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ORIGINAL ARTICLE

Green chemistry: the emergence of a transformative framework

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Since the Twelve Principles of Green Chemistry were formulated in the 1990s, there have been tremendous successes in developing new products and processes to be more compatible with human health, the environment, and sustainability goals. This review gives a sampling of research successes from the last 20 years, including advances in synthetic efficiency, application of alternative synthetic methods, use of less hazardous solvents and reagents, and development of renewable resources for chemical feedstocks. The future of green chemistry will depend on innovations that consolidate and integrate these achievements that have been made, using all Twelve Principles as a framework for intentional design. Designing for sustainability and reduced hazard should not be viewed as constraining, but rather as providing the freedom to explore and invent, bridging continents and scientific disciplines to create new solutions.

Keywords: Sustainable design, Twelve Principles, synthetic efficiency, catalysis, alternative synthetic methods, alternative solvents, renewable feedstocks

Introduction

The achievements of green chemistry in the years since it emerged as a cohesive field in the early 1990s have been remarkable. It is important to recognize the scientific breakthroughs that have been made through excellent research as well as through the other elements of education, industrial engagement, and outreach that are required to provide the broader structure needed to drive the field. It is also necessary, however, to use this understanding of how far green chemistry has come as a field to analyze where the greatest opportunities and challenges for the future lie, and what essential steps need to be taken to advance the field so that it can reach its power and potential of advancing sustainability through fundamental chemistry.

When looking at the historical roots of green chemistry, it is important to recognize the foundational building blocks that are central to the field. Chemistry has made tremendous advances over the past century and a half or more in facilitating the skills of synthesis and analysis to the point that we can make virtually any molecule that can be drawn and obtain a characterization of molecules, materials, and complex molecular systems. As these skills emerged, selectivity was emphasized to make our construction of com-

pounds more efficient, and properties such as rudimentary biodegradability were addressed in making new products. These and other chemistry skills directly relevant to green chemistry goals were important advances.

Green chemistry emerged from this disparate collection of skills and sought to provide a structured design framework that could exploit the abilities of chemists and molecular designers to consciously and intentionally address the issues of the fundamental impact of chemicals on human health, the environment, and sustainability. The work of the green chemistry community, globally, has resulted in significant progress in illustrating that this approach, this design framework, can be a reality in practice and not merely a design theory.

With the introduction of the Twelve Principles of Green Chemistry, guidelines were provided for chemists to develop clean, environmentally benign methodologies that are sustainable for the long term (1). This overview highlights some advances made in major green chemistry research areas:

- Increased use of addition reactions and rearrangements, and decreased reliance on elimination and substitution reactions. Research aimed at improving the selectivity of this chemistry is crucial, and often depends on advances in catalysis.

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- Alternative driving forces for reaction, such as microwave irradiation, sonochemistry, and photochemical reactions.
- Reduction of, or, ideally, elimination of solvents. Use of alternative, environmentally benign solvents.
- Avoiding toxic materials and designing for reduced environmental exposure.
- Switching from petroleum-based feedstocks to renewable resource-based feedstocks.

This paper does not aim to be a comprehensive review, but rather seeks to provide a useful sampling of the past successes associated with green chemistry research since the early 1990s as a foundation to consider the future potential of the field as it continues to emerge.

Important advances for green chemistry

Assessing synthetic efficiency

Chemists have long admired elegance in synthetic pathways, but streamlining synthesis by reducing the number of steps and avoiding inherently wasteful chemical transformations has taken on a greater sense of urgency. Efficient synthetic pathways are at the heart of many green chemistry principles: reducing the use of non-renewable materials, eliminating waste, and reducing emissions. There are clear benefits for safety and sustainability. The concept of “atom economy” encourages chemists to seek out synthetic methods that incorporate all the atoms of a reactant into the product molecule (2) (Figure 1). A similar philosophy is described by “step economy,” achieving the complexity of the target molecule in the fewest possible steps, using carefully selected reactions (3). Explicit assessments of complexity can be devised, allowing for strategic design of molecules requiring multiple carbon–carbon bond-forming steps (4).

Efficiency may also be measured in terms of an “E-factor,” or how much waste is generated per kg of product (5). Reaction mass efficiency (RME) takes into account a calculation of atom economy as well as the stoichiometry and yield of each step (6). These metrics have been successfully applied in industry to devise greener processes, for example in pharmaceutical production (7). Atom economy and RME calculations typically do not account for use of hazardous reagents, or solvents, which may constitute the primary source of waste in a synthesis. In developing more sophisticated green chemistry me-

trics, there are challenges in defining safety and waste in terms of scope and environmental impact. Life-cycle assessment (LCA) aspires to provide a more comprehensive analysis of environmental impact, taking into account not only the product but also cradle-to-grave aspects such as the raw materials needed and ultimate fate upon disposal. The scope of LCA may include potential for global warming, eutrophication, energy consumption, and human and ecological toxicity (8).

Catalysis

The 2005 Nobel Prize in Chemistry awarded to Chauvin, Grubbs, and Schrock for their olefin metathesis catalysts specifically highlighted the potential of their research to provide access to “greener” synthetic routes (9). The recognition of their work is just one indicator of the paramount role catalysis has played in expanding the range of reactions available to green chemists.

Olefin metathesis is an example of a very atom-economical reaction, with potential to eliminate the waste associated with alternate multi-step synthetic routes. A versatile method for forming carbon–carbon bonds in both organic and aqueous media, it has many applications in polymer chemistry (living polymerization, preparation of block copolymers, and synthesis of liquid crystal materials). It has been used to construct ring systems for total synthesis of natural products, and can cyclize or crosslink polypeptides (10). Olefin metathesis has also been useful in deriving useful materials from renewable resources. Unsaturated fatty acid esters and various natural oils and fats can be used to produce valuable chemical feedstocks and macrocyclic frameworks for natural product synthesis (11). Further “greening” of homogeneous olefin metathesis has been achieved by developing catalysts that can be easily separated from the products, which is particularly important in applications such as pharmaceutical synthesis (12). Homogeneous transition metal catalysts have also proven to be extremely useful in other carbon–carbon bond-forming reactions. Cycloaddition and cycloisomerization can produce a variety of organic molecule structural skeletons, often replacing sequential, stoichiometric reduction and oxidation steps with one-step, highly atom-economical reactions (13).

Hydrogenation using H₂ gas is another major atom-economical reaction of high utility in designing green synthetic pathways. There is a need for new synthetic methods based on H₂, in order to phase out hazardous and wasteful hydride and borane reagents. Progress has been made in asymmetric hydrogenation. For example, highly enantioselective, high-yielding

$$\text{Atom economy} = \left(\frac{\text{m.w. of desired product}}{\text{m.w. of all reactants}} \right) \times 100\%$$

Figure 1. A calculation of atom economy.

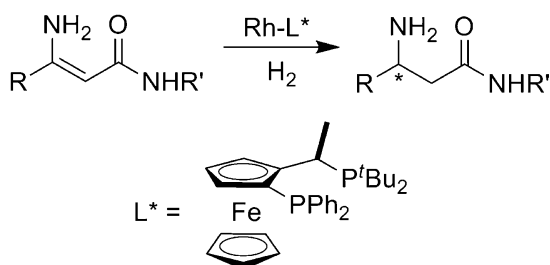


Figure 2. Asymmetric hydrogenation of enamines without an N-acyl protecting group (14).

reactions have been developed for preparation of β -amino acids from unprotected enamines, using metal catalysts with ferrocenophosphine ligands (14) (Figure 2). The chemistry has been applied to streamline synthesis of the pharmaceutical sitagliptin from eight to three steps, and it is expected that the method will be useful in preparing other pharmaceutical targets as well (15). A “toolbox” of chiral ligands for asymmetric hydrogenation has been developed by researchers at Penn State University. A wide variety of olefins, ketones, and imines can be converted into chiral building blocks including amino acids, amines, alcohols, aminoalcohols, esters, and carboxylic acids (16). This technology is being used in commercial synthesis of the pharmaceutical atorvastatin (17).

Enantioselective C–C bond formation promoted by H_2 has emerged as a green chemistry method for avoiding organometallic reagents, and Professor Michael J. Krische was awarded the 2007 Presidential Green Chemistry Challenge Academic Award for developing the chemistry (18). In conventional synthetic routes, it is not unusual to rely on a sequence of three stoichiometric organometallic reagents (some having pyrophoric properties) to achieve a single transformation, but Krische’s catalytic method eliminates stoichiometric byproducts, incorporating all the atoms of the reactants into the final product (19) (Figure 3).

The opportunity for catalysis to increase the safety of industrial processes, provide alternatives to toxic reagents, and avoid the generation of persistent pollutants is highlighted by iron-based “Fe-TAML” catalysts. Fe-TAML catalysts activate environmentally benign oxidizing agents including H_2O_2 and O_2 , providing an alternative to polluting chlorine- and

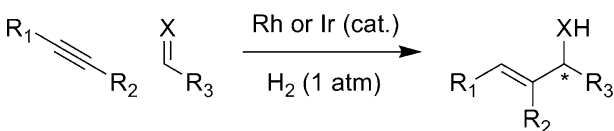


Figure 3. Enantioselective, hydrogen-mediated C–C bond formation, avoiding the use of preformed organometallic stoichiometric reagents ($X=O, NR$) (19).

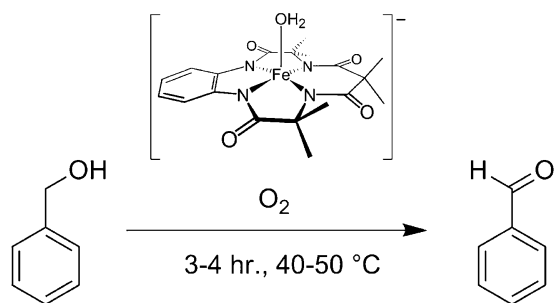


Figure 4. Dioxygen activated by a Fe-TAML catalyst (21).

metal-based oxidants (20,21) (Figure 4). Fe-TAML-activated oxidants can be used instead of dangerous ClO_2 gas in applications such as bleaching of kraft paper pulp (22), and deactivation of biological warfare agents (23).

A growing field of research in green chemistry is the development of recyclable catalysts, including heterogeneous catalysts on inorganic or polymer supports, catalysts for biphasic reactions, and catalysts that can be recovered by adjusting pH or temperature (24). In addition to using smaller amounts of metals, a chemical synthesis based on a recyclable catalyst prevents waste that would be generated by quenching conventional catalysts or separating them from the product at the end of the reaction. Heterogeneous catalysts based on porous solids are an example of the green chemistry benefits that can be realized from this strategy. They have been applied to promote solvent-free reactions, can replace corrosive reagents and aggressive oxidants, and activate molecular oxygen at low temperature. They have also been designed for shape-, regio-, and enantioselectivity (25,26). There are many opportunities for improving conventional industrial processes. For example, nanoporous aluminophosphate catalysts with a distribution of acidic and redox-active sites have been used to develop a new route to the Nylon-6,6 precursor ϵ -caprolactam. The one-step, solvent-free reaction eliminates hazardous reagents and reduces generation of waste byproducts (27) (Figure 5). Mesoporous solids have also been used to design recyclable catalysts with Bronsted- and Lewis-acidity. These have shown promise in eliminating hazardous waste associated with conventional acid catalysts such as $AlCl_3$. Applications include production of alkylbenzenes and alkylphenols, and oligomerization of alkenes to produce low-molecular weight thermoplastics (28). Oxidation catalysts based on mesoporous solids can use the environmentally friendly oxidant O_2 under mild conditions (29). In general, inorganic solid supports are not associated with safety or toxicity concerns, but in some cases the entire life-cycle of the support material should be

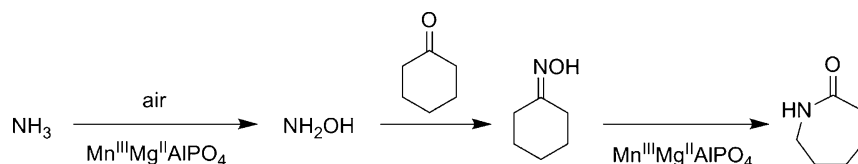


Figure 5. One-step, solvent-free synthesis of ϵ -caprolactam from NH_3 , air, and cyclohexanone, using a bifunctional nanoporous solid catalyst (27).

considered: for example, TiO_2 production via intermediate TiCl_4 is known to generate chlorinated dioxins and furans (30). Immobilization of catalysts on polymer supports also improves catalyst recyclability and performance. Progress has been made in using polymer supports based on natural resources; for example, chemically modified chitosan films have been used to support catalysts for Suzuki and Heck reactions (31), and materials made from corn starch show promise in heterogeneous base catalysis (32).

Photocatalysis, the conversion of light energy into chemical energy, has proven to be extremely important in oxidation chemistry. TiO_2 is a well known photocatalyst for decomposition of water pollutants by UV light (33). Sensitization of TiO_2 to visible light presents opportunities for a wider range of industrially useful photocatalysis, such as hydroxylation of C–H bonds and oxidation of water to evolve O_2 or provide a source of oxygen atoms in alkene epoxidation (34).

While new synthetic catalysts are often of biomimetic design, another green chemistry strategy is to use enzymes to achieve transformations that are reagent- or synthetic-step intensive. An increasing amount of information about enzyme function is available to chemists; for example, an online database maintained by the University of Cologne compiles data on 3500 enzymes, including reaction types, products, and substrates (35). Challenges for successful biocatalytic systems include achieving high activity toward xenobiotic substrates and avoiding inhibition by substrate or products (36). Nevertheless, numerous biotransformations have been reported for production of organic chemicals (37). One-pot “cascade” reactions have been developed, based purely on enzymatic processes, or with enzymatic and

chemical reactions working in concert. As many as 12 distinct enzymatic transformations have been carried out in sequence without recovery of intermediates (Figure 6). Typically, low-value carbohydrates are converted into chiral building blocks with very high enantioselectivity (38).

A promising field of research aims to modify enzyme active sites to increase biocatalyst “promiscuity”: enzymes may be induced to accept a wider variety of substrates, to catalyze different reactions depending on the substrate introduced, or to produce different products from a single substrate. Potentially high regio- and stereospecificity are a driving force for applying these engineered enzymes in asymmetric synthesis. Further development of non-natural activity should make biocatalysts more broadly useful (39). Directed evolution, or optimization of enzymes by mutation and screening, emerged in the 1990s as a powerful technique to produce broadly useful biocatalysts (40). Recently, performance of a halohydrin dehydrogenase enzyme was increased $\sim 4,000$ -fold by introduction of 35 mutations; the new enzyme is used to produce a precursor of the pharmaceutical atorvastatin (41). The enzymatic process reduces waste, phases out dangerous reagents, uses less solvent, and eliminates purification steps known to interfere with product yield (42). Catalysis by enzymes also provides routes to both natural and non-natural polymers, in many cases with precise control of structure (43). An enzymatic polymerization process has been used to produce macromolecules with superior antioxidant properties, having potential applications in a variety of industries. Production of the antioxidants is environmentally benign and requires only one step (17).

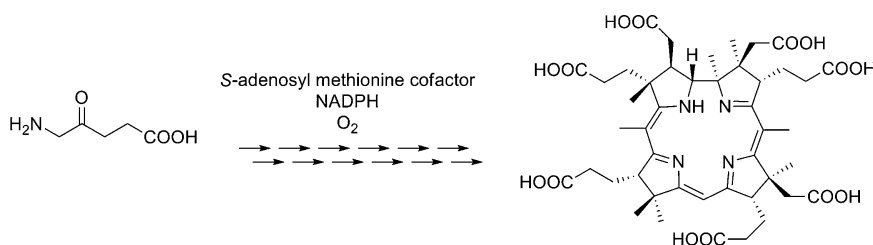


Figure 6. One-pot, 12-enzyme synthesis of a vitamin B_{12} precursor from δ -aminolevulinic acid (44).

Aldol reactions, another class of carbon–carbon bond-forming techniques, conventionally require a tradeoff between inefficiency and selectivity. New biomimetic catalytic methods are improving the environmental profile of aldol chemistry. Proline, for example, can be used to give excellent regio- and stereoselectivity in many cases (45). Aldol reactions are common in nature; engineered aldolase enzymes can convert a variety of substrates to chiral products with excellent selectivity (46).

Alternative synthetic methods

Cascade reactions can lead to reductions in the amounts of solvents, reagents, and unwanted byproducts. In the absence of biocatalysts, they typically proceed by cationic, anionic, radical, or pericyclic mechanisms. Intramolecular radical cascades are useful in streamlining synthesis of polycyclic natural products. With careful planning, cyclizations, 1,2-group migrations, hydrogen shifts, fragmentations, and substitutions can be “programmed” in a useful order (47) (Figure 7).

Since the late 1980s, microwave-assisted organic synthesis has developed rapidly; specialized commercial equipment is now available for measuring and controlling power input, temperature, and pressure, allowing for improved reproducibility. Often the major benefit of microwave energy is reaction acceleration due to increased temperature, but microwave techniques can also facilitate green chemistry methods such as solvent-free reactions, use of high-temperature water as a reaction medium, and use of recyclable solid-supported materials. Microwave heating potentially allows shorter residence time at high temperatures and more rapid cooling, enabling preservation of thermally unstable reaction products. Rapid heating of organic material under closed conditions is a well-known safety hazard, but with properly designed reactors the ability to rapidly remove the source of heat is an advantage over conventional heating systems (49,50). There is no

evidence that shortened reaction times and higher yields are related to anything but thermal effects, but the enhancements may be difficult to achieve by classical techniques. Energy savings compared to conventional heating depends on efficiency in converting electric energy to microwave energy, as well as the characteristics of the reactor, the amount of reaction mixture, and the capability of the reaction components to absorb microwave energy. The use of microwave heating on an industrial scale is relatively unexplored (51).

Sonochemistry, the use of ultrasonic waves to promote chemical reactions, is similar to microwave-assisted synthesis in that rate and yield enhancements are usually the primary benefits. In many cases, the chemical pathway is not affected; the benefits can be explained by mechanical effects analogous to high-speed stirring. However, unlike microwaves, ultrasound can indirectly induce homolytic cleavage of chemical bonds. Transition metal complexes may be activated, and “sonochemical switching” can occur: the reaction mechanism changes depending on the application of ultrasound. Green chemistry benefits have been demonstrated, including use of milder reaction conditions, less aggressive reagents, and access to selectivity that conventionally requires material-intensive routes (52).

Photochemistry provides methods for achieving chemical transformations without added reagents. Photon absorption can occur independently of temperature and solvent, providing flexibility in environmentally friendly synthetic design (53). Solvent-free “solid-to-solid” photochemical reactions have been developed as a technique for synthesizing molecules with adjacent quaternary stereogenic centers (54) (Figure 8).

Microreactors (in which reaction components are manipulated in channels as small as 10 μm in diameter) can result in reduced reaction time and increased yields, because of improved mixing. Some autocatalytic, UV-light-intensive, or highly exothermic (“run-away”) reactions are more safely performed in

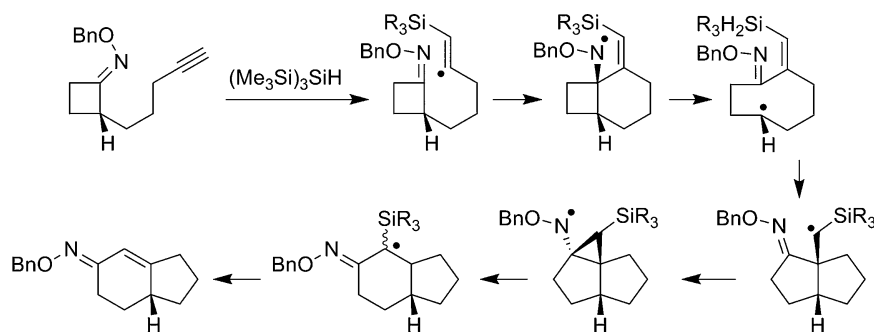


Figure 7. One-pot cascade of radical cyclization and fragmentation reactions, giving 70% product yield (48).

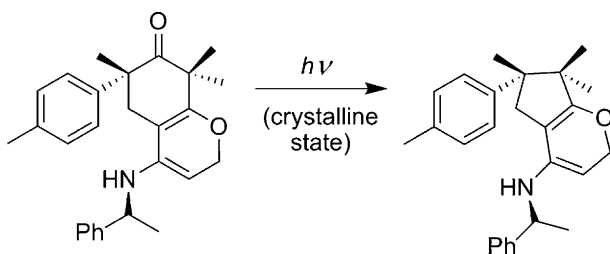


Figure 8. Stereospecific, solid-state photodecarbonylation of an intermediate in the synthesis of (–)-(α)-cuparenone (54).

microreactors, with high attenuation of increases in temperature. Precise control of temperature resulting from the high surface area-to-volume ratio can eliminate unwanted side reactions in temperature-sensitive pathways. In some cases this can improve regioselectivity, for example the ratio of E/Z isomers in a Wittig reaction. There are relatively few examples of enantioselective reactions performed in microreactors, but in those cases the enantiomeric excess matches or exceeds that of conventional reactors. Rapid heat transfer can reduce solvent requirements, allowing reactions under more concentrated (or even solvent-free) conditions. Intermediates may be generated *in situ* and then used in subsequent reactions, providing a way to minimize risks associated with toxic reagents. Microreactors can be placed in series, and progress has been made toward multistep microreactions; a 5-step synthesis of ciprofloxacin has been reported that eliminated chromatographic purification, relying on only minimal workup steps. While potentially capital-intensive, scale-up of reactions is said to be safer with microreactors because only the number of reactors increases, not the size of each reactor (so-called “numbering up”). Real-time, in-reactor monitoring to precisely control reaction conditions is an additional advantage of microreactor technology, another way to avoid waste and formation of hazardous materials (55,56).

Alternative solvents

Solvents can account for 85% of mass in pharmaceutical synthesis, and coupled with low recovery rates, can be a major source of waste regardless of the atom economy of the reaction. Toxicity, flammability, corrosivity, and volatility are human safety and environmental concerns. These problems typically arise due to difficulties in containment, recovery, and reuse (57).

When possible, “the best solvent is no solvent” (57). Many examples of solventless reactions have been reported, often in conjunction with new synthetic techniques such as microwave-assisted or microreactor chemistry, as discussed previously. Advan-

tages include increased reactivity and access to mechanisms dependent on weak interactions that would ordinarily be disrupted by solvent. Use of solid supports (such as clays, zeolites, and silica) is common, and the support material may behave as a Lewis acidic or basic catalyst. Specific interactions between the reagents and the support material can influence selectivity. As these reactions are activated by heating, they often benefit from microwave exposure. In reactions activated by anions, phase transfer catalysts are extremely useful (58). A selection of solvent-free reactions reported in recent years:

- Claisen–Schmidt condensation was achieved using a solid base (59).
- Fatty acid esters for use in cosmetic applications were prepared by solid acid-catalyzed reaction of alcohols and carboxylic acids or alkylation of carboxylates with alkyl bromides using a phase-transfer catalyst (60).
- Aldol condensations have been achieved by grinding the solid reagents with NaOH, resulting in better selectivity than when solvent was present (61).
- Supramolecular ligand–metal complexes having two- or three-dimensional topography (including double helical structures) were formed much more rapidly under solventless conditions (62).

Another innovation in solid-state chemistry is “non-covalent derivatization,” the use of hydrogen bonding, π -stacking, lipophilic–lipophilic interactions, and electrostatic interactions to manipulate the physical properties of a molecule. By identifying auxiliary reagents having specific intermolecular interactions with the target compound, changes in melting point, solubility, vapor pressure, diffusivity, and other physical properties can be induced. There is excellent potential for eliminating pollution associated with the solvents, purification steps, and energy inputs needed for covalent chemistry. The use of supramolecular aggregates in Polaroid Instant Photography is an example of the viability of non-covalent chemistry on the industrial scale (63,64).

Carbon dioxide (CO_2), an abundant and cheap waste material, has been extensively studied as a replacement for conventional solvents. It is non-toxic, non-flammable, and having a relatively low critical temperature (31°C) and critical pressure (73.8 bar), both liquid and supercritical phases are easily accessible. One of the first “green” applications of CO_2 was decaffeination of coffee beans by extraction with supercritical CO_2 , replacing earlier technology which often relied on toxic solvents such as dichloromethane (65). CO_2 has been used as a medium for a wide range of synthetic chemistry. Examples include hydroformylation (66,67), epoxida-

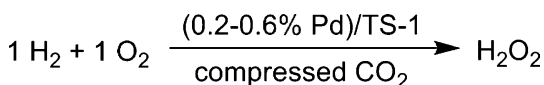


Figure 9. Direct synthesis of H_2O_2 in CO_2 over a titanium silicalite catalyst, an alternative to industrial processes using anthraquinone and organic solvents (70).

tion (67), and Diels-Alder reactions (68,69). Hydrogen peroxide can be synthesized directly from H_2 and O_2 using CO_2 as a solvent, eliminating waste from the conventional autoxidation process, and allowing a higher non-explosive limit for the $\text{H}_2 + \text{O}_2$ mixture (70) (Figure 9). H_2O_2 produced in CO_2 can be used to oxidize propylene to propylene oxide, providing an alternative to the conventional synthesis from chlorohydrin that generates 2 pounds of salt waste per pound of product in addition to large volumes of wastewater (71). In addition to the environmental and safety benefits associated with solvent replacement, the tunability of CO_2 density often offers additional advantages such as increased reaction rates and control over selectivity (72).

The solvent power of CO_2 is crucial in the success of a CO_2 -based application. CO_2 is a good solvent for non-polar molecules and some low-molecular weight polar molecules. With few exceptions, highly polar molecules and high-molecular weight compounds are poorly soluble (73). A major area of research has been elucidation of CO_2 -philicity. Identification of CO_2 -philic chemical structural motifs has expanded the range of chemistry possible in the medium. CO_2 -solubility can be imparted by covalently linking CO_2 -philic groups to a target molecule, adding stabilizers, or using surfactants. The invention of stabilizers for heterogeneous polymerization in CO_2 greatly expanded the usefulness of CO_2 as a medium for polymerization (74,75). Surfactants for water-in- CO_2 microemulsions have made it possible to dissolve ionic compounds, a wider range of catalysts, and even biomolecules in CO_2 (76). Early research was based on perfluorinated and silicone compounds (77,78), but toxicity concerns led to development of hydrocarbon-based surfactants (79,80), some based on renewable resources (81). Recently, it was shown that ionic liquids can form reverse micelles in supercritical CO_2 , providing another strategy for dissolving highly polar chemicals in CO_2 (82).

In the last decade, CO_2 has shown success in commercialization and industrial usage. It has been used in dry cleaning, replacing the bioaccumulating chemical perchloroethylene, and in paint spraying applications (83,84). Continuous hydrogenation (85), Friedel-Crafts acylation (86), and hydroformylation (66) processes based on CO_2 were developed at the University of Nottingham and, in collaboration with

Thomas Swan & Co., have led to the construction of a demonstration plant (87).

Water has been increasingly used to replace conventional solvents; the major green chemistry benefits are water's non-flammability and elimination of volatile emissions. The scope of chemistry that can be carried out in water is vast, as highlighted in extensive reviews of C-C bond forming reactions (88,89). Grignard-like reactions are known (90,91). Even dehydration reactions forming esters, ethers, and acetals can be carried out in water using surfactant-like acid catalysts (92). Selective oxidation of various alcohols has been carried out in water, not only obviating the need for organic solvent and facilitating catalyst recycling, but using environmentally-friendly O_2 as a replacement for stoichiometric toxic metals (93). In some cases increased selectivity can be seen compared to conventional solvents, for example as the result of hydrophobic effects and hydrogen bonding (94,95). Heterogeneous reactions between water-insoluble reactants are sometimes accelerated compared to solvent-free conditions (so-called "on-water" catalysis) (96,97).

Polyethylene glycol (PEG) and aqueous solutions of PEG have low toxicity and volatility. PEG is biodegradable but stable to acids, bases, high temperature, and some oxidizing and reducing conditions. Its solvent properties vary depending on molecular weight but various PEGs can dissolve both organic compounds and inorganic salts. PEG can complex metal ions and be used as a phase-transfer catalyst in biphasic systems (98).

A "smart" solvent has been developed, able to alternate between an ionic liquid and a binary mixture of non-ionic constituents depending on exposure to CO_2 or N_2 . The polarity can switch from chloroform-like to dimethylformamide-like. Providing the solvent is suitably inert, it should be possible to induce phase separation of products after reaction, eliminating problems associated with solvent waste and recycling (99).

An especially fast growing field in the last two decades was research on ionic liquids (ILs), particularly those that remain liquid at and below room temperature. The primary green chemistry benefit of ILs is non-volatility, resulting in reduced exposure to industrial workers and easier containment of the solvents. The wide range of room-temperature ILs now known allows these "neoteric solvents" to replace conventional solvents for many synthetic applications (100,101). However, there is growing concern that claims of non-toxicity have not been adequately supported, and that risk analysis and lifecycle considerations are rarely taken into consideration in the development of novel ILs

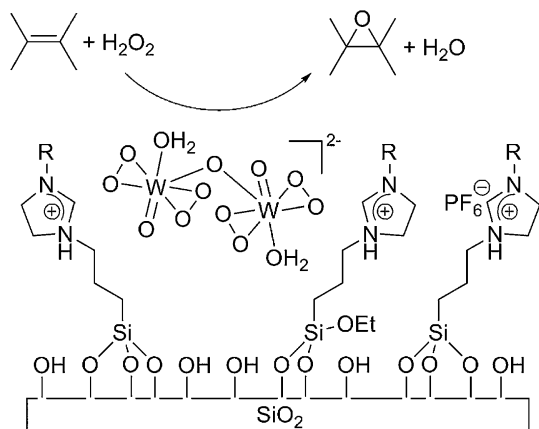


Figure 10. Peroxotungstate immobilized on ionic liquid-modified silica, an example of supported ionic liquid phase catalysis (107).

(102,103). The wide range of IL materials reported highlights the “designer” nature of the new solvents; it is hoped that the growing body of information related to IL toxicity (104) will be used in designing the next generation of ILs. Improved biodegradability and recyclability are also suggested research goals for the IL field (105). Supported ionic liquid phase (SILP) catalysis is one area of IL research that has achieved additional green chemistry goals such as reduced solvent use and catalyst recyclability and reusability. The SILP catalyst materials are stable and heterogeneous-like but can achieve high activity and selectivity more typical of heterogeneous catalysts. These catalyst systems have been applied to effect a wide variety of synthetic transformations (106).

Design of safer chemicals

The publication of *Silent Spring* by Rachel Carson in 1962 was one of the early alerts to chemists about the toxicity of the products they design. Besides DDT, alarms have been sounded for many chemicals and classes of chemicals, for example vinyl chloride (108)

and organochlorine compounds in general (109), perfluorooctanoic acid (110), polybrominated diphenyl ethers (111), phthalate plasticizers (112), and bisphenol A (113). The phenomenon of endocrine disruption by manmade chemicals has emerged as a leading threat to sustainable civilization (114,115). Compared to 1962, chemists now have more information available to design chemicals that are less likely to result in toxicity “surprises.” Considerations for design of safer chemicals have been outlined, including: environmental mobility and fate; uptake, metabolism, and excretion by organisms; and avoiding toxic functional groups (116).

Many compendia of chemical toxicity information have been published (117), such as *A Comprehensive Guide to the Hazardous Properties of Chemical Substances* (Wiley: Hoboken, NJ, 2007) and *Handbook of Green Chemicals* (Synapse Information Resources, Inc.: Endicott, NY, 2004). Systems for benchmarking chemicals according to green properties have been developed such as GreenScreen (118), and CleanGredients (for product formulations) (119). Some industries are adopting similar metrics, notably SC Johnson & Son, Inc., which employs a proprietary ‘Greenlist’ methodology to develop safer chemical formulations for its commercial products (120).

Some examples of design for reduced toxicity by green chemists in the last two decades:

- Dimethyl carbonate has been developed as an alternative to phosgene for carbonylation and alkyl halides for alkylation reactions. Dimethyl carbonate is non-toxic and biodegradable (121). Phosgene can also be eliminated from isocyanate production by generating isocyanates from CO₂, amines, and *o*-sulfobenzoic acid anhydride (122) (Figure 11).
- Polymers of N-vinylformamide have been applied as alternatives to polyacrylamides. Acrylamide monomer is a potential carcinogen and neurotoxin (123).
- Atom transfer radical polymerization, a widely used technique for living radical polymerization, can be performed using significantly reduced amounts of

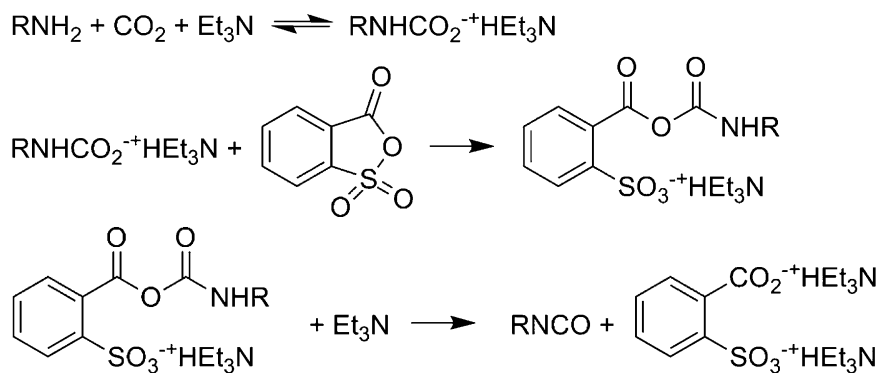


Figure 11. Phosgene-free synthesis of isocyanates. The *o*-sulfobenzoic acid salt is recyclable (122).

copper catalyst. Non-toxic ascorbic acid is used as a reducing agent to regenerate the active catalyst (124).

- Tributyltin hydride, a known neurotoxin, can be replaced by a hypophosphite salt in reductive termination of free-radical reactions (125). Organotin antifoulants (e.g. tributyltin oxide) used on ships are bioaccumulative and have reproductive toxicity; an isothiazolone alternative was developed having low bioconcentration properties and excellent biodegradability (126).
- The use of structure-activity relationships has revealed that the acute toxicity of nitrile compounds is related to the ease of radical formation at the α -carbon. This elucidated a simple design guideline for synthetic chemists to prepare less toxic nitriles (127).

The rapidly growing field of nanotechnology has seen the invention of myriad novel materials, but very little evaluation of environmental and human health risks. Nanoparticles based on arsenic, cadmium, and other toxic materials present clear concerns, but other hazards have not been fully explored. Some nanoparticles are able to cross the blood-brain barrier; others may pass through cell membranes, increasing the risk of mutagenicity and carcinogenicity. Activity at the nanoparticle surface, such as generation of damaging radicals, adsorption and transport of substances, and interactions with biochemicals are largely unknown (128). A recent review has focused on green nanosynthesis, the wet chemistry that has been invented to produce and manipulate nanomaterials. The review proposes guidelines for design and evaluation of novel materials according to green chemistry principles. Progress in development of green synthetic methods has been summarized, such as reduced dependence on solvents and reagents (reducing agents for metals, stabilizers, and phase-transfer reagents), use of more efficient purification techniques, and use of microreactors for better control of reaction conditions and facilitation of scale-up. Biology also offers greener routes to nanoparticles, through use of biomolecules as templates for growth of inorganic structures, or production of nanoparticles by whole organisms (129).

Designing molecules for biodegradability reduces the chance that a molecule can exert a toxic effect on a life form. A recent review of small molecule biodegradability presents some generalizations that can be made from examining structure-degradability relationship data, and provides commentary on specific cases with relevance to industrial chemistry. A summary of modeling software and database information is also provided (130). Additional examples of design for degradation have been reported for textile dyeing auxiliaries (131). With the exception of

natural polymers, and those derived from renewable resources, most high-molecular weight chemicals are extremely resistant to microbial attack. One strategy for imparting degradability to traditional polymers is chemical modification with degradable functional groups; a poly(styrene-co-maleic anhydride) was derivatized with monosaccharides and disaccharides, leading to a significant increase in biodegradation rate (132). Biodegradable polymers will be further discussed under the heading of 'renewable resources' below.

Renewable resources

One of the major goals of green chemistry is to derive chemical feedstocks from renewable resources instead of petroleum. Renewable biomass is produced by nature on the scale of about 180 billion metric tons/year, of which only about 4% is currently utilized by humans. Most (about 75%) is in the form of carbohydrates, about 20% is lignin, and the remainder includes fats, proteins, and terpenes. A recent review summarizes strategies for converting biomass into useful materials, including chemistry of glucose fermentation products, chemical transformations of mono- and disaccharides, and reactions of oils, fatty acids, and terpenes (133). Currently, the major non-food uses of carbohydrates are production of ethanol, furfural, d-sorbitol sweetener, lactic acid, surfactants, and pharmaceuticals (e.g. penicillin). However, routes are available for converting low-value carbohydrates into a much wider range of industrially useful products (134).

Biomass has been utilized in many inventive ways by green chemists:

- Amino acids and vegetable oils can be used to prepare antimicrobial surfactants having low toxicity and excellent biodegradability. In many cases the synthesis can be achieved through biocatalysis (135).
- Simple amino acids, by adsorbing onto metal surfaces, behave as natural corrosion inhibitors, slowing damage to steel or aluminum in concentrated HCl solution (136,137). The amino acids can replace conventional inhibitors such as nitrites, benzoates, phosphonates, and quaternary ammonium salts, which are often biohazardous and difficult to dispose of safely (138).
- All-natural UV protectant can be prepared by enzymatically incorporating ferulic acid (derived from plants) into soybean oil. By encapsulation in starch, aqueous dispersions of the material can be prepared without surfactants, and the UV-blocking properties were enhanced (139).
- While terpenes comprise only a small percentage of biomass, they can be used to prepare thermoplastics

- with properties comparable to polystyrene and poly(methyl methacrylate) (140).
- The DNA base thymine is known to undergo $2\pi + 2\pi$ photocyclization, so incorporation of thymine into synthetic polymers presents opportunities for reversible crosslinking. Polymers of vinylbenzyl thymine are promising photoresistant materials that allow for water-based processing. Use of thymine crosslinking in biodegradable polymers may enhance durability (141).
- Defatted soy flour, an inexpensive commercial product consisting mainly of soy protein and carbohydrates, can be crosslinked and used in biodegradable composite materials with plant fibers such as flax, hemp, or bamboo. The environmentally friendly composites show promise as a building material that could replace non-degradable composites such as polypropylene/glass (142). Soy flour has also been chemically modified to mimic adhesive proteins found in mussels; the resulting material has been commercialized as a wood adhesive, replacing toxic urea-formaldehyde resins conventionally used in plywood and particleboard (143).
- Cargill developed a commercial process for converting vegetable oils into polyols for manufacturing polyurethane foam, replacing petroleum-derived polyols. In addition to reducing dependence on non-renewable feedstocks, the mild process conditions save energy (144).
- Biomass-derived γ -valerolactone (Figure 12) has properties that make it an ideal sustainable liquid fuel: it has a low melting point, high boiling point and flash point, low vapor pressure, minimal peroxide formation after prolonged storage, and can be blended with gasoline. It is a naturally occurring chemical found in fruits, and has been used as a food additive. It is miscible with water and biodegradable (145,146).

Renewable resources are at the heart of efforts to develop biodegradable polymers. Biodegradable plastics can be produced from biopolymers such as

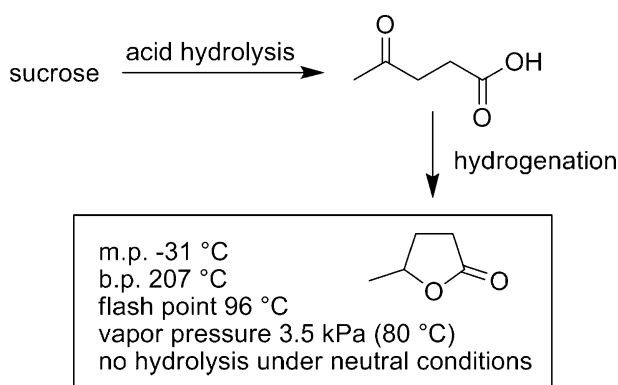


Figure 12. γ -Valerolactone, a biomass-derived liquid fuel (145,146).

cellulose and starches. Polyester materials like poly-hydroxylalkanoates (PHAs) and poly(lactic acid) (PLA) have also been successful. Water-soluble biodegradable polymers include chemically modified cellulose and starches, microbially produced polysaccharides (e.g. xanthan and pullulan), and poly(amino acid)s (147).

PHAs have been commercialized by Metabolix and Archer Daniel Midlands Co., with a facility under construction for producing >100 million pounds per year (148). The process relies on genetically engineered microbes, achieving the polymer synthesis through fermentation of the renewable raw materials (149).

Large-scale production of PLA was pioneered by NatureWorks, owned by Cargill. The production process has been noted for following all Twelve Principles of Green Chemistry in its avoidance of organic solvent, high yields achieved by efficient catalysis, and waste reduction through recycle streams. The process is estimated to use 20–50% less petroleum resources compared to conventional polymers (150). Lactic acid is typically derived from corn, but it can be derived from other materials as well, for example waste sugarcane bagasse (151). Composites of PLA have been developed using fillers made from renewable resources. Polymer composites derived from fossil fuels are non-degradable and difficult to recycle. While PLA itself is currently more expensive than conventional polymers, the use of plant-derived fillers makes the costs of composites competitive. Sugar beet pulp and residue from oilseed crops are examples of low-cost fillers. Milkweed showed a plasticizing effect, imparting ductility to PLA (152,153).

Utilization of process wastes is another way to reduce dependence on petroleum feedstocks. Restaurant oil waste can undergo fermentation to produce large quantities of sophorolipids, natural surfactants that also have cosmetic and therapeutic properties (154). Cashew nut shell liquid (CNSL), a waste product of the cashew nut industry, is distilled to give predominantly cardanol, a mixture of long-chain alkyl-phenol oils. Cardanol modified with benzoxazine has been used to prepare biocomposites with jute fibers, resulting in materials with useful mechanical properties (155). Cardanol has also been used as a non-petroleum feedstock for non-covalent synthesis of organic nanotubes (156). Agricultural byproducts such as rice and nut hulls, fruit peels, and olive mill wastewater contain phenolic compounds with high antioxidant activity (157). These natural anti-oxidants are alternatives to the food additives butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), and *t*-butylhydroquinone (TBHQ), synthetic antiox-

idants of questionable safety (158). Polycarbonate waste can be converted into starting materials for polyurethane; in a one-pot procedure, the waste polymer is converted into bisalkoxylated diols of Bisphenol A, which is then polymerized with urea (159).

Production of biofuels generates large quantities of glycerol (about 1 kg for every 10 kg of biofuel); finding valuable applications has been a challenge. Using a green chlorodehydroxylation technique (160), a Belgian company has built a facility to produce epichlorohydrin from glycerol and hydrochloric acid instead of propylene and chlorine (161). Glycerol can also be converted into propylene glycol by reactive distillation and hydrogenation, providing an alternative to the traditional route based on propylene oxide (162) (Figure 13). Archer Daniel Midlands Co. has announced plans to build a large scale glycerol-to-propylene oxide manufacturing facility (163). The company IUCT in Barcelona, Spain uses glycerol from biodiesel production as a starting material for new solvents and fuels.

The use of CO₂ as a renewable source of carbon has been recently reviewed (164). While use of CO₂ as a raw material is not expected to mitigate the “green-house gas” effects of CO₂ in the atmosphere, the non-toxic, non-flammable gas is considered to be an environmentally friendly reagent. Currently, the most industrially promising uses of CO₂ as a feedstock are in the formation of carbonate small molecules and polymers. Dimethyl carbonate, as discussed earlier, is a green alternative to phosgene in polycarbonate and polyurethane synthesis. Ironically, dimethyl carbonate is conventionally synthesized from phosgene. New methods for dimethyl carbonate synthesis have been devised, for example a one-pot conversion based on a cyclic carbonate, using methanol and a heterogeneous Mg-based catalyst (165) (Figure 14). Cyclic carbonates, useful intermediates for polycarbonate synthesis, can now be prepared directly from alkenes instead of preformed epoxides, avoiding extra synthetic steps. The synthesis from alkenes has additional green characteristics: it is performed in water without use of metal catalysts (166). The development of highly active polymerization catalysts operating under mild conditions has been key in preparing polycarbonates from CO₂ and epoxide compounds (167). The

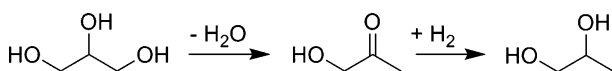


Figure 13. Reactive distillation of glycerol over copper-chromite catalyst yields propylene oxide. The process is carried out at relatively low temperature and pressure, producing less byproduct than previous systems (162).

resulting polymers have variable plastic properties but poly(cyclohexene carbonate) shows promise as an alternative to polystyrene.

A CO₂ sequestration and utilization process known as Supramics captures waste CO₂ from flue gas and incorporates it into cement-fiber composites. The process has low energy requirements, and the product replaces building materials that result in emission of CO₂ and other waste byproducts (168).

The path forward

As we consider the past accomplishments outlined in the preceding sections, it is useful to try and identify conceptual perspectives of green chemistry that will help take the field to the next level of maturity. While the advances above have been of the highest quality science, many of the advances have been made well within a single sub-discipline within chemistry. Other advances, while rigorous and useful, have been incremental steps forward in making our chemical design more sustainable and environmentally benign. A large portion of our resources of time, funding, and intellectual dedication to the subject of sustainability has been devoted to convincing policy makers, consumers, and members of the scientific community of the magnitude of the problems confronting the world that are due to our historical and present-day unsustainable products, processes, and systems. Green chemistry needs to continue to be a driving force in addressing these serious issues by identifying the future possibilities. These possibilities will not happen small step by small step. We simply do not have the luxury of time. Dramatic transformative advances will need to be part of the portfolio of future green chemistry technologies in order to get us where we need to be within the timeframe required.

1. The Twelve Principles of Green Chemistry need to be understood – not as a collection of individual isolated goals but rather as a design framework. Design is the conscious statement of human intention. While it may be possible to make products and processes less hazardous or more efficient as a by-product of research endeavors, green chemistry is a framework for the design of products and processes such that the goals themselves, e.g. degradability or less toxic products, are essential performance criteria. It will not be enough to simply consider these goals as “added features” that are ancillary to the central purpose of the molecules, materials and transformations. It will be important that these goals are intrinsic design specifications. In that way, it will be obvious that when a hazardous and unsustainable product or process is produced, there are only two explanations: (1) there is a design flaw or (2) it was designed to be hazardous.

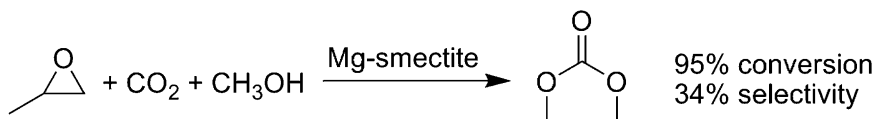


Figure 14. Progress toward a viable phosgene-free synthesis of dimethyl carbonate: one-pot reaction using a heterogeneous catalyst (165).

2. Innovation is the lifeblood of green chemistry. Too often throughout the past, any new technology that has benefited human health and the environment has been focused on what you are not allowed to do or what you must do less of. The historical approaches were to eliminate, minimize, lessen, reduce, etc. The approach was usually about design constraints. In green chemistry, the strategy is to see what you can create and what you can invent. New materials, transformations, methodologies, solvents, molecules, analyses, and tools are the hallmark of green chemistry, and the research portfolio of the field reflects this orientation. Rather than having to consider design constraints, the new chemistry is providing new design opportunities in the way that all new perspectives and advances have.
3. Green chemistry must have a solutions orientation. As we look at advancing sustainability, there has been a tremendous effort on measuring, monitoring, reviewing, assessing, and characterizing problems. These problems include energy, climate, water availability, food production, health and medicine, pollution, and much more. While it is important to understand the nature of the problems we face in order to effectively address them, green chemistry focuses on the solutions to these problems: what are the new alternatives, the next generation of substances that will make sure that the energy and material basis of our society and economy more sustainable? As important as fully understanding a problem is, a diagnosis is only good if it assists in creating a cure. Having a "solutions orientation" often requires a broader perspective than has traditionally been the case when approaching our science from a "problem orientation." More than mere semantics, the distinction between these two approaches can be the difference between asking the question "how do I change this molecule or this transformation?" versus "how do I get the service or function that I hope to achieve regardless of the particular molecule or particular transformation?"
4. Green chemistry and the set of design principles is a cohesive system, not a list of unrelated goals. Many of the advances in green chemistry technologies have been important incremental advances that have illustrated the ability to achieve various goals. Research has focused on particular principles within the Twelve Principles of Green Chemistry such as solvent replacement or atom economy. As we see green chemistry evolving, there is a recognition that the most transformative breakthroughs will occur when we view the Twelve Principles as an integrated system.

This system will be used to design synergies and minimize or avoid trade-offs between the Principles. The leap-frog innovations that will come through using the systems approach will be necessary to truly address many of the sustainability challenges we face.

In all, there is reason for excitement that the nascent research field of green chemistry has only begun to demonstrate its power and potential for using fundamental sciences for the benefit of man, the environment, and the economy. Now that the concepts have been dramatically and unequivocally demonstrated over the course of recent years, both in the scientific and industrial realms, we are now entering the phase of exploring the breadth, range and scope of the possible achievements in green chemistry. It has been said that the term green chemistry was derived from the dual connotations of the word "Green" – concerned with the environment and the color of the US dollar. There is an additional connotation of the word "green" which is young, fresh, and new. The science of green chemistry is showing that the creativity of thoughtful practitioners of every continent are generating young, fresh, and new chemistry that will help drive this transformation of both theory and practice.

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