1

Understanding the Principles of Sustainable Chemistry

Learning Objectives

By the end of this chapter, you should be familiar with the core principles of green chemistry and its key metrics. You should understand elemental and material cycles – including the carbon and nitrogen cycles – and recognize the human impact on these systems. You should also be able to discuss how a shift to renewable resources and sustainable materials can create new business opportunities. Finally, you should understand how green chemistry contributes to the development of a circular economy.

This book is aimed at students who are interested in setting up new businesses based on innovations that are related to sustainability and the circular economy. It is based on a course that I have been teaching in Amsterdam for the past five years as part of the 'Science, Business and Innovation' bachelor, as well as on graduate workshops on innovation that I have been teaching in Europe and China. Since the students have different backgrounds, the introduction is broader, covering also the concepts of material cycles, waste management and environmental impact. We then discuss in more depth the principles of green chemistry, grouping them into six themes: preventing waste; reducing hazard and toxicity; using fewer solvents and reagents; saving energy; switching to renewable resources and making the most of catalysis and catalytic cycles.

An important recurring theme in this book is the emphasis on recognising **real value** [1]. This is especially important when dealing with sustainability and the circular economy. When people, governments and companies talk about these subjects, they tend to get starry-eyed and imagine how things *could* turn out if our world was an ideal place. The world, however, is not an ideal place, and most investors know this. This is especially true for industrial chemical processes, which require a large capital outlay. I am all for optimism, and there is much personal satisfaction in developing products that will make the world a better place. **But this 'green premium' cannot replace real value** [2]. If you want to turn sustainability ideas into businesses, you need to learn how to recognise and assess real value.

But first, we must understand enough chemistry to talk with the scientists and engineers in their own jargon. You don't have to know the details of every reaction and unit operation,

Innovation Management in Sustainable Chemistry, First Edition. Gadi Rothenberg.

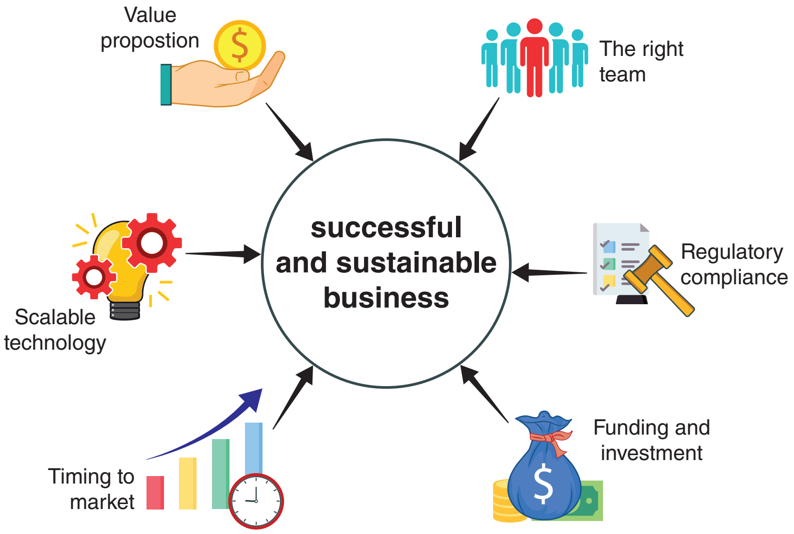

Figure 1.1 The key 'ingredients' for transforming an idea in sustainable chemistry into a successful and sustainable business.

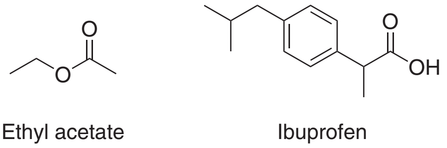

Figure 1.2 Chemical structures of ethyl acetate and ibuprofen.

but the more you learn about what happens inside the reactor, the easier it will be for you to evaluate someone's new discovery (Figure 1.1). An invention or innovation often begins with a scientific/technical discovery. Sometimes, this discovery creates the possibility for new products that can open new markets or increase market demand. The technical solution is only one part of the process, but it's an essential part. Understanding the different drivers of sustainable chemistry will help you in recognising businesses that can be both 'green' and profitable.

After explaining the principles, we take a look at two real-life successful industrial examples that highlight both the chemical and economic benefits of sustainable chemistry: The first is the production of **ethyl acetate**, a common solvent used in many food applications, with a global production of over 4800 ktpa and a market value of ca. €4 billion. The second is the popular nonsteroidal anti-inflammatory drug **ibuprofen**, with a global production of 45 ktpa and a market value of over €600 million (Figure 1.2). We follow the story of the manufacturing of these chemicals from the original processes to the new, sustainable alternatives, examining the drivers for change in each case.

1.1 Background: Chemistry and the Global Importance of Sustainability

Of all the fields of science, chemistry is the one that has the most impact on our modern society, even if this impact is not obvious at first glance. Man-made chemicals are all around us. The chemical and petrochemical industries have shaped our lives by supplying us with energy, medicines, crop protection, foodstuffs and new materials. Considering the 20,000-year timeline of human history, these are recent developments. They began in the second half of the 19th century and expanded throughout the 20th century, the period correlating with what we term 'modern society'. Thanks to the chemical industry, people in the 21st century live longer and healthier lives than in any other period in history. We have abundant food and enjoy an unprecedented quality of life with ample access to energy, shelter and modern medicines. Worldwide distribution of resources is not ideal, but this reflects bad management and greed rather than actual shortages. Even in rich, developed countries, people are bound to complain. But trust me – as a species, we never had it so good.

Ironically, modern life has changed so much since the advent of the large-scale chemical industry in the late 19th century that these positive changes have caused a population increase that is itself creating problems on a global scale [3]. More people means more pressure on the world's fresh water, arable and habitable land, and energy resources. But more people also means more garbage and a larger environmental footprint, affecting biodiversity, polluting the air and the oceans, and even changing the Earth's climate.

Solving these problems is beyond the scope of this book. Indeed, there is no technological short-term 'magic solution', because these problems are caused by long-term societal and demographic changes [4]. We can optimise government regulations, management, planning and safety procedures, but the challenges of resource scarcity and end-of-life product disposal will remain. The best we can do is understand the problems' origin and try and adapt our lives to create a more sustainable environment.

The problems we face are complex because they involve many connected factors that affect each other both in the short term and in the long term. Two such examples are energy scarcity and plastic garbage. Are we really going to run out of fossil fuels in our lifetimes? Or before 2100? Is this the reason that oil prices are (sometimes) increasing? No, we are not, and it is not [5]. The short-term prices of fossil-based raw materials fluctuate because of geopolitics and national and regional economic policies. There are enough fossil carbon resources available to cover humanity's needs for centuries to come. But these resources will run out eventually, and exploiting some of them carries a large environmental penalty. The bigger and much more urgent problem is that burning fossil fuels is changing the climate – so much so that 198 countries that participated in the 28th Conference of the Parties (COP28) in Dubai in 2023 agreed that they should gradually phase out the use of fossil fuels to try and limit the long-term effects of the resulting greenhouse gases [6]. Whether they will actually do it is another issue [4].

Similarly, while we all enjoy the abundance and attractive price/performance ratios of plastic bottles and plastic packaging in general, the accumulation of plastic garbage and the effects of microplastics and persistent pollutants are making people realise the importance of product life cycles [7, 8]. To put it simply, we must transform our 'produce-use-waste' linear economy into a circular one where the waste, if it cannot be avoided, is recycled back into resources and raw materials (Figure 1.3).

A key aspect of this transition is how we view waste and resources. The so-called **waste management pyramid** indicates an order of preference for reducing and managing waste, starting from prevention (the most favoured option) all the way down to disposal (see Figure 1.4) [9]. Moving from a linear economy to a circular one is a sensible idea that is easily understood by scientists and laypeople alike. Yet understanding something and doing it are two different things. Everyone agrees that a circular economy is much

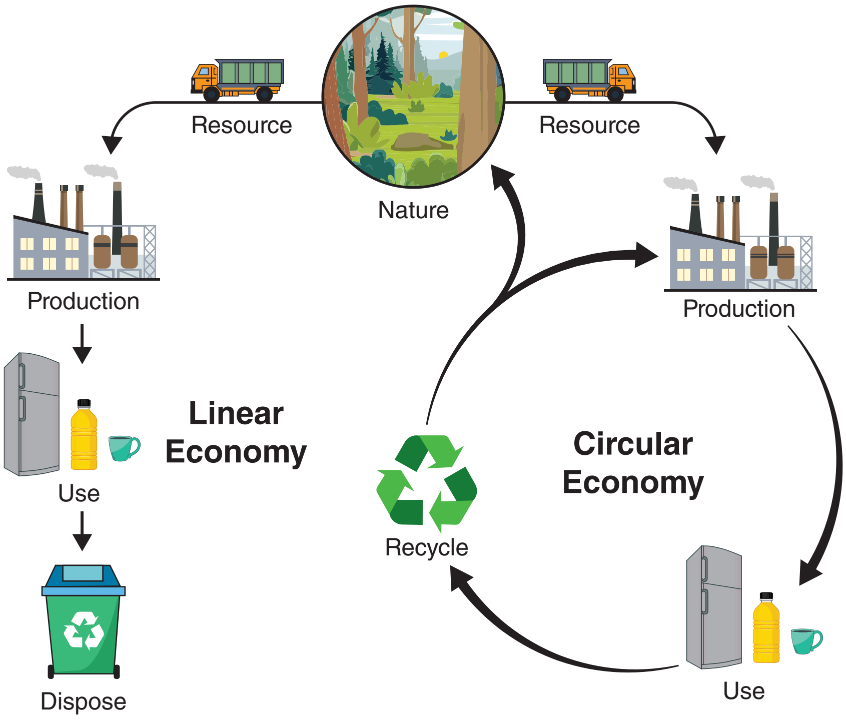

Figure 1.3 Comparing the linear economy and the circular economy.

better in the long term, but the transition is costly and risky in the short term [4]. For example, recycling plastics is better for the environment than sourcing 'pristine' raw materials, but as long as new raw materials are available and cheap, there is no incentive for companies to switch their production processes. Governments may set sustainability goals, but it is up to companies, and the people heading those companies, to carry them out. This is the difference between wishful thinking ('recycling waste back to raw materials is good for the environment and therefore good for everyone') and reality ('switching our process will cost a lot in the next five years, it's risky, and I may not see the long-term benefit') [10].

As we shall see in the following chapters, many worthy ideas are never implemented because of short-term economic considerations. A perfect circular economy is a utopian concept. It cannot be realised in practice in the world we live in today. But the transformation process itself creates many opportunities for businesses. This book will help you recognise these opportunities, assess their economic value, and hopefully benefit from them while making the world a better place.

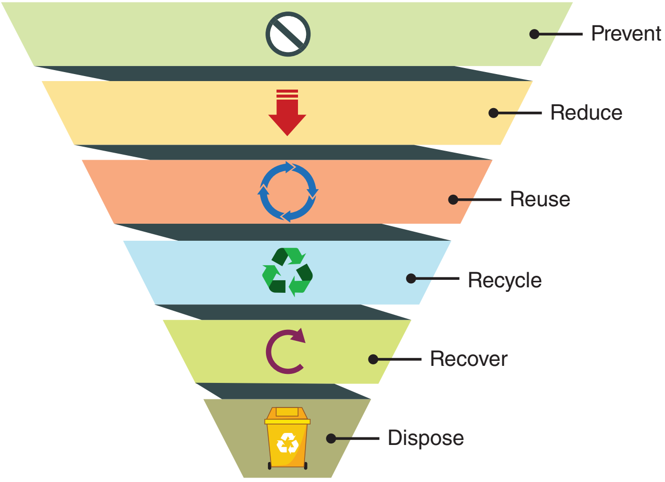

Figure 1.4 The waste management pyramid.

1.2 Sustainable Chemistry as the Key to Sustainable Development

Two popular terms associated with the change from a linear economy to a circular one are **sustainability** and **sustainable development**. A sustainable society is one that 'meets the needs of the current generation without sacrificing the ability of future generations to meet their own needs'. Sustainable development is a strategic goal. It can be reached using various approaches, and this is where **sustainable chemistry**, also known as **green chemistry**, comes in. Figure 1.5 shows the relationship between the strategic goals, the practical approaches, and the day-to-day operational and monitoring tools. Green chemistry is just one step on the road to sustainability, but our dependence on industrial chemicals makes it an essential step. Anyone stepping outside in mega cities such as Delhi, Guangzhou or Mexico City, for example, will tell you that the air pollution from power stations and chemical factories cannot be ignored (in fact, air pollution is now a serious problem even in Europe [11]). Accidents such as the Deepwater Horizon oil spill in the Gulf of Mexico in 2010, where over 4.9 million barrels of oil were discharged into the ocean, haven't helped improve the industry's image either [12].

1.3 What Is 'Sustainable Chemistry'?

In the 1990s, the concept of 'green chemistry' was initiated in both the United States and Europe and has since been adopted widely by the chemical industry [13]. Green chemistry deals with designing chemical products and processes that generate and use less (or preferably no) hazardous substances. By applying the **principles of green chemistry**, companies embrace cleaner and more efficient technologies, with an *a priori* commitment to a cleaner and healthier environment. The message is simple: 'Seek prevention, not cure'. In 1998, Anastas and Warner formulated the 12 principles of green chemistry [14, 15]:

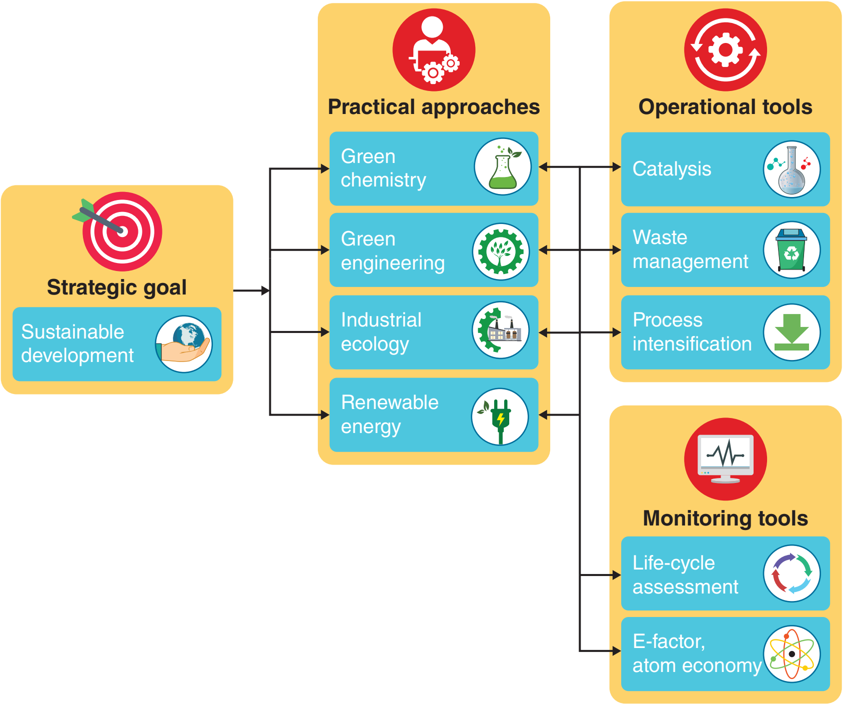

Figure 1.5 The strategic goal of sustainable development relies on practical approaches such as green chemistry, industrial ecology and green engineering. These approaches use various operational tools (such as catalysis) and monitoring tools (such as life-cycle assessment).

I Prevent waste instead of treating it.
II Design atom-efficient synthetic methods.
III Choose synthetic routes using nontoxic compounds where possible.
IV Design new products that preserve functionality while reducing toxicity.
V Minimise the use of auxiliary reagents and solvents.
VI Design processes with minimal energy requirements.
VII Preferably use renewable raw materials.
VIII Avoid unnecessary derivatisation.
IX Replace stoichiometric reagents with catalytic cycles.
X Design new products with biodegradable capabilities.
XI Develop real-time and online process analysis and monitoring methods.
XII Choose feedstocks and design processes that minimise the chance of accidents.

Sustainable chemistry has three drivers : Government legislation, societal pressure and economic benefit (Figure 1.6) [16]. The EU directive on the registration, evaluation and assessment of chemicals (REACH) has changed the chemical industry across Europe [17]. Similar regulations are expected worldwide in the coming decades. But legislation is just one of the drivers. Societal pressure is another: The public favours industrial green chemistry initiatives, as they lead to safer and eco-friendly products and processes. This creates goodwill for the company, something that is difficult to quantify but undoubtedly important.

The third and most important driver is economic benefit. Applying sustainable chemistry principles can decrease both your capital investment and your operating costs. If you use

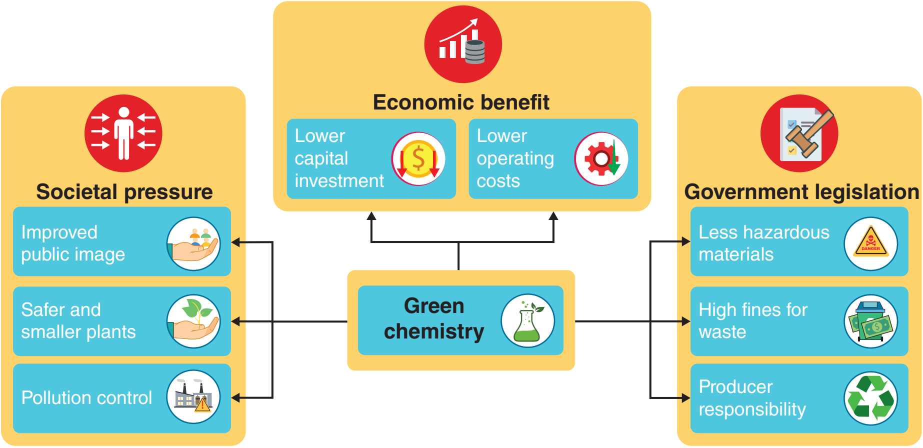

Figure 1.6 The three drivers of sustainable chemistry are government legislation, societal pressure and economic benefit.

less (or no) solvent, your reactor space-time yields go up. If you replace costly reagents with cheaper and more abundant ones by switching to catalytic cycles, your chemicals bill goes down. Processes running at moderate (or even ambient) temperatures are less energy-intensive, requiring less utilities. This means making the same products using smaller and safer equipment. Eliminating waste also removes the need for costly treatment and disposal, and replacing toxic reagents with benign ones saves on safety costs during transportation and storage. Producing the same amount of product with a smaller plant footprint saves a lot of money on the capital required for building the plant as well as on the operational costs. Getting permits for building smaller and less energy-intensive plants is easier, and people are less likely to object to them. This means that sustainable chemistry plants can be placed in more varied locations, which in turn makes finding operators for these plants easier. As the awareness of these benefits grows, more companies adopt sustainable chemistry practices simply because it improves their bottom-line performance.

As we will see in the industrial case studies in the following chapters, economic benefit is an essential driver for the success of sustainable processes and products. A '**green premium**' (the additional amount that a customer is willing to pay for a product just because it is environmentally friendly) can enhance a company's public image and increase sales. It is also an important factor in recruiting enthusiastic employees (especially millennials and generation Z). But your product or process should compete in the market even without a green premium. If, on top of that, you have the appeal of sustainability, it's a bonus.

In the following sections, we will examine more closely the principles of green chemistry. In each case, I will explain the challenges involved in putting the principles into practice and see whether we can turn these challenges into economic opportunities. The original 12 principles were written aimed at chemists, who have a broad knowledge of the subject and typically specialise in a specific area. For simplicity, and because this textbook focuses on applications, I will divide these principles here into six groups (Table 1.1).

1.3.1 Preventing Waste and Maximising Atom Efficiency (Principles I and II)

The first principle is a no-brainer. After all, waste is, by definition, something that nobody wants. Anything that comes out of your process that is not a product is basically waste and

Table 1.1 Division of the 12 principles of sustainable chemistry.

Content	Principles
Prevent waste and maximise atom efficiency	I and II
Reducing overall toxicity and hazard	III, IV, XI and XII
Use fewer reagents, solvents and derivatisation	V and VIII
Save energy	VI
Use renewable resources and make biodegradable products	VII and XI
Replace stoichiometric reagents with catalytic cycles	IX

costs you money. Chemical waste incurs multiple costs: first, when you purchase the raw materials, because if there is waste, it means that you've paid for kilograms of something that you are not using. The second cost is in your plant footprint and reactor space-time yield. Chemical plants are expensive, and the larger they are, the more they cost. Waste also needs to be separated from your products and any unused reactants. Such separation requires costly equipment that takes up space and uses energy. Building a moderately sized plant, that produces 100,000 tpa of product, can easily cost €300–400 million, and much of this cost is product separation and post-reaction treatment. Once you have separated it, you must also pay money to *dispose* of your waste. In nearly all countries, the days when companies could simply dump their waste in rivers, in the sea or even in landfills are long gone.

In recent years, chemical waste has developed another cost factor: the environmental cost of using wasteful suppliers. Many companies operating in developed countries commit to a sustainable supply chain, sourcing their chemicals and materials from less wasteful producers. The economic impact of this effect is still small, because there are enough buyers who disregard the environmental consequences of their suppliers' processes (just like most of us don't buy organic milk or free-range chicken). But waste is costing more and more money.

There are some specific rulers for measuring the 'wastefulness' of processes and products. One such measure is the **E-factor**, introduced by **Roger Sheldon** in 1994 [18, 19]. A reaction's E-factor equals the quotient $\mathrm{kg}_{waste}:\mathrm{kg}_{product}$ (here 'waste' is everything formed in the reaction except the desired product). The waste can be gases such as CO_2 or NO_x, water, common inorganic salts (e.g. NaCl, Na_2SO_4 or $(NH_4)_2SO_4$), heavy metal salts and/or organic compounds. Table 1.2 compares the production tonnage and E-factors of various

Table 1.2 Annual production and E-factors in the chemical industry.

Industrial sector	Production ton/year	E-factor
Petrochemicals	10^6–10^8	<0.01
Bulk chemicals	10^4–10^6	1–5
Fine chemicals	10^2–10^4	5–50
Specialities/pharmaceuticals	10–10^3	20–100

industrial sectors. Note that the petrochemicals and the bulk chemicals sectors have the lowest E-factors. In fact, E-factors increase substantially when going from bulk chemicals to fine chemicals and specialties. This is because producing fine chemicals and pharmaceuticals often involves multi-step syntheses, which require protecting groups and other reagents that are absent from the final product.

This brings us to the second principle of maximising atom efficiency. The concept of **atom economy**, introduced by **Barry Trost** in 1991, is similar to the E-factor [20]. Here, one considers how many and which atoms of the reactants are incorporated into the products. With these two concepts, we can evaluate chemical reactions and get a quantitative result.

Example: Calculating the E-factor and Atom Economy

In this worked-out example, we look at the classic oxidation of diphenylmethanol to benzophenone, one of the most commonly used photosensitisers in photochemistry (Figure 1.7). We will evaluate this reaction using the measures of product yield, product selectivity, E-factor and atom economy. In this reaction, three equivalents of diphenylmethanol react with two equivalents of chromium trioxide and three equivalents of sulphuric acid, giving three equivalents of benzophenone. First, let us see how the reaction measures with respect to product yield and selectivity. Assume that this is an ideal chemical reaction that goes to completion, or 100% conversion. If no other (organic) by-product is obtained, the selectivity to benzophenone is also 100%. The yield, in this ideal case, would also be 100% (remember: yield = conversion × selectivity). If we focus on the organic compounds, this looks like a high-yielding reaction.

Figure 1.7 The oxidation of diphenylmethanol to benzophenone using stoichiometric amounts of chromium trioxide and sulphuric acid.

However, examining the **E-factor** for this reaction, we see that for every 3 mol of benzophenone, we produce 1 mol of chromium sulphate and 6 mol of water. The molecular weight of benzophenone is 182.2 g/mol, so every kg of benzophenone contains 5.48 mol of benzophenone. This means that for every kilogram of benzophenone, we generate 5.48/3 = 1.83 mol (or 0.717 kg) of chromium sulphate and 10.96 mol (or 0.197 kg) of water. The overall E-factor is therefore:

$$\text{E-factor} = \frac{\text{kg}_{\text{waste}}}{\text{kg}_{\text{product}}} = \frac{0.717 + 0.197}{1} = 0.914 \qquad (1.1)$$

Nearly a whole kilogram of waste for every kilogram of product! Remember, this is for the ideal case of 100% yield and 100% selectivity. In real life, the E-factor is usually

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higher, because product yields are less than 100% and reagents are sometimes used in excess. Furthermore, in many cases, you need to neutralise acid or base side products, so the overall waste amounts are even higher.

We can also calculate the **atom economy** for the same reaction using the molar masses and the reaction stoichiometry, as shown in Eq. (1.2):
The molar masses are:

Diphenylmethanol ($C_{13}H_{12}O$) = 184.23 g/mol
CrO_3 = 99.99 g/mol
H_2SO_4 = 98.08 g/mol
Benzophenone ($C_{13}H_{10}O$) = 182.21 g/mol

The total mass of the reactants (for 3 mol of product):

$= 3 \times 184.23 + 2 \times 99.99 + 3 \times 98.08$
$= 552.69 + 199.98 + 294.24$
$= 1046.91\text{ g}$

The mass of the desired product (3 mol benzophenone):

$= 3 \times 182.21 = 546.63\text{ g}$

$$\text{Atom economy} = \frac{\text{Mass of desired product}}{\text{Total mass of reactants}} \times 100\% = \frac{54{,}663}{104{,}691} \times 100\% \ = {\sim}52\% \tag{1.2}$$

The challenges that arise from the first two principles come hand-in-hand with opportunities. Wherever there is waste in your process you can try and redesign the chemistry and/or the engineering operations to avoid generating it. The earlier you avoid the waste in your product chain, the better: fewer separation steps, smaller reactor and plant footprints, and, of course, less capital and lower operational costs. Sometimes the opportunity comes in the form of new chemistry: Can you make a different molecule or material that incurs less waste yet delivers the same performance? Or can you perhaps engineer the process such that the waste is recycled back into the reactor as new raw material (perhaps with an additional step, but if you're not throwing away anything, it's probably still worthwhile) [21].

Alternatively, if you cannot avoid making this extra stuff, maybe you can find a use for it and then find someone who will buy it. Then your 'waste' is not waste anymore, but a by-product that is generating income. This is a little tricky, because it ties your original product-market combination to another product-market combination. Sometimes, the two fit well together, but there is no guarantee. For example, if you are a phenol producer and you choose to produce your phenol via the cumene oxidation route (see Figure 1.8) you also get one mole of acetone for every mole of phenol. You probably have buyers for your phenol, since this is your main business, but you must also now find buyers for an equivalent amount of acetone.

Sometimes this is not a problem, especially if you're also making the second product in-house. For example, a few years ago, my colleague **Raveendran Shiju** invented a niobia-catalysed ammoximation route to caprolactam that avoided the generation of the

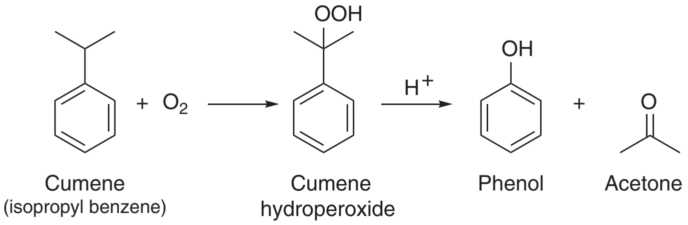


Figure 1.8 The catalytic oxidation of cumene (isopropyl benzene) to phenol + acetone proceeds via a hydroperoxide intermediate.

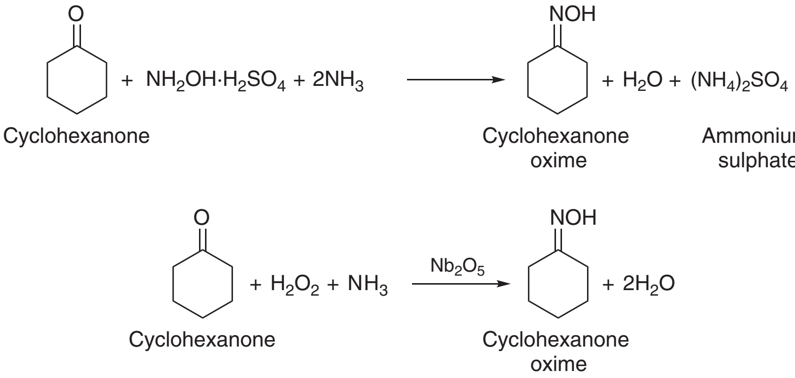


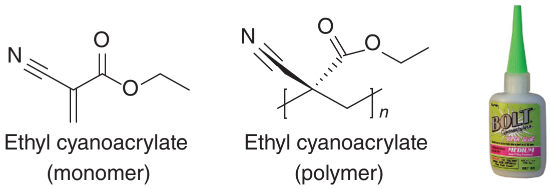
Figure 1.9 The classical ammoximation route (top) and the new route improved by Shiju's catalyst, which avoids the ammonium sulphate by-product (bottom).

ammonium sulphate by-product (see Figure 1.9) [22]. We tried selling this catalyst to BASF, and they agreed that our process was both elegant and less wasteful than theirs, saving the ammonium sulphate waste. However, they didn't mind the few extra thousand tons of ammonium sulphate, for a simple reason: they just went and poured this on the 'mountain' of ammonium sulphate they had in Ludwigshafen anyway, BASF being a producer of both ammonia and sulphuric acid for making ammonium sulphate fertiliser. We then realised that we would have a better chance of selling the patent to Sumitomo or to DSM, since both of these companies had at that time business units that produced and sold caprolactam, but not ammonium sulphate. After some interesting negotiations, we sold the patent to DSM.

1.3.2 Reducing Overall Toxicity and Hazard (Principles III, IV, XI and XII)

Most people recognise the risks associated with toxic chemicals, yet still accept a certain level of toxicity based on functionality. For example, cyanoacrylate glue ('superglue') is toxic and hazardous, but many people keep a small tube of it at home (Figure 1.10). Yet as far as possible, we look for non-toxic products, especially when dealing with long exposures and/or large amounts. The fourth principle of green chemistry, 'Design new products that preserve functionality while reducing toxicity', makes a lot of sense. We want to replace toxic products with non-toxic ones, while keeping the same functionality and performance.

Toxicity is not always apparent at first glance. Sometimes years pass before studies show that a compound is toxic. In some sectors, namely food and medicines, the issue of toxicity



Ethyl cyanoacrylate (monomer)

Ethyl cyanoacrylate (polymer)

Figure 1.10 Chemical structures of the ethyl cyanoacrylate monomer and 'superglue' polymer. *Source*: BUPAK Ltd / Wikimedia Commons / public domain.

must be settled by official bodies (e.g. the American Food & Drug Administration, or FDA) before you can start making and selling your products. Approvals can take several years, another good reason to start from non-toxic materials (this does not guarantee that your products will be approved, but it could help you register them under 'lighter' constraints). And every toxicity problem with a chemical product is also an opportunity for replacing this product (and overtaking its market) with a non-toxic alternative.

The third principle is about choosing synthetic routes using nontoxic and/or non-hazardous compounds. Sometimes the end product is non-toxic, but its synthesis involves toxic and/or hazardous materials. Some reagents or intermediates are so toxic that they may not be transported between factories and must be prepared and consumed on-site. Phosgene, $COCl_2$, is such an example. It is a toxic, colourless, dense gas. During WW I, it was used as a chemical weapon, killing tens of thousands of people.[1] Yet the same phosgene is also an important industrial building block, especially for producing the precursors of polyurethanes and polycarbonate plastics. The global market size of these two polymers was >100 billion US$ in 2022 (more than the market value of BASF and General Motors combined) and is expected to grow to 135 billion US$ by 2032.

Today, phosgene is still used on a large scale in the production of polyurethane and polycarbonate precursors, but it is considered too dangerous to transport or store. Therefore, it is usually produced on demand and immediately consumed within the same plant. By maintaining equivalent rates of production and consumption, the amount of phosgene at any one time is kept low, reducing the risks in the event of an accident. Nevertheless, few people want such a chemical plant in their neighbourhood. There are ample opportunities here for enterprising chemists, especially since the two chlorine atoms are not part of the end product (see Figure 1.11). Considering that these atoms account for 72% of the weight of phosgene, replacing it with something more benign would also follow principles **I** and **II**.

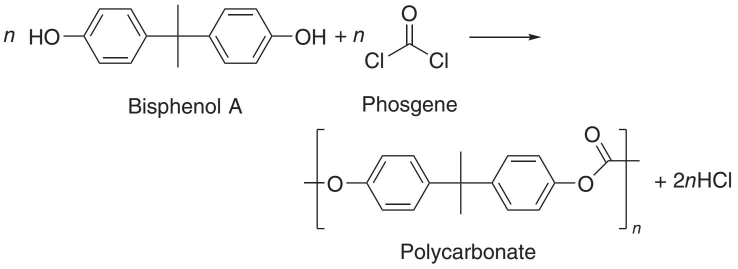


Figure 1.11 The reaction of phosgene with bisphenol A gives polycarbonate plus two equivalents of hydrochloric acid as a by-product.

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[1] Phosgene was especially effective in trench warfare, because its density of 4.5 g/L is over three times that of air (1.3 g/L). It would settle in the trenches, attacking and killing the sheltering soldiers.

However, the challenge of replacing phosgene as a reagent is a difficult one because of its high reactivity and selectivity. Another barrier to replacement is that these polymerisations are large-scale processes. Global production of polyurethanes exceeded 25 million tons in 2020. As we shall see in the next chapters, companies rarely change large-scale processes, because such a change involves a large short-term economic risk that often outweighs the uncertain future benefit [23].

In this group, I also include principles **XI** and **XII**, since online monitoring and design for safety go hand-in-hand. Accidents are best avoided, but some will happen. When they do, online monitoring systems of the different process steps can shorten response times and increase the efficiency of treatment and remediation. This is one area that benefits from the amazing advances in physics, electronics and computer science. Monitoring devices that used to weigh kilograms and cost thousands of dollars are made today on single chips so light and cheap that they are disposable (this leads to another waste problem, so using such devices still requires a cost/benefit analysis, but it's often worth it). Coupling online analysis to large-scale data processing can also reduce the risk of accidents and even predict where accidents are likely. Such systems are part of the so-called '4th industrial revolution', also known as '4IR' or **Industry 4.0**, which refers to the integration of computerised agents in industrial processes [24]. Simulated 'digital twins' are now used to check processes for weak points and predict their sensitivity to different conditions [25].

1.3.3 Using Fewer Reagents, Solvents and Derivatisation (Principles V and VIII)

Chemical reactions are aimed at specific products. The routes to these products vary, depending on what you start from, what reagents you use and even what kind of equipment you have. Companies often depend on locally available resources. Equipment is expensive, so you often end up using whatever is already available. Some routes require additional reagents (auxiliary reagents). These lower your atom efficiency and increase the amount of waste. They can also pose toxicity and/or hazard problems. Finding simpler routes to the same product, with fewer steps or using fewer reagents, makes a lot of sense. Similarly, solvents are handy in the lab when you use small amounts of reagents, but in industry they take up much reactor space and can be a fire hazard and a problem to separate, not to mention the cost involved in sourcing, buying, storing and recycling them. Finally, the number of steps in your reaction sequence also plays a role: fewer steps and fewer derivatives mean less separation, less reagents and less time, increasing both the atom efficiency and the reactor space-time yield.

Here, too, there are opportunities for innovation and new businesses. If you can design a simpler synthesis route, you can overtake incumbent producers, who might be reluctant to change their process (see the two industrial examples at the end of this chapter).

1.3.4 Saving on Energy (Principle VI)

This is something that the chemical industry is already doing well. In any large chemical plant, exothermic processes are coupled to endothermic ones. The energy is typically shuttled around the plant in the form of 'hot' and 'cold' steam that gives/takes heat to/from processes using heat exchangers.

Figure 1.12 Going large: The latest large-scale 5 MW water electrolyser designed and built in May 2025 by the Chinese company Goldshine Lever in Ordos, Inner Mongolia. From left: Yang Wang, Vitaly Gitis, Gadi Rothenberg, Weizhen Sun (Goldshine Lever CEO).

One notable change that has occurred in the 21st century is that, especially in Europe, both the *source* and *type* of energy used matter. Until recently, chemical plants obtained their energy in the form of hot steam from a central boiler that typically ran on oil or gas. Today, more and more companies are switching to (clean) electricity. But if your process is energy-intensive, getting enough electricity can be difficult. Siemens Energy, for example, builds and markets state-of-the-art water electrolysers in their plant in Erlangen in Germany. These electrolysers are about the size of a small bus and produce 1.25 MWh worth of hydrogen from water. Siemens can test two electrolysers simultaneously at their Erlangen site. They are planning on expanding their production and testing facilities, but they cannot do this in Erlangen because this would ‘drink up’ all of the city’s electricity supply. When we compare this effect of one additional 1.25 MWh electrolyser with the 2.980 TWh of energy that was consumed in Germany in 2023, we get a feeling of how large this challenge is [26] (we’ll return to Siemens Energy for a different type of electrolyser and its application in CO_2 conversion in Chapter 5). State-of-the-art water electrolysers are getting bigger (see photo in Figure 1.12), but there is still a long way to go [27].

1.3.5 Renewable Resources and Biodegradable Products (Principles VII and XI)

The increasing public attention paid to these two principles opens many new business opportunities for chemistry-minded entrepreneurs. Using renewable resources is essential for building a true circular economy. With ‘renewable’, I mean that these resources can be renewed on a human time scale. Certain species of bamboo can grow almost a meter a day. Industrial hemp cultivars, *Cannabis sativa,* which are grown for their fibre, can reach maturity within 12–16 weeks. Douglas fir trees, which are popular as Christmas trees and also used in managed forestry for softwood timber, take 15 years. All of these can be considered as 'renewable carbon sources' (fir trees are planted at a density of about 250 trees/acre; if you have 15 acres of land, you can plant one acre every year and cut down and process one acre every year). Crude oil, natural gas or coal deposits are not considered renewable because they formed over tens of millions of years.

1.3.5.1 Historical Context: The Century of Change

To realise the global importance of switching to renewable resources, we need to understand first how the chemical industry shaped our modern society over the past century. The chemical products that we use are typically made from carbon, oxygen, hydrogen, nitrogen, sulphur, phosphorous and a few other elements. In addition to these, the steel and concrete industries, which are not perceived as part of the 'chemical' industry, use a lot of iron and calcium, but luckily Earth has an abundance of both.[2] In each case, we talk about an elemental cycle, for example, the **carbon cycle** or the **nitrogen cycle**, showing us where the raw material is coming from and where it ends up after use. We can also track the cycles of compounds and materials, as in the **water cycle**. Normally, these cycles change only slowly with time. Continental changes due to the movement of tectonic plates take millions of years. Glacial periods (ice ages) take tens of thousands of years. The Earth is now in the *Holocene*, an interglacial period that started about 10,000 years ago. We're coming out of an ice age. The problem is that we are coming out of it a little too quickly for our own good.

For most of human history, our impact on planet Earth has not been large enough to change elemental cycles significantly. This small impact reflected the Earth's relatively small human population, which remained under a billion people until the end of the 19th century. But in the early 20th century, everything changed. Abundant coal-based power drove industrialisation and economic growth forward, creating massive new opportunities for development in Europe and North America. The invention of petroleum refining in the 1920s compounded these opportunities, giving mankind access to what was, at the time, practically limitless energy.

This coincided with two crucial discoveries: In 1921, Alexander Fleming, a physician working at St. Mary's Hospital in London, accidentally discovered lysozyme, the first antimicrobial protein [28]. Across the English Channel in Ludwigshafen, Carl Bosch and Alwin Mittasch at BASF were optimising the catalytic Haber-Bosch process for making ammonia, invented by Fritz Haber a decade earlier [29, 30]. The combination of antibiotics and plentiful fertiliser, combined with abundant energy from coal and crude oil, led to an exponential increase in prosperity and population, from less than two billion people a century ago to eight billion today. With this increase in population and quality of life came an increasing demand for energy, almost all of it from fossil fuels. In 2020, CO_2 emissions reached a staggering 35 billion tons. The good news, if we could call it that, is that the emissions *per capita* have not increased so much (cf. the slopes of CO_2 emissions and population growth in Figure 1.13). In some countries, the emissions per capita even

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[2] Although the principles of sustainability apply also to the steel and concrete sectors, the market size and large entry barriers make these sectors a tough challenge for new technology start-ups. See the discussion on process scale in Chapter 2.

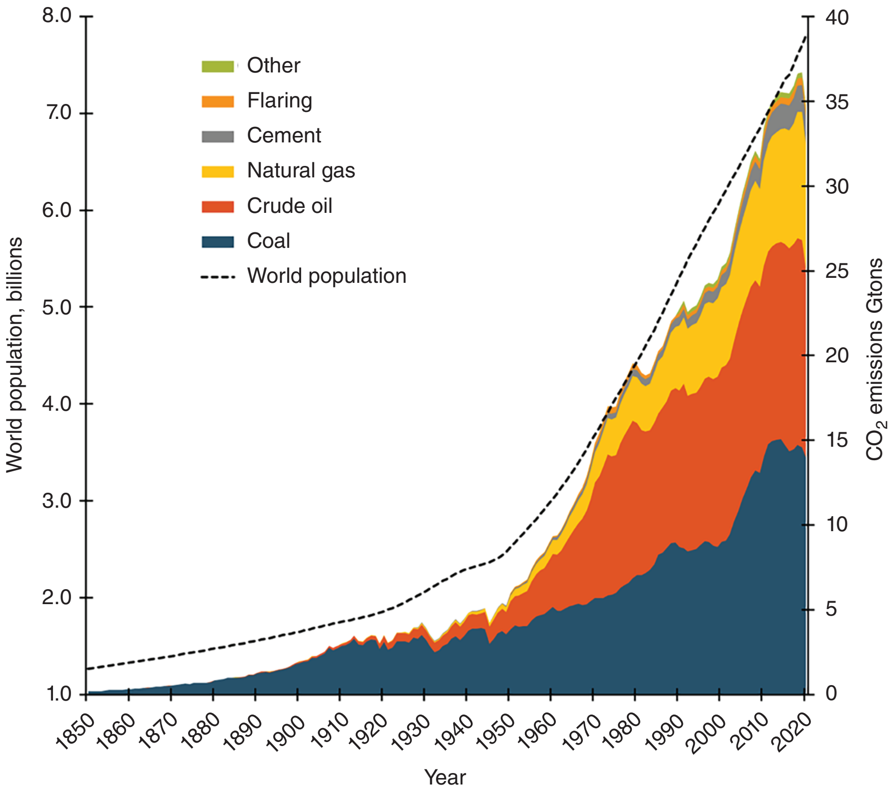

Figure 1.13 Annual worldwide anthropogenic CO_2 emissions, in gigatons from 1850 until 2020 (right ordinate) and their cause. The dashed curve shows the world population for the same period (left ordinate). *Source*: [4] / Elsevier / CC BY 4.0.

decreased. However, this also shows that the problem of CO_2 emissions is a direct result of this population increase, and this is not going down anytime soon. **For the first time in history, human intervention has become so large that it is disrupting global elemental cycles**. Mankind is affecting the environment as much as a large volcanic eruption or a long-term reduction in solar activity would do. And just like these extreme cases, there are worldwide consequences.

By understanding the human effects on elemental cycles and especially by figuring out where do resources come from and what is the fate of waste, we can try and locate points for improvement. These often come hand-in-hand with new business opportunities. In the two examples below, I will discuss the carbon and nitrogen cycles, but the principles apply to all elements and compounds.

1.3.5.2 Human Impact on the Carbon Cycle

In today's linear economy, carbon is derived mainly from fossil sources. These differ per location: crude oil and natural gas are abundant in the Middle East, the United States, Europe and Russia; coal and natural gas in China and coal in South Africa and Australia. The carbon produced from these sources enters the chemical production chain in various molecular formats: C1 (methane, CO, methanol), C2 (ethane, ethene, acetylene, ethanol), C3 (propane, propene, propanol), C4 (butane, butenes, 1,3-butadiene) and C6–C8 (hexane, hexenes and benzene/toluene/xylenes or BTX). Most of these hydrocarbons, about 90%, are used for generating energy. The remaining 10% are used for making so many of the products in our everyday lives: polymers (plastics), bulk chemicals, fine chemicals and pharmaceuticals. This division also determines where the waste goes: 90% of the carbon we use ends up as CO_2 emissions in the atmosphere, and 10% ends up as solid or other waste. The main problem with using carbon from fossil sources is that we cannot replace these on a human time scale. The coal, petroleum and natural gas that we use today have accumulated underground over tens of millions of years. They have stayed underground for tens of millions of years. Now, we are releasing them back into the environment, and especially into the atmosphere (as CO_2) and the oceans (as microplastics) in just a few decades.

There is an alternative source of carbon: biomass. This is not a new invention – mankind used biomass for fuel way before fossil carbon, simply because it was more readily available. Even today, lignocellulosic biomass accounts for about 10% of the global energy supply. Yet biomass can be used for much more than energy [31]. Once broken down into its main components of cellulose, hemicellulose and lignin, you can use it for making polymers, alcohols, acids and other bulk and fine chemicals [32]. Oils and fats can be hydrolysed to give glycerol and fatty acids, both of which can be converted to useful products. Using carbon from biomass has two important advantages: First, biomass *can* be renewed on a human time scale. Second, every carbon atom in every tree, bush or blade of grass comes directly from CO_2 in the atmosphere. Using biomass as a renewable carbon source makes lots of sense. The problem is that the amount of biomass that is available worldwide is only about 10% of the total carbon that we use.

Thus, we can envisage a world where the carbon needed for chemicals and materials comes from biomass sources (because these account for about 10% of the total carbon we use, so the amounts are similar). Yet even changing this 10% is a formidable challenge. Despite the increased media hype, renewable carbon accounted for a measly 0.2% of the plastics industry in 2022. The following chapters will explain in more detail the challenges in this area, but the most important message is that companies will switch to biobased carbon sources only if this brings them economic benefit [33]. Companies may say on their websites that they want to save the environment, but what they want is to make profits. As long as we, the customers, are unwilling to pay more for biobased products, biomass will not replace petroleum-based carbon.

Energy is a completely different story. We *cannot* use biomass to meet our energy needs simply because there is not enough biomass to meet even a quarter of the world's energy demand. We must find another solution for our energy needs.

1.3.5.3 Human Impact on the Nitrogen Cycle

Nitrogen molecules are available everywhere. They make up 80% of the air around us. The problem is that the stability of the $N{\equiv}N$ triple bond severely limits their direct use in chemical reactions. This can be a good thing – nitrogen gas is used in inert packaging, in electronic devices and in various industries to prevent fires. Here, however, we are interested in incorporating nitrogen atoms into molecules and materials, from polyamides (nylons) to antibiotics. Unlike carbon, which comes from several sources, the nitrogen atoms that we use in the chemical industry are sourced via just one molecule: Ammonia. And practically all of the ammonia today is synthesised from nitrogen and hydrogen (the latter typically made from natural gas) via the Haber-Bosch process. This process is so large that it stands in a class all on its own: worldwide production of ammonia in 2021 was a mind-boggling 235 million tons. Today, the ammonia process alone accounts for >2% of the world's energy consumption (roughly the same amount of energy consumed by Mexico in a year).

Man-made nitrogen is essential for making fertilisers, nylons, explosives and many other chemicals. Many of these products are made using nitric acid, HNO_3, of which 70 million tons were produced in 2021. This impacts the environment, as the nitrogen atoms eventually end up in the bio ecosystem, and the amounts are too large for nature to deal with. The result is increased amounts of nitrogen oxides (which are potent greenhouse gases) in the atmosphere, and higher concentrations of nitrate and ammonium ions in terrestrial and aquatic systems. These ions are basically 'food additives' for the ecosystem, and they create a celebration of growth, causing eutrophication and decreasing biodiversity. All these disturb the natural nitrogen cycle. Just like with carbon, we need to rethink our impact on the nitrogen cycle, and just like with carbon, this need opens opportunities for start-ups and new businesses [34].

1.3.5.4 The Importance of Biodegradable Products

One way to reduce our ecological footprint is by making products that can be readily decomposed under natural conditions. Ideally, this decomposition should not have an adverse effect on the environment. This is a very big challenge, for two reasons: First, consumers strongly prefer new-looking and long-lasting products, so the decomposition should happen only when the product reaches its end-of-life. Second, even when the product decomposes only at the disposal, there is no guarantee that its remains will not affect the environment. Additional nitrogen or phosphorous in the soil, for example, can enrich it and promote the growth of different plants and microorganisms, changing the ecosystem. Often, these changes are observed only after many years, but the knowledge that this can happen creates barriers for approval of product use.

Nevertheless, biodegradable products, and especially biodegradable plastics, are extremely important for dealing with our enormous waste problem. In 1950, each person on Earth used on average 1.7 kg of plastic. Today the figure is >150 kg. The total production of plastics in 2019 was 370 million tons per annum, and biodegradable plastics formed less than 2% of this [35]. Figure 1.14 shows the material flow analysis for plastics in 2019. Recycling accounted for only 23 million tons, while landfill and mismanaged waste together accounted for 165 million tons. That's a lot of plastic that ends up in the environment. Unfortunately, landfills and mismanaged waste are the major causes of microplastics in the environment. Between 15% and 40% of mismanaged plastics enter the oceans from coastal cities [36]. Most of the microplastics that form in these conditions (soil and coastlines) are difficult to quantify [37]. Estimates of microplastics released in the soil in Europe are comparable to those reported for the oceans in the same region.

There is clearly a case for switching to biobased and biodegradable plastics. But this switching will take decades, if it happens at all. The reason is that the current processes for making durable plastics from fossil-based carbon are mature and highly optimised. Replacing them incurs a short-term risk that currently offsets any future gain. Regulations for separation and recycling of traditional plastics can help this transition, because they turn plastic waste from an externality (i.e. somebody else's problem) to something with a defined cost and therefore value.

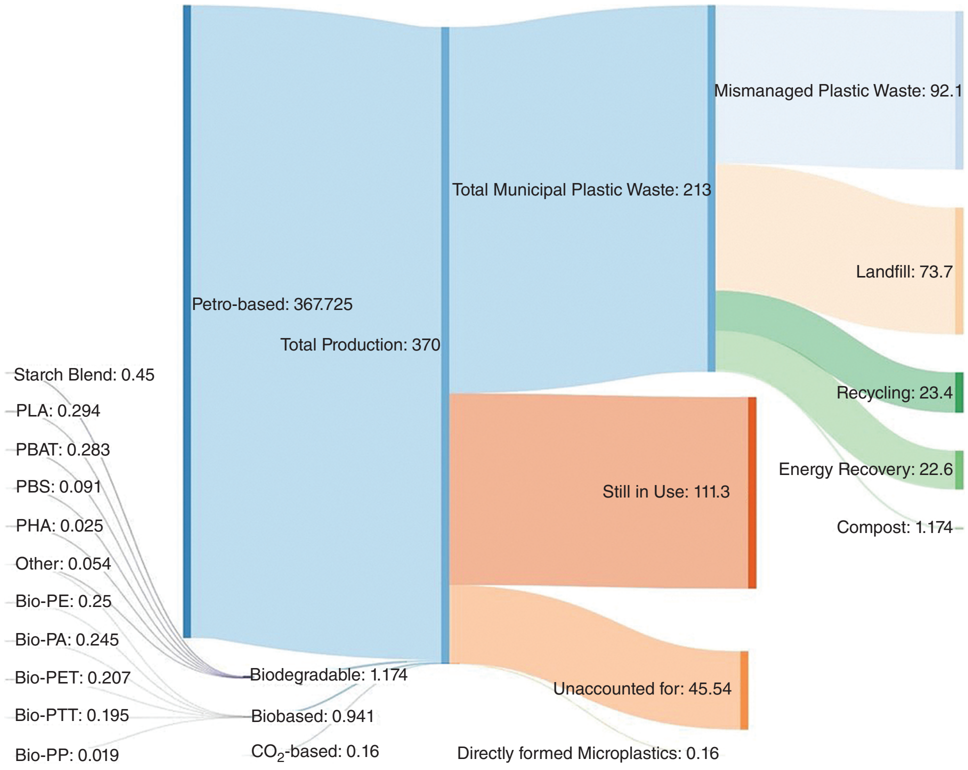

Figure 1.14 Sankey diagram showing the material flow analysis (MFA) for fossil-carbon-based, biodegradable, biobased, and CO_2-based plastics in 2019. All values are in millions of tons. *Source*: [35] / John Wiley & Sons.

Yet moving from traditional plastics to eco-friendly ones is a tricky challenge. The very definitions of ‘biobased’ and ‘biodegradable’ are unclear. Adjectives such as ‘green’, ‘circular’ or indeed ‘eco-friendly’ are even vaguer. Producers, consumers and policy-makers are faced with a plethora of choices and approaches, where relevant information is hard to come by. But one thing is certain: There is a large market out there for biobased and biodegradable plastics, if these can be made economically viable. I will discuss the subject of product-market combinations in more detail in Chapter 2, but even now, we can see that biodegradability, which is an end-of-life characteristic, is not trivial. When we throw something away, biodegradability is an advantage as the waste goes back into the ecosystem and is eventually recycled by nature into new raw material. But as long as the product is functioning, we don’t want it to degrade.

Biodegradable products are suitable in some cases, especially when collection, recycling and reuse are difficult. Otherwise, keeping the material performance parameters can be essential for efficient recycling and reuse. Polyethylene can stay in the environment for hundreds of years, but this also means that if you can collect it and clean it, you can reprocess and reuse it again and again. In this way, the carbon atoms that form the polymer backbone remain ‘stored’ there instead of being released as CO_2. Even from a societal viewpoint, biodegradability is a two-edged sword, as it can also encourage single-use and wastage.

Ultimately, it all depends on the application. Biodegradable plastic packaging and film make sense, but Lego bricks, for example, are made from a copolymer called acrylonitrile butadiene styrene (ABS) for a reason: They last for decades and are valued for their durability and long-term performance. Chapters 8 and 9 tell the respective stories of the companies Avantium and Plantics, whose main value proposition centres on biobased and/or biodegradable products.

1.3.6 Replacing Stoichiometric Reagents with Catalytic Cycles (Principle IX)

Although I have left this one to the end, catalysis is one of the most important principles of green chemistry [38]. In fact, catalysis is the key to sustainability [39]. Catalysis also creates many business opportunities. Finding the right catalyst can disrupt large markets and sometimes even create whole new markets. One such example is the discovery of the zeolite ZSM-5, which enabled the selective formation of terephthalic acid and with it the

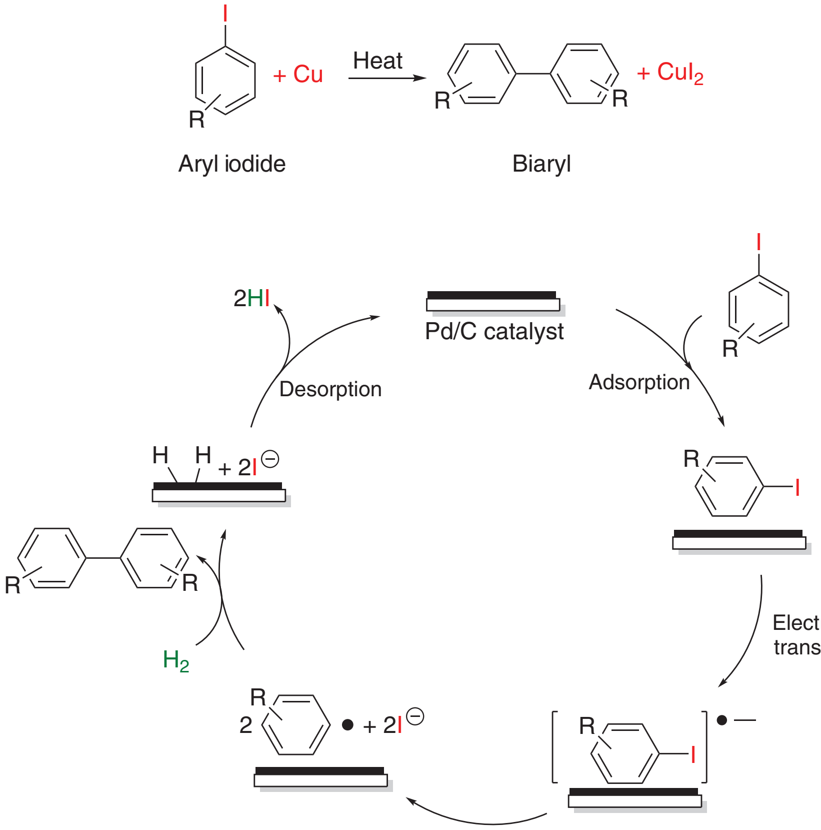

Figure 1.15 The Ullmann coupling of aryl iodides uses stoichiometric amounts of copper metal (top). Yet the copper is only used as a reducing agent (a source of electrons). The alternative Pd-catalysed cycle takes the electrons from a much lighter (and cheaper!) *source*: hydrogen gas (bottom), generating less waste. Switching from iodoaryls to bromo- and ultimately chloroaryls will further reduce both the price and weight of the waste part in the reagent. However, it also requires a catalyst that can activate the aromatic C—Cl bond, which is more stable than the C—I bond.

cheap production of high-grade polyethylene terephthalate (PET). Patented by the Mobil Oil Company in 1975, ZSM-5 revolutionised the plastics industry, so much that the product, PET, has become in itself a global pollution problem.

Note that one cannot literally 'replace stoichiometric reagents with catalytic cycles'. Every chemical reaction uses stoichiometric reagents, including all catalytic reactions. What we actually mean is 'replace heavy and/or toxic (and usually expensive) stoichiometric reagents with catalytic cycles that can use lighter, eco-friendlier (and hopefully cheaper) reagents'.

For example, consider the reaction of two iodoaryls with copper metal to give the corresponding biaryl and copper(II) iodide (Figure 1.15, top). This type of aryl-aryl coupling is known as the **Ullmann reaction**. Discovered by the German chemist Fritz Ullmann over 100 years ago, this reaction is still used today, owing to its high selectivity. Yet we see that the copper is not part of the desired product but is just used as a reagent and discarded as waste. The reaction only uses two electrons from the copper (because we start with Cu^0 and end with Cu^{2+}). That's a lot of expensive waste for just two electrons. We can try and replace the copper with another reducing agent that would give the same two electrons. One option is using hydrogen gas and thus swapping our CuI_2 waste for 2 mol of hydrogen iodide (HI, see Figure 1.15, bottom). This is where catalysis can help, because this reaction does not run spontaneously with hydrogen, but does run in the presence of small amounts of a Pd/C (read: palladium on carbon) catalyst [40].

Can we improve this reaction even further? We reduced the waste associated with the two electrons to two protons, and we cannot go much lower than that. But how about the iodide ions? Iodide is not only expensive – it is heavy! This is important because chemicals react based on their stoichiometry, but they're bought and sold by their mass. The molar mass of iodide is 127 g/mol. This means that when you purchase a tonne of iodobenzene, you're buying 680 kg of 'iodo' and only 320 kg of 'benzene'. So you're paying a lot of money for something that is over 2/3 garbage! Definitely not the best deal. We can improve here by using chlorobenzene instead. This reduce the weight of the waste by a factor of 3.5, and chlorine compounds are cheaper and more readily available than iodine ones. The catch is that breaking the C—Cl bond is more difficult and therefore requires a better catalyst [41].

The Importance of Aryl-Aryl bonds

Joining two aromatic rings is an important chemical reaction, useful in many industrial chemical processes. This is because monoaromatics (benzene, toluene and xylenes) are readily available from crude oil reforming, whereas many fine chemicals, agrochemicals and pharmaceutical intermediates contain two connected rings or have a molecular size that is roughly that of two connected rings with some substituents. The reason for this is that many biological receptors are triggered by molecules that are roughly the size of two connected rings, and the chemical industry makes and sells products that target these receptors (think of flavours and fragrances, but also medicines, drugs and pesticides, some examples of which are shown in Figure 1.16).

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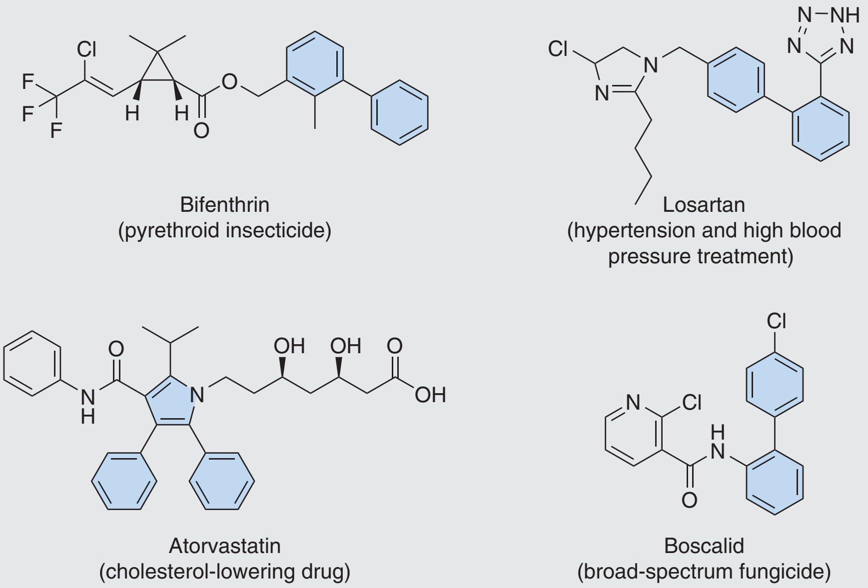


Bifenthrin
(pyrethroid insecticide)

Losartan
(hypertension and high blood pressure treatment)

Atorvastatin
(cholesterol-lowering drug)

Boscalid
(broad-spectrum fungicide)

Figure 1.16 Examples of agrochemicals and pharmaceutical compounds that contain two connected aromatic or heterocyclic rings.

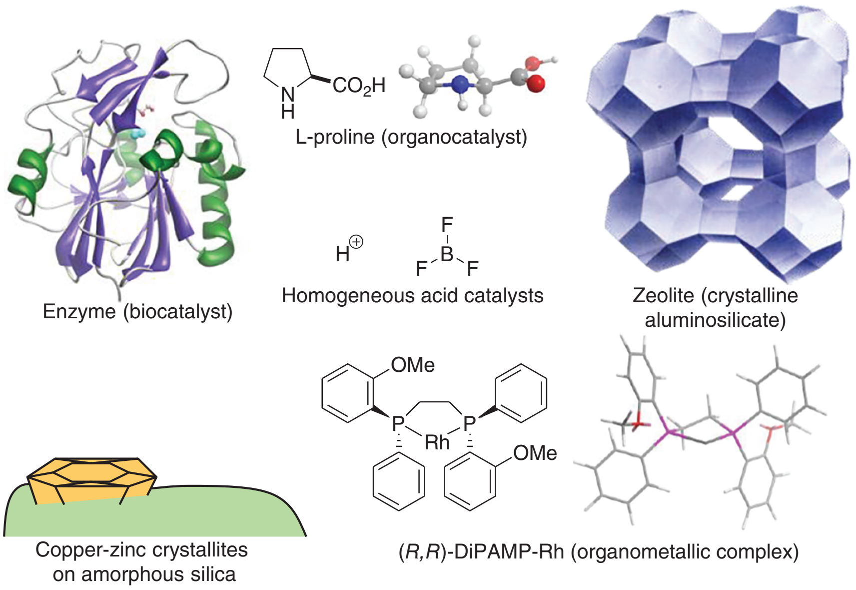
Literally, catalysis means the breaking down of stuff (from Ancient Greek: κατά = down, λυσις = loosening or dissolving). Today, we use the term catalysis to mean the speeding up of chemical reactions. For an outside observer, it seems that adding a catalyst ‘makes the reaction go faster’. In fact, in most cases, the catalyst enables a different, faster reaction pathway. However, at this stage, we will use the following general definition:

A catalyst is something that makes a reaction go faster, without being consumed in the process.

In theory, each catalyst molecule or unit can participate in many consecutive cycles, so we need only a small amount of catalyst relative to the substrate. In practice, catalysts eventually deactivate and must be regenerated and/or replaced. The substrate:catalyst ratio reflects the catalyst’s efficiency, which is measured as **turnover number** (TON) or **turnover frequency** (TOF).

Note that catalysis is a kinetic phenomenon – you can make your reaction go faster towards the thermodynamic equilibrium. But catalysis *cannot* change the thermodynamic equilibrium. This is important: you cannot use catalysis to circumvent the laws of thermodynamics. For example, CO_2 conversion is a ‘hot topic’ these days, but reacting CO_2 incurs a thermodynamic energy penalty, and no catalyst can avoid (or even lower) this penalty.

There are many types of catalysts (Figure 1.17). These range from simple ions like H^+ and OH^-, through Lewis acids, various metals, organometallic complexes, organic and inorganic polymers and all the way to enzymes. To simplify things, we divide catalysis into three categories: homogeneous catalysis, heterogeneous catalysis, and biocatalysis. Although the catalysts and the process conditions in each category can be very different, the principles of



Enzyme (biocatalyst)

L-proline (organocatalyst)

Homogeneous acid catalysts

Zeolite (crystalline aluminosilicate)

Copper-zinc crystallites on amorphous silica

(*R*,*R*)-DiPAMP-Rh (organometallic complex)

Figure 1.17 Catalysts come in many shapes and sizes – from a single proton all the way to millimetre-sized particles of solid materials. Yet they all share a common factor: they open a more effective chemical pathway from the reactants to the products.

catalysis are the same. Once you understand these principles, you can easily apply them in all three categories.

Most people are simply unaware of the role that catalysis plays, literally, in their lives. Practically all of the reactions in all living cells are catalytic ones. Our bodies burn fuel, for example (by reacting oxygen with sugar), yet they do so at the amazingly low temperature of 37°C, thanks to complex catalytic cycles. Our modern society is also highly dependent on catalysis: the manufacturing of petrochemicals, plastics, medicines, agrochemicals and modern materials all use catalytic processes.

The Different Types of Selectivity

The main advantage of using catalysis is that you can get the desired product faster, using less resources and generating less waste. A catalyst can open a selective route to the desired product. There are various kinds of product selectivity (compare the examples in Figure 1.18). Chemical selectivity, or **chemoselectivity**, denotes a situation where two different chemical reactions can occur, giving two different products. Similarly, **regioselectivity** is when the same chemical reaction at different regions of the molecule leads to different products. When a reaction gives two (or more) diastereomers, the selectivity to each one of those is called **diastereoselectivity**. In the special case when two products are mirror-image diastereomers, or enantiomers, we talk about **enantioselectivity**.

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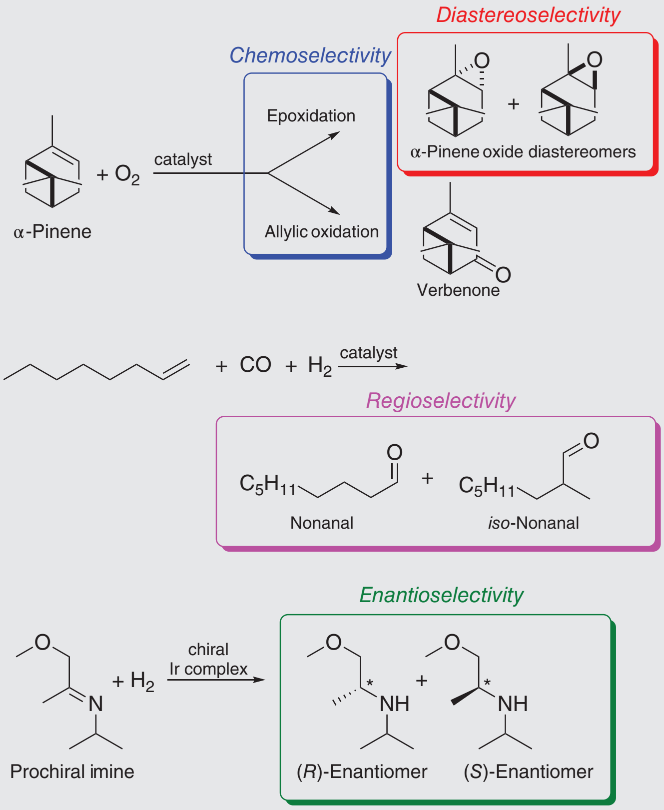

Figure 1.18 Examples of chemoselectivity and diastereoselectivity in the oxidation of α-pinene (top), regioselectivity in the hydroformylation of 1-octene (middle) and enantioselectivity in the hydrogenation of the prochiral isopropyl(2-methoxyisopropyl)imine (bottom). '*' indicates the asymmetric carbon atoms.

These same advantages also form the basis for new business opportunities in the context of sustainable chemistry and the circular economy. Catalysis can help us switch from fossil-based material and energy sources to renewable ones, and/or replace expensive, toxic or hazardous reagents with cheap and environmentally benign ones. Nature gives here amazing inspirations: Some strains of bacteria can bind nitrogen from the air at ambient temperatures and pressures, and all plants use photosynthesis to bind and react CO_2 to lignocellulosic biomass. This doesn't mean that this is the best way. Bacteria typically grow in dilute solutions, and industry needs large amounts of pure or highly concentrated chemicals. Similarly, growing trees takes years, while companies want to manufacture chemicals in minutes or hours. But nature does show us what is possible when the right catalyst is found.

1.4 Industrial Examples

1.4.1 The BHC Synthesis of Ibuprofen

In 1992, BASF opened a 35,000 tpa ibuprofen production plant in Bishop, Texas. This plant was the result of the elegant green chemistry route developed by the Boots Hoechst Celanese (BHC) consortium. The clean synthesis of ibuprofen is an excellent example of how combining catalysis and green chemistry can yield both commercial success and environmental benefits. Ibuprofen is a nonsteroidal, anti-inflammatory painkiller. It is a popular over-the-counter drug against headache, toothache and muscular pains. You may know it better as Ibux, Advil, Motrin or Nurophen.

Like many other drugs, ibuprofen is a rather simple chemical compound. It was first patented by Boots in 1962. The original production route consisted of six steps, starting from 2-methylpropylbenzene and acetic anhydride. Each of these steps involved additional reagents, many of which are absent from the final product molecule (Figure 1.19, left). The overall atom economy of the process was only 40%. This means that more than half of the materials that entered the process were thrown away as waste (in addition to large amounts of water and salt waste from separation steps). For example, note the addition of hydroxyl amine, NH_2OH, in step 4: This functional group is used to create the imine **7**, which is then converted to the cyano derivative **8** and finally oxidised to give the carboxylic acid product **9**. Effectively, what happens is that the hydroxyl amine is first added to the molecule and then removed and thrown away. This type of ‘roundabout synthesis’ is precisely what green chemistry aims to avoid.

Ibuprofen quickly became a popular painkiller, and Boots made good profits. But they knew that this would not last forever. Patents give limited protection to their owners, but they also expire after 20 years. When the patent rights on ibuprofen were about to expire, Boots knew that the market would soon be flooded with cheap generic alternatives. Moreover, thanks to strict regulatory procedures, the ibuprofen in the generic pills would be just as good as that in their own, and most customers would opt for the cheaper alternative. Think about it: when you purchase painkillers at the supermarket, do you choose the original brand name, or do you buy the cheaper supermarket brand, which is chemically just as good?

To keep their market share, Boots *had* to innovate. It was not a question of doing something for the environment, but simply a question of economics. Boots teamed with Hoechst Celanese and formed the BHC consortium, developing a new process for making ibuprofen [42]. The consortium started from the same raw materials but replaced the stoichiometric six-step process with a three-step catalytic one (Figure 1.19, right). The overall atom economy of this new process was 77%, with acetic acid as the only by-product. The consortium then also developed methods for recovering and recycling the acetic acid, increasing the atom utilization to 99%, and creating an essentially waste-free synthesis. Using anhydrous hydrogen fluoride (HF) as both catalyst and solvent offers important advantages in reaction selectivity and waste reduction, as the new route also eliminates the large volumes of aqueous salt waste associated with the old ibuprofen manufacturing process.

The BHC ibuprofen process is an innovative, efficient technology that has revolutionized bulk pharmaceutical manufacturing. The process provides an elegant solution to

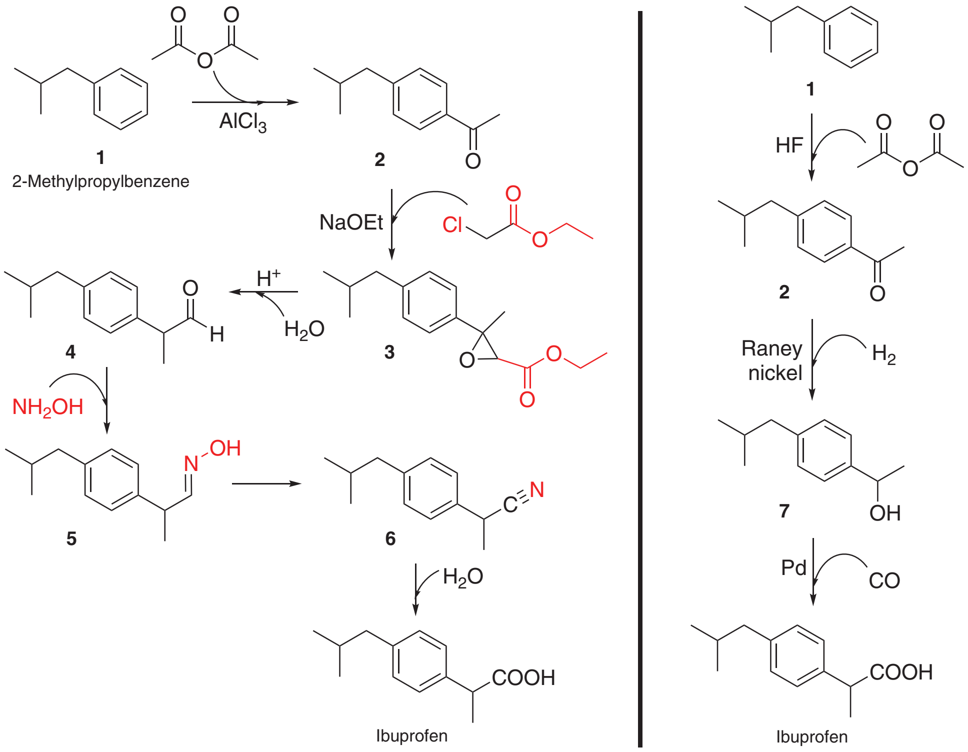

Figure 1.19 Synthesis of ibuprofen: The six-step Boots route (left; additional reagents highlighted in red) and the three-step BHC route (right).

a prevalent problem encountered in bulk pharmaceutical synthesis: It avoids the large quantities of solvents and waste (especially aqueous salt waste streams) associated with the traditional stoichiometric reagent use. The anhydrous HF catalyst is recovered and recycled with greater than 99.9% efficiency. No other solvent is needed in the process, simplifying product recovery and minimising emissions. The new ibuprofen process became a model for environmental excellence in chemical technology, and BHC received the Kirkpatrick Achievement Award for ‘outstanding advances in chemical engineering technology’ in 1993 and the U.S. Presidential Green Chemistry Award in 1997. It was also a commercial success: the BHC consortium sold the process to BASF for more than $100 million.

And a short postscript: In 2013, I was on the train going to the Amsterdam Science Park, and a British gentleman sitting across from me asked, ‘excuse me, but are you a chemist?’ (I was reading the *Journal of Organic Chemistry*, so he less clairvoyant than you might think). I pleaded guilty and we started talking. He was also a chemist, currently working for Philips. We exchanged business cards (this was before QR codes and WeChat), and I looked at his card and said – ‘You’re Graham Mott! You invented the BHC process – I teach about you in my class!’

As coincidence would have it, this was indeed the same man who used to head the R&D division at Hoechst. Graham was surprised (and pleased!) to learn that he was so famous and even agreed to come to our institute’s Christmas Event and tell the story. He gave us a rare view into what went on behind the scenes during the setting up of the consortium and the process development. For example, one of the biggest hurdles was convincing the management of Hoechst Celanese, a company then focused on producing large-scale bulk chemicals and materials, to enter the pharmaceuticals market and manufacture something as esoteric and small-scale as ibuprofen (bulk chemicals are produced in millions of tons, three orders of magnitude larger than medicines). But Boots needed Graham and his team because they wanted the know-how and facilities for using anhydrous HF, which was the key to the new process. Very few companies knew how to do this, and Hoechst was one of them. It all worked out well in the end, and the consortium made a handsome profit. But companies are often wary of entering new markets, especially in cases where there is a mismatch between market sizes.

1.4.2 The BP AVADA Ethyl Acetate Process

Ethyl acetate is a common solvent known since the mid-18th century. It has a fruity odour and is widely used in paints, pharmaceuticals and fragrances. A simple ester, the classic way of making it is by **Fischer esterification** of ethanol and acetic acid (Eq. (1.3)). This is an equilibrium reaction, which gives about 65% of the ester product at room temperature. The reaction can be accelerated by using an acid catalyst, and the equilibrium can be shifted to the right by removing the water by-product. Alternatively, ethyl acetate can also be prepared using the **Tishchenko reaction**, by reacting two equivalents of acetaldehyde in the presence of an alkoxide catalyst (Eq. 1.4).

$$CH_3CO_2H + CH_3CH_2OH \rightleftharpoons CH_3CO_2CH_2CH_3 + H_2O \tag{1.3}$$

$$2CH_3CHO \rightarrow CH_3CO_2CH_2CH_3 \tag{1.4}$$

Both of these reactions rely on liquid acid/base catalysts that result in large aqueous waste streams. For many years, this was not a problem. But in the 1990s, BP Chemicals, one of the large manufacturers of ethyl acetate, underwent restructuring. Business unit managers had to either come up with new technological solutions that would make their units more profitable or close down plants. BP's new AVADA process (AdVanced Acetates by Direct Addition), which went on stream in Hull in a 220 ktpa plant in June 2001, is an excellent example of how combining heterogeneous catalysis and process innovation can create economic value *and* environmental benefits [43]. The process (Figure 1.20) converts ethene and acetic acid directly to ethyl acetate, cutting out the intermediate esterification step and the need for ethanol. Instead of using a liquid Brønsted acid, it uses a solid heteropolyacid, which is supported on porous silica for additional stability. The process gives 99.98% pure ethyl acetate, in what is now the largest EtOAc plant worldwide. Moreover, the simpler design requires fewer operators and saves ~20% on energy costs compared to the conventional routes. In 2002, the AVADA process won the 2002 AstraZeneca Award for Excellence in Green Chemistry and Engineering.

The AVADA process combines several green chemistry principles: It uses simple, non-toxic feedstocks, converting these directly to the desired product. It features 100% atom economy – all of the atoms in the reactants are incorporated in the product. Using a solid catalyst, the process is practically waste-free, avoiding waste stream problems. AVADA is an excellent example of sustainable chemistry. But it also illustrates another

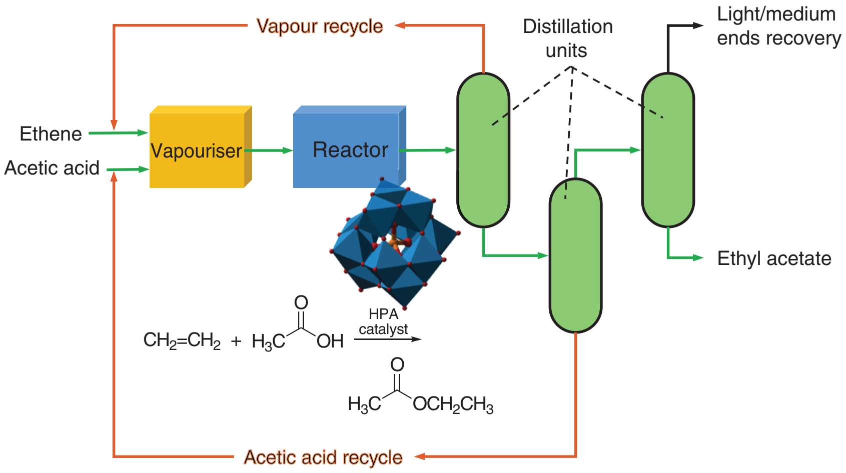

Figure 1.20 Chemical reactions and simplified process schematic for BP's AVADA ethyl acetate process. The exact structure of the catalyst is undisclosed; it is most probably a 'superacid' (a Keggin-type phosphotungstic heteropolyacid, shown in dark blue, with the general formula $H_3PW_nM_{12-n}O_{40}$, wherein M is tungsten or another metal). Such heteropolyacids are used in the laboratory both in solution and as solid salts [44]. Their industrial application is limited, however, due to rapid deactivation [45]. To solve this problem, BP impregnated the heteropolyacid in porous silica beads.

important point: BP developed it purely out of commercial considerations, demonstrating again how economic benefit drives green chemistry.

Exercises

Q1.1 a) Examine the 12 principles of Green Chemistry. Which three of these principles are, in your opinion, the most important ones? Explain your answer (100–150 words).

b) Explain the concepts of E-factor, atom economy, and environmental quotient Q. Discuss and compare these factors for the petrochemical industry and the pharmaceutical industry. Which industry is more sustainable? (100–150 words)

c) Hydroquinone is used in cosmetics as a skin-lightening agent. It can be made by reacting benzoquinone with metallic iron and water (Figure 1.21). Calculate the E-factor for this reaction and estimate its environmental quotient. What type of reaction is this? What is the iron used for in this reaction?

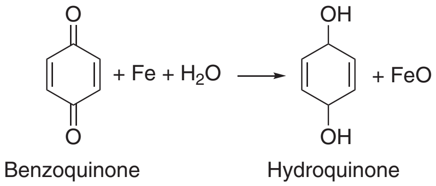

Figure 1.21 The reaction of benzoquinone with metallic iron and water to give hydroquinone.

Q1.2 Polyethylene terephthalate (PET) is the most common 'plastic'. It has become so thanks to the invention of ZSM-5, a zeolite solid acid catalyst that enabled the selective synthesis of *p*-xylene, the precursor of terephthalic acid.

a) Write down the chemical equation for the acid-catalysed reaction for making xylenes from toluene and methanol.
b) Draw a schematic showing how ZSM-5 catalyses the selective reaction between toluene and methanol to give over 99.99% of *p*-xylene.
c) Explain why this high selectivity is important for the production of PET, and how it contributes to the economic efficiency and sustainability of the process (100–150 words).

Q1.3 In 2008, when the price of crude oil peaked at \$110 per barrel, governments and companies looked towards biomass as an alternative source for gasoline and diesel. The transesterification of oils and fats (triglycerides) to fatty acid methyl esters (FAME) was thought to be the answer.

a) List two advantages and two disadvantages of using FAME as biodiesel.
b) Examine the reaction profiles for the acid-catalysed esterification of dodecanoic acid with 2-ethylhexanol shown in Figure 1.22. What is the advantage of using a solid acid as the catalyst in this reaction? What are the disadvantages?
c) Today, governments and companies focus on biofuels made from lignocellulosic material. What caused the shift away from fatty acids towards cellulose and hemicellulose?

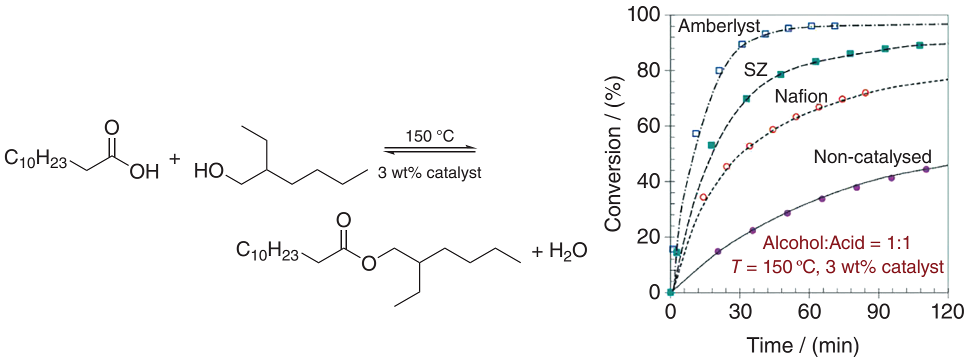

Figure 1.22 Time-resolved reaction profiles for the esterification of dodecanoic acid with 2-ethylhexanol in the presence of different solid acid catalysts. *Source*: [46] / John Wiley & Sons.

Q1.4 Anthropogenic emissions of CO_2 are related to global warming and climate change. In the past decade, annual CO_2 emissions averaged at over 35 Gton per year! There are three main solutions to this problem: burn less fossil carbon, capture the CO_2 and store it somewhere (CCS) or capture the CO_2 and make something from it (CCU).

a) Compare these three options and explain which one is the most suitable in your opinion and why (150–200 words).

b) What are the main challenges for the CCU route? Can you address these challenges using sustainable chemistry? Support your answer with quantitative arguments (150–200 words).

Q1.5 Converting CO_2 emissions back to chemical products is said to be the solution to CO_2 emissions and global warming.

a) Do you think this is true? Explain your answer (100–150 words).
b) Draw a catalytic cycle for converting CO_2 and hydrogen to methanol in the presence of a copper catalyst. Assuming a methanol yield of 100%, calculate the E-factor for this reaction and estimate its environmental quotient Q.
c) There are other greenhouse gases than CO_2. List two of them and suggest how you can convert them into useful products, and which markets you would address.

Q1.6 The Suzuki reaction is a method for coupling organoboronic acids to organohalides. It is typically catalysed by small amounts of homogeneous organometallic Pd complexes and requires water and 1.5–2 equivalents of base. An example is shown in Figure 1.23.

a) Balance the reaction equation and calculate for this example the E-factor and the Atom Economy and estimate the value of the environmental quotient.
b) Suggest two methods for reducing the amount of waste generated by this reaction and explain the pros and cons of each method.
c) Company **A** uses the Suzuki reaction for synthesising a drug for fighting a rare disease. Company **B** uses the reaction for synthesising a pesticide against a bug that attacks bananas. Explain the considerations of each company when choosing their reagents and process in this reaction.

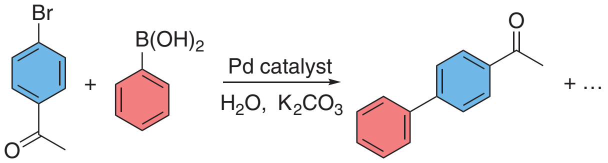

Figure 1.23 The Suzuki cross-coupling of 4-bromoacetophenone with phenylboronic acid.

Q1.7 The hydro-dehalogenation of chlorobenzene with zinc powder and water (Figure 1.24, top) is a method for removing Cl atoms from organics. This reaction gives >99% yield.

a) Balance the reaction equation, calculate its E-factor and Atom Economy, and estimate the value of the environmental quotient.
b) Another version of this reaction uses hydrogen gas as the reducing agent, in the presence of 1 mol% Pt/Al_2O_3 catalyst (Figure 1.24, bottom). This reaction gives 100% conversion, but only 80% yield. Balance the reaction equation and calculate its E-factor and Atom Economy, and estimate the value of the environmental quotient.

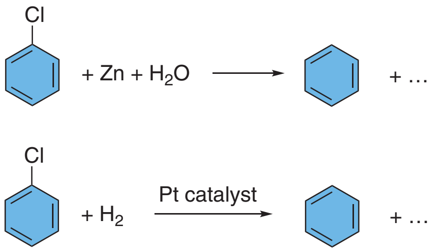

Figure 1.24 Hydro-dehalogenation of chlorobenzene with zinc and water (top) and the Pt-catalysed variant with hydrogen gas (bottom).

c) Compare the two reaction alternatives and explain which one you would use for making a drug on a 500 kg scale and which one you would use for making a pesticide a 10,000-ton scale.

Q1.8 Phenol, C_6H_5OH, is an important bulk chemical, with a worldwide production of 11 million tons in 2024. Today, it is produced almost exclusively via the partial oxidation of cumene (isopropylbenzene, see Eq. (1.1)). This process is used on a multi-million-ton scale per year, yet there are several alternatives. One is the oxidation of toluene, developed by Dow Chemical (Eq. (1.2)).

$$C_6H_5CH(CH_3)_2 + O_2 \rightarrow C_6H_5OH + (CH_3)_2CO \tag{1.5}$$

$$C_6H_5CH_3 + 2O_2 \rightarrow C_6H_5OH + CO_2 + H_2O \tag{1.6}$$

a) Calculate the E-factor and estimate the size of the environmental quotient for both processes.
b) List two advantages and two disadvantages for each process, explaining which process you favour. If you favour the Dow process, how do you explain the fact that over 95% of phenol production worldwide goes via the cumene route?

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