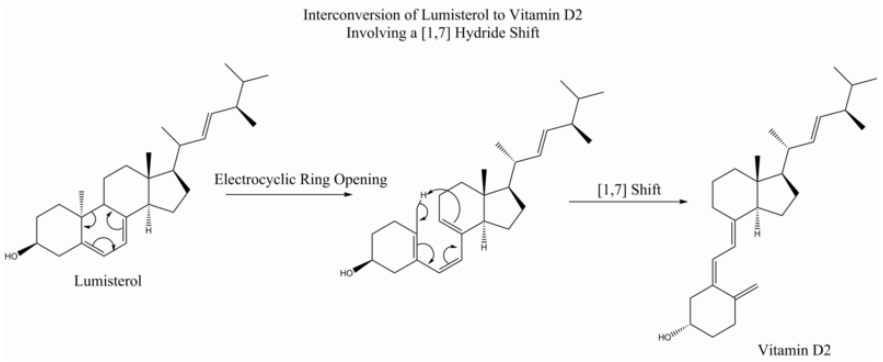
Photochemical shifts

A [1,5] shift involves the shift of 1 substituent (hydride, alkyl, or aryl) down 5 atoms of a π system. Hydrogen has been shown to shift in both cyclic and open-chain compounds at temperatures at or above 200 ˚C These reactions are predicted to proceed suprafacially, via a Hückel-topology transition state.



1,5 Shift

[1,7] sigmatropic shifts are predicted by the Woodward–Hoffmann rules to proceed in an antarafacial fashion, via a Mobius topology transition state. An antarafacial [1,7] shift is observed in the conversion of lumisterol to vitamin D2, where following an electrocyclic ring opening to previtamin D2, a methyl hydrogen shifts.



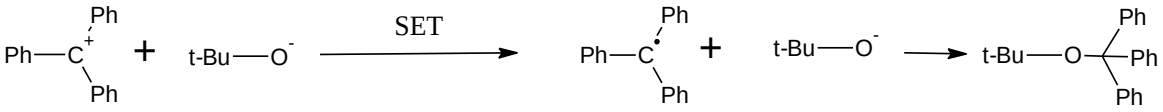
Single Electron Transfer (SET)

In some nucleophilic substitution reaction where SN1 is highly probable,free radicals are involved and has been proved by ESR spectroscopy.

In such reactions carbocations is good electron acceptor and nucleophile is a good electron donors.

Example:

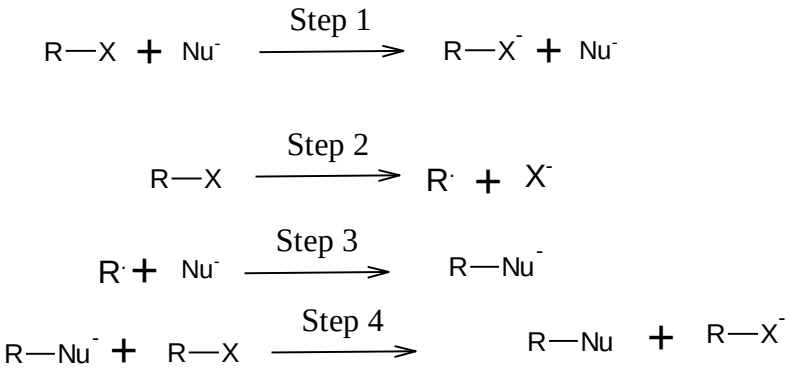
1.Reaction between triphenyl methyl cation and tertiary butoxide ion.



In this reaction carbocation is a good electron acceptor and nucleophile is a good electron donor.

In this type of mechanism where transfer of single electron is involved so it is known as SET mechanism.

2.SN2 reaction via SET mechanism



SET mechanism involves free radicals, radical-anions and radical cations. The intermediate are paramagnetic and helps in detection of these species using a reaction by ESR is a proof that SET mechanism is being followed.

Activation of substrate by suitable mechanism often increases its reactivity. here electron transfer also enhances reactivity.

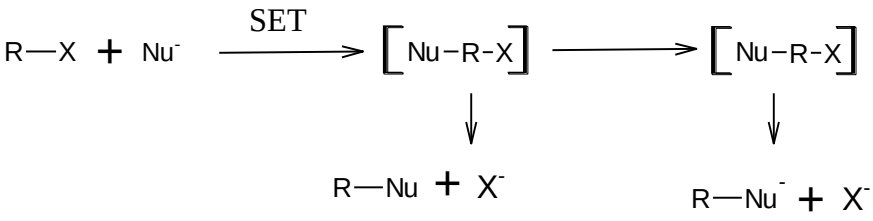
Electron transfer reactions are of two types:

1. Photoinduced electron transfer (PET)

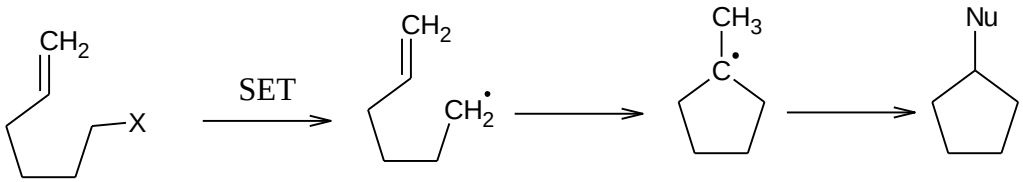
2. Chemically induced electron transfer(CET)

Stereochemistry of SET mechanism:

These reactions show inversion of configuration.Howeverin many cases some racemisation has also been observed. If the reaction involves intermediary of a simple free radical (R' ,a completely racemised product (R-Nu) would have been observed.Therefore it has been suggested that Nucleophile approaches, R-X from backside and radical is tied up in a solvent cage having a nucleophile on the back.



Sometimes cyclic side products are also formed



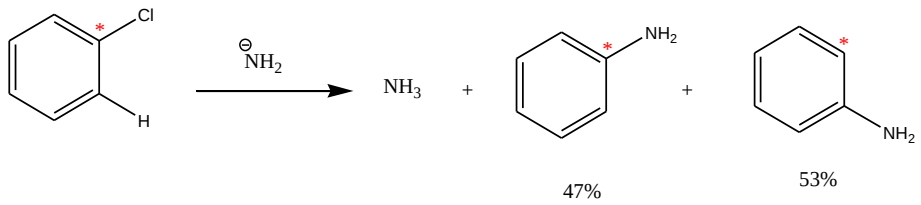
Addition – Elimination Reactions

Benzyne Mechanism

In several cases of nucleophilic aromatic substitution the entering group does not occupy the position vacated by the expelled group. Such reactions are called cine substitution.

Example

When chlorobenzene labelled with C^{14} at the carbon atom of C-Cl group is treated with Sodamide in liquid ammonia the amino group enter party at the labelled carbon and party at the ortho atom.

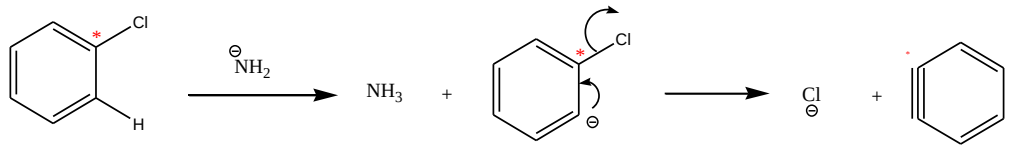


Mechanism

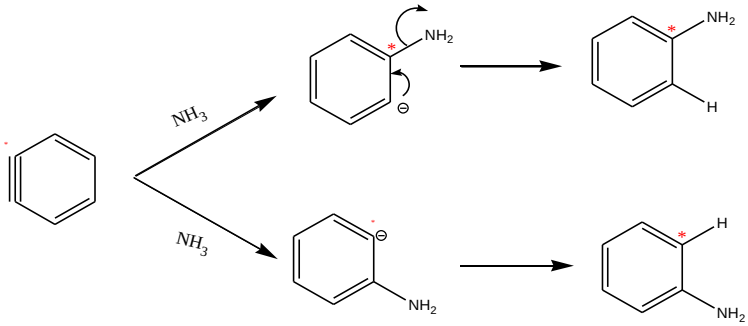
i. Benzyne is formed by a stepwise elimination

ii. Benzyne undergoes stepwise addition to give the final product aniline

STEP 1 ELIMINATION

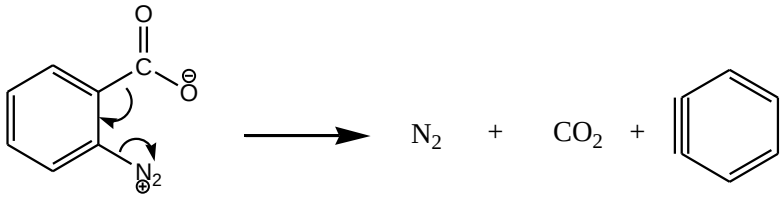


STEP II ADDITION

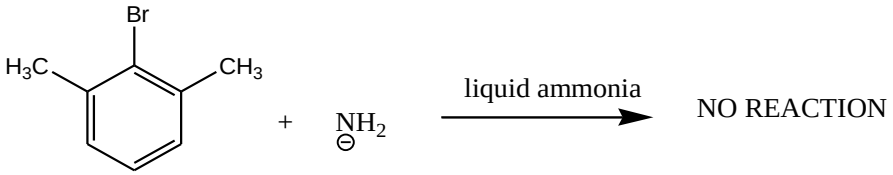


Evidence for benzyne mechanism

i. Benzyne has detected by the combination of flash photolysis and mass spectrometry in the decomposition of benzenediazonium o-carboxylate.



ii. The formation of intermediate does not occur if the aryl halide contain two ortho substituent



Coupling reaction

i. The term 'coupling reaction' means the class of organic reactions that involve the joining of two chemical species. It is usually done with the help of a metal catalyst.

ii. There is an important type of coupling reaction, which is the reaction of an organic halide with an organometallic compound having the general formula R-M that helps in the new carbon-carbon formation of chemical bonding.

iii. The compound formed as a result will have the formula R-R'; if the organic halide in this reaction has the general formula R'-X.

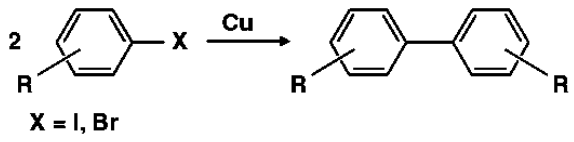
Types of Coupling Reactions

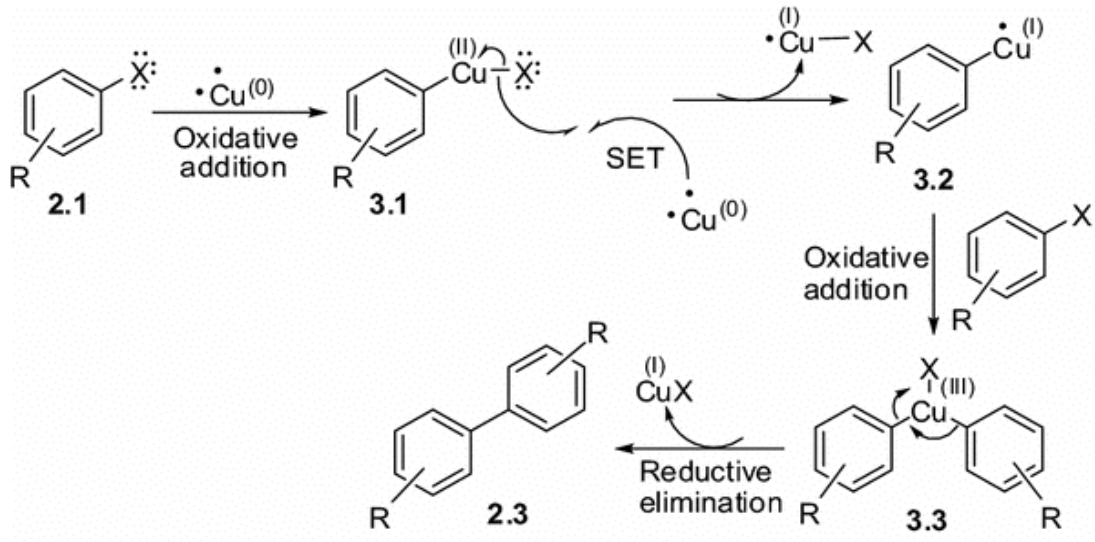
Coupling reactions can be classified into two types based on the chemical species that are combined by them:

- **Homo-coupling reactions:** Here, two identical chemical species are combined to yield a single product.
- **Hetero-coupling reactions (also known as cross-coupling reactions):** Here, two dissimilar chemical species are joined together to afford a single product.

Homo-Coupling Reactions

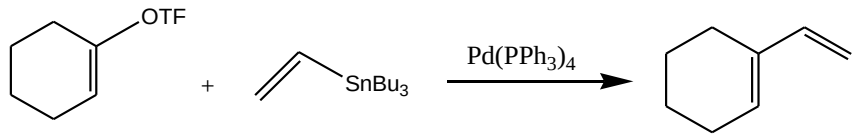
An important example of homo-coupling reactions is the Ullmann reaction,



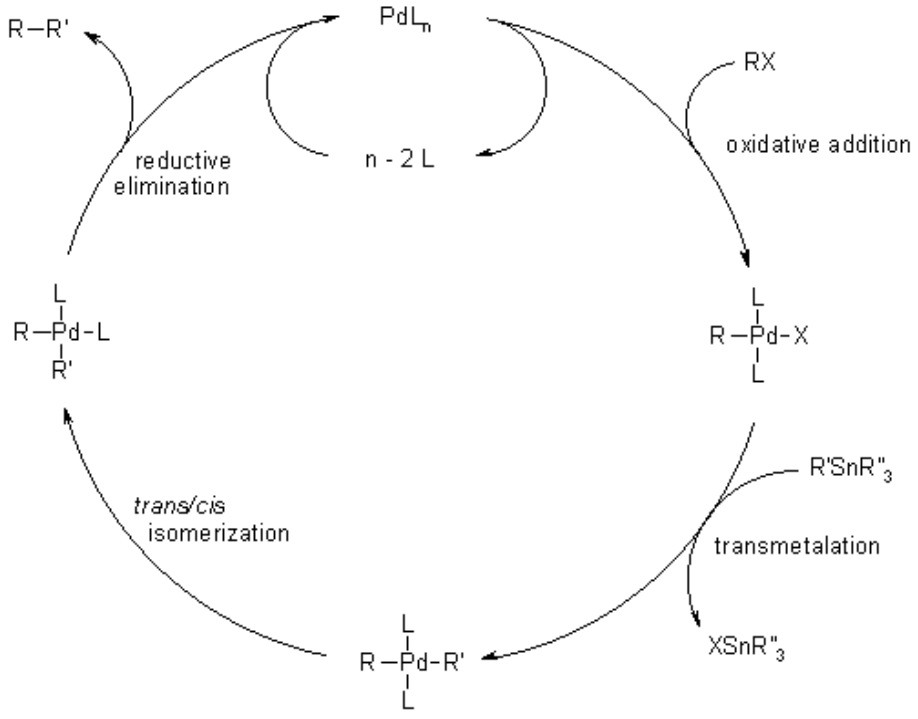


Hetero-coupling reactions

The stille reaction is an important example of a cross-coupling reaction. The stille reaction of an aryl halide and an alkene

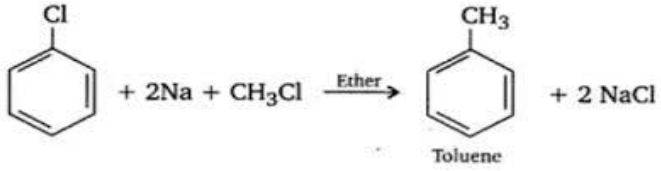


Catalytic cycle

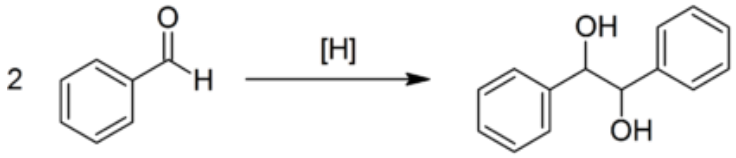


Another example for homocoupling:

Wurtz reaction



Pinacol coupling



Mechanism of oxidation reactions: halides and amines

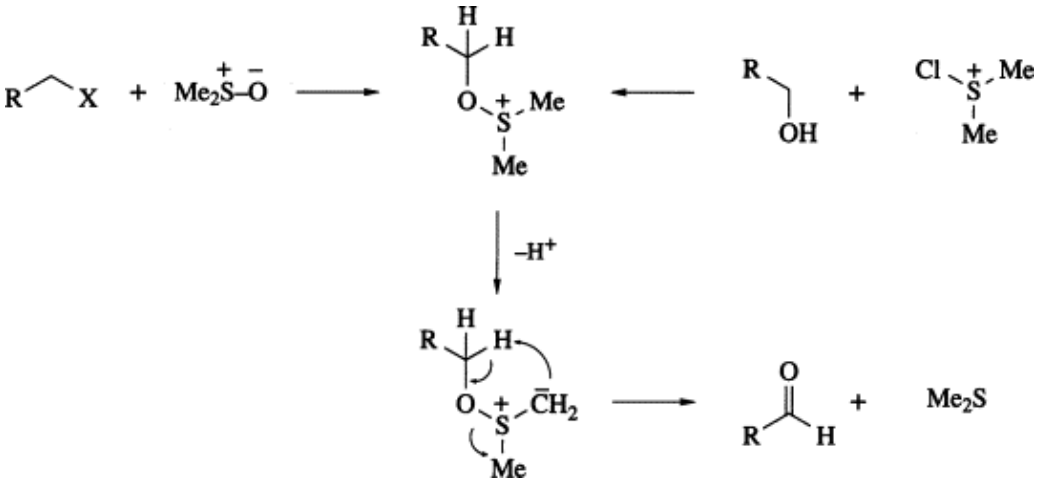
A oxidation reaction is a chemical reaction that involves the loss of electrons or increase in the oxidation state of a molecule, atom or ion.

Oxidation reaction of halides:

Kornblum oxidation reaction:

The Kornblum oxidation named after Nathan kornblum is an organic oxidation reaction that converts alkyl halides and tosylates into carbonyl compounds.

Mechanisms



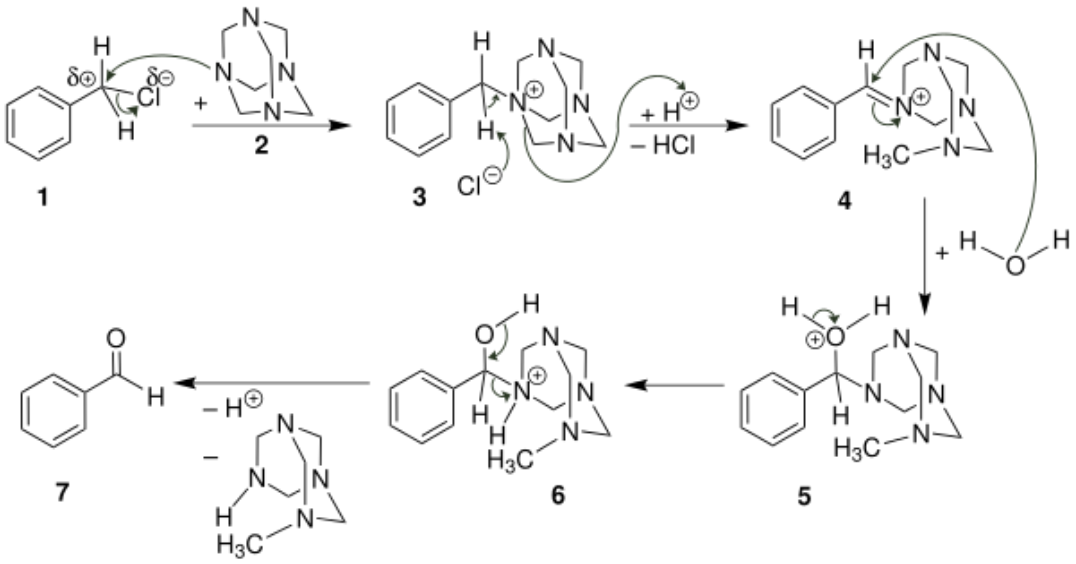
Kornblum oxidation is best for halides oxidation it follows S_N2 reaction ,displacement of halide by oxygen atom of DMSO to form sulfonium salt. Proton is removes to generate sulfur ylide. Affords the oxidized product . However in path B α halocarbonyl compound loses an α proton to generate carbonyl groups since the proton adjacent to it more acidic than methyl group pf sulfonium.

Note: more acidic = more polarity = easily tends to leave.

Kornblum oxidation well known method for oxidizing halides. **The Ganem oxidation reaction** is modification of this uses pyridine-N-oxide or similar reagent instead of DMSO.

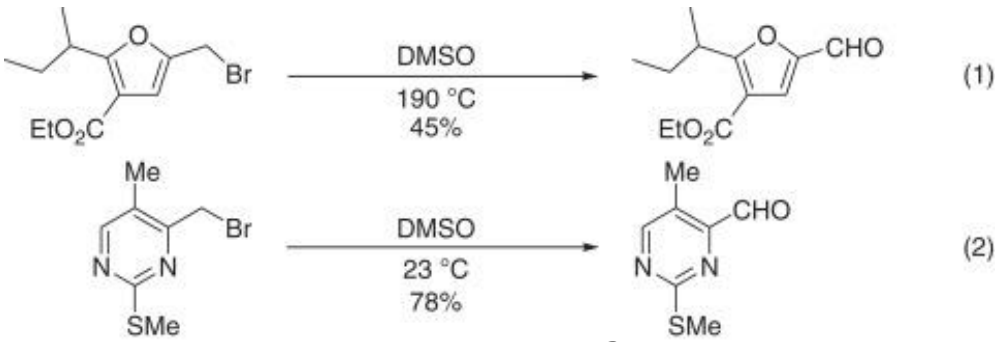
Sommelet reaction:

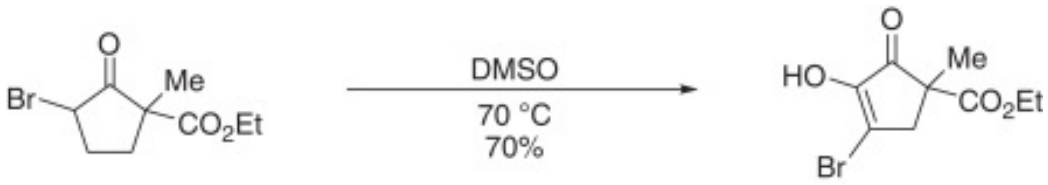
Sommelet reaction use hexamethylenetetramine(HMT) to convert benzylic halides into aldehydes. The reaction requires mild acidic condition.

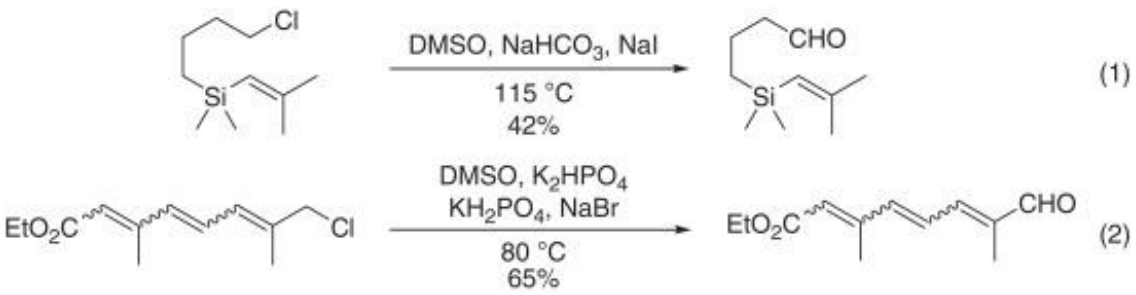


The benzyl halide reacts with hexamine to a quarternary ammonium salt each time just alkylating the nitrogen atom. The benzylammonium undergoes an acid-catalysed hydrolysis process. Depends on hydrolysis the hexamine unit break leaving a benzaldehyde .

Application and examples:

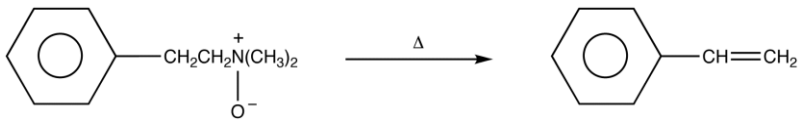




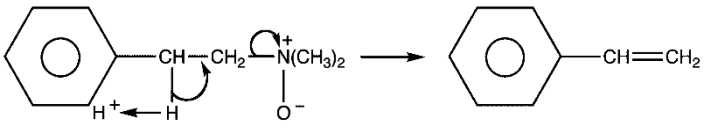


The cope elimination or cope reaction is a reaction that forms an alkene and hydroxylamine from an N-Oxide. It is syn periplanar elimination, meaning six electrons move in a five membered ring to produce the alkene and hydroxylamine

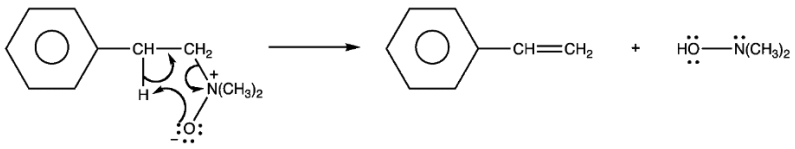
When a tertiary amine oxide bearing one or more beta hydrogens is heated, it is converted to an alkene. The reaction is known as *Cope elimination* or *Cope reaction*, not to be confused with Cope Rearrangement. For example:



The net reaction is 1,2-elimination, hence the name Cope elimination.

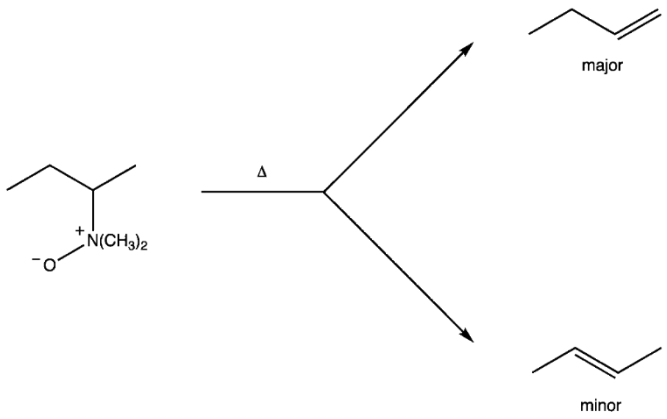


mechanism: Cope elimination is an intramolecular E2 reaction. It is also a pericyclic reaction.



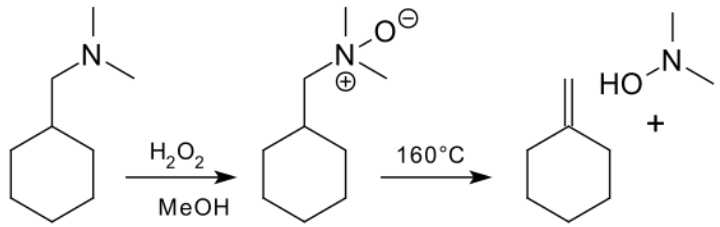
Cope elimination is regioselective. Unlike intermolecular E2 reactions, it does not follow Zaitsev's rule; the major product is always the least stable alkene, i.e the alkene with the least highly substituted double bond.

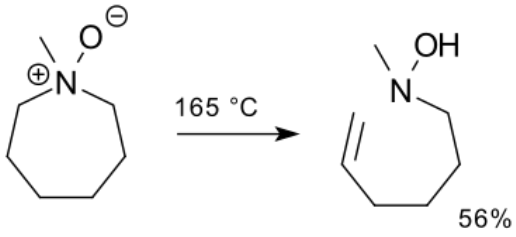
For example:



Application:

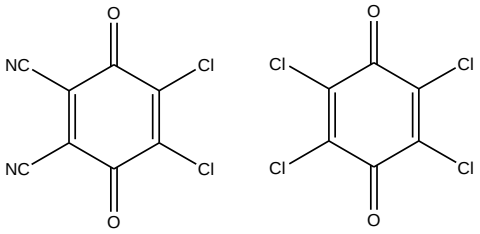
1. Synthesis of methylene cyclohexane:





Dehydrogenation by Quinone (DDQ)

- Quinones are generally used for dehydrogenation Two important quinones are chloranil and DDQ (2,3- Dichloro- 5,6 dicyano-1,4-benzoquinone)

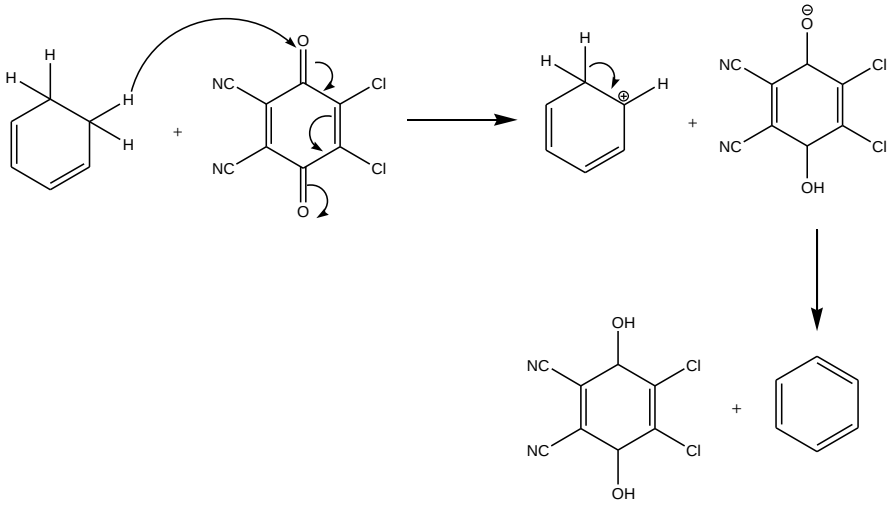


DDQ chloranil

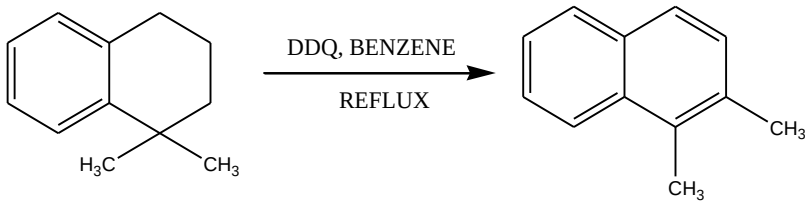
- DDQ is very reactive and may be used in case where the substrate is difficult to dehydrogenate. DDQ is used under anhydrous conditions because it decomposes in pressure of H_2O.
- The reaction may be carried out in inert solvent (benzene, toluene, THF)
- Solution DDQ in benzene is red because the formation of charge transfer complex after dehydrogenation DDQ reduced to hydroquinone which is yellow colour solid ,in soluble in benzene

Mechanism of dehydrogenation

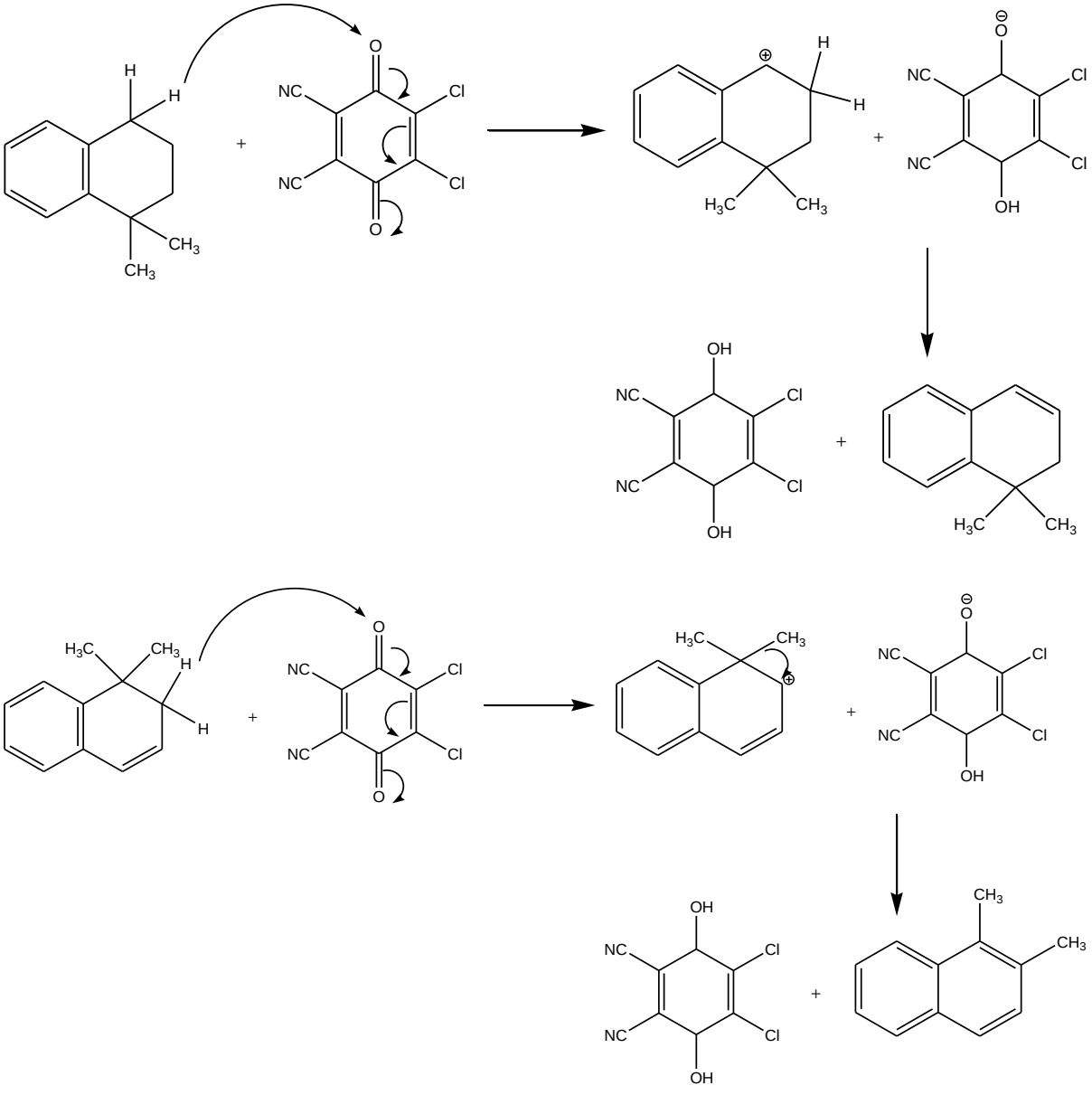
- DDQ involves the transfer of hydride ion form hydrocarbon to quinone oxygen followed by the transfer of a proton to the phenolate ion. Thus DDQ is reduced to hydroquinone.



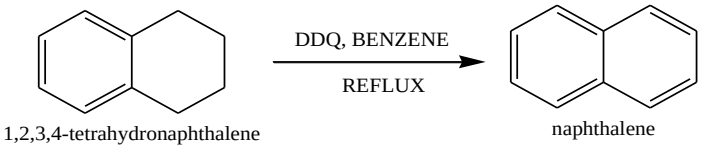
Example. 2



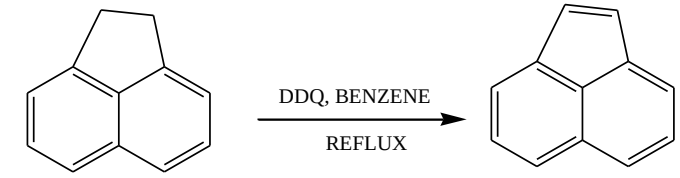
Mechanism



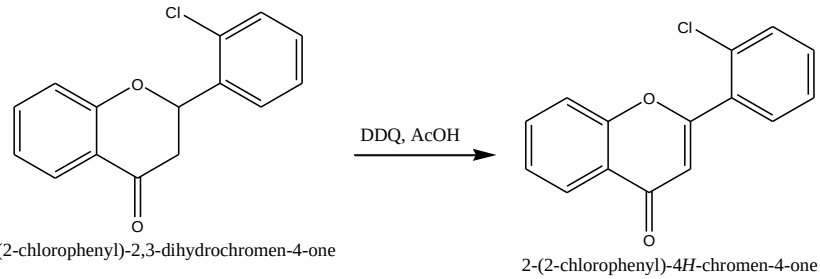
Applications of DDQ



1,2,3,4-tetrahydronaphthalene — naphthalene



1,2-dihydroacenaphthylene — acenaphthylene



2-(2-chlorophenyl)-2,3-dihydrochromen-4-one — 2-(2-chlorophenyl)-4*H*-chromen-4-one

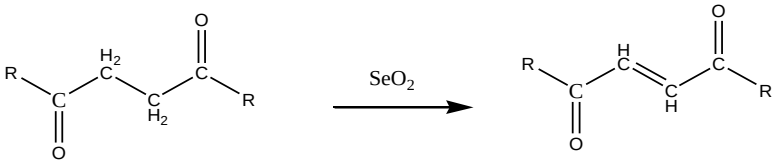
Dehydrogenation by Selenium dioxide

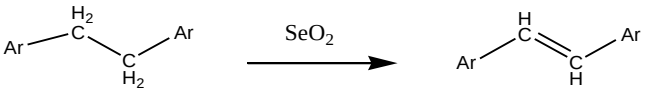
Preparation

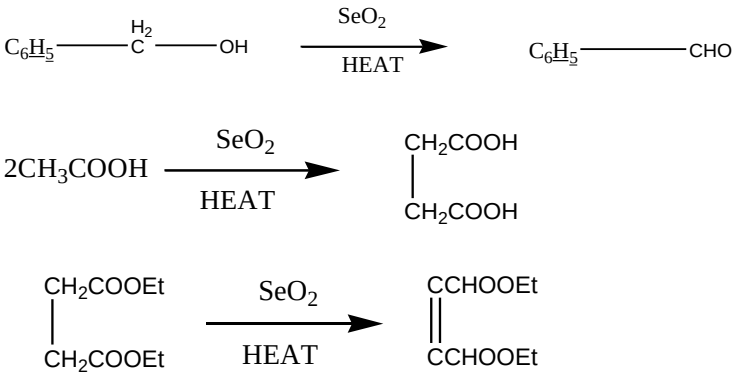
When selenium is strongly heated with air in the presence of trace of nitrogen peroxide as catalyst then we get selenium oxide.

$$Se + O_2 \longrightarrow SeO_2$$

- Colour needle like crystals melting point 340 º C
- Dissolves in water to form selenium oxide.
- SeO_2 is an oxidising agent but in certain case it converts carbonyl compounds to α,β- unsaturated carbonyl compounds by removing hydrogen.
- For ex : SeO_2 has been used to dehydrogenate 1,4-diketones and 1,2-diaryethane

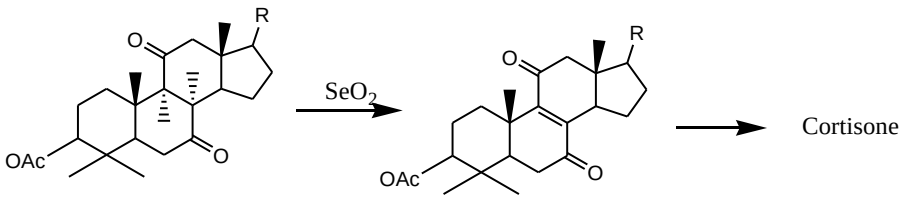






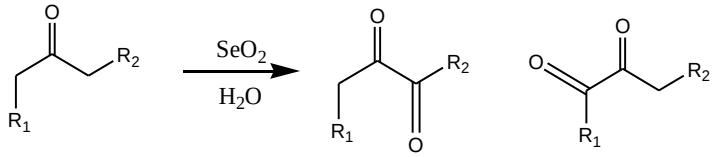
Applications

- Dehydrogenation of 12-ketobile acid with SeO_2 where a 9,11-double bond is introduced. this is key step in the syn of cortisone .



Riley oxidation

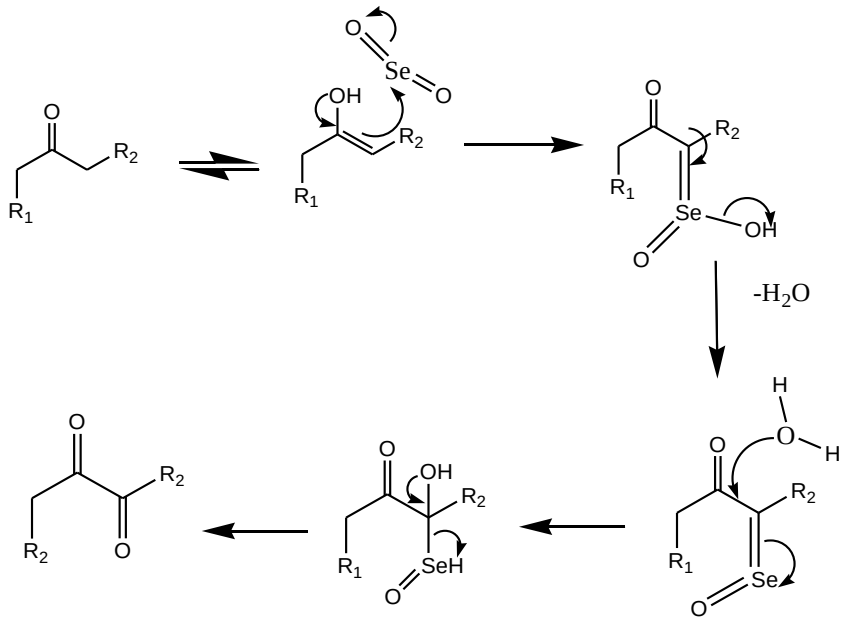
Selenium dioxide mediated oxidation of methylene group to alpha ketones and at allylic position of olefins is known as the Riley oxidation.



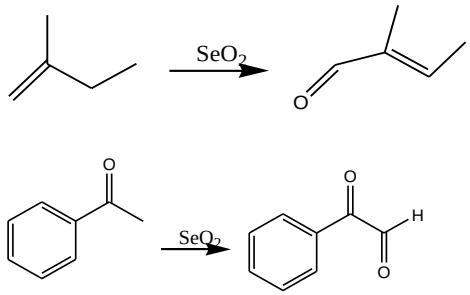
Mechanism:

The oxidation of carbonyl alpha methylene position begins with attack by the enol tautomer at the electrophile selenium centre.

Following rearrangement and loss of water, second equivalent of water attack to alpha position selenic acid is liberated in the final step to give the 1,2-dicarbonyl product.



Applications:

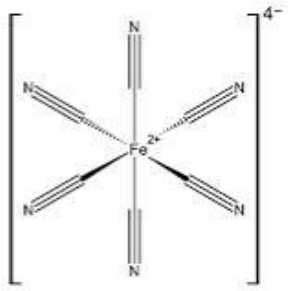


Mechanism of oxidation reaction reactions – Ferricyanide, Mercury acetate, Lead tetra acetate

Ferricyanide:

Potassium ferricyanide dissociate to give potassium ion and ferricyanide ion Potassium ferricyanide, with the chemical formula $K_3Fe(CN)_6$, is a coordination compound that contains iron in its +3 oxidation state. It is a bright red crystalline solid and is commonly used in analytical chemistry and photography. In laboratory settings, it serves as an oxidizing agent. However, it's important to handle it with care, as it can be toxic.

Structure:



Preparation:

Potassium ferricyanide can be prepared on an industrial scale by obtaining a solution of potassium ferricyanide and passing chlorine gas through it. When the chlorine gas is passed through the potassium ferrocyanide solution, the red-colored potassium ferricyanide is formed. This compound goes on to separate itself from the potassium ferrocyanide solution. The chemical equation for this reaction is provided below.

$2K_4[Fe(CN)_6] + Cl_2 \rightarrow 2KCl + 2K_3[Fe(CN)_6]$

Therefore, it can be understood that two molar equivalents of potassium chloride are obtained for each molar equivalent of chlorine gas passed through the potassium ferrocyanide solution.

Mechanism of ferricyanide – oxidation of thiols

The mechanism is

$$RSH + HO^- \rightleftharpoons RS^- + H_2O \quad \text{(fast)} \quad (1)$$

$$RS^- + Fe(CN)_6^{3-} \rightleftharpoons RSFe(CN)_6^{3-} + CN^- \quad \text{(fast)} \quad (2)$$

$$RSFe(CN)_6^{3-} \longrightarrow RS^{\bullet} + Fe(CN)_6^{3-} \quad \text{(slow)} \quad (3)$$

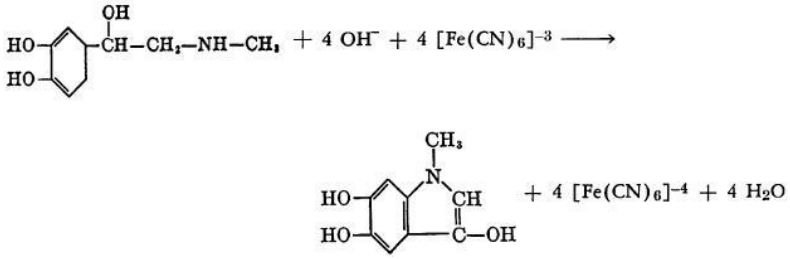
$$Fe(CN)_6^{3-} + CN^- \longrightarrow Fe(CN)_6^{4-} \quad \text{(fast)} \quad (4)$$

$$RS^{\bullet} \longrightarrow RSSR \quad \text{(fast)} \quad (5)$$

Application :

1, $3\ FeSO_4 + 2\ K_3[Fe(CN)_6] \rightarrow Fe_3[Fe(CN)_6]_2 + 3K_2SO_4$.

When ferrous sulfate reacts with potassium ferricyanide to give the important compound called Turnbull's blue. It is deep blue color often used in analytical chemistry and colorimetry.

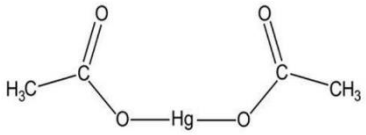


Mercury acetate:

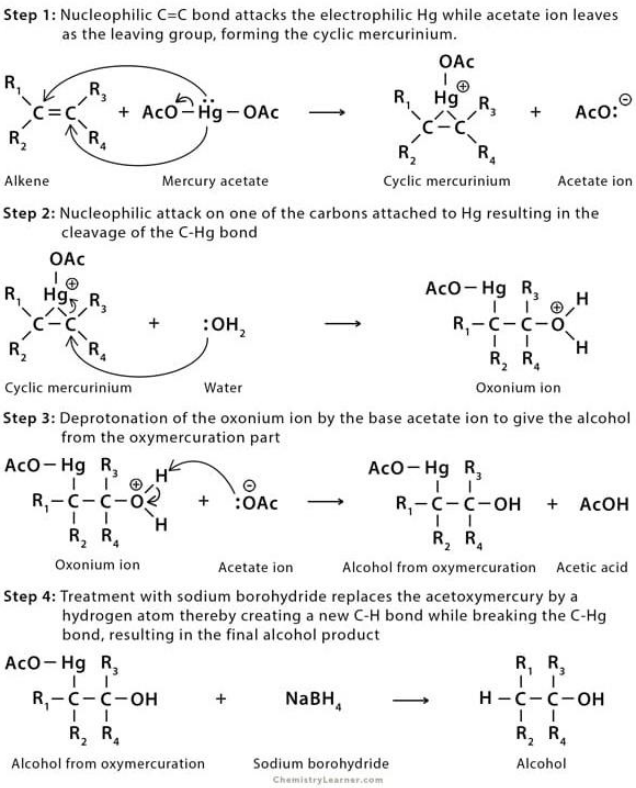
Preparation:

Mercury acetate (MA) can be obtained by metallic mercury immersed in a mixture of deionised, bidistillated water (dbw) and acetic acid.

Structure:

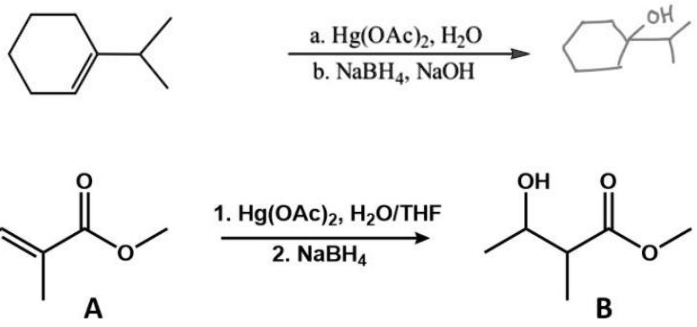


Oxidation mechanism:



Application:

It is used to convert alkenes to corresponding alcohols.



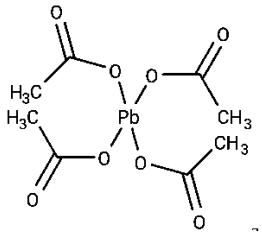
Lead tetraacetate:

Lead tetraacetate, also known as lead(IV) acetate, is a chemical compound with the molecular formula $Pb(CH_3CO_2)_4$. It is a yellow-brown crystalline solid and is a powerful oxidizing agent. This compound has been used historically as a reagent in organic synthesis for oxidizing certain organic compounds, particularly alkenes and alkynes.

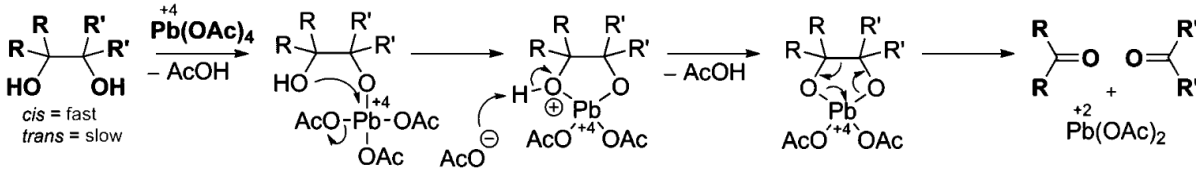
Preparation:

It can be prepared by adding red lead oxide,Pb_3O_4, to a mixture of acetic acid and acetic anhydride at 70°c.

Structure:

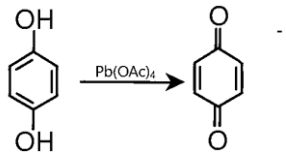


Oxidation mechanism:

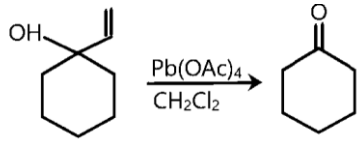


Application:

1. It is used to oxidise vicinal diols into corresponding aldehydes and ketones.



2. It is used to convert corresponding alcohols into ketones.



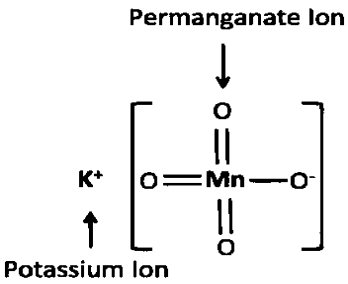
Oxidation using Permanganate and Manganese dioxide

Potassium Permanganate:

A German-Dutch chemist Johann Rudolf Glauber was the first to discover the production of $KMnO_4$ IN 1659. It is also known as Condy's crystals or permanganate of potash. It is considered as strong oxidizing agent.

It dissolves in water,acetic acid, acetone ,methanol and pyridine.

Structure:



Preparation:

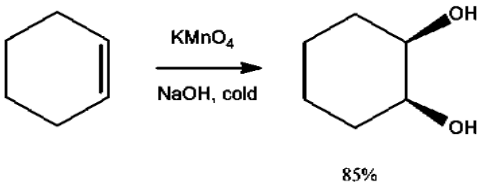
$$2MnO_2 + 4KOH + O_2 \xrightarrow{\text{heat}} \underset{\text{Potassium magnate}}{2K_2MnO_4} + 2H_2O$$

$$\underset{\text{Potassium magnate}}{2K_2MnO_4} + 4HCl \longrightarrow \underset{\text{Potassium Permagnate}}{2KMnO_4} + MnO_2 + H_2O + 4KCl$$

Powdered manganese oxide is added to KOH with oxidizing agent like potassium chlorate. Then the mixture is evaporated by boiling and residue is heated in iron pans. Obtained potassium permanganate is boiled with water and current of chlorine. CO_2 and ozonized air is passed into it until it is converted to permanganate.

Oxidation Of Alkenes [Mild Condition]

Bayer's Reaction ⟶ Cis –dihydroxylation

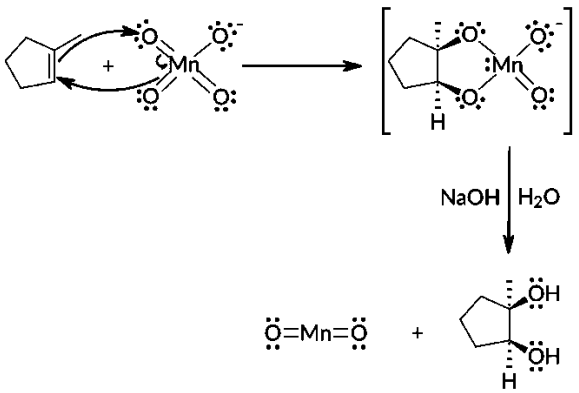


85%

Alkene undergo oxidation in presence of $KMnO_4$ to give syn-addition product – Cis-diol.

In this reaction pink or purple $KMnO_4$ is reduced to MnO_2, a brown solid. This change in colour is the basis of a test for the presence of double and triple bonds known as Baeyer's test for unsaturation.

Mechanism

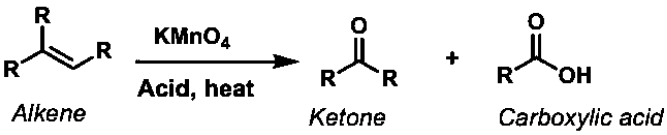


In the above mechanism, the diols obtained are cis-diol. The hydroxylation of alkenes with $KMnO_4$ involves a cyclic intermediate, a manganite ester. The intermediate breaks down in water to give cis-1, 2-diol. The manganate ion is converted to MnO_4

Oxidation of alkenes [strong condition]

Here the reaction is carried out in acidic medium of $KMnO_4$ at high temperature. The product is based on reagents used.

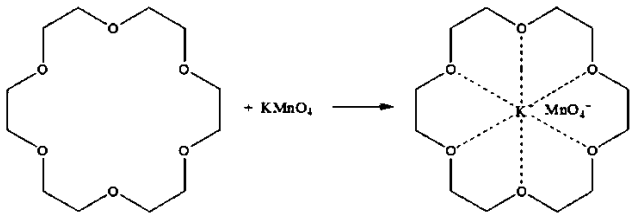
Oxidative Cleavage of alkenes with $KMnO_4$



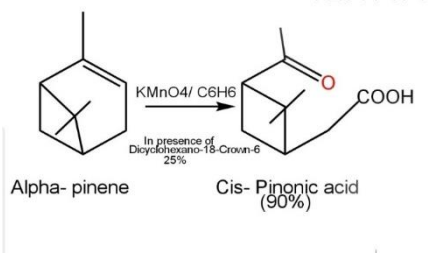
Key bonds formed	Key bonds broken
C–O (2)	C–C
C–O (π) (2)	C–C (π)
C–OH	C–H

Role of Crown Ethers and Phase Transfer Catalyst:

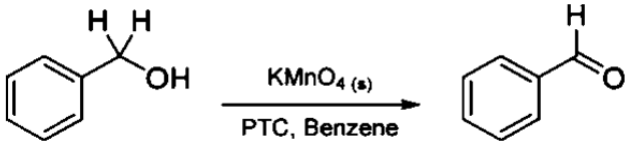
Oxidation of alkenes can also be affected by presence of Phase Transfer Catalyst [PTC] and crown ethers with aqueous solution of $KMnO_4$. The catalytic action of quarternary salt [PTC] is due to the ability of their organic soluble cations to transfer anions [eg.MnO_4] from aqueous into organic phase. The crown ethers form permanganate complex with potassium permanganate and take part in reaction.



Reaction:

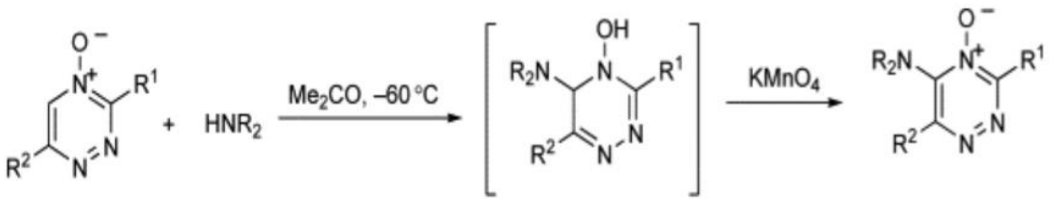


Alpha -pinene gives pinonic acid by using crown ether as catalyst.

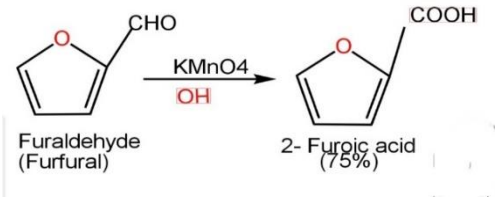


Application:

1. A new version of chichibabin amination of azaaromatics in liquid ammonia in the presence of potassium permanganate, suggested by H.C.Van der plas, has been applied successfully in the series of 1,2,4-triazines.



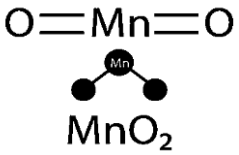
2)Synthesis of Furoic acid from furfural



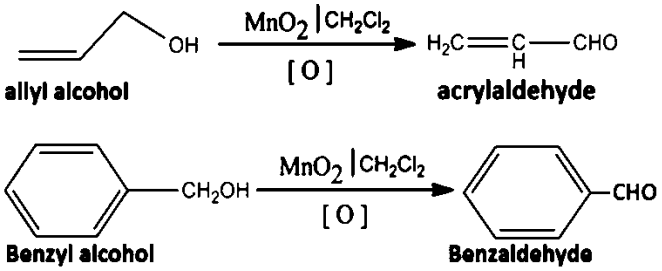
Oxidative Mechanism of Manganese Dioxide:

Manganese dioxide is the selective mild oxidizing reagent with the formula MnO_4 that exist as black brown solid. It is also known as pyrolusite.

Structure:

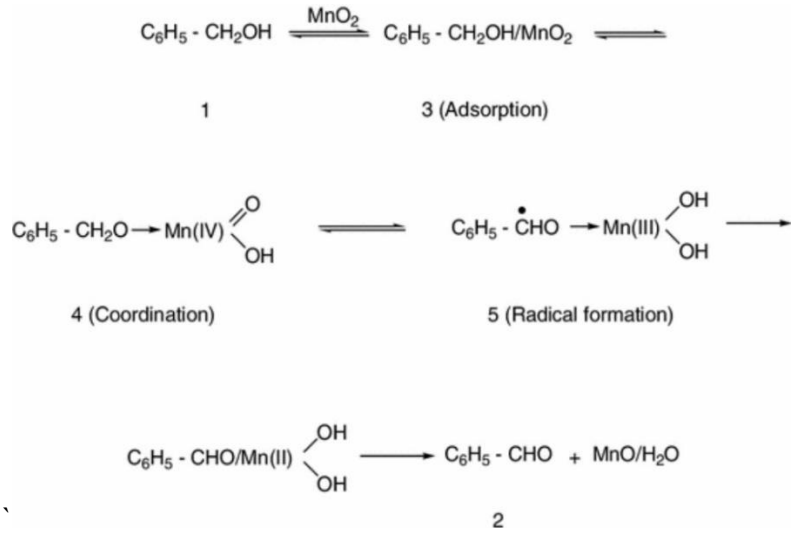


Oxidation of Alcohol:



MnO_2 is a specific oxidizing agent for allylic and benzylic alcohols. The reaction takes place in mild condition and in neutral solvent. For oxidation MnO_2 must be freshly prepared.

Mechanism:

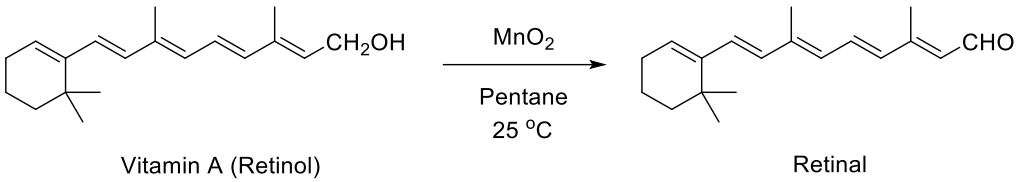


Goldman and Henbest proposed that the oxidation of alcohol to carbonyl compounds proceeds via a radical intermediate . Here the alcohol is observed on manganese dioxide followed by the formation of co-ordination complex. This complex generate electron transfer and form a radical further Mn [IV] is reduced to Mn [III]. The second electron transfer generates carbonyl product and Mn $[OH]_2$ .Finally loss of water molecule and carbonyl desorption results in the formation of carbonyl product and manganese [II] oxide.

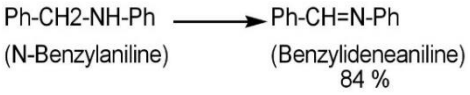
MnO_2 allow selective oxidation of allylic and benzylic hydroxyl groups.

Application:

1. Synthesis of Retinal

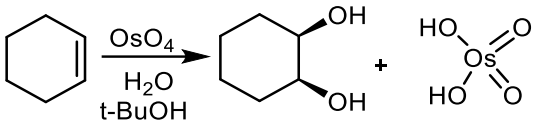


2. Oxidation of amines



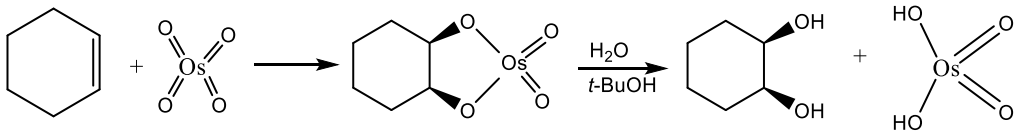
Osmium Tetraoxide (OsO_4)

Osmium tetroxide is highly toxic and has high vapour pressure. It is very useful reagent for the *syn*-hydroxylation of alkenes. It oxidises sulfoxides to sulfones but not oxidises sulfides.



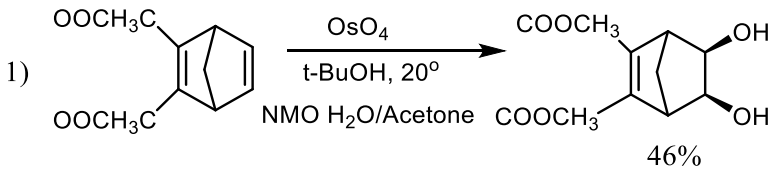
Mechanism

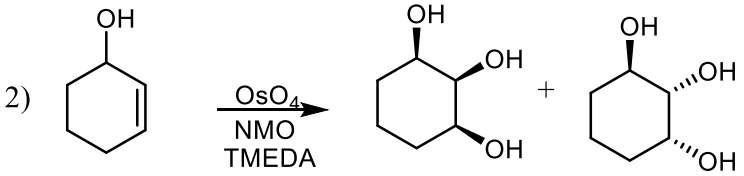
Osmium tetroxide adds to the double bond of an alkene by cyclic mechanism in which the two carbon-oxygen bonds simultaneously. The resulting cyclic osmate ester has the oxygen atoms bonded to the same face of the original bond. Then the osmium-oxygen bonds of the reactive intermediate are hydrolysed to from *syn*-diol.

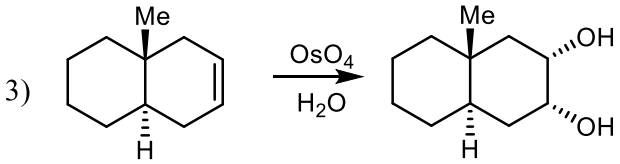


Application

Due to the electrophilic nature of OsO_4, the presence of electron withdrawing groups to the alkene double bond retard the hydroxylation. Thus, when more then one double bond is present, hydroxylation occurs at the most electron rich double bond.

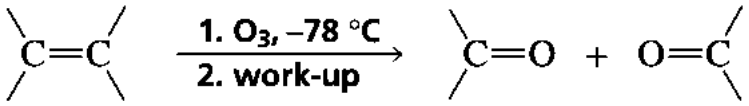






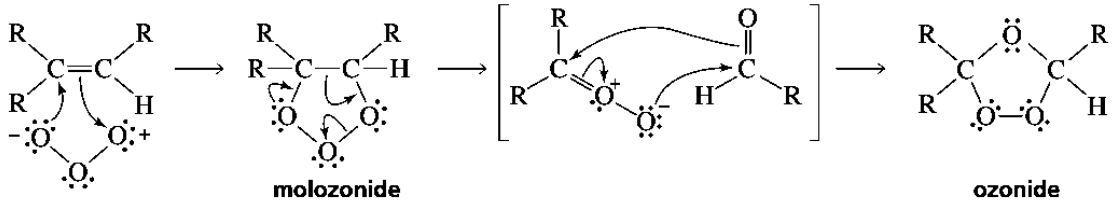
Reactions involving cleavage of C – C Bonds: Cleavage of Double bonds

When an alkene is treated with ozone at low temperatures, the double bond breaks and the carbons that were doubly bonded to each other find themselves doubly bonded to oxygens instead. This oxidation reaction is known as **ozonolysis**.



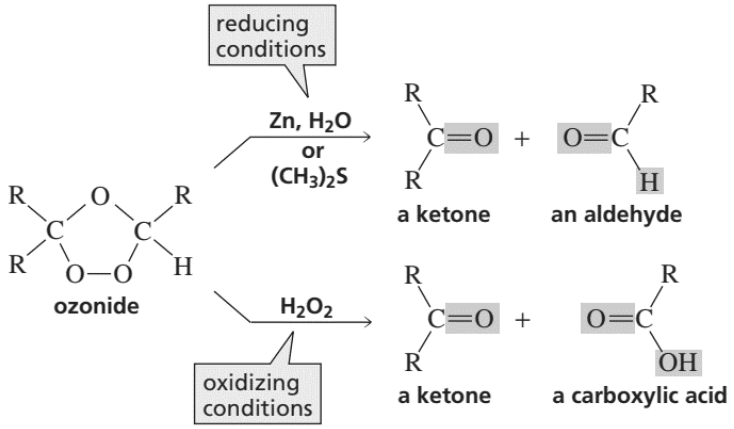
An electrophile adds to one of the carbons, and a nucleophile adds to the other. The electrophile is the oxygen at one end of the ozone molecule, and the nucleophile is the oxygen at the other end. The product of ozone addition to an alkene is a molozonide. (The name "molozonide" indicates that one mole of ozone has added to the alkene.) The molozonide is unstable because it has two bonds; it immediately rearranges to a more stable ozonide.

Mechanism for ozonide formation



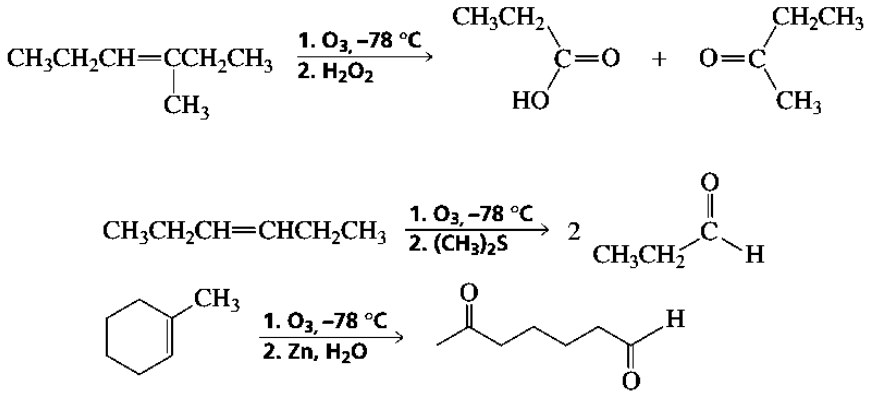
Ozonides are explosive, so they are seldom isolated. In solution, they are easily cleaved to carbonyl compounds. If the ozonide is cleaved in the presence of a reducing agent such as zinc or dimethyl sulfide, the products will be ketones and/or aldehydes. (The product will be a ketone if the carbon of the alkene is bonded to two carboncontaining substituents; the product will be an aldehyde if at least one of the substituents bonded to the carbon is a hydrogen.)

The reducing agent prevents aldehydes from being oxidized to carboxylic acids. Cleaving the ozonide in the presence of zinc or dimethyl sulfide is referred to as "working up the ozonide under reducing conditions.

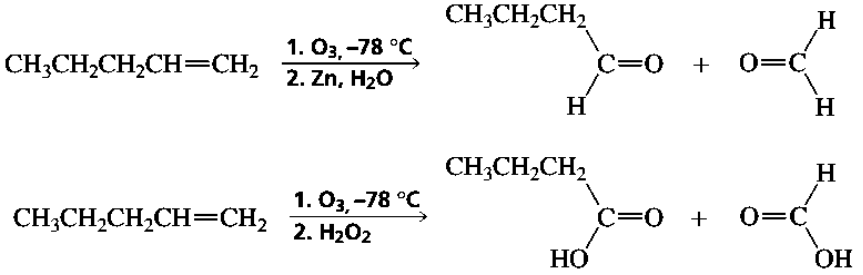


If the ozonide is cleaved in the presence of an oxidizing agent such as hydrogen peroxide the products will be ketones and/or carboxylic acids. Carboxylic acids are formed instead of aldehydes because any aldehyde that is initially formed will be immediately oxidized to a carboxylic acid by hydrogen peroxide. Cleavage in the presence of is referred to as "working up the ozonide under oxidizing conditions."

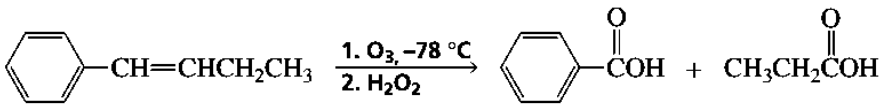
The following reactions are examples of the oxidative cleavage of alkenes by ozonolysis:



The one-carbon fragment obtained from the reaction of a terminal alkene with ozone will be oxidized to formaldehyde if the ozonide is worked up under reducing conditions and to formic acid if it is worked up under oxidizing conditions.

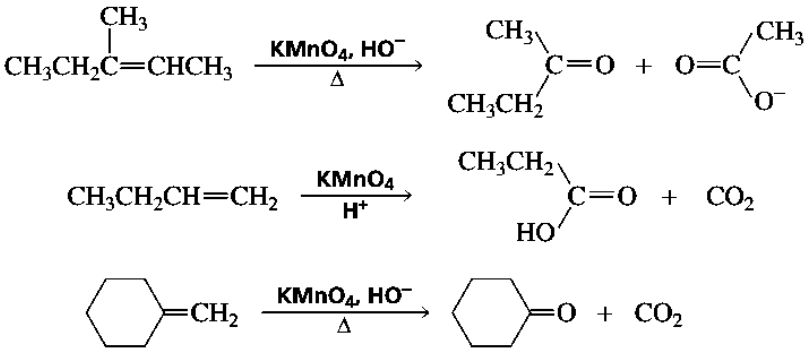


Only the side-chain double bond will be oxidized in the following reaction because the stable benzene ring is oxidized only under prolonged exposure to ozone.



Permanganate Cleavage

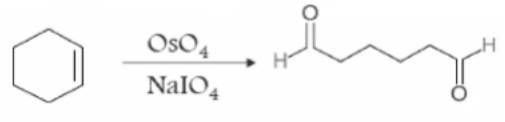
We have seen that alkenes are oxidized to 1,2-diols by a basic solution of potassium permanganate at room temperature or below, and the 1,2-diols can subsequently be cleaved by periodic acid to form aldehydes and/or ketones. If, however, the basic solution of potassium permanganate is heated or if the solution is acidic, the reaction will not stop at the diol. Instead, the alkene will be cleaved, and the reaction products will be ketones and carboxylic acids. If the reaction is carried out under basic conditions, any carboxylic acid product will be in its basic form if the reaction is carried out under acidic conditions, any carboxylic acid product will be in its acidic form (RCOOH). Terminal alkenes form as a product.



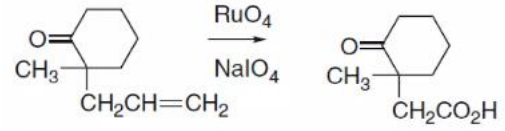
Cleavage using Sodium Periodate

Sodium periodate ($NaIO_4$) is an oxidising agent which is mainly used for oxidation of vicinal glycols. It performs oxidation of alkenes cleaving the double bonds and converting to aldehydes or ketones or carboxylic acids.

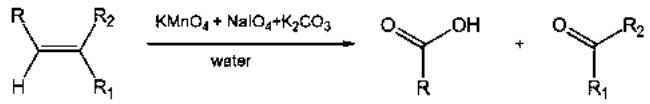
Oxidation of alkenes using $NaIO_4$ with Osmium Tetroxide (OsO_4). This reagent is also called Lemieux – Johnson reagent.



Oxidation of alkenes using $NaIO_4$ with Ruthenium Tetroxide (RuO_4)



Oxidation of alkenes using $NaIO_4$ with Potassium Permanganate ($KMnO_4$). This reaction is also called Lemieux – Von Rudloff reaction.

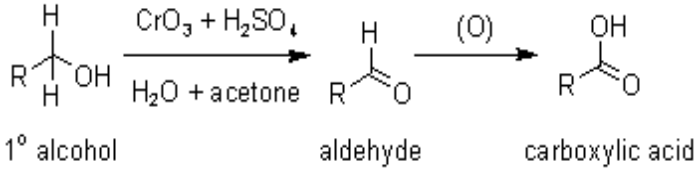


Oxidation of Alcohols

Alcohol oxidation is a collection of oxidation reactions in organic chemistry that convert alcohols to aldehydes, ketones, carboxylic acids, and esters where the carbon carries a higher oxidation state. The reaction mainly applies to primary and secondary alcohols.

Jones Oxidation:

The Oxidation of alcohols with chromium trioxide-acetate sulfuric acid reagent (Jones Reagent) is known as Jones Oxidation. This reagent is very selective as it is useful for oxidation of alcohols which contain C-C double or triple bonds, allylic or benzylic C-H bonds and other sensitive groups. The reaction is carried out at 0-20^{0}C. The primary alcohols are initially oxidized to aldehydes, which are finally oxidized to carboxylic acids. A mixture of sodium dichromate or potassium dichromate in dilute sulfuric acid and acetone can also be used as Jones reagent.



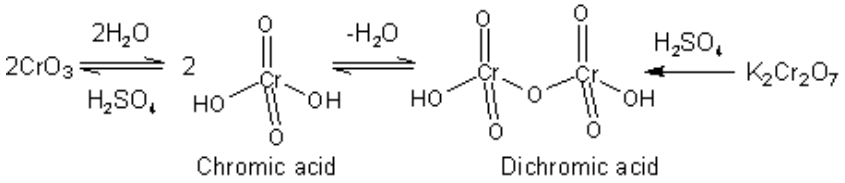
This oxidation is usually referred to as **Jones oxidation.**

Reaction Conditions:

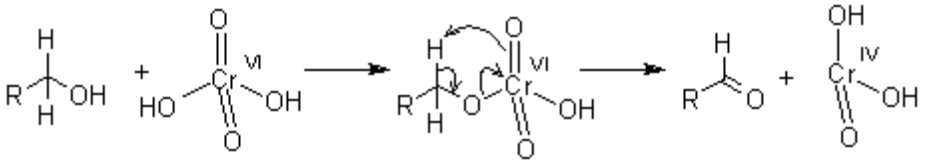
- The Jones reagent is prepared by adding chromic anhydride to dilute sulfuric acid in acetone and is added to the alcohol at 0-25^{o}C.
- The orange or yellow colored Cr(VI) is reduced to blue green Cr(III) species during the oxidation.
- The excess Cr(VI), if any is remained, is destroyed in the reaction workup by adding isopropyl.

Mechanism:

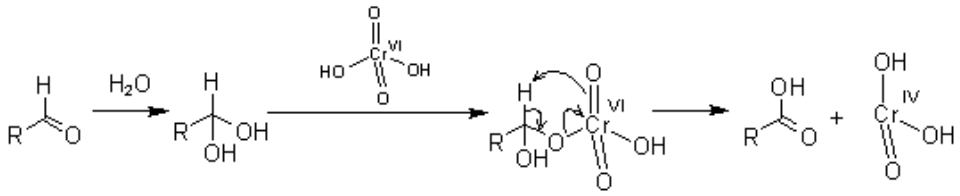
Initially, chromic acid(VI) is generated is situ from the mixture of chromic trioxide and dilute sulfuric acid.



The alcohol and chromic acid form chromium (VI) monoester, which may react intra-molecularly or inter-molecularly in presence of a base (H_2O in this case) to give the corresponding carbonyl compound and chromium(IV) acid. The intra-molecular reaction occurs by way of a β-elimination through a cyclic transition state.



The aldehydes, which can form hydrates in presence of water can further undergo oxidation to yield carboxylic acids in Jones reaction.

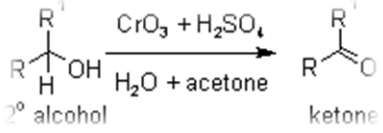


Hence oxidation of primary alcohols with Jones reagent usually results in the formation of carboxylic acids due to presence of water. However benzyl and allyl alcohols do not form hydrates in water and hence can be selectively oxidized to aldehydes.

If the oxidation is carried out in anhydrous conditions, it is possible to stop the reaction at aldehyde level.

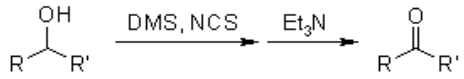
Secondary Alcohol – Ketone:

Secondary alcohols on oxidation with Jones Reagent gives Ketones



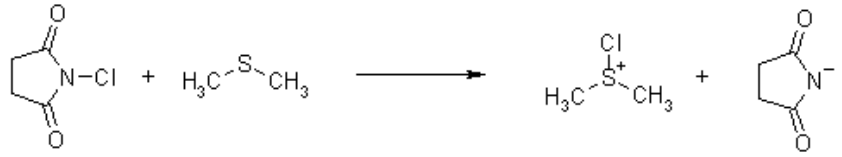
Corey Kim Oxidation:

Oxidation of alcohol to the corresponding aldehyde or ketone using NCS / DMS followed by treatment with a base.

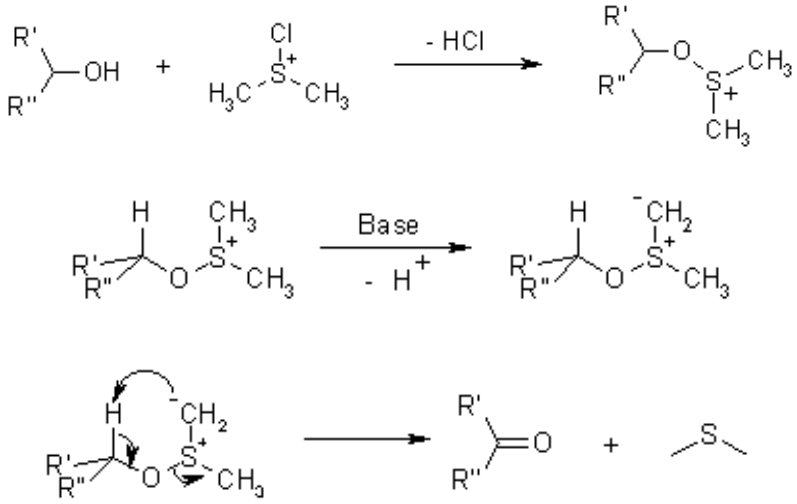


Mechanism:

Dimethylchlorosulphonium ion is generated *in situ* from NCS and DMS:

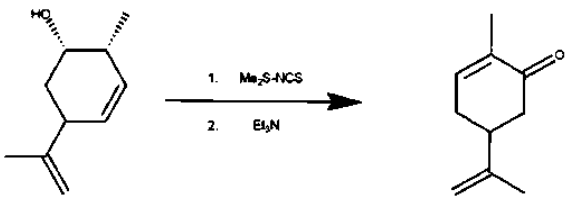


The following steps are comparable to the Swern Oxidation:



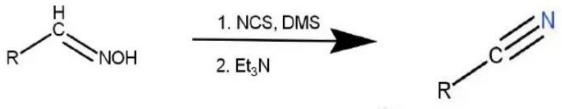
Applications:

i. Alcohols containing a double bond at the β,γ- position can be converted to α,β, -unsaturated carbonyl compounds.



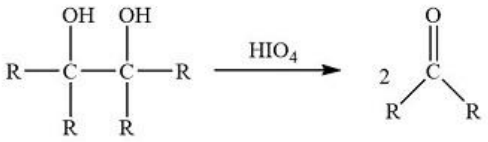
ii. **Nitrile Synthesis:**

The Corey-Kim Reaction can also be used to synthesize Nitrile from Aldoximes.



Periodic Acid:

Periodic Acid is used for the oxidative cleavage of bonds with adjacent oxidisable groups.Eg: 1,2 diols, α hydroxy carbonyl compounds, 1,2-diketones and α amino acids.

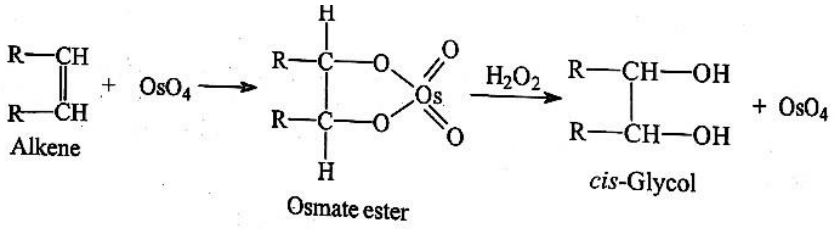


Oxidation of Alkyl Groups

Oxidation of Alkene:

Osmium Tetraoxide:

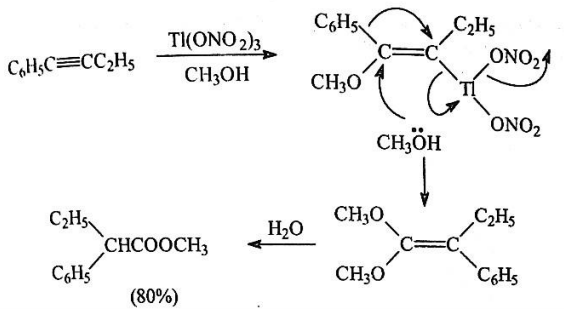
The Hydroxylation of alkene with osmium tetraoxide in inert solvent gives cyclic osmate ester, which undergoes hydrolytic cleavage under reducing conditions, such as aqueous conditions, such as aqueous sodium sulfite, to give 1,2 diols. However, cis-hydroxylation can be effected by using catalytic amount of OsO4 together with H2O.



Oxidation of Alkynes:

Thallium Nitrate:

With Alkyl Aryl Alkynes, a mixture of products is obtained in acid solution. But in methanolic solution, a smooth rearrangement takes place to give methyl esters of α-alkylaryl acetic acids. α–Alkylarkylacetic acid are valuable intermediates in organic synthesis and the above reaction provides a very effective route.



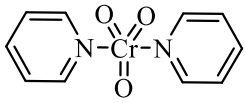
Oxidation using CrO_3.Pyridine (Collin's Reagent)

Introduction

Collin's reagent is an oxidising agent which is used for oxidation of alcohols. It is a mild reagent. It is a chromium based oxidising agent for organic reactions. It is used with the solvent CH_2Cl_2 (Dichloromethane-DCM).

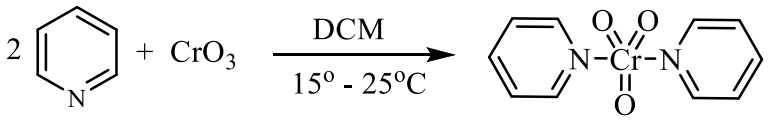
Collin's reagent is the complex of Chromium (VI) Oxide with pyridine in DCM. It is a red coloured metal-pyridine complex.

Structure



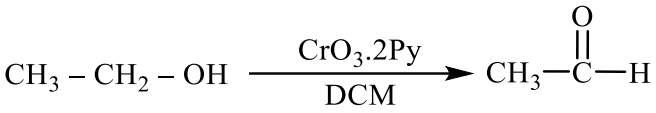
Preparation

Collin's reagent (or) Dipyridine chromium (VI) oxide is prepared by the addition of one equivalent of chromium trioxide to a stirred solution of 2 equivalents of Pyridine in DCM. It precipitates a yellow microcrystalline form and a continuous stirring at 15°*C*, it reverts a deep red microcrystal form.

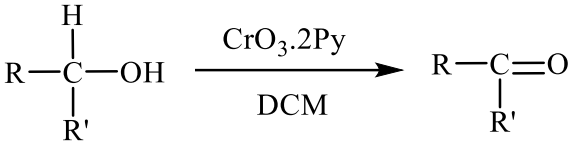


Collin's Reagent Reaction

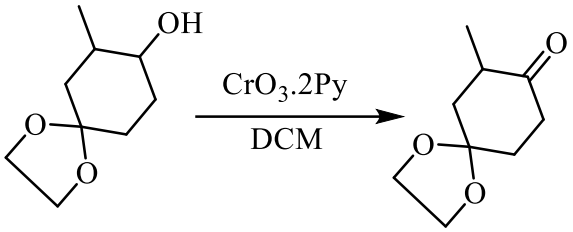
1. Primary alcohol is to be converted into aldehyde. Future oxidation of aldehyde is not possible at here because this reagent is a mild reagent.



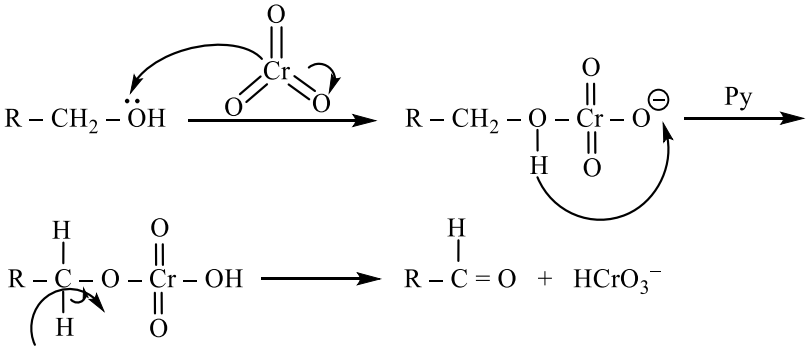
2. Secondary alcohol is converted into ketone.



3. The reagent can oxidise alcohol in carbonyl group without affecting an acid (or) acid sensitive group.

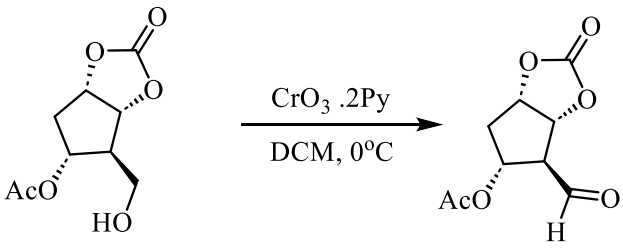


Mechanism

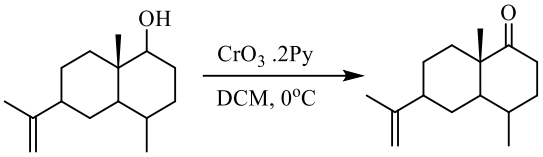


Applications

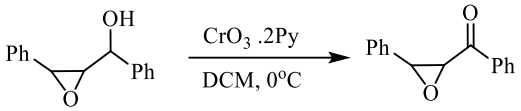
1)



2)



3)



Disadvantages

1. Must use a large excess of reagent
2. It is moisture sensitive and loses its activity in aqueous solution.

Allylic Oxidation

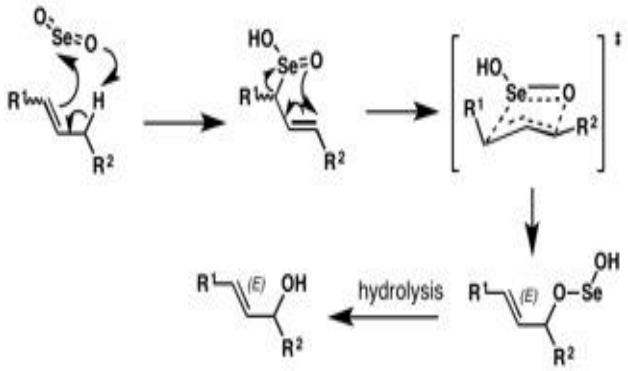
SeO_2 Oxidizes allylic $–CH_3/CH_2$-gp units , Selenium dioxide, SeO_2 is an oxidizing agent generally employed in the allylic oxidation of alkenes to furnish allylic alcohols, which may be further oxidized to conjugated aldehydes or ketones

$R_2C=CR'-CHR''_2 + [O] \rightarrow R_2C=CR'-C(OH)R''_2$

R, R', R'' may be alkyl or aryl substituents.

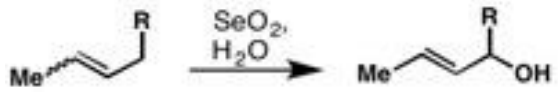
Mechanism

Allylic oxidation using selenium-dioxide proceeds via an ene reaction at the electrophilic selenium center. A 2,3-sigmatropic shift, proceeding through an envelope-like transition state, gives the allylselenite ester, which upon hydrolysis gives the allylic alcohol. The (*E*)-orientation about the double bond, a consequence of the envelope-like transition state, is observed in the penultimate ester formation, is retained during the hydrolysis step giving the (*E*)-allylic alcohol product

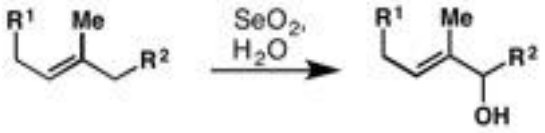


Examples:

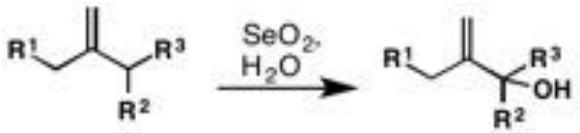
1.Allylic oxidation can be predicted by the substitution pattern on the olefin. In the case of 1,2-disubstituted olefins, reaction rates follow CH > CH_2 > CH_3



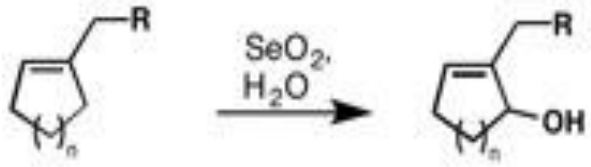
2.Trisubstituted alkenes experience reactivity at the more substituted end of the double bond. The order of reactivity follows that CH_2 > CH_3 > CH



3. Due to the rearrangement of the double bond, terminal olefin s tend to give primary allylic alcohols

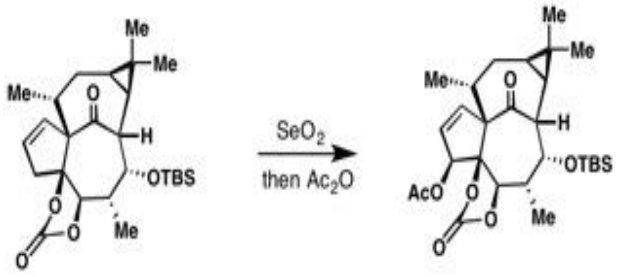


4. Cyclic alkenes prefer to undergo allylic oxidation within the ring, rather than the allylic position at the sidechain. In bridged ring systems, Bredt's rule is followed and bridgehead positions are not oxidized



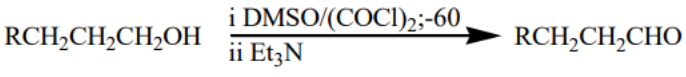
Application:

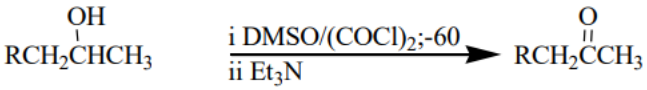
1. Selenium dioxide mediated allylic oxidation to access ingenol



Swern Oxidation:

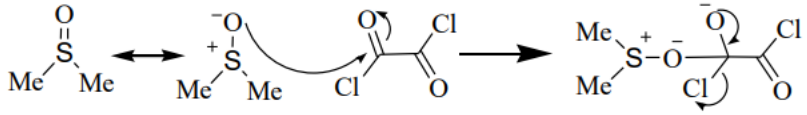
The oxidation of primary or secondary alcohol by dimethyl sulfoxide (DMSO), oxalyl chloride ($COCl_2$) and trimethyl amine form aldehydes or ketones respectively.



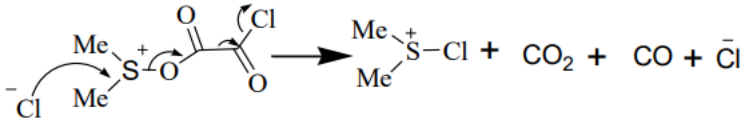


Mechanism

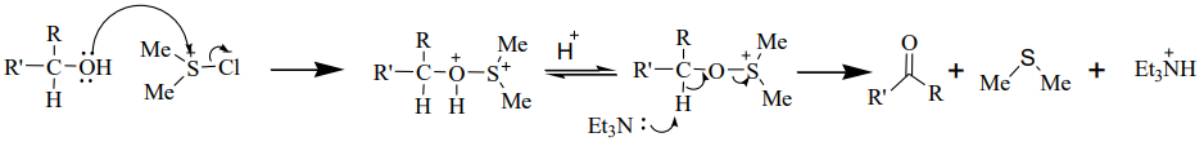
Firstly, oxalyl chloride react with dimethyl sulfoxide gives dimethyl sulfonium ion.



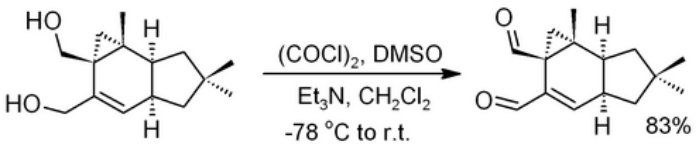
Dimethyl chlorosulfonium ion reacts with alcohol.



Like chromic acid oxidation the swern oxidation uses an E2 reaction to form the aldehyde or ketone.



Applications

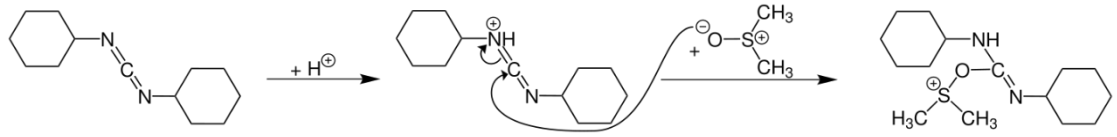


Pfitzner–Moffatt oxidation:

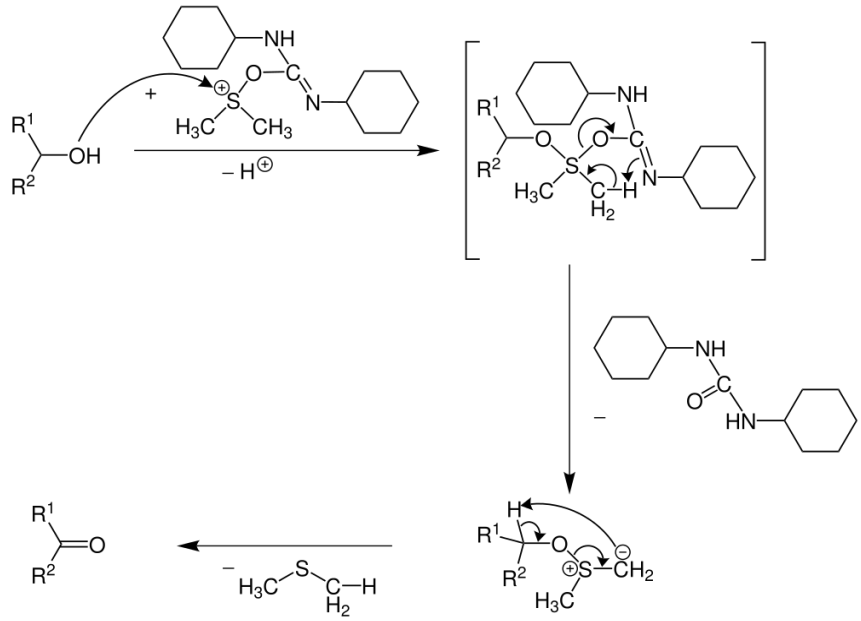
The Pfitzner–Moffatt oxidation, sometimes referred to as simply the Moffatt oxidation, is a chemical reaction for the oxidation of primary and secondary alcohols to aldehydes and ketones, respectively. The oxidant is a combination of dimethyl sulfoxide (DMSO) and dicyclohexylcarbodiimide (DCC). The reaction was first reported by J. Moffatt and his student K. Pfitzner in 1963

Mechanism :

In terms of mechanism, the reaction is proposed to involve the intermediary of an sulfonium group, formed by a reaction between DMSO and the carbodiimide.



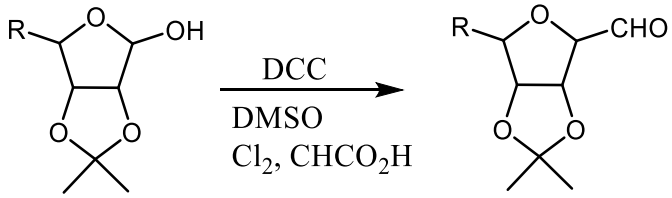
This species is highly reactive and is attacked by the alcohol. Rearrangement give an alkoxysulfonium ylide which decomposes to give dimethyl sulfide and the carbonyl compound.



This reaction has been largely displaced by the Swern oxidation, which also uses DMSO as an oxidant in the presence of an electrophilic activator. Swern oxidations tend to give higher yields and simpler workup; however, they typically employ cryogenic conditions.

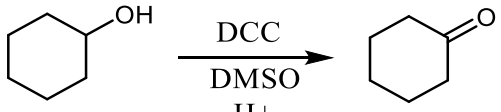
Application

1)



Primary alcohol

2)



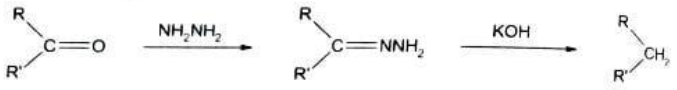
2° Alcohol Hexanone

Mechanism of reduction reactions

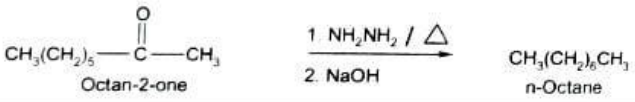
Wolff-Kishner reduction

The aldehydes and ketones can be reduced to the corresponding hydrocarbon by wolff kishner reduction.

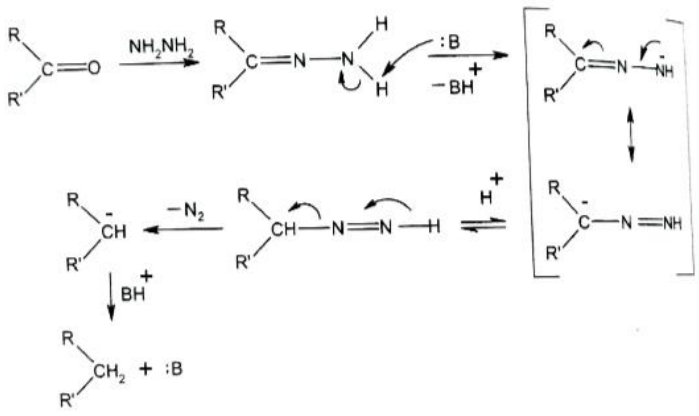
Reaction;



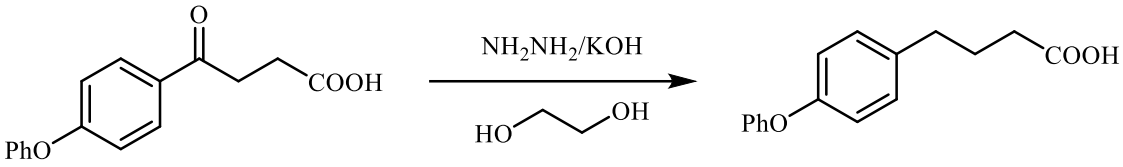
Another example of wolff-kishner reduction is synthesis of n-octane from 2-octanone.



Mechanism:



Applications:

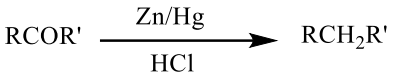


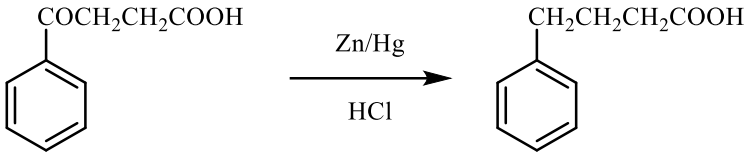
Clemmensen reduction:

Ketones and aldehyde on reduction with zinc amalgam and hydrochloric acid give the corresponding hydrocarbon

Example; carbonyl group is converted into methylene group

This is known as clemmensen reduction.

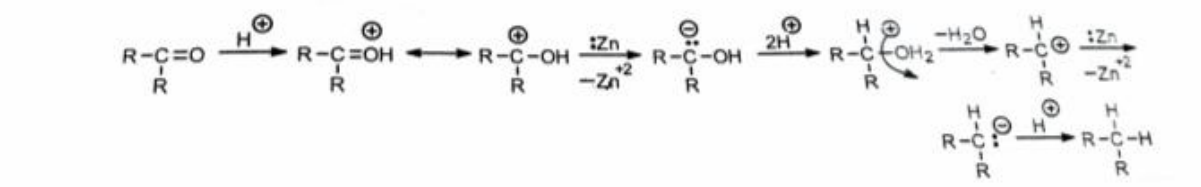




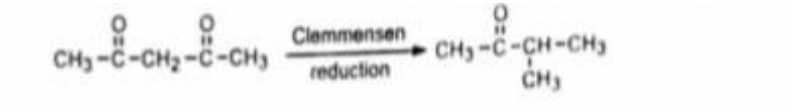
Mechanism :

Various mechanisms have been suggested which are so contradictory that no conclusion can be drawn . A mechanism suggesting the intermediate formation of alcohol was rejected since the reagent fails to reduces most alcohols to hydrocarbons.

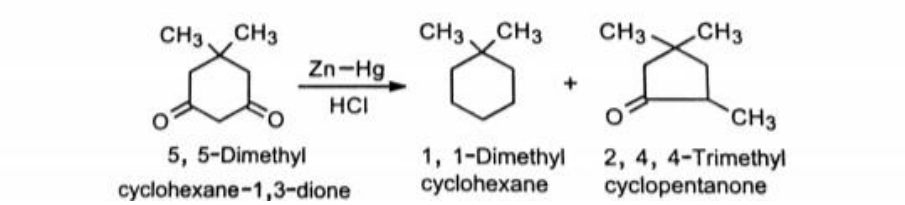
Nakabayaski has suggested a mechanism on the assumption that the reduction under acid condition involves protonated carbonyl group to which electrons are transferred from the metal.



Certain types of aldehydes and ketones do not give the normal reduction products alone. Thus *alpha* hydroxyl ketones gives either ketones through hydrogenolysis of OH group or olefins and 1,3 diketones give exclusively monoketons with rearrangement.

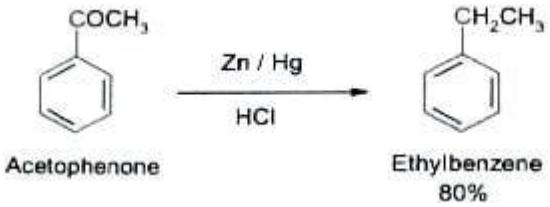


Certain cyclic 1,3diketones give under Clemmensen reduction a fully reduced product along with a monoketone with Ring Contraction.

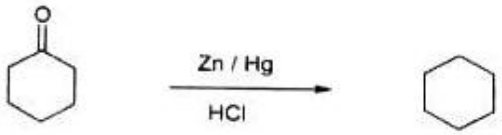


Applications:

The method is used for the reduction of aromatic aliphatic ketones, thus acetophenone is reduced by clemmensen method to ethylbenzene.

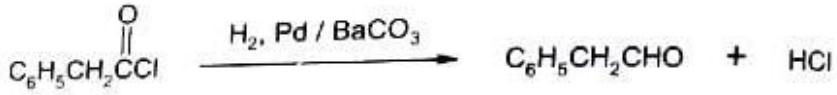


Alicyclic ketones can also be reduced by this method for example , cyclohexanone is reduced to cyclohexane .



Rosenmund reduction :

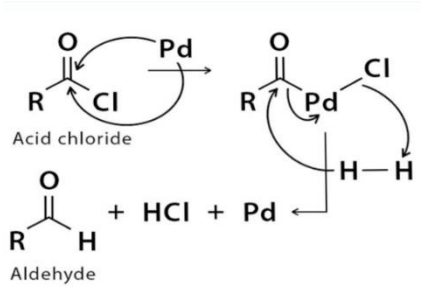
Acid chloride are catalytically reduced with hydrogen in boiling xylene to give aldehydes.this reduction is known as rosenmund reduction.



The reation is used for the synthesis of aromatic and heterocyclic aldehydes . palladium on barium sulphate poisoned with quinoline and Sulphur is used as a catalyst to bring about the desired reduction . In order to prevent further reduction . the reaction is carried out at lower

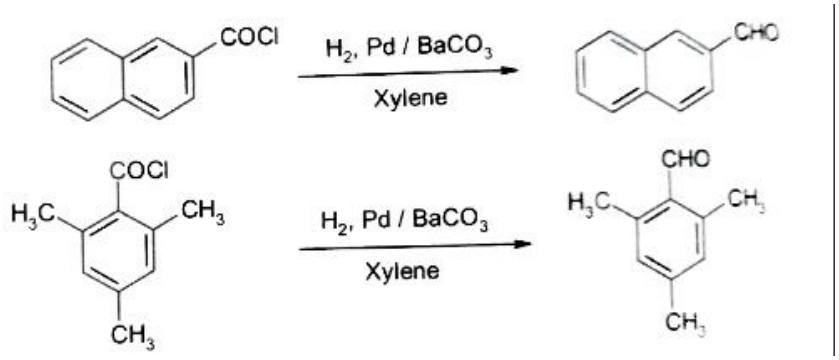
temperature .The reduction is applicable to acyl chloride carrying halogen , nitro or ester group .

Mechanism :



Application :

2 – Na phthalaldehyde and 2,4,6- trimethyl benzaldehyde are prepared from 2-naphthoyl chloride and 2,4,6-trimethyl benzoyl chloride respectively.



Reduction with Trialkyltinhydride and Triphenyltin hydride

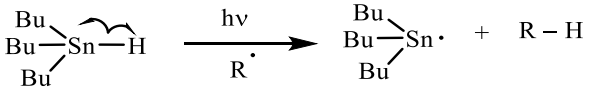
Reduction with Trialkyltinhydride [Bu_3SnH] :

The compound is produced by reduction of tributyltinoxide with polymethylhydrosiloxane.

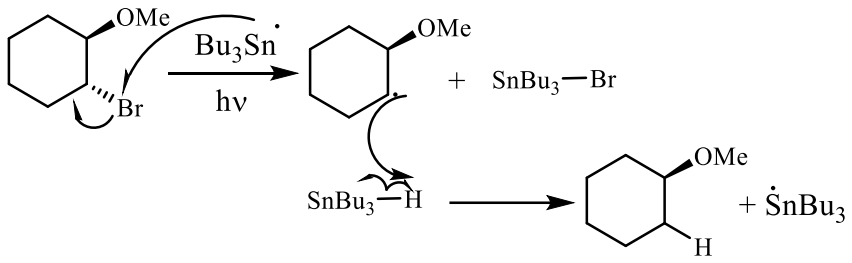
2 "$[MeSi(H)O]_n$" + $(Bu_3Sn)_2O$ → "$[MeSi(OH)O]_n$" + 2 Bu_3SnH

Bu_3SnH –Reducing agent

Reducing agent generally used to form a C-H bond, removal of halogens , formation of C-C bond and also used for intramolecular reactions.



Example :



By adding a reducing agent $Bu_3Sn^{\cdot}$, orthobromomethoxy cyclohexane is converted into methoxy cyclohexane radical and tinbromide. [Sn –H bond will break and this tributyltin radical will abstract this bromine radical and hydrogen radical will replace bromine radical, so why this happened and why we are using tributyltin hydride ,because

i. Sn-H bond much weaker than carbon hydrogen bond
ii. Sn-X bond is stronger than Sn-H bond therefore Bu_3Sn-H bond will break and it will attach with this halide. So the bond of tin with halide is stronger than bond with hydrogen]

Further reaction of methoxy cyclohexane radical with Bu_3SnH gives methoxy cyclohexane and tributyltin radical.

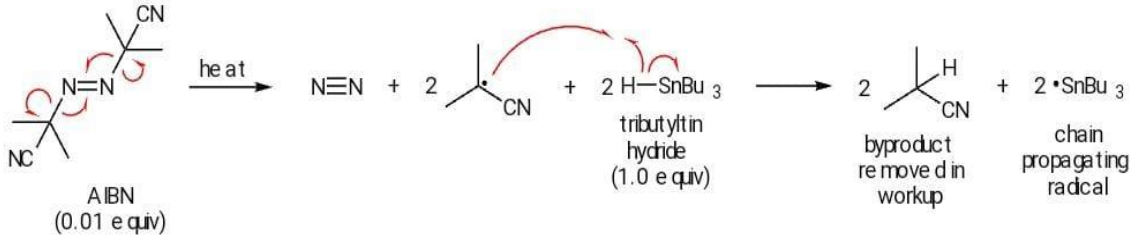
Role of AIBN (Azobisisobutyro nitrile):

AIBN is produced in two steps from acetone cyanohydrin. Reaction with hydrazine gives the substituted dialkylhydrazine. In the second step the hydrazine is oxidized to the azo derivative.

$$2\ (CH_3)_2C(CN)OH + N_2H_4 \rightarrow [(CH_3)_2C(CN)]_2N_2H_2 + 2\ H_2O$$

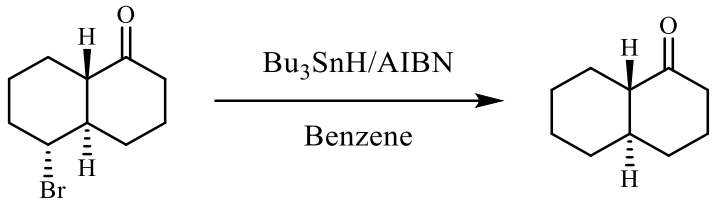
$$[(CH_3)_2C(CN)]_2N_2H_2 + Cl_2 \rightarrow [(CH_3)_2C(CN)]_2N_2 + 2\ HCl$$

AIBN is a good radical initiator because it has two stable Nitrile group symmetrically linked by an azo group.



AIBN on heating at 60-70^{0}c, the reactant is homolytically cleaved and azo group is elimination with a formation of isobutyl nitrile radical . Then this radical on reaction with tributyl tin hydride, homolytically cleaved to give trialkyl tin radical and isobutyl nitrile .

Example :



5,Bromobicyclo[4.4.0]Decal-1-one on adding reducing agent Bu_3SnH and AIBN in the presence of benzene gives Bicyclo [4.4.0] Decal-1-one.

The reactivity of alkyl halide ,

Alkyl iodide > Alkyl bromide > Alkyl chloride >Alkyl fluoride .

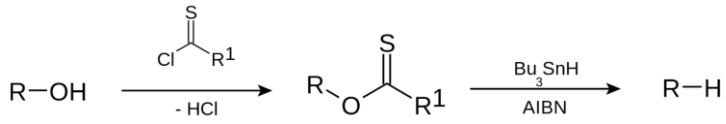
Reactivity of reaction also depends on stability of substrate radical

Allyl > Benzyl > 3^0 >2^0>1^0 > Vinyl

Barton –McCombie deoxygenation:

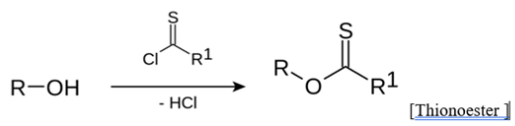
The Barton –McCombie deoxygenation is an organic reaction in which a hydroxy functional group in an organic compound is replaced by a hydrogen to give an alkyl group. It is named after British chemists Sir Derek Harold Richard Barton and Stuart W.McCombie.

Ex :



Mechanism :

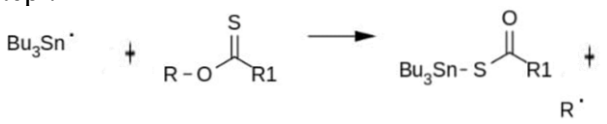
Step :1



Step :2

Step :3

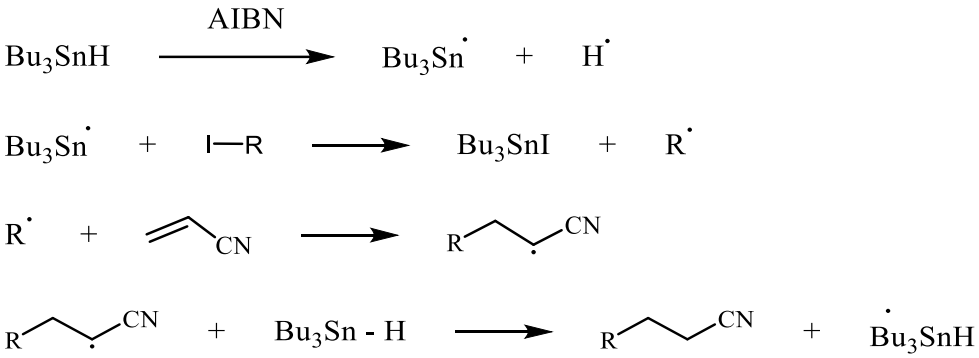
Step :4



Step :5

Applications :

Intermolecular reaction :

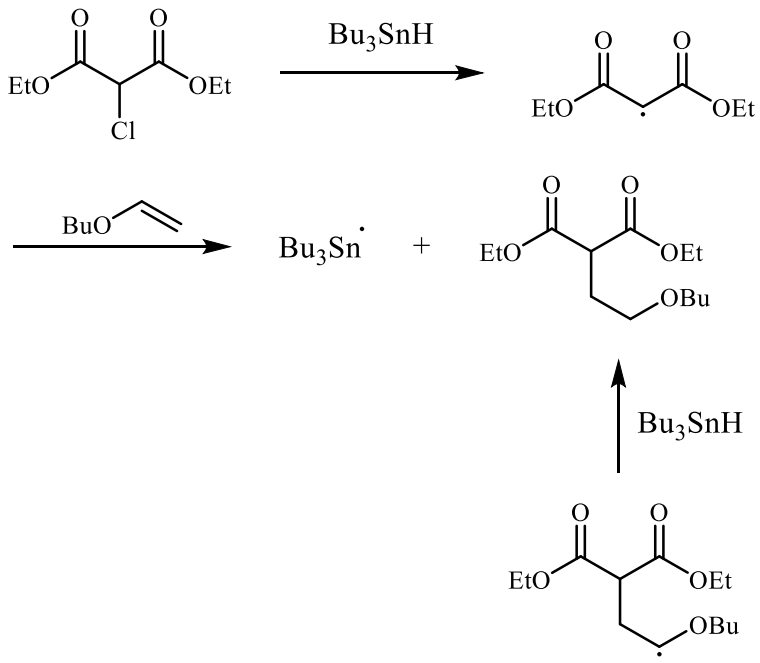


Radicals are two types,

i. Electrophilic radical (EWG attached to the radical)
ii. Nucleophilic radical (ERG attached to the radical)

Example :

Electrophilic radical :



Nucleophilic radical :

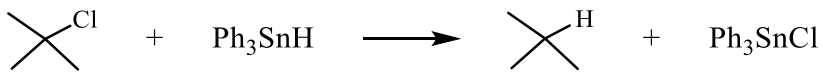
Reduction with Triphenyltinhydride [Ph_3SnH]:

Triphenyltinhydride is prepared from $LiAlH_4$ and Ph_3SnCl.

$$Ph_3SnCl + LiAlH_4 \rightarrow Ph_3SnH$$

Ph_3SnH is used as source of hydrogen radical. It is a milder reducing agent and less reactive than $LiAlH_4$.

Example :

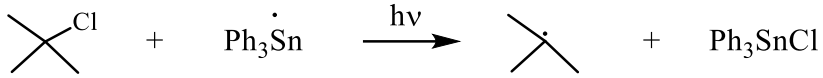


Mechanism :

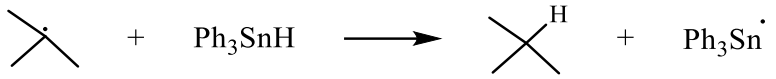
Step : 1

$Ph_3SnH \xrightarrow{h\nu} Ph_3Sn\cdot + H\cdot$

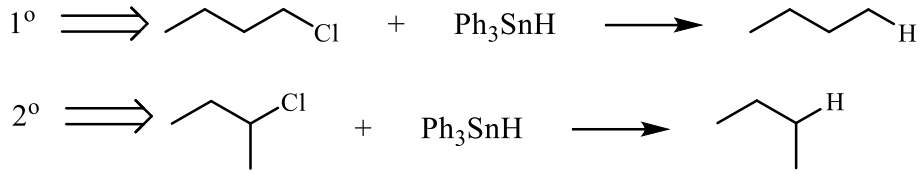
Step : 2



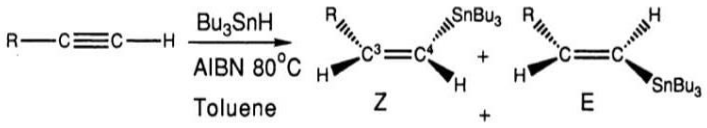
Step : 3



Examples of primary and secondary alkylhalides :



Applications:

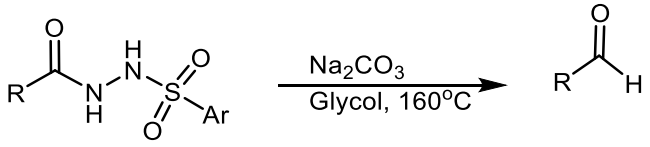


- Triphenyltinhydride is used as a source of hydrogen radical to generate radicals or cleave carbon oxygen bonds, also used in anti- fouling paints.
- It is used in thin film deposition,industrial chemistry,Pharmaceuticals,LED manufacturing .

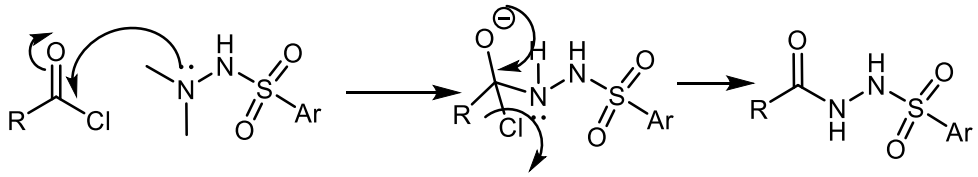
Mc – Fayden – Steven Reduction Reaction

Introduction

- It is a chemical reaction best described as a base catalysed thermal decomposition of “allyl sulfonylhydrazides” to “aldehydes”.
- R = Aryl (or) Alkyl with no alpha protons.

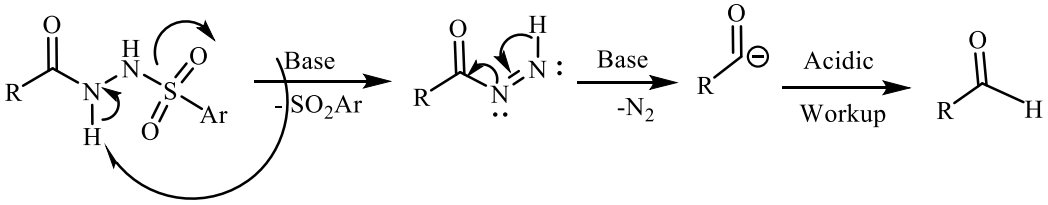


Starting Material Preparation

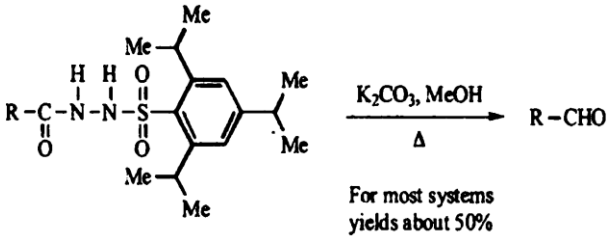


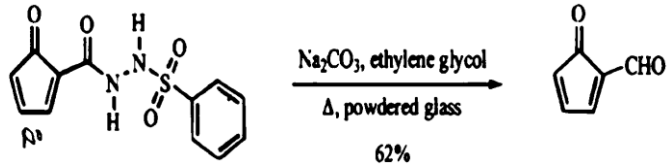
Mechanism

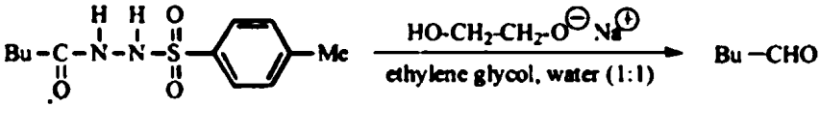
- Two groups have independently proposed a heterolytic fragmentation mechanism
- The mechanism involves the deprotonation of acylsulfonamide followed by a 1,2 hydride migration to give the alkoxide. The collapse of the alkoxide result in the fragmentation producing the desired aldehyde, aryl sulfinate ion and nitrogen gas.



Synthetic applications





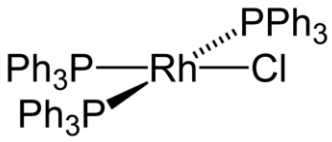


Uses

- Used in the presumptive diagnosis of anthrax in animals.
- Polychrome methylene blue staining technique is currently used to confirm anthrax sample as a reliable diagnostic test.

Homogeneous hydrogenation

Wilkinson's catalyst (**chloridotris(triphenylphosphene)rhodium(I)**) is a coordination complex of rhodium with the formula [$RhCl(PPh_3)_3$], where 'Ph' denotes a phenyl group. It is a red-brown colored solid that is soluble in hydrocarbon solvents such as benzene, and more so in tetrahydrofuran or chlorinated solvents such as dichloromethane. The compound is widely used as a catalyst for hydrogenation of alkenes. It is named after chemist and Nobel laureate Sir Geoffrey Wilkinson



Preparation of Wilkinston catalyst

Wilkinson’s catalyst can be prepared by reacting hydrated rhodium(III) chloride with excess triphenylphosphine in the presence of ethanol (which acts as a refluxing agent). Here, the triphenylphosphine(denoted by the chemical formula $P(C_6H_5)_3$) acts as a reducing agent which has the ability to oxidize itself from an oxidation state of +3 to an oxidation state of +5.

During the synthesis of Wilkinson’s catalyst, one equivalent of triphenylphosphine reduces rhodium(III) to rhodium(I) while three other equivalents bind themselves to the metal as ligands in the final product.

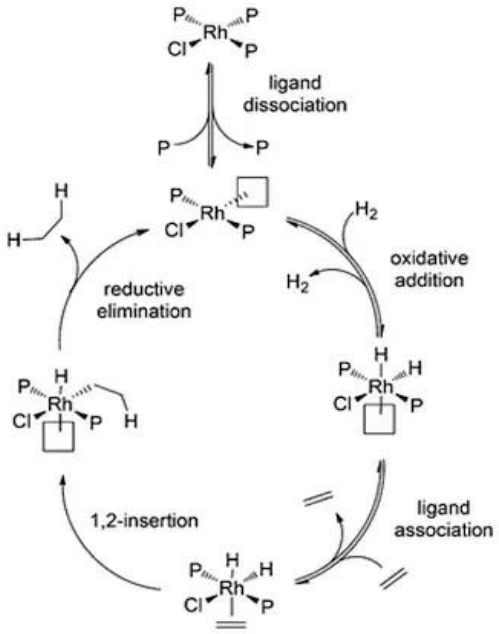
$$\mathbf{4P(C_6H_5)_3 + RhCl_3(H_2O)_3 \rightarrow RhCl(P(C_6H_5)_3)_3 + OP(C_6H_5)_3 + 2HCl + 2H_2O}$$

The chemical reaction for the synthesis of Wilkinson’s catalyst is provided above.

Mechanism

- Initially, a 14-electron or 12-electron complex is formed from the dissociation of 1 or 2 tri phenyl phosphine ligands.

- Now, the oxidative addition of molecular hydrogen (H_2) to the metal core of Wilkinson's catalyst (rhodium) occurs.
- The third step of the mechanism involves the formation of a pi complex with the alkene.
- The hydrogen is inserted into the complex via migratory insertion which could proceed through intramolecular hydride transfer or through olefin insertion.
- Finally, reductive elimination occurs at the pi complex to regenerate the catalyst and afford the required alkene product.



Applications

- For the hydrogenation process of unsaturated hydrocarbons, the Wilkinson catalyst is commonly utilized (olefins). It introduces molecular hydrogen into the molecule at an unsaturated carbon site.
- In the addition of a hydrogen-acyl group to alkenes, the Wilkinson catalyst can be utilized.
- It is very important in the alkene hydroboration process.
- In the selective hydrogenation of alkenes, the Wilkinson catalyst is utilized. It prefers to add hydrogen to the unsaturated carbon position that is least inhibited.
- In the presence of hydrogen and a strong base, functionalized tri-substituted alkenes and internal alkynes can be hydrogenated using Wilkinson's catalyst. A highly reactive Rh(I) species with considerably higher catalytic activity is produced in this

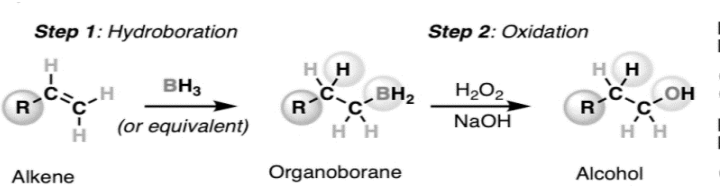
Hydroboration:

Hydroboration is an addition reaction between an alkenes(olefin) and a borane.In hydroboration, a C-C pi bond is broken and a C-H bond as well as C-B bond is formed.

Typical reagents for hydroboration include borane ((BH3) and it's relative's (B2H6,BH3.THF,BH3.OEt,9-BBN). Hydroboration is stereoselective for syn addition and follow the **'anti Markovnikov rule**'.

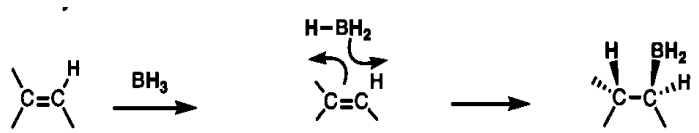
In this reaction, the H and B are delivered to the same face of the alkene. The resulting organoborane is not isolated, instead of it is oxidised using H2O2 and base like NaOH or KOH. Oxidation resulting the replace of the C-B bond with a C-O bond.

Regioselectivity refer to the tendancy for the reaction to selectively form one constitutional isomer over others. In hydroboration, alcohol are selectively formed at the least substituted carbon of the alkene. This is called '**anti-Markovnikov selectivity'.**

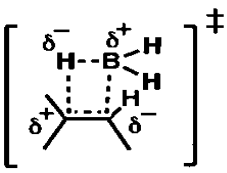


Mechanism:

The mechanism of hydroboration is happens via a four membered acyclic transition state. It is a one step reaction and intermediate is not not formed.



There is an transition state formed instead of intermediate**.**

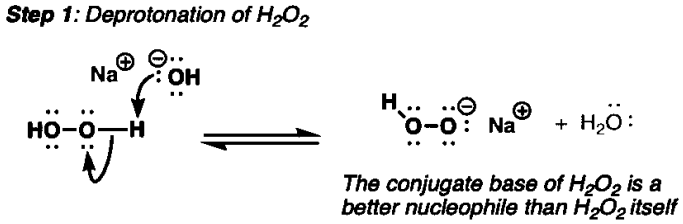


This mechanism observe the syn product. The electronegativity of carbon is 2.55 and the electronegativity of boron is 2.04. Therefore, the boron gains a partially negative charge whereas the more substituted carbon gains a partially positive charge and stable carbocation in the four-membered transition state. Then H adds to the more substituted carbon whereas B adds to the less substituted carbon.

However there is one more explanation for it. Out of the H and BH2, more bulky group goes to the less hindered carbon. So we get H on more more alkylated(more hindered).

Oxidation mechanism:

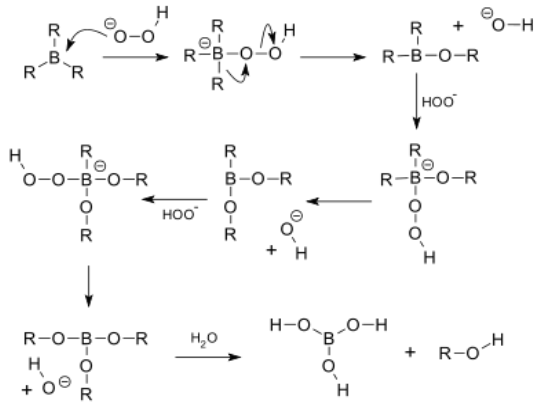
In this mechanism a rearrangement occurs where the C-B bond is broken and a new C-O bond is formed. This is usually done under basic conditions.



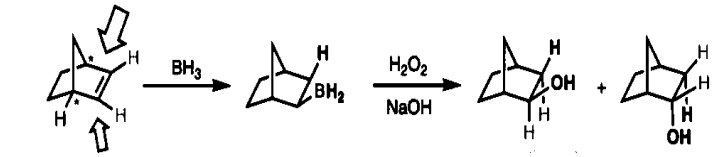
Step 2 : Attack of peroxide on boron

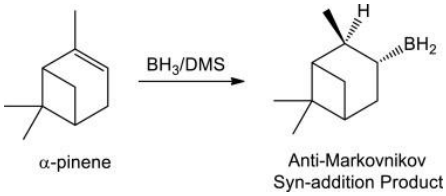
In this step a pair of electrons in the C-B bond migrates over to oxygen (form C-O, break C-B). The O-O bond breaks, liberating the hydroxide ion HO(-) as a leaving group.After migration, the resulting compound (a “boronic ester”) then undergoes hydrolysis by hydroxide ion to eventually

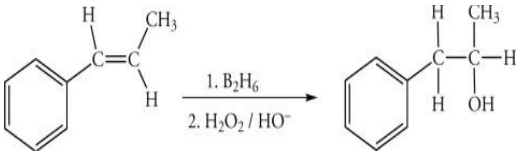
Note that stereochemistry is conserved throughout the rearrangement process. The C-B bond is converted to C-O with perfect fidelity. The yield of this reaction is have more than 90% conversation rate.

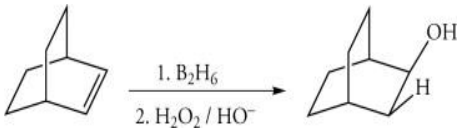


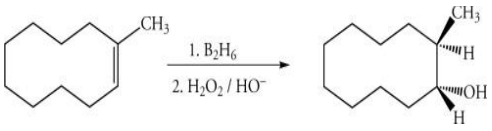
Applications

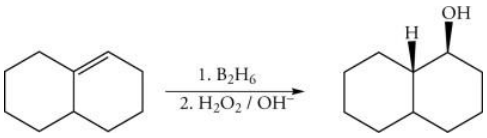


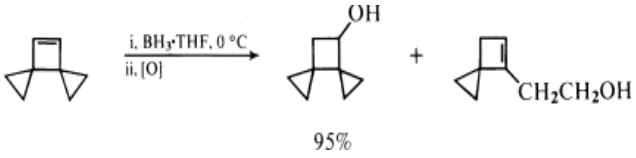






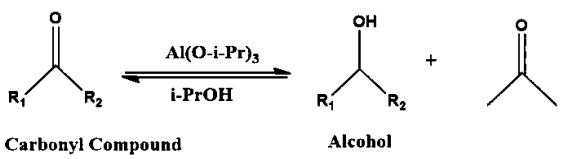






Meerwein - Ponndorf - Verley Reduction

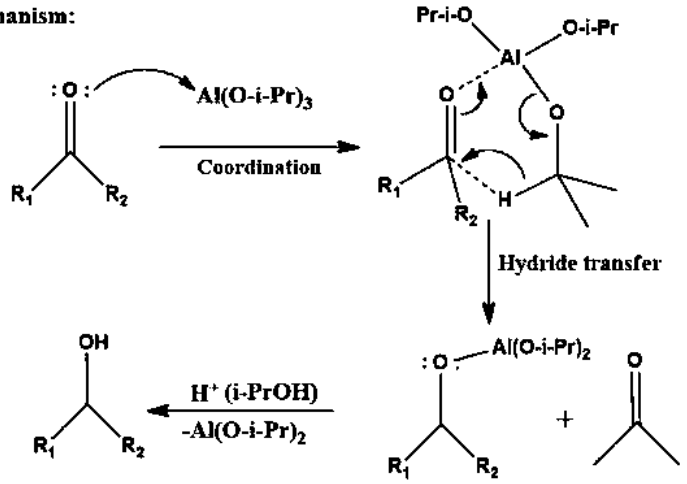
The reaction involves the reduction of aldehydes or ketones to alcohols by treatment with aluminum isopropoxide in excess of isopropyl alcohol.



The reaction is reversible. The reverse reaction called oppenauer oxidation, is used for the oxidation of alcohols using aluminum t-butoxide as catalyst in the presence of excess of acetone.

This reaction occurs under mild condition and it takes place rapidly. The by-products are neglibile and the yield is high.

Mechanism:



This reaction is specific for carbonyl group other reducible group such as olefinic bond, No_2, etc…present in the substrate remains unaffected. If a compound contains two carbonyl groups one may be protected by acetal formation and the other is then reduced. Ketones with high enol content example β-diketones, β-ketoesters etc... do not give this reduction. For reduction one hydrogen is supplied by the catalyst and the other hydrogen by the solvent.

Specificity of aluminium isopropoxide:

Aluminium isopropoxide is less polar than alkali metal alkoxides. Since Al – O bond is nearly covalent in nature. Hence, this undergoes very little dissociation to give alkoxide ions which causes some polymerization of the carbonyl compounds specially the sensitive aldehydes. The by-product is negligible. The boiling point is 140℃ - 150℃. Thus, the acetone which has low boiling point (56℃) distills out easily.

Applications:

1. α, β unsaturated aldehyde to α, β unsaturated alcohol

$$CH_2{=}CH\text{-}CHO \xrightarrow[CH_3CHOH]{Al\,(OCHMe_2)} CH_2{=}CH\text{-}CH_2\,OH$$

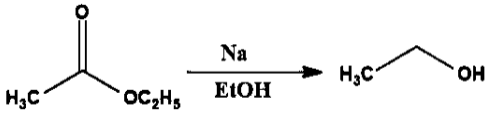
Acraldehyde — allyl alcohol

2. Reduction of aromatic ketones

$$C_6H_5\text{-}CO\text{-}CH_3 \xrightarrow[CH_3CHOH]{Al\,(OCHMe_2)} C_6H_5\text{-}CHOH\text{-}CH_3$$

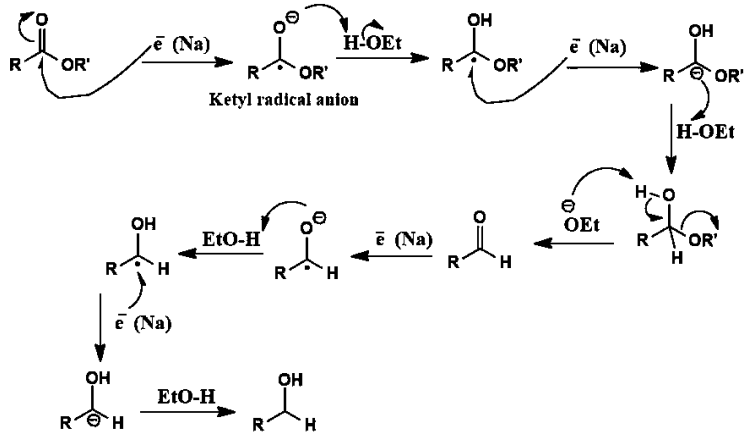
Boveault - blanc reduction

Formation of primary alcohols by reduction of ester using absolute alcohol and sodium.



- It is a single electron transfer mechanism
- Sodium serves as single electron transfer reducing agent and ethanol is the proton donor.

Mechanism:



Application

1. butyl oleate to oleyl alcohol

$$CH_3(CH_2)_7CH{=}CH(CH_2)_7CO_2C_4H_9 \xrightarrow{Na,\ C_4H_9OH} CH_3(CH_2)_7CH{=}CH(CH_2)_7CH_2OH$$

2. Diethyl sebacate to 1,10 decanediol

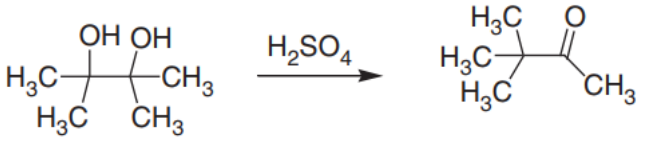
UNIT – III

REARRANGEMENTS

Rearrangement to Electron Deficient Carbon

(1) Pinacol – Pinacolone Rearrangement

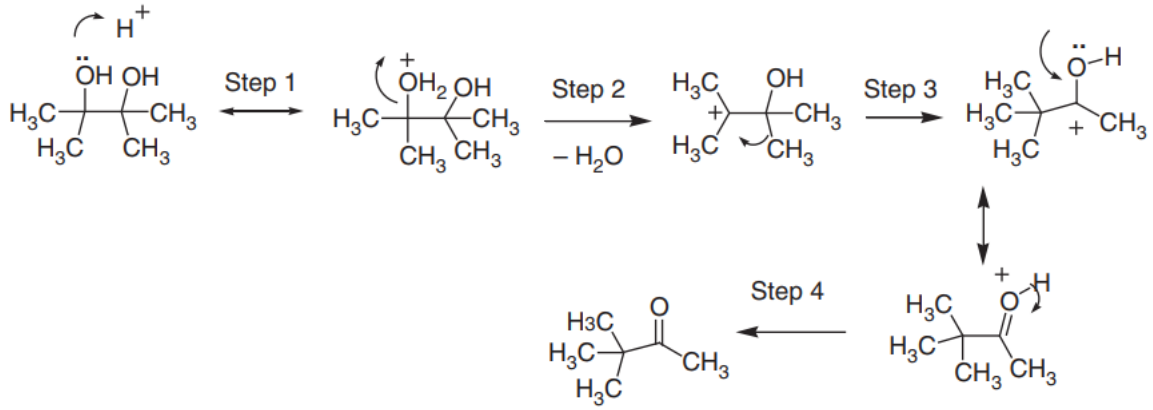
The pinacol–pinacolone rearrangement is an acid-catalyzed conversion of a 1,2-diol to a carbonyl compound. The name of this reaction comes as pinacol rearranges to pinacolone.



Pinacol Pinacolone

Mechanism

If both the –OH groups are not similar, then the one that gives a more stable carbocation participates in the reaction. Subsequently, an alkyl group from the adjacent carbon migrates to the carbocation center.



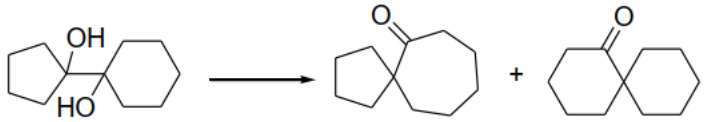
Step 1: Protonation of one hydroxyl group.

Step 2: Elimination of water and formation of a carbocation.

Step 3: Migration of one methyl group.

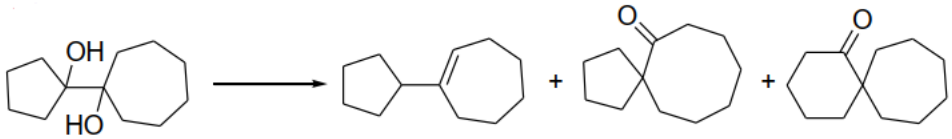
Step 4: The loss of proton and formation of final product.

Application



Conc. H_2SO_4	0 °C	major	minor
Conc. H_2SO_4	97 °C	minor	major

B. P. Mundy, R. Srinivasa, *Tetrahedron Lett.* **1979**, *20*, 2671.

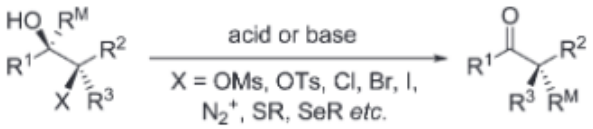


Conc H_2SO_4	0 °C	0	5	95
25% Conc. H_2SO_4	0 °C	30	1	69

B. P. Mundy, R. Srinivasa, R. D. Otzenberger, A. R. DeBernardis, *Tetrahedron Lett.* **1979**, *20*, 2673.

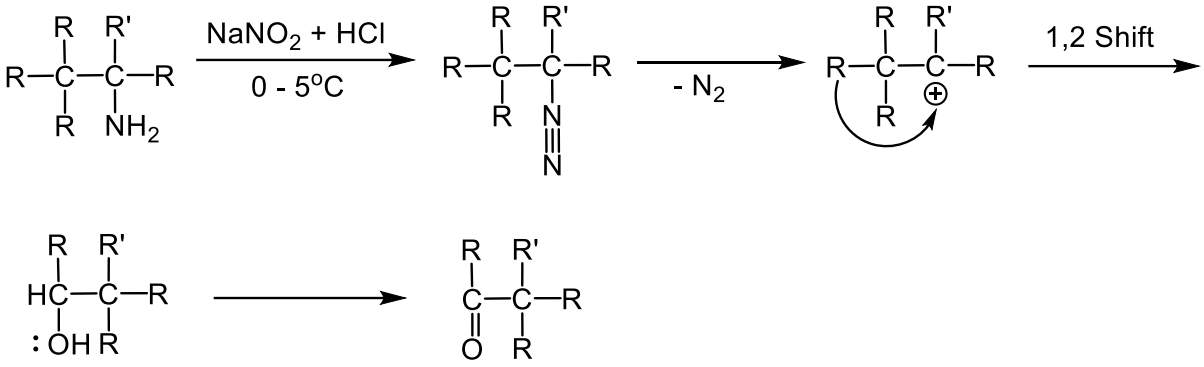
(2) Semi – Pinacolone Rearrangement

The semipinacol rearrangement is a rearrangement reaction in organic chemistry involving a heterosubstituted alcohol of the type $R_1R_2(HO)C–C(X)R_3R_4$. The hetero substituent can be a halogen (Cl, Br, I), a tosylate, a mesylate or a thiol group.



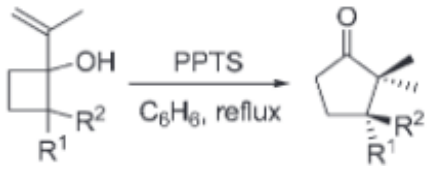
Mechanism

This reaction proceeds by removal of the leaving group X forming a carbocation as electron deficient center. One of the adjacent alkyl groups then migrates to the positive carbon in a 1,2-shift. Simultaneously with the shift, a pi bond forms from the oxygen to carbon, assisting in driving the migrating group off its position. The result is a ketone or aldehyde. In another definition all semipinacol rearrangements "share a common reactive species in which an electrophilic carbon center, including but not limited to carbocations, is vicinal to an oxygen-containing carbon and can drive the 1,2-migration of a C–C or C–H bond to terminate the process, generating a carbonyl group.



Application:

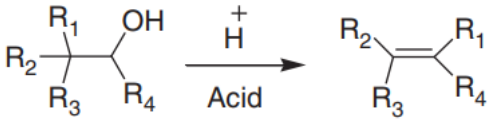
For the total synthesis of (±) α-Cuparenone



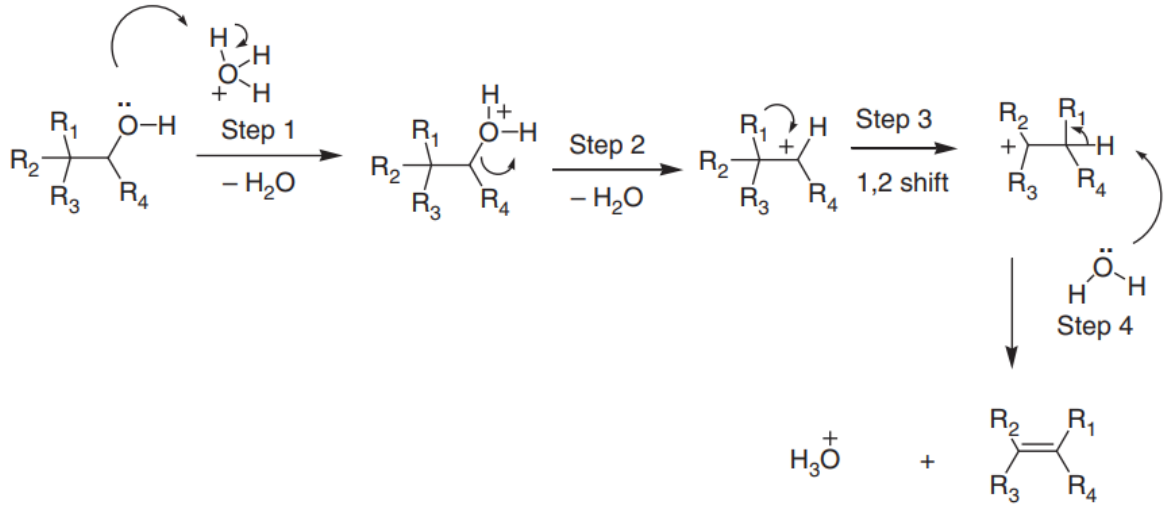
R1 = Me, R2 = C_6H_4-4-Me

(3) Wagner – Meerwein Rearrangement

The Wagner–Meerwein rearrangement is an acid-catalyzed alkyl group migration of an alcohol to give an olefin with more substituted. This is a cationic-sigmatropic rearrangement reaction. This reaction has been applied to synthesize complex natural products and drug molecules.



Mechanism



Step 1: Protonation of the alcohol with the acid.

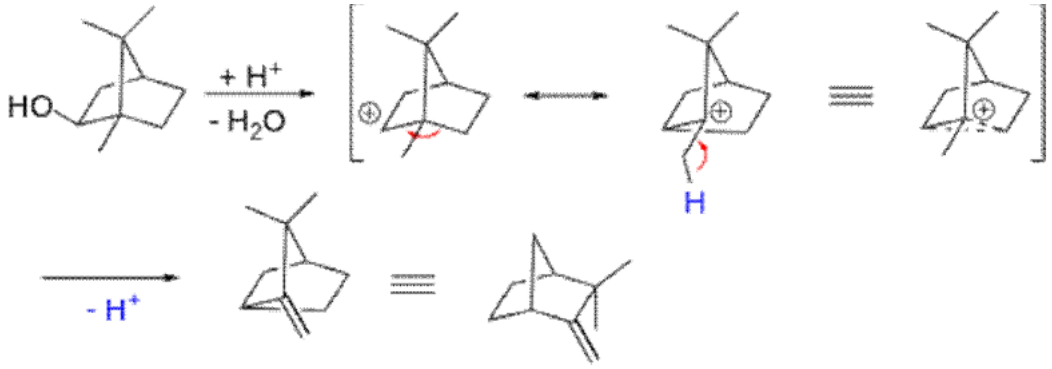
Step 2: Elimination of water forms a carbocation.

Step 3: A 1,2-shift (R1 group migration) forms a more stable carbocation.

Step 4: Deprotonation with water gives a more substituted olefin and regeneration of acid catalyst.

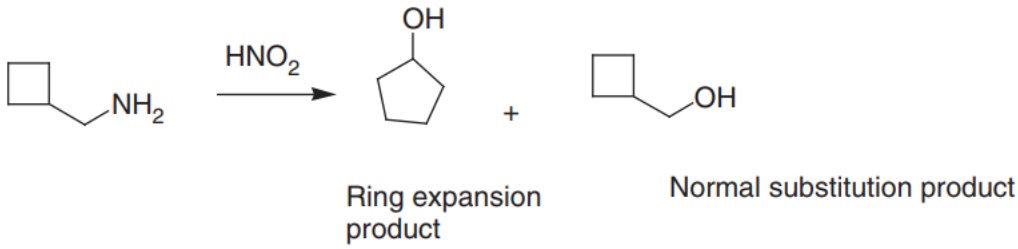
Application

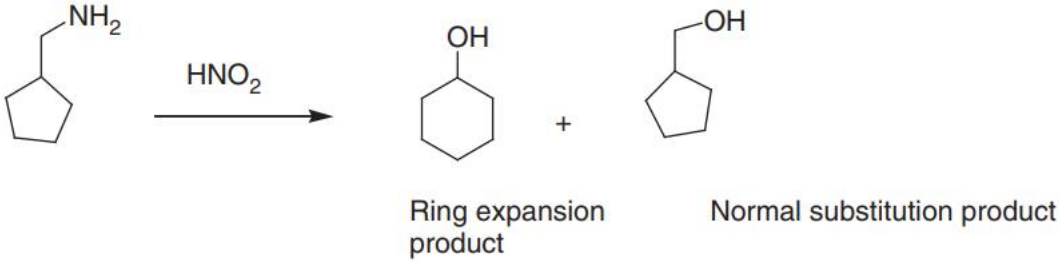
For preparation of Camphene

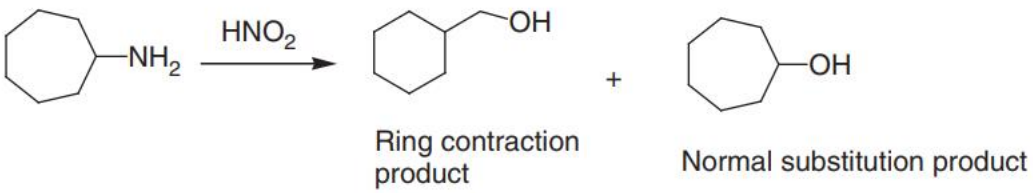


(4) Demjanov Rearrangement

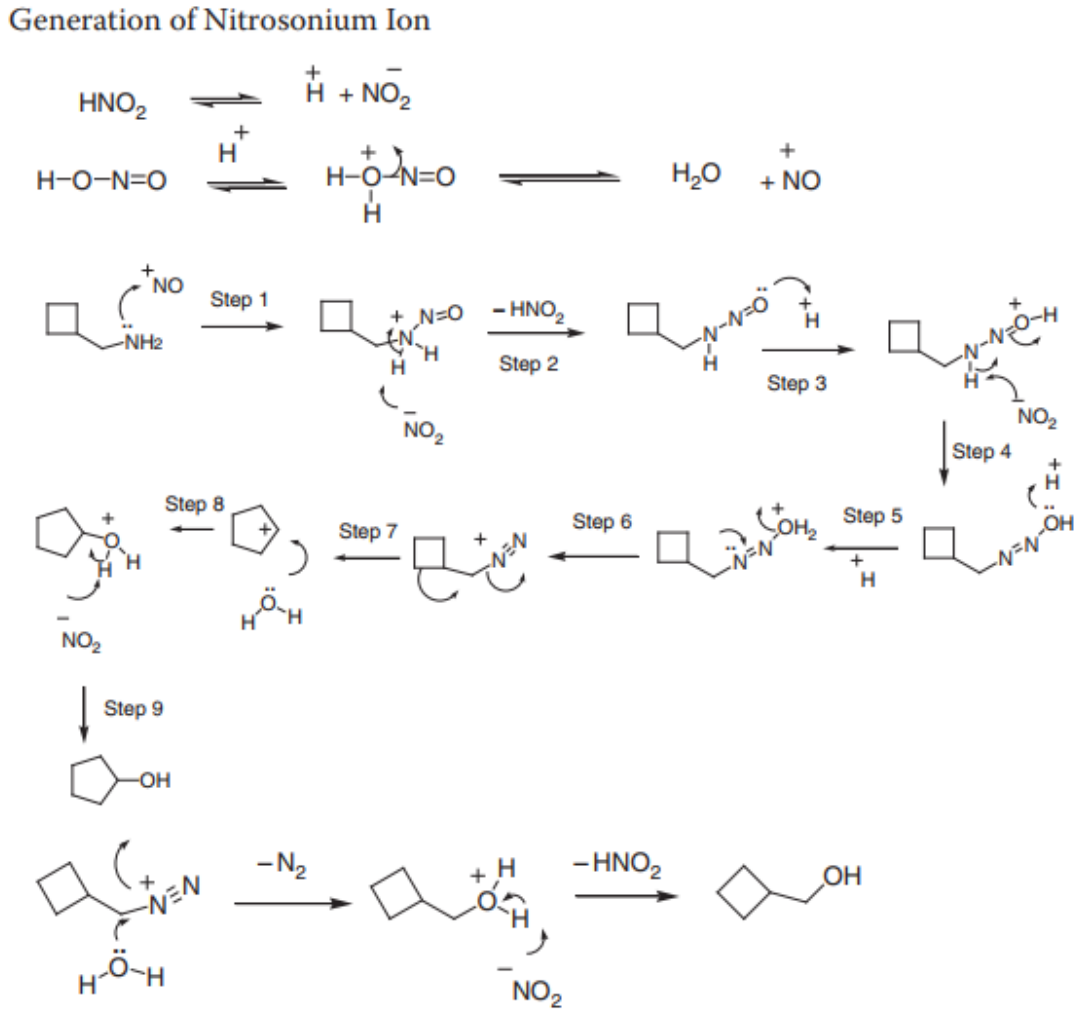
The Demjanov rearrangement is an organic reaction of primary amine with nitrous acid to form rearranged alcohols. The reaction proceeds via diazotization followed by ring expansion or ring contraction.







Mechanism



Step 1: The nitrosonium ion reacts with the primary amine.

Step 2: Abstraction of proton from the amine.

Step 3: Protonation.

Step 4: Deprotonation.

Step 5: Protonation.

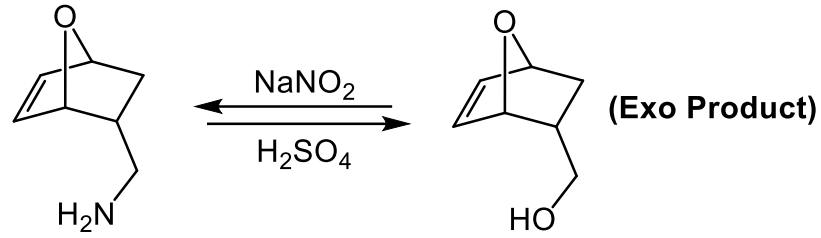
Step 6: Elimination of water and formation of diazonium ion.

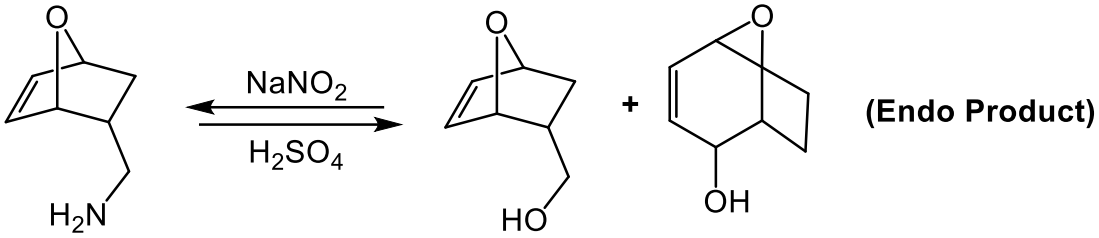
Step 7: Rearrangement and formation of carbocation.

Step 8: Nucleophilic attacks by water.

Step 9: Deprotonation and formation of the product.

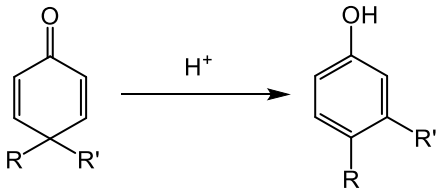
Application



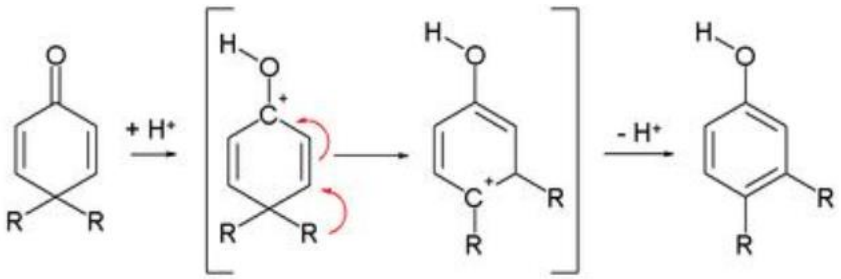


(5) Dienone – Phenol Rearrangement

The Dienone – Phenol rearrangement can be considered as the reversal of pinacol-pinacolone rearrangement. The driving force of the reaction is the formation of aromatic rings.

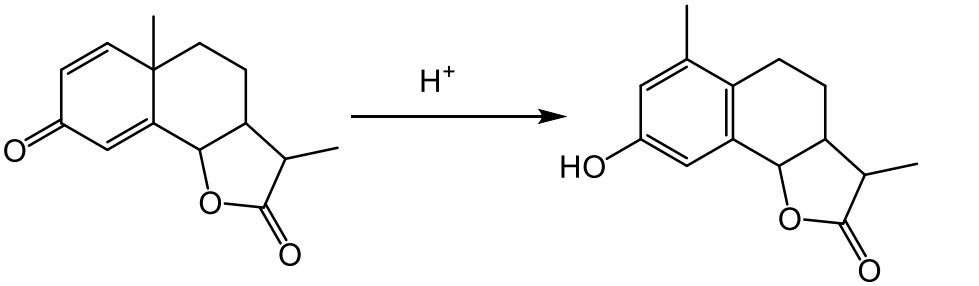


Mechanism



Application

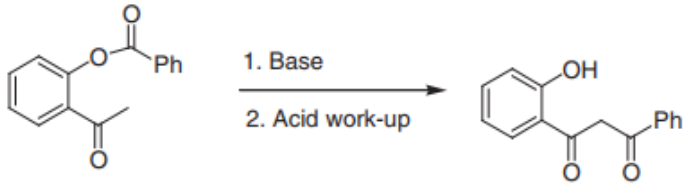
For the synthesis of desmotropo sanontonin from sanotonin



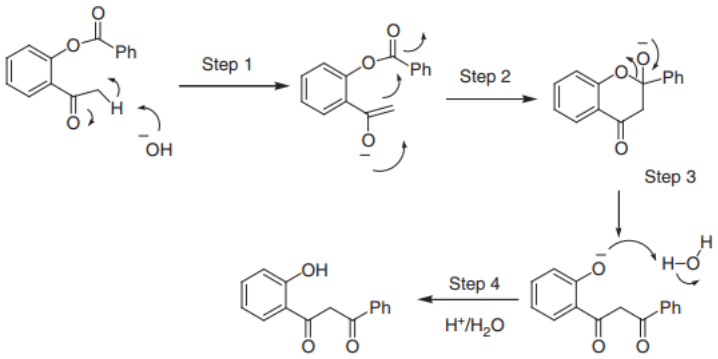
Sanotonin **Desmotroposanotonin**

(6) Baker – Venkataraman Rearrangement

The Baker–Venkataraman rearrangement is a base-catalyzed acyl transfer reaction of aromatic ortho-acyloxyketones to aromatic β-diketones.



Mechanism



Step 1: The hydroxide abstracts an α-hydrogen atom to form an enolate.

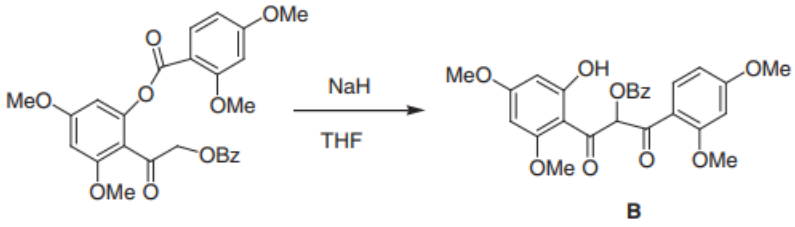
Step 2: The nucleophilic attacks by the enolate to the ester carbonyl to form a cyclic alkoxide.

Step 3: Ring opening and transfer of the acyl group.

Step 4: Protonation from acidic work-up gives the desired product

Application

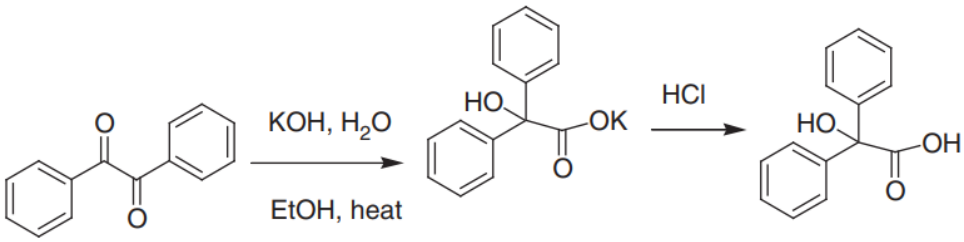
Synthesis of 2,4-Dimethoxyphenyl-3-(2-hydroxy-4,6-dimethoxyphenyl)-2- propyl-1,3-dicarbonyl-benzoate



B

(7) Benzilic acid rearrangement

The benzilic acid rearrangement reaction is an organic reaction used to convert 1,2-diketones to 2-hydroxycarboxylic acids using strong base (KOH or NaOH) and then acid work-up. Benzil reacts with base to give benzilic acid that bears the name of the reaction. The reaction works well with aromatic 1,2-diketones. Aliphatic diketones with adjacent enolizable protons undergo aldol-type condensation. The aryl groups with electron-withdrawing groups work the best.



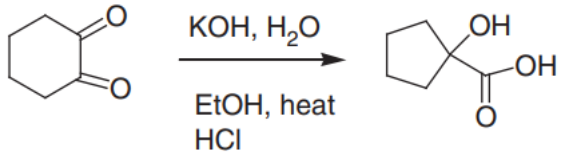
Benzil

1,2-diketone

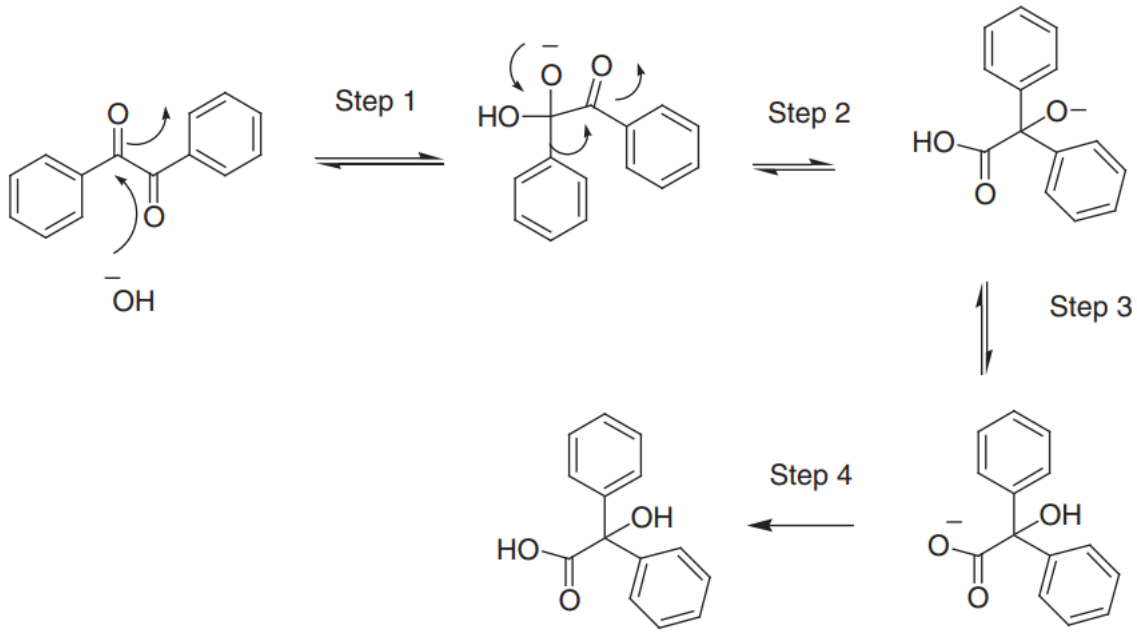
Benzilic acid

2-hydroxylcarboxylic acid

Cyclic diketones lead to form ring contraction products.



Mechanism



Step 1: Nucleophilic attack by hydroxide at the electron-deficient carbonyl carbon atom.

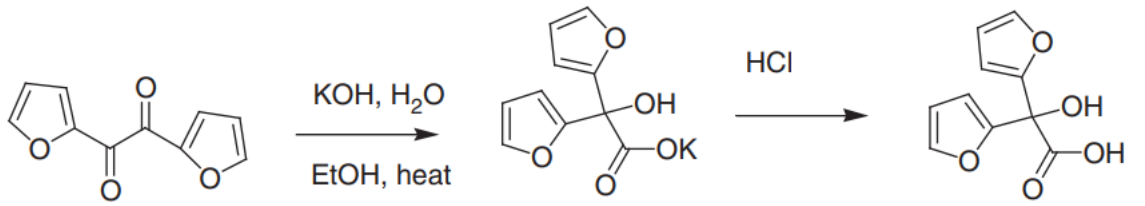
Step 2: Migration of phenyl group.

Step 3: Proton transfer.

Step 4: Acidic work-up gives the desired product.

Application

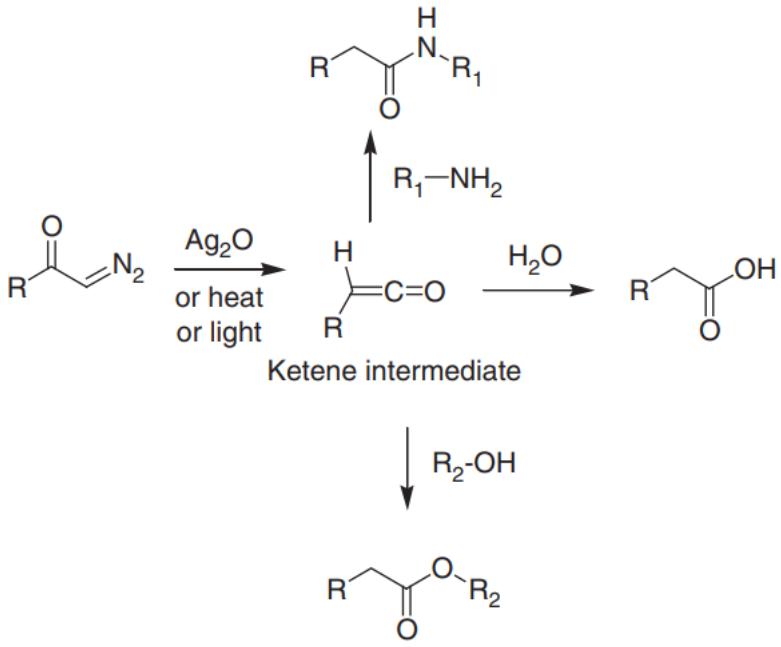
Synthesis of Ferulic acid from Furil



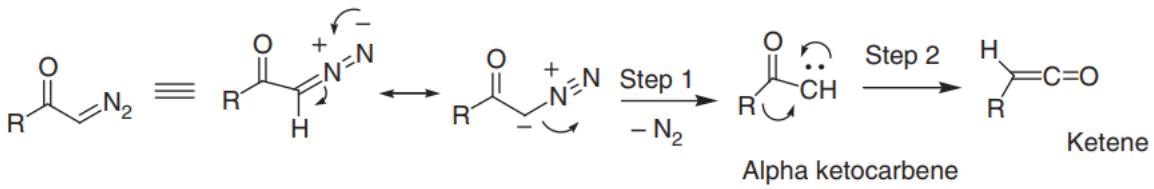
Furil Ferulic acid

(8) Wolff rearrangement

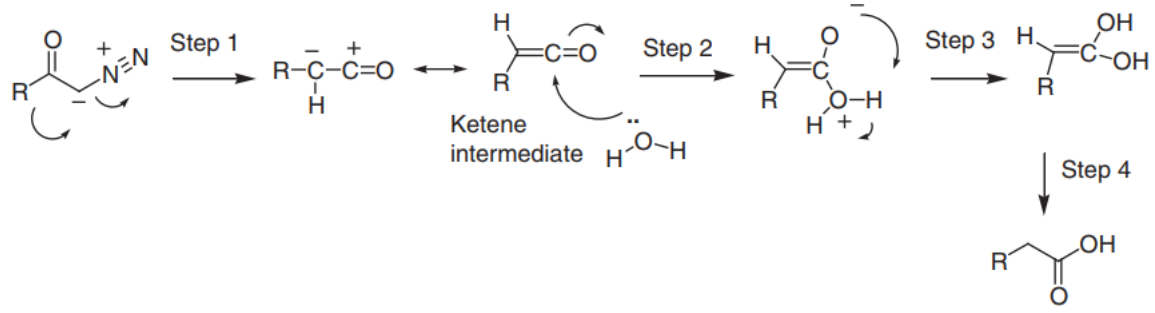
The Wolff rearrangement is a conversion of an α-diazoketone to a ketene with the loss of molecular nitrogen accompanying 1,2-rearrangement using a silver oxide catalyst or thermal or photochemical conditions. Generally, these ketenes are not stable to isolate. These can undergo a nucleophilic attack by water or alcohol or amine to form one carbon homologation of acid or ester or amide (having one carbon more from starting material).



Mechanism



Alternatively



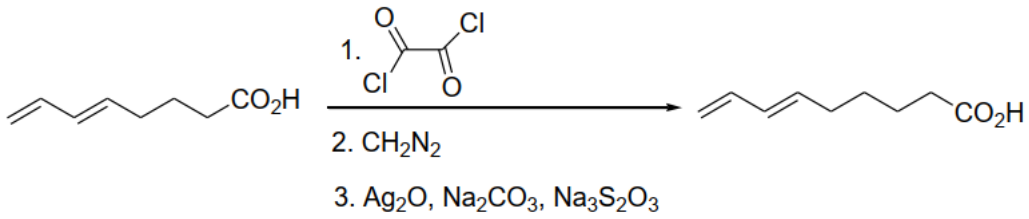
Step 1: Elimination of a molecule of nitrogen gas, R group migration, and formation of ketene intermediate.

Step 2: Water attacks as a nucleophile to the ketene.

Step 3: Proton transfer.

Step 4: Tautomerization gives the desired product.

Application

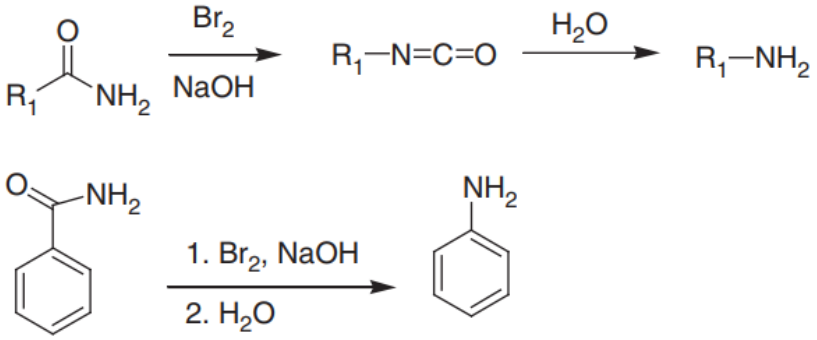


T. Hudlicky, J. P. Sheth, *Tetrahedron Lett.* **1979**, *29*, 2667.

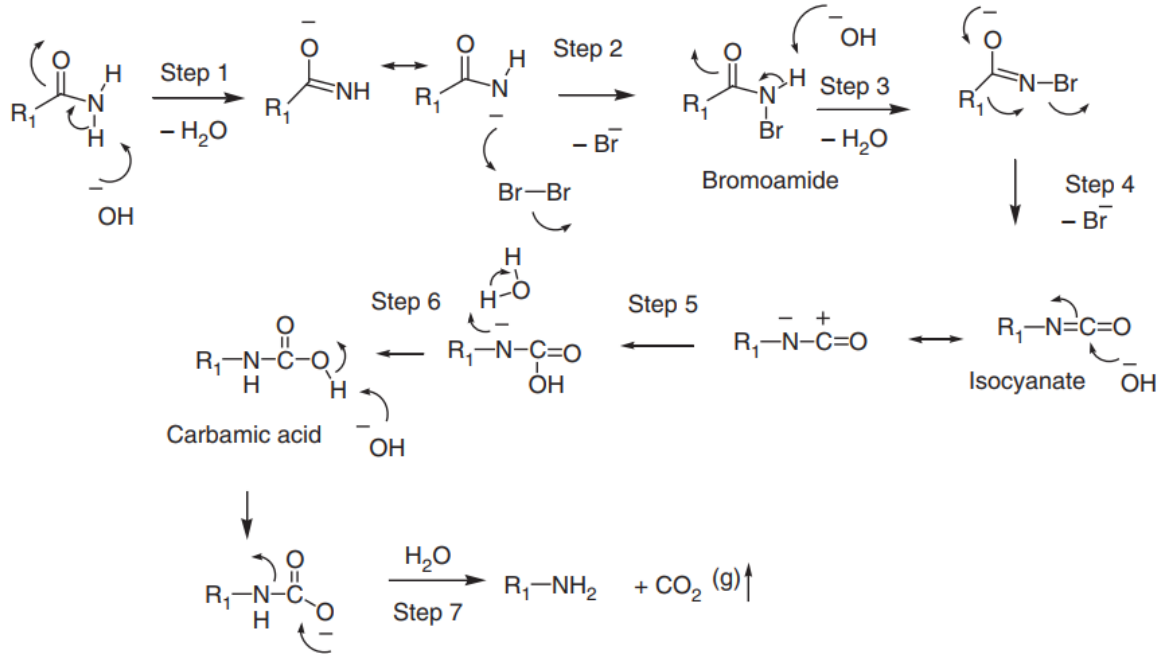
Rearrangements to Electron deficient Nitrogen

(1) Hoffman Rearrangement

The Hofmann rearrangement is a conversion reaction of primary amide to primary amine with one carbon atom less (via the intermediate isocyanate formation) using alkali (NaOH) and halogen (chlorine or bromine) or hypohalite (NaOCl or NaOBr). This reaction is also referred to as the Hofmann degradation of amide.



Mechanism



Step 1: Hydroxide abstracts an acidic N–H proton.

Step 2: The anion reacts with bromine to form an N-bromoamide.

Step 3: Hydroxide abstracts another acidic H atom from N–H.

Step 4: Elimination of bromide and migration of R1 group to nitrogen atom occur simultaneously to form an isocyanate.

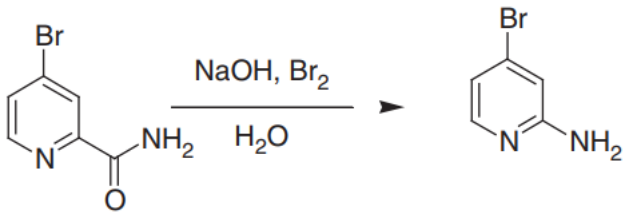
Step 5: Water or hydroxide reacts with isocyanate.

Step 6: Proton transfer produces a carbamic acid.

Step 6: Abstraction of proton with hydroxide.

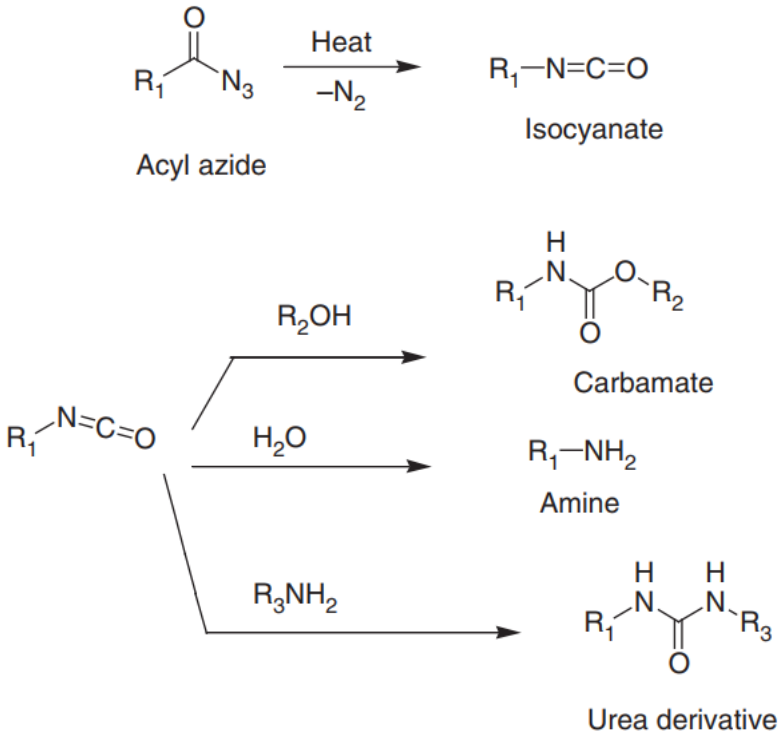
Step 7: Carbamic acid loses CO2 and after protonation gives the amine product

Application

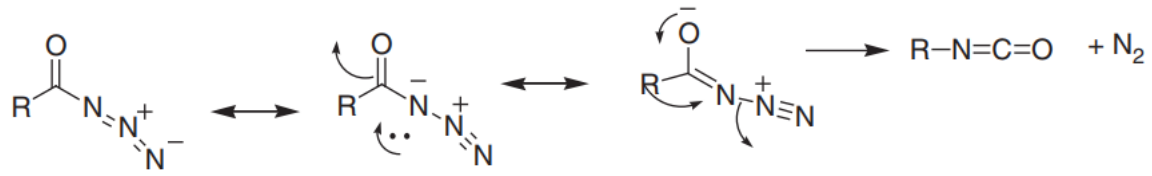


(2) Curtius Rearrangement

The Curtius rearrangement is the thermal conversion of an acyl azide to an isocyanate. The isocyanate is the intermediate of several products such as urea, amine, carbamate-protected amine, amino acid, and other products. Several improvements on this reaction using different reaction conditions and mechanistic studies have been successfully accomplished.

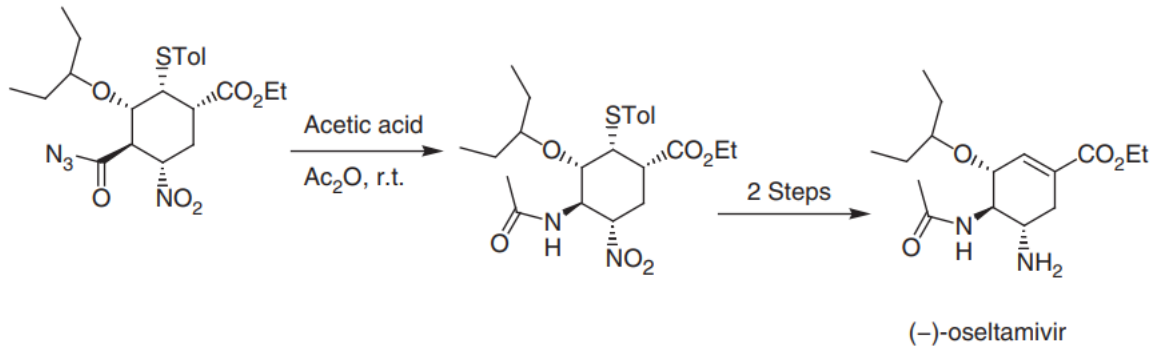


Mechanism



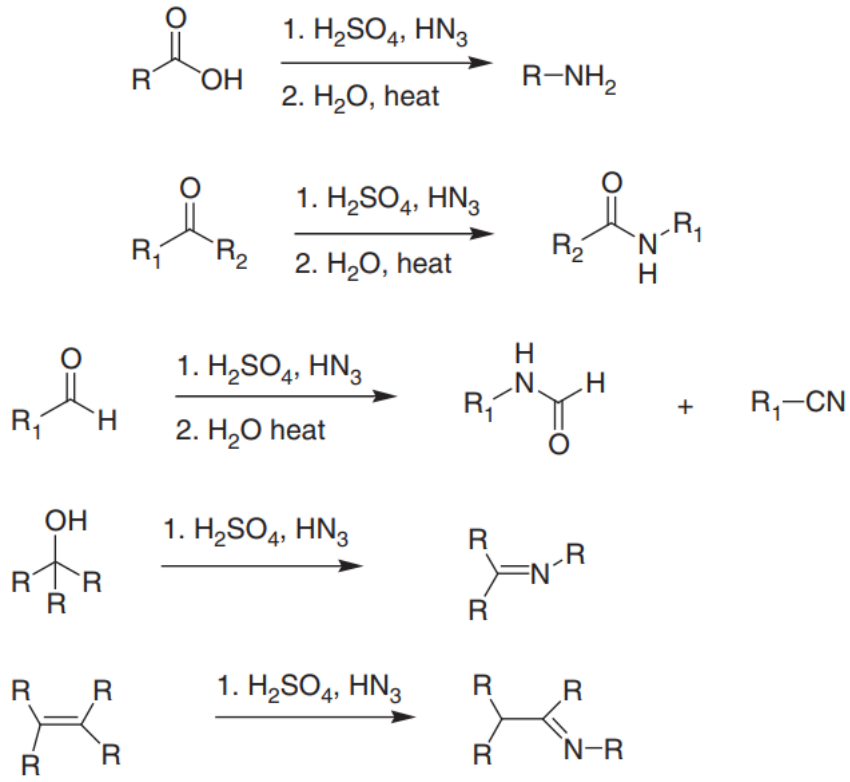
Application

The Curtius rearrangement has been used for the synthesis of several medicines including oseltamivir, tranylcypromine, candesartan, gabapentin, benzydamine, bromadol, igmesine, tecadenoson, terguride, and others

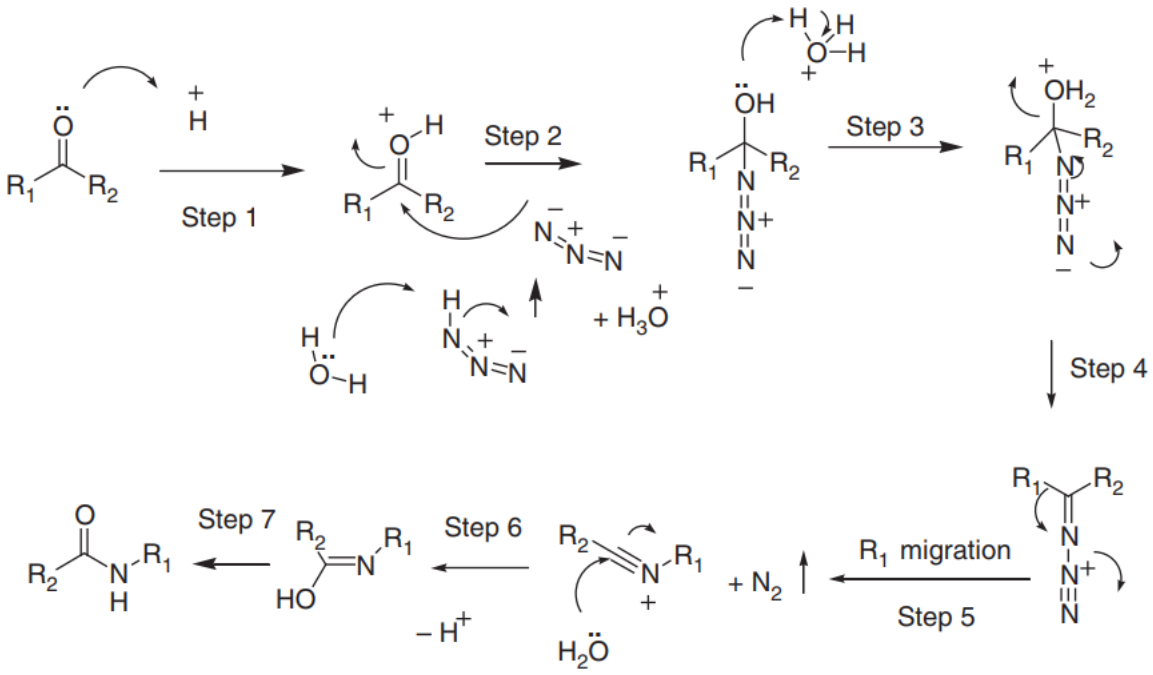


(3) Schmidt Rearrangement

The Schmidt reaction or rearrangement is an acid-catalyzed reaction of hydrogen azide with a carbonyl compound such as an aldehyde, a ketone, or a carboxylic acid to give an amine, amide, or nitrile, respectively, after a rearrangement and the loss of a molecule of nitrogen gas.



Mechanism



Step 1: Protonation of oxygen atom of the carbonyl compound.

Step 2: Nucleophilic attack by an azide to the electron-deficient carbonyl carbon atom.

Step 3: Protonation.

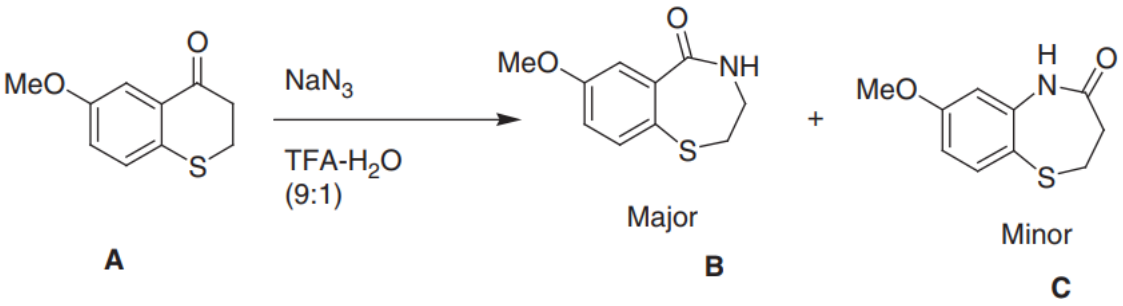
Step 4: Elimination of water.

Step 5: R1 group migration and formation of nitrilium ion.

Step 6: Nucleophilic attack by water and deprotonation.

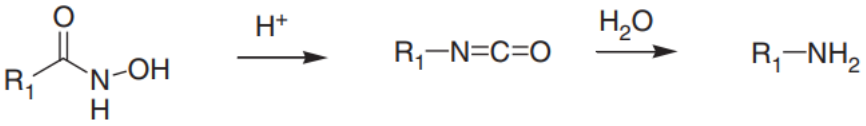
Step 7: Tautomerization gives the desired product.

Application

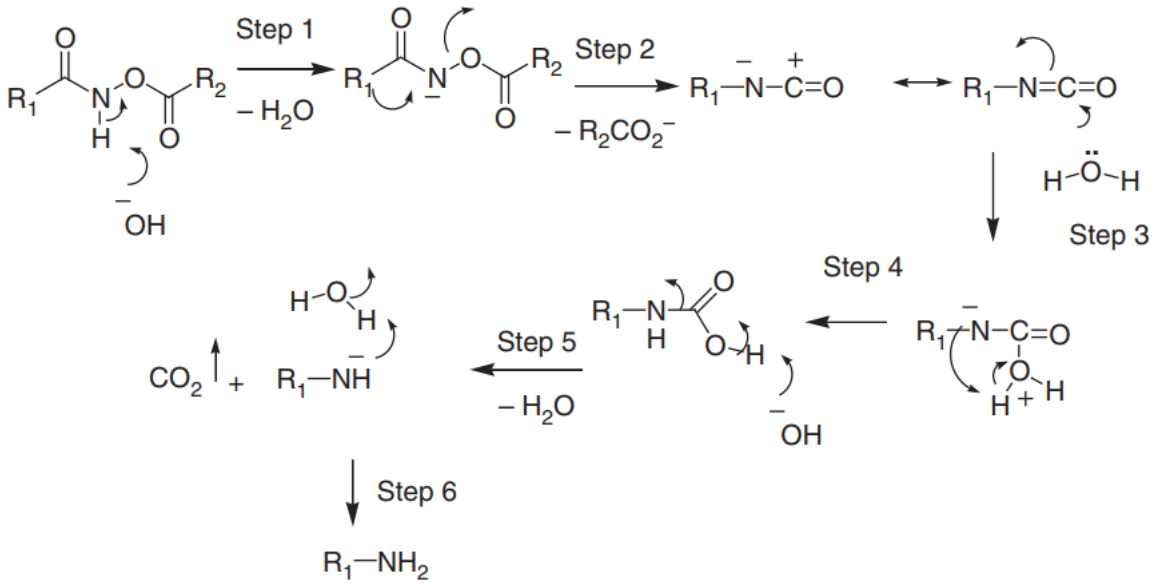


(4) Lossen Rearrangement

The Lossen rearrangement is the intramolecular conversion of hydroxamic acids or their O-acetyl, O-aroyl, and O-sulfonyl derivatives into isocyanates under thermal or in the presence of acid or base catalysts. Isocyanate can be converted to the corresponding primary amine with water.



Mechanism



Step 1: Abstraction of the proton from the N atom.

Step 2: Migration of R1 group to the N-atom and elimination of carboxylate.

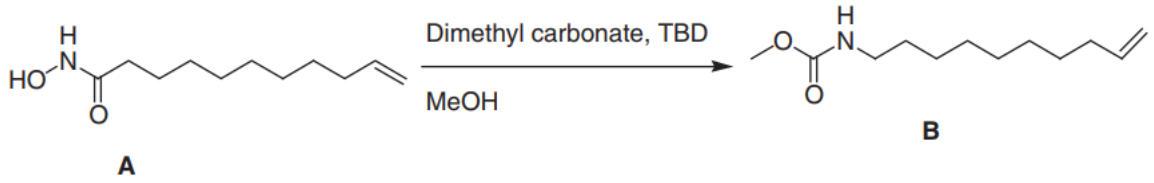
Step 3: Hydrolysis of isocyanate and nucleophilic attack by water.

Step 4: Proton transfer.

Step 5: Decarboxylation and liberation of carbon dioxide.

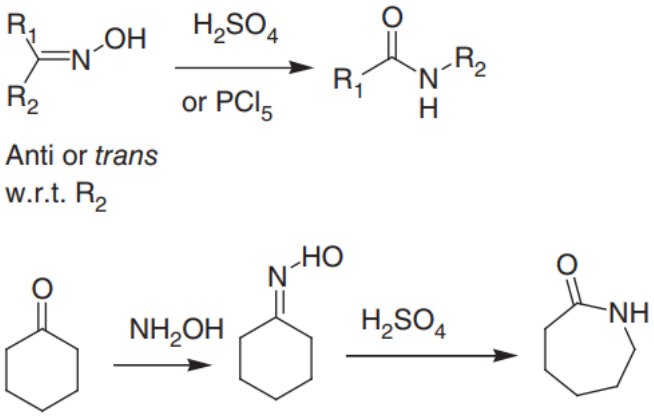
Step 6: Proton transfer and formation of an amine product.

Application

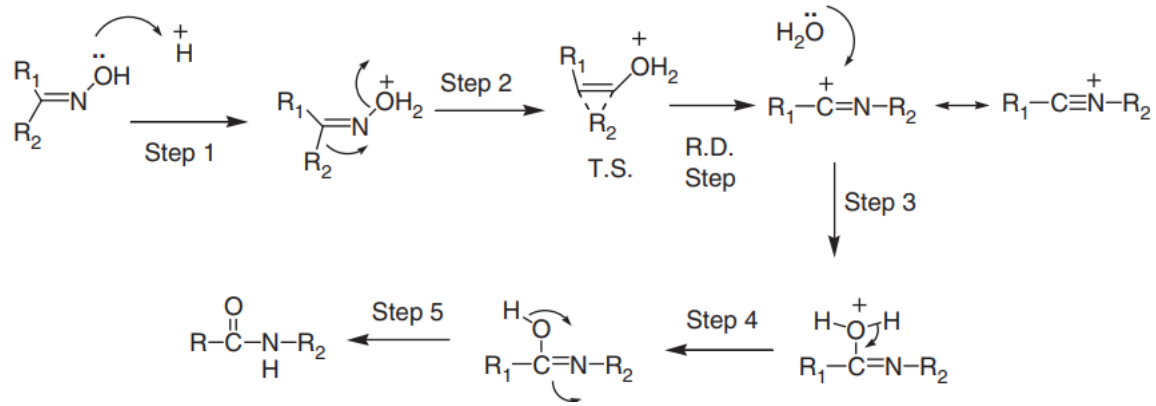


(5) Beckmann Rearrangement

The Beckmann rearrangement, named after the German chemist Ernst Otto Beckmann, is a conversion of an oxime to an N-substituted amide in the presence of acid catalyst. The acid catalysts are used including HCl, H_2SO_4, PCl_5, $SOCl_2$, P_2O_5, tosyl chloride, SO_3, BF_3, etc. These catalysts require the excess amounts and produce a large amount of by-products. Most recently, this reaction has been utilized by using a catalytic amount of new types of catalysts such as $RuCl_3$, $BiCl_3$, etc.



Mechanism



Step 1: Protonation of hydroxyl group and formation of a better leaving group

Step 2: Migration of R2 group trans or anti to the leaving group and loss of water group leading to formation of carbocation. This trans (1,2) shift predicts the regiochemistry for this reaction.

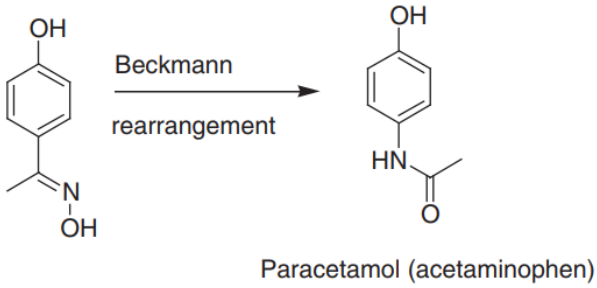
Step 3: Water molecule attacks as a nucleophile with a lone pair of electrons to the carbocation.

Step 4: Deprotonation.

Step 5: Tautomerization affords an N-substituted amide, the final product.

Application

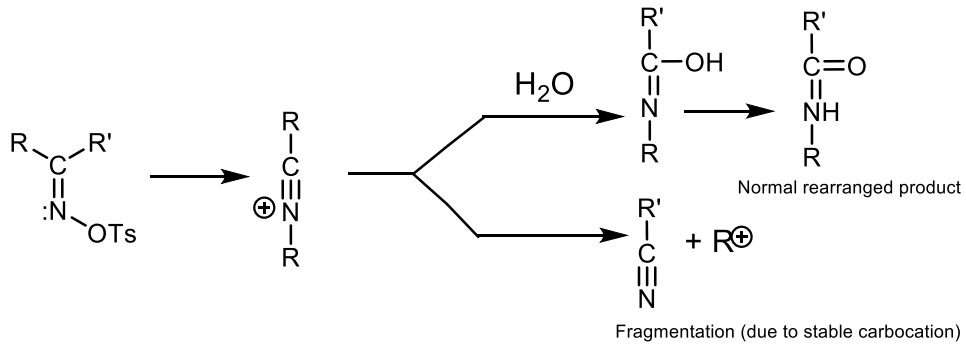
For the synthesis of Paracetemol



Paracetamol (acetaminophen)

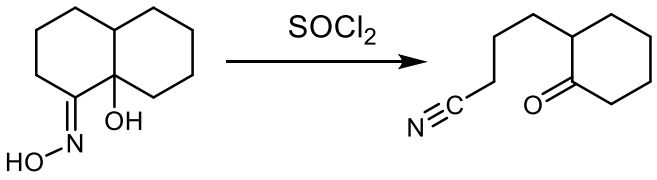
(6) Abnormal Beckmann Rearrangement

Abnormal Beckmann (or) Beckmann fragmentation is a reaction that frequently competes with Beckmann rearrangement. When the group α to the oxime is capable of stabilizing carbocation formation, the fragmentation becomes a viable reaction pathway. The reaction generates a nitrile and a carbocation, which quickly forms various products. The nitrile can be hydrolyzed to give carboxylic acids.



Fragmentation (due to stable carbocation)

Application



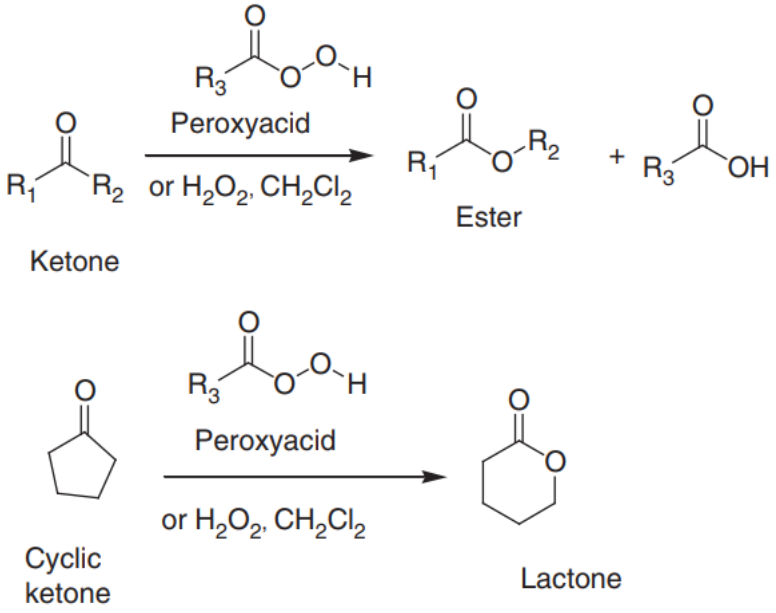
Rearrangements to electron deficient Oxygen

(1) Baeyer-Villiger oxidation

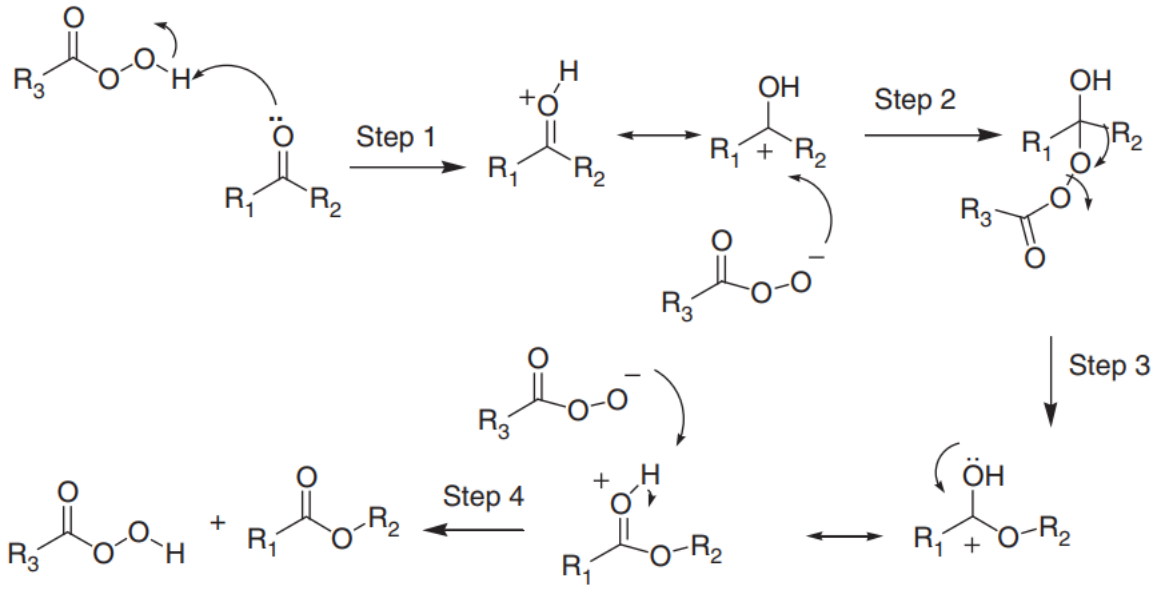
The Baeyer–Villiger oxidation is an organic reaction that converts a ketone to an ester or a cyclic ketone to a lactone in the presence of hydrogen peroxide or peroxy acids. The reaction was discovered in 1899 by Adolf von Baeyer and Victor Villiger. It is an intramolecular anionotropic rearrangement where an alkyl group migrates from the carbonyl carbon atom (migration origin) to an electron-deficient oxygen atom (migration terminus). The most electron-rich alkyl group (most substituted carbon) that is able to stabilize a positive charge migrates most readily.

The migration order is as follows: Tertiary alkyl > cyclohexyl > secondary alkyl >phenyl >primary alkyl > CH3 > H.

Several new catalysts including organics, inorganics, and enzymes have been developed for this reaction. Amine or alkene functional groups are limitations, however, because of their easy and undesirable oxidation.



Mechanism



Step 1: The oxygen atom of the ketone is protonated to form a carbenium ion.

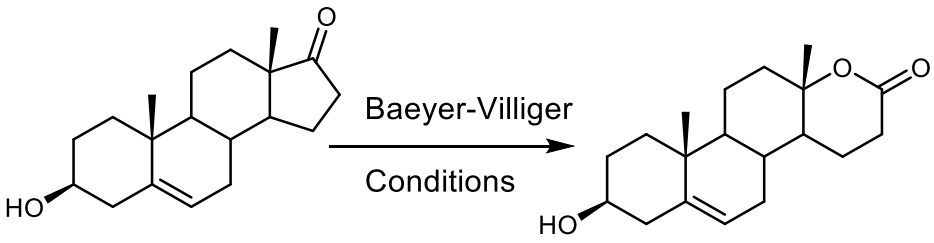
Step 2: Nucleophilic attacks by aperoxycarboxylate ion at electron-deficient carbonyl carbon atom.

Step 3: One of the alkyls on the ketone migrates to the oxygen of the peroxide group, while a carboxylic acid departs.

Step 4: Deprotonation of the oxocarbenium ion produces the desired ester

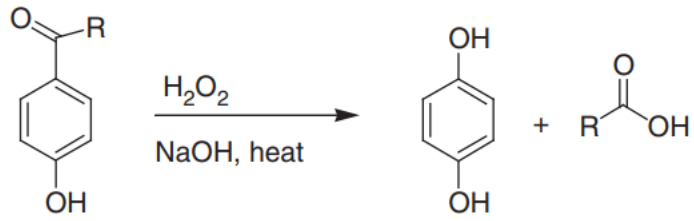
Application

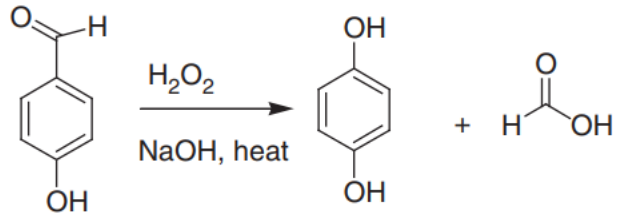
Synthesis of Testolactone



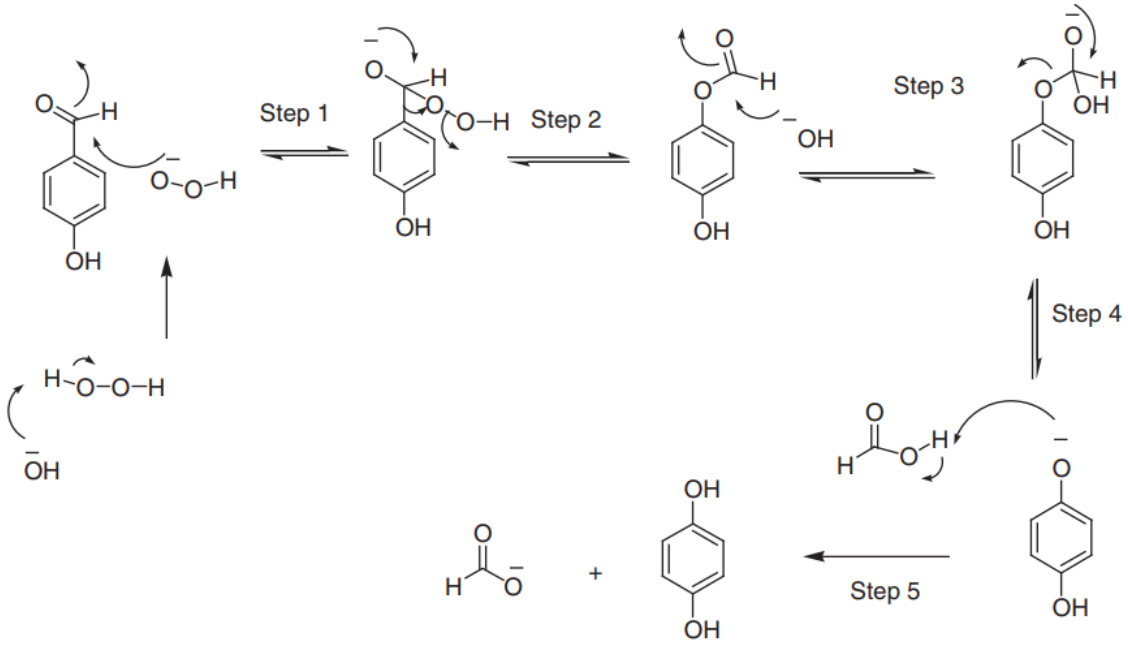
(2) Dakin Reaction

Dakin reaction is a redox reaction used to convert an *ortho*- or *para*-hydroxylated phenyl aldehyde or a ketone to a benzenediol with alkaline hydrogen peroxide.





Mechanism



Step 1: Nucleophilic attack by a hydroperoxide anion to the electron-deficient carbonyl carbon atom forms a tetrahedral intermediate.

Step 2: Aryl migration, elimination of hydroxide, and formation of an aryl ester.

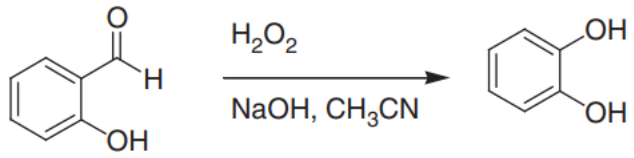
Step 3: Nucleophilic addition of hydroxide to the ester carbonyl carbon atom forms a second tetrahedral intermediate.

Step 4: The unstable tetrahedral intermediate collapses to eliminate a phenoxide and forms a carboxylic acid.

Step 5: Proton transfers from carboxylic acid to phenoxide.

Application

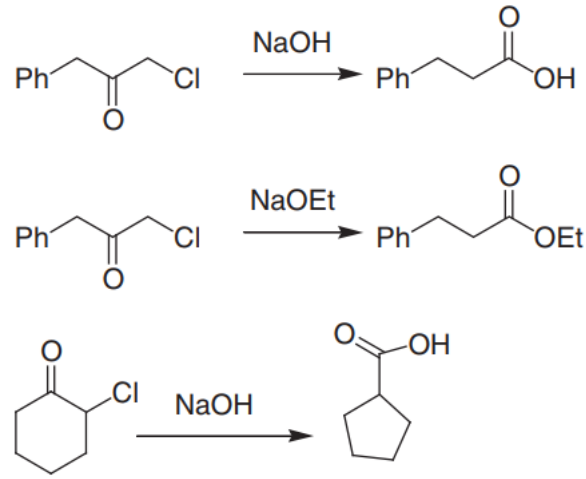
Preparation of Catechol (o-Dihydroxybenzene)



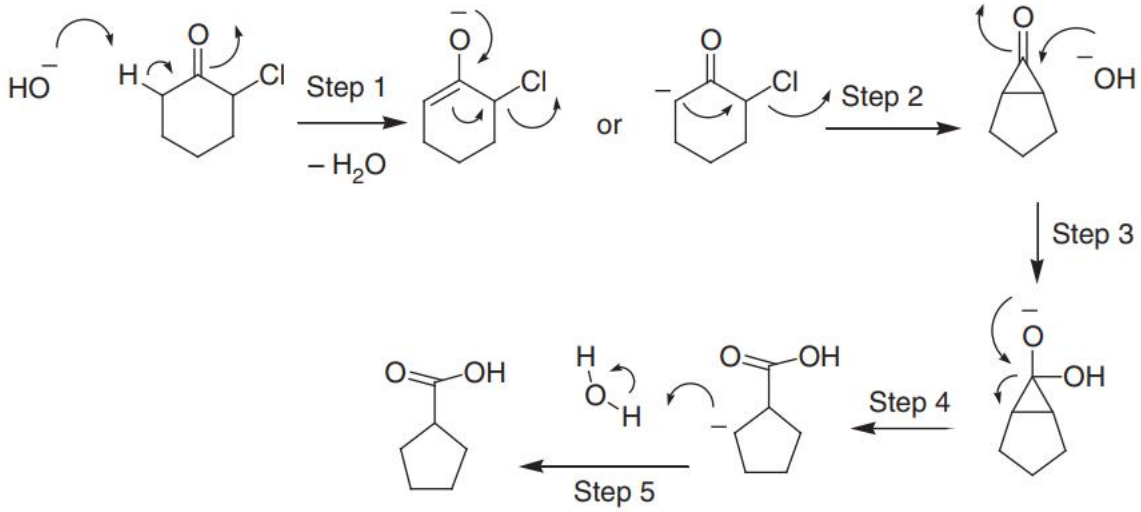
Rearrangements to electron rich atom

(1) Favorskii Rearrangement

The Favorskii rearrangement is an organic reaction used to convert an α-haloketone to a rearranged acid or ester using a strong base (hydroxide or alkoxide). In case of cyclic α-haloketone, this reaction gives a ring contracted product.



Mechanism



Step 1: Abstraction of α-H on the side of the ketone away from the chlorine atom forms an enolate.

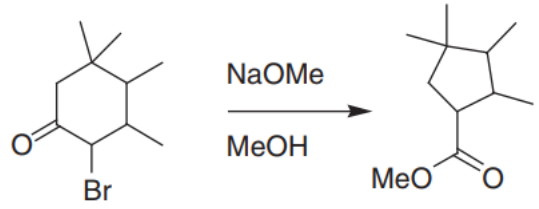
Step 2: SN_2-type reaction and formation of cyclopropanone ring intermediate.

Step 3: Hydroxide as a nucleophile attacks at the ketone.

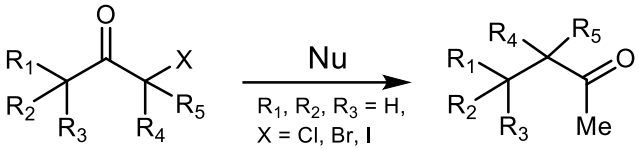
Step 4: Ring opening gives an anion.

Step 5: Proton transfers from water or solvent gives the final product.

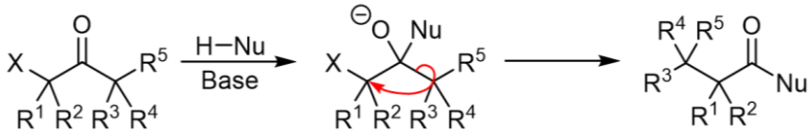
Application



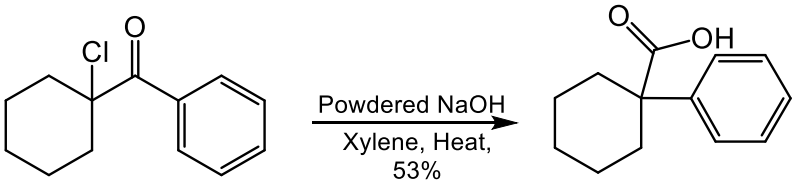
(2) Quasi – Favorskii Rearrangement



Mechanism

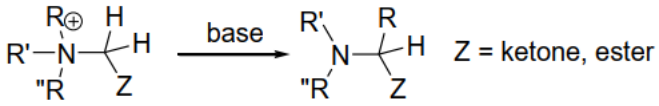


Application



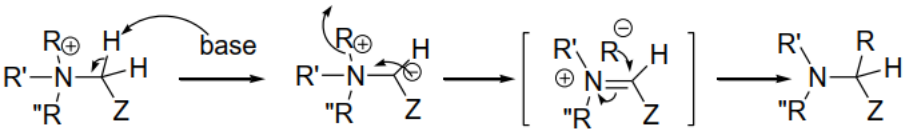
(3) Stevens Rearrangement

In case of quaternary ammonium salts containing β-ketone or ester or aryl group, an α −hydrogen is removed by base to give an ylide and then the rearrangement occurs.

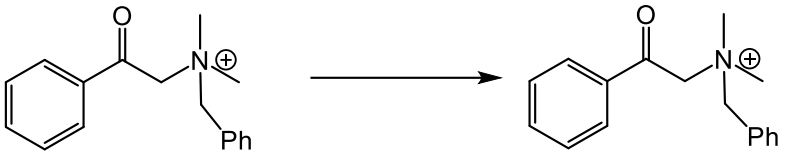


Migratory Aptitude R = propargyl > allyl > benzyl > alkyl

Mechanism

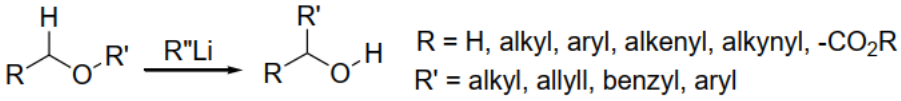


Application

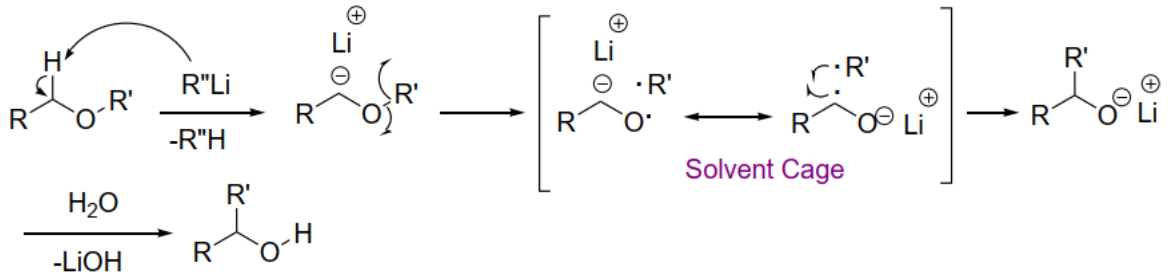


(4) [1,2] Wittig Rearrangement

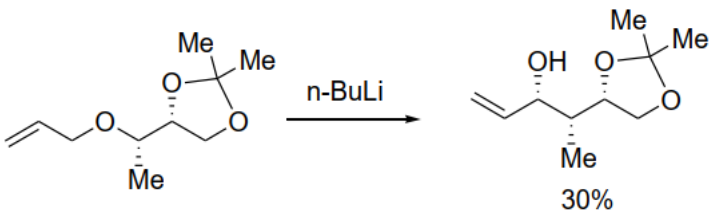
Ethers undergo [1,2]-sigmatropic rearrangement in the presence of strong base such as amide ion or phenyllithium to give more stable oxyanion. The mechanism is analogous to that of Stevens rearrangement.



Mechanism



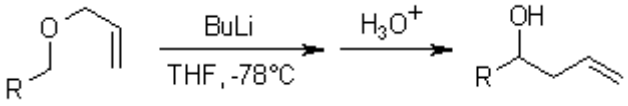
Application



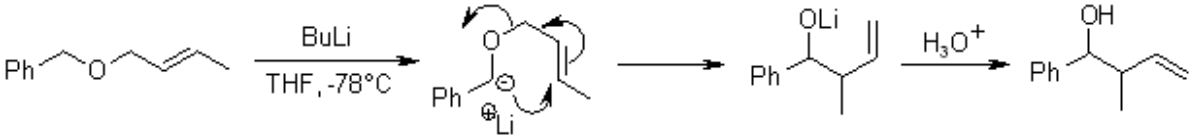
R. E. Maleczka, Jr., F. Geng, *J. Am. Chem. Soc.* **1998**, *120*, 8551.

(5) [2,3] Wittig Rearrangement

The [2,3]-Wittig rearrangement is the transformation of an allylic ether into a homoallylic alcohol via a concerted, pericyclic process. Because the reaction is concerted, it exhibits a high degree of stereocontrol, and can be employed early in a synthetic route to establish stereochemistry. The Wittig rearrangement requires strongly basic conditions, however, as a carbanion intermediate is essential. [1,2]-Wittig rearrangement is a competitive process.

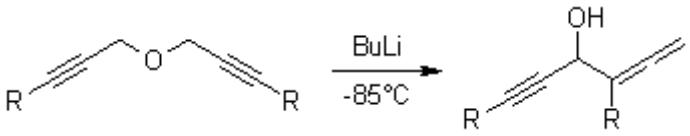


Mechanism



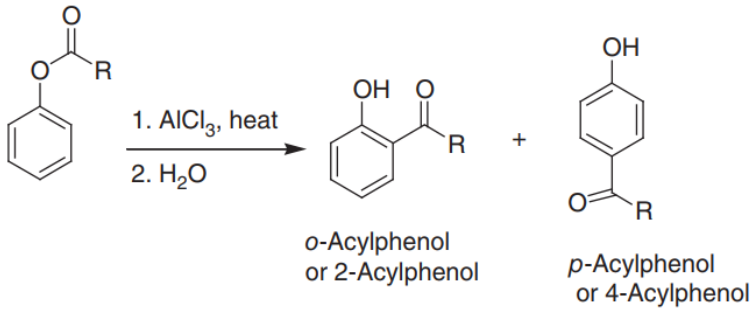
Application

2,3]-Wittig Rearrangements of propargyl ethers can afford allenic alcohols, but the scope is relatively limited and the process is not general.



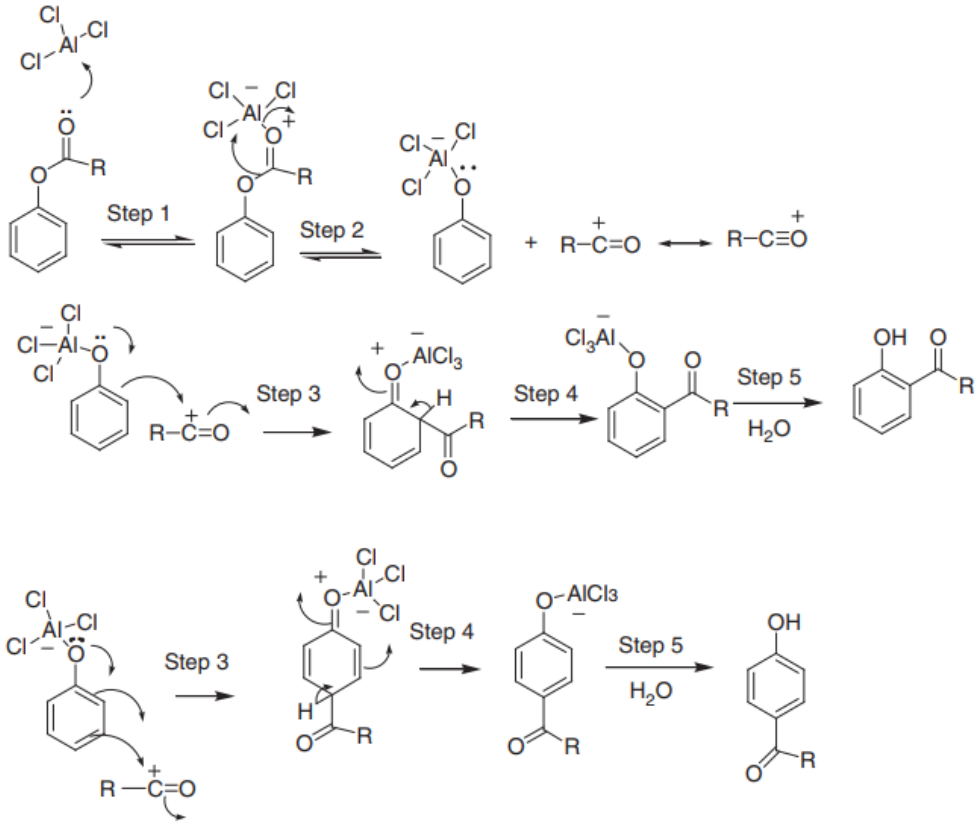
(6) Fries Rearrangement

Mostly $AlCl_3$, BF_3, $TiCl_4$, or $SnCl_4$ catalyzed rearrangement of phenolic esters to 2-hydroxy aryl ketone or 4-hydroxy aryl ketone is called the Fries rearrangement, named after the German chemist Karl Theophil Fries. The rearrangement can proceed with other acids such as HF, CF_3CO_2H, and $MeSO_3H$ in an inert solvent or without any solvent. The acids are generally required in excess of the stoichiometric amounts, particularly with the Lewis acids (most common is AlCl3) since they form complexes both with the starting materials and the products.



R = Alkyl or aryl group

Mechanism



Step 1: $AlCl_3$ forms a complex with phenolic ester. $AlCl_3$ coordinates with carbonyl oxygen atom of carbonyl acyl group as this oxygen atom is more electron rich than phenolic oxygen atom. It is a stable and preferred Lewis base.

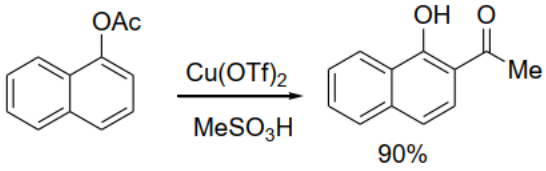
Step 2: Reversible formation of an acylium carbocation.

Step 3: Electrophilic attacks by the acylium carbocation at ortho and para positions of the aromatic ring to give a resonance-stabilized σ-complex.

Step 4: Deprotonation and aromatization.

Step 5: Hydrolysis liberates an acylphenol (or called hydroxyl aryl ketone).

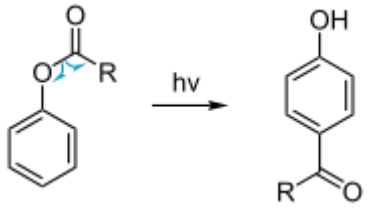
Applications



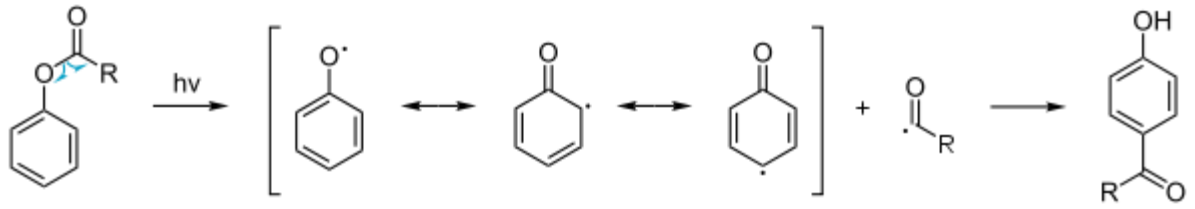
O. Mouhtady, H. Gaspard-Iloughmane, N. Roques, C. LeRoux, *Tetrahedron Lett.* **2003,** *44,* 6379.

(7) Photo Fries Rearrangement

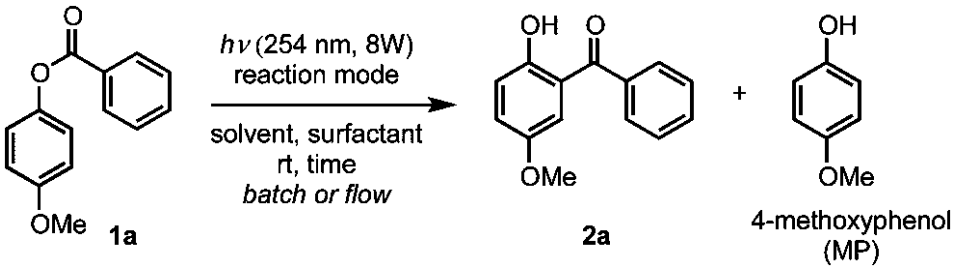
Photo-Fries Rearrangement: Similar transformation of phenolic esters into hydroxy ketones occurs during the Photo-Fries rearrangement when UV light is present and no catalyst is used.



Mechanism



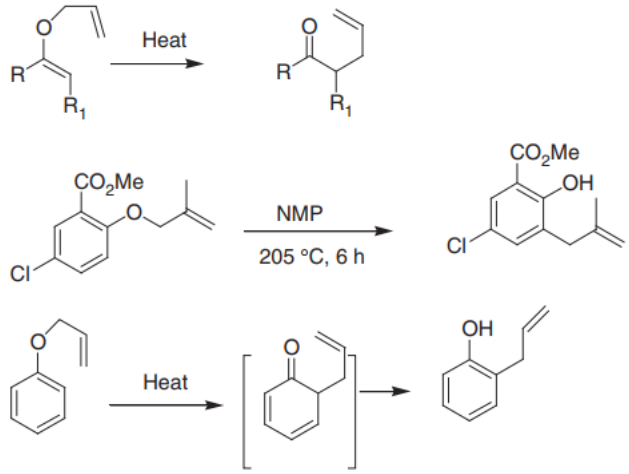
Application



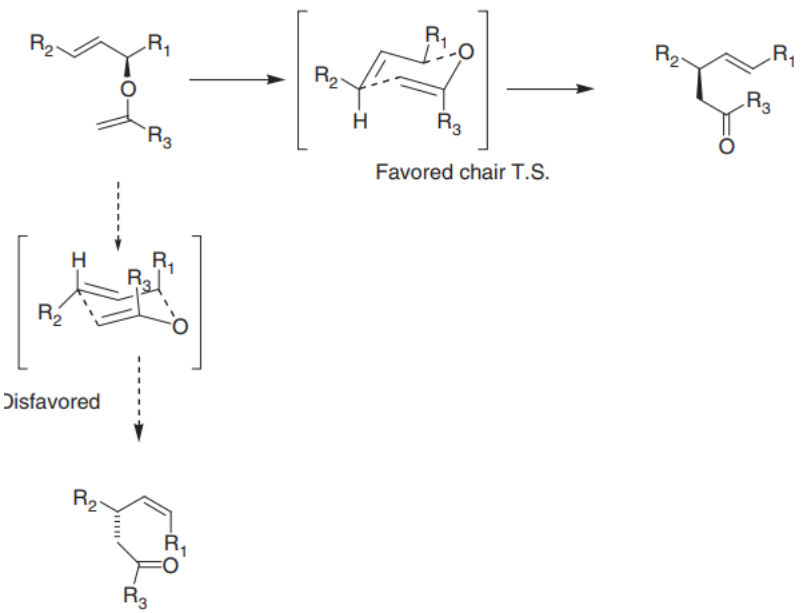
Intramolecular Rearrangements

(1) Claisen Rearrangement

The Claisen rearrangement is a [3,3]-sigmatropic rearrangement of an allyl vinyl ether to form a γ,δ-unsaturated carbonyl compound under heating or acidic conditions. The reaction is a concerted process where bonds are forming and breaking at the same time.



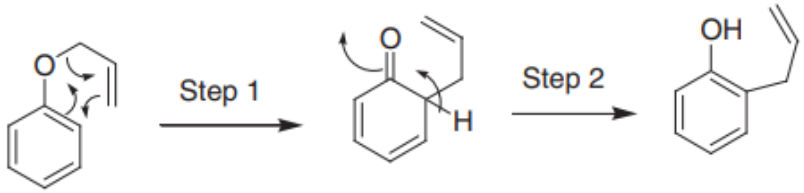
Mechanism



When large groups are in equatorial positions, the 1,3-interaction is minimized.

When large groups are in axial positions, the 1,3-diaxial unfavorable interaction is maximized.

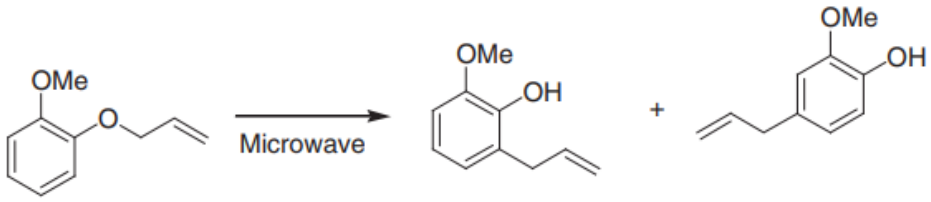
The aromatic Claisen rearrangement undergoes [3,3]-sigmatropic rearrangement accompanied by a rearomatization.



Step 1: [3,3]-Sigmatropic rearrangement.

Step 2: Rearomatization gives the desired product.

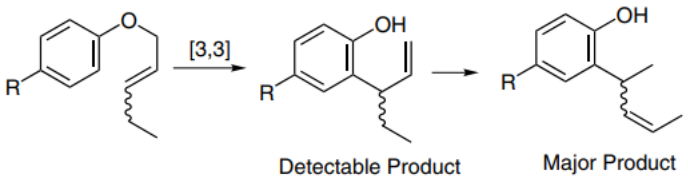
Application



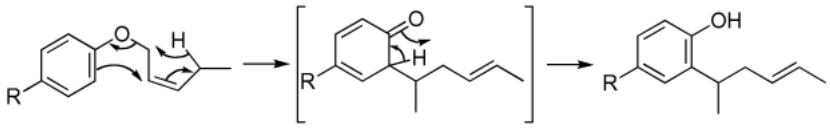
(2) Abnormal Claisen Rearrangement

the abnormal Claisen rearrangement usually occurs for the allyl aromatic ethers. A similar reaction also occurs for the thermal rearrangement of cyclopropyl ketones to homoallylic ketones. The abnormal Claisen rearrangement is believed to proceed via two consecutive

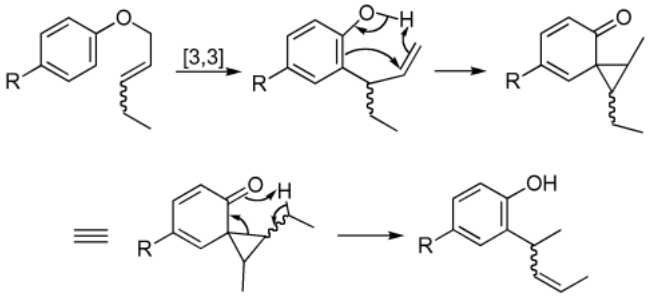
processes, i.e., the normal ortho Claisen rearrangement of γ-alkylallyl aryl ether to an o-(α-alkylallyl) phenol and the isomerization of the resulting phenol. In general, this type of abnormal Claisen rearrangement does not occur smoothly, except when in the presence of Lewis acids $FeCl_3$, even though other Lewis acids (e.g., $HfCl_4$, $GaCl_3$, $ZrCl_4$) have limited ability to accelerate such reaction.



Mechanism

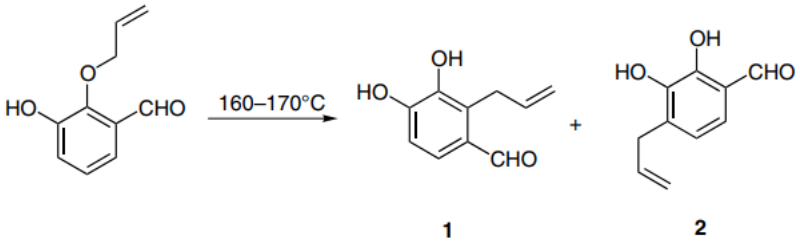


SCHEME 1. *Concerted mechanism for abnormal Claisen rearrangement.*



SCHEME 2. *Stepwise mechanism for abnormal Claisen rearrangement.*

Application



(3) Cope Rearrangement

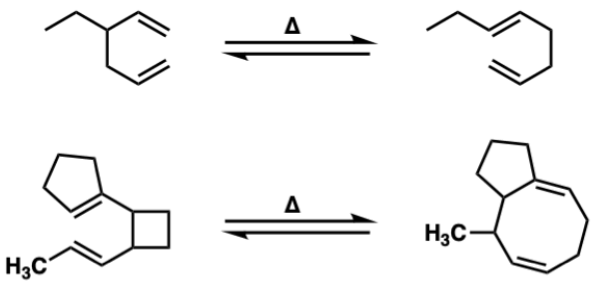
The Cope rearrangement is a [3,3]-sigmatropic rearrangement of 1,5-dienes under thermal conditions to produce regioisomeric 1,5-dienes.

Mechanism

Chair-like T.S.

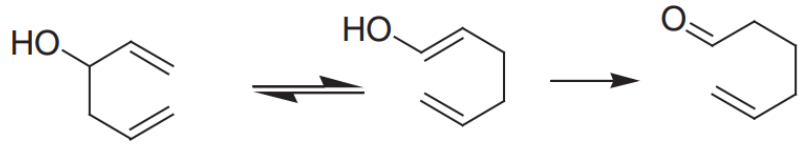
Boat-like T.S.

Application

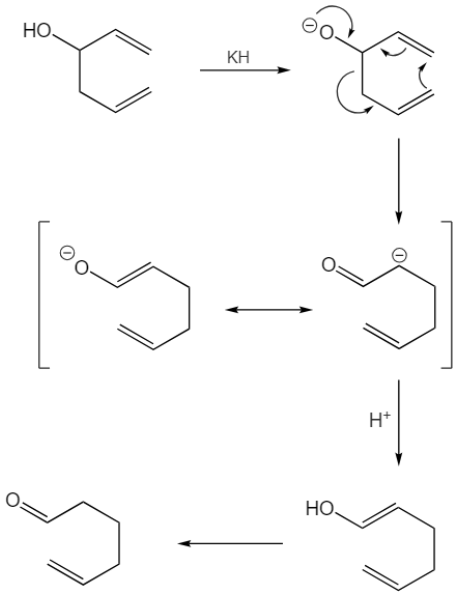


(4) Oxy-Cope Rearrangement

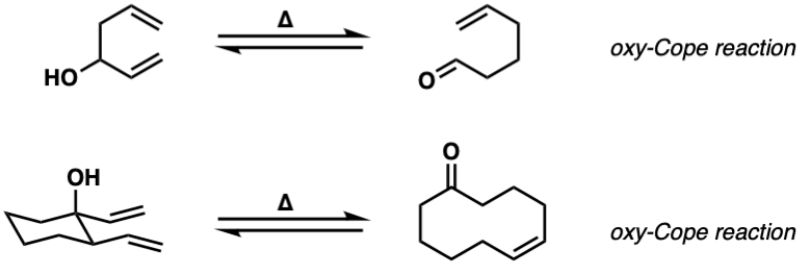
The oxy-Cope rearrangement has a hydroxy group on C-3 (sp3-hybridized carbon), forming enal or enone after keto–enol tautomerization.



Mechanism



Application



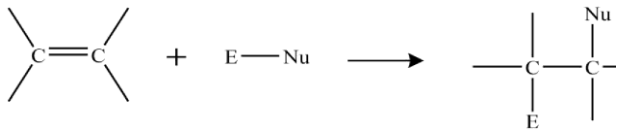
UNIT – IV
ADDITION TO CARBON MULTIPLE BONDS

a) Addition to carbon-carbon multiple bonds

We know that addition reactions in organic chemistry are the chemical transformations where two or more molecules combine to yield a usually single but bigger molecule called an adduct. Since these addition reactions are restricted to chemical compounds with multiple bonds, molecules with carbon-carbon multiple bonds (alkenes, alkynes, or many cyclic species like benzene derivatives or cyclo-alkene/alkynes), or with carbon-heteroatom multiple bonds (like carbonyl C=O or imine C=N derivatives) are suitable candidates. Furthermore, these addition reactions can be classified into polar addition (electrophilic and nucleophilic) and non-polar addition (free radical and cycloaddition) reactions. Nevertheless, in this section, we will only discuss the mechanistic and stereochemical aspects of electrophilic, nucleophilic, and free radical addition to the carbon-carbon multiple bonds

Addition reactions involving electrophiles

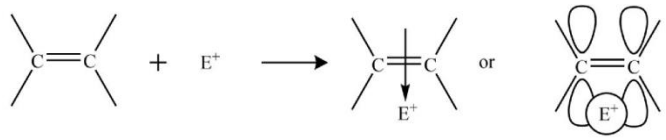
We know from the wave-mechanical treatment that space below and above the chemical bond is quite rich in electron density due to π-overlap; which makes the carbon-carbon multiple bonds very susceptible to electrophilic attacks. The general reaction showing the electrophilic attack on carbon-carbon multiple bonds is shown below.



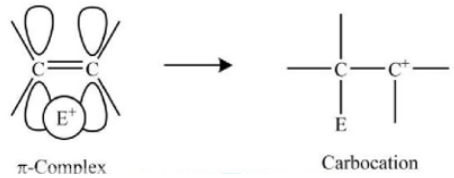
Now first we will discuss the mechanism responsible for this transformation and then we will study the stereochemical aspects of the same.

Mechanism:

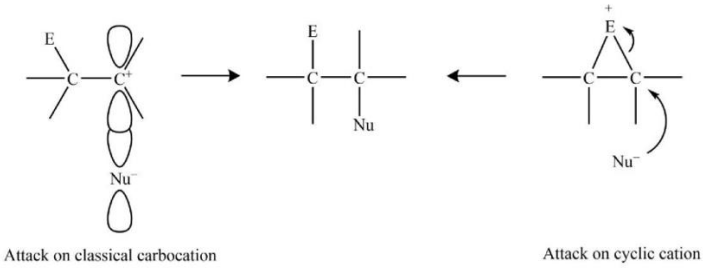
Since the reaction between the reagent and substrate requires them to get close to each other first, some attractive force is needed to do so. This can be achieved by considering the attacking reagent as a species that can be fragmented into electrophile (E^+) and nucleophile (Nu^-).



Now because the double bond is a Lewis base (and nucleophile), it will attract the electrophilic part of the attacking reagent towards itself, forming π-complex. One might ask the since we have a nucleophilic part too in the attacking reagent then why we don't call the nucleophilic addition; the answer would be that the electrophilic part attacks first, and therefore, dictates almost everything. Also, we can not assign the electrophile to any specific carbon because the empty orbital of the attacking electrophile is overlapping with π-bond and not with any particular atomic orbital. However, this π-complex so formed will get convert into carbocation with real sigma bonds as shown below.



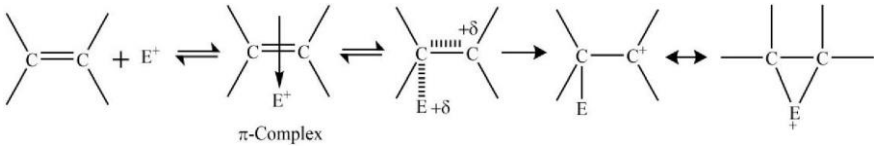
Furthermore, if the attacking electrophile is having a lone pair of electrons, which can be donated to neighboring carbon, a three-membered cyclic cation will be obtained which can be represented via three resonating structures as shown below.



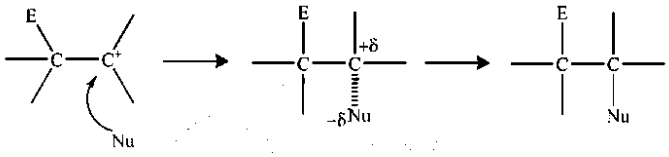
Now depending upon the relative stability of three resonating structures, the intermediatory carbocation becomes "more cyclic" or even acyclic at the extreme. In other words, the intermediate carbocation will be cyclic if structure II is more stable (and hence more contributing) and will be acyclic if the structure I and III are more stable (and hence more contributing). This cyclic (or acyclic) cation is then attacked by the nucleophilic part of the attacking reagent to give rise to the final product.

The whole process of the electrophilic attack on the carbon-carbon multiple bonds can be fragmented into two steps as shown below.

1st Step:

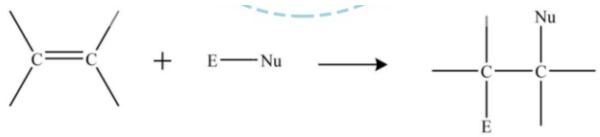


2nd Step:



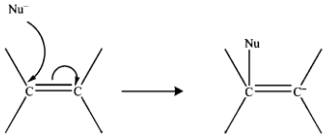
Nucleophilic addition to Carbon-Carbon Multiple bond

The nucleophilic addition in organic chemistry is an addition reaction where an organic compound with an electrophilic multiple bond reacts with an attacking nucleophile in such a way that the multiple bond is broken. It is different from the electrophilic additions because it involves the group, to which atoms are being attached, accepts electron pairs; whereas in electrophilic addition, the group, to which atoms are being attached, donates electron pairs. The reaction of nucleophilic attack on C-C multiple bonds is shown below.

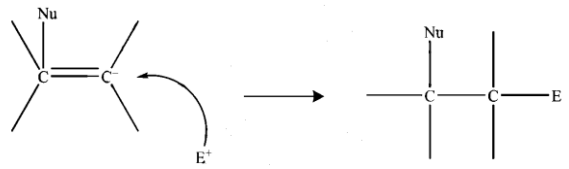


Mechanism: The mechanism of nucleophilic addition to the carbon-carbon multiple bonds follows a two-step pathway as shown below.

Step I: The driving force for the addition to the alkenes is the generation of a nucleophile X^- that creates a covalent bond with an electron-deficient unsaturated system −C=C− (first step); and the negative charge on nucleophile is shifted to the C−C bond.

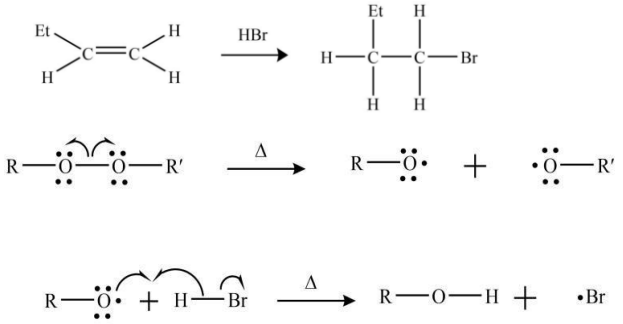


Step II: In the second step, the carbanion binds with the electrophilic part of the reagent (E^+) that is electron deficient to form another covalent bond. Simple alkenes are not vulnerable to a nucleophilic attack due to the non-polar nature of the bond.



Addition reactions involving free radicals

Besides electrophiles and nucleophiles, the reactive species that can initiate addition reactions to carbon-carbon multiple bonds are free radicals. All this started with the regioselectivity HBr additions where the product from Markonikov rule wasn't the 'major' product suggesting some other route than the normal electrophilic addition. Further research in this field showed that the reason for the anti-markonikov product is the contamination of the reactants by peroxide; which in turn initiated an entirely different pathway called the free-radical mechanism. Nevertheless, if extremely pure HBr 1-butene, 1-bromobutane (Markovnikov product) was the main yield. The reaction of nucleophilic attack on carbon-carbon multiple bonds shown below.

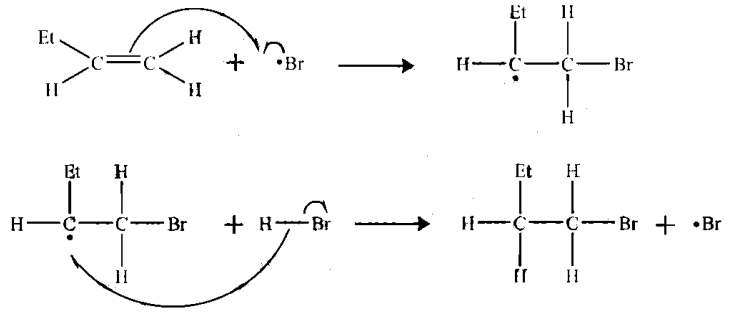


Free-radical reactions depend on a reagent having a (relatively) weak bond, allowing it to homolysis to form radicals (often with heat or light). Reagents without such a weak bond would likely proceed via a different mechanism.

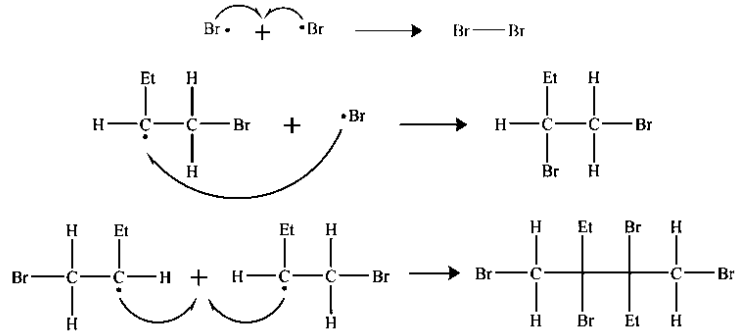
Mechanism: The mechanism of radical addition to the carbon-carbon multiple bonds follows a three-step pathway as shown below.

Initiation: In this step, a catalytic amount of organic peroxide is needed to abstract the acidic proton from HBr and generate the bromine radical.

Propagation: In this step, the radical initiated addition to carbon-carbon multiple bonds propagates via the attack of free radicals.



Termination



Reaction of alkenes with carbenes – cyclopropanation

The highly strained nature of cyclopropane compounds makes them very reactive and interesting synthetic targets. Additionally cyclopropanes are present in many biological compounds. One common method of cyclopropane synthesis is the reaction of carbenes with the double bond in alkenes or cycloalkenes. Methylene, H_2C, is the simplest carbene, and in general carbenes have the formula R_2C. Other species that will also react with alkenes to form cyclopropanes but do not follow the formula of carbenes are referred to as carbenoids.

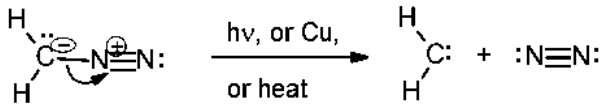
Introduction

Carbenes were once only thought of as short lived intermediates. The reactions of this section only deal with these short lived carbenes which are mostly prepared *in situ*, at the time of the main reaction. However, there do exist so called persistent carbenes, which are stabilized by a variety of methods often including aromatic rings or transition metals. In general a carbene is neutral and has six valence electrons, two of which are non bonding. These electrons can either occupy the same sp^2 hybridized orbital to form a singlet carbene (with paired electrons), or two different sp^2 orbitals to form a triplet carbene (with unpaired electrons), but we will focus exclusively on the more common singlet carbenes.

The reactivity of a singlet carbene is concerted and similar to that of electrophilic or nucleophilic addition. The highly reactive nature of carbenes leads to very fast reactions in which the rate determining step is generally carbene formation.

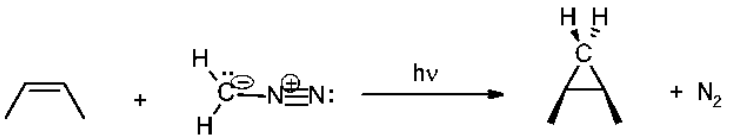
Preparation of methylene (:CH_2)

The preparation of methylene starts with the yellow gas diazomethane, CH_2N_2. Diazomethane can be exposed to light, heat or copper to facilitate the loss of nitrogen gas and the formation of the simplest carbene methylene. The process is driven by the formation of the nitrogen gas which is a very stable molecule.

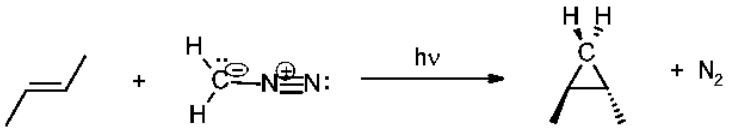


Carbene reaction with alkenes

A carbene such as methylene will react with an alkene which will break the double bond and result with a cyclopropane. The reaction will usually leave stereochemistry of the double bond unchanged. As stated before, carbenes are generally formed during the reaction; hence the starting material is diazomethane not methylene.

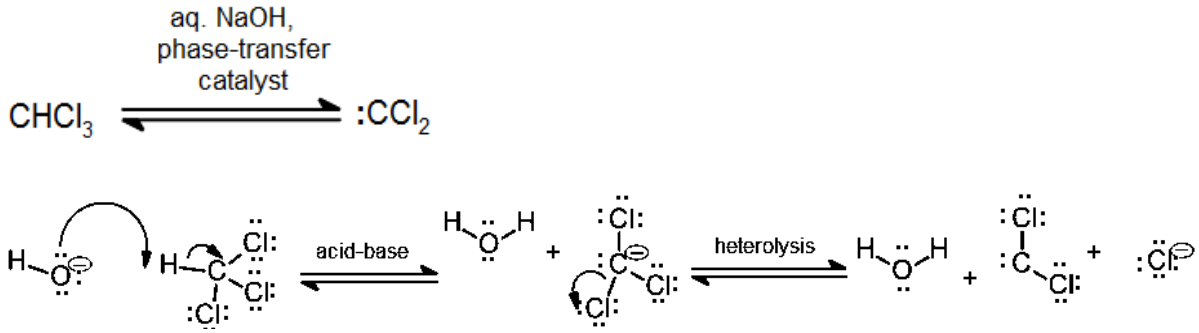


In the above case *cis*-2-butene is converted to *cis*-1,2-dimethylcyclopropane. Likewise, below the *trans* configuration is maintained.



Other carbenes

In addition to the general carbene with formula R_2C: there exist a number of other compounds that behave in much the same way as carbenes in the synthesis of cyclopropane derivatives. **Halogenated carbenes** such as dichlorocarbene, Cl_2C:, are more stable than simple alkyl carbenes. Dichlorocarbene can be conveniently prepared from chloroform ($CHCl_3$) with base in the presence of a phase transfer catalyst:



Regioselectivity chemoselectivity reactivity and orientation of addition reaction

Reactivity

The case of electrophilic addition reactions:

As in electrophilic aromatic substitution electron-donating groups increase the reactivity of a double bond toward electrophilic addition and electron- withdrawing groups decrease it. Similarly the reactivity toward electrophilic addition of a group of alkenes increased in the order.

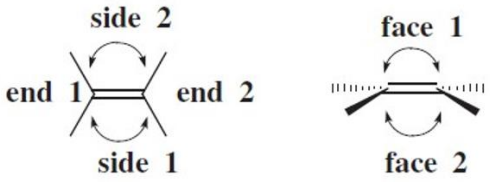
$CCl_3CH=CH_2 < Cl_2CHCH=CH_2 < ClCH_2CH=CH_2 < CH_3CH_2=CH_2$

The case of nucleophilic addition reactions

For nucleophilic addition the situation is reversed. These reactions are best carried out on substrates containing three or four electron-withdrawing groups, two of the most common being $F_2C=C_F2$ and $(NC)_2C=C(CN)_2$. The effect of substituents is so great that it is possible to make the statement that simple alkenes do not react by the nucleophilic mechanism, and polyhalo or polycyano alkenes do not generally react by the electrophilic mechanism

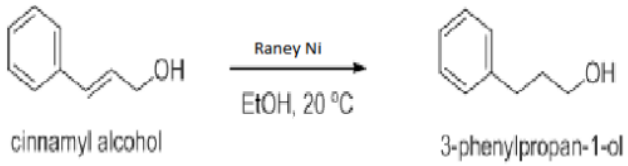
Orientation

When an unsymmetrical reagent is added to an unsymmetrical substrate, the question arises: Which side of the reagent goes to which side of the double or triple bond?

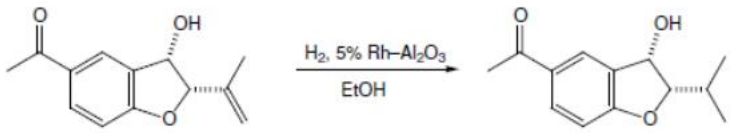


Hydrogenation of double bonds

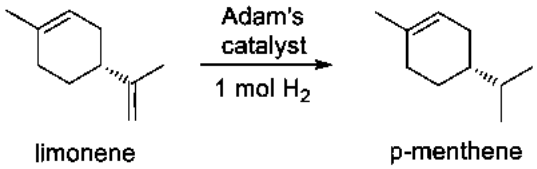
Hydrogenation of alkenes takes place easily and in most cases can be effected under mild conditions. However, as hydrogenation is sensitive to steric hindrance, highly hindered alkenes are resistant to hydrogenation, but even these can generally be hydrogenated under more vigorous conditions. Pd and Pt are the most frequently used catalysts. Both are very active and their use depends upon the type of substrate and degree of selectivity required. In general, Pt is more active than Pd-catalysts.



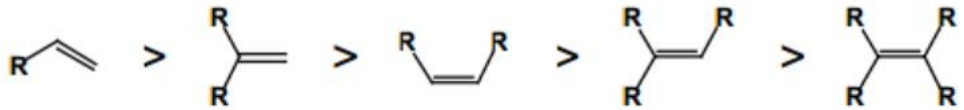
Other catalysts that can be used are Raney-Nickel (only in some cases as it is highly reactive) and Rhodium and Ruthenium catalysts. Rh and Ru catalysts sometimes show useful selectivity. For example, in the reaction shown below, rhodium allows hydrogenation of alkenes without affecting the hydrogenolysis of the ether (an oxygen functional group).



The degree of substitution of the double bond decreases the ease of reduction of an alkene, and this sometimes selectively reduce one double bond over other in a molecule with more than one double bond. Out of the exocyclic and endocyclic double bonds, exocyclic double bonds are easier to be reduced. For example, limonene can be converted into p-menthene by hydrogenation over Adam's catalyst if the reaction is stopped after absorption of one molar equivalent of hydrogen.

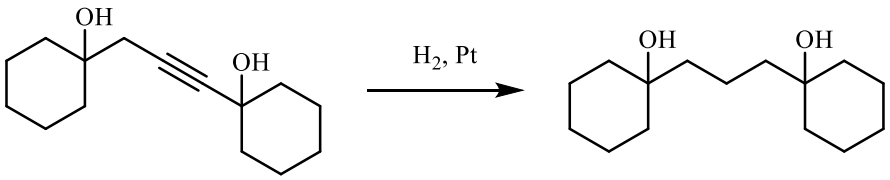


Order of reactivity of various alkenes

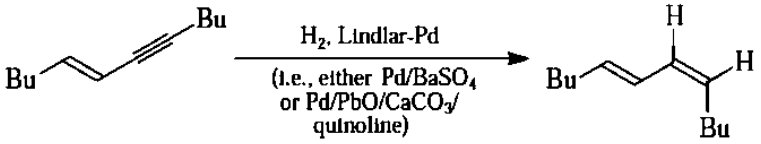


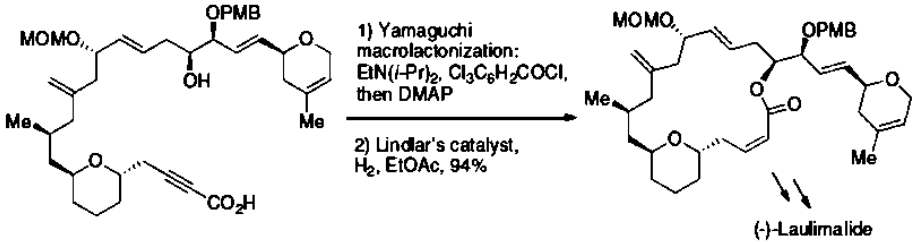
Hydrogenation of Triple bonds

Alkynes are catalytically hydrogenated to alkene and further to alkane in a step-wise manner as discussed earlier. Both alkene and alkane may be isolated. For complete conversion of alkyne to alkane, Pt, Pd catalysts or Raney-Nickel are used. However, if a propargylic alcohol group is present, it may occasionally undergo hydrogenolysis, especially when Pt-catalysts are used.



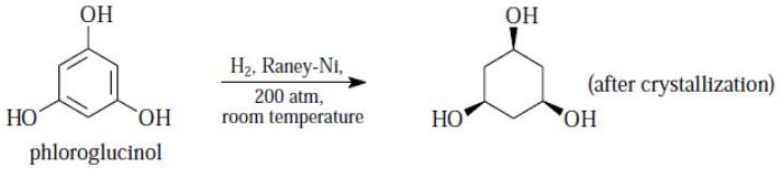
As mentioned earlier, it is possible to partially hydrogenate alkynes to alkenes by the use of catalyst poisons. The use of Lindlar's catalyst to get Z-alkenes is a most important example of such transformation. More electrophilic alkynes absorb more strongly on the electron-rich catalyst surface than the corresponding alkenes, aids such partial hydrogenations. However, when using Lindlar's catalyst, it is important to prevent over-hydrogenation by carefully monitoring the reaction conditions and limiting the hydrogen consumption to around 1 mol. Such selective hydrogenation to Z-alkenes has found significant use in the synthesis of natural products and some pharmaceutically important intermediates.



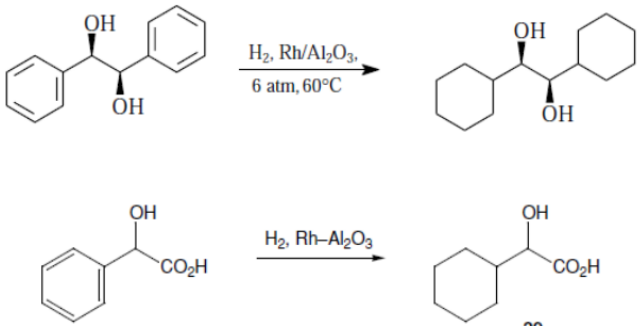


Hydrogenation of aromatic rings

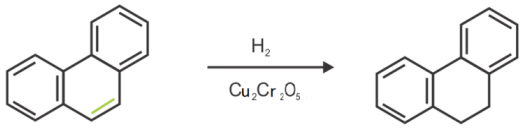
Aromatic rings are among the hardest to be hydrogenated and even with precious metal catalysts, require higher temperatures and pressures. But, once a benzene ring starts to hydrogenate, there is nothing like partial hydrogenation, and it hydrogenates to cyclohexane. This is because when benzene has been converted to cyclohexadiene (the first hydrogenation and the hardest, endothermic step), it is associated with the loss of resonance energy and the subsequent hydrogenations are exothermic and faster than the first one.



Pt and Rh catalysts are common and used at ordinary temperatures whereas Raney-Nickel or Rucatalysts require higher temperatures and pressures and Raney-Nickel is used for large scale hydrogenations involving heating at 150 ^{O}C at high pressures (100-200 atm). Rh over Alumina is another prominent catalyst used and requires milder conditions than others. Also, it does not cause hydrogenolysis of the sensitive C—O bonds present in the molecule.



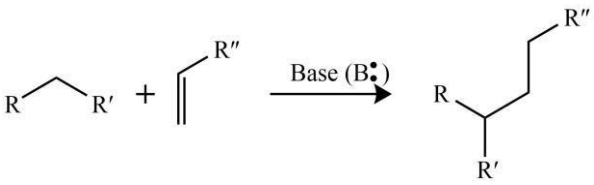
Hydrogenation of polycyclic aromatic rings such as naphthalenes and phenanthrenes are also performed and by varying the reaction conditions, partially hydrogenated or fully hydrogenated products may be obtained. For example, Raney-Nickel may be used to obtain tetrahydro or decahydro-naphthalene by varying the reaction conditions. Similarly, 9,10-dihydro phenathrenes or anthracenes can be obtained by reduction over copper-chromite and to fully reduce them, more active catalysts are required.



Michael Addition

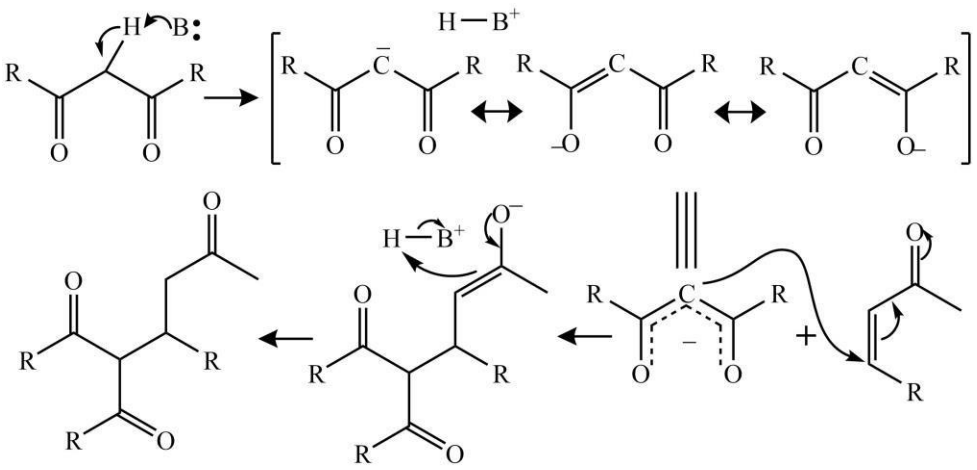
The Michael addition (or Michael reaction) may simply be defined as the addition of a nucleophile like a carbanion to an α, β-unsaturated carbonyl compound with an electron-withdrawing group. It is a type of conjugated addition, and this process is one of the most practical approaches for the formation of C-C bonds.

Illustrative Reaction: The typical organic reaction showing this type of addition is shown below.



Where R and R' on thenucleophile symbolizethe electron-withdrawing groups such ascyano and acyl, making the nearby methylene H enough acidic to give rise to a carbanion when treated with a base (B). The R" group on the activated olefin (Michael acceptor) is generally a ketone to makes the molecule an enone; nevertheless, it can also be a sulfonyl fluoride or nitro group.

Mechanism Involved: In the first step, the carbanion is formed due to the deprotonation of the substates, which isstabilized byelectron-withdrawinggroups.Threeresonating structures(2A, 2B, and2C)can bedrawn for this hybrid species with two enolate ion types. The electrophilic alkene reacts with this nucleophile via conjugated addition mode. Finally, the abstraction of a proton by the enolate from solvent (or protonated base) gives rise to the final product.



It is also worthy to note that the Michael addition is primarily dominated by the orbital picture rather than the electrostatic interactions. The lowest unoccupied molecular orbital (LUMO) of α-, β- unsaturated carbonyl systems have a hefty magnitude of the coefficient for β-carbon, whereas the HOMO of resonance stabilized enolates have a large magnitude of the coefficient for carbon. Therefore, owing to the similar-energy polarized frontier orbitals and softens, they are suitable for generating a good C–C bond.

Applications

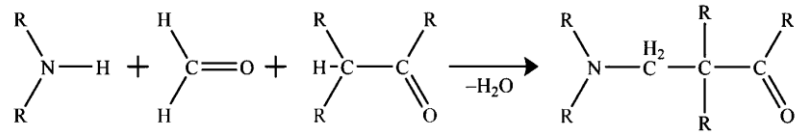
- It is used as inhibitor drugs, cancer drugs such as Ibrutinib and Rociletinib have an acrylamide functional groups as a michael acceptor.it is an active site of an enzyme.
- Towards the total synthesis of brevetoxinA, Azaspiracid, Cortistain A, (+)-conical, Aspergilide A and B, Indoxamycin etc.

(b) Addition to carbon-hetero atom multiple bonds

Mannich Condensation

The Mannich condensation may simply be defined as an organic chemical transformation where a carbonyl functional group's neighboring proton (acidic in nature) undergoes amino alkylation by formaldehyde and ammonia (or a secondary, or primary amine), giving rise to a β-amino-carbonyl compound called Mannich base.

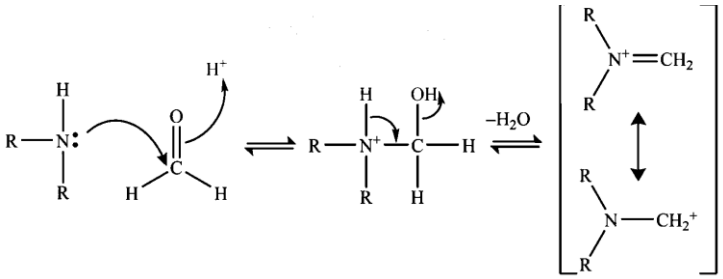
This reaction was invented by an eminent German chemist Carl Mannich in 1912; and therefore, is also named after him



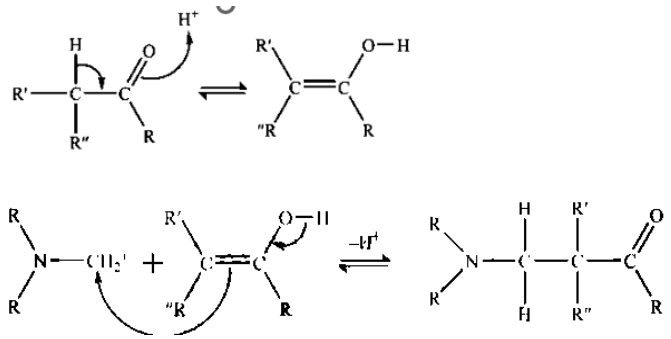
The Mannich condensation is a case of nucleophilic addition of an anime to carbonyl group trailed by the dehydration to yield a Schiff base, which in turn, reacts in an electrophilic addition mode with a compound acidic hydrogen (next step).

Mechanism of Mannich reaction:

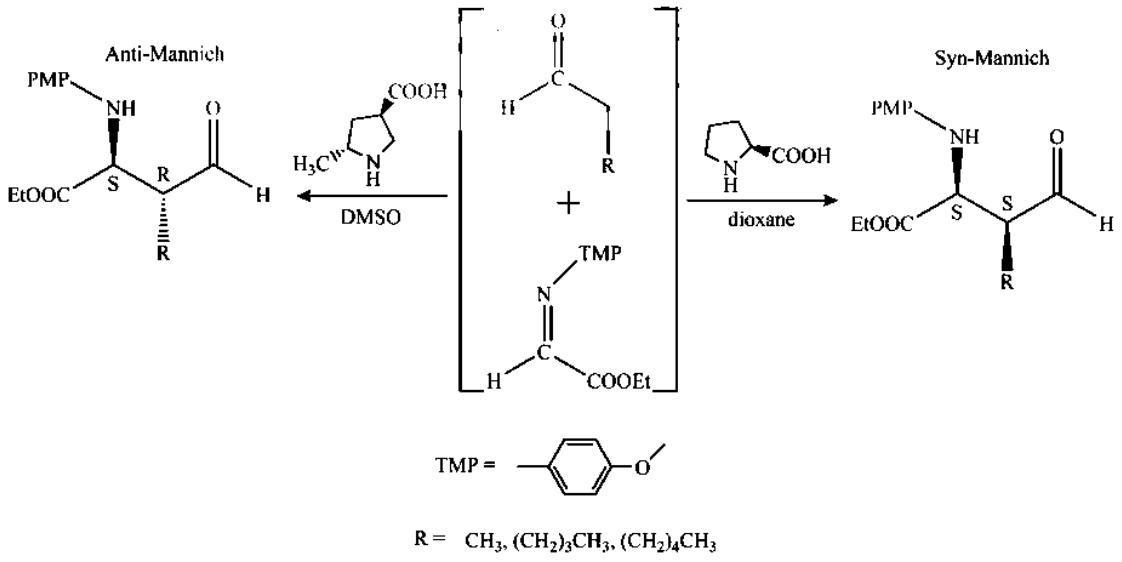
The Mannich condensation's mechanism begins with the generation of an iminium ion from the formaldehyde and the amine used. The protonated oxygen is highly acidic with a pKa value of -2. The reaction will be stopped when the carbonyl gets deprotonated by amine base; and therefore, it is necessary to perform at a pH of about 5. Hence, the right pathway should begin with a nucleophilic attack at carbonyl's carbon by the nitrogen atom.



The carbonyl compound like ketone will undergo tautomerization to yield enol form, which can attack the iminium ion afterward. It is also important to note that the enolization and Mannich addition can occur twice with methyl ketones, trailed by an β-elimination to give rise to β-amino enones.



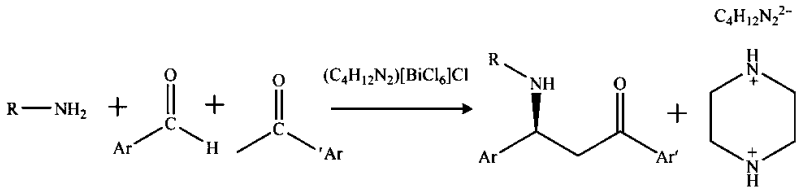
Stereochemistry of Mannich condensation: Asymmetric Mannich reactions have also been studied in the recent era. It has been observed that if two prochiral centers are present in an appropriately functionalized ethylene bridge of Mannich adduct, two diastereomeric pairs of enantiomers are obtained. One of the most commonly reported examples (also first) of asymmetric Mannich reaction was performed using (S)-proline as a naturally occurring chiral catalyst.



R = CH_3, $(CH_2)_3CH_3$, $(CH_2)_4CH_3$

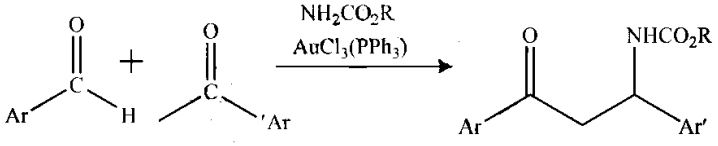
Examples of Mannich condensation: Some of the most common examples of organic chemical transformation Mannich condensation are given below.

1. The reaction between aniline, benzaldehyde, and an aromatic ketone.



R = Ar, Bu

2. The reaction between amide, benzaldehyde, and an aromatic ketone.



R = Et, Bn

Applications of Mannich condensation:

Some of the most common applications of organic chemical transformation involving Mannich condensation are given below.

1. The Mannich condensation is used in the synthesis of peptides, alkyl amines, antibiotics, nucleotides, alkaloids like tropinone, and many important agrochemicals.

2. Mnay polymers, Formaldehyde tissue crosslinking, catalysts, Pharmaceutical drugs like rolitetracycline (fluoxetine (antidepressant), tolmetin (anti-inflammatory drug), and tramadol are formed via Mannich condensation.

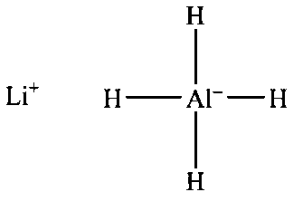
3. Many detergents and soaps are synathesized via Mannich condensation which find applications in cleaning industry, epoxy coatings, and automotive fuel treatments.

4. The thermal decay of Mannich reaction products gives rise to α, β-unsaturated ketones by (e.g. methyl vinyl ketone through 1-diethylamino-butan-3-one).

Metal hydride reduction of acids

Many metal hydrides can be used to reduce the saturated and unsaturated carbonyl compounds like carboxylic acid.

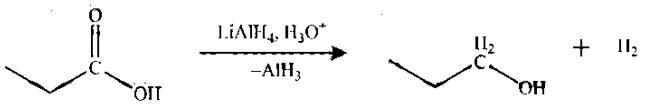
1. Reduction by lithium aluminium hydride: The lithium aluminium hydride (LiAlH4) is one of the most common sources of the hydride nucleophile. The hydride anion is produced in the course of reaction because of the polar nature of the metal-hydrogen bond.



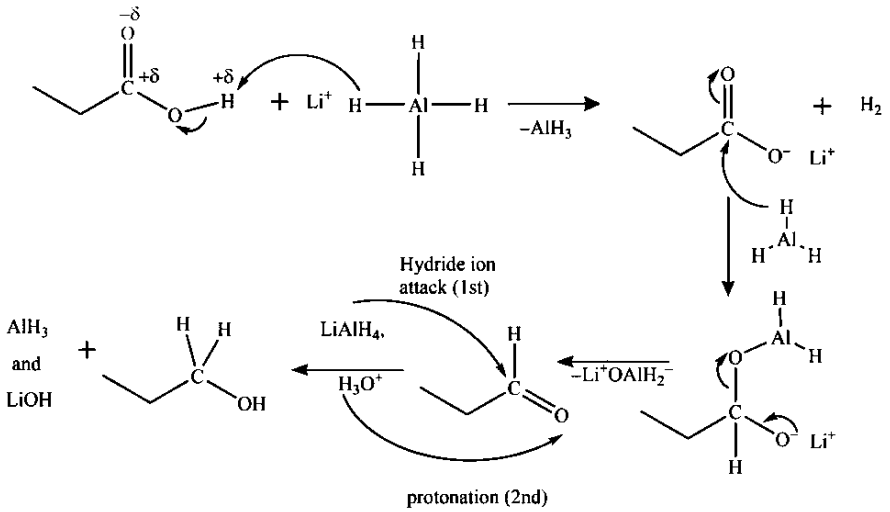
Lithium aluminium hydride

The hydride anion's addition to carbonyl compound results in an alkoxide anion which in turn gives rise to a reduced product.

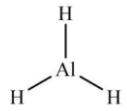
The hydride anion's attack on carboxylic acid results in a carboxylate anion, which in turn, is attacked by AlH_3 to yield aldehyde. This aldehyde then gives rise to primary (1°) alcohols after 1, 2-addition.



The mechanism for the carboxylic acid's reduction by metal hydride (by LiAlH4 in this case) to give primary alcohols is given below.



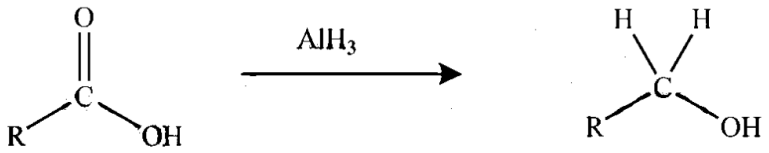
Reduction by aluminium hydride: The aluminum hydride, i.e., AlH_3, is one of the most common types of electrophilic addition for the reduction of carboxylic acid because simple borohydride cannot reduce carboxylic acids.



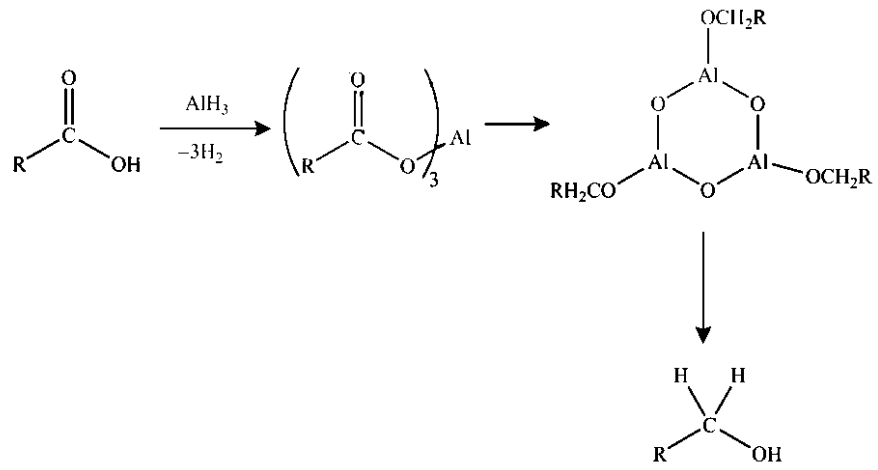
Aluminium hydride

In some cases, the reactivity of aluminium hydride is like lithium aluminium hydride; whereas sometimes it acts as borane (BH_3).

The hydride anion's addition to carboxylic acid results in a complex series of transition states which in turn gives rise to primary (1°) alcohols on protonation.



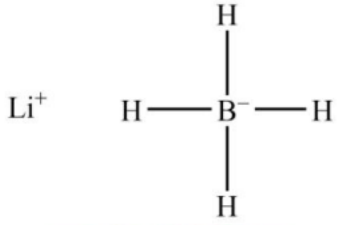
The mechanism responsible for the reduction of carboxylic acids by aluminium hydride involves the following steps.



Metal Hydride reduction of esters

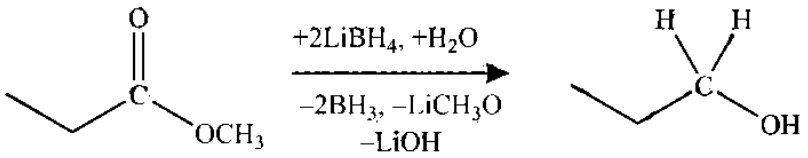
Metal hydrides like lithium borohydride and lithium aluminium hydride can be used to reduce the carbonyl compounds like esters.

1. Reduction by lithium Borohydride: The lithium borohydride ($LiBH_4$) is one of the most common sources of the hydride nucleophile. The hydride anion is produced during reaction because of the polar nature of the metal-hydrogen bond.

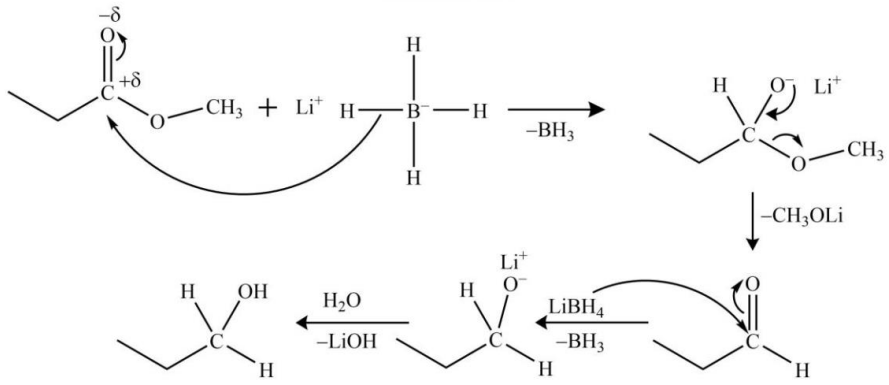


The hydride anion's addition to carbonyl compound results in an alkoxide anion which in turn gives rise to the reduced product.

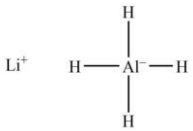
Two subsequent hydride anions' additions to ester result in an alkoxide anion which in turn gives rise to primary (1°) alcohols on protonation.



The mechanism for the ester reduction by metal hydride ($LiBH_4$ in this case) that involves the nucleophilic addition of the hydride ion to the carbonyl carbon is given below.



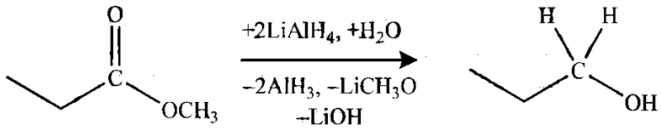
Reduction by Lithium aluminium hydride: The lithium aluminium hydride (LiAlH4) is one of the most common sources of the hydride nucleophile. The hydride anion is produced during reaction because of the polar nature of the metal-hydrogen bond.



Lithium aluminium hydride

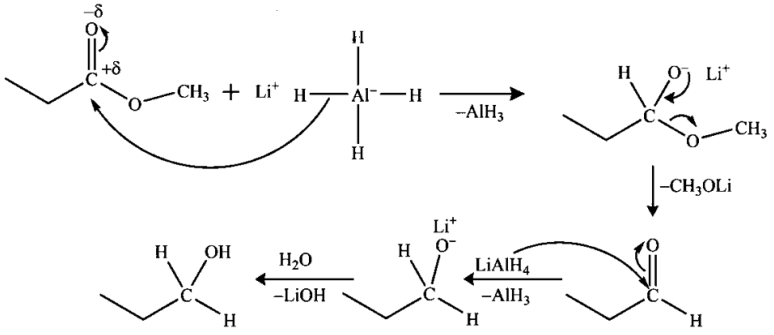
The hydride anion's addition to carbonyl compound results in an alkoxide anion which in turn gives rise to the reduced product.

Two subsequent hydride anions' additions to ester result in an alkoxide anion which in turn gives rise to primary (1°) alcohols on protonation.



The mechanism for the ester reduction by metal hydride ($LiAlH_4$ in this case) that involves the nucleophilic addition of the hydride ion to the carbonyl carbon is given below.

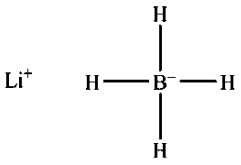
The mechanism for the ester reduction by metal hydride ($LiAlH_4$ in this case) that involves the nucleophilic addition of the hydride ion to the carbonyl carbon is given below.



Metal Hydride Reduction of Nitriles

The nitriles' reduction may simply be defined as the chemical transformation in which a nitrile is reduced to either an aldehyde or an amine by the use of a suitable reagent. Many metal hydrides can be used to reduce the nitrile compounds to amines but LiBH4 and LiAlH4 are most common.

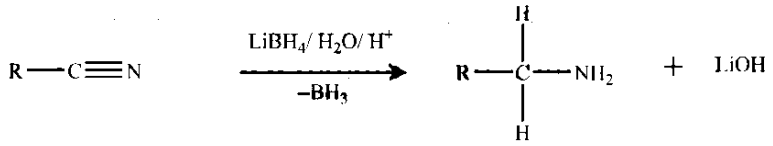
1. Reduction by lithium borohydride: The lithium borohydride (LiBH4) is one of the most common sources of the hydride nucleophile. The hydride anion is produced during the reaction because of the polar nature of the metal-hydrogen bond.



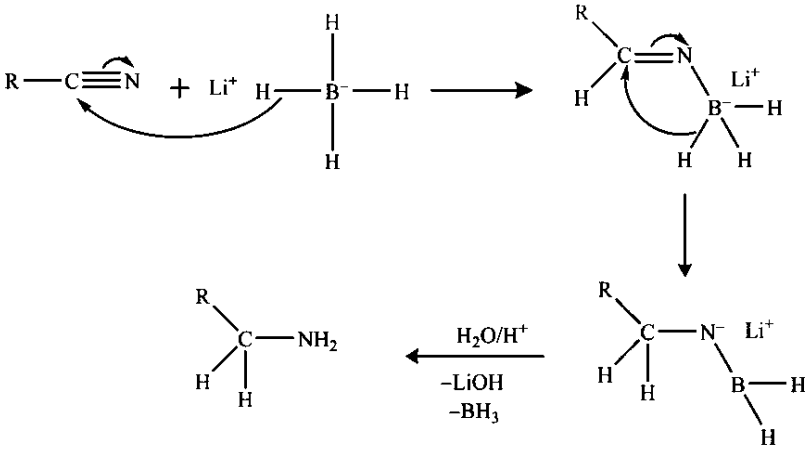
Lithium borohydride

The hydride anion's addition to nitrile compounds results in an anion which in turn gives rise to a reduced product.

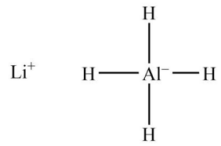
Two subsequent additions of hydride anions to the carbon-nitrogen bond result in a lithium salt which in turn gives rise to primary (1°) amines on protonation.



The mechanism for the nitriles' reduction by metal hydride ($LiBH_4$ in this case) that involves the nucleophilic addition of the hydride ion to the carbon-nitrogen bond is given below.



Reduction by Lithium aluminium hydride: The lithium aluminium hydride (LiAlH4) is one of the most common sources of the hydride nucleophile. The hydride anion is produced during reaction because of the polar nature of the metal-hydrogen bond.



Lithium aluminium hydride

The hydride anion's addition to nitrile compounds results in an anion which in turn gives rise to a reduced product.

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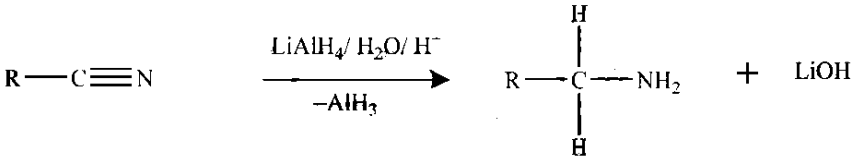

The mechanism for the nitriles' reduction by metal hydride ($LiAlH_4$ in this case) that involves the nucleophilic addition of the hydride ion to the carbon-nitrogen bond is given below.

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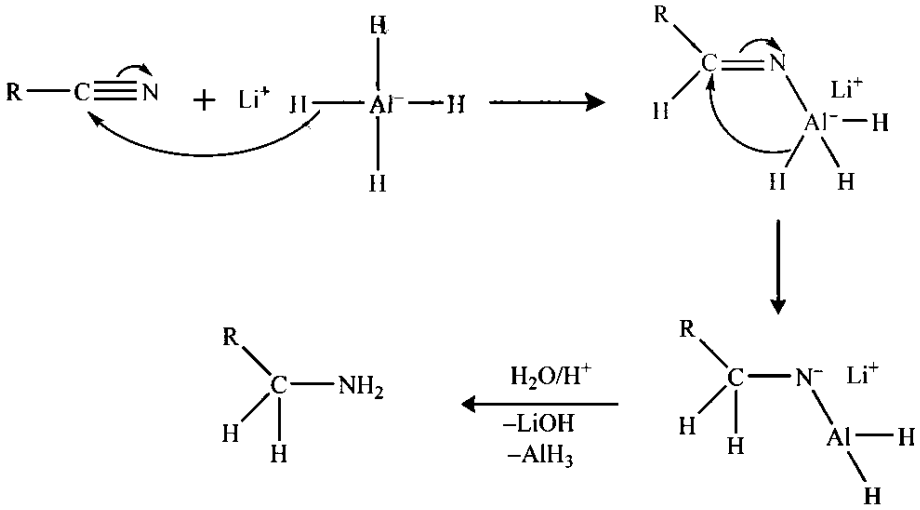


Addition of Grignard reagents :

A Grignard reagent is an organo magnesium compound which can be described by the ***chemical formula 'R-Mg-X'*** where R refers to an alkyl or aryl group and X refers to a halogen.

They are generally produced by reacting an aryl halide or an alkyl halide with magnesium.

These reagents were discovered by the **French chemist Victor Grignard**, who won the Nobel Prize in Chemistry in the year 1912 for his work on these compounds.

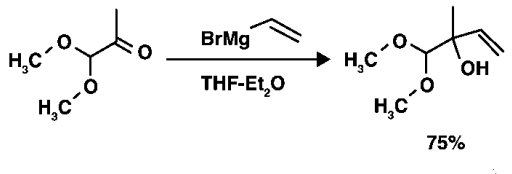
Reactions of Grignard Reagents

During a reaction involving Grignard reagents, it is necessary to ensure that no water is present which would otherwise cause the reagent to decompose rapidly. Therefore, the majority of Grignard reactions occur in solvents such as anhydrous diethyl ether or tetrahydrofuran because the oxygen in these solvents stabilizes the magnesium reagent.

Grignard reagents are very important reagents in organic chemistry since they can be reacted with a wide range of compounds to form different products. Some of the reactions of these reagents are listed below.

1. Reactions with Carbonyl Group

These reagents form various products when reacted with different carbonyl compounds. The most common reaction of Grignard reagents is the alkylation of ketones and aldehydes with the help of R-Mg-X.



This reaction depicted above is also referred to as the Grignard reaction. The solvents that are used in this reaction include tetrahydrofuran and diethyl ether.

2. Reactions with Non-Carbon Electrophiles

For the ***formation of new carbon-heteroatom bonds, Grignard reagents and some organolithium compounds are very useful.*** These reagents can also undergo a transmetallation reaction with cadmium chloride, yielding dialkyl cadmium. This reaction can be written as follows.

$2R\text{-}Mg\text{-}X + CdCl_2 \rightarrow R_2Cd + 2Mg(X)Cl$

Alkyl chains can be attached to many metals and metalloids with the help of these reagents.

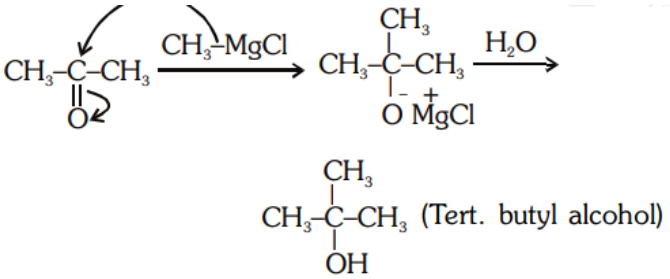
3. Reactions with Organic Halides

Typically, these reagents are quite unreactive towards organic halides which highly contrasts their behaviour towards other halides. However, carbon-carbon coupling reactions occur with Grignard reagents acting as a reactant when a metal catalyst is introduced.

An example of such a coupling reaction is the reaction between methyl p-chlorobenzoate and nonyl magnesium bromide which yields the compound p-nonyl benzoic acid in the presence of the catalyst – Tris(acetylaceto) iron(III).

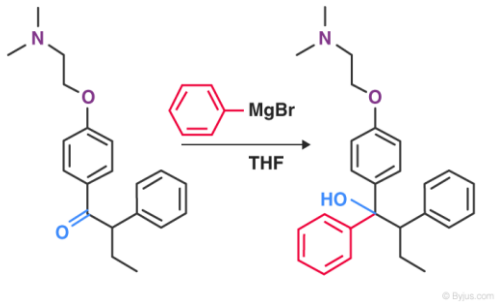
4. Reaction between Acetone and Methyl Magnesium Chloride

The reaction of methyl magnesium bromide with acetone followed by hydrolysis gives tertiary alcohol. Acetone reacts with methyl magnesium bromide followed by hydrolysis to give secondary alcohols.



5. Industrial Reactions

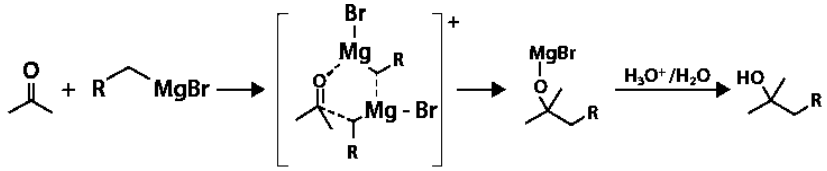
For the production of Tamoxifen, a type of medication used to prevent and treat breast cancer, the Grignard reagent is a vital part of the non-stereoselective process.



An illustration detailing the Grignard reaction that takes place in the manufacturing process of tamoxifen can be found above.

Grignard Reaction Mechanism

The synthesized Grignard reagent is highly nucleophilic as discussed earlier. This reagent attacks the electrophilic carbon in the polar bond of the carbonyl group. The mechanism of this Grignard reaction proceeds through a six-membered ring transition state, as shown below:



Other reactions of Grignard reagents may proceed through a single electron transfer process. Some of these processes involve the formation of a carbon-phosphorus bond, carbon-silicon bond, and carbon-boron bond. In a rate-controlling step, the grignard reagent coordinates with the ketone on the simultaneous displacement of an ether molecule of solvation. This is followed by a rapid reaction with a second monomeric Grignard reagent to form alcohol via a six membered transition state. It has been proposed that the reaction can proceed with RMgX, RMg or both of these organometallic compounds.

Barbier Reaction :

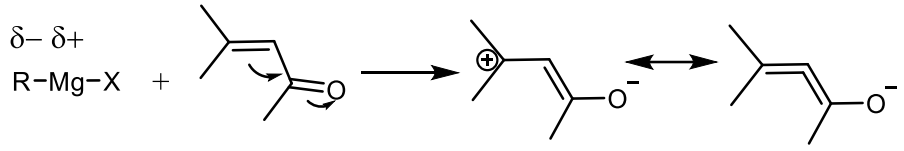
The **Barbier reaction** is an organometallic reaction between an alkyl halide (chloride, bromide, iodide), a carbonyl group and a metal.

- The reaction can be performed using magnesium, aluminium, zinc, indium, tin, samarium, barium or their salts.
- The reaction product is a primary, secondary or tertiary alcohol.
- The reaction is similar to the Grignard reaction but the crucial difference is that the organometallic species in the Barbier reaction is generated in situ, whereas a Grignard reagent is prepared separately before addition of the carbonyl compound.
- Unlike many Grignard reagents, the organometallic species generated in a Barbier reaction are unstable and thus cannot be stored or sold commercially.
- Barbier reactions are nucleophilic addition reactions that involve relatively inexpensive, water insensitive metals (e.g zinc powder) or metal compounds.
- For this reason, it is possible in many cases to run the reaction in water, making the procedure part of green chemistry.

- In contrast, Grignard reagents and organolithium reagents are highly moisture sensitive and must be used under an inert atmosphere without the presence of water.
- The Barbier reaction is named after Philippe Barbier, who was Victor Grignard's teacher.

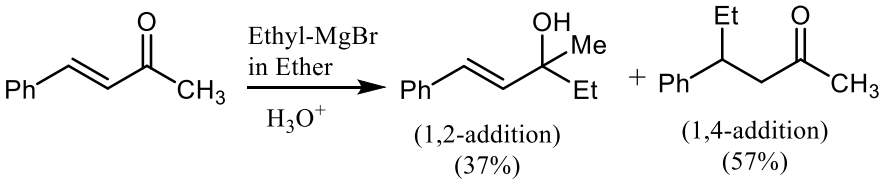
Addition of α ,β − unsaturated compound

Grignard reaction usually prefers 1,2-addition but in some cases 1,4-addition ,1,6-addition also takes place .

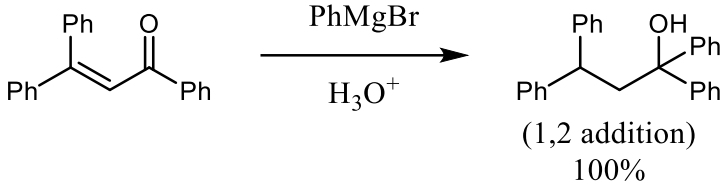


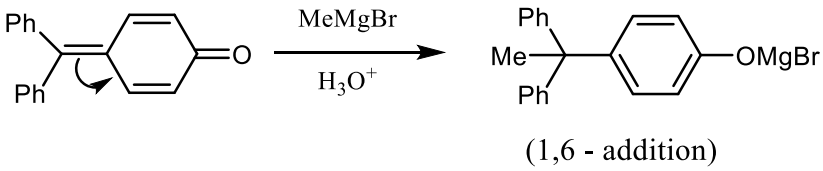
Usually Grignard id hard .α is attached to electro negative oxygen ,so it harder. β is far apart from the oxygen so it is softer electrophilic center .

Some examples for exceptional cases :



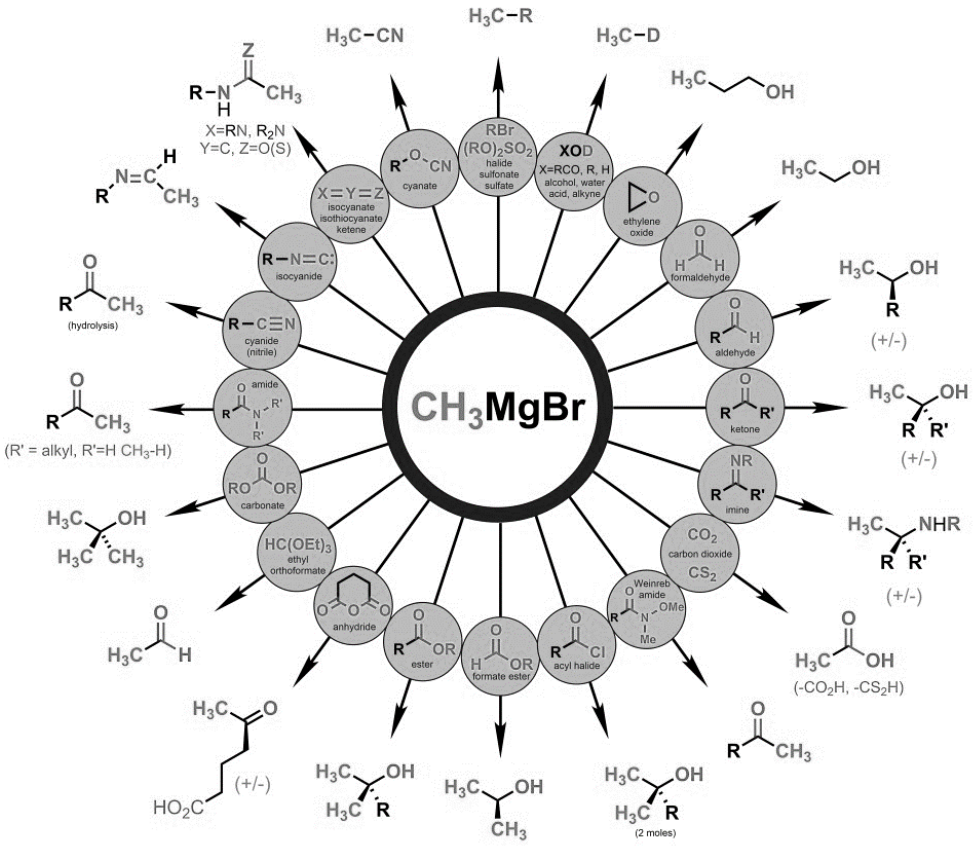
Here addition on aldehyde is favored over ketones because ketone is more crowded and bulky





Here resonance takes place to maintain aromaticity and 1,6 -addition takes place

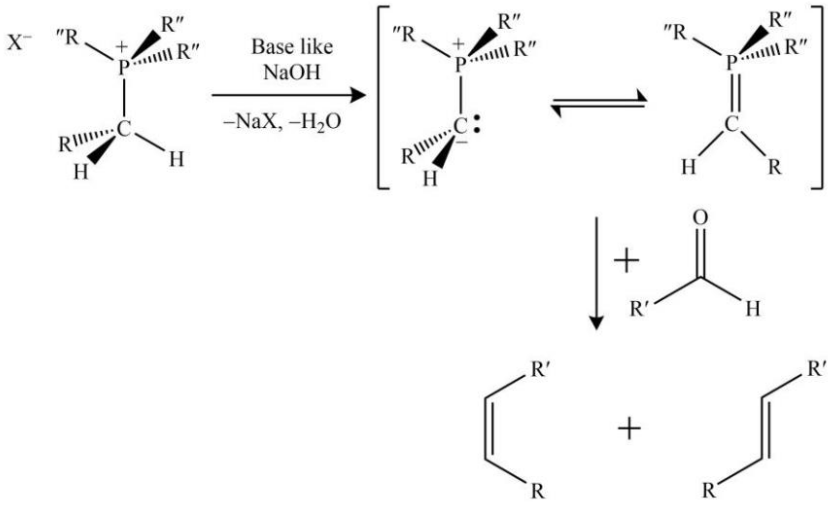
Applications:



Wittig Reaction

The Wittig olefination (or Wittig reaction) may simply be defined as a chemical transformation where a ketone or aldehyde reacts with a triphenyl phosphonium ylide (Wittig reagent).

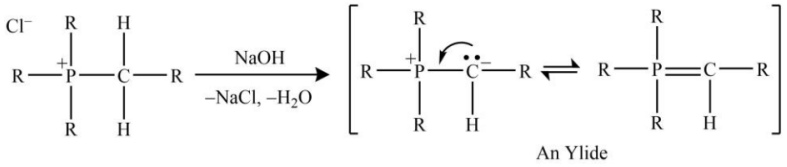
The conversion of aldehydes and ketones to alkenes is one of the most common uses of Wittig reactions. Usually, the Wittig reaction is employed to add a methylene group using Ph3P=CH2 (methylenetriphenylphosphorane or Wittig reagent). The importance of Wittig reaction can be imagined by the fact that George Wittig, who invented this reaction, was awarded the Nobel prize in 1979 for the same work.



With help of Wittig reagent, a camphor-like ketone, which has a very much sterically hindered carbon, can also be transformed into its methylene derivative. Now before we proceed further to study different aspects of Wittig reaction, we need to first know what a Wittig reagent actually is and how does it behave around different kinds of substrates.

The Wittig Reagent (An Organophospborus Ylide)

The Wittig reagent is a ylide, and a ylide may be defined as a compound with opposite charges on adjacent atoms both of which have complete octets. These ylides are obtained as the zwitterionic conjugate bases of the cationic part of phosphonium salts.



An Ylide

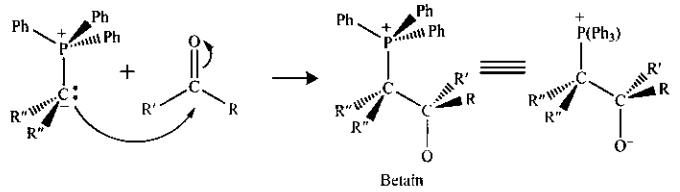
Since these ylides are stabilized by $p\pi$-$d\pi$ bonding, the carbanions adjacent to the phosphonium centers also get stability benefits from the same. It is also obvious that the phosphorus's ability to hold more than eight valence electrons permits for a resonance structure with double-bonded; and therefore, enhances the stability.

Mechanism of Wittig Reaction

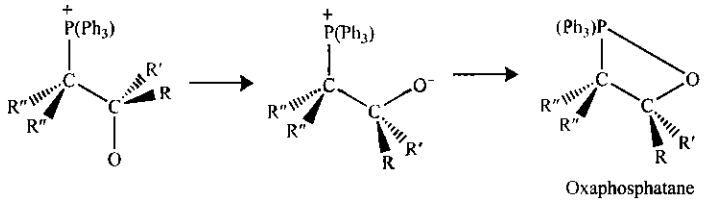
The NMR studies have confirmed the formation of two intermediates after the generation of the first carbon-carbon bond during the Wittig reaction, the betaine (a dipolar species) and oxaphosphatane (a four- membered heterocyclic structure). The final product will be obtained by the cleavage of oxaphosphatane to alkene and phosphine oxide which is irreversible and

exothermic in nature. Precisely, the mechanism can primarily be divided into three steps as given below.

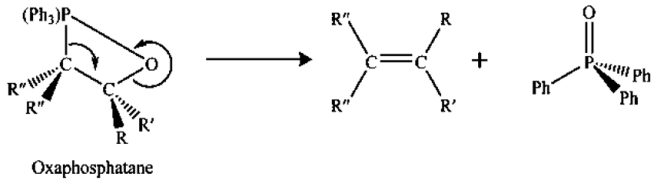
1. Nucleophilic attack on the carbonyl:



2. Formation of four-membered ring:

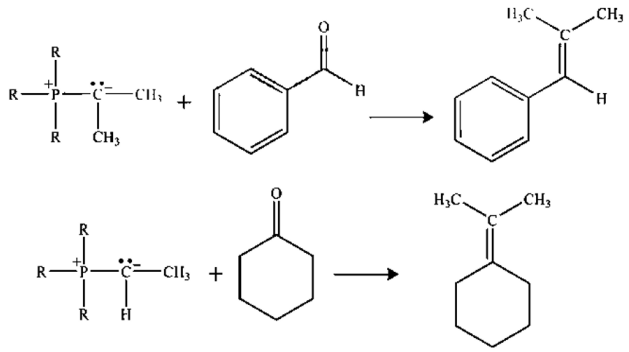


3. Generation of the alkene:



A major benefit of the alkene synthesis via Wittig's route is that, unlike alcohol dehydration, the site of the double bond is fixed absolutely.

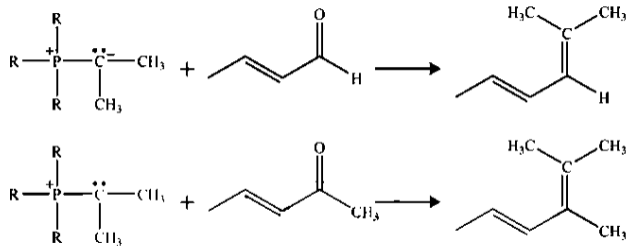
Examples:



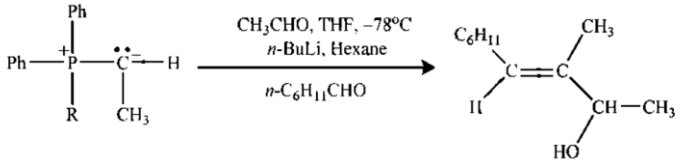
It has been observed that the Wittig reagents usually tolerate carbonyl compounds with numerous types of functional groups like OH, OR, epoxide, aromatic nitro, and ester groups.

Applications

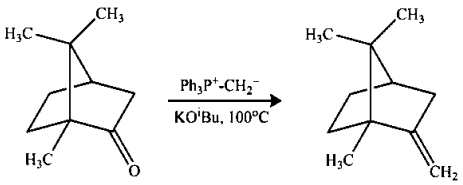
1. The conversion of aldehydes and ketones to alkenes is one the most common uses of wittig reactions.



2. The Schlosser modification Wittig reaction can be used to get allylic alcohols by the reaction of the betaine ylide with a secondary aldehyde.



3. Even a sterically hindered ketone such as camphor can be converted to its methylene derivate.



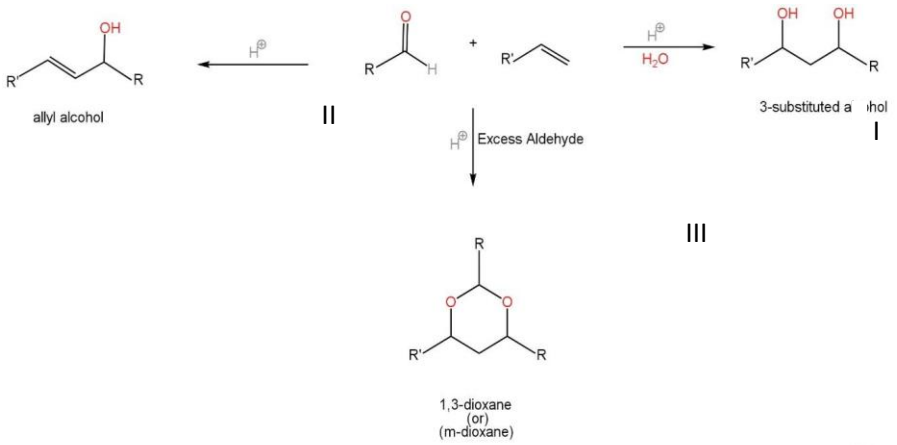
Prins Reaction

The Prins reaction is an electrophilic addition of an aldehyde or ketone to an alkene or alkyne followed by capture of a nucleophile. The outcome (product) of the reaction depends on reaction conditions.

i. With water and a protic acid such as sulfuric acid as the reaction medium and formaldehyde the reaction product is a 1,3-diol (or) 3-substituted alcohol.

ii. When water is absent dehydration takes place to an allyl alcohol.

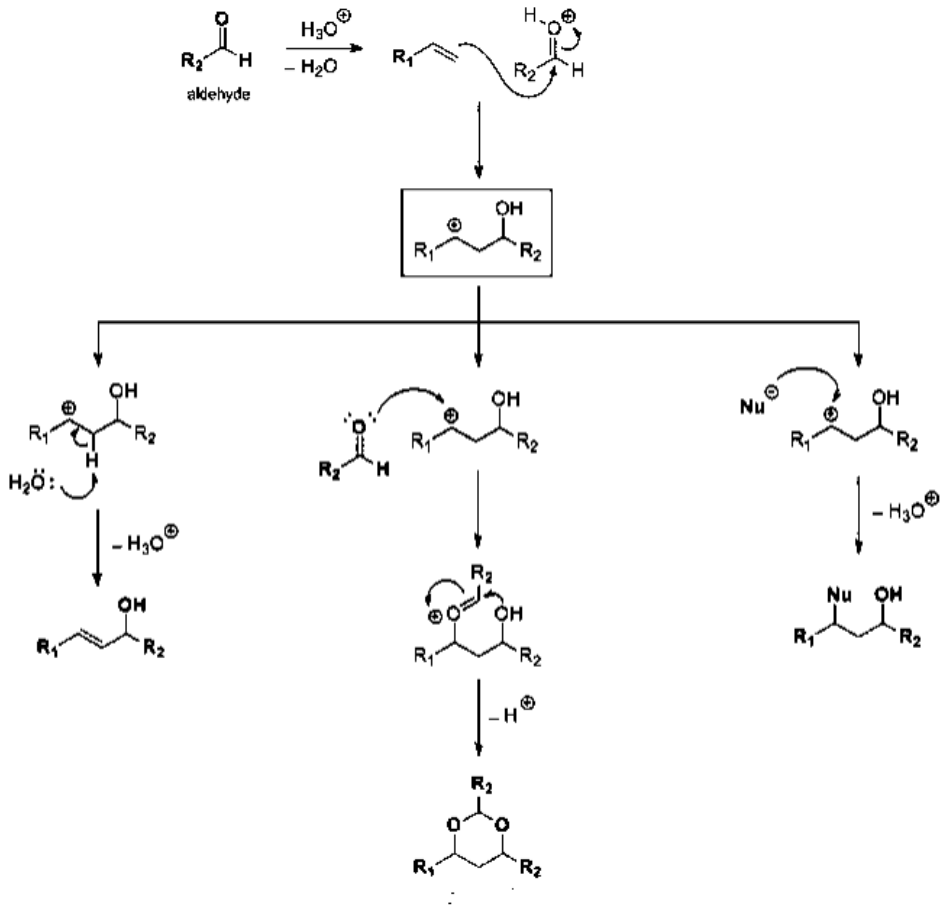
iii. With an excess of formaldehyde and a low reaction temperature the reaction product is a dioxane.



Over all Mechanism

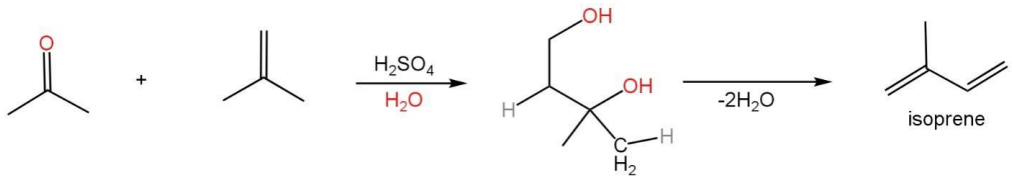
- The carbonyl reactant is activated by protonation.
- The resulting oxonium ion undergoes electrophilic addition with the alkene.
- The carbocationic intermediate is then captured by water or any suitable nucleophile or undergoes proton abstraction in an elimination reaction.

Mechanism



Application

- By using prins reaction we can obtain allyl alcohols, dioxanes and 3-susbstituted alcohols can be obtained.
- It is used in rubber industries to synthesis isoprene formaldehyde and 2-methyl propene.



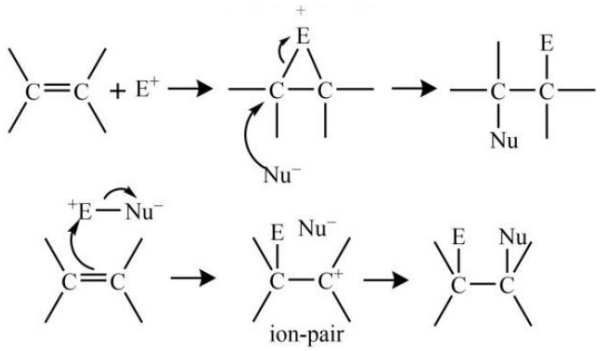
Stereochemistry of addition reactions

Stereochemistry: The stereochemistry of electrophilic addition to carbon-carbon multiple bonds is affected by two primary factors as discussed below.

i) The electrophile can attach itself to the double bond on the same or different side of the nucleophile i.e., syn- or anti-additions, respectively.

ii) In addition to the geometrical profile of addendum E^+ and Nu^-, the stereochemistry of the final product is also decided by the configuration of the addition product i.e., the orientation w.r.t rest of the molecule.

In other words, the electrophilic addition at the carbon-carbon multiple bonds can be cis- (syn) or trans- (anti), and may or may not be stereospecific. The only way for the nucleophile to attack is from backward if the intermediate is a cyclic cation; resulting in a syn addition product. Furthermore, if the reagent forms a 4-membered ring intermediate (instead of three), the addition will still be 'syn'.



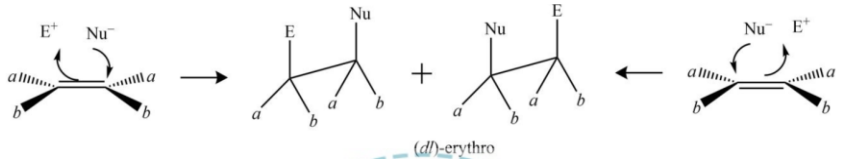
Conversely, if the classical carbocations dominate as intermediate and are having a sufficiently longer lifespan, they can show rotation about carbon-carbon single to yield a non-stereospecific product. However, if the classical carbocationic intermediate is short-lived, the nucleophile coming after the electrophilic attack may generate an ion-pair leading to a syn-addition product.

To find whether the addition is syn or anti for a certain reagent (E−Nu), we need to use a substrate of form *ab*C=C*ab* where $a \neq b$ but E may or may not be the same as Nu. At this point, two scenarios can be realized, one when E ≠ Nu, and the other is when E = Nu; and

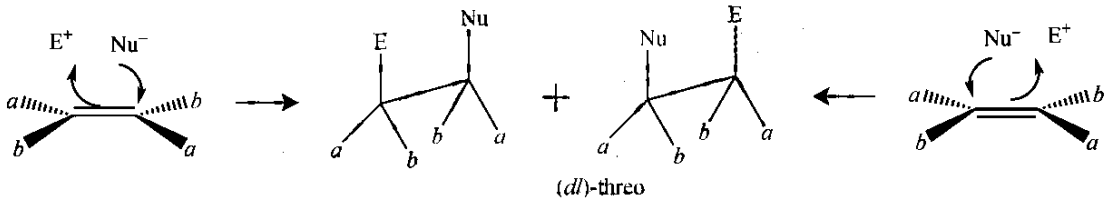
we will discuss them one by one.

Case-I (E ≠ Nu):

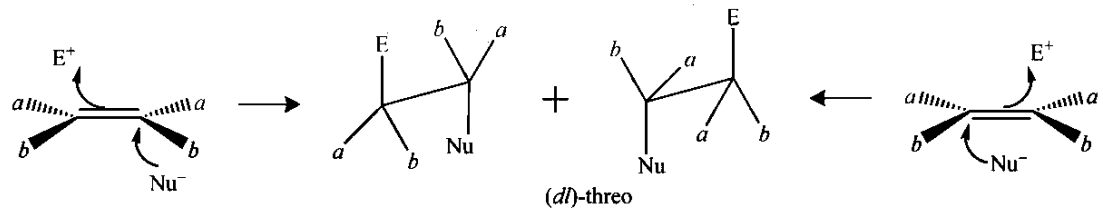
If the addition is syn but on cis-compound, we will get a (*dl*)-erythro form via such type of transformation as shown below.



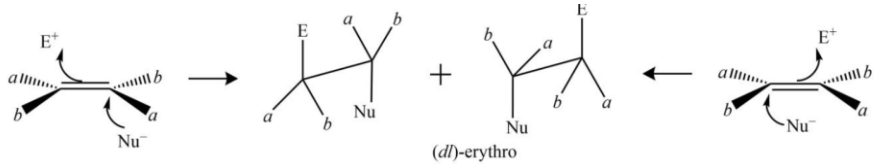
On the other hand, if the addition is syn but on trans-compound, we will get a (dl)-threo form via such type of transformation as shown below.



Similarly, If the addition is anti but on cis-compound, we will get a (*dl*)-threo form via such type of transformation as shown below.

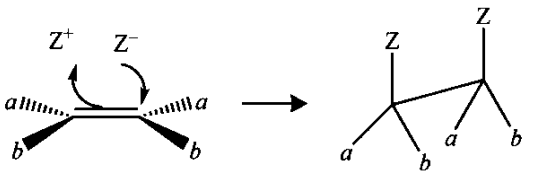


On the other hand, if the addition is anti but on trans-compound, we will get a (dl)-erythro form via such type of transformation as shown below.

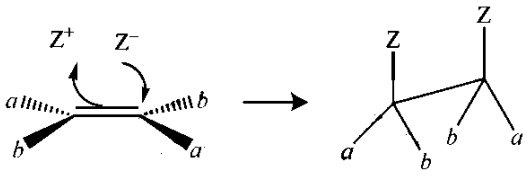


Case-II (E = Nu):

In these types of cases, the (*dl*)-erythro forms will become meso-products; whereas the threo-forms will remain the same as shown below.



meso form



(*dl*)-threo form

Therefore, we may conclude that if the configuration of both the product and substrate are identified, the reaction pathway along with the addition mode can simply be predicted.

(c) Addition to Carbon-Hetero atom Multiplebonds:

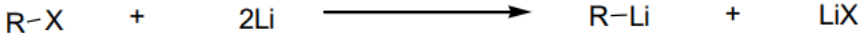
Organozinc and organolithium reagents to carbonyl and unsaturated carbonyl compounds.

Organolithium reagent

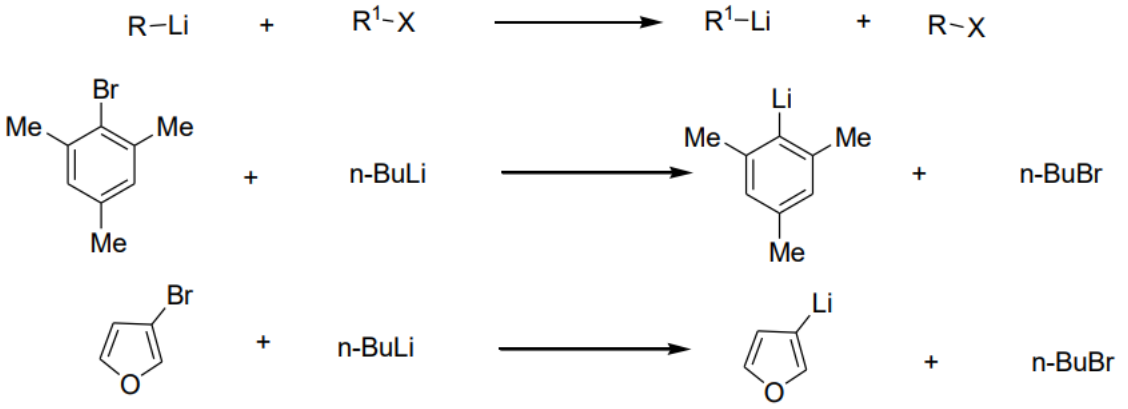
Organolithium reagents are one of the most useful nucleophillic reagents in organic synthesis. They are also highly basic in nature. However, due to their thermal instability and extremely high reactivity they require elaborate precautions during use. Many organolithiums are commercially available as dilute solution in hydrocarbon solvents. In such solvents they are polymeric species with n = 4 to 6. In ethers, however, they are mostly tetrameric in nature. In the presence of strong donating molecules such as HMPA and DMPU, the degree of association decreases and they exist as monomeric species. This leads to an enhancement in their reactivity. Tetrameric structures are based on distorted cubic structures where the lithium atoms occupy alternate corners of the cube and the alkyl groups occupy a face of the cube.

Preparation:

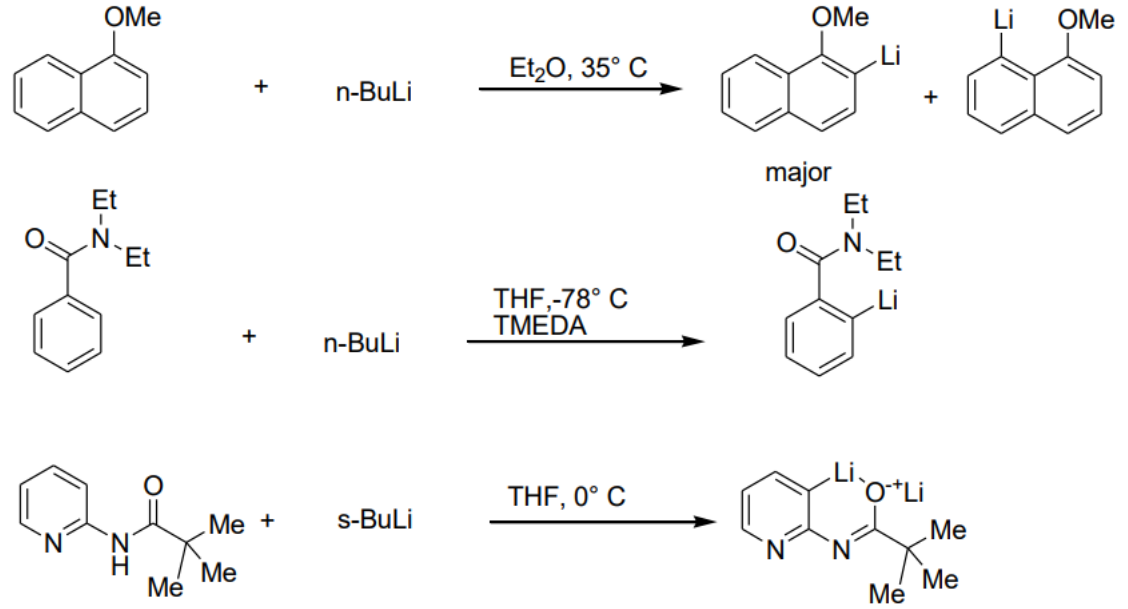
Organolithium reagents are usually prepared by the reaction of organic halides with lithium. The order of reactivity of the organic halides decreases in the following order RI > RBr > RCl.



Another route to organolithium compounds is the use of metal halogen exchange reactions. In these reactions the equilibirium lies to the right if the organic group is able to accommodate the electron density than the organic species on the left



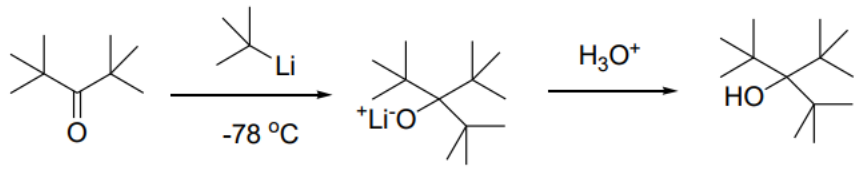
The replacement of a hydrogen by a lithium (known as lithiation) can also be used to generate organolithium species. This reaction is essentially an acid base reaction. However in case, where there is activation by a coordinating group, the reaction occurs with considerable ease. This type of activation is particularly helpful in introducing an ortho substituent to a preexisting coordinating group.



The ortho-directing groups are usually arranged in the following order in order of their reactivity: SO_2NR_2 > SO_2Ar > $CONR_2$ > oxazolinyl > CONHR > CSNHR, CH_2NR_2 > OR > NHAr > SR > CR_2O - . . .

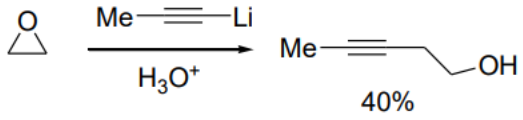
Reaction with Carbonyl Compounds:

Organolithium reacts with carbonyl compounds as that of the Grignard reagents. In comparison to Grignard reagents, organolithium reagents are less susceptible to steric factors and react with hindered ketones to give the corresponding tertiary alcohols.



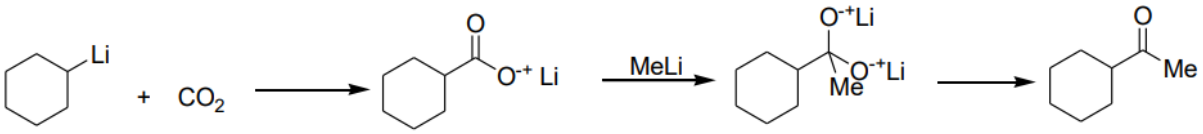
Reactions with Epoxides:

Epoxides react with organolithium reagents to give primary alcohols (as in the case of Grignard reagents). Use of unsaturated organolithium reagent gives unsaturated alcohols.



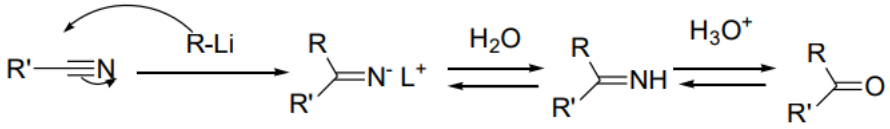
Reactions with Carbon Dioxide

A major difference between the reactivity of Grignard reagents and organolithium reagent is observed in their reactivity towards CO_2. The reaction of Grignard reagents with CO_2 stops at the carboxylate stage, while in case of organolithium reagents, the carboxylate ion formed reacts with another equiv of organolithium to generate a ketone.



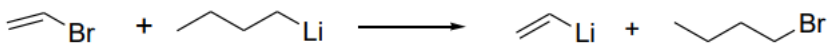
Reactions with Alkyl Cyanide

As in the case of Grignard reagents, the reactions of organolithium reagents with alkyl cyanides give imine salts, which undergo hydrolysis in the presence of water to give ketones.



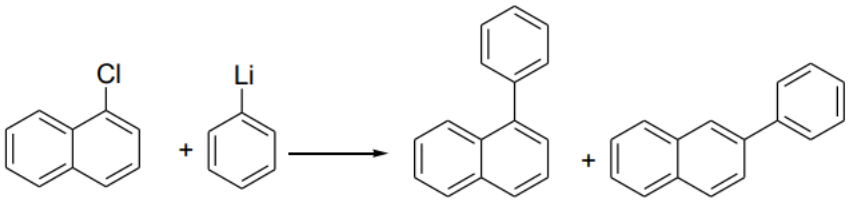
Electrophilic Displacement

Reaction of an organic halide with an organometallic compound is known as metalhalogen exchange reaction is example for electrophilic displacement. This reaction is useful for the synthesis of vinyl- and phenyl lithium.

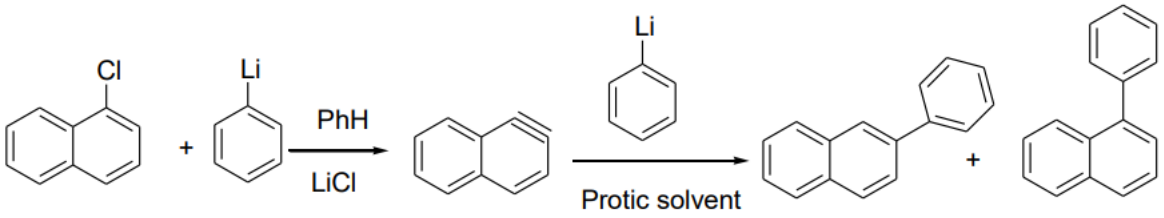


Nucleophilic Displacement

Reactions of alkyl and aryl halides can be reacted with alkyl and aryl lithium reagents to give hydrocarbons. The reaction of alkyl halides with alkyl lithium takes place by S_N2 mechanism. While aryl halides react with aryl lithum via addition-elimination process.

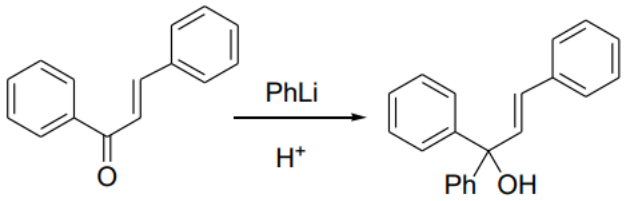


Mechanism

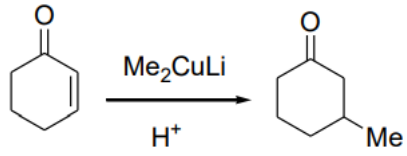


Reaction with α,β-Unsaturated Carbonyl Compounds

In the case of Grignard reagents, α,β-unsaturated carbonyl compounds undergo reaction either at 1,2- or 1,4-addition depending on the structure of the carbonyl compound. The main reason is steric hinderance. While the organolithium reagents undergo reaction exclusively to give 1,2-addition products.

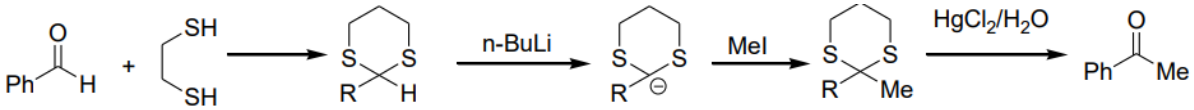


Exclusive formation of 1,4-addition product, however, can be achieved using lithium dialkylcuprates.



Deprotonation

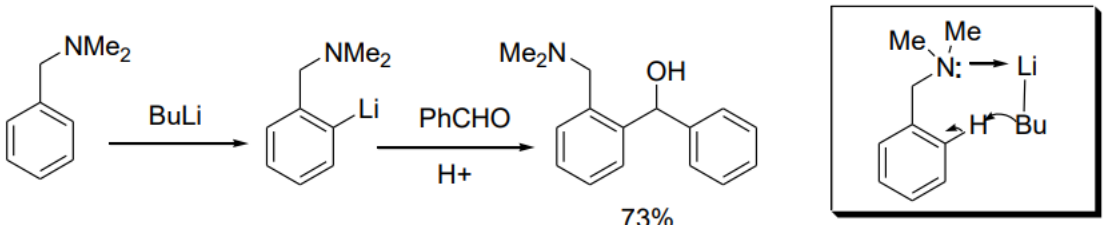
The basic nature of organolithiums can also be put to good use in achieving umpolang at the carbonyl centre of an aldehyde. In this protocol a C=O function is first protected by 1, 3-dithiane and then the proton is removed by an organolithium.



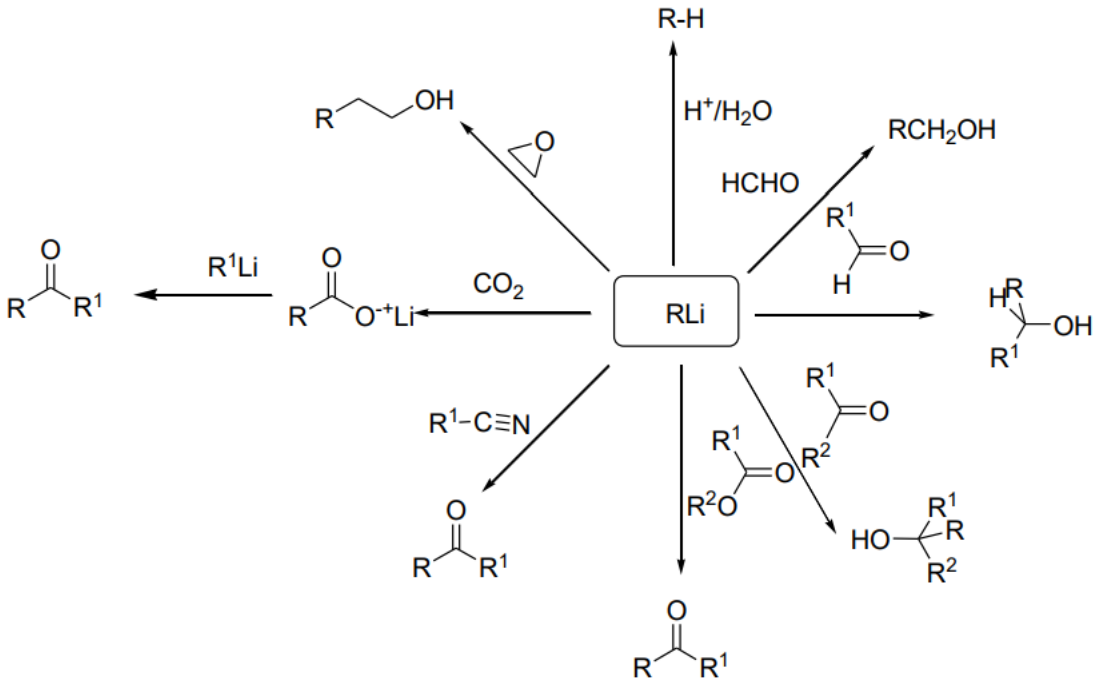
The stereochemical outcome of the nucleophillic addition of organolithiums is similar to that of Grignard reaction. It can be predicted on the basis of Cram's rule.

Ortholithiation

It is useful because the starting material does not need to have a halogen atom. For example, in the case of benzyldimethylamine, the nitrogen atom directs attack of the butyllithium.

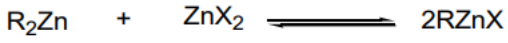


Summary of the Reactions of Organolithium Reagents



Organo Zinc Compounds

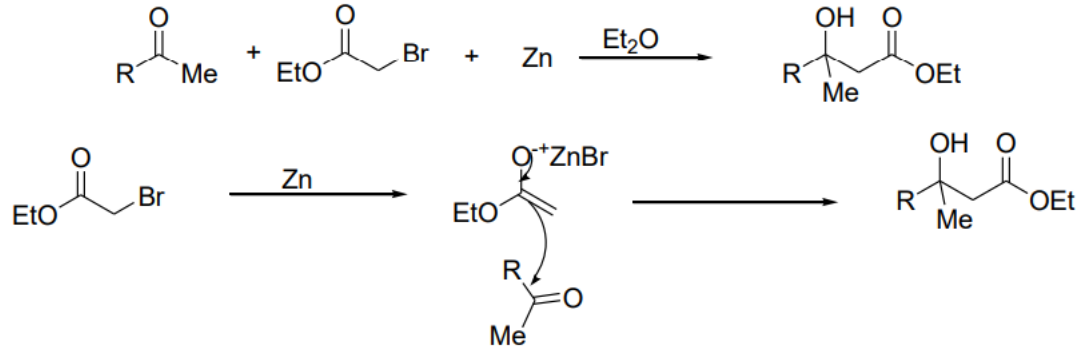
Organozinc reagents are one of the most important of organometallic compounds. The first instance of an organozinc compound goes back to 1849 when Edward Frankland discovered that heating a mixture of zinc and ethyl iodide gives highly pyroporric diethyl zinc. Organozinc compounds in general are sensitive to oxidation, dissolve in a wide variety of solvents whereas protic solvents cause decomposition. Organozinc compounds also exhibit the Schlenck equilibrium like Grignard reagents.



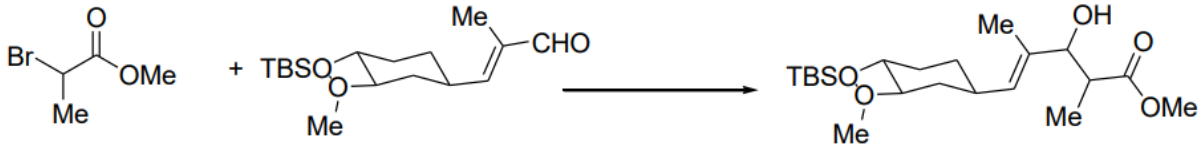
In terms of reactivity, organozinc compounds are less reactive than Grignard reagents. This can be explained on the basis of relative position of Mg and Zn in the periodic table. Since zinc is more electropositive than Mg thus the Zn-C bonds have a higher degree of covalency compared to the Mg-C bond. In a typical case, the electrons forming the C-Zn bond reside in two sp hybridized molecular orbitals resulting in linear geometry about the zinc centre.

Nucleophilic Addition by Organozinc Reagents

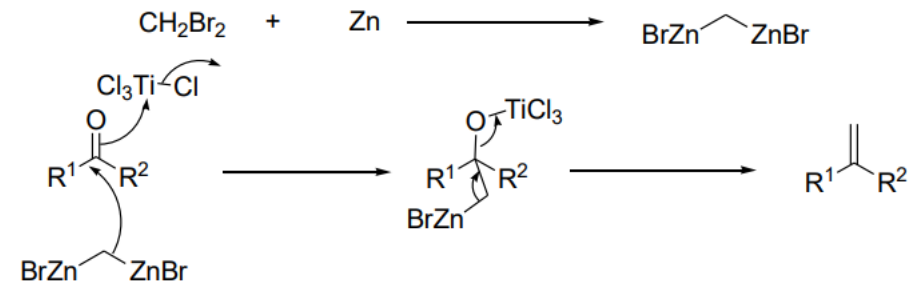
Organozinc reagents are less reactive than organomagnesium and organolithium reagents thereby allowing a higher functional group tolerance. However, this low reactivity means that they need to be often aided by additives or catalysts. Reformatsky reaction is one of the most important applications of organozinc reagent formed in situ. In this reaction zinc, α-haloester and a carbonyl compound react to give βhydroxyester. The reaction involves the formation of a zinc enolate which attacks the carbonyl group. As the zinc enolate is only weakly basic so the reaction works even in the presence of highly enolisable carbonyl partner. Sterically hindered ketones do not pose a problem for this reaction.



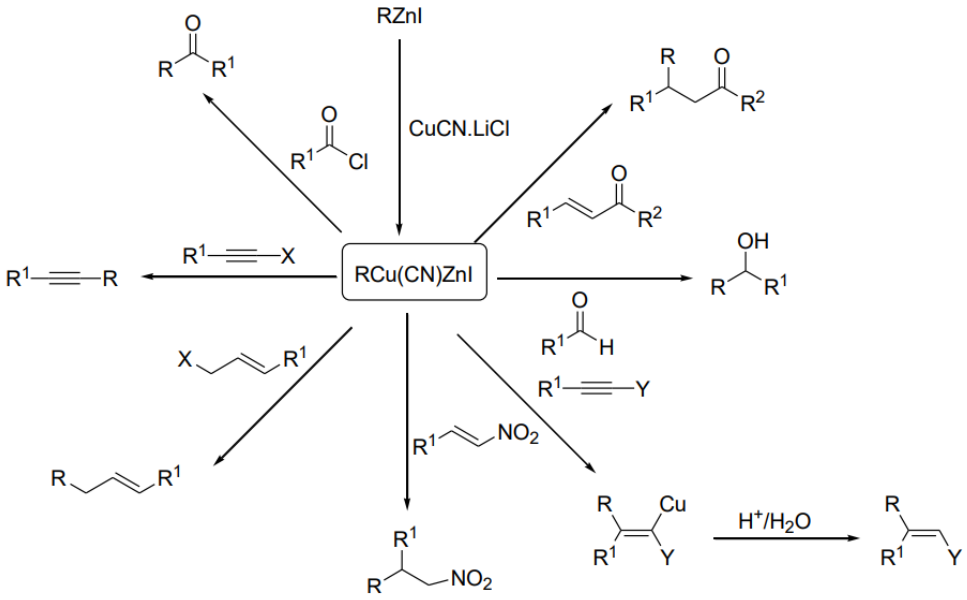
In case of α,β-unsaturated carbonyl compound the addition takes place regioselectively in a 1,2 fashion.



The combination of Zn/CH2Br2/TiCl4 is known as Lombordo's reagent which can convert ketones to methylene group. The reaction is believed to proceed through a dimetalated intermediate which adds to the ketone.

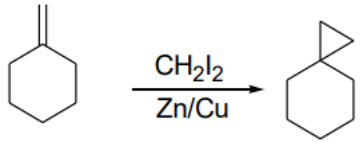


Organozinc reagents readily undergo transmetallation thereby making them suitable candidates to be used in conjunction with transition metal salts. Thus, RZnI reacts with THF soluble salt CuCN·LiCl to form new copper-zinc reagents which are usually formulated as RCu(CN)ZnI.

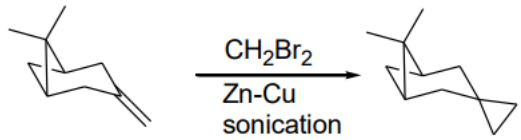


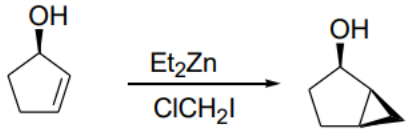
Cyclopropanation by Organozinc Reagents

Alkenes may be conveniently converted into cyclopropanes by treatment with methylene iodide and Zn/Cu couple. This reaction is known as Simmons Smith reaction. The reactive species is iodomethylzinc iodide.

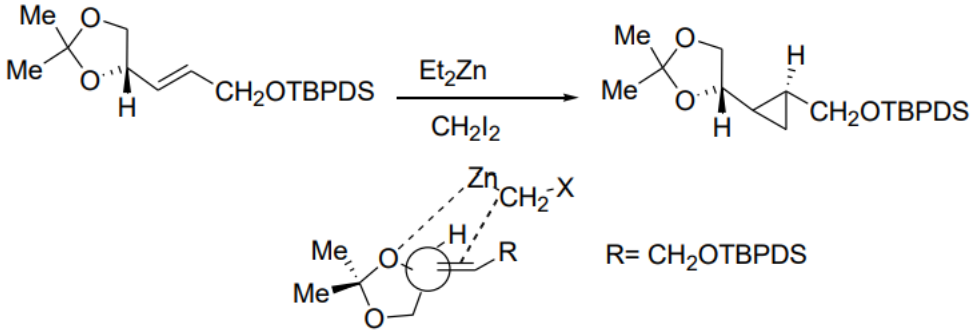


Several modifications are available to allow the use of less reactive methylene group donors like chloroiodomethane. Such methods employ the use of Lewis acids like TiCl4 or organic reagents like acetyl chloride or trimethylsilyl chloride. This reaction is also sensitive to the purity of zinc. Thus electrochemically prepared zinc is more effective than metallurigically prepared zinc.





Simmons Smith reaction is highly stereospecific reaction as it does not involve a carbene intermediate (:CH2). In case of additional directing groups, the reaction exhibits considerable stereoselectivity. In Scheme 8, the stereoselectivity of the reaction is explained by the coordination of zinc to allylic oxygen in the transition state.

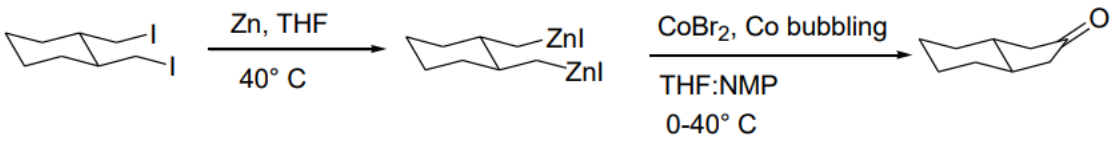


Other reagents have been developed having aryloxy or acetoxy anions. These reagents are effective for cyclopropanation of unactivated alkenes. They are prepared by the reaction of diethyl zinc with a suitable oxyanion precursor such as trifluoroacetic acid followed by reaction with methylene iodide to generate reagents having formula $ROZnCH_2I$. The reactivity of the oxyanions are in the order $CF_3COO^- > ArO^- > RO^-$.

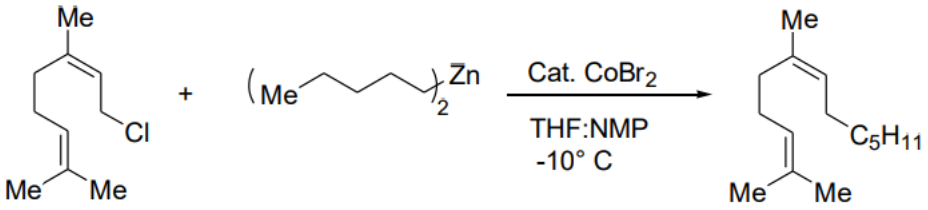
Transition Metal Mediated Addition of Organozinc Reagents

As mentioned earlier, organozinc reagents can be used in conjunction with various transition metal salts which may be added in either stoichiometric amount or catalytic amount. This transmetallation reaction has been already discussed in the previous section for copper salts. In this section we will see the effect of Pd, Ni, Fe and Co salts on the addition of organozinc reagents.

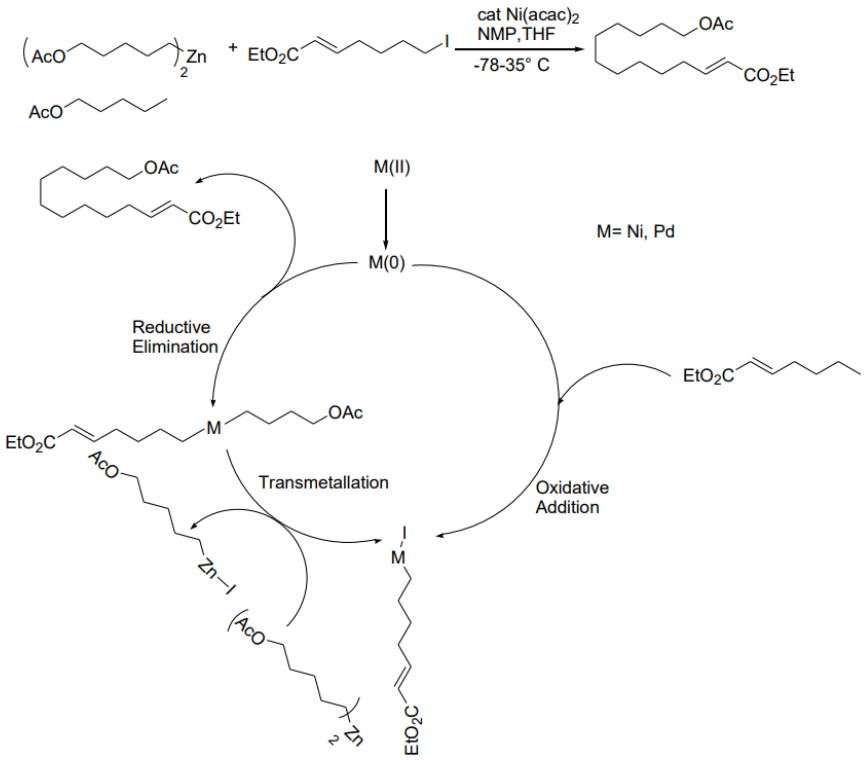
One of the most useful reactions using Co is the carbonylation reaction. Organozinc reagents when treated $CoBr_2$ generate organocobalt reagents which are stable for several hours at low temperature. Carbonylation is now possible by simply bubbling CO through such a solution.

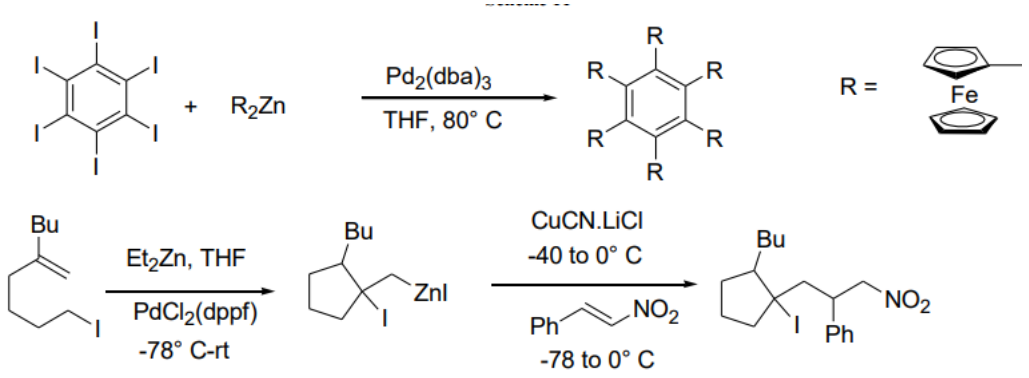


Addition of cobalt salts in catalytic amount is known for acylation and allylation reaction of diorganozincs. The reaction occurs in a S_N2 fashion but, not by S_N2' fashion, thereby leading to a complete retention of double bond geometry



The reaction between organozinc compound and an organic halide in the presence of Pd(0) or Ni(0) species is known as Negishi cross-coupling reaction which is one of the most widely used cross-coupling reactions. The mechanism of this reaction involves oxidative addition followed by transmetallation with the zinc compound and subsequent reductive elimination. This reaction can be applied to highly substituted substrates. An interesting example of application of Negishi coupling is the synthesis of hexaferrocenyl benzene. Besides Negishi cross-coupling, Ni and Pd salts are also known to catalyze the cyclization reactions of organozincs via a radical pathway. In these cases, an intermediate Ni(0) or Pd(0) is formed which initiates a radical chain providing a new zinc derivative which can further undergo reaction with other electrophiles.

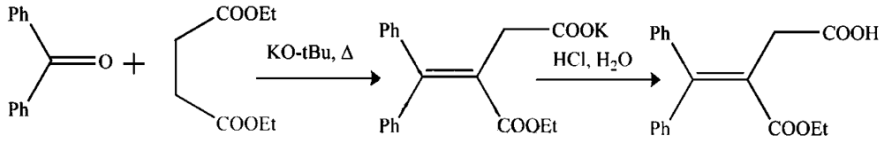




Stobbe Condensation

The Stobbe condensation may simply be defined as a modification to Claisen condensation where the diethylesters of succinic acid react with aldehydes (or ketones) to give rise to alkylidene succinic acids or their monoesters inpresence of a relatively less strong base.

This reaction is a modification to Claisen condensation and was invented by a German chemist Hans Stobbe; and therefore, is also named after him. The initial reaction was observed in 1893 when H. Stobbe observed that the reaction between acetone and diethyl succinate (in the presence of C_2H_5ONa) yielded an a-unsaturated ester (tetraconic acid) and its monoethyl ester, instead of a 1, 3-diketone product via normal Claisen condensation.



In the later years, Stobbe and his co-workers observed that this is quite common when succinic acid's esters are treated with aldehyde or ketones.

Mechanism of Stobbe condensation: The most widely accepted mechanism for Stobbe condensation that can explain the generation of an ester group, as well as the formation of a carboxylic acid group is a function of a lactone intermediate as shown below.

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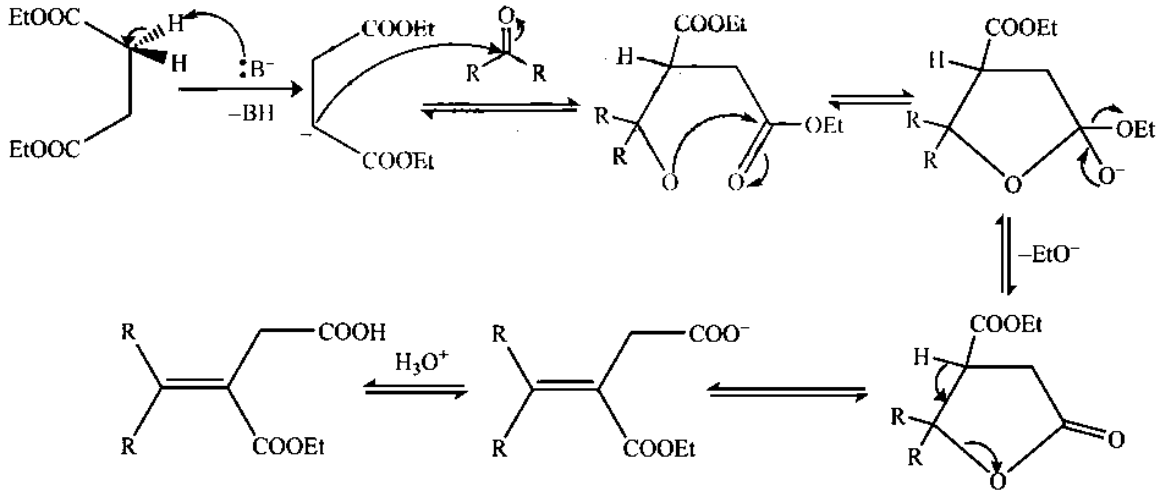
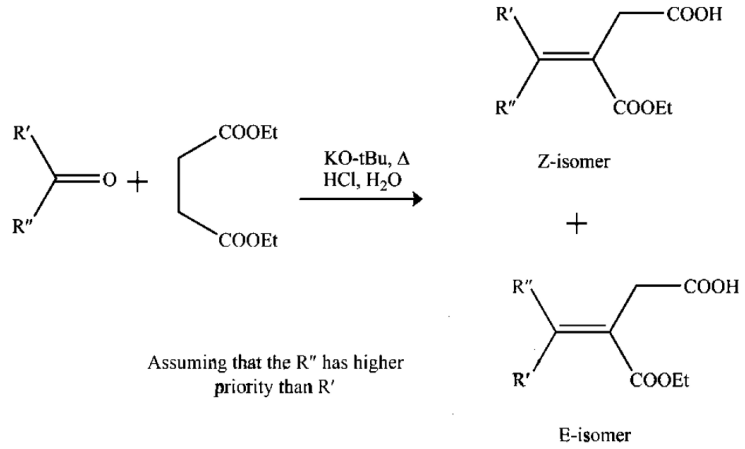


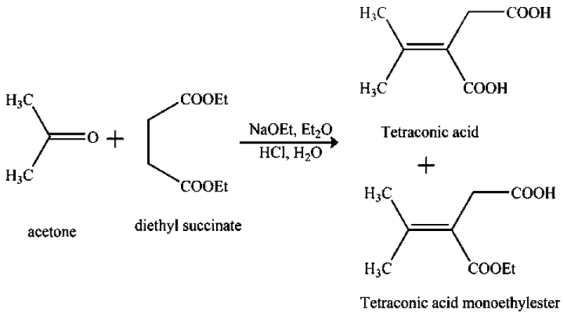
The carbonyl component isn't restricted in Stobbe condensation; and therefore, it even can have α-hydrogens. Nevertheless, if α-hydrogens are present in the carbonyl component, the double bond migration can trigger the formation of many types of final products.

Stereochemistry of Stobbe condensation: Only one alkene stereoisomer will be obtained if symmetrica ketones are used; nevertheless, unsymmetrical ketones will give rise to a mixture of alkene stereoisomers.

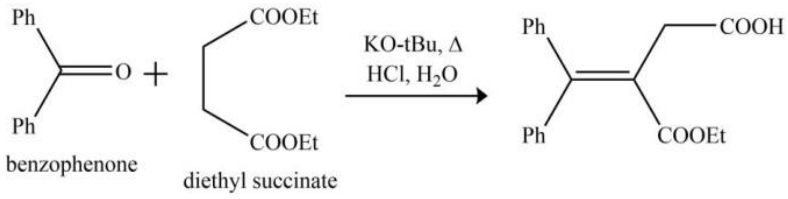


Examples of Stobbe condensation: Some of the most common examples of organic chemical transformation Stobbe condensation are given below.

1. One of the most popular examples of Stobbe condensation is the reaction between acetone and diethyl succinate to give tetraconic acid and its monoethyl ester.

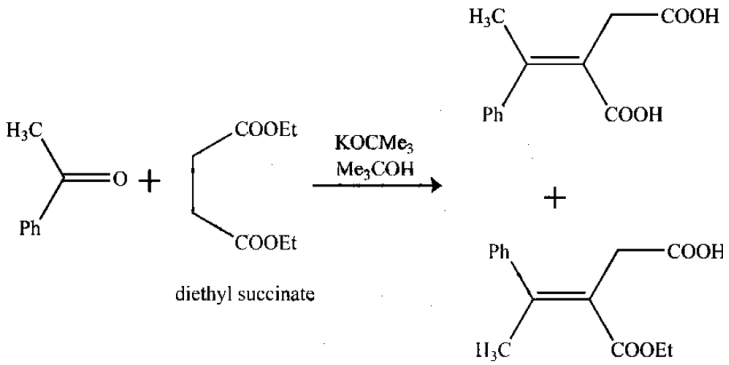


2. The reaction between benzophenone and diethyl succinate to give corresponding monoethyl ester is also an example of Stobbe condensation.



benzophenone diethyl succinate

3. One more example of Stobbe condensation includes the generation of acids and monoethyl esters from the reaction between alkyl aryl ketone with diethyl succinate.



diethyl succinate

Applications of Stobbe condensation: Some of the most common applications of organic chemical transformation involving Stobbe condensation are given below.

1. Stobbe condensation is widely used to synthesize different types of organic acids.
2. one of the major applications of Stobbe condensation is the synthesis of polycyclic ring systems. For instance, the Stobbe products from aryl ketones can give rise to naphthol or indenone derivatives when undergoes dehydration route.
3. Tetralone and phenenthren derivatives can also be obtained using Stobbe condensation.
4. Reinhard Sarges' synthesis of tametraline and synthesis of dimefadane are also based upon the employment of Stobbe condensation in the first step.

Hydrolysis of Esters and Amides

In this section, we will discuss the mechanism of acid - and base-catalyzed hydrolysis of esters and amides (both are the derivatives of carboxylic acid) in detail.

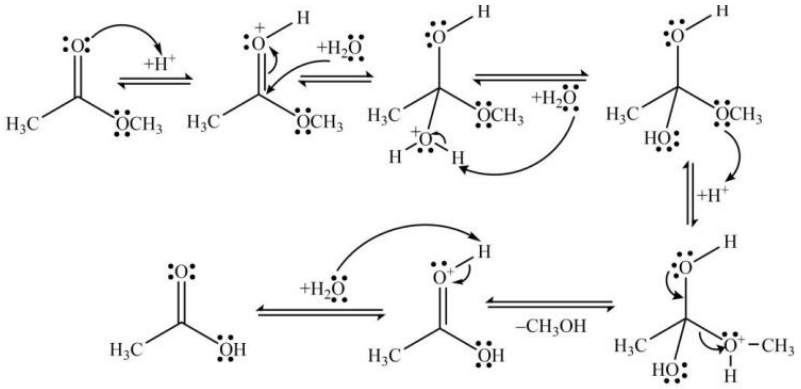
Hydrolysis of Esters

Although the esters are derived from acids, they are generally neutral compounds. In an archetypal ester reaction , the OR group (i.e., alkoxy) of the ester is swapped by another group. One such type of reaction is the ester hyd rolysis where the OH group (generated by the water-splitting) replaces the alkoxy group of esters under consideration. The ester hyd rolysis can either be catalyzed by an acid or by a base.

Illustrative Reaction: The typical organic chemical reaction depicting acid hydrolysis of esters is shown below.

i) Acid-catalyzed mechanism of ester hydrolysis:

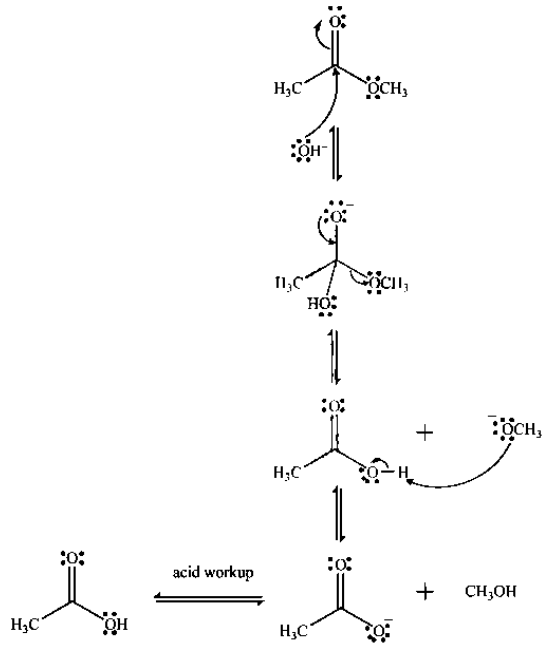
The mechanism for acid-catalyzed ester hydrolysis is a case of 'less reactive system type', and all the steps involved are shown below.



Furthermore, it is also worthy to note that the acidic hydrolysis of esters is just the reverse of esterification where an ester is heated with a large amount of water in the presence of a strongly acidic catalyst. Also, acidic ester hydrolysis is a reversible process and does not complete with 100% yield (like esterification).

ii) Base catalyzed mechanism of ester hydrolysis:

The mechanism for base-catalyzed ester hydrolysis is a case of 'reactive system type', and all the steps involved are shown below.

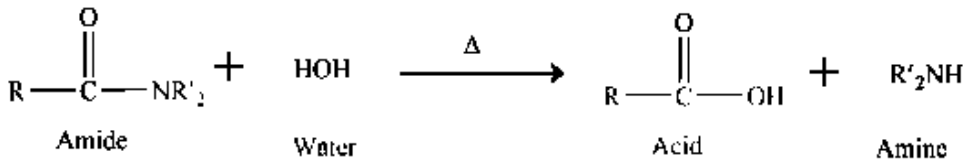


The mechanism given above gives rise to the breakage of the acyl-oxygen bond (second step); and is supported by experimental pieces of evidence through if the compound is isotopically labeled (i.e., $^{18}0$). A similar conclusion was drawn if esters of chiral alcohols were used. The base-catalyzed ester hydrolysis is popularly known as the "saponification" process due to its use of soap-synthesis.

Hydrolysis of Amides

Amides are derivatives of carboxylic acid where the OH group has been substituted by NR_2, NH_2, NHR, or amine. Since the reaction between an amine and a carboxylic acid giving amide occurs via the release of the water molecule (condensation reaction), the amides' hydrolysis can be labeled as the reverse of condensation reaction as the amine and acid are being reproduced. The amides' hydrolysis isn't easy and requires conditions like the heating of amide with aqueous acid for a long interval of time. Like the hydrolysis of esters, the amide hydrolysis can either be catalyzed by an acid or by a base.

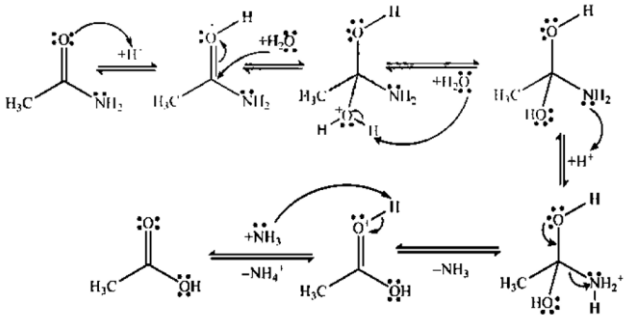
Illustrative Reaction: The typical organic chemical reaction depicting acid hydrolysis of amides is shown below.



Mechanism involved: Since the amide hydrolysis can either be catalyzed by an acid or by a base; a brief overview for both kinds must be discussed for a better understanding.

i) Acid-catalyzed mechanism of amide hydrolysis:

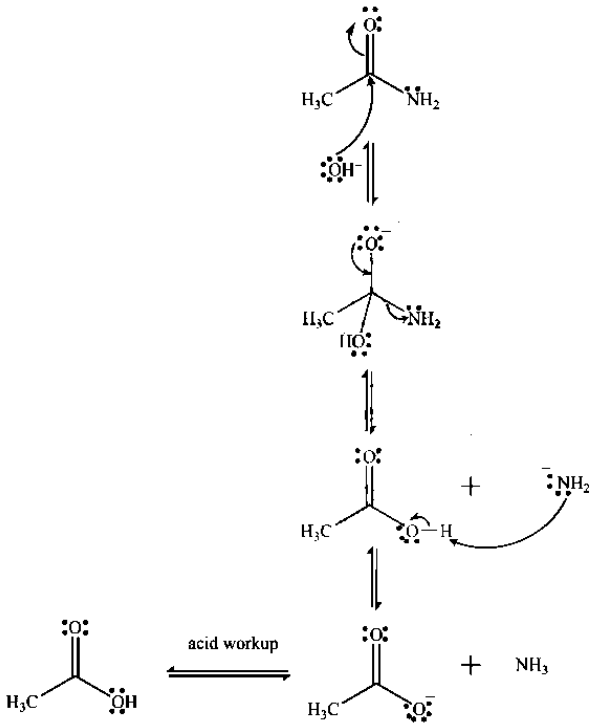
The mechanism for acid catalyzed amide hydrolysis is a case of 'less reactive system type', and all the steps involved are shown below.



It is obvious from the mechanism given above that the acid catalysed amide hydrolysis is quite analogous to the acid catalysed esters' hydrolysis; and proceed via the protonation of the carbonyl group and not the amide one.

ii) Base catalyzed mechanism of amide hydrolysis:

The base-catalyzed amide hydrolysis is extremely difficult to carry out but possible if the amide is heated for a very long span of time. All the steps involved in the base-catalyzed hydrolysis of amide are shown below.

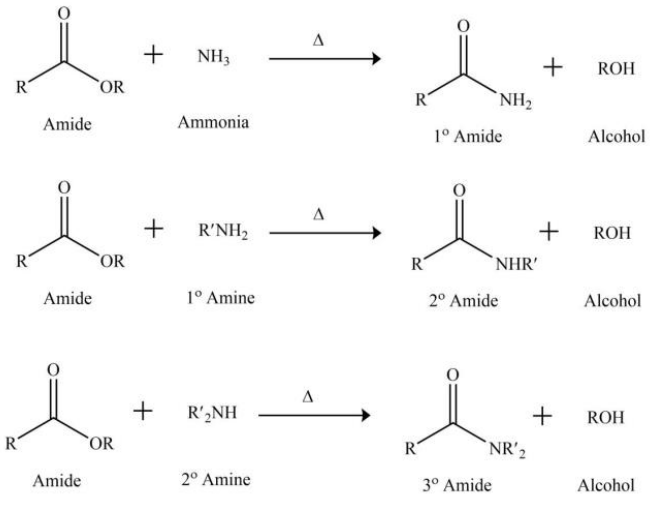


It is obvious that the major problem in the way of substitution to happen is the need for a good leaving group; however, the deprotonated amine so strongly basic that it is almost the opposite of a good leaving group. Consequently, the breaking of amide is proved to be extremely difficult even if we couple very high temperatures with a base like KOH.

Ammonolysis of Esters

Before we study the ammonolysis of esters, we need to distinguish the term 'ammonolysis' from the term 'aminolysis' first. The precise definition of 'ammonolysis' includes the chemical reactions in which a compound is split into two parts by its reaction with ammonia; however, in broader terms, admins can also be used. On the other hand, the precise definition of 'aminolysis' includes the chemical reactions in which a compound is split into two parts by its reaction with amine; nevertheless, in broader terms, ammonia can also be used . Hence, we can conclude that the terms 'ammonolysis' and 'aminolysis' are pretty much similar not only w.r.t names but also in their approach; and therefore, are used in an exchangeable manner in different textbooks.

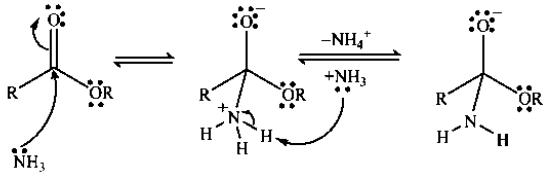
Ammonolysis of esters, which popularly means that the esters can be converted into primary, secondary, and tertiary amides (along with alcohols) by treating them with ammonia, primary amines, and secondary amines respectively.



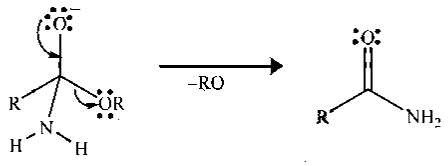
Since the RO- is a very poor leaving group, the conventional nucleophilic addition-elimination pathway will not be useful as far the practicality is concerned. Hence, unlike the reaction of acyl chlorides with amines, the corresponding nucleophilic addition-elimination in case esters requires much stronger conditions.

Mechanism of Ammonolysis of Esters

Before we discuss the mechanism of ammonolysis of esters, we understand different outcomes first. Initially, an ammonia molecule (or amine) attacks the carbonyl via nucleophilic addition ; whilst a large amount of ammonia still present in the reaction solution, followed by the formation of an anionic tetrahedral intermediate due to deprotonation.



At this point, C=O double bond can only be restored only if either the alkoxy (RO^-) or the amide (NH_2^-) group is detached. Now although both are very poor leaving groups; the pKa values of alcohol and ammonia suggested that alkoxy groups (RO^-) are much weaker bases than ammonia's conjugate base (i.e., NH_2^-), and therefore, is a better leaving group. Consequently, the reassortment of the C=O bond will happen via loss of alkoxy group giving rise to an amide product.



However, it is also worthy to note that the relative betterment of alkoxy as a leaving group doesn't make it a good leave group on the absolute scale; and therefore , the ammonolysis of esters isn't a very effective route for the amides ' synthesis, indicating acyl chlorides as more suitable substrates.

UNIT-V

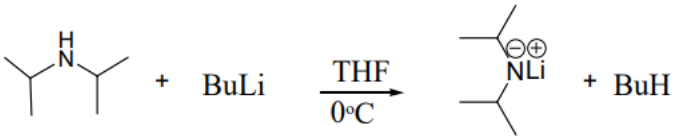
REAGENTS AND MODERN SYNTHETIC REACTIONS:

5.1 Lithium diisopropylamine:

Lithium Diisopropylamide (LDA) is a Chemical Compound. LDA is a colorless solid and its molecular formula is $[(CH_3)_2CH]_2NLi$. LDA is used as a strong base and it has good solubility in non-polar organic solvents. LDA is also a nonnucleophilic as well as highly polar in nature.

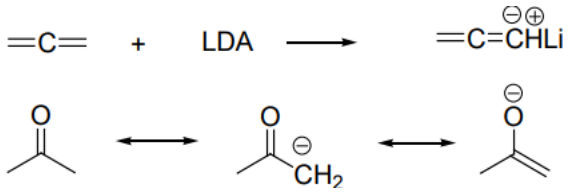
Preparation

LDA is prepared with the reaction of diisopropylamine with butyllithium in presence of tetrahydrofuran (THF) at 0°C to -75°C.

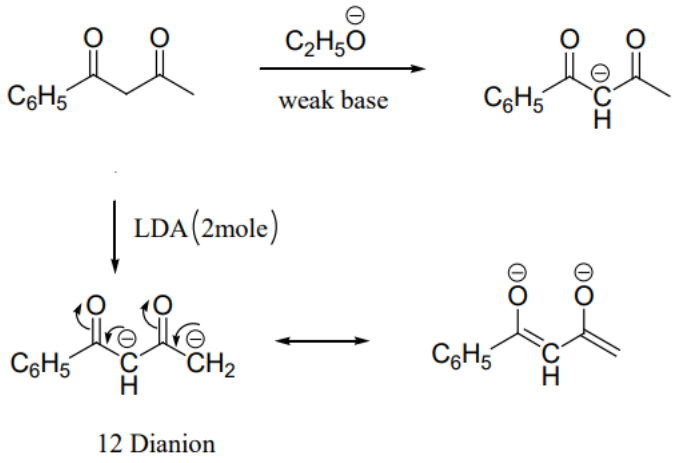


Applications

1) LDA is hindered non-nucleophilic strong base.
2) LDA is a poor nucleophile and does not give nucleophilic substitution even with alkyl halides and tosylates (R-O-Ts). It does not give nucleophilic addition with aldehydes, ketones and nitriles.
3) In THF its structure is primarily that of a solvated dimer.
4) LDA forms a temperature-dependent oligomer equilibrium, in non- polar solvents such as toluene. At room temperature trimers and tetramers are the most likely structures. With increasing temperature the aggregation extends to pentameric and higher oligomeric structures.
5) Solid LDA is pyrophoric but its solutions are generally not.
6) It is strong base that it abstracts hydrogen from active carbon.

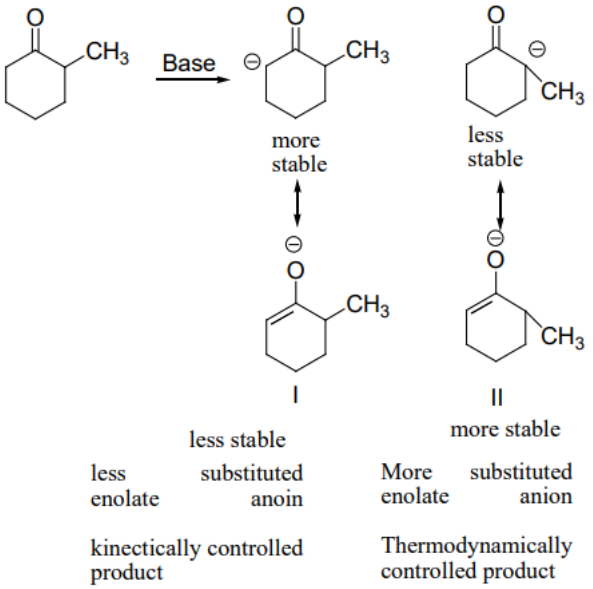


7) A compound possessing two activated CH groups of different acidity forms dianion in a very good yield



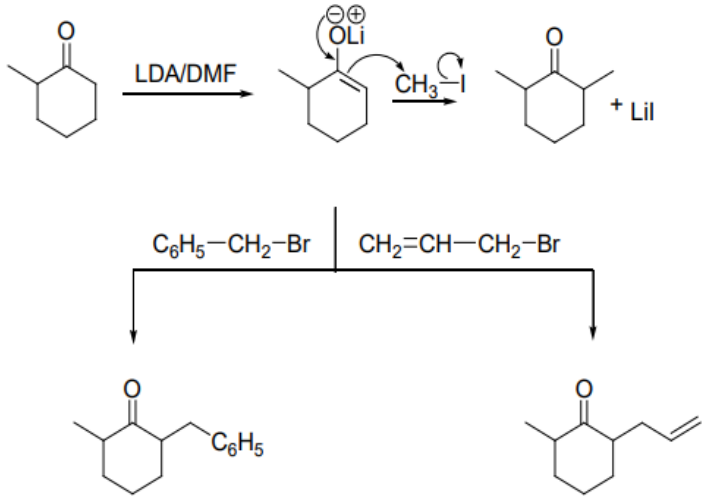
12 Dianion

8) For a ketone with two sets of non-equivalent α-hydrogens, formation of enolate anion has high degree of regioselectivity and regioselectivity depends on experimental condition



9) Direct Alkylation and Acylation of ketones

The alkylation reaction is SN2. Enolate anions are strong bases, successful alkylation occurs only when primary alkyl, primary benzyl and primary alkyl halides are used in this reaction. With secondary and tertiary, elimination becomes the main course of the reaction.

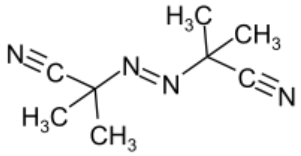


5.2 Azobisisobutyronitrile

Azobisisobutyronitrile (abbreviated AIBN) is an organic compound with the formula $[(CH_3)_2C(CN)]_2N_2$. This white powder is soluble in alcohols and common organic solvents but is insoluble in water. It is often used as a foamer in plastics and rubber and as a radical initiator.

As an azo initiator, radicals resulting from AIBN have multiple benefits over common organic peroxides. For example, they do not have oxygenated byproducts or much yellow discoloration. Additionally, they do not cause too much grafting and therefore are often used when making adhesives, acrylic fibers, detergents, etc.

Structure



Preparation

AIBN is produced in two steps from acetone cyanohydrin. Reaction with hydrazine gives the substituted dialkylhydrazine. In the second step, the hydrazine is oxidized to the azo derivative:

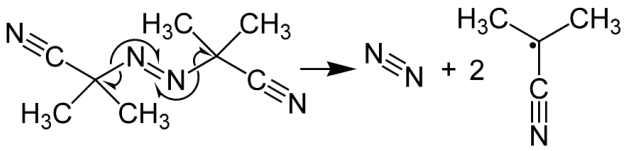
Related azo compounds behave similarly, such as 1,1′-azobis(cyclohexanecarbonitrile). Water-soluble azo initiators are also available.

$$2\ (CH_3)_2C(CN)OH + N_2H_4 \rightarrow [(CH_3)_2C(CN)]_2N_2H_2 + 2\ H_2O$$

$$[(CH_3)_2C(CN)]_2N_2H_2 + Cl_2 \rightarrow [(CH_3)_2C(CN)]_2N_2 + 2\ HCl$$

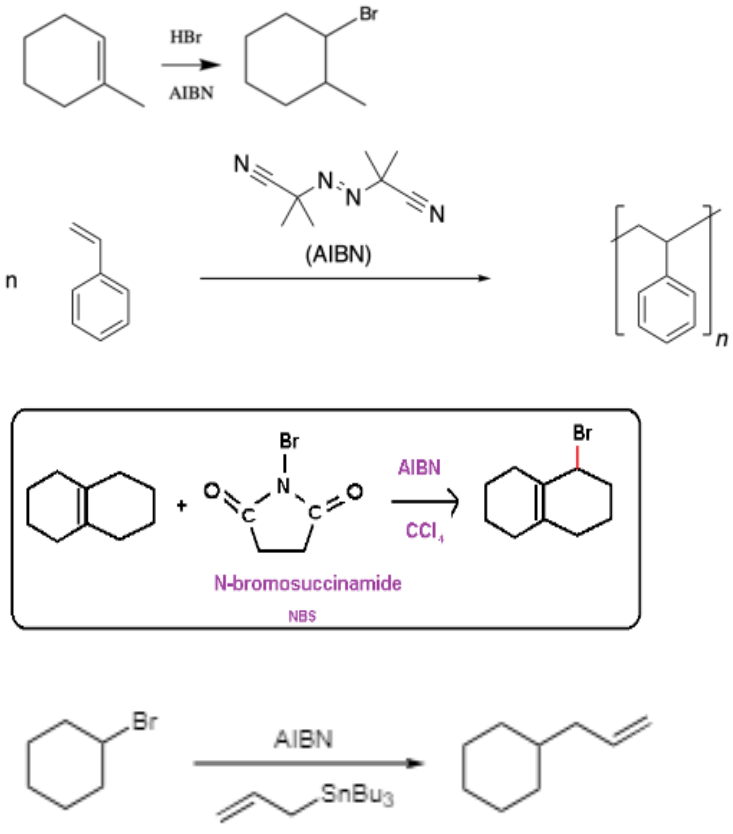
Mechanism of decomposition

n its most characteristic reaction, AIBN decomposes, eliminating a molecule of nitrogen gas to form two 2-cyanoprop-2-yl radicals:



Because azobisisobutyronitrile readily gives off free radicals, it is often used as a radical initiator. This happens at temperatures above 40 °C, but in experiments is more commonly done at temperatures between 66 °C and 72 °C. This decomposition has a ΔG‡ of 131 kJ/mol and results in two 2-cyano-2-propyl (carbon) radicals and a molecule of nitrogen gas. The release of nitrogen gas pushes this decomposition forward due to the increase in entropy. And the 2-cyano-2-propyl radical is stabilized by the −CN group.

Reactions



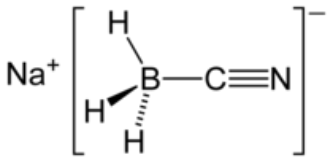
5.3 Sodium cyanoborohydride

odium cyanoborohydride ($NaBH_3CN$) is a mild reducing agent that is commonly used in reductive aminations. The presence of the electron-withdrawing cyano (CN) group makes it less reactive than sodium borohydride ($NaBH_4$). This reduced reactivity allows $NaBH_3CN$ to be employed at neutral or slightly acidic conditions for the selective reduction of iminium ions in the presence of ketones and aldehydes.

Reductive amination by $NaBH_3CN$ is sometimes done in the presence of certain Lewis acids (ex. $Ti(OiPr)_4$, $TiCl_4$, or $ZnCl_2$). The aldehyde or ketone is typically pre-stirred with the amine in the presence of the Lewis acid, then treated with $NaBH_3CN$. This procedure is useful in cases where imine formation is poor, when the use of excess amine isn't possible, or acidic conditions aren't well tolerated.

NaBH3CN can effectively be used in H_2O and protic solvents (ex. MeOH or EtOH), unlike sodium triacetoxyborohydride (STAB) which is quickly degraded by H_2O and protic solvents.

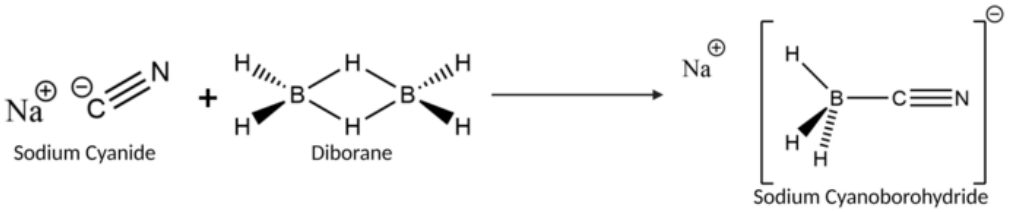
Structure



Preparation

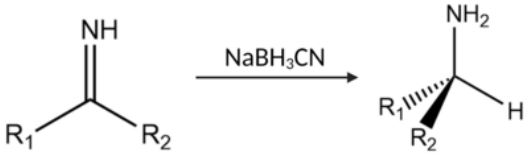
Sodium cyanoborohydride can be synthesized from sodium cyanide and diborane.

This method of preparation can be used for other compounds of the formula RBH_3CN where R is an alkali metal, a quaternary ammonium radical, or a phosphonium radical. The final products are useful as hydrolysis stable reductants and as synthetic intermediates.

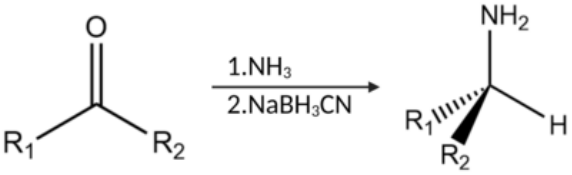


Applications

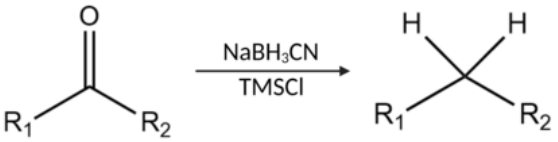
Reduction of imines



Reductive imination



Reductive deoxygenation of ketones



5.4 *m*-chloro perbenzoic acid

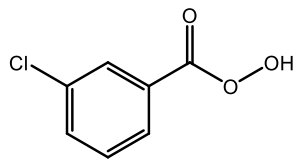
m-CPBA is versatile regent in organic synthesis. It is a efficient oxidizing agent. This reagent is used for the oxidation of carbonyl compounds, olefins, imines alkanes, ethers N and s - heterocycles, cyclic acetals, furans and phosphates.

It has exceptional reactivity and oxidative potential. Having characteristics of weak O-O bond and nucleophilic -OH group present in m-CPBA.

The weak O-O bond of m-CPBA transfers an oxygen atom to electron-rich substrates, nucleophilic attack of m-CPBA on substrates could result oxidation. This has one of the abundant applications is the formation of epoxides from alkenes.

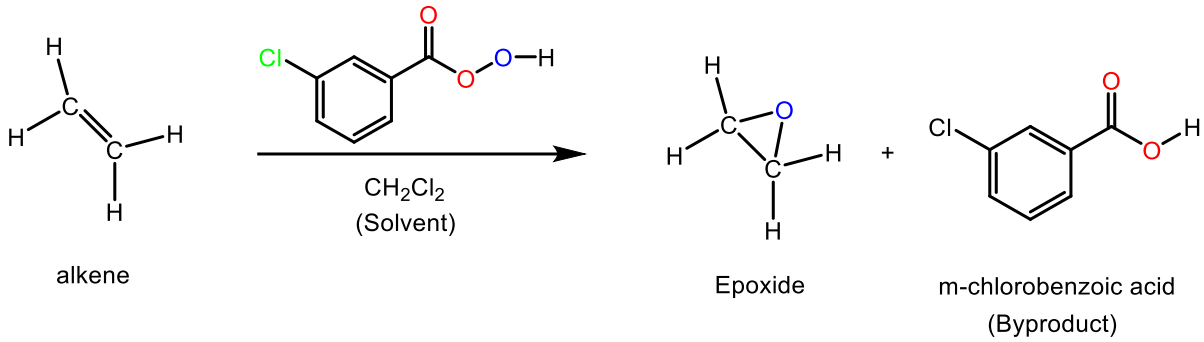
The suitable solvent which has used for the m-CPBA reactions is dichloromethane (CH_2Cl_2) which is a non-polar solvent. It could be efficient of soluble in numerous non-polar solvents, but it has insoluble in water.

Structure



Preparation of m-CPBA:

m-CPBA can be prepared by the reaction of m-chlorobenzoyl chloride with hydrogen peroxide in presence of magnesium sulphate and aqueous sodium hydroxide and dioxane.



alkene

Epoxide

m-chlorobenzoic acid
(Byproduct)

Epoxide chemistry:

Epoxides are also known as oxiranes (3-membered cyclic ethers). It having bond angle of approximately 60º. They have possessed considerable ring strain about 13 kcal/mol. It has useful for ring opening reactions.

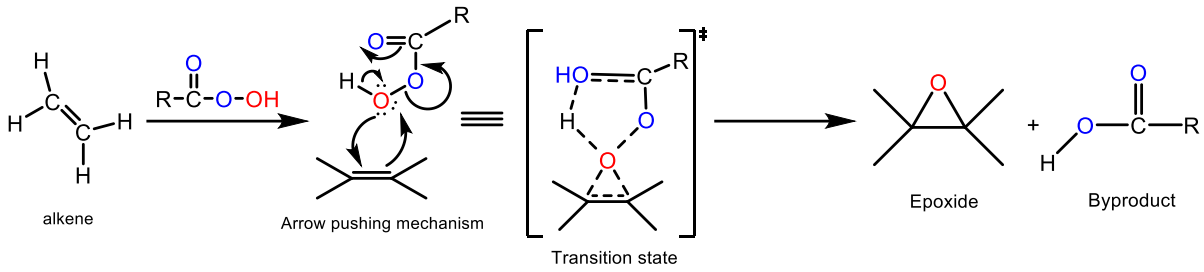
Epoxidation of alkenes with m-CPBA is an example of 'syn-addition'. C-C pi bond is broken in alkene, two new C-O sigma bonds are formed on the same face of the alkene pi bond. (syn-addition)

Epoxidation of alkene is stereospecific reaction. The configuration of atoms about C-C bond is always conserved.

Epoxidation of alkenes with m-CPBA:

Reactions & mechanism:

When alkenes are treated with m-CPBA, two new C-O bonds are formed and C-C pi bond is broken, resulting is in the formation of epoxide. It could also be broken the O-O bond present in m-CPBA, which is the source of oxygen in epoxide. At the end of the reaction, the byproduct has formed is m-chlorobenzoic acid.



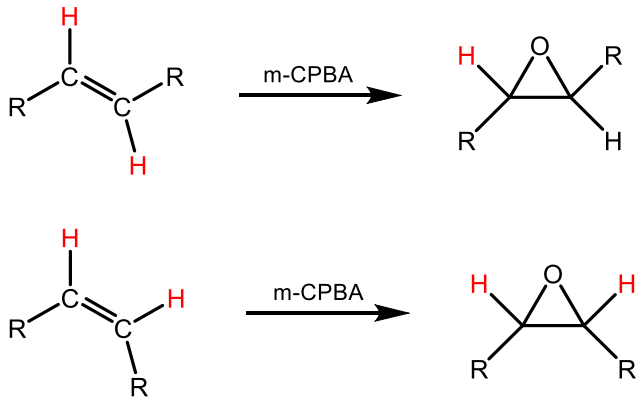
O-O bond is relatively weak. It having Bond Dissociation Energy (BDE) of 45 kcal/mol. C-C pi bond having BDE of 60 kcal/mol. We have used m-CPBA as a driving force to apply to break the bonds, which has formed two relatively strong C-O sigma bonds.

The transition state has occurred is as like butterfly shaped T.S.

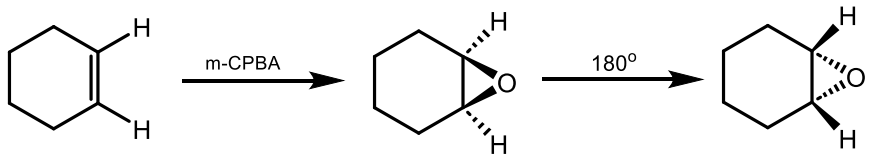
C-C pi bond breaks, the two new C-O sigma bond form, the weak O-OH bond breaks.

The mechanism is 'concerted' (one step mechanism) which is the second order reaction.

Streospecific reactions:



Syn-addition:



Important points to be noted:

Electron-rich alkenes has reacted more quickly than electron-poor alkenes. Adding electron withdrawing groups to the R group pf the peroxyacid makes it more reactive.

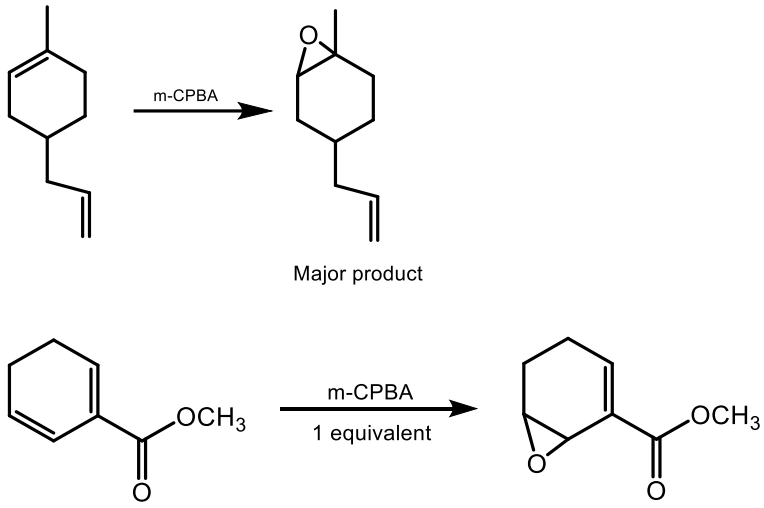
Thus m-CPBA having chlorine atom on the meta position makes m-CPBA as an electron deficient molecule and thus it has ability to react more with electron-rich substances like alkene compounds which has undergo epoxidation.

[When multiple alkenes are present on a molecule, the more substituted alkene tends to react more quickly with m-CPBA.]

Alkene which acts as a nucleophile and m-CPBA act as an electrophile. Increasing the number of alkyl groups on the alkene, has made the compound the more electron rich and which it helps to stabilize the electron poor carbons in the transition state.

In despite of this, the rate of reaction is more sensitive to electronic effects rather than steric effects.

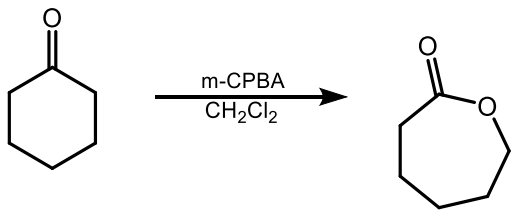
Example:



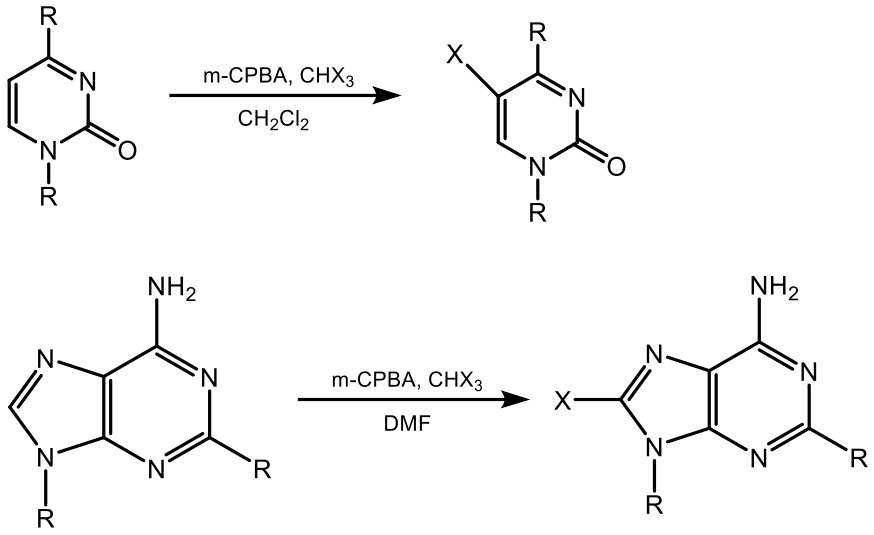
More applications:

Baeyer-villiger oxidation:

It is one of the naming reactions which has been used any peroxyacids as the reagent. This has been used for the conversion of ketones into esters.



Halogenation of purine & pyrimidine derivatives:

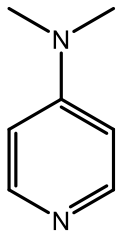


5.5 Dimethyl Amino Pyridine (DMAP)

DMAP can be used for the numerous numbers of reaction as nucleophilic catalyst.

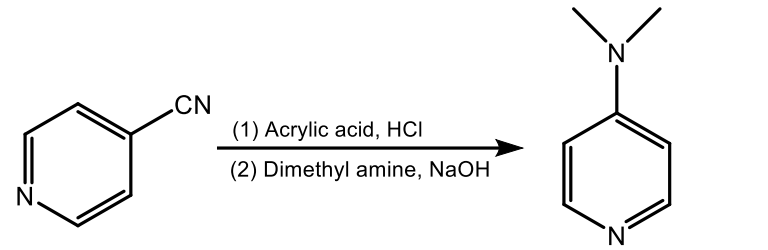
It can be also used as a catalyst with involvement of other reagents to be more reactive in the reactions. It has been used as speed up the esterification of hindered alcohols via acid anhydrides.

Structure



Preparation:

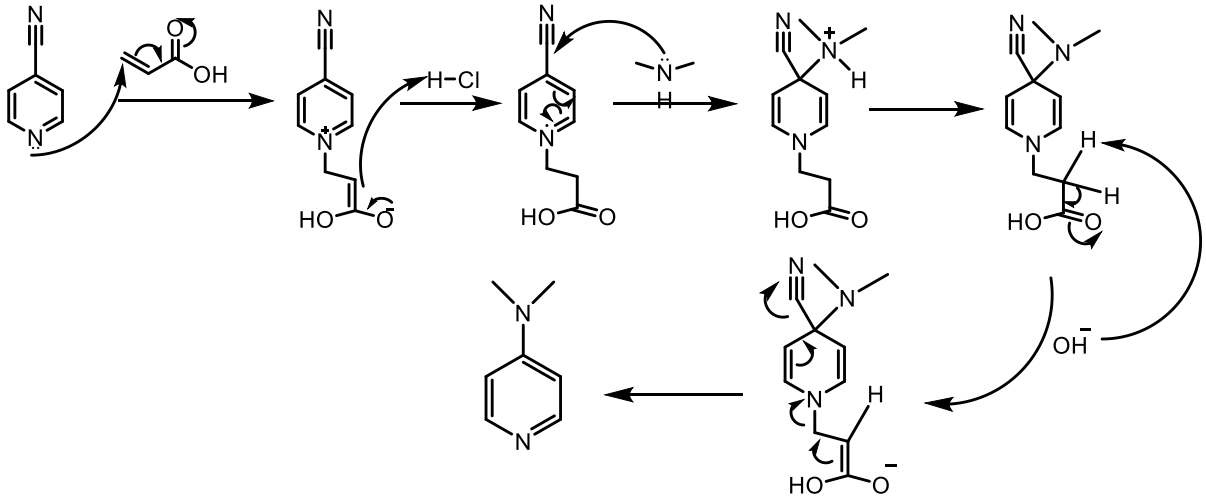
It can be prepared by treatment of 3-cyanopyridine with acrylic acid and hydrochloric acid, Dimethyl amine in presence of NaOH as a solvent to produce 4-Dimethylaminopyridine.



3-cyanopyridine

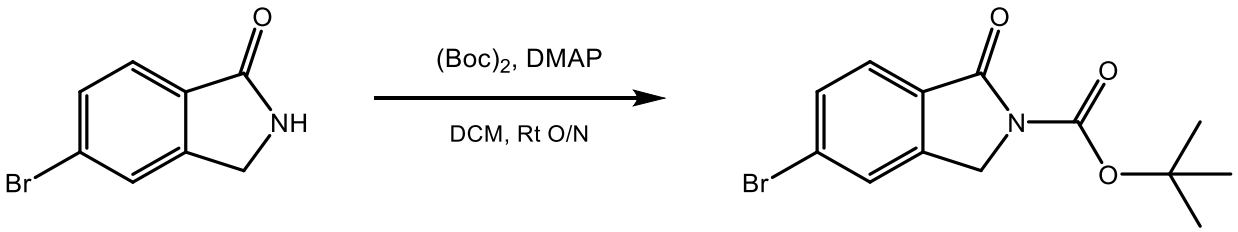
4-Dimethylaminopyridine

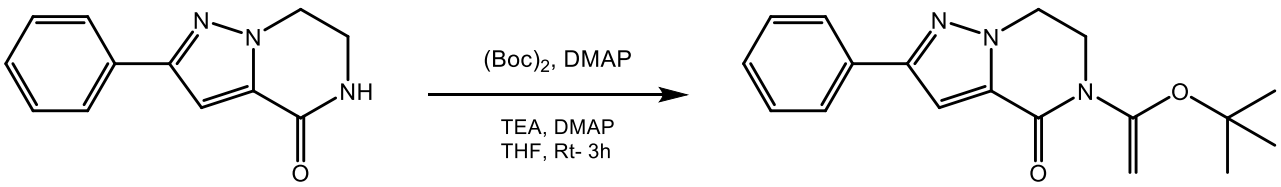
Mechanism:



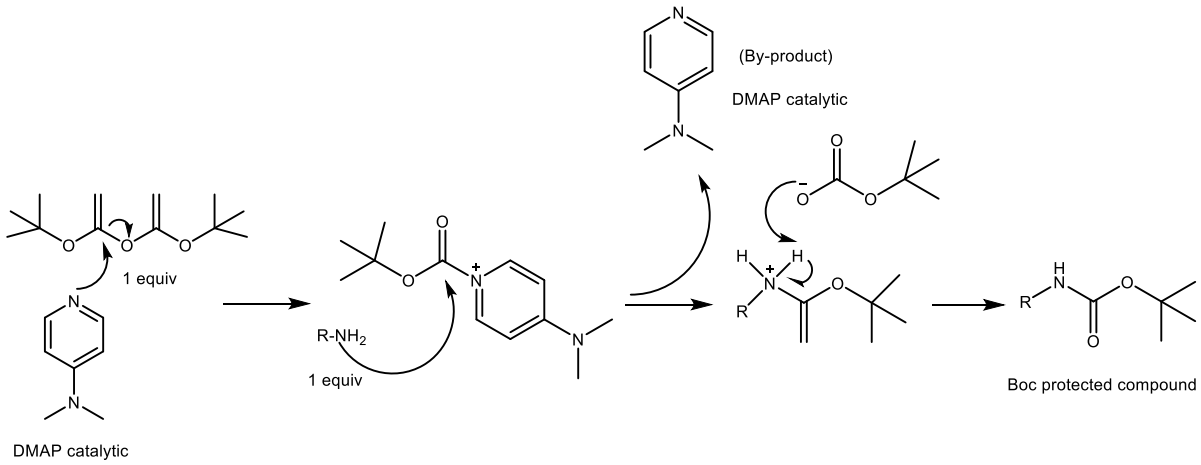
Applications:

(1) Nucleophilic catalyst for (BOC) protection:

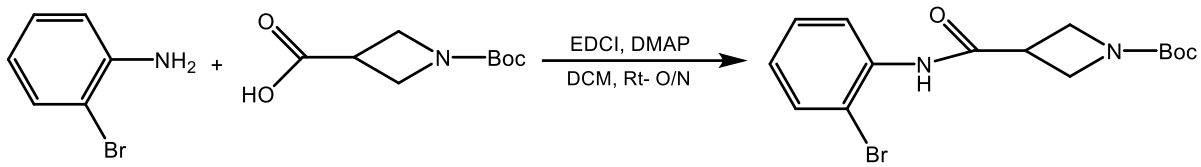




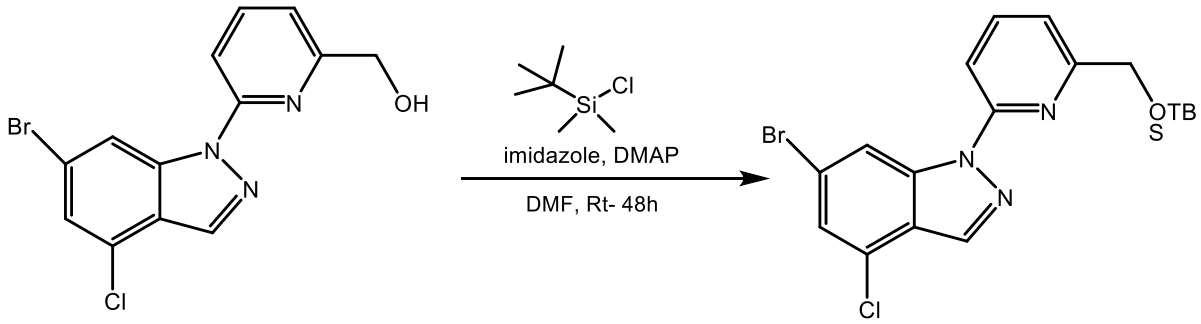
Mechanism:



(2) Reagent for amide coupling:



(3) Nucleophilic catalyst for tbs protection:

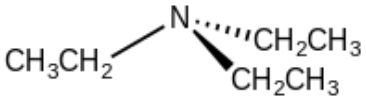


5.6 Triethyl amine

Triethylamine is the chemical compound with the formula $N(CH_2CH_3)_3$, commonly abbreviated Et_3N. It is also abbreviated TEA, yet this abbreviation must be used carefully to avoid confusion with triethanolamine or tetraethylammonium, for which TEA is also a common abbreviation. It is a colourless volatile liquid with a strong fishy odor reminiscent of

ammonia. Like diisopropylethylamine (Hünig's base), triethylamine is commonly employed in organic synthesis, usually as a base.

Structure



Preparation

Triethylamine is prepared by the alkylation of ammonia with ethanol

$$NH_3 + 3\ C_2H_5OH \rightarrow N(C_2H_5)_3 + 3\ H_2O$$

Applications

Triethylamine is commonly employed in organic synthesis as a base. For example, it is commonly used as a base during the preparation of esters and amides from acyl chlorides.Such reactions lead to the production of hydrogen chloride which combines with triethylamine to form the salt triethylamine hydrochloride, commonly called triethylammonium chloride. (R, R' = alkyl, aryl):

$$R_2NH + R'C(O)Cl + Et_3N \rightarrow R'C(O)NR_2 + Et_3NH^+Cl^-$$

Like other tertiary amines, it catalyzes the formation of urethane foams and epoxy resins. It is also useful in dehydrohalogenation reactions and Swern oxidations.

Triethylamine is readily alkylated to give the corresponding quaternary ammonium salt:

$$RI + Et_3N \rightarrow Et_3NR^+I^-$$

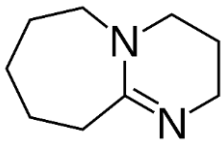
Triethylamine is mainly used in the production of quaternary ammonium compounds for textile auxiliaries and quaternary ammonium salts of dyes. It is also a catalyst and acid neutralizer for condensation reactions and is useful as an intermediate for manufacturing medicines, pesticides and other chemicals.

Triethylamine salts, like any other tertiary ammonium salts, are used as an ion-interaction reagent in ion interaction chromatography, due to their amphiphilic properties. Unlike quaternary ammonium salts, tertiary ammonium salts are much more volatile, therefore mass spectrometry can be used while performing analysis.

5.7 Diazobicyclo[5.4.0]undec-7-ene (DBU)

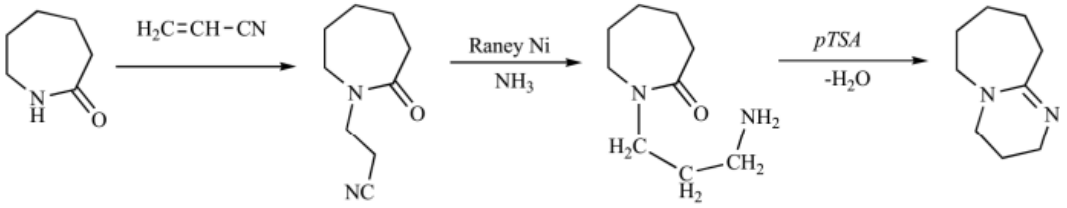
1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU), is a sterically hin-dered amidine base. It is a liquid with a boiling point of 261°C. It is one of the strongest organic neutral base. The presence of adjacent nitrogen in the molecule stabilizes the proto-nated species. It is a non-nucleophilic base and due to this it has found to be useful in reactions where side reactions due to inherent nucleophilicity of a basic nitrogen poses problem. Although, traditionally DBU is considered to be a non-nucleophilic base, but there are few reports where DBU has been employed as a nucleophilic base also. It is advantageous to use DBU in organic reactions as it is cheap, commercially available, homogenous and most importantly recoverable. In recent years, DBU has been used as a catalyst, complexing ligand and a nucleophilic/non-nucleophilic base in organic reactions.

Structure



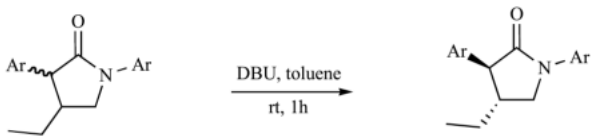
Preparation

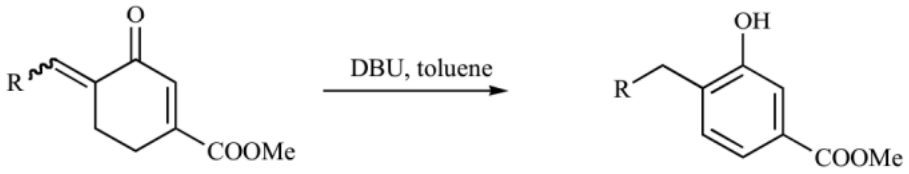
It is synthesized starting from a lactam, azepan-2-one. N-Cyanoethylation of lactam is carried out using acrylonitrile in the presence of a base such as potassium hydroxide producing the nitrite, which is reduced catalytically using Raney-nickel in the presence of ammonia to give N-(3-aminopropyl)-azepan-2-one and this further undergoes loss of water in the presence of p-toluenesulphonic acid to finally yield DBU.



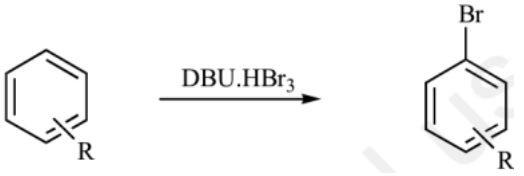
Applications

Isomerization Reactions

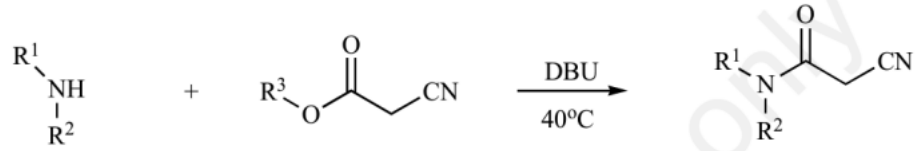




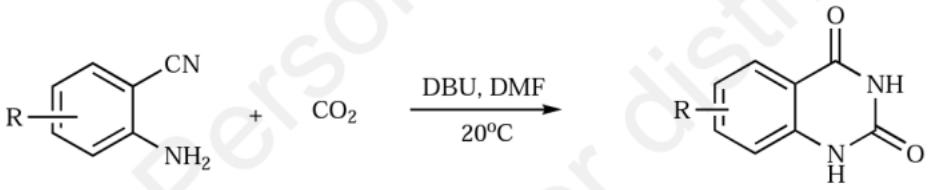
Halogenation Reactions



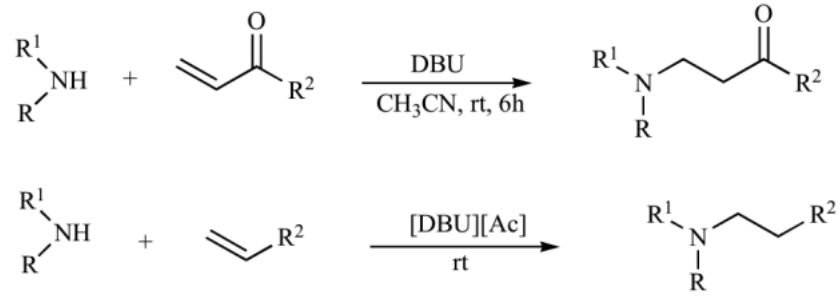
Amidation reactions



Cycloaddition reactions



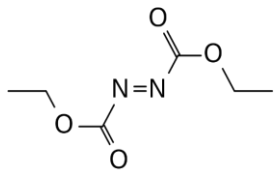
Addition reactions



5.8 DEAD - Diethyl azodicarboxylate

Diethyl azodicarboxylate, is an organic compound with the structural formula $CH_3CH_2{-}O{-}C(=O){-}N{=}N{-}C(=O){-}O{-}CH_2CH_3$. Its molecular structure consists of a central azo functional group, RN=NR, flanked by two ethyl ester groups. This is a orange-red liquid and it is a valuable reagent but quite dangerous and explodes upon heating

Structure:



Properties:

DEAD is an orange-red liquid which weakens its colour to yellow or colourless upon dilution or chemical reaction. This colour change is conventionally used for visual monitoring of the synthesis. It dissolves in most common organic solvents, such as toluene, chloroform, ethanol, tetrahydrofuran and dichloromethane but has low solubility in water or carbon tetrachloride.

Melting point of DEAD is 6^{o} C.

Boiling point of DEAD is 104.5 ^{o}C.

Density of DEAD is 1.11 g/cm^{3}

Preparation of DEAD

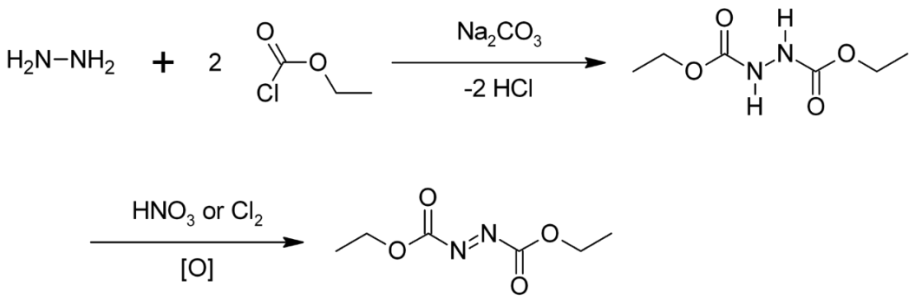
diethyl azodicarboxylate can be prepared fresh in the laboratory, especially if required in pure, non-diluted form. It is a two-step synthesis.

Step 1:

Alkyation of Hydrazine with ethylchloroformate.

Step 2:

Oxidation of diethyl hydroazodicarboxylate.



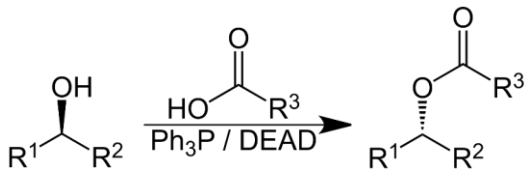
Mitsunobu Reaction

This reaction was discovered by Oyo Mitsunobu. The Mitsunobu reaction is an organic reaction that converts an alcohol into a variety of functional groups, such as an ester. The alcohol reacts with the phosphine to create a good leaving group then undergoes an inversion of stereochemistry in classic S_N2 fashion as the nucleophile displaces it. it. A common side-product is produced when the azodicarboxylate displaces the leaving group instead of the desired nucleophile.

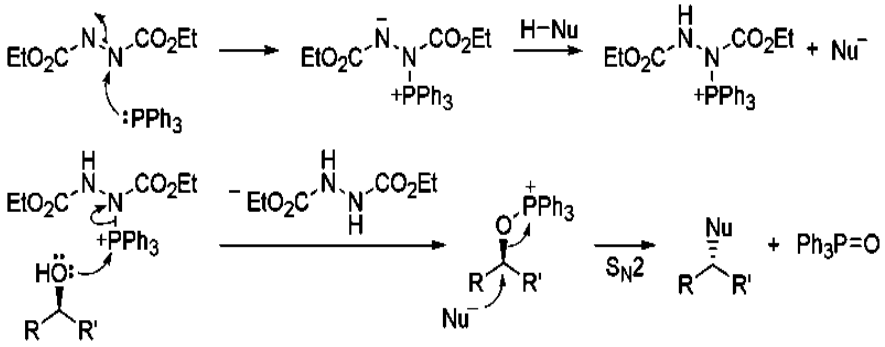
Reaction process:

In a typical protocol, one dissolves the alcohol, the carboxylic acid, and triphenylphosphine in tetrahydrofuran or other suitable solvent (e.g. diethyl ether), cool to 0 °C using an ice-bath, slowly add the DEAD dissolved in THF, then stir at room temperature for several hours.

Reaction:



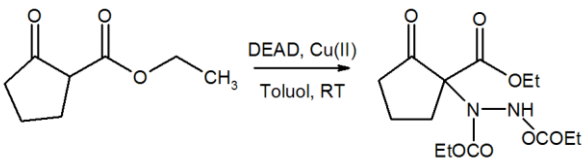
Mechanism:



Application:

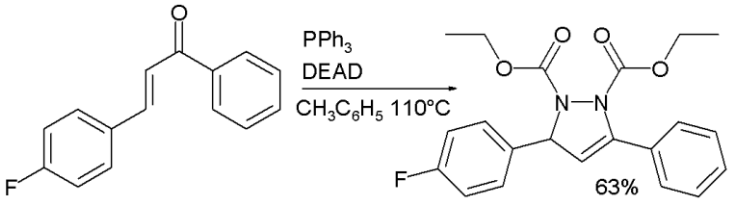
1. **Michael Reaction.**

   The azo group in DEAD is a Michael acceptor. In the presence of a copper(II) catalyst, DEAD assists conversion of β-keto esters to the corresponding hydrazine derivatives.

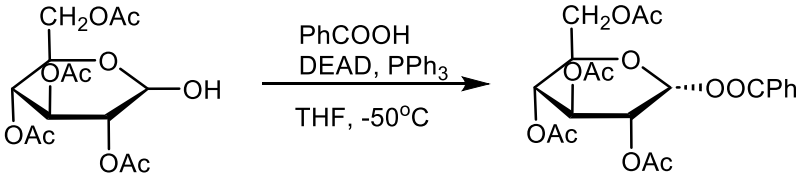
2. 

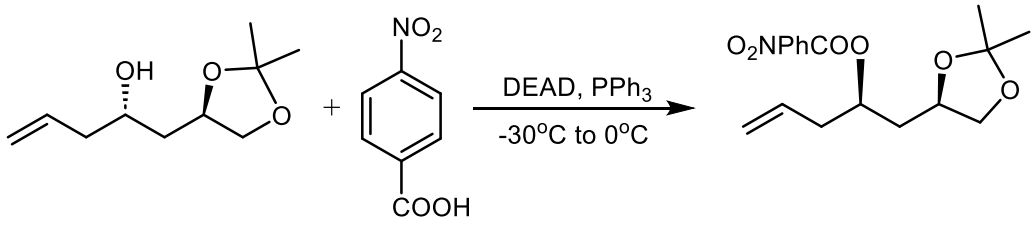
3. **Synthesis of Heterocyclic Compound:**

DEAD can be used for synthesis of heterocyclic compounds. Thus, pyrazoline derivatives convert by condensation to α,β-unsaturated ketones.



Other Application:

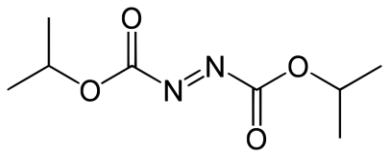
1) 

2) 

5.9. DIAD – diisopropyl azodicarboxylate

Diisopropyl azodicarboxylate (**DIAD**) is the diisopropyl ester of azodicarboxylic acid. It is used as a reagent in the production of many organic compounds. It is a orange liquid with melting point of 3 to 4^0C and boiling point of 75^0C. It is generally insoluble in water.

Structure



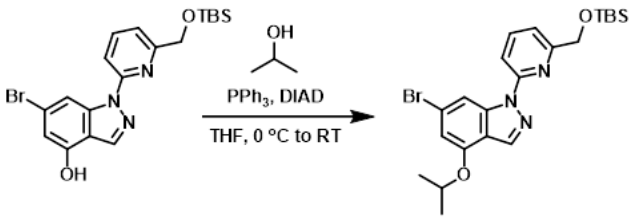
Preparation of DIAD

under protection of inert gas, add alkali and solvent, add carbazic acid isopropyl ester and diethyl carbonate successively, reacting by heating 2 ~ 6h at 100 ~ 180 DEG C, by solution acid for adjusting pH value to 4.5 ~ 7.5, suction filtration, obtains hydrodiazo dioctyl phthalate diisopropyl ester;

at-20 DEG C ~ 25 DEG C, hydrodiazo dicarboxylate being added massfraction is in the sulphuric acid soln of 40% ~ 50%, after dissolving, adds catalyzer, control temperature of reaction at-15 DEG C ~-5 DEG C, drip the hydrogen peroxide extremely no longer heat release that massfraction is 10% ~ 15%, drip Bi Jixu and react 5 ~ 10h, cancellation, extraction, be washed to neutrality, drying, filters, and concentrates and obtains diisopropyl azodiformate.

Mitsunobu reaction

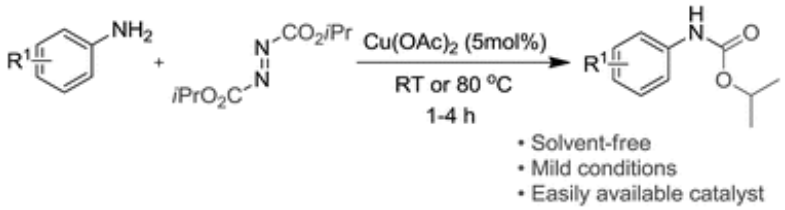
PPh3 (0.55 g, 2.1 mmol) was added to a solution of the **indazole** (0.65 g, 1.5 mmol) and IPA (0.16 mL, 2.1 mmol) in THF (7.6 mL). The mixture was cooled in an ice-H2O bath, then treated slowly with DIAD (0.41 mL, 2.1 mmol). The mixture was allowed to reach RT while stirring over the weekend. The mixture was diluted with EtOAc then washed with H2O, brine, dried (MgSO4), and concentrated. The resulting material was purified by silica gel flash chromatography (24 g silica gel, 0-40% EtOAc/heptane) to provide the product.



Application of DIAD:

1. Copper catalysed Carbonylation of Aniline to form Carbamates.

   A Cu-catalyzed efficient methodology for the direct carbonylation of anilines has been developed. The N–H bond cleavage and N–C bond formation were notably achieved under solvent-free conditions and a variety of carbamates were synthesized from readily available anilines using diisopropyl azodicarboxylate (DIAD) as the carbonylating source.



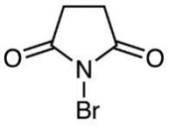
2. **Copper catalysed reaction of oxime.**

   A new Cu-catalyzed efficient protocol is described for the transformation of oximes to the corresponding carbonate derivatives. Diisopropyl azodicarboxylate acted as a selective new precursor for the synthesis of oxime carbonates in high yields. The O–H bond cleavage and O–C bond formation occur in the presence of a copper catalyst providing a synthetically useful process, which tolerates a wide range of functional groups.

5.9 *N*-bromosuccinimide (NBS)

The IUPAC name of NBS is 1- Bromo – 2,5 pyrrolidinedione. It is commonly known as *N*-Bromosuccinamide. This is a convenient source of bromine used for both radical substitution and electrophilic addition reaction. It is used by accomplished with non-polar solvents such as CCl_4.

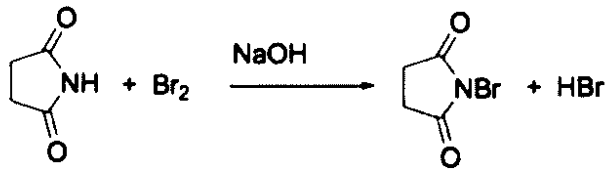
Structure



Preparation

NBS can be prepared from succinamide in the presence of sodium hydroxide solution, a white product is washed with water and recrystallized from hot water or acetic acid . It is stored in refrigerator and protected from moisture to avoid decomposition. It is easier and safer to handle than bromine.

Preparation:



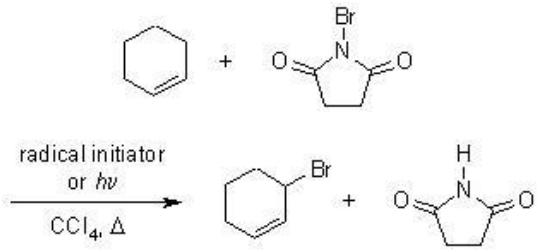
Applications

1. Allylic and benzylic bromination

Alkenes are brominated at allylic positionon refluxing a solution of alkene and recrystallized NBS in anhydrous CCL4. The reaction is initiated by peroxide or light.

For example,

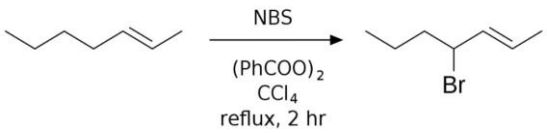
Reaction of NBS with cyclohexene gives 3 – Bromo cyclohexene in the presence of catalytic amount of radical initiator such as benzoyl peroxide or AIBN. Olefins can be brominated in the allylic position by a number of reagents but NBS is the most common. When this reagent is used the reaction is known as Wohl – Ziegler reaction



3 – Bromocyclohexane (50 – 80%)

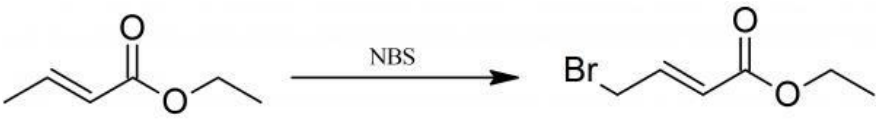
If these are two allylic positions, then two monobromo derivatives may be obtained. Bromine is attached to allylic methylene groups much more rapidly than allylic methyl groups

Example, In 2 – heptene, a secondary position is substituted more rapidly than primary.



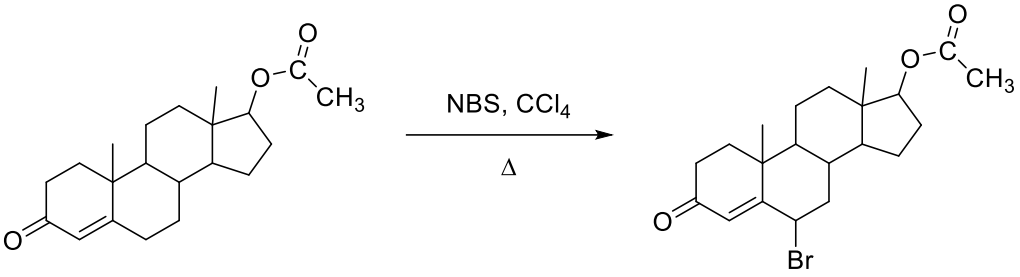
2. Allylic bromination of unsaturated acids, esters, aldehyde, ketone

Ethyl 4- bromo crotonate is readily prepared from ethyl crotonate using NBS in the presence of benzoyl peroxide as initiator



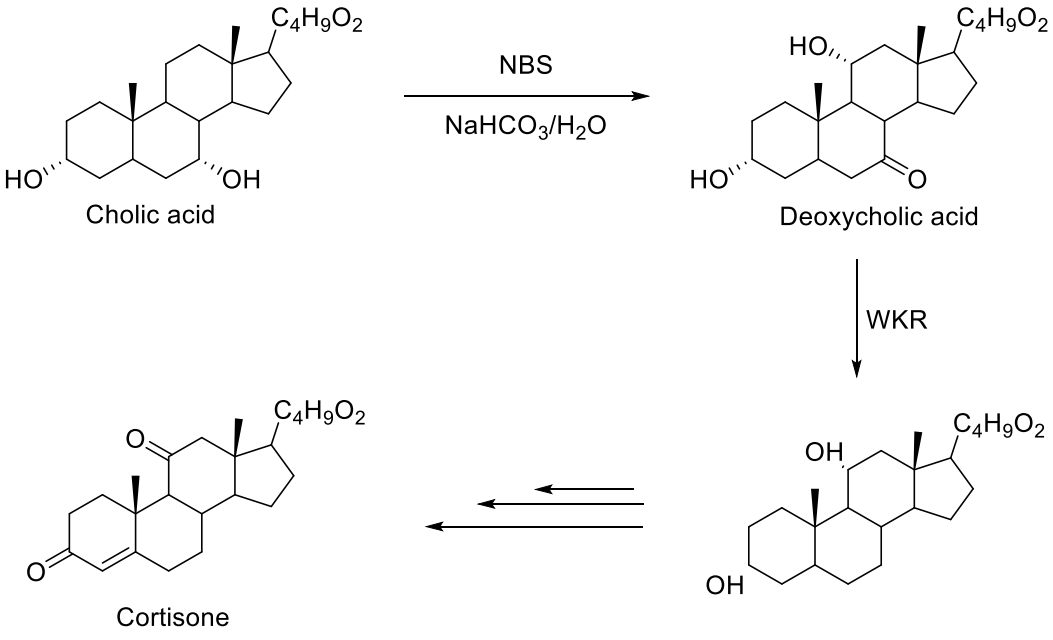
Ethyl crotonate Ethyl 4 – bromo crotonate

Under similar conditions , testosterone acetate (5) is converted into 6 – Bromotestosterone acetate by NBS



Testosterone acetate 6-Bromo Testosterone acetate

3. Selective oxidation of cholic acid (9) with NBS in the presence of H_2O provides an efficient route to deoxycholic acid (10) required as starting material for the synthesis of cortisone.



Cholic acid Deoxycholic acid

Cortisone

Advantages of N Bromosuccinamide

1. NBS facilitates selective bromination of allylic and benzylic position in the presence of other reactive sites such as double bonds or aromatic rings.

2. It is stable solid compound, easy to handle and store.

3. NBS exhibits good regioselectivity favouring the bromination of less hindered positions in many cases leading to predictable in outcomes in synthetic routes.

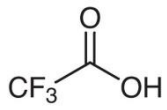
Disadvantages

1. Highly reactive substrates or under harsh conditions overbromination may occurs
2. NBS is sensitive to moisture, reactivity can be affected by exposure to air or humid condition.
3. NBS is not prohibitively expensive, it may be costlier compared to alternative bromination reagents particularly for large scale.

5.10 Trifluoroacetic acid (TFA)

TFA was discovered by swarts in 1922 at early 20th century. It was widely used in organic synthesis as solvent, catalyst, and reagent, chemical transformation done with TFA. And it is mainly used as deprotecting reagent of BOC (N tert- Butyloxycarbonyl) boc is an protecting group for specific functional group like amine.

Structure



Preparation of TFA

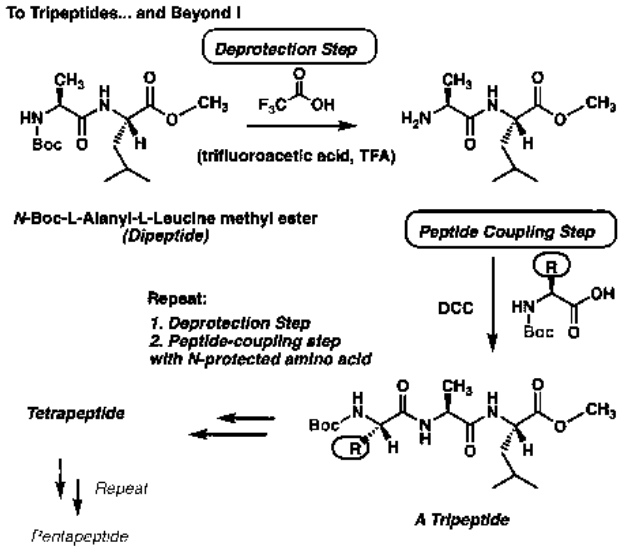
Trifluoroacetic Acid is prepared by the electrochemical fluorination of acetylchloride or acetic anhydride in anhydrous hydrogen fluoride using Simon's process.

$$CH_3COCl + 4\ HF \rightarrow CF_3COF + 3\ H_2 + HCl$$
$$CF_3COF + H_2O \rightarrow CF_3COOH + HF$$

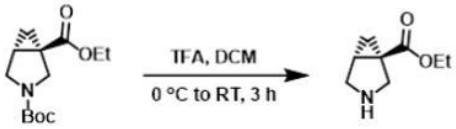
Applications

1. Deprotection of BOC in peptide synthesis

TFA is popularly used as a strong acid to remove protecting groups such as BOC used in organic chemistry and peptide synthesis.



2.



3.

4. Good solubility of peptides in TFA, fewer side reactions during deprotection, and mildness make it useful not only for removal of temporary protecting groups but also for the final deprotection step.

Uses

TFA is popularly used as a strong acid to remove protecting groups such as BOC used in organic chemistry and peptide synthesis. At a low concentration, TFA is used as an ion pairing agent in liquid chromatography (HPLC) of organic compounds, particularly peptides and small proteins.

Advantages

Wide range of reactions are promoted by TFA including esterification, condensation, and oxidation.

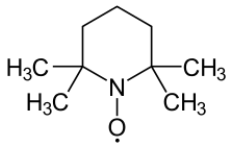
Disadvantages

TFA is a corrosive chemical contact can severely irritate and burn the skin and eyes cause eye damage.

5.11 Tetramethyl piperiridin-1-oxyl (TEMPO)

(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl or (2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl, commonly known as TEMPO, is a chemical compound with the formula $(CH_2)_3(CMe_2)_2NO$. This heterocyclic compound is a red-orange, sublimable solid. As a stable aminoxyl radical, it has applications in chemistry and biochemistry. TEMPO is used as a radical marker, as a structural probe for biological systems in conjunction with electron spin resonance spectroscopy, as a reagent in organic synthesis, and as a mediator in controlled radical polymerization

Structure

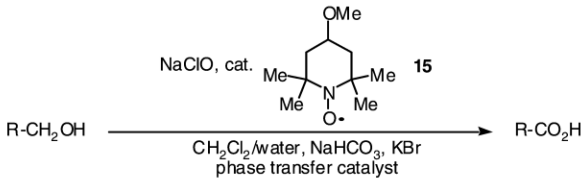


Preparation

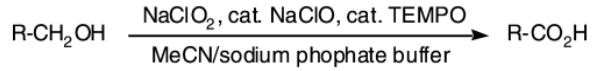
TEMPO (**13**)

Applications

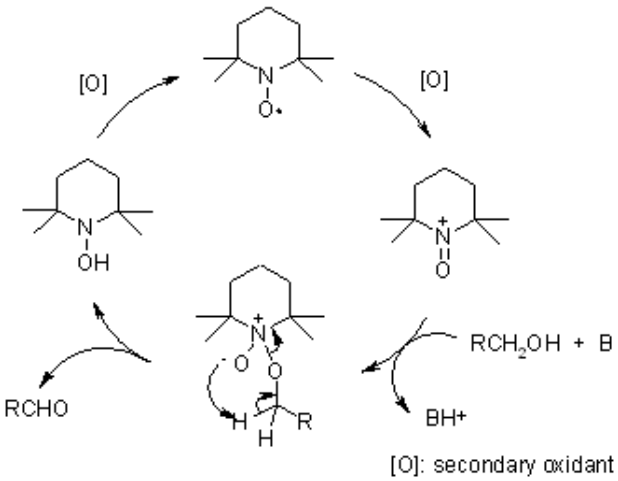
1. Anelli's oxidation of primary alcohols



2. Zhao's modification of Anelli's oxidation



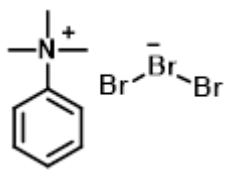
Catalytic cycle



5.12 Phenyltrimethylammonium tribromide (PTAB)

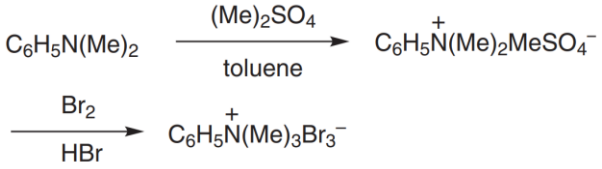
Phenyltrimethylammonium tribromide (PTAB) is known to be a convenient oxidizing and brominating agent. It is an orange crystal and easy to handle, with a melting point at 113–115 °C.1 It has been used for various oxidative transformations.

Structure



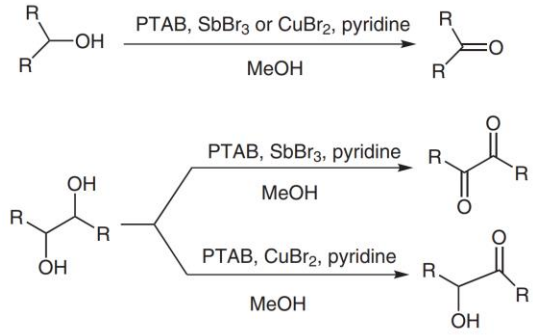
Preparation

Phenyltrimethylammonium tribromide is commercially available now. It can be readily prepared from N,N-dimethylaniline and dimethyl sulfate, followed by treatment with 48% hydrobromic acid and bromine.

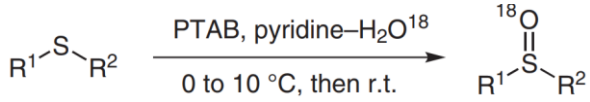


Applications

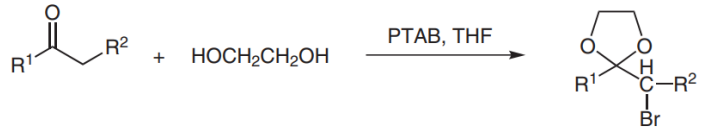
(A) Oxidation of Secondary Alcohols to the Corresponding Carbonyl Compounds



(B) Selective Oxidation of Sulfides to Sulfoxides:



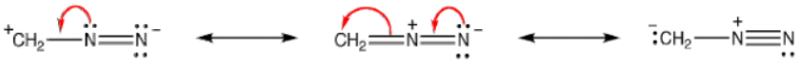
(C) One-Pot a-Bromoacetalization of Carbonyl Compounds:



5.13 Diazomethane and Zn-Cu

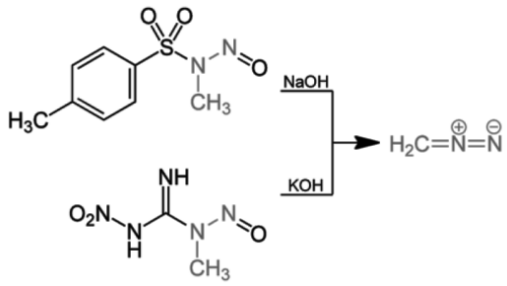
Diazomethane is the chemical compound CH_2N_2, discovered by German chemist Sir. Hans von Pechmann in 1894. Diazomethane is a yellow, poisonous, potentially explosive compound, which is a gas at room temperature.

Structure



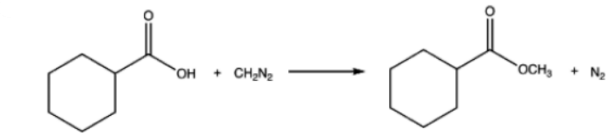
Preparation

Diazomethane is prepared by hydrolysis of an ethereal solution of an *N*-methyl nitrosamide with aqueous base.

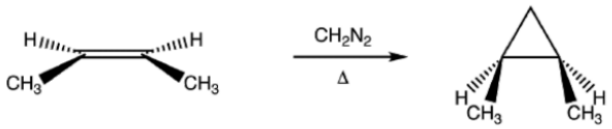


Applications

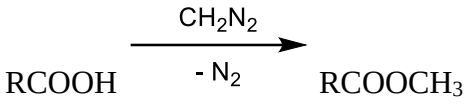
1. Conversion of carboxylic acids to methyl esters



2. Conversion of alkenes to cyclopropanes

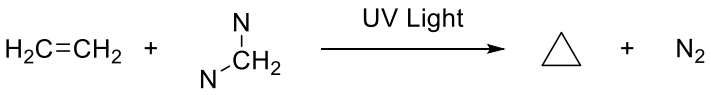


3. It is used as methylating agent for acidic compounds, alcohols, carbonyl compounds, amines



4. For synthesis of Heterocyclic compounds

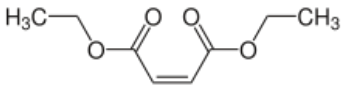
Diazomethane condense with ethylenic and acetylenic bonds to give heterocyclic compounds.



5.14 Diethyl maleate (DEM)

A maleate ester resulting from the formal condensation of both carboxy groups of maleic acid with ethanol. A colourless liquid at room temperature (m.p. -10°C) with boiling point 220°C at 1 atm., it is commonly used as a dienophile for Diels-Alder-type cycloaddition reactions in organic synthesis.

Structure



Preparation

Dimethyl maleate can be synthesized from maleic anhydride and methanol, with sulfuric acid acting as acid catalyst, via a nucleophilic acyl substitution for the monomethyl ester, followed by a Fischer esterification reaction for the dimethyl ester.

Applications

Dimethyl maleate is used in many organic syntheses as a dienophile for diene synthesis. It is used as an additive and intermediate for plastics, pigments, pharmaceuticals, and agricultural products. It is also an intermediate for the production of paints, adhesives, and copolymers.

Dimethyl maleate has also found use in applications where improvements in the hardness and toughness of polymer films are desired. This includes, in particular, the improvement of anti-blocking properties of copolymers of vinyl acetate with DMM. It is also used as an internal modifier to increase the glass transition temperature of styrene or vinyl chloride polymers.

5.15Copper diacetylacetonate ($Cu(acac)_2$)

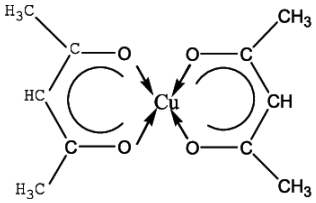
Copper acetylacetonate, also known as copper(II) acetylacetonate or copper acetylacetonate hydrate, is a coordination compound with the chemical formula $Cu(acac)_2$. The term "acac" refers to the acetylacetonate ligand, which is a beta-diketone ligand.

The chemical structure of copper acetylacetonate can be represented as $Cu(O_2C_5H_7)_2$, and it is commonly found in a hydrated form. The hydrated form may have water molecules associated with the copper ions in the crystal lattice.

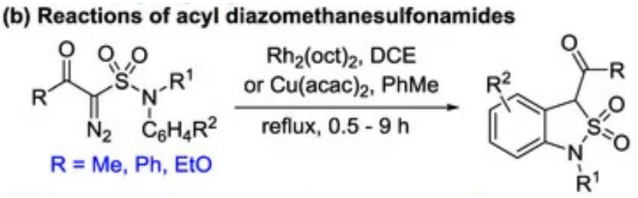
This compound is often used in various applications, including as a precursor for the deposition of thin films in electronics, a catalyst in organic reactions, and as a component in the synthesis

of other copper-containing compounds. It has interesting optical and electronic properties that make it useful in certain technologies and research fields.

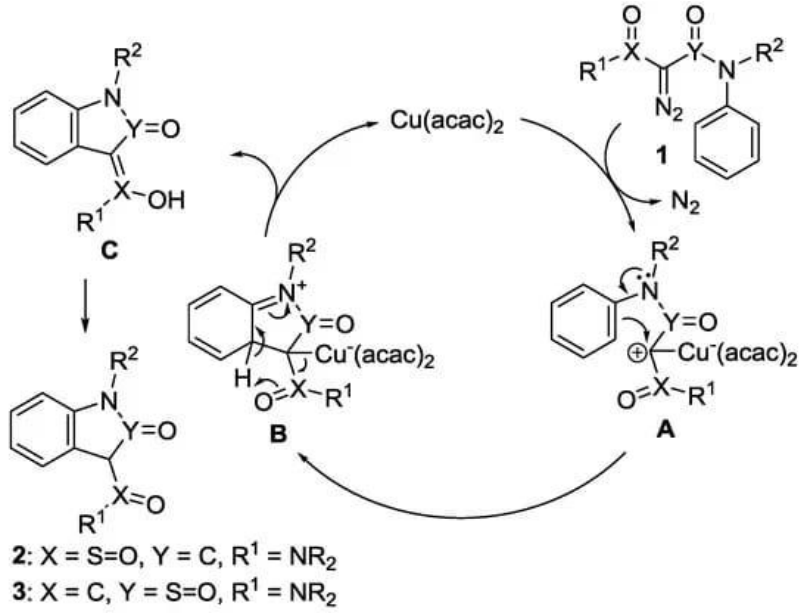
Structure



Reaction Scheme

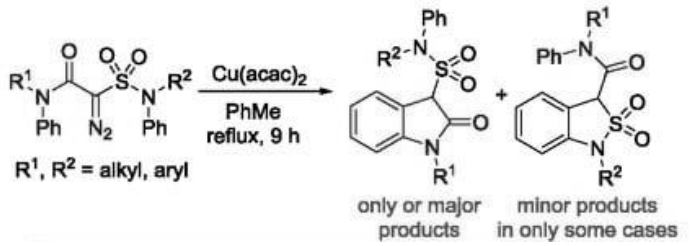


Mechanism



Diazosulfamoylacetamides **1** react with $Cu(acac)_2$ to generate Cu-carbon ylides A, of which the carbocation electrophilically attacks the benzene ring in the N-phenyl group in the amide moiety (in the sulfonamide moiety only for 2-diazo-N,N-dialkyl(N-rylsulfamoyl)acetamides) to yield cyclized intermediates B (Frediel–Craft alkylation). After releasing $Cu(acac)_2$ catalyst and the proton transfer, the intermediates **B** convert to aromatic 1,5-inserted enolic intermediates **C**, which tautomerize into final products **2** and/or **3.**

Applications



The electron density of the phenyl group controlled chemoselectivity.

The chemoselectivity is controlled by the electron density of the phenyl group in the intramolecular competitive aromatic 1,5 – C – H insertion of *N*-aryl-2-diazo-2-(*N*-arylsulfamyl)acetamides.

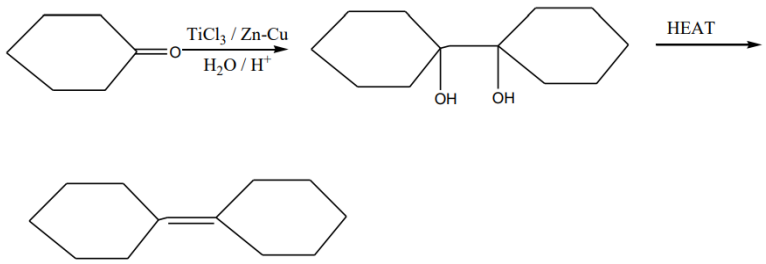
5.16 $TiCl_3$

Preparation

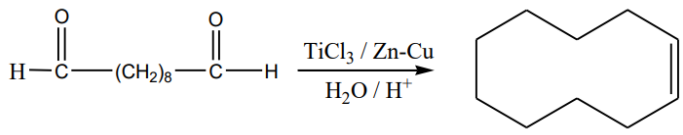
$2\ TiCl_4 + H_2 \rightarrow 2\ HCl + 2\ TiCl_3$

Applications

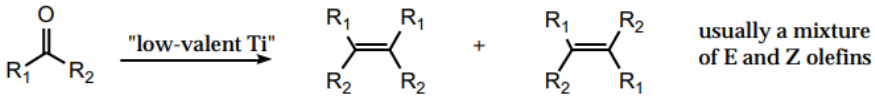
1. Mc-Murry Reaction



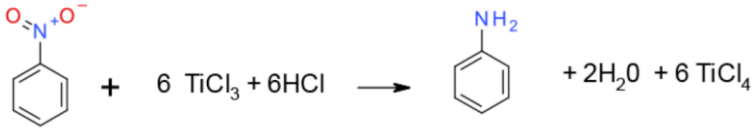
This reaction can also occur in the dialdehyde of the long hydrocarbon chain by the intramolecular fashion.



3. Reductive coupling of carbonyls with low valent transition metals, to give olefins



4. Mild and efficient reagent for nitro reduction.

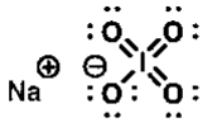


5. $TiCl_3$ is the main Ziegler-Natta catalyst, responsible for most industrial production of polypropylene. The catalytic activities depend strongly on the polymorph and the method of preparation.

6. $TiCl_3$ is also a reagent in organic synthesis, useful for reductive coupling reactions, often in the presence of addedreducing agents such as zinc. It reduces oximes to imines.

5.17 $NaIO_4$

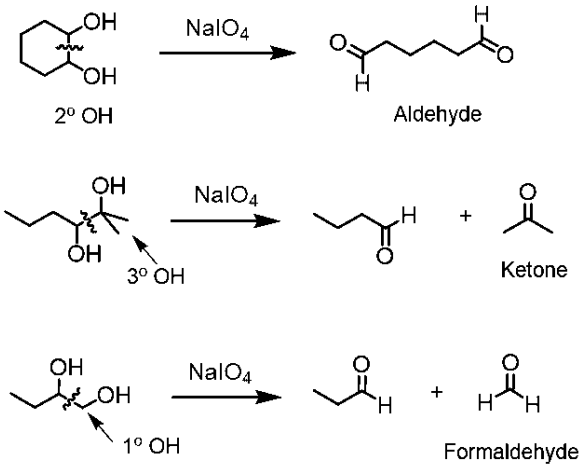
Structure

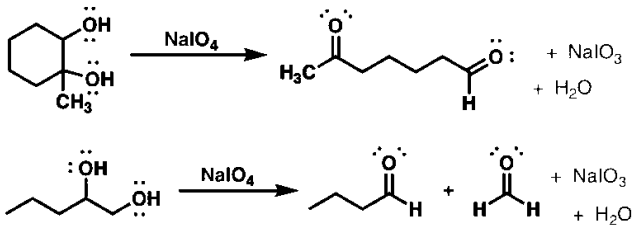


Sodium periodate ($NaIO_4$)

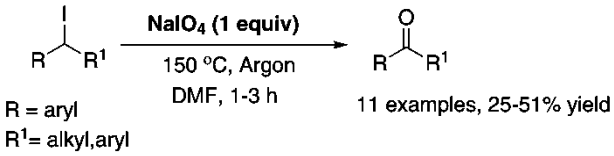
Applications

1. Sodium periodate ($NaIO_4$), is a strong oxidizing agent mainly used for the oxidative cleavage of 1,2-diols (vicinal diols) forming aldehydes and ketones depending on the structure of the alcohol



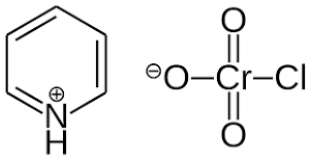


2. Oxidation of iodomethyl group



5.18 Pyridinium chlorochromate (PCC)

- The history of this reagent goes back to 1975 when ELIAS JAMES COREY and WILLIAM SUGGS suggested it as an oxidizing agent.
- It is commonly referred as Collins reagent, named after its developer Thomas L. Collins.
- This reagent used in the organic synthesis of converting primary alcohol to aldehyde and secondary alcohol to ketone.
- It is a yellow orange colored salt.
- It oxidizes the alcohol (OH) group and does not affect any other functional group or double bond present in the compound.
- It can oxidize both aliphatic and aromatic alcohol.
- The chemical formula for pyridinium chlorochromate (PCC) is $C_5H_5NH^+$ CrO_3Cl^-. It consists of a pyridinium cation ($C_5H_5NH^+$) and a chlorochromate anion (CrO_3Cl^-).

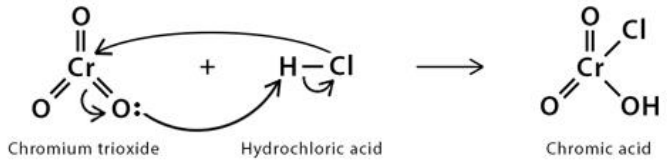


- It is soluble in DCM and it is non- hygroscopic in nature.

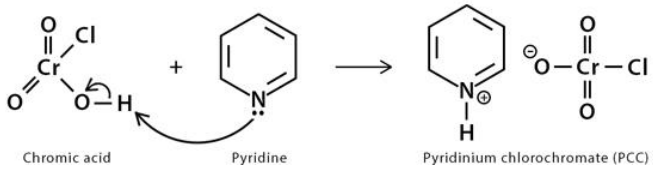
Preparation:

PCC reagent is prepared by adding 1ml of solid chromium trioxide to concentrated hydrochloric acid followed by rapid stirring. The solution is cooled to 0^0 C. To this solution, 1ml of pyridine is added until the final mixture turns into a yellow orange solid. The solid product is filtered and dried in a vacuum.

Step 1

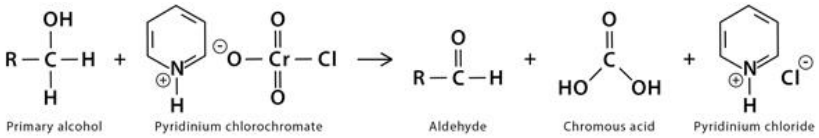


Step 2

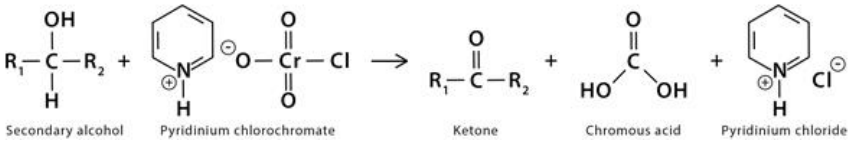


Example:

1. Oxidation of primary alcohols to aldehyde,



2. Oxidation of secondary alcohols to ketone,



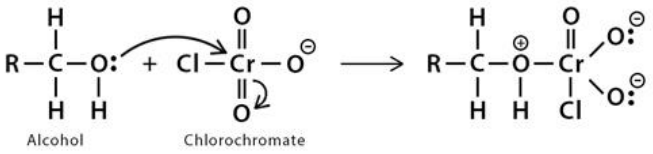
3. Oxidation in tertiary alcohol is not possible.

Mechanism:

The alcohol co-ordinates with the chromium (IV) atom, displacing chlorine. The chlorine then acts as the base, resulting in oxidation of alcohol and reduction of chromium (VI) to chromium (IV).

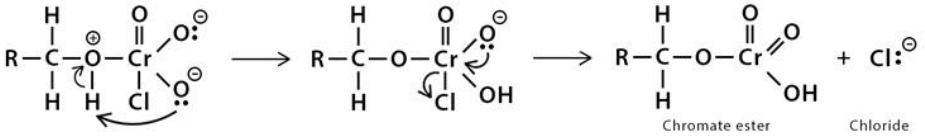
Step 1

Attack of the oxygen atom by the chromium atom to form a Cr-O bond.



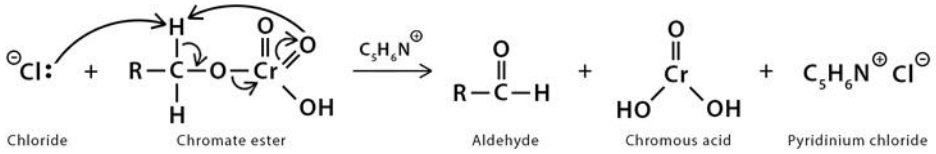
Step 2

Transfer of proton from the O-H bond to one of the oxide ions, followed by displacement of the chloride ion to form a chromate ester.



Step 3

Deprotonation of the chromate ester by a strong base like chloride, resulting in a C-O double bond and hence, an aldehyde. Breakage of Cr-O bond, resulting in the reduction of Cr (VI) to Cr (IV).

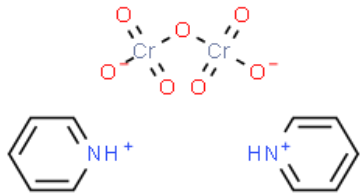


5.19 Pyridinium dichromate (PDC)

- In 1962, The Australian British Chemist Sir John Warcup Cornforth introduced PDC.
- It is also known as Cornforth reagent.
- It is a red/orange solid.

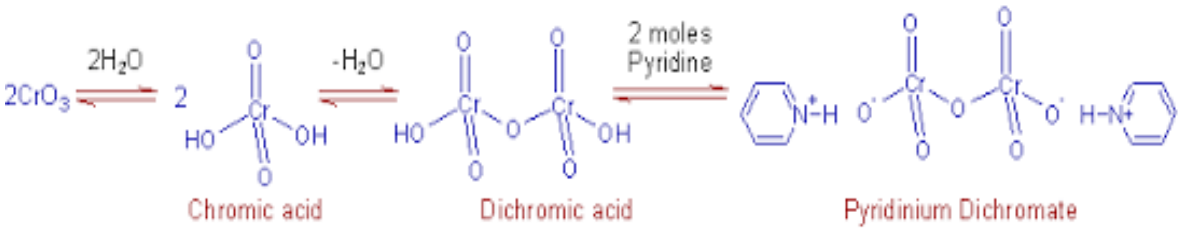
- It is used in the organic synthesis of converting primary alcohol to aldehyde and secondary alcohol to ketone.
- It is less acidic than PCC.
- The reaction conditions are mild.
- The chemical formula of PDC is $[C_5H_5NH^+]^2[Cr_2O_7]$.

Structure



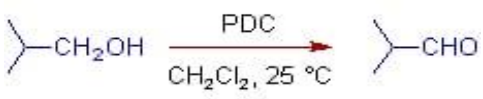
Preparation

It is obtained by gradual addition of a solution of chromic anhydride in water to pyridine in ice cold conditions.

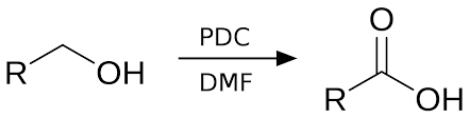


Example:

1. Primary alcohols are conveniently oxidized to aldehydes with PDC in dichloromethane at room temperature.

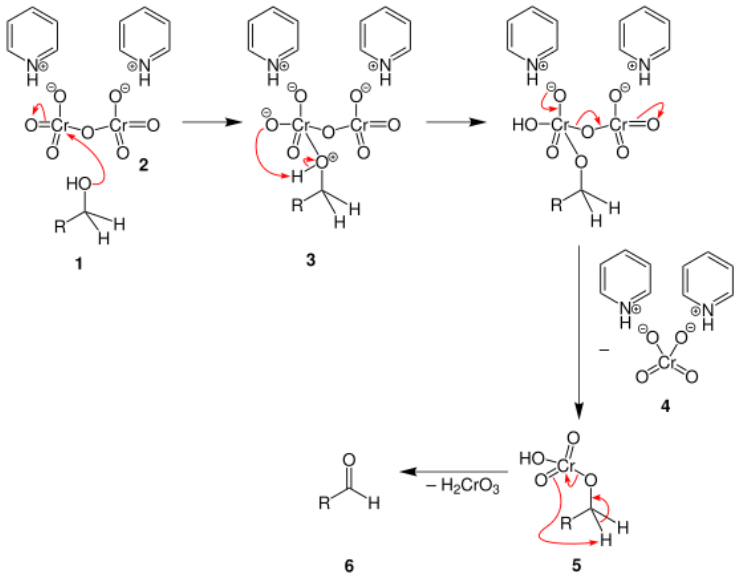


2. The secondary alcohols are oxidized to ketones with PDC.



3. Oxidation of tertiary alcohol does not exist.

Mechanism:



- **Composition:**

PCC: Contains chromium (VI) in the form of chromate (CrO_3) and chloride ions.

PDC: Contains chromium (VI) in the form of dichromate (Cr_2O_7) and chloride ions.

- **Oxidizing power:**

PCC: Generally considered to be milder than PDC.

PDC: More aggressive oxidizing agent compared to PCC.

- **Selective oxidation:**

PCC: Selectively oxidizes primary alcohols to aldehydes and secondary alcohols to ketones.

PDC: Also selectively oxidizes primary and secondary alcohols, similar to PCC.

- **Stability:**

PCC: Relatively stable under normal storage conditions.

PDC: Less stable than PCC and can decompose over time, especially in the presence of moisture.

- **Solubility:**

PCC: Typically, soluble in organic solvents like dichloromethane and chloroform.

PDC: Solubility properties are similar to PCC, generally soluble in organic solvents.

- **Applications:**

PCC: Widely used in organic synthesis for mild and selective oxidation reactions.

PDC: Also employed in organic synthesis for selective oxidation reactions, but may be preferred for more aggressive oxidation conditions.

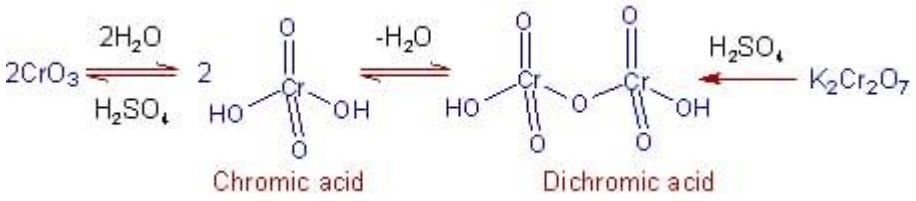
- **Safety:**

PCC: Generally considered safer and easier to handle compared to PDC.

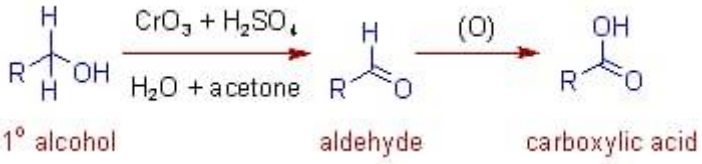
PDC: More hazardous due to its higher oxidizing power and potential for decomposition.

Some Oxidizing Reagents Containing Chromium;

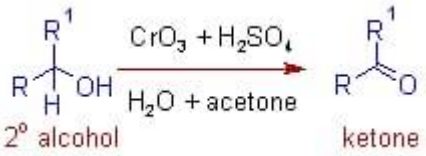
- Fiser reagent: CrO_3 in acetic acid.
- Thile reagent: CrO_3 + acetic anhydride + H_2SO_4.
- Jones reagent: (CrO_3 + dil. H_2SO_4 + H_2O) in acetone.
- Jones reagent can also be made from the,



- In Jones reagent, the primary alcohols are initially oxidized to aldehydes, which are finally oxidized to acids.

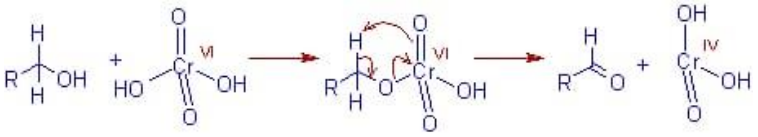


- The secondary alcohols are oxidized to ketone.

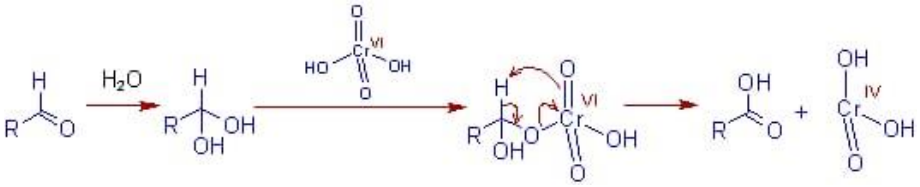


Mechanism:

- The primary alcohols are oxidized with chromic acid to give aldehyde.

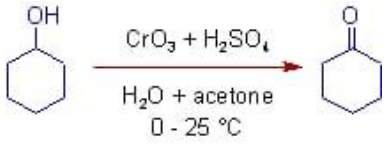


- The secondary alcohols are oxidized with chromic acid to give ketone.

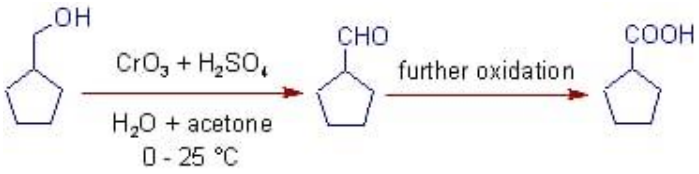


Applications:

- The secondary alcohols are oxidized to corresponding ketones in jones reaction.

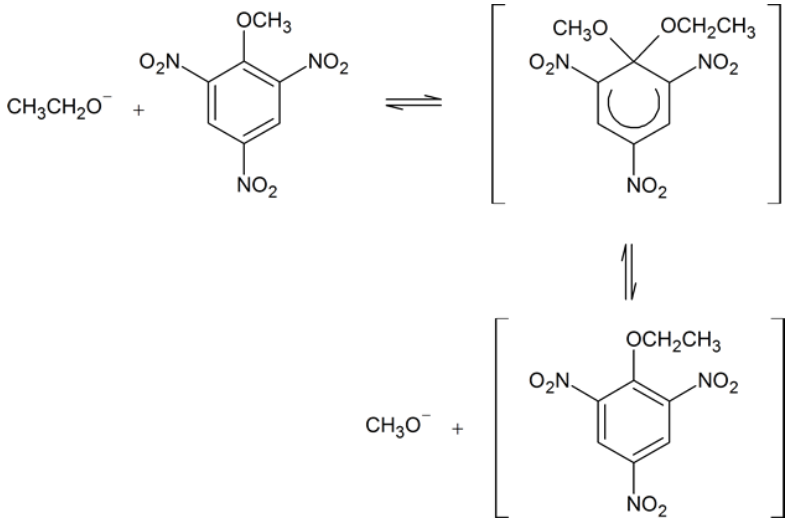


- The primary alcohols are oxidized to carboxylic acid via aldehydes with jones reagent.



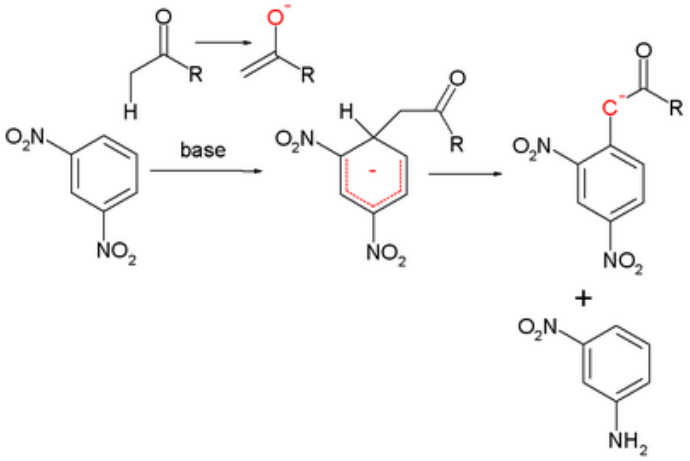
5.20 Meisenheimer complex

A Meisenheimer complex is a negatively charged intermediate formed by the attack of a nucleophile upon one of the aromatic-ring carbons during the course of a nucleophilic aromatic substitution reaction. A typical Meisenheimer complex is shown in the reaction scheme below. Notice how this particular complex can be formed from two different starting materials by using a different nucleophile in each case.



Applications

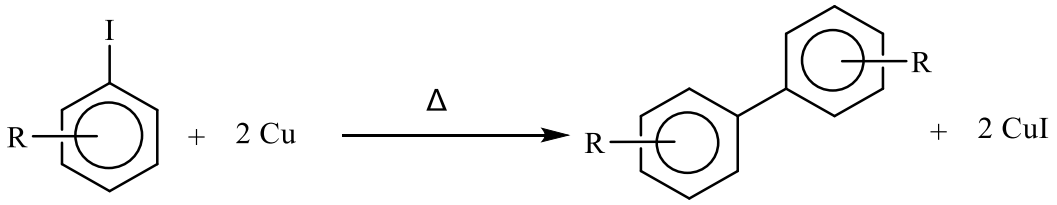
In the Zimmermann reaction the Janovski adduct is oxidized with excess base to a strongly colored enolate with subsequent reduction of the dinitro compound to the aromatic nitro amine. This reaction is the basis of the Zimmermann test used for the detection of ketosteroids.



Palladium catalysed C – C Cross Coupling Reactions

Introduction

C – C bond formation is one of the important reactions, in organic chemistry. Non-catalytic traditional aryl – aryl coupling (or) aryl – alkene coupling involves many steps. Copper mediated aryl – aryl homocoupling using Aryl Iodide was introduced by Ulman in the year 1901.

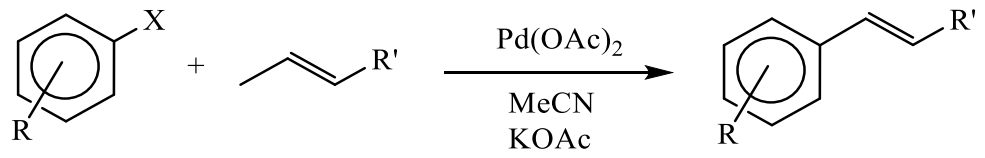


Chem. Ber. 1901, 34, 2174

The major discoveries in the cross-coupling reactions, catalysed by Palladium, begain in 1972 with the Heck reaction (Aryl Halide + Alkene) and the Kumada reaction (Aryl Halide + RMgX). The most important contribution of all cross-coupling reactions however came from Prof. Akira Suzuki. In 1979, the seminal paper of Suzuki and Miyaura in *Tetrahedron Letters* laid the ground work, which is most important and useful in modern day Synthetic Organic Chemistry. Since, then research by various groups over past 30 years has lead to vast improvement of this reaction. Sonogoshira brought in Palladium catalyzed Aryl-Alkyne coupling in 1975. Buchwald and Hartwig introduced aryl C-N and aryl C-O coupling with Pd catalyst.

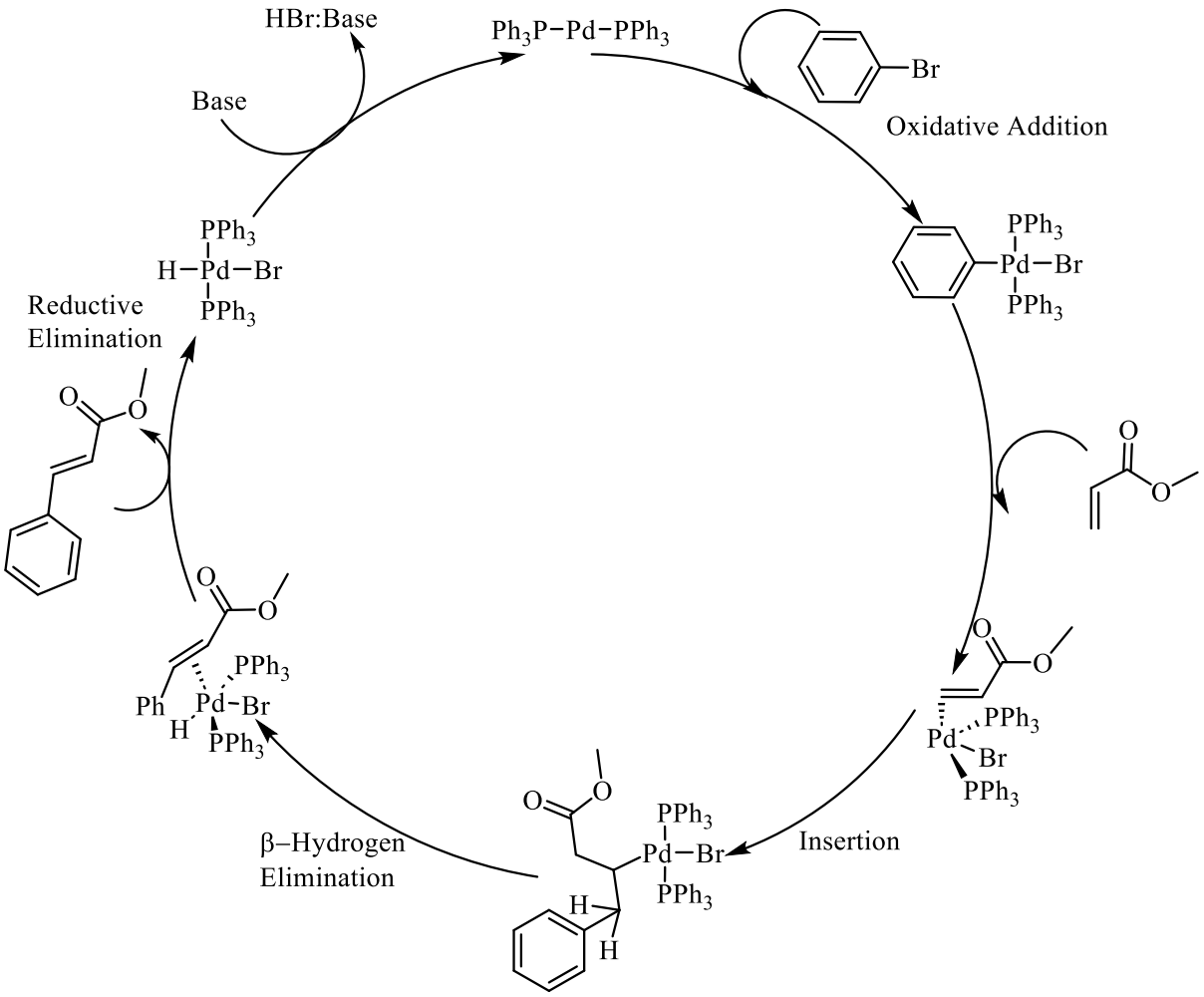
5.21 The Heck Reaction (T Mizorki and R F Heck)

The classical Heck Reaction involves the Palladium catalysed substitution of vinyl, aryl or benzyl group. Palladium as Pd(II) in the form of salt or complex or as Pd(0) with concentration of 1-5 mole% is the most widely used catalyst in this reaction. A base is necessary to remove the liberated acid HX. Typical catalysts are Pd(0) – Phosphine complexes, $Pd(PPh_3)_4$, $Pd(OAc)_2/PPh_3$, $Pd_2(dba)_3$ and (π-allyl) Pd complexes.

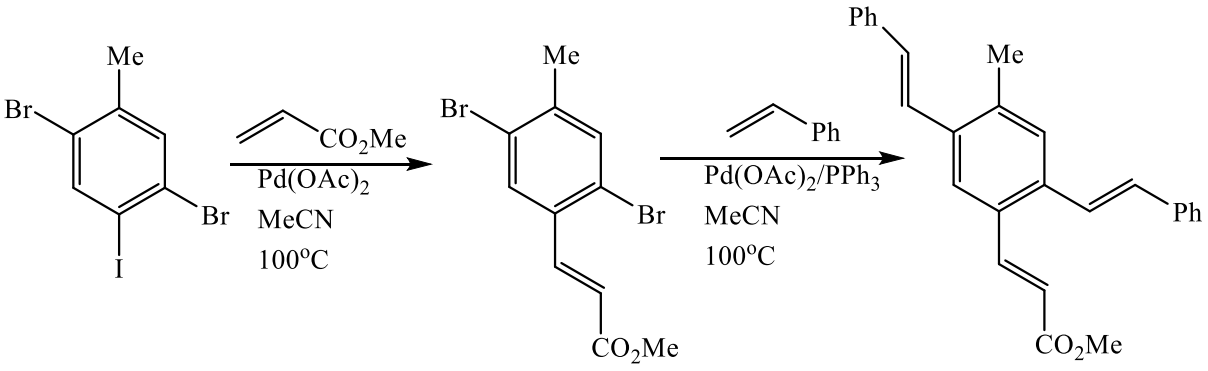


Generally, such reactions are conducted in polar aprotic solvents like MeCN, DMSO (or) DMAc (Dimethylacetamide). The reaction time depends on the nature of organohalide to be activated. Iodo are more reactive and hence ligands are avoided. In these cases polar solvents DMF, DMAc in combination with NaOAc as a bases are especially used. Many functional groups are compatible with Heck conditions which enables the synthesis of carbo and heterocyclic compounds and C – C bonded isomerized products including natural products.

Catalytic Cycle



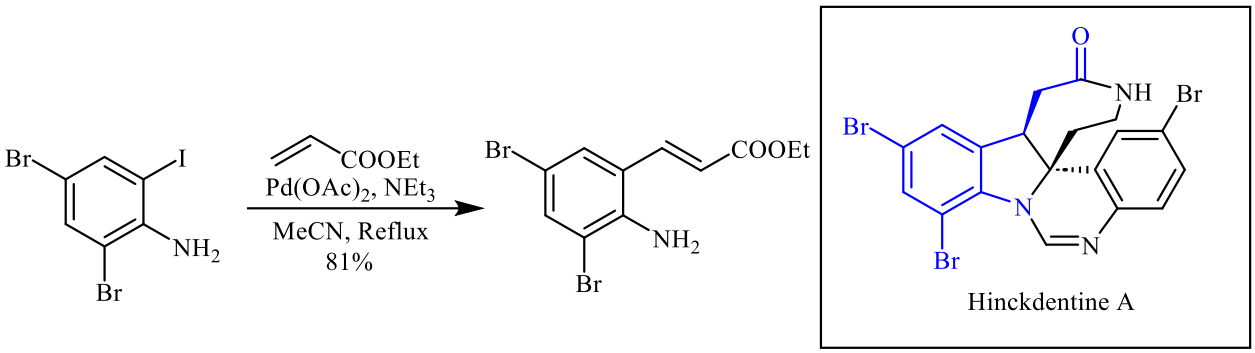
Examples



Discrimination in reactivity is possible in Heck reactions by controlling the reaction conditions. In the above condition when PPh_3 is not added, only iodide is replaced by acrylate whereas upon addition of PPh_3, the bromides also reacts with the tri alkenyl substituted toluene.

Applications

Towards the Total synthesis of Hickdentine A



Org. Lett. 2021, 23, 2169

5.22 The Suzuki – Miyaura Coupling

The Suzuki coupling can ne described as a palladium catalysed cross coupling reaction of organoboron compounds with organic halides.

$$R - BY_2 \; + \; R' - X \xrightarrow{[Pd],\ Base} R - R'$$

Where, BY_2 = $B(OH)_2$, $B(OR'')_2$, $B(CHCH_3CH(CH_3))_2$

X = I, Br, OSO_2 ($C_n F_{2n+1}$) and also Cl (with bulky electron rich phosphines)

R = Aryl, Alkenyl

R' = Aryl, Alkenyl, Alkynyl, Benzyl, Allyl

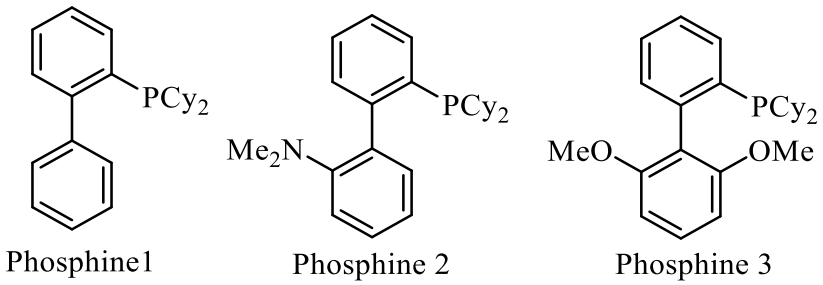
[Pd] = $Pd(PPh_3)_4$, $Pd(OAc)_2$, $Pd_2(dba)_3$

Base = Na_2CO_3, NaOEt, Net_3, K_3PO_4, CsF

This is one of the most powerful reactions in the synthetic organic chemistry for C – C bond formation as it can tolerate the presence of functional groups in coupling partners. The Suzuki reaction requires conditions milder than that of Heck reaction. The boronic acids are air and water stable and as well as non-toxic.

There has been vast improvement and increase in the scope and utility of this reaction. This includes aryl chlorides as substrates, the ability to conduct reaction at very low catalyst loading, to carry out reaction at room temperature, to couple highly hindered substrates and to

carryout asymmetric synthesis. The phosphine component in the metal catalyst has undergone wide changes. An important breakthrough came in 1998 from the work of Stephen Buchwald and Gregory Fu of MIT. They found systems that would catalyse coupling of aryl chlorides under mild conditions. They used Pd with an electron rich phosphine bearing biphenyls, aliphatic phosphines like P(*t*-Bu)$_3$.

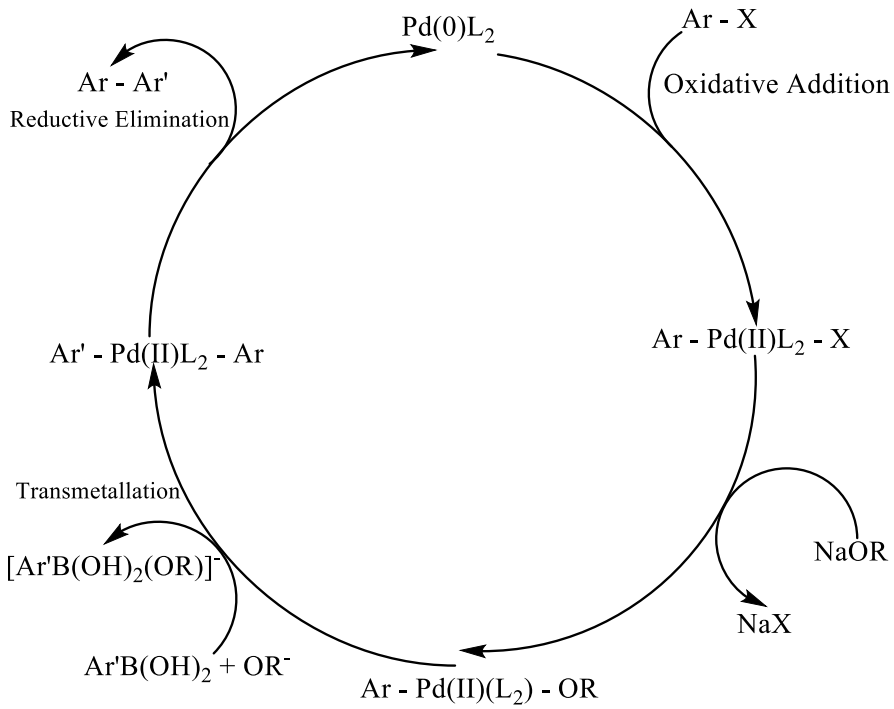


Phosphine1 Phosphine 2 Phosphine 3

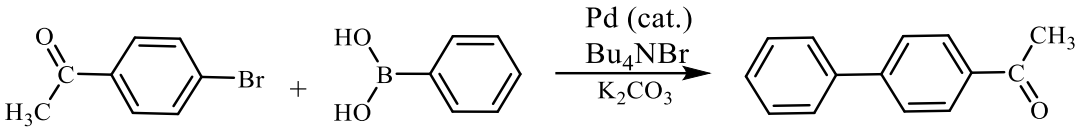
The success of these ligands is due to

1. Their electron richness enhances the rate of oxidative addition to Pd and prevents precipitation of the Pd complex.
2. Their steric bulkiness enhances the rate of reductive elimination.

Catalytic Cycle

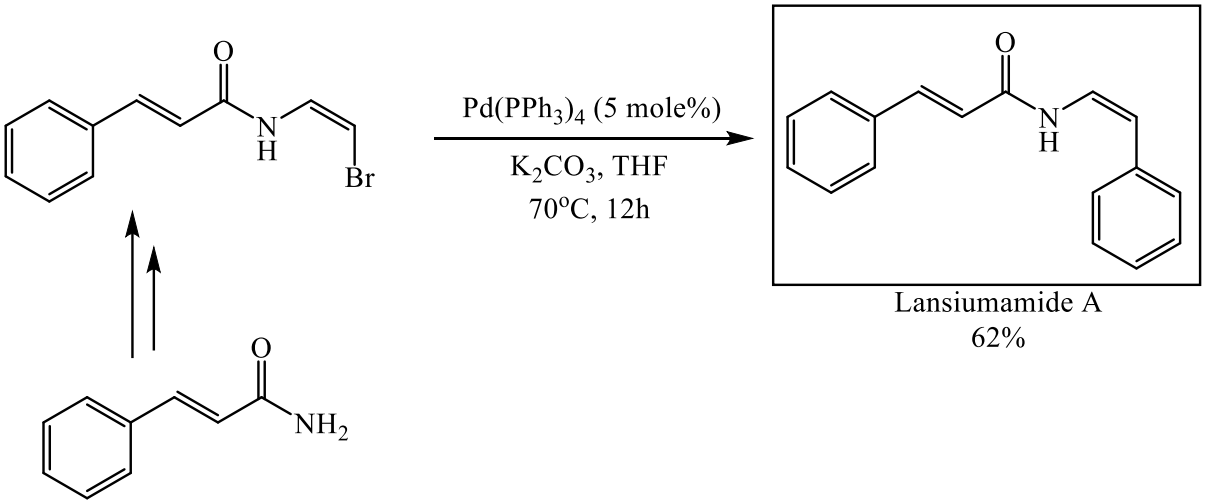


Example



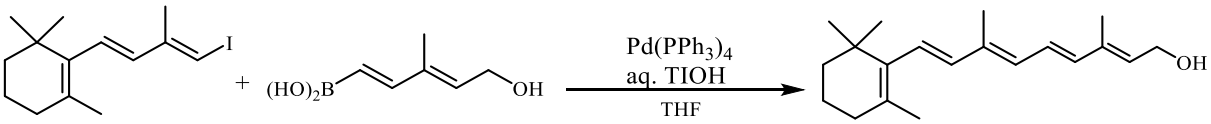
Applications

(i) Towards the total synthesis of Lansiumamide A



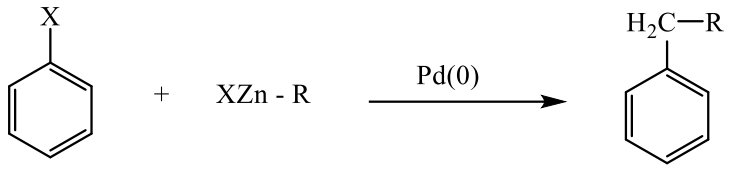
Tetrahedron Lett. 2014, 55, 6042

(ii) For the synthesis of Retinol

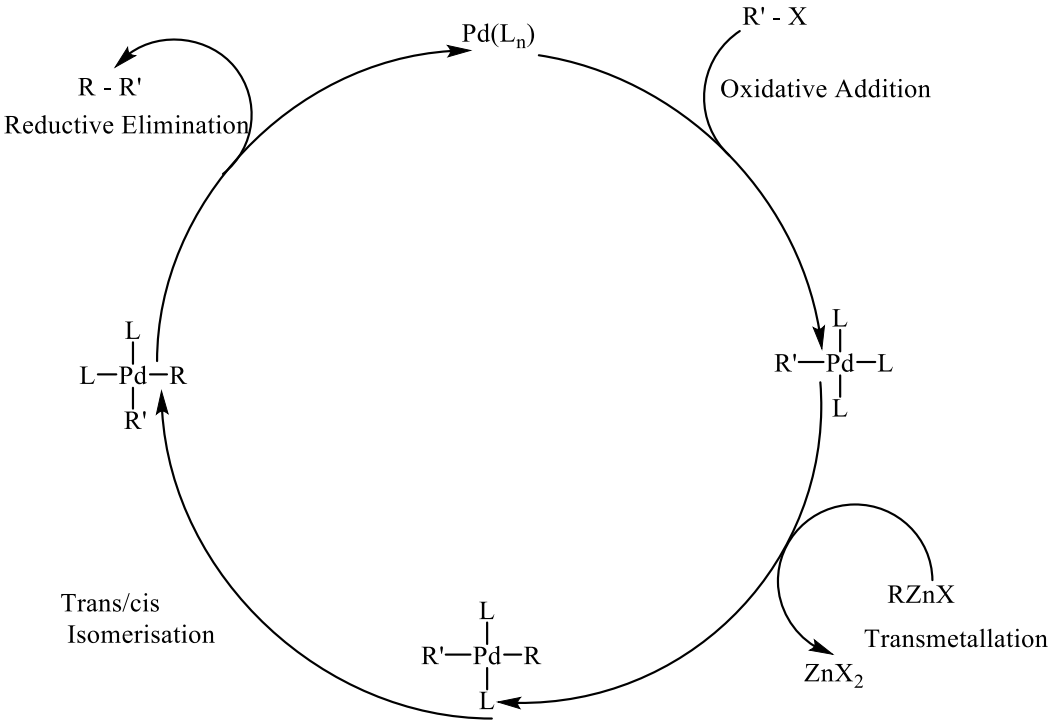


5.23 The Negishi Coupling

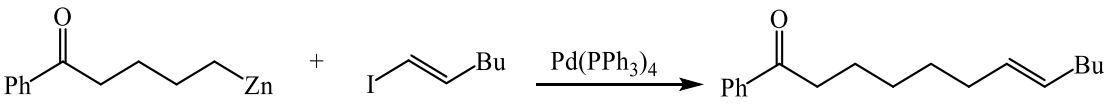
Negishi coupling is a cross coupling reaction that involves an organozinc compound, an organic halide and a palladium/nickel catalyst and creates a new C – C bond. The Negishi coupling, reported in 1977, was the first reaction that allowed the preparation of unsymmetric biaryls and coupling of heterocyclic rings. The active catalyst in this reaction is Pd(0) or Nickel and the reaction generally proceeds through oxidative addition of organic halide, followed by transmetallation with the Zinc compound and finally reductive elimination.



Catalytic Cycle

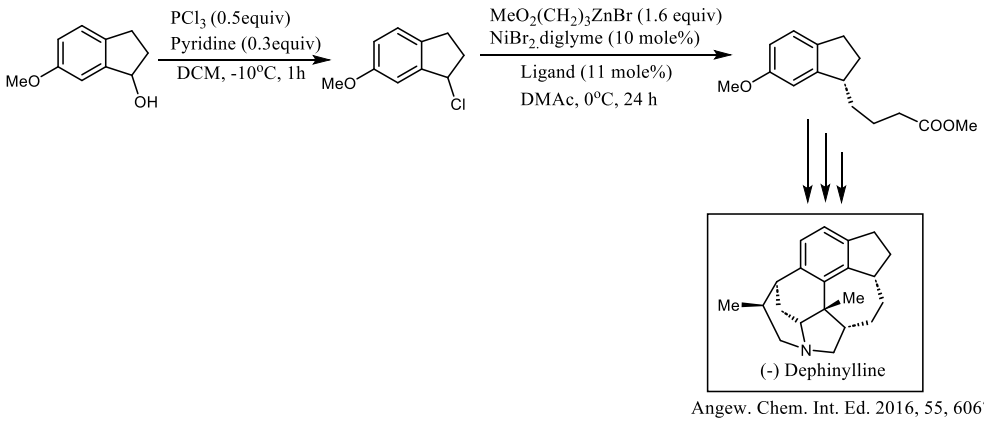


Example



Applications

(i) Towards the Total Synthesis of (-) Dephenylline



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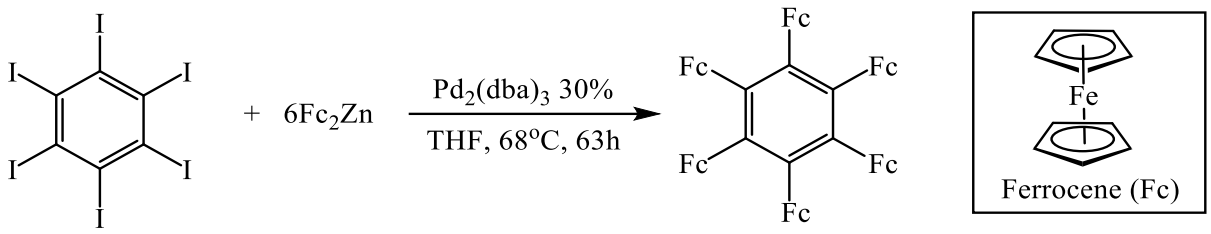
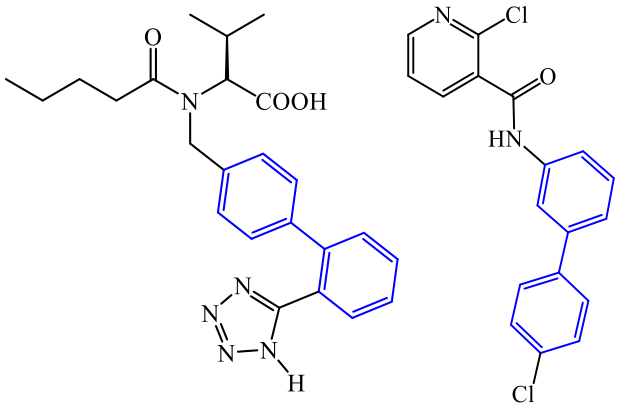
(ii) For Synthesis of Hexa Ferrocenyl Benzene



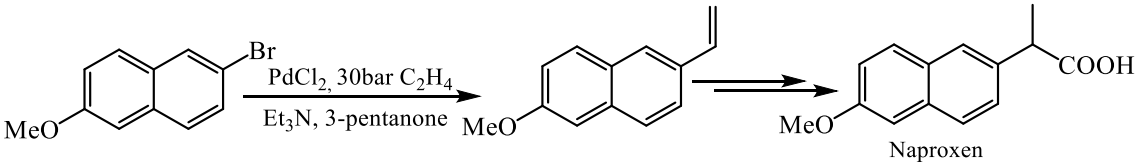
Industrial Applications of Cross Coupling Reactions

As biaryls are common substructures in many natural products, Suzuki cross coupling has been used in the industrial preparation of many natural products and bioactive compounds. The well-known antihypertensive drug Valsartan, is manufactured by Novartis. The use of Suzuki coupling had considerably reduced the number of steps in its synthesis. Another compound manufactured in bulk quantities by BASF using Suzuki coupling is the fungicide Boscalid, used on food crops.



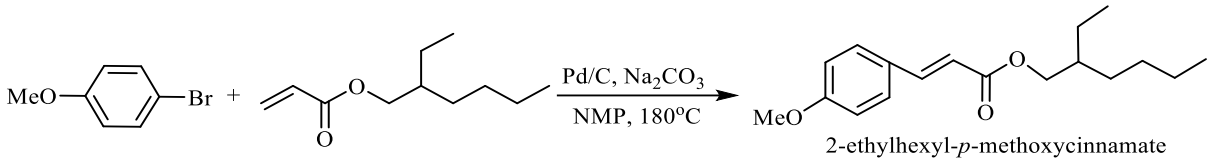
Valsartan Boscalid

The Suzuki coupling had been used in making many advanced materials such as light emitting polymers (such as polyphenylene vinylenes and polythiophenes). Organic LED manufactures use Suzuki coupling in large measures. Other cross coupling reactions also find use in many industrial applications. Albermarle Corporation uses the Heck reaction in the synthesis of drugs like Naproxen and Ketoprofen.



Naproxen

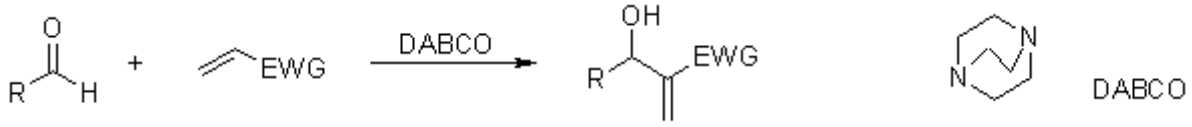
The Heck reaction is also used for the industrial synthesis of common sunscreen agent 2-ethylhexyl-*p*-methoxycinnamate, herbicide Prosulfuron and Singulair, an anti-asthma agent.



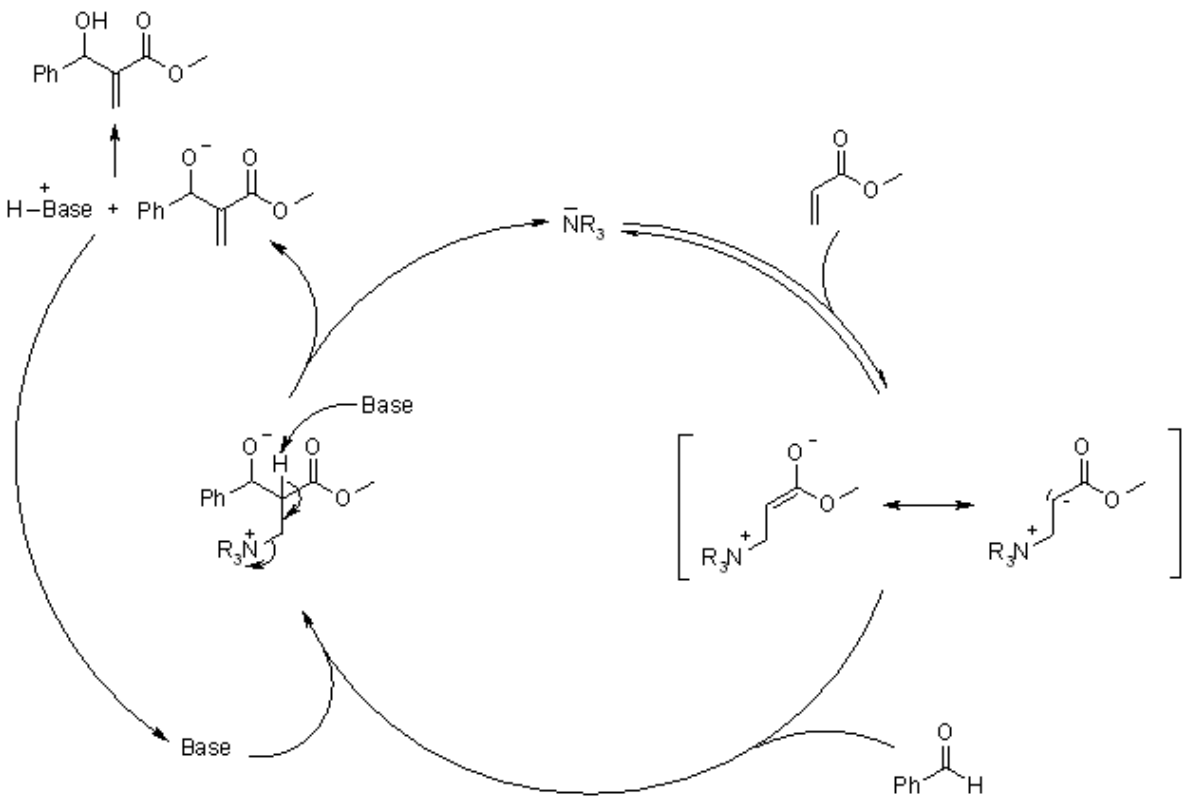
2-ethylhexyl-*p*-methoxycinnamate

5.24 Baylis-Hillman reaction

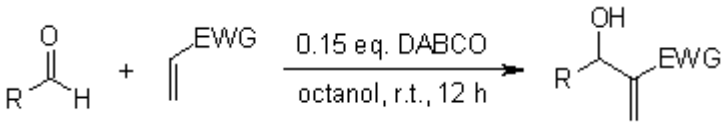
This coupling of an activated alkene derivative with an aldehyde is catalyzed by a tertiary amine (for example: DABCO = 1,4-Diazabicyclo[2.2.2]octane). Phosphines can also be used in this reaction, and enantioselective reactions may be carried out if the amine or phosphine catalyst is asymmetric.

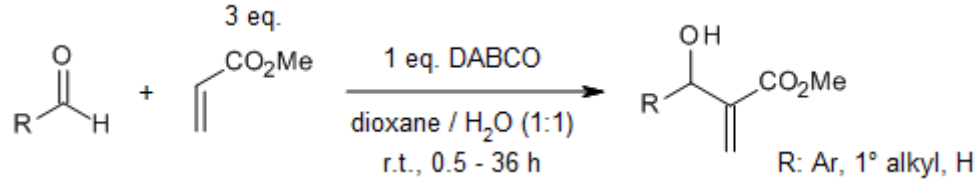


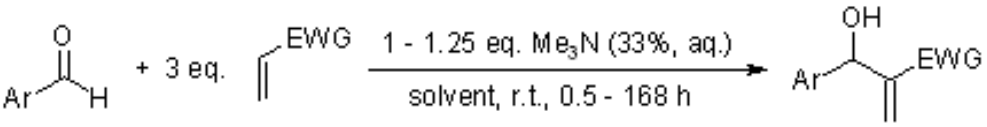
Catalytic Cycle



Applications

1. 

2. 

3. 

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