General aspects of 12 basic principles of green chemistry with applications

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The present review article focuses upon the key advancements made in green chemistry, its different areas and its 12 basic principles along with applications. It also highlights how chemists are now ready to introduce the applications of green chemistry and study its vital role in our daily life.

Keywords: Basic principles, clean technology, green chemistry, sustainable development.

THE first principle of the Rio Declaration on Environment and Development states that 'Human beings are at the centre of concerns for sustainable development. They are entitled to live a healthy and productive life in harmony with nature'[1] which highlights the challenge to all of us to define the objectives of sustainable development and to provide scientific, technological and social tools to achieve these objectives. We do not have to look too far back to see how a society could lose its sustainability: the rise and fall of Easter Island, discovered by the Polynesians around AD 400 (ref. 2). Its population reached a peak, perhaps more than 10,000, far exceeding the capabilities of the local system. The forests were cleared for agriculture and to move the giant stone monoliths, known as 'Moais' from 1400 AD to 1600 AD. Core sampling from the island has shown deforestation, soil depletion and erosion resulting in over population, food shortage and ultimately the collapse of the society. Thus, the history of Easter Island indicates that the sustainability of our civilization depends on whether we can supply the rapidly increasing population with enough energy, food and chemicals simultaneously without compromising on the long-term health of our planet.

The role of chemistry is essential in ensuring that our next generation of chemicals, materials and energy is sustainable. Worldwide demand for environment-friendly chemical processes and products requires the development of novel and cost-effective approaches for preventing pollution. The most important goals of sustainable development are to reduce the adverse consequences of the substances that we use and generate. Foremost among the fundamental changes this calls for, is the shifting of the production of energy and carbon-based chemicals from fossil fuels to renewable resources. Since it is difficult to predict the exact date of depletion of fossil fuels, the transition to renewable materials should be accelerated because of the frequently and unexpectedly changing political/economic environment, resulting in limited access and rising costs. But perhaps of equal significance is the need to deal with toxicities that are threatening the welfare of essentially all living things in real time. At the apex of these predicaments sits the need of the chemical enterprise to adjust to the threats of anthropogenic chemicals that disrupt the chemical signals controlling cellular development, i.e. the so-called 'endocrine disruptors'.

It is a challenge before the chemists to develop synthetic methods that are less polluting, i.e. to design clean or 'green' chemical transformations. Industries and scientific organizations have put clean technology as an important R&D concern. The area of chemistry which is particularly directed to achieve such goals is termed as 'green chemistry'. Green chemistry is a central issue, in both academia and industry, with regard to chemical synthesis in the 21st century[3]. Without this approach, industrial chemistry is not sustainable. Our health and daily life relies on man-made substances such as pharmaceuticals, fine chemicals, synthetic fibres and plastics, which are produced by multistep chemical conversion of petroleum or biomass-based feedstock. Many existing chemical processes, though beneficial produce unwanted waste along with target products, and inefficient recovery of solvents causes environmental problems[4]. Thus, the development of environmentally benign and clean synthetic technology is a goal of the researchers and industry.

The term 'green chemistry' was coined by Paul Anastas, who is also considered as the father of green chemistry. Green chemistry is defined as: the invention, design and application of chemical products to reduce or to eliminate the use and generation of hazardous substances[5]. A striking aspect of the above definition is the concept of invention and design. Another aspect is the phrase 'use and generation'. Rather than focusing only on those undesirable substances that might be inadvertently produced in a process, green chemistry also includes all substances that are part of the process. Therefore, green chemistry is not a tool only for minimizing the negative impact of those procedures aimed at optimizing efficiency, although clearly both impact minimization and process optimization are legitimate and complementary

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objects of the subject. Green chemistry, however, also recognizes that there are significant consequences to the use of hazardous substances ranging from regulatory, handling and transport and liability issues. To limit the definition to waste only would be to address only a part of the problem.

Finally, the definition of green chemistry includes the term 'hazardous'. It is important to note that green chemistry is a way of dealing with risk reduction and pollution prevention by addressing the intrinsic hazards of the substances, rather than those circumstances and conditions of their use that might increase their risk. Risk, in its most fundamental terms is the product of hazard and exposure[6].

$$\text{Risk} = \text{Hazard} \times \text{Exposure}.$$

The definition of green chemistry also illustrates another important point about the use of the term 'hazard'. This term is not restricted to physical hazards such as explosiveness, flammability and corrodibility, but also includes acute and chronic toxicity, carcinogenicity and ecological toxicity. Furthermore, for the purpose of this definition, hazards must include global threats such as global warming, stratospheric ozone depletion, resource depletion and persistent chemicals. But more importantly, intrinsically hazardous properties constitute those issues that can be addressed through the proper design or redesign of chemistry and chemicals.

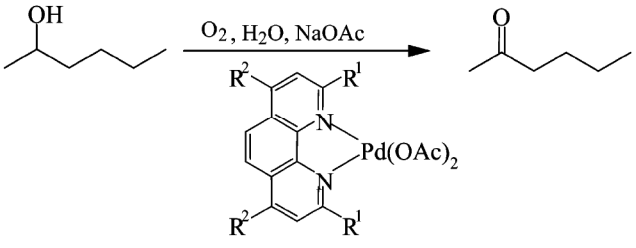
Green solvents

Today, in the chemical industry solvents are used in large quantities. In particular, fine-chemical and pharmaceutical production requires large amounts per mass of final products. Therefore, solvents define a major part of the environmental performance of processes in the chemical industry and 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. Usage of solvents is often an integral part of the chemical or manufacturing process. The unavoidable choice of a specific solvent for a desired chemical reaction can have profound economical, environmental and societal implications. The pressing need to develop alternative solvents to some extent originates from these implications and constitutes an essential strategy under the emerging field of green chemistry.

In the context of green chemistry, there are several issues which influence the choice of a solvent. It should be relatively non-toxic and non-hazardous, e.g. not inflammable or corrosive. Removal of residual solvent from products is usually achieved by evaporation or distillation and most popular solvents are therefore highly volatile. Spillage and evaporation inevitably leads to atmospheric pollution, a major environmental issue of global proportions. Moreover, the exposure of workers to volatile organic compounds (VOCs) is a serious health issue. Many chlorinated hydrocarbon solvents already have been banned, or are likely to be banned in the near future. Another class of solvents which presents environmental problems comprises the polar aprotic solvents, such as dimethyl formamide and dimethylsulphoxide that are used in many reactions, e.g. nucleophilic substitutions. They have a high boiling and not easily removed by distillation. They are also water-miscible, which enables their separation by washing with water. Unfortunately, this inevitably leads to contaminated aqueous effluent.

These issues surrounding a wide range of volatile and non-volatile, polar aprotic solvents have stimulated the fine chemical and pharmaceutical industries to seek more benign alternatives. The best solvent is no solvent at all, but if a solvent is needed, then water is the preferred option. Water is non-toxic, non-flammable, abundantly available and inexpensive. Moreover, owing to its highly polar character, one can expect novel reactivities and selectivities for organometallic catalysis in water. Furthermore, this provides an opportunity to overcome a serious shortcoming of homogeneous catalysis, viz. the cumbersome recovery and recycling of the catalyst. Thus, performing the reaction in an aqueous biphasic system, whereby the catalyst resides in the water phase and the product is dissolved in the organic phase[7], allows for recovery and recycling of the catalyst by simple phase separation. An example of a large-scale application of this concept is the Ruhrchemie/Rhone-Poulene process for the hydroformylation of propylene to *n*-butanol, which employs a water-soluble rhodium (I) complex of trisulphonated triphenylphosphine (tppts) as the catalyst[8]. The palladium (II) complex of sulphonated bathophenanthroliine was used in a highly effective aqueous biphasic aerobic oxidation of primary and secondary alcohols to the corresponding aldehydes and ketones respectively[9] (Scheme 1).

In recent years, other non-classical reaction media have attracted increasing attention from the viewpoint of avoiding environmentally unattractive solvents and/or facilitating catalyst recovery and recycling[10]. For example, supercritical carbon dioxide has been receiving increasing attention as an alternative reaction medium in recent years[11]. Several features of $scCO_2$ make it an attractive



Scheme 1.

solvent in the context of green chemistry and catalysis. For carbon dioxide, the critical pressure and temperature are moderate, 74 bar and 31°C respectively. Hence, the amount of energy required to generate supercritical carbon dioxide is relatively small. In addition, carbon dioxide is non-toxic, chemically inert towards many substances, non-flammable, and simple depressurization results in its removal. It is miscible with say, for example, hydrogen, making it an interesting solvent for hydrogeneration[12] and hydroformylation[13]. Furthermore, the physical properties of CO_2, e.g. polarity, can be tuned by manipulation of temperature and pressure. Although CO_2 is a greenhouse gas, its use involves no net addition to the atmosphere. Its main use is as a replacement of VOCs in extraction processes. For example, it is widely used for the decaffeination of coffee, where it replaces the use of chlorinated hydrocarbons.

Room-temperature ionic liquids exhibit certain properties which make them attractive media for performing green catalytic reactions. Ionic liquids are simple liquids that are composed entirely of ions[14]. They are generally salts of organic cations, e.g. tetraalkyl ammonium, alkylpyridinium, 1.3-dialkylimidazolium and tetraalkylphosphonium. They have essentially no vapour pressure and are thermally robust with liquid boiling point 300°C, compared to 100°C for water. Polarity and hydrophilicity/hydrophobicity can be tuned by a suitable combination of cation and anion; hence the name, 'designer solvent'. Ionic liquids have been extensively studied in the last few years as media for organic synthesis and catalysis in particular[15], e.g. the hydroformylation of higher olefins[16]. The use of ionic liquids as reaction media for biotransformations has several potential benefits compared to conventional organic solvents, e.g. higher operational stabilities and enantioselectivities[17], and activities are generally as high as those observed in organic solvents. They are particularly attractive for performing bioconversion with substrates which are sparingly soluble in conventional organic solvents, e.g. carbohydrates[18] and nucleosides.

Poly(ethyleneglycol) (PEG) and poly(propyleneglycol) (PPG) have attracted interest as novel solvents for catalytic processes. They are both relatively inexpensive and also readily available. They are essentially non-toxic and biodegradable. PPG finds use as a solvent for pharmaceutical and cosmetic preparations, and both PPG and PEG are approved for use in beverages. Also, they are immiscible with water, non-volatile, thermally robust, and can in principle be recycled after removal of the product. Hence, combinations of PEG or PPG with say water or $scCO_2$ are of interest as media for biphasic catalysis.

Recently, the following measures have been taken to develop green solvents:

(i) Substitution of hazardous solvents with those which show better EHS (environmental, health and safety) properties such as increased biodegradability or reduced ozone section[19–21].

(ii) Use of biosolvents, i.e. solvents produced from renewable resources such as ethanol produced by fermentation of sugar-containing feeds, starchy feed materials or lingo cellulosic materials[22].

(iii) Substitution of organic solvents with supercritical fluids that are environmentally harmless[23–26].

(iv) Substitution of organic solvents with ionic liquids, that show low vapour pressure and thus less emission to atmosphere[27,28]. Environmental improvements are achieved with all alternatives in different ways.

The extent up to which a solvent is green can be measured by two methods. The first is the EHS assessment method[29], which is a screening method that aims to identify potential hazards of chemicals. The second method, i.e. the life-cycle assessment method (LCA)[30] can be used for a detailed assessment of emissions to the environment as well as resource use over the full life cycle of a solvent, including the production, use, potential recycling and disposal. For the selection of the environmentally best performing solvent or solvent mixture, the results of the two assessment methods are combined.

It has come to be recognized in recent years, that the science of chemistry is central to addressing the problems faced by the environment. The utilization of various subdisciplines of chemistry and the molecular sciences has increased an appreciation in the emerging area of the *green chemistry* which is needed to design and attain sustainable development. A central driving force for this increasing awareness is that green chemistry accomplishes both economic and environmental goals simultaneously through the use of sound, fundamental scientific principles.

In the glorious days of the 1950s and 1960s, chemists envisioned chemistry as a solution to a host of society's needs. They discovered many things, which improved the quality of life on earth like dyes, plastics, cosmetics and other materials. At the same time, chemistry also brought about medical revolution, i.e. through antibiotics which conquered infectious diseases. All these prove Du Pont's slogan: 'Better things for better living through chemistry'[31]. But there are some adverse outcomes due to the discovery of certain drugs, insecticides, herbicides, fertilizers, etc. leading to air, water, soil and noise pollution on earth. For example, DDT which accumulates in birds and causes thinning of the egg shell and nesting failure results in species decline. Refrigerants like chlorofluorocarbons (CFCs) which deplete the ozone layer that protects our earth from harmful UV rays of the sun. So, there are several advantages and disadvantages of chemistry. The main disadvantage is pollution and this marked the beginning of green chemistry by the middle of the 20th century.

Green chemistry is not different from traditional chemistry in as much as it embraces the same creativity and innovation that has always been central to classical chemistry. However, there lies a difference in that, historically synthetic chemists have not been seen to rank the environment very high in their priorities. But with an increase in environmental consciousness throughout the world, there is a challenge for the chemists to develop new products, processes and services that achieve necessary social, economic and environmental objectives. Since the type of chemicals and the type of transformation vary, so do the green chemistry solutions that have been proposed. Of course, fundamental research will play a central role in achieving these objectives. What we call green chemistry may in fact embody some of the most advanced perspectives and opportunities in chemical sciences.

Areas of green chemistry

Economic considerations and environmental evaluations have pushed the chemical industry to adopt new eco-friendly technologies to survive in a market that becomes more demanding everyday. Green chemistry will be one of the fields in which these sometimes conflicting forces will contend.

The areas for the development of green chemistry have been identified as follows:

- Use of alternative feedstock.
- Use of innocuous reagents.
- Employing natural processes.
- Use of alternative solvents.
- Design of safer chemicals.
- Developing alternative reaction conditions.
- Minimizing energy consumption.

The challenge for chemists is to develop new products, processes, procedures and services that achieve societal, economic and environmental benefits. This requires a new approach which sets out to reduce the materials and energy intensity of chemical processes and products, minimize or eliminate the dispersion of harmful chemicals in the environment, maximizing the use of renewable resources, and extend the durability and recyclability of products – in a way increasing industrial competitiveness. Mature chemical processes that are often based on technology developed in the first half of the 20th century, may no longer be acceptable now. The drive towards clean technology in the chemical industry, with an increasing emphasis on the reduction of waste at source, will require a level of innovation and new technology.

Green chemistry concerns the development of chemical technology and processes that are designed to be incapable of causing pollution (Figure 1). We humans have dealt with toxicity and pollution throughout our entire history, but only recently we have understood its sources and consequences.

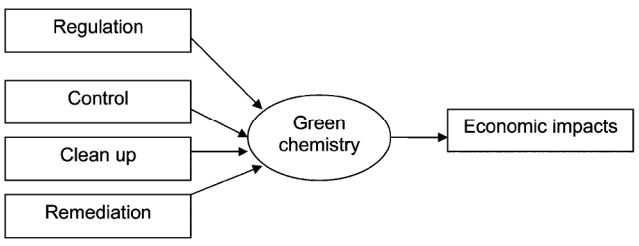


Figure 1. Environmental protection activities that require the intervention of green chemistry to minimize impact.

Principles of green chemistry

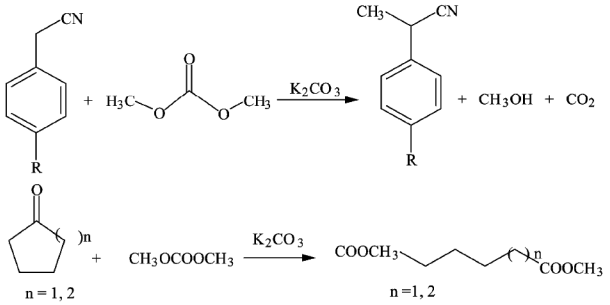
The principles of green chemistry can guide chemists towards fulfilling their unique and vital role in achieving sustainable development. These principles[5] are summarized here.

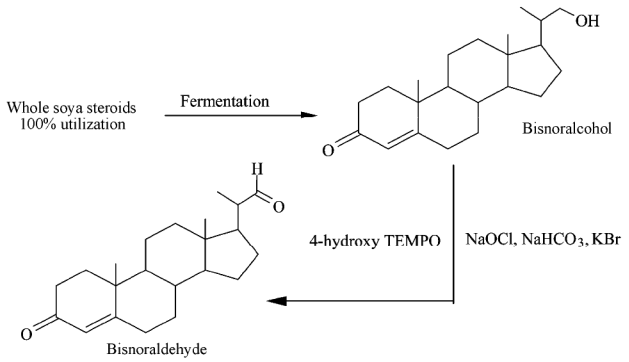
Principle 1

'Prevention: It is better to prevent waste than to treat or clean up waste after it has been created.'

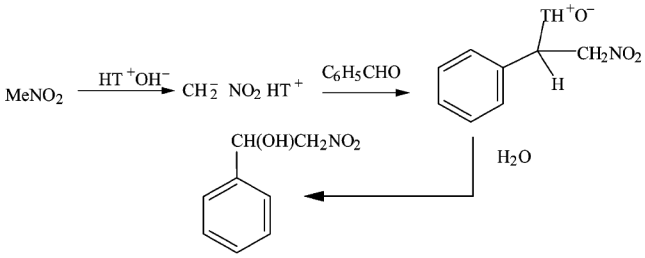
Perhaps this principle is the most intuitively obvious. Waste prevention brings both environmental and economic benefits. By consciously designing a reaction that does not generate waste, the need for separation, treatment and disposal of hazardous substances is eliminated.

Tundo and co-workers[33,34] have demonstrated the applications of dimethylcarbonate (DMC) as an alternative to phosgene in carbonylation reactions and as a substitute to MeCl in methylation reactions. The DMC process generates no organic by-products or salts, and demonstrates excellent selectivity when used with environment-friendly catalysts such as zeolite and K_2CO_3. Whereas the traditional synthesis of DMC also utilized phosgene, there is now an environmentally benign process which involves oxidative carbonylation of methanol[35,36]. Methylation reactions using DMC rather than phosgene also fulfil principles 3 (non-toxic reagents) and 12 (accident prevention).

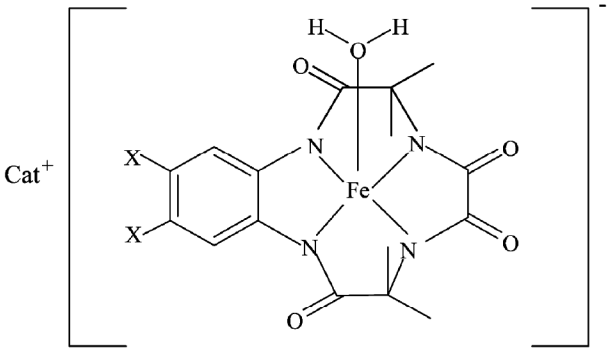




Scheme 2.



Scheme 3.



$Cat^+ = Li^+, [Me_4N]^+, [Et_4N]^+, [PPh_4]^+$

$X = Cl, H, OCH_3$

Figure 2.

$$Na^+Y^-_{aq} + Q^+X^-_{org} \rightleftharpoons Na^+X^-_{aq} + Q^+Y^-_{org}$$

$$Q^+Y^-_{org} + R-X \rightleftharpoons R-Y + Q^+X^-_{org}$$

Scheme 4.

Acid catalysis is a widely used area of catalysis with application in all sectors of chemicals, pharmaceuticals and allied industries[37]. Traditionally, most organic reactions have been catalysed by strong Brønsted acids such as H_2SO_4 and hydrogen fluoride (HF) and soluble Lewis acids such as $AlCl_3$ and BF_3. These acids have many important advantages – they are cheap, readily available and active. Unfortunately, they also suffer from serious disadvantages which lead to large volumes of hazardous waste. So, there is a need to develop reagents which could either replace these acids or minimize their hazardous nature.

In industrial applications, the oxidation of alcohols to carbonyl groups traditionally employs a heavy-metal catalyst, a process that generates a significant amount of hazardous waste. Pharmacia and Upjohn have developed an alternative method that employs bleach (NaOCl) and a catalyst/co-factor system[38]. These reagents are used to convert bisnoralcohol to bisnoraldehyde, producing non-toxic aqueous waste stream and avoids toxic reagents such as organic peroxides (Scheme 2).

The Henry reaction[39] is an important class of C–C bond-forming reactions catalysed by bases. It gives nitroalkanols which are important intermediates for various useful compounds such as aminoalcohols. Difficulties that give rise to waste include dehydration and Cannizaro reaction of aldehyde component. Mg–Al hydrotalcites seem to overcome these problems giving selective and clean reaction under mild conditions, thereby reducing the production of hazardous waste (Scheme 3).

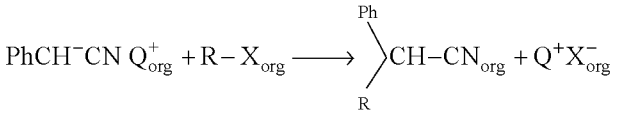
The pulp and paper industry employs chlorine oxidants as bleaching agents. As a result, chlorine-containing organics, a class of compounds with toxicity concerns, are produced as by-products. The development of a new iron catalyst/hydrogen peroxide system (Figure 2) by Collins[40] permits the chlorine-free bleaching of paper in addition to preventing waste. This innovative process generates less toxic substances (principle 3) and uses a safer oxidizing agent (principle 12).

Another methodology that generates less waste is through the use of phase-transfer catalysis (PTC). This is used in various organic synthesis. PTC-catalysed reactions of organic anions are mechanistically more complicated. In these cases, the inorganic phase contains bases such as concentrated aqueous or solid NaOH or KOH or solid K_2CO_3, whereas the organic phase contains the anion precursor, an electrophilic reactant and eventually a solvent[41,42] (Scheme 4).

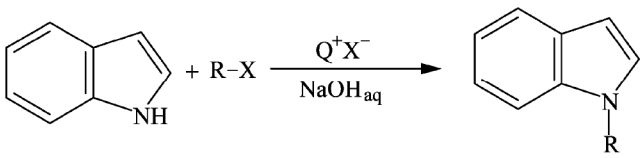
Alkylation of phenylacetonitrile via reaction of its carbanion with alkyl halide examplifies application of this methodology and helps describe how the system operates.

$$PhCH_2CN_{org} + Na^+OH^-_{aq} \rightleftharpoons PhCH^-CNNa^+_{int} + H_2O_{aq}$$

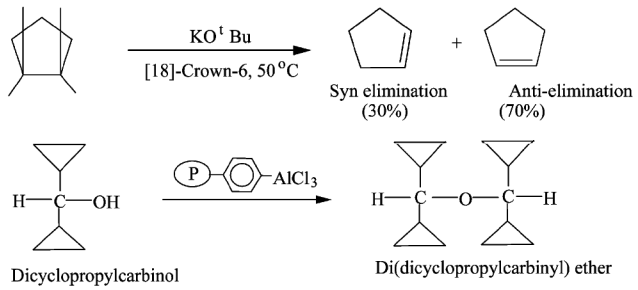
$$PhCH^-CN\ Na^+_{int} + Q^+X^-_{org} \rightleftharpoons PhCH^-CNQ^+_{org} + NA^+X^-_{aq}$$



In a similar way, numerous other CH acids, alcohols and NH acids are efficiently alkylated as exemplified with *N*-alkylation of indole[43]:



The commonly used catalysts for solid–liquid systems are crown ether, polyglycol ether, TBAB and polymer-supported reagents[44,45].



Principle 2

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

Traditionally, chemists have judged the success of a reaction by percentage yield of the product formed. This narrow focus ignores the quantity and nature of by-products generated by the reaction. The concept of atom economy[46] considers the efficiency with which the reagents are incorporated into the final product. It has proven to be a popular tool in the evaluation of the 'greenness' of a chemical process[47]. It is also reveals to compare sectors of chemical manufacturing.

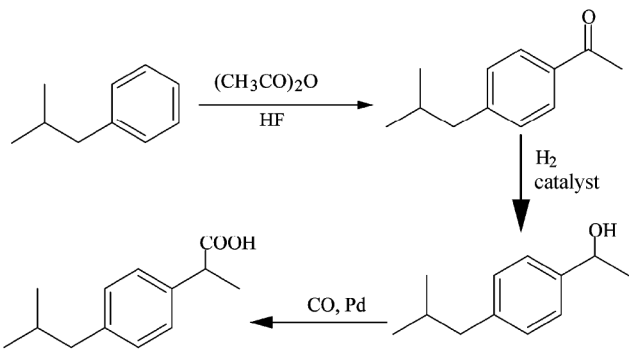
There are many ways to define the efficiency of a chemical reaction, each approximate in its own way. Yield and selectivity are commonly employed; these however, are not especially useful in measuring the amount of waste generated in a process. From an environmental (and interestingly, economic) point of view, it is more important to know how many atoms of the starting material are converted to useful products and how many to waste materials. Attempts at qualifying this have been made by Prost and Sheldon[48]. Prost's atom economy or atom utilization approach is simple, looking at, for example, the percentage of reactant carbon atoms that end up in desired products. One of the benefits of this approach is that it can be done theoretically; before any chemistry is done, chemists can evaluate alternative routes. Of course, yield and selectivity are also important, but if a route giving only a maximum 30% atom utilization is chosen even with a quantitative yield, it will still produce lot of waste.

The various reactions commonly used in the synthesis can have different degrees of impact on human health and environment. Addition reactions, for example, completely incorporate the starting materials into the final product and therefore, do not produce waste that needs to be treated, disposed-off or otherwise dealt with. Substitution reactions, on the other hand, necessarily generate stoichiometric quantities of substances as by-products and wastes.

The application of catalysts is ubiquitous in increasing the atom economy of reactions. More than 90% of all industrial processes are based on catalysis[49]. The widespread utilization of catalytic processes by the industry reflects the economic and environmental benefits achieved through catalysis.

Ibuprofen is one of the most commonly used over-the-counter pain reliever. The traditional synthesis requires six steps that use large volumes of solvent, corrosive reagents and stoichiometric quantities of materials. This protocol also exhibits poor atom economy, only 40% of the atoms in the starting material are incorporated into the final product. In contrast, the BHC synthesis[50] of Ibuprofen is accomplished in only three steps with atom economy reaching 80% (99% recovered with acetic acid) (Scheme 5).

Catalytic amounts of reagents are used, and greater than 99% of the HF catalyst is recycled and reused about three times. Atom economy doubles to 80%, significantly reducing the amount of waste generated. Since there is concern that this improved synthesis of ibuprofen relies



Scheme 5.

on anhydrous HF, it however does serve as both catalyst and solvent and maximizes the reaction efficiency. Other examples are as follows.

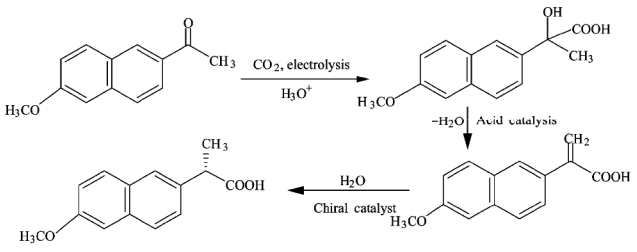
Synthesis of naproxen[51]*:* The anti-inflammatory drug, naproxen, can be synthesized in high yield via a catalytic route (Scheme 6). The final step in the synthetic sequence employs a chiral transition metal catalyst containing BINAP [2,2′-bis(diarylphospheno)-1,1′-binaphthyl] to produce the desired enantiomer in 97% yield. This chiral catalyst is recyclable for at least three consecutive runs without much loss of activity, rendering the process more economical.

The high selectivity of the transition metal catalyst is attributed to steric factors that restrict rotation. Improved selectivity through catalysis minimizes or eliminates the need for production, separation, reducing the use of solvents and separation agents.

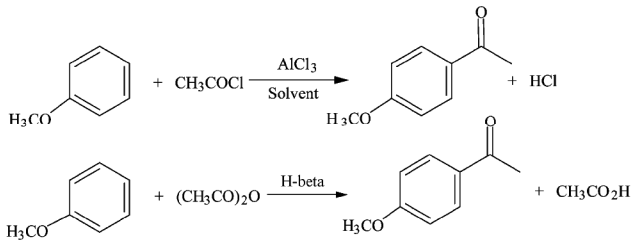
Friedel–Crafts acylation[52]*:* Catalytic methods can provide safer alternatives to reagents, especially heterogenous catalysts, e.g. in Friedel–Crafts acylation, H-beta was used as that heterogeneous catalyst (Scheme 7).

Traditional Friedel–Crafts reaction takes place in the presence of Lewis acids and solvents with the generation of a large volume of effluents. However, the H-beta catalysed reaction does not require any solvent, the catalyst is regenerable, recyclable several times without much loss of activity and only traces of effluents are produced.

Amidocarbonylation[53]*:* Another elegant example of a 100% atom-efficient carbonylation is the one-step conversion of an aldehyde, CO and an amide to an acylamino acid via palladium-catalysed amidocarbonylation (Scheme 8).

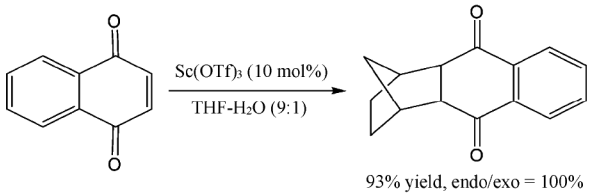


Scheme 6.

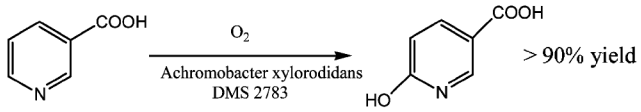


Scheme 7.

Diels–Alder reaction[54]*:* The Diels–Alder reaction in water at room temperature without using any catalyst is one of the greenest reactions. The Diels–Alder reaction also illustrates the concept of atom economy. The Diels product is 100% atom-efficient, i.e. all of the atoms in diene and dienophile are included in the final product. Lanthanides can be used as highly selective catalysts in both Diels–Alder and aza Diels–Alder reactions. Wang *et al.*[55] used scandium triflate catalyst for Diels–Alder reaction.



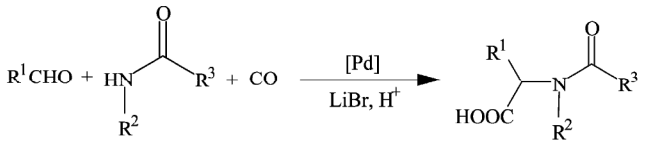
Biocatalysts[55,56]*:* Usually chemical reactions are carried out in rigorous conditions, whereas biocatalysts offer the possibility of carrying the reactions without the formation of toxic and carcinogenic products and also improve the atom economy.



Principle 3

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

As in the selection of a starting material, the selection of a reagent must include an evaluation to identify what the hazards associated with a particular reagent are. This includes analysis of the reagent itself as well as the analysis of synthetic transformations associated with the use of that reagent (i.e. to determine product selectivity,



Scheme 8.

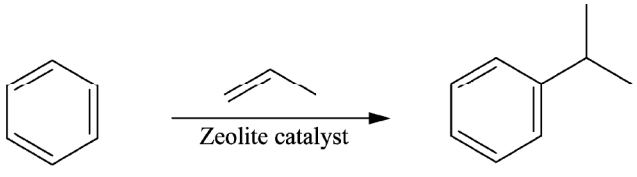
reaction efficiency, separation needs, etc). In addition, a study should be undertaken to determine if more alternative reagents are available that are either themselves more environmentally benign or are able to carry out the necessary synthetic transformation in more environmentally benign way.

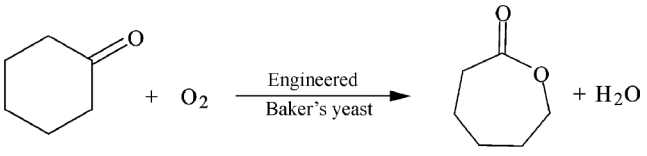
One example of an innocuous reagent (which is produced from non-toxic intermediates) is DMC[57,58]. Any waste generated must also be assessed. Just as all chemical products are not equal in terms of their hazards, neither are chemical waste streams. Waste streams therefore must also be assessed for any hazard properties that they possess. In this regard, it is obvious that oxidation reactions involving oxygen and H_2O_2 will be of outstanding priority, as they produce water as the by-product.

Green oxidation reactions require the use of non-toxic solvents (water or CO_2) and mild reaction conditions. Oxidations using air as a reagent are difficult to control, being either too slow or too fast for industrial applications, and intrinsically non-selective when selectivity is often a crucial parameter. Hydrogen peroxide[59] is a clean reagent; however its use for fine chemical production is currently limited by its poor reactivity and ease to undergo radical decomposition. Therefore, there is effort to develop systems that are able to selectively activate oxygen and hydrogen peroxide for oxidative transformations. In this context, both homogenous and heterogeneous catalysis play a key role.

Risk is a function of both hazard and exposure and therefore, risk can be reduced by minimizing either of these parameters. Since exposure controls can fail, reducing intrinsic toxicity succeeds in eliminating risk by eliminating hazard. Reactions that utilize non-toxic reagents and yield non-toxic products are preferable to those that use or generate hazardous substances, from both environmental and often economic perspectives. Reactions and process design should consider the use of safer alternatives wherever possible. Here are some examples.

Synthesis of cumene[60]*:* Approximately seven million metric tonnes of cumene is produced annually on a global scale. The traditional cumene synthesis employs benzene alkylation with propene over a solid phosphoric acid or aluminium chloride catalyst. Both catalysts are corrosive and are categorized as those producing hazardous wastes. A zeolite catalyst is featured in the Mobil/Badger cumene process.





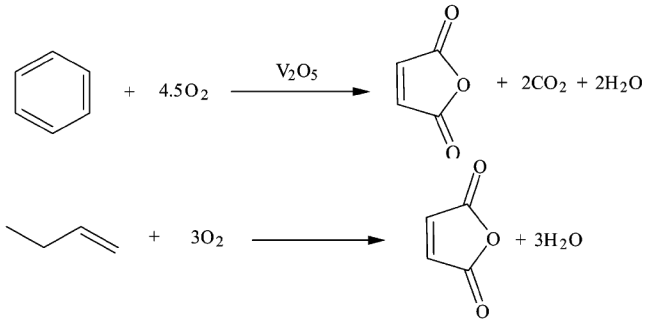
Scheme 9.

The catalyst is environmentally inert and gives high yield of products. The new process generates less waste (principle 1), requires less energy (principle 6), and employs a less corrosive catalyst (principle 12).

Bayer–Villiger reaction: The Bayer–Villiger oxidation is a classical organic reaction for converting a ketone into ester. The most commonly used reagent for this transformation is *m*-chloroperoxy benzoic acid (*m*CPBA), a substance that is shock-sensitive and explosive. Stewart[61] has used genetically engineered Baker's yeast to convert cyclohexanone to lactone (Scheme 9).

In addition to principle 3, the enzymatic Bayer–Villiger reaction satisfies principle 5 (benign solvents) and principle 12 (accident prevention).

Production of maleic anhydride: Another example is the production of maleic anhydride. Maleic anhydride finds widespread use in the manufacture of 1,4-butanediol and butyrolactone.



The process essentially involves passing the feedstock over a promoted vanadium pentoxide at 3–5 bar pressure and 350–450°C temperature. Apart from the toxicity of benzene, it is clear that the aliphatic feedstock provides 'green' routes, whereas the butane route probably comes out on top.

Principle 4

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

An increased understanding of reaction mechanisms and toxicology/functional groups may pose an environmental hazard. This information assists in the design of safer

chemicals, while maintaining the desired purpose of the product. This is true even in cases where the function of the product is toxicity (e.g. pesticides). The design of safer chemicals is a process that utilizes an analysis of the chemical structure to identify what part of the molecule is providing the characteristic property that is desired from the products and what part of a molecule is responsible for toxicity or hazard. By this, it is possible to maintain efficacy of function while minimizing the hazard. This goal of designing safer chemicals can be achieved through several different strategies, the choice of which is largely dependent on the amount of information that exists on the particular substance.

The overall development of green materials or chemicals can be characterized into three parts.

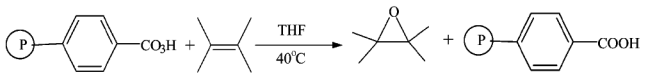
(i) *Green reagents:* The criteria for efficacy, availability and effect of green reagents on the environment are used to carry out the transformation of selected feedstock into the target molecules. Various types of green reagents are used, but those commonly used are DMC and polymer-supported reagents.

Some applications of DMC in organic synthesis are as follows[62,63]:

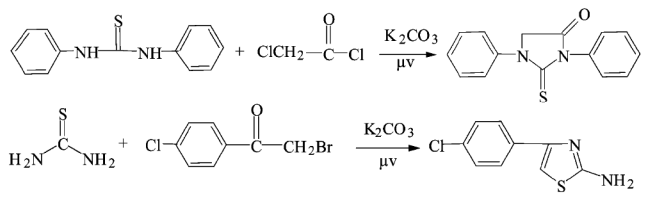
$$R{-}CH_2{-}SO_2R_1 + CH_3OCOOCH_3 \xrightarrow{K_2CO_3} R{-}\underset{\displaystyle CH_3}{\underset{|}{CH}}{-}SO_2R_1 + CH_3OH + CO_2$$

$$ArNH_2 + CH_3OCOOCH_3 \xrightarrow{\text{Zeolite}} ArNHCH_3 + CH_3OH + CO_2.$$

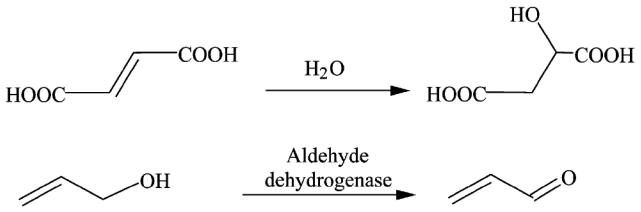
Polymer-supported reagents are those in which ordinary reagents are bound to polymer support, e.g. polymer-supported peracids[63] used for the conversion of alkenes into epoxides.



(ii) *Green catalysts:* Nowadays, traditional catalysts like HF are replaced by green catalysts[64,65]. K_2CO_3 has been used as a green reagent[66,67] for the synthesis of various heterocyclic compounds. The usage of K_2CO_3 eliminates the requirement of solvent and requires only water for work-up. Also, K_2CO_3 serves as a base, eliminating the need for an external base.



(iii) *Biocatalysts:* There are many valuable compounds made in lower volume[68] by biocatalysis. These include lactic acid, maleic acid, *L*-aspartic acid and other amino acids[69], flavours and fragrances[70], steroids, vitamins, human growth harmones and many enzymes[71,72].



Pheromones are not widely used as other insecticides due to the high cost of manufacturing. This economic challenge has been addressed by Knipple, who has explored the enzyme-catalysed synthesis of lepidopteran (moth) pheromone precursor[73]. Pheromones are volatile chemicals released by insects and have been used for pest control.

Principle 5

'The use of auxiliary substances (e.g. solvents, separating agents, etc.) should be made unnecessary wherever possible and innocuous when used.'

Auxiliary substances are used to promote a reaction, but are not incorporated into the final product. As such, they become part of the waste stream and many pose an environmental hazard. The use of solvents in the chemical industry is ubiquitous. With increasing regulatory pressure focusing on solvents, there is a significant attention for compressible fluid, whereas $scCO_2$ has relatively high liquid-like densities and low gas-like viscosities. The solvency of $scCO_2$ is often compared to that of fluorocarbon solvents. Many small molecules are soluble in CO_2 (ref. 74); including high vapour pressure solvents like methanol, acetone and tetrahydrofuran, many vinyl monomers, azo- and peroxy-initiators.

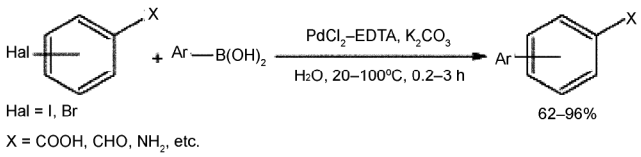
In CO_2, few polymers, typically amorphous fluoropolymers can be synthesized by a homogenous solution polymerization. Many insoluble polymers can be synthesized by a heterogeneous chain-growth process, such as precipitation, emulsion, dispersion or suspension. Due to the solubility of many vinyl monomers and free-radical initiators in CO_2, and the ability to design appropriate CO_2-soluble polymeric surfactants, dispersion polymerization is a common heterogeneous polymerization method. Step growth polymerization can also be conducted in CO_2 with advantages over other processes.

The use of $scCO_2$ as a reaction medium in organic synthesis provides an excellent example of the evolution from fundamental academic research into a commercial process. In collaboration with Thomas Swan and Co Ltd,

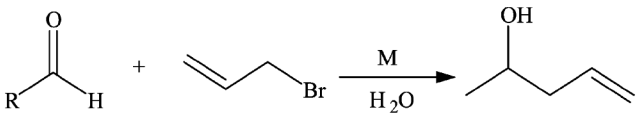
researchers at the University of Nottingham[75] have developed synthetic methodologies in $scCO_2$ that are being employed in new supercritical fluids in such key technologies as hydrogenation, Friedel–Crafts alkylations and acylations, hydroformylations and etherification.

Organic reactions in water have received much attention, because H_2O is a readily available, safe and environmentally benign solvent. The increased focus on water in synthetic organic chemistry during the past few decades has resulted in a large number of reactions that can now be performed successfully in an aqueous medium. The use of water as a solvent has been an active area of research in green chemistry[76]. Some examples pertaining to this principle are given below.

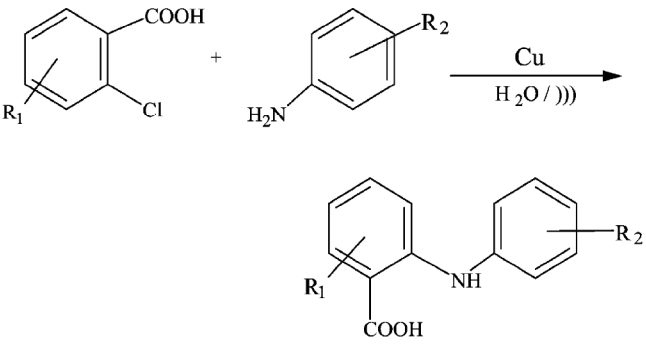
Suzuki reaction[77,78]*:*



Metal-mediated reaction of an aldehyde and allyl halide in H_2O (ref. 79):



Synthesis of N-phenylanthranilic acid derivatives using water as solvent in the presence of ultrasound irradiation[80]*:*



Ionic liquids, a relatively new area of solvents, are attractive because of their negligible vapour pressure and their use in polar systems to generate new chemistries[81–84]. A plethora of ionic liquids can be produced by varying the cations and anions, permitting the synthesis of ionic liquids tailored for specific applications. The potential for the design of next-generation ionic liquids holds significant promise for improved environmental benefits.

Principle 6

'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.'

The design of chemical transformations can reduce the required energy input in terms of mechanical, thermal and other energy inputs and the associated environmental impacts of excessive energy usage. Design for energy minimization is inherently coupled to the design for material efficiency in many aspects. For instance, when utilizing new solvents such as $scCO_2$ (ref. 85), it often affects the ease of separation, which requires significant energy inputs. Therefore, the intrinsic design changes are being appreciated, which are providing extensive benefits for energy minimization through the use of green chemistry methodologies.

Catalysis provides an excellent tool for lowering energy requirements in a particular reaction. Changes in ligand design or metal selection can provide significant improvements in selectivity, energy consumption and solvent utilization.

Parciello *et al.*[86] employed molecular modelling as a tool in designing catalysts with improved selectivity in the hydroformylation of olefins. The rhodium catalysts typically used in the hydroformylation process contain chelating ligands such as biphosphanes and biphosphites. A calixarene biphosphite ligand (Figure 3) was found to give high regioselectivety (99.5%) in the conversion of 1-octene to *n*-nonanal. The green chemistry benefits of this ligand include increased selectivity and decreased energy demands in the form of lower temperature and pressure requirements.

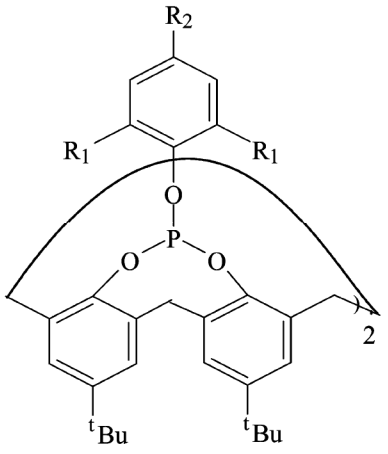
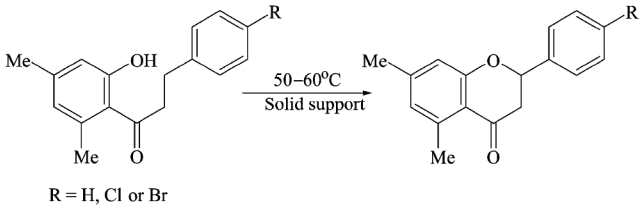
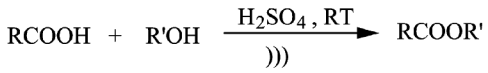


Figure 3. Calixarene biphosphite ligand.

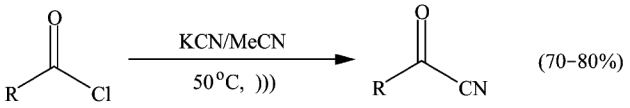
The use of solid supports in various reactions has been widely reported for minimization of energy use, e.g. Michael-type addition[87]:



Use of ultrasound is another tool which minimizes energy, e.g. esterification[88]:



and substitution reaction[89]:



Principle 7

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

In addition to the direct hazard associated with a particular chemical substance, the implications of using a renewable versus a depleting feedstock need to be included in the selection of that substance as a starting material in a synthetic transformation. The utilization of benign, renewable feedstock is a needed component for addressing the global depletion of resources. More than 98% of all organic chemicals are derived from petroleum[90]. Yet, we are rapidly depleting our petroleum reserves and must look for alternative feedstock if we have to develop a sustainable chemical industry. Achieving a sustainable chemical industry dictates switching from depleting finite sources to renewable feedstock. Therefore, the feasibility and benefits of using bio-based instead of petroleum-based feedstock, for example, is actively being researched in both academia and the chemical industry.

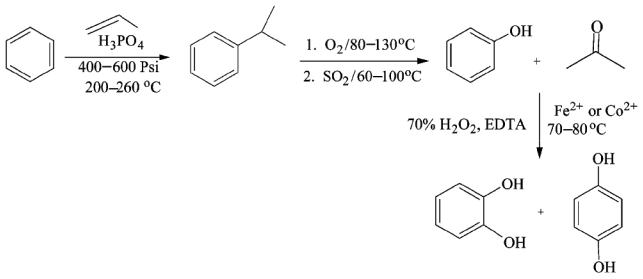
Research in this area has focused on both the macro- and molecular levels. Oleo chemistry is a branch of chemistry that uses vegetable oils and fats as renewable resources. Together with carbohydrates and proteins, fatty oils are important renewable resources compared to fossils and mineral raw materials. The carbohydrate economy provides a rich source of feedstock for synthesizing commodity[91] and specially chemicals. For example, agricultural wastes have been converted into useful chemical intermediates such as levulinic acid[92], alcohols, ketones and carboxylic acids[93]. Shells, crabs, etc. serve as a valuable and plentiful source of chitin, which can be processed into chitosan, a biopolymer with a wide range of potential application that are being currently explored for use in oil-drilling industry[94]. At the molecular level, advances in genetic engineering permit the customization of organisms to catalyse specific transformations that are currently finding applications in numerous chemical processes.

Draths and Frost[95,96] have utilized renewable feedstock in the synthesis of adipic acid (Figure 4) and catechol.

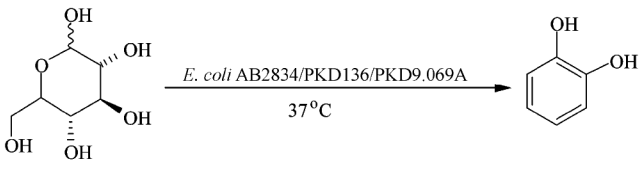
The traditional synthesis of catechol (Scheme 10) begins with benzene, a known carcinogen, which is obtained from petroleum, a non-renewable feedstock. Using genetically-engineered *Escherichia coli*, catechol may be obtained in a single step from *D*-glucose (Scheme 11). The biocatalytic pathway eliminates the use of hazardous substances present in the synthesis of catechol (principle 3) and decreases the energy demands of the reaction (principle 6).

Starch is the second largest biomass and represents one of the most important renewable resources for the future needs of a sustainable society[97]. The potential of such materials has been evaluated through the preparation of solid acids and bases through chemical modification of expanded corn starch (Figures 5 and 6). These solid acids and bases were found to be recyclable for many consecutive runs without much loss of activity rendering the process more economic and fall in the area of green chemistry.

Pd can be covalently anchored with chitosan[98] according to Scheme 12. This Pd(II)-complex catalyses Suzuki and Heck reactions in xylene, K_2CO_3 and stirred at 140°C. Recyclability was studied in heterogeneous catalyst.



Scheme 10.



Scheme 11.

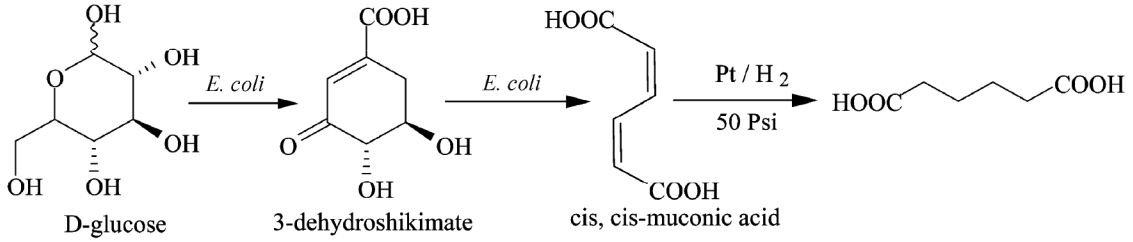


Figure 4. Bio-catalytic synthesis of adipic acid.

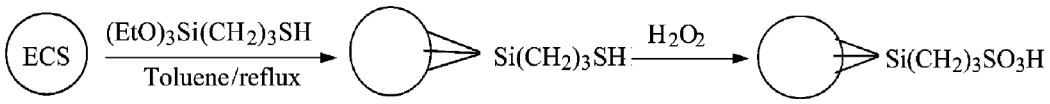
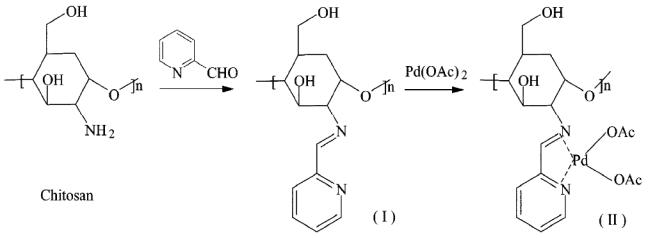


Figure 5. Monitoring the formation of one form of sulphonic acid-modified corn starch.



Scheme 12.

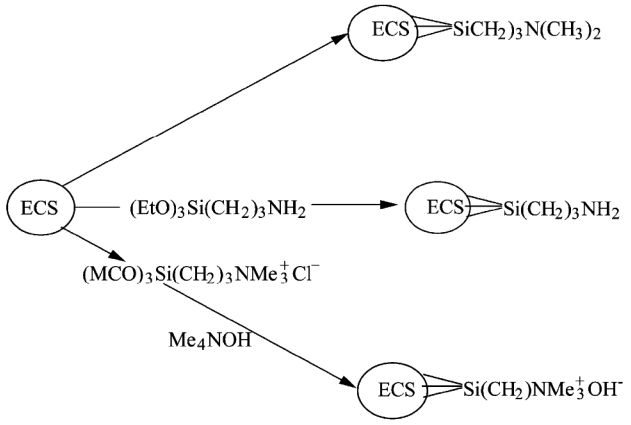


Figure 6. Synthetic routes to solid bases.

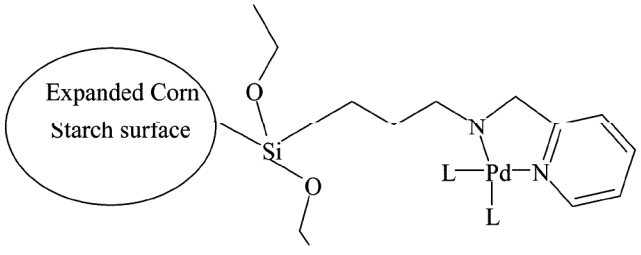


Figure 7. Starcat.

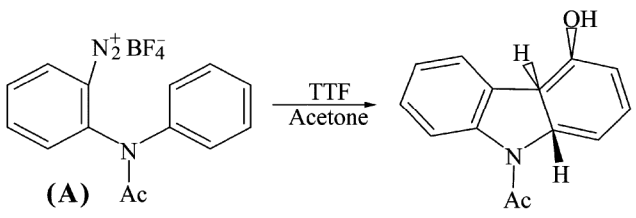
Similarly, starch-supported palladium catalyst[98,99] (starcat) has been found to be highly active in Suzuki, Heck and Sonogashira coupling reactions (Figure 7).

The untrapped sources of renewable feedstock are waste biomass. These waste resources include sewage sludge, municipal solid waste, agricultural residues and manure. Holtzapple has used rumen micro-organisms in an anaerobic fermentor to convert waste biomass into volatile fatty acid salts, which may be concentrated and transformed into chemicals or fuels[100]. Commercial utilization of waste biomass eliminates disposal costs, both economic and environmental, and conserves non-renewable resources, such as petroleum.

Principle 8

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

It is often necessary when executing a multi-step synthesis to protect a sensitive functional group from unwanted reaction or to temporarily convert a compound to its salt for ease of formation. For example, the diazonium salt of (**A**) provides protection from attack on the lower face of the carbon.



Both of these reactions, however, require additional steps with attendant increase in materials, time and energy. Catalytic reactions can often offer enhanced selectivity and minimize the number of modifications required in a reaction sequence.

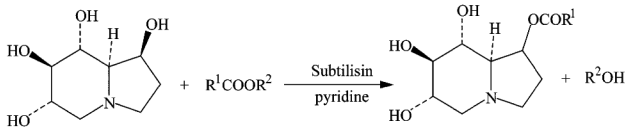
Traditional catalysts may be complemented by enzymes that provide remarkable selectivity in organic synthesis. Analogues of castanospermine, a potential AIDS drug, may be synthesized using the enzyme catalyst subtilisin[101] (Scheme 13). The regioselectivity of the catalyst permits acylation exclusively at the C-1 hydroxyl group, leaving the remaining three secondary hydroxyl groups untouched.

Typically, the synthesis of individual esters of castanospermine requires protection and deprotection of the neighbouring hydroxyl groups. Enzymatic synthesis of castanospermine derivatives permits simple isolation and purification of the product, recovery and re-use of unreacted starting material, and elimination of protection/deprotection steps.

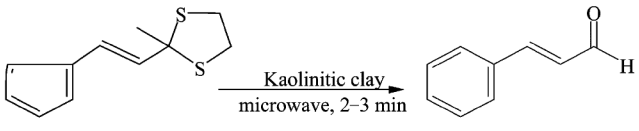
Bandgar *et al.*[102,103] have developed a protocol to deprotect the carbonyl group under microwave irradiation and solvent-free conditions. Conventional cleavage and removal of thioacetals and thioketals frequently employs heavy metals such as mercury(II) chloride and selenium dioxide. Less toxic alternativs to mercury salts are desirable because of the environmental problems associated with the use of mercury. Irradiation of the thioacetals or thioketals with a catalytic amount of kaolinitic clay under microwaves regenerates the carbonyl compound in good yield (Scheme 14).

Altus Biologics[104] has developed cross-linked enzyme catalysts (CLECs) to increase the versatility of enzymes in organic reactions. Unlike free enzymes, CLECs can withstand extremes of temperature and pH, and exposure to both aqueous and organic solvents. The CLEC-mediated synthesis of the antibiotic cephalexin eliminates the need for *N*-protection of *D*-phenylglycine (Scheme 15).

Another example is the preparation of hetero-biaryl compounds[105] via Suzuki–Miyaura coupling reaction of hetero-aryl moieties containing an unprotected $-NH_2$ group and aryl boronic acid. D-T-BPF was found to be an efficient ligand for cross-coupling of NH_2-unprotected hetero-arylchlorides with phenylboronic acid (Scheme 16).



Scheme 13.



Scheme 14.

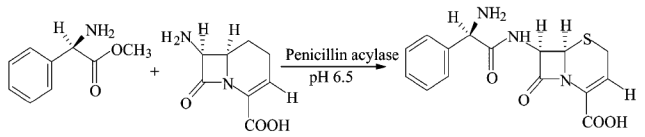
Principle 9

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

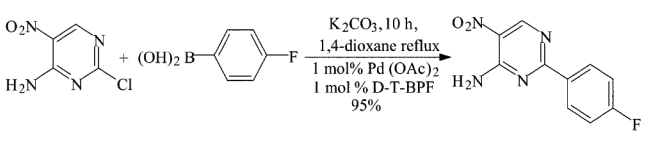
Catalysis offers advantages over stoichiometric reactions in terms of both selectivity and energy minimization. The specificity of a catalyst favours one stereoisomer over another, one regioisomer over another, or monosubstitution over disubstitution. By driving the reaction to a preferred product, the amount of undesired by-product is decreased thereby reducing the waste generated. The amount of energy required for a given transformation is also reduced as the catalyst decreases the activation energy of the reaction.

The primary cause of waste generation is the use of stoichiometric reagents. Fine chemicals manufacture is rampant with antiquated classical 'stoichiometric' technologies; for example, stoichiometric reductions with metals (Na, Mg, Fe, Zn) and metal hydrides ($LiAlH_4$, $NaBH_4$), and oxidations with permanganate or chromium(VI) reagents. Another major cause of waste is the widespread use of minerals (H_2SO_4, H_3PO_4, etc.) and Lewis acids ($AlCl_3$, $ZnCl_2$, etc.), often in stoichiometric amounts, which cannot be easily recovered and recycled. Hence there is marked trend towards their replacement by recyclable solid acids such as zeolites, acidic clays and heteropolyacids.

A pertinent example is the Friedel–Crafts acylation[106], which is widely used in fine chemicals manufacture. In contrast to Friedel–Crafts alkylations, acylations require more than one equivalent of $AlCl_3$ or BF_3 owing to strong complexation of the Lewis acid by the ketone product. Although zeolites have already widely replaced mineral and Lewis acids in Friedel–Crafts alkylations, the more difficult acylations have proven recalcitrant.



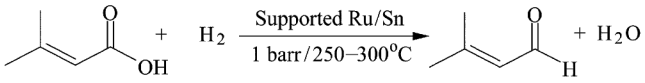
Scheme 15.



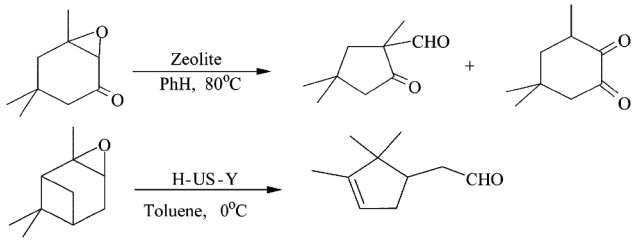
Scheme 16.

Acid-catalysed rearrangement of epoxide to carbonyl compounds is another widely used reaction in fine chemicals manufacture. Lewis acids such as $ZnCl_2$ are generally used, often in stoichiometric amounts, to perform such transformations. Zeolites can be used as recyclable solid acid catalysts for these reactions. Two commercially relevant examples are shown in Scheme 17 (ref. 22).

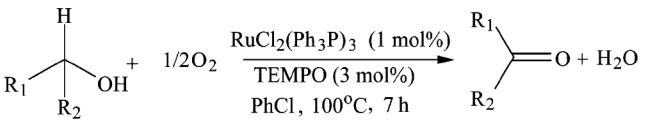
Catalytic reduction: Catalytic hydrogenation is widely used in industrial organic synthesis. A wide variety of functional groups can be effectively hydrogenated, often with high degree of chemo-, regio- and stereoselectivities. Nevertheless, new advances still continue to appear. For example, Rhone Poulenc[107] has succeeded in developing a catalyst for the direct hydrogenation of aromatic and aliphatic carboxylic acids. The reaction is performed in the vapour phase over a supported ruthenium/tin alloy catalyst at 250–300°C and 1 bar H_2 pressure. 1-Dodecanoic acid and trifluoroacetic acid afforded 1-dodecanal and fluoral respectively and an α,β-unsaturated acid underwent chemoselective reduction to the corresponding α,β-unsaturated aldehyde in 91% yield.



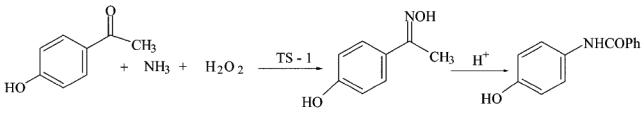
Catalytic oxidation: The selective oxidation of the corresponding carbonyl compounds plays a central role in the organic synthesis. Methods should preferably use a clean oxidant (e.g. O_2 or H_2O_2) and be effective with a broad range of alcohol substrates. Recently, a method has been developed for the aerobic oxidation of alcohols (Scheme 18) using a combination of $RuCl_2(Ph_3P)_3$ and TEMPO(2,2′,6,6′-tetramethylpiperidine-*N*-oxyl) as the catalyst[108]. The method is effective for the conversion of a broad range of primary, secondary and allylic alcohols to the corresponding aldehydes or ketones. Many other examples of selective catalytic aerobic oxidation of alcohols have been reported[109].



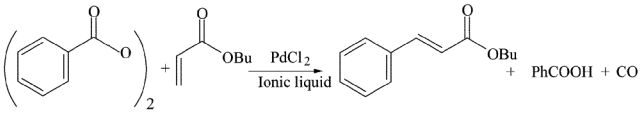
Scheme 17.



Scheme 18.



Scheme 19.



Scheme 20.

Ammoximation proceeds via *in situ* formation of hydroxylamine by titanium-catalysed oxidation of ammonia with hydrogen peroxide in the micropores of the catalyst. Subsequent reaction of hydroxylamine with ketone occurs in the bulk reaction, which means that it is applicable, in principle, to any ketone (or aldehyde). For example, 4-hydroxyacetophenone was converted to the corresponding oxime[110]. Beckmann rearrangement of the latter affords the analgesic, paracetamol (Scheme 19).

Another useful reaction is the palladium-catalysed coupling of aryl halides with alkenes (Heck reaction). It has been found that many palladium complexes dissolved in ionic liquids[111] allow the products and by-products of the Heck reaction to be extracted with either water or alkane solvents (Scheme 20)[112]. This allows the expensive catalyst to be easily recycled as it remains in the ionic phase. This differs from the conventional Heck reaction, in which the catalyst is usually lost at the end of the reaction and noxious dipolar aprotic solvents are used.

Principle 10

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

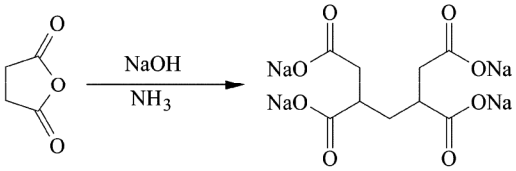
It was often the goal of the chemists to design substances which were robust and could last as long as possible. This philosophy has resulted in a legacy of wastes, persistent toxic and bio-accumulative substances and lingering toxic waste sites. It is now known that it is more desirable to avoid substances that persist indefinitely in the environment or a landfill and to replace them with those that are designed to degrade after their useful life is over. Therefore, the design of safer chemicals cannot be limited to only hazards associated with the manufacture and use of chemicals, but also that of their disposal and ultimate end of life cycle.

Polymeric materials, for instance, should not have any negative effect on the environment during their production or service and at the end of their life. The durability

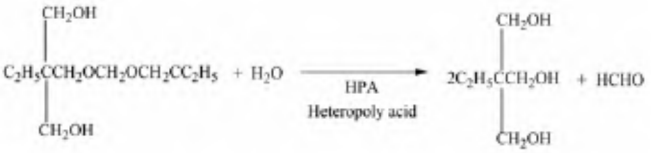
of polymers can present problems for the wildlife and long-term disposal. As a result, focus is on for the design of bio-degradable polymers. Natural polyhydroxy alkanoates (PHAs) are microbial polyesters that are synthesized enzymatically by bacteria. Gross and co-workers[113] have focused their attention on the use of PEG in controlling the molecular weight and therefore the properties of PHAs. In addition to being biodegradable, PHA polyesters may also be synthesized from the renewable resources (principle 7).

Other examples which lead to safe products are as follows.

Synthesis of sodium iminodisuccinate, a biodegradable chelating agent[114]*:*



Hydrolysis of bistrimethylol propane monoformal[115,116]*:*



In some cases, the design of safer chemicals could possibly proceed by removing the toxic functionality which defines the Green Chemistry class. In these cases, such as masking the functional group as a non-toxic derivative form and only releasing the parent functionality when necessary.

Catalysts play a key role in the manufacture of biodegradable polymers. The Donlar corporation[117], for example, employs a catalytic process to polymerize thermal pyroaspartic acids (TPA). TPA is a non-toxic biodegradable polymer and a viable replacement for poly-acrylic acids (PAA).

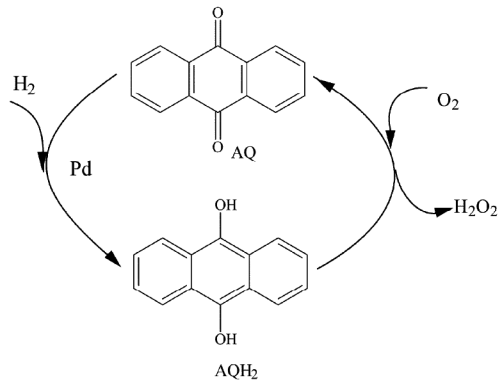


Figure 8. Catalytic production of hydrogen peroxide.

Hydrogen peroxide is widely accepted as a green oxidant because it is relatively non-toxic and breaks down readily in the environment to benign by-products[118]. The schematic representation for the production of hydrogen peroxide is shown in Figure 8.

An unusual application of bio-degradability is in the area of road deicers. Millions of tonnes of NaCl and other inorganic salts is spread on the roadways each winter. These salts enter the surface and groundwater supplies, thus damaging sensitive ecosystems. Salt usage during the winter months also contributes to the corrosion of automobiles and deterioration of roadways. Mathews[119] used biocatalysis to convert whey effluence into the biodegradable road deicers, calcium magnesium acetate and calcium magnesium propionate. Utilization of waste biomass generated by the dairy industry enhances the value of these waste products, eliminates the need for treatment and disposal and provides an economical feedstock for manufacturing alternative road deicers.

Principle 11

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

Analytical chemistry plays a key role in the environmental concerns by detecting, measuring and monitoring environmental contaminants. As we move towards prevention and avoidance technology, analytical methods are being incorporated directly into the process in real-time in an effort to minimize or eliminate the generation of waste before it is formed[120]. Continuous process monitoring assists in optimizing the use of feedstock and reagents while minimizing the formation of hazardous substances and unwanted by-products. In addition, analytical methodologies have themselves historically used and generated hazardous substances and are being redesigned with green chemistry goals using benign mobile and stationary phases and placing greater emphasis on *in situ* analysis.

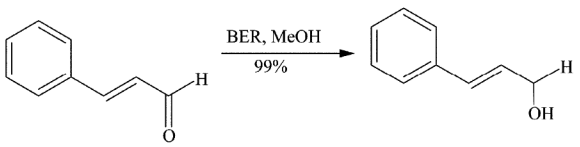
Reaction conditions can be adjusted to control the generation of unwanted by-products. The use of excess reagents can be minimized by monitoring the process of reaction. Subramanian[121] used on-line GC quantitative analysis to monitor alkylation of 1-butene/isobutene. This process replaces the traditional hydrofluoric and sulphuric acid catalysts with solid acid catalysts such as HY zeolite, sulphated zirconia or Neflon.

The current interest in solid-phase organic synthesis has led to a renewed interest in a complimentary technique in which solid-supported reagents (SSRs) are used in solution-phase chemistry. This technique obviates the need for attachment of the substrate to a solid support and enables the chemists to monitor the reaction using familiar analytical techniques. Medicinal chemists are now routinely utilizing solid-phase organic synthesis to pre-

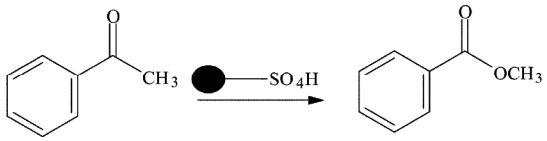
pare libraries of small organic molecules for screening[122]. The advantages of this methodology have been well described: excess reagents can be used to drive reactions to completion; impurities and excess reagents can be removed by simple washing of solid phase and enormous number of compounds can be created using the mix-and-split technique. Synthesis using SSRs[123] is attractive and suitable for parallel synthesis because the reactions are often clean and high-yielding, and the work-up involves simple filtration and evaporation of the solvent. Here are some examples.

Reductions: The selective reduction of functional groups is a common need in organic synthesis. Borohydride exchange resin[124] was introduced and has proved to be of considerable value.

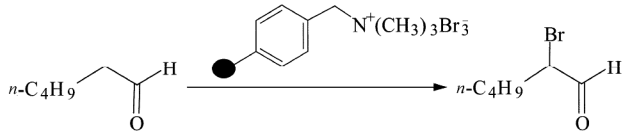
Selective reduction of α,β-unsatured carbonyl compounds[125]:



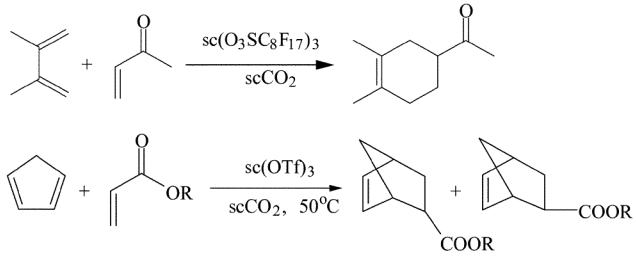
Oxidations using polymer-supported persulphonic acid[126]:



Halogenations: Bromination with amberlyst A-26 perbromide[127]:



Although water works as a Lewis base to coordinate to Lewis acid, coordination occurs under equilibrium conditions and Lewis acid catalysis has been efficiently performed in such media. Similarly, it was expected that the Lewis acid works well in $scCO_2$ to accomplish benign chemical reactions[128]. Coke retention in the pores of the catalyst is also minimized through the use of $scCO_2$ as solvent.



Principle 12

'Substances 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.'

Chemical accidents can have a devastating effect on the local community. Perhaps the most notorious chemical disaster was the accidental release of methyl isocyanate in Bhopal (India), resulting in thousands of deaths. As accidents cannot be completely prevented, it is desirable to use the most benign form of a substance available.

Of special interest has been the use of water (either alone or with co-solvents) as a medium for reactions with organic or organometallic reagents[129–131]. In the organometallic field, particular attention has been paid to the use of allyl and allyl-like tin-halides as well as $BuSnCl_3$ as reactant in water for carbon–carbon[132–135] and C–O–C[136–138] bond-forming reactions under homogeneous or heterogeneous conditions. A versatile procedure based on the mediation of zinc powder[139,140] has been adopted for the preparation of homoallylic alcohols. The various examples are discussed in principles 1–11.

Conclusion

In conclusion, while designing any chemical reaction or process, attention should now be paid to all the 12 principles of green chemistry. One of the main challenges to the chemists is to develop clean and efficient methodologies. Green chemistry helps make our environment neat and clean and opens up a new area of chemistry to make the environment free from pollution.

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