

TARGET TO MAKE WORLD POLLUTION FREE IN PILOT PLANT SYNTHESIS BY GREEN CHEMISTRY

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ABSTRACT

This paper provides an overview of applicability by 12 principles and future trends of Green Chemistry. Green or Sustainable Chemistry is a term that refers to the creation of chemical products and processes that reduce or eliminate the use and production of harmful substances. They are used exclusively chemicals and chemical processes that do not have negative consequences for the environment. It is based on twelve principles that can be used to initially create or recreate molecules, materials, reactions and processes that are safer for human health and the environment. The processes of the Green Chemistry that have been developed to date include almost all areas of chemistry, including organic, inorganic, biochemistry, polymer, toxicology, environmental, physical, technological, etc. Through the several prevailing trends of the green program such as catalysis, bio catalysis and the use of alternative: renewable feedstock (biomass), reaction media (water, ionic liquids and supercritical fluids), reaction conditions (microwave irradiation) and new synthetic pathways (photocatalytic reaction), the dual goals – environmental protection and economic benefit can be achieved. This article shows examples of the prevailing trends in ways that Green Chemistry reduces the impact of chemical processes and technologies on the environment.

KEYWORDS: Atom Economy, Safer solvents, Catalysts, In-situ synthesis, Reuse, Renewables, Safer Chemicals, Waste Prevention, Safer chemistry.

INTRODUCTION

Accelerated progress in science and technology in the second half of the twentieth century has led to significant economic development and an increase in living standards in developed parts of the world. However, such

economic development has also caused considerable environmental degradation, which is manifested by more pronounced climate change, the emergence of ozone holes and the accumulation of non-destructive organic pollutants in all parts of the biosphere.



Figure 1: Green Chemistry.

The newly established situation required the search for a solution to balance the use of natural resources,

economic growth and environmental conservation. As a result of such reflections in the last two decades,

awareness of the need for environmental protection has increased, so great attention is paid to the so-called "Green and viable technologies. The new laws and regulations aim to protect the ecosystem from harmful chemicals, while the chemical community through the processes of green chemistry is geared towards developing new compounds and processes that are less dangerous to human health and the environment. Green or Sustainable Chemistry is a term related to the creation of chemical products and processes that reduce or eliminate the use and production of harmful substances. As a new branch of chemistry with ecological approaches it involves reducing or eliminating the use of harmful substances in chemical processes as well as reducing harmful and toxic intermediates and products. To be called "green," each reaction should have three green components: solvent, reagent/catalyst and energy consumption. Green chemistry is based on twelve principles that can be used to create or recreate

molecules, materials, reactions and processes that are safer for human health and the environment, and the processes of green chemistry developed to date include mainly all areas of chemistry, including organic, inorganic, biochemical, polymeric, toxicological, environmental, physical, technological, etc. Basic principles of green chemistry cover a wide spectrum of synthetic organic synthesis: designing processes in organic synthesis to reduce by-product/waste generation, reduce the use of hazardous chemicals/raw materials and enhance the use of safer or more environmentally-safe solvents and (bio) catalysts, renewable raw materials and how Would improve energy efficiency. In addition, green chemistry is interested in the best form of waste disposal and designing the process of degradation of chemical products after use, all in accordance with pollution prevention and sustainable development measures.^[1]



Figure 2: Twelve principles of Green Chemistry.

The goals of green chemistry in environmental protection and economic profit are achieved through several dominant directions such as catalysis, bio catalysis, the use of alternative renewable raw materials (biomass), alternative reaction media (water, ionic liquids, supercritical fluids), alternative reaction conditions (microwave activation, Mechanochemistry and ultrasound) as well as new photocatalytic reactions. This paper aims to contribute to a better understanding of the principles and processes underlying green chemistry, and through examples and dominant trends to point to the ways in which green chemistry reduces the impact of chemical processes and technology on the environment.

Definition of Green Chemistry: According to the EPA definition, green chemistry is defined as a chemistry that designs chemical products and processes that are harmless to the environment, thus preventing the formation of pollution. Chemical products should be made so that they do not remain in the environment at the end of their application and that they are broken down into components that are harmless to the environment. Saving based on efficient synthesis without the use of "exotic" reagents, reducing the required energy, and replacing organic solvents with water are significant even at the laboratory level, while in industrial scale possible millions of savings.^[2]

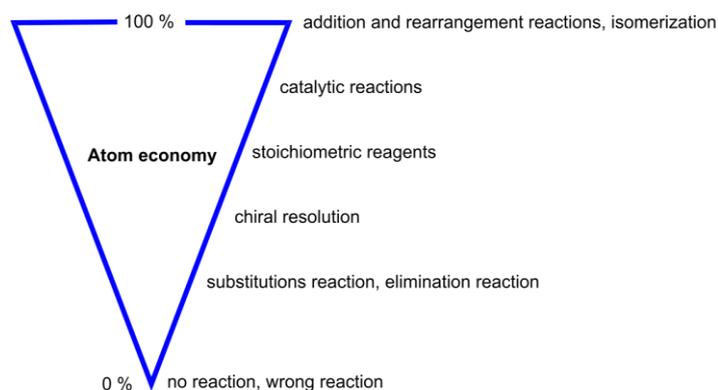
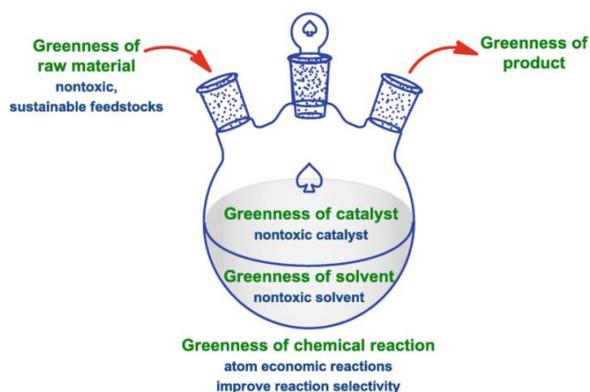


Figure 3: Atom Economy.

Green chemistry is not a separate scientific discipline, but a responsible interdisciplinary approach to science, based on chemical, ecological and social responsibility, which enables creativity and the advancement of innovative research.^[3] As a propulsive area of research, it tries to find and maintain a balance between the use of natural resources, economic growth and environmental conservation. In the field of synthetic chemistry, the greenness of the reaction process is required such as the greenness of raw materials, catalyst, solvent, and product as depicted in Scheme-1. The key content of the green synthesis would be atom economy. Therefore, discussion on atom economic reactions and how to improve the atom economy are mainly given in this chapter in combination with both fundamental research and industrial respects.

Generally speaking, atom economic reaction is considered with high ratio of atom utilization. Therefore, features are born with (1) maximizing the conversion of raw materials and (2) minimizing the waste emission: e.g., ideal "zero emission" process. According to the concept, the higher the atom efficiency is, the less waste is produced; as a result of less pollution to the environment.

Additionally, Trost puts forward the perception of synthetic efficiency for guiding the synthetic methodology to be developed preferentially.^[4] Two aspects in synthetic efficiency are referred as below: (1) selectivity such as chemo-selectivity, regioselectivity, enantioselectivity, and diastereoselective and (2) atom economy of chemical reaction, namely, how many atoms in the raw material and reagent are incorporated into the target product.



Scheme-1: Green Synthesis.

Calculation & Reaction: Atom economy is defined as the ratio, namely, molecular weight of the expected product/total molecular weight of all resultants $\times 100\%$. In fact, the molecular weight (MW) of some unknown by-products with uncertain atom constitutes is not be determined in many processes. Therefore, it is difficult to calculate the atom efficiency directly. As a supplementary method, atom utilization rather than atom economy is defined here. Generally, atom economic reaction is considered as the transformation with high percentage of atom utilization. In the practical work, atom utilization is useful tool for selecting the synthetic route with high atom economy.^[5]

Equation-1: Atom utilization (%) = (Atoms in the product/Atoms in all reactants) × 100%

In addition, several concepts including conversion, yield, and selectivity are also introduced herein. Among them, conversion, an important indicator of the reaction, is used to describe the reaction stage or efficiency. In addition, the yield and selectivity are used to directly evaluate the reaction outcome. Especially, in many processes, side reaction is generally accompanied simultaneously. Therefore, the selectivity is one of the most key indicators to assess the specificity on the target transformation.

Equation-2: Conversion (%) = (Transformed quantity of substrate A/Total amount of substrate A) × 100%

Equation-3: Yield (%) = (Experimental quantity of the target product/Theoretical quantity of the target product) × 100%

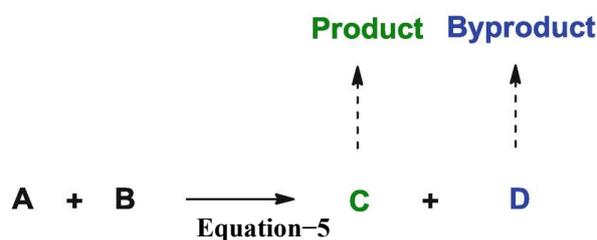
Equation-4: Selectivity (%) = (Quantity of the target product/Total quantity of reactants subtracts the remaining reactants) × 100%

Atom Economic Reaction: In traditional synthetic chemistry, great efforts have been devoted to improve the product yield; however, much waste is still generated even in a process with 100% yield. Therefore, through “yield” to evaluate the productivity and greenness of the process without considering the by-products is

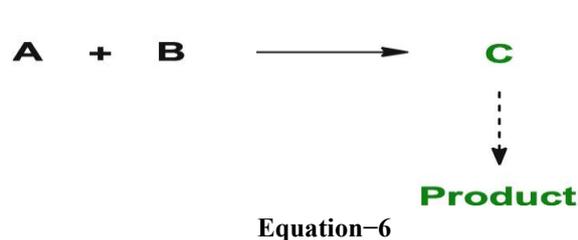
insufficiently comprehensive. Luckily, the concept of atom economy is created, and development of ideal atom economic reaction is a main target for green synthetic chemistry. Ideal synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product. Herein, the classical examples for the atom economic reaction are overviewed and discussed, and an inspiration is given to readers on what is the atom economic reaction and how to achieve the goal with a greenness of synthetic chemistry and engineering.

In an efficient synthetic reaction, high yield and selectivity are generally required. But in fact, atom economy of the reaction is also a key factor in consideration of green chemistry. In an ideal route, the raw material is used fully without side reaction; namely, all of the atoms are transferred into the products through catalytic process. For example, Equation-5 displays the conventional reaction pattern along with the by product. Although the high selectivity of C is gained, atom economy of the reaction is still low due to the ineffective atom shift into the by-product D. In addition, Equation 6 represents the 100% atom economic reaction with full utilization of the raw materials (by-product D is inhibited: “zero emission”).^[6]

1) Traditional reaction



2) Atom economic reaction



Wittig reaction, a useful tool for C=C bond construction developed by Wittig and Brown (Equation-7) has been widely applied in the synthesis of the complicated natural products and was awarded the Nobel Prize in 1979. It features as easily available raw materials, simple experiment procedure, and high yield. Even though a nice yield is obtained, the atom economy of this reaction is very low (29.8%). For methyl bromide

triphenylphosphine PPh_3 , only methylene species is incorporated into the target product, namely, only 4% $[14/(118 + 278) \times 100\%]$ atom efficiency is acquired. Meanwhile, large ratio of triphenylphosphine oxide as a waste is generated. Therefore, the exploration of atom economic reaction together with high selectivity is of much importance in practical synthetic chemistry.



$$\text{Atom economy (\%)} = \frac{118}{118 + 278} \times 100\% = 29.8\%$$

Equation-7.

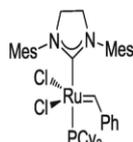
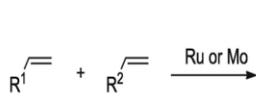
The Nobel Prize in Chemistry in 2005 was awarded jointly to Yves Chauvin, Robert H. Grubbs, and Richard R. Schrock “for the development of the metathesis method in organic synthesis.” Olefin metathesis, an excellent model in green chemistry, is described as an

atom economic reaction with “zero emission” bearing with the salient features of diversity, high efficiency, and wide applications (selective examples in Equation-8 and 9). According to the classification of molecular skeleton, there are five types including

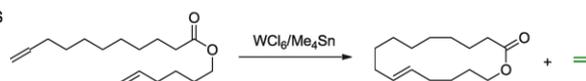
ring-opening metathesis, ring-opening metathesis polymerization, acyclic diene metathesis polymerization, ring-closing metathesis, and cross metathesis. Now, it has been an important method in numerous fields such as organic synthesis and polymer material chemistry and so on. The by-product, e.g., ethylene, is a valuable

industrial material rather than the waste. As appraised in Press Release “This represents a great step forward for ‘green chemistry’, reducing potentially hazardous waste through smarter production. Metathesis is an example of how important basic science has been applied for the benefit of man, society and the environment.”^[7]

Cross Metathesis



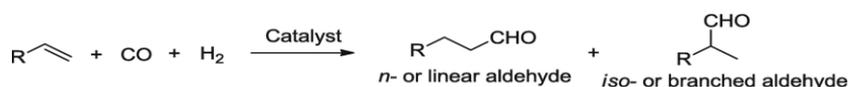
Ring Closing Metathesis



Equation-8 and Equation-9.

In addition, there are many classical examples on atom economy in the industrial production. These types of atom economic reactions include olefin hydroformylation with CO and hydrogen, carbonylation of methanol to acetic acid, olefin polymerization by Ziegler-Natta catalyst, and addition reaction of 1,3-butadiene, and HCN for the preparation of adiponitrile. Take hydroformylation as an example,

hydroformylation is the addition of synthesis gas (“syngas”), a mixture of CO and H₂, to olefins in the presence of a metal catalyst with the production of aldehydes. In this reaction, hydrogen (“hydro”) and a formyl group (H-C=O) are added in an atom-economical manner with 100% atom efficiency (Equation-10).



$$\text{Atom economy (\%)} = 100\%$$

Equation-10.

Acetic acid, an important commodity chemical, has been found a broad range of applications. For example, it is used as a raw material for the synthesis of vinyl acetate monomer and acetic anhydride and as a solvent for the purified terephthalic acid production. Global demand on virgin acetic acid market stands at 13 million tons in 2015 with annual growth rate of around 5%. Catalytic carbonylation of methanol is one of the most significant methods for the production of acetic acid (Equation-11). Nowadays, most acetic acid is produced via methanol carbonylation. In this process, methanol reacts with carbon monoxide to produce acetic acid without the generation of any waste; thus, atom economy reaches 100%.^[8]

Equation-11: CH₃OH+CO→Catalyst CH₃COOH

Atom economy (%) = 100%

CH₃OH+CO→Catalyst CH₃COOH

Atom economy (%) = 100%

Criteria for Evaluation on Reaction/Process: For an appointed chemical reaction, atom economy could well reflect the greenness of the reactions and chemical processes. But for a whole process, it is difficult to effectively assess in one standard only via atom economy because various reagents may be used and much waste is generated beyond the reaction itself. In addition, it is too simple to evaluate the different process only through the amount of by-product or waste materials, i.e., the metric of atom efficiency. Therefore, a much precise evaluation method should be put forward to calculate both the

quantity and the property of by product or waste, e.g., environment factor (E factor). Based on the debates and the impact of reaction route on the environment, Sheldon proposes E factor (kg waste per kg of desired product) as a metric for quickly assessing the environmental footprint of chemical processes. For a specific chemical, any material can be regarded as waste beyond the desired products.

According to the value of E factor, chemical industry is divided into four sectors by Sheldon as described in Table-1. The data indicate that the deeper the product is refined; the more waste is produced. This is because fine chemicals are obtained through a number of procedures, and the amount of the total waste from each process could be large. As a result, the large amount of waste further restricts industrial application. Therefore, the exploration of atom economy reaction with “zero emission” is of much significance and urgently required.^[9]

Table 1: E factor in the chemical industry. (The Royal Society of Chemistry).

| Industry segment | Tons per annum | E factor (kg waste per kg product) |
|------------------|----------------------------------|------------------------------------|
| Oil refining | 10 ⁶ -10 ⁸ | < 0.1 |
| Bulk chemicals | 10 ⁴ -10 ⁶ | < 1-5 |
| Fine chemicals | 10 ² -10 ⁴ | 5-50 |
| Pharmaceuticals | 10-10 ³ | 25-> 100 |

In Sheldon's subsequent research, the concept of E factor has been expanded. The pollution level being from the waste discharged into the environment is considered to be related to the toxicological properties and toxic behaviour in the corresponding surroundings. Therefore, to evaluate the synthetic method precisely, the amount of the waste and its behaviour essence in the environment should be taken into account, and the integrated performance is described as environmental quotient (EQ, E: Environmental factor; Q: Quotient, Equation-12). Q describes the abstracted degree of unfriendliness according to the behaviour of the waste in the environment. For example, the Q value of innocuous NaCl is assigned as 1, and the Q value of heavy metal salt, such as chromium, is 100~1000 depending on its toxicity, ease of recycling, etc.

Although EQ value is distinguishing in different department, production area, and the region, the EQ method is calculated simply with direct results on the

environmental toxic and therefore used as an important indicator to assess the environmental impact of specific process. This metric is beneficial to quantify the amount of waste generated per kilogram of product. Therefore, it is a means to assess the "environmental acceptability" of a manufacturing process. In the viewpoint of green chemistry, the reaction should behave the minimal EQ value.^[10]

Equation-12: $EQ = E \times Q$

The E factor metric is based on the mass of the waste generated from any given process. Notably, during recent years, other mass metrics such as process mass intensity (PMI, Scheme-2) focused on the total mass of materials are proposed as the key and high-level mass metric used for evaluating and benchmarking progress towards sustainable manufacture as listed in Table-2. In addition, Andraos adopts a general formula of Relative Mass Efficiency (RME) for sake of unification of mass metrics and applies it for assessing organic syntheses.

$$\text{Process mass intensity (PMI)} = \frac{\text{total mass in a process or process step (kg)}}{\text{mass of product (kg)}}$$

$$\text{E factor} = \frac{\text{total mass of waste (kg)}}{\text{mass of product (kg)}}$$

$$= \frac{\text{total mass used in process or process step} - \text{mass of product (kg)}}{\text{mass of product (kg)}} = \text{PMI} - 1$$

Scheme-2: The relationship between PMI and E factor.

Table 2: Mass metrics. (Copyright M. Gabriela T.C. Ribeiro and Adélio A.S.C. Machado).

| Name | Expression | Aim | Ideal value | References |
|---------------------------------|---|----------|-------------|------------|
| Environmental factor (E factor) | mass of waste / mass of the product | Decrease | 0 | 29 |
| Mass intensity (MI) | total mass of all the reagents / mass of the product | Decrease | 1 | 15 |
| Atom economy (AE) | molecular weight of the product / sum of molecular weights of all the stoichiometric reagents | Increase | 100% | 17 |
| Atom utilization (AU) | mass of the product / total mass of all the substances produced | Increase | 100% | 29 |
| Relative mass Efficiency (RME) | mass of the product / total mass of all the stoichiometric reagents | Increase | 100% | 15 |
| Element (X) Efficiency (XEE) | mass of the element in the product / total mass of the element in the stoichiometric reagents | Increase | 100% | 15 |

Based on all the principles indicated in the previous reports, the ideal chemical synthetic process may include: 100% atom efficiency, 100% yield and selectivity, easily available raw materials, renewable, simple, one-step, safe, and environmentally friendly. Although great advances have been made in the evaluation metric for the reaction and chemical process, herein, main attention is paid to the atom economic

reaction and improvement strategies in the subsequent sections.^[11]

Strategies to Improve Atom Economy.

The Design of Greener Synthetic Pathways: It is one of the most important aims to develop highly efficient methodology for organic synthesis. In 1993, Wender proposed the concept of step economy, in which shortest

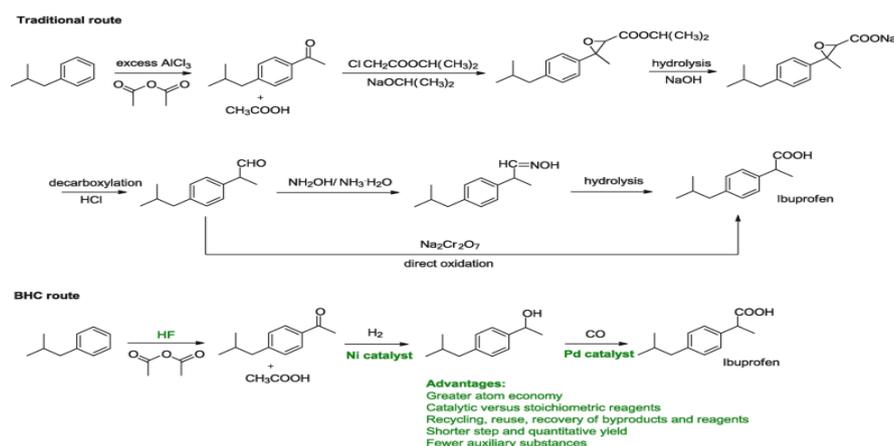
reaction route is required for facile synthesis of the target product with overall consideration of the factors such as route length, cost, time, total yield, procedure, and environment. It has been developed to be one important method to achieve the goal through the development of step economic process. But in fact, plenty steps including multistep synthetic procedure, separation, and purification are commonly required in the synthesis of most complicated molecules. Therefore, it is a pivotal task to develop step economic processes in modern organic synthesis.

As an example, in this aspect, Ibuprofen is the main component in the painkiller such as Motrin, Advil, and Medipren. It has been widely applied since it was firstly synthesized in 1961 by Boots Company. In early stage, six steps are required including Friedel–Crafts acylation of isobutyl benzene to give isobutyl acetophenone, followed by Darzens condensation, and oxidation or oximate/hydrolysis. This route is bore with complicated steps, low atom economy (Table–3, atom efficiency 40%), and intensive energy consumption. More than half of the raw material is wasted. In addition, several other disadvantages cover much generated inorganic salt, complicated refinement for the product, high cost, and serious pollution. During 1990s, BASF and Hoechst

Celanese Company (BHC co–partnership) have developed the carbonylation route of 1–(4–isobutylphenyl) ethanol to improve Ibuprofen synthesis, as shown in Scheme–3. In traditional route, stoichiometric AlCl_3 is required to gain high yield in the first step, and a large amount of $\text{Al}(\text{OH})_3$ is generated simultaneously. On the other hand, in the BHC method, high yield is obtained through HF catalysis, and meanwhile the catalyst could be recovered and reused so that no waste is produced. As a result, the target product is acquired through only three steps in the alternative route, resulting in great improvement of the atom efficiency with saving energy, short period of production (Table–3, up to 77.4%). Besides, the other two steps in BHC process use Raney nickel and palladium catalysts that also could be recovered and reused. Furthermore, given the recovery of the by–product, i.e., acetic acid, the atom economy reaches up to 99%. Therefore, this new synthetic route could remarkably reduce the pollution and the production cost in comparison with traditional process, thus representing the improved process with harvesting both economic and environmental benefits. In 1997, BHC process for the synthesis of ibuprofen was awarded “Presidential Green Chemistry Challenge Award.”¹²¹

Table 3: Calculation of the atom economy in the synthesis of ibuprofen.

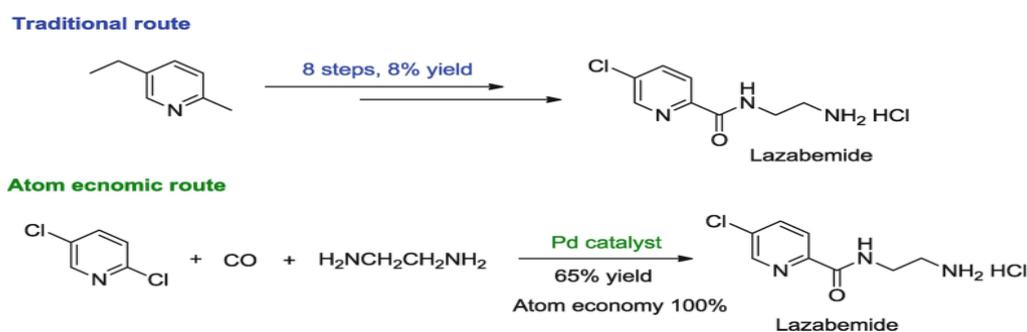
| Reagent | | Used in ibuprofen | | Unused in ibuprofen | |
|--|-------|--|-----|---|-------|
| Formula | MW | Formula | MW | Formula | MW |
| $\text{C}_{10}\text{H}_{14}$ | 134 | $\text{C}_{10}\text{H}_{13}$ | 133 | H | 1 |
| $\text{C}_4\text{H}_6\text{O}_3$ | 102 | C_2H_3 | 27 | $\text{C}_2\text{H}_3\text{O}_3$ | 75 |
| $\text{C}_4\text{H}_7\text{ClO}_2$ | 122.5 | CH | 13 | $\text{C}_3\text{H}_6\text{ClO}_2$ | 109.5 |
| $\text{C}_2\text{H}_5\text{ONa}$ | 68 | | 0 | $\text{C}_2\text{H}_5\text{Ona}$ | 68 |
| H_3O | 19 | | 0 | H_3O | 19 |
| NH_3O | 33 | | 0 | NH_3O | 33 |
| H_4O_2 | 36 | | 33 | H_3 | 3 |
| Total | | Ibuprofen | | Wastes | |
| $\text{C}_{20}\text{H}_{42}\text{NO}_{10}\text{ClNa}$ | 514.5 | $\text{C}_{13}\text{H}_{18}\text{O}_2$ | 206 | $\text{C}_7\text{H}_{24}\text{NO}_8\text{ClNa}$ | 308.5 |
| Atom economy = $206/(206 + 308.5) \times 100\% = 40\%$ | | | | | |
| Reagent | | Used in ibuprofen | | Unused in ibuprofen | |
| Formula | Mw | Formula | Mw | Formula | Mw |
| $\text{C}_{10}\text{H}_{14}$ | 134 | $\text{C}_{10}\text{H}_{13}$ | 133 | H | 1 |
| $\text{C}_4\text{H}_6\text{O}_3$ | 102 | $\text{C}_2\text{H}_3\text{O}$ | 43 | $\text{C}_2\text{H}_3\text{O}_2$ | 59 |
| H_2 | 2 | H_2 | 2 | | 0 |
| CO | 28 | CO | 0 | | 0 |
| Total | | Ibuprofen | | Wastes | |
| $\text{C}_{13}\text{H}_{22}\text{NO}_4$ | 266 | $\text{C}_{13}\text{H}_{18}\text{O}_2$ | 206 | $\text{C}_2\text{H}_4\text{O}_2$ | 60 |
| BHC route: Atom economy = $206/(206 + 60) \times 100\% = 77.4\%$ | | | | | |



Scheme-3.

Synthetic routes to ibuprofen: Lazabemide, one kind of antiparkinsonian drug, is prepared via catalytic carbonylation with high atom economy by Hoffmann-La Roche Company. In traditional synthetic route from 2-methyl-5-ethylpyridine, 8 steps are required and only 8% aimed product is obtained as illustrated in Scheme 4.

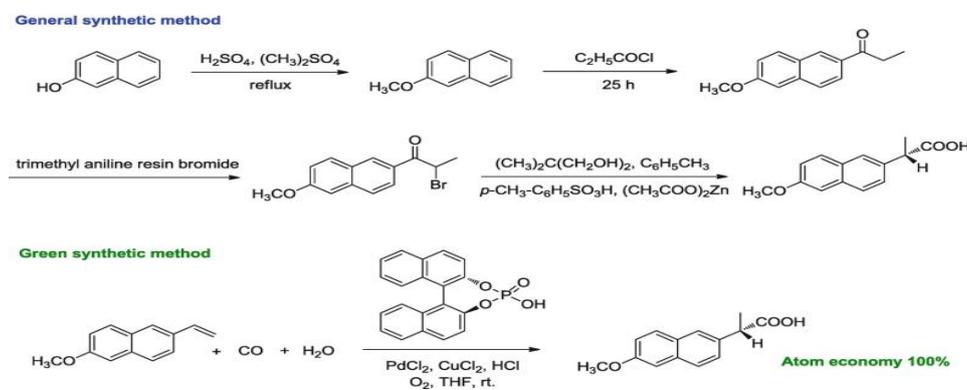
In the alternative route, only single step is needed through the Pd-catalyzed carbonylation of 2,5-dichloropyridine, carbon monoxide, and 1,2-ethylenediamine. The atom economy is up to 100% with the production capacity of more than 3000 tons per year.^[13]



Scheme-4.

Synthetic access to Lazabemide: Naproxen, one antiphlogistic and analgesic drug [(S)-(+)-1-(6-methoxy-2-naphthyl) propionic acid], is used for killing numerous diseases such as rheumatoid arthritis, rheumatic arthritis, ankylosing spondylitis, various rheumatic tendinitis and scapulothoracic periarthritis, and so on. Its synthetic route started from

β -naphthol includes etherification, Friedel-Crafts acylation, bromination, oxidation, hydrogenation, and subsequent chiral separation process. This method features as multistep, high cost, and serious pollution from the process of concentrated sulfuric acid catalysis and pH regulation through sodium hydroxide solution and hydrochloric acid, as illuminated in Scheme-5.



Scheme-5.

Asymmetric synthesis of Naproxen: In the alternative synthetic route, the chiral phosphoric acid ligands are explored to assist and control the tandem asymmetric

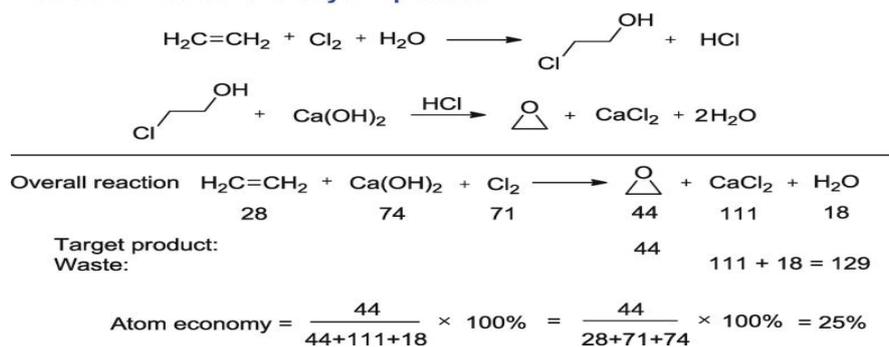
hydrogenation/carboxylation of olefins with high yield and selectivity under ambient conditions. Compared with previous process, this pathway has advantages with

shorter reaction steps, milder reaction conditions, avoidable organic solvent such as toluene, methanol, and dichloroethane, etc., simple posttreatment, nearly no waste generation, and high atom economy.^[14]

The traditional method for the preparation of ethylene oxide in industry is chlorohydrination as shown in Scheme-6. Initially, the reaction of ethylene and chlorine gives chloroethyl alcohol. Subsequently, the chloroethyl alcohol reacts with the aqueous solution of calcium hydroxide through elimination reaction. In the process, chlorine is harmful and is not incorporated finally into

the product and in contrast is converted into calcium chloride which is discharged along with the waste water. Therefore, atom economy of this process is low with the generation of a large amount of the salt residue and waste water which could further pollute the environment. The atom utilization of this process is just 25% which means the three times of the waste amount than the target product (i.e., 1 kg product/3 kg waste). In addition, separation and purification are necessary to obtain the target product. Therefore, the method does not meet the requirement of green chemistry.

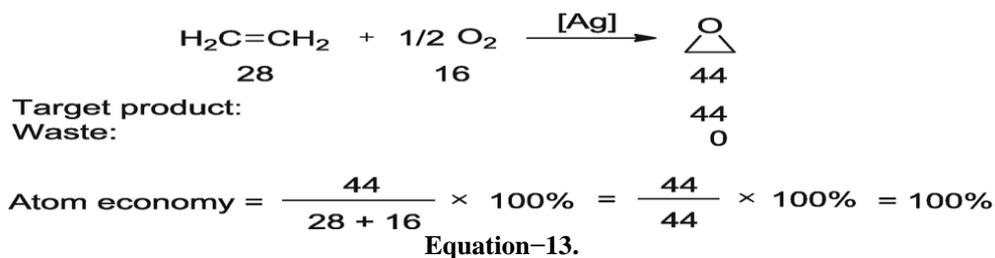
Traditional method: chlorohydrin process



Scheme-6.

Traditional synthetic method of ethylene oxide: A one-step atom economic method to produce ethylene oxide through epoxidation of ethylene has been well developed already (Equation-13). The alternative method employs oxygen as oxidant through silver

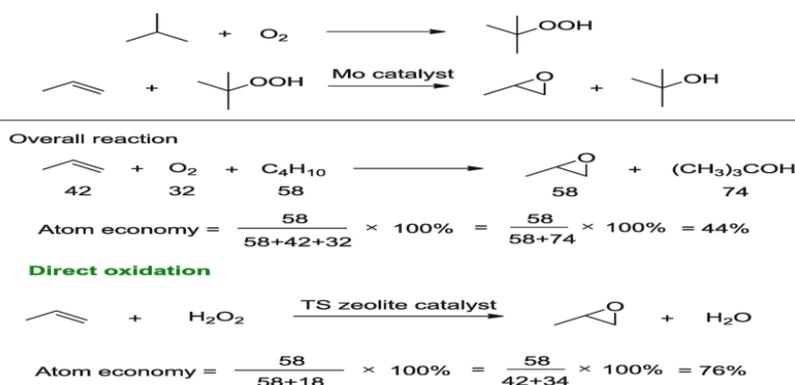
catalysis with up to 99% yield and 100% atom efficiency without separation or purification process. Therefore, this method can be regarded as an environmentally friendly approach for the production of ethylene oxide.^[15]



Equation-13.

In addition, the atom economy reaches up to 44% in the synthesis of propylene oxide from propylene through a two-step oxidative process as depicted in Scheme-7. Meanwhile, large amount of by-product,

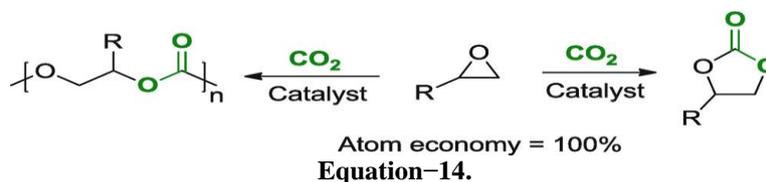
i.e., *tert*-butanol, is generated. The atom economy of the alternative method is greatly enhanced through the direct TS zeolite catalysis oxidation and nearly two times than the former process.



Scheme-7.

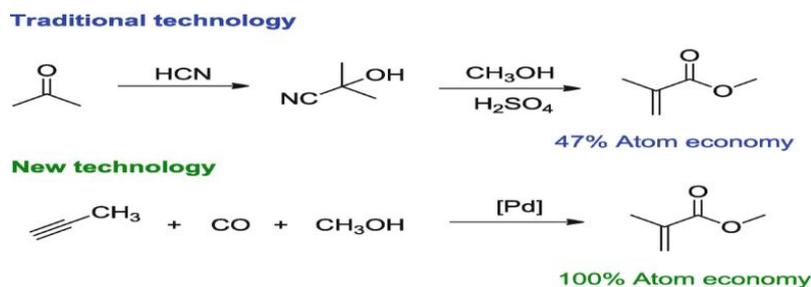
Synthetic access to propylene oxide: The 100% atom economic reaction between epoxides and carbon dioxide to give cyclic carbonates (Equation-14) is extremely attractive as part of preparing sustainable material and chemicals in the future. Cyclic carbonates have found extensive application as nontoxic solvents, fuel additives, and monomers for polymers and intermediates in the

production of pharmaceuticals and fine chemicals. Polycarbonates could also be prepared via this route as replacement for conventional polycarbonates from phosgene and as polyols for the production of polyurethanes. These carbonates have successfully been realized industrial production via the reaction of CO₂ with epoxides.^[16]



In traditional two-step process for the synthesis of methyl methacrylate via condensation of acetone and hydrogen cyanide, toxic hydrocyanic acid and strong corrosive sulfuric acid are needed, and total 47% atom economy is obtained (Scheme-7). However, in the alternative method, one-pot three-component reaction of propyne, carbon monoxide, and methanol is

performed directly to prepare the target product without using virulent reagent with 100% atom economy. As developed by Shell Company, this process produces methyl methacrylate in one step reaction in 99% yield using the catalyst system consisting of palladium acetate, phosphine ligand, and Brønsted acid (Scheme-8).^[17]

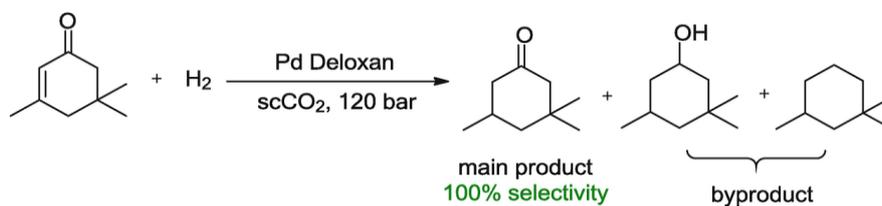


Scheme-8.

The synthetic method of methyl methacrylate

Selectivity Improvement: Here is an example, in traditional hydrogenation of isophorone, the byproducts of deep hydrogenation such as trimethyl cyclohexanol and trimethyl cyclohexane are generated in the step of trimethyl cyclohexanone production. Unfortunately, the similar boiling points of these compounds make the separation and purification tedious. Therefore, to overcome the low selectivity could bring a plethora of

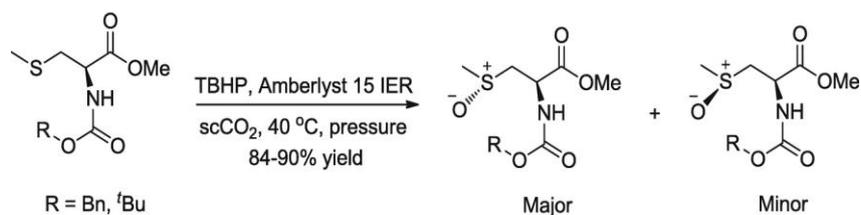
benefits for industrial production. In 2002, Martyn Poliakoff et al. developed an alternative process of isophorone hydrogenation through using supercritical CO₂ (scCO₂) as reaction media in the industrial process. As a result, the full conversion with 100% selectivity can successfully be obtained which greatly facilitates the separation and purification procedure too, thus remarkably improves the atom economy of the reaction (Equation-15).^[18]



Equation-15.

In conventional solvents, no diastereo selectivity can be observed in the sulfoxidation of chiral sulfides derived from methionine and cysteine. But using scCO₂ as a medium, Rayner et al. have found that *tert*-butyl hydroperoxide and Amberlyst™ 15 ion exchange resin work particularly effective for sulfoxide formation, and a dramatic pressure-dependent increase in diastereo

selectivity is attained with cysteine derivatives (Equation-16, up to >95% de). The high diastereo selectivity simplifies the separation and purification of the target isomer and meanwhile increases the synthetic efficiency and also reduces the cost in place of expensive chiral ligand.^[19]

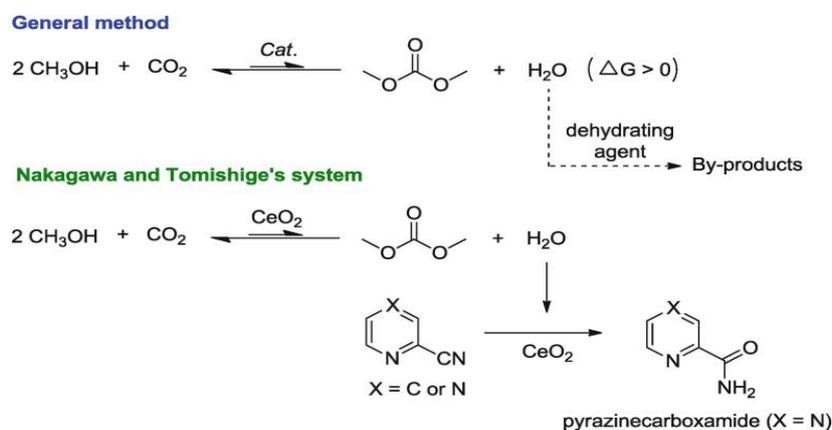


Make Good Use of By-products: In some cases, the by-products could also be used as raw materials directly for other transformation or through further derivatization indirectly. Consequently, less waste is in total emitted, thereby atom economy is further improved in view of the whole process.

Reusing of By-product or Derivatization: Olefin metathesis is a representative and classical example as previous description in this chapter (Equations-8 and 9). On the one hand, ethylene is co-generated in the reaction and could damage atom economy a little bit. On the other hand, ethylene is also an important industrial chemical which could be further reused, rather than a waste. Therefore, in view of the whole process, the atom economy could be reached up to 100%.

Dimethyl carbonate (DMC), one of the most useful organic carbonates, has been used as electrolyte in lithium-ion batteries and as starting material for polycarbonate resins. A future promising and large-volume use is to act as an additive to gasoline and diesel fuels. The green route to prepare DMC is the

carboxylation/dehydration of methanol and CO₂ (Scheme-9). The reaction analogous to the reaction of ethylene glycol and carbon dioxide is also thermodynamically unfavorable. On the one hand, the production of by-product water lowers the atom economy although it is not harmful. On the other hand, the low yield is obtained with the generation of the water. Therefore, how to remove the water during the reaction through suitable dehydrating agent is the key step to improve the reaction efficiency. But in the traditional method, large amount of waste is produced through using stoichiometric or excess dehydrating agent because the by-product is useless. Therefore, it is a promising method to explore the use of inexpensive dehydrating agent or concurrent production of valuable co-products. Nakagawa and Tomishige *et al.* have developed CeO₂-catalyzed carboxylation/dehydration of methanol and CO₂ using 2-cyanopyridine as dehydrating agent. The by-product could be recycled through reversible dehydration or directly used as synthetic intermediate/medicine. For example, the by-product pyrazine carboxamide could be used as a medicine for tuberculosis.^[20]

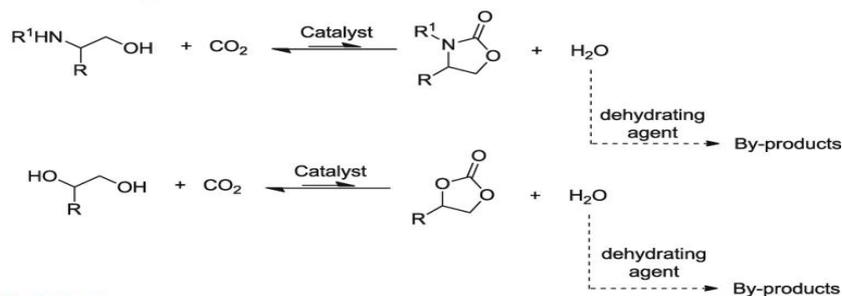


Scheme-9.

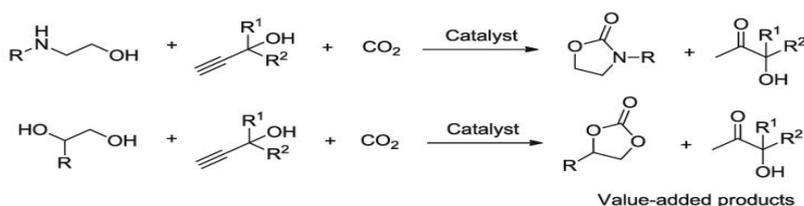
Synthetic access to of dimethyl carbonate from methanol: An alternative cascade reaction has been developed for the synthesis of 2-oxazolidinones/cyclic carbonates from terminal propargylic alcohols, carbon dioxide, and 2-aminoethanols/vicinal diols by He's group (Scheme-10). Compared with direct condensation of 2-aminoethanols/vicinal diols with CO₂, this protocol provides a thermodynamically favorable route to 2-oxazolidinones/cyclic carbonates and α -hydroxyl ketones with 100% atom economy. In this work, cyclic carbonate/ β -oxopropylcarbamate intermediate is

designed and the direct dehydration process can be avoided with successive generation of 2-oxazolidinones/cyclic carbonate and useful co-product α -hydroxyl ketone.^[21]

Traditional strategies



He's strategy

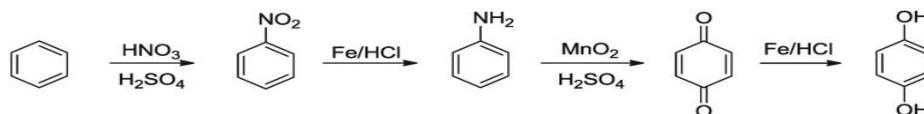


Scheme-10.

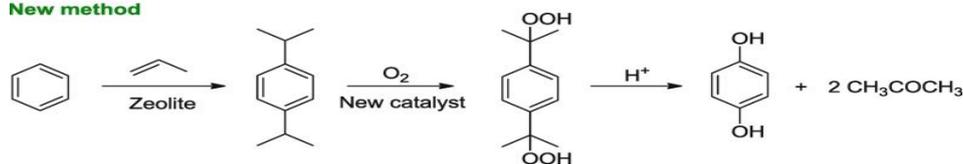
The synthetic strategy of heterocyclic compounds: In traditional method for the synthesis of hydroquinone, the procedure is complicated such as four steps, a series of oxidation and reduction, a large amount of metal reagent used with generation of by-products (salt, waste), and many strong corrosive acids are needed (Scheme-11), whereas the alternative method provides an atom

economic route with less waste which uses environmentally friendly and effective catalyst and dioxygen as oxidant in this three-step route. Notably, the by-product acetone is an important industrial building block, and therefore, it could be reused which further improves the atom economy.^[22]

Traditional method



New method

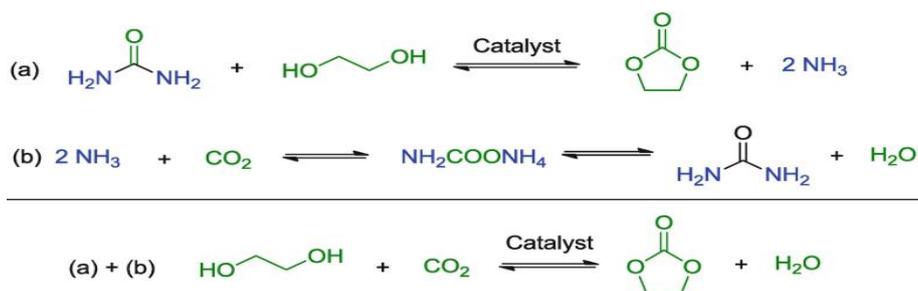


Scheme-11.

Synthetic route to hydroquinone

By-product Recycling: The reaction of ethylene glycol and carbon dioxide is limited by the equilibrium, and the maximum conversion and yield of ethylene carbonate are low. For example, even under harsh reaction conditions (20 MPa CO₂, 180 °C and 12 h), only 2.2% ethylene carbonate yield is obtained through the Sn(IV) (0.05 mol%) catalysis. To break through the limitation, urea as the substitute of CO₂ reacts with ethylene glycol to give

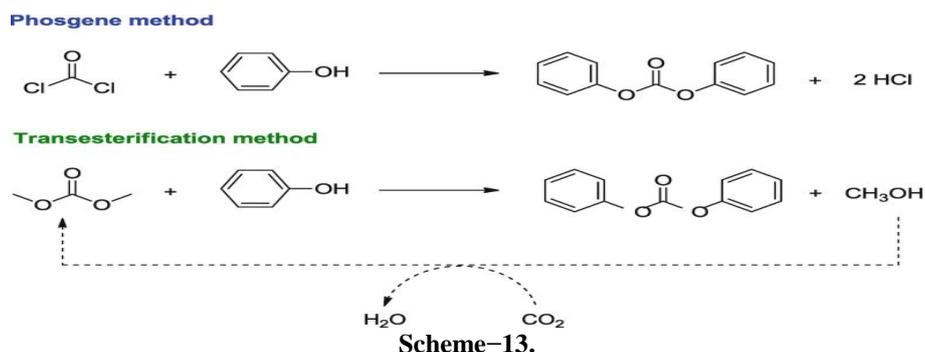
ethylene carbonate in high yield and concurrent ammonia as illustrated in Scheme-12. The ammonia molecule could be recycled into urea through the carboxylation with CO₂. Therefore, the overall process could be described as the synthesis of ethylene carbonate through the carboxylation of ethylene glycol and carbon dioxide with the formation of water. The recycling of ammonia increases the atom efficiency of the whole process.^[23]



Scheme-12.

Synthesis of ethylene carbonate from ethylene glycol and urea: Diphenyl carbonate is a kind of useful chemicals and finds many applications in pharmaceutical, pesticide, organic synthetic, and polymers. For example, it is mainly used as synthetic building block for the preparation of polycarbonates, *p*-hydroxybenzoic acid and isocyanate, and also as solvent and plasticizer of cellulose nitrate and polyamide. Take the industrial production of diphenyl carbonate as an example. In the traditional method, hypertoxic phosgene is used as carbonylation reagent

with generation of large amount of hydrogen chloride. In contrary, the green route to diphenyl carbonate is the transesterification of phenol and nontoxic dimethyl carbonate. The coproduct methanol could be recycled through the carboxylation/dehydration of methanol and CO₂ with formation of dimethyl carbonate as indicated in Scheme-13. Therefore, the transesterification method is much better than the phosgene pathway in view of green chemistry, and the atom economy is also greatly improved through recyclable process in the later method.^[24]



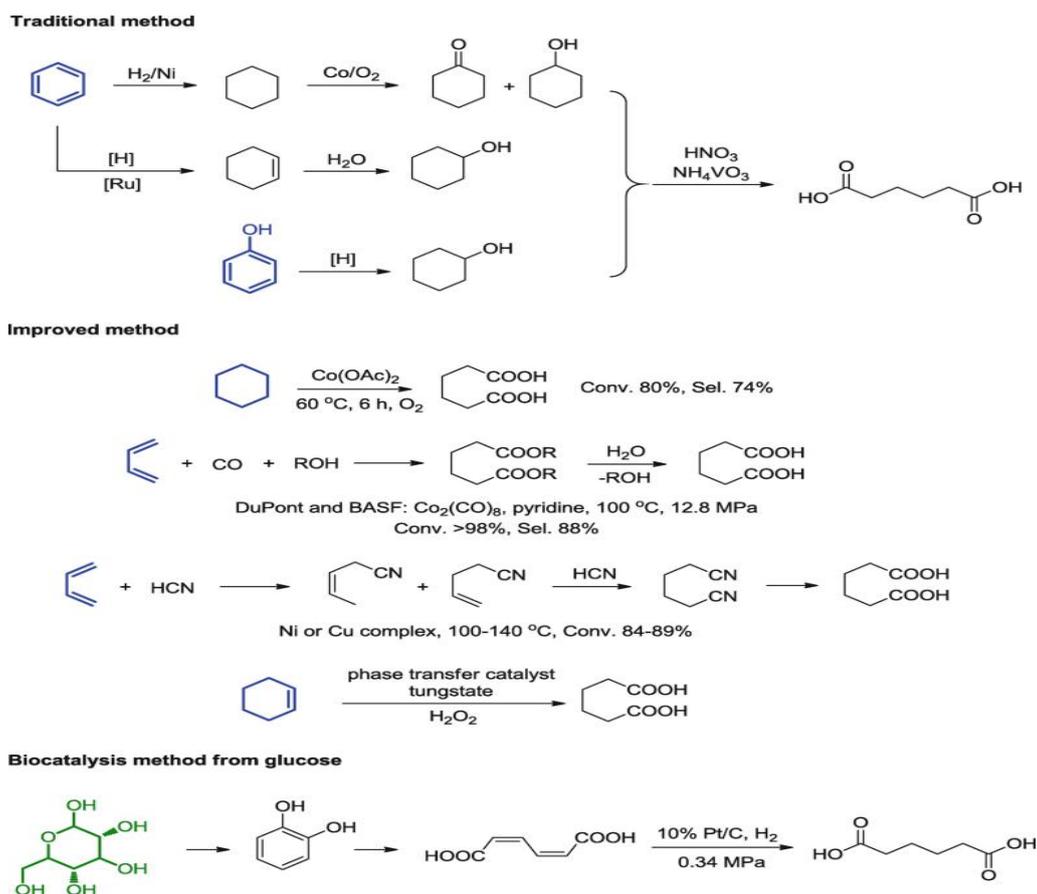
Synthesis of diphenyl carbonate from phenol

Summary and Further Directions: The Nobel Prize for Chemistry for 2005 is shared by three chemists, Y. Chauvin, R. H Grubbs, and R. R Schrock, who have made fundamental discoveries in olefin metathesis and its application in organic synthesis and polymerization. This great discovery has been appraised as "Examples of important basic sciences that benefit mankind, society and the environment" and "Olefin metathesis is an important weapon in the search for drugs for the treatment of major human diseases" by Royal Swedish Academy of Sciences official press release who declared that the fruit has been applied in the industrial production of pharmaceuticals and advanced plastic materials every day. As the Chairman of the jury of the Nobel Prize in Chemistry Per Ahlberg puts it, scientific theory is really useful to improve the human life only in combination with industry to explore the new development and creation.^[25]

With the development of green chemistry, it is of more and more importance to explore clean synthetic chemistry/technology. Therefore, the reaction with 100% atom economy, namely, atom economic reaction, is urgently required. Several strategies to improve atom economy including (1) designing alternative synthetic methodology, (2) selectivity improvement, (3) making good use of byproducts have been discussed with representative examples. In the ideal transformation, the waste could be prevented at a source, and the "zero emission" with step-economy process is the final ideal aim for the atom economic reaction. During the past several decade years, great progress in organic synthesis

has been seen such as oxidation reaction, addition reaction, pericyclic reaction (i.e., Diels-Alder reaction, Ene reaction etc.), transition metal-catalyzed [2+2+2] addition reaction, hydrogenation of amines, C-H bond activation and functionalization, and radical reaction, and so on. Therefore, the exploration of highly effective economic reaction is a promising field. On the basis of atom economic reaction and the knowledge of the reaction mechanism, excellent yields and selectivity are also necessary to acquire high atom economy. Therefore, for a specified reaction, it is also crucial how to develop robust and environmentally friendly catalysts to achieve a real atom economic reaction.^[26]

Take the industrial production of adipic acid for an example as shown in Scheme-14. Adipic acid is a kind of important raw material in the preparation of many industrial products such as nylon. In 1998, "Presidential Green Chemistry Challenge Award" was granted to J. W. Frost and K. M. Draths for their contribution to the exploration of adipic acid route based on biomass.. The process represents the green technology associated with the use of renewable feedstocks in combination of biotechnology (glucose to adipic acid) and chemical methodology (hexadienic acid to adipic acid). Biocatalysis using intact microbes allows the Draths-Frost syntheses to use water as reaction solvent, near-ambient pressure, and temperature. In contrast, several key limitations in the traditional routes are as follows: (1) petroleum feedstock such as cancer-causing benzene, (2) nitric acid as oxidant is corrosive, (3) high pressure and temperature are required, and so on.^[27]



Scheme-14.

Synthetic routes to adipic acid: Poor atom efficiency, i.e., much waste generation in the chemical process, can be overcome with the tool of green chemistry and environmental concerns. Therefore, to improve the atom economy through reduction/avoidance of the waste emission in the whole process or by-product recycle on large-scale production is another significant direction.^[28]

How is atom economy used in industry? Atom economy is an important concept of green chemistry philosophy and one of the most widely used ways to measure the "greenness" of a process or synthesis. improved upon by careful selection of starting materials and a catalyst system. Atom economy is just one way to evaluate a chemical process.^[29]

What is a good atom economy? The highest possible value of atom economy is 100%, when all the reactant atoms end up in the desired product. If the atom economy is 50%, for example, then half the reactant atoms end up in the desired product or products.^[30]

CONCLUSION

The greatest blight affecting the modern time is the apathy associated with ignorance. We tend to strongly adhere to wrongful beliefs—all manufacturing and industrial processes are failsafe in protecting humans and the environment. The truth is that Murphy's Law more

often than not is RIGHT. Thus, the need for pre-emptive measures as embodied by the principles of green chemistry is of paramount significance. Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product.

REFERENCES

1. McKenzie RH. Use of fertilizers, manures and pesticides for sustainable farm management. [http://www1.agriculture.alberta.ca/\\$department/deptdocs.nsf/all/agdex12413](http://www1.agriculture.alberta.ca/$department/deptdocs.nsf/all/agdex12413)
2. Gardel ML Synthetic polymers with biological rigidity. *Nature*, 2013; 493: 618–619.
3. Grant G. Integrative medicine, the medicine of the future. *MOJ Clin Med Case Rep*, 2014; 1(1): 00002.
4. Freeman HS, Sokolowska J. Developments in dyestuff chemistry. *Color Technol*, 1999; 29(1): 8–22.
5. Kampa M, Castanas E. Human health effects of air pollution. *Environ Pollut*, 2008; 151: 362–367.
6. Mabahwi NAB, Leh OLH, Omar D. Human health and wellbeing: human health effect of air pollution. *Proc Soc Behav Sci.*, 2014; 153: 221–229.
7. Anastas PT, Warner JC *Green chemistry: theory and practice*. Oxford University Press, New York, 1998.
8. Tundo P, Anastas P, Black DS, Breen J, Collins T, Memoli S, Miyamoto J, Polyakoff M, Tumas W.

- Synthetic pathways and processes in green chemistry. Introductory overview. *Pure Appl Chem.*, 2000; 72(7): 1207–1228.
- Winterton N. Twelve more green chemistry principles. *Green Chem.*, 2001; 6(1): G73–G75.
 - Anastas P, Eghbali N. Green chemistry: principles and practice. *Chem Soc Rev.*, 2010; 39: 301–312.
 - Enze M, Jun F. Advance of green chemistry. *Chem Bulletin*, 1999; 1: 10–15. (in Chinese).
 - Trost BM The atom economy – a search for synthetic efficiency. *Science*, 1991; 254: 1471–1477.
 - Trost BM On inventing reactions for atom economy. *Acc Chem Res.*, 2002; 35: 695–705.
 - Gabriela M, Ribeiro TC, Machado AASC Greenness of chemical reactions – limitations of mass metrics. *Green Chem Lett Rev.*, 2013; 6(1): 1–18.
 - Constable DJC, Curzons AD, Cunningham VL Metrics to ‘green’ chemistry – which are the best? *Green Chem.*, 2002; 4: 521–527.
 - Wittig G, Geissler G. Zur Reaktionsweise des Pentaphenyl-phosphors und einiger Derivate. *Justus Liebigs Ann Chem (Eur J Org Chem)*, 1953; 580(127): 44–57.
 - Wittig G, Schöllkopf U. Über Triphenyl-phosphin-methylene als olefinbildende Reagenzien I. *Chem Ber*, 1954; 87(9): 1318–1330.
 - Wittig G, Haag W. Über Triphenyl-phosphin-methylene als olefinbildende Reagenzien II. *Chem Ber*, 1955; 88(11): 1654–1666.
 - Hoffmann RW Wittig and his accomplishments: still relevant beyond his 100th birthday. *Angew Chem Int Ed.*, 2001; 40(8): 1411–1416.
 - Schrock RR High-oxidation-state molybdenum and tungsten alkylidene complexes. *Acc Chem Res.*, 1986; 19(11): 342–348.
 - Astruc D. The metathesis reactions: from a historical perspective to recent developments. *New J Chem.*, 2005; 29(1): 42–56.
 - Press Release: The Nobel Prize in Chemistry (2005) Nobelprize.org. Nobel Media AB 2014. Web. 20 Nov 2017.
 - Evans D, Osborn JA, Wilkinson G. Hydroformylation of alkenes by use of rhodium complex catalyst. *J Chem Soc.*, 1968; 33(21): 3133–3142.
 - Cornils B, Herrmann WA (eds) *Aqueous-phase organometallic catalysis*. VCH, Weinheim, 1998.
 - Ojima I, Tsai CY, Tzamarioudaki M, Bonafoux D. The hydroformylation reaction. *Org React*, 2000; 56: 1–354.
 - Yoneda N, Kusano S, Yasui M, Pujado P, Wilcher S. Recent advances in processes and catalysts for the production of acetic acid. *Appl Catal A Gen*, 2001; 221(1–2): 253–265.
 - Pal P, Nayak J. Acetic acid production and purification: critical review towards process intensification. *Sep Purif Rev.*, 2017; 46(1): 44–61.
 - Sunley GJ, Watson DJ High productivity methanol carbonylation catalysis using iridium: the Cativa™ process for the manufacture of acetic acid. *Catal Today*, 2000; 58: 293–307.
 - Sheldon RA Consider the environmental quotient. *ChemTech.*, 1994; 24(3): 38–47.
 - Sheldon RA Catalysis: the key to waste minimization. *J Chem Technol Biotechnol*, 1997; 68(4): 381–388.