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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 specialized subjects in catalysis.

1.1

Green Chemistry and Sustainable Development

In the 20th century, chemistry changed our lives. It has shaped our modern technological society by supplying us with energy, medicines, crop protection, foodstuffs, and new materials worldwide. Unfortunately, even though chemistry is the science with the highest impact on our everyday lives, chemicals and the chemical industry have a poor public image. This is partly due to misconceptions and media scares, but there is also a valid reason: the traditional chemical industry, certainly until the 1980s, was a hazardous and polluting one. It generated stoichiometric amounts of waste, causing much pollution of both air and water. A number of major chemical accidents have reinforced this image in recent decades [1,2]. The most infamous are the Bhopal catastrophe in 1984, where 3000 people were killed and more than 40 000 injured [1], and the grounding of the *Exxon Valdez* [3] in the Prince William Sound in Alaska in 1989, that still affects the marine ecosystem nearly 20 years later [4].

Apart from the immediate health and environmental hazards, there is also the problem of resource management. The chemical industry during the past 200 years drew heavily on resources. Today, the escalating costs of petrochemicals, and the increasing energy and raw material demands in Asia's emerging markets, are forcing a change. Two popular terms associated with this change are **sustainability**, or

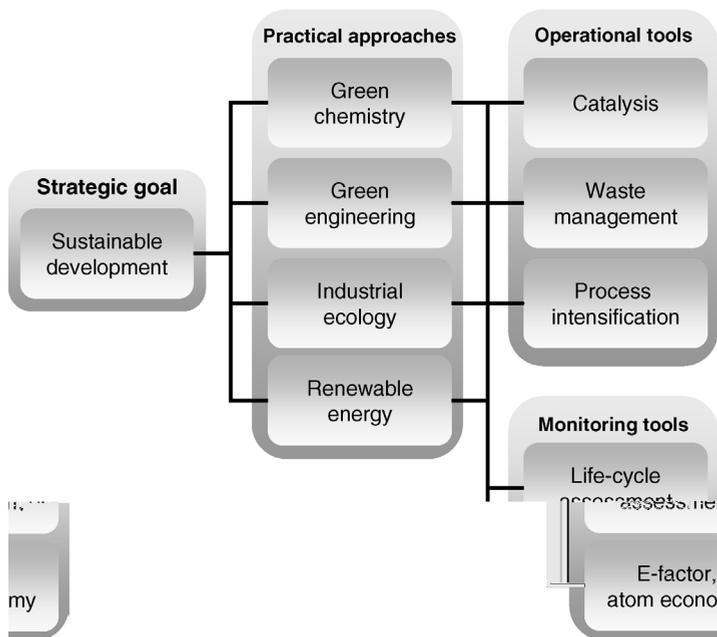


Figure 1.1 The strategic goal of sustainable development relies on practical approaches such as green chemistry, industrial ecology, and green engineering. These approaches use various operational tools (e.g., catalysis), and monitoring tools (e.g., life-cycle assessment).

sustainable 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) along 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 [5]. Green chemistry deals with designing chemical products and processes that generate and use fewer (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 12 principles of green chemistry [6,7] (I have rephrased these in the active voice, in keeping with the spirit of this book):

- Prevent waste instead of treating it.
- Design atom-efficient synthetic methods.
- Choose synthetic routes using nontoxic compounds where possible.
- Design new products that preserve functionality while reducing toxicity.
- Minimize the use of auxiliary reagents and solvents.
- Design processes with minimal energy requirements.
- Preferably use renewable raw materials.
- Avoid unnecessary derivatization.
- Replace stoichiometric reagents with catalytic cycles.
- Design new products with biodegradable capabilities.
- Develop real-time and on-line process analysis and monitoring methods.
- Choose feedstocks and design processes that minimize the chance of accidents.

Green chemistry offers an alternative to the traditional environmental protection agenda, mainly because it deals with avoiding hazards, rather than treating and solving exposure problems. Three forces drive the green chemistry initiative [8]: Government legislation, societal pressure, and economic benefit (Figure 1.2). The new 800-page EU Directive on the registration, evaluation, and assessment of chemicals (**REACH**) [9] is changing the chemical industry across Europe. Similar regulations are expected worldwide in the coming decade. But legislation is just one of the drivers. Societal pressure is also important: the public favors industrial green chemistry initiatives, as they lead to safer and eco-friendly products and processes.

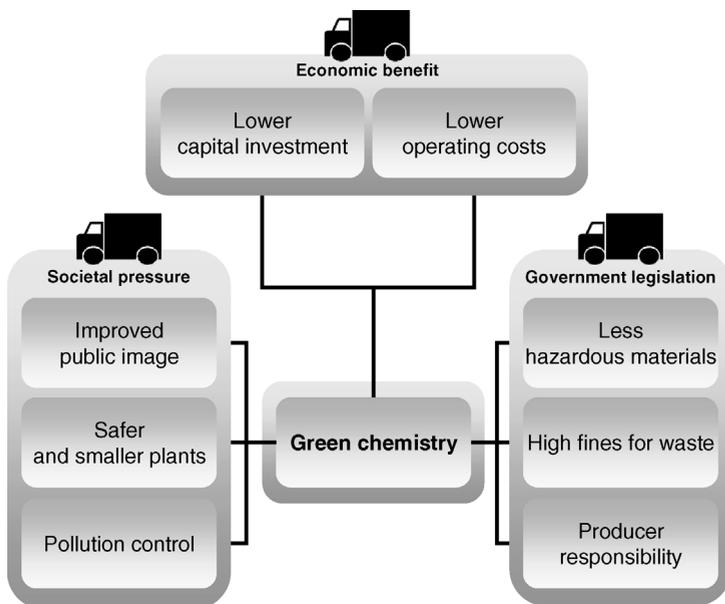


Figure 1.2 Green chemistry initiatives are driven by government legislation, societal pressure, and economic benefits.

This creates goodwill for the company, something that is difficult to quantify but undoubtedly important.

The third driver is *bona fide* economic benefit. Applying the principles of green chemistry decreases both capital investment and operating costs. If you use less (or no) solvent, and replace stoichiometric reagents with catalytic cycles, your reactor space–time yields go up. 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. Replacing toxic reagents with benign ones saves on safety costs during transportation and storage. Thus, more and more companies are adopting green chemistry because it simply improves their bottom-line performance.

1.1.2

Quantifying Environmental Impact: Efficiency, *E*-factors, and Atom Economy

Everyone agrees that green chemistry and “green manufacture” are good things. The websites and pamphlets of all the major chemical companies emphasize 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?

First, let us define 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 reactant conversion is the 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 \times 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, there are specific rulers for measuring the “greenness” or “ecofriendliness” of processes and products. One such measure is the ***E*-factor**, introduced by Roger Sheldon in 1994 [10,11]. A reaction’s *E*-factor is the quotient $\text{kg}_{\text{waste}}/\text{kg}_{\text{product}}$ (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 $(\text{NH}_4)_2\text{SO}_4$), 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 are used to thinking of such chemicals as pollutants. In fact, *E*-factors increase substantially when going from bulk chemicals to fine chemicals and specialties. This is partly because fine-chemicals production often involves multistep syntheses, and partly because stoichiometric reagents are more often used for producing fine chemicals and pharmaceuticals.

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

Industrial sector	Production/ton y ⁻¹	<i>E</i> -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

The concept of **atom economy**, introduced by Barry Trost in 1991, is similar to that of the *E*-factor [12]. 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 to get a quantitative result.

As an example, let us consider the stoichiometric oxidation of diphenylmethanol to benzophenone, one of the most commonly used photosensitizers 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 diphenylmethanol react with two equivalents of chromium trioxide and three equivalents of sulfuric 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 which goes to completion, so one obtains 100% yield of the product, benzophenone. If no other (organic) by-product is obtained, the product selectivity is also 100%. This is all well and good, and indeed for many years this has been the way that chemical processes were evaluated, both in academia and in the (fine-) chemical industry.

However, examining the *E*-factor for this reaction, we see that for every three moles of benzophenone we produce one mole of chromium sulfate and six moles of water. The molecular weight of benzophenone is 182.2 g mol⁻¹, so every kilogram of benzophenone contains 5.48 moles of benzophenone. This means that for every kilogram of benzophenone we generate 5.48/3 = 1.83 moles (or 0.717 kg) of

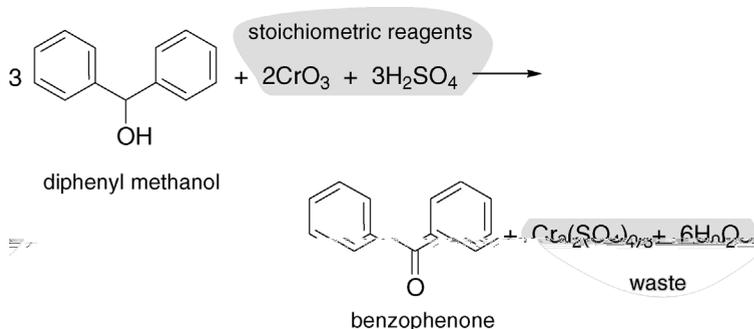


Figure 1.3 Oxidation of diphenylmethanol to benzophenone using chromium trioxide and sulfuric acid.

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
Nonmetal salts	medium	persistent materials	high

chromium sulfate and 10.98 moles (or 0.197 kg) of water. The overall E -factor is therefore given by Eq. (1.1).

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

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

The E -factor and atom economy can be used for comparing reaction alternatives, but we should remember that there are different types of “waste”. The reaction example above has two by-products: chromium sulfate and water. Obviously, water is “good waste”, while chromium sulfate is “bad waste”, so evaluating a synthetic protocol on the basis of only the amount of waste produced is insufficient. To solve this problem, Sheldon put forward the concept of the **environmental quotient** (EQ) [10]. By multiplying the E -factor by Q , an arbitrarily assigned hazard quotient, this measure takes both the amount and the nature of the waste into account. 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 EQ 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 hazards and consequences of acquiring and transporting the raw materials. Additionally, it should factor in the overall energy demand. A reaction can have 100% atom economy, yet 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

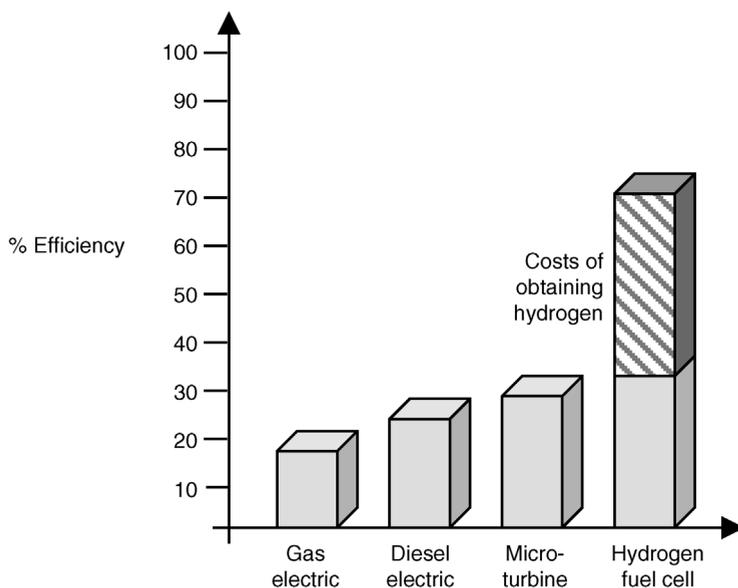


Figure 1.4 Relative efficiency of various engine types. The column on the right also shows the estimated “hidden costs” of obtaining hydrogen in the case of fuel cells.

and/or transporting these highly toxic reagents is problematic. To understand this better, let us look at two examples: hydrogen-powered fuel cells and oxidation of propene to propene oxide.

Hydrogen-powered fuel cells are a “hot topic.” In principle, such fuel cells can provide us with energy, while at the same time reducing emissions. They are highly efficient and, because they burn hydrogen, the only by-product is water, or “good waste.” Moreover, because fuel cells require high-purity hydrogen, the resulting water waste is also pure [13]. Figure 1.4 compares the efficiency of a hydrogen-powered fuel cell with those of various gas-powered and diesel-powered energy sources. Adding this high efficiency to the environmental benefits (no emission of CO_2 , NO_x , SO_x , or hydrocarbon particulates), it seems that fuel cells are the ideal source of power. But there is a catch: Where does the hydrogen come from? There is no natural source of pure hydrogen on Earth. It must be manufactured from fossil fuels, biomass, or water. This manufacture costs time, capital, and energy. Then the hydrogen must be transported and stored. This also requires dedicated infrastructure. All these factors must be taken into account when evaluating the overall efficiency of fuel cells. Further, hydrogen manufacture generates waste. This waste should also be taken into account when calculating the overall environmental impact of fuel cells compared to conventional energy sources.

Propene oxide is an important bulk chemical, used for making propylene glycol (**propane-1,2-diol**), polyethers, glycerol (**propane-1,2,3-triol**), and other products. Currently there is no catalytic process for oxidizing propene directly to propene oxide using molecular oxygen. The classic manufacturing route goes via chlorohydrin

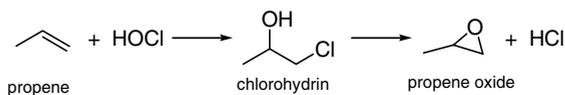


Figure 1.5 Traditional route to propene oxide. Note how the choice of HOCl as reagent adds another step and another reagent (NaOH) to the process.

(Figure 1.5). The HCl by-product is neutralized with caustic soda or lime. Although this process is wasteful and polluting, it still accounts for 40% of the global manufacture of propene oxide.

There are several alternatives to the polluting chlorohydrin route. One is the styrene monomer propene oxide (SMPO) process, used by Shell and Lyondell (Figure 1.6a) [14]. It is less polluting, but couples the epoxide production to that of styrene, a huge-volume product. Thus, this route depends heavily on the styrene market price. Another alternative, the ARCO/Oxirane process, uses a molybdenum

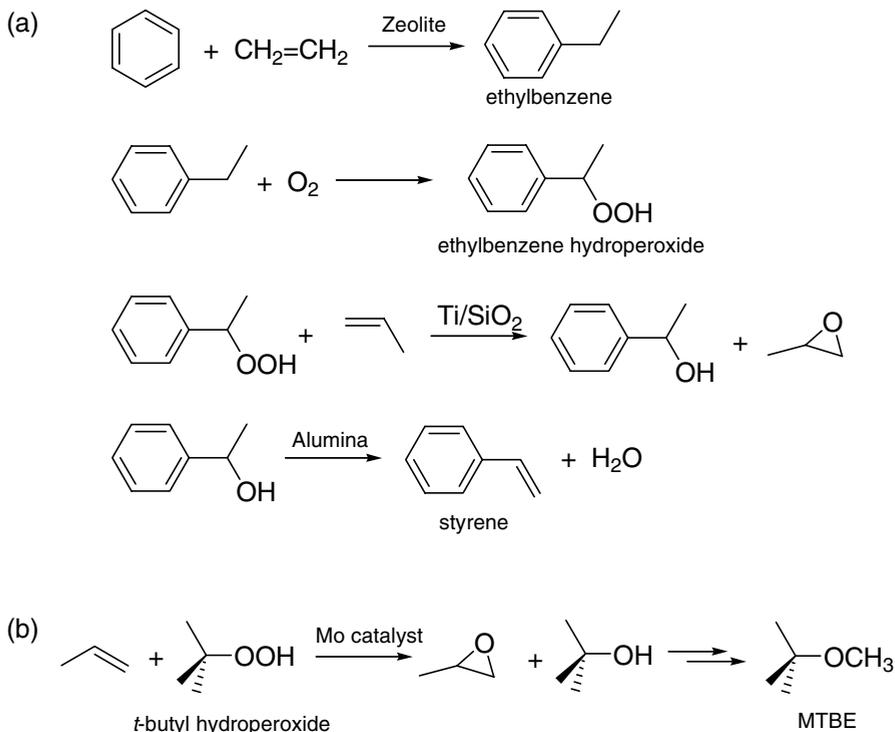


Figure 1.6 a SMPO process; b the catalytic oxidation of propene with *tert*-butyl hydroperoxide in the presence of a molybdenum-oxo complex.

catalyst, and couples the epoxidation of propene to isobutene oxidation (Figure 1.6b). The *t*-butanol that this generates as a by-product is then used as a gasoline additive and a starting material for making methyl *t*-butyl ether (MTBE). The disadvantages here are that Mo is a toxic heavy metal, and MTBE use is being phased out in the US and Europe.

In theory, one can also use N_2O as an epoxidation agent, with supported iron catalysts or homogeneous polyoxometallate Mn/Zn catalysts [15]. N_2O already contains an activated oxygen atom, and the only by-product is harmless molecular nitrogen. Furthermore, N_2O itself is a greenhouse gas, so reacting it with propene to give a valuable product seems like an ideal solution. However, the fact that N_2O is a greenhouse gas does not mean that it is generally available. This solution, like the hydrogen process above, depends on raw material availability.

1.1.4

Product and Process Life-Cycle Assessment (LCA)

The examples above show that we must take into account the overall environmental impact of chemical processes for an unbiased comparison. 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 overall view. This includes raw-material extraction and acquisition, chemical reactions, processing, manufacture, packaging, transportation, distribution, consumer use, and end-of-life management [16]. LCA has four main stages: (1) defining the assessment scope and boundaries; (2) quantifying energy and materials flows (inventory analysis); (3) impact analysis, determining the effects on the environment and human health; and (4) improvement analysis, which can include methods such as green chemistry and green engineering, and environmental design [17]. Figure 1.7 shows the four stages in life-cycle assessment. Note that LCA is not limited to chemistry. It is applied in diverse areas, from assessment of roof types [18] to groundwater remediation technologies [19].

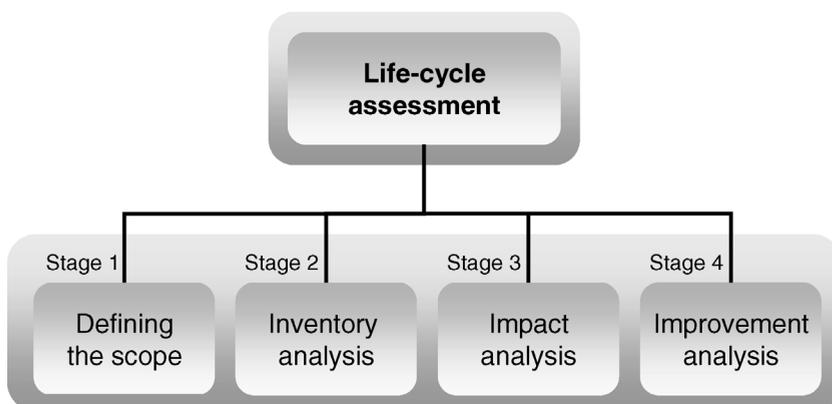


Figure 1.7 The four stages in life-cycle assessment.

The first step in LCA is defining the scope and goal of the study [20]. In this stage, functional units are defined, so that products can be compared on the basis of the functions they fulfill, rather than by their amount. For example, a milk bottle that is collected, cleaned, and reused 20 times fulfills the same function as 20 disposable milk cartons. Defining the scope of the study and its 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 totaled for all the processes. Such inventory tables can contain over 100 entries, e.g., the total emission of lead, SO_2 , or hydrocarbon particulates. The third step is impact analysis. First, impact categories are classified. These usually pertain to common environmental threats, such as global warming, 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. This is often the most problematic step, because quantifying the environmental impact of a process is complex and subjective. Finally, the results are interpreted and an improvement analysis tries to pinpoint the process elements that can be changed by using a different technology or 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 minimization. Moreover, we learned that a sustainable process is one that optimizes 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 [21].

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 opens 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, which 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, organometallic complexes, organic and inorganic polymers, all the way to enzymes. To simplify things, we divide catalysis into three



Figure 1.8 Different types of catalysts.

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 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 definitions, however, vary slightly among the three catalysis fields. In homogeneous catalysis, the TON is the number of cycles that a catalyst can run through before it deactivates, i.e., the number of **A** molecules that one molecule of catalyst can convert (or “turn over”) into **B** molecules. The TOF is simply TON/time, i.e., the number of **A** molecules that one molecule of catalyst can convert into **B** molecules in one second, minute, or hour. In heterogeneous catalysis, TON and TOF are often defined per active site, or per gram catalyst. This is because one does not 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.

- **CAUTION!** Chemists can have different meanings for TON and TOF. To minimize misunderstandings, 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 fewer resources and generating less waste. The catalyst opens a selective route to the desired product. There are various kinds of product selectivity. Chemical selectivity, or **chemoselectivity**, denotes a situation where two different chemical reactions can occur, giving two different products. Similarly, **regioselectivity** occurs when the same chemical reaction in different regions of the molecule leads to different products. When a reaction gives two (or more) diastereomers, the selectivity to each of these is called **diastereoselectivity**. In the special case when two products are mirror-image diastereomers, or enantiomers, we talk about **enantioselectivity**. Figure 1.9 shows examples of the various product selectivity types.

1.2.1

Homogeneous Catalysis, Heterogeneous Catalysis, and Biocatalysis

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 catalyzed by hydroxide (OH^-) ions. This is an important process for making fatty acid methyl esters which are then used as biodiesel.

Notice that in Figure 1.10 I have written the “ OH^- ” above the reaction arrow, rather than on the same line as the reactants and products. This notation reminds us that the catalyst, 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 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 catalyzes many consecutive cycles.

The easiest way to illustrate this is using an example. Figure 1.11a shows the classic catalytic cycle for the Pd-catalyzed cross-coupling between an alkene and an aryl halide. This reaction, discovered independently by Heck and Mizoroki in 1968, is known as the Heck reaction [22]. Since its discovery it has become ubiquitous in organic chemistry, and is used today in several fine-chemical processes [23]. 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 catalyze the coupling reaction of two new substrate molecules. Figure 1.11b shows

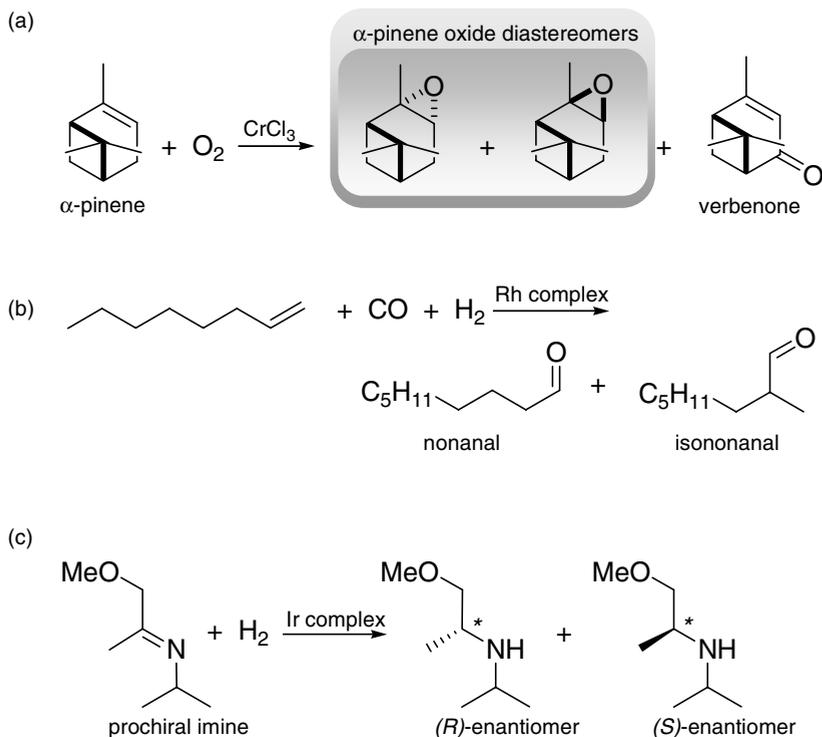


Figure 1.9 Examples of a chemoselectivity and diastereoselectivity in the oxidation of α -pinene, b regioselectivity in the hydroformylation of 1-octene, and c enantioselectivity in the hydrogenation of the prochiral isopropyl(2-methoxyisopropyl) imine (* indicates the asymmetric carbon atoms).

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 stabilized by a **ligand**. The ligand is usually an organic molecule that attaches to the metal atom. By changing this ligand, one can change the catalyst's properties.

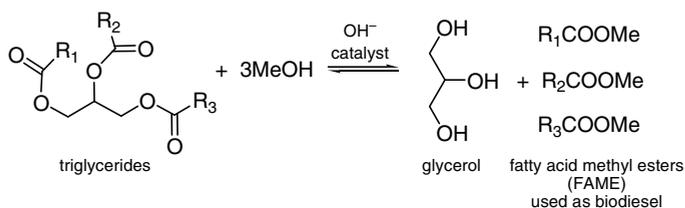


Figure 1.10 Base-catalyzed transesterification of triglycerides.

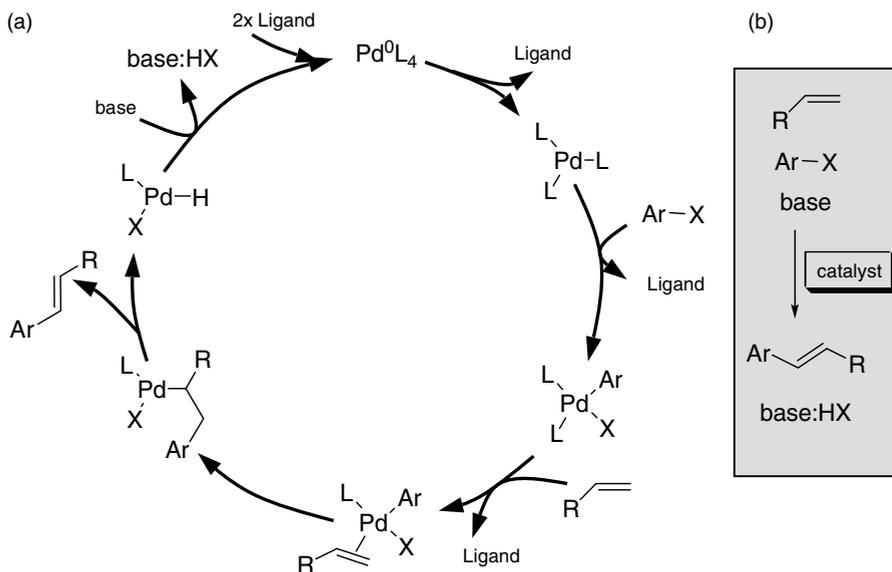


Figure 1.11 Proposed catalytic cycle for the Heck reaction, showing a the various catalytic intermediates and b the “black box” version. Some Pd catalysts exhibit TONs and TOFs of over 100 000 in this reaction.

Selecting the right metal and the right ligand can improve the catalyst’s activity, selectivity, and stability. In some cases, it also allows the use of renewable feedstocks and reagents, an important aspect of green chemistry. One such example is the alternating copolymerization of limonene oxide and CO₂, catalyzed by a β-diiminato–zinc acetate complex (Figure 1.12). CO₂ is an important raw material – it is abundant,

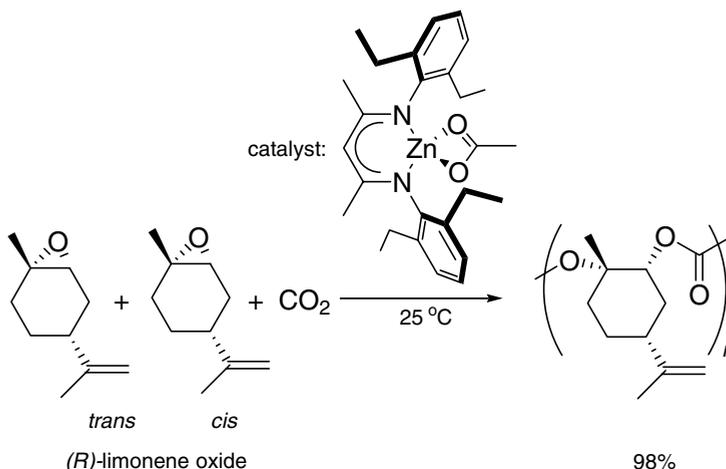


Figure 1.12 Copolymerization of limonene oxide and CO₂ in the presence of β-diiminato–zinc acetate complex.

inexpensive, and nontoxic. Likewise, limonene oxide is easily obtained from limonene, which is the most common terpene in citrus peel oil and has a world production of $>150 \times 10^3$ tpa (tons per annum). Its abundance, low cost, and structural similarity to cyclohexene oxide make (*R*)-limonene oxide an excellent choice as a biorenewable epoxide monomer for copolymerization with CO_2 . By optimizing the steric and electronic parameters of the ligand, Byrne et al. succeeded in copolymerizing limonene oxide and CO_2 , obtaining polymers with a mass of 9.3 kg mol^{-1} and 98% *trans* configuration [24].

Heterogeneous catalysis covers all the cases where the catalyst and the substrate are in different phases. However, when chemists speak about heterogeneous catalysis, they usually refer to a system where the catalyst is a solid and the reactants are (most often) 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 origins: most “classic” heterogeneous catalysis was developed in the petrochemicals and bulk-chemicals industry. Due to reactivity and process size considerations, these industries favor continuous processes at high temperatures. This meant that working with solid catalysts and gaseous reactants was often the best, and often 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, while the catalyst changes 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 catalyst (Ni, Pd, or Pt). The catalytic cycle (Figure 1.13) involves several steps. First, a propene molecule is adsorbed on the catalyst surface. The carbon–carbon π -bond breaks and bonds with the surface are created. Meanwhile, H_2 molecules are also adsorbed 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 at the other C atom also, 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 platinum 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 catalyzes 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(propylene) and other polymers.

Olefin hydrogenation by heterogeneous catalysis has an interesting history. 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 Ni catalyst. This

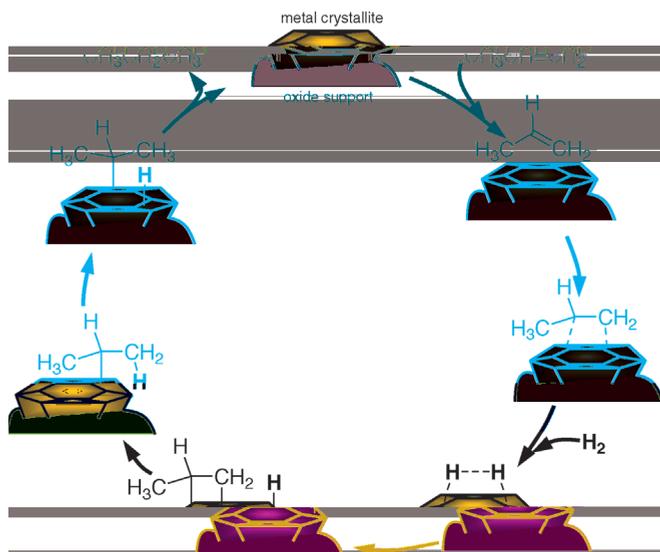


Figure 1.13 Hydrogenation of propene to propane in the presence of a supported metal catalyst (the reverse arrows are omitted for clarity).

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. In 2007, the company is worth over €37 billion (\$50 billion).

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, aluminum, 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 catalyze liquid/solid reactions, as in the example of geraniol cyclization [25] by zeolite Y (Figure 1.14a–b; see Chapter 4 for a discussion of zeolite types). Geraniol and its corresponding cyclic derivatives are important intermediates in the flavor and fragrance industry [26]. The suggested reaction mechanism involves both carbocation formation, via protonation of the double bond at a Brønsted acid site [27], and 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 catalyzes the reactions in living cells. Enzymes are extremely efficient catalysts. An enzyme typically completes 1000 catalytic cycles in one second. Compared to this, conventional homogeneous and heterogeneous catalysts are slow and inefficient (100–10 000 cycles per hour). Speed, however, is not the only advantage: enzymes specialize in converting one specific reactant into another

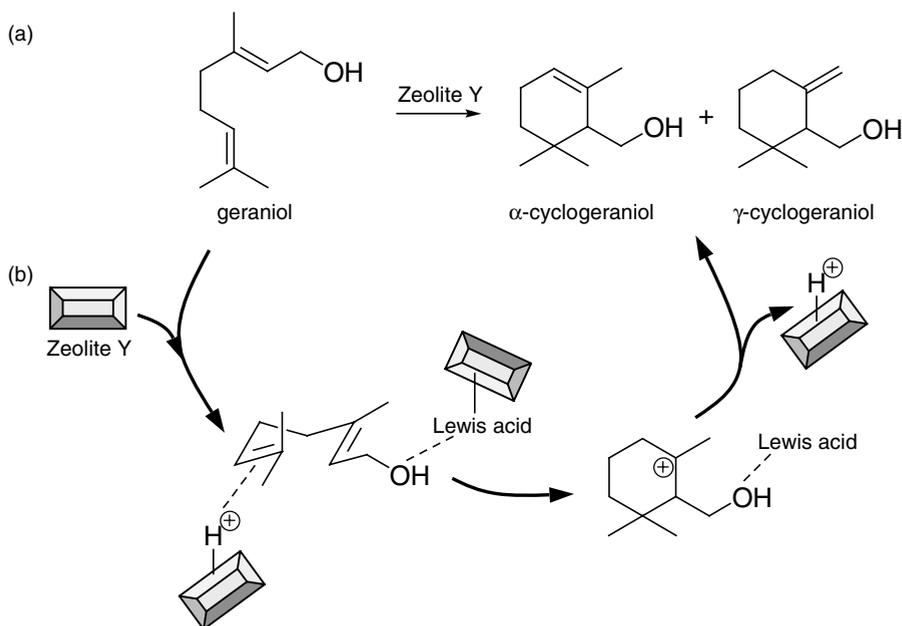


Figure 1.14 a Equation for the cyclization of geraniol, and b possible mechanism in the presence of zeolite Y, a solid acid catalyst that has both Brønsted and Lewis acid sites.

specific product. This specificity even includes chiral centres, so an enzyme will catalyze the reaction of one substrate enantiomer, but not of the other. Such enantiospecific reactions are extremely important in the pharmaceutical and food industries, because often only one enantiomer has the desired activity. This is the case for many drugs, food additives, flavorings, and fragrances.

Further advantages of biocatalysis over “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 which catalyze reactions in water and even in organic solvents [28]. Despite these advantages, the activity and stability of most wild-type enzymes do not meet the demands of industrial processes. Fortunately, modern protein engineering methods can be used to change enzyme properties and optimize desired characteristics. In Chapter 5 we will outline these optimization 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 manufacture. One reason for this is that biocatalysts give sustainable alternatives to chemical manufacture, and not just for making chiral products. The synthesis of acrylamide via an enzyme-catalyzed water addition to acrylonitrile (2-propenenitrile) is a classic example (Figure 1.15). It uses the *Rhodococcus* enzyme nitrile hydratase. Commercialized in 1985 by Nitto Chemicals in

Japan, this process replaced an acid-catalyzed process, and also avoided the acrylic acid by-product [29]. Biocatalytic acrylamide processes are now running at 50 000 tpa worldwide.

Recent advances in genetic engineering are bringing forth new and exciting possibilities for biocatalysis. One example is the synthesis of important bulk industrial chemicals from renewable feedstocks. Adipic acid, for example, is a key monomer for making nylon 6.6. The world production of adipic acid is 2.2 million tons per annum. Practically all of this is produced from benzene, via cyclohexane and cyclohexanol/hexanone (Figure 1.16, left). Although the process itself is quite efficient, it has three main drawbacks: First, it relies on petroleum, a nonrenewable fossil fuel, 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.

In 2002, Frost and co-workers successfully constructed a mutated *Escherichia coli* bacterium that can convert D-glucose to *cis,cis*-muconic acid, which is then easily hydrogenated to adipic acid (Figure 1.16, right) [30]. 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 (€230, or \$300, per ton) and renewable raw material. Switching from benzene to glucose gives a process that is inherently safer and more sustainable. A similar approach was used to convert D-glucose to hydroquinone, an important intermediate in the synthesis of antioxidants and polymerization inhibitors [31].

Will such biocatalytic processes really replace the traditional chemical manufacturing routes? Yes, but it will take time. Although petroleum prices are increasing, 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-chemical industry is very conservative, and enzymes are

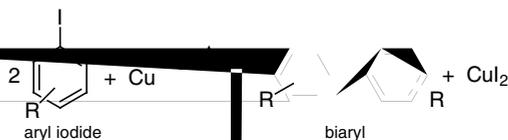


Figure 1.17 The classic Ullmann reaction for coupling aryl iodides by reaction with copper metal at high temperatures.

which are key building blocks for various agrochemical and pharmaceutical products. Although the Ullmann reaction is over 100 years old, it is still used in industry today. The problem is that it consumes stoichiometric copper 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) come out as chemical waste.

Using the principles of green chemistry, let us 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, ultimately generating two $\text{C}_6\text{H}_5\cdot$ radicals that couple to give biphenyl. The copper metal reduces the iodine atoms, giving Cu^{2+} and 2I^- . The same stoichiometric reaction can be brought about by using palladium instead of copper (Figure 1.18a). This does not look so useful, because Pd is much more expensive than Cu. However, the advantage of Pd is that it is easily reduced back from Pd^{2+} to Pd^0 . This reduction can happen, for example, using

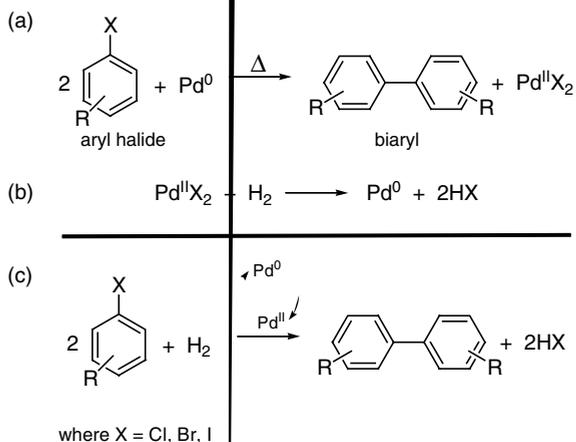


Figure 1.18 Combination of two stoichiometric reactions: a the reductive coupling of haloaromatics with Pd^0 and b the reduction of Pd^{II} with hydrogen gas creates c a catalytic cycle where the Pd catalyst shuttles between the Pd^0 and Pd^{II} species.

hydrogen gas [32], giving Pd^0 and 2H^+ (Figure 1.18b). If we then combine these two reactions, we get the catalytic cycle shown in (Figure 1.18c). This is a very simple representation of the catalytic cycle, but it demonstrates 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 . Usefully, this catalytic cycle also works with bromo- and chloroarenes, improving the *E*-factor of the reaction and the atom economy.

Can we improve the atom economy even further, and avoid using any halide? The “greenest solution” for making biphenyl, $\text{C}_{12}\text{H}_{10}$, is to use 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 (Figure 1.19a). 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, obtained by, e.g., oxidative coupling of two benzene molecules to form biphenyl (Figure 1.19b). This reaction can be effected by using stoichiometric amounts of PdCl_2 in acetic acid as solvent [33], or by using a Pd catalyst and regenerating it with air as the oxidant, giving water as the only by-product (an additional homogeneous $\text{Co}(\text{OAc})_2$ catalyst is used for activating the oxygen in solution) [34]. 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 $\sim 80\%$.

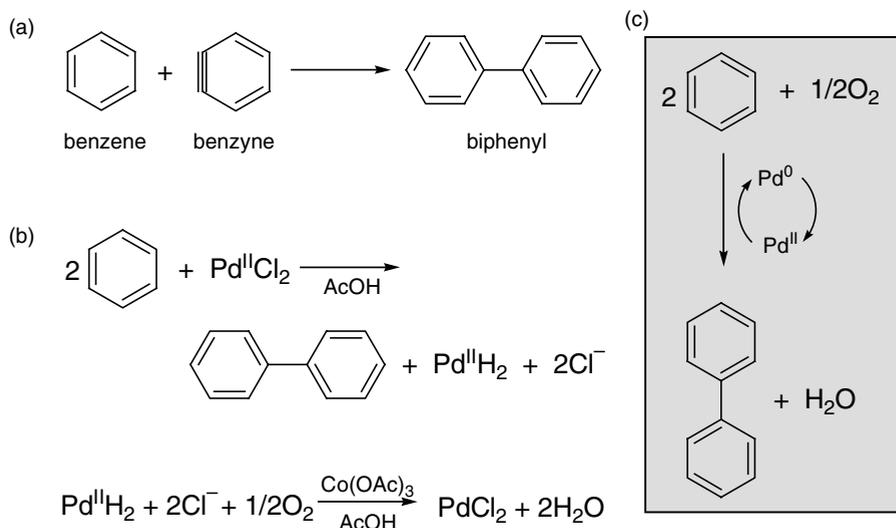


Figure 1.19 a Theoretical waste-free route to biphenyl starting from benzene and benzyne; b oxidative coupling of two benzene molecules with stoichiometric $\text{Pd}^{\text{II}}\text{Cl}_2$ and regeneration of Pd^{II} with molecular oxygen; c the resulting catalytic cycle for oxidative coupling.

Another interesting alternative combines catalysis and electrochemistry [35]. In the reductive coupling cycle of two bromobenzene molecules to biphenyl, the Pd catalyst provides just two electrons. This reaction can be performed in an electrochemical cell, where the electrons are supplied from an outside source [36]. 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 tons per year 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 Nurofen.

Ibuprofen, like many other drugs, is a fairly 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 stoichiometric reagents (Figure 1.20a–b). 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. For example, note the addition of hydroxylamine, NH_2OH , in step 4: This group is used to create the imine **5**, which is then converted to the cyano derivative **6** and finally oxidized to give the carboxylic acid product **7**. Effectively, what happens is that the hydroxylamine is first added to the molecule and then removed. This type of “roundabout synthesis” is precisely what green chemistry tries to avoid.

When the patent rights on ibuprofen expired, Boots teamed with the Hoechst Celanese Corporation and formed the BHC consortium, developing a new process for making ibuprofen. They started from the same raw materials, but replaced the stoichiometric six-step process with a three-step catalytic one (Figure 1.20b). 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 utilization 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 has also eliminated the large volumes of aqueous salt waste associated with ibuprofen manufacture.

The BHC ibuprofen process is an innovative, efficient technology that has revolutionized bulk pharmaceutical manufacture. 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

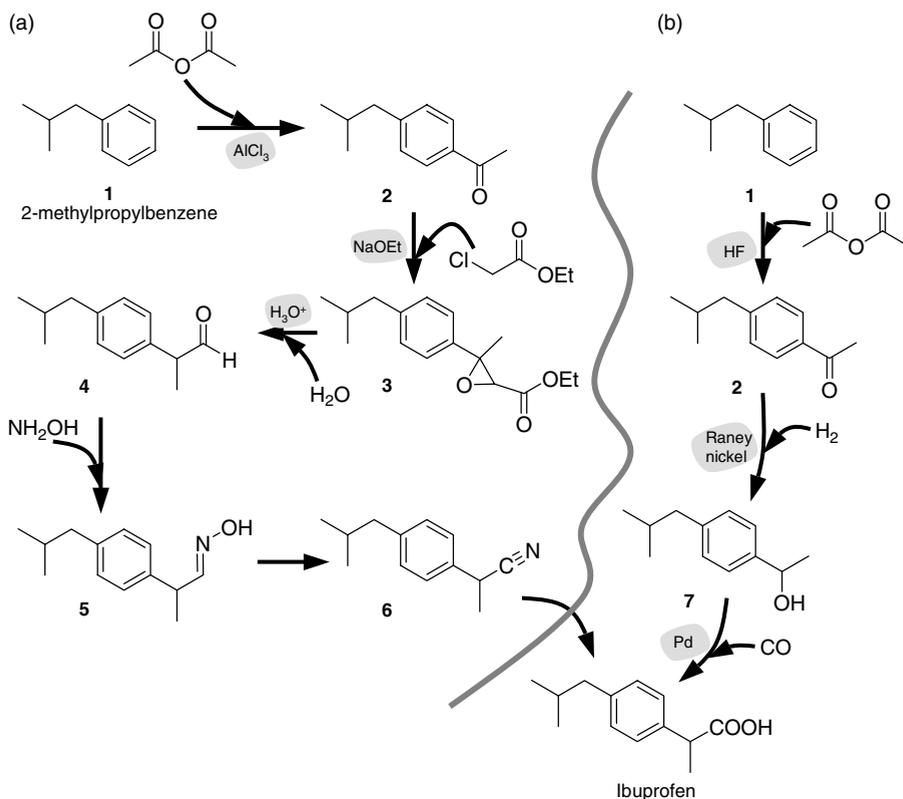


Figure 1.20 Synthesis of ibuprofen: a the six-step Boots route; b the three-step BHC route. In each case, the catalysts are highlighted in gray.

streams) associated with traditional stoichiometric reagent usage. The anhydrous HF catalyst is recovered and recycled with efficiency greater than 99.9%. No other solvent is needed in the process, simplifying product recovery and minimizing 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.

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 into three

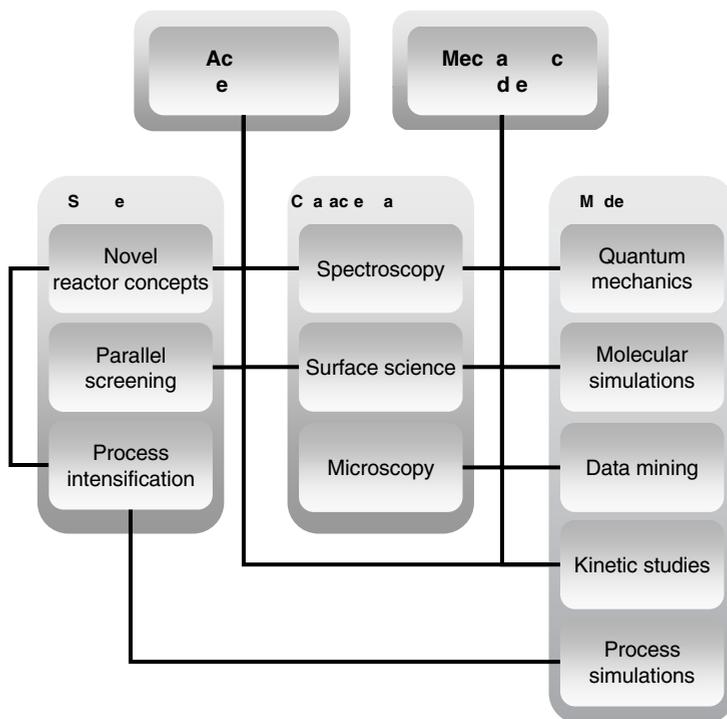


Figure 1.21 Block diagram of the various tools used in catalysis research.

groups: synthesis and testing tools, characterization tools, and modeling/mechanistic studies tools (see Figure 1.21).

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 still take place 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 [37].

Traditionally, research in catalyst discovery and optimization followed a cyclic workflow of synthesis, characterization, activity testing, and mechanistic studies. Because carrying out reactions was considered costly and labor-intensive, chemists favored 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 Alejandro Zaffaroni and Peter Schultz, who founded the company Symyx in

1994. Symyx adapted the concepts of miniaturization and parallel synthesis, used in pharmaceutical and biomedical research, to catalysis and materials science [38]. The main advantages were higher efficiency, and the ability to carry out reactions using smaller amounts of reactant and quantities of catalyst. This was especially important for homogeneous catalysis, where ligand cost and availability are often a problem. Diphosphine ligands, for example, typically cost €75–€370 (\$100–\$500) per gram, while 1 g of Rh costs €120 (\$160) and 1 g of Pt “only” about €24 (\$32). Moreover, performing many experiments in parallel can improve data quality, as repeating experiments is easier, and systematic errors can be minimized. Similar advantages were obtained by “one-pot” reaction systems, where multiple substrates and catalysts were tested simultaneously [39]. Although these new tools were initially viewed with skepticism by the chemical industry, they are used today by most companies that develop catalysts and catalytic processes.

Most of the parallel reactors on the market today are basically arrays of scaled-down batch reactors. There are also several novel concepts for high-throughput catalyst screening based on new microreactor technology [40]. One such example is the mixed-pulse reactor developed by Claude de Bellefon in 2000, which enables the fast sequential screening of catalysts in liquid/liquid and gas/liquid systems [41]. Here, two liquid carriers flow continuously through a micromixer which is connected to a plug-flow reactor. The two carriers can be mutually 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. They mix perfectly in the micromixer, with a residence time of less than 10 ms. This creates a “reaction pulse” which then moves through the reactor and can be analyzed by standard gas chromatography (GC) or high-performance liquid chromatography (HPLC) at the reactor outlet. Using this approach, one can test truly minute amounts of catalyst, without sacrificing the high accuracy and precision of chromatographic analysis. This system can also be adapted to high-throughput screening using spectroscopy (Figure 1.22). This involves adding a third valve that injects air bubbles before and after each pulse, and sending the pulses through a spectrophotometric flow cell.

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, and lithographic techniques were 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 was well defined [42]. Today, libraries of hundreds, even thousands, of catalysts are prepared in this way, using very small amounts of metal precursors.

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 [43]. 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. Two years later, Maier and co-workers refined this concept, screening 50

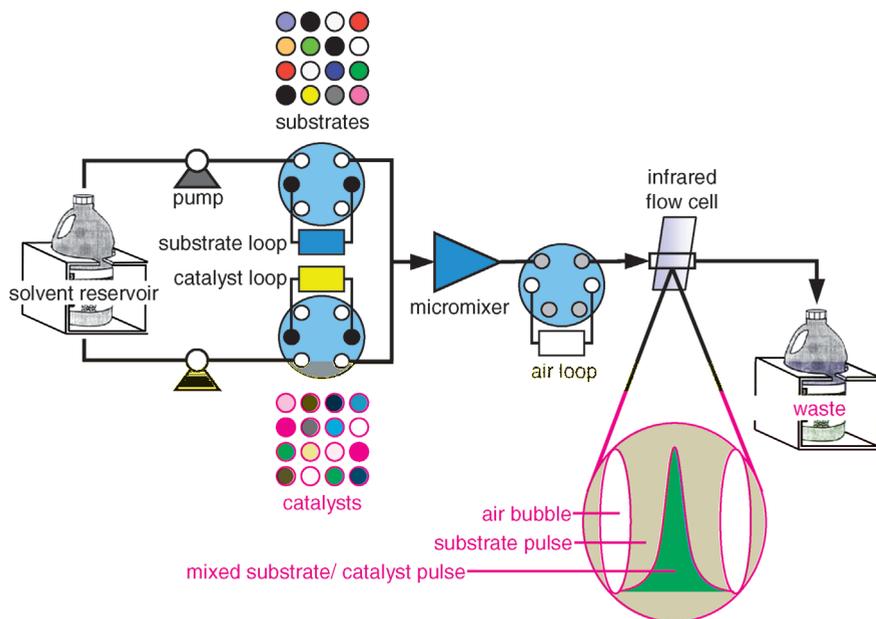


Figure 1.22 Schematic of the sequential pulse injection system developed by de Bellefon, adapted for high-throughput screening using on-line spectroscopy.

catalysts simultaneously and using only 200 μg of catalyst per sample [44]. Higher camera sensitivity enabled the screening of less exothermic reactions, such as the hydrogenation of hexyne at 100 $^{\circ}\text{C}$ and the oxidation of isooctane and toluene at 350 $^{\circ}\text{C}$.

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 of solving this problem is to attach the homogeneous catalysts to a solid support, such as polymer beads [45] peptide scaffolds [46], or inorganic monoliths [47].

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. In 1998, Taylor and Morken combined solid-phase bead supports with IR thermography, for synthesizing and screening large libraries of supported homogeneous catalysts using the split/pool approach [48].

1.3.2 Catalyst Characterization Tools

Catalysis is still very much a “black box” discipline, and catalyst characterization tools help us look inside this box. Characterization is done on several levels: On the first, the

macroscopic level (the reactor level), engineers search for the optimal formulation and operating conditions of the catalytic process. The second, the 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, the nanoscopic) level, chemists and physicists probe catalyst molecules, clusters, and atoms, trying to understand the fundamental steps that make up the catalytic cycle. A discussion of catalyst formulation on the macroscopic level is outside the scope of this book – the reader is referred to specialized texts on industrial catalysis [49]. We will cover the subject of kinetic studies in Chapter 2, and give further specific examples from homogeneous, heterogeneous, and biocatalysis in Chapters 3, 4 and 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 characterization on the microscopic level, especially in the area of spectroscopy and imaging of solids [50]. Instruments for transmission electron microscopy (TEM) and scanning electron microscopy (SEM) are now almost commonplace. They can resolve images to within a few nanometers. High-resolution atomic force microscopes are also available which can 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 [51]. Similar spectroscopic techniques are also used in homogeneous catalysis and biocatalysis.

One way of circumventing the high complexity of catalytic systems is by analyzing 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* characterization 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 which 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 [52,53].

Alternatively, one can characterize the catalytic intermediates *in situ*, under conditions that are closer to the real reaction conditions. Recent advances in 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 [54]. In some cases, one can combine the characterization with activity/selectivity analysis, examining the catalyst in real-time operation. This

simultaneous catalyst characterization and activity analysis is known as *operando* spectroscopy, a term coined by Miguel Banares in the 1990s [55]. *In situ* and *operando* characterization studies are increasingly popular, as more and more chemists concede the advantages of studying catalytic processes under realistic conditions.

1.3.3

Tools for Modeling/Mechanistic Studies

The meteoric rise in computer power (and meteoritic decline in hardware prices) has opened exciting avenues for computer modeling in all branches of science. Today, computer models are used in three main areas of catalysis research: modeling of reaction pathways and catalytic cycles, modeling 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.

Quantum mechanics calculations are used for solving the wavefunction 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-functional theory (DFT) enable the modeling of complex reactions in all three catalysis fields. In heterogeneous catalysis and biocatalysis, where the size of the system prohibits costly computations, hybrid methods are used. For example, one 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 hypothetical activated complexes associated with transition states. Thus, computer modeling can provide a picture of the elusive transition states, which can never be observed directly by experiment (because by definition, transition states have a zero lifetime). In this way, one can model the reaction pathways, and the corresponding reaction kinetics in detail, gaining insight into the various elementary steps in the catalytic cycle.

Classical molecular simulations are used for modeling 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 dynamics of the system are modeled by solving Newtonian equations. The computational cost here depends on the size of the system and on the level of detail. For example, a butane molecule, C_4H_{10} , can be modeled as a collection of 14 atoms (all-atom model), or as a chain with four links (coarse-grained model), or as one particle. In this way, one can tune the system size and the degree of detail to the requirements of the problem at hand.

Another important modeling 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. However, as this book deals primarily with the chemical aspects of catalysis, the reader is referred to the literature on industrial catalysis and process simulations for further information [49,56].

The third type of modeling deals with catalyst descriptors, structure/activity and structure/property relationships [57,58]. 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 modeling methods, descriptor models are often used for explaining the behavior of catalytic systems. Following the advances in drug discovery, however, predictive descriptor modeling is emerging as an exciting new field in catalysis research [59]. By combining the data from high-throughput experimentation with statistical analysis and descriptor models, you can predict the properties and performance of new catalysts [60,61]. Chapter 6 explains the basics of predictive modeling and *in silico* catalyst screening.

1.4 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 below were in print and commercially available in August 2007.

Homogeneous Catalysis, S. Bhaduri and D. Mukesh, Wiley-Interscience: 2000, 239 pp., ISBN 0-471-37221-8. This introductory textbook emphasizes the practical side, with a chapter dedicated to chemical engineering basics and process unit operations. The authors cover several examples of industrial homogeneous catalysis processes. Although the book is aimed at graduate students, it contains relatively few references to the primary literature. Each chapter is accompanied by a good selection of review questions and problems.

Homogeneous Catalysis, P.W.N.M. van Leeuwen, Kluwer Academic: 2004, 407 pp., ISBN 1-4020-1999-8. This is an advanced textbook aimed at graduate students with prior knowledge in synthetic, inorganic, and physical-organic chemistry. It gives a comprehensive overview on metal–ligand complexes, especially phosphorus ligands. All the subjects are clearly presented, with many useful references. The author explains ligand effects and the elementary steps in homogeneous catalysis with good examples which also include important process aspects of hydroformylation, hydrogenation, polymerization, and a variety of Rh- and Pd-catalyzed reactions.

The Organometallic Chemistry of the Transition Metals, R. H. Crabtree, Wiley-Interscience: 2005 (4th edn.), 546 pp., ISBN 0-471-66256-9. 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 also contains exercises and up-to-date references.

Applied Homogeneous Catalysis with Organometallic Compounds, B. Cornils and W. A. Herrmann, Eds., VCH: 1996, 1246 pp. in two volumes, ISBN 3-527-29286-1. Although it is over 10 years old, this large collection of essays covers many important applications of organometallic homogeneous catalysis. Some chapters are written from an industrial perspective, discussing scale-up and process challenges also.

Concepts of Modern Catalysis and Kinetics, I. Chokendorff and J. W. Niemantsverdriet, Wiley-VCH: 2003, 452 pp., ISBN 3-527-30574-2. This specialized book deals only with classic gas/solid heterogeneous catalysis. It contains excellent technical explanations and has a strong mathematical and physical approach, which makes for rather heavy reading. It covers many surface reaction mechanisms and catalyst characterization techniques.

Principles and Practice of Heterogeneous Catalysis, J. M. Thomas and W. J. Thomas, Wiley-VCH: 1996, 688 pp., ISBN 978-3-527-29239-4. A comprehensive textbook on classic heterogeneous catalysis which covers catalyst preparation and characterization methods. It also includes a chapter on solid-state chemistry and surface chemistry, and a chapter on process engineering.

Spectroscopy in Catalysis, J. W. Niemantsverdriet, VCH: 1995, 288 pp., ISBN 3-527-28726-4. This is an excellent book on heterogeneous catalysis characterization. It is highly specialized, and aimed at advanced graduate students and researchers. It covers only classic gas/solid heterogeneous catalysis, but if you want to specialize in characterizing solid catalysts, this is the book for you.

Catalysis: An Integrated Approach, R. A. van Santen, P. W. N. M. van Leeuwen, J. A. Moulijn, and B. A. Averill, Eds., Elsevier: 1999, 582 pp., ISSN 0167-2991 (Vol. 123 in the *Studies in Surface Science and Catalysis* series). This is one of the few books that cover all categories of catalysis. It is written by 25 different authors, and like many other such collections, this is both a blessing and a curse. The advantage is that each chapter is written by specialists who are discussing research subjects dear to their hearts. The disadvantage is that the overall result is somewhat disjointed.

Handbook of Green Chemistry and Technology, J. H. Clark and D. J. Macquarrie, Eds., Blackwell Publishing: 2002, 540 pp., ISBN 0-632-05715-7. This collection of 22 review essays covers all the important areas of green chemistry, including environmental impact and life-cycle analysis, waste minimization, catalysts and their industrial applications, new synthesis methods, clean energy, and novel solvent systems. The chapters are well referenced and contain pertinent examples and case studies.

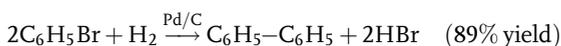
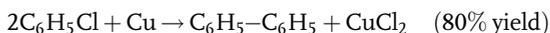
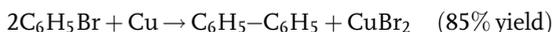
Green Chemistry and Catalysis, R. A. Sheldon, I. W. C. E. Arends, and U. Hanefeld, Wiley-VCH: 2007, 433 pp., ISBN 3-527-30715-9. An up-to-date advanced reference book, containing a collection of chapters on green chemistry applications in academia and industry. The subjects are ordered by reaction (oxidations, reductions, etc.) and are well presented.

An Introduction to Enzyme and Coenzyme Chemistry, T. Bugg, Blackwell Science: 1997, 247 pp., ISBN 0-86542-793-3 (paperback). This is a superb undergraduate/postgraduate textbook about enzymes. It is well written and illustrated, with interesting examples and well-thought-out exercises.

Biocatalysis, A. S. Bommarius and B. R. Riebel, Wiley-VCH: 2004, 611 pp., ISBN 3-527-30344-8. This is a comprehensive advanced textbook covering all aspects of biocatalysis. There are many good examples with references. It is a serious book, definitely not light reading, but one to have on the shelf if you are going to work in biocatalysis.

1.5 Exercises

- Examine the list of the 12 principles of green chemistry shown at the beginning of this chapter. Which of these principles relate to the concepts of atom economy, the *E*-factor, and the environmental quotient *Q*?
- (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.



- 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.
 - If using 100 mg of catalyst gives 98% conversion after 40 min, what are the TON and TOF of this catalyst?
- 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 1.23 shows two routes for this oxidation, a stoichiometric reaction using chromium trioxide, and a catalytic alternative using sodium hypochlorite (bleach) in the presence of 1 mol% osmium tetroxide catalyst.
- Calculate the *E*-factors and atom economy values for both options.
 - Given that both CrO_3 and OsO_4 are equally toxic, estimate the *Q*-values in both cases, and explain which option you favor and why.

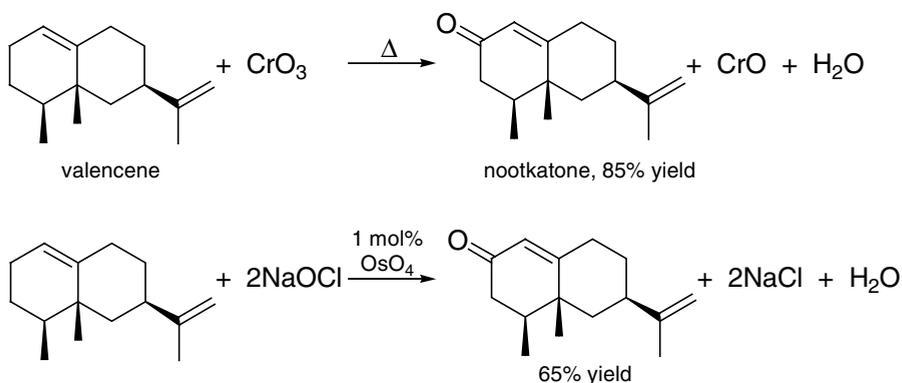


Figure 1.23 Alternative synthesis routes from valencene to nootkatone.

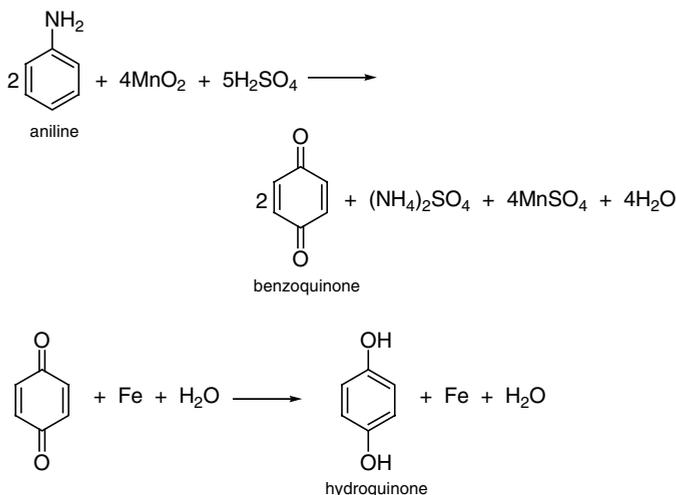


Figure 1.24 The classic synthesis route to hydroquinone starting from aniline.

- The classic synthesis of hydroquinone starts with aniline, and uses stoichiometric MnO_2 , sulfuric acid, and iron (Figure 1.24).
 - Calculate the atom economy for this process.
 - Aniline itself is made by nitration of benzene to nitrobenzene, followed by hydrogenation. Using the principles of green chemistry, draw a scheme for a new process for making hydroquinone, starting directly from benzene (feel free to invent any catalysts you need).
 - Search on 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?
- Fluorescent light bulbs contain mercury, which is released into the environment when the bulbs are disposed of in landfills [62]. Incandescent (regular) 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 into the environment. A typical fluorescent bulb consumes 11 W h^{-1} and burns for 5000 h, while a typical incandescent one consumes 75 W h^{-1} and burns for 1000 h.
 - Construct two life-cycle charts, one for fluorescent light bulbs and one for incandescent light bulbs.
 - Assuming that coal contains typically 20 ppm mercury impurities, which type of light bulb is better, fluorescent or incandescent, for the environment?
- A typical 1 L glass bottle for storing milk or juice weighs $\sim 400 \text{ g}$, while a 1 L tetra pak carton weighs only 35 g. This implies a big difference in raw material and transportation costs. Glass bottles, however, are often washed, reused, and

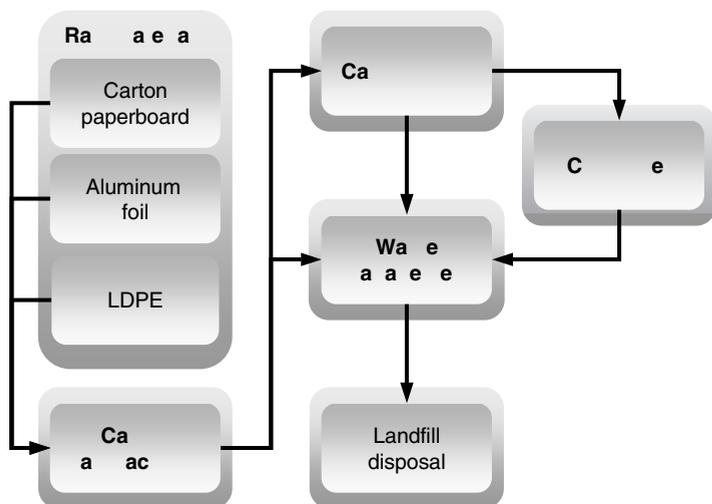
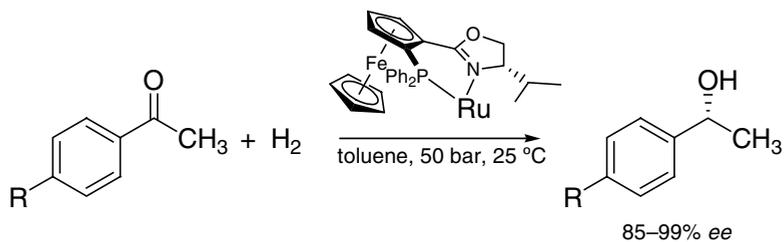


Figure 1.25 Life-cycle flow diagram for milk cartons.

eventually recycled, while cartons are disposed of in landfills (tetra paks are hard to recycle because they contain thin layers of low-density poly(ethylene) and aluminum, and because their collection is costly; the only municipality that currently recycles them is Sao Paolo, in Brazil). Figure 1.25 shows the life-cycle flow diagram for tetra-pak 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?
7. 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 [63]. Figure 1.26 shows the different substrates tested, along with the time, conversion, and substrate/catalyst ratio. Using these data, calculate the catalyst TON and TOF in each case.
 8. Monosodium glutamate (MSG) is a common food additive with a “meaty” flavor, used commercially for nearly 100 years. It was originally produced in Japan by extracting glutamic acid (2-aminopentanedioic acid) from wheat flour, and marketed under the trade name Ajinomoto (*Aji no moto* means “the origin of flavor” in Japanese) [64]. After WWII and the discovery of hydroformylation, the Ajinomoto company replaced the extraction with a continuous chemical process, starting from acrylonitrile, CO, and H₂ (see Figure 1.27).
 - (a) Calculate the overall atom economy and *E*-factor for the glutamic acid synthesis.



R	b	a e:ca a	e,	c e	, %
Cl-	50,000	78	99		
CH ₃ O-	20,000	1	92		
F-	500	1	100		

Figure 1.26 Catalytic hydrogenation of various aryl ketones and the corresponding kinetic data.

- (b) Recalculate 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 *Corynebacterium*

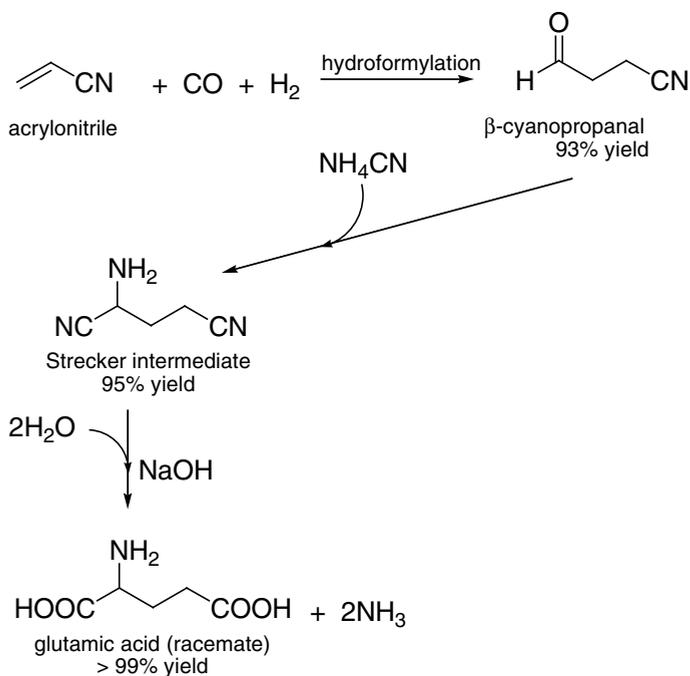


Figure 1.27 Three-step chemical synthesis of glutamic acid, starting from acrylonitrile.

glutamicum bacteria. This process gives ~60% conversion, with a final glutamic acid concentration of ~100 g L⁻¹. List two possible disadvantages of the fermentation route compared to the chemical synthesis route.

- Jack Daniel's "Old No. 7" whiskey has been 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 aging in oak barrels. All these steps are done in-house, including making the filter charcoal from locally grown sugar maple trees (unfortunately, Lynchburg is classified as 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").

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