1
Introduction to Green Chemistry, Organic Synthesis and Pharmaceuticals

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1.1
The Development of Organic Synthesis

The well-being of modern society is unimaginable without the myriad products of industrial organic synthesis. Our quality of life is strongly dependent on, *inter alia*, the products of the pharmaceutical industry, such as antibiotics for combating disease and analgesics or anti-inflammatory drugs for relieving pain. The origins of this industry date back to 1935, when Domagk discovered the antibacterial properties of the red dye, prontosil, the prototype of a range of sulfa drugs that quickly found their way into medical practice.

The history of organic synthesis is generally traced back to Wöhler's synthesis of the natural product urea from ammonium isocyanate in 1828. This laid to rest the *vis vitalis* (vital force) theory, which maintained that a substance produced by a living organism could not be produced synthetically. The discovery had monumental significance, because it showed that, in principle, all organic compounds are amenable to synthesis in the laboratory.

The next landmark in the development of organic synthesis was the preparation of the first synthetic dye, mauveine (aniline purple) by Perkin in 1856, generally regarded as the first industrial organic synthesis. It is also a remarkable example of serendipity. Perkin was trying to synthesize the anti-malarial drug quinine by oxidation of *N*-allyl toluidine with potassium dichromate. This noble but naïve attempt, bearing in mind that only the molecular formula of quinine ($C_{20}H_{24}N_2O_2$) was known at the time, was doomed to fail. In subsequent experiments with aniline, fortuitously contaminated with toluidines, Perkin obtained a low yield of a purple-colored product. Apparently, the young Perkin was not only a good chemist but also a good businessman, and he quickly recognized the commercial potential of his finding. The rapid development of the product, and the process to make it, culminated in the commercialization of mauveine, which replaced the natural dye, Tyrian purple. At the time of Perkin's discovery Tyrian purple, which was extracted from a species of Mediterranean snail, cost more per kg than gold.

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This serendipitous discovery marked the advent of the synthetic dyestuffs industry based on coal tar, a waste product from steel manufacture. The development of mauveine was followed by the industrial synthesis of the natural dyes alizarin and indigo by Graebe and Liebermann in 1868 and Adolf Baeyer in 1870, respectively. The commercialization of these dyes marked the demise of their agricultural production and the birth of a science-based, predominantly German, chemical industry.

By the turn of the 20th century the germ theory of disease had been developed by Pasteur and Koch, and for chemists seeking new uses for coal tar derivatives which were unsuitable as dyes, the burgeoning field of pharmaceuticals was an obvious one for exploitation. A leading light in this field was Paul Ehrlich, who coined the term chemotherapy. He envisaged that certain chemicals could act as 'magic bullets' by being extremely toxic to an infecting microbe but harmless to the host. This led him to test dyes as chemotherapeutic agents and to the discovery of an effective treatment for syphilis. Because Ehrlich had studied dye molecules as 'magic bullets' it became routine to test all dyes as chemotherapeutic agents, and this practice led to the above-mentioned discovery of prontosil as an antibacterial agent. Thus, the modern pharmaceutical industry was born as a spin-off of the manufacture of synthetic dyestuffs from coal tar.

The introduction of the sulfa drugs was followed by the development of the penicillin antibiotics. Fleming's chance observation of the anti-bacterial action of the penicillin mold in 1928 and the subsequent isolation and identification of its active constituent by Florey and Chain in 1940 marked the beginning of the antibiotics era that still continues today. At roughly the same time, the steroid hormones found their way into medical practice. Cortisone was introduced by the pharmaceutical industry in 1944 as a drug for the treatment of arthritis and rheumatic fever. This was followed by the development of steroid hormones as the active constituents of the contraceptive pill.

The penicillins, the related cephalosporins, and the steroid hormones represented considerably more complicated synthetic targets than the earlier mentioned sulfa drugs. Indeed, as the target molecules shifted from readily available natural compounds and relatively simple synthetic molecules to complex semi-synthetic structures, a key factor in their successful introduction into medical practice became the availability of a cost-effective synthesis. For example, the discovery [1] of the regio- and enantiospecific microbial hydroxylation of progesterone to 11α-hydroxyprogesterone (Figure 1.1) by Peterson and Murray at the Upjohn Company led to a commercially viable synthesis of cortisone that replaced a 31-step chemical synthesis from a bile acid and paved the way for the subsequent commercial success of the steroid hormones. According to Peterson [2], when he proposed the microbial hydroxylation, many outstanding organic chemists were of the opinion that it couldn't be done. Peterson's response was that the microbes didn't know that. Although this chemistry was invented four decades before the term Green Chemistry was officially coined, it remains one of the outstanding applications of Green Chemistry within the pharmaceutical industry.

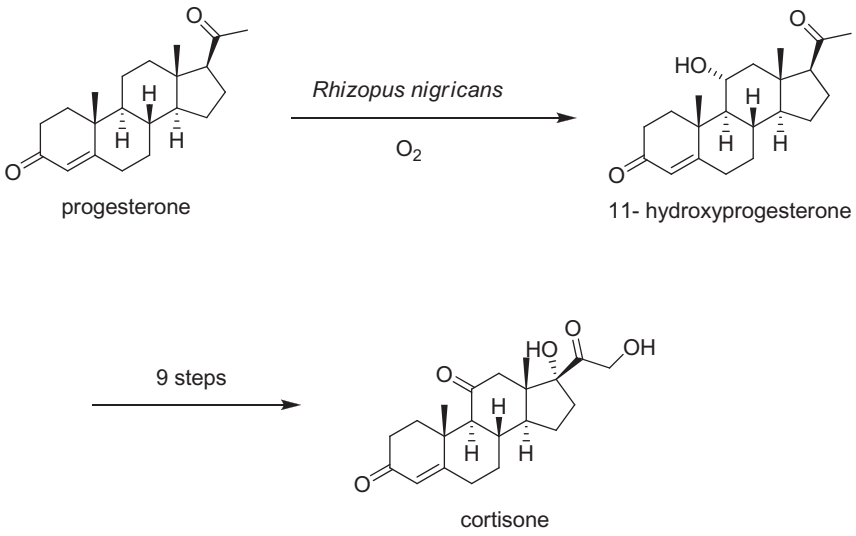


Figure 1.1 Cortisone synthesis.

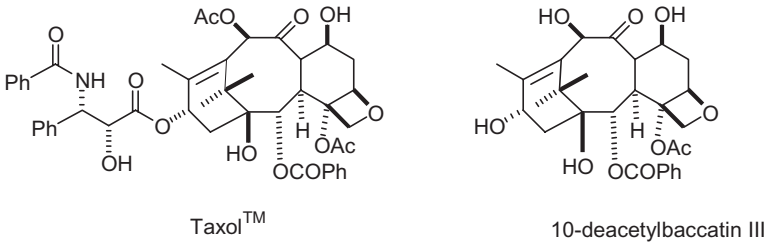


Figure 1.2 Structure of the anticancer drug Taxol® and 10-deacetylbaccatin III.

This monumental discovery marked the beginning of the development, over the following decades, of drugs of ever-increasing molecular complexity. In order to meet this challenge, synthetic organic chemists aspired to increasing levels of sophistication. A case in point is the anticancer drug, Taxol® [3], derived from the bark of the Pacific yew tree, *Taxus brevifolia,* and introduced into medical practice in the 1990s (see Figure 1.2). The breakthrough was made possible by Holton's invention [4] of a commercially viable and sustainable semi-synthesis from 10-deacetylbaccatin III, a constituent of the needles of the English yew, *Taxus baccata*. The Bristol-Myers Squibb Company subsequently developed and commercialized a fermentation process that avoids the semi-synthetic process (see Chapter 7).

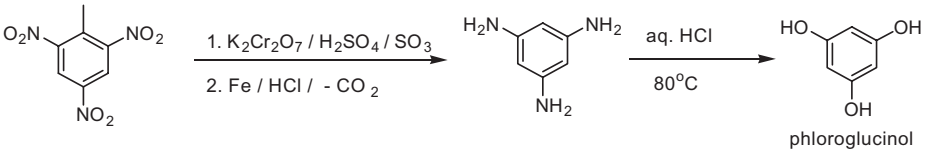
In short, the success of the modern pharmaceutical industry is firmly built on the remarkable achievements of organic synthesis over the last century. However, the down side is that many of these time-honored and trusted synthetic methodologies were developed in an era when the toxic properties of many reagents and

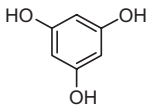
solvents were not known and the issues of waste minimization and sustainability were largely unheard of.

1.2 The Environmental Factor

In the last two decades it has become increasingly clear that the chemical and allied industries, such as pharmaceuticals, are faced with serious environmental problems. Many of the classical synthetic methodologies have broad scope but generate copious amounts of waste, and the chemical industry has been subjected to increasing pressure to minimize or, preferably, eliminate this waste. An illustrative example is provided by the manufacture of phloroglucinol, a reprographic chemical and pharmaceutical intermediate. Up until the mid-1980s it was produced mainly from 2,4,6-trinitrotoluene (TNT) by the process shown in Figure 1.3, a perfect example of vintage nineteenth-century organic chemistry.

For every kg of phloroglucinol produced ca. 40 kg of solid waste, containing $Cr_2(SO_4)_3$, NH_4Cl, $FeCl_2$, and $KHSO_4$, were generated. This process was eventually discontinued as the costs associated with the disposal of this chromium-containing waste approached or exceeded the selling price of the product. That such an enormous amount of waste is formed is easily understood by examining the stoichiometric equation (see Figure 1.3) of the overall process, something very rarely done by organic chemists. This predicts the formation of ca. 20 kg of waste per kg of phloroglucinol, assuming 100% chemical yield and exactly stoichiometric quantities of the various reagents. In practice, an excess of the oxidant and reductant and a large excess of sulfuric acid, which subsequently has to be neutralized with base,





+ $Cr_2(SO_4)_3$ + 2 $KHSO_4$ + 9 $FeCl_2$ + 3 NH_4Cl + CO_2 + 9 H_2O

M W = 126	392	2 X 136	9 X 127	3 X 53.5	44	9 X 18
Product		Byproducts				

Atom efficiency + 126 / 2282 = ca. 5%

E factor = ca. 40

Figure 1.3 Manufacture of phloroglucinol from TNT.

Table 1.1 E factors in the chemical industry.

Industry segment	Volume ($t\,y^{-1}$)[a)]	E factor (kg waste/kg product)
Bulk chemicals	10^4–10^6	<1–5
Fine chemicals industry	10^2–10^4	5– > 50
Pharmaceutical industry	10–10^3	25– > 100

a) Annual production of the product world-wide or at a single site.

is used, and the isolated yield of phloroglucinol is less than 100%. This explains the observed 40 kg of waste per kg of desired product.

Indeed, an analysis of the amount of waste formed in processes for the manufacture of a range of fine chemicals and pharmaceuticals intermediates has revealed that the generation of tens of kilograms of waste per kilogram of desired product was not exceptional in the fine chemical industry. This led to the introduction of the E (environmental) factor (kilograms of waste per kilogram of product) as a measure of the environmental footprint of manufacturing processes [5] in various segments of the chemical industry (Table 1.1).

The E factor represents the *actual amount* of waste produced in the process, defined as everything but the desired product. It takes the chemical yield into account and includes reagents, solvent losses, process aids, and, in principle, even fuel. Water was generally excluded from the E factor as the inclusion of all process water could lead to exceptionally high E factors in many cases and make meaningful comparisons of processes difficult. A higher E factor means more waste and, consequently, a larger environmental footprint. The ideal E factor is zero. Put quite simply, it is the total mass of raw materials minus the total mass of product, all divided by the total mass of product. It can be easily calculated from a knowledge of the number of tons of raw materials purchased and the number of tons of product sold, the calculation being for a particular product or a production site or even a whole company.

It is clear from Table 1.1 that the E factor increases substantially on going from bulk chemicals to fine chemicals and then to pharmaceuticals. This is partly a reflection of the increasing complexity of the products, necessitating multistep syntheses, but is also a result of the widespread use of stoichiometric reagents (see below). A reduction in the number of steps of a synthesis will in most cases lead to a reduction in the amounts of reagents and solvents used and hence a reduction in the amount of waste generated. This led Wender to introduce the concepts of step economy [6] and function oriented synthesis (FOS) [7] of pharmaceuticals. The central tenet of FOS is that the structure of an active lead compound, which may be a natural product, can be reduced to simpler structures designed for ease of synthesis while retaining or enhancing the biological activity. This approach can provide practical access to new (designed) structures with novel activities while at the same time allowing for a relatively straightforward synthesis.

As noted above, a knowledge of the stoichiometric equation allows one to predict the theoretical minimum amount of waste that can be expected. This led to the concept of *atom economy* [8] or *atom utilization* [9] to quickly assess the environmental acceptability of alternatives to a particular product before any experiment is performed. It is a theoretical number, that is, it assumes a chemical yield of 100% and exactly stoichiometric amounts and disregards substances which do not appear in the stoichiometric equation.

In short, the key to minimizing waste is precision or *selectivity* in organic synthesis which is a measure of how efficiently a synthesis is performed. The standard definition of selectivity is the yield of product divided by the amount of substrate converted, expressed as a percentage. Organic chemists distinguish between different categories of selectivity:

- Chemoselectivity (competition between different functional groups)
- Regioselectivity (selective formation of one regioisomer, for example ortho vs para substitution in aromatic rings)
- Diastereoselectivity (the selective formation of one diastereomer)
- Enantioselectivity (the selective formation of one of a pair of enantiomers)

However, one category of selectivity was, traditionally, largely ignored by organic chemists: the *atom selectivity* or *atom utilization* or *atom economy*. The virtually complete disregard of this important parameter is the root cause of the waste problem in chemicals manufacture. As Lord Kelvin remarked, 'To measure is to know'. Quantification of the waste generated in chemicals manufacturing, by way of E factors, served to bring the message home and focus the attention of fine chemical and pharmaceutical companies on the need for a paradigm shift from a concept of process efficiency, which was exclusively based on chemical yield, to one that is motivated by elimination of waste and maximization of raw materials utilization. Indeed, the E factor has been widely adopted by the chemical industry and the pharmaceutical industry in particular [10]. To quote from a recent article [11]: 'Another aspect of process development mentioned by all pharmaceutical process chemists who spoke with Chemical and Engineering News is the need for determining an E factor.'

The Green Chemistry Institute (GCI) Pharmaceutical Roundtable has used the Process Mass Intensity (PMI) [12], defined as the total mass used in a process divided by the mass of product (i.e. PMI = E factor + 1) to benchmark the environmental acceptability of processes used by its members (see the GCI website). The latter include several leading pharmaceutical companies (Eli Lilly, GlaxoSmithKline, Pfizer, Merck, AstraZeneca, Schering-Plow, and Johnson & Johnson). The aim was to use this data to drive the greening of the pharmaceutical industry. We believe, however, that the E factor is to be preferred over the PMI since the ideal E factor of 0 is a better reflection of the goal of zero waste.

The E factor, and derived metrics, takes only the mass of waste generated into account. However, the environmental impact of waste is determined not only by its amount but also by its nature. Hence, we introduced [13] the term 'environmental quotient', EQ, obtained by multiplying the E factor by an arbitrarily

assigned unfriendliness quotient, Q. For example, one could arbitrarily assign a Q value of 1 to NaCl and, say, 100–1000 to a heavy metal salt, such as chromium, depending on factors like its toxicity or ease of recycling. Although the magnitude of Q is debatable and difficult to quantify, 'quantitative assessment' of the environmental impact of waste is, in principle, possible. Q is dependent on, *inter alia*, the ease of disposal or recycling of waste and, generally speaking, organic waste is easier to dispose of or recycle than inorganic waste.

1.3 The Role of Catalysis

The main source of waste is inorganic salts such as sodium chloride, sodium sulfate, and ammonium sulfate that are formed in the reaction or in downstream processing. One of the reasons that the E factor increases dramatically on going from bulk to fine chemicals and pharmaceuticals is that the latter are more complicated molecules that involve multi-step syntheses. However, the larger E factors in the fine chemical and pharmaceutical industries are also a consequence of the widespread use of classical stoichiometric reagents rather than catalysts. Examples which readily come to mind are metal (Na, Mg, Zn, Fe) and metal hydride ($LiAlH_4$, $NaBH_4$) reducing agents and oxidants such as permanganate, manganese dioxide, and chromium(VI) reagents. For example, the phloroglucinol process (see above) combines an oxidation by stoichiometric chromium (VI) with a reduction with Fe/HCl. Similarly, a plethora of organic reactions, such as sulfonations, nitrations, halogenations, diazotizations, and Friedel-Crafts acylations, employ stoichiometric amounts of mineral acids (H_2SO_4, HF, H_3PO_4) or Lewis acids ($AlCl_3$, $ZnCl_2$, BF_3) and are major sources of inorganic waste.

Once the major cause of the waste has been recognized, the solution to the waste problem is evident: the general replacement of classical syntheses that use stoichiometric amounts of inorganic (or organic) reagents by cleaner, catalytic alternatives. If the solution is so simple, why are catalytic processes not as widely used in fine and specialty chemicals manufacture as they are in bulk chemicals? One reason is that the volumes involved are much smaller, and thus the need to minimize waste is less acute than in bulk chemicals manufacture. Secondly, the economics of bulk chemicals manufacture dictate the use of the least expensive reagent, which was generally the most atom economical, for example O_2 for oxidation H_2 for reduction, and CO for C–C bond formation.

A third reason is the pressure of time. In pharmaceutical manufacture 'time to market' is crucial, and an advantage of many time-honored classical technologies is that they are well tried and broadly applicable and, hence, can be implemented rather quickly. In contrast, the development of a cleaner, catalytic alternative could be more time consuming. Consequently, environmentally (and economically) inferior technologies are often used to meet stringent market deadlines, and subsequent process changes can be prohibitive owing to problems associated with FDA approval.

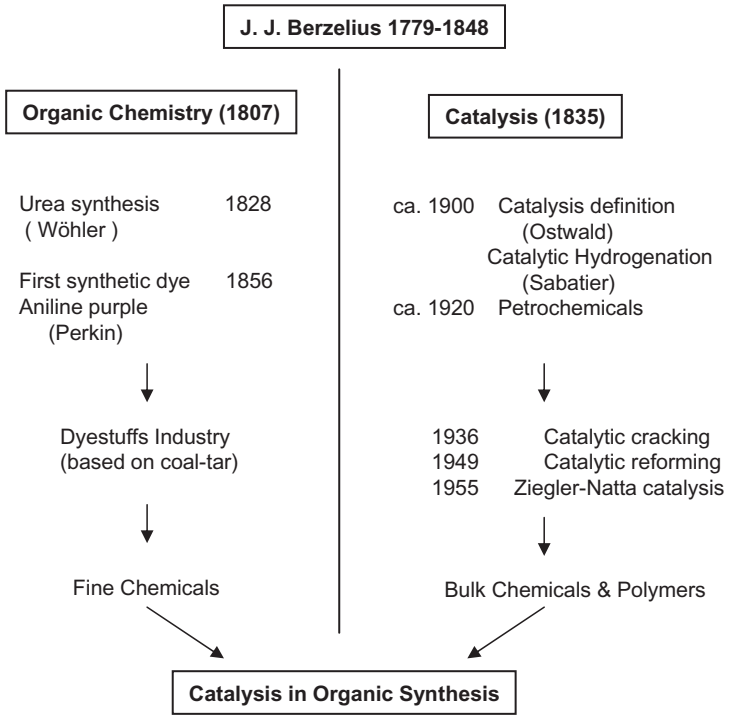
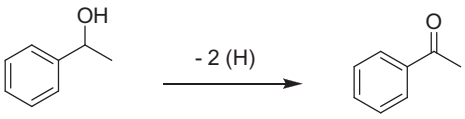


Figure 1.4 The development of organic synthesis and catalysis.

Another reason, however, is the more or less separate paths of development of organic synthesis and catalysis (see Figure 1.4) since the time of Berzelius, who coined the terms 'organic chemistry' and 'catalysis', in 1807 and 1835, respectively [14]. Subsequently, catalysis developed largely as a sub-discipline of physical chemistry. With the advent of petrochemicals in the 1930s, catalysis was widely applied in oil refining and bulk chemicals manufacture. However, the scientists responsible for these developments were, generally speaking, not organic chemists but were chemical engineers and surface scientists.

Industrial organic synthesis, in contrast, followed a largely 'stoichiometric' line of evolution that can be traced back to Perkin's synthesis of mauveine, the subsequent development of the dyestuffs industry based on coal tar, and the fine chemicals and pharmaceuticals industries, which can be regarded as spin-offs from the dyestuffs industry. Consequently, fine chemicals and pharmaceuticals manufacture, which is largely the domain of synthetic organic chemists, is rampant with classical 'stoichiometric' processes. Until fairly recently, catalytic methodologies were only sporadically applied, with the exception of catalytic hydrogenation which, incidentally, was invented by an organic chemist, Sabatier, in 1905.

The desperate need for more catalytic methodologies in industrial organic synthesis is nowhere more apparent than in oxidation chemistry. For example, as any



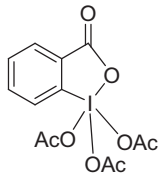
Oxidant	Atom Efficiency
CrO_3/H_2SO_4	44%
	22%
$(CH_3)_2SO / (COCl)_2$	37%
NaOCl	48%
O_2	87%

Figure 1.5 Atom efficiencies of alcohol oxidations.

organic chemistry textbook will tell you, the reagent of choice for the oxidation of secondary alcohols to the corresponding ketones, a pivotal reaction in organic synthesis, is the Jones reagent. The latter consists of chromium trioxide and sulfuric acid and is reminiscent of the phloroglucinol process referred to earlier. The introduction of the storage-stable pyridinium chlorochromate (PCC) and pyridinium dichromate (PDC) in the 1970s, represented a practical improvement, but the stoichiometric amounts of carcinogenic chromium(VI) remain a serious problem. Other stoichiometric oxidants that are popular with synthetic organic chemists are the Swern reagent [15] and Dess-Martin Periodinane [16] (DMP). The former produces the evil smelling dimethyl sulfide as the by-product, the latter is shock sensitive, and oxidations with both reagents are abominably atom inefficient (see Figure 1.5).

Obviously there is a definite need in the fine chemical and pharmaceutical industry for catalytic systems that are green and scalable and have broad utility [10]. More recently, oxidations with the inexpensive household bleach (NaOCl) catalyzed by stable nitroxyl radicals, such as TEMPO [17] and PIPO [18], have emerged as more environmentally friendly methods. It is worth noting at this juncture that 'greenness' is a relative description and there are many shades of green. Although the use of NaOCl as the terminal oxidant affords NaCl as the by-product and may lead to the formation of chlorinated impurities, it constitutes a dramatic improvement compared to the use of chromium(VI) and other

reagents referred to above. Moreover, we note that, in the case of pharmaceutical intermediates, the volumes of NaCl produced as a by-product on an industrial scale are not likely to present a problem. Nonetheless, catalytic methodologies employing the green oxidants, molecular oxygen (air) and hydrogen peroxide, as the terminal oxidant would represent a further improvement in this respect. However, as Dunn and coworkers have pointed out [10], the use of molecular oxygen presents significant safety issues associated with the flammability of mixtures of oxygen with volatile organic solvents in the gas phase. Even when these concerns are reduced by using 10% oxygen diluted with nitrogen, these methods are on the edge of acceptability [10]. An improved safety profile and more acceptable scalability are obtained by performing the oxidation in water as an inert solvent. For fine chemicals or large volume pharmaceuticals the environmental and cost benefits of using simple air or oxygen as the oxidant would justify the capital investment in the more specialized equipment required to use these oxidants on a large scale.

1.4 Green Chemistry: Benign by Design

In the mid-1990s Anastas and coworkers [19] at the United States Environmental Protection Agency (EPA) were developing the concept of *benign by design*, that is designing environmentally benign products and processes to address the environmental issues of both chemical products and the processes by which they are produced. This incorporated the concepts of atom economy and E factors and eventually became a guiding principle of *Green Chemistry* as embodied in the 12 Principles of Green Chemistry [20], the essence of which can be reduced to the useful working definition:

Green chemistry efficiently utilizes (preferably renewable) raw materials, eliminates waste, and avoids the use of toxic and/or hazardous reagents and solvents in the manufacture and application of chemical products.

Raw materials include, in principle, the source of energy, as this also leads to waste generation in the form of carbon dioxide. Green Chemistry is primary pollution prevention rather than waste remediation (end-of-pipe solutions). More recently, the twelve Principles of Green Engineering were proposed [21], which contain the same underlying features – conservation of energy and other raw materials and elimination of waste and hazardous materials – but from an engineering standpoint. Poliakoff and coworkers [22] proposed a mnemonic, PRODUCTIVELY, which captures the spirit of the twelve Principles of Green Chemistry in a single slide.

Another concept which has become the focus of attention, both in industry and society at large, in the last decade or more is that of sustainable development, first introduced in the Brundtland report [23] in the late 1980s and defined as:

Meeting the needs of the present generation without compromising the ability of future generations to meet their own needs.

Sustainable development and Green Chemistry have now become a strategic industrial and societal focus [24–27], the former is our ultimate goal and the latter is a means to achieve it.

1.5
Ibuprofen Manufacture

An elegant example of a process with high atom efficiency is provided by the manufacture of the over-the-counter, non-steroidal anti-inflammatory drug, ibuprofen. Two routes for the production of ibuprofen via the common intermediate, *p*-isobutylacetophenone, are compared in Figure 1.6. The classical route, developed by the Boots Pure Drug Company (the discoverers of ibuprofen), entails 6 steps with stoichiometric reagents, relatively low atom efficiency, and substantial inorganic salt formation. In contrast, the elegant alternative, developed by the Boots-Hoechst-Celanese (BHC) company, involves only three catalytic steps [28]. The first step involves the use of anhydrous hydrogen fluoride as both catalyst and solvent in a Friedel-Crafts acylation. The hydrogen fluoride is recyclable and waste is essentially eliminated. This is followed by two catalytic steps (hydrogenation and carbonylation), both of which are 100% atom efficient.

The BHC ibuprofen process was commercialized in 1992 in a ca. 4000 tons per annum facility in Texas. The process was awarded the Kirkpatrick Achievement Award for outstanding advances in chemical engineering technology in 1993 and a Presidential Green Chemistry Challenge Award in 1996. It represents a benchmark in environmental excellence in chemical processing technology that revolutionized bulk pharmaceutical manufacturing. It provides an innovative and excellent solution to the prevalent problem of the large volumes of waste associated with the traditional stoichiometric use of auxiliary chemicals. The anhydrous hydrogen fluoride is recovered and recycled with greater than 99.9% efficiency. No other solvent is used in the process, simplifying product recovery and minimizing fugitive emissions. This combined with the almost complete atom utilization of this streamlined process truly makes it a waste-minimizing, environmentally friendly technology and a source of inspiration for other pharmaceutical manufacturers.

1.6
The Question of Solvents: Alternative Reaction Media

Another important issue in green chemistry is the use of organic solvents. The use of many traditional organic solvents, such as chlorinated hydrocarbons, has been severely curtailed. Indeed, so many of the solvents that are favored by organic chemists have been blacklisted that the whole question of solvent use requires rethinking and has become a primary focus, especially in the manufacture of pharmaceuticals [29, 30]. In our original studies of E factors of various processes,

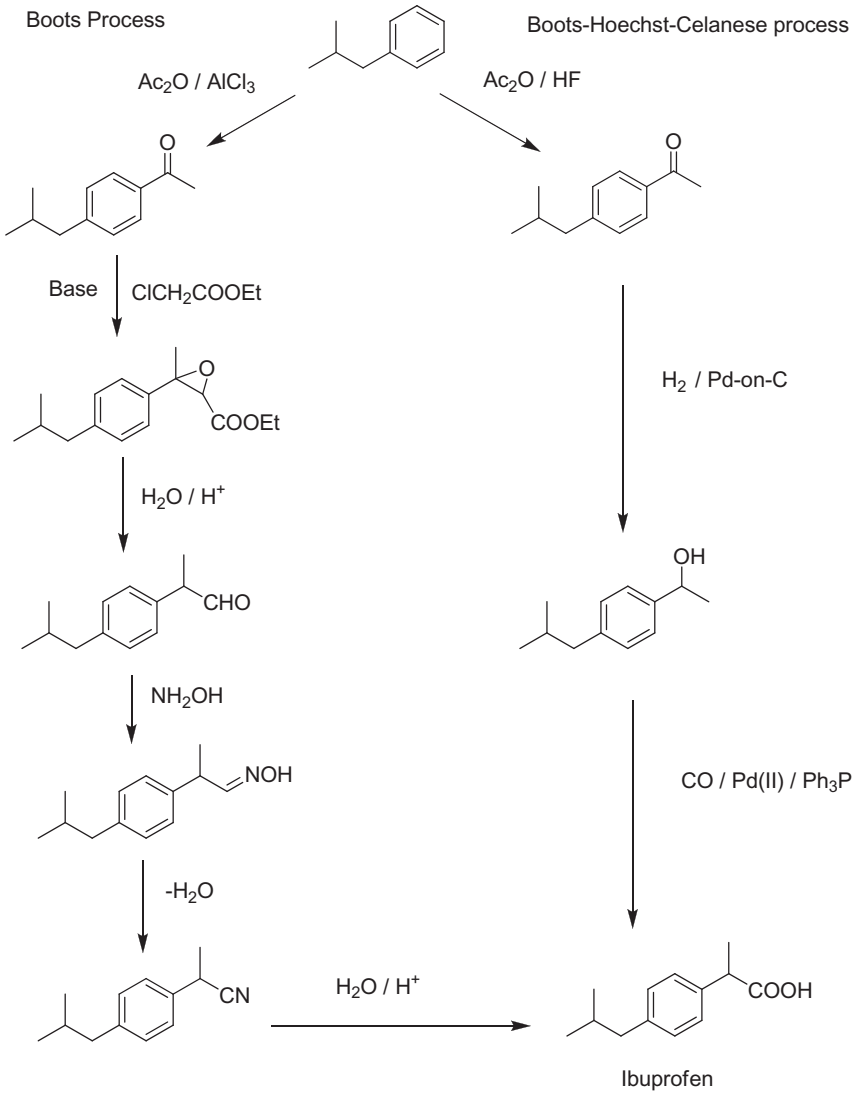


Figure 1.6 Two processes for ibuprofen.

we assumed, if details were not known, that solvents would be recycled by distillation and that this would involve a 10% loss. However, the organic chemist's penchant for using different solvents for the various steps in multistep syntheses makes recycling difficult owing to cross contamination. A benchmarking exercise performed by the GCI Pharmaceutical Roundtable (see above) revealed that solvents were a major contributor to the E factors of pharmaceutical manufacturing processes. Indeed, it has been estimated by GlaxoSmithKline workers [31] that ca.

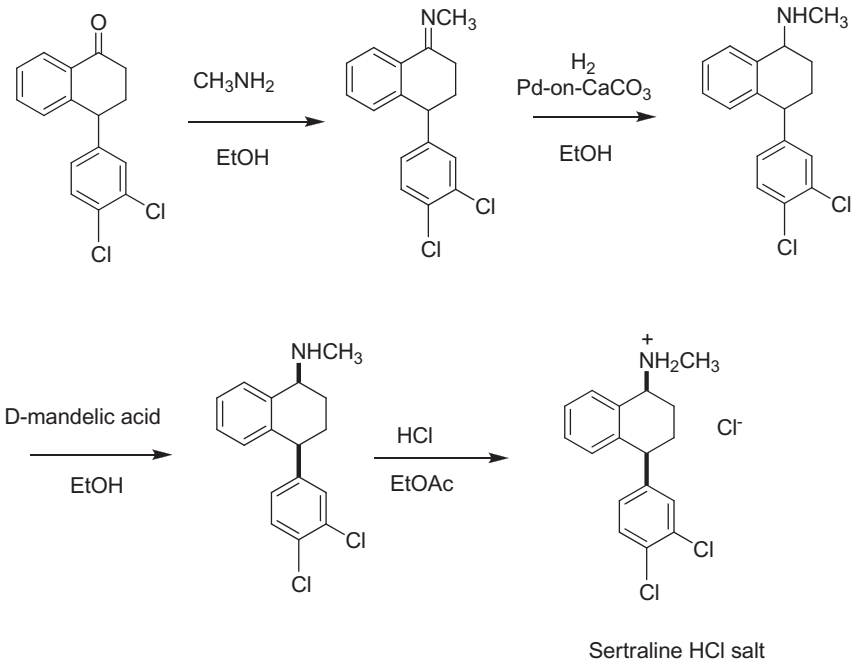


Figure 1.7 The new sertraline process.

85% of the total mass of chemicals involved in pharmaceutical manufacture comprises solvents. Consequently, pharmaceutical companies are focusing their effort on minimizing solvent use and in replacement of many traditional organic solvents, such as chlorinated and aromatic hydrocarbons, by more environmentally friendly alternatives.

An illustrative example is the redesign of the sertraline manufacturing process [32], for which Pfizer received a Presidential Green Chemistry Challenge Award in 2002. Among other waste-minimizing improvements, a three-step sequence was streamlined by employing ethanol as the sole solvent (see Figure 1.7). This eliminated the need to use, distill, and recover four solvents (methylene chloride, tetrahydrofuran, toluene, and hexane) and resulted in a reduction in solvent usage from 250 to 25 liters per kilogram of sertraline.

Similarly, Pfizer workers also reported [33] impressive improvements in solvent usage in the process for sildenafil (Viagra®) manufacture, reducing the solvent usage from 1700 liters per kilogram of product used in the medicinal chemistry route to 7 L kg^{-1} in the current commercial process with a target for the future of 4 L kg^{-1}. The E factor for the current process is 8, placing it more in the lower end of fine chemicals rather than with typical pharmaceutical manufacturing processes.

These issues surrounding a wide range of volatile and nonvolatile, polar aprotic solvents have stimulated the fine chemicals and pharmaceutical industries to seek

more benign alternatives. There is a marked trend away from hydrocarbons and chlorinated hydrocarbons toward lower alcohols, esters, and, in some cases, ethers. Inexpensive natural products such as ethanol have the added advantage of being readily biodegradable, and ethyl lactate, produced by combining two innocuous natural products, is currently being promoted as an environmentally attractive solvent for chemical reactions. The problem with solvents is not so much in their use but in the seemingly inherent inefficiencies associated with their containment, recovery, and reuse. The best solvent is no solvent at all, but if a solvent is needed there should be provisions for its efficient removal from the product and reuse.

The subject of alternative reaction media also touches on another issue that is important from both an environmental and an economic viewpoint: recovery and reuse of the catalyst. An insoluble solid, that is heterogeneous, catalyst is easily separated by centrifugation or filtration. A homogeneous catalyst, in contrast, presents more of a problem, the serious shortcoming of homogeneous catalysis being the cumbersome separation of the catalyst from the reaction products and its quantitative recovery in an active form. In pharmaceutical manufacture, another important issue is contamination of the product. Attempts to heterogenize homogeneous catalysts by attachment to organic or inorganic supports have, generally speaking, not resulted in commercially viable processes for a number of reasons, such as leaching of the metal, poor catalyst productivity, irreproducible activity and selectivity, and degradation of the support.

There is a definite need, therefore, for systems that combine the advantages of high activity and selectivity of homogeneous catalysts with the facile recovery and recycling characteristic of their heterogeneous counterparts. This can be achieved by employing a different type of heterogeneous system, namely liquid-liquid biphasic catalysis, whereby the catalyst is dissolved in one liquid phase and the reactants and product(s) are in a second liquid phase. The catalyst is recovered and recycled by simple phase separation. Preferably, the catalyst solution remains in the reactor and is reused with a fresh batch of reactants without further treatment or, ideally, it is adapted to continuous operation.

Various nonconventional reaction media have been intensively studied in recent years, including *water* [34], *supercritical* CO_2 [35], *fluorous biphasic* [36], *and ionic liquids* [37] alone or in liquid-liquid biphasic combinations. The use of water and supercritical carbon dioxide as reaction media fits with the current trend toward the use of renewable, biomass-based raw materials, which are ultimately derived from carbon dioxide and water.

Water has many benefits: it is nontoxic, nonflammable, abundantly available, and inexpensive. Furthermore, performing the reaction in an aqueous biphasic system [38], whereby the catalyst resides in the water phase and the product is dissolved in the organic phase, allows for recovery and recycling of the catalyst by simple phase separation. A case in point is the BHC process for ibuprofen manufacture (see above). The key carbonylation step involves a homogeneous palladium catalyst, and contamination of the product (the active pharmaceutical ingredient) with unacceptably high amounts of palladium necessitates an expensive purification. Replacing the organic soluble palladium(0) triphenylphosphine complex with

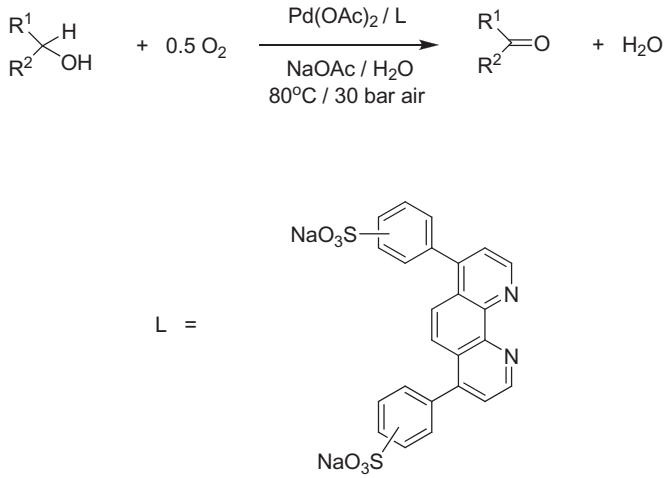


Figure 1.8 Aqueous biphasic aerobic oxidation of alcohols.

an analogous complex of the water-soluble trisulfonated triphenylphosphine, TPPTS, affords a catalytic system for the aqueous biphasic carbonylation of alcohols [39]. For example, when the above-mentioned ibuprofen synthesis was performed with TPPTS in an aqueous biphasic system, product contamination by the catalyst was essentially eliminated.

Similarly, a water-soluble palladium complex of a sulfonated phenanthroline ligand catalyzed the highly selective aerobic oxidation of primary and secondary alcohols in an aqueous biphasic system in the absence of any organic solvent (Figure 1.8) [40]. The liquid product could be recovered by simple phase separation, and the aqueous phase, containing the catalyst, used with a fresh batch of alcohol substrate, affording a truly green method for the oxidation of alcohols.

1.7 Biocatalysis: Green Chemistry Meets White Biotechnology

Biocatalysis has many attractive features in the context of green chemistry: reactions are generally performed in water under mild conditions of temperature and pressure using an environmentally compatible, biodegradable catalyst (an enzyme) derived from renewable raw materials. High activities and chemo-, regio-, and stereoselectivities are obtained in reactions of multifunctional molecules without the need for the functional group activation and protection often required in traditional organic syntheses. This affords more environmentally attractive and cost-effective processes with fewer steps and, hence, less waste. Illustrative examples are provided by the substitution of classical chemical processes with enzymatic counterparts in the synthesis of semi-synthetic penicillins and cephalosporins [41].

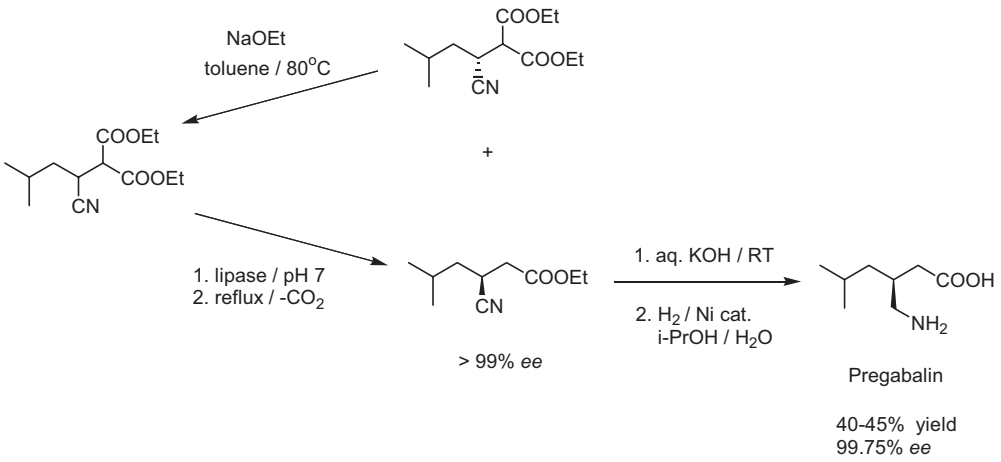


Figure 1.9 Chemoenzymatic process for pregabalin.

If biocatalysis is so attractive, why was it not widely used in the past? The answer is that only recent advances in biotechnology have made it possible. First, the availability of numerous whole-genome sequences has dramatically increased the number of potentially available enzymes. Second, *in vitro* evolution has enabled the manipulation of enzymes such that they exhibit the desired properties: substrate specificity, activity, stability, and pH profile [42]. Third, recombinant DNA techniques have made it, in principle, possible to produce virtually any enzyme for a commercially acceptable price. Fourth, the cost-effective techniques that have now been developed for the immobilization of enzymes afford improved operational stability and enable their facile recovery and recycling [43].

An illustrative example of the replacement of a traditional organic synthesis by a more economically and environmentally attractive chemoenzymatic process is provided by the manufacture of pregabalin (see Chapter 8) [44]. The key step is an enzymatic kinetic resolution of an ester (see Figure 1.9) using the readily available lipase from *Thermomyces lanuginosus* (Lipolase). The stereochemistry at C2 is not important as it is lost in the subsequent thermal decarboxylation step. The unreacted substrate was racemized by heating with a catalytic amount of sodium ethoxide in toluene at 80 °C and was then recycled to the resolution step. Subsequent hydrolysis and hydrogenation affords pregabalin in 40–45% overall yield.

The chemoenzymatic route afforded a dramatic improvement in process efficiency compared to the first-generation process. This was reflected in the E factor which decreased 7-fold, from 86 to 12, and the substantial reduction in organic solvent usage resulting from a largely aqueous reaction medium.

The enzymes found in Nature are the result of aeons of cumulative natural selection, but they were not evolved to perform biotransformations of non-natural, pharmaceutical target molecules. In order to make them suited to these tasks they generally need to be re-evolved, but we don't have millions of years to do it. Fortunately, modern advances in biotechnology have made it possible to accomplish

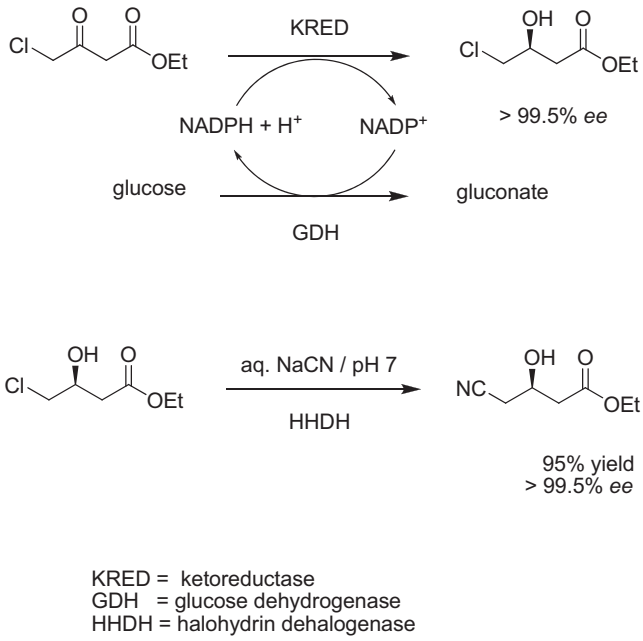


Figure 1.10 Codexis process for atorvastatin intermediate.

this in weeks in the laboratory using *in vitro* techniques such as gene shuffling [45].

An illustrative example is provided by the Codexis process for the production of an intermediate for Pfizer's blockbuster drug Atorvastatin (Lipitor®). The two-step process (Figure 1.10), for which Codexis received a 2006 Presidential Green Chemistry Challenge Award, involves three enzymes (one for cofactor regeneration). The low activities of the wild-type enzymes formed a serious obstacle to commercialization, but *in vitro* evolution of the individual enzymes, using gene shuffling, afforded economically viable productivities [46].

The highly selective biocatalytic reactions afford a substantial reduction in waste. The overall isolated yield is greater than 90%, and the product is more than 98% chemically pure with an enantiomeric excess of >99.9%. All three evolved enzymes are highly active and are used at such low loadings that counter-current extraction can be used to minimize solvent volumes. Moreover, the butyl acetate solvent is recycled with an efficiency of 85%.The E factor (kgs waste per kg product) for the overall process is 5.8 if process water is excluded (2.3 for the reduction and 3.5 for the cyanation) [47]. If process water is included, the E factor for the whole process is 18 (6.6 for the reduction and 11.4 for the cyanation). The main contributors to the E factor are solvent losses which accounted for 51% of the waste, sodium gluconate (25%), NaCl and Na_2SO_4 (combined circa. 22%). The three enzymes and the NADP cofactor account for <1% of the waste. The main waste streams are aqueous and directly biodegradable.

1.8 Conclusions and Prospects

Over the last fifteen years the manufacture of pharmaceuticals has undergone revolutionary changes. Target molecules have become increasingly complex, and legislative pressure, starting in the late 1980s, has stimulated the marketing of chiral molecules as pure enantiomers [47]. This, in turn, stimulated the development of cost-effective methods for the manufacture of enantiomerically pure compounds. On top of this, there has been a paradigm shift from the traditional concept of process efficiency to one that assigns economic value to conserving energy and raw materials, eliminating waste, and avoiding the use of toxic and/or hazardous chemicals. Indeed, the concepts of E factors, atom economy, and step economy have gradually become incorporated into mainstream organic synthesis in both industry and academia [48–50].

The pharmaceutical industry has risen to the occasion and is making substantial progress in replacing traditional processes with greener, more sustainable alternatives, though there is much still to do. It has adopted the E factor, or its direct equivalent, as its measuring staff, and recent publications have identified key areas where improvement is most needed [51–53]. In short, we conclude that the challenge of sustainability and Green Chemistry is leading to fundamental, game-changing innovations in organic synthesis that will ultimately lead to economic, environmental, and societal benefits in the pharmaceutical industry and in the chemical and allied industries at large.

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