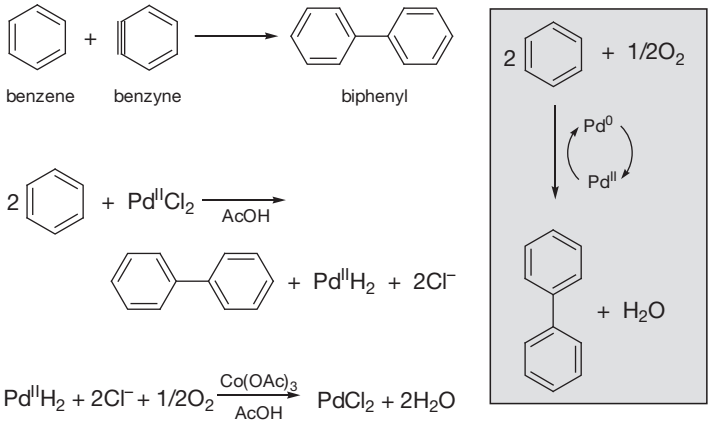


Figure 1.18 Theoretical waste-free route to biphenyl starting from benzene and benzyne (top left), oxidative coupling of two benzene molecules with stoichiometric $Pd^{II}Cl_2$ and regeneration of Pd^{II} with molecular oxygen (bottom left), and the resulting catalytic cycle for oxidative coupling (grey 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.

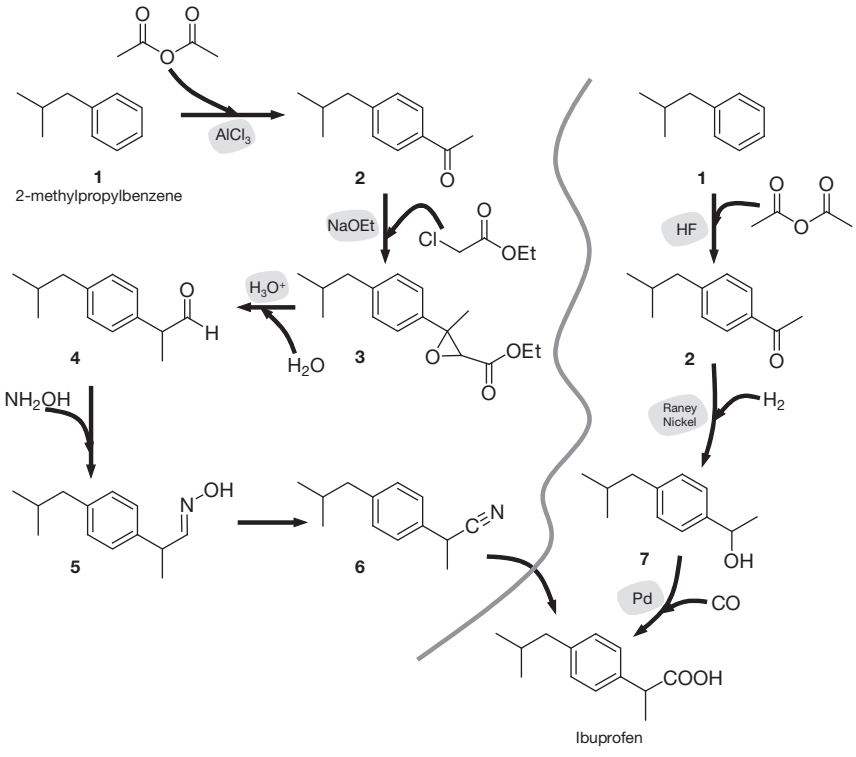


Figure 1.19 Synthesis of ibuprofen: The six-step Boots route (left) and the three-step BHC route (right). In each case, the catalysts are highlighted in grey.

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-

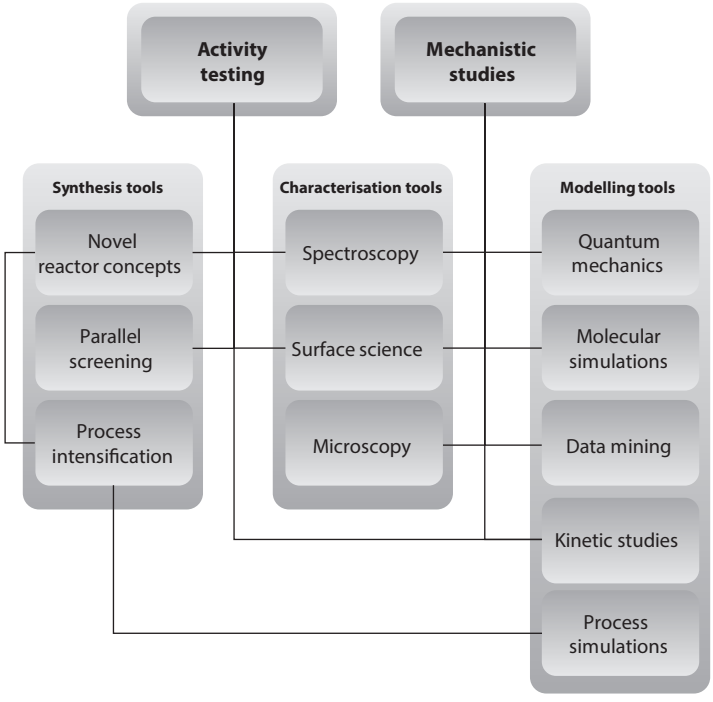


Figure 1.20 Block diagram of the various tools used in catalysis research.

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

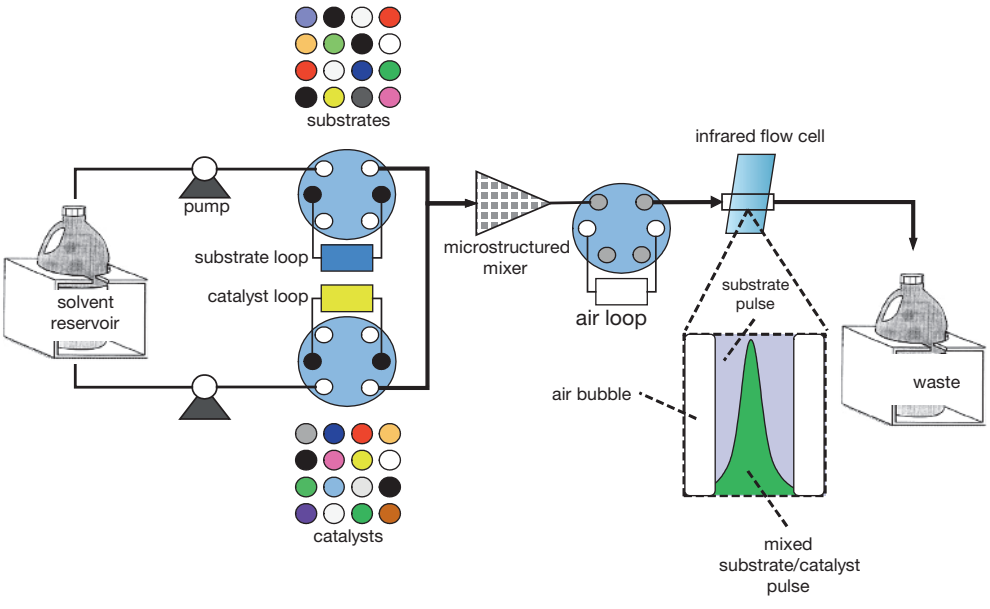


Figure 1.21 Schematic of a sequential pulse injection system for high-throughput catalyst screening using on-line spectroscopy.

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 ultravi-

olet 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 coworkers [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-

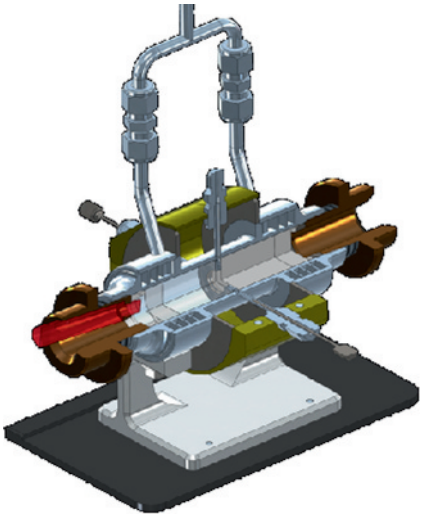


Figure 1.22 Schematic of a flow cell for measuring IR spectroscopy during a catalytic reaction (courtesy of Dr. Frederic Thibault-Starzyk).

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].

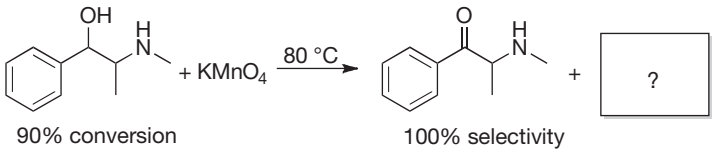


Figure 1.23 The oxidation of 2-(methylamino)-1-phenyl-propan-1-ol with potassium permanganate.

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?

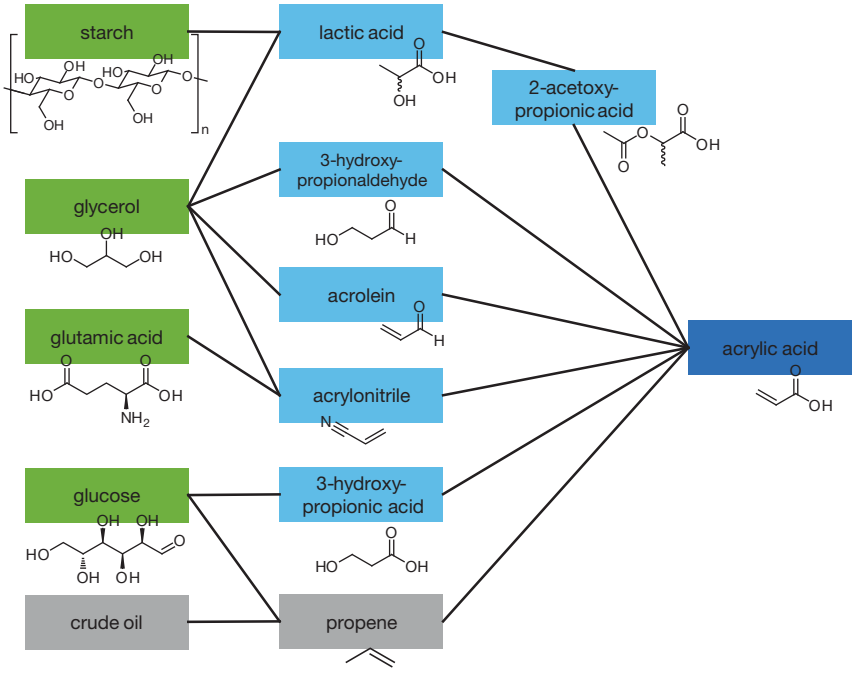


Figure 1.24 Different production routes to acrylic acid, showing biobased feedstocks (green), biobased platform chemicals (light blue), and existing petrobased routes (grey).

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 alter-

native using 5 wt% Pd/C and hydrogen gas.

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

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.

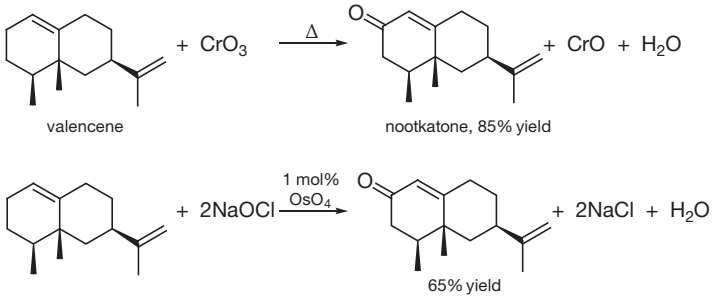


Figure 1.25 Alternative synthesis routes from valencene to nootkatone.

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?

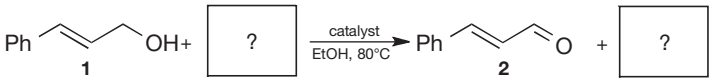


Figure 1.26 The catalytic oxidation of cinnamyl alcohol to cinnamaldehyde.

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).

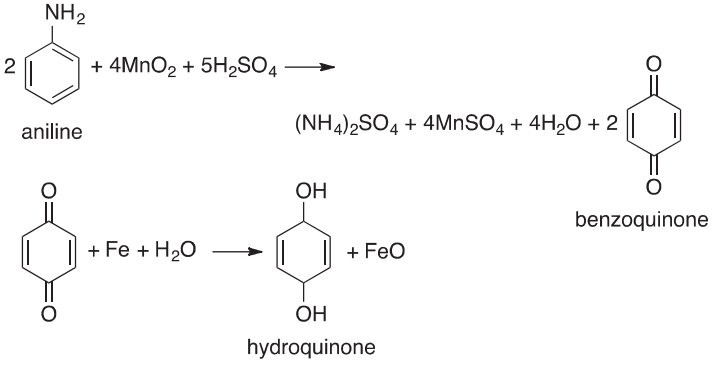


Figure 1.27 The classic synthesis route to hydroquinone starting from aniline.

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 ~ 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

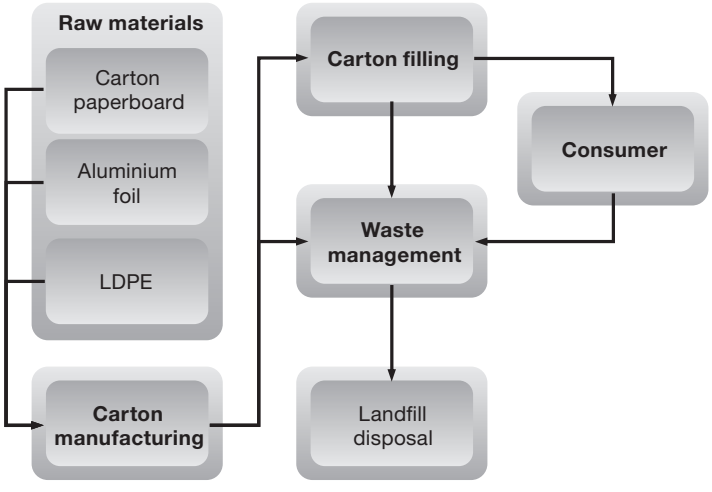
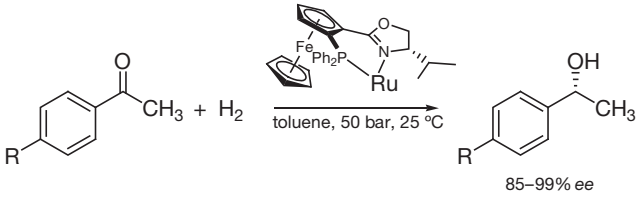


Figure 1.28 Life-cycle flow diagram for milk cartons.



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

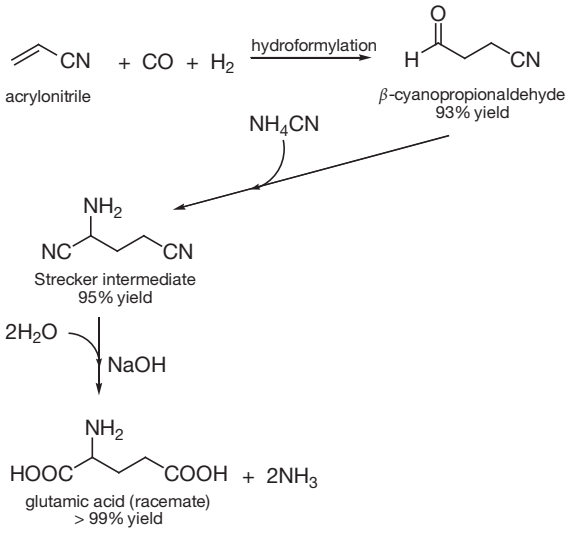


Figure 1.30 Three-step chemical synthesis of glutamic acid, starting from acrylonitrile.

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.

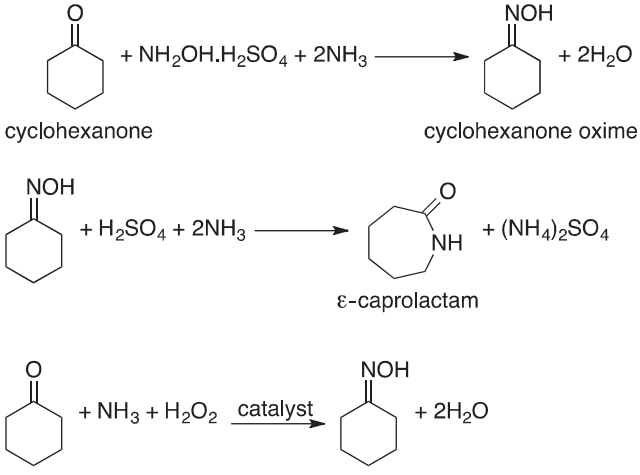


Figure 1.31 Production routes to ε-caprolactam: (a) the classic BASF route; (b) the Sumitomo/EniChem ammoximation process.

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').

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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.