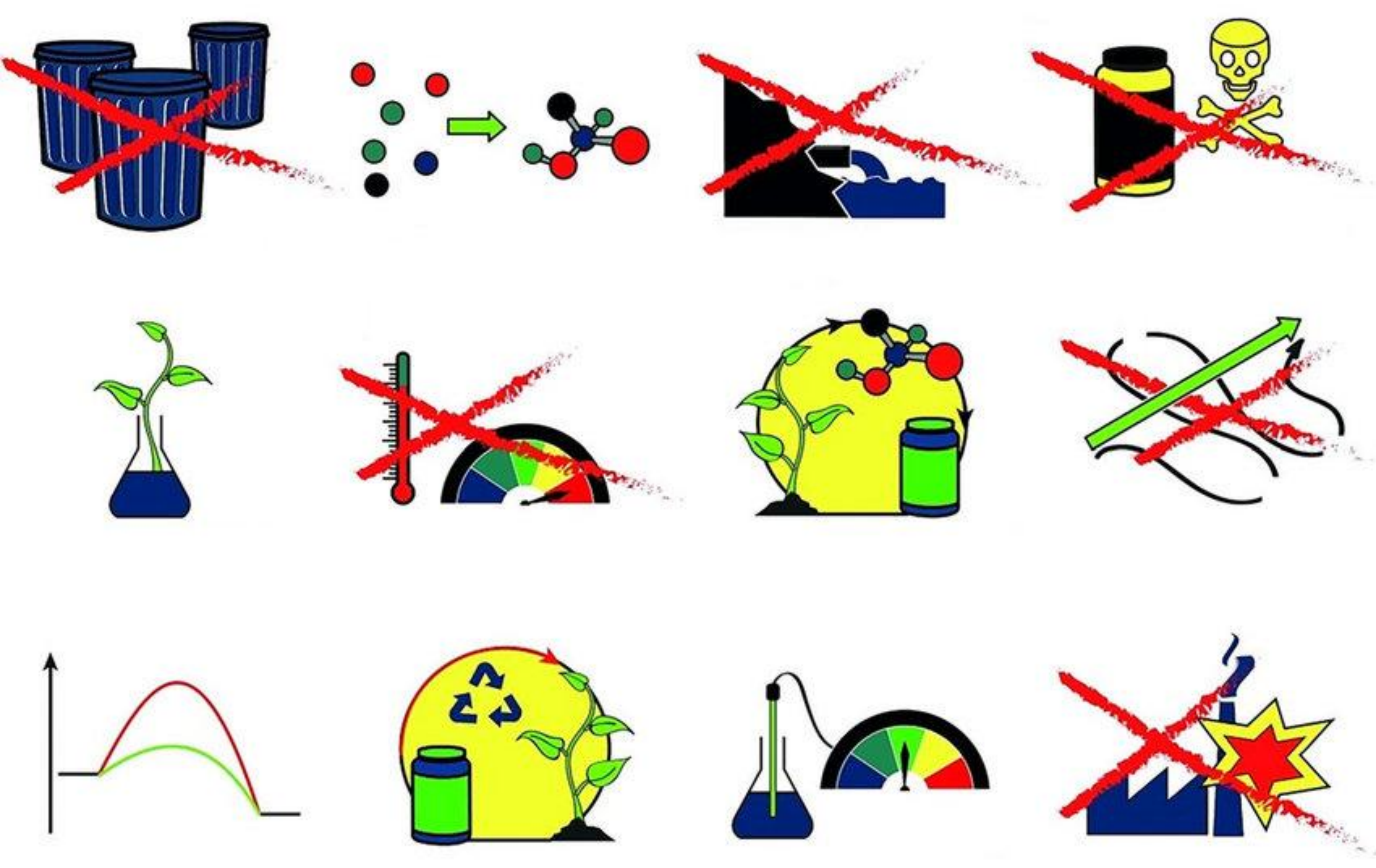
Chapter 2

Principles of Green Chemistry



Green Chemistry is the utilization of a set of principles that reduces or eliminates the use or generation of hazardous substances in the design, manufacture and application of chemical products

GREEN CHEMISTRY IS ABOUT

- Waste Minimization at Source
- Use of Catalysts in place of Reagents
- Using Non-Toxic Reagents
- Use of Renewable Resources
- Improved Atom Efficiency
- Use of Solvent Free or Recyclable Environmentally Benign Solvent systems

The 12 Principles of Green Chemistry

1. **Prevention**
   - It is better to prevent waste than to treat or clean up waste after it has been created.
2. **Atom Economy**
   - Synthetic methods should be designed to maximise the incorporation of all materials used in the process into the final product.
3. **Less Hazardous Chemical Synthesis**
   - Wherever practicable, synthetic methods should be designed to use and generate substances that possess little or no toxicity to people or the environment.
4. **Designing Safer Chemicals**
   - Chemical products should be designed to effect their desired function while minimising their toxicity.

5. **Safer Solvents and Auxiliaries**

   The use of auxiliary substances (e.g., solvents or separation agents) should be made unnecessary whenever possible and innocuous when used.

6. **Design for Energy Efficiency**

   Energy requirements of chemical processes should be recognised for their environmental and economic impacts and should be minimised. If possible, synthetic methods should be conducted at ambient temperature and pressure.

7. **Use of Renewable Feedstocks**

   A raw material or feedstock should be renewable rather than depleting whenever technically and economically practicable.

8. **Reduce Derivatives**

   Unnecessary derivatization (use of blocking groups, protection/de-protection, and temporary modification of physical/chemical processes) should be minimized or avoided if possible, because such steps require additional reagents and can generate waste.

9. **Catalysis**

   Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.

10. **Design for Degradation**

    Chemical products should be designed so that at the end of their function they break down into innocuous degradation products and do not persist in the environment.

11. **Real-time Analysis for Pollution Prevention**

    Analytical methodologies need to be further developed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances.

12. **Inherently Safer Chemistry for Accident Prevention**

    Substances and the form of a substance used in a chemical process should be chosen to minimize the potential for chemical accidents, including releases, explosions, and fires.

Prevention

It is better to prevent waste than to treat or clean up waste after it is formed

- Disposal of waste adds to the cost of chemical products
- Waste is a serious concern for economic, environmental, and social liability.
- It poses a threat the health of workers and general public.

What is Waste?

1. Resources consumed by inefficient or non-essential activities.
2. Unwanted material left from a production process or output which has no market value.
3. Process or material that does not (from the viewpoint of customer) add value to a goods or service.
4. Material discharged to, deposited in, or emitted to an environment in such amount or manner that may cause a harmful change.

Chemical waste includes:

- Unreacted starting materials,
- By-products (may be waste if not used as the starting material),
- Very large amount of solvent, and other auxiliary materials

- It is very expensive to store, transport, treat, and dispose of the waste
- If the waste is hazardous, then regulatory cost, liabilities, workers' health and safety are other concerns
- All these factors add up to the expense of material to be synthesized
- The expense due to waste of the unused starting material is paid two times-once as a feedstock and secondly for its disposal.

- Thus, it is very important to design and carry out a synthesis in such a manner that formation of waste is minimized.

E-factor (environmental impact factor)

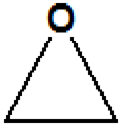
$$E = \frac{kg\ of\ biproduct\ produced}{kg\ of\ desired\ product}$$

Higher the value of E, higher is the amount of waste generated

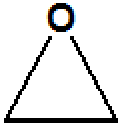
1. Two-step synthesis

$H_2C = CH_2 + Cl_2 + H_2O \longrightarrow ClCH_2{=}CH_2OH{+}HCl$

Chlorohydrin hydrate

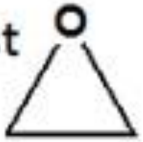
$ClCH_2{=}CH_2OH + Ca(OH)_2 \longrightarrow$  $+CaCl_2 + 2H_20$

Overall reaction:

$H_2C{=}CH_2 + Cl_2 + Ca\ (OH)_2 \longrightarrow$  $+CaCl_2 + 2H_20$

E-factor = 4.0

2. One-step synthesis

$H_2C{=}CH_2{+}0.5O_2 \xrightarrow{Catalyst}$ 

E-factor=0.3

Calculation of E-factor for various methods of hydrogen synthesis:

1. Production of hydrogen by steam reforming combined with water gas shift reaction of methane.

$$CH_4 + 2H_2O \xrightarrow{\qquad} CO_2 + 4H_2$$

E-factor= 44/8 = 5.5

2. Partial oxidation of hydrocarbons (butane) and the water gas shift reaction.

$$C_4H_{10} + 20_2 + 4H_20 \xrightarrow{\qquad} 4C0_2 + 9H_2$$

E-factor = 9.8

3. Bacterial fermentation

$C_6H_{10}O_5 + 7H_2O \longrightarrow 6CO_2 + 12H_2$

E-factor = 11.0

i.e. all hydrogen production processes produce waste. The higher the carbon content, the higher is the E-value

Practicing Green chemistry in Undergraduate lab

Various types of waste in the lab are as follows:

(a) Used solvents.

(b) Unwanted chemicals after experiments are over

(e) Other reagents intended to be discarded.

A chemist who is not careful may

(a) Dump solvents and solutions over the sink.

(b) Dump outside somewhere.

(c) Leave them lying around the lab.

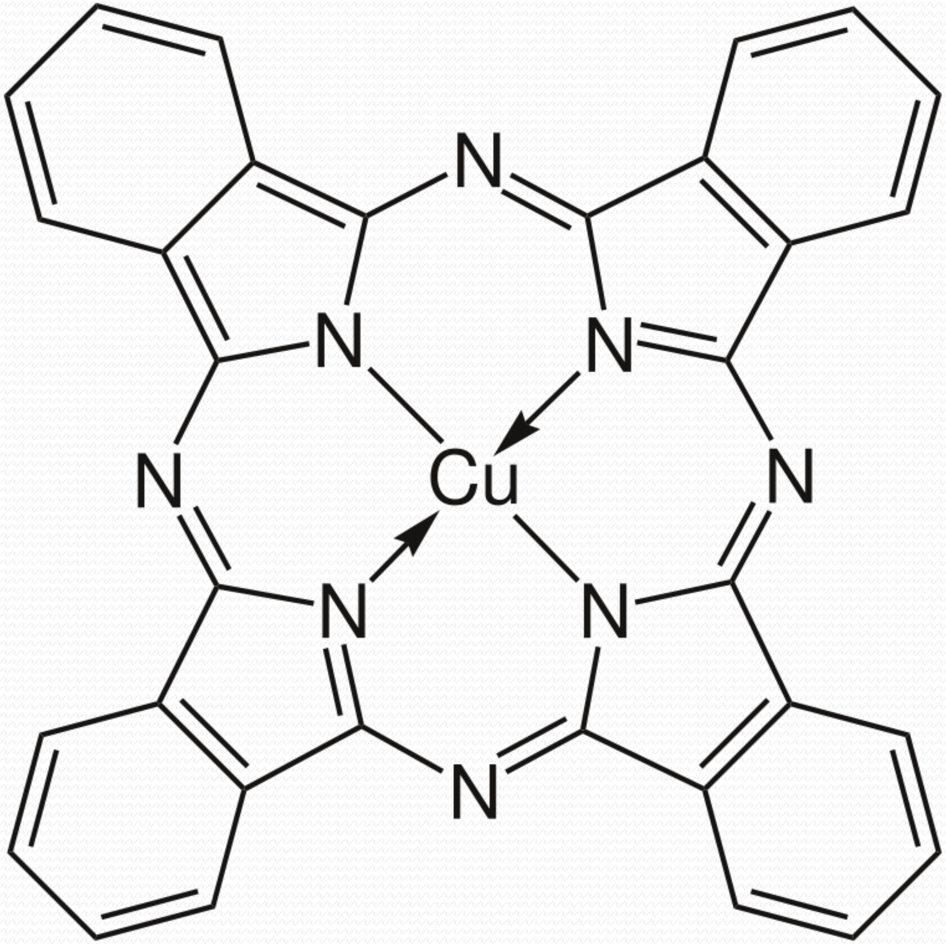
(d) Throw chemicals in the trash.

Following are the examples of utilization of waste in the lab:

(a) Organic derivatives prepared in the lab can be given for extra element detection in the class.

(b) Pththalic anhydride as derivative should be collected and used as the starting material for copper Pthalocyanine.

(c) Solid waste generated in the gravimetric experiments should be collected and experiments designed for several projects of students.


N
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Cu
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Examples of minimization of waste in the lab

(a) Qualitative analysis of inorganic mixture done by semi-micro analysis and micro techniques instead of macro analysis.

(b) Spot tests for cations and anions done.

(c) Qualitative organic analysis for preliminary test and functional groups by spot tests. Spot tests save time, energy, reagents and cost.

(d) Synthesis of inorganic compounds and organic derivatives is done with milligrams of the starting materials, wherever possible, instead of grams.

(e) Solvent-free synthesis should be done for organic derivative and inorganic preparations wherever possible.

Principle 2

Atom Economy

Synthetic methods should be designed to maximise the incorporation of all materials used in the process into the final product

Most of the chemical reactions carried out in a lab are assessed by percentage yield

$$\text{Yield (\%)} = \frac{\text{Actual quantity of the desired product}}{\text{Theoritical Quantity of desired product}} \text{X100}$$

Cones:
By-products that might be generated are not taken into consideration and can access 100% yield

Ideally, there is never a 100% yield. This may be due to
1. Improper mixing while conducting an experiment.
2. There are spills and splashes.
3. Some products may have been lost during the process of transferring
4. Reaction may not have been proceeded to 100%, especially in reversible reaction.

- Upon reaction of 1.274 g of copper sulfate with excess zinc metal, 0.392 g copper metal was obtained according to the equation:

$CuSO_4(aq)+Zn(s)\longrightarrow Cu(s)+ZnSO_4(aq)$

What is the percent yield?

Selectivity $$S = \frac{\text{Yield of the desired product}}{\text{yield of thesubstrate converted}} X100$$

$$\text{Atom economy (\%)} = \frac{\text{Mass of atoms in the desired product}}{\text{Mass of atoms in the reactants}} X\ 100$$

.

Salient Features of Atom Economy

1. The percentage atom economy is calculated theoretically using the balanced equation of a chemical reaction.

2. There is no practical work required to calculate atom economy.

3. Atom economy is a measure of the amount of starting material that will end up as useful products.

4. Calculation of atom economy helps at the planning stages of a reaction. Lots of waste is generated if atom economy is low, which requires redesigning of the synthetic process.

5. Reactions which give only one product has maximum atom economy, of 100%. An ideal reaction would incorporate all the reactants into the desired product. Higher atom economy means less material is wasted, less energy used, making the process more economic, greener, and sustainable.

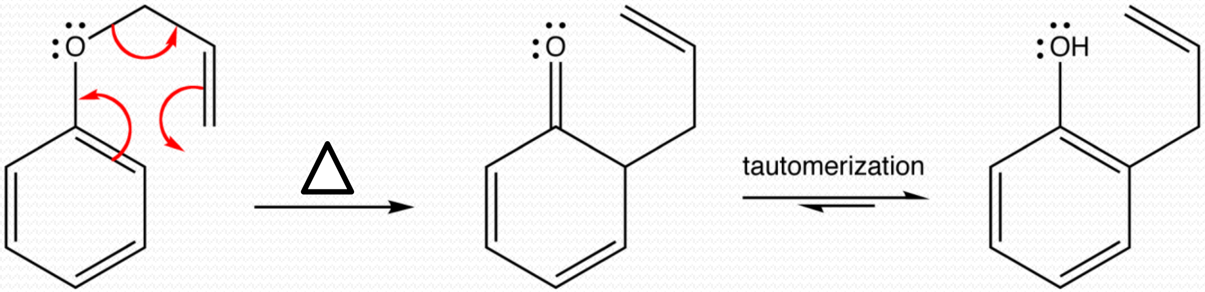
6. Atom economy is calculated from a balanced equation. Percentage yield on the other hand is calculated after a product has been prepared in the laboratory.

Calculation of atom economy

$$\text{Atom economy (\%)} = \frac{\text{Mass of atoms in the desired product}}{\text{Mass of atoms in the reactants}} \times 100$$

Atom economy in rearrangement reaction:

- Claisen rearrangement:



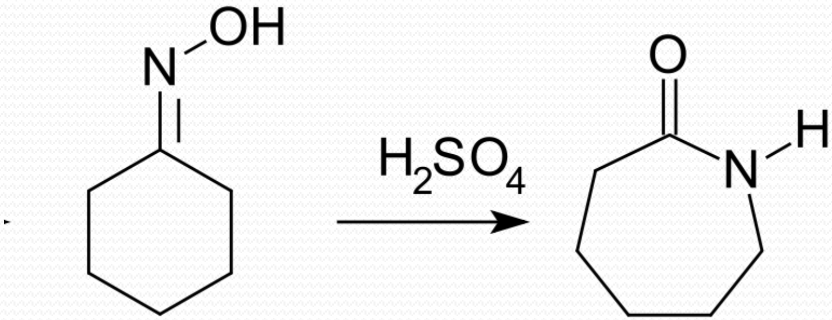
Allyl phenyl ether

o-allyl phenol

	Reagent formula	FW(g /mol)	Utilized formula	FW	Unutilized formula	FW
	$C_9H_{10}O$	134.173	$C_9H_{10}O$	134.173	----	----
Total	$C_9H_{10}O$	134.173	$C_9H_{10}O$	134.173	----	----

% Atom Economy: 100%

Beckman rearrangement:

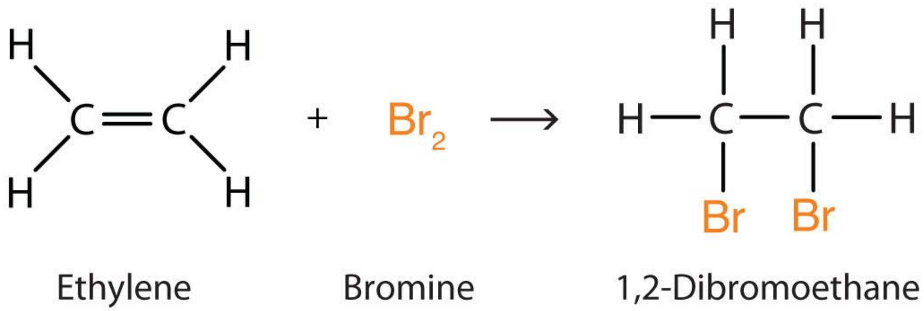


cyclohexanoxime caprolactam

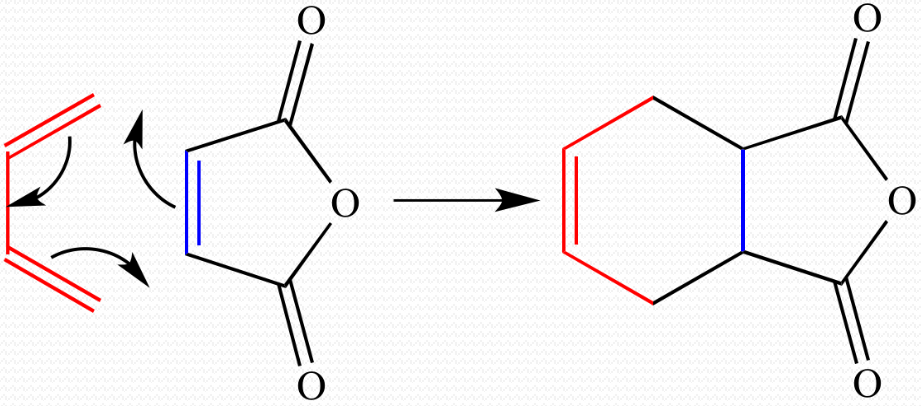
	Reagent formula	FW(g/ mol)	Utilized formula	FW	Unutilized formula	FW
Total	C6H11NO C6H11NO	113.16 113.16	C6H11NO C6H11NO	113.16 113.16	---- ----	---- ----

% Atom Economy: 100%

Atom economy in addition reaction :

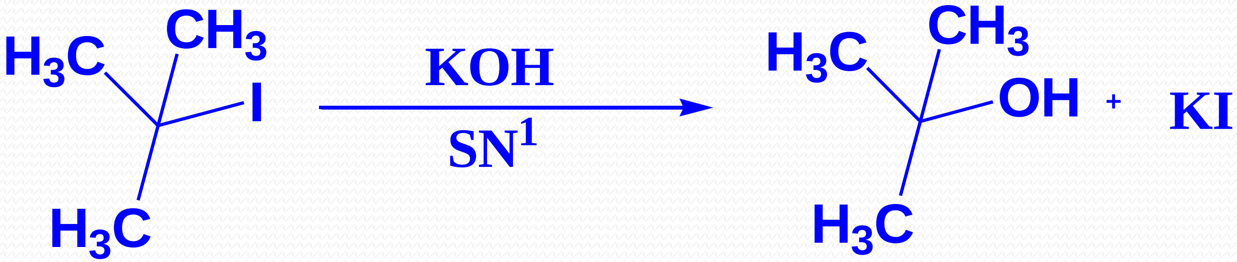


Atom economy: ____________________

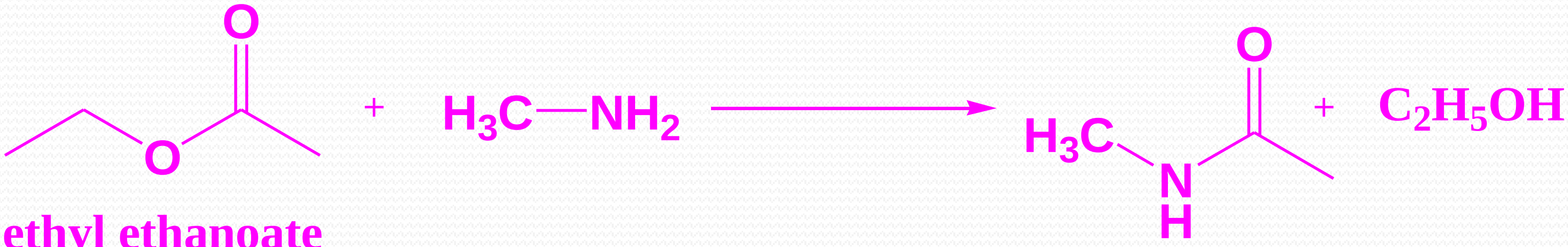


Atom economy: ____________________

Atom economy in substitution reaction:



Atom economy: ______________



ethyl ethanoate

***N*-methylacetamide**

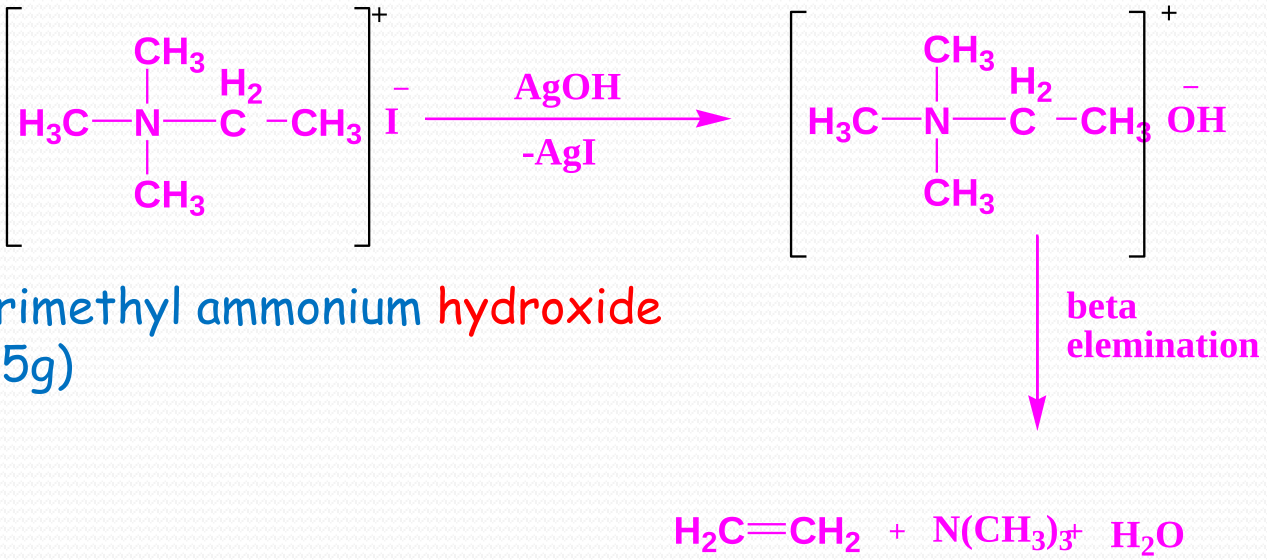
Atom economy: ______________

$$H_3C-I \quad + \quad NaOCH_3 \xrightarrow{\text{dry } Et_2O} H_3C-O-CH_3$$

Atom economy: ______________

Atom economy in elimination reaction:

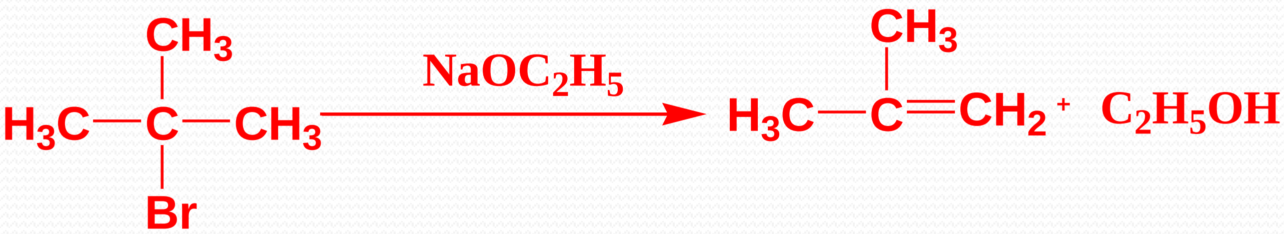
Hofmann's Elimination:



Ethyl trimethyl ammonium hydroxide (FW:105g)

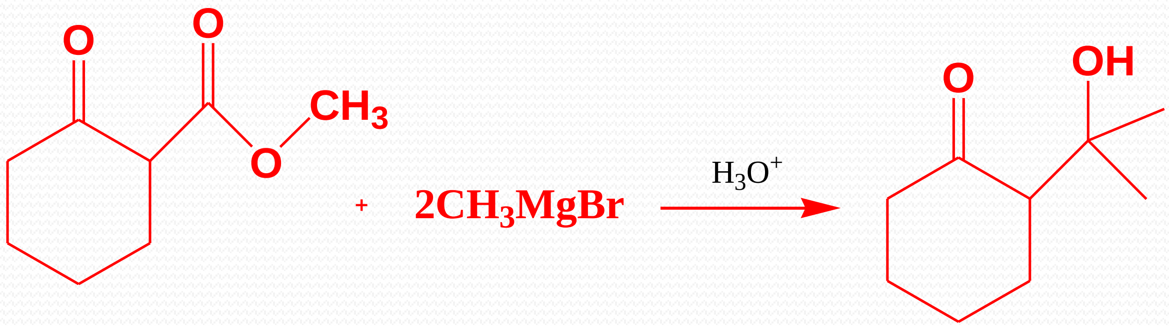
Ethene (FW: 28g)

Dehydrohelogenation: of 2-bromo 2-methylpropane:



2-bromo 2-methylpropane Isobutylene:

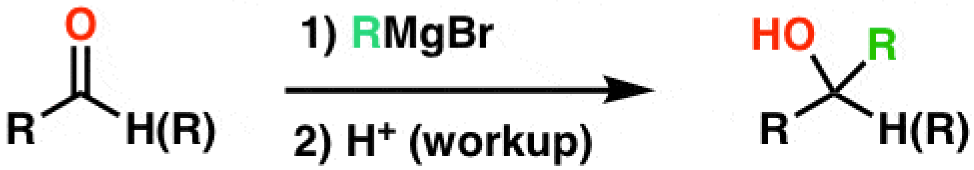
Besides 4 different types of reactions we come across another type of reaction based on selectivity of two different types of groups present in the molecule



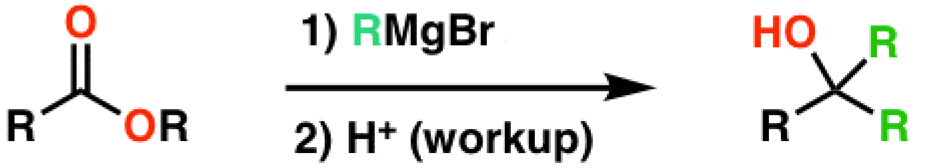
Key Reactions of Grignard Reagents

- **Reaction with Epoxides**

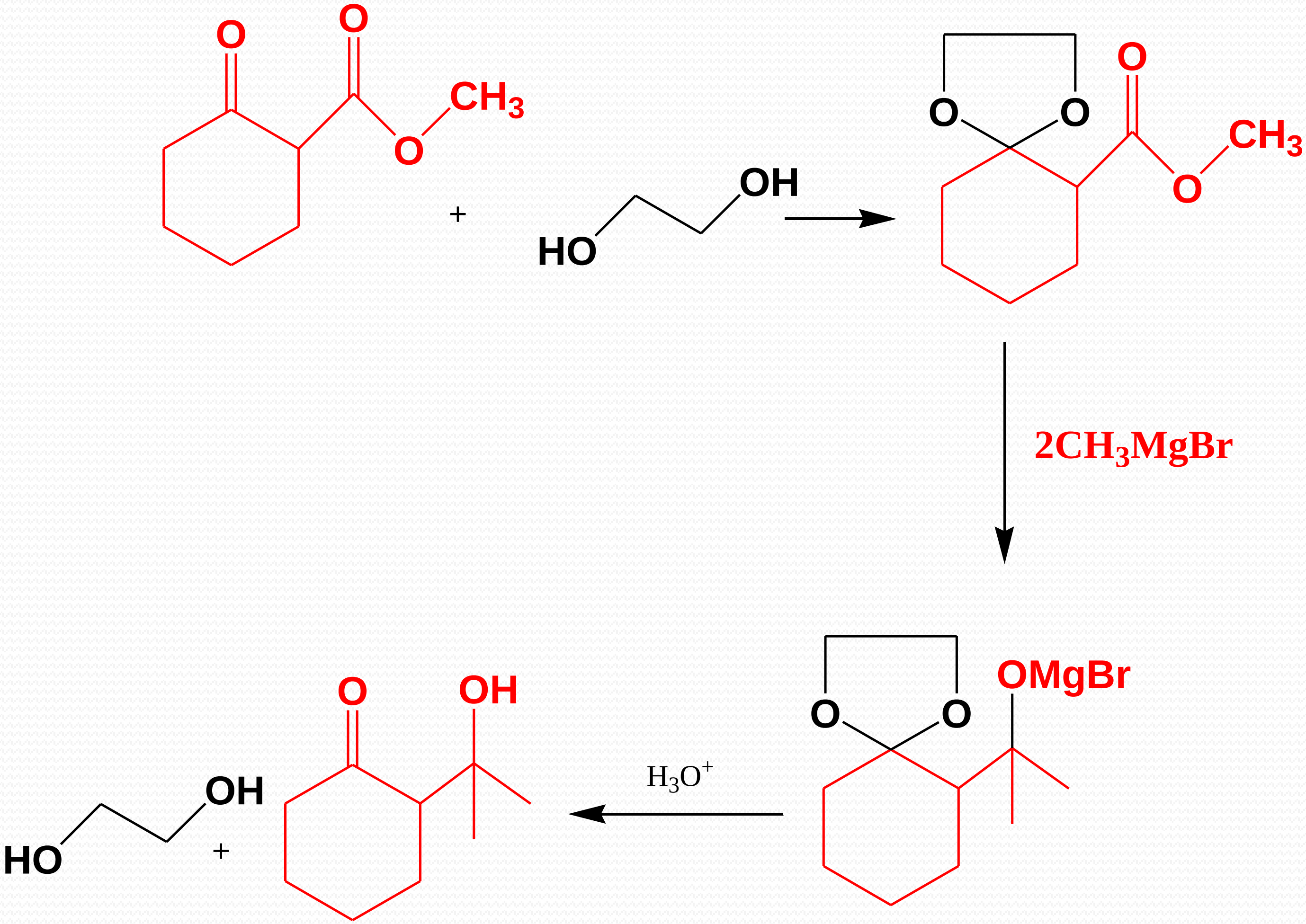
- **Reaction with Aldehydes & Ketones**



- **Reaction with Esters**

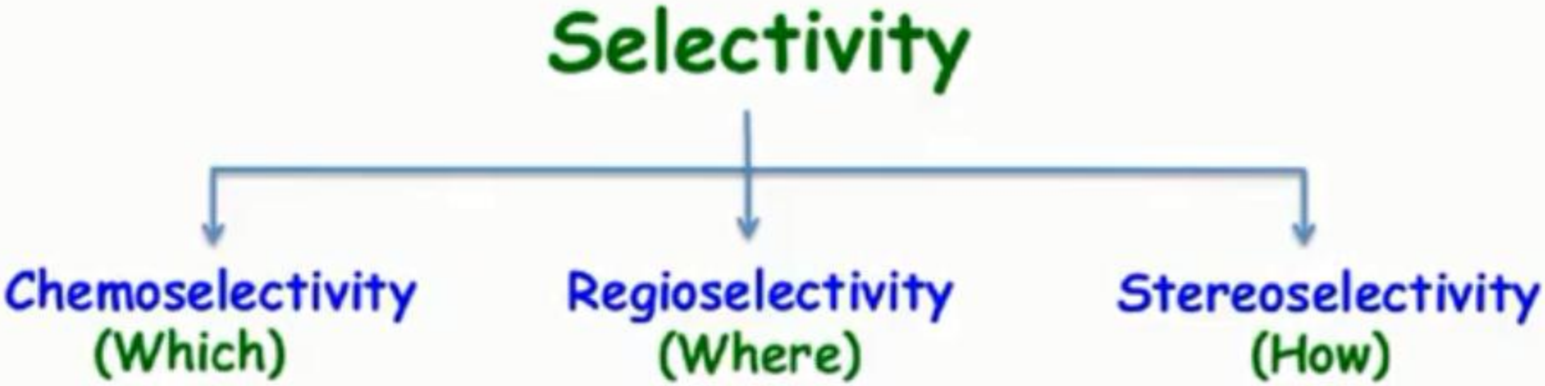


Form	Break	Notes
C–C O–H	C–O	Adds to least sub. carbon
C–C O–H	C–O(π)	
C–C C–C O–H	C–O(π) C–OR	Adds twice!



This reaction involves chemoselectivity problem

Selectivity



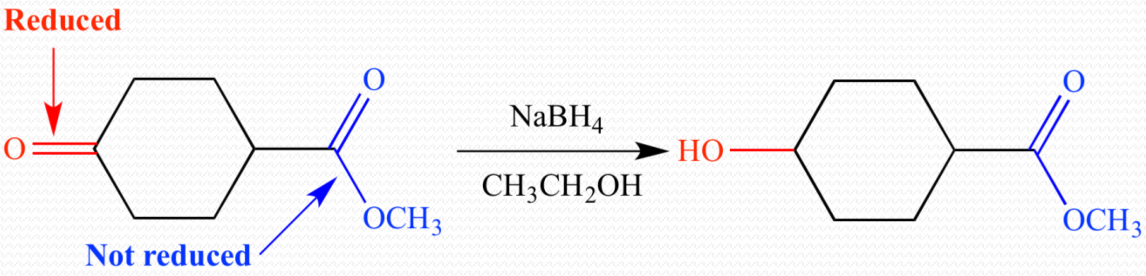
Selectivity

- Chemoselectivity (Which)
- Regioselectivity (Where)
- Stereoselectivity (How)

Selectivity:

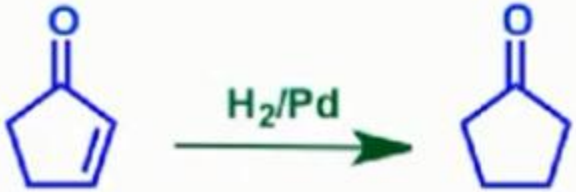
Chemoselectivity :

Chemoselectivity is a term that describes the ability of a reagent or intermediate to react with one group or atom in a molecule in preference to another group or atom present in the same molecule



Selective Reduction:

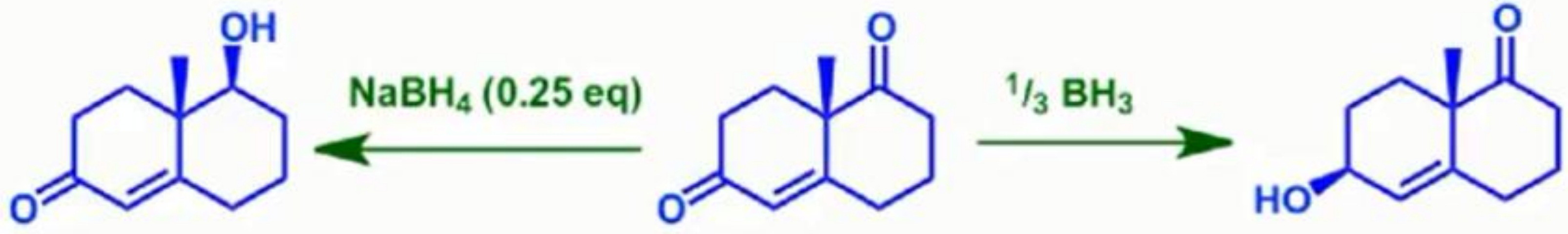
Chemoselective reduction of C=C over C=O:



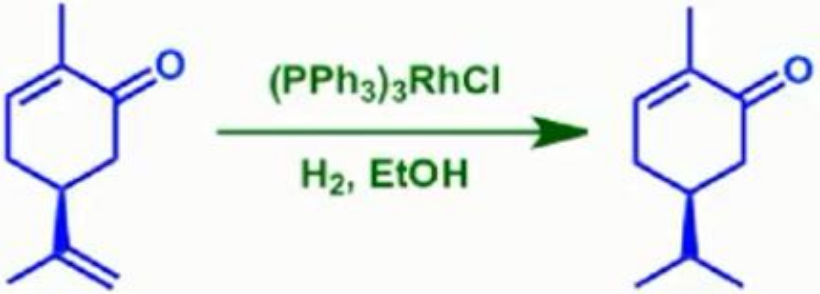
Chemoselective reduction of C=O over C=C:

Chemoselectivity

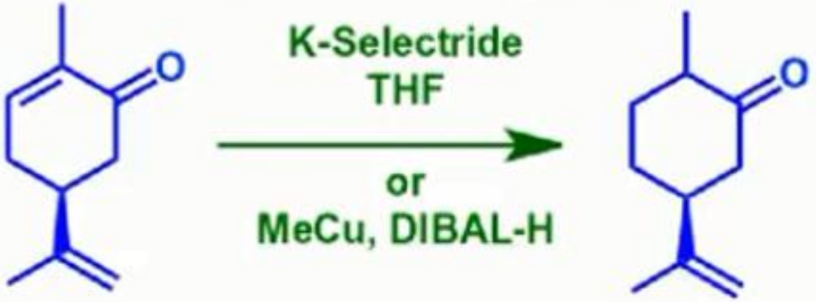
Selective Reduction:



Chemoselective reduction of alkenes over alkenones:



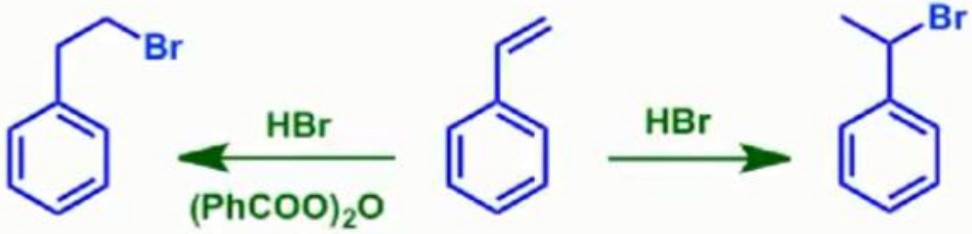
Chemoselective reduction of alkenones over alkenes:



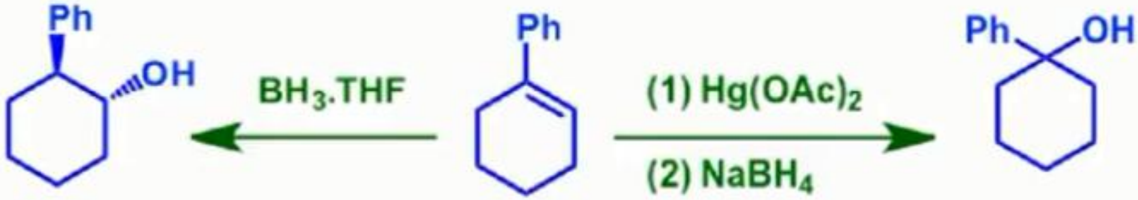
Regioselectivity

Preferential reactivity of one site over the other site of the same functional group

Addition of HBr to alkenes:



Hydration of alkenes:



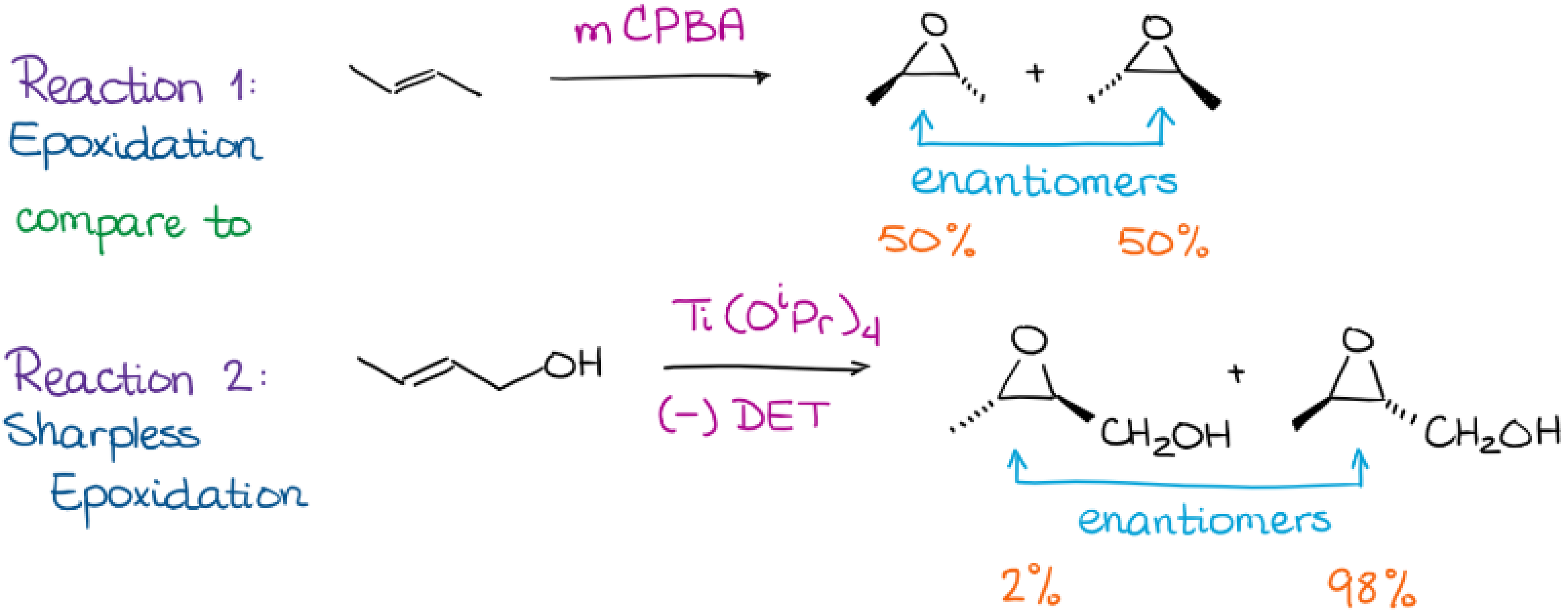
Oxymercuration-Demercuration of Alkenes

Regioselectivity

Diels-Alder Reaction:

Stereoselectivity

These are reactions that can give two different stereoisomers but one of those stereoisomers is major while the other one is minor.



tert-butyl hydroperoxide

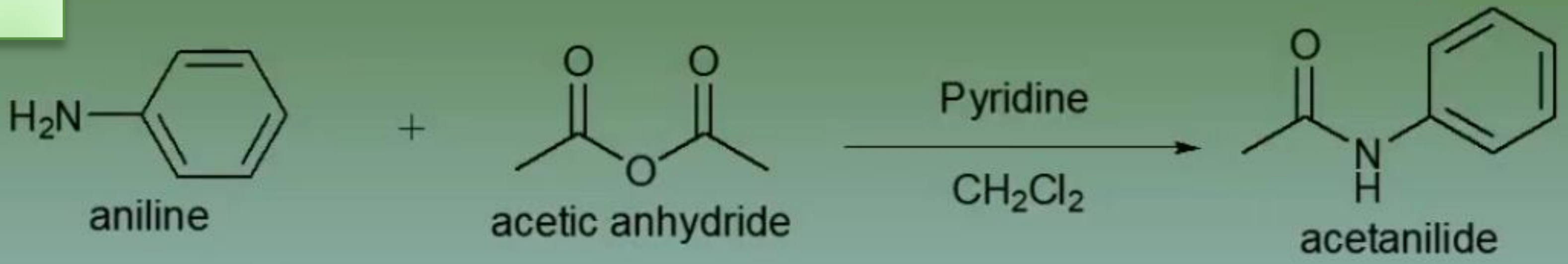
- Virtually all organic reactions fall into the category of substitution, addition, elimination and rearrangement reactions.
- From prospective of atom economy, addition and rearrangement reactions are environmentally preferable.
- Along with atom economy selectivity of a reaction is also important while designing a green synthesis.
- Use of solvent, nature of waste generated and energy consumption are also important factors under consideration while designing a green synthesis.

Principle 3

Less Hazardous Chemical Synthesis

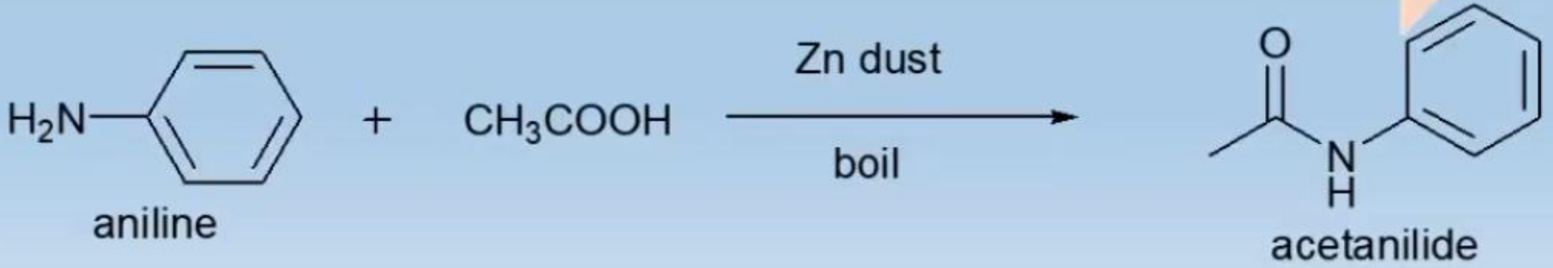
- Wherever practicable, synthetic methods should be designed to use and generate substances that possess little or no toxicity to people or the environment.

Acetanilide Synthesis: Conventional process



- ✓ Non-green components : CH_2Cl_2 , Pyridine
- ✓ Not atom – economic : 1 mole of acetic acid unused.

Acetanilide Synthesis: Green process



Synthesis of urethane(Ethyl carbamate)

Phosgene method:

$$RNH_2 + COCl_2 \longrightarrow RNCO + 2HCl \xrightarrow{R'OH} RNHCOOR'$$

Non- Phosgene method:

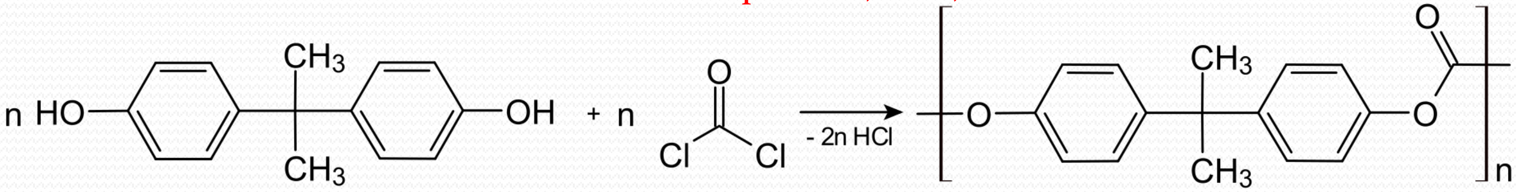
$$RNH_2 + CO_2 \longrightarrow RNCO + H_2O \xrightarrow{R'OH} RNHCOOR'$$

Urethane is commonly used as a sealant, but it has several other uses because it is resistant to water, oil, and oxidation. As an elastomer, it has outstanding tensile and tear strength. It is also resistant to abrasion and retains its durability in a wide range of temperature extremes.

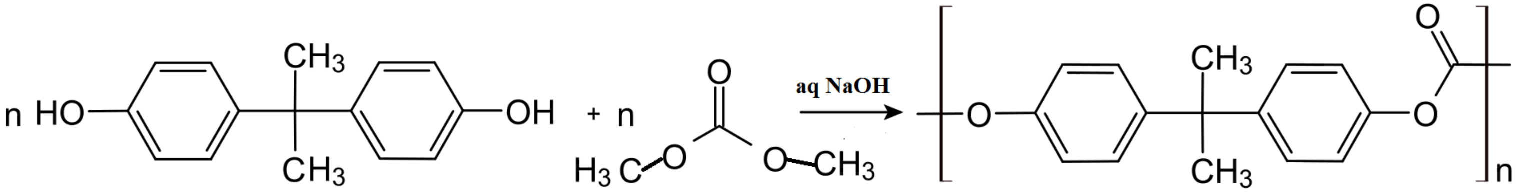
Synthesis of Polycarbonate:

Phosgene method

aq NaOH, PTC, CH_2Cl_2



Phosgene free method using dimethyl carbonate



Advantages of phosgene free synthesis:

- Ethanol is obtained as a by-product and can be recycled
- Eliminate the use of CH2Cl2(DCM)
- Eliminate use of hazardous HCl
- No need of crystallization
- Superior quality polycarbonate.

Phosgene ($COCl_2$) is a **highly toxic gas** or liquid that is classified as a pulmonary irritant. Exposure to phosgene gas produces delayed-onset noncardiogenic pulmonary edema. Its high toxicity arises from the action of the phosgene on the –OH, –NH_2 and –SH groups of the proteins in pulmonary alveoli(the site of gas exchange), respectively forming ester, amide and thioester functional groups Inhalation of such high doses can eventually result in fatality within hours up to 2–3 days of the exposure

Designing Safer Chemicals

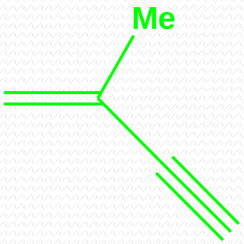
Chemical products should be designed to effect their desired function while minimising their toxicity.

A safer chemical should have the following characteristic:

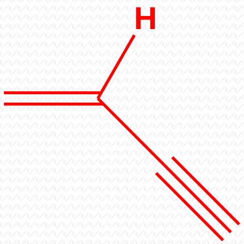
1. Small amount should be sufficient to carry out specific functions efficiently.
2. Less chemicals used for synthesis; less waste is generated to handle.
3. Its preparation does not directly or indirectly contribute to environmental pollution.
4. Minimal toxicity to human and other ecological receptors (e.g. birds, fish, etc.)
5. Non-explosive, non-flammable (physical hazard).
6. Does not persist in the air, and degradation products should be non-hazardous.
7. Safe to handle and use.
8. Does not bioaccumulate or biomagnify in the food chain.

Types of safer chemical:

1. Safer structural analog of another commercially available chemical

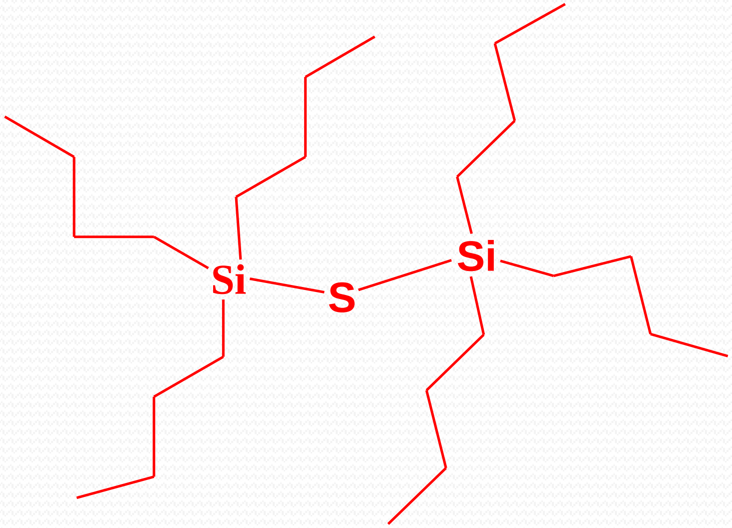


Methylacrylonitrile

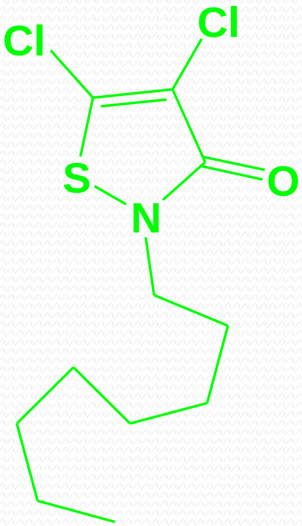


Acrylonitrile

Antifouling agent



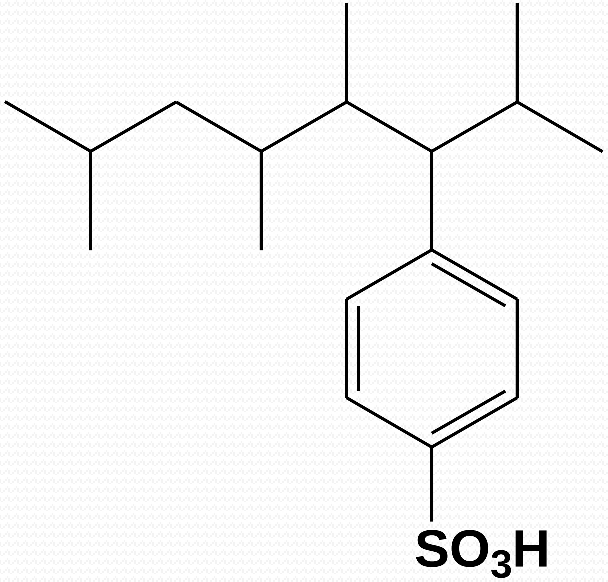
bis(tri -n-butyl tin)oxide



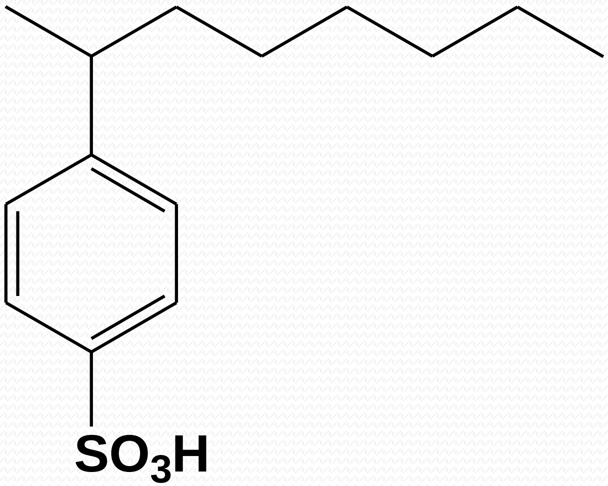
4,5-dichloro-2-octylisothiazol-3(2*H*)-one

Substituted thiazole

Detergent



low degradatio rate



high degradatio rate

Synthesis of $FeSO_4$: Two possible ways of making $FeSO_4$ are as follows:

$$Fe(s) + H_2SO_{4\ (aq)} \longrightarrow H_2\ (g) + FeSO_{4(aq)}$$

$$FeO(s) + H_2SO_4\ (aq) \longrightarrow FeSO_4\ (aq) + H_2O\ (aq)$$

Scheme : Synthesis of $FeSO_4$ using iron filings and iron oxide.

Safer solvent and Auxiliaries:

The use of auxiliary substances (e.g., solvents or separation agents) should be made unnecessary whenever possible and innocuous when used.

Syllabus:

- Green solvents- supercritical fluids, water as a solvent for organic reactions, ionic liquids, fluorous biphasic solvent, PEG, solventless processes, immobilized solvents and how to compare greenness of solvents.

Solvents:

- A solvent is a substance that dissolves a solute, resulting in a solution. A solvent is usually a liquid but can also be a solid, a gas, or a supercritical fluid
- Types:-

  -polar

  -nonpolar

-------Amalgam..

PHYSICAL PROPERTIES OF SOLVENT'S:-

- The physical properties of solvents greatly influence the choice of solvent for a particular application.
- The solvent should be liquid under the temperature and pressure conditions at which it is employed.
- thermodynamic properties:- density & vapor pressure, temperature & pressure coefficients, as well as the heat capacity surface tension.
- transport properties:- such as viscosity, diffusion coefficient, & thermal conductivity, also need to be considered

- Electrical, optical, and magnetic properties, such as the dipole moment, dielectric constant, refractive index, magnetic susceptibility, and electrical conductance are relevant, too.
- Molecular characteristics, such as the size, surface area, and volume, as well as orientational relaxational times, have appreciable bearing on the applicability of a solvent or on the interpretation of solvent effects.

Health effect of solvents:

General health hazards associated with solvent exposure include :

- Toxicity to the nervous system,
- reproductive damage,
- liver and kidney damage,
- respiratory impairment,
- cancer, and
- Dermatitis

-Many solvents can lead to a sudden loss of consciousness if inhaled in large amounts

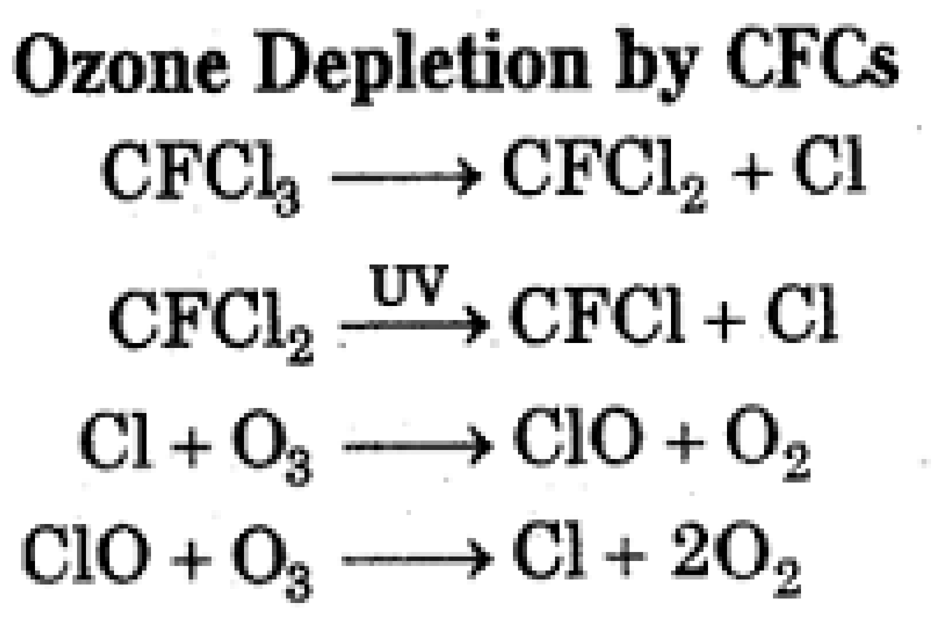
-Solvents like diethyl ether and chloroform have been used in medicine as anesthetics, sedatives, and hypnotics

- Ethanol is a widely used and abused psychoactive drug.

-Diethyl ether, chloroform, and many other solvents have harmful long term health effects like neurotoxicity or cancer.

-If ingested, the so-called toxic alcohols (other than ethanol) such as Methanol, propanol, and ethylene glycol metabolize into toxic aldehydes and acids, which cause potentially fatal metabolic acidosis.

-The commonly available alcohol solvent methanol can cause permanent blindness or death if ingested



Ozone Depletion by CFCs

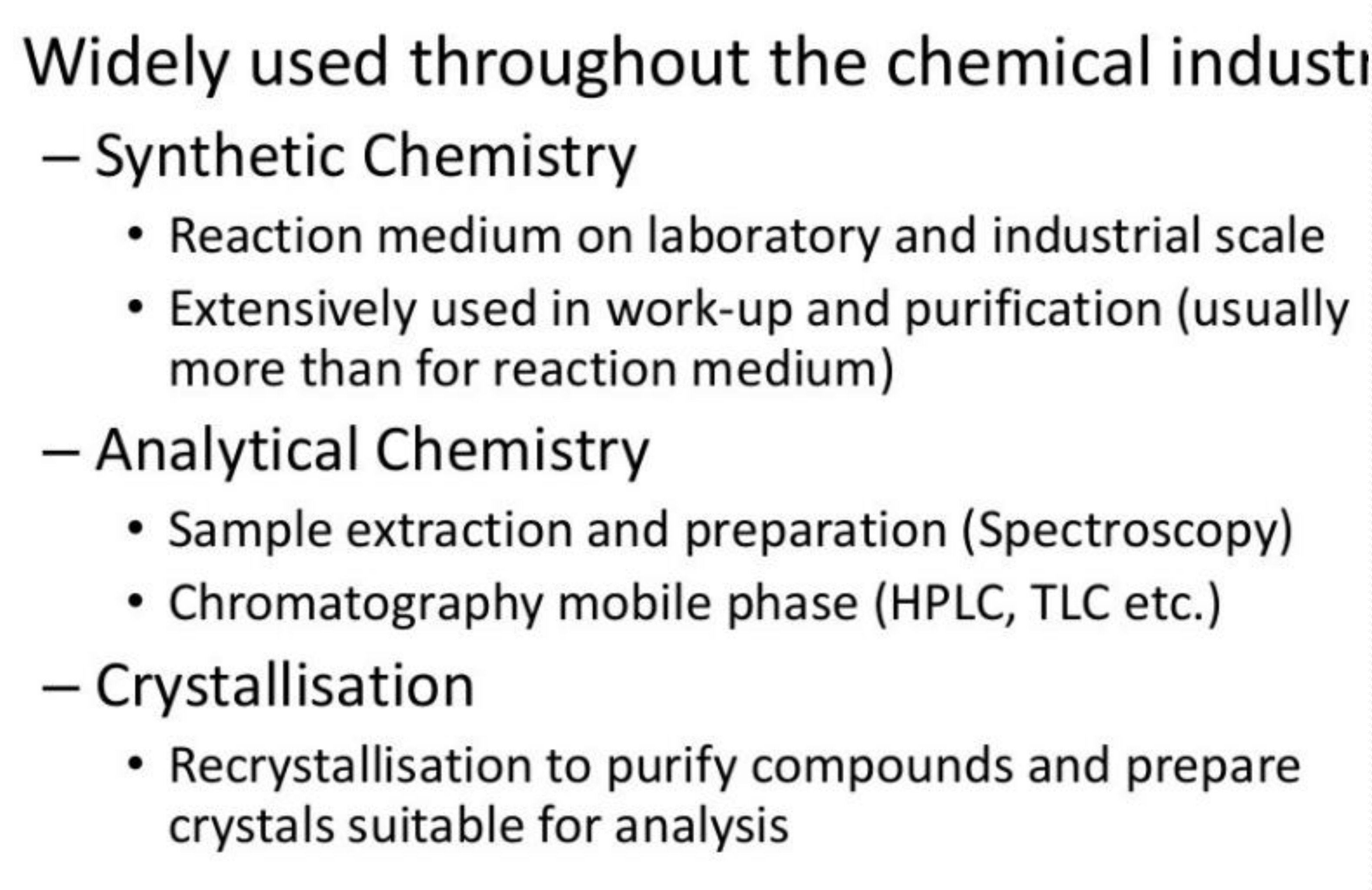
$$CFCl_3 \longrightarrow CFCl_2 + Cl$$

$$CFCl_2 \xrightarrow{UV} CFCl + Cl$$

$$Cl + O_3 \longrightarrow ClO + O_2$$

$$ClO + O_3 \longrightarrow Cl + 2O_2$$

For every reactive chlorine atom generated in stratosphere 100000 molecules of ozone are depleted

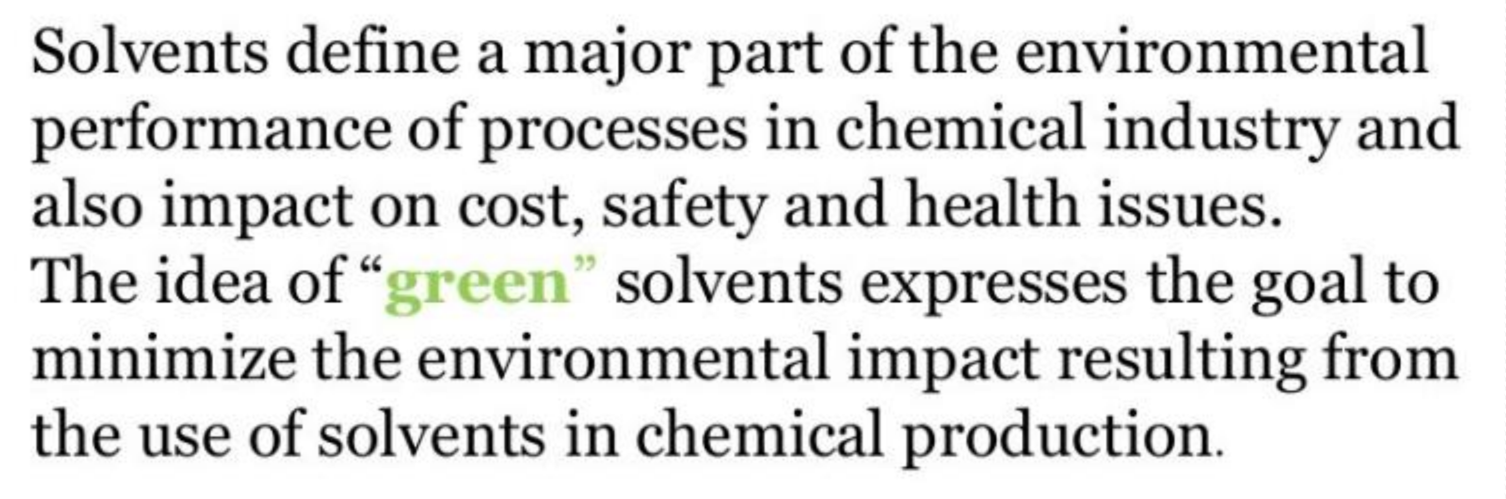


Widely used throughout the chemical industr

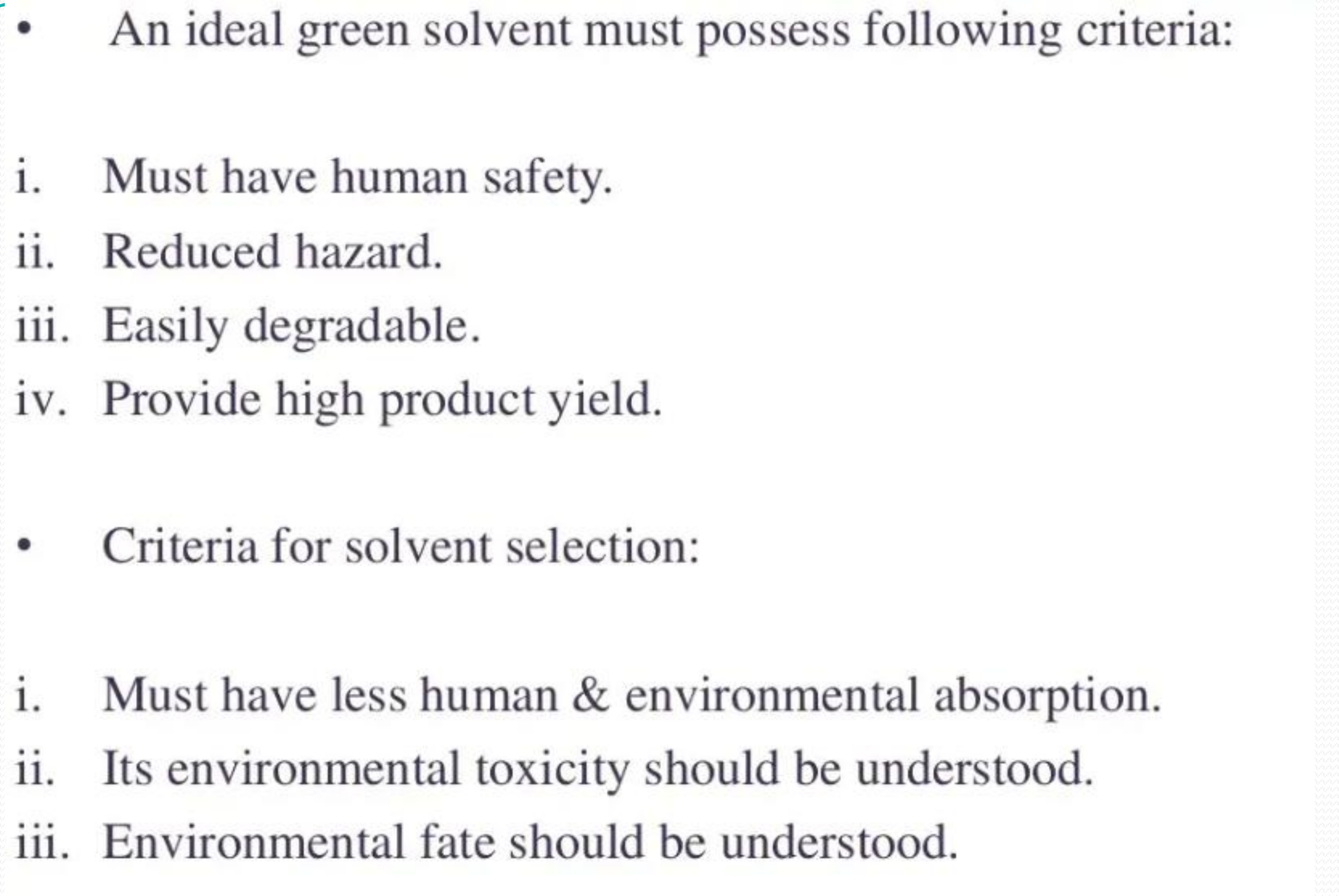
- Synthetic Chemistry
  - Reaction medium on laboratory and industrial scale
  - Extensively used in work-up and purification (usually more than for reaction medium)
- Analytical Chemistry
  - Sample extraction and preparation (Spectroscopy)
  - Chromatography mobile phase (HPLC, TLC etc.)
- Crystallisation
  - Recrystallisation to purify compounds and prepare crystals suitable for analysis

- Used much more widely than just synthetic chemistry
- Coatings:
  - Paints, adhesives
    - Solvent usually removed by evaporation after application leaving coating behind
    - Coating removal
- Cleaning
  - E.g. Dry cleaning – extensive use of perchloroethylene, a known cancer suspect agent, which also contaminates groundwater supplies
- Extraction
  - E.g. Coffee decaffeination (benzene, CH_2Cl_2)

oil extraction



Solvents define a major part of the environmental performance of processes in chemical industry and also impact on cost, safety and health issues.
The idea of “**green**” solvents expresses the goal to minimize the environmental impact resulting from the use of solvents in chemical production.



- An ideal green solvent must possess following criteria:

i. Must have human safety.
ii. Reduced hazard.
iii. Easily degradable.
iv. Provide high product yield.

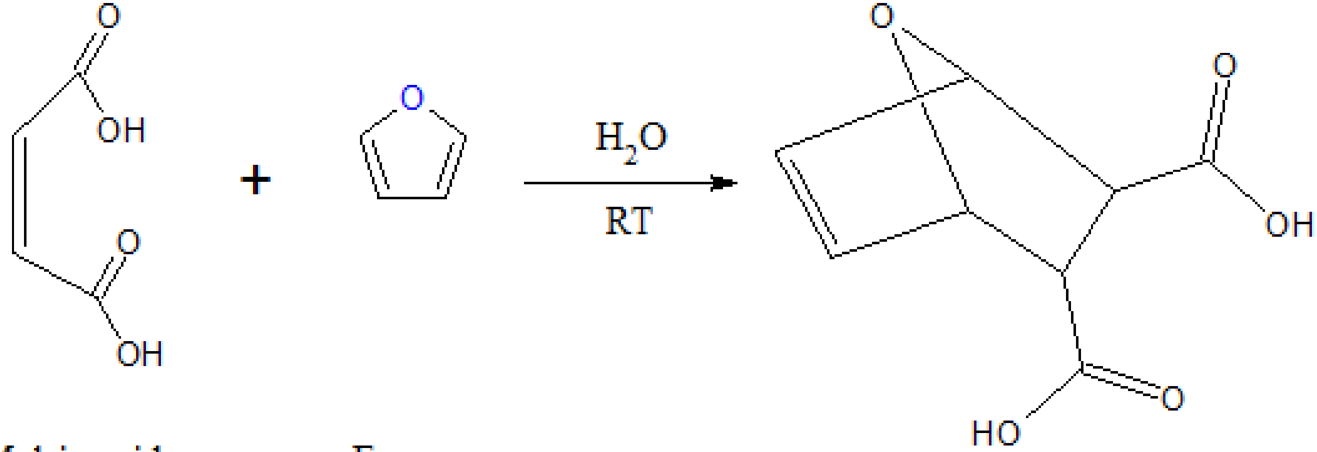
- Criteria for solvent selection:

i. Must have less human & environmental absorption.
ii. Its environmental toxicity should be understood.
iii. Environmental fate should be understood.

Water as a reaction medium

- One of the most obvious alternatives to VOCs.
- Cheap, readily available, and plentiful

- Useful for certain types of reaction but limited because of:
  - Low solubility of organic substrates
  - Compatibility with reagents
- Clean up of aqueous waste difficult
- Useful in biphasic processes in conjunction with other solvents



Maleic acid

Furan

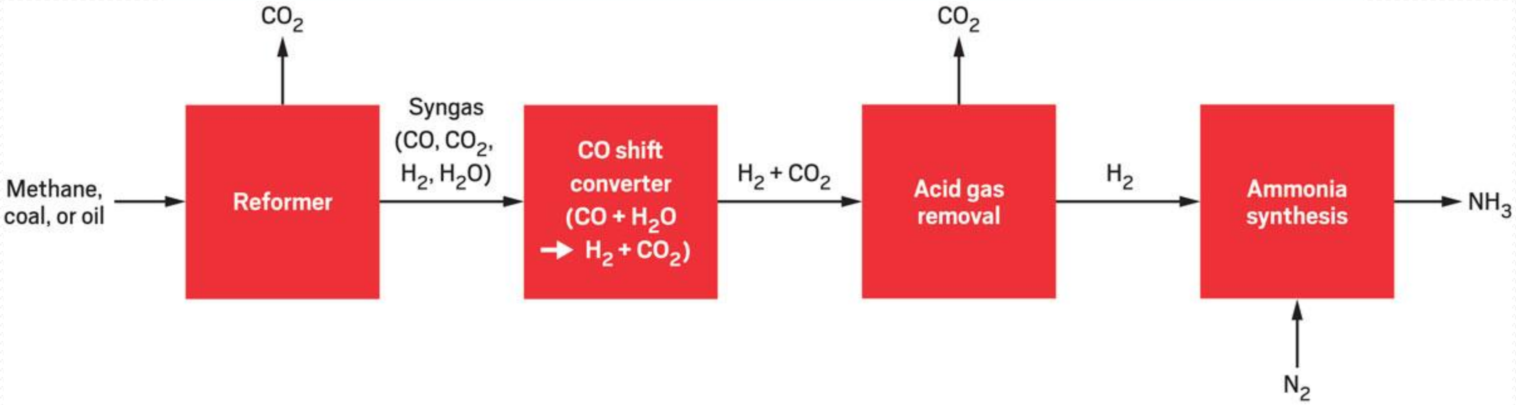
Adduct

Carbon Dioxide

- Similar advantages to water
  - Natural, cheap, plentiful (too much of it!)
  - Available in >99.9% pure form, £70/$110 per 25kg.
  - By-product of brewing, ammonia synthesis, combustion
- Already being adopted in a variety of commercial processes (see later)
- Non-toxic and properties well understood
  - asphyxiant at high concentrations
- Easily removed and recycled, and can be disposed of with no net increase in global CO_2
  - Simple product isolation by evaporation, to 100% dryness.
- No solvent effluent
- Potential for product processing (extraction, particle formation, chromatography etc.)

$$\text{glucose} \xrightarrow{\text{yeast}} \text{ethanol} + \text{carbon dioxide}$$

$$C_6H_{12}O_{6(aq)} \xrightarrow{\text{yeast}} 2C_2H_5OH_{(aq)} + 2CO_{2(aq)}$$



$$2\,CH_3OH + 3\,O_2 \longrightarrow 2\,CO_2 + 4\,H_2O$$

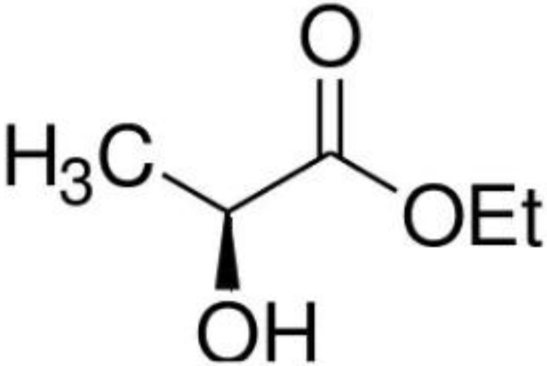
Methanol

$$C_3H_6O + 4\,O_2 \longrightarrow 3\,CO_2 + 3\,H_2O$$

Acetone

Ethyl lactate – a renewable solvent

- Derived from processing corn
- Variety of lactate esters possible
- Renewable source (non-petrochemical)
- Attractive solvent properties
  - Biodegradable,
  - Easy to recycle,
  - Non-corrosive,
  - Non-carcinogenic
  - Non-ozone depleting
  - Good solvent for variety of processes
- Commonly used in the paint and coatings industry
  - Potentially has many other applications.



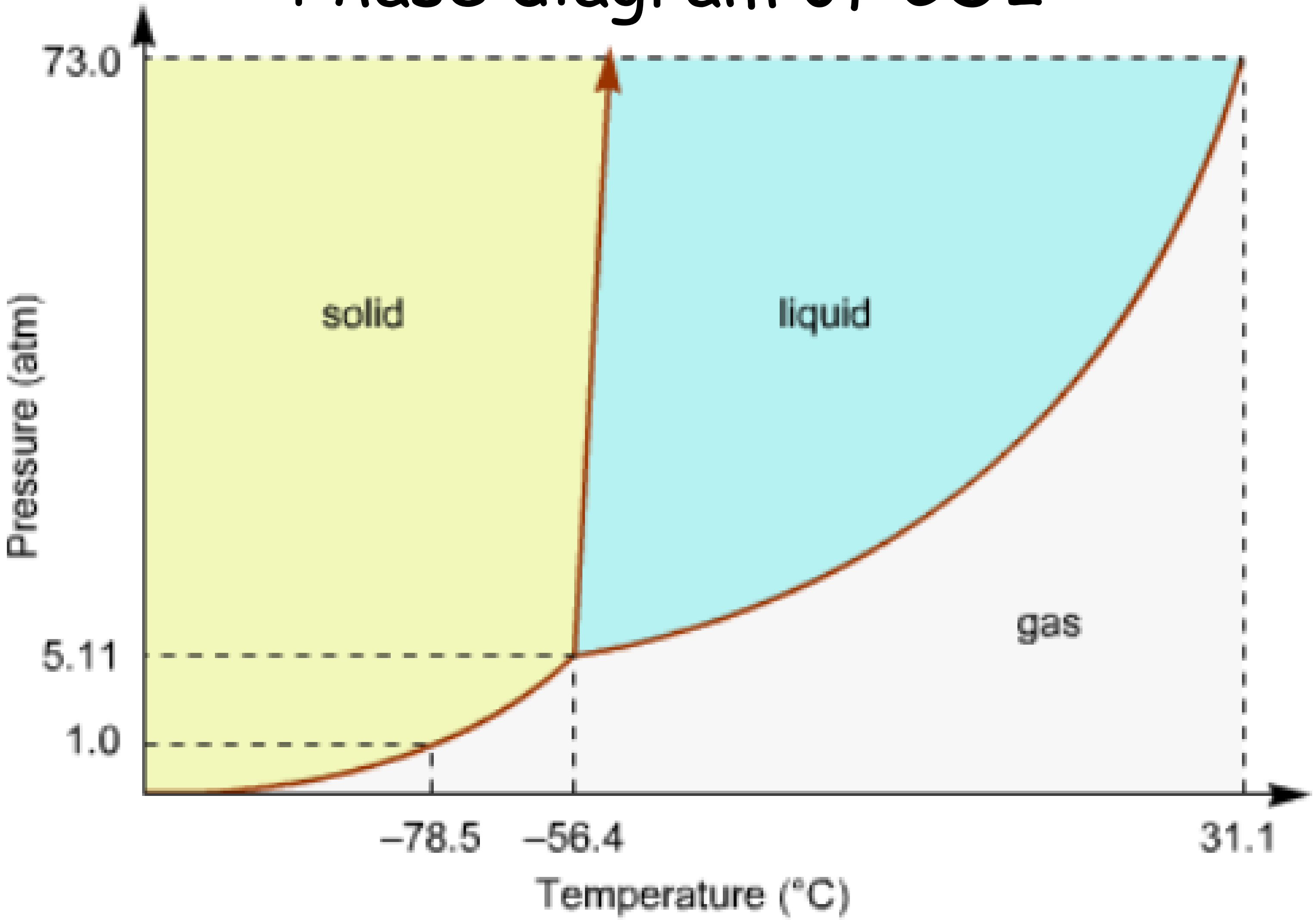
Supercritical fluids

- **Supercritical fluids** are rather interesting substances that are neither liquid nor gas once a certain critical temperature and pressure have been exceeded.

- In this state they are almost as dense as a liquid, but have a similar viscosity to gas.

- Supercritical CO_2 offers clear advantages, as it is easily available, inexpensive, non-toxic, non-explosive, not an organic solvent, and ensures gentle treatment of the product at moderate temperatures ($<100°C$) as well as easy separation of solvent and extract.

Phase diagram of CO2

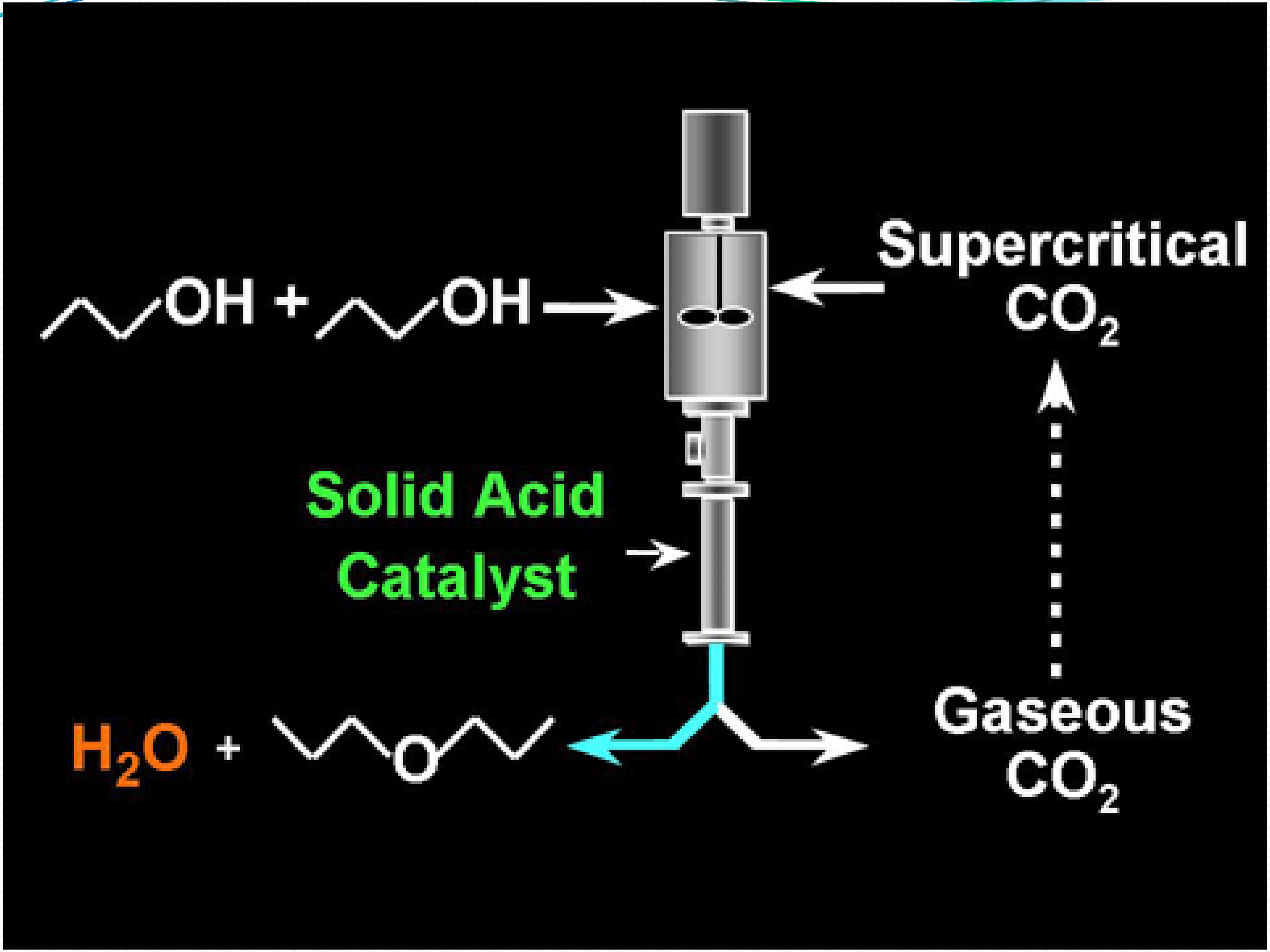


Advantages of supercritical CO2

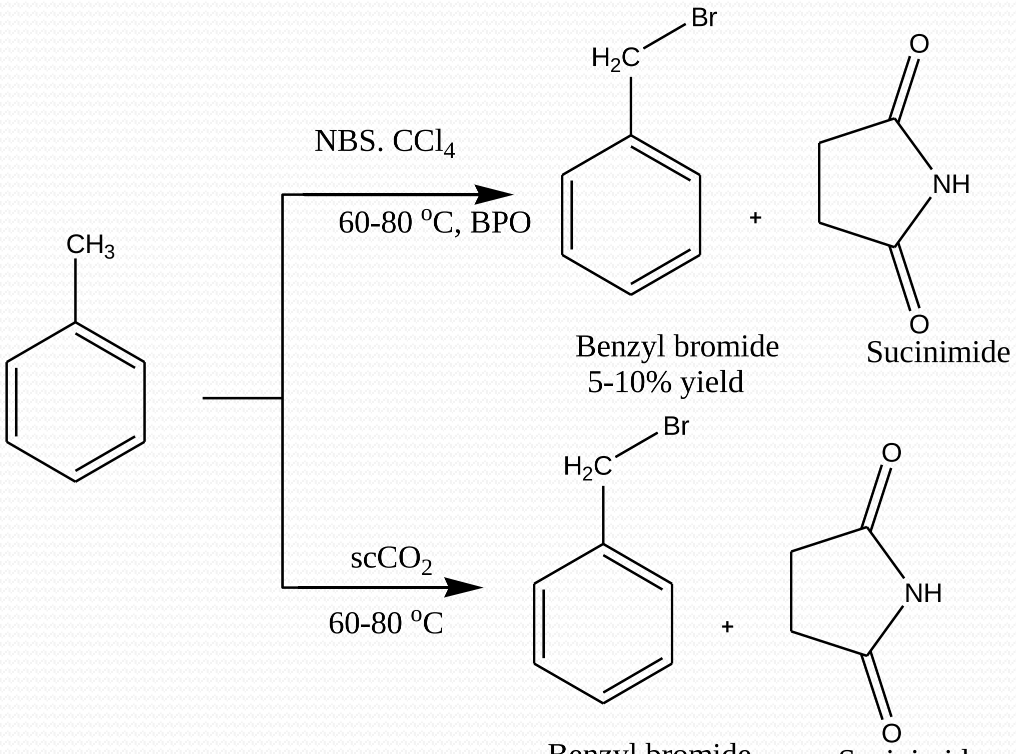
- Non-toxic
- Non-flammable
- Inexpensive
- Environmentally benign
- non-explosive
- Not an organic solvent
- Workable at moderate temperature

Use of super critical CO2

- To make decaffeinated coffee.
- In dry cleaning replacing perchloroethylene(C_2Cl_4), a suspected carcinogen and groundwater contaminant
- As an extraction solvent for essential oils and other herbal distillates.
- Estimatimation of polycyclic aromatics in soil
- To produce micro and nanoscale particles
- As foaming agent during polymer manufacturing(in polystyrene replacing CFC)


OH + OH
Supercritical
CO_2
Solid Acid
Catalyst
H_2O +
O
Gaseous
CO_2

Example :1(Wohl-Ziegler Bromination)



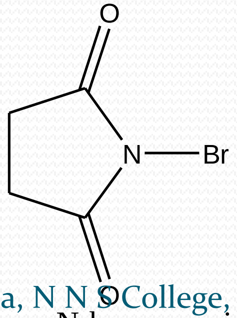
Benzyl bromide
5-10% yield

Sucinimide

Benzyl bromide
100%

Sucinimide

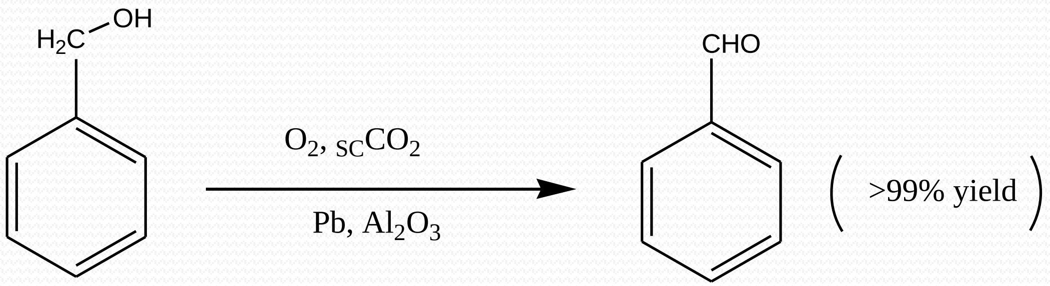
NBS:



N-bromo sucinimide

(Brominating agent for allylic and Benzylic sites)

Example 2:Synthesis of Benzaldehyde from benzyl alcohol



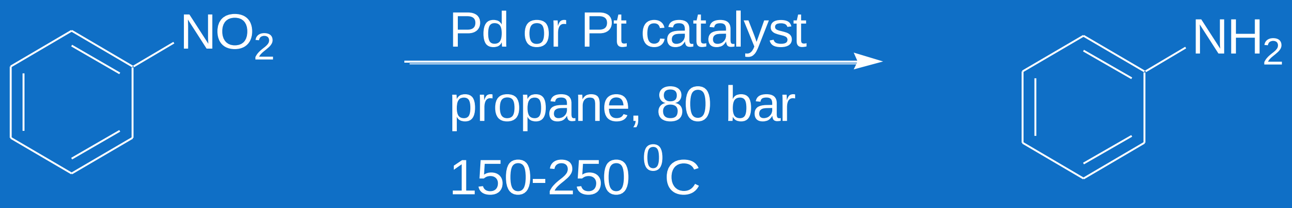
Here oxidation process becomes smooth and straightforward as O2 is highly soluble in supercritical CO2

Reactions in Supercritical Fluids

- Formation of cyclic ethers

acid catalyst

- Hydrogenation



Pd or Pt catalyst

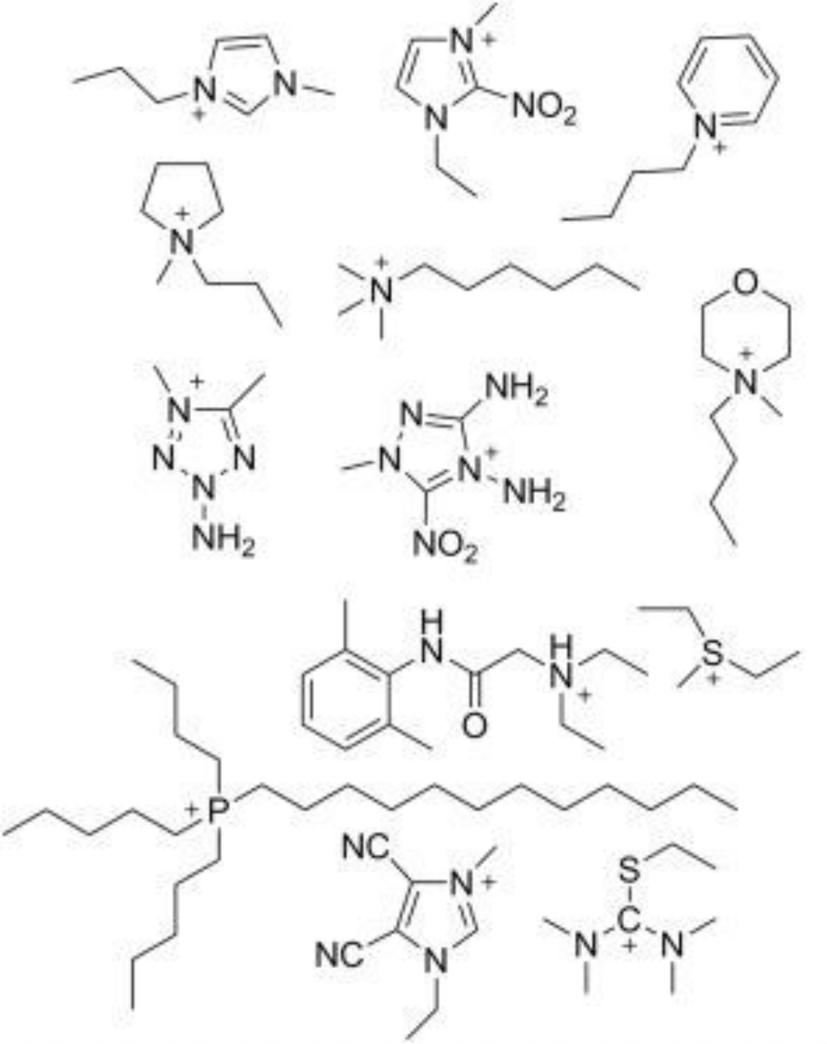
propane, 80 bar

150-250 ^{0}C

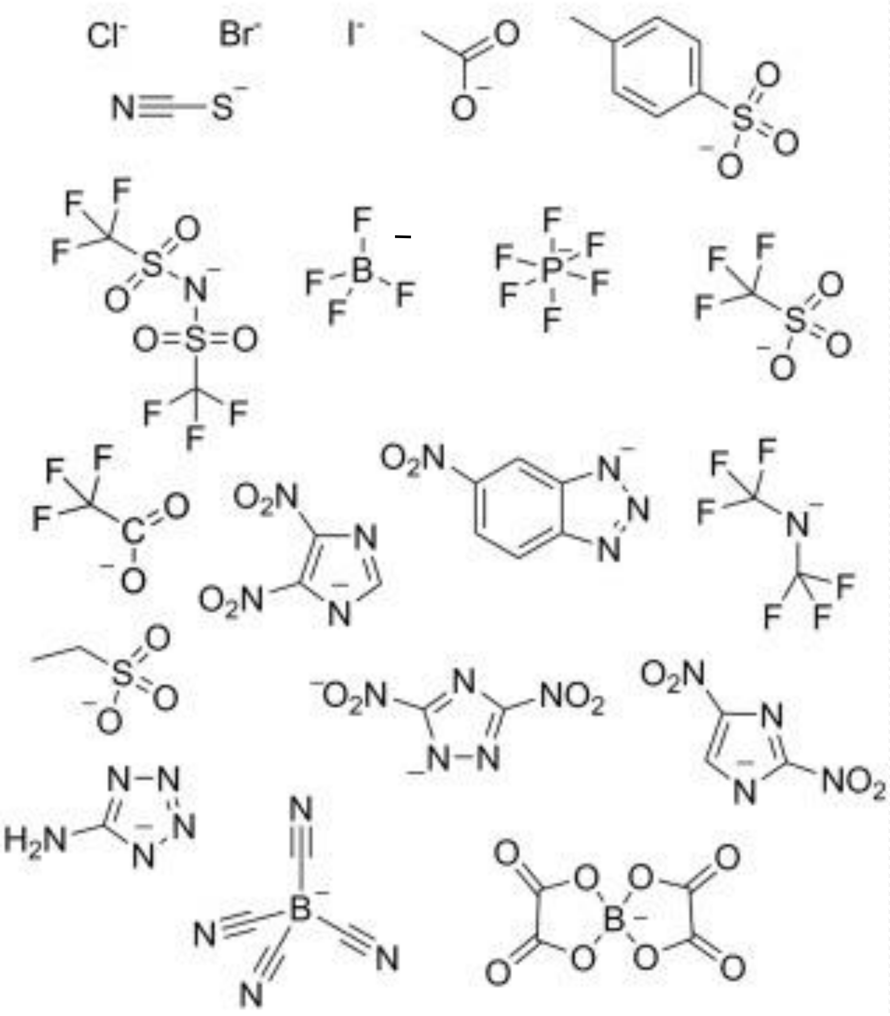
Ionic liquids:

- Ionic liquids (ILs) are **salts that exist as liquid at temperatures below 100°C**,
- They are usually composed of a combination of **organic cations** and **organic/inorganic anions**.
- To remain in liquid state at room temperature organic cations should be **unsymmetrical** in structure.

Cations



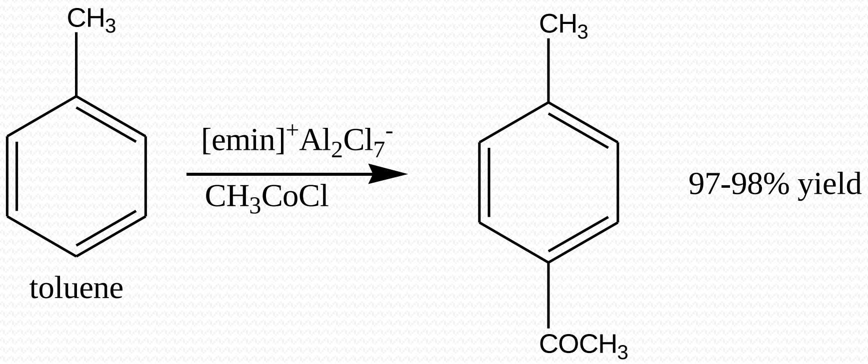
Anions



Characteristics

- Ionic liquids are often moderate to poor conductors of electricity, non-ionizing,
- highly viscous and frequently exhibit low vapor pressure.
- Their other properties are diverse: many have low combustibility, are thermally stable, with wide liquid regions, and favorable solvating properties for a range of polar and non-polar compounds.
- Many classes of chemical reactions, such as Diels-Alder reactions and Friedel-Crafts reactions, can be performed using ionic liquids as solvents.
- The miscibility of ionic liquids with water or organic solvents varies with side chain lengths on the cation and with choice of anion.
- They can be functionalized to act as acids, bases, or ligands, and are precursors salts in the preparation of stable carbenes.

Example: Friedel-Crafts Acylation



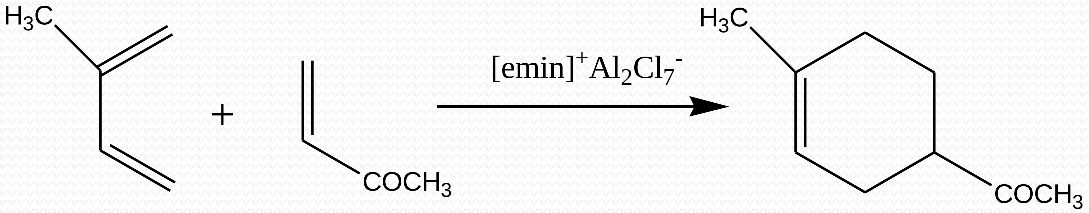
4-methyl acetophenone

$[emin]^+$: 1-ethyl 3-methyl imidazolium

Advantages over conventional method:

1. Use of nitrobenzene solvent is avoided as it is a cancer suspect
2. It gives predominantly a para-product
3. The ionic liquid can be reused.

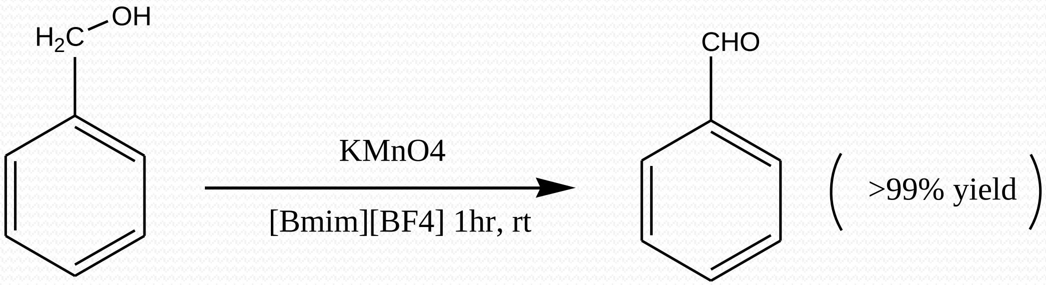
Example: Diels-Alder Reaction:



Advantages:

1. Ionic liquids can be reused
2. Reaction can be carried out at ambient conditions

Example: Oxidation of benzyl alcohol to benaldehyde by KMnO4 in RTIL



The ionic liquid used here is 1-butyl-3-methyl imidazolium tetrafluoroborate, can be reused after the reaction

Potential applications:

- Catalysis :

  ILs improve the catalytic performance of palladium nanoparticles. Furthermore, ionic liquids can be used pre-catalysts for chemical transformations.

- Pharmaceuticals:

  Approximately 50% of commercial pharmaceuticals are salts, ionic liquid forms of a number of pharmaceuticals have been investigated. Combining a pharmaceutically active cation with a pharmaceutically active anion leads to a Dual Active ionic liquid in which the actions of two drugs are combined

Biopolymer processing:

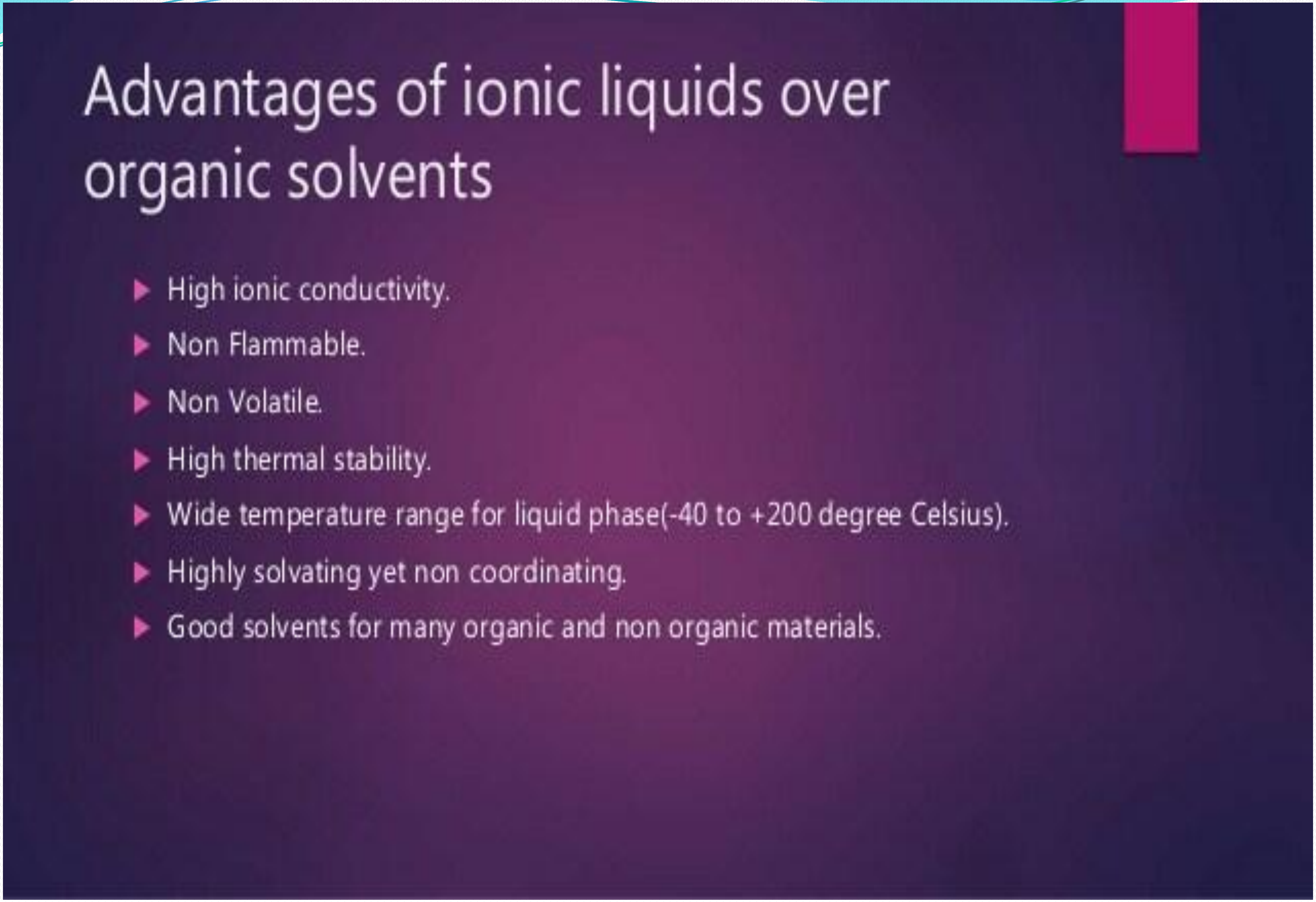
ILs have also shown potential in the dissolution, extraction, purification, processing and modification of biopolymers such as cellulose chitin/chitosan, starch, alginate, collagen, gelatin, keratin, and fibroin.

Nuclear fuel reprocessing:

The IL 1-butyl-3-methylimidazolium chloride has been investigated for the recovery of uranium and other metals from spent nuclear fuel and other sources

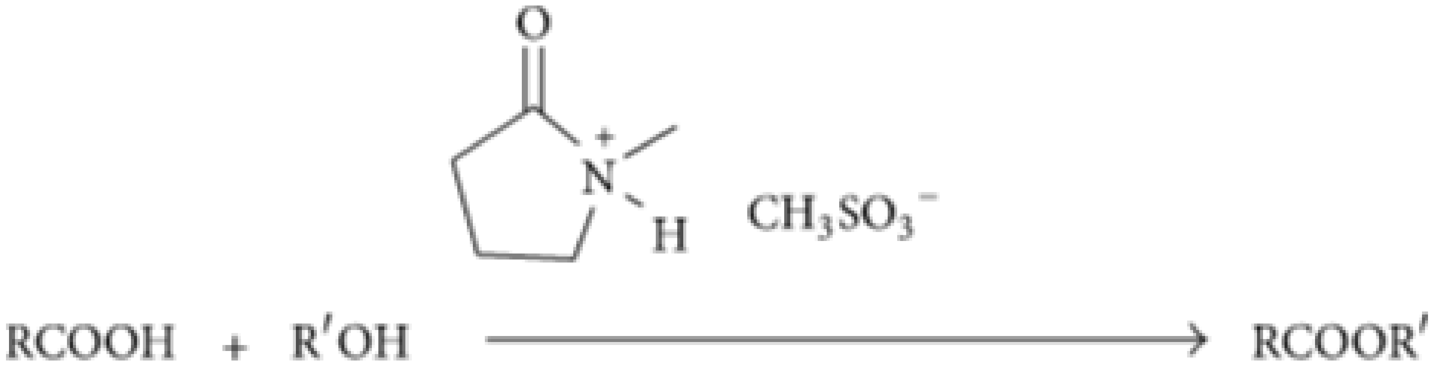
Batteries:

ILs can replace water as the electrolyte in metal-air batteries. ILs are attractive because of their low vapor pressure. Furthermore, ILs have an electrochemical window of up to six volts (versus 1.23 for water) supporting more energy-dense metals



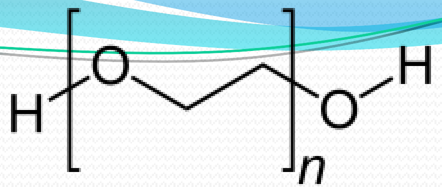
Advantages of ionic liquids over organic solvents

- High ionic conductivity.
- Non Flammable.
- Non Volatile.
- High thermal stability.
- Wide temperature range for liquid phase(-40 to +200 degree Celsius).
- Highly solvating yet non coordinating.
- Good solvents for many organic and non organic materials.



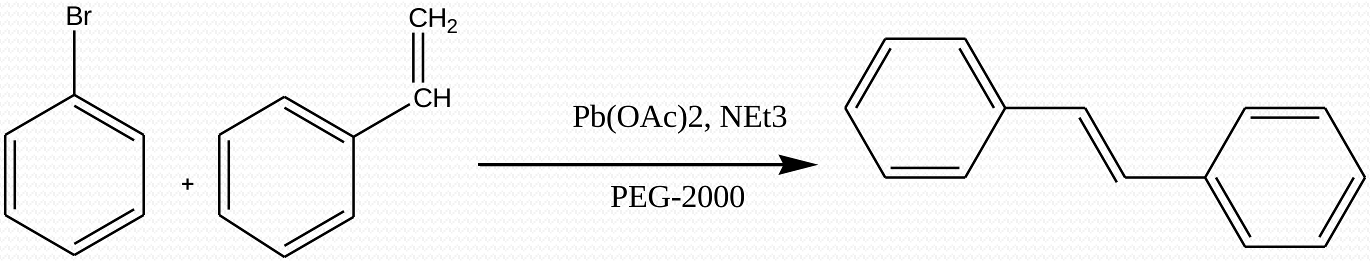
Esterification of alcohols by carboxylic acids has been carried out in a halogen-free Bronsted acidic ionic liquid, N-methyl-2-pyrrolidinium methyl sulphonate under mild conditions, and without additional solvent

PEG(Polyethylene Glycol)



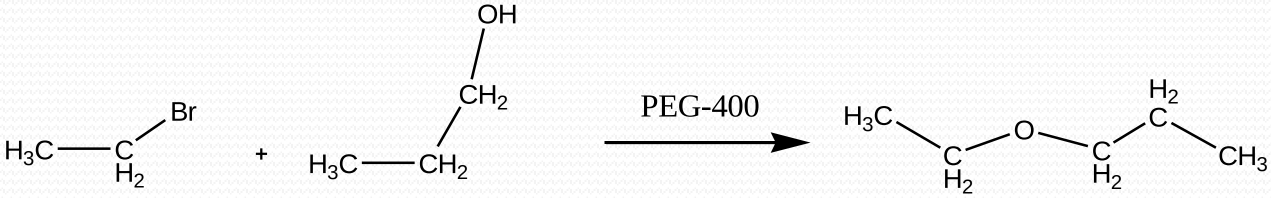
- Low flamability
- Low volatility
- Biodegradable
- Stable in acidic and Basic medium even in high temperature.

Example: Heck reaction

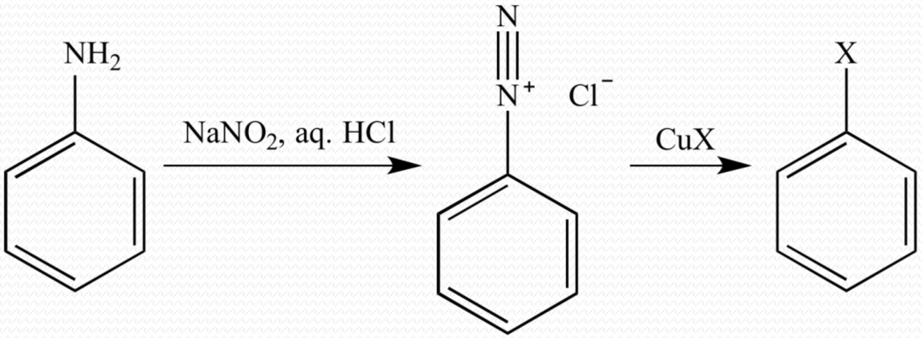


stilbene

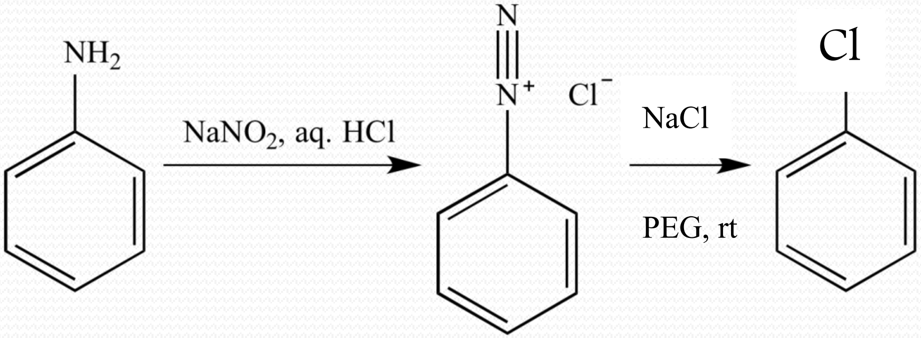
Example: Williamson ether synthesis



Sandmayer reaction:



Yield of above reaction is poor however if the reaction is carried out in PEG yield of corresponding chloride is excellent.



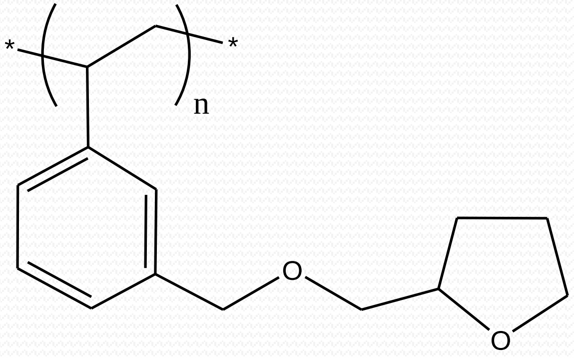
Immobilized Solvent:

- Immobilization of any substance means to restrict the flowing capacity of any substance.
- A major problem with many solvents in relation to human health and the environment, is their volatility and thus have a detrimental effect by exposing individuals and contaminating the air.
- Use of immobilized solvents may be one solution of this problem.
- Immobilization has taken several forms but the goal of each is the same, to maintain the solvency of a material while making it non-volatile .

How to do immobilization:

- By tethering the solvent molecule to a solid support.
- By binding the solvent molecule directly on to the backbone of a polymer.
- New polymer substances themselves are being developed that have solvent properties and yet do not possess the properties that would make them a hazard

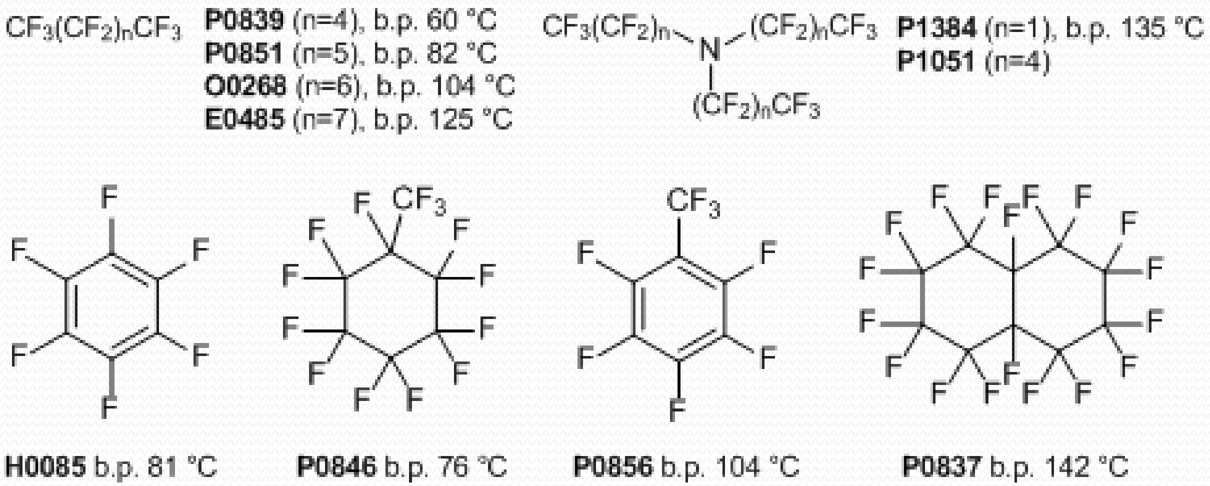
- This concept for solvent design and synthesis offers the potential for significant source reduction in air and water pollution. Example:



An derivatized THF(oligomer solvent)

Fluorous Biphasic Solvent(FBS)

- Solvents containing fluorine with a relatively large component in molecules are called fluorous solvents. Most fluorous solvents have high thermostability and chemostability and are low in toxicity.



Fluorous fluids have very unusual in their properties such as, they have:

- high density
- high stability
- low solubility in water and organic solvent, although they are miscible at high temperature.
- low surface tension
- low intermolecular interactions
- low di-electric constants

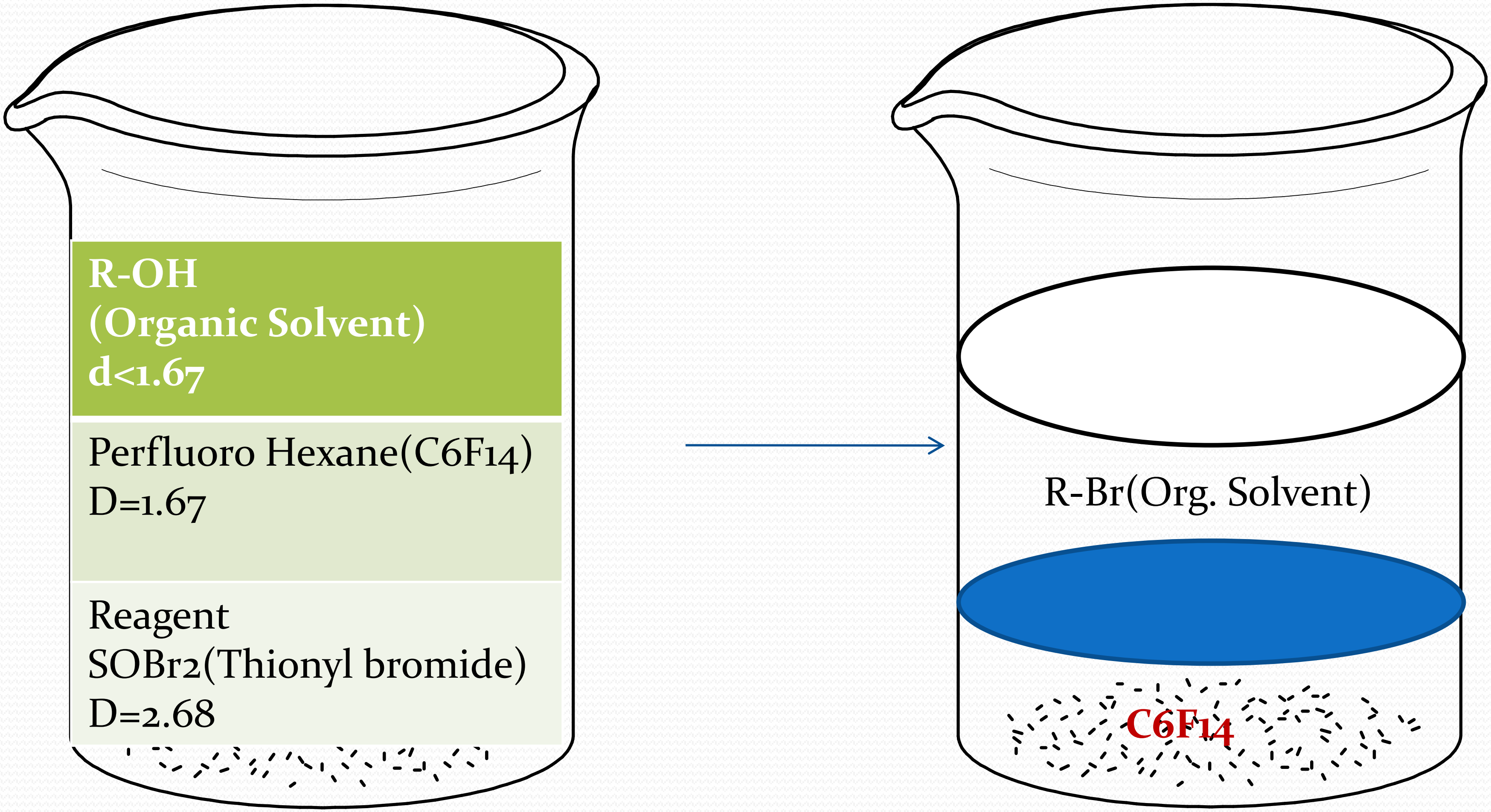
Characteristics of FBS

- They mix with neither common organic solvents nor water at room temperature thus forming biphasic systems.
- They dissolve fluorine-rich compounds well.
- To utilize these features, a method of separation and purification called a fluorous biphase system (FBS) has been developed.

How reaction is done?

- In FBS, a highly fluorous soluble reagent / catalyst resides in the fluorous phase whereas the starting materials are dissolved in an immiscible solvent phase, which can be either an organic solvent, water or a non-organic solvent.
- These two distinct layers are made homogeneous upon heating and the reactants are put into contact and the reaction takes place.
- The layers separate again when the temperature is lowered, products remain in the organic layer while the catalyst or any unreacted fluorous regent stay the fluorous phase.
- This allows an easy separation of products and recycling of catalyst with using any other organic solvent.

Example: PV reaction(Phase vanishing reaction method)



R-OH
(Organic Solvent)
d<1.67

Perfluoro Hexane(C_6F_{14})
D=1.67

Reagent
$SOBr_2$(Thionyl bromide)
D=2.68

R-Br(Org. Solvent)

C_6F_{14}

Comparing Greenness of solvents:

- To compare the greenness of solvents, many chemical characteristics have to be considred like :

Human health - relating to

- toxicity,
- reproductive effects,
- developmental effects,
- neurotoxicity,
- mutagenicity genotoxicity and
- carcinogenicity.

- Ecological effect: relates to
- Bioaccumulation,
- aquatic toxicity
- eutrophication potential,
- acidification potential,
- smog formation potential,
- ozone depleting potential
- persistence in the atmosphere

- N.B.: **Eutrophication** is the process by which an entire body of water or parts of it, becomes progressively enriched with minerals and nutrients.

Pfizer medicinal chemistry has given a solvent selection guide in conformity to ACS

Code	Colour
Score-1-3	Green
Score 4-7	Yellow
Score 8-10	Red

Gree Solvents Colour code - 1-3 (Green) (Preferred solvents):

Water, Acetone, Ethanol, Isopropyl alcohol, Ethyl acetate, Iso propyl acetate , methanol, MEK (methyl ethyl ketone) , 1-Butanol & Tertiary butyl alcohol) etc.

Yellow solvents colour code (4-7): Usable

Cyclohexane, Heptane, Toluene, Methylcyclohexane, TBME (Tertiary Butyl Methyl Ether), Isooctane, Acetonitrile, 2-methylTetrahydrofuran, Tetra hydrofuran (THF), xylenes, DMSO (Dimethyl sulphoxide) Aceticacid, ethylene glycol.

Red Solvent colour code (8-10): Undesirable

Benzene, Carbon Tetrachloride, Pentane, Hexane, Di-isopropyl ether, Diethyl ethter, DCM(Dichloro Methane), DCE(Dichloro ethane), Chloroform, NMP (N-methyl piperidine), DMF(N, N-dimethylformamide), Pyridine, DMAC (N-N-dimethyl acetamide), Dioxane, DME (dimethoxyethane)] etc.

<u>physical properties</u> relates to :

- flammability,
- flashpoint,
- Boiling point reactivity,
- explosivity,
- corrosive tendency,
- odour behaviour,
- water reactivity etc.

Design for Energy Efficiency

Energy requirements of chemical processes should be recognised for their environmental and economic impacts and should be minimised. If possible, synthetic methods should be conducted at ambient temperature and pressure.

- Most chemists mainly think about energy in terms of the reactions it creates. They do not think of where it comes from or the need to minimize its use. And they almost never think of its cost.

- The 6th principle asks that thought is given to the issue of energy efficiency which is a key issue for the 21st century.
- Most energy is based on fossil fuels which actually deliver a very small amount of energy to the end use. Much is lost in transport and transmission.
- Chemists could help to change this. To do so they need to minimise as far as possible the steps taken to achieve the desired result, and to use lower cost materials.
- Trying to run reactions as far as possible at ambient temperatures and pressure is also a way to be green and have impact less on the planet.

Conventional heating method:

What is to be Done? Design for Energy Efficiency

- Following measures should be taken:
- 1. A reaction should be designed with fewer number of steps, which uses less energy, less solvents, higherwater economy, and less waste.
- 2. Energy requirement to be kept at minimum so that the reaction should be carried out at an ambient temperature and pressure.
- 3. Use of a catalyst is a common way to minimize energy use. With a catalyst reaction can be more efficient and selective. A typical catalyst will lower the activation energy by 100 kJ/mol. A reduction of just 6.3 kJ/mol will reduce the temperature by 200°C. This provides an enormous energy saving. This also reduces the risk of explosion or other high-temperature hazards.
- 4. Use of biocatalyst should be encouraged as they work at ambient temperatures and mildest conditions, such as water as a solvent.
- 5. Process design should be such that separation and purification is not needed, for example, mechano-chemical synthesis.
- 6. Instead of thermal energy, energy can be supplied by photochemical means, microwave, sonification,etc.
- 7. Improve process efficiency: To minimize the use of equipment in a lab, equipment should be turnedoff when not in use. This will conserve energy and save money.

Improved Processes and Energy Efficiency.

- **Drawbacks of thermal energy:**
- Thermal sources of energy for most chemical reactions use fossil fuels.
- The energy supplied is not specific, which means that it is not directed to the chemical bond of the molecule of the reactants.
- Most of the energy is used up (wasted) in heating the container and the solvent, while some is lost to the environment.
- Therefore, corrective measures need to be taken to reduce the environmental impact, cost, and increasing efficiencies of fuel.

Measures to be taken….

- 1. Temperature control is very important and should be monitored digitally.
- 2. Regular maintenance of equipment, pumps, tubing, and lubrication should be done.
- 3. Waste energy should be used for other heating purposes.
- 4. Instead of big boilers, smaller boilers should be used

- The following alternatives which are more specific forms of energy may be beneficial if applied:
- 1. Microwave-assisted irradiation
- 2. Light-induced photochemical reaction.
- 3. Sonochemistry-ultrasound irradiation

Use of Microwave

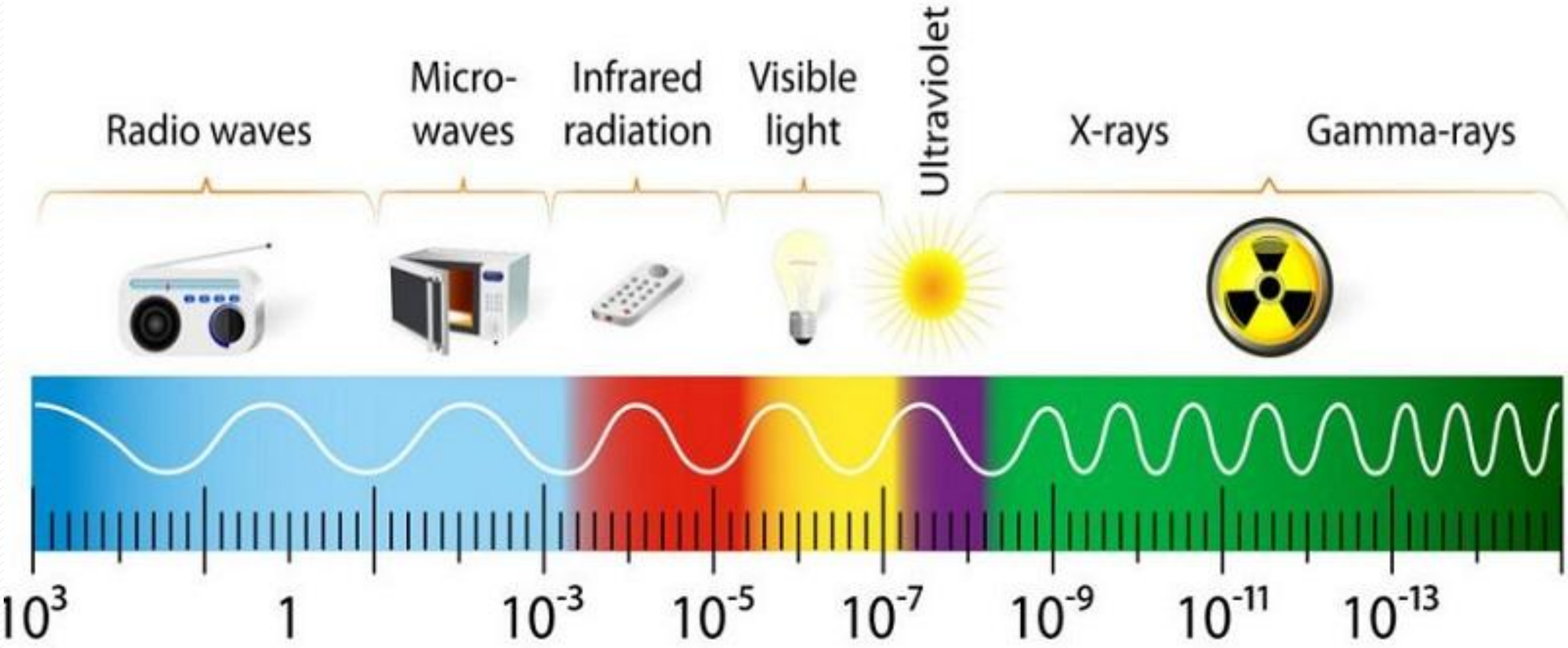
- Microwave irradiation technique is an unconventional energy source. The selective absorption of microwave in the range of 10^9-10^{11} by polar molecules leads to reaction acceleration. The reactions experiencing polar transition state are favored by MWI. Main benefits by using Microwave technique are:

  (i) quick reaction time

  (ii)no requirement of long heating or reflux conditions (saves energy)

  (iii) Most of the MW assisted reactions do not require any medium i.e. solvent free reaction condition, which avoids the disposal problem of solvents.

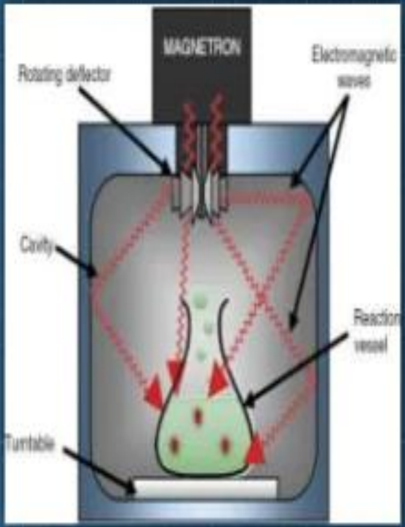
THE ELECTROMAGNETIC SPECTRUM

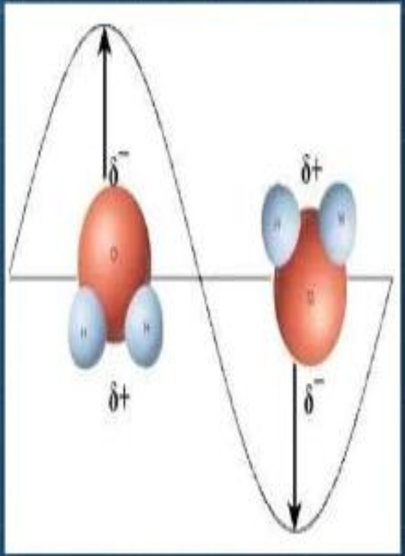


➤ Working Principles

- Microwave oven works by passing non-ionizing microwave radiation , usually at a frequency 2.45 GHz(a wavelength of 12.24 cm), through the food...water, fat & other substances in the food absorb energy from the microwaves in a process called dielectric heating .

- Many molecules (water) are electric dipoles, meaning that they have “+”charge at one end & “-” charge at other end therefore rotate as they try to align themselves & this rotation put them into motion which creates heat.



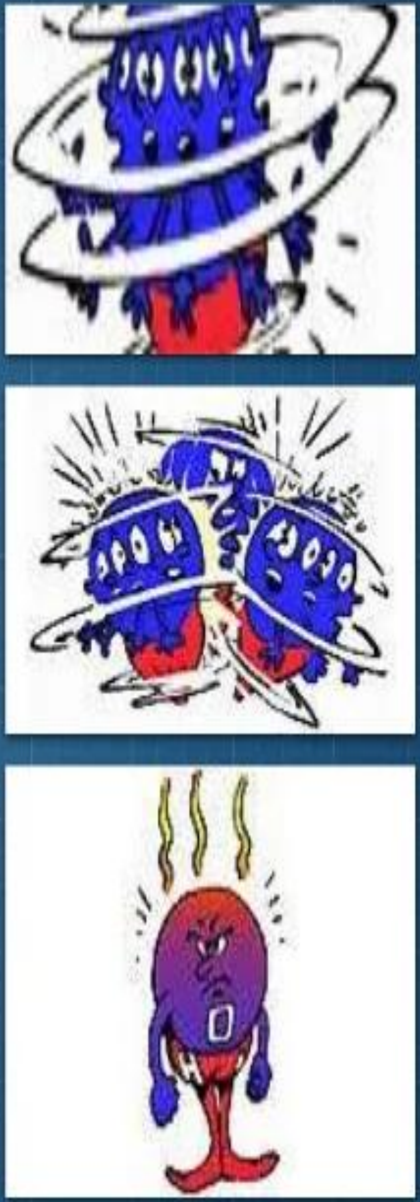


- Microwave Oven generates electromagnetic waves(called microwaves), which makes water move.

- Microwave causes molecules to vibrate.

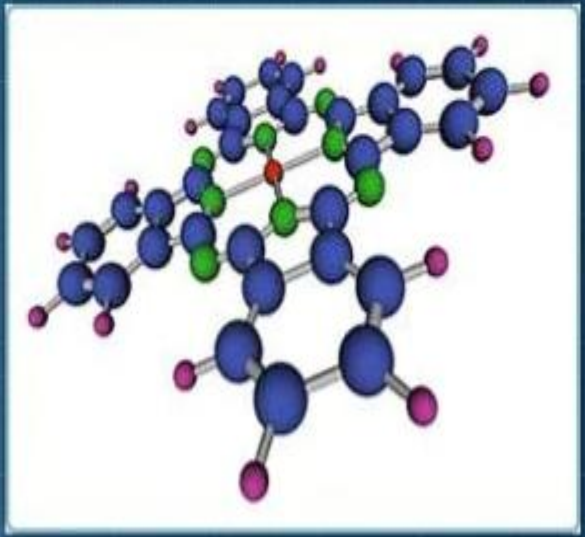
- Vibration creates friction.

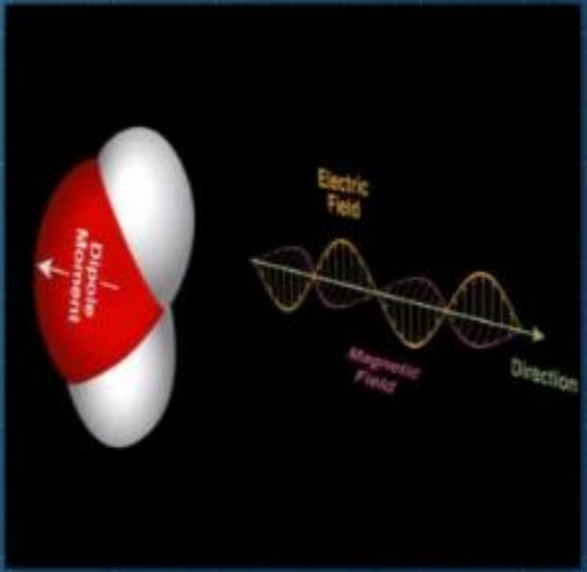
- Friction produces the heat that cook the food.

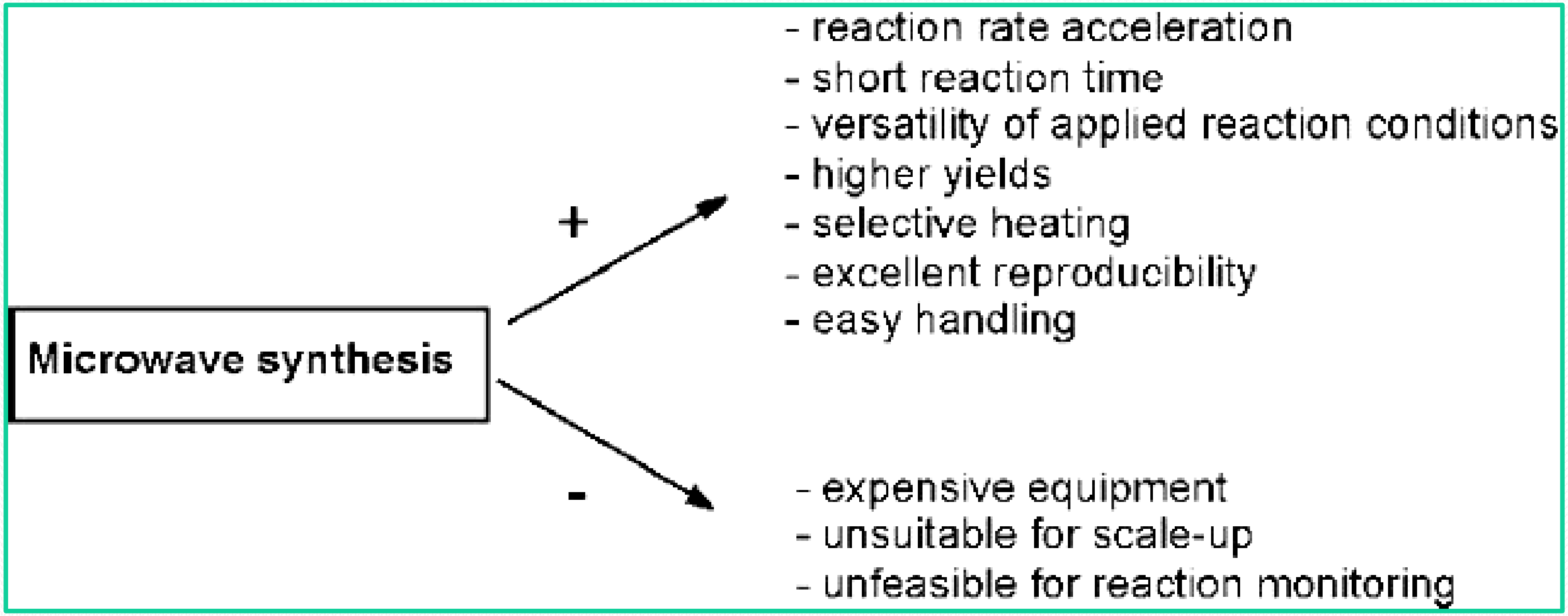


Heating Effect

- Microwave heating is more efficient on liquid water.
- Much less so on fats & sugars(which have less molecular dipole moment).
- And frozen water (where the molecules are not free to rotate).







Microwave synthesis

+

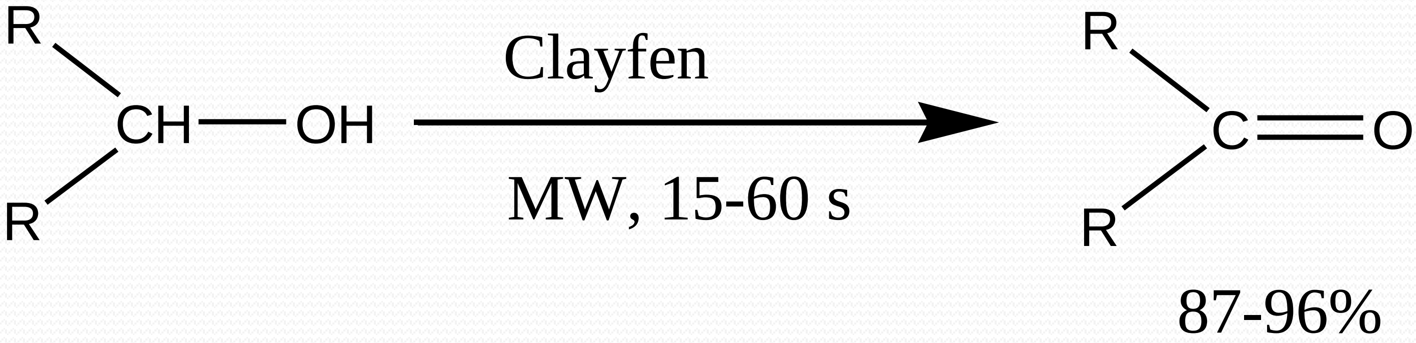
- reaction rate acceleration
- short reaction time
- versatility of applied reaction conditions
- higher yields
- selective heating
- excellent reproducibility
- easy handling

-

- expensive equipment
- unsuitable for scale-up
- unfeasible for reaction monitoring

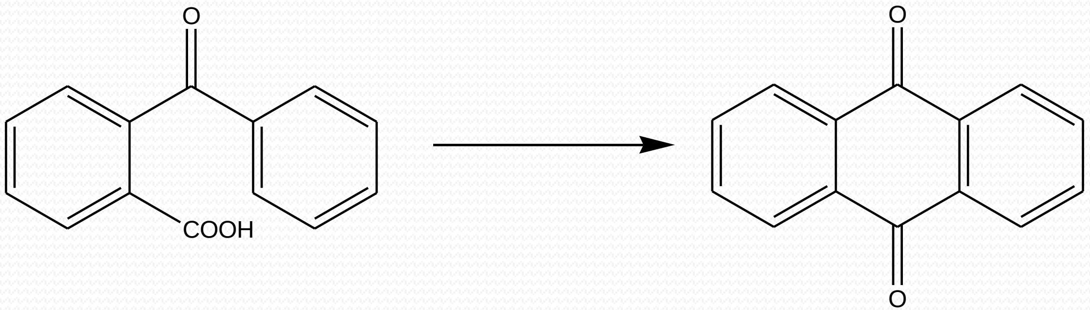
Example 1

- The conventional oxidants like peracids, peroxides, MnO,, (Manganese dioxide)potassium permanganate (KMnO4.), chromium Trioxide (Cr2O3), potasium Dichromate K2Cr2O7) are used as oxidising agents, do have their own limitations in terms of toxicity, work-up procedure and associated waste disposal problems because all of them are stoichiometric oxidising agents, but their use can be avoided by using MWI technique in solvent free oxidation with clayfen [Ferric nitrate]



Example 2

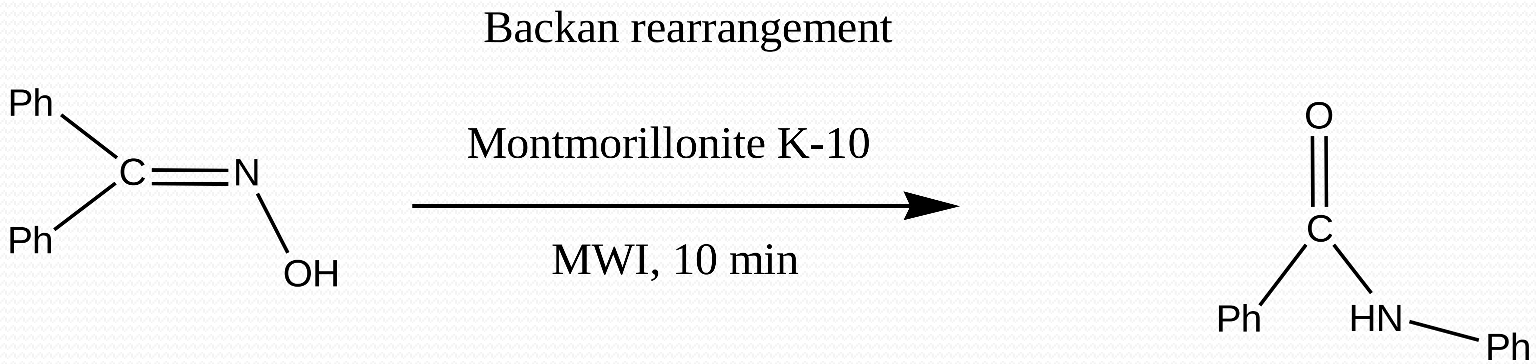
Anthraquinone is obtained by cyclisation of o-benzoyl benzoic acid using microwavein presence of acidic clay



o-benzyl benzoic acid

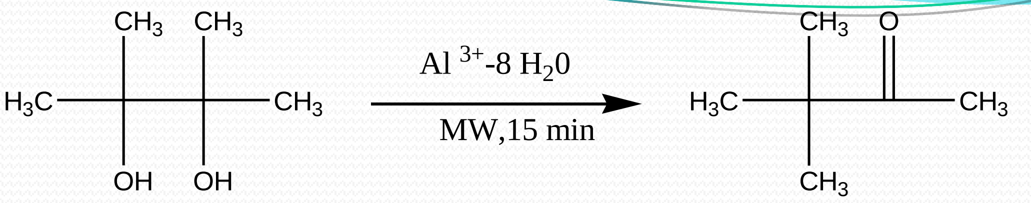
Anthraquinone

Benzanilide is obtained by Beckmann rearrangement of benzo phenone oxime with monotmorillonite K-10 clay in dry media under MW irradiation



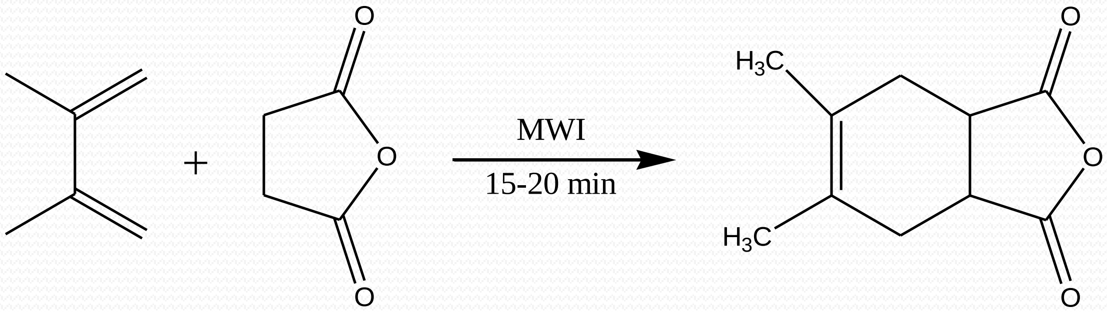
Ph: C_6H_5

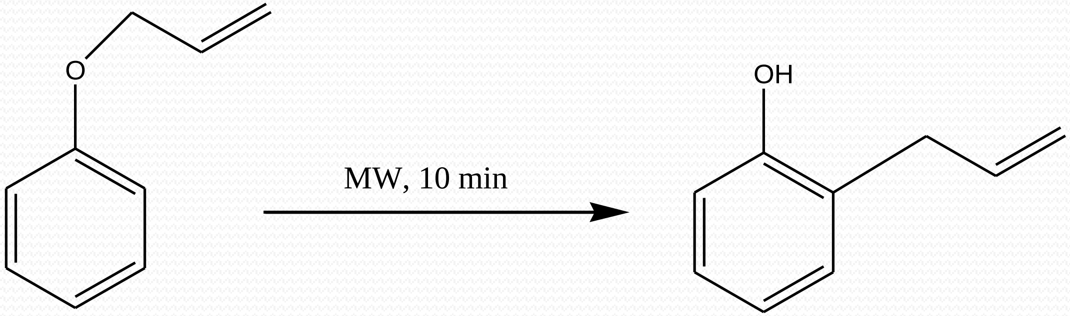
N-phenyl benzamide



pinacol

pinacolon





allyl phenyl ether

O-allyl phenol

Advantages of microwave over conventional synthesis:

1. The reaction rate gets accelerated.
2. It is more efficient as the energy is directly aimed at the reactants rather than first heating the vessel.
3. It has lower relative energy consumption, efficient, and cost-efficient.
4. It is environmentally benign.
5. It has higher production yield.
6. The use of catalyst can be avoided.
7. The formation of side product is reduced. This reduces waste generation.
8. Milder reaction conditions are employed.
9. Different reaction selectivity.

Advantages of solvent free reactions :

- Solid state organic reactions do not require any solvent, so they are the best examples of green reactions.

- They save a lot of energy. In fact the best solvent is no solvent.

- Use of organic solvents is objectionable from standpoint of environmental hazard. That is why solvent free reaction addition is an important objective of green chemistry

Use of sound wave (sonication technique)

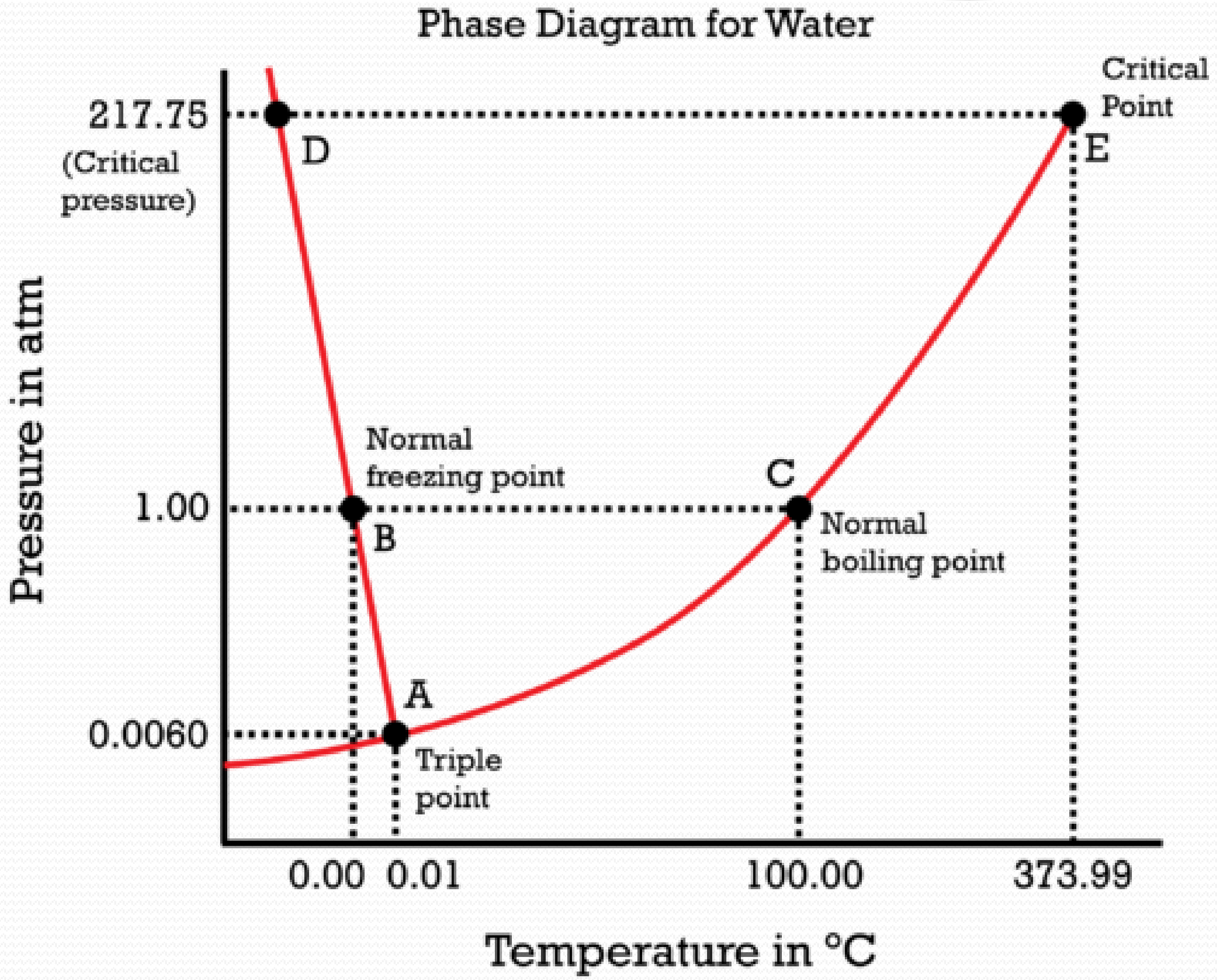
- Ultrasound covers the range 20 kHz to 10 MHz. In sonochemistry, it generally uses the range 20 kHz to 100 kHz
- Sound waves can not directly interact with the molecular vibration because the wave length of sound wave in much longer than the molecular dimension.
- In fact, sonication in homogeneous solution produces accoustic cavitation which is responsible for chemical effects.
- A solvent medium irradiated with ultrasonic waves leads to production and collapse of microbubbles which is called as accoustic cavitation
- During the propagation of ultrasonic waves through a solvent medium, the oscillating particles produce the region of compression and rarefaction successively. Bubbles produced in the region of rarefaction collapse.
- Collapse of these bubbles releases high energy locally to produce high temperature (Ca. 5000°C) and high pressure (Ca. 2 x 10'atm). This gives the activation energy to the molecules present within the bubbles and the liquid surrounding the collapsing bubbles.

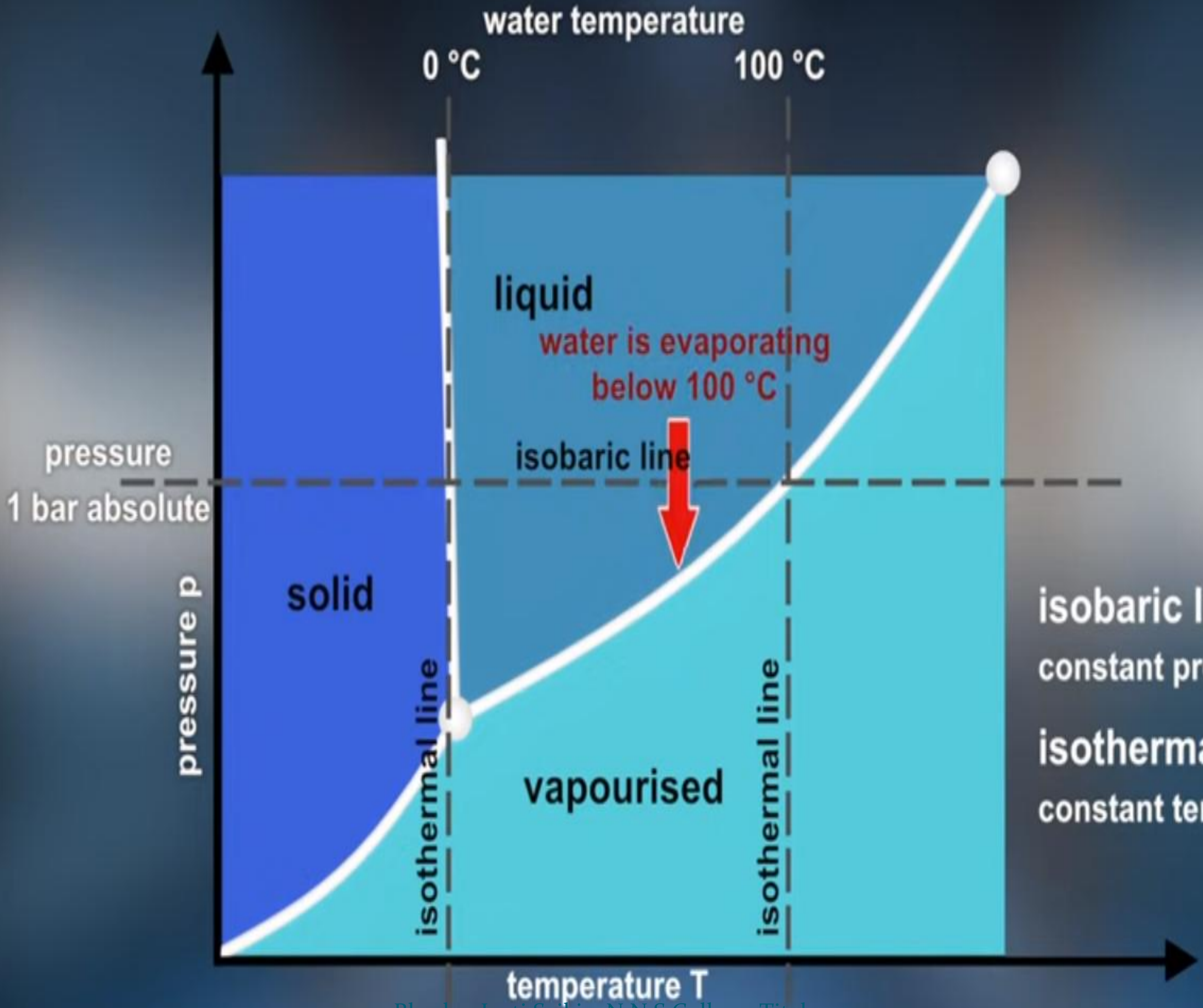
- This accelerates the rate of chemical transformation.
- The symbol)))))) denotes ultrasound assisted reaction.
- Using sonication technique a large no of organic transformations like Diels Alder reaction, Simmon-Smith reaction, Cannizzaro's reaction, Reformatsky Reaction etc. has been carried out.

What is cavitation?

Rapid formation and collapse of vapour bubbles within a liquid.

Cavitation occurs mainly when the static pressure becomes smaller than the liquid's vapour pressure.


Phase Diagram for Water
217.75
(Critical pressure)
D
Critical Point
E
Normal freezing point
1.00
B
C
Normal boiling point
A
0.0060
Triple point
0.00
0.01
100.00
373.99
Pressure in atm
Temperature in °C

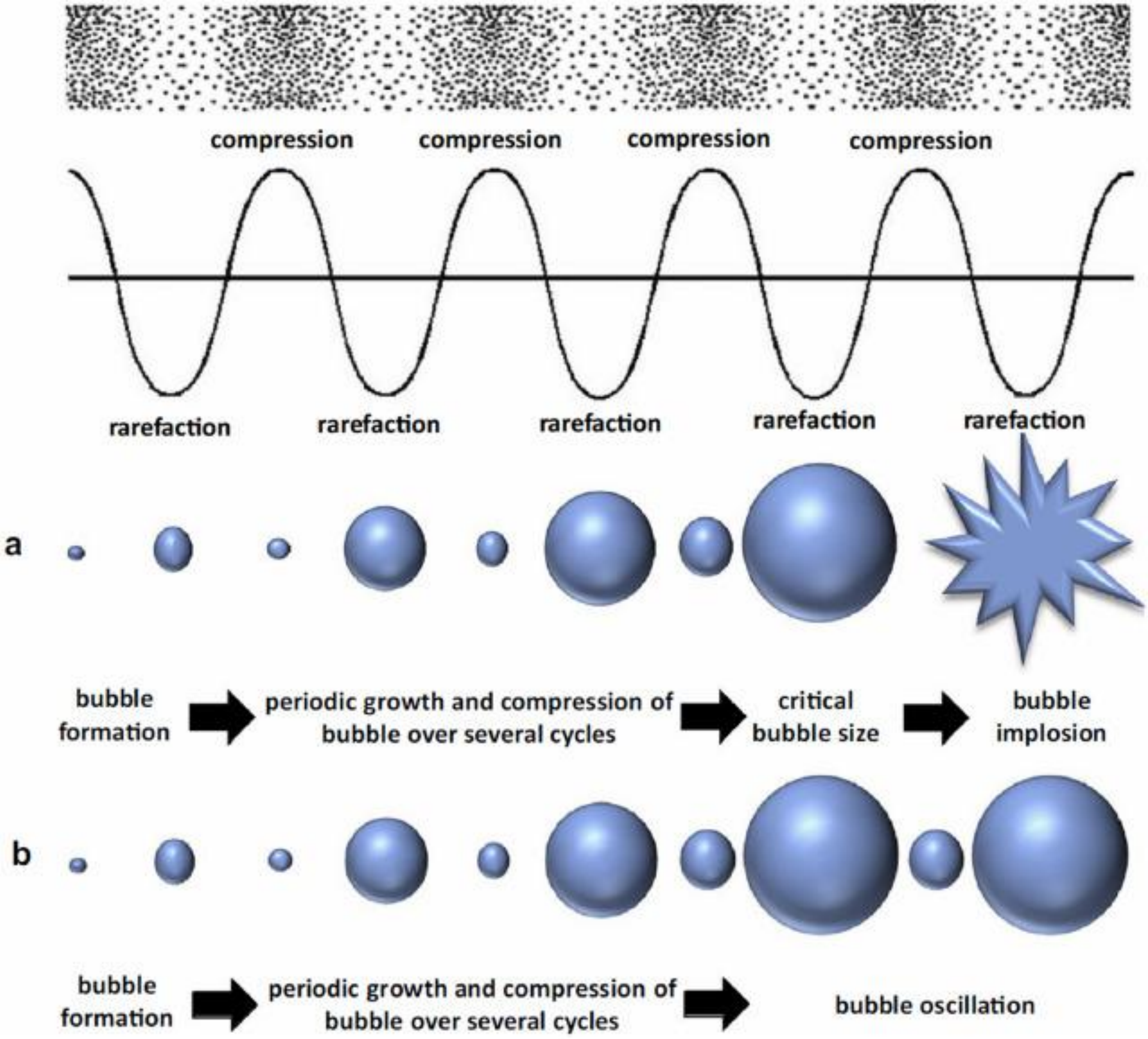


isobaric line:

constant pressure

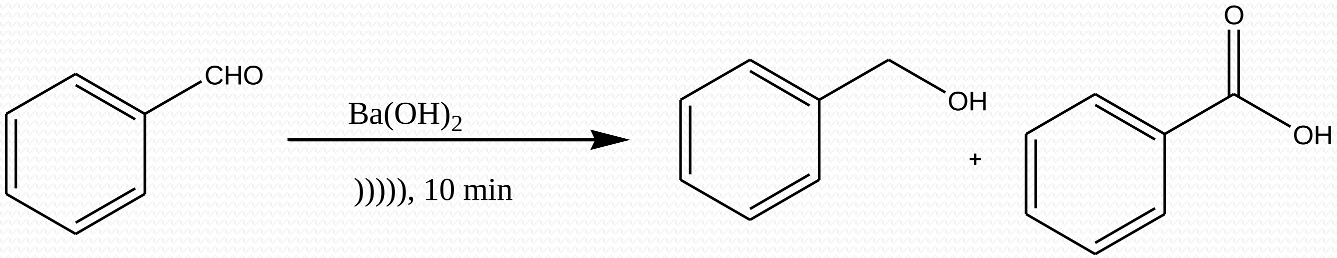
isothermal line:

constant temperature


compression
compression
compression
compression
rarefaction
rarefaction
rarefaction
rarefaction
rarefaction
a
bubble formation
periodic growth and compression of bubble over several cycles
critical bubble size
bubble implosion
b
bubble formation
periodic growth and compression of bubble over several cycles
bubble oscillation

- Collapse of these bubbles releases high energy locally to produce high temperature (Ca. 5000°C) and high pressure. This gives the activation energy to the molecules present within the bubbles and the liquid surrounding the collapsing bubbles.
- So the bubble site acts as a tiny reactor.
- It generates free radical and activated molecule accelerating reaction rate.

Example 1: Cannizzaro's Reaction:

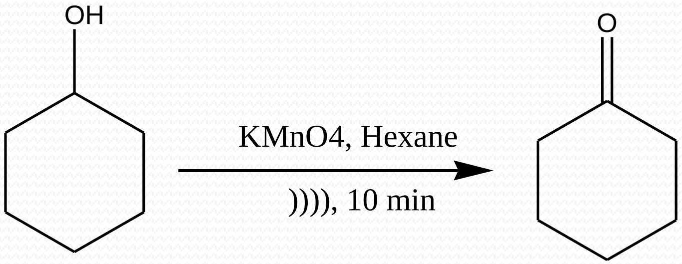


Benzaldehyde

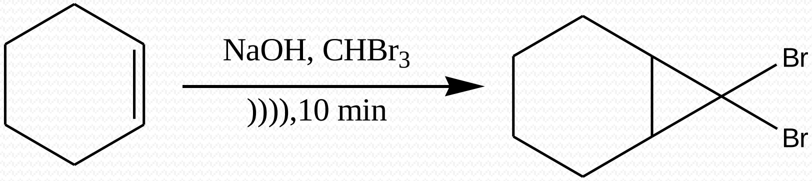
Benzyl alcohol

benzoic acid

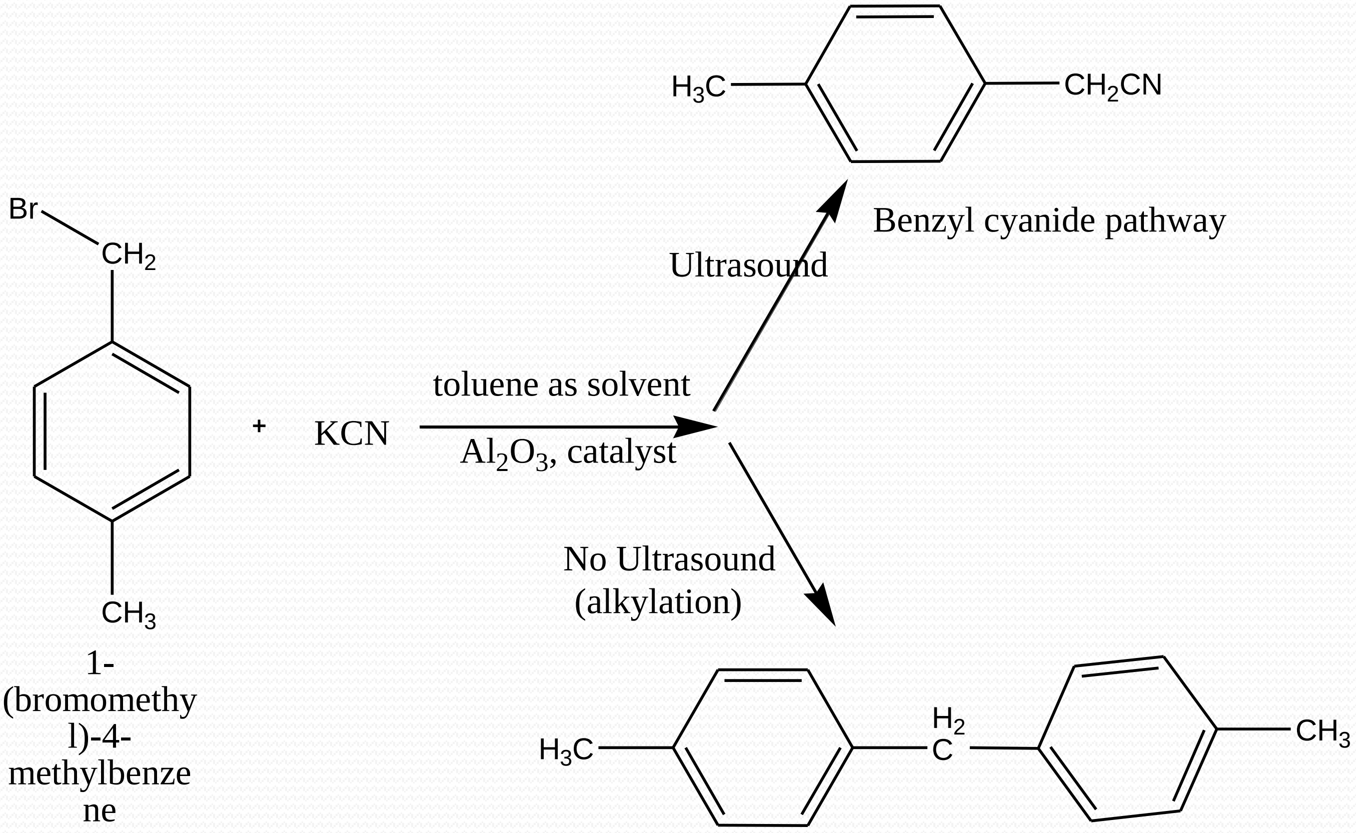
Example 2: Oxidation of Cyclohexanol



Synthesis of bicyclo derivatives:



Switching Pathway



+ KCN

toluene as solvent

Al_2O_3, catalyst

Ultrasound

Benzyl cyanide pathway

No Ultrasound (alkylation)

1-(bromomethyl)-4-methylbenzene

Sonochemical assisted switching pathways

Limitation:

- Always requires liquid medium for bubble formation.

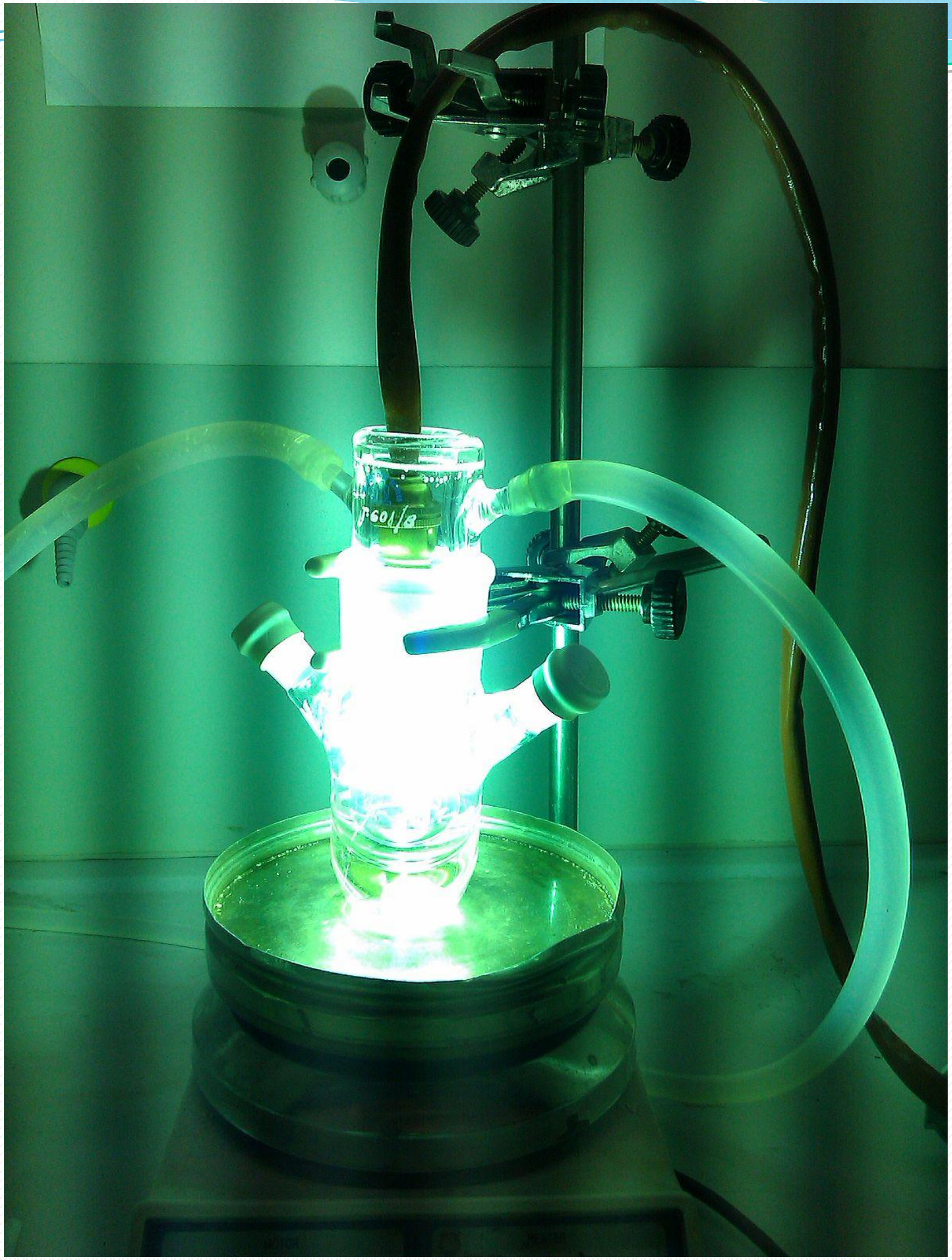
Advantages of sonochemistry

1. There is enhancement of reaction rates upto million times.
2. There is better yield in milder temperature conditions.
3. The reaction may follow different pathways in US-assisted chemical reactions.
4. The very high temperature and very short time of cavitational collapse makes sonochemistry a unique interaction of energy and matter.
5. The equipment is relatively inexpensive.
6. The US is well-suited for industrial application since the reaction liquid itself carries the sound, and there is no barrier to its use with large volume.

Photochemical Reactions

Advantages of photochemical reactions

- 1. Photons are clean reagents and do not leave any residue.
- 2. Photon-initiated process has advantage over catalyst-initiated process, as fewer raw materials are used.
- 3. Use of less harsh reaction conditions as well as solvents.
- 4. Temperature has little effect on the rate of photochemical reactions whereas intensity of light has a marked effect.
- 5. Reaction temperature is generally low as the energy is more directed. This results in higher selectivities there by reduction in by-product formation.
- 6. Sometimes different pathways are easily available for the formation of product, which is not possible by other methods.



Example:

Photochemical protocol for the oxidation of alcohols to aldehydes and ketones

- Mild, Cheap Photochemical reaction conditions
- No need for stoichiometric oxidants
- Environmentally friendly
- No formation of toxic wastes

Use of Renewable Feed stocks

A raw material or feedstock should be renewable rather than depleting whenever technically and economically practicable.

This principle becomes very important due to the following two issues:

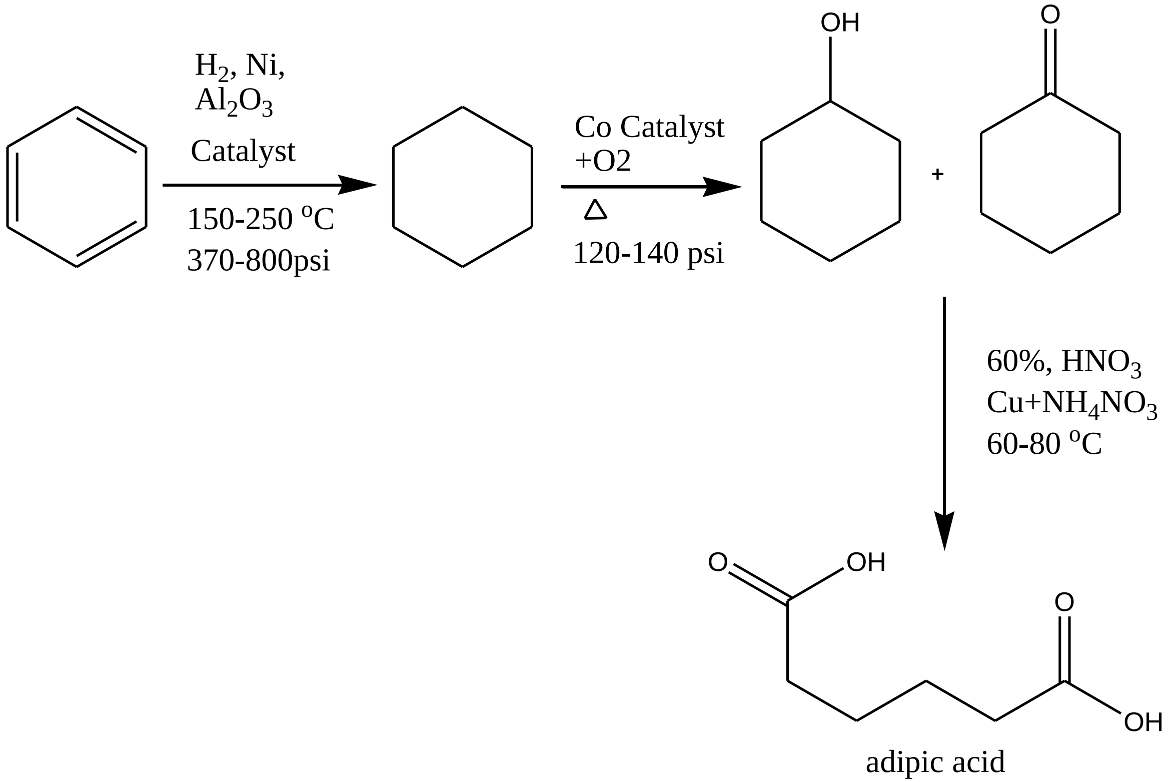
- Sustainability issue:
- Environmental issue:

Some examples of renewable raw materials are as follows:

- (a) Ethanol from plants.
- (b) Polyethylene can be made from ethylene, which is a product of bio-ethanol.
- (c) Polyurethane can be synthesized from soya (polyhydroxy compounds known as polyols).
- (d) Enzymes from biomass.
- (e) Oils and carbohydrates from plants are used for surfactants.
- (f)Starch-based plastics.
- (g) Biodiesel from plant oil.
- (h) 2-MeTHF as a solvent.

Some Alternative Chemicals Derived from Natural Resources

- Adipic Acid from Conventional method:



H_2, Ni, Al_2O_3 Catalyst

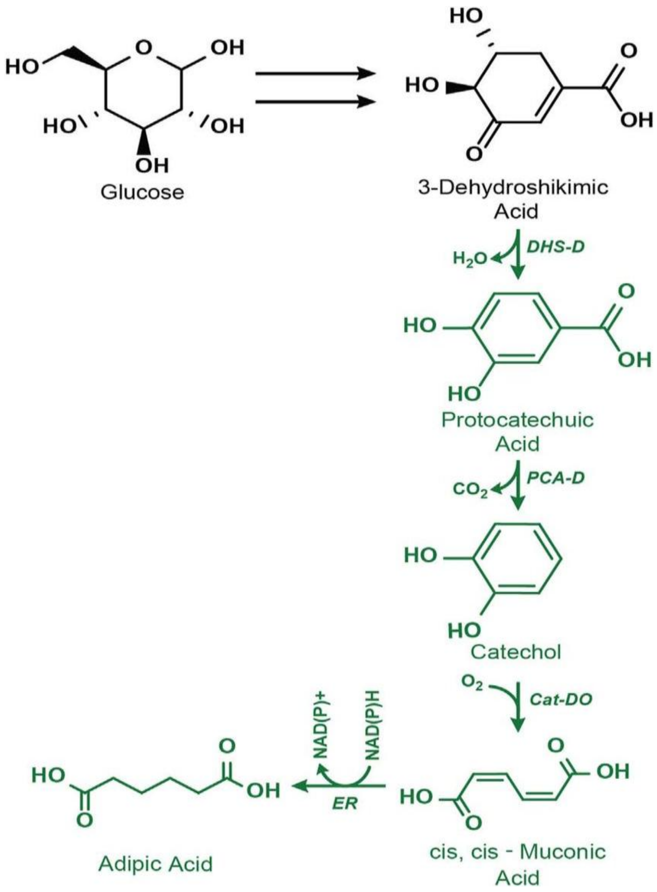
150-250 °C
370-800psi

Co Catalyst
+O2
△
120-140 psi

60%, HNO_3
$Cu+NH_4NO_3$
60-80 °C

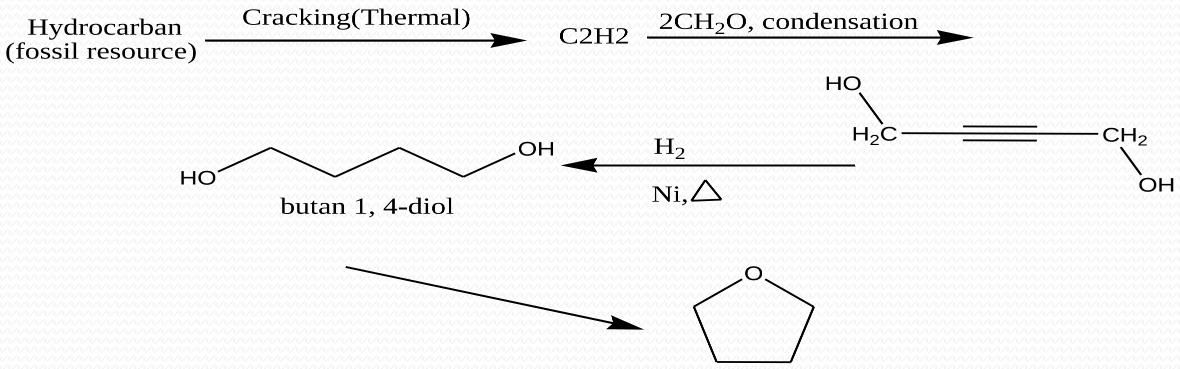
adipic acid

Adipic Acid from Corn Starch:

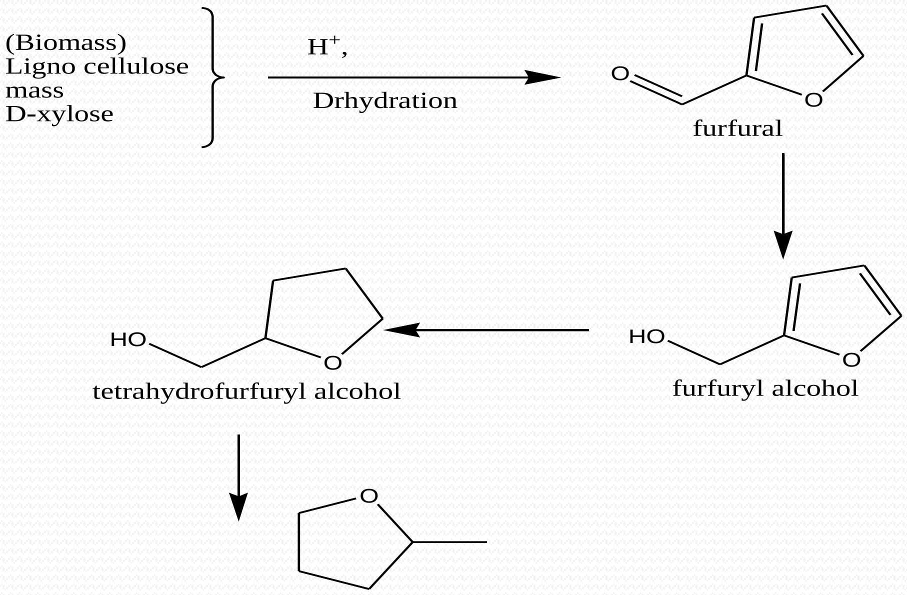


Example 2:

Chemical Synthesis of THF



Synthesis of 2- methyl tetrahydrofuran (MTHF) from Biomass



Biofuels:

- Biofuel is a fuel that is produced through contemporary processes from biomass, rather than by the very slow geological processes involved in the formation of fossil fuels, such as oil.

- The two most common types of biofuel are

  1. **bioethanol** and
  2. **biodiesel**

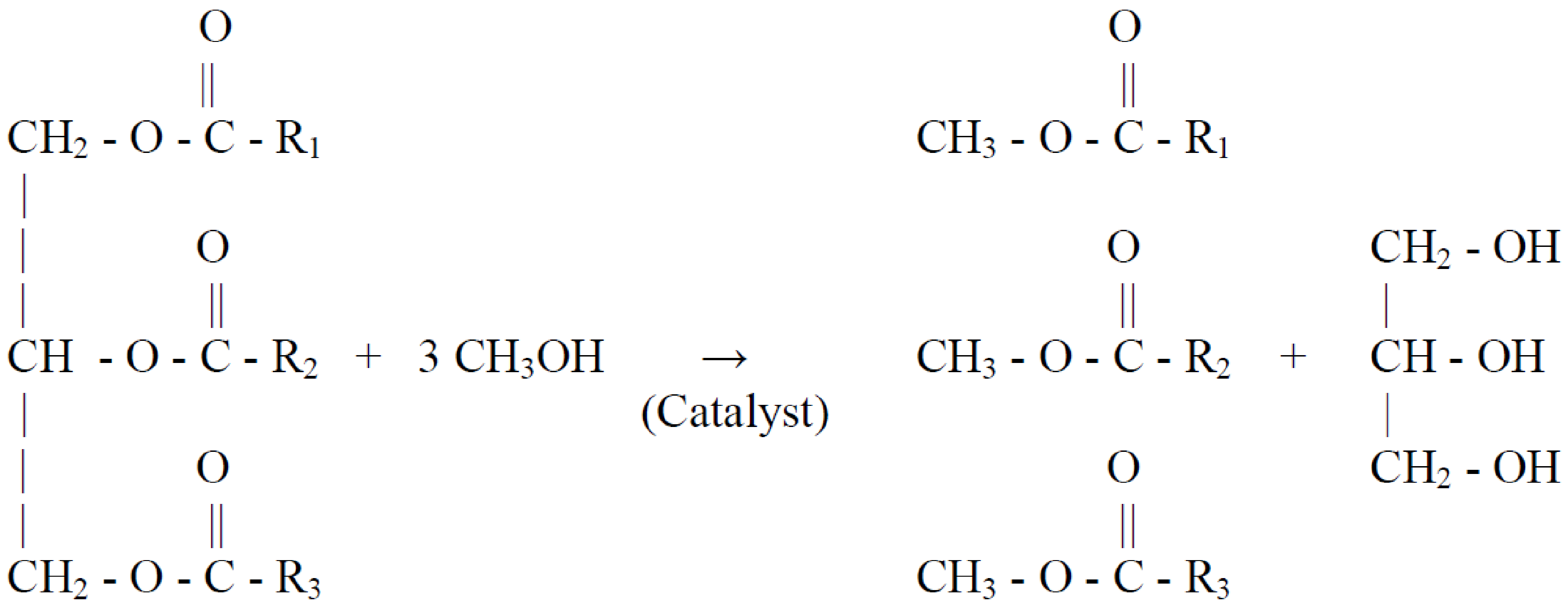
Biodiesel

- Biodiesel is a form of diesel fuel derived from plants or animals
- It consist of long-chain fatty acid esters.
- It is typically made by chemically reacting lipids such as animal fat, soybean oil, or some other vegetable oil with an alcohol, producing a methyl, ethyl or propyl ester by the process of transesterification.

- FEEDSTOCK:

  The feedstock for transesterification can be any fatty acids from vegetable or animal origin, or used cooking oils . Typically used vegetable oils originate from rapeseed, sunflower, soy and oil palms

Biodiesel from vegetable oil:



$$\begin{matrix} \mathrm{CH_2-O-\overset{O}{\overset{\|}{C}}-R_1} \\ | \\ \mathrm{CH\ -O-\overset{O}{\overset{\|}{C}}-R_2} \\ | \\ \mathrm{CH_2-O-\overset{O}{\overset{\|}{C}}-R_3} \end{matrix} \quad + \quad 3\ \mathrm{CH_3OH} \quad \xrightarrow[\text{(Catalyst)}]{} \quad \begin{matrix} \mathrm{CH_3-O-\overset{O}{\overset{\|}{C}}-R_1} \\ \mathrm{CH_3-O-\overset{O}{\overset{\|}{C}}-R_2} \\ \mathrm{CH_3-O-\overset{O}{\overset{\|}{C}}-R_3} \end{matrix} \quad + \quad \begin{matrix} \mathrm{CH_2-OH} \\ | \\ \mathrm{CH-OH} \\ | \\ \mathrm{CH_2-OH} \end{matrix}$$

triglyceride methanol mixture of fatty esters glycerol

Biodiesel

Oil

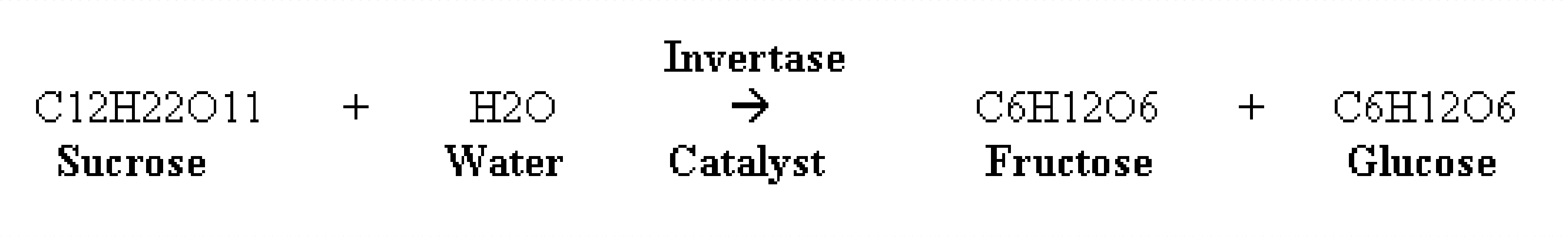
Green chemistry principle used in the process:

- Principle 1: Waste prevention(glycerol can be used in the food and cosmetic industries, as well as in the oleochemical industry)
- Principle3: Less hazardous chemical synthesis.
- Principle6: Design for energy efficiency
- Principle7: Renewable resources.
- Principle 12: Safer Chemistry.

Bioethanol

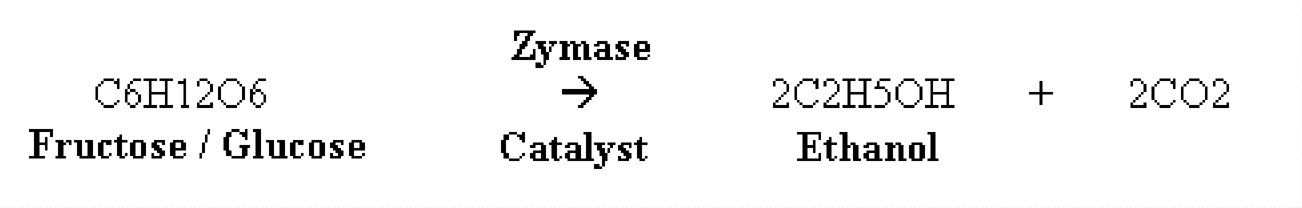
- Bioethanol is an alcohol made by fermentation, mostly from carbohydrates produced in sugar or starch crops such as corn, sugarcane etc.
- Cellulosic biomass, derived from non-food sources, such as trees and grasses, is also being developed as a feedstock for ethanol production.
- Ethanol can be used as a fuel for vehicles in its pure form (E100), but it is usually used as a gasoline additive to increase octane and improve vehicle emissions.

- The hydrolysis process breaks down the cellulostic part of the biomass or corn into sugar solutions that can then be fermented into ethanol



$$\underset{\text{Sucrose}}{C_{12}H_{22}O_{11}} + \underset{\text{Water}}{H_2O} \xrightarrow[\text{Catalyst}]{\text{Invertase}} \underset{\text{Fructose}}{C_6H_{12}O_6} + \underset{\text{Glucose}}{C_6H_{12}O_6}$$

The fructose and glucose sugars then react with another enzyme called zymase, which is also contained in the yeast to produce ethanol and carbon dioxide.



$$\underset{\text{Fructose / Glucose}}{C_6H_{12}O_6} \xrightarrow[\text{Catalyst}]{\text{Zymase}} \underset{\text{Ethanol}}{2C_2H_5OH} + 2CO_2$$

Advantages of bioethanol as a biofuel include:

- **high octane number (108),**
- **low boiling point,**
- **higher heat of vaporization, and**
- **comparable energy content**

Formula equation:

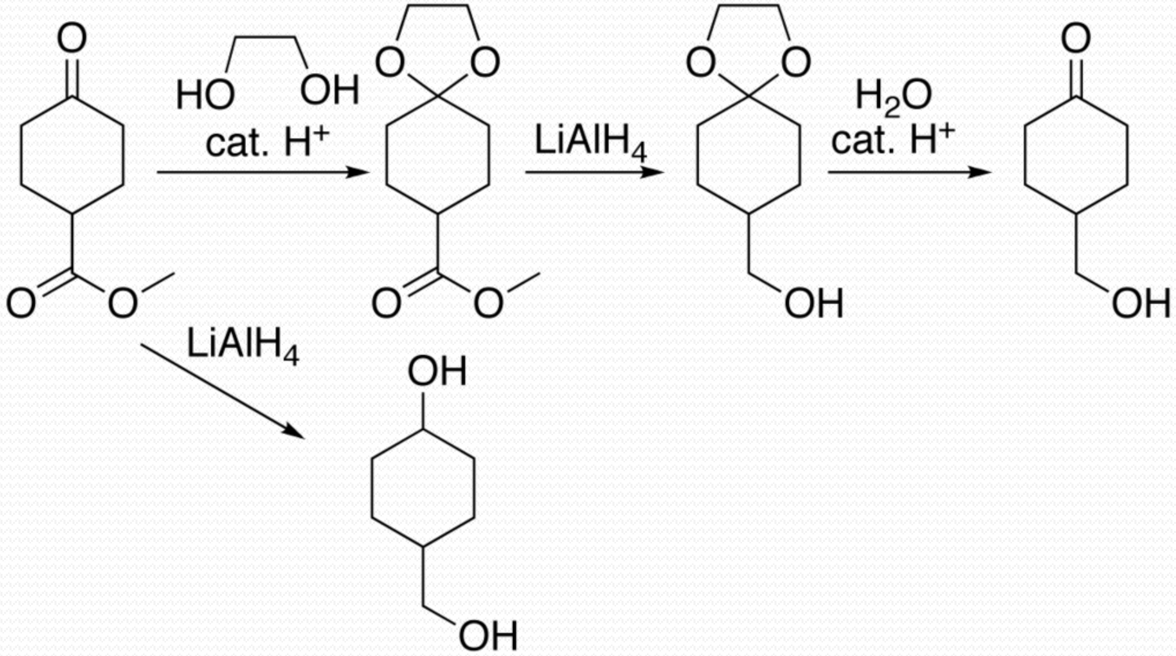
$$C_2H_5OH + 3O_2 \longrightarrow 2CO_2 + 3H_2O$$

8. Reduce Derivatives

Unnecessary derivatization (use of blocking groups, protection/de-protection, and temporary modification of physical/chemical processes) should be minimized or avoided if possible, because such steps require additional reagents and can generate waste.

What is protecting group?

- A protecting group is introduced into a molecule by chemical modification of a functional group to obtain chemoselectivity in a subsequent chemical reaction.
- They are easy to insert and easy to remove

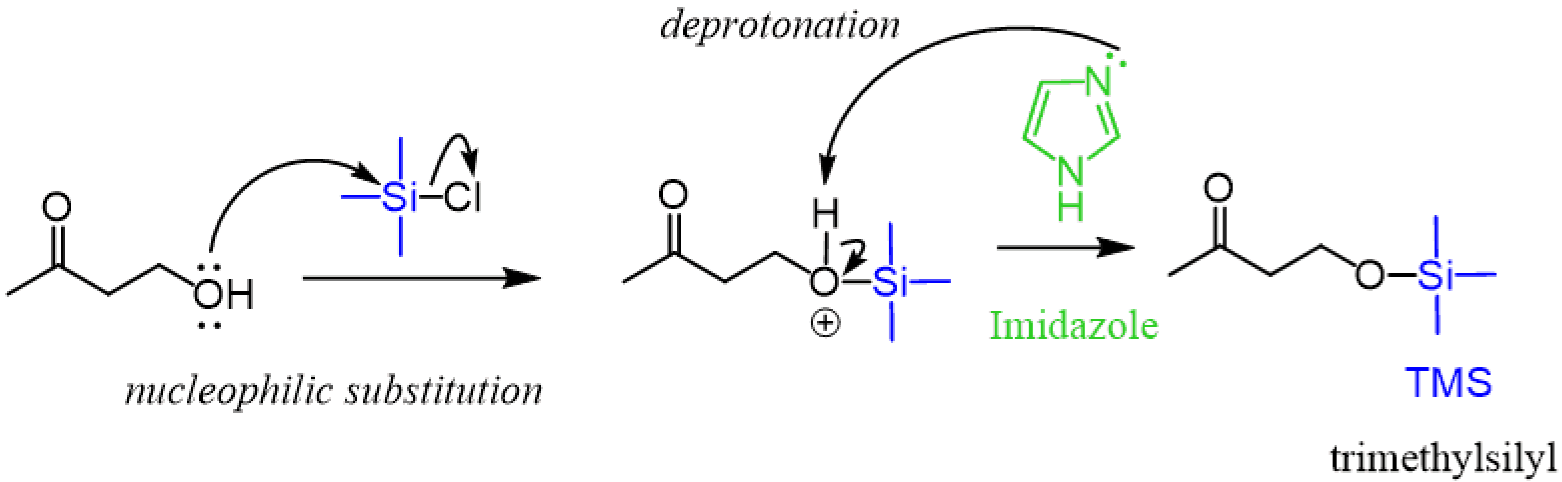


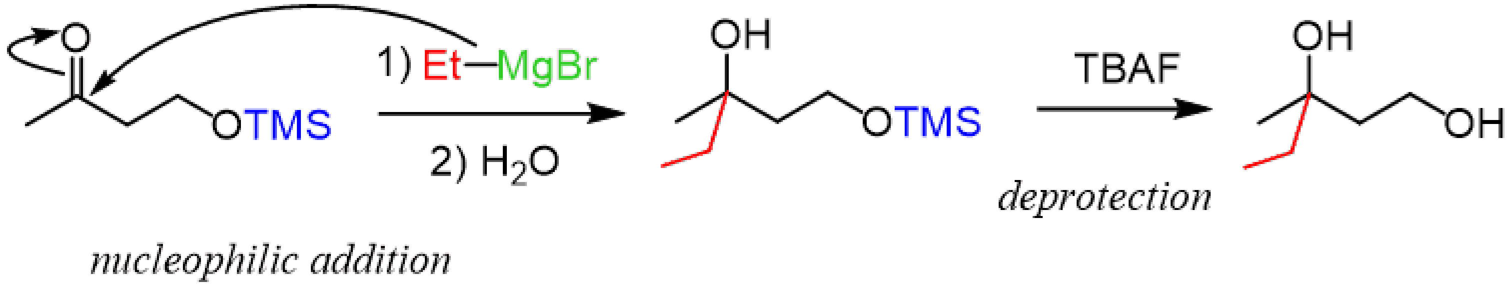
Acetal protection of a ketone with ethylene glycol during reduction of an ester, vs. reduction to a diol when unprotected.

Alcohol protecting groups:

- Acetyl (Ac) – Removed by acid or base.
- Benzoyl (Bz) – Removed by acid or base
- Benzyl (Bn) – Removed by hydrogenolysis.
- β-Methoxyethoxymethyl ether (MEM) – Removed by acid.
- Dimethoxytrityl, [bis-(4-methoxyphenyl)phenylmethyl] (DMT) – Removed by weak acid.
- Methoxymethyl ether (MOM) – Removed by acid.
- Methoxytrityl [(4-methoxyphenyl)diphenylmethyl] (MMT) – Removed by acid and hydrogenolysis.
- p-Methoxybenzyl ether (PMB) – Removed by acid, hydrogenolysis, or oxidation - commonly with DDQ .
- p-Methoxyphenyl ether (PMP) – Removed by oxidation.
- Methylthiomethyl ether – Removed by acid.
- Pivaloyl (Piv) – Removed by acid, base or reductant agents. It is substantially more stable than other acyl protecting groups.
- Tetrahydropyranyl (THP) – Removed by acid.
- Tetrahydrofuran (THF) – Removed by acid.
- Trityl (triphenylmethyl, Tr) – Removed by acid and hydrogenolysis.
- **Silyl ether (most popular ones include trimethylsilyl (TMS), tert-butyldimethylsilyl (TBDMS or TBS), tri-iso-propylsilyloxymethyl (TOM), and triisopropylsilyl (TIPS) ethers) – Removed by acid or fluoride ion. (such as NaF, TBAF (tetra-n-butylammonium fluoride, HF-Py, or HF-NEt3)). TBDMS and TOM groups are used for protection of 2'-hydroxy function in nucleosides, particularly in oligonucleotide synthesis.**
- Methyl ethers – Cleavage is by TMSI in dichloromethane or acetonitrile or chloroform. An alternative method to cleave methyl ethers is BBr3 in DCM
- Ethoxyethyl ethers (EE) – Cleavage more trivial than simple ethers e.g. 1N hydrochloric acid

Protection and deprotection of alcohols by a common silyl ether - trimethylsilyl (TMS)



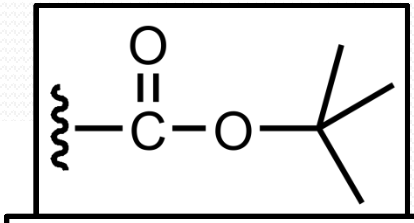


TBAF = Tetrabutylammonium fluoride

Protection of amines

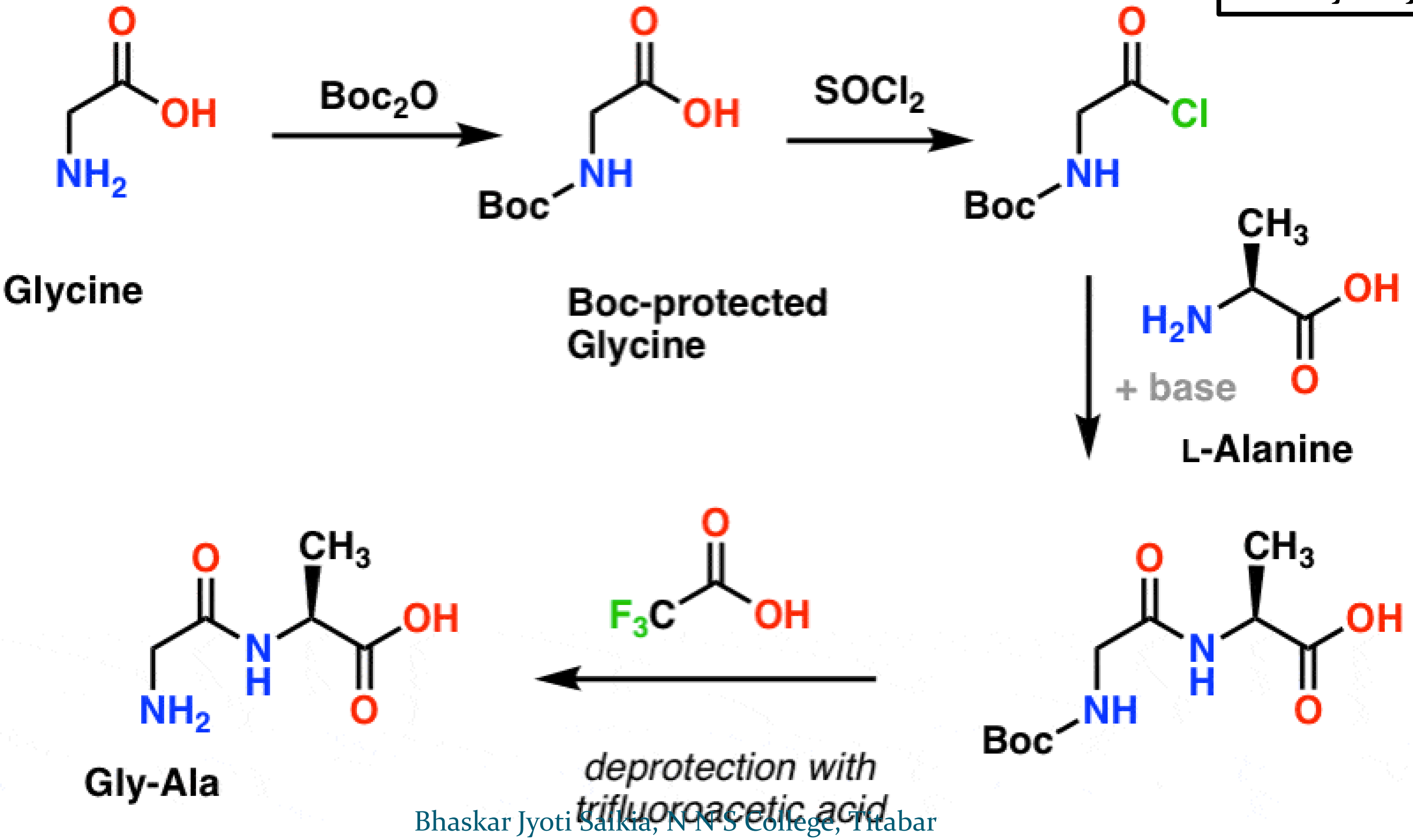
- Carbobenzyloxy (Cbz) group – Removed by hydrogenolysis
- p-Methoxybenzyl carbonyl (Moz or MeOZ) group – Removed by hydrogenolysis, more labile than Cbz
- tert-Butyloxycarbonyl (BOC) group - Removed by concentrated strong acid (such as HCl or CF3COOH), or by heating to >80 °C.
- 9-Fluorenylmethyloxycarbonyl (Fmoc) group (Common in solid phase peptide synthesis) – Removed by base, such as piperidine
- Benzyl (Bn) group – Removed by hydrogenolysis
- Carbamate group – Removed by acid and mild heating.
- p-Methoxybenzyl (PMB) – Removed by hydrogenolysis, more labile than benzyl
- 3,4-Dimethoxybenzyl (DMPM) – Removed by hydrogenolysis, more labile than p-methoxybenzyl
- p-Methoxyphenyl (PMP) group – Removed by ammonium cerium(IV) nitrate (CAN)
- Tosyl (Ts) group – Removed by concentrated acid (HBr, H2SO4) & strong reducing agents (sodium in liquid ammonia or sodium naphthalenide)
- Troc (trichloroethyl chloroformate) group – Removed by Zn insertion in the presence of acetic acid

Protection and deportation of amine via Boc



t-Butyloxycarbonyl

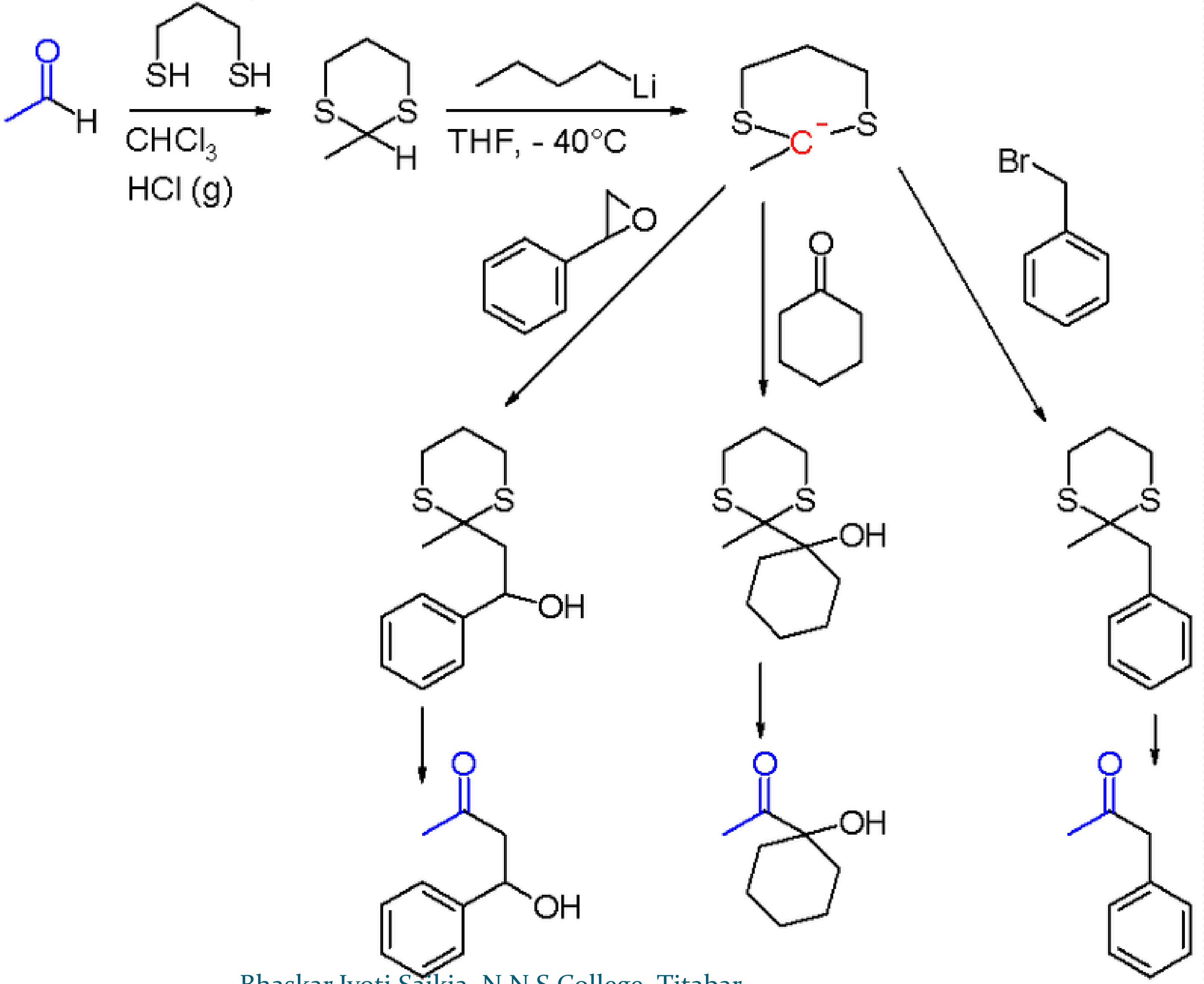
Dipeptide synthesis with Boc *via* acid chloride



Protection of carbonyl groups:

- Acetals and Ketals – Removed by acid. Normally, the cleavage of acyclic acetals is easier than of cyclic acetals.
- Acylals – Removed by Lewis acids.
- Dithianes – Removed by metal salts or oxidizing agents.

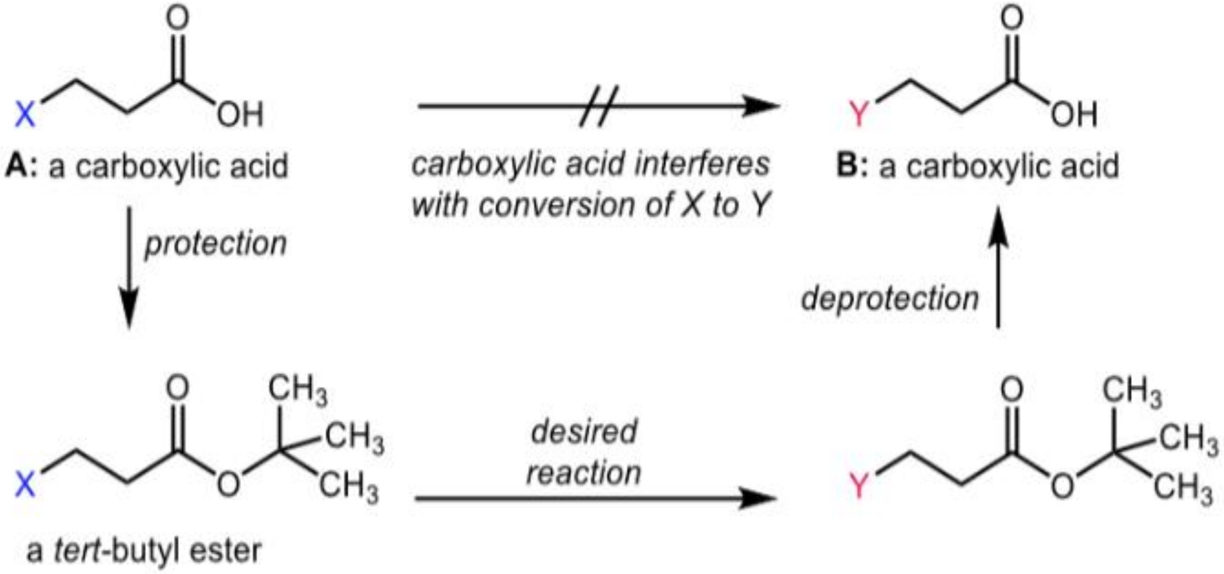
Carbonyl protection by 1,3 –Dithianes:



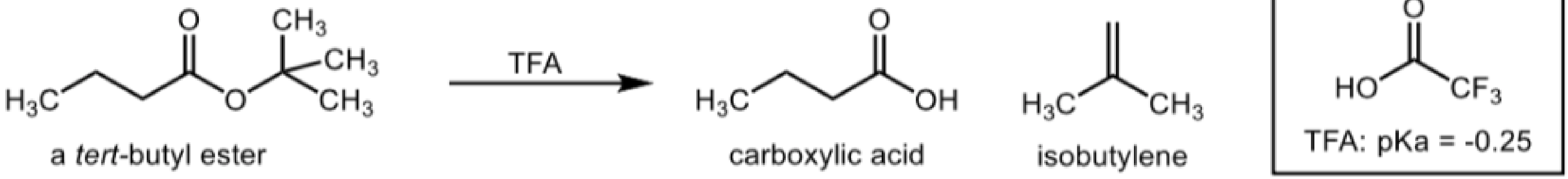
Carboxylic acid protecting groups

- Methyl esters – Removed by acid or base.
- Benzyl esters – Removed by hydrogenolysis.
- tert-Butyl esters – Removed by acid, base and some reductants.
- Esters of 2,6-disubstituted phenols (e.g. 2,6-dimethylphenol, 2,6-diisopropylphenol, 2,6-di-tert-butylphenol) – Removed at room temperature by DBU-catalyzed methanolysis under high-pressure conditions
- Silyl esters – Removed by acid, base and organometallic reagents.
- Orthoesters – Removed by mild aqueous acid to form ester, which is removed according to ester properties.
- Oxazoline – Removed by strong hot acid ($pH < 1$, $T > 100$ °C) or alkali ($pH > 12$, $T > 100$ °C), but not e.g. LiAlH4, organolithium reagents or Grignard (organomagnesium) reagents

Carboxylic acid protection and deprotection:



Deprotection of a *tert*-butyl ester in acid



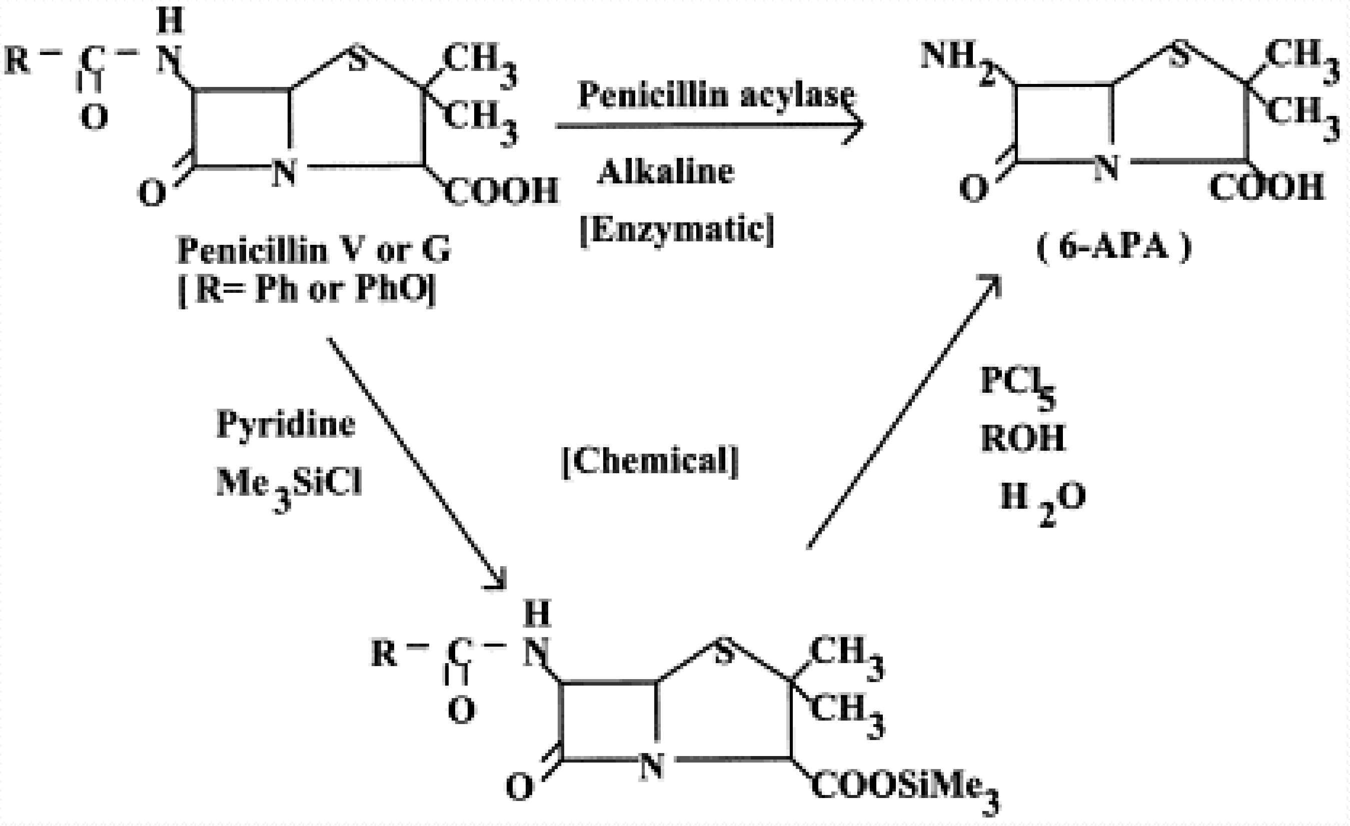
Terminal alkyne protecting groups:

- Propargyl alcohols in the Favorskii reaction,
- Silyl groups, especially in protection of the acetylene itself

Disadvantages of Protection:

1. More steps are involved.
2. Additional reagents.
3. Generation of more waste
4. More time for synthesis
5. Higher cost of production.
6. Poor atom economy.

Schematic representation of synthesis of penicillin:



Advantages of enzymatic process:

- 1. No silyl group is required (no protecting/ deprotecting step).
- 2. No use of corrosive PCI, and ozone depleting CH_2Cl_2.
- 3. No need of cooling as reaction occurs at room temperature.
- 4. Aqueous medium is involved.

9. Catalysis

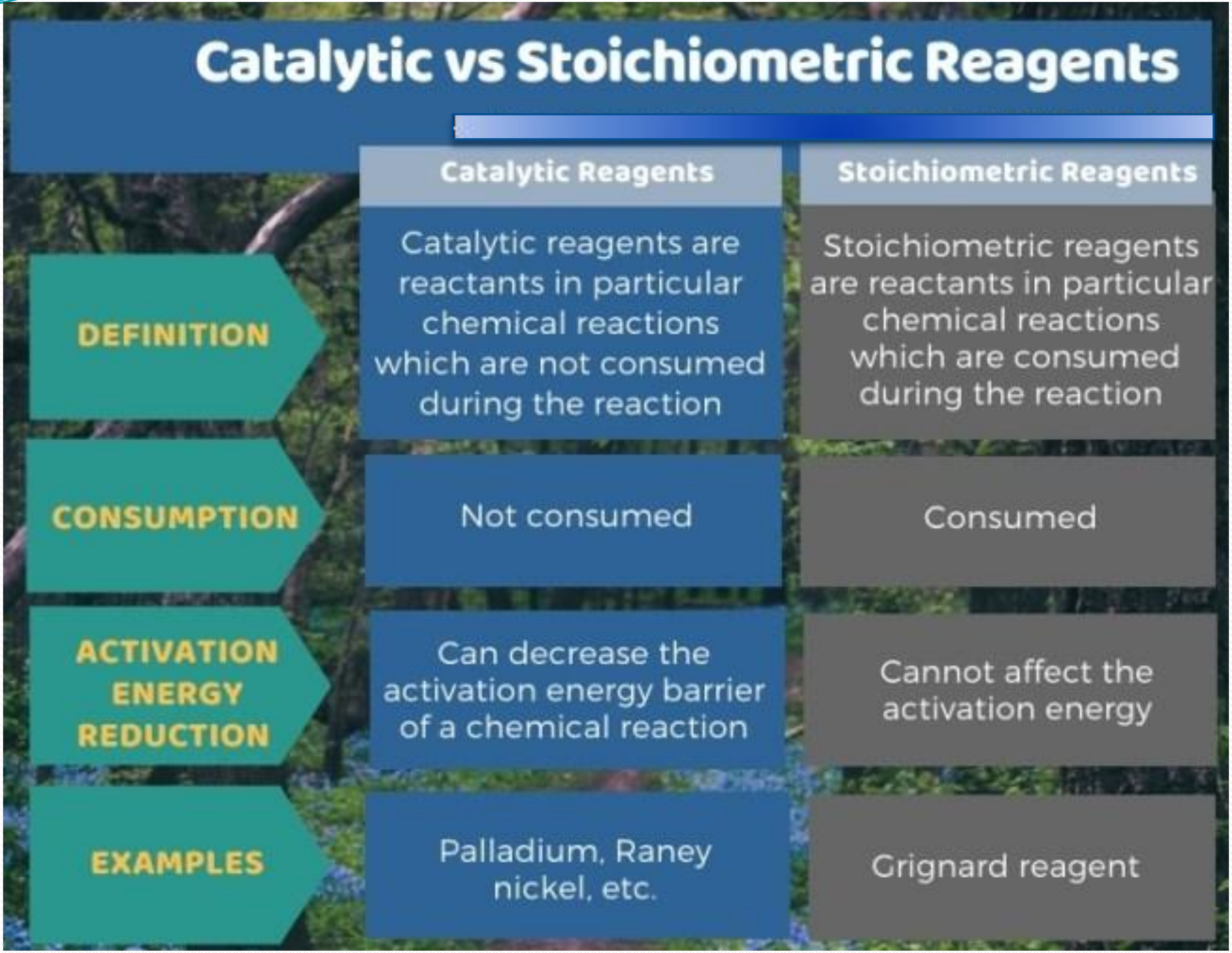
Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.

Stoichiometric reagents

Stoichiometric reagents are reactants in a chemical reaction that are consumed during the reaction. Therefore, a stoichiometric reagent actively participates in the chemical reaction. Due to this consumption, stoichiometric reagent does not regenerate after the completion of the reaction.

Catalytic reagents

- Catalytic reagents are reactants in particular chemical reactions which are not consumed during the reaction.
- Catalyst is a substance that can increase the reaction rate of a particular chemical reaction.
- The process of increasing the reaction rate is “catalysis”.
- We need only a small amount of the catalyst for the catalysis of a chemical reaction.
- Chemical reactions occur faster when there is a catalyst

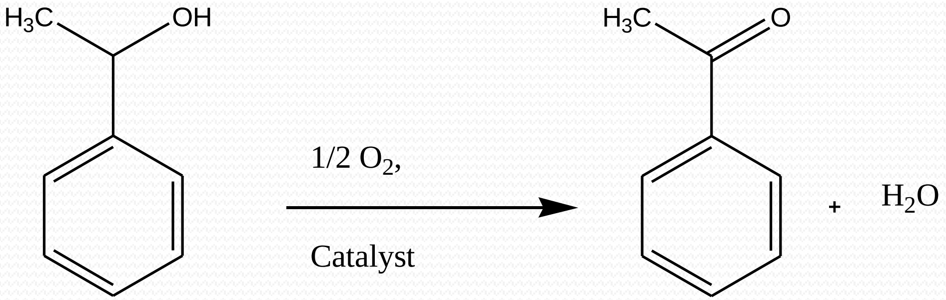


Catalytic vs Stoichiometric Reagents

	Catalytic Reagents	Stoichiometric Reagents
DEFINITION	Catalytic reagents are reactants in particular chemical reactions which are not consumed during the reaction	Stoichiometric reagents are reactants in particular chemical reactions which are consumed during the reaction
CONSUMPTION	Not consumed	Consumed
ACTIVATION ENERGY REDUCTION	Can decrease the activation energy barrier of a chemical reaction	Cannot affect the activation energy
EXAMPLES	Palladium, Raney nickel, etc.	Grignard reagent

Catalytic Reagents will save energy and reduce the burden of by-product. The principle of green chemistry states that catalytic reagents are superior to stoichiometric reagents, Use of catalysts is preferred because of the following advantages.

- (i) 100% atom economy because the true catalysts are fully recovered without change in their chemical and physical properties
- (ii) The catalyzed reactions are faster as they save energy
- (iii) Reaction yield is better
- (iv) Selective reaction products are obtained
- (v) Maximum utilization of starting material and minimum generation of waste.

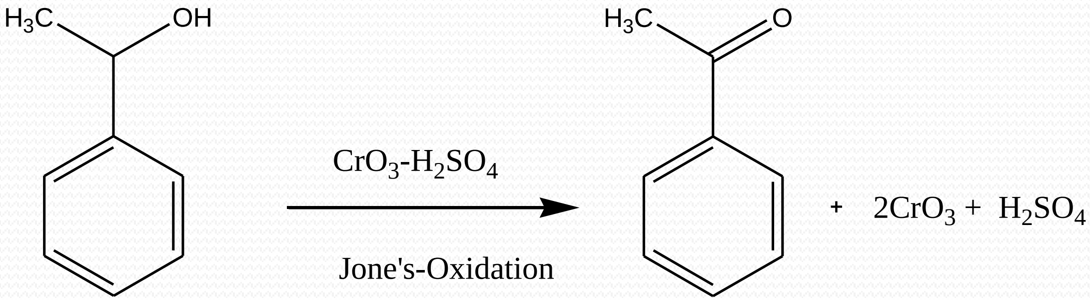


$$\text{1-phenyl ethanol} \xrightarrow[\text{Catalyst}]{1/2\ O_2,} \text{acetophenone} + H_2O$$

1-phenyl ethanol

acetophenone

Atom economy: 120/138 * 100=87 %



$$\text{1-phenyl ethanol} \xrightarrow[\text{Jone's-Oxidation}]{CrO_3\text{-}H_2SO_4} \text{acetophenone} + 2CrO_3 + H_2SO_4$$

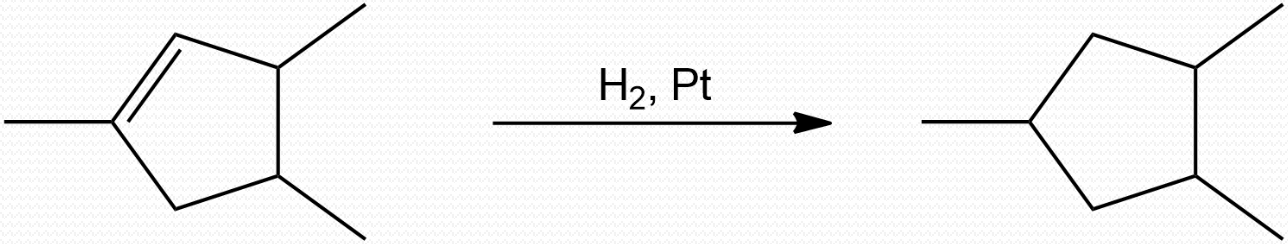
1-phenyl ethanol

acetophenone

Atom economy: 360/860 * 100=42 %

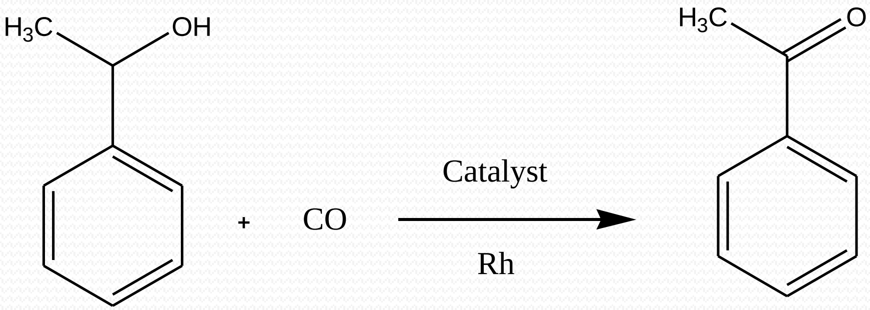
Catalytic Hydrogenation:

- Reaction is Catalytic Hydrogenation of alkene to alkane

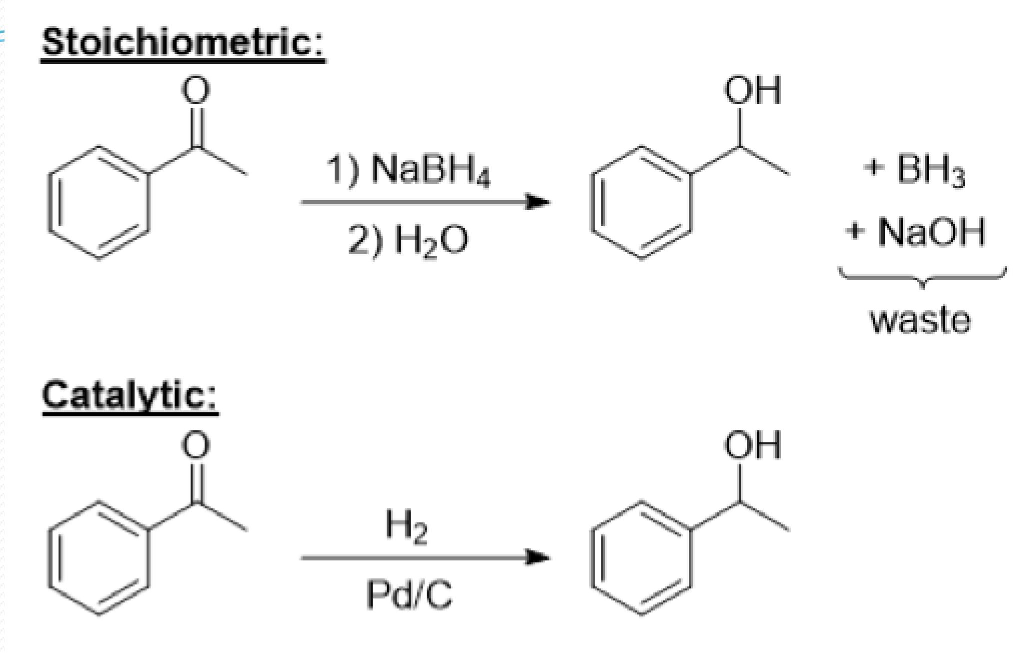


1,3,4-trimethylcyclopentene

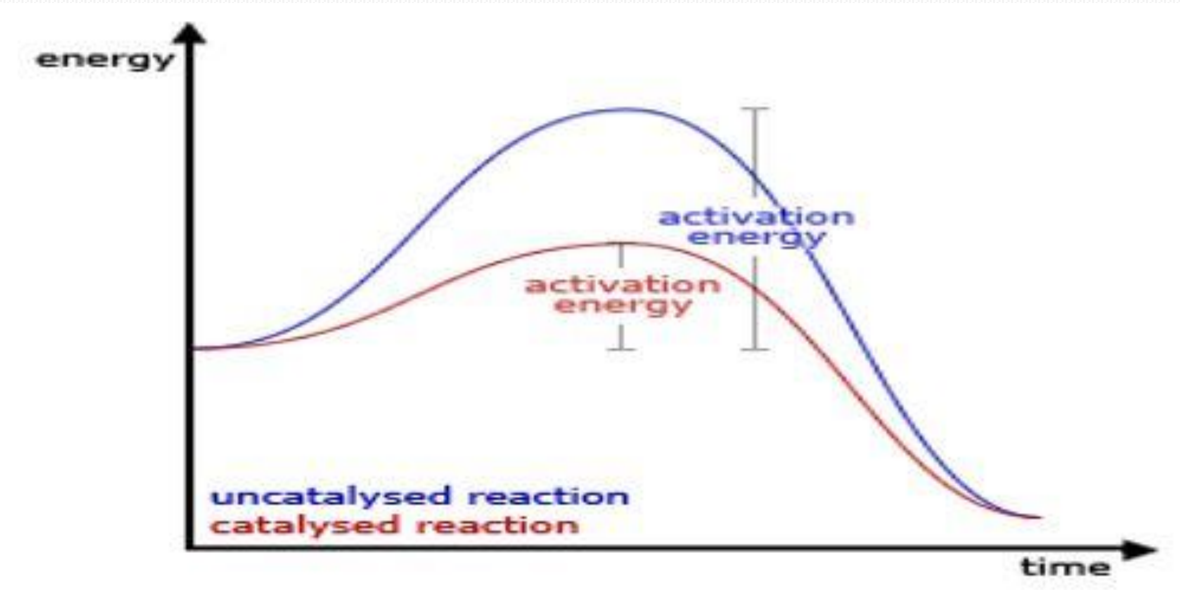
Carbonylation: (Monsanto process)



100% atom economical


Stoichiometric:

Catalytic:



Types of catalyst:

- Homogeneous
- Heterogeneous

In Homogeneous catalysis processes,

✓Mild reaction conditions required,

✓They are often highly selective,

✓They are associated with ease of heat transfer from a solution.

Disadvantages:

✓Separation of product,

✓Recycling of catalysts,

✓Most often product gets contaminated.

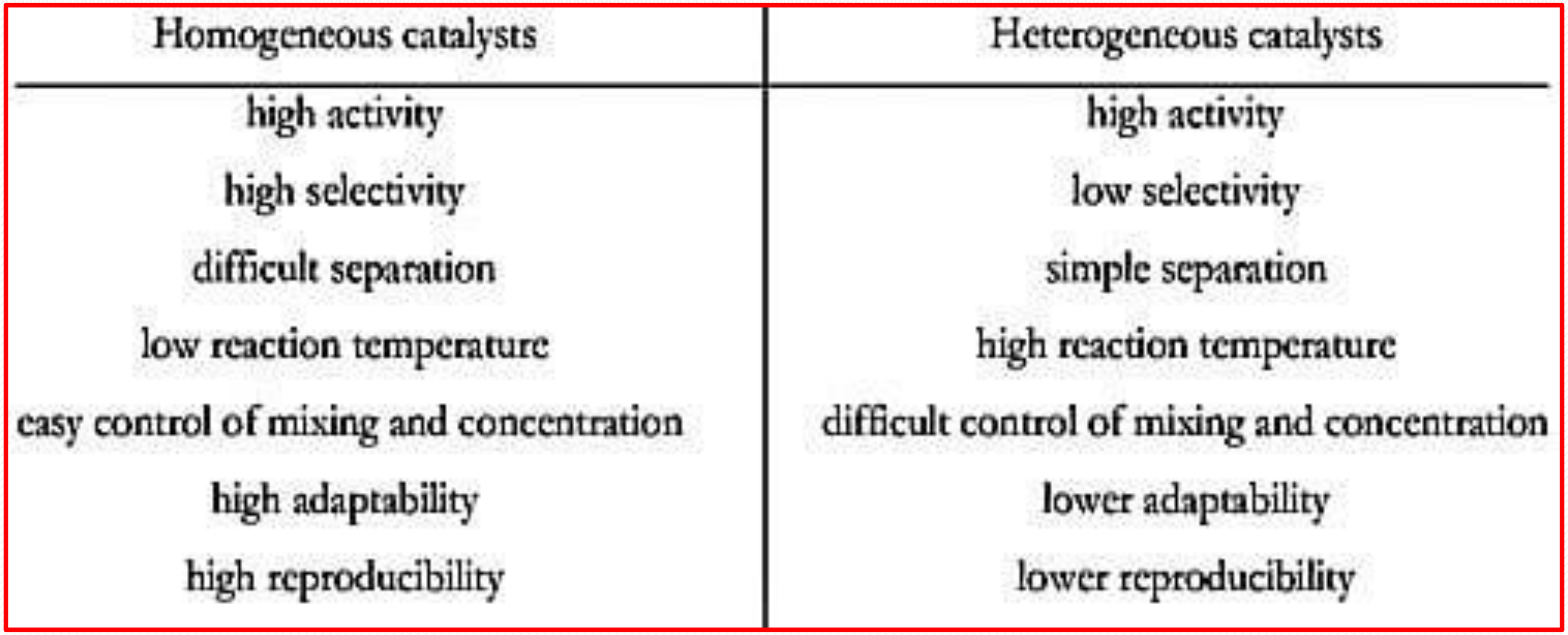
- **Homogeneous catalysis**
- Homogeneous catalysts are catalytic compounds that are in a similar phase as the substances which are going into the reaction phase.
- These types of catalysts usually are common in either the liquid phase or gas phase
- Operative temperature for homogeneous catalysis is generally low except only when under high pressure.
- The recovery of homogeneous catalysts is complicated and exclusive.
- The partition of homogeneous catalyst from the reaction mixture is complex.
- The heat transfer in homogeneous catalysis is very high as all the molecules of reactants and catalysts are in the same phase.
- Recycling methods are not very cost effective as it’s a long drawn process and as it’s a difficult treatment method for spent catalysts
- Modification of homogenous catalysts is very easy as it depends upon the tuning of electronic and steric properties on metal
- The recycling of homogeneous catalysts is not easy. The reaction mechanism is easier to find as varied techniques are available.
- The dynamic site of homogeneous catalysts is well-defined and has good selectivity.
- The thermal constancy of homogeneous catalysts is poor.

Heterogeneous catalysis

In heterogeneous catalysis systems:

- Product separation is easier and straight forward with continuous processing.
- Heat transfer problem lies with heterogeneous catalysis
- Attractive feature is that many of the solid catalysts are robust at high temperature and therefore make available in a wide range of operating conditions.

- Heterogeneous catalysts are catalytic compounds that are in a contradictory phase from that of the phase of the reaction combination.
- Heterogeneous catalysis is found in the liquid phase, gas phase, and solid phase.
- Operative temperature for heterogeneous catalysis is harsh as compared to the homogeneous process.
- The recovery of heterogeneous catalysts is simple and inexpensive.
- The severance of heterogeneous catalyst from the reaction combination is simple.
- The heat transfer is relatively low as compared to homogeneous catalysis as the reactant molecules and catalysts are in a different phase.
- These catalysts although require reactivating treatment process but still quite cost effective.
- The modification of heterogeneous catalysts is relatively difficult as the controlling methods of particle size, as well as the active size at a molecular level, is really difficult.
- The recycling of heterogeneous catalysts is simple. The reaction mechanism is difficult to fins as the techniques utilized as the product is scrutinized and not the catalysts.
- The dynamic site of heterogeneous catalysts is not well-defined and has deprived selectivity.
- The thermal constancy of heterogeneous catalysts is superior. The severance of the catalyst from the reaction combination is simple.



Homogeneous catalysts	Heterogeneous catalysts
high activity	high activity
high selectivity	low selectivity
difficult separation	simple separation
low reaction temperature	high reaction temperature
easy control of mixing and concentration	difficult control of mixing and concentration
high adaptability	lower adaptability
high reproducibility	lower reproducibility

Design for Degradation

Chemical products should be designed so that at the end of their function they break down into innocuous degradation products and do not persist in the environment.

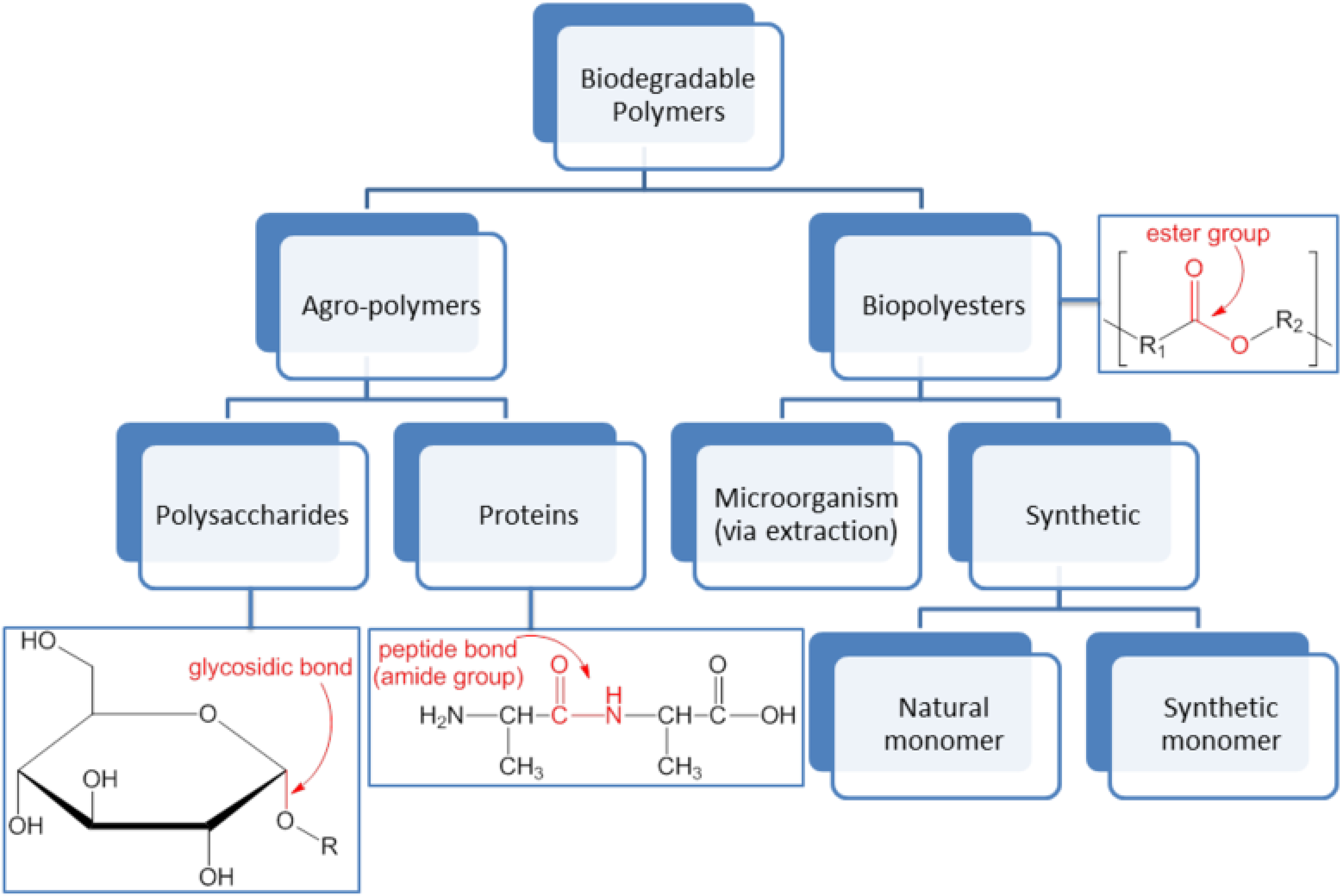
Persistent chemicals:

- Chemicals that are resistant to degradation in the environment are called persistent.
- Persistent chemicals are distributed widely, often globally, and reach (much) higher concentrations than short-lived chemicals emitted at the same rate.

Biodegradable polymers:

- Biodegradable polymers are a special class of polymer that breaks down after its intended purpose by bacterial decomposition process to result in natural byproducts such as gases (CO2, N2), water, biomass, and inorganic salts.

- These polymers are found both naturally and synthetically made, and largely consist of ester, amide, and ether functional groups.



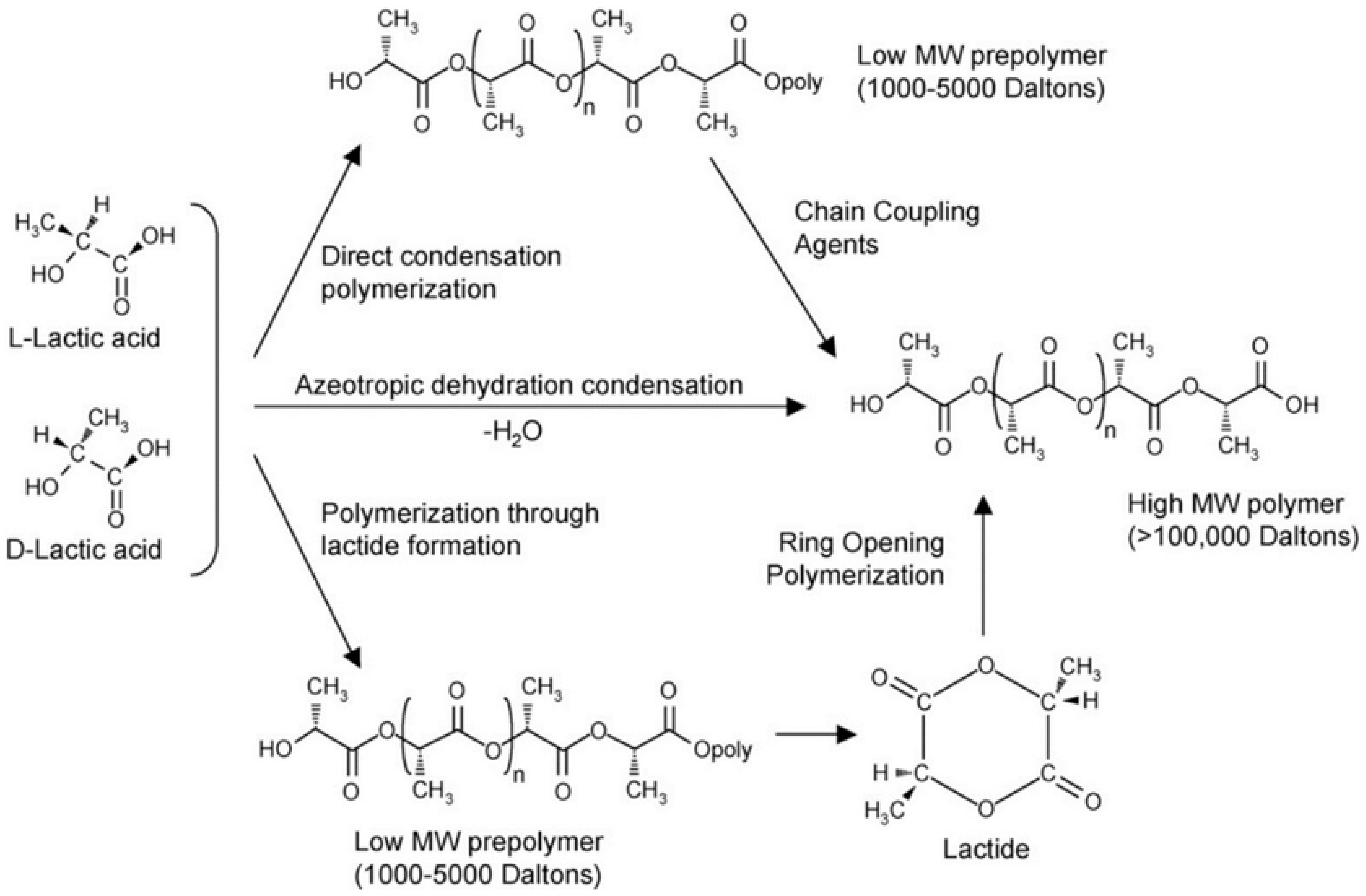
- Biodegradable Polymers
  - Agro-polymers
    - Polysaccharides
    - Proteins
  - Biopolyesters
    - Microorganism (via extraction)
    - Synthetic
      - Natural monomer
      - Synthetic monomer

Polylactic Acid

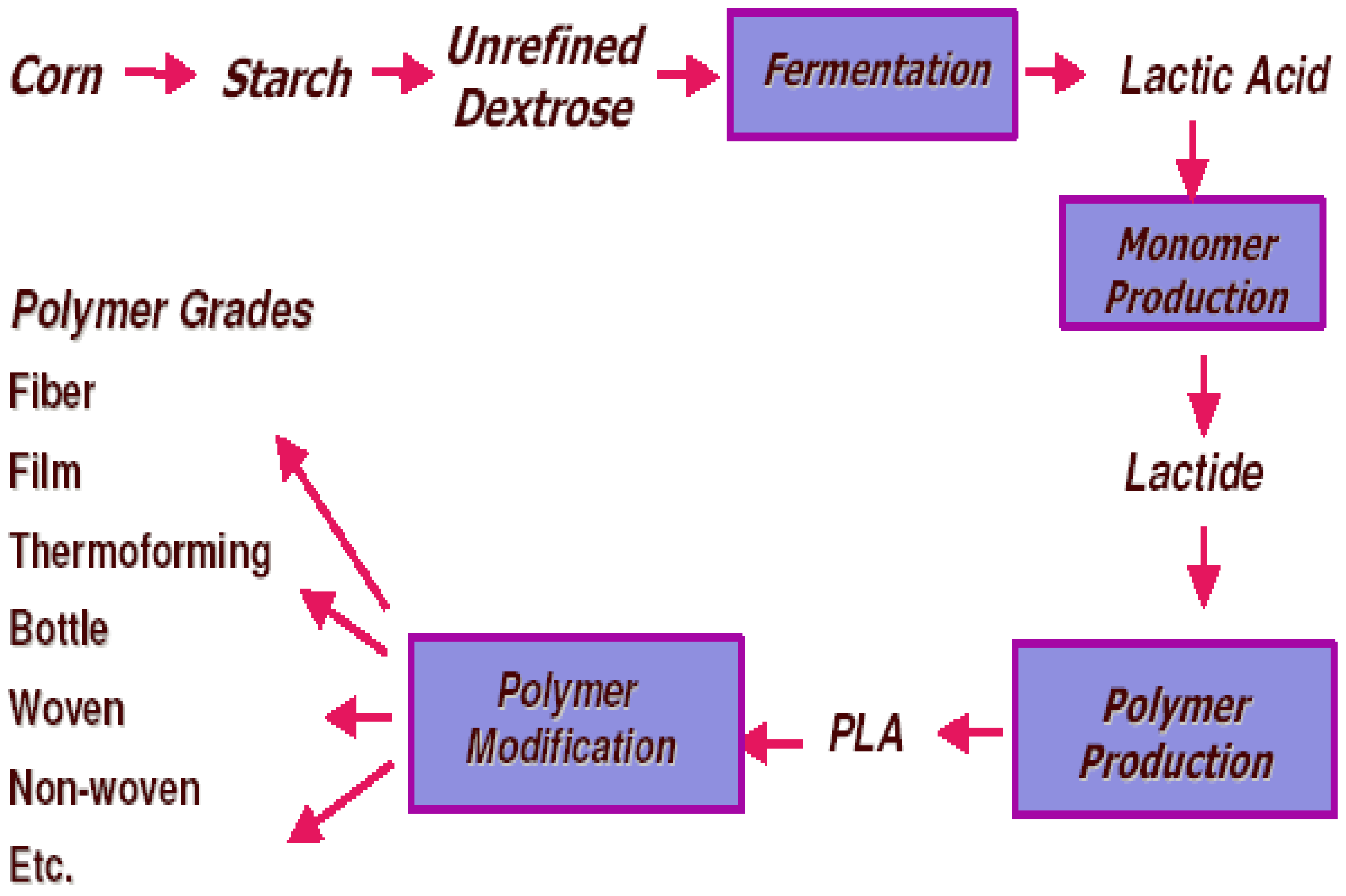
- Manufactured from renewable resources
  - Corn or wheat; agricultural waste in future
- Uses 20-50% fewer fossil fuels than conventional plastics
- PLA products can be recycled or composted

Alternative solvents

- Solvent-free synthesis of polylactic acid polymers (PLA)
  - lactic acid obtained from corn and sugar beets
  - condensation of aqueous lactic acid yields PLA pre-polymer
  - pre-polymer thermally depolymerized into L- and meso-lactide diastereomers
  - tin-catalyzed ring opening polymerization of lactide produces PLA high polymer


L-Lactic acid
D-Lactic acid
Direct condensation polymerization
Low MW prepolymer (1000-5000 Daltons)
Chain Coupling Agents
Azeotropic dehydration condensation
$-H_2O$
High MW polymer (>100,000 Daltons)
Polymerization through lactide formation
Ring Opening Polymerization
Low MW prepolymer (1000-5000 Daltons)
Lactide
Opoly

Poly lactic acid (PLA) for plastics production



Alternative products

- Eastman Biodegradable Copolyester 14766
  - Copolyester of adipic acid, terephthalic acid, and 1,4-butanediol
  - Totally biodegrades to H_2O, CO_2, biomass
  - Reduces waste sent to landfills and incinerators

Sutures made from polyglycolic acid. These sutures are absorbable and will be degraded by the body over time.

A trash bag made of a poly(lactic acid) blend

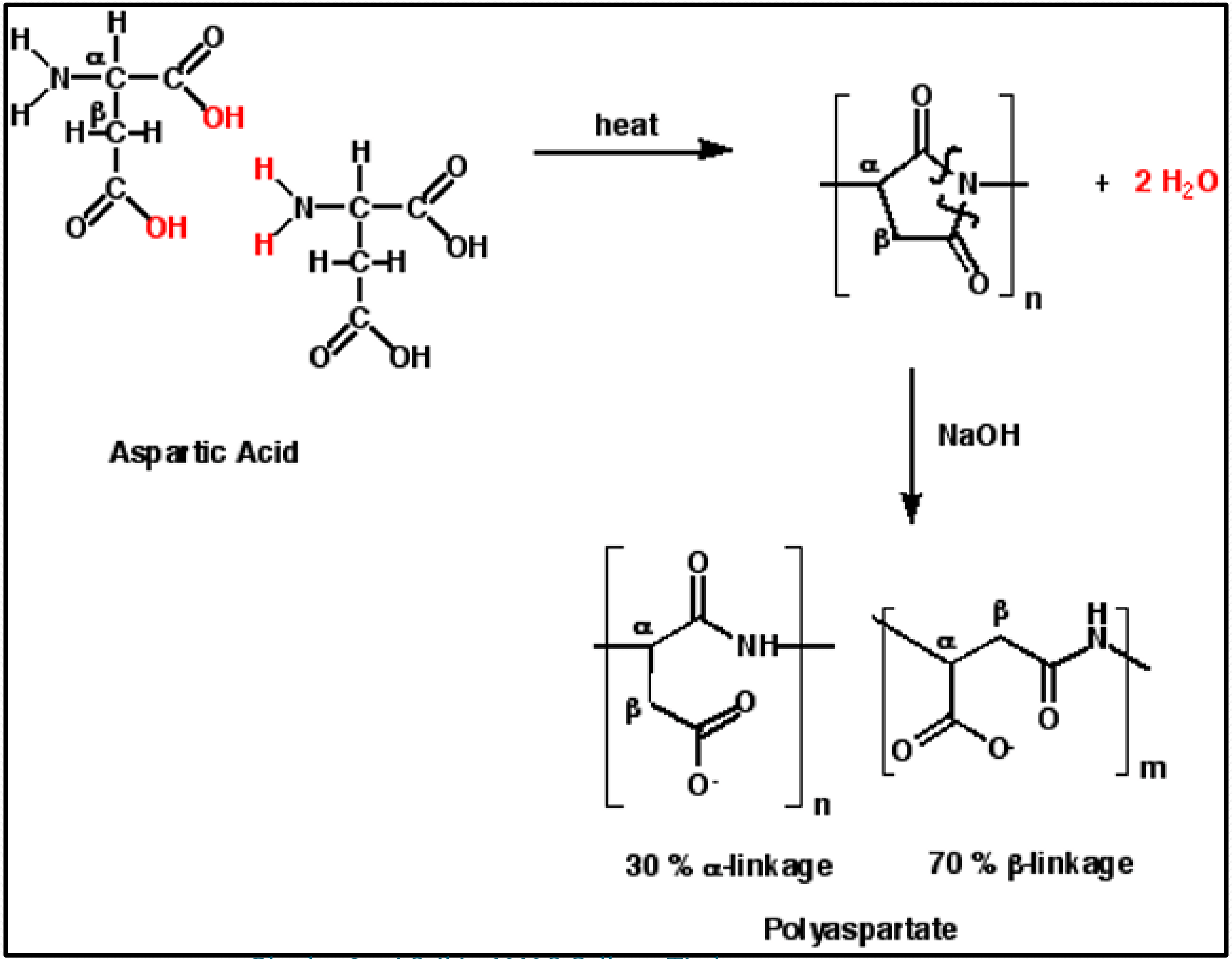
Thermal poly Aspartate (TPA) Polymers – A biodegradable polymer to replace PAC (Poly acrylate) as scale inhibitor:

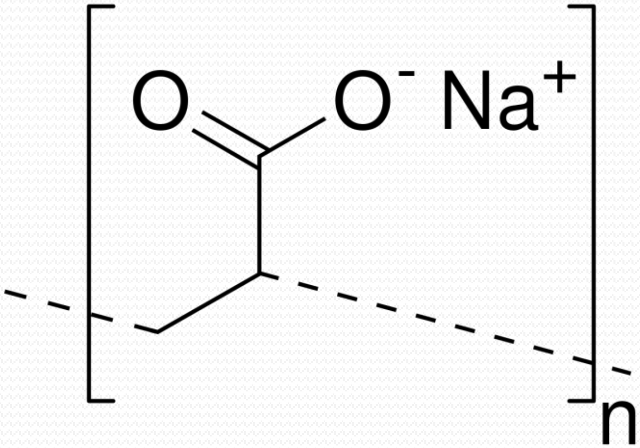
The different industries use anionic poly acrylate (PAC) polymer as an anti-scalanat to prevent the formation of scales (insoluble salt, like BaSO4, CaSO4, CaCO3, MgCO3, etc) in pipes, pumps, boilers etc.

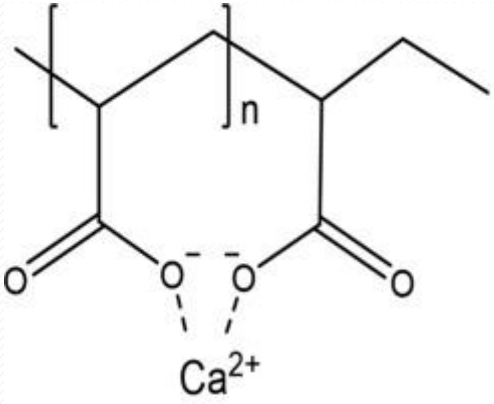
The scale formation prevents the flow of fluid and heat transfer.
PAC is used as an anti scalant. It is not toxic, but it is not biodegradable thus it causes a heavy waste load on the environment.

PAC acts as an anti scalant, as its carboxylate anion binds metal ions like Ca2+, Mg2+ and Ba2+ and other scale forming metal ions through complex formation, but it is non biodegradable, thus it is replaced by an alternative green polymer named as TPA (Thermal poly aspartate), prepared from aspartic acid by heat treatment through polymerization.

Preparation of thermal polyasparate:







AA

TPA offers several environmental benefits:

- TPA is biodegradable, it does not cause any disposal problem
- TPA is a very good anti scalant
- Its synthesis procedure is ecofriendly as it is prepared from a naturally occurring amino acid (aspartic acid)

Whenever a chemical is being designed it should be ascertained that it is biodegradable. It is also equally important to see that degradation products does not possess any toxicity and it does not cause any detrimental effect on the ecosystem.

Real-time Analysis for Pollution Prevention

Analytical methodologies need to be further developed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances

What is the Meaning of Real Time ?

- ❑Real-time analysis for a chemist is the process of checking the progress of a chemical reaction as it happens, that is, the result of the analysis should be obtained instantaneously.

- ❑It means that for the analysis of a sample, no pre-treatment or digestion is required. If a chemical reaction has to be carried out for the preparation of sample, then the kinetics should be fast.

- ❑Analytical methodologies should be developed or modified so that continuous monitoring and control prior to the formation of by-product or formation of hazardous material takes place.

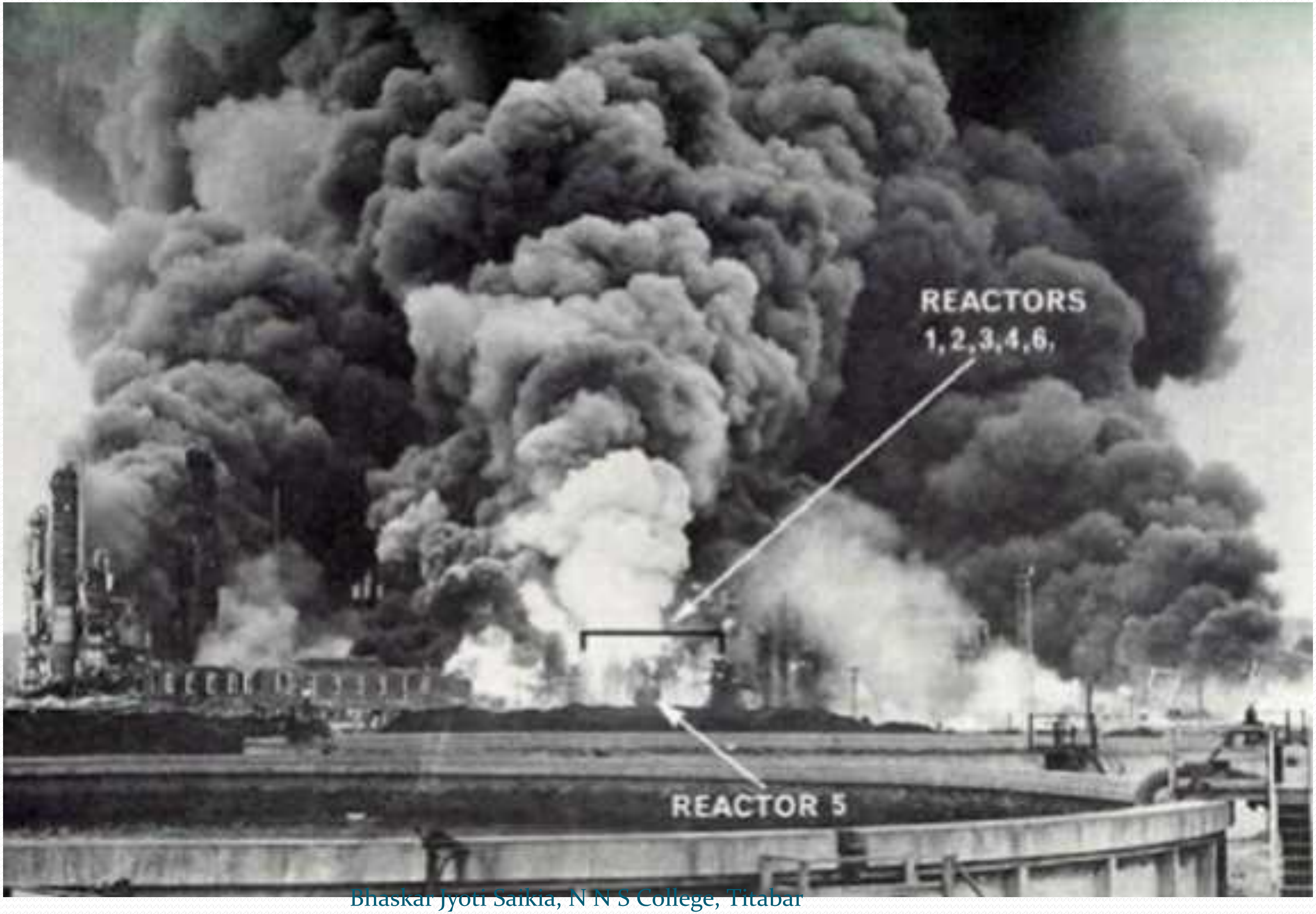
- ❑Once these are observed, then parameters of such reactions and processes could be adjusted to eliminate or reduce their formation. After optimizing conditions, an online process can be automated.


IN A 9900

Inherently Safer Chemistry for Accident Prevention

Substances and the form of a substance used in a chemical process should be chosen to minimize the potential for chemical accidents, including releases, explosions, and fires.

Flixborough accident:



- ❑The Flixborough disaster was an explosion at a chemical plant close to the village of Flixborough England on 1 st June 1974.

- ❑It killed 28 people and seriously injured 26

☐The chemical plant, owned by Nypro (UK) and in operation since 1967.

☐Produced caprolactam, a precursor chemical used in the manufacture of nylon.

☐The process involved oxidation of cyclohexane with air in a series of six reactors to produce a mixture of cyclohexanol and cyclohexanone.

- Two months prior to the explosion, a crack was discovered in the number 5 reactor.
- It was decided to install a temporary 50 cm (20 inch) diameter pipe to bypass the leaking reactor to allow continued operation of the plant while repairs were made.

The Disaster:

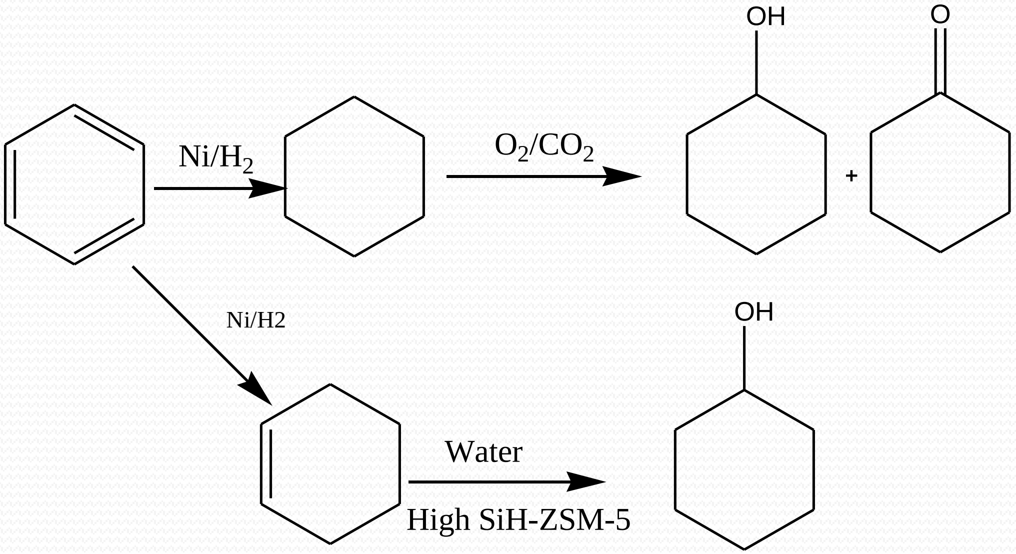
- At 1653 on Saturday 1 June 1974, the temporary bypass pipe (containing cyclohexane at 150C and 1 MPa) ruptured, possibly as a result of a fire on a nearby 8 inch (20 cm) pipe which had been burning for nearly an hour.
- Within a minute, about 40 tonnes of the plant's 400 tonne store of cyclohexane leaked from the pipe and formed a vapour cloud 100200 metres in diameter.

- The cloud, on coming in contact with an ignition source (probably a furnace at a nearby hydrogen production plant) exploded, completely destroying the plant.

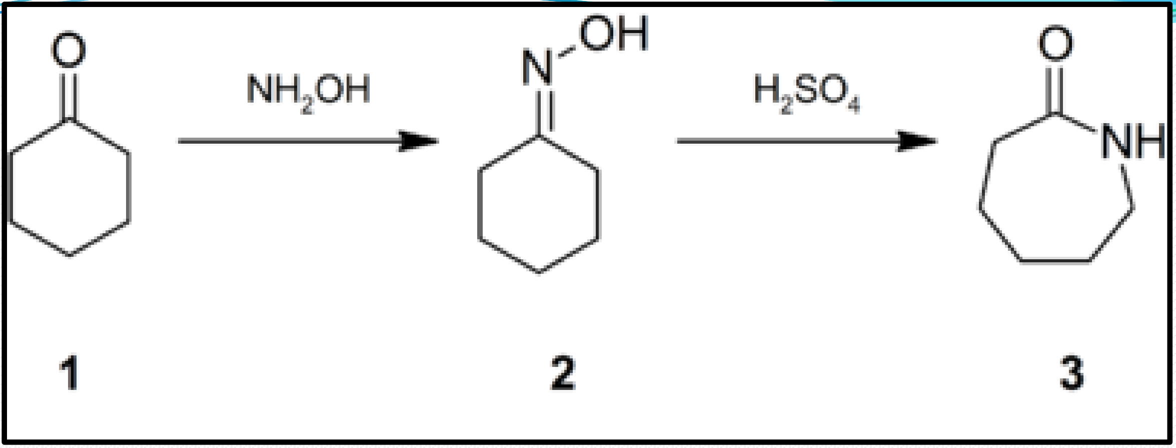
- Around 1,800 buildings within a mile radius of the site were damaged.

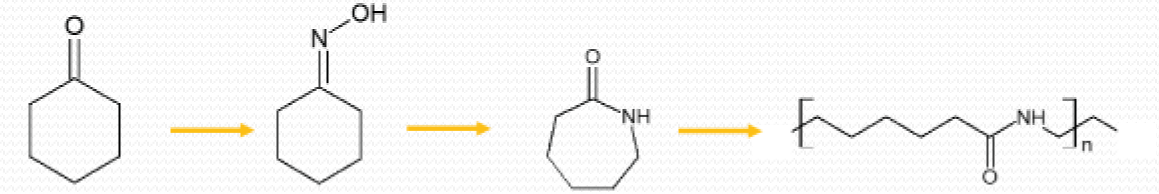
- The fuel-air explosion was estimated to be equivalent to 15 tonnes of TNT and it killed all 18 employees in the nearby control room.
- Had the explosion occurred on a weekday, more than 500 plant employees would likely have been killed.

- Flixborough plant in UK was synthesizing cyclohexanone
- In this proces, benzene on hydrogenation gave cyclohexane which on aerial oxidation with homogeneous cobalt catalysts resulted in 50% cyclohexanone and 50% cyclohexanol (by-product and waste).
- Since the conversion of cyclohexane to the product was low, so it was necessary to circulate cyclohexan through six reactors arranged in series.
- This was done by injecting O2 into cyclohexane at a working pressure of 9 bar and temperature of 155°C

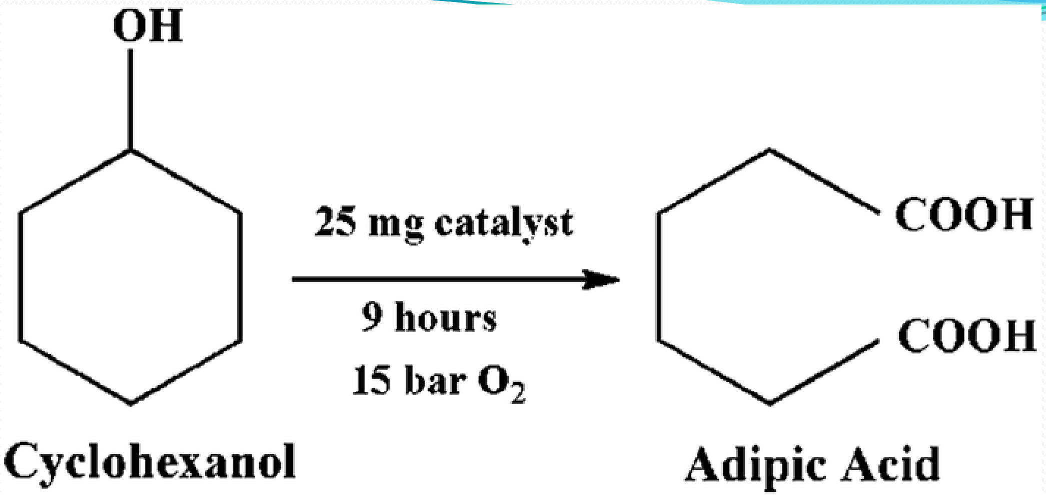


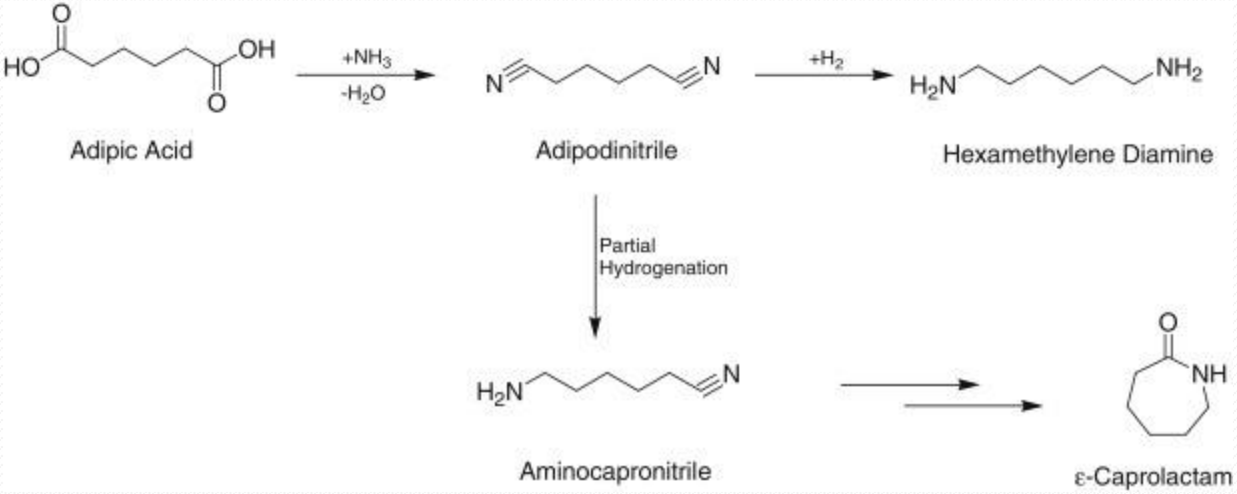
Safer ISD process does not produce flammable cyclohexane and is energy efficient. Atom economy is 100% as only the required product cyclohexanol is obtained.It uses water and high-silica pentasil zeolite as catalyst. This is ISD(Inheriently safer design), as cyclohexane is not formed, which responsible for the accident.





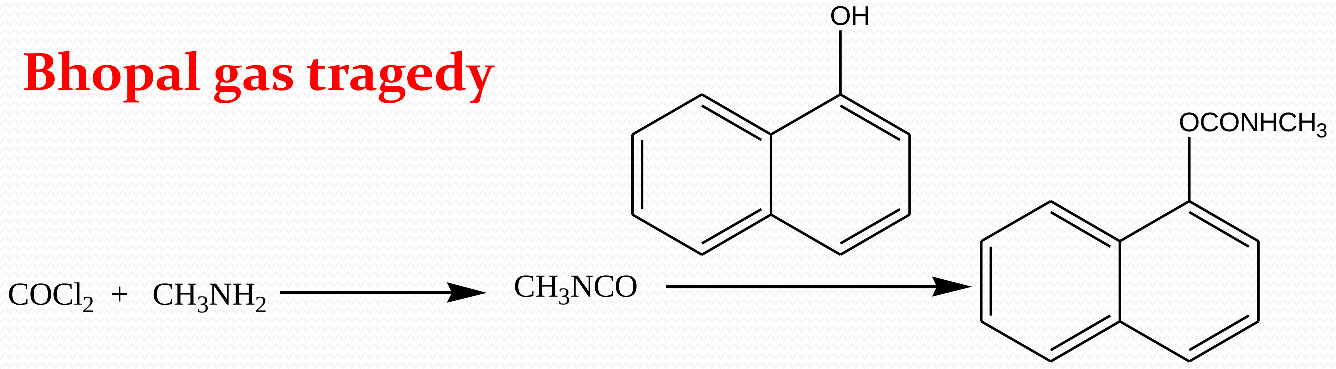
Cyclohexanone Cyclohexanone oxime Caprolactam Nylon 6


OH
25 mg catalyst
9 hours
15 bar O2
COOH
COOH
Cyclohexanol
Adipic Acid


O
HO
OH
O
+NH3
-H2O
N
N
+H2
H2N
NH2
Adipic Acid
Adipodinitrile
Hexamethylene Diamine
Partial
Hydrogenation
H2N
N
O
NH
Aminocapronitrile
ε-Caprolactam

Bhopal Gas tragedy:

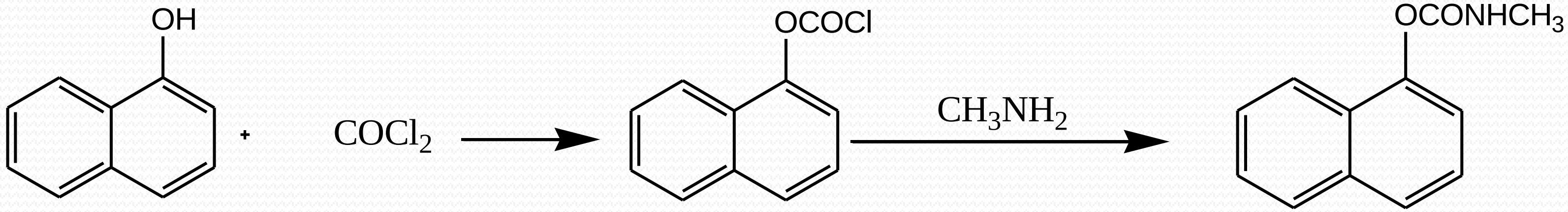
Bhopal gas tragedy



MIC

Carbaryl(insectiside)

Inherently safer design



The important role played by green chemistry in inherent safer processes is explained by Anastas and Hammond in 2016.

1.This is achieved by replacing hazardous substances in chemical synthesis, as shown in Bhopal gas tragedy and Flixborough accidents.
2. employing in-situ production instead of transporting hazardous substances,
3. Limited storage of hazardous substances, and there should be on-demand production.
4. Reducing the dependence on irreplaceable hazardous chemicals.
5. Preventing accidents by design modifications using the knowledge of accidents already taken place.