Green Chemistry in Organic Synthesis

T. Deligeorgiev[1,*], N. Gadjev[1], A. Vasilev[1], St. Kaloyanova[1], J.J. Vaquero[2] and J. Alvarez-Builla[2]

[1]University of Sofia, Faculty of Chemistry, 1164 Sofia, Bulgaria

[2]University of Alcalá, Faculty of Pharmacy, 28871 Alcalá de Henares, Madrid, Spain

Abstract: The development of the concepts for "Green Chemistry" and the main principles of this field are reviewed. Examples of the application of these principles in different areas of chemistry are included. The frequently used alternative solvents (green solvents – water, PEG, perfluorinated solvents, supercritical liquids) in preparative organic chemistry are described. The present and the future developments of green chemistry in education and organic chemical technology are considered.

Key Words: Green chemistry, green solvents, organic synthesis, principles of green chemistry.

WHAT IS GREEN CHEMISTRY?

The term "Green Chemistry" was introduced for the first time by Anastas [1, 2] in 1991 in a special program created by the US Environmental Protection Agency (EPA) in order to stimulate a substantial development in chemistry and chemical technology. The program was also aimed at changing the outlook of chemists and was directed at protecting the environment by focusing on lower risks or their complete elimination as far as human health is concerned.

Green Chemistry can be comprehensively illustrated as a set of 12 pripciples, which were proposed by Anastas and Warner [1-3]. These principles include instructions for professional chemists concerning the creation of new substances, new syntheses and new technological processes.

The first principle describes the basic idea of Green Chemistry – environmental protection from pollution. The other principles focus on such problems as atom economy, toxicity, solvents, energy consumption, use of raw materials from renewable resources and
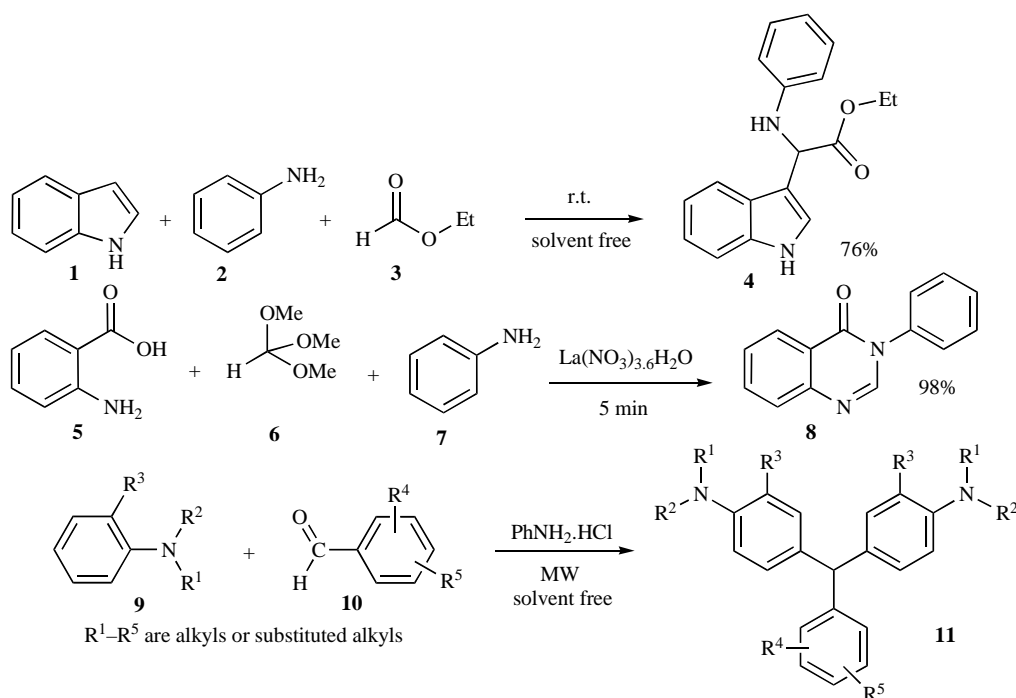
Scheme 1. Organic syntheses in the absence of solvent.

THE CONCEPT OF GREEN CHEMISTRY

The Green Chemistry concept appeared in the USA as a general scientific program, originating from the interdisciplinary cooperation of research groups in universities, independent research groups, scientific societies and government agencies, with members of each of these bodies having their own program dedicated to lowering levels of environmental pollution. Green Chemistry comprises a new approach to the synthesis, processing and application of chemical substances, thus diminishing the hazards for human health and environmental pollution.

decomposition of the chemical products to simple non-toxic substances that are compatible with the environment.

THE 12 PRINCIPLES OF GREEN CHEMISTRY

1. Prevention

It is better to prevent the formation of waste materials and/or by-products than to process or clean them.

Organic syntheses in the absence of solvents. This principle has stimulated so-called "grinding chemistry", in which the reagents are mixed without solvent, sometimes by simply grinding them in a mortar. Chen *et al.* [4] described a good example of a three-component Friedel–Crafts reaction on indoles, leading to the functionalized indole **4**. In a similar way, Venkateswarlu *et al.* [5] de-

*Address correspondence to this author at the University of Sofia, Faculty of Chemistry, 1164 Sofia, Bulgaria, Tel: (+3592)8161269; Fax: (+3592)9625439; E-mail: toddel@chem.uni-sofia.bg

veloped a synthesis of 4-quinazolinone **8** using a rapid method without solvent. "Grinding chemistry" has recently been reviewed [6]. An expanding area of chemistry without solvents involves the use of microwaves to irradiate mixtures of neat reagents. One example of this approach is the synthesis of 4,4'-diaminotriphenyl-methanes (**11**) using microwave irradiation [7] (Scheme **1**).

2. Atom Economy [8]

Synthetic methods should be designed in such a way that all products participating in the reaction process are included in the final product.
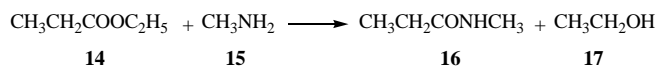
Chemists all over the world consider a reaction to be 'perfect' when the yield is 90% or more. However, such a reaction could create considerable amounts of waste. The concept of atom economy was developed by Trost [8, 9] and is represented as follows:

% atom economy = (FW of the atoms used) / (FW of the reactants in the reaction) × 100
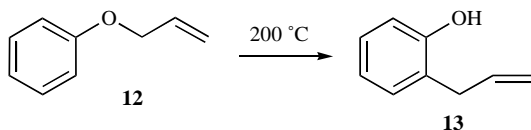
Scheme 2. Allylic rearrangement with 100% atom economy.

This reaction has an atom economy of 100% because all reactants are included in the final product (Scheme **2**).

$$CH_3CH_2COOC_2H_5 + CH_3NH_2 \longrightarrow CH_3CH_2CONHCH_3 + CH_3CH_2OH$$
$$\quad\; \textbf{14} \qquad\qquad \textbf{15} \qquad\qquad\qquad \textbf{16} \qquad\qquad \textbf{17}$$

Scheme 3. Preparation of an amide with 65.4% atom economy.

In the above reaction (Scheme **3**), the leaving group (OC_2H_5) and a proton from the methylamine (**15**) are not used. The rest of the atoms are used and for this reason:

% atom economy = 87.106/133.189 × 100 = 65.40%

4. Designing Safer Products

The design of products should be safe in terms of human health and the environment.

A typical example of a hazardous drug is thalidomide (**20**) (Fig. **1**), which was introduced in 1961 in West Germany. This drug was prescribed to pregnant women against nausea and vomiting. Pregnant women who had taken the drug gave birth to babies with a condition called phocomelia – abnormally short limbs with toes sprouting from the hips and flipper-like arms. Other infants had eye and ear defects or malformed internal organs such as unsegmented small or large intestines [11]. This drug is now prescribed for treatment of patients with *multiple myeloma* and for the acute treatment of the cutaneous manifestations of *erythema nodosum leprosum*.
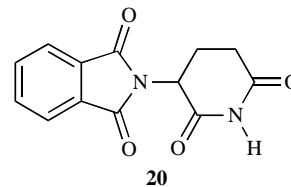
Fig. (1). Chemical structure of Thalidomide – 2-(2, 6-dioxopiperidin-3-yl)-1,3-dione.

Dow AgroSciences designed spinosad (**21**), a highly selective, environmentally friendly insecticide [12]. Spinosad demonstrates both rapid contact and ingestion activity in insects, which is unusual for a biological product (Fig. **2**). Spinosad has a favorable environmental profile. It does not leach, bioaccumulate, volatilize, or persist in the environment. Spinosad will degrade photochemically when exposed to light after application. Spinosad strongly adsorbs to soils and, as a result, it does not leach through soil to groundwater when used properly and buffer zones are not required. Spinosad has a relatively low toxicity to mammals and birds and, although it is moderately toxic to fish, this toxicity represents a reduced risk to fish when compared with many synthetic insecticides currently in use. In addition, 70–90% of

Table 1. Used and Unused Atoms from the Reactants in the Preparation of the Amide Shown on Scheme 3

| Reactants		Used		Unused	
Formula	FW	Formula	FW	Formula	FW
$C_5H_{10}O_2$	102.132	C_3H_5O	57.057	C_2H_5O	45.061
CH_5N	31.057	CH_4N	30.049	H	1.008
Total $C_6H_{15}NO_2$	133.189	C_4H_9NO	87.106	C_2H_5OH	46.069

The most important principle of Green Chemistry is to eliminate or at least to decrease the formation of hazardous products, which can be toxic or detrimental to the environment.

3. Avoidance or Minimization of Hazardous Products

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

An example of this principle is the oxidation of cyclohexene (**18**) to adipic acid (**19**) with 30% hydrogen peroxide [10] (Scheme **4**).

Scheme 4. Oxidation of cyclohexene to adipic acid with 30% hydrogen peroxide.

beneficial insects and predatory wasps are left unharmed by spinosad. The unique mode of action of spinosad, coupled with the high degree of activity on targeted pests, low toxicity to non-target organisms (including many beneficial arthropods), and resistance management properties make spinosad an excellent new tool for integrated pest management.

Spinosad is an example of a technological development that demonstrates how the creation and production of safer chemicals is possible. Changes in the chemical structure are the means to achieve this goal.

5. Safer Solvents and Auxiliaries

The solvent chosen for a given reaction should not pollute the environment or be hazardous to human health.

The use of ionic liquids or supercritical CO_2 is recommended. If possible, the reaction should be carried out in an aqueous phase or in the absence of solvent. A better method is to conduct the reaction
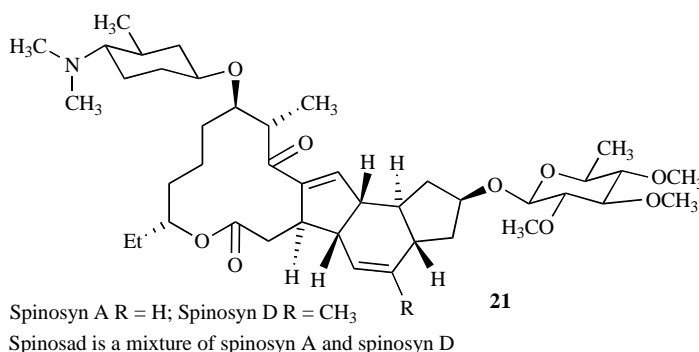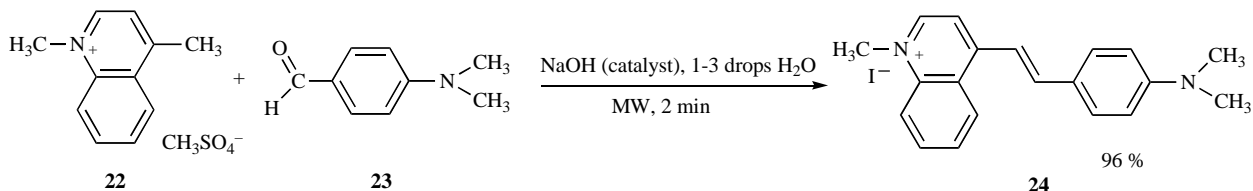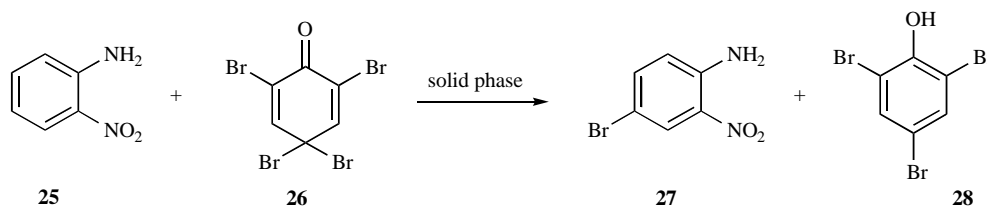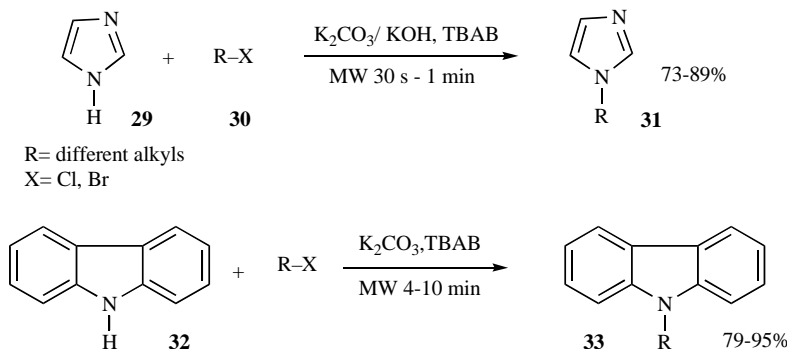
Spinosyn A R = H; Spinosyn D R = CH$_3$
Spinosad is a mixture of spinosyn A and spinosyn D

Fig. (2). Chemical structure of spinosad – an environmentally friendly insecticide.

Scheme 5. Preparation of styryl dyes under solvent-free conditions and microwave irradiation.

Scheme 6. Bromination of anilines in the solid phase.

Scheme 7. N-alkylation of azaheterocycles under microwave conditions.

in the solid phase and one example of this approach is the preparation of styryl dyes. A series of styrylpyridinium, styrylquinolinium (**24**) and styrylbenzothiazolium dyes have been synthesized by novel environmentally benign procedures. The condensation of 4- methylpyridinium methosulfate, 2- or 4-methylquinolinium methosulfate (**22**) or 2-methylbenzothiazolium methosulfate with aromatic aldehydes (**23**) was performed under solvent-free conditions and microwave irradiation in the presence of different basic or acidic reagents (Scheme **5**) [13].

Another example of this approach is the preparation of brominated anilines (**27**) and phenols in the solid phase (Scheme **6**) [14].

The volatility of solvents is also a fundamental problem as these materials can be hazardous to human health and the environment. One possibility of overcoming this problem is the use of immobilized solvents or solvents with low volatility, e.g. ionic liquids, and the use of these systems is growing.

6. Energy Efficiency

The energy requirements involved in the chemical processes should be accounted for, in view of their influence on the environment and the economic balance, and the energy requirements should be diminished. If possible, the chemical processes should be carried out at room temperature and atmospheric pressure.

The reaction energy could be photochemical, microwave or ultrasonic irradiation. A boom is currently occurring in the use of these green energy sources and this is also associated with a marked decrease in the reaction time, to higher yields and, very often, to higher product purity.

A number of azaheterocycles [i.e. pyrrole, imidazole (**29**), indole and carbazole (**32**)] react remarkably quickly with alkyl halides (**30**) to give exclusively N-alkyl derivatives (**31**, **33**) under microwave conditions [15, 16] (Scheme **7**).

A series of imines (**36**) was synthesized by an ultrasound-assisted reaction of aldehydes (**34**) and primary amines (**35**) using silica as the promoter [17] (Scheme **8**).
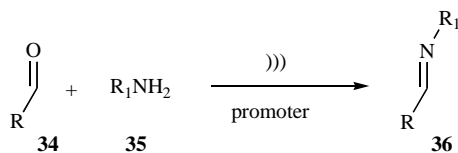
Scheme 8. Preparation of imines using alternative energy source.

7. Use of Renewable Feedstocks

The intermediates and materials should be renewable rather than depleting (which is the case with, e.g., crude oil) whenever this is technically and economically advantageous.

Biodiesel (**40**) is a diesel-equivalent biofuel that is usually produced from vegetable oil and/or animal fat (**37**) by re-esterification with methanol (**38**) or ethanol (Scheme **9**) and this material can be used in cars and other motors.
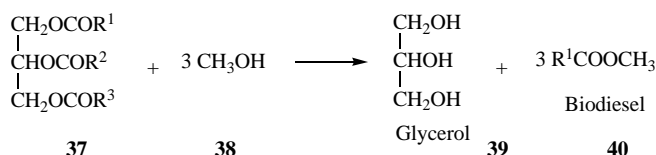
Scheme 9. Re-esterification of vegetable or animal fat for biodiesel production.

Interest in biodiesel as an alternative fuel has increased tremendously as a result of recent regulations requiring a substantial decrease in the hazardous emissions from motor vehicles, as well as the high crude oil prices. Biodiesels are biodegradable in water and are not toxic. Upon combustion, much less hazardous emissions are formed (less sulfur is emitted, 80% less carbohydrates and 50% less solid particles) as compared to petro-diesel. Biodiesel can be used in modern diesel motors without the need for alteration of the motor. With a flash point of 160 ºC, biodiesel is classified as a non-flammable liquid. This property makes it far safer in accidents involving motor vehicles when compared to petro-diesel and gasolines. Biodiesel production is, and will continue to be, related to a new revival in agriculture in some regions that are at present in decline [2, 18].

8. Decrease and/or Elimination of Chemical Stages

Derivatizations, such as protection/deprotection and various other modifications, should be decreased or avoided wherever possible since these stages require additional amounts of reagents and waste products could be formed.

Bromination at the *para-* or *ortho*-position of anilines (**41**, **42**) without protection of the amino group (Scheme **10**) [19] is a process in which the protection/deprotection steps have been removed.

9. Use of Catalysts

It is well known that catalysts increase substantially the chemical process rates, without their consumption or insertion into the final products.
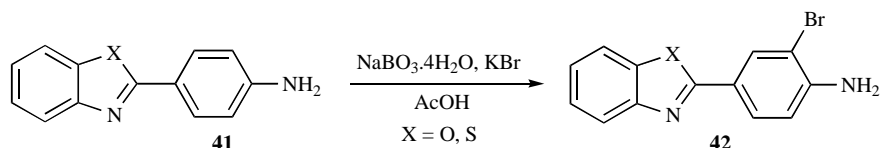
It follows that, wherever possible, a catalyst should be used in a chemical process. The advantages of using catalysts include:

- higher yield;
- shorter reaction time;
- the reaction proceeds in the presence of a catalyst but does not take place in its absence;
- increase in selectivity.

An example of this approach is the preparation of ketimines (**45**) from 1,3-dicarbonyl compounds (**43**) at room temperature in the presence of an $NaAuCl_4$ catalyst (Scheme **11**) [20].

R^1–R^4 = alkyl or phenyl
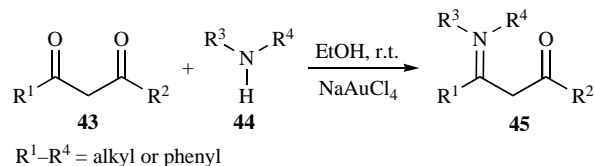
Scheme 11. Preparation of ketimines at room temperature in the presence of an $NaAuCl_4$ catalyst.

10. Design of Degradable Products

The design of the final chemical products should be such that, after fulfilling their functions, these products should easily degrade to harmless substances that do not cause environmental pollution.

This approach is exemplified by the creation of biodegradable "green" polymers [21, 22]. Conventional polymers such as polyethylene and polypropylene persist for many years after disposal. Built for the long haul, these polymers seem inappropriate for applications in which plastics are used for short time periods prior to disposal. In contrast, biodegradable polymers (BPs) can be disposed of in bioactive environments and degrade by the enzymatic action of microorganisms such as bacteria, fungi, and algae. The worldwide consumption of biodegradable polymers has increased from 14 million kg in 1996 to an estimated 68 million kg in 2001. Target markets for BPs include packaging materials (trash bags, wrappings, loose-fill foam, food containers, film wrapping, laminated paper), disposable nonwovens (engineered fabrics) and hygiene products (diaper back sheets, cotton swabs), consumer goods (fast-food tableware, containers, egg cartons, razor handles, toys), and agricultural tools (mulch films, planters) [21]. For example, poly(ε-caprolactone) (**46**), PCL, and poly(alkylenesuccinate)s (**47**) are biodegradable polymers. PCL is a thermoplastic biodegradable polyester that is synthesized by chemical conversion of crude oil, followed by ring-opening polymerization. PCL has good water, oil, solvent, and chlorine resistance, has a low melting point and low viscosity, and is easily processed thermally. To reduce manufacturing costs, PCL may be blended with starch – for example, to make trash bags. The blending PCL with fiberforming polymers (such as cellulose) has been used to produce hydro-entangled nonwovens (in which bonding of a fiber web into a sheet is accomplished by entangling the fibers using water jets), scrub-suits, incontinence products, and bandage holders. The rate of hydrolysis and biodegradation of PCL depends on its molecular weight and degree of crystallinity. However, many microbes in nature produce enzymes that are capable of complete PCL biodegradation (Fig. **3**) [22].
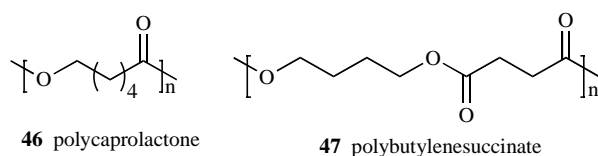
Scheme 10. Bromination of anilines without protection of the amino group.

46 polycaprolactone   **47** polybutylenesuccinate

Fig. (3). Chemical structures of biodegradable polymers polycaprolactone (**46**) and polybutylenesuccinate (**47**).

11. Real Time Analysis for the Avoidance of Contamination. Increase in the Role of Analytical Chemistry in Green Technologies

Analytical methodologies should be developed in such a way that the process can be monitored in real time.

New analytical tools are needed for real-time monitoring of industrial process and to prevent the formation of toxic materials. The growing field of process analytical chemistry is aimed primarily at obtaining the analytical data close to the production operation. A real-time field measurement capability is desired for continuous environmental monitoring and this would replace the common approach of sample collection and transport to a central laboratory [23].

The sensor in analytical chemistry will have a particularly important role to play, but in the future it is expected that traditional and instrumental analytical chemistry will also play a fundamental part in green technologies.

The environmental and industrial interest in biosensor technology has been driven by the need for faster, simpler, cheaper, and better monitoring tools [24]. Microfabricated microfluidic analytical devices, in which multiple sample-handling processes are integrated with the actual measurement step on a microchip platform, have been of considerable interest in recent times [25, 26]. For obvious reasons, such devices are referred to as "lab-on-a-chip" devices. In this respect complete assays, involving sample pretreatment (e.g., preconcentration/extraction), chemical/biochemical derivatization reactions, electrophoretic separations, and detection, have been carried out on single microchip platforms.

The dramatic downscaling and integration of chemical assays make these analytical microsystems particularly attractive as "green analytical chemistry" screening tools and hold considerable promise for faster and simpler onsite monitoring of priority pollutants. A large number of environmental applications of CE/EC microchips have already appeared, including rapid separation and detection of chlorophenols, nitroaromatic explosives, hydrazines and organophosphate pesticides [27, 28].

The revolution in green chemistry has provided new challenges and exciting opportunities for analytical chemistry and for the development of greener analyses, in general.

At this point it is worth highlighting that Van Aken *et al.* [29] developed an EcoScale, a semi-quantitative tool to select an organic preparation based on economical and ecological parameters. A novel post-synthesis analysis tool is presented that evaluates the quality of the organic preparation based on yield, cost, safety, conditions and ease of workup/purification. The proposed approach is based on assigning a range of parameters to the process. This semi-quantitative analysis can easily be modified by other synthetic chemists who can change some of the parameters as appropriate. This approach is a powerful tool to compare several preparations of the same product based on safety, economical and ecological features.

12. Inherently Safer Chemistry for Accident Prevention

The reagents used to carry out chemical processes should be chosen with caution in order to avoid accidents, such as the release of poisonous substances into the atmosphere, explosions and fires.

The oxidation of isatins (**48**) to isatoic anhydrides (**50**) has been achieved using a safe, cheap, stable and green oxidizing agent – urea/hydrogen peroxide complex (**49**) and ultrasound irradiation at room temperature (Scheme **12**) [30]. The oxidant is safer than liquid hydrogen peroxide.

Green Solvents [31]

The organic solvents used in numerous syntheses are quite hazardous to the environment. Volatile organic solvents are released into the environment by evaporation or flow in substantial amounts, since they are used in much higher proportions than the reagents themselves. A new approach to overcome this problem is to carry out the chemical reactions in the absence of such media, i.e., without solvents or by the use of non-volatile solvents that are harmless to humans and the environment. The ideal "green" solvent should have a high boiling point and it must be non-toxic, dissolve numerous organic compounds, cheap and, naturally, recyclable. Clearly such requirements strongly limit the choice of substance or class of compound as a green solvent. The substantial efforts of research groups throughout the world have led to the establishment of good alternatives to the common organic solvents, including: supercritical liquids, ionic liquids, low-melting polymers, perfluorinated (fluorous) solvents and water.

Alternative Solvents in Organic Syntheses

Water

Water is the basis and bearer of life. For millions of years, water has been at work to prepare the earth for the evolution of life. Water is the solvent in which numerous biochemical organic reactions (and inorganic reactions) take place. All of these reactions affect living systems and have inevitably occurred in an aqueous medium. On the other hand, modern organic chemistry has been developed almost on the basis that organic reactions often have to be carried out in organic solvents. It is only within the last two decades or so that people have again focused their attention on carrying out organic reactions in water.

Why should we consider using water in organic reactions as a green solvent?

There are many potential advantages:

- **Cost.** Water is the cheapest solvent available on earth; using water as a solvent can make many chemical processes more economical.

- **Safety.** Many organic solvents are flammable, potentially explosive, mutagenic, and/or carcinogenic. Water, on the other hand, has none of these adverse properties.
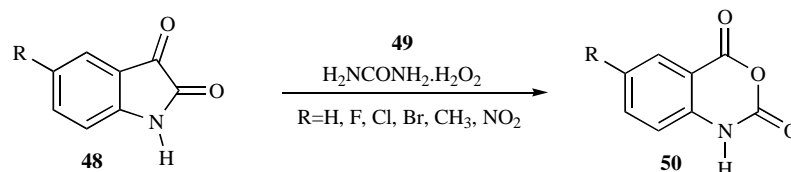
Scheme 12. Oxidation of isatins with urea/hydrogen peroxide complex and ultrasound irradiation at room temperature.
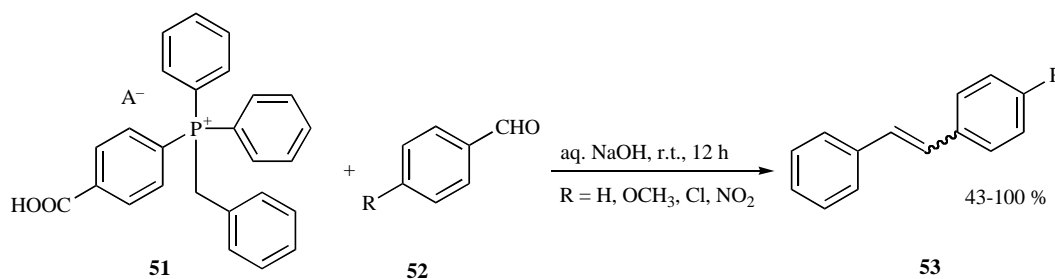
Scheme 13. Wittig reaction in aqueous media.

- **Synthetic efficiency.** In many organic syntheses it may be possible to eliminate the need for the protection and deprotection of functional groups, thus saving numerous synthetic steps. Water-soluble substrates can be used directly and this would be especially useful in carbohydrate and protein chemistry.

- **Simple operation.** In large industrial processes, isolation of the organic products can be performed by simple phase-separation. It is also easier to control the reaction temperature, since water has one of the highest heat capacities of all substances.

- **Environmental benefits.** The use of water may alleviate the problem of pollution by organic solvents since water can be recycled readily and is benign when released into the environment (when harmful residues are not present).

- **Potential for new synthetic methodologies.** Compared to reactions in organic solvents, the use of water as a reaction medium has been explored to a much lesser extent in organic chemistry. Furthermore, there are many opportunities to develop novel synthetic methodologies that have not been discovered before [32].

On the basis of the above characteristics water is probably the greenest solvent in view of its price, availability, safety and environmental effects. The drawbacks of using water, however, are that many organic compounds are insoluble or slightly soluble in water, and with some reagents (e.g., organometallic compounds) water is highly reactive. The use of water is often restricted to hydrolysis reactions, but in the early 1980s it was shown that water has unique properties that can lead to surprising results. The use of co-solvents or surfactants helps to increase the solubility of non-polar reagents by disrupting the dense hydrogen bonding network of pure water [33].

The Wittig reaction has been investigated in aqueous conditions [34, 35]. Wittig olefination reactions with stabilized ylides (known as the Wittig–Horner or Horner–Wadsworth–Emmons reaction) are sometimes performed in an organic/aqueous biphasic system [36, 37]. In many cases a phase-transfer catalyst is used. Recently, the use of water alone as the solvent has been investigated [38] and the reaction proceeded smoothly with a much weaker base such as K_2CO_3 or $KHCO_3$. In addition, a phase-transfer catalyst was not required. Recently, water-soluble phosphonium salts (**51**) were synthesized and their Wittig reactions with substituted benzaldehydes (**52**) were carried out in aqueous sodium hydroxide solution (Scheme **13**) [39].

The assessment of how green a solvent is requires the consideration of various aspects, such as environmental impacts arising from industrial productions, recycling and disposal processes, as well as EHS (environmental, health and safety) characteristics. 26 organic solvents have been studied [40] and results show that simple alcohols (methanol, ethanol) or alkanes (heptane, hexane) are environmentally preferable solvents, whereas the use of dioxane, acetonitrile, acids, formaldehyde and tetrahydrofuran is not recommendable from an environmental perspective.

Ionic Liquids

Ionic liquids are the most widely explored alternatives to organic solvents, as confirmed by the incredible number of publications in the literature dedicated to this topic. In our opinion, this is a new branch in applied organic chemistry and organic chemical technology [41].

The great interest in these compounds is due to the fact that they possess some quite attractive properties, such as negligible vapor pressure, good chemical and thermal stability, they are inflammable, have high ionic conductivity, wide electrochemical potential and, in addition, they can act as catalysts.

In contrast to conventional solvents that consist of single molecules, ionic liquids consist of ions and are liquid at room temperature or have a low melting temperatures (usually below 100 °C). Due to their ionic nature, these materials reveal different properties when used as solvents in comparison to conventional molecular liquids. A huge variety of ionic liquids can be envisaged by simple combination of different cations and anions. By changing the anion or the alkyl chain of the cation, physical properties, such as hydrophobicity, viscosity, density and solvating ability can be varied. The application of ionic liquids (**54**, **55**, Fig. **4**) is not limited only to the replacement of organic solvents in the reaction media of organic reactions. In some cases, ionic liquids can act as reagents, catalysts or media for catalyst immobilization or to induce chirality.
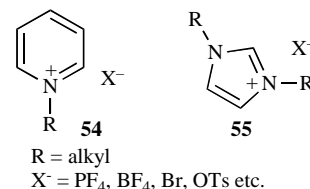

R = alkyl
$X^- = PF_4$, BF_4, Br, OTs etc.

Fig. (4). Chemical structures of some widely used ionic liquids.

The presence of Lewis acid species in chloroaluminate ionic liquids has also been used to bring about various acid-catalysed transformations that do not require additional catalysts. For example, acidic ionic liquids are ideally suited to Friedel–Crafts acylation reactions. In a traditional Friedel–Crafts acylation an acylium ion is generated by reaction between an acyl chloride and $AlCl_3$ or $FeCl_3$. Acidic chloroaluminate ionic liquids are able to generate acylium ions and are therefore ideally suited to Friedel–Crafts reactions. Acylation of mono-substituted aromatic compounds (**56**) in acidic chloroaluminate ionic liquids (**58**) leads almost exclusively to substitution at the 4-position (**59**) on the ring [42] (Scheme **14**).
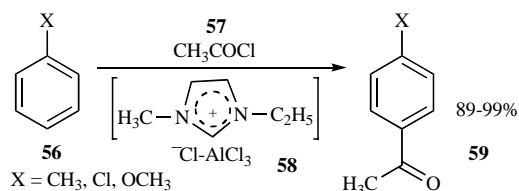
Scheme 14. Acylation of aromatic compounds in acidic chloroaluminate ionic liquid.
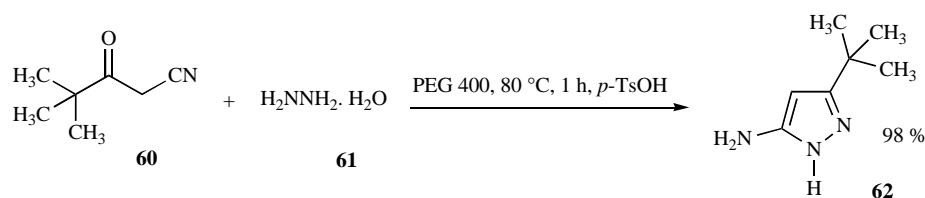
Scheme 15. Synthesis of 3-amino 1*H*-pyrazoles using PEG-400 as an efficient and reusable reaction medium.

Essentially, there is no limit to the number of different ionic liquids that can be engineered with specific properties for chemical applications. However, a number of problems still need to be overcome before their use becomes widespread.

The current problems associated with ionic liquids include:

1. Many are difficult to prepare in a pure form, and the current methods that provide pure ionic liquids are generally very expensive. Scale-up could be a problem in certain cases.

2. The viscosity of ionic liquids is often quite high. In addition, impurities can have a marked influence and may increase the viscosity of the ionic liquid. In the worse case scenario the addition of a catalyst and substrate to an ionic liquid can increase the viscosity to such an extent that it becomes gel-like and therefore difficult to process.

3. Some ionic liquids (e.g. chloroaluminates) are highly sensitive to oxygen and water, which means that they can only be used in an inert environment and all substrates must be dried and degassed before use.

4. Catalysts immobilized in ionic liquids are sometimes leached into the product phase. It may therefore be necessary to design new catalysts for use in ionic liquids.

Despite these problems, ionic liquids are currently attracting considerable attention as alternatives to volatile organic solvents in many different reactions, including oligomerization and polymerization, hydrogenation, hydroformylation and oxidation, C–C coupling and metathesis. In particular, ionic liquids containing BF_4^- or PF_6^- anions have been very widely used and several general properties have emerged:

1. These ionic liquids form separate phases with many organic materials and can therefore be used in biphasic catalysis.

2. These liquids are non-nucleophilic and present an inert environment that often increases the lifetime of the catalyst.

3. The rate of diffusion of gases is very high compared to many conventional solvents and this leads to increased reaction rates in catalysed reactions involving gaseous substrates such as hydrogenation, hydroformylation and oxidation [43].

Poly(ethylene glycol)

Poly(ethylene glycol) (PEG) is a linear polymer obtained by polymerization of ethylene oxide. The term PEG is used to designate a polyether with a molecular mass lower than 20000. It is known that PEG is a cheap, thermally stable, biocompatible, non-toxic material that can be recycled [44, 45]. In addition, PEG and its monomethyl ethers have low vapor pressures, are inflammable and can be separated from the reaction medium by a simple procedure. For this reason, it is believed that PEG is a green alternative to volatile organic solvents and is a very convenient medium for organic reactions. PEG is used as an effective medium for phase transfer catalysis and, in some cases, as a polyether catalyst in the phase transfer catalysis reaction.

Recently, PEG was used as a reaction medium for organic reactions; low molecular weight (< 20000) derivatives are usually applied since they have low melting points or are liquids at room tem-

perature. Despite the fact that PEGs are less widely used, they are commercial products and are much cheaper than ionic liquids but, unlike the latter, their properties cannot be changed easily. One of the greatest disadvantages of PEGs (which also holds for ionic liquids) is that organic solvents must be used for the extraction of the reaction products – although supercritical carbon dioxide ($scCO_2$) could also be used in both cases. The literature examples of the use of PEG are scarce but, in recent years, polyethylene glycol-promoted reactions have attracted the attention of organic chemists due to the solvating power of these compounds and their ability to act as a phase transfer catalyst, negligible vapor pressure, easy recyclability, reusability, ease of work-up, eco-friendly nature, and low cost.

An efficient and facile method for the synthesis of 3-amino 1*H*-pyrazoles (**62**) in the presence of *p*-toluenesulfonic acid using PEG-400 as an efficient and reusable reaction medium has been reported (Scheme **15**) [46]. This method does not require expensive reagents or special care to exclude the moisture from the reaction medium.

Perfluorinated (Fluorous) Solvents

The term "fluorous" was introduced for the first time by Horvath and Rabai [47] by analogy with "aqueous" or "aqueous medium". Fluorous compounds have recently been defined by Gladysz and Curran [48] as substances that are fluorinated to a high degree and are based on sp^3-hybridised carbon atoms. Perfluorous solvents, such as perfluoroalkanes, perfluoroalkyl ethers and perfluoroalkylamines, are chemically stable and are harmless to the environment since they are non-toxic (unlike the freons), inflammable, thermally stable and could be recycled. These compounds have a high ability to dissolve oxygen, which is an advantage used in medical technology. In fluorous solvents or liquids, the fluorine atoms are substituents on the carbon atoms (C–F bond).

Fluorous liquids have quite unusual properties and these include high density, high stability (mainly due to the stability of the C–F bond), low dissolving ability and extremely low solubility in water and organic solvents [49], although they are miscible with the latter at higher temperatures. The low solubility of the perfluorinated solvents can be explained in terms of their low surface tension, the weak intermolecular interactions, high densities and low dielectric constants.

The reactions that take place in perfluorous solvents show a somewhat different trend in comparison to the other alternative green solvents. Although they are solvents, they cannot be considered as substitutes for solvents. Due to the fact that they are extremely non-polar, they are inappropriate to perform most chemical reactions and are used together with conventional organic solvents to give biphasic mixtures.

In such a biphasic mixture, the soluble reagent or catalyst is in the fluorous phase while the starting materials are dissolved in the immiscible solvent phase, which could be an organic solvent, water or non-organic solvent. These two distinct layers are homogenized upon heating, the reactants come into contact with one another and the reaction takes place. The layers separate again upon cooling, with the reaction products remaining in the organic phase while the unreacted substances and the catalyst remain in the perfluorous phase. This situation allows an easy separation of the reaction prod-
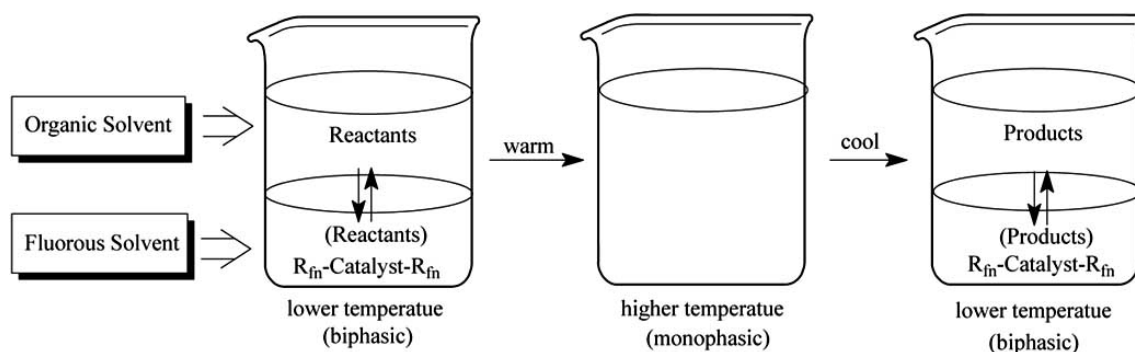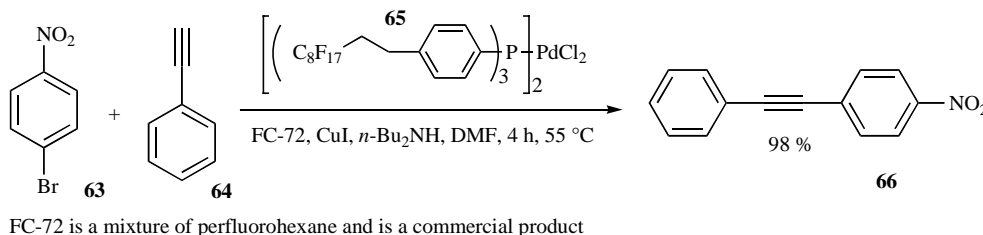
Fig. (5). Schematic representation of organic syntheses in fluorous solvents.

FC-72 is a mixture of perfluorohexane and is a commercial product

Scheme 16. Sonogashira coupling in a liquid/liquid fluorous biphasic system.

ucts and catalyst recycling without the use of an organic solvent for extraction. Such a system combines the advantages of a monophasic system with the ease of product separation in the biphasic system; this system is non-toxic, can be used several times, and allows the easy separation of the catalyst from the reagents and products (Fig. **5**) [50].

One example of this approach is the Sonogashira coupling in a liquid/liquid fluorous biphasic system for the preparation of 1-(4-nitrophenyl)-2-phenylacetylene (**66**) (Scheme **16**) [51].

In some cases the reaction takes place very rapidly at lower temperatures in a two-phase system.

A disadvantage of the fluorous solvents is that they are expensive and toxic gaseous fluorine or HF is required for their production [21].

Supercritical Liquids

A supercritical liquid (SCL) is defined as a substance above its critical temperature (Tc) and critical pressure (Pc). The properties of an SCL are between those of its liquid and gaseous phases. These properties can be specifically changed by varying the temperature and pressure.

The most widely used SCL is carbon dioxide (scCO$_2$). The critical point of CO$_2$ is at 73 atm and 31.1 °C – conditions that can easily be achieved in the laboratory. Other supercritical solvents are not as useful because of the extreme conditions required to achieve the critical point. For instance, the critical point of water is at 218 atm and 374 °C. Recently, examples have appeared in the literature of reactions in scH$_2$O [52].

The advantages of using scCO$_2$ are as follows: CO$_2$ is inflammable and is less toxic than most organic solvents, it is relatively inert toward reactive substances, it is a natural gas found in the atmosphere and there are no regulations concerning its use, it can be easily removed by decreasing the pressure, which provides the possibility of its easy removal from the reaction products, it has a high gas-dissolving ability, a low solvating ability, a high diffusion rate and good mass transfer properties. The selectivity of a reaction can be dramatically changed when conducted in sc liquids when compared to the use of traditional organic solvents.

In 1992 it was demonstrated that scCO$_2$ works as an alternative solvent to chlorofluorocarbons (CFCs) for the homogeneous free-radical polymerization of highly fluorinated monomers [53]. The homogeneous polymerization of 1,1-dihydroperfluorooctyl acrylate (**67**) using azobisisobutyronitrile (AIBN) (**68**) in scCO$_2$ (59.4 °C, 207 bar) gave perfluoropolymer (**69**) in 65% yield with a molecular weight of 270000 (Scheme **17**).

In 1994, the first example of free-radical dispersion polymerization using amphiphilic polymers as stabilizers in scCO$_2$ was reported [54]. ScCO$_2$ has also been successfully employed in cationic polymerizations. One example is the polymerization of isobutyl vinyl ether (IBVE) (**70**) using an adduct of acetic acid and IBVE (**71**) as the initiator, ethylaluminum dichloride as a Lewis acid and ethyl acetate as a Lewis base deactivator.
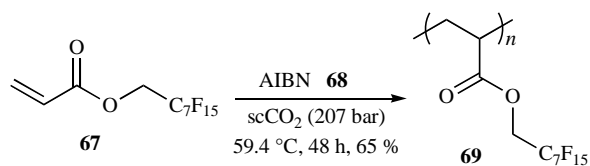
Scheme 17. Polymerization of an acrylate perfluoromonomer to perfluoropolymer in scCO$_2$.
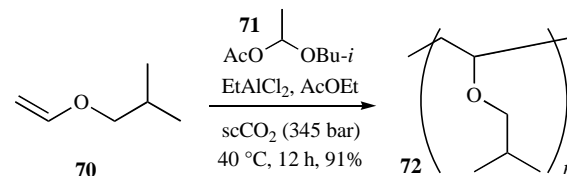
Scheme 18. Dispersion polymerization in scCO$_2$.

The reaction proceeded via a heterogeneous precipitation process in scCO$_2$ (40 °C, 345 bar) to form poly(IBVE) (**72**) in 91% yield with a molecular weight distribution of 1.8 (Scheme **18**) [55]. Several reviews have been published covering the history and recent developments of homogeneous and heterogeneous polymerizations in scCO$_2$ [56-58].
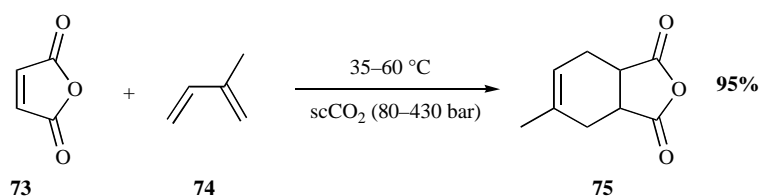
Scheme 19. Diels–Alder reaction in scCO$_2$.

Stoichiometric and catalytic Diels–Alder reactions in scCO$_2$ have been studied extensively and the first report appeared in 1987 [59]. The reaction of maleic anhydride (**73**) and isoprene (**74**) was conducted in scCO$_2$ and the effect of CO$_2$ pressure (80–430 bar) on the reaction rate was investigated (Scheme **19**).

The disadvantages of supercritical fluids should also be mentioned and these include the following: reactivity towards strong nucleophiles, specialized and expensive equipment is required to achieve the critical conditions, low dielectric constant and hence low dissolving ability, and the fluid behaves as a hydrocarbon solvent – for this reason it dissolves catalysts and/or reagents with some difficulty.

Where Does Public Opinion Stand on Chemistry?

Chemistry plays a key role in maintaining and improving the quality of our lives. Unfortunately, the majority of people and governments do not fully appreciate this role. In fact, chemists, chemistry and chemicals are regarded by many as the source of environmental protection problems. An investigation in the USA in 1994 showed that 60% of the people have a negative attitude towards the chemical industry. At the same time, pharmaceutical and polymer chemistry both have a better image, probably due to the natures of their products and respective benefits. Public opinion is more negative towards the chemical industry than towards the petro-, wood-processing and paper industries. The main reason for this is the opinion that the chemical industry has an unfavorable impact on the environment [60].

Only one third of the individuals interviewed believed that the chemical industry is concerned about the protection of the environment and only one half admit that intensive work is done to solve environmental problems. The negative public opinion contradicts the tremendous economic success of the chemical industry. The scope of chemical products is huge and these products have an invaluable part to play in improving of our quality of life. In the fabrication of these products, millions of tons of waste products are formed and the solution to this problem is a basic aim for industry, governments, education and society.

The challenges to chemists and other specialists related to the chemical industry and education are to create new products, new processes and a new approach to education in order to achieve social and economic benefits, as well as benefits for the environment, which cannot be postponed any longer. A change in public opinion is also important, but this is expected to require many years. All of the aspects outlined above form part of the vocation of Green Chemistry.

It is obvious that, after two centuries of the development of modern chemistry and more than a century of industrial chemical production, mankind has arrived at the invisible point where two issues are clear: (i) without chemistry (meaning new materials, effective drugs, plant protection systems, dyes, computers, fuels etc. – the list could be extended) mankind cannot exist at the present stage of development and (ii) in its present form, chemical production should not exist.

CONCLUSIONS

- Green Chemistry is not a new branch of science. It is a new philosophical approach that, through the introduction and expansion of its principles, could lead to a substantial development in chemistry, the chemical industry and environmental protection.

- Future generations of chemists should be trained in the principles of Green Chemistry and should possess knowledge and habits that should be applied in practice.

- At present, one can easily find in the literature quite interesting examples of the use of the rules of Green Chemistry. These principles could be applied not only to the synthesis, but to the processing and use of chemical substances. Numerous new analytical methodologies have been described and these are carried out according to the rules of Green Chemistry. These approaches are particularly important in conducting chemical processes and assessing their impact on the environment.

- In the coming decades Green Chemistry will continue to be attractive and practical. It is expected that this approach will solve numerous ecological problems. The development of waste-free technologies as well as technologies that have a lesser impact on the environment at the research stage does not guarantee their adoption on an industrial scale. The implementation of such technologies in industry can be ensured by more flexible legislation, new programs for the acceleration of the technological transfer between academia and governments and, last but not least, tax advantages for companies for the industrial application of cleaner technologies.

- All of us, by using the comforts of modern civilization, contribute to environmental pollution and are in debt to Mother Nature. The education in Green Chemistry of future generations of chemists will contribute to the solution of numerous ecological problems on the national, regional and global scale and will allow the specialists trained by us to be competitive within the global economy.

- By starting education in Green Chemistry right now we should travel a long way along the path to fulfill our mission and to enjoy the results of our efforts for future generations of chemists and other specialists.

Finally, let us cite Raveendran [61] "The Nobel Prize for Green Chemistry will definitely boost the efforts for a sustainable chemistry"

In our opinion this will inevitably happen in the very near future.

The biggest challenge to Green Chemistry is to put its rules into practice.

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