How to plan a Green Synthesis?

1. **The synthetic methods should be such that all the starting materials be converted into the final product.**
   This means that a reaction should be a 100% atom economical.

2. **Unnecessary derivation such as blocking group protection or deprotection should be avoided whenever possible.**
   The use of protecting group or blocking group is also a factor in the atom economy of a reaction. Though sometimes it is necessary to use protecting group to solve a chemo selectivity problem, these should be added to the reaction mixture in stoichiometric amount and then removed after completion of the reaction.

3. **Use of an environmentally benign solvent.**
   A number of halogenated solvents like dimethyl chloride (CH_2Cl_2), chloroform ($CHCl_3$), perchloroethylene (PCE), carbon tetrachloride (CCl_4), etc. are generally used in reactions due to their excellent solvent properties but they have been identified as human carcinogens. Another solvents which are responsible for destroying the ozone layer are chloroflurocarbons (CFCs).
   - **Water** has been used as a solvent in a number of chemical reactions. Water is the cheapest available solvent and does not cause problems of pollution. Super critical water, critical temperature is 374^{o}C and 22.1 MPa, has also been used as a good medium for organic reaction. Also microwave assisted organic reactions and bio catalytic reactions have been performed in water.
   - **Super critical carbon dioxide (SC-CO_2)** has also been used as a solvent in organic reaction. SC-CO_2 is a fluid state of carbon dioxide where it is held at or above critical temperature and critical pressure. SC-CO_2 is becoming an important commercial and industrial solvent due to its role in chemical extraction in addition to its low toxicity and environmental impact. SC-CO_2 is used as the extraction solvent for creation of essential oils and other herbal distillates. Its main advantages over solvents such as hexane and acetone in this process are that it is non-toxic and non-flammable.
   - **Ionic liquids** are emerging as novel replacement for volatile organic solvents used traditionally as industrial solvents. These are liquid at ambient temperature and are colourless, have low viscosity and can be easily handled. The ionic liquids have virtually no vapour pressure and possess good thermal stability.
   - **Polyethylene glycol (PEG)** and its solutions are believed to be a green reaction medium of the future for a number of organic reactions because it has low flammability and is biodegradable. Polyethylene glycol, HO-$(CH_2CH_2O)_n$-H, is available in a variety of molecular weights. It is also stable to acid, base and high temperatures and can be recovered and recycled.

4. **The requirement of energy should be minimized to a bare minimum.**
   The time required for completion of a reaction should be minimum, so that minimum amount of energy is required. Use of catalyst is beneficial for lowering the requirement of energy for a reaction. It is now well known that the energy requirement can be kept bare minimum by using microwaves sonication or photo activation.

5. **Use of catalyst.**
   Catalysts are known to facilitate chemical transformations, which are effected in much short time, consuming less energy and giving good yields. An additional advantage is that the catalysts are not consumed in the reaction and can often be recycled.

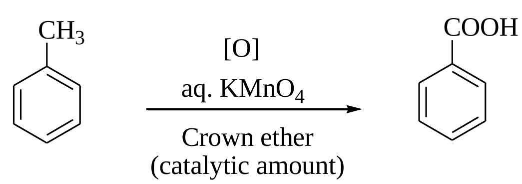
$$\underset{\text{Acetylene}}{HC{\equiv}CH} \xrightarrow[H_2SO_4]{HgSO_4} \underset{\text{Acetaldehyde}}{H_3C{-}CHO}$$

$$\underset{\text{Propyne}}{H_3C{-}C{\equiv}CH} + H_2 \xrightarrow{Pd\text{-}BaSO_4} \underset{\text{Propene}}{H_3C{-}\underset{H}{C}{=}CH_2}$$

Another type of catalysts which are commonly used for reactions which give low yields or those reactions which do not take place, are **phase transfer catalysts (PTC)**. Phase transfer catalysts are ionic substances, usually quaternary ammonium salts, where the size of the hydrocarbon group in the cation is large enough to confer solubility of the salt in organic solvents. PTC catalyzed reactions describes a methodology for accelerating reactions between water insoluble organic compounds and water soluble reactants.

$$\underset{\text{Chlorooctane}}{CH_3(CH_2)_6CH_2Cl} \xrightarrow[\substack{CH_3(CH_2)_{15}P^{+}(n\text{-}Bu)_3Br^{-} \\ \triangle,\ 105^{o}C,\ 2\ hr}]{NaCN,\ H_2O,\ decane} \underset{\text{Cyanooctane}}{CH_3(CH_2)_6CH_2CN}$$

Crown ethers are a family of cyclic polyether and like PTC, these can be used in a number of transformations.



Toluene Benzoic acid

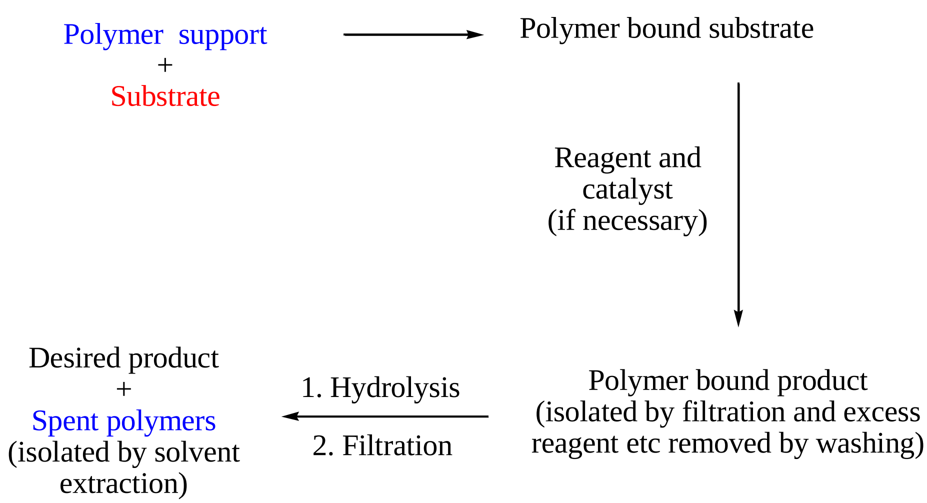
6. Use of polymer supported substrates or polymer supported reagents.

Advantages:

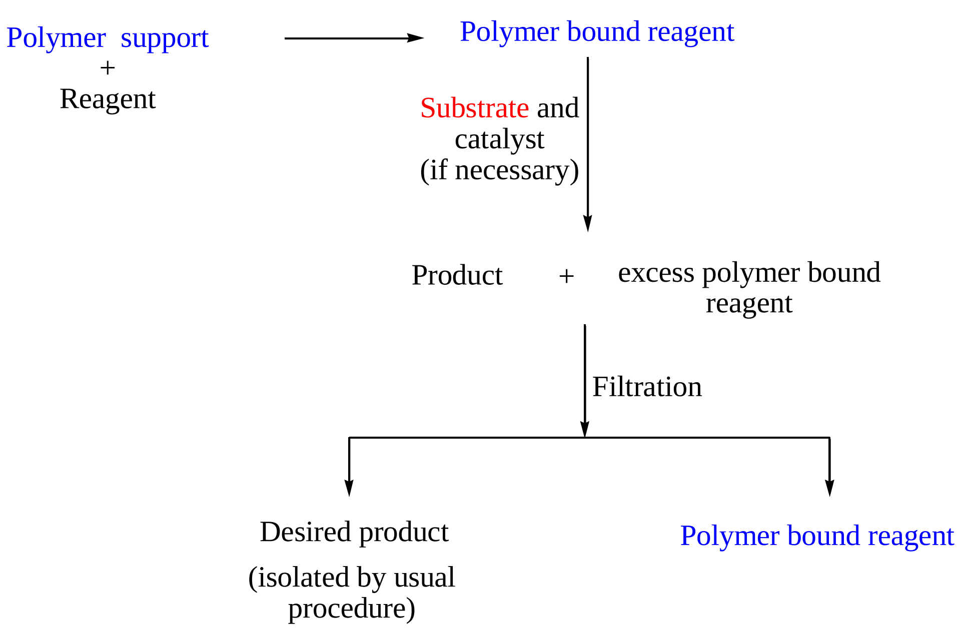
a) The reaction can be carried out easily and the isolation of product become easier.
b) The purification of the product is simplified.
c) Polymer supported reactions can be carried out cleanly, rapidly and in high yields under mild conditions.
d) After isolation of the polymer supported product, the polymer support is cleaved to get the final desired product.

There are three types of polymer supported organic synthesis:

- ***Type- 1:***



- ***Type- 2:***



- ***Type- 3:***

This is polymer supported catalytic reaction. In this type of reaction, conventional catalysts, which are normally used in the homogeneous phase is linked to a polymer support and used in this form to catalyze the reaction.

7. **Nature of waste products or byproducts should not be toxic or environmentally harmful.**

8. Synthetic methodologies should be designed in such a way that the products or byproducts generated should possess no toxicity to human health and environment.

9. The raw materials should be renewable rather than depleting, whenever technically and economically practicable.

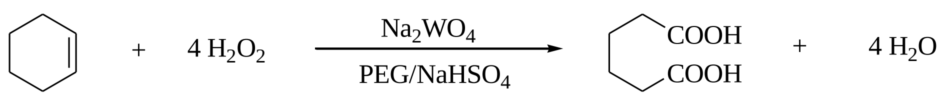
❖Example of Green Synthesis OR Reaction:

Green synthesis of Adipic Acid:

Adipic acid (1,6-Hexanedioic acid) is a dicarboxylic acid which is an important industrial chemical used in the synthesis of nylon-6,6. The commercial synthesis of adipic acid uses petroleum derived benzene and releases significant quantities of greenhouse gases.

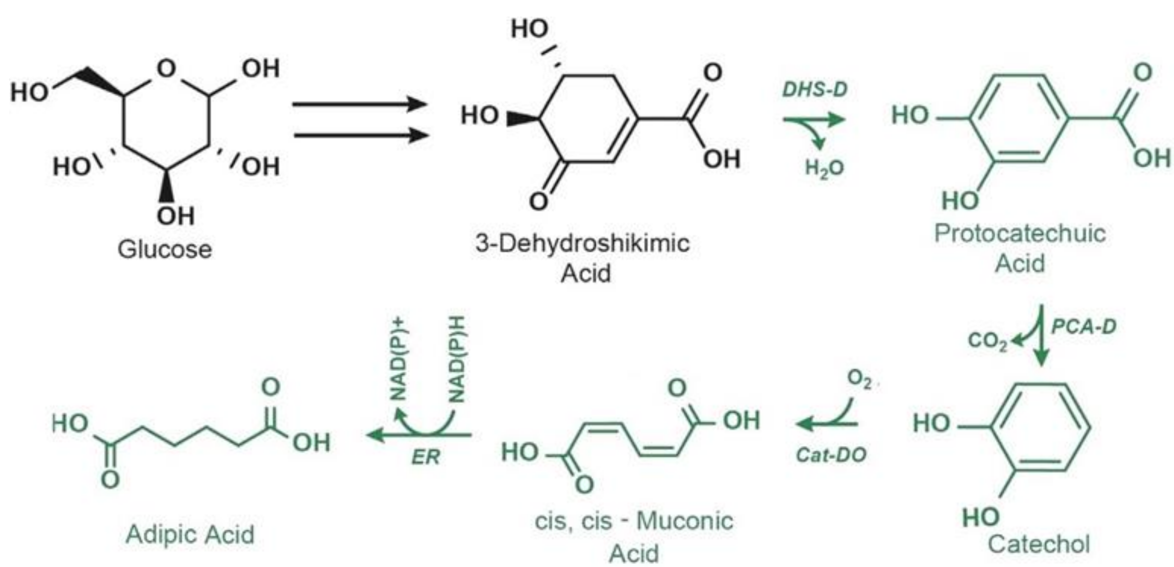
Biocatalytic production of adipic acid from renewable feedstocks could potentially reduce the environmental damage and need for fossil fuel precursors.

1. Synthesis using Polyethylene glycol (PEG): (greener approach): An elegant, environmentally benevolent synthesis of adipic acid from cyclohexene in polyethylene glycol is based on aqueous biphasic system using sodium tungstate and (30%) hydrogen peroxide.



Cyclohexene Adipic acid

2. Synthesis from D-Glucose: (greener approach): Recently another greener approach of adipic acid synthesis have been demonstrated from D-glucose. D-glucose is currently derived primarily from corm starch. In this synthetic pathway it is expressed that the Bacillus coagulans ER in a *Saccharomyces cerevisiae* strain producing muconic acid and developed a three stage fermentation process enabling the synthesis of adipic acid from glucose.



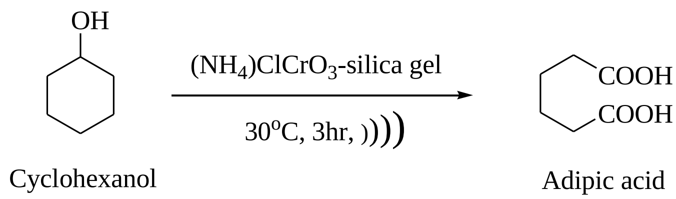
DHS-D: 3-Dehydroshikimate Dehydratase

PCA-D: Protocatechuate Decarboxylase

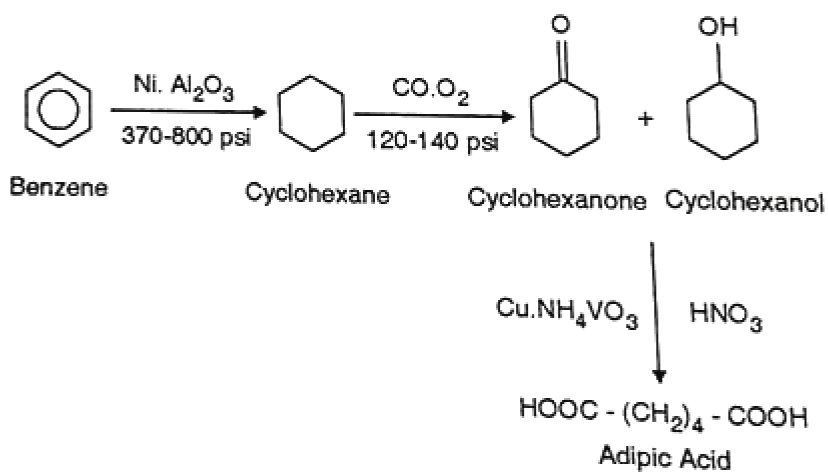
Cat-DO: Catechol 1,2-Dioxygenase

ER: Enoate Reductase

3. Ultrasound Assisted Synthesis: (non-green approach): Another synthetic pathway of adipic acid using ultrasound is from cyclohexanol in present of ammonium chlorochromate as oxidizing agent. But this synthesis is not considered as green synthesis as cyclohexanol derivative is derived from benzene derivative which is obtained from non-renewable fossil fuel. Also for oxidation nitric acid (HNO_3) is required which itself gets oxidized to nitrous acid (HNO_2), a greenhouse gas, responsible for ozone layer depletion.

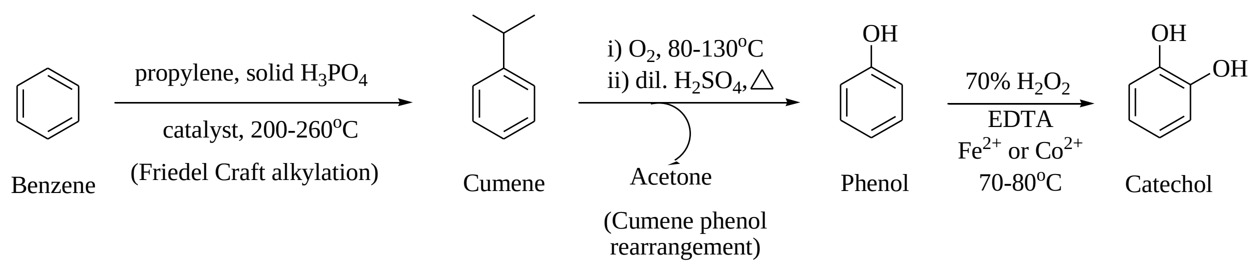


4. Another traditional pathway: (non-green approach): Adipic acid can also be synthesized from benzene which is a carcinogenic solvent. Benzene is also included by the Environmental Protection Agency on the list of chemicals covered by the Chemical Manufacturing Rule that requires drastic reductions in emissions of hazardous organic air pollutants. Thus this is not a greener approach.

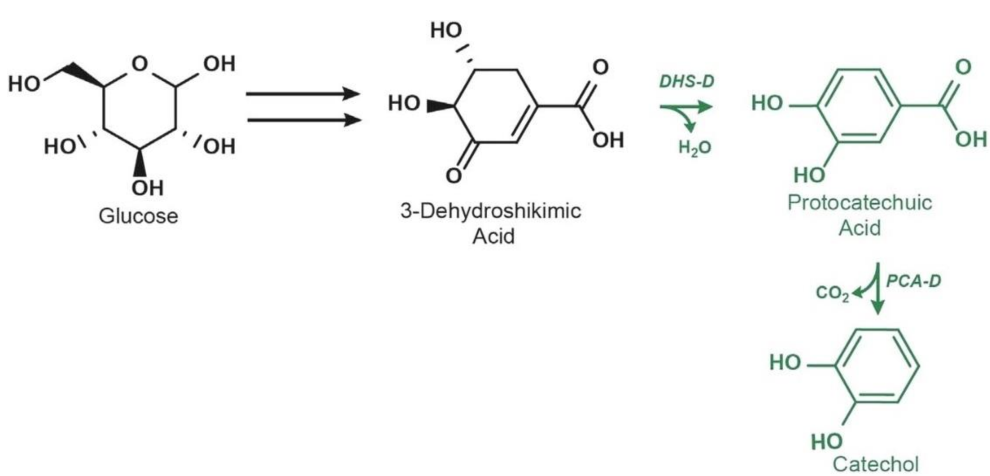


Green synthesis of Catechol:

1. Synthesis from benzene: (non-green approach): Several aspects of contemporary catechol manufacture are environmentally problematic. Petroleum is a non-renewable resource that has been historically provoked by inadvertent releases into the environment. The benzene starting material used in catechol synthesis is carcinogenic and intermediate phenol is toxic. Hydrogen peroxide used as the oxidant in catechol synthesis is a highly energetic, corrosive material which requires special safety precautions to ensure safe storage and handling.



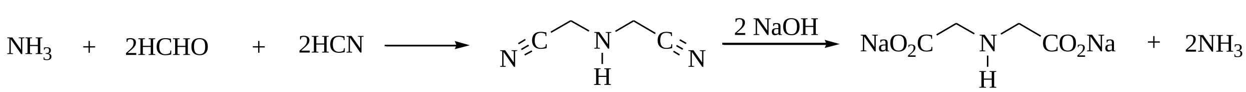
2. Synthesis from D-Glucose: (greener approach): A synthesis of catechol has now been elaborated that utilizes D-glucose as starting material and genetically modified microbe, *Escherichia coli* as a catalyst. D-glucose is currently derived primarily from corm starch. Future sources of D-glucose will likely include plants such as switchgrass that require minimal chemical inputs during cultivation and can be harvested multiple times during a single growing season.



Green synthesis of Disodium Iminodiacetate:

1. Traditional synthesis of Disodium iminodiacetate by Strecker Synthesis: (non-green approach):

Disodium iminodiacetate (DSIDA) is a key intermediate in the production of Monsanto's Roundup herbicide, an environmentally friendly, nonselective herbicide. Traditionally Monsanto have manufactured DSIDA using Strecker process requiring ammonia, formaldehyde, hydrochloric acid and hydrogen cyanide. Hydrogen cyanide is acutely toxic and requires special handling to minimize risk to workers, the community and the environment. Furthermore, the chemistry involves the exothermic generation of potentially unstable intermediates and special care must be taken to repel the possibility of a runaway reaction. The overall process also generates up to 1 pound of waste for every 7 pounds of product, and this waste must be treated to prior to safe disposal.

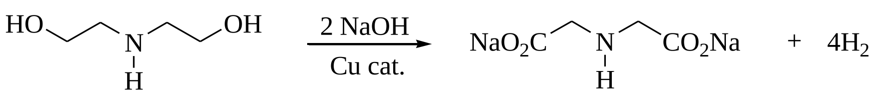


Disodium Iminodiacetate

2. Alternative synthesis of Disodium iminodiacetate by Catalytic Dehydrogenation: (greener approach):

Monsanto have developed and implemented an alternative DSIDA process that relies on the copper-catalyzed dehydrogenation of diethanolamine. The raw materials have low volatility and are less toxic. Process operation is inherently safer because the dehydrogenation reaction is endothermic and therefore does not present the danger of a runaway reaction. Moreover, this zero waste route to DSIDA produces a product stream that, after filtration of the catalyst, no purification or waste cut is necessary for subsequent use in the manufacture of Roundup.

The new technology represents a major breakthrough in the production of DSIDA because it avoids the use of cyanide and formaldehyde, is safer to operate, produces higher yield and has fewer process steps.



Diethanolamine

Disodium Iminodiacetate