UNITED NATIONS
INDUSTRIAL DEVELOPMENT ORGANIZATION

GREEN CHEMISTRY

THE 12 PRINCIPLES OF GREEN CHEMISTRY

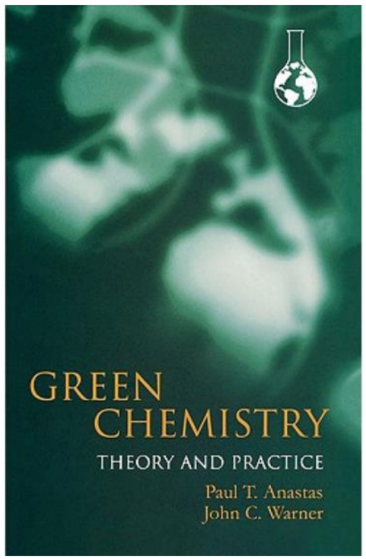
Image: Wikimedia Commons, Author: Steve Jurvetson

DAY 2 SESSION II
4-DAY PRESENTATION

www.greenchemistry-toolkit.org

THE 12 PRINCIPLES OF GREEN CHEMISTRY

GREEN CHEMISTRY



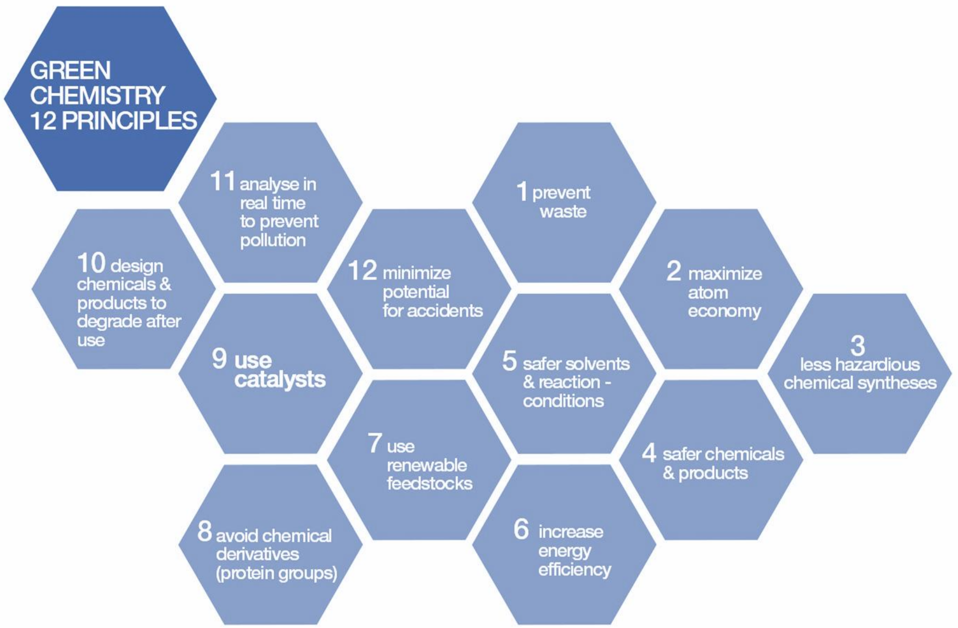
Anastas, P. T.; Warner, J.C. Green Chemistry: Theory and Practice, Oxford University Press,1998

THE 12 PRINCIPLES OF GREEN CHEMISTRY

GREEN CHEMISTRY

The principles address:

- **Toxicity**
  - Reducing the hazard
- **Feedstocks**
  - Use of renewable resources
- **Designing safer products**
  - Non toxic products by design
- **Biodegradability**
  - Enhancing break down at the end of life
- **Energy**
  - Reducing the energy needs
- **Accidents**
  - Eliminating accidents
- **Efficiency**
  - Shorter processes and synthesis



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

Image: Harshaw Chemical Company discharges waste water into the Cuyahoga river
Source: National Archives and Records Administration

What is waste?

Waste is anything that is a leftover from the product/process and cannot be re-used.

Waste can be produced in any stage of a process life-cycle:

- Origins of feedstock
- Manufacturing
- Distribution
- Use
- End of life

When is waste *not* waste?

- When it can be reused, becoming a feedstock.
- When it can be reduced or completely eliminated.

Waste generated by different industry segments:

Industry segment	Annual product tonnage	Kg waste/Kg product
Oil refining	10^6–10^8	*ca.* 0.1
Bulk chemicals	10^4–10^6	<1–5
Fine chemicals	10^2–10^4	5–>50
Pharmaceuticals	10–10^3	25–>100

Production of pharmaceuticals produces a lot of waste due making complex molecules with demanding quality standards, often requiring batch processing; there are greater regulatory constraints and often high value and low volume products are manufactured.

Many industry sectors try to decrease waste generation by decreasing the number of synthetic steps to generate the product and by implementing a solvent recovery system.

R. A. Sheldon, *Chem. Ind.*, 1992, 903–906
R. A. Sheldon, *Chem. Ind.*, 1997, 12–15

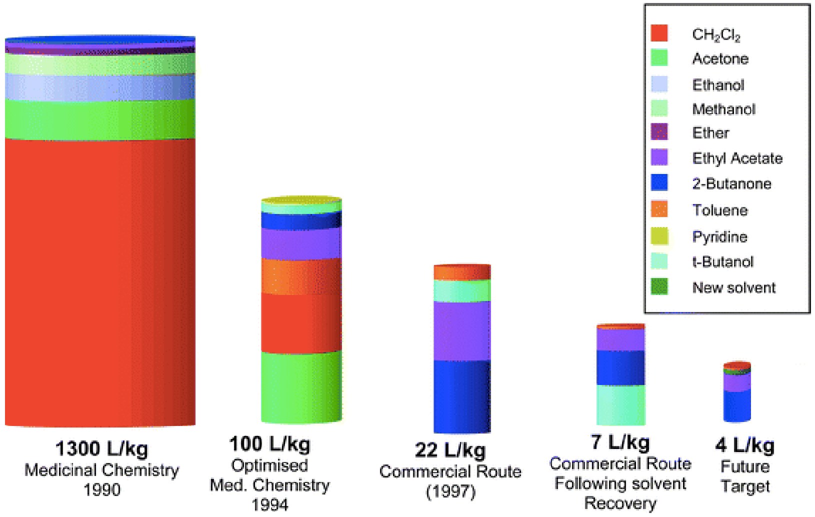
Case study: Sildenafil citrate production

Sildenafil citrate, commonly known as Viagra, is a selective inhibitor of phosphodiesterase 5 (PDE5). This new drug immediately became a major seller, achieving sales of more than $1 billion during its first year on the market. With such a rapid sales take off it was critical that the environmental performance of the synthesis was good from the outset.

Conventional sildenafil citrate synthesis included:

- 11 step synthesis, which gave a 4.2% overall yield.
- Tin chloride, a heavy metal and a major environmental polluter.
- The use of stoichiometric quantities of thionyl chloride in a solvent. This has a high environmental impact.
- Hydrogen peroxide, which causes burns upon skin contact and is a fire and transportation hazard, especially when in contact with organic materials.
- Produced over 1300 L of waste per 1 kg of product.

Dunn, P.J et al *Green Chem.*, 2004, **6**, 43-48

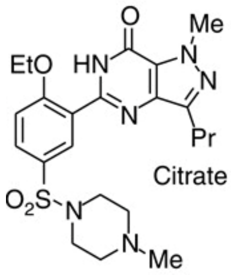


The amount of organic waste produced by the sildenafil citrate processes at various time points

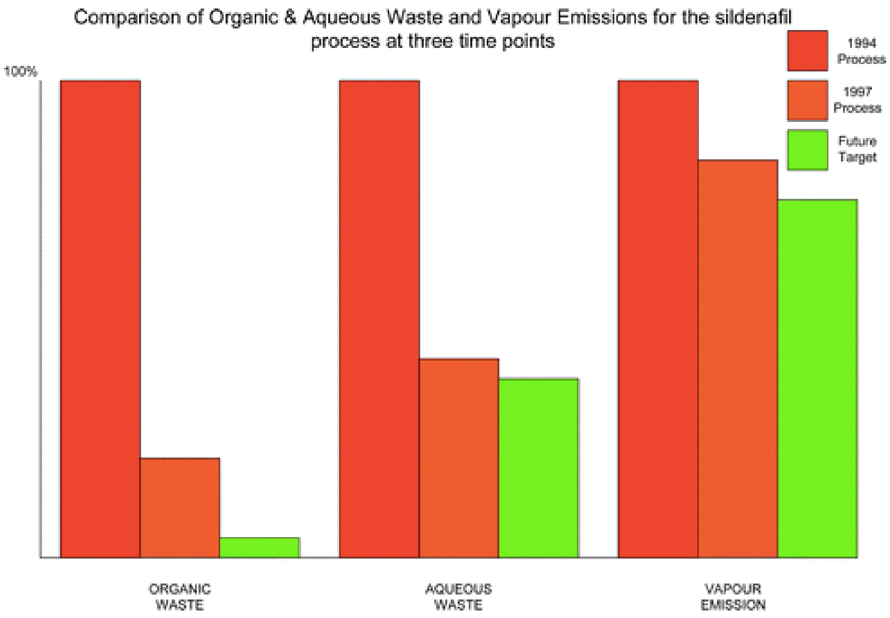
Case study: Sildenafil citrate production

Alternative production of sildenafil citrate:

- Average yield of last three steps = 97% yield.
- Reduction of the ratio of solvent waste/kg product over 17 years from 1300 L/kg to only 7 L/kg by minimizing solvent use, increasing solvent recovery, improving solvent selection, and telescoping steps.
- Only the solvents *t*-butanol, ethyl acetate, 2-butanone, and a trace of toluene still require disposal.



Citrate salt



Dunn, P.J et al *Green Chem.*, 2004, **6**, 43-48

Case study: Phenols

Phenols are widely used in household products and as intermediates for industrial synthesis. They are often referred to as drop-in platform chemicals.

Conventional method of obtaining phenols from petroleum:

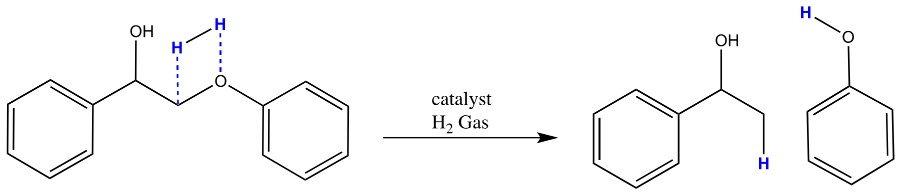
- Petroleum $\longrightarrow$ Phenols (benzene, toluene, xylenes)
- The method is not sustainable – it is dependent on depleting resources.

Image: Pixabay

Case study: Phenols

Alternative production of phenols from biomass waste using depolymerization:

- This method uses abundant product (waste) as a starting material.



Biomass

Phenols

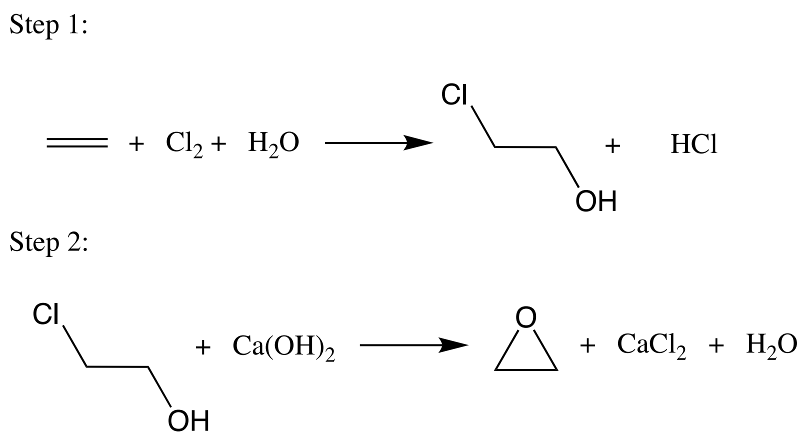
Image: Pixabay

Case study: Production of ethylene oxide

Ethylene oxide is used as an intermediate in the production of several industrial chemicals, the most notable of which is ethylene glycol. It is also used as a fumigant in certain agricultural products and as a sterilant for medical equipment and supplies.

Conventional ethylene oxide synthesis included:

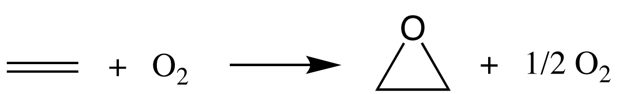
- A 2-step synthesis with a chlorohydrin intermediate.
- For each kilogram of product, 5 Kg of waste were disposed.



Case study: Production of ethylene oxide

Alternative production of ethylene oxide:

- Use of molecular oxygen removes the need for chlorine.
- New process generates more than 16 times less waste than the original one, and eliminates the formation of waste water.



E-factor = 0.3

Image: Wikimedia Commons, Author: LHcheM

Case study: Revalorization of biofuel byproducts

When byproducts cannot be avoided, other innovative solutions should be considered. One productive solution is to seek an industrial ecology approach where the waste can become a new raw material with significant value for another process as it re-enters the life-cycle. This approach is currently being applied to the production of biofuel.

1. Biofuel → Energy + Waste

2. Waste → Energy + Material

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

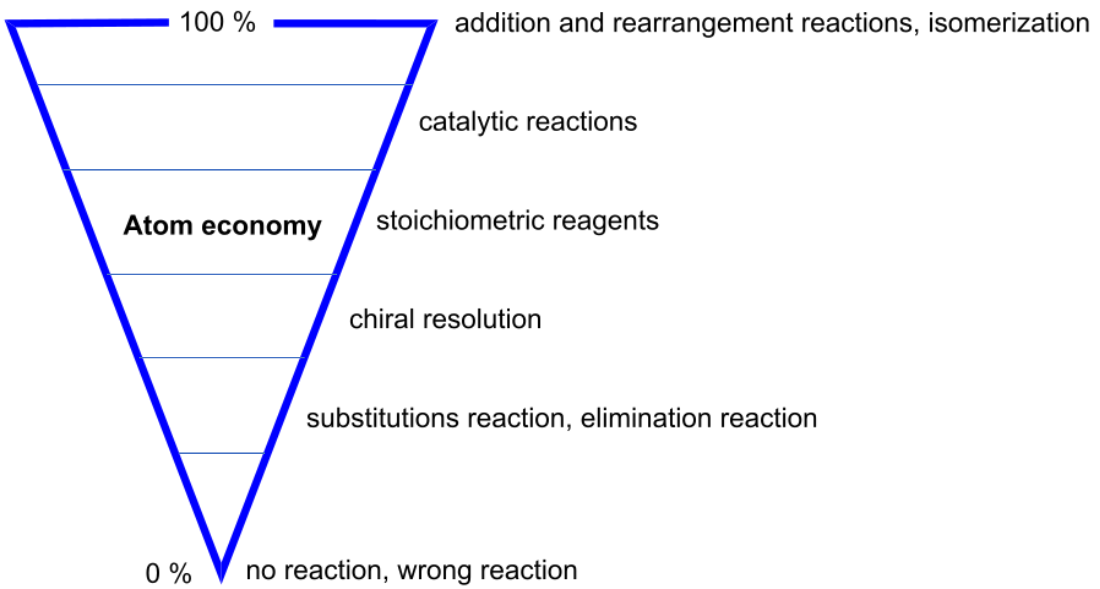


Image: Wikimedia Commons, Author: Astrid 91

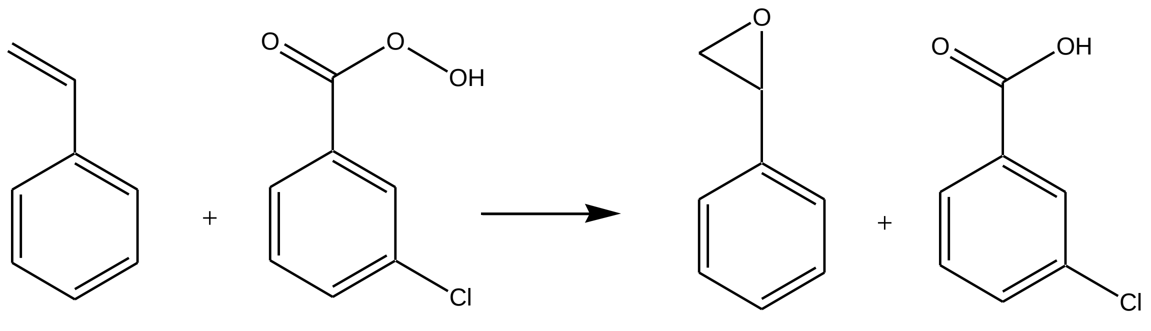
In 1990 Barry Trost introduced the concept of synthetic efficiency: Atom Economy (AE). It refers to the concept of maximizing the use of raw materials so that the final product contains the maximum number of atoms from the reactants.

The ideal reaction would incorporate all of the atoms of the reactants.

The AE is measured as the ratio of the molecular weight of the desired product over the molecular weights of all reactants used in the reaction.

Additional considerations when designing a green reaction:
Generation of co-products and waste, toxicity of co-products and waste, energy needs, purification steps, solvent and catalyst usage

Example: Epoxidation of styrene



styrene

desired epoxide

waste

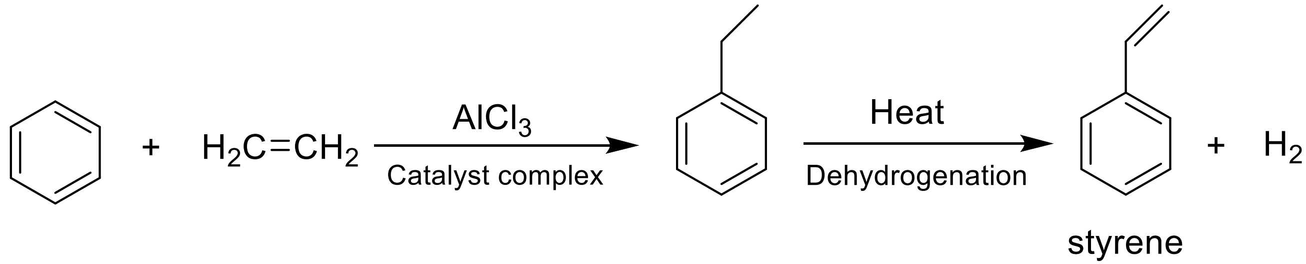
- Assume 100% yield.
- 100% of the desired epoxide product is recovered.
- 100% formation of the co-product: m-chlorobenzoic acid.
- A.E. of this reaction is 23%.
- 77% of the products are waste.

Case study: Styrenes

Conventional method of styrene production:

Styrenes are precursors to polystyrene. Polystyrene is one of the most widely used plastics, the scale of its production being several million tons per year.

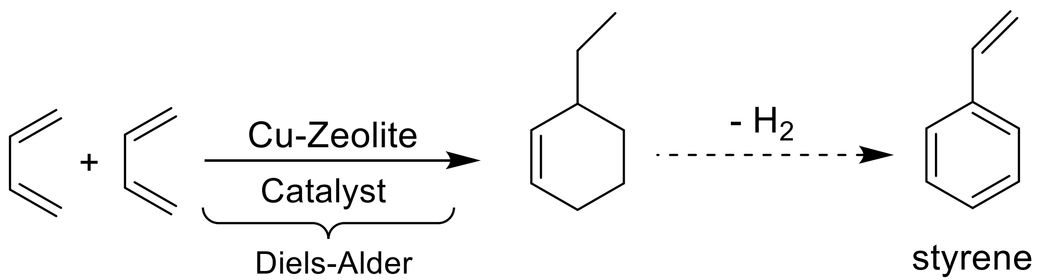
- Use of benzene, a known carcinogen, as a starting material.
- High temperature (800-950 ^{0}C).



Case study: Styrenes

Alternative method of styrene production from butadiene using Diels-Alder reaction:

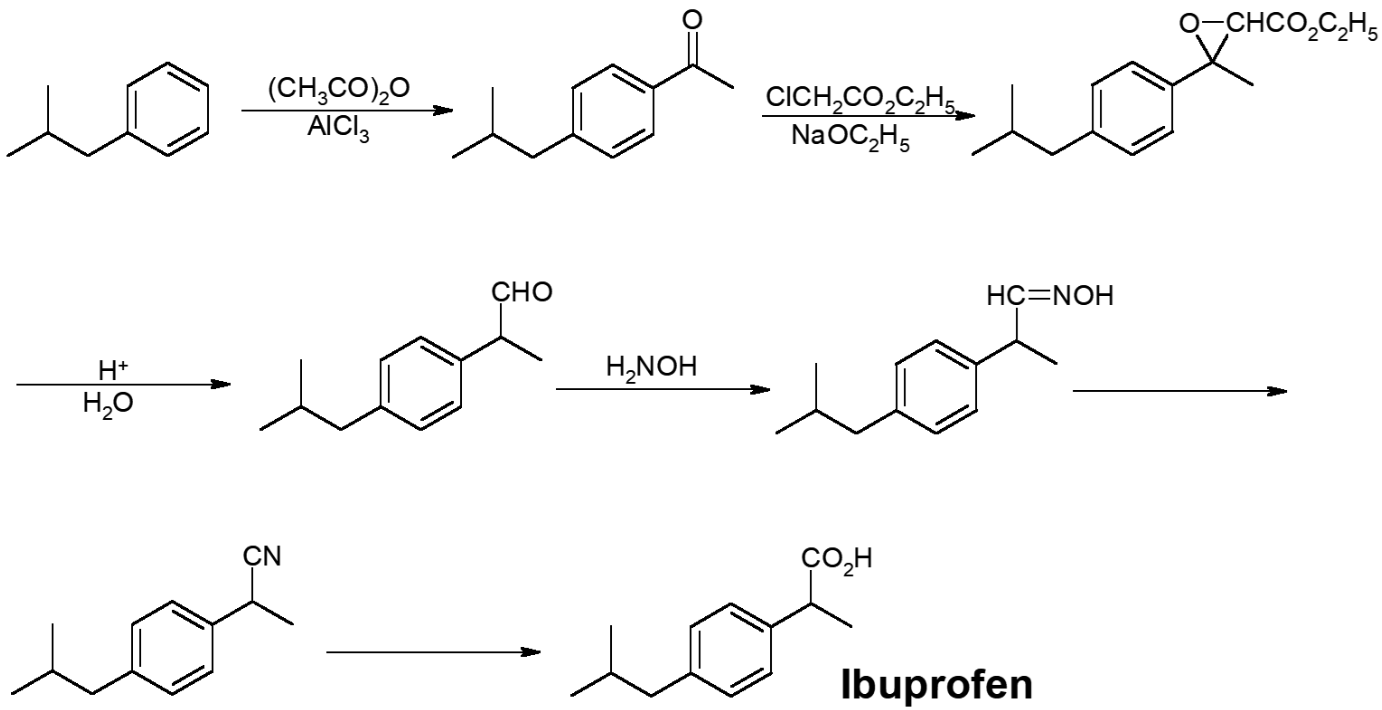
- Diels-Alder reaction = 100% atom economy.
- Use of non-toxic starting material.



Case study: Ibuprofen

Conventional synthesis of ibuprofen:

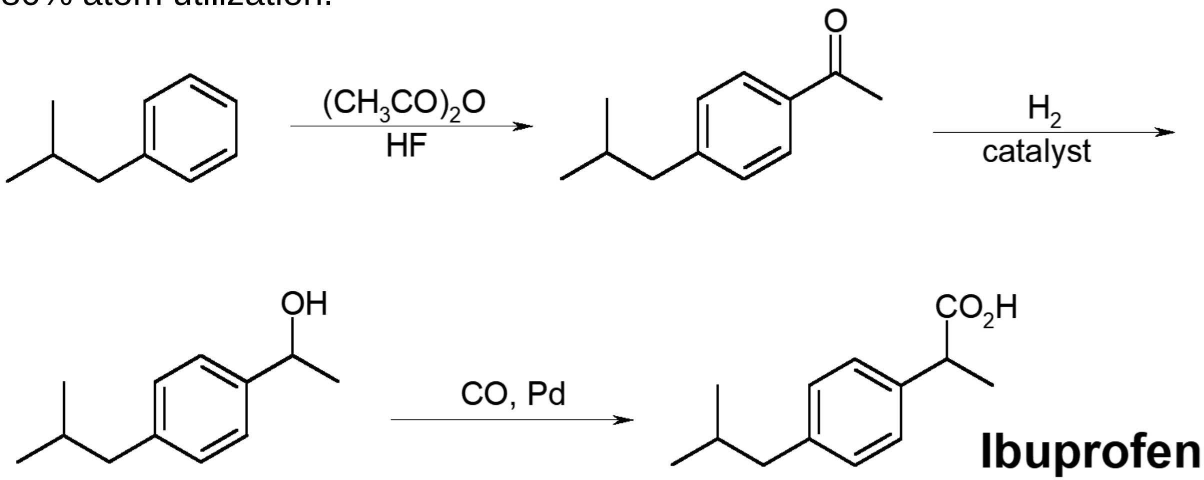
- 6 stoichiometric steps.
- <40% atom utilization.



Case study: Ibuprofen

Alternative catalytic synthesis of ibuprofen:

- 3 catalytic steps.
- 80% atom utilization.



BHC

3 LESS HAZARDOUS CHEMICAL SYNTHESIS

GREEN CHEMISTRY

Whenever practicable, synthetic methodologies should be designed to use and generate substances that possess little or no toxicity to human health and the environment.

Image: Wikimedia Commons, Center for Biofilm Research Laboratory Montana State University

Ideally, non-toxic substances are used to synthesize a chemical product.

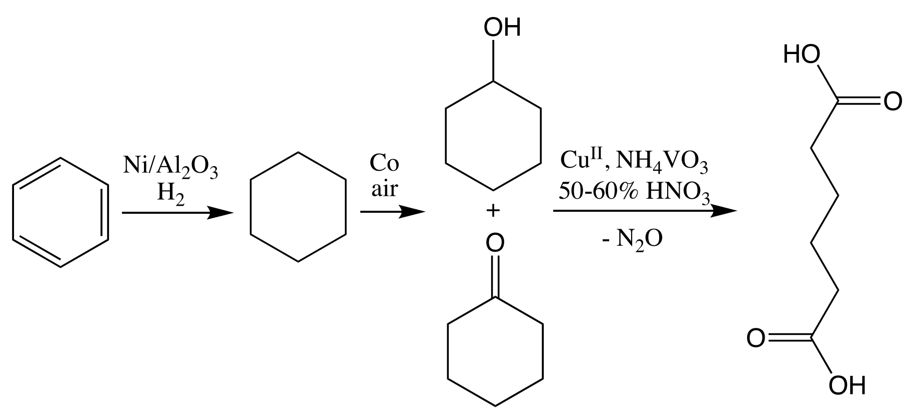
Organic chemistry's synthetic toolbox has been significantly improved over the past decade by the innovative work of green chemists and the many new reactions that have been developed.

Cascade, or tandem reactions, such as C–H activation, metathesis, and enzymatic reactions are some excellent examples of the cleaner and more efficient synthetic tools that are now available to organic chemists.

Case study: Synthesis of adipic acid

Adipic acid (AA), also referred to as hexanedioic acid, is one of the most produced commodity chemicals worldwide. With a projected global market size of more than 7 billion US dollars by 2019, AA is a versatile building block for an array of processes in the chemical, pharmaceutical and food industries. Its primary use is as a precursor for the synthesis of the polyamide Nylon-6,6.

Conventional synthesis of adipic acid:
- Uses benzene, a known carcinogen, as a starting material.
- Involves oxidation with an excess of HNO3, and production of greenhouse gas nitrous oxide (N_2O), the latter accounting for approximately 5–8% of the worldwide anthropogenic N_2O emissions.

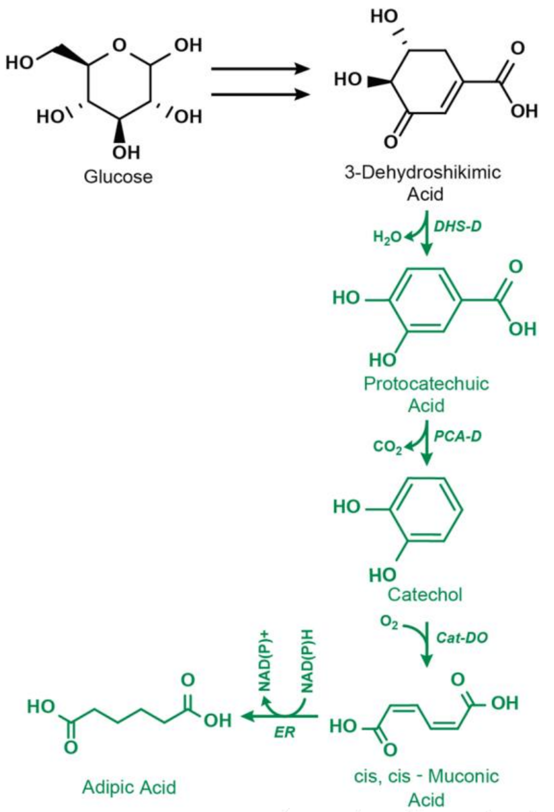


Case study: Synthesis of adipic acid

Alternative synthesis of adipic acid:

- Development of biocatalytic processes for producing adipic acid and catechol from sugars.
- Biocatalytic process using yeast converts sugars to cis,cis-muconic acid, and this intermediate stage allows ready access to catechol and adipic acid.
- Uses water as solvent at ambient temperature and pressure.

Raj, K et al. Biocatalytic production of adipic acid from glucose using engineered Saccharomyces cerevisiae. Metabolic Engineering Communications. 6, 2018, 28-32



Case study: Paper Bleaching

Conventional paper bleaching with Chlorine dioxide (ClO_2):

- Produces unacceptable quantities of chlorinated pollutants.
- Many of these pollutants are exceptionally toxic.

Alternative technology for paper bleaching with TAML/H_2O_2:

- Alternative catalytic breakdown of H_2O_2 provides the oxidative equivalent.
- Lower temperature and time requirements.

Image: Wikimedia Commons, Author: Sammutawe

Chemical products should be designed to preserve efficacy of the function while reducing toxicity.

Image: Wikimedia Commons, Author: Sentryair

The modern motto of toxicology:

"Everything is toxic. It is simply depends on the dose"

Often otherwise phrased as

"The dose makes the poison."

Risk = Hazard x Exposure

Green chemistry and engineering focus on reducing risk by **reducing hazard.**

Hazard types to avoid:

❑ **Toxicological/Eco-toxicological**

- Carcinogenicity
- Reproductive
- Developmental
- Neurological
- Global warming potential
- Ozone depleting potential
- Bioaccumulation
- Persistence

❑ **Physical**

- Explosivity
- Flammability
- Corrosivity

Physical/Chemical Properties to consider:

- Water solubility
- Log Kow
- Volatility
- Molar volume
- Aspect ratio
- Radical formation
- Nucleophilicity
- Electrophilicity
- pH/pKa
- Surface area
- Reducing potential
- Oxidizing potential
- Polarizability

Chemists can design chemicals which have reduced toxicity by:

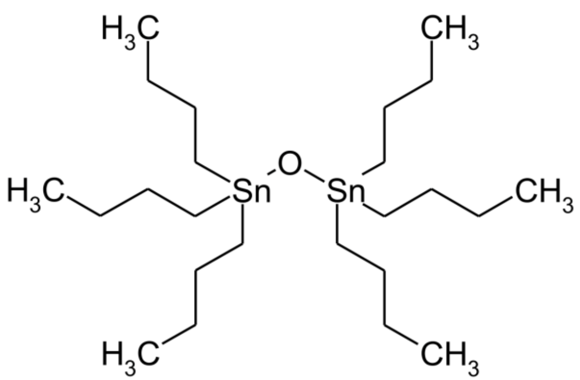
- ❑ Manipulation of chemical bonds, chemical functional groups.
  - Reactive functional groups have a greater potential to be toxic. Removing these groups is likely to reduce toxicity.
- ❑ Elimination of the molecular initiating event that activates pathway
  - While difficult to achieve, if the chemical is modified not to interact with the biological pathway, no biological effect is triggered and the toxicity can be avoided.
- ❑ Reducing or eliminating bioavailability.
  - If a chemical does not absorb into a body, it cannot cause harm.

Case study: Antifoulants

Antifoulants are generally dispersed in the paint as it is applied to the hull. Organotin compounds such as tributyltin oxide (TBTO) have traditionally been used. TBTO works by gradually leaching from the hull and killing the fouling organisms in the surrounding area.

Conventional use of organotin compounds as antifoulants:

- TBTO and other organotin antifoulants have long half-lives in the environment (the half-life of TBTO in seawater is over 6 months).
- They bioconcentrate in marine organisms (the concentration of TBTO in marine organisms has been found to be up to 104 times greater than in the surrounding water).
- Organotin compounds are chronically toxic to marine life and can enter food chain.
- They are bioaccumulative.

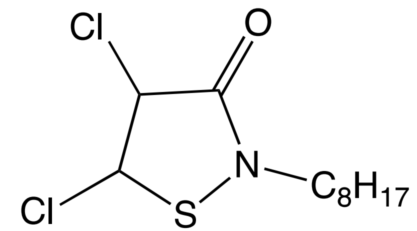


Tributyltin oxide (TBTO)

Case study: Antifoulants

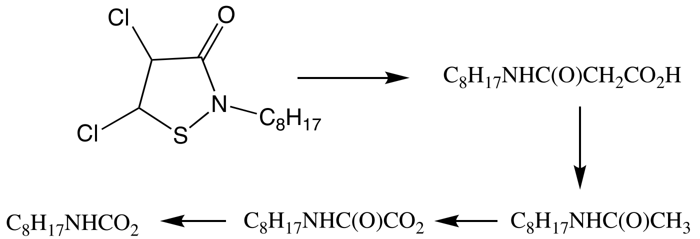
Alternative antifoulants:

- Sea-Nine® 211 works by maintaining a hostile growing environment for marine organisms. When organisms attach to the hull (treated with DCOI), proteins at the point of attachment with the hull react with the DCOI. This reaction with the DCOI prevents the use of these proteins for other metabolic processes. The organism detaches itself and searches for a more hospitable surface to grow upon.
- Only organisms attached to hull of ship are exposed to toxic levels of DCOI.
- Readily biodegrades once leached from ship (half-life is less than one hour in sea water).



4,5-dichloro-2-octylisothiazolidin-3-one

DCOI



Deposition of DCOI in Natural Seawater

In 2014, the Solberg Company earned an award for its halogen-free RE-HEALING Foams for use in fighting fires. Traditionally, firefighting foams used fluorinated surfactants, persistent chemicals that have the potential for negative environmental impacts.

The RE-HEALING firefighting foam concentrates use a blend of non-fluorinated surfactants and sugars. This works well and with far less environmental impact.

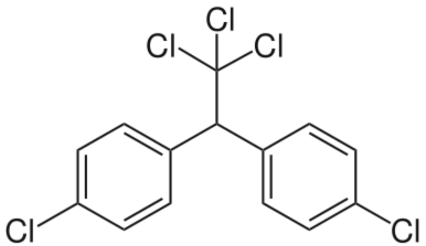
Control, extinguishing time, and burnback resistance are paramount to the safety of firefighters everywhere, and the new foams have excellent performance in each category. The RE-HEALING Foams also achieve full regulatory compliance with existing fire protection standards.

https://www.epa.gov/greenchemistry/presidential-green-chemistry-challenge-2014-designing-greener-chemicals-award

Case study: Pesticides

Conventional use of agricultural pesticide and a malarial control agent Dichlorodiphenyltrichloroethane (DDT):

- Carcinogenic.
- The threat to wildlife - especially birds – has almost led to the extinction of a bald eagle population.



DDT

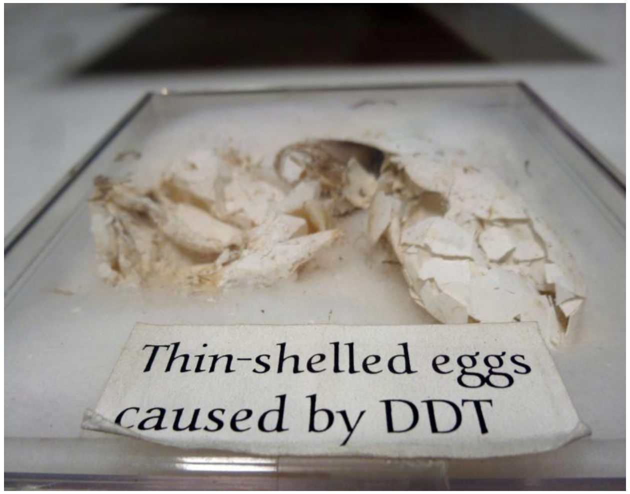


Image Source: http://www.avoidingregret.com/2014/06/photo-essay-eggs-and-nests-of-bird.html

Case study: Pesticides

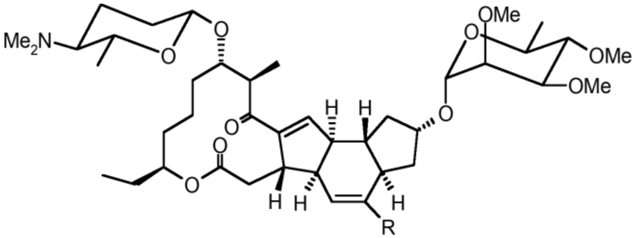
***Alternative (and natural) use of Spinosad* for insect control:**

- Produced by bacteria *Saccharopolyspora spinosa.*
- Isolated from Caribbean soil samples (sugar mill).
- It selectively targets nervous system of insects.
- Demonstrates high selectivity, low mammalian toxicity, and a good environmental profile.

Toxicity scorecard

Rat: LD_{50}>5000 mg/kg
Duck: LD_{50}>5000 mg/kg
Fish: $LC_{50\text{-}96h}$=30.0 mg/L
Bee:
LD_{50}=0.0025 mg/bee

Saccharopolyspora spinosa



Spinosyn A: R = H
Spinosyn D: R = CH_3

Dow AgroSciences

5

SAFER SOLVENTS AND AUXILIARIES

GREEN CHEMISTRY

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

Image: Dr. El Sayed Arafat from NAWCAD's Materials Lab, U.S. Navy

Solvents account for the vast majority of mass wasted in syntheses and processes. Moreover, many conventional solvents are toxic, flammable, and/or corrosive.

Solvents volatility and solubility have contributed to air, water and land pollution, have increased the risk of workers' exposure, and have led to serious accidents.

Recovery and reuse, when possible, is often associated with energy-intensive distillation and sometimes cross contamination. In an effort to address all those shortcomings, chemists have started to search for safer solutions.

SAFER SOLVENTS AND AUXILIARIES

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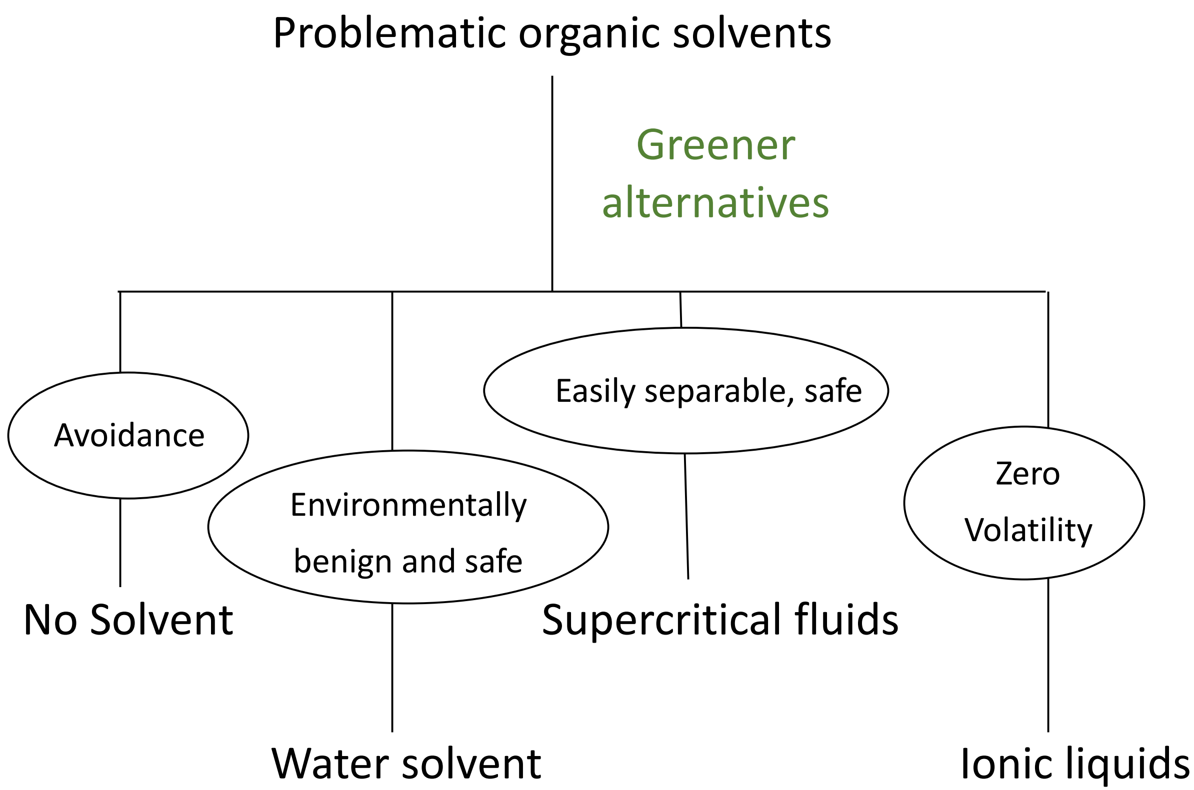


Case study: Coffee decaffeination

Conventional method of coffee decaffeination:

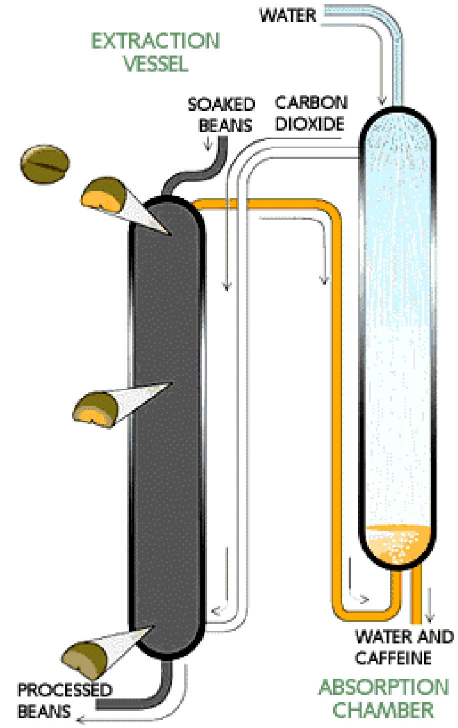
- Coffee decaffeination was performed in a chlorinated organic solvent, dichloromethane (DCM), exposure to which can lead to headaches, mental confusion, nausea, vomiting, dizziness and fatigue.
- Coffee beans were heated with steam and then exposed to DCM for decaffeination.

Image: Wikimedia Commons, Coffee Mechanical Separator, Aquapulp

Case study: Coffee decaffeination

Alternative method for coffee decaffeination:

- Soaking green coffee beans in water doubles their size, allowing the caffeine to dissolve into water inside the bean.
- Caffeine removal occurs in an extraction vessel (70 feet high,10 feet in diameter), suffused with carbon dioxide at roughly 90 °C and 250 atm. Caffeine diffuses into this $scCO_2$. The beans enter at the top of the chamber and move toward the bottom over 5 hours.
- Decaffeinated beans at the bottom of the vessel are removed, dried and roasted.
- Recovery of dissolved caffeine occurs in an absorption chamber. A shower of water droplets leaches the caffeine out of the supercritical carbon dioxide. The caffeine in this aqueous extract is then often sold to soft-drink manufacturers and drug companies. The purified carbon dioxide is recirculated for further use.



Zosel, K. Practical Applications of Material Separation with Supercritical Gases. *Angew. Chem., Int. Ed.* **1978**, *17*, 702-709

Case study: Medical sterilization

Conventional medical sterilization:

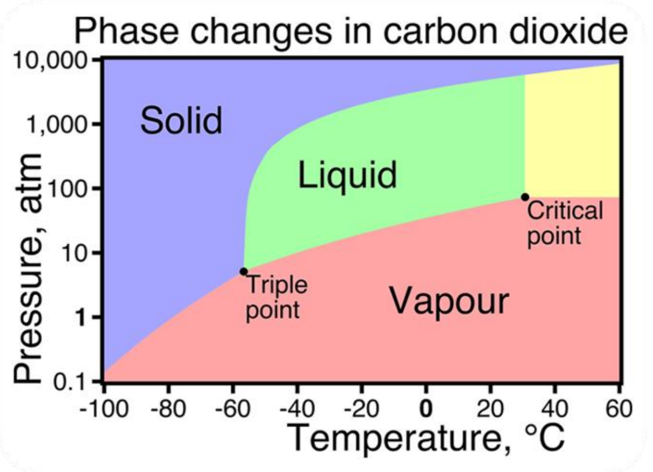
- Delicate biomedical materials such as vaccines and tissues are conventionally sterilized with ethylene oxide - a carcinogenic, mutagenic, toxic, and flammable gas - or with gamma radiation, which is lethal to all cells.
- Both methods damage the materials they are sterilizing.
- Ethylene oxide persists in tissue.

Image: Svetlana Pohovey, 359th Medical Group, U.S. Air Force photo/Staff Sgt. Kevin Iinuma

Case study: Medical sterilization

Alternative medical sterilization:

- Development of a supercritical carbon dioxide ($scCO_2$) based method for sterilization of biological material.
- NovaSterilis sterilization uses $scCO_2$, peracetic acid, and small amounts of water at low temperatures and modest pressures to achieve rapid sterilization of sensitive biomaterials.

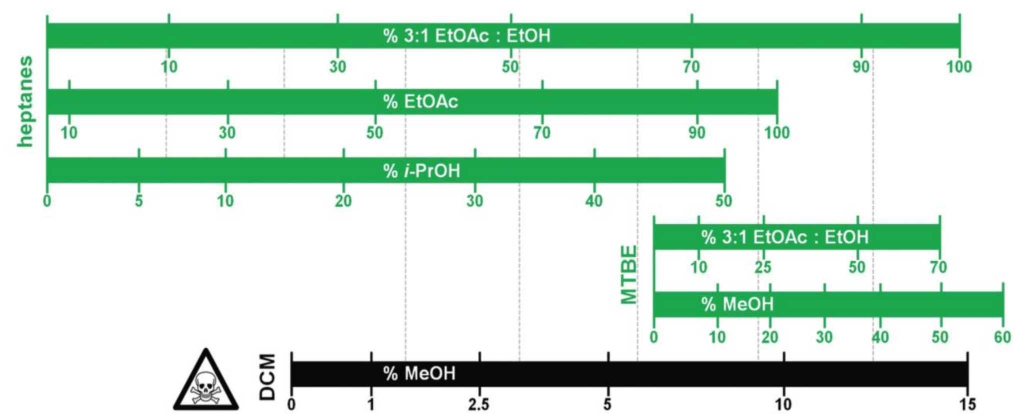


NovaSterilis Inc.

Case study: Replacing dichloromethane (DCM) in chromatography

Amgen developed a guide to replace DCM with greener alternatives. DCM is known to be associated with respiratory and cardiovascular toxicity in humans, carcinogenicity, and genotoxicity.

The guide on the right compares the eluting power of different greener solvent mixtures with reference to DCM-Methanol.



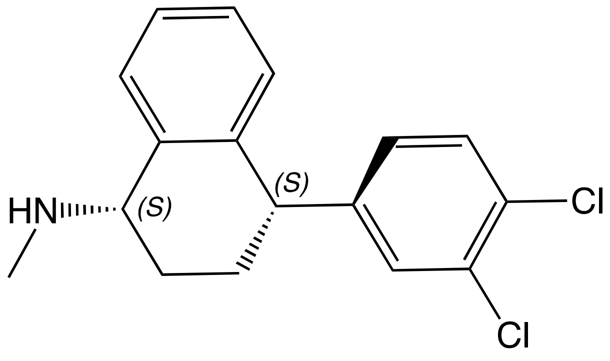
Amgen's Green Solvents for Chromatography in practice. If a compound suitably elutes in 5% DCM–MeOH, the bar chart predicts that 60% 3 : 1 EtOAc : EtOH in heptanes or 40% i-PrOH in heptanes would be a suitable starting point to evaluate greener solvent alternatives.

Case study: Manufacturing process for sertraline, the active ingredient in the popular drug Zoloft®

Zoloft® is an anti-depressant and was once one of the best selling pharmaceuticals on the market.

Conventional sertraline synthesis:

- Synthesis was a three step process.
- Used 4 hazardous solvents (methylene chloride, tetrahydrofuran, toluene, and hexane).



Zoloft®

Case study: Manufacturing process for sertraline, the active ingredient in the popular drug Zoloft®

Alternative sertraline synthesis:

- The process was streamlined to a single step that is carried out in ethanol, a much less toxic solvent.
- The new process is also catalytic, cutting down on starting materials by 60%, 45%, and 20% for the three components of the reaction.
- The combined steps eliminated 310,000 pounds of titanium tetrachloride, 220,000 pounds of 50% sodium hydroxide, 330,000 pounds of 35% hydrochloric acid waste, and 970,000 pounds of solid titanium dioxide waste per year.

Image: Wikimedia Commons, Author: Ragesoss

Pfizer, Inc

Energy requirements should be recognized for their environmental and economic impacts and should be minimized. Synthetic methods should be conducted at ambient temperature and pressure.

Image: U.S. Air Force photo/Bill Evans

6 DESIGN FOR ENERGY EFFICIENCY

GREEN CHEMISTRY

Most energy is used for heating, cooling, separations and pumping.

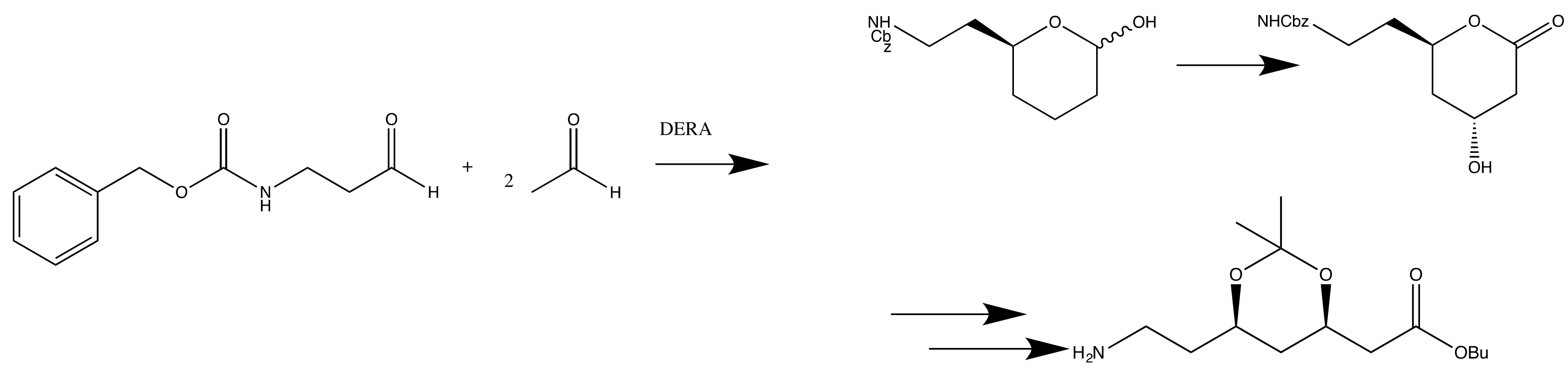
Ideally, all reactions are performed at 'ambient' conditions – room temperature and atmospheric pressure – in order to minimize energy usage.

Image: Wikimedia Commons, Janicki Omni Processor Pilot Plant in Dakar, Senegal , Author: Janicki Bioenergy

Case Study: Atorvastatin

Atorvastatin, a cholesterol-lowering drug, suffers from an energy-demanding synthesis as a result of two cryogenic reactions at - 70 ^{o}C

New ***biocatalytic*** synthesis uses enzyme DERA and shortens the process by removing two energy intensive chemical steps.



Sono-, microwave-, and photo-assisted chemistry are known to save energy, improve reaction time, and catalytic activity.

Sonochemistry

- Uses of high frequency (20-100 kHz) sound waves to promote chemical reaction.
- The collapse of bubbles formed in a solution generates a very high temperature and a higher pressure than conventional heating.
- Used in the production of triglycerides from methyl transesterification.

Microwave

- Uses a high-frequency electric field to heat or cool the local environment with electrical charges.
- Avoids unnecessarily prolonged residence time at a given temperature.

Photo-assisted

- Naturally occurring, such as using the sun as a catalyst.
- Used in photo-driven acylation for the production of valuable synthetic intermediates and commercial fragrances in bulk.
- Used by BASF to develop automotive primer coating, a precursor readily able to be crosslinked under photo irradiation, as opposed to its conventional energy-intensive thermally driven variation.

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

Image: Wikipedia, Pongamia Pinnata Seeds

Biomaterials [Carbohydrates, Proteins, Lipids]
Highly Functionalized Molecules

↓

Petroleum Products [Hydrocarbons]

↓

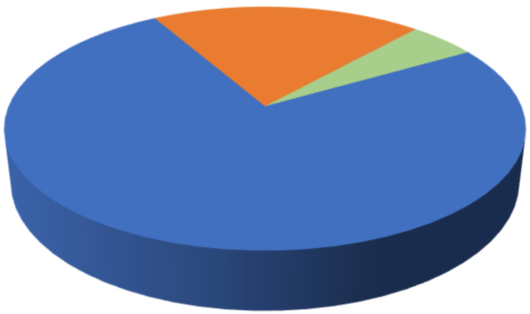
Functionalized Compounds [Olefins, Alkylchlorides]

↓

Highly Functionalized Molecules

Biomass production in nature: 180 billion metric tons/year

Only about 4% utilized by humans (food, ethanol, sweeteners)



Carbohydrates Lignin Fats, proteins, terpenes, etc.

Building blocks for a diverse chemical platform.

Nature's richest source of aromatic carbon. Used in polymers, adhesives, production of phenolic chemicals.

Converted into polymers, lubricants, and detergents.

Case study: Producing polymers from renewable resources (PHAs)

Polyhydroxyalkanoates (PHAs) are a broadly useful family of natural, environmentally friendly, and high-performing, bio-based plastics.

- The development of microorganisms that produce polyhydroxyalkanoates (PHAs) are from renewable feedstocks such as cornstarch and cellulose hydrolysate.
- The microorganisms have proven to be applicable to conventional commercial equipment and can even be recycled using this same equipment.
- They can be used in biodegradable products, such as credit cards.
- They are comparable with polyolefins - which are made from petroleum feedstocks - in terms of strength, melting point, and can be manufactured with the existing equipment.

Image: Alpha Stock Images, Author: Nick Youngson

Metabolix

Case study: Carpet tile backings

Conventional synthesis:

- Carpet tile backings were usually comprised of bitumen, polyvinyl chloride (PVC), or polyurethane - which are all derived from petroleum.
- PVC - the most common base for carpet tile backings - is made from vinyl chloride, a toxic substance which releases toxic dioxins and hydrochloric acid as byproducts upon combustion.

Image: Wikimedia Commons, Swatches of Carpet, Author: Quadell

Case study: Carpet tile backings

Alternative synthesis:

- The development of a new, recoverable carpet backing.
- Utilizing a combination of low-toxicity polyolefin resins, the backing can be separated from any fiber and recovered by elutriation, grinding, and air separation.
- Collection, transportation, elutriation, and reprocessing is less expensive than using fresh starting material.

Shaw Industries, Inc

Image: Flickr, Author: Emily May

Case study: Development and commercialization of toners

Conventional synthesis:

- Over 400 million pounds of toner are consumed in the U.S. each year.
- Conventional petroleum-based resin toners are difficult to remove from paper, making paper recycling more intensive.

Image: Wikimedia Commons, Black toner container, Author: Adamantios

Case study: Development and commercialization of toners

Alternative process:

- The development of a novel, bioderived printer toner that is easier to deink from paper.
- This technology incorporates functional groups in their toners that are susceptible to chemical degradation for recycling.
- These toners are biobased, derived from soybean oil and corn.
- At 25% market penetration, this technology could reduce CO_2 emissions by 360,000 tons/year.

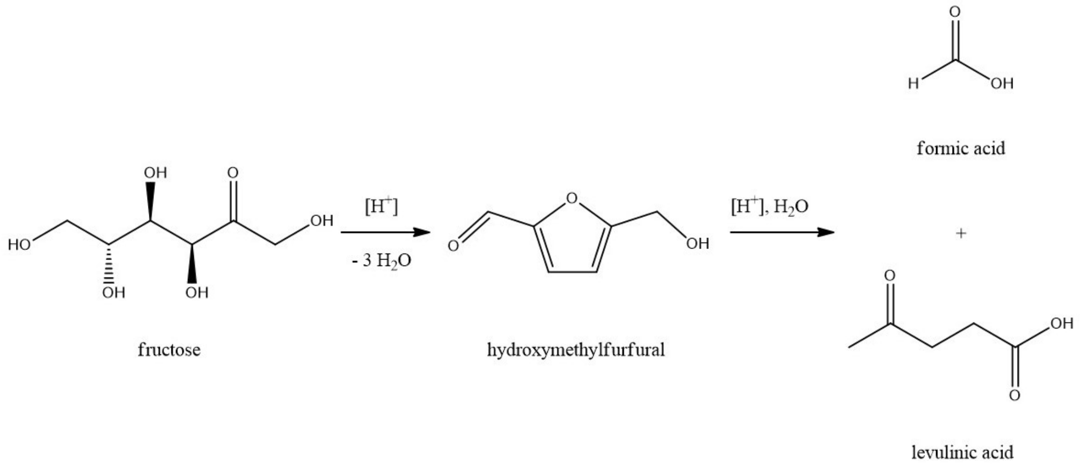
Battelle

Case study: Production of levulinic acid

Levulinic acid is used as a precursor for pharmaceuticals, plasticizers, and various other additives. It is also widely used as a building block or starting material for a wide number of compounds.

Conventional synthesis:

- Obtained by heating hexoses (glucose, fructose) or starch in dilute hydrochloric acid or sulfuric acid.
- The yield depends on the nature of the acid, acid concentration, temperature, and pressure.
- The reaction also produces hard to remove by-products.



Case study: Production of levulinic acid

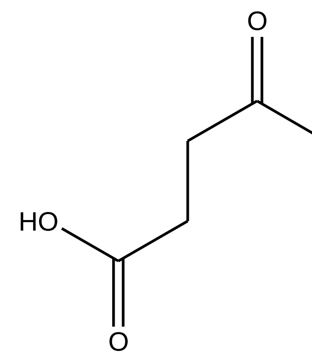
Alternative synthesis:

- Levulinic acid can be obtained from paper mill sludge, agricultural and municipal waste and paper.
- Utilizes a high-temperature, dilute-acid hydrolysis process that converts cellulosic biomass.

Agricultural residues, waste wood

Municipal solid waste and waste paper

Paper mill sludge

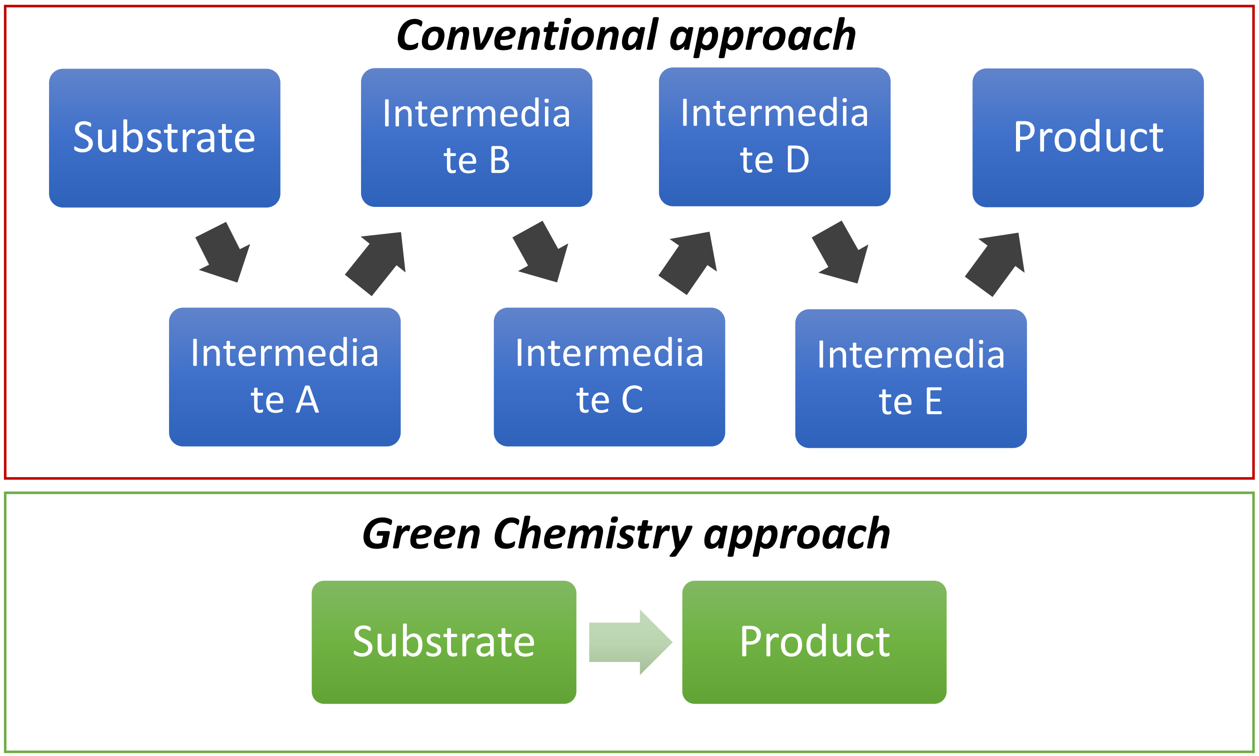


Levulinic acid

Biofine, Inc

Unnecessary derivatization (blocking group, protection/deprotection, temporary modification of physical/chemical processes) should be avoided whenever possible.

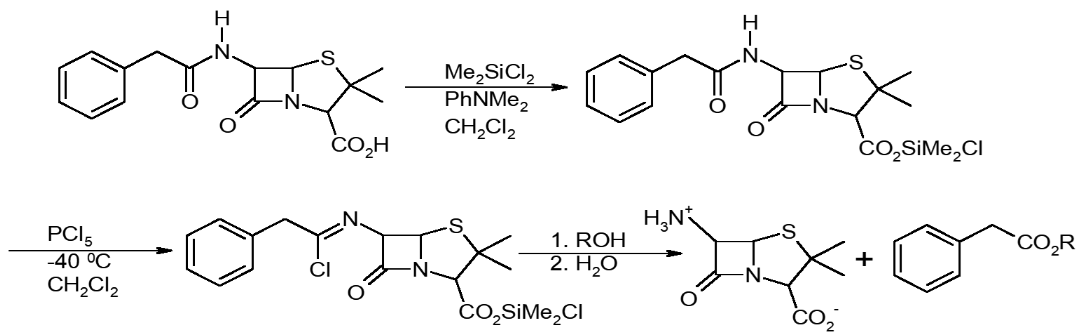
Image: Wikimedia Commons, Center for Biofilm Research Laboratory Montana State University


Conventional approach
Substrate
Intermedia te B
Intermedia te D
Product
Intermedia te A
Intermedia te C
Intermedia te E
Green Chemistry approach
Substrate
Product

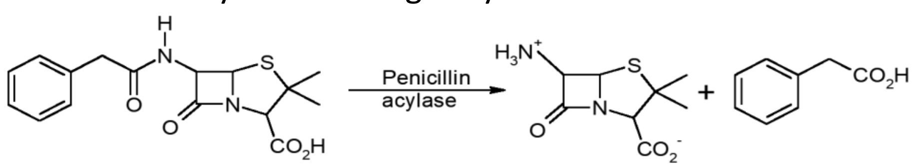
Case study: 6-aminopenicillanic acid

Synthesis of 6-aminopenicillanic acid – core moiety of penicillin

Conventional synthesis of 6-aminopenicillanic acid using 3 steps and intermediate products:



Alternative synthesis using enzyme and fewer derivatives:



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

Image: Flickr, Catalysts, Author: BASF Catalysts

Catalysts can facilitate complex reactions by:

- Lowering the activation energy of the reaction.
- Reducing temperature necessary to achieve a reaction.
- Controlling the site of the reaction (selectivity enhancement).

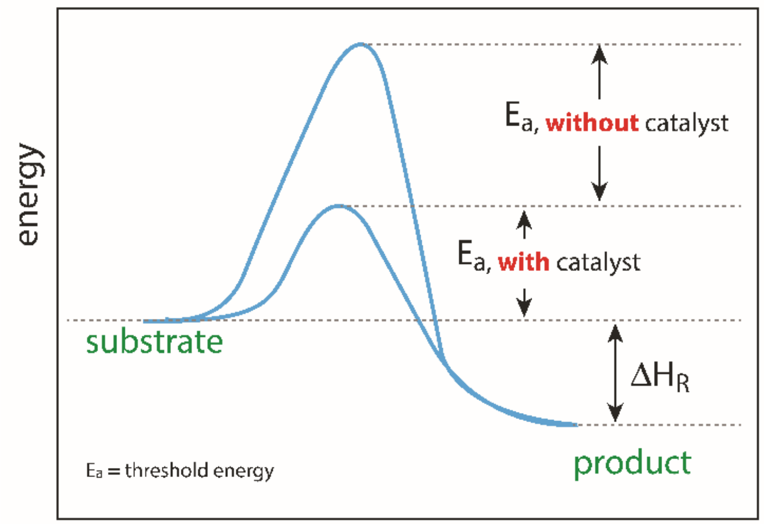


Image source: Adobe stock

Heterogeneous vs Homogeneous

- Distinct solid phase
- Readily regenerated & recycled
- Readily separated
- Rates not as fast
- Diffusion limited
- Sensitive to poisons
- Lower selectivity
- Long service life
- High energy process
- Poor mechanistic understanding

- Same phase as rxn medium
- Expensive and/or difficult to separate
- Difficult to separate
- Very high rates
- Not diffusion controlled
- Robust to poisons
- High selectivity
- Short service life
- Mild conditions
- Mechanisms well understood

Heterogeneous vs Homogeneous

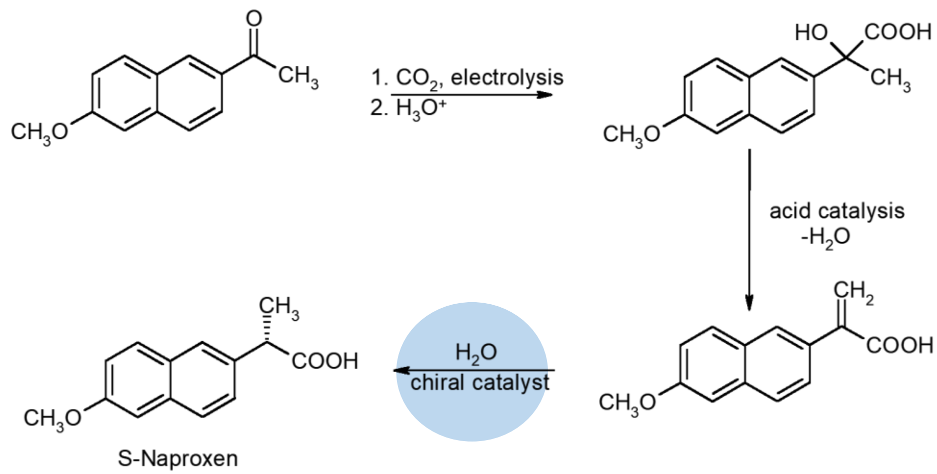
- Distinct solid phase
- **Readily regenerated & recycled**
- **Readily separated**
- Rates not as fast
- Diffusion limited
- Sensitive to poisons
- Lower selectivity
- **Long service life**
- High energy process
- Poor mechanistic understanding

Green catalyst

- Same phase as rxn medium
- Expensive and/or difficult to separate
- Difficult to separate
- **Very high rates**
- Not diffusion controlled
- **Robust to poisons**
- **High selectivity**
- Short service life
- **Mild conditions**
- Mechanisms well understood

Case study: Green naproxen synthesis

Nonsteroidal anti-inflammatory drug (NSAID) of the propionic acid class (the same class as ibuprofen) that relieves pain, fever, swelling, and stiffness; COX inhibitor



97% yield in three steps

Dartt and Davis

Case study: Paper production

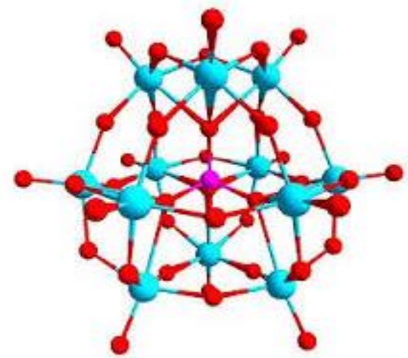
- Polyoxometalate (POM) catalysts
  - non-toxic, inorganic cluster compounds
  - selectively delignify wood
  - utilize only air and water
- Allows use of oxygen instead of chlorine as the whitener of paper pulp and water as the solvent
- Generates only CO_2 and H_2O, instead of chlorinated organics

1st step

2nd step

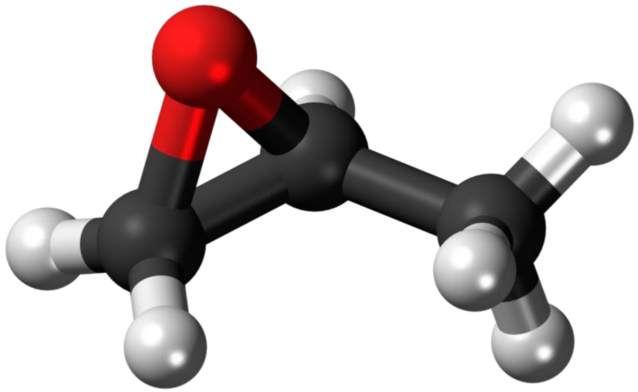
3rd step

4th step



Hill, Emory University;
Hill et al, *Nature* **2001**, *414*, 191–195

One of Dow Chemical's awards is for a green catalyst that reduces the environmental footprint associated with producing propylene oxide, one of the biggest volume industrial chemicals in the world. The Hydrogen Peroxide to Propylene Oxide (HPPO) process, which was developed jointly with BASF, serves as a chemical building block for a vast array of products including detergents, polyurethanes, de-icers, food additives, and personal care items. The new process reduces the production of wastewater by as much as 70–80 percent and reduces the use of energy by 35 percent over conventional technologies.

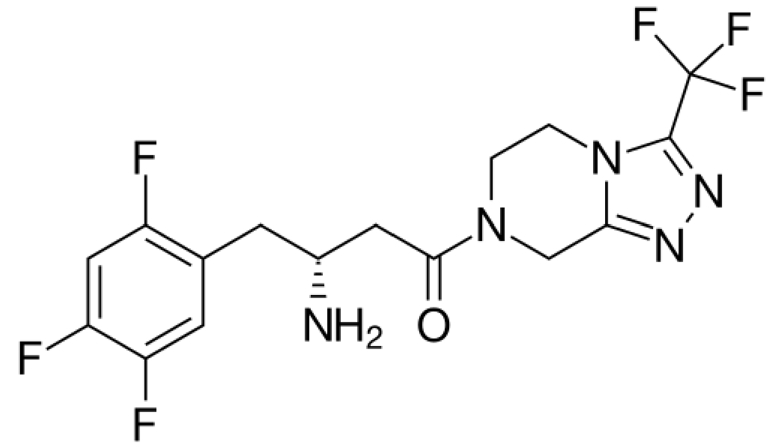


propylene oxide molecule

Image: Wikipedia, propylene oxide molecule, Author: Jynto

https://www.epa.gov/greenchemistry/presidential-green-chemistry-challenge-2010-greener-synthetic-pathways-award

A new catalyst developed by pharmaceutical companies Merck and Codexis for the green synthesis of sitagliptin - the active ingredient in the type 2 diabetes treatment Januvia™ - may also be useful in the manufacturing of other drugs. For example, recent clinical trial showed that it may help patients with acute coronary syndrome.



sitagliptin

Image: Wikipedia, sitagliptin, Author: NEUROtiker

https://www.epa.gov/greenchemistry/presidential-green-chemistry-challenge-2010-greener-reaction-conditions-award

CATALYSIS

An example of green catalysts with the potential to reduce the pharmaceutical industry's environmental impact is the powerful series of tetra-amido macrocyclic ligand (TAML) catalysts modelled on natural peroxidase enzymes developed by Terry Collins of Carnegie Mellon University. Collins thinks that using the catalysts at a late stage in the sewage treatment process would allow them to break down a wide variety of chemical residues - including those from Lipitor, Prozac, Zoloft, the contraceptive pill, and more - before they enter the environment.

Image: Wikicommons, Pipes of the Minsk sewage treatment plant, Author: Homoatrox

https://www.epa.gov/greenchemistry/presidential-green-chemistry-challenge-1999-academic-award

10 DESIGN FOR DEGRADATION

GREEN CHEMISTRY

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

Image: Wikicommons, a landfill in Dryden, Ontario, Author: Michelle Arseneault

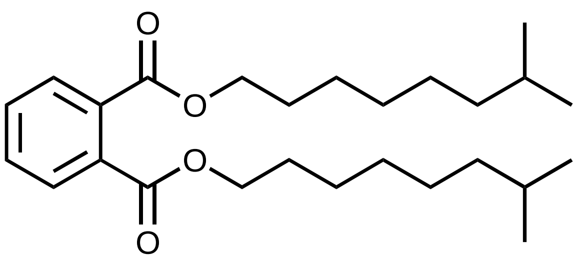
Early examples:

- ❑ Sulfonated detergents
  - Alkylbenzene sulfonates – 1950's & 60's
  - Foam in sewage plants, rivers, and streams
  - Persistence was due to long alkyl chain
  - Introduction of an alkene group into the chain increased degradation
- ❑ Chlorofluorocarbons (CFCs)
  - Do not break down, persist in atmosphere and contribute to destruction of the ozone layer.
- ❑ DDT
  - Bioaccumulate and cause thinning of egg shells

Case study: Plasticizers

Plasticizers for plastics are additives, most commonly phthalate esters in PVC applications. Almost 90% of plasticizers are used in PVC, giving this material improved flexibility and durability. The majority of PVC is used to produce films and cables.

Conventional plasticizers, such as DiNP, are an additive used to soften plastics:

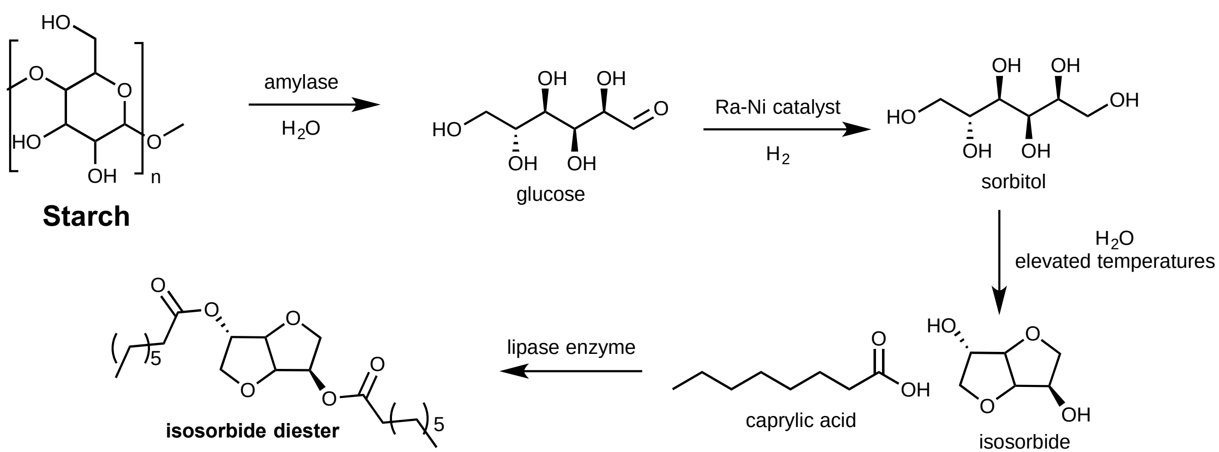


Diisononyl phthalate, DiNP

- DiNP exposure has been linked to liver toxicity, endocrine disruption, and carcinogenicity.
- The additives persist in the environment.

Case study: Plasticizers

Alternative plasticizers, such as isosorbide diester, can be derived from starch:

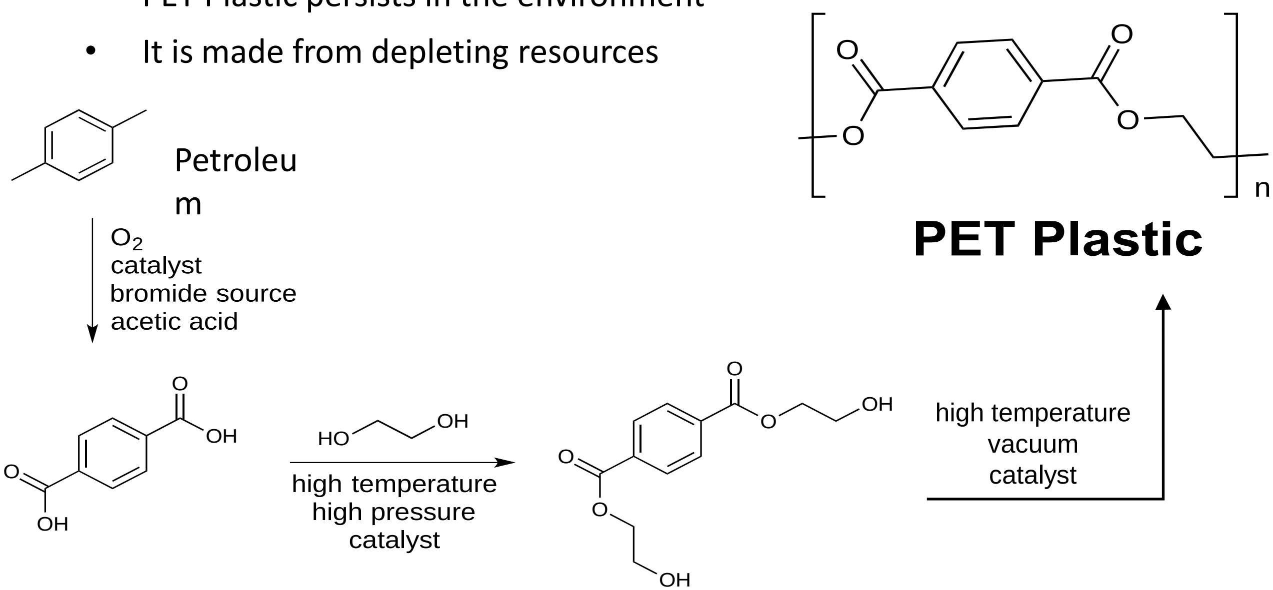


- Offers 1 to 1 substitution of DiNP in plastics.
- Isosorbide diester is thermally stable and biodegradable.

Case study: Plastics

Conventional plastics (PET) are made from petroleum:

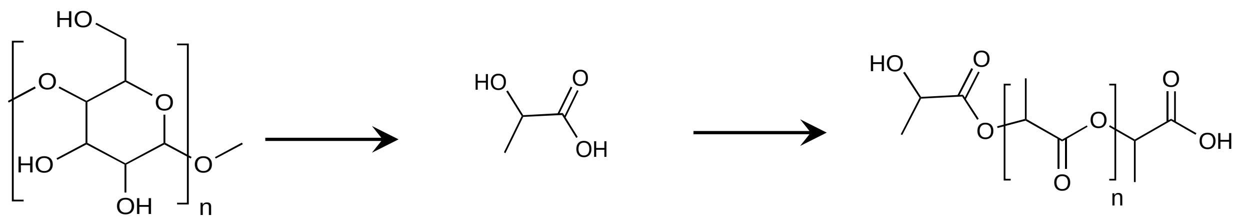
- PET Plastic persists in the environment
- It is made from depleting resources



Case study: Plastics

Synthesis of PolyLactic Acid (PLA) from starch:

Alternative process:



Starch **Lactic Acid** **PolyLacticAcid PLA**

- The development of a biobased, compostable, and recyclable polylactic acid (PLA) polymer that uses 20–50 percent less fossil fuel resources than comparable petroleum-based polymers.
- It is the first family of polymers derived entirely from renewable resources that can compete cost-effectively with traditional fibers and plastic packaging materials.
- The manufacturing process consists of three solvent-free steps that lead to the production of lactic acid, lactide, and PLA high polymer with very high yields and internal recycling schemes that reduce waste.
- PLA is fully biodegradable or can be readily hydrolyzed into lactic acid for recycling back into the process.

Cargill Dow LLC

Case study: Fire extinguishers

Conventional approaches:

- Chemical additives or alternatives to water for firefighting applications can have negative long-term environmental and health effects.
- Halon gases are destructive to the ozone layer.
- Aqueous film-forming foams release both toxic hydrofluoric acid and fluorocarbons when used.
- Fluorosurfactant compounds are resistant to microbial degradation, often leading to contamination of groundwater supplies and failure of wastewater treatment systems.

Image: Wikimedia Commons, Author: Caduser2003

Case study: Fire extinguishers

Alternative production:

- The development of a fire extinguishing foam that is nontoxic and highly biodegradable.
- PYROCOOL F.E.F. (Fire Extinguishing Foam) is an alternative formulation based on a biodegradable surfactant.
- PYROCOOL F.E.F. has a low application volume.
- Extinguishing an oil tanker fire estimated to take 10 days can be put out in 12.5 minutes.

Image: Wikimedia Commons, Kyrgyz Republic firefighters,
Author: Senior Airman Brett Clashman, U.S. Air Force

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

Image: Wikimedia Commons,
Author: Hindustanilanguage

Real time analysis for a chemist is the process of "checking the progress of chemical reactions as it happens".

Knowing when your product is "done" can save a lot of waste, time, and energy!

The Role of Analytical Chemistry

Analytical chemistry has been at the heart of the environmental movement since its inception. It’s been used in:

- Identification
- Monitoring
- Measurement
- Characterization

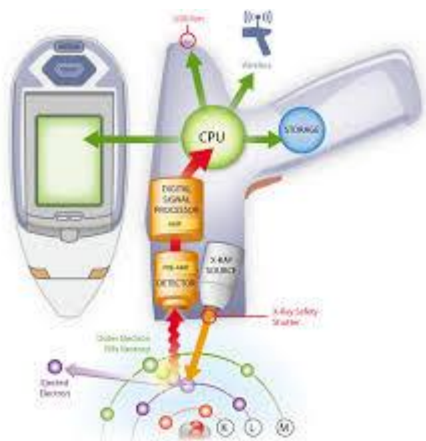
What Does Green Analytical Chemistry Mean?

Green Chemistry is applicable to all chemical processes, including the methods, protocols and processes of environmental analytical chemistry.

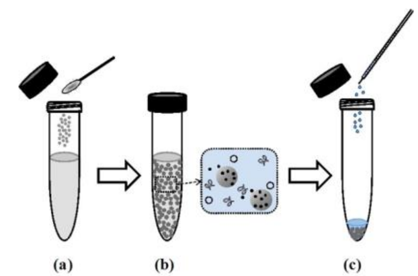
Image: Wikipedia

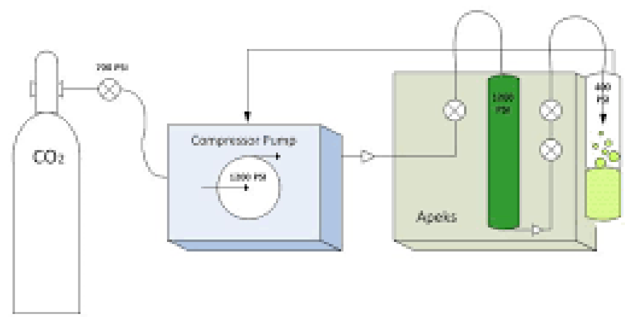
Examples of Green Analytical Chemistry Methodologies

X-ray fluorescence detection for multi-metal matrix



Solid-phase extraction and micro-extraction





Supercritical Fluid Extraction

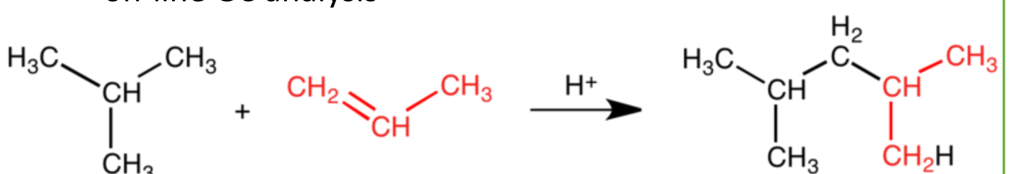
Image Sources: https://www.thermofisher.com, https://www.intechopen.com/books/herbicides-advances-in-research/recent-advances-in-the-extraction-of-triazines-from-water-samples, http://soviethammer.info/thlon/s/supercritical-fluid-extraction-co2/

Process Analytical Chemistry to Minimize Waste Generation

Through the use of real-time, in-process monitors, sensors, etc., pollution and hazardous waste generation can be prevented rather than simply measured after it is produced.

Solid-acid catalyzed 1-butene/isobutane alkylation process:

- replaces HF and H_2SO_4 catalysts
- process utilizes supercritical CO_2 to prevent coke accumulation in pores of solid catalyst
- on-line GC analysis



Subramaniam, University of Kansas
Ind. Eng. Chem. Res., 2001, 40 (18), pp 3879–3882

Image: Wikimedia Commons, Author: Smokefoot

Continuous Flow Reactors

Replacing batch reactors on large, medium, and even small scale has distinct advantages:

- Precise control of reaction conditions.
- Reproducible reaction outcome (product purity).
- Minimizes waste, and provides increased safety.

Image Sources: http://encyclopedia.che.engin.umich.edu/Pages/Reactors/menu.html, https://www.technologynetworks.com/drug-discovery/product-news/automated-compound-library-production-294622

Case study: Real-time analysis in cooling systems

Conventional Cooling Systems:

- They consume large amounts of water.
- Microbial growth and mineral scale decrease the efficiency and increase energy consumption of heat-exchange.
- However, high levels of biocide to prevent microbial growth increases the risk of leaks in the system.
- Biocide and metal-byproducts from corrosion are then released into the environment with the waste water.

Image: Wikimedia Commons, Cooling tower and cooling water discharge at a Philippsburg nuclear power plant, Author: Michael Kauffmann

https://www.epa.gov/greenchemistry/presidential-green-chemistry-challenge-2008-greener-reaction-conditions-award

Case study: Real-time analysis in cooling systems

In 2008 Naclo Company won the EPA Greener Reaction Conditions Award for their innovative 3D TRASAR® Technology.

Alternative Cooling System with 3D TRASAR® Technology:

- The 3D TRASAR® System allows for the real-time monitoring of mineral scale buildup.
- This system can also utilize poor-quality water.
- 3D Scale Control prevents mineral scale formation to increase efficiency.
- 3D Bio-control performs a real-time check for planktonic and sessile bacteria. This reduces the amount of biocide used since biocides are then added only when necessary, rather than on a set schedule.
- The 3D TRASAR® System greatly reduces the amount of wastewater discharged from cooling systems.

https://www.epa.gov/greenchemistry/presidential-green-chemistry-challenge-2008-greener-reaction-conditions-award

Image: Wikipedia, A lavender-colored nonpotable water pipeline in Mountain View, California, Author: Grendelkhan

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

Image: Flickr, Author: sea turtle

Accidents can be avoided by minimizing hazards

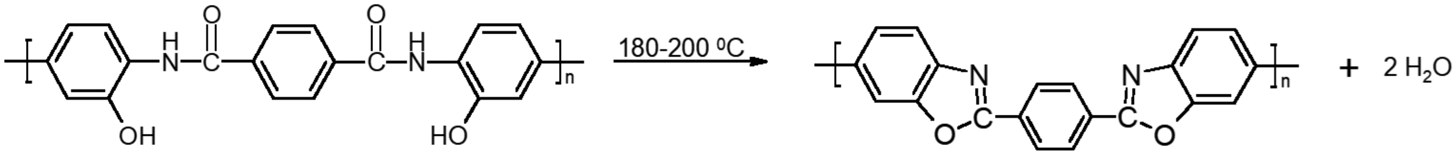
- Approaches to design safer chemistry can include the use of solids or low vapor pressure substances in place of volatile liquids.
- Other approaches include avoiding the use of molecular halogens in large quantities.
- Continuous flow processes can help to minimize chemical hazards.

Case study: Designing safer polymers for use in airplanes

Polyhydroxyamide (PHA):

- Can be molded into seats, bins, and wall panels.
- It is synthesized under mild conditions.
- It decomposes into fire-resistant polybenzoxazole (PBO) and water upon heating.

Image Source: https://videohive.net/item/plane-interior-flying-in-the-clouds/9895121



PHA

PBO

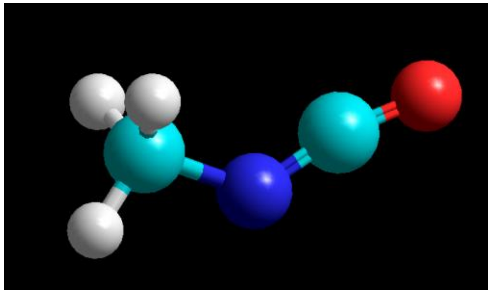
Westmoreland, UMass Amherst

Tragedy in Bhopal, India - 1984

In arguably the worst industrial accident in history, 40 tons of methyl isocyanate were accidentally released when a holding tank overheated at a Union Carbide pesticide plant, located in the heart of the city of Bhopal. 15,000 people died and hundreds of thousands more were injured.

Image: Wikimedia Commons, Bhopal Plant in 2010, Author: Julian Nitzsche

Chemists try to avoid things that explode, light on fire, are air-sensitive, etc. When these things happen in the "real world", lives are lost.



methyl isocyanate

Tragedy in Bhopal, India - 1984

December 3, 1984 – toxic gas leaked from a Union Carbide factory, killing thousands instantly and injuring many more (many of who died later of exposure). Up to 20,000 people have died as a result of exposure (3-8,000 instantly). More than 120,000 still suffer from ailments caused by exposure

What happened?

- ❑ Methyl isocyanate - used to make pesticides - was being stored in large quantities on-site at the plant.
- ❑ Methyl isocyanate is highly reactive, exothermic molecule.
- ❑ Most safety systems either failed or were inoperative.
- ❑ Water was released into the tank holding the methyl isocyanate.
- ❑ The reaction occurred and the methyl isocyanate rapidly boiled, producing large quantities of toxic gas.

Case study: Production of gasoline alkylate with AlkyClean® Technology

In 2016 Albemarle and CB&I won the EPA green chemistry award for their inherently safer AlkyClean® process technology.

Conventional alkylate production:

- Alkylate is typically produced from the reaction of isobutane and light olefins.
- This requires the use of liquid acid catalyzed processes, such as hydrofluoric acid.
- Hydrofluoric acid is extremely toxic. When released it forms clouds that can be lethal for up to five miles.

AlkyClean® Technology:

- The AlkyClean® solid acid alkylation process produces high quality alkylate without using liquid acid catalysts.
- The solid acid alkylation process is safer for both people working directly in production and for people in the area surrounding the production facility.
- There are also environmental and economic benefits since neither acid-soluble oils nor spent acids are produced.

More examples available

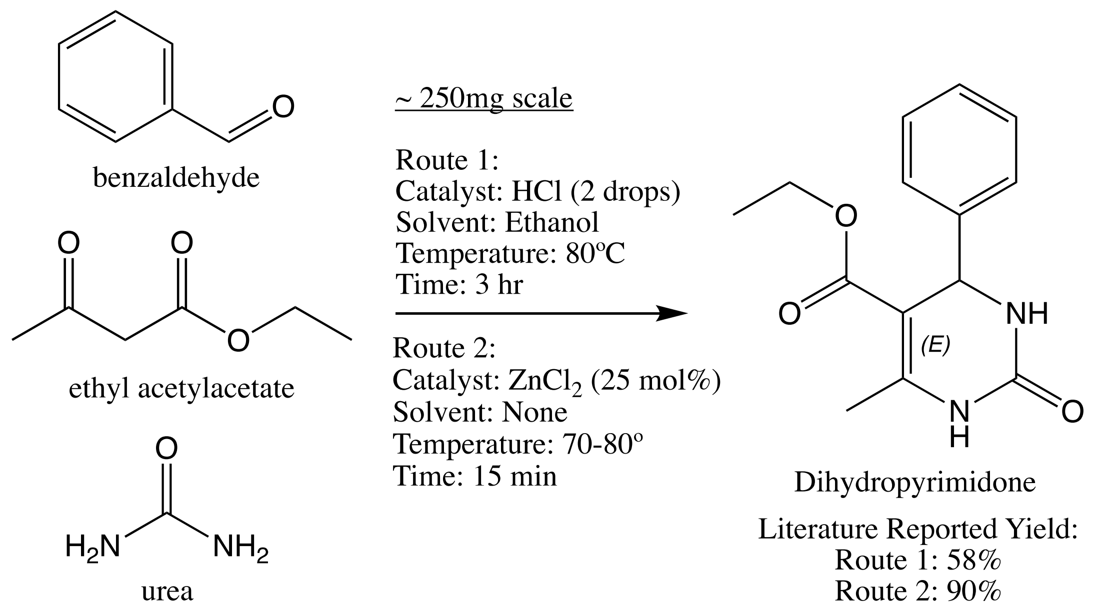
- Presidential Green Chemistry Challenge Winners

  https://www.epa.gov/greenchemistry/presidential-green-chemistry-challenge-winners

- How Industrial Applications in Green Chemistry Are Changing Our World (white paper) by American Chemical Society

Synthesis Comparison Exercise

Dihydropyrimidone is a pharmaceutical compound that displays medicinal properties as vasodilatory calcium-channel blockers and anti-viral, anti-bacterial, and anti-inflammatory agents. More than one synthetic schemes have been proposed for its synthesis since the late 1800s. Compare the two synthetic routes and analyze which pathway is greener. In your argument, be sure to consider and compare all aspects of the reaction.



THANK YOU!

QUESTIONS?

This training material was developed in close collaboration with the Center for Green Chemistry and Green Engineering at Yale University.

www.greenchemistry-toolkit.org