Green Chemistry: Principles and Practice

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Green Chemistry is a relatively new emerging field that strives to work at the molecular level to achieve sustainability. The field has received widespread interest in the past decade due to its ability to harness chemical innovation to meet environmental and economic goals simultaneously. Green Chemistry has a framework of a cohesive set of Twelve Principles, which have been systematically surveyed in this review. This article covers the concepts of design and the scientific philosophy of Green Chemistry with a set of illustrative examples. Future trends in Green Chemistry are discussed with the challenge of using the Principles as a cohesive design system (93 references).
I Introduction

Green Chemistry is defined as the “design of chemical products and processes to reduce or eliminate the use and generation of hazardous substances.”¹ ² This definition and the concept of Green Chemistry were first formulated at the beginning of the 1990s nearly 20 years ago.³ In the years since, there has been international adoption that resulted in the creation of literally hundreds of programs and governmental initiatives on Green Chemistry around the world with initial leading programs located in the U.S., United Kingdom, and Italy.⁴ These have played a significant role in informing sustainable design. Examples include the US Presidential Green Chemistry Challenge Awards established in 1995, 1997,⁷ and the publication of the first volume of the now well-established Green Chemistry journal of the Royal Society of Chemistry.
The most important aspect of Green Chemistry is the concept of design. Design cannot do design by accident. It includes novelty, planning and systematic conception as “design rules” to help chemists achieve the intentional goal of sustainability. Green Chemistry is characterized by careful planning of chemical synthesis and molecular design to reduce adverse consequences—not merely trade-offs.

The Green Chemistry approach strives to achieve sustainability at the molecular level. Because of this goal, it has been applied to all industry sectors. From aerospace, automobile, cosmetic, electrical, pharmaceutical, to agriculture, there are hundreds of examples of successful applications of award-winning, economically competitive technologies.

The concept of Green Chemistry has had this large impact due to the fact that it has touched industry, education, environment, and the general public. The field of Green Chemistry has demonstrated how chemists can design next generation products and processes so that they are profitable while being good for human health and the environment. Following the scientific enthusiasm of Green Chemistry, teaching initiatives, governmental funding, and the establishment of Green Chemistry Research Centers have multiplied in the past two decades. Many universities now offer classes on Green Chemistry and Green Engineering. Some institutions offer degrees in the field.

II Framework of Green Chemistry

The three main points about the Green Chemistry framework can be summarized as:

1. Green Chemistry designs across all stages of the chemical life-cycle.
2. Green Chemistry seeks to design the inherent nature of the chemical products and processes to reduce their intrinsic hazard.
3. Green Chemistry works as a cohesive system of principles or design criteria.

The Twelve Principles of Green Chemistry are design criteria or guidelines that provide the framework for sustainable design. They constitute an overarching construct for the design of safer chemicals and chemical transformations. Chemistry has long been perceived as a dangerous science and often the public associates the word “chemical” with “toxic.” There are ways to reduce risk by using safety precautions such as protective gear. When safety protections fail, the risk, which is defined as a function of the hazard and exposure, increases (Fig. 1). If the hazard is high and exposure controls fail, the consequences can be catastrophic (injury or death). By minimizing the hazard portion of the equation instead of focusing only on exposure controls, the risk can be limited even in cases of undesirable circumstances (accident, spills, sabotage, etc…). Designing safer sustainable chemicals and processes requires striving to reduce the intrinsic hazards to a minimum and therefore limiting the risk.

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\text{Risk} = f(\text{hazard} \times \text{exposure})
\]
The aim of Green Chemistry, to reduce hazards across all the life-cycle stages, has been shown to be economically profitable. Hazard is defined as the ability to cause adverse consequence to humans or the environment. Intrinsic hazard of a substance or a chemical process can be designed to be minimized at every level of a process, whether it is toxicity, physical hazards (e.g., explosion, flammability) or global hazards such as stratospheric ozone depletion. Risks based on these hazards may arise from the nature of the feedstock and raw materials that are used in the chemical transformation as well as the final products that are made. Careful design will reduce or eliminate intrinsic hazards within chemicals and processes. A design based on the integration of the Twelve Principles as one cohesive set.

III The Twelve Principles

The Twelve Principles of Green Chemistry were introduced in 1998 by Paul Anastas and John Warner. They provide a framework for the design of new chemical products and processes, applying to all aspects of the process life-cycle from the raw materials used to the efficiency and safety of the transformation, the toxicity and biodegradability of products and reagents used. They were summarized recently into the more convenient and memorable acronym, PRODUCTIVELY, intended to provide a general knowledge about Green Chemistry. For the convenience of the reader, technical examples are cited for each principle.
Fig. 2 The Twelve Principles of Green Chemistry.

1. Prevention. It is better to prevent waste than clean up waste after it is formed.

2. Atom Economy. Synthetic methods should be designed to maximize the incorporation of all materials into the final product.

3. Less Hazardous Chemical Synthesis. To the extent practicable, synthetic methodologies should be designed to use and generate substances that pose little or no risk to human health and the environment.

4. Designing Safer Chemicals. Chemical products should be designed to preserve efficacy of the function while reducing toxicity.

5. Safer Solvents and Auxiliaries. The use of toxic solvents (e.g., solvents, separation agents, etc.) should be made unnecessary whenever possible and, if used, innocuous.

6. Design for Energy Efficiency. Energy requirements of chemical processes should be recognized and minimized. Shall be conducted at ambient temperature and pressure.

7. Use of Renewable Feedstocks. A raw material should be renewable rather than depleting.

8. Reduce Derivatives. Unnecessary derivatization (i.e., blocking groups, protection/deprotection, modification of physical/chemical processes) should be minimized or avoided if possible, because additional reagents and can generate waste.

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

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

11. Real-Time Analysis for Pollution Prevention. Such methodologies need to be further developed to allow for real-time, in-process monitoring and control to prevent or significantly reduce the formation of hazardous substances.

12. Inherently Safer Chemistry for Accident Prevention. Substances and the forms of substances used in a process should be chosen to minimize the potential for chemical accidents, including releases, explosions, or fires.
Waste prevention is the first of the Twelve Principles of Green Chemistry. It is better to prevent the formation of waste rather than to clean it up after the fact. The generation of any material that does not have realized value or the loss of unutilized energy can be considered a waste. As mentioned above, waste can take many forms and may impact the environment differently depending on its nature, its toxicity, its quantity, or the way it is released.\(^{12}\) When large portions of the initial raw materials used in a process are lost because of the original design of the process itself then it will inexorably generate waste which is by definition undesirable.

In 1992, the concept of what is now widely accepted as the E-Factor, or Environmental Impact Factor, was introduced by Roger Sheldon.\(^{13}\) This metric helps to quantify the amount of waste generated per kilogram of product. It is a means to assess the “environmental acceptability” of a manufacturing process.

The environmental factor which has been adopted by many in the chemical industry underscores how inefficient certain industrial processes have been and opened the door to creative solutions. One well-known example is the early synthesis of oxide which was prepared through a chlorohydrin intermediate (Fig. 3a). The E-Factor for the entire synthesis as stated above was equal to 5. For each kilogram of product, 5 Kg of waste were to be disposed. This does not take into consideration the waste contaminated by chlorine by-products.\(^{12–14}\) When the synthesis was modified to use molecular oxygen, thus removing the need for chlorine, the E-Factor dropped to 0.3 Kg of waste. The new process was generating more than 16 times less waste than the original one, eliminating the formation of waste water as well.\(^{15}\)
When byproducts cannot be avoided, other innovative solutions should be considered and a productive one is to seek an industrial ecology approach where 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.

2 Atom economy

In 1990 Barry Trost introduced the concept of synthetic efficiency: Atom Economy. Atom Economy is 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 Atom Economy is measured as the ratio of the molecular weight of the desired product over the molecular weights of all reactants used in the reaction. This allows one to quickly assess how efficient a reaction will be.
To illustrate this concept, a few examples such as the Grignard reaction, A3 coupling and the Diels–Alder reaction are presented below. The Grignard reaction, which received the recognition of the scientific community for its importance in organic synthesis, is unfortunately a relatively poor atom-economical reaction due to the use of a stoichiometric amount of metal reactant and the necessity to prepare the Grignard reagent separately.\footnote{Fig. 4 presents a typical Grignard reaction Grignard reagent to build a propargylic amine type structure.} The values of the AE respectively are 44 and 56% which reflect a loss of half of the raw material. A solution in respect to the last example was proposed by C.-J. Li (Alkyne, Aldehyde and Amine).\footnote{This one-step multicomponent coupling reaction of the original atoms used are found in the final product. The Diels–Alder reaction is an excellent example of an atom-economical reaction\footnote{Fig. 4} (Fig. 4). Its AE is equal to 100% since all atoms from the reactants are incorporated into the final product.}
Diels–Alder type reactions belong to the category of cycloaddition which is among the greenest types of reactions in traditional chemistry.

3 Synthesis

As illustrated in Fig. 5, the synthetic toolbox of organic chemists has been improved by a significant amount of innovative work in the past decade. Many of the new reactions that have been developed add to the already existing reactions discovered during the past century. Reactions based on cycloaddition, rearrangement reactions were already known and constitute one category of efficient reactions. Cascade or tandem reactions, metathesis, and enzymatic reactions are rather new approaches and illustrate cleaner, more efficient synthetic tools available to organic chemists. The Grubbs catalyst, for example, allows similar to Wittig-type reactions such as the Horner–Wadsworth–Emmons reaction (formation of a four membered ring as reaction intermediate, Fig. 5). It is an essential tool for the construction of larger molecules. The metathesis reaction does not produce a large amount of waste. The formation of phosphonium reaction is unfortunately unavoidable since it is part of the design of the reaction.
C–H activation is another relatively new area of chemistry which holds great promise for the future. Traditional coupling reactions, activated carbon–halogen bonds are usually used because of their high reactivity. Since halogenated molecules are rarely natural, it implies additional steps to produce the precursor. The replacement of traditional coupling reactions with C–H activation eliminates the need for halogenated precursors and therefore the halogenated waste byproduct generated.

Two famous examples of C–H activation were published in 1993 by Murai and in 2007 by Fagnou.
employed a ruthenium catalyst to couple the inactivated substrates acetophenone and aromatic compounds selectively without the need for any activating or directing group. This represents a milestone in the field of C–H activation in advancing Green Chemistry.

4 Molecular design

While there has been significant focus on designing chemicals for various functions ranging from medicines to materials, there has been a surprising lack of interest in taking into consideration hazard in the design process. Understanding the properties of a molecule that have an impact on the environment and the transformations that take place in the biosphere is essential to sustainability. Through a mastery of this understanding, chemistry will be able to genuinely design molecules that are safer for humans and the environment. Work by Ariëns in 1984 and by Garrett and Devito in 1996 showed that designing safer chemicals is not only highly needed for the advancement of Green Chemistry, but is also possible.

In recent decades, there has been a significant amount of work in the field of toxicology that has moved it from being a descriptive science to one that has a large mechanistic component, and even more recently progressively towards the incorporation of an *in-silico* component. Because of that transition, it has been possible to create correlations, equations, and models that relate structure, properties, and function. These approaches provide the basis for the work being pursued in the development of a comprehensive design strategy. For instance, the existing understanding of medicinal chemistry can already help establish some ground rules for designing less toxic chemicals via incorporation of specific design features that block their access into humans and many animal organisms.

5 Solvents

Solvents are perhaps the most active area of Green Chemistry research. They represent an important challenge for Green Chemistry because they often account for the vast majority of mass wasted in syntheses and processes. Conventional solvents are toxic, flammable, and/or corrosive. Their volatility and solubility have contributed to air 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 started a search for safer solutions. Solventless systems, recently ionic liquids are some examples of those new “green” answers.

Where possible, the ideal situation would be to not use any solvent because the decision to include an auxiliary always implies efforts and energy to remove it from a designated system. Efforts have therefore been devoted to developing solventless systems. This idea was reinforced by the finding that solvents account for most of the industrial waste.

properties of the reagents used or the desired outcome of the transformation, the approach often requires a new or redesigned chemistry to allow the reaction to proceed without the original solvent.
Water is the most abundant molecule on the planet and is sometimes referred to as a benign "universal solvent" for large scale process chemistry. The properties of water have even led to increased reaction rates through the hydrophobic effect and easier separation since a lot of organic substances do not dissolve in water. A reaction in water is one of the useful examples illustrating the advantages of water as a solvent for large scale process chemistry. The risk of water contamination that can be very energy intensive to clean is yet to be addressed.

SCF are another alternative to traditional organic solvents and have been extensively studied in the past decades. Common SCF are generated from water, carbon dioxide, methane, methanol, ethanol, and others which have been simultaneously heated and compressed above their critical point. The resulting scCO\textsubscript{2} has proven to be a versatile solvent, safe, and easy to handle as demonstrated by the work of Poliakoff, Leitner, Jessop, DeSimone, and others. What makes SCF so attractive in general and particularly scCO\textsubscript{2} is the change of state that occurs when cooling down the vessel or reducing the pressure. Above critical points, CO\textsubscript{2} will be a gas in which reactions can be performed and below, it will be a gas. Degassing the system allows the complete removal of the CO\textsubscript{2} gas. scCO\textsubscript{2} has found a wide range of industrial applications with the most famous being the decaffeination of green coffee beans and the replacement of perchloroethylene in dry cleaning. Supercritical fluids have proven to be one valuable alternative to traditional solvents.

Another example of greener solvents would be ionic liquids pioneered in modern times by Seddon. ionic liquids, or sometimes called room temperature ionic liquids, are liquid salts at room temperature. They have virtually no vapor pressure and very low flammability. What was discovered recently by Jessop et al. is 

![Image of pressure-temperature phase diagram showing supercritical region.](image-url)
solvent” generated *in situ* just like the liquid scCO$_2$. Addition of pressurized carbon dioxide into an ionic liquid, generating a safer solvent *in situ*. Releasing the pressure reverses the phenomenon and the ionic liquid is retransformed into the original mixture, thus removing completely the solvent and steps.

Another example based on the same concept is the development of fluorous biphasic catalysis advanced by Horvath. Phase or solvent containing a catalyst suited for the desired transformation is usually not miscible with organic reagents at ambient temperature. When heated, they form a single media, allowing the reaction to proceed. Fluous solvent separate, simplifying the purification process. This is an attractive approach with the restriction that fluorous solvents are expensive.

These last examples are good illustrations of one of chemistry’s major challenges: separation. Apart from certain solventless systems, the new improved green solvents remain auxiliaries and therefore must be isolated from the desired product. If their use cannot be avoided then the issue of separation must be taken into consideration when choosing the appropriate solvents.

### 6 Energy

Rising concerns over the depletion of petroleum feedstocks and the increase in energy consumption have pushed the development of more energy efficient processes and for the search for renewable energies; non-depleting resources in a time frame relevant to human scale.$^{49}$

As mentioned in the first section (first principle), unutilized energy may also be reactions or systems that do not require intensive energy use is highly desirable. Reducing the energy barrier of a chemical reaction or choosing appropriate reactants so that the transformation may proceed at room temperature is one example of what chemists can do to reduce energetic requirements, with all the direct and indirect benefits associated with it.

Increasing the energy efficiency of a chemical system is merely one part of the solution. Alternative energies are also needed. Several of those renewable energies have been identified in biofuels production,$^{49,50}$ wind power, hydro power, geothermal energy,$^{49}$ and hydrogen fuel cells.$^{49,54}$ Once again, green chemists have an important role to play in this new challenge as they have the ability to design both energy efficient transformations and materials or chemical systems that can be used to harvest some of those renewable natural energies.

Solar energy, the primary sustainable energy source on earth, is one of those alternatives to petroleum. Considerable efforts have been dedicated to understand and design chemical systems that can convert solar radiations into voltaic energy. Inorganic and hybrid solar cells have received interest although more focus has been higher efficiency. The principle of those cells relies on the ability of the material used to absorb photonic energy from solar radiations. The absorption leads to the formation of excited states that can be relayed and generate electronic current. Building materials and polymers that can efficiently transform light into current remain a challenge and are key to the success of this approach.

Proton Exchange Membrane (PEM) fuel cells using hydrogen and oxygen gases c
upcoming increase in energy demand (Fig. 7). PEM fuel cells have generated research interest, especially in the past decade with the development of increasingly efficient catalysts such as nanoparticles or even hydrogenase enzymes. Consideration in this approach is the hazard of handling hydrogen gas, which is highly flammable and explosive.

Fig. 7 General concept of a hydrogen fuel cell.

### 7 Renewable materials

It has been estimated that the vast majority of our manufacturing products are derived from petroleum feedstock or natural gas. The depletion of those resources will touch many aspects of our consumer life and our economy. Turning towards renewable feedstocks both for material and fuel has now become more urgent. The material available from living organisms is bio-mass, the material available from living organisms. Examples of renewable material include cellulose, lignin, suberin and other wood compounds, chitin, starch, glycerol and oil. Lignin, for instance, is a major waste of the pulp and paper industry. In recent years it has found new applications as dispersants, additives, and raw materials for the production of chemicals such as vanilin, DMSO, and can be transformed into chitosan by deacetylation. Numerous applications of chitosan have been described from purification, biomedical applications and other industrial uses. Reusing this waste of the bio-industries should provide a large amount of raw materials to replace the current petroleum feedstocks.

### 8 Derivatives

Covalent derivatization is a ubiquitous technique in chemistry whether it is employed for organic synthesis or analytical chemistry. In the early 1990s, an innovative concept surfaced called non-covalent derivatization, which relies on intermolecular interactions rather than on covalent bonding. The work by Warner was developed as a means to use little energy and less material to achieve chemical modifications from the original system. An early example of non-covalent derivatization illustrated by the controlled diffusion and solubility of hydroquinones used in Polaroid films.
release hydroquinones at elevated pH. Instead of relying on base-labile covalent protecting group approach, they developed a non-covalent protecting group in the form of a co-crystal with bis-((N,N-dialkyl)terephthalamides (Fig. 8). This approach was successful and viable for the industrial process. It solved the problem without modification of the original hydroquinone structures and minimized waste material.

**Fig. 8** Hydroquinones protected by non-covalent interactions with bis-((N,N-dialkyl)terephthalamides.

### 9 Catalysis

In many cases, the formation of waste is linked to the traditional use of a stoichiometric amount of reagents. The transition from stoichiometric methodologies to catalytic processes is perceived as one major way to improve the efficiency of the synthetic toolbox. Catalysis can improve the efficiency of a reaction by lowering the energy input required, by avoiding the use of a stoichiometric amount of reagents, and by greater product selectivity. This implies less energy, less feedstock and less waste. Moreover, it often opens the door to innovative chemical reactions and bring unconventional solutions to traditional chemical challenges.

Oxidation and reduction reactions illustrate this concept. Reduction employing DIBAL-H as the established procedure used by organic chemists. It generates a significant amount of waste since a stoichiometric amount of reducing agent is needed to complete the reaction. Switching to catalytic hydrogenation decreases the need for stoichiometric reagents and in consequence decreases the amount of waste generated (Fig. 9).
Beyond efficiency, catalysis can allow for otherwise unfavorable reactions to be realized. This was the case for the reaction and the development of the Grubbs catalyst.\textsuperscript{27} As illustrated in Fig. 5, the development of a groundbreaking approach to the formation of unsaturated compounds. The environmental benefit was significant and the innovation was important.

Biocatalysis is yet another example of “green” chemistry as it is a biomimetic approach relying on natural or modified enzymes.\textsuperscript{28–29,71} It usually refers both to the direct use of purified enzymes and the transformations accomplished by engineered living organisms. Reaction conditions are relatively mild as the transformation can be performed in mild and ambient temperature. Moreover, enzymes have proven to be more chemo-, regio- and stereoselective.

\section*{10 Biodegradation}

The problem of persistence has been known for a long time and became apparent in the early stages of industrial development. In the 1950s for instance, tetrapropylene alkylbenzene sulfonate (TPPS) was used as an detergent and accumulated into the water supply due to an incomplete degradation. The situation was so critical that there were examples where “water tended to foam when coming out of the tap.”\textsuperscript{73,74} The public outcry prompted the industry to seek an immediate solution and it was found that replacing the methyl branched chain of TPPS by a linear carbon chain reduces the biopersistence. A common example is the replacement of TPPS by linear alkylbenzene sulfonate (LAS).
Designing biodegradable materials and chemicals is not a simple task as illustrated by continuing problems of environmental pollution. Trends have emerged following decades of data collection. Certain chemical structures such as halogenated moieties, branched chains, quaternary carbons, tertiary amines, and certain heterocycles may possess enhanced persistence and are avoided. On the other hand, integrating functional groups such as esters or amides which are recognized by ubiquitous enzymes may help the design of environmental degradable products.\textsuperscript{73,75} This strategy was applied to surface-active compounds used as household fabric softeners.\textsuperscript{76} Until the 1990s, long chain ammonium salts dimethyl ammonium chloride (DHTDMAC) were released into the environment. It was then discovered that their rate of biodegradation in aqueous sediment was low and the intrinsic ecotoxicity, high. In response, hydrolyzable amide or ammonium salts were introduced. The new ammonium salts have proven to be more biodegradable as illustrated by di(ethyl-ester) dimethyl ammonium chloride (DEEDMAC) which was followed by di(ethyl-ester)dimethyl ammonium chloride (DEEDMAC) - Biodegradation.

\textbf{11 Analysis}

It is the goal of green analytical chemistry to measure chemicals without generating waste. Problems associated with analytical chemistry are usually linked to the analytical approach itself. Real-time monitoring is defined as the ability to monitor a transformation and act immediately upon it to prevent unwanted outcomes. It is not always possible, and therefore waste may be generated when the sample is analyzed. Green chemists must take into consideration the functional requirements of analytical methods since it will be counterproductive if the chosen methods contribute to further environmental problems. Green analytical chemistry can be defined as the use of analytical procedures that generate less waste and are safer to human health and the environment.\textsuperscript{79} This definition includes both aspects of "live" monitoring of a chemical transformation and the environmental shortcomings associated with traditional analysis.
reaction has significant advantages in terms of Green Chemistry. When action can be taken quickly, it may prevent accidents, save energy, and/or prevent the formation of significant amounts of by-products that would otherwise require additional treatment.

When it comes to the analytical methods themselves, most of them share two problems linked to the two major steps of a method: a pretreatment of the sample which includes extraction, separation or even sometimes chemical modification of the sample, and a signal acquisition step. Since the pretreatment step usually calls for the use of analytical chemists concerns. If the use of solvents can not be avoided for an extraction, Accelerated Solvent Extraction (ASE) or SCF extraction should be considered.

Material used in the manufacture of analytical apparatus should be taken into consideration. Both green chemists and green engineers building new sensors should be aware of the toxicity and any potential environmental problems related to the material they handle. Mercury electrodes, for example, are often used for electrochemistry. Replacing them with carbon-based materials such as nanotubes or nanofibers has proven to be an effective solution.

12 Accident prevention

Dangerous substances and processes have multiplied in our working environment. According to the “Chemical accident prevention and the clean air act amendments of 1990,” preventing accidents starts by identifying hazards whether it is toxicity, physical hazards such as explosivity or flammability, and global hazards should be addressed in the design of chemicals and processes in order to prevent accidents such as Bhopal or Love Canal.

A recent and shocking illustration of these dangers and hazards can be found in the UCLA accident that occurred in January 2009. Handling of the very common and highly flammable butyllithium reagent resulted unfortunately in a terrible outcome with the death of the research assistant involved. This accident should be a strong reminder to the scientific community that many chemicals we still use present serious hazards and should be replaced by safer alternatives.

IV Accomplishments by industry

There are numerous examples of successful industrial changes using Green Chemistry. Instead of presenting an exhaustive list of the awards winners but rather introduce a few key examples to show how the industry has been adapting to the new challenges of Green Chemistry.

As a first example, a greener synthetic pathway which was attributed to Eastman for its enzymatic esterifications. The biocatalytic process runs under mild conditions, minimizes the formation of byproducts, and saves energy, resulting in increased efficiency. Overall hundreds of litres of organic solvents were eliminated from the previous process.

In 2008, researchers at Dow AgroSciences were rewarded for the design of green pesticides with structure–activity relationships of natural biopesticides in an effort to predict analogues that would be more active, they designed Spinetoram. The company expects that the production of this new pesticide will el organophosphate insecticides during its first five years of use.”
In 2006, Merck developed a greener synthetic pathway for Sitagliptin, a chiral amino acid derivative used for the treatment of type 2 diabetes. The approach was based on a novel asymmetric catalytic hydrogenation to eliminate the need of excessive derivatization (Fig. 11). Merck presented a three-step synthesis, claiming an increase in the overall yield. Implementing the new route on a manufacturing scale showed a significant reduction in process costs, making it a more cost-effective option.

In 2004, BMS developed a new approach to Paclitaxel, the active ingredient in the anticancer drug, which is commercially produced from the naturally occurring precursor 10-deacetylbaccatin III. The "semisynthetic route", which was first developed as an economically viable approach to the molecule, was not without certain environmental concerns. A more sustainable process was therefore investigated by BMS using the latest biotechnological advances. Instead of synthesizing Paclitaxel from a precursor, the active compound was extracted directly from a plant cell culture. This method eliminated all organic solvents, hazardous reagents, and additional steps associated with the previous process. BMS is now manufacturing Paclitaxel using only plant cell cultures.

In 2002, Pfizer developed a new greener synthetic pathway for the redesigned synthesis of an antidepressant drug (Fig. 12). The new process offered substantial environmental benefits while improving the overall efficiency and selectivity of the synthesis. Specifically, a three-step sequence in the original manufacturing process was streamlined to a single step. Raw material use was significantly cut and the process was optimized so that all steps could be performed in a single solvent. The last change eliminated the need to use, distill, and recover four toxic solvents (methylene chloride, toluene, hexane, and benzene).
One final noteworthy example is the work accomplished in 1998 by Solutia, Inc. on the elimination of chlorine from the synthesis of 4-aminodiphenylamine ([Fig. 13](#)). Researchers at the company explored new routes to a variety of aminodiphenylamine (4-ADPA), in order to eliminate the formation of aqueous waste streams containing high levels of salts. There were also concerns about the hazard associated with storage and handling of large quantities of chlorine gas. The solution came with a new synthesis to 4-ADPA that utilizes the base-promoted, direct coupling of environmental benefits were significant and included a dramatic reduction in waste.

**V Future challenges**

The accomplishments in the field of Green Chemistry thus far are impressive due to the scientists in academia, industry, and research institutes around the world. However, the accomplishments achieved thus far are a prelude to the grand challenges still to
be addressed by the field. A few notable challenges are mentioned below.

**Twelve Principles as a cohesive system**

The design framework of the Twelve Principles of Green Chemistry has been a template for many advances in the field, however, the Twelve Principles were not meant to be twelve independent goals but rather an integrated cohesive system of design. Only through the applications of all principles can one hope to achieve a truly sustainable process. By seeking out the mutually reinforcing aspects of the principles, systemic sustainable design is possible and can facilitate transformative innovation rather than incremental improvement.

**Multi-functional catalysts**

Catalysis has made significant progress during the past two decades. However, even today, most transformation only and little is known about multi-functional catalysts, defined as the ability of one catalyst to perform a series of transformations. If the same catalyst could be used for various independent reactions or achieve an entire synthesis in one pot, it will bring chemistry to a new level as more complex molecules could be made with higher material and energy efficiency.

**Mastering weak forces for synthesis and properties**

Non-covalent and weak-force interactions are likely to play an increasingly important role in the future of chemistry. Imparting properties through weak-forces and guiding synthetic pathways in the same manner while minimizing the amount of bond breaking and bond forming can result in significant advantages. These include reducing the amount of waste, and an increase in efficiencies. Mastering the weak forces in the way that the field of chemistry has mastered covalent forces holds great potential to help in reaching sustainability at the molecular level.

**Integrative systems thinking**

The traditional approach to scientific investigation has been largely based on the reductionist approach. This approach has brought about a depth of understanding and discovery that have made the things of modern life—from communication to transportation to medicine—possible. It has also resulted in tremendous unintended and unforeseen consequences that have had a damaging impact on humans and the environment. By thinking in terms of systems, Green Chemistry can pursue significant innovations while avoiding unintended results. Coupling reductive and integrated thinking can result in truly transformative innovations.

**Conclusion**

For generations, molecular scientists have invented the molecules, materials, and processes that have allowed economic and societal development. Green Chemistry is ensuring that all of that creative ability that is the long tradition of the field of chemistry is practised in a way that builds in impact on people and the planet as a whole.
has shown that through innovation companies can be economically more profitable and more environmental benign at the same time. Although an impressive amount of work has been done by practitioners of Green Chemistry around the world, the achievements of the past pale by comparison to the power and potential of the field.

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Green chemistry: principles and practice, freud.

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