Promoting Green Engineering through Green Chemistry

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The decisions made by chemists in designing chemical products and processes directly impact the options available to engineers. The physical and chemical properties of a material, for example, dictate the type of reactor that must be used in a given process. The task of the engineer is simplified when chemists design products and processes that reduce or eliminate the use and generation of hazardous substances. Green chemistry provides a foundation on which to build green engineering. This paper highlights green chemistry technologies that minimize the need for engineering safeguards in the areas of feedstocks, reagents, solvents, and syntheses.

Introduction

Green chemistry is an integral part of green engineering. The definitions share common language, and the application of both chemistry and engineering principles is needed to advance the goals of sustainability.

Green Chemistry: The design of chemical products and processes that reduce or eliminate the use and generation of hazardous substances (*1*).

Green Engineering: The design, commercialization, and use of processes and products that are feasible and economical while minimizing pollution at the source and risk to human health and the environment (*2*).

The connection between green chemistry and engineering is particularly strong in ensuring that inputs and outputs, both materials and energy, are as inherently safe as possible (*3*). Green chemistry focuses on the design of chemical products and processes that reduce or eliminate the use and generation of hazardous substances. Green chemistry provides the foundation on which to design the green engineering technologies needed to implement sustainable products, processes, and systems. Using inherently safer materials eliminates the need to "engineer out" environmental concerns later in the process.

The Twelve Principles of Green Chemistry serve as a guide in designing environmentally benign products and processes (*4*). Tradeoffs may be necessary in applying the Principles to a specific situation however. For example, the energy required to remove water from the product, when substituting water for an organic solvent, needs to be taken into account in assessing the environmental benefits of competing processes. These Principles provide guidance in assisting the molecular designer to create new products or evaluate existing processes.

Green chemistry enhances the safety of a process by employing inherently safer substances throughout the design process, including the selection of feedstocks, reagents, and solvents, and designing the final product so that it too is

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innocuous. We have a much better understanding of the interaction between functional groups in a molecule and biological organisms thanks to advances in toxicology and mechanistic chemistry. We can more accurately measure substances released into the environment because analytical chemists have developed instruments and methods capable of detecting pollutants at very small concentrations. Armed with this information, chemists can design the hazard out of molecular structures by avoiding functional groups that interact with living organisms, designing syntheses to eliminate the use of volatile organic solvents, transforming functional groups using less toxic reagents, and developing products that do not persist in the environment.

Energy inputs are also an important consideration in product and process design since many environmental problems can be traced directly to the combustion of fossil fuels. Biomass alternatives to coal, oil, and natural gas have been commercialized to a limited degree, but burning hydrocarbons to produce energy is not a sustainable option. The application of green chemistry principles guides the development of fossil fuel alternatives, such as fuel cells and photovoltaics. In addition, numerous green chemistry technologies employ catalysts to benefit existing processes by decreasing the amount of energy required. Not only do catalytic processes lower energy requirements, they also increase selectivity, thereby minimizing the need for separation technologies at the end of a process.

The following sections highlight green chemistry advances in four areas: feedstocks, reagents, solvents, and syntheses. These examples are simply illustrative of the breadth of green chemistry applications and do not represent a comprehensive overview of the field. Additional examples of green chemistry may be found in recent volumes dedicated to green chemistry technologies (*5*–*9*).

Feedstocks

When choosing a feedstock, factors such as source, toxicity, and environmental fate should be considered. Because petroleum is the basis for the vast majority of organic chemicals in use (*10*), but the supply of fossil fuels is limited, increasing research efforts have been directed toward the development of renewable feedstocks. Agricultural biomass (*11*), carbon dioxide (*12*), chitin (*13*), and waste byproducts (*14*) all provide sources of renewable feedstocks. These alternatives are not widely used, however, because most are not economically competitive with petroleum-based feedstocks. In addition, the petrochemical industry is well-established and highly efficient.

Biobased feedstocks present several advantages over petroleum-based sources. Biomass-derived carbohydrates are more highly functionalized than hydrocarbon sources, minimizing the need for oxidative chemistry that often requires the use of toxic heavy metals. New crops can provide a continuous supply of raw materials. Despite these advantages, furfural is the only unsaturated large-volume organic chemical derived from carbohydrate sources (*15*). A high-temperature, acid hydrolysis process converts forestry and agricultural wastes into furfural, which can subsequently be transformed into a variety of industrial chemicals. New applications transforming biobased feedstocks into chemicals and fuels are being commercialized however.

Cargill Dow manufactures NatureWorks polylactic acid (PLA) from renewable resources, such as corn and sugar beets (*16*). Fewer fossil fuel resources are used to make PLA because annually renewable resources replace petroleum-based feedstocks. The manufacturing process uses no organic

SCHEME 1. Catalytic Oxidation of Cyclohexanol to Cyclohexanone

FIGURE 1. TAML catalyst.
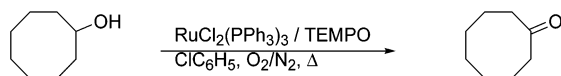
solvents, and the final product is biodegradable, compostable, and recyclable. Products made from PLA can be hydrolyzed with water to lactic acid, yielding prime polymer following purification and polymerization. Cargill Dow eventually plans to use lower value biomass, such as agricultural waste, as a feedstock. PLA fibers perform as well as petroleum-based polymers in consumer goods, including beverage containers, food packaging, and clothing.

The transformation of lignocellulosic biomass into ethanol has been widely studied with efforts focused on developing commercially competitive processes. Two significant improvements have led to substantial decreases in the cost of bioethanol in recent years (*17*). First, the optimization of pretreatment conditions and the development of better cellulase enzymes have improved rates, yields, and concentrations. Second, the design of genetically modified organisms has increased ethanol yields while decreasing disposal costs of unused sugars.

Ethanol is considered a potential hydrogen source for fuel cells. Optimization of conditions for oxidative steam reforming of ethanol over a $Ni-Cu/SiO_2$ catalyst has recently been reported (*18*). On-board conditions were used in the investigation of re-forming ethanol for use in a solid polymer fuel cell, which has potential applications in light-duty vehicles and buildings. High activity, selectivity, and efficiency coupled with near-zero emissions promise further interest in ethanol, particularly bioethanol, as a source for fuel cells.

Not all renewable resources are derived from biomass however. Combustion of fossil fuels provides a ready source of carbon dioxide as a feedstock. For example, CO_2 has been used as a raw material in the manufacture of building materials (*19*). CO_2 is stripped from flue gases and made supercritical by increasing its temperature and pressure. This supercritical fluid is combined with the hydrated products, derived from cement paste, to convert metal hydrates into carbonates. Products such as roofing tiles and wallboard are stronger, tougher, and more durable than conventional molded products. This process, termed the Supramics process, converts industrial wastes (CO_2 and fly ash) into valuable building materials.

Reagents

A number of reagents used to carry out chemical transformations are toxic, corrosive, or hazardous to handle. Substitutes have been developed that carry out the same reactions in a safer manner. Oxidation chemistry is one area in which effective alternatives are available. Alcohols are commonly oxidized to carbonyl compounds using heavy metals such as chromium(VI). Sheldon and co-workers (*20*) have designed greener catalytic systems to convert alcohols to aldehydes and ketones. One system combines a ruthenium catalyst with TEMPO (2,2,6,6-tetramethylpiperidinyl-1-oxy) under aerobic conditions to oxidize a wide range of alcohols (Scheme 1). The oxidation can be run under solvent-free conditions, and the only coproduct formed is water.

Hydrogen peroxide is another reagent that can be used for oxidations. The Collins group has designed a series of catalysts that activate hydrogen peroxide to bleach wood pulp (*21*). Termed TAML (TetraAmidoMacrocyclicLigand) activators (Figure 1), these catalysts are selective, effective over a wide pH range, consume less energy, and eliminate the problem of chlorinated byproducts. This technology has applications in the pulp and paper industry, which is gradually shifting toward better reagents for pulp deligni-
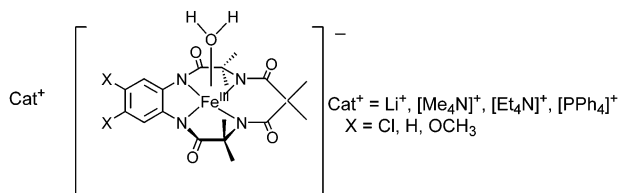
fication and bleaching. Chlorine dioxide has largely replaced chlorine as a bleaching agent because it produces fewer chlorinated organic byproducts, many of which are linked to cancer and endocrine disruption. Bleaching with chlorine dioxide, however, uses stoichiometric amounts of reagents, is energy intensive, and generates trace amounts of chlorinated organics. Combining minute quantities of TAML activators with hydrogen peroxide offers a totally chlorine-free approach for pulp bleaching. Furthermore, this technology is effective in bleaching the highly colored effluent streams associated with paper mills.

Hydrogen peroxide is finding applications in epoxidation reactions as well (*22*). Alkenes are commonly epoxidized using oxygen, peroxides, or peracids. However, these methods are plagued by overoxidation and the generation of stoichiometric amounts of coproducts and waste. Key to the effectiveness of hydrogen peroxide as an epoxidizing agent is catalyst design, and a variety of catalyst systems have been developed to activate hydrogen peroxide. A polyoxometalate catalyst, for example, selectively epoxidizes 1-hexene in a mixture of aqueous hydrogen peroxide and toluene (*23*). Once the hydrogen peroxide is consumed, the catalyst precipitates out, facilitating recovery and reuse.

Alternatives to phosgene, a highly toxic reagent widely used in industry, are also being developed. Dimethyl carbonate (DMC) is being used for methylations and carbonylations in place of methyl halides and phosgene, respectively (*24*). DMC is nontoxic and is synthesized in a phosgene-free process from methanol and oxygen or methanol and carbon dioxide (*25*). Although reactions using DMC commonly employ elevated temperatures and pressures, these processes are safer and generate less waste than other alkylation methods, which produce inorganic salts as byproducts.

Solvents

Solvents are widely used in the chemical industry as reaction media, separation agents, and processing aids. Many solvents are volatile organic compounds, hazardous air pollutants, flammable, or toxic. These concerns have promoted research into alternative solvents that create fewer environmental problems. An increasing number of reactions are being run in solvents such as supercritical fluids, ionic liquids, and water as well as under solvent-free conditions.

The properties and uses of supercritical carbon dioxide ($scCO_2$) have been widely investigated. Carbon dioxide is a nontoxic, nonflammable, inexpensive renewable resource with a critical point that is easily accessible. Numerous types of reactions can be run in $scCO_2$, including organometallic catalysis. Leitner (*26*) has demonstrated enhanced catalyst efficiency by hydrogenating imines in $scCO_2$ rather than CH_2-Cl_2 (Scheme 2). A chiral iridium catalyst yields the amine product in 80% ee with over 99% conversion.

The use of supercritical carbon dioxide as a solvent has seen several commercial applications. Collaboration between the University of Nottingham and Thomas Swan & Company, for example, led to operation of a full-scale plant carrying out continuous hydrogenation reactions in supercritical carbon dioxide (*27*). The conversion of isophorone to trimethylcyclohexanone (TMCH) (Scheme 3) was the first

SCHEME 2. Enantioselective Hydrogenation of Imines in scCO$_2$

80% ee
>99% conversion
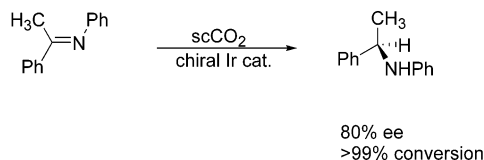
SCHEME 3. Hydrogenation of Isophorone in scCO$_2$
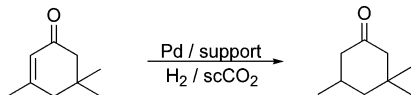
reaction to be run in this plant, which began operations in June 2002. Conventional hydrogenation of isophorone yields over-hydrogenated byproducts along with TMCH, requiring extensive separation and purification. Producing TMCH in scCO$_2$ has eliminated the need for downstream purification. The plant is a multi-purpose facility, allowing catalysts within the reactor to be changed to alter the chemistry.

A rapidly expanding area of research on alternative solvents focuses on ionic liquids (ILs). These potentially green solvents are an attractive alternative to volatile organic solvents because of their very low vapor pressures and the potential to design ILs that are nonhazardous by varying the anion and cation. Widespread applications of ionic liquids, however, will require efficient, economical syntheses of the ionic liquids themselves.

One challenge in the synthesis of ionic liquids is the large quantity of organic solvent needed to remove impurities, primarily unreacted starting material and byproducts. New methods that generate less waste are being developed to prepare ionic liquids. One such preparation uses microwaves to produce ionic liquids in high yields and purity (*28*). A multimode microwave system was used to control and monitor temperature, pressure, and reaction time. Pyridinium, imidazolium, pyrazolium, and thiazolium ionic liquids were prepared using this protocol, using a small molar excess of haloalkane.

Most ionic liquids are prepared using an alkyl halide. When these salts are used in metathesis reactions to produce a different IL, the resulting product is often contaminated with halide, altering the physical properties and potentially deactivating catalysts in subsequent reactions. 1-Alkylimidazoles can be combined with dimethyl sulfate or diethyl sulfate to yield halide-free ionic liquids (*29*) (Scheme 4). The

reaction proceeds faster than its counterpart using an alkyl halide as the alkylating agent and produces no waste. Alkyl sulfate ionic liquids can also be used as intermediates in the preparation of other ionic liquids.

Water is also finding new applications as a reaction medium. Syntheses that have historically been conducted in organic solvents can also be accomplished in water, thanks in part to the design of catalysts that facilitate many reactions. For example, an acidic solid resin has recently been used to synthesize tetrahydropyranols in water (*30*). The reaction is promoted by sonication and is run at room temperature, and the catalyst can be recovered and reused (Scheme 5). This variation on the Prins cyclization is a cross-molecular isomerization that demonstrates complete atom economy. The cis isomer is favored due to thermodynamic control. Interestingly, the reaction does not occur in the absence of sonication.

The Heck reaction, widely used in the specialty chemical and pharmaceutical sectors, can also be conducted in water using a palladium catalyst (*31*) (Scheme 6). An Amberlite IRA-400 resin acts as a base and is converted into a quaternary ammonium salt. The quaternary ammonium salt is proposed to stabilize the palladium catalyst, thereby accelerating the reaction rate.

In some cases, reactions can be carried out in the absence of solvent. A recent example by Clark uses sulfated Zirconia to catalyze the Fries rearrangement of benzoate esters in the absence of solvent (*32*). The catalyst is more selective than other solid acid catalysts, such as zeolites and transition metal triflates. Furthermore, the catalyst can be recovered and reused by suspension in acetone, followed by filtration. The Fries rearrangement is frequently used in the manufacture of pharmaceuticals and pesticides.

Dihydropyrimidinones, with applications as calcium channel blockers, antihypertensive agents, and anticancer drugs, have recently been synthesized in a solvent-free process (*33*). A variation of the Biginelli reaction, the procedure combines a 1,3-dicarbonyl, aldehyde, and urea without solvent or catalyst (Scheme 7). The reactants are heated for 1 h, and the product was filtered and recrystallized from hot ethanol, yielding analytically pure product. This protocol eliminates the use of Lewis acid catalysts and solvents such as acetonitrile and methylene chloride.
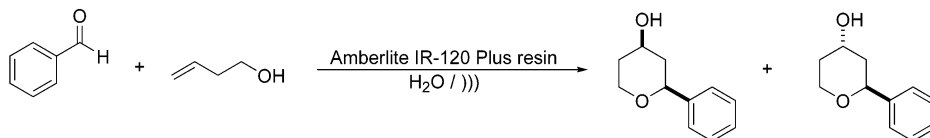
Syntheses

Applying green chemistry principles to synthetic pathways can yield more efficient reactions that generate less waste and improve worker safety. Environmental benefits can be
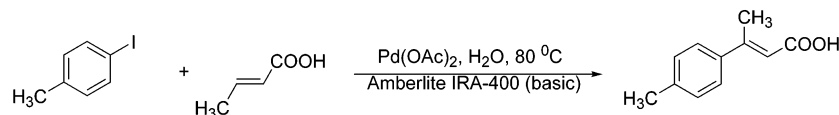
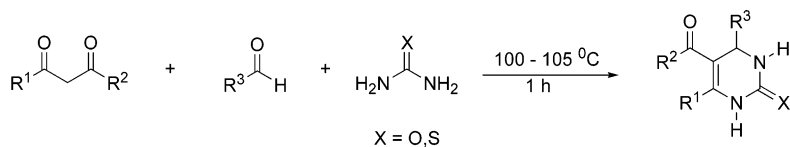## SCHEME 4. Preparation of 1,3-Dialkylimidazolium Alkyl Sulfate Ionic Liquids
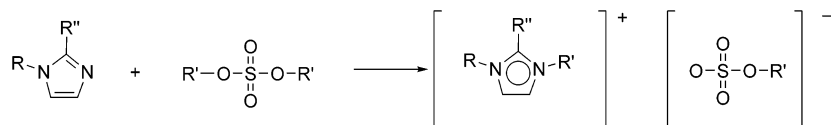
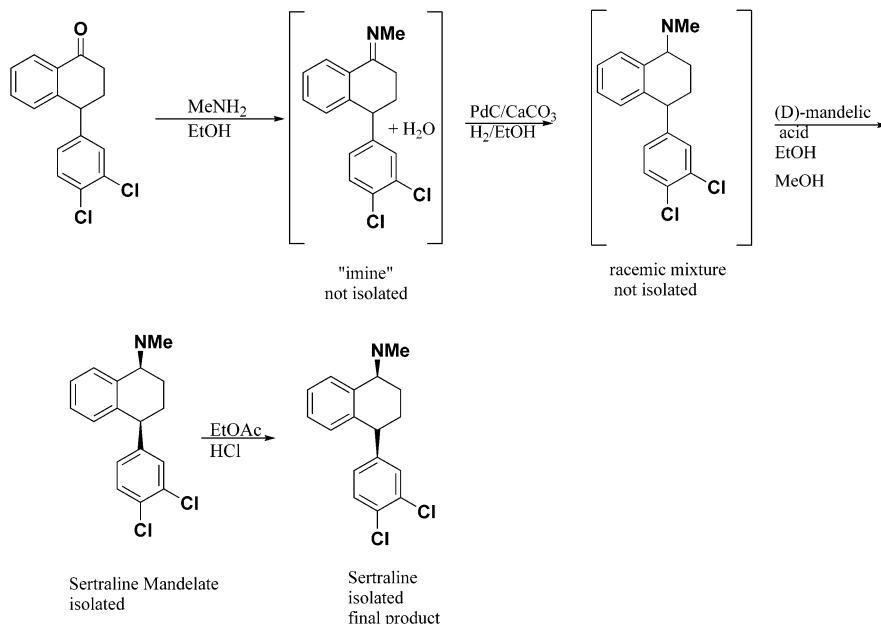## SCHEME 5. Synthesis of Tetrahydropyranol Derivatives in Water

SCHEME 6. Aqueous Heck Reaction

SCHEME 7. Solvent- and Catalyst-Free Synthesis of Dihydropyrimidinones

$X = O, S$

SCHEME 8. Redesigned Synthesis of Sertraline

"imine"
not isolated

racemic mixture
not isolated

Sertraline Mandelate
isolated

Sertraline
isolated
final product

realized from feedstock through product. An excellent example of synthetic redesign can be found in Pfizer's production of sertraline, the active ingredient in the anti-depressant Zoloft (*16*). The new manufacturing process (Scheme 8) has doubled product yield while eliminating 140 t of TiCl$_4$, 440 t of solid TiO$_2$ waste, 150 t of 35% HCl, and 100 t of 50% NaOH on an annual basis. Key to improving the manufacture of sertraline was changing from a mixture of four organic solvents, used in the first step, to a single solvent, ethanol. Solvent usage decreased from 60 000 L/1000 kg of product in the discovery phase to 6000 L/1000 kg of product in the combined process. The new commercial process provides improved safety and material handling and de-creased energy and water usage, while doubling the overall yield.

Another pharmaceutical, Cytovene, is also manufactured via a cleaner process (*34*). Cytovene is an antiviral agent used to treat cytomegalovirus retinitis infections in AIDS patients and those who have received solid tissue transplants. In redesigning the synthesis of this drug, Roche Colorado reduced the number of reagents and intermediates from 22 to 11, eliminated 1.12 million kg of liquid waste/yr and 25 300 kg of solid waste/yr, while increasing product yield by 25%. The approach used in the production of Cytovene is applicable to the synthesis of other biologically active purine-based antivirals.

Eli Lilly engaged elements of chemical engineering and microbiology in developing a new synthesis for a drug candidate (*35*). In reducing a ketone to a chiral alcohol, researchers employed a three-phase system to prevent product buildup from deactivating the yeast biocatalyst. The alcohol product preferentially adsorbed to the surface of the solid polymer resin, thereby simplifying isolation and purification. In a subsequent step, a combination of air, NaOH, and DMSO replaced chromium oxide as the oxidation reagent. These changes have eliminated 100 kg of hexavalent chromium waste and 34 000 L of solvent for every 100 kg of product synthesized, while increasing product yield 3-fold.

Biocatalysis plays an increasingly important role in synthetic protocols. DuPont has designed an enzymatic route for producing 1,3-propanediol, a monomer in the production of commercial polymers (*36*). Current synthetic pathways to 1,3-propanediol start with either ethylene oxide or acrolein, both of which are toxic, flammable, and classified as hazardous air pollutants. The new approach combines biosynthetic pathways from three microorganisms into a single organism to convert glucose, a renewable resource obtained from cornstarch, into 1,3-propanediol. Metabolic engineering enables the production of this important mono-mer without the need for petroleum-based feedstocks, high temperatures and pressures, and organic solvents.

Conclusion

The need for engineering solutions to prevent pollution from being released into the environment is minimized when green chemistry principles are incorporated into feedstock and reagent selection, solvent use, and overall synthetic design. Combining green chemistry with green engineering at the earliest design stages is an effective strategy for maximizing efficiency, minimizing waste, and increasing profitability.

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