1
Introduction

This chapter outlines the principles of green chemistry, and explains the connection between catalysis and sustainable development. It covers the concepts of environmental impact, atom economy, and life-cycle analysis, with hands-on examples. Then, it introduces the reader to heterogeneous catalysis, homogeneous catalysis, and biocatalysis, explaining what catalysis is and why it is important. The last two sections give an overview of the tools used in catalysis research, and a list of recommended books on specialised subjects in catalysis.

1.1
Green Chemistry and Sustainable Development

Chemistry affects every day of our lives. The chemical and petrochemical industry has shaped our modern technological society by supplying us with energy, medicines, crop protection, foodstuffs and new materials. Thanks to the chemical industry people in the twentyfirst century live longer, have abundant food, and enjoy an unprecedented quality of life. Yet despite these benefits, chemicals and the chemical industry suffer from a negative public image. Most of this is due to misconceptions and media scares, but there are also real reasons: If they are mismanaged, petrochemical plants and chemical factories can cause serious environmental hazards. Anyone who has stepped outside in mega-cities such as Delhi, Beijing or Mexico City, for example, will tell you that the air pollution from energy and chemical factories cannot be ignored. 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 this image either [1].

But even with superb management, planning and safety procedures, the challenges of resource scarcity and end-of-life product disposal remain. The short-term prices of fossil-based raw materials fluctuate because of politics, but these resources will run out sooner or later. Similarly, while we enjoy the attractive price/performance ratios of chemical products such as plastic bottles, the accumulation of plastic garbage is making more and more people realise the importance of product life-cycles. All these factors are slowly causing a change. Two popular terms associated with this change are **sustainability** and **sustainable**

Catalysis, Second Edition. Gadi Rothenberg.

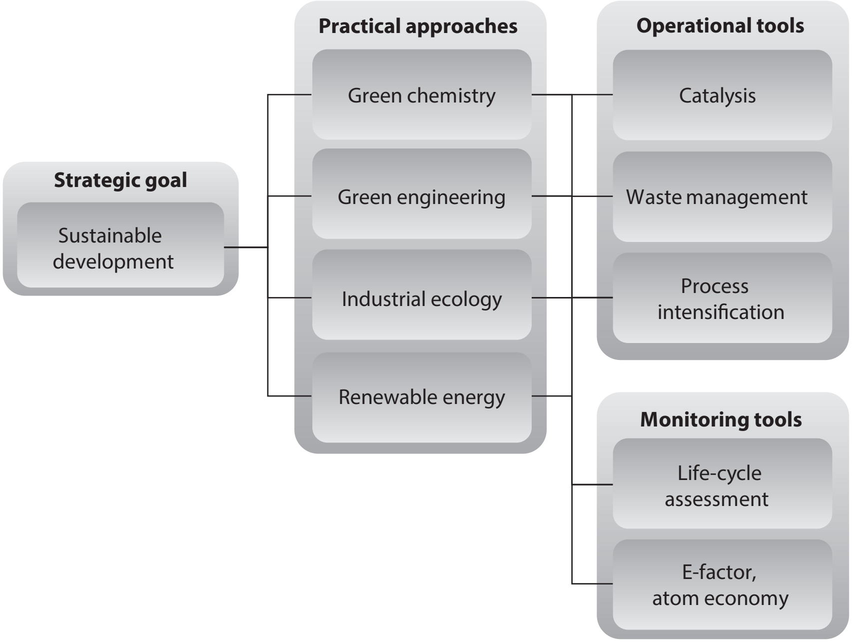


Figure 1.1 The strategic goal of sustainable development relies on practical approaches such as green chemistry, industrial ecology, and green engineering. These approaches use various operational tools (such as catalysis), and monitoring tools (such as life-cycle assessment).

development. A sustainable society is one that 'meets the needs of the current generation without sacrificing the ability to meet the needs of future generations'. Sustainable development is a strategic goal. It can be reached using various approaches, and this is where green chemistry comes in. Figure 1.1 shows the relationship between the strategic goals, the practical approaches, and the operational and monitoring tools. Thus, green chemistry is just one step (albeit an important one) on the road to sustainability.

1.1.1
What Is 'Green Chemistry'?

In the 1990s, the concept of 'green chemistry' was initiated in both the US and Europe, and has since been adopted widely by the chemical industry [2]. 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 green chemistry message is simple: 'Seek prevention, not cure'. In 1998, Anastas and Warner formulated the following twelve principles of green chemistry [3, 4] (I've rephrased these in the active voice, in keeping with the spirit of this book):

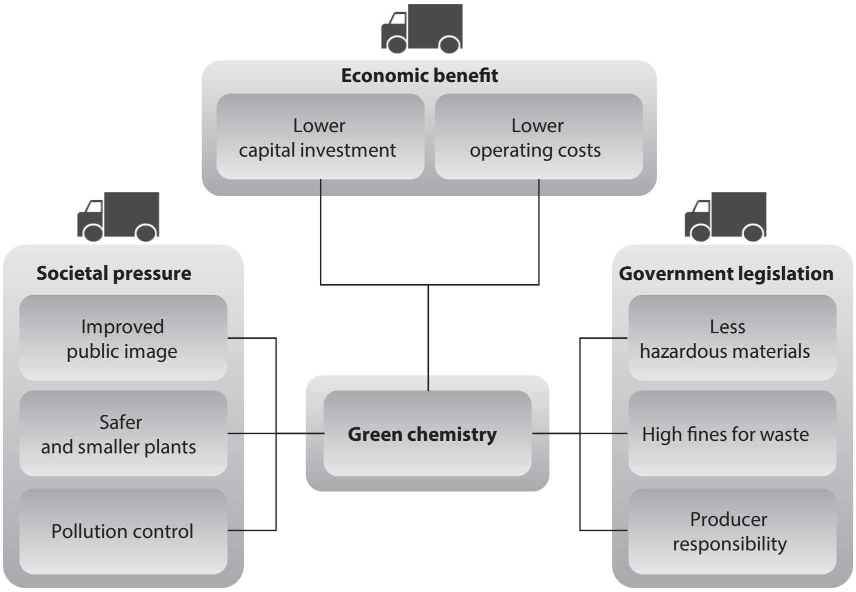


Figure 1.2 Green chemistry initiatives are driven by government legislation, societal pressure, and economic benefits.

I Prevent waste instead of treating it.
II Design atom-efficient synthetic methods.
III Choose synthetic routes using non-toxic 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 on-line process analysis and monitoring methods.
XII Choose feedstocks and design processes that minimise the chance of accidents.

Green chemistry offers an alternative to the traditional environmental protection agenda, mainly because it deals with avoiding hazard, rather than with treating and solving exposure problems. Three forces drive the green chemistry initiative: Government legislation, societal pressure, and economic benefit (Figure 1.2) [5]. The EU directive on the registration, evaluation, and assessment of chemicals (**REACH**), has changed the chemical industry across Europe [6]. Similar regulations are expected worldwide in the coming decade. But legislation is just one of the drivers. Societal pressure is also important: 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 driver is real economic benefit. Applying the principles of green chemistry decreases both capital investment and operating costs. If you use less (or no) solvents, your reactor space-time yields go up. If you replace costly reagents with cheaper and more abundant ones by using catalytic cycles, your chemicals bill goes down. Similarly, processes running at ambient temperatures are less energy-intensive. This means doing the same work using smaller and safer equipment. Eliminating waste also eliminates the need for waste treatment and disposal, and replacing toxic reagents with benign ones saves on safety costs during transportation and storage. Thus, more and more companies are adopting green chemistry practices simply because it improves their bottom-line performance.

1.1.2
Quantifying Environmental Impact: Efficiency, E-Factors, and Atom Economy

Everyone agrees that green chemistry and ‘green manufacturing’ are good things. The websites of all the major chemical companies emphasise their concern for the environment. They all say that their processes and products are ‘efficient’, ‘green’, and ‘environmentally friendly’. But how should we compare these processes? How should we judge such claims?

Let’s define first some key terms. One method for quantifying a reaction’s efficiency is by examining the **reactant conversion**, the **product selectivity**, and the **product yield** over time. The conversion is that fraction of reactant molecules that have transformed to product molecules (regardless of which product it is). The selectivity to product **P** is the fraction (or percentage) of the converted reactant that has turned into this specific product **P**. The yield of **P** is simply conversion × selectivity. High conversions in short time spans mean smaller and safer reactors. Similarly, high selectivity means less waste, and simpler and cheaper separation units. Thus, conversion, selectivity, and yield are all measures of the **reaction efficiency**.

In addition to those, there are specific rulers for measuring the ‘greenness’ or ‘eco-friendliness’ of processes and products. One such measure is the **E-factor**, introduced by Roger Sheldon in 1994 [7, 8]. A reaction’s E-factor equals the quotient $\mathrm{kg}_{\mathrm{waste}} : \mathrm{kg}_{\mathrm{product}}$ (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 1.1 compares the production tonnage and E-factors of various industrial sectors. Note that the petrochemicals and the bulk chemicals sectors are the least polluting. This is surprising, as we’re used to think of such chemicals as pollutants. In fact, E-factors increase substantially when going from bulk chemicals to fine chemicals and specialties. This is because the production of fine-chemicals and pharmaceuticals often involves multi-step syntheses, which

Table 1.1 Annual production and E-factors in the chemical industry.

Industrial sector	Production ton/y	E-factor
Petrochemicals	10^6–10^8	< 0.1
Bulk chemicals	10^4–10^6	1–5
Fine chemicals	10^2–10^4	5–50
Specialities/pharmaceuticals	10–10^3	20–100

require protecting groups and other reagents that are absent from the final product.

The concept of **atom economy**, introduced by Barry Trost in 1991, is similar to the E-factor [9]. 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.

As an example, let us consider the classic oxidation of diphenyl methanol to benzophenone, one of the most commonly used photosensitisers in photochemistry (Figure 1.3). We will evaluate this reaction using the measures of product yield, product selectivity, E-factor and atom economy. In this reaction, three equivalents of diphenyl methanol react with two equivalents 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.

However, examining the E-factor for this reaction, we see that for every three moles of benzophenone we produce one mole of chromium sulphate and six moles of water. The molecular weight of benzophenone is 182.2 g/mole, so every kg of benzophenone contains 5.48 moles of benzophenone. This means that for every kg of benzophenone we generate 5.48/3 = 1.83 moles (or 0.717 kg) of chromium sulphate and 10.98 moles (or 0.197 kg) of water. The overall E-factor is therefore:

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

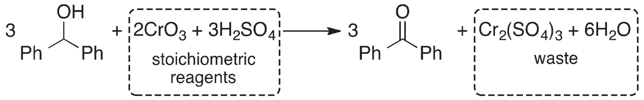


Figure 1.3 The oxidation of diphenyl methanol to benzophenone using stoichiometric amounts of chromium trioxide and sulphuric acid.

Table 1.2 Hazard quotient (*Q*) values for some common chemical by-products.

Compound	*Q*-value	Compound	*Q*-value
Nitrogen gas	Zero	Acids	Medium
Carbon dioxide	Low	Bases	Medium
Water	Low	Heavy metal salts	High
NaCl	Low	CFC gases	High
Non-metal salts	Medium	Persistent materials	High

Nearly a whole kg of waste for every kg of product! Remember, this is for the ideal case of 100% yield and 100% selectivity. In real life, the E-factor is usually much higher, because product yields are less than 100% and reagents are sometimes used in excess. Furthermore, in many cases one needs to neutralise acid or base side-products, so the overall waste amounts are even higher.

The E-factor and the atom economy can be used for comparing reaction alternatives, but there are different types of 'waste'. The example reaction above has two by-products: chromium sulphate and water. Obviously, water is 'good waste', while chromium sulphate is 'bad waste', so evaluating a synthetic protocol based only on the amount of waste produced is insufficient. To solve this problem, Sheldon put forward the concept of the **environmental quotient** (*EQ*) [7]. This measure takes both the amount and the nature of the waste into account, by multiplying the E-factor by *Q*, an arbitrarily assigned hazard quotient. Table 1.2 shows some possible *Q*-values for different by-products. Assigning absolute *Q*-values to waste streams is difficult, because cases differ according to location and type of waste. Nevertheless, the environmental quotient gives a better measure of the environmental impact of a process than the E-factor or the atom economy alone.

1.1.3
Just How 'Green' Is This Process?

Some processes and products seem more eco-friendly than others. Often this is because we see only part of the process. An overall environmental impact analysis should take into account not only the chemical reactions, but also the hazard and consequences of acquiring and transporting the raw materials. Moreover, it should also factor in the overall energy demand. A reaction can feature 100% atom economy, and still be problematic because of hazardous reagents. Adding Br_2, HF or HCN to a double bond, for example, is 'clean' from the atom economy perspective, but storing and/or transporting these highly toxic reagents is problematic. To understand this better, let us look at two examples: Clean energy from hydrogen-powered fuel cells, and industrial oxidation of propene to propene oxide.

1.1.3.1 **Example: the 'Hydrogen Economy' and Fuel Cell Engines**

The term 'Hydrogen Economy', coined by John Bockris in 1970, originally pertained to burning hydrogen as fuel in internal combustion engines. Today, it applies more to using hydrogen-powered fuel cell devices to produce electricity. Fuel cells are an attractive alternative to combustion engines, because their efficiency is much higher. A combustion engine's efficiency is limited by the thermodynamic constraints of the Carnot cycle. Most engines are made of steel, with a theoretical thermodynamic limit of 37%. In practice, their average efficiency is only 18–20% [10]. Conversely, fuel cells convert chemical energy directly into electrical energy using a catalytic process [11]. They have no moving parts, and their theoretical efficiency is a whopping 82% (in practice, today's fuel cells reach 50–60% efficiency).

The operation of the hydrogen fuel cell was demonstrated already in 1842 by William Grove. It is the opposite of water electrolysis. In water electrolysis an electric current is passed through the water, dissociating it to hydrogen and oxygen (see Figure 1.4). In a fuel cell, the recombination of hydrogen and oxygen produces an electric current.

To avoid 'short-circuiting', the anode and cathode are isolated from each other by a membrane that is permeable to only one species, while the electrons are transported through an external circuit. At the membrane/electrode interface there's a thin layer of catalyst (most commonly platinum nanoparticles supported on high-surface-area carbon). Fuel cells are divided based on their electrolyte/membrane types. Proton-exchange membrane fuel cells (PEMFCs)[1] transfer protons, molten carbonate fuel cells transfer CO_3^{2-} anions [12], and solid oxide fuel cells (SOFCs) transfer oxide O^{2-} anions across ceramic membranes [13]).

At first glance, hydrogen-powered fuel cells seem ideal: They are highly efficient and produce only electricity and water [14]. Low-temperature PEMFCs are

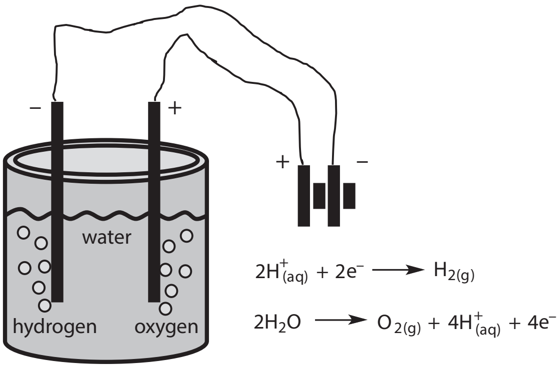


Figure 1.4 Electrolysis of water showing the anode and cathode reactions in an acidic environment.

---

[1] PEMFCs were first commercialised by General Electric in 1950s, and used by NASA in the *Gemini* and *Apollo* space projects.

compact and light. They don't emit any pollutants and are suitable for automotive applications. But looking at the larger picture shows two serious disadvantages. The first problem is that today's PEMFCs require relatively large amounts of noble metals (most commonly Pt) as catalysts for H_2 dissociation. This is a problem because there is simply not enough platinum to go around. We're already using 70% of the world platinum production for emission reduction in automotive exhaust catalysts (see Chapter 4 for details). If cars were to be powered by today's PEMFCs, we would need ten times that [15]. Chemists are researching metal-free PEMFC catalysts, but these are still far from application (the most promising materials are nitrogen-doped graphitic carbons [16]).

But even if we solve the catalyst problem, where will the hydrogen come from? While hydrogen is the most common element in the universe, there is no natural source of pure hydrogen on Earth. It must be manufactured from fossil fuels, biomass, or water. This manufacturing costs time, capital, and energy. Then, the hydrogen must be purified, transported and stored. This also requires special infrastructure. All these factors must be taken into account when evaluating the overall efficiency of fuel cells. Furthermore, the hydrogen manufacturing also generates waste, and this waste should also be taken into account when calculating the overall environmental impact of fuel cells compared to conventional energy sources. Figure 1.5 compares the efficiency of a hydrogen-powered fuel cell with that of various gas-powered and diesel-powered energy sources. Looking at this

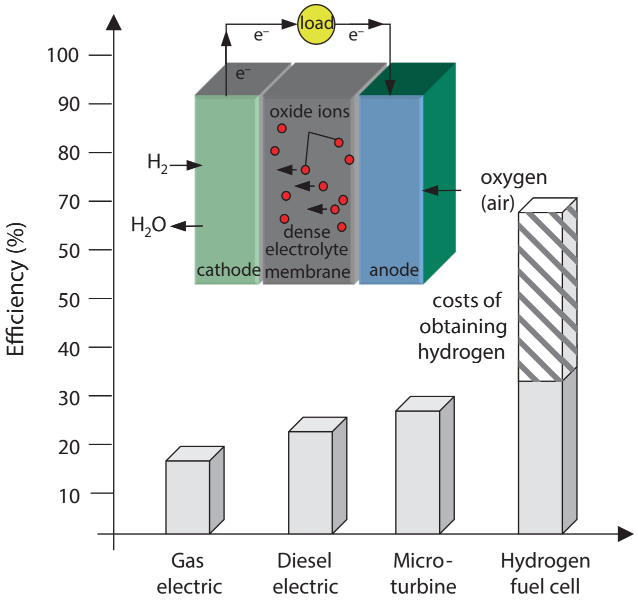


Figure 1.5 Relative efficiency of various engine types. The column on the right shows also the estimated 'hidden costs' for obtaining hydrogen in the case of fuel cells. The inset shows a schematic of a solid oxide fuel cell that converts fuel (in this case, hydrogen) directly to electricity.

figure, we see that the real environmental benefits of hydrogen-powered fuel cells are lower than we first thought. Fuel cells that can use methane or biogas as fuel are in fact 'greener'.

1.1.3.2 Example: the Oxidation of Propene to Propene Oxide

Propene oxide is an important bulk chemical, with a global production of 8.7 million tpa. It is used for making polyurethanes, propylene glycol, and polyethers. These are made into many products, from car bumpers and matrasses all the way to detergents and diving suits. Ideally, it would have been made by direct oxidation of propene with air (similar to the ethene oxide process). But there is no selective catalyst for doing this, and therefore for decades the classic manufacturing route went via chlorohydrin (see Figure 1.6b). The HCl by-product is neutralised with caustic soda or lime (note how the choice of HOCl as reagent adds another step and another reagent to the process). Although this process is wasteful, it still accounts for 40% of the global manufacturing of propene oxide.

There are several alternatives to the chlorohydrin route. One is the styrene monomer propene oxide (SMPO) process, used by Shell and Lyondell (Figure 1.6c) [17]. It is less polluting, but it couples the epoxide production to that of styrene, which is a huge-volume product. Thus, this route depends heavily on

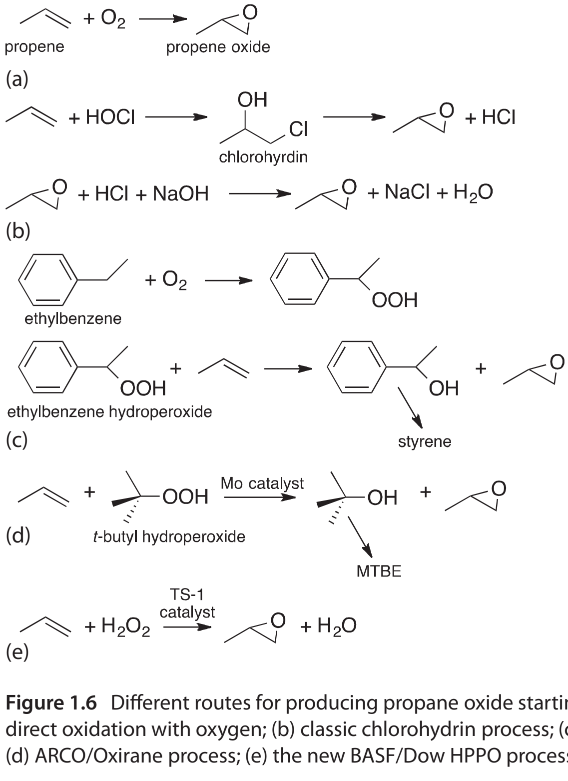


Figure 1.6 Different routes for producing propane oxide starting from propene: (a) the ideal direct oxidation with oxygen; (b) classic chlorohydrin process; (c) Shell/Lyondell SMPO process; (d) ARCO/Oxirane process; (e) the new BASF/Dow HPPO process.

Table 1.3 Comparison of the various propene oxide routes by type and by-product.

Process route	Reagents	Intermediates	By-products and recycles, ton[a)]
Chlorohydrin	Cl_2, H_2O	HOCl, chlorohydrin	Cl^- salts > 2; H_2O > 40
SMPO	Ethylbenzene	EB hydroperoxide	Styrene > 2.2
MTBE	Isobutane	*t*-Butyl hydroperoxide	*t*-Butanol > 2.4
Cumene	Cumene	Cumene hydroperoxide	Cumyl alcohol ~ 1.5
HPPO	H_2O_2	H_2O_2	H_2O ~ 0.3

a) For every ton of propene oxide produced.

the styrene market price. Another alternative, the ARCO/Oxirane process, uses a molybdenum catalyst, and couples the epoxidation of propylene to isobutane oxidation (Figure 1.6d). This generates *t*-butanol as a by-product, that is then used as a gasoline additive and a starting material for making methyl-*t*-butyl ether (MTBE). Another analogous alternative uses cumene, producing cumyl alcohol as by-product.

Several companies set forth to develop a greener and more efficient alternative, using hydrogen peroxide (H_2O_2) as the oxidising agent combined with TS-1, a solid acid titanium-silicate zeolite catalyst. In 2008, a joint venture of BASF and Dow commercialised the first hydrogen peroxide propene oxide (HPPO) process in Antwerp, Belgium [18]. Compared with the chlorohydrin route, the HPPO process generates 80% less wastewater and uses 35% less energy (see Table 1.3). The Antwerp plant manufactures 300 ktpa of propene oxide, and a second plant with a capacity of 390 ktpa was opened in 2012 in Map Ta Phut, Thailand (in collaboration with SCG Chemicals). Dow and BASF have received much recognition for the HPPO process, including the US Presidential Green Chemistry Challenge Award in 2010.

1.1.4
Product and Process Life-Cycle Assessment (LCA)

The above examples show that if we want to make an unbiased comparison of chemical processes, we must take into account their overall environmental impact. One tool that helps us evaluate the environmental impact of a chemical product or process is **life-cycle assessment** (LCA). The main advantage of LCA is that it gives an overview. This includes raw materials extraction and acquisition, chemical reactions and separations, processing, manufacture, packaging, transportation, distribution, consumer use, and end-of-life management [19]. Each LCA has four main stages: (i) defining the assessment scope and boundaries; (ii) quantifying energy and materials flows (inventory analysis); (iii) impact analysis, determining the effects on the environment and human health; and (iv) improvement analysis, which can include methods such as green chemistry, green engineering, and environmental design [20]. Figure 1.7 shows the four stages in life-

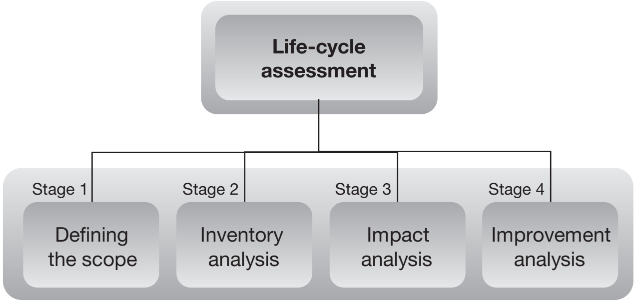


Figure 1.7 The four stages in life-cycle assessment.

cycle assessment. Note that LCA is not limited to chemistry. It is applied in many diverse areas, from assessing roof types [21] to groundwater remediation technologies [22].

The first step in every LCA is defining the scope and goal of the study [23]. In this stage, functional units are defined, so that products can be compared based on the functions they fulfil, rather than by their amount. For example, a milk bottle that is collected, cleaned, and reused 20 times, fulfils the same function as 20 disposable milk cartons. Defining the study scope and goal within your sphere of influence is useful, because then you can actually carry out the recommendations once the assessment is completed.

The second step is making an inventory of all the environmental interventions, such as emissions to air and water and the acquisition of raw materials. This is done using mass- and energy-balances. The interventions are then clustered by type, and totalled for all the processes. Such inventory tables can contain over 100 entries (for example, the total emission of lead, SO_2, or hydrocarbon particulates).

The third step is an impact analysis. First, impact categories are classified. These usually pertain to common environmental threats, such as water pollution, acid rain, or ozone depletion. The environmental interventions from step 2 are then translated into scores in each impact category. These scores are used for calculating an overall environmental impact profile for the original product or process. Often, this is the most problematic step, because quantifying the environmental impact of a process is complex, causing much debate.

Finally, the results are interpreted and an improvement analysis tries to pinpoint the process elements that can be changed, by using for example a different technology, or by adapting the technology to a different design. This is where we apply the tools of green chemistry and green engineering.

1.2
What Is Catalysis and Why Is It Important?

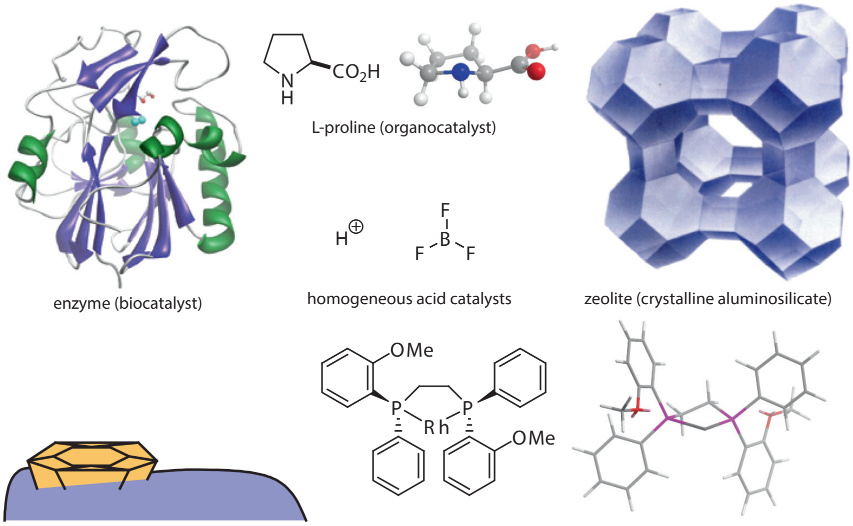
In the previous section we saw that one of the key objectives of green chemistry is waste minimisation. Moreover, we learned that a sustainable process is one that optimises the use of resources, while still leaving sufficient resources for future generations. Catalysis is an important tool in both cases. In fact, as far as chemistry is concerned, catalysis is the key to sustainability [24].

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. A catalyst is a substance that facilitates a chemical reaction. For an outside observer, it seems that the catalyst 'makes the reaction go faster'. As we shall see in Chapter 2, this is an oversimplification. In most cases, the catalyst in fact 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.

Because the catalyst is not consumed in the process, each catalyst molecule can participate in many consecutive cycles, so we need only a small amount of catalyst relative to the substrate. The substrate : catalyst ratio reflects the catalyst's efficiency, that is measured as turnover number or turnover frequency (see below).

There are many different types of catalysts (Figure 1.8). They range from the proton, H^+, through Lewis acids, various metals, organometallic complexes, or-



enzyme (biocatalyst)

L-proline (organocatalyst)

homogeneous acid catalysts

zeolite (crystalline aluminosilicate)

copper-zinc crystallites on amorphous silica

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

Figure 1.8 Different types of catalysts.

ganic and inorganic polymers and all the way to enzymes. To simplify things, we divide catalysis in 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 catalysis are the same. Once you understand these principles, you can easily apply them in all three categories.

The catalyst **turnover number** (**TON**) and the **turnover frequency** (**TOF**) are two important quantities used for comparing catalyst efficiency. Their definition, however, varies slightly between the three catalysis fields. In homogeneous catalysis, the TON is defined as the number of cycles that a catalyst can run through before it deactivates. In other words, the TON is the number of **A** molecules that one molecule of catalyst can convert (or 'turn over') into **B** molecules. The TOF is simply TON/time. In other words, the TOF is the number of **A** molecules that one molecule of catalyst can convert into **B** molecules in one second (or minute, or hour, depending on your time units). In heterogeneous catalysis, TON and TOF are often defined per active site, or per gram catalyst. This is because one doesn't know exactly how many 'catalyst molecules' there are on the surface. In biocatalysis, the TON and TOF are defined by the rate measured when all the enzyme molecules are complexed with a reactant, divided by the total enzyme concentration.

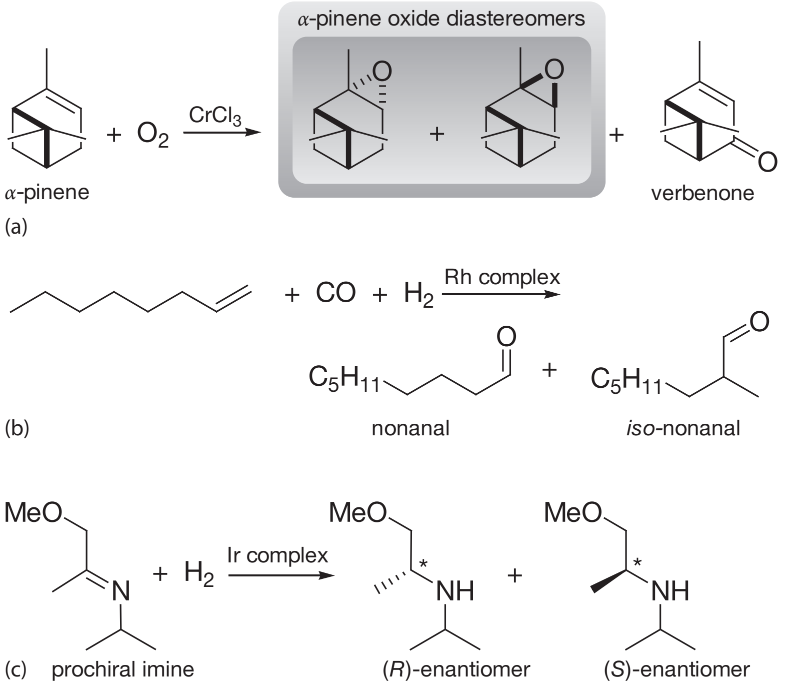


Figure 1.9 Examples of chemoselectivity and diastereoselectivity in the oxidation of α-pinene (a), regioselectivity in the hydroformylation of 1-octene (b) and enantioselectivity in the hydrogenation of the prochiral isopropyl(2-methoxyisopropyl)imine (c, the '★' indicates the asymmetric carbon atoms).

CAUTION! Chemists can have different meanings for TON and TOF, so always include the units of these values when discussing catalytic activity.

The main advantages of catalysis is that you get the desired product faster, using less resources and generating less waste. The catalyst opens a selective route to the desired product. There are various kinds of product selectivity (compare the examples in Figure 1.9). 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**.

Most people are simply unaware of the role that catalysis plays, literally, in their lives. To begin with, 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 an 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. Without catalysis we would still live as an Athenian society (if we're lucky) or in the middle ages.

1.2.1
Homogeneous Catalysis, Heterogeneous Catalysis, and Biocatalysis: Definitions and Examples

In **homogeneous catalysis**, the catalyst is in the same phase as the reactants and products. Here we will concentrate on homogeneous catalysis in the liquid phase. In the classic case, the reactant (also called the substrate) molecules and the catalyst are reacted in a solvent. For example, the transesterification of fatty acid triglycerides with methanol (Figure 1.10) is catalysed by hydroxide (OH^-) ions. The products, fatty acid methyl esters, are then used as biodiesel.

Note that I wrote the 'OH^-' above the reaction arrow, rather than in the same line as the reactants and products. This notation reminds us that the catalyst,

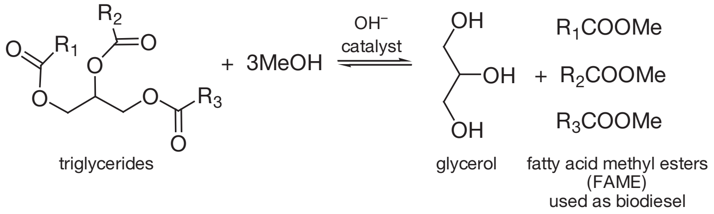


Figure 1.10 Base-catalysed transesterification of triglycerides. The reactants and products are written as part of the stoichiometric reaction equation, but the catalyst is written above the reaction arrow, to show that it is unchanged at the end of the reaction.

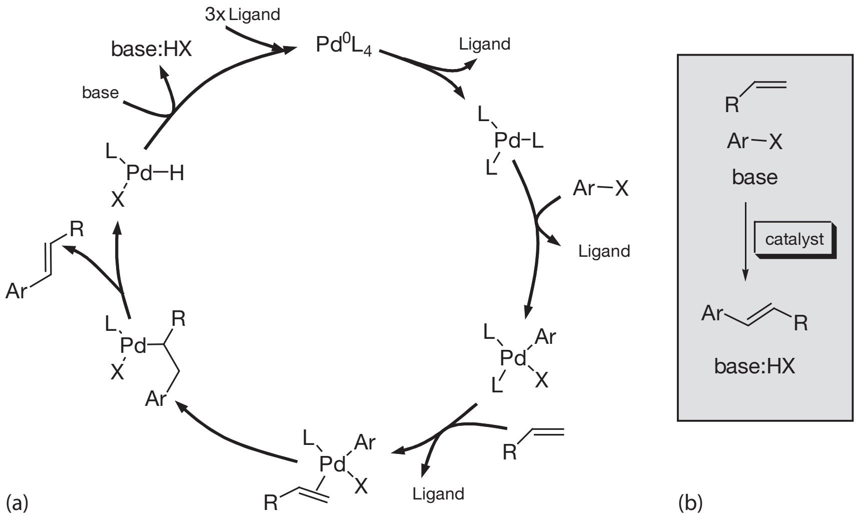


Figure 1.11 Proposed catalytic cycle for the Mizoroki–Heck reaction, showing the various catalytic intermediates (a) and ‘black box’ version (b).

although it participates in the reaction, remains unchanged when the reaction is completed. This does not mean that the catalyst does not change during the reaction. A catalytic reaction is made up of several steps. These form together a cyclic process, called a **catalytic cycle**. Although the catalyst can (and often does) change *during* the catalytic cycle, it returns to its original form at the ‘end’ of the cycle. Typical TONs for this reaction are ~ 1000, so each OH^- anion can catalyse many consecutive cycles.

The easiest way to illustrate this is using an example. Figure 1.11a shows the classic catalytic cycle for the Pd-catalysed cross-coupling between an alkene and an aryl halide. This reaction, discovered independently by Mizoroki in 1971 and Heck in 1972, is known as the Mizoroki–Heck reaction [25, 26]. Since then it has become ubiquitous in organic chemistry[2] and is used today in several fine-chemical processes [27]. We see that the catalyst goes through at least six different structures (these are called the **catalytic intermediates**). Each of these is ‘the catalyst’ as much as any other. The point is, however, that at the end of the cycle the original catalyst is regenerated and is ready to catalyse the coupling reaction of two new substrate molecules. Figure 1.11b shows a ‘black box’ version of the same catalytic cycle. This is what we actually observe: The substrates (aryl halide and alkene) enter the reactor, and the products and by-products leave it. The catalyst remains in the reactor and, for all practical purposes, remains unchanged.

Many homogeneous catalysts are based on a (transition) metal atom that is stabilised by a **ligand**. The ligand is most often an organic molecule that attaches to

---

2) Heck, Negishi and Suzuki shared the Nobel Prize in Chemistry in 2010 for their contributions to palladium-catalysed cross-couplings in organic synthesis (Mizoroki, sadly, died in 1980).

the metal atom. By changing this ligand, one can change the catalyst's properties. Selecting the right metal and the right ligand can improve the catalyst's activity, selectivity, and stability.

Heterogeneous catalysis covers all the cases where the catalyst and the substrate are in different phases. However, the term usually refers to a system where the catalyst is a solid and the reactants are fluids (gases or liquids). In fact, the solid/gas combination is so common that some books and journals refer to it as 'classic' heterogeneous catalysis or even simply as 'catalysis'. This has historical reasons: Most of the 'classic' heterogeneous catalysis was developed in the petrochemicals and bulk-chemicals industry. Due to reactivity and process size considerations, these industries favour continuous processes at high temperatures. This meant that working with solid catalysts and gaseous reactants was the best option (often, it was the only option). One important advantage of heterogeneous catalysis is the ease of catalyst separation. In gas/solid systems the catalyst is easily separated and cleaned, and in liquid/solid systems it can be simply filtered.

Once again, reactants enter the catalytic cycle and products leave it. The catalyst may change during the cycle but regains its original form at the 'end' of the cycle. A simple example of gas/solid heterogeneous catalysis is the hydrogenation of propene to propane. In this reaction, a hydrogen molecule is added to the propene double bond, in the presence of a group VIII metal crystallite (Ni, Pd, or Pt) which is itself supported on a porous support such as silica. The catalytic cycle (Figure 1.12) involves several steps: First, a propene molecule adsorbs on the catalyst surface. The carbon-carbon π-bond breaks and bonds with the surface are created. Meanwhile, H_2 molecules also adsorb on the catalyst. The H–H bond then breaks, and the H atoms move across the metal surface. Eventually, an H atom diffuses close to one of the bonded C atoms. The C–Metal bond is then replaced by a C–H bond. When this happens also at the other C atom, the connection with the surface breaks and the new propane molecule diffuses back into the gas phase.

Note that each of these simple **elementary reactions** is reversible, and so the entire catalytic cycle is also reversible. This is known as the principle of **microscopic reversibility**. Consequently, if the combination platinum/tin supported on alumina is a good hydrogenation catalyst, then it must also be a good dehydrogenation catalyst. In fact, as we will see later, catalysts change only the reaction rate, not the equilibrium. Every catalyst catalyses both the 'forward' and the 'reverse' reactions in the same proportions. In the above example, the reverse reaction is actually more interesting for industry, because propene is a valuable monomer for making (poly)propene and other polymers.

Olefin hydrogenation by heterogeneous catalysis has some interesting stories. In 1927, two manufacturers in Oss (the Netherlands) bought the rights to a French patent for hydrogenating the double bonds in vegetable oil using a nickel catalyst. This yielded a fatty substance – a vegetable-based margarine. They named their joint venture the *Margarine Unie*. Later, they teamed up with two English margarine manufacturers, the Lever brothers, and formed Unilever. Today Unilever employs 168 000 people, with a turnover of €52.7 billion in 2016.

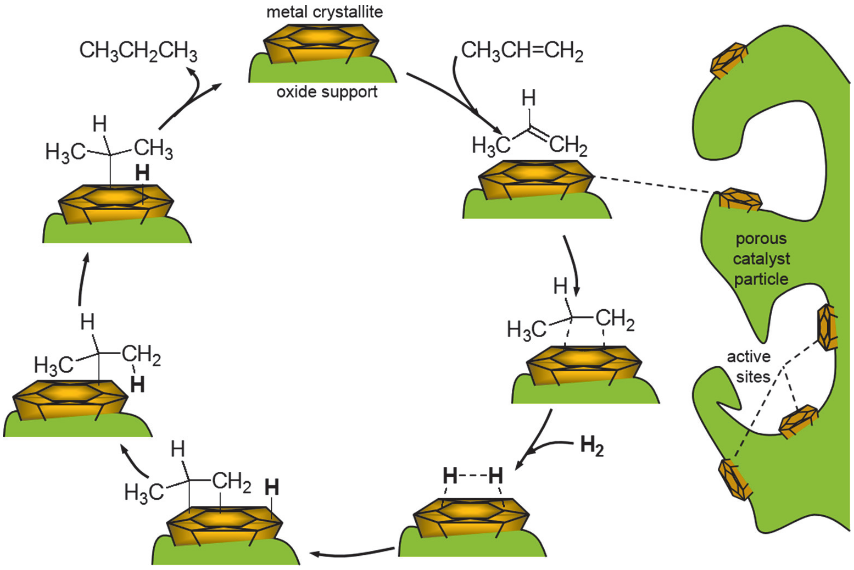


Figure 1.12 Catalytic cycle for the hydrogenation of propene to propane in the presence of a supported metal catalyst. The metal crystallite is one of many so-called 'active sites' on the porous catalyst particle (right). All of the reactions in this cycle are reversible (the reverse arrows are omitted for clarity).

Not all heterogeneous catalysis occurs on metal surfaces. **Zeolites**, for example, are excellent solid acid catalysts. These are porous crystalline structures of metal oxides, often made from silicon, titanium, aluminium, and oxygen. By substituting cations in the zeolite framework, one can create Brønsted and/or Lewis acid sites. As we shall see in Chapters 2 and 4, zeolites are widely used in industry for enriching gasoline octane numbers via gas/solid catalysis. Nevertheless, they can also catalyse liquid/solid reactions, as in this example of geraniol cyclisation by zeolite Y [28] (Figure 1.13, see Chapter 4 for a discussion of zeolite types). Geraniol and its corresponding cyclic derivatives are important intermediates in the flavour and fragrance industry [29]. The suggested reaction mechanism involves both carbocation formation, via protonation of the double bond at a Brønsted acid site [30], as well as complexation of the hydroxy group with a Lewis acid site.

Biocatalysis is a rather special case, somewhere between homogeneous and heterogeneous catalysis. In most cases, the biocatalyst is an enzyme – a complex protein that catalyses all the different reactions in living cells. Enzymes are extremely efficient catalysts. An enzyme typically completes a million catalytic cycles in one second. Compared to this, conventional homogeneous and heterogeneous catalysts are slow and inefficient (100–10 000 cycles/second). Speed, however, is not the only advantage: many enzymes specialise in converting one specific reactant into one specific product. This specificity even includes chiral centres, so an enzyme will catalyse the reaction of one substrate enantiomer, but not of the other. Such enantiospecific reactions are extremely important in the pharmaceuti-

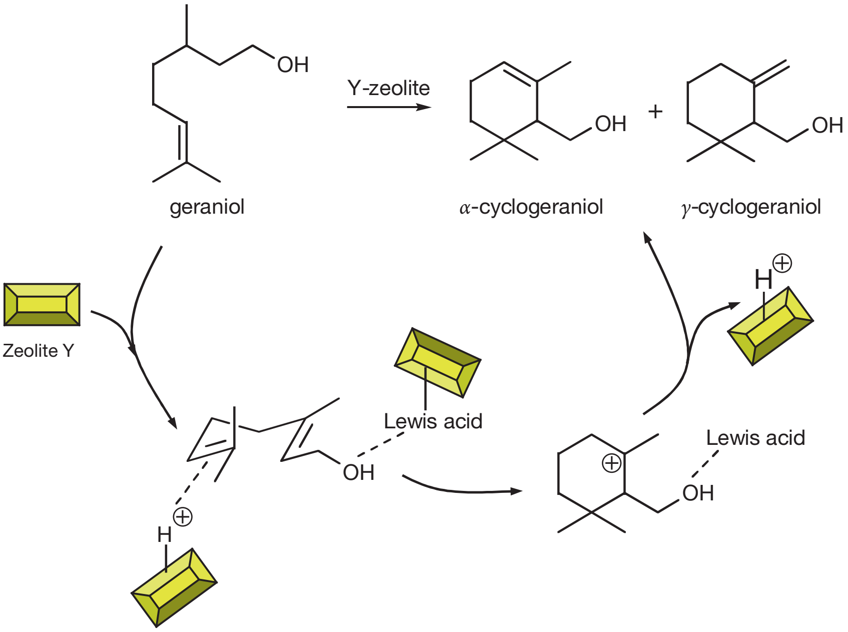


Figure 1.13 Cyclisation of geraniol (top left) and possible mechanism (bottom left) in the presence of zeolite Y, a solid acid catalyst that has both Brønsted and Lewis acid sites.

cal and food industry, because often only one enantiomer has the desired activity. This includes many drugs, food additives, flavourings and fragrances.

Further advantages of biocatalysis compared to 'chemical catalysis' include shorter synthesis routes, and milder reaction conditions. Enzymatic reactions are not confined to *in vivo* systems – many enzymes are also available as isolated compounds, that catalyse reactions in water and even in organic solvents [31]. Despite these advantages, the activity and stability of most wild-type enzymes are insufficient for the demands of industrial processes. Fortunately, modern genetic engineering methods can be used to synthesise proteins 'on demand', changing enzyme properties and optimising desired characteristics. In Chapter 5 we will outline these optimisation methods, including **site-directed mutagenesis** and **directed evolution**.

Although biocatalysis is the 'new kid on the block', more and more companies are using enzymes for chemical manufacturing. One reason for this is that biocatalysts give sustainable alternatives to chemical manufacturing, and not just for making chiral products. The synthesis of acrylamide via an enzyme-catalysed water addition to acrylonitrile is a classic example (Figure 1.14). It uses the *Rhodococcus* enzyme nitrile hydratase. Commercialised in 1985 on a 10 000 ton/year scale by Nitto Chemicals in Japan, this process replaced an acid-catalysed process, and also avoided the acrylic acid by-product [32]. In 2014, the global biocatalytic acrylamide production was over 800 000 tons.

Advancements in genetic engineering are opening exciting opportunities for biocatalysis. One example is the synthesis of important bulk industrial chemicals

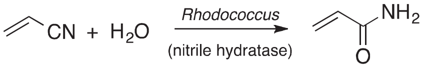


Figure 1.14 In the biocatalytic synthesis of acrylamide from acrylonitrile the bacterial cells are immobilised in a (poly)acrylamide gel, and the process is run at pH 8.0–8.5 in semi-batch mode, keeping the substrate concentration below 3%.

from renewable feedstocks. Adipic acid, for example, is a key monomer for making nylon 6.6. In 2016, the world production of adipic acid was 2.7 million tons. Practically all of this is produced from benzene, via cyclohexane and cyclohexanol/hexanone (Figure 1.15, left). Although the process itself is quite efficient, it has three main drawbacks: First, it relies on petroleum as a raw material. Second, it uses benzene, a known carcinogen. Third, it requires high pressures of hydrogen and oxygen, and uses concentrated HNO_3 in the intermediate oxidation step, generating N_2O as a by-product.

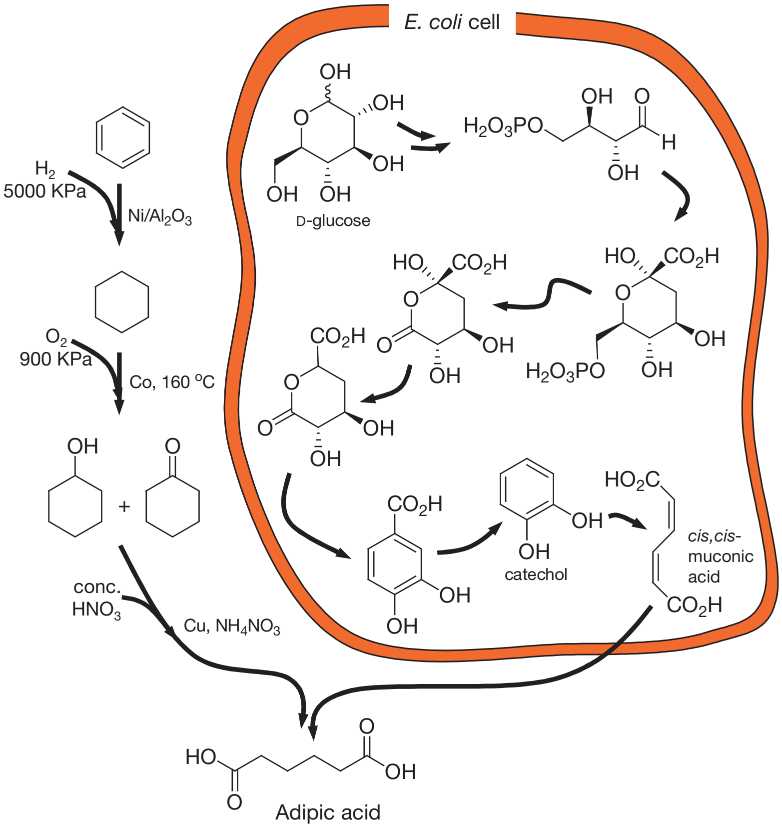


Figure 1.15 The classic Du Pont route to adipic acid (left) and Frost's biosynthetic route using a genetically modified *E. coli* cell (right, the enzymes and the reagents are omitted for clarity).

In 2002, Frost and co-workers successfully constructed a mutated *E. coli* bacterium that can convert D-glucose to *cis,cis*-muconic acid, which is then easily hydrogenated to adipic acid (Figure 1.15, right) [33]. The biosynthetic route is certainly more complex than the conventional synthesis: It has nine steps, and uses eight different enzymes. But the first eight steps are carried out inside the *E. coli* cell, at 37 °C and ambient pressure. The bacterium simply eats D-glucose, and produces *cis,cis*-muconic acid. Moreover, D-glucose is a cheap (∼ $400/ton) and renewable raw material. Benzene is a known carcinogen, while glucose is food. Switching from benzene to glucose gives a process that is inherently safer. A similar approach was used to convert D-glucose to hydroquinone, an important intermediate in the synthesis of antioxidants and polymerisation inhibitors [34].

Will such biocatalytic processes really replace the traditional chemical manufacturing? Yes, but it will take time. There is still no shortage of benzene for chemical production (> 90% of the worldwide petroleum demand ends up as transportation fuel; chemicals production accounts only for ∼ 7%). The bulk chemicals industry is very conservative, and enzymes are expensive compared to conventional catalysts. Biosynthetic process alternatives will only enter the market when they are deemed commercially viable. Nevertheless, biotechnology, and with it biocatalysis, is progressing fast. In the 1980s, such a *tour de force* of genetic engineering could only be found in the science fiction section. Now it is commonplace research. Designed metabolic biosynthesis is here, and it is here to stay.

1.2.2
Connecting Catalysis and Sustainability: Saving Resources by Using Catalytic Cycles

As we saw in the previous sections, atom economy is an important concept in green chemistry. Preferably, every atom that you put into a process should come out as product. Classic organic synthesis protocols often require additional reagents that are not incorporated in the products and must be disposed of. This is not only bad for the environment, but also costly, because you pay twice: Once for buying the additional reagents, and once for disposing of the waste.

A classic example is the homocoupling of aryl iodides in the presence of copper, known as the **Ullmann reaction** (Figure 1.16). This reaction gives symmetric biaryls, which are key building blocks in various agrochemical and pharmaceutical processes. Although the Ullmann reaction is over 100 years old, it is still used in industry today. The problem is that it consumes a mole of copper for every mole of product, and generates large amounts of waste. The reaction works best with iodoaryls, which increases the waste problem. This is because chemicals react by their molarity, but are quantified (and bought and sold!) by their mass. One ton of iodobenzene contains 620 kg of 'iodo' and only 380 kg of 'benzene'. Thus, two-thirds of the reactant (PhI) and all of the reagent (Cu) comes out as chemical waste.

Using the principles of green chemistry, let's first see if we can replace the stoichiometric reagent (copper) with a catalytic cycle. The iodine atoms are not part of the product. They act as leaving groups, generating ultimately two $C_6H_5^\bullet$ radicals

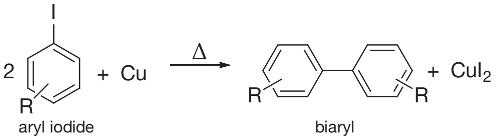


Figure 1.16 The classic Ullmann reaction for coupling aryl iodides by reaction with copper metal at high temperatures.

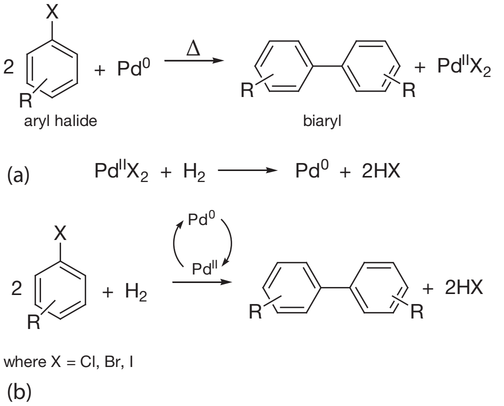


Figure 1.17 Combining two stoichiometric reactions (a, the reductive coupling of halobenzene with Pd^0 and the reduction of Pd^{II} with hydrogen gas) creates a catalytic cycle where the Pd catalyst shuttles between the Pd^0 and Pd^{II} species (b).

that couple to give biphenyl. The copper metal reduces the iodine atoms, giving Cu^{2+} and $2I^-$. The same stoichiometric reaction can be done using palladium instead of copper (Figure 1.17, top). This doesn't look so useful, because palladium is much more expensive than copper. However, the advantage of Pd is that it is easily reduced back from Pd^{2+} to Pd^0. This reduction can be done, for example, using hydrogen gas [35], giving Pd^0 and $2H^+$. If we then tally these two reactions, we get the catalytic cycle shown on the bottom of Figure 1.17. This is a very simple representation of the catalytic cycle, but it shows the principle: iodobenzene and hydrogen go in, and biphenyl and HI come out, while the Pd catalyst remains in the cycle and shuttles between Pd^{2+} and Pd^0. We're still using a stoichiometric reagent (hydrogen gas) but a mole of hydrogen weighs only 2g, while a mole of copper metal weighs 63g. As an added bonus, the Pd-catalysed cycle also works with bromo- and chloroarenes, improving the reaction's E-factor and the atom economy even more.

Can we improve the atom economy even further, and avoid using any halide? The 'greenest solution' for making biphenyl, $C_{12}H_{10}$, is using no leaving group, starting from 12 C atoms and 10 H atoms. This can be done (in theory) by coupling benzene, C_6H_6, with benzyne, C_6H_4. Although this route gives 100% atom economy on paper, generating benzyne is very difficult. More practically, the smallest leaving group that is easily available is a hydrogen atom, that is oxidative coupling

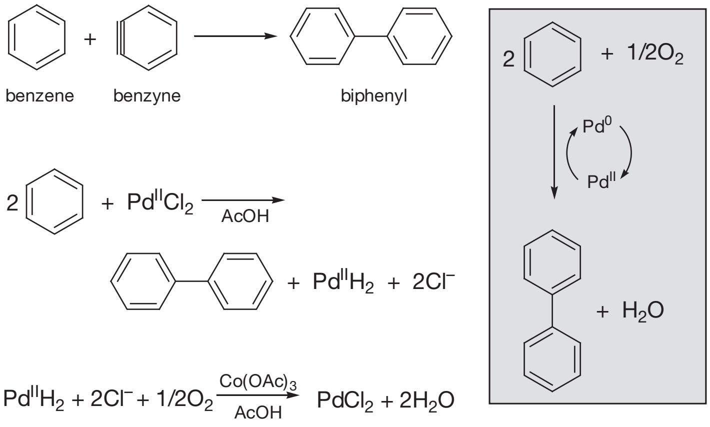


Figure 1.18 Theoretical waste-free route to biphenyl starting from benzene and benzyne (top left), oxidative coupling of two benzene molecules with stoichiometric Pd^{II}Cl$_2$ and regeneration of Pd^{II} with molecular oxygen (bottom left), and the resulting catalytic cycle for oxidative coupling (grey inset).

of two benzene molecules to form biphenyl (Figure 1.18). This reaction can be done using stoichiometric amounts of $PdCl_2$ in acetic acid as solvent [36], or by using a Pd catalyst and regenerating it with air as the oxidant, giving water as the only by-product (an additional homogeneous $Co(OAc)_2$ catalyst is used for activating the oxygen in solution [37]). Although the actual catalytic cycle involves many steps and intermediates, the principle is simple: Benzene and oxygen go in, and biphenyl and water come out. Currently, the highest yields reported for this system are ~ 80%.

Another interesting alternative combines catalysis and electrochemistry [38]. In the reductive coupling cycle of two benzene molecules to biphenyl, the Pd catalyst provides just two electrons. This reaction can be done in an electrochemical cell, where the electrons are supplied from an outside source [39]. We thus see that catalysis gives us a variety of green alternatives to the classic stoichiometric process. There are no hard and fast rules as to which route to choose – it all depends on the reaction conditions, and on the chemicals available.

1.2.3
Industrial Example: the BHC Ibuprofen Process

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 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 Advil, Motrin, or Nurophen.

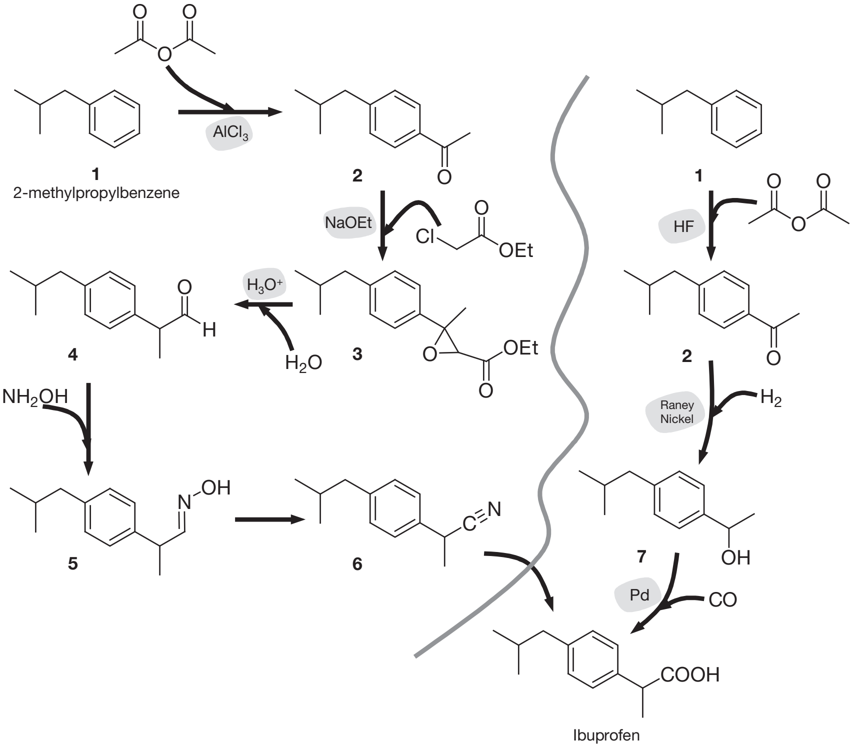


Figure 1.19 Synthesis of ibuprofen: The six-step Boots route (left) and the three-step BHC route (right). In each case, the catalysts are highlighted in grey.

Ibuprofen, like many other drugs, is a rather simple 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 do not appear in 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 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. Effectively, what happens is that the hydroxyl amine is first added to the molecule and then removed. This type of 'roundabout synthesis' is precisely what green chemistry wishes to avoid.

When the patent rights on ibuprofen expired, Boots teamed with Hoechst Celanese and formed the BHC consortium, developing a new process for making ibuprofen [40]. They 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 also developed methods for recovering and recycling the acetic acid, increasing the atom utilisation to 99%, and creating an essentially waste-free synthesis. Using anhydrous HF as both catalyst and solvent offers important advantages in reaction selectivity and waste reduction, as the new route also eliminated the large volumes of aqueous salt waste associated with ibuprofen manufacturing.

The BHC ibuprofen process is an innovative, efficient technology that has revolutionised bulk pharmaceutical manufacturing. The process provides an elegant solution to 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 > 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 US Presidential Green Chemistry Award in 1997. It was also a commercial success: the consortium sold the business to BASF for more than $100 million.

1.3
Tools in Catalysis Research

Catalysis plays an integral role in many chemical reactions, all the way from petrochemistry to pharmaceutical chemistry. Because catalysis covers such a wide area, researchers use a variety of tools. These can be roughly divided in three groups: Synthesis and testing tools, characterisation tools, and modelling/mechanistic studies tools (see Figure 1.20).

1.3.1
Catalyst Synthesis and Testing Tools

The reactors used in organic and organometallic chemistry research did not change much from the 1850s to the 1990s. The chemical industry is a conservative one, so the majority of liquid-phase reactions are still done in batch reactors in one form or another, while most gas-phase reactions are carried out in flow reactors. Nevertheless, recent developments in reactor design and process intensification are now changing the picture [41].

Traditionally, research in catalyst discovery and optimisation followed a cyclic workflow of synthesis, characterisation, activity testing, and mechanistic studies. Because doing reactions was considered costly and labour-intensive, chemists favoured working on a few model compounds, learning as much as possible from each reaction. The 1990s saw a paradigm shift, with the entry of parallel screening and high-throughput experimentation in catalysis research. This was pioneered by Zaffaroni and Schultz, who founded the company Symyx in 1994. Symyx adapt-

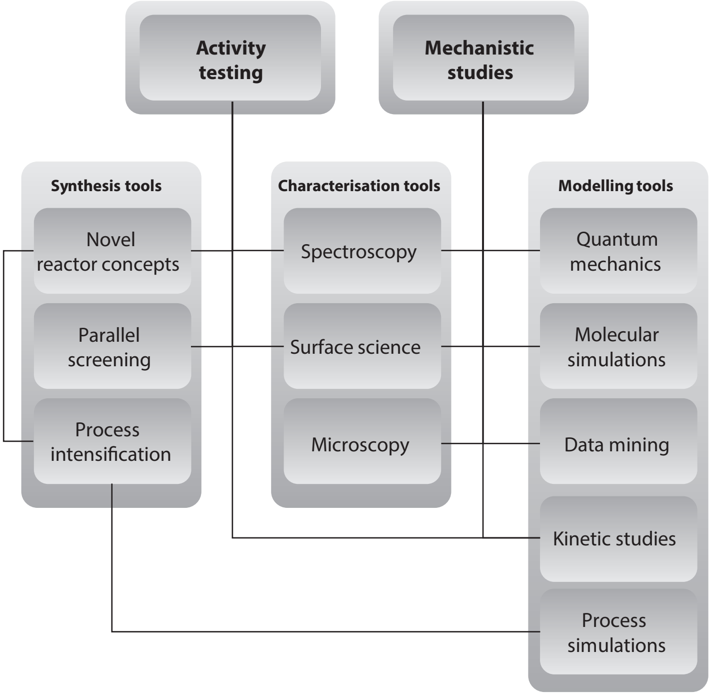


Figure 1.20 Block diagram of the various tools used in catalysis research.

ed the concepts of miniaturisation and parallel synthesis, used in pharmaceutical and biomedical research, to catalysis and materials science [42]. The main advantages were higher efficiency, and the ability to run reactions using less reactant and catalyst quantities. This was especially important for homogeneous catalysis, where ligand cost and availability is often a problem. Diphosphine ligands, for example, cost typically €75–€370 per gram, while the average cost of a gram of Pt in 2016 was 'only' €32. Moreover, running many experiments in parallel improves data quality, as repeating experiments is easier, and systemic errors can be minimised. Similar advantages are obtained by 'one-pot' systems, where multiple substrates and catalysts are tested simultaneously [43], as well as by using multicomponent reactions [44]. Today, most companies that develop catalysts and catalytic processes use such tools.

Some of the parallel reactors on the market today are basically arrays of scaled-down batch or flow reactors. Others employ microreactor technology for high-throughput catalyst synthesis and screening [45]. Structured reactors are the twentyfirst-century equivalent of the round-bottomed flask, enabling efficient mixing, mass- and heat transfer [46, 47]. One such example is the mixed pulse reactor developed by de Bellefon, that enables the fast sequential screening of catalysts in liquid/liquid and gas/liquid systems [48]. Here, two liquid carriers are flown continuously through a micromixer, that is connected to a plug flow

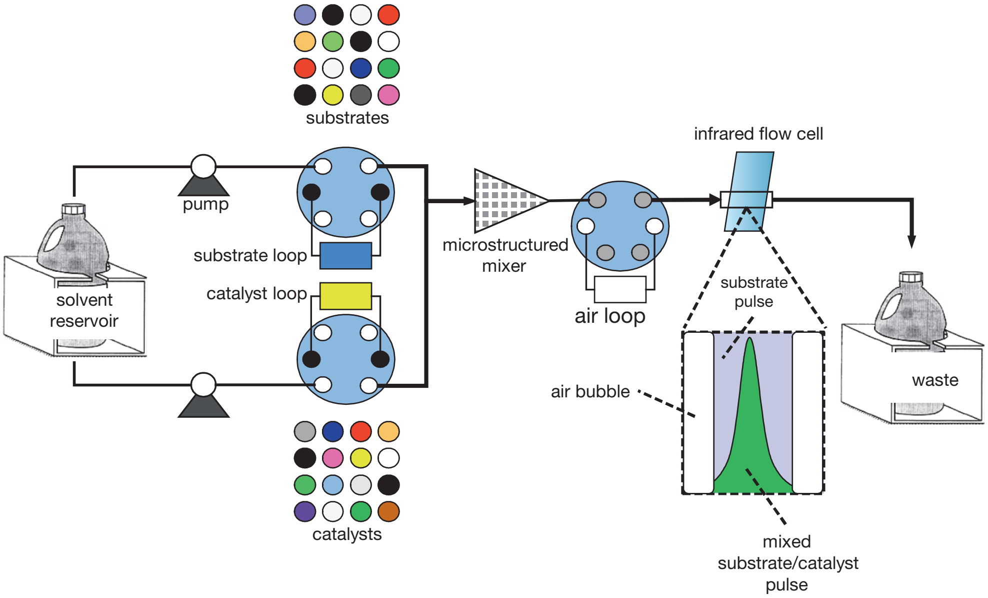


Figure 1.21 Schematic of a sequential pulse injection system for high-throughput catalyst screening using on-line spectroscopy.

reactor. The two carriers can be miscible (e.g. pentane and cyclohexane) or immiscible (e.g. heptane and water). The first carrier contains the substrates, while the second contains the catalyst. Pulses of the two carriers are injected simultaneously into a micromixer, with a residence time of < 10 milliseconds. This creates a 'reaction pulse' that then moves through the reactor and can be analysed by gas chromatography (GC) or high performance liquid chromatography (HPLC) at the reactor outlet. This approach enables the testing of small catalyst amounts without sacrificing the high accuracy and precision of chromatographic analysis. This type of system can also be adapted to high-throughput screening using spectroscopy, by adding a third valve that injects air bubbles before and after each pulse, and sending the pulses through a spectrophotometric flow cell (Figure 1.21).

Parallel synthesis and testing of heterogeneous catalysts for gas/solid reactions has also seen a number of ingenious developments, especially in the preparation and screening of catalyst libraries. Masking, sputtering, inkjet printing and lithography techniques are now applied for depositing arrays of metal catalyst precursors on ceramic or silicon wafers. Subsequent oxidation (or reduction) of these wafers gave solid catalyst libraries (mixed metal alloys or mixed metal oxides, depending on the treatment), wherein both the composition and the position of each catalyst are well defined. Today, libraries of hundreds and even thousands of catalysts are prepared in this way, with promising candidates scaled up for commercial production [49].

In 1996, Willson and co-workers reported the first parallel screening of such a library using infrared (IR) thermography, using a grid of alumina pellets [50]. By taking infrared photos of the catalyst array through a sapphire window, and measuring the ignition temperature, they tested the catalytic activity for hydrogen oxidation. Later, Maier and co-workers refined this concept, screening 50 catalysts simultaneously and using only 200 μg catalyst per sample [51]. Higher camera sensitivity enabled the screening of less exothermic reactions, such as the oxidation of isooctane and toluene at 350 °C.

The main advantage of the grid approach is that the catalyst position is well defined. This is easy to do with solid catalysts, but not with homogeneous ones in solution. One way for solving this problem is attaching the homogeneous catalysts to a solid support, such as polymer beads peptide scaffolds, or inorganic monoliths [52]. The resulting supported catalysts are heterogeneous, but still similar to their homogeneous analogues. Such solid-phase synthesis is common in pharmaceutical chemistry, where it is often used in combination with split/pool synthesis.

1.3.2
Catalyst Characterisation Tools

Catalysis is still very much a ‘black box’ discipline, and catalyst characterisation tools help us look into this box. Characterisation is done on several levels: On the macroscopic level (the reactor level), engineers search for the optimal formulation and operating conditions of the catalytic process. The second, mesoscopic level includes surface analysis and temperature-programmed techniques (in heterogeneous catalysis), as well as kinetic studies, with the aim of finding composition/activity and structure/activity relationships. Finally, on the microscopic (or, more accurately, nanoscopic) level, chemists and physicists probe catalyst molecules, clusters, and atoms, trying to understand the fundamental processes that make up the catalytic cycle. A discussion of catalyst formulation on the macroscopic level is out of the scope of this book – the reader is referred to specialised texts on industrial catalysis [53]. We will cover the subject of kinetic studies in Chapter 2, and give further specific examples from homogeneous, heterogeneous, and biocatalysis in Chapters 3–5, respectively. In heterogeneous catalysis, much information on the mesoscopic level is gained using classic surface science techniques for measuring surface area, porosity, and particle size distribution. Chapter 4 gives an overview of these methods.

The last two decades have witnessed rapid developments in catalyst characterisation on the microscopic level, especially in the area of spectroscopy and imaging of solids. Instruments for transmission electron microscopy (TEM) and scanning electron microscopy (SEM) are now almost commonplace, and can resolve images to within a few nanometres. High-resolution transmission electron microscopes and atomic force microscopes can now resolve rows of atoms and single crystal facets. Using such tools, chemists can ‘see’ the catalyst surface, and sometimes follow the reactions in real time. Other techniques such as Raman spectroscopy, solid-state nuclear magnetic resonance (SS-NMR), and diffuse reflectance ultraviolet spectroscopy (DRIFTS) also give important information regarding the active sites on the surface [54]. Similar spectroscopic techniques are also used in homogeneous catalysis and biocatalysis.

One way of circumventing the high complexity of catalytic systems is by analysing isolated samples of catalyst precursors or intermediates. The advantage of this *ex situ* approach is that one works with simplified systems, under well-defined conditions (e.g. polished crystals under ultra-high vacuum, or diluted solutions of pure analytes). *Ex situ* characterisation can give important information on the catalyst structure, from which one can deduce key structure/activity relationships, and learn about the reaction mechanism. The disadvantage is that the analysis conditions differ from the real reaction conditions. Typical gas/solid catalysis is performed at high temperatures and pressures, not in ultra-high vacuum. Similarly, liquid-phase homogeneous catalysis takes place in solutions and mixtures of numerous species, and enzymes work inside living cells that contain a plethora of compounds, not with 'pure analytes'. This difference in pressure, composition, and temperature between the analysis conditions and the real reaction conditions, is known as 'the gap'. Bridging this gap is an important challenge in catalysis research [55, 56].

Alternatively, one can characterise the catalytic intermediates *in situ*, under conditions that are closer to the real reaction conditions. High-pressure IR and NMR equipment, for example, enable the measurement of spectra at up to 200 bar and 150 °C, similar to the reaction conditions in high-pressure autoclaves [57]. In some cases, one can combine the characterisation with activity/selectivity analysis, examining the catalyst in real-time operation. This simultaneous catalyst characterisation and activity analysis is known as *operando* spectroscopy, a term coined by Miguel Bañares in the 1990s [58, 59]. *In situ* and *operando* characterisation studies are increasingly popular, as more and more chemists see the advantages of studying catalytic processes under realistic conditions. Figure 1.22 shows a flow cell for *operando* IR spectroscopy, developed by Thibault-Starzyk and co-workers [60].

1.3.3
Modelling/Mechanistic Studies Tools

The meteoric rise in computer power (and meteoritic decline in hardware prices) has opened exciting opportunities for computer modelling in all branches of science. Today, computer models are used in three main areas of catalysis research: Modelling of reaction pathways and catalytic cycles, modelling of process kinetics and reaction performance, and computing structure/activity relationships on various levels. The models cover a wide range of approaches and system types, and are discussed in detail in Chapter 6.

Quantum mechanics calculations are used for solving the wave function equations of catalytic systems, giving a detailed picture of the reaction dynamics on the molecular scale. Two decades ago, such *ab initio* computations were so expensive, that they were limited to very simple systems. Now, algorithms based on density-

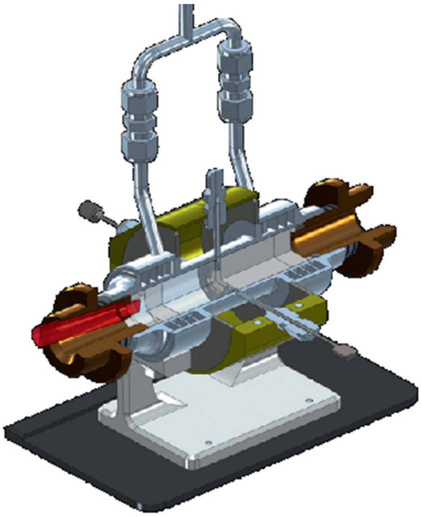


Figure 1.22 Schematic of a flow cell for measuring IR spectroscopy during a catalytic reaction (courtesy of Dr. Frederic Thibault-Starzyk).

functional theory (DFT) enable the modelling of complex reactions in all three catalysis fields [61]. In heterogeneous catalysis and biocatalysis, where the size of the system prohibits costly computations, hybrid methods are used. For example, you can model the active site of an enzyme using high-level computations, and the rest of the enzyme using low-level methods. Importantly, such models are not limited to energy minima (i.e. reactants, catalytic intermediates and products). They can also be used for computing the structures of the activated complexes associated with transition states. Thus, computer modelling can provide a picture of the elusive transition states, which can never be observed experimentally (because by definition, transition states have a zero lifetime). In this way, you can model the reaction pathways and the corresponding reaction kinetics in detail, gaining insight on the various elementary steps in the catalytic cycle.

Classical molecular simulations are used for modelling large systems, such as solid surfaces, enzymes, or large numbers of solvent molecules. In these simulations, the electronic interactions are averaged out using a classical potential, and the system's dynamics are modelled by solving Newton's equations. The computational cost here depends on the system's size and level of detail. For example, a butane molecule, C_4H_{10}, can be modelled as a collection of fourteen atoms (all-atom model), or as a chain with four links (coarse-grained model), or as a single particle. This way, you can tune the system size and the degree of detail to the requirements of the problem at hand.

Another important modelling aspect is the simulation of catalytic process parameters and reactor configurations. Such models are typically associated with process engineering, and involve computational fluid dynamics and heat- and mass-transfer calculations. They are essential in the process planning and scale-up. But as this book deals primarily with the chemical aspects of catalysis, the reader is referred to texts on industrial catalysis and process simulations for further information [53, 62].

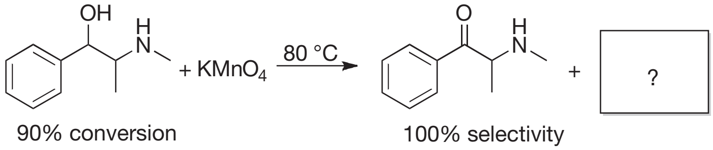


Figure 1.23 The oxidation of 2-(methylamino)-1-phenyl-propan-1-ol with potassium permanganate.

The third type of modelling deals with catalyst descriptors, structure/activity and structure/property relationships [63, 64]. There are various levels of catalyst descriptors, ranging from very simple ones based on composition parameters (in heterogeneous catalysis) or connectivity matrices (in homogeneous catalysis) to ones based on high-level quantum computations and thermodynamic calculations. Like other modelling methods, descriptor models are often used for explaining the behaviour of catalytic systems. Following the advances in drug discovery, however, predictive descriptor modelling has now become an exciting new field in catalysis research [65, 66]. By combining the data from high-throughput experimentation with statistical analysis and descriptor models, you can predict the properties and performance of new catalysts [67]. Chapter 6 also covers the basics of predictive modelling and *in silico* catalyst screening.

1.4
Exercises

Q1.1 Examine the list of the twelve principles of green chemistry shown in the beginning of this chapter. Which of these principles relate to the concepts of atom economy, the E-factor, and the environmental quotient Q?

Q1.2 (RS)-2-(methylamino)-1-phenyl-propan-1-one (more commonly known as **ephedrone**, and sometimes called 'Jeff' or 'Charlie') is an alkaloid psychoactive stimulant. It is used as a recreational drug and considered to be addictive. Like many other drugs, it is a rather simple molecule, and can be synthesised by the selective oxidation of the corresponding alcohol in the presence of stoichiometric potassium permanganate, $KMnO_4$ (see Figure 1.23). This reaction gives 90% conversion and 100% selectivity at 80 °C.

a) Balance the reaction and then calculate its E-factor and estimate its Q-value.
b) Write a balanced chemical equation of an alternative oxidation route, which uses H_2O_2 instead of $KMnO_4$, in the presence of 1 mol% of $FeCl_3$ catalyst. This catalytic process gives only 30% conversion but with 100% selectivity at 80 °C. What causes this low conversion? How can you increase the conversion without lowering the selectivity?

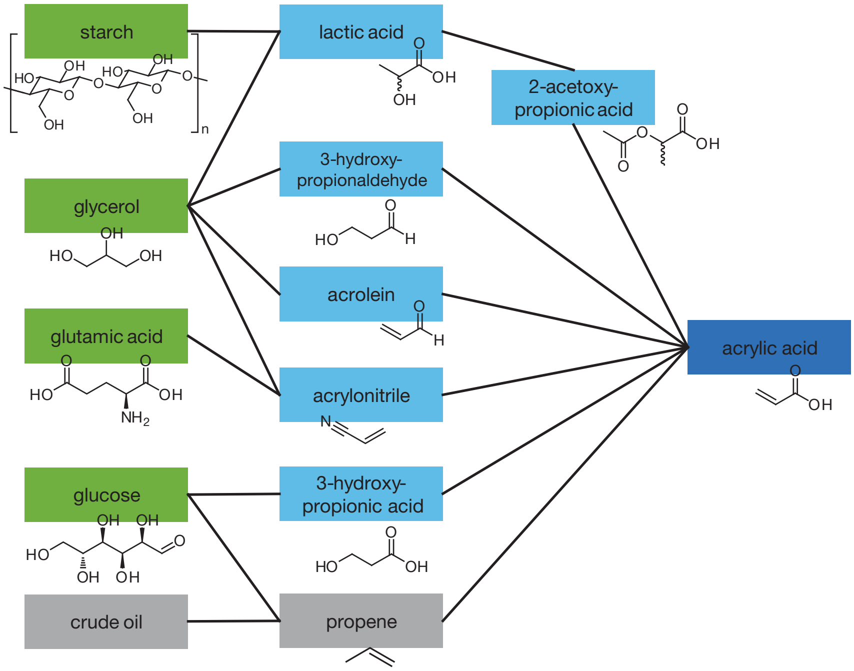


Figure 1.24 Different production routes to acrylic acid, showing biobased feedstocks (green), biobased platform chemicals (light blue), and existing petrobased routes (grey).

Q1.3 Acrylic acid, $H_2C{=}CH{-}COOH$, is an important bulk chemical. Its esters feature in many applications, including plastics, synthetic rubber and superabsorbent polymers for diapers. In 2012, the worldwide production of acrylic acid was over 4.5 million tons, with prices ranging from 1600 \$/ton for low-grade up to 2200 \$/ton for glacial-grade. Figure 1.24 shows eight different possible production routes to acrylic acid starting from different biomass sources as well as from crude oil [68].

a) Choose three of these routes and compare their pros and cons based on starting material, number of steps, and atom economy.
b) In practice, all the industrial production plants of acrylic acid today still follow the conventional propene route starting from crude oil. What are the chances of this changing in the next decade? Explain your answer.

Q1.4

a) Calculate the E-factors and estimate the *Q*-values for the following three Ullmann reactions using stoichiometric copper, as well as for the catalytic alternative using 5 wt% Pd/C and hydrogen gas.

$$\begin{aligned}
&2C_6H_5I + Cu \rightarrow C_6H_5{-}C_6H_5 + CuI_2 && \text{(100\% yield)}\\
&2C_6H_5Br + Cu \rightarrow C_6H_5{-}C_6H_5 + CuBr_2 && \text{(85\% yield)}\\
&2C_6H_5Cl + Cu \rightarrow C_6H_5{-}C_6H_5 + CuCl_2 && \text{(80\% yield)}\\
&2C_6H_5Br + H_2 \rightarrow C_6H_5{-}C_6H_5 + 2HBr && \text{(89\% yield)}
\end{aligned}$$

b) Compare the E-factors and *Q*-values for these four situations, and discuss the pros and cons of replacing the stoichiometric protocol with a catalytic cycle.
c) If using 100 mg of catalyst gives 98% conversion after 40 min, what are the TON and TOF of this catalyst?

Q1.5 The most important (and also the most expensive) grapefruit aroma compound is the bicyclic terpene nootkatone. It is manufactured by oxidation of valencene, which is extracted from Valencia oranges. Figure 1.25 shows two routes for this oxidation, one using chromium trioxide, and one using sodium hypochlorite (bleach) in the presence of 1 mol% osmium tetraoxide catalyst.

a) Calculate the E-factors and atom economy values for both options.
b) Given that CrO_3 and OsO_4 are equally toxic, estimate the *Q*-values in both cases, and explain which option do you favour and why.

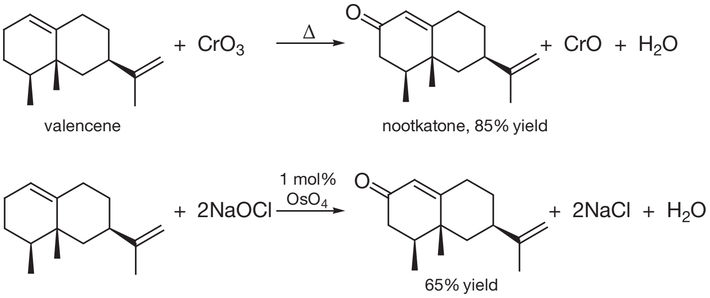


Figure 1.25 Alternative synthesis routes from valencene to nootkatone.

Q1.6 Revisit the section on propene oxide manufacturing and write down the chemical equations for the classic chlorohydrin route and the Dow-BASF HPPO process. Then, consider an alternative route that uses nitrous oxide, N_2O, as an epoxidation agent. This reaction can be catalysed by supported iron catalysts.

a) Write a balanced chemical equation for the epoxidation of propene to propene oxide using N_2O. Then, calculate the E-factor and atom economy values for this reaction, and estimate its *Q*-value. Compare these values with the ones for the chlorohydrin and the HPPO routes. Which route is more favourable?
b) Search the Internet for information about N_2O and list two advantages and two disadvantages for using it as an oxidant in this reaction. Why doesn't industry use the nitrous oxide route?

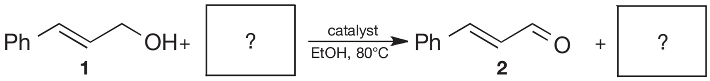


Figure 1.26 The catalytic oxidation of cinnamyl alcohol to cinnamaldehyde.

Q1.7 The catalytic oxidation of cinnamyl alcohol **1** to cinnamaldehyde **2** runs at 80 °C and 1 atm with various oxidants and ethanol as solvent (Figure 1.26). When using air as the oxidant, the conversion is 100% but the product selectivity is only 30%. When using hydrogen peroxide as the oxidant, the conversion is only 30% but the product selectivity is 100%. Acetaldehyde and acetic acid are not observed in any of the reactions.

a) Complete and balance this oxidation using molecular oxygen, and then calculate the E-factor and estimate the *Q*-value of this reaction. What are the possible by-products in this reaction?
b) Complete and balance the reactions for the analogous oxidation using hydrogen peroxide. Estimate the environmental quotient of this reaction. What are the possible by-products in this case?
c) Which oxidation option is preferable? Explain your answer.
d) Would this catalyst be suitable for oxidation of alcohols in fine-chemical synthesis? Would it be suitable for alcohol oxidation in bulk chemical processes? Explain your answer.

Q1.8 The classic synthesis of hydroquinone starts with aniline, and uses stoichiometric MnO_2, sulphuric acid, and iron (Figure 1.27).

a) Calculate the atom economy for this process.
b) Aniline itself is made by nitration of benzene to nitrobenzene, followed by hydrogenation. Using the principles of green chemistry, draw a new process for making hydroquinone, starting directly from benzene (feel free to invent any catalysts you need).

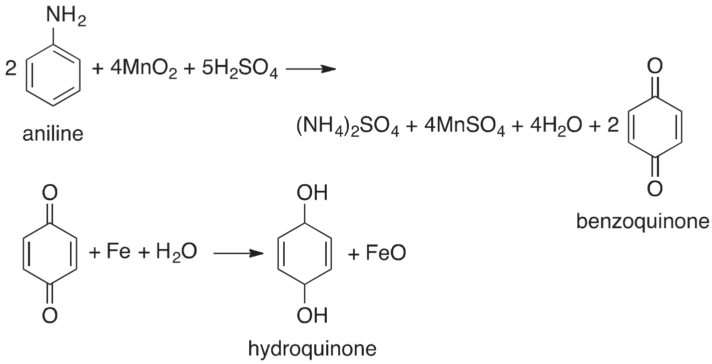


Figure 1.27 The classic synthesis route to hydroquinone starting from aniline.

c) Search the Internet for information on the Upjohn hydroquinone process, and compare that with your synthesis route. What are the advantages of the Upjohn process and of your synthesis compared to the classic route? Are there any disadvantages?

Q1.9 Fluorescent light bulbs contain mercury, that is released to in the environment when the bulbs are disposed of in landfills [69]. Incandescent light bulbs contain no mercury, and so disposal is not a problem. However, regular bulbs use more electricity than fluorescent ones, which means burning more coal at the power station, and burning coal also releases mercury to the environment. A typical fluorescent bulb consumes 11 W and burns for 5000 h, while a typical incandescent one consumes 75 W and burns for 1000 h.

a) Construct two life-cycle charts, one for fluorescent light bulbs and one for incandescent light bulbs.
b) Assuming that coal contains typically 20 ppm mercury impurities, which type of light bulb is better, qua mercury, for the environment?
c) A typical LED light can burn for 20 000 h, and consumes only 7 W. It releases no mercury into the environment, but it does contain rare-earth elements, and costs ten times the price of a fluorescent bulb. How do LED lights compare, in terms of life-cycle, to the fluorescent and incandescent ones?

Q1.10 A typical 1 L glass bottle, for storing milk or juice, weighs $\sim$ 400 g, while a 1 L Tetrapak™ carton weighs only 35 g. This is a big difference in raw materials and transportation costs. Glass bottles, however, are often washed, reused, and eventually recycled, while cartons are disposed of in landfills (Tetrapaks are hard to recycle because they contain thin layers of low-density polyethylene and aluminium, and because their collection is costly; the only municipality that currently recycles them is Sao Paolo, in Brazil). Figure 1.28 shows the life-cycle flow diagram for Tetrapak cartons.

a) Draw an analogous diagram for glass bottles, and consider the energy input and transport costs associated with 1000 L milk in cartons compared to 1000 L milk in bottles.
b) Compare the prices of 1 L milk in glass bottles and cartons in your local supermarket. Which packaging method is more sustainable?

Q1.11 The asymmetric hydrogenation of aryl ketones is an important step in the synthesis of many pharmaceutical intermediates. Blaser and co-workers showed that Ru complexes with Fe-cyclopentadienyl ‘sandwich complexes’ are good catalysts for this reaction [70]. Figure 1.29 shows the different substrates tested, along with the time, conversion, and substrate : catalyst ratio. Using this data, calculate the catalyst TON and TOF in each case.

Q1.12 Monosodium glutamate (MSG) is a common food additive with a ‘meaty’ flavour, used commercially for nearly 100 years. It was originally produced in Japan by extracting glutamic acid from wheat flour, and marketed under the trade

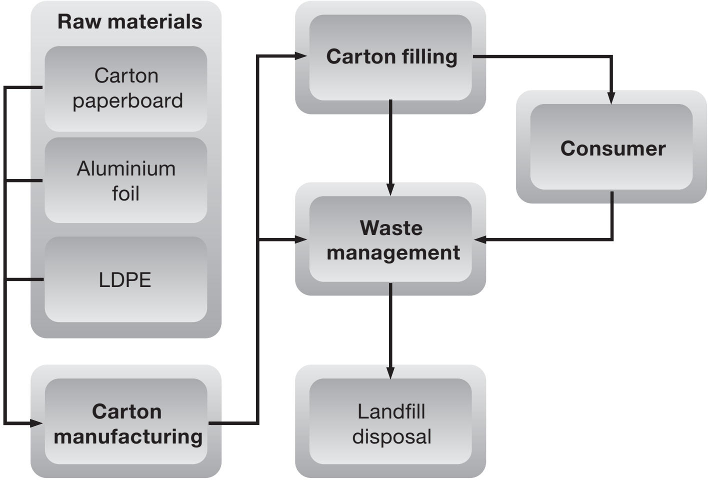
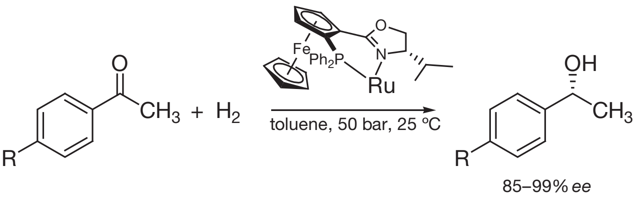


Figure 1.28 Life-cycle flow diagram for milk cartons.



R–	substrate : catalyst	time, h	conversion, %
Cl–	50 000	78	99
CH_3O–	20 000	1	92
F–	500	1	100

Figure 1.29 Catalytic hydrogenation of various aryl ketones and the corresponding kinetic data.

name Ajinomoto (*Aji no moto* means 'the origin of flavour' in Japanese) [71]. After WW II and the discovery of hydroformylation, the Ajinomoto company replaced the extraction with a continuous chemical processes, starting from acrylonitrile, CO and H_2 (see Figure 1.30).

a) Calculate the overall atom economy and E-factor for the glutamic acid synthesis.
b) Re-calculate these values, assuming that the ammonia by-product is recycled with 80% yield back to ammonium cyanide. Does this recycling of ammonia make a big change?
c) Today, glutamic acid is produced by large-scale batch fermentation in 200 000 L reactors, starting from sugar, oxygen and ammonia and using the bacteria *C. glutamicum*. This process gives ~ 60% conversion, with a final glutamic acid

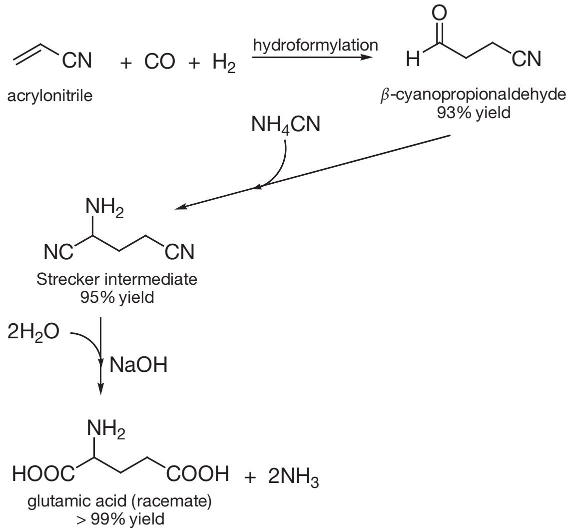


Figure 1.30 Three-step chemical synthesis of glutamic acid, starting from acrylonitrile.

concentration of ~100 g/L. List two possible disadvantages of the fermentation route compared to the chemical synthesis route.

Q1.13 Cyclohexanone oxime is a key intermediate in the synthesis of ε-caprolactam, which is one of the 50 most important bulk chemicals worldwide. Caprolactam is the monomer for making Nylon-6, and its annual demand is over 5 million tons. The classic production route, shown in Figure 1.31a, is still used today by BASF.

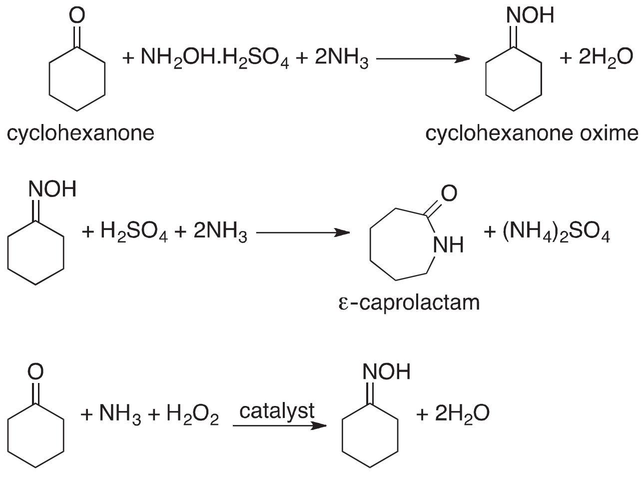


Figure 1.31 Production routes to ε-caprolactam: (a) the classic BASF route; (b) the Sumitomo/EniChem ammoximation process.

In 2009, Sumitomo and EniChem have introduced a new catalytic process for making cyclohexanone oxime in situ using NH_3 and an oxygen-containing reagent (Figure 1.31b). This approach, known as ammoximation, avoids the use of bulk amounts of hydroxyl amine. Moreover, the only theoretical by-product is water.

a) Calculate the E-factor and estimate the *Q*-value for making cyclohexanone oxime via each of these two routes.
b) Give three reasons why the Sumitomo/EniChem route is preferred over the BASF route.
c) Search the Internet for information on BASF, and give two reasons why the world's largest chemical company has decided to stay with the classic production route.

Q1.14 Phenol, C_6H_5OH, is one of the most important bulk chemicals. Today, it is produced almost exclusively via the partial oxidation of cumene (isopropylbenzene):

$$C_6H_5CH(CH_3)_2 + O_2 \rightarrow C_6H_5OH + (CH_3)_2CO$$

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:

$$C_6H_5CH_3 + 2O_2 \rightarrow C_6H_5OH + CO_2 + H_2O$$

a) Calculate the E-factor and estimate the size of the environmental quotient, for both processes.
b) List at least 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?

Q1.15 Jack Daniel's 'Old No. 7' whiskey is produced in Lynchburg, Tennessee, using the same recipe and methods since 1866. The production involves cooking and fermenting the corn mash, distillation, filtration over charcoal, and ageing in oak barrels. All these steps are done in-house, including making the filter charcoal from locally-grown sugar maple trees (unfortunately, Lynchburg is a 'dry county', so you will not be served any whiskey if you visit the distillery). Search The Internet for information and draw a life-cycle diagram for the whiskey-making process, indicating the on-site stages (also called the 'foreground system') and the outside resources and effects (the 'background system').

References

1 (2011) On-Scene Coordinator Report Deepwater Horizon Oil Spill. https://www.uscg.mil/foia/docs/dwh/fosc_dwh_report.pdf (accessed 05 August 2017)

2 Clark, J.H. (2006) Green chemistry: Today (and tomorrow). *Green Chem*, **8**, 17–21.

3 Anastas, P.T. and Warner, J. (2000) *Green Chemistry: Theory and Practice*, Oxford University Press.

4 Anastas, P.T. and Kirchhoff, M.M. (2002) Origins, current status, and future challenges of green chemistry. *Acc Chem. Res.*, **35**, 686–694.

5 Clark, J.H. and Smith, P. (2005) Basic principles of Green Chemistry. *Innov. Pharma. Technol.*, 94–97.

6 REACH (2006) REGULATION (EC) No 1907/2006. *Off. J. Eur. Union 3961*.

7 Sheldon, R.A. (1994) Consider the environmental quotient. *Chemtech*, **24**, 38–47.

8 Sheldon, R.A. (1997) Catalysis: The key to waste minimization. *J. Chem. Technol. Biotechnol.*, **68**, 381–388.

9 Trost, B.M. (1991) The atom economy – a search for synthetic efficiency. *Science*, **254**, 1471–1477.

10 Lutz, A.E., Larson, R.S., and Keller, J.O. (2002) Thermodynamic comparison of fuel cells to the Carnot cycle. *Int. J. Hydrog. Energy*, **27**, 1103–1111.

11 Wright, S.E. (2004) Comparison of the theoretical performance potential of fuel cells and heat engines. *Renew. Energy*, **29**, 179–195.

12 Selman, J.R. (2006) Molten-salt fuel cells – Technical and economic challenges. *J. Power Sources*, **160**, 852–857.

13 Chuang, S.S.C. (2005) Catalysis of solid oxide fuel cells. *Catalysis*, **18**, 186–198.

14 Carrette, L., Friedrich, K.A., and Stimming, U. (2000) Fuel cells: Principles, types, fuels, and applications. *Chem. Phys. Chem.*, **1**, 163–193.

15 Gröger, O., Gasteiger, H.A., and Suchsland, J.-P. (2015) Review – Electromobility: Batteries or fuel cells? *J. Electrochem. Soc.*, **162**, A2605–A2622.

16 Eisenberg, D., Stroek, W., Geels, N.J. *et al.* (2016) A simple synthesis of an N-doped carbon ORR catalyst: Hierarchical micro/meso/macro porosity and graphitic shells. *Chem. Eur. J.*, **22**, 501–505.

17 Buijink, J.K.F., van Vlaanderen, J.J.M., Crocker, M., and Niele, F.G.M. (2004) Propylene epoxidation over titanium-on-silica catalyst – the heart of the SMPO process. *Catal. Today*, **93–95**, 199–204.

18 Bassler, P., Goebbel, H.G., and Weidenbach, M. (2010) The new HPPO process for propylene oxide: From joint development to worldscale production. *Chem. Eng. Trans.*, **21**, 571–576.

19 Lankey, R.L. and Anastas, P.T. (2002) Life-cycle approaches for assessing green chemistry technologies. *Ind. Eng. Chem. Res.*, **41**, 4498–4502.

20 McDonough, W., Braungart, M., Anastas, P.T., and Zimmerman, J.B. (2003) Applying the principle of green engineering to cradle-to-cradle design. *Env. Sci. Technol.*, **37**, 434A–441A.

21 Saiz, S., Kennedy, C., Bass, B., and Pressnail, K. (2006) Comparative life cycle assessment of standard and green roofs. *Env. Sci. Technol.*, **40**, 4312–4316.

22 Bayer, P. and Finkel, M. (2006) Life cycle assessment of active and passive groundwater remediation technologies. *J. Contam. Hydrol.*, **83**, 171–199.

23 Tukker, A. (2002) Life-cycle assessment and the precautionary principle. *Env. Sci. Technol.*, **36**, 70A–75A.

24 Sheldon, R.A. (2000) Atom efficiency and catalysis in organic synthesis. *Pure Appl. Chem.*, **72**, 1233–1246.

25 Mizoroki, T., Mori, K., and Ozaki, A. (1971) Arylation of olefin with aryl iodide catalyzed by palladium. *Bull. Chem. Soc. Jpn.*, **44**, 581–581.

26 Heck, R.F. and Nolley, J.P. (1972) Palladium-catalyzed vinylic hydrogen substitution reactions with aryl, benzyl, and styryl halides. *J. Org. Chem.*, **37**, 2320–2322.

27 de Vries, J.G. (2001) The Heck reaction in the production of fine chemicals. *Can. J. Chem.*, **79**, 1086–1092.

28 Yu, W., Bian, F., Gao, Y. *et al.* (2006) Y-zeolite-catalyzed cyclizations of terpenols. *Adv. Synth. Catal.*, **348**, 59–62.

29 Clark, G.S. (1998) An aroma chemical profile. Geraniol. *Perfum Flav.*, **23**, 19.

30 Vlad, P.F. (1993) Superacidic cyclization of terpenoids. *Pure Appl. Chem.*, **65**, 1329–1336.

31 Castro, G.R. and Knubovets, T. (2003) Homogeneous biocatalysis in organic solvents and water-organic mixtures. *Crit. Rev. Biotechnol.*, **23**, 195–231.

32 Yamada, H. and Kobayashi, M. (1996) Nitrile hydratase and its application to industrial production of acrylamide. *Biosci. Biotechnol. Biochem.*, **60**, 1391–1400.

33 Niu, W., Draths, K.M., and Frost, J.W. (2002) Benzene-free synthesis of adipic acid. *Biotechnol. Prog.*, **18**, 201–211.

34 Ran, N.Q., Knop, D.R., Draths, K.M., and Frost, J.W. (2001) Benzene-free synthesis of hydroquinone. *J. Am. Chem. Soc.*, **123**, 10927–10934.

35 Mukhopadhyay, S., Rothenberg, G., Wiener, H., and Sasson, Y. (1999) Palladium-catalyzed aryl-aryl coupling in water using molecular hydrogen: Kinetics and process optimization of a solid-liquid-gas system. *Tetrahedron*, **55**, 14763–14768.

36 Van Helden, R., and Verberg, G. (1965) The oxidative coupling of aromatic compounds with palladium salts. *Recl. Trav. Chim. Pays-Bas*, **84**, 1263–1273.

37 Mukhopadhyay, S., Rothenberg, G., Lando, G. *et al.* (2001) Air oxidation of benzene to biphenyl – A dual catalytic approach. *Adv. Synth. Catal.*, **343**, 455–459.

38 Kweon, D., Jang, Y., and Kim, H. (2003) Organic electrochemical synthesis utilizing Mg electrodes. 1. Facile reductive coupling reactions of aromatic halides. *Bull. Kor. Chem. Soc.*, **24**, 1049–1050.

39 Durán Pachón, L., Elsevier, C.J., and Rothenberg, G. (2006) Electroreductive palladium-catalysed ullmann reactions in ionic liquids: Scope and mechanism. *Adv. Synth. Catal.*, **348**, 1705–1710.

40 Hendricks, J.D. and Mott, G.N. (1992) Method for producing ibuprofen. US5166418 A, filed Dec. 4, 1991 and issued Nov. 24, 1992.

41 Reay, D., Ramshaw, C., and Harvey, A. (2013) *Process Intensification*, 2nd edn, Elsevier.

42 Jandeleit, B., Schaefer, D.J., Powers, T.S. *et al.* (1999) Combinatorial materials science and catalysis. *Angew. Chem. Int. Ed.*, **38**, 2495–2532.

43 Satyanarayana, T. and Kagan, H.B. (2005) The multi-substrate screening of asymmetric catalysts. *Adv. Synth. Catal.*, **347**, 737–748.

44 Ruijter, E., Scheffelaar, R., and Orru, R.V.A. (2011) Multicomponent reaction design in the quest for molecular complexity and diversity. *Angew. Chem. Int. Ed.*, **50**, 6234–6246.

45 Frost, C.G. and Mutton, L. (2010) Heterogeneous catalytic synthesis using microreactor technology. *Green Chem.*, **12**, 1687–1703.

46 Hessel, V., Loeb, P., and Loewe, H. (2009) Industrial microreactor process development up to production. *Micro Process Eng.*, **3**, 183–247.

47 Luisi, R., Musio, B., and Degennaro, L. (2011) Microreactor technology as tool for the development of a sustainable synthetic chemistry. *Chim. E. Ind.*, **93**, 114–123.

48 de Bellefon, C., Tanchoux, N., Caravieilhes, S. *et al.* (2000) Microreactors for dynamic high throughput screening of fluid/liquid molecular catalysis. *Angew. Chem. Int. Ed.*, **39**, 3442–3445.

49 Mayer, R.W., Quandt, T., Schimmer, K. *et al.* (2006) Development of tools and methods for the high-throughput preparation of commercial heterogeneous catalysts, in *Studies in Surface Science and Catalysis*, vol 162, Elsevier, pp. 235–242.

50 Moates, F.C., Somani, M., Annamalai, J. *et al.* (1996) Infrared thermographic screening of combinatorial libraries of heterogeneous catalysts. *Ind. Eng. Chem. Res.*, **35**, 4801–4803.

51 Holzwarth, A. and Maier, W.F. (2000) Catalytic phenomena in combinatorial libraries of heterogeneous catalysts detection of activation and deactivation by

emissivity-corrected IR thermography. *Platin. Met. Rev.*, **44**, 16–21.

52 Kingsbury, J.S., Garber, S.B., Giftos, J.M. *et al.* (2001) Immobilization of olefin metathesis catalysts on monolithic sol–gel: Practical, efficient, and easily recyclable catalysts for organic and combinatorial synthesis. *Angew. Chem. Int. Ed.*, **40**, 4251–4256.

53 Hagen, J. (2015) *Industrial Catalysis: A Practical Approach*, Wiley-VCH, Weinheim.

54 Wachs, I.E. (2005) Recent conceptual advances in the catalysis science of mixed metal oxide catalytic materials. *Catal. Today*, **100**, 79–94.

55 Freund, H.J., Kuhlenbeck, H., Libuda, J. *et al.* (2001) Bridging the pressure and materials gaps between catalysis and surface science: Clean and modified oxide surfaces. *Top Catal*, **15** (2–4), 201–209.

56 Stoltze, P., and Nørskov, J.K. (1985) Bridging the 'pressure gap' between ultrahigh-vacuum surface physics and high-pressure catalysis. *Phys. Rev. Lett.*, **55** (22), 2502–2505.

57 Elsevier, C.J. (1994) NMR at elevated gas pressures and its application to homogeneous catalysis. *J. Mol. Catal.*, **92** (3), 285–297.

58 Bañares, M.A., and Wachs, I.E. (2002) Molecular structures of supported metal oxide catalysts under different environments. *J. Raman Spectr.*, **33**, 359–380.

59 Beale, A.M., Hofmann, J.P., Sankar, M. *et al.* (2014) Recent trends in operando and ln situ characterization: techniques for rational design of catalysts. *Heterog. Catal. Clean Technol.*, 365–411.

60 El-Roz, M., Kus, M., Cool, P., and Thibault-Starzyk, F. (2012) New operando IR technique to study the photocatalytic activity and selectivity of TiO_2 nanotubes in air purification: Influence of temperature, UV intensity, and VOC concentration. *J. Phys. Chem. C*, **116** (24), 13252–13263.

61 Hellman, A., Baerends, E.J., Biczysko, M. *et al.* (2006) Predicting catalysis: Understanding ammonia synthesis from first-principles calculations. *J. Phys. Chem. B*, **110**, 17719–17735.

62 Dimian, A.C. and Bildea, C.S. (2008) *Chemical Process Design: Computer-Aided Case Studies*, Wiley-VCH, Weinheim.

63 Klanner, C., Farrusseng, D., Baumes, L. *et al.* (2004) The development of descriptors for solids: Teaching 'catalytic intuition' to a computer. *Angew. Chem. Int. Ed.*, **43**, 5347–5349.

64 Burello, E. and Rothenberg, G. (2006) In silico design in homogeneous catalysis using descriptor modelling. *Int. J. Mol. Sci.*, **7**, 375–404.

65 Ras, E.-J. and Rothenberg, G. (2014) Heterogeneous catalyst discovery using 21st century tools: a tutorial. *RSC Adv.*, **4**, 5963–5974.

66 Maldonado, A.G. and Rothenberg, G. (2010) Predictive modeling in homogeneous catalysis: a tutorial. *Chem. Soc. Rev.*, **39**, 1891–1902.

67 Madaan, N., Shiju, N.R., and Rothenberg, G. (2016) Predicting the performance of oxidation catalysts using descriptor models. *Catal. Sci. Technol.*, **6**, 125–133.

68 Beerthuis, R., Rothenberg, G., and Shiju, N.R. (2015) Catalytic routes towards acrylic acid, adipic acid and ε-caprolactam starting from biorenewables. *Green Chem.*, **17**, 1341–1361.

69 Aucott, M., McLinden, M., and Winka, M. (2003) Release of mercury from broken fluorescent bulbs. *J. Air Waste Manag. Assoc.*, **53**, 143–151.

70 Naud, F., Malan, C., Spindler, F. *et al.* (2006) Ru-(phosphine-oxazoline) complexes as effective, industrially viable catalysts for the enantioselective hydrogenation of aryl ketones. *Adv. Synth. Catal.*, **348**, 47–50.

71 Ault, A. (2004) The monosodium glutamate story: The commercial production of MSG and other amino acids. *J. Chem. Educ.*, **81**, 347–355.

Further Reading

There are several books available in the field of catalysis. Here are the important ones, with a short synopsis of my thoughts about each book. All the books listed here were in print and commercially available in April 2017.

- *Sustainable Energy Without the Hot Air*; David McKay, UIT Cambridge: 2009, 366 pp., ISBN 978-0-9544529-3-3 (paperback).
  This book is mandatory reading for all students in my group. It's basically the clearest and most honest introduction to the subject of sustainable energy. It is also an excellent example for students who wish to learn how to present complex subjects in a simple and accessible way.
- *Chemical Technology: An Integral Textbook;* Andreas Jess and Peter Wasserscheid, Wiley-VCH Verlag GmbH, 2013, 888 pp., ISBN 978-3-527-30446-2.
  A heavy volume in a large format, this excellent book bridges the fields of chemistry and chemical engineering. The authors explain clearly the key principles that govern industrial processes, with many relevant examples. They also discuss resource management, sustainability, and economic implications, all from the chemical process perspective.
- *Homogeneous Catalysis;* Piet van Leeuwen, Kluwer Academic: 2004, 407 pp., ISBN 978-1402031762.
  This advanced textbook gives a comprehensive overview on metal-ligand complexes, especially phosphorous ligands. The subjects are clearly presented, with many useful references. The author explains the elementary steps in homogeneous catalysis, as well as the catalytic process aspects of hydroformylation, hydrogenation, and other Rh- and Pd-catalysed reactions.
- *The Organometallic Chemistry of the Transition Metals;* Robert Crabtree, John Wiley & Sons: 2014 (6th edn), 520 pp., ISBN 978-1-118-13807-6.
  This is the best graduate-level textbook in organometallic chemistry. It is clear and well written, covering all of the fundamental reactions of organometallic complexes, plus some applications. Each chapter contains also exercises and up-to-date references.
- *Principles and Practice of Heterogeneous Catalysis;* J.M. Thomas and W.J. Thomas, Wiley-VCH Verlag GmbH: 2014 (2nd edn), 768 pp., ISBN 978-3-527-31458-4.
  A comprehensive textbook on classic heterogeneous catalysis that covers catalyst preparation and characterisation methods. It also includes a chapter on solid state chemistry and surface chemistry, and a chapter on process engineering.
- *Concepts of Modern Catalysis and Kinetics;* Ib Chokendorff and Hans Niemantsverdriet, Wiley-VCH Verlag GmbH: 2007 (2nd edn), 477 pp., ISBN 978-3-527-31672-4.
  This specialised book deals only with gas/solid heterogeneous catalysis. It contains excellent technical explanations and has a strong mathematical and phys-

ical approach, which makes for rather heavy reading. It covers many surface reaction mechanisms and catalyst characterisation techniques.

- *Spectroscopy in Catalysis;* Hans Niemantsverdriet, Wiley-VCH Verlag GmbH: 2007 (3rd edn), 344 pp., ISBN 978-3-527-31651-9.
  This is an excellent book on solid catalyst characterisation. It is highly specialised, and aimed at advanced graduate students and researchers. It covers only classic gas/solid heterogeneous catalysis, but if you want to specialise in characterising solid catalysts, this is the book for you.
- *Introduction to Enzyme and Coenzyme Chemistry;* Timothy Bugg, John Wiley & Sons: 2012 (3rd edn), 290 pp., ISBN 978-1-119-99595-1 (paperback).
  This is a superb undergraduate textbook about enzymes. It is well written and illustrated, with interesting examples and well-thought-out exercises.