1

Catalysis and Prerequisites for the Modern Pharmaceutical Industry Landscape

In the sum of the parts there are only the parts

Wallace Stevens, Poet

1.1 Introduction

The global market for active pharmaceutical ingredients (APIs) is in a very good state. The market was valued at US $119.7 billion in 2014 and is predicted to rise to US $185.9 billion by 2020 [1]. It is expected to increase at a compound annual growth rate (CAGR) of 6.50% from 2014 to 2020. The global API market is driven by the rising abbreviated new drug applications (ANDAs) [1]. It was also noted in 2011 that 90% of chemicals are derived from catalytic processes, and that the worldwide demand for catalysts was estimated to be about 850 000 tons in 2007 and the market value of products generated by catalysis reached about US $900 billion [2].

In the history of humanities' brief time on this planet, the need for more potent and efficient APIs has never been more critical than it is today. This has become a crucial issue particularly due to the exponential increase in the world population, the ever-increasing aging world population, the impact of global climate change on world health, the ever-diminishing set of natural resources, the greater propensity for the spread of disease, the rise in urban pollution, as well as lifestyle changes that are leading to serious health issues, such as obesity, and neurological problems, such as depression. For these reasons, there is an increased demand on world governments to improve their health care services. Within this context there is the requirement to provide new and efficacious drugs to treat a large panoply of diseases, including emerging ones, that are generally viral or spread by other microorganisms. This is no easy task, and two of the parameters that have to be considered are the cost of the drug (so that it can be acquired by governments and patients alike) and the speed of putting such entities on the market. However, quality is also a very important factor, and catalytic methods allowing for cleaner reaction conditions can make this an easier and more cost-effective task. In both cases, catalysis can provide the answer as both economical and efficient/rapid catalytic routes can reduce the cost and accelerate the time to market.

Active Pharmaceutical Ingredients in Synthesis: Catalytic Processes in Research and Development, First Edition. Anthony J. Burke.

Without a doubt during the past number of decades, catalysis has played a very important role in the development of APIs. When working at its optimum level, it is one of the most efficient and desirable ways of accessing APIs, particularly at the large scale over a prolonged period of time. Catalysis is desirable for accessing APIs, particularly in the pharmaceutical industry, for a number of reasons: it reduces waste, so the environmental footprint is reduced; the catalysts can be recycled, so that the process becomes more economical in the long run; low loadings can be attained for a number of metal-based catalysts (like palladium), so that the overall cost is reduced; chiral catalysts can be used to afford enantiomerically pure chiral APIs [3]; specific catalysts that are eco-friendly like enzymes (whether used as part of a whole cell, or as the isolated enzymes) with no metal contamination, organocatalysts can also be used which require facile working conditions (air reactions and water as solvent, and with no metal contamination issues); and catalysis can be easily integrated in continuous manufacturing processes, such as continuous-flow chemistries (see subsequent text) that can really speed up production times.

However, with the new developments in enabling technologies, catalytic methods leading to APIs are undergoing a major revolution; the great advances in continuous-flow methods in the context of continuous manufacturing [4] have certainly enhanced the effectiveness of catalytic routes in the past number of years (we return to this topic in Section 1.3) [5]. This technology is now highly integrated in an automatic or back-to-back setup, which includes not only the actual chemical transformation but the separations, crystallizations, drying, and formulations, as well! [4, 5].

It should also be noted that over the past three decades, there has been an increased application of the principles of green chemistry, particularly the incorporation of catalytic steps in API production [6, 7]. Catalysis is one of the 12 principles of green chemistry – i.e. principle 9 – [6] and for inherent sustainable catalytic processes it is crucial that it is integrated with the other key principles like atom economy (No. 2), safer solvents (No. 5), design for energy efficiency (No. 7), use of renewable feedstocks (No. 7), and inherently safer chemistry for accident prevention (No. 12). These issues are addressed in Chapter 2.

The impact of catalysis for the synthesis of APIs by the pharmaceutical industry has been reviewed previously [2, 3, 8]. In the context of green engineering for sustainable manufacture, both biocatalysis and continuous processing have been identified as key enabling technologies [4].

Before describing some of the landmark API synthesis that have been accomplished over the past number of decades, in the next section we describe the historical development of the field of catalysis as a major scientific area, and include some of the key discoveries in the area and their industrial applications over the past 100 years or so.

1.2 Key Historical Moments in Catalysis Development

A catalyst is a substance that when added to a chemical reaction in small quantities affects the reaction rate (generally increasing it) and the selectivity (generally

improving it) but without being consumed. Historically, it was Wilhelm Ostwald who introduced chemical thermodynamics into the physical chemical definition of catalysis, and stated that it was a substance that did not effect the equilibrium of the reaction or, in Ostwald's exact words, "a catalyst is a substance which affects the rate of a chemical reaction without being part of its end products" [9, 10]. Oswald won the Nobel Prize in Chemistry in 1909, for his work on catalysis and on the conditions of chemical equilibria and velocities of chemical reactions (see Table 1.1). He also developed the industrial-scale catalytic oxidation of ammonia to nitric acid (known as the Ostwald process (Table 1.2)) [12]. This area gained traction with the work of Paul Sabatier who studied the heterogeneous catalytic hydrogenation of organic compounds using finely divided metals, and who won the Nobel Prize in Chemistry in 1912, for his method of hydrogenating organic compounds in the presence of finely divided metals (Table 1.1). (In fact, it would be several decades later that homogeneous catalytic hydrogenation became a stable academic and industrial process with the work of Fischer and Wilkinson using organometallic compounds; see subsequent text).

Sabatier introduced the concept of formation of reaction intermediates of intermediate stability on the surface of the catalyst; if they were too stable, they would not decompose into products and if too unstable, the products would not be formed [10]. He introduced for the first time the notion of a catalytic cycle, with the formation of transient complexes between the catalyst and the reagent. Together with the thermodynamic and physical chemical concepts of Oswald, this led to a greater understanding of the molecular basis of catalysis [10]. The area of catalysis began to build up steam and gain much importance with the development of the Haber–Bosch (HB) process – essentially the reaction of hydrogen with nitrogen to form ammonia over a metal catalyst – which was invented in 1913 by Fritz Haber in collaboration with Carl Bosch (Table 1.2) [10]. With this technology, large quantities of fertilizer for global food production could be obtained. In this process, dinitrogen from the air is split using a catalyst – which is usually iron – to synthesize ammonia [10]. Fritz Haber won the Nobel Prize in Chemistry for this discovery in 1918 (actually Carl Bosch won the Nobel Prize jointly with Friedrich Bergius for the invention and development of chemical high-pressure methods in chemistry in 1931) for the synthesis of ammonia (Table 1.1). It was in fact the first high-pressure industrial process on record [10]. However, insight into the actual mechanism of this process was only obtained by the groundbreaking, careful, and painstaking experiments of Gerhard Ertl – one of the fathers of modern surface chemistry – who was the recipient of the Nobel Prize in Chemistry in 2007 [13]. Ertl, having been inspired by developments in the semiconductor field in the 1960s and 1970s, conducted groundbreaking experimental studies of chemical processes, mainly catalytic, on surfaces (http://www.nobelprize.org/nobel_prizes/chemistry/laureates/2007/advanced-chemistryprize2007.pdf). When asked at his first interview – after been informed that he had received the prize – if it was possible to improve the efficiency of the HB process, he responded by saying that it was impossible to improve the process from the chemical side, as it had undergone so many improvements/optimizations over the past 90 years; the only improvements possible would be in the engineering context [12]. Ertl not only clarified the

Table 1.1 Relevant Nobel Prizes in Chemistry with a link to catalysis (https://www.nobelprize.org/nobel_prizes/chemistry/laureates/) [11].

Years	Winner	Theme
1907	Eduard Buchner	For biochemical researches and his discovery of cell-less formation
1909	Wilhelm Ostwald	For his work on catalysis and on the conditions of chemical equilibrium and velocities of chemical reactions
1912	Paul Sabatier (one half) Victor Grignard (one half)	For his methods of hydrogenating organic compounds in the presence of finely divided metals (PS). For the discovery of the so-called Grignard reagent, which in recent years has greatly advanced the progress of organic chemistry (VG)
1913	Alfred Werner	For his work on the linkage of atoms in molecules by which he has thrown new light on earlier investigations and opened up new fields of research, especially in inorganic chemistry
1918	Fritz Haber	For the synthesis of ammonia from its elements, nitrogen and hydrogen
1932	Irving Langmuir	For discoveries and investigations in surface chemistry
1946	James B. Sumner/John H. Northrop/Wendell M. Stanley	For his discovery that enzymes could be recrystallized (JBS) For the preparation of enzyme and virus proteins in a pure form (JHN/WMS)
1963	Karl Ziegler/Giulio Natta	Catalytic polymer synthesis
1973	Geoffrey Wilkinson Ernst Otto Fischer	For pioneering work on the chemistry of the organometallic so-called sandwich compounds
1983	Henry Taube	For work on electron transfer reactions, especially in metal complexes
1989	Sidney Altman Thomas R. Cech	For their discovery that RNA acts as a biological catalyst as well as a carrier of genetic information
1993	Kary B. Mullis	For his invention of the polymerase chain reaction (PCR) method
2001	K.B. Sharpless/R. Noyori/W. Knowles	For their work on chirally catalyzed hydrogenation and oxidation reactions
2005	Robert H. Grubbs/ Richard R. Schrock/ Yves Chauvin	For the development of the metathesis method in organic synthesis
2007	Gerhard Ertl	For studies of chemical processes on solid surfaces
2010	Richard F. Heck/Ei-ichi Negishi/Akira Suzuki	For palladium-catalyzed cross couplings in organic synthesis

mechanism of the HB process but also provided a road map for the elucidation of heterogeneous catalytic processes in general [12]. It should be noted that prior to Ertl, Irving Langmuir (known for Langmuir–Blodgett films, Langmuir circulation, Langmuir waves, and the Langmuir probe) who incidentally originally

Table 1.2 Relevant catalytic processes applied in the chemical industry.

Years	Inventor	Process
1908	W. Ostwald	The Ostwald process for nitric acid synthesis
1913	F. Haber C. Bosch	Haber–Bosch ammonia synthesis
1926	F. Fischer H. Tropsch	Production of saturated/unsaturated hydrocarbons from synthesis gas
1938	O. Roelen	The CO-catalyzed hydroformylation reaction
1953	K. Ziegler G. Natta	Ziegler, Natta polymerization
1948	W. Reppe	The Reppe acrylic acid synthesis and benzene and cyclooctatetraene synthesis
1959	J. Smidt	Wacker reaction – selective oxidation of ethylene to acetaldehyde
1969	H.P. Wulff F. Wattimena (Shell)	Heterogeneous Ti-catalyzed epoxidation
1972	W. Keim	Shell higher olefin process
1972	C.D. Chang/A.J. Silvestri/W.H. Lang (Mobil)	Methanol to gasoline with zeolite catalyst ZSM-5

started out investigating light bulbs, was very influential in developing the field of surface chemistry with his pioneering work on simple heterogeneous catalytic reactions. For his work he received the Nobel Prize in Chemistry in 1932. His remarkable studies included insights on the physicochemical behavior of mixtures of oxygen and hydrogen over a tungsten filament at low pressures at high temperatures in a light bulb (http://www.nobelprize.org/nobel_prizes/chemistry/laureates/1932/langmuir-lecture.pdf). He showed that the oxygen, in fact, was adsorbed and disassociated into its individual atoms on the surface of the tungsten filament; subsequently, all of the hydrogen was consumed, and the monoatomic oxygen layer on the filament was removed through reaction with the individual hydrogen atoms. He deduced that although the hydrogen atoms could not react in the gas phase with the oxygen atoms, they could react with the adsorbed oxygen atoms. These amazing insights heralded the age of surface chemistry/heterogeneous catalysis.

A number of other key industrial applications of catalysis occurred in the following decades (the most important of which are listed in Table 1.2). The Wacker reaction had been originally developed in 1894, when it was observed that palladium chloride formed acetaldehyde directly from ethylene [14]. However, the problem of catalysis was only resolved in the 1950s by chemists from Wacker-Chemie and Farbwerke Hoechst, when they developed a procedure of reoxidizing Pd(0) to Pd(II) (http://www.nobelprize.org/nobel_prizes/chemistry/laureates/1932/langmuir-lecture.pdf) [15]. This was achieved using Cu(II). The problem with the reaction was the formation of the linear and branched aldehyde products; and, subsequently, phosphines were used as ligands, to compete with the CO, affording the more

valuable linear aldehyde (http://www.nobelprize.org/nobel_prizes/chemistry/laureates/1932/langmuir-lecture.pdf). This process was later developed commercially by Shell. In the 1970s, the Cu was replaced by Rh, and even better results in terms of regioselectivity, favoring, of course, the linear aldehyde, were obtained. The aldehydes produced can be reduced to valuable alcohols via catalytic hydrogenations.

It must be noted that the seminal contributions of Werner in the 1920s (Nobel Prize 1923) on coordination chemistry with metals underpinned much of these developments, particularly from the theoretical point of view, and laid the groundwork for the field of organometallic chemistry and homogeneous catalysis (see subsequent text).

In the 1940s, Walter Reppe developed a method for the synthesis of acrylic acid from acetylene using a nickel carbonyl catalyst – which is commonly known as the Reppe catalyst (http://www.nobelprize.org/nobel_prizes/chemistry/laureates/1932/langmuir-lecture.pdf) [16]. The reaction was dangerous as the acetylene would explode without proper reason. For many years this was the prime industrial method to synthesize acrylic acid, an important feedstock chemical for the polymer industry. However, this method was later replaced by safer industrial methods developed at Rohm and Haas (methyl methacrylate, 1948) and Nippon Shokubai in 1976. In the 1960s, Lutz developed a Ti carbonyl catalyst [17].

Also, in the 1940s, Reppe synthesized both benzene and cyclooctatetraene via the cycloaddition of alkynes with Ni catalysts [18].

Another important metal-catalyzed process with a tremendous industrial impact was the hydroformylation discovered in the 1930s. Otto Roelen at Ruhrchemie discovered that when carbon monoxide, hydrogen (the mixture of CO and H_2 is called synthesis gas and is derived from methane), and ethylene were reacted in the presence of cobalt salts, propionaldehyde was obtained [9, 12, 19]. It can be applied to a range of terminal olefins, which includes styrenes. This process is in fact a carbonylation process. Actually, this process was born of the Fischer–Tropsch reaction (discovered in 1926), which involves the production of saturated and unsaturated hydrocarbons, including alcohols and esters by the reaction of synthesis gas (CO/H_2) with heterogeneous Fe and Co catalysts. The Fischer–Tropsch method is currently used to produce clean diesel fuel from coal and natural gas [9]. Further studies in the 1960s shed light on its mechanism and then it was later taken over by Shell. We discuss applications of this important process for API synthesis in Chapter 4. These studies also gave rise to new types of carbonylation reactions that led to the Monsanto process – discovered by D. Forster in 1976 – which involves the carbonylation of methanol (from syngas) to give acetic acid[1] via insertion of a carbonyl group within the C—O bond of methanol (http://www.nobelprize.org/nobel_prizes/chemistry/laureates/1932/langmuir-lecture.pdf) [20]. This process is catalyzed by a Rh catalyst in the presence of iodine and is very selective, fast, and high yielding. It replaced the Wacker process that was dangerous. However, there is constant interest in improving this process for the manufacture

[1] There is in fact another analogous process known as the Cativa process.

of acetic acid (http://www.nobelprize.org/nobel_prizes/chemistry/laureates/1932/langmuir-lecture.pdf).

This was then followed by the remarkable discovery by Ziegler and Natta on the Ti-catalyzed room temperature and ambient pressure polymerization of ethylene and propylene to both polyethylene and polypropylene – two very valuable polymeric products [9, 12, 21]. In this process, a $TiCl_3$ catalyst was used; this was a major advancement because prior to this discovery, these polymers could only be made using high-pressure reactions (exceeding 1000 atm with small quantities of oxygen) and temperatures (the Imperial Chemical Industries (ICI) process) (http://www.nobelprize.org/nobel_prizes/chemistry/laureates/1932/langmuir-lecture.pdf). In fact, it was Karl Ziegler who first accidently [22] polymerized ethylene when he used an autoclave contaminated with a colloidal nickel residue. In 1953, the catalytic system was improved using $TiCl_4$ with Et_3Al (Ziegler catalyst) [23]. The isotactic version was discovered by Giulio Natta, who used a different catalytic system – $TiCl_3$ with Et_3Al (Natta catalyst) – and who studied the polymerization of propylene. Natta also took Ziegler's catalyst, applied it in the propylene polymerization reaction and obtained crystalline polypropylene. The reaction was unique for the following reasons: it did not involve radicals and, secondly, as was the case with polypropylene, it occurred with great stereochemical fidelity. For their efforts, these workers received the Nobel Prize in Chemistry in 1963. When the new metallocene catalysts came on the scene, like ferrocene (Cp_2Fe), dichlorodicyclopentadienyltitanacene (Cl_2Cp_2Ti), and zirconocenes (see subsequent text), they were successfully used to replace the former iron and titanium catalysts (http://www.nobelprize.org/nobel_prizes/chemistry/laureates/1932/langmuir-lecture.pdf). In fact, some of the pioneering studies of Natta in 1964 concerned a ring-opening metathesis polymerization (ROMP) that laid the groundwork for the future Nobel Prize studies of Grubbs, Schrock, and Chauvin on alkene metathesis (see subsequent text) [24]. This process is discussed in Chapter 7.

Victor Grignard won one-half of the Nobel Prize in Chemistry in 1912 for his studies using organomagnesium compounds for the creation of C—C bonds, and taking this a step further in the early 1940s Kharasch exploited the use of Grignard reagents in the presence of catalytic quantities of cobalt, nickel, and iron salts to form biaryl compounds via a homocoupling process [25]. This was followed in the 1950s by the copper-catalyzed coupling between methylmagnesium bromide and methyl iodide by Gilman et al. [26].

In 1965, Wilkinson discovered a new catalytic system for homogeneous catalytic hydrogenation. This was an enormously big advancement, and it opened up the modern era of both organometallic chemistry and of catalytic asymmetric synthesis (see subsequent text), which is a key technology used in the pharmaceutical industry, and also the enormous field of metal-catalyzed cross-coupling reactions which is currently crucial for the development of APIs (see Chapter 6).

Underpinning the developments and advances in the field of metal-based catalysts were the seminal contributions of Henry Taube (Nobel Prize 1983) for his contribution to the understanding of the mechanism of electron transport in metal complexes.

Wilkinson also introduced the now famous $RhCl(PPh_3)_3$ catalyst which bears his name. What was remarkable about this catalytic system was that the catalyst

could be tuned by the type of phosphine ligand used. Besides opening up the field of metal-catalyzed hydrogenation, it laid the groundwork for and the key principles of the field of metal-catalyzed C—C coupling, where the ligand is endowed with the special role of being able to modulate the reactivity. This key development led to at least three Nobel Prizes in the past 20 years: Sharpless/Noyori/Knowles (asymmetric catalytic oxidation and hydrogenation, 2001), Grubbs/Schrock/Chauvin (metathesis reactions, 2005), and Heck/Suzuki/Negishi, palladium-catalyzed cross-coupling reactions, 2010), for processes that rely heavily on the formation of catalysts by the interaction of metals with key ligands (many of which are phosphines).

Wilkinson, in fact, won the Nobel Prize in 1973 (jointly with Ernst Fischer) for his seminal contributions to the field of metallocene chemistry (or sandwich compounds), which includes ferrocene (Fe), titanocene dichloride (Ti), and zirconocene dichloride (Zr) (Figure 1.1). Again, these developments fortified the field of catalysis, introducing new concepts, which underpinned many of the catalytic processes, like olefin metathesis, polymerization reactions, cyclopropanations, C—H, N—H insertions, cycloaromatization processes, and so on. In fact, Pauson and coworker [27] and Miller et al. [28] were the first to synthesize ferrocene (it should also be noted that chiral ferrocene-based phosphine ligands are a very successful class of ligands for asymmetric catalysis, particularly, asymmetric hydrogenation, take, for instance, the highly successful xyliphos ligand that is used in the large-scale synthesis of the herbicide (*S*)-*Metolachlor*, commonly known as Dual Magnum®, that is sold by Syngenta) (Figure 1.1). But, it was both Wilkinson and Fischer who independently observed that this complex had a stable C—Fe π-bond. With this discovery, the new era of organometallic chemistry was born.

Inspired by developments with Wacker-type processes, Tsuji et al. in the mid-1960s reported the reaction of π-allylpalladium chloride with malonates to give – via the formation of a new C—C bond – allylated malonates [29]. (These reactions are now called Tsuji–Trost reactions [22] as Barry Trost from Stanford University also contributed greatly to developing this chemistry, and these reactions are discussed in Chapter 6.) By homing into these developments, Heck in the late 1960s published a series of back-to-back papers on his work studying the arylation of olefins [30], including a mechanistic paper in 1969 [31]. These seminal papers revolutionized the field. Motivated by key studies from Mizoroki's laboratory [32] (who incidentally had been inspired by the previous work of Heck), Heck later made key modifications to this reaction, the main one being the generation

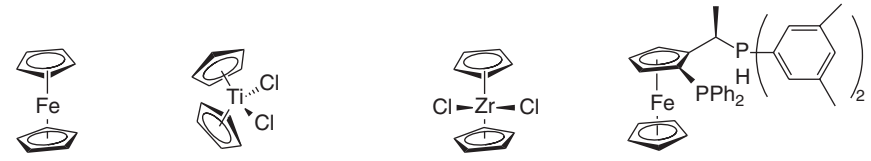


Figure 1.1 Some key metallocene (sandwich) compounds, including the ferrocene-derived chiral ligand Xyliphos.

of the organopalladium complex RPdX by oxidative addition of an organohalide to the Pd(0) complex [33]. (In many cases, advances in science come about through synergies and stimuli between various scientists, as we have seen here.) The reaction is commonly known as the Mizoroki–Heck reaction. In 2010, he won the Nobel Prize in Chemistry with Akira Suzuki and Ei-ichi Negishi for their pioneering work (https://www.nobelprize.org/nobel_prizes/chemistry/laureates/2010/advanced-chemistryprize2010.pdf). Some examples of the application of these reactions to API synthesis are given in Section 1.2 and of course in Chapter 6.

Inspired by the earlier work by Dieck and Heck in the mid-1970s [34], in the late 1970s Suzuki and coworkers (including Miyaura) developed a Pd-catalyzed coupling reaction between vinyl and aryl halides, which involved organoboron compounds [35]. This process involved the transmetalation of the organic group on the boron to the Pd. The transmetalation only occurs when base is present [36]. The reaction was later extended to include coupling with alkyl groups. It was found that the reaction works best with arylboronic acids, their stability and weak nucleophilic character made this reaction very practical [33]. The reaction is commonly known as the Suzuki–Miyaura (SM) reaction and it has heavy usage in the pharmaceutical industry (an example is given in Section 1.2, and there are more examples in Chapter 6). It should also be noted that, in general, this reaction works best with organobromides and iodides, but Fu and coworker developed a procedure that uses cheaper organochlorides and sterically hindered phosphine ligands [37]. Incidentally, Thomas and Denmark, through a recent combination of three methods (spectroscopic analysis, independent synthesis, and kinetic studies), have unambiguously identified and characterized three pre-transmetalation species that undergo the SM reaction [38]. There are other cross-coupling methods that have been used with success for the production of APIs; examples include the Migita-Kosugi-Stille, Kumada–Tamao–Corriu, Hiyama–Denmark, and the exceedingly useful Buchwald–Hartwig reaction that has become very useful (see Section 1.3 and Chapter 6) [36].

There have also been very remarkable discoveries of new chiral catalysts for producing single enantiomer and enantiomer-enriched chiral molecules, such as amino acids, alcohols, epoxides, amines, nitriles, cyanohydrins, etc. which have become the stalwarts in a number of pharmaceutical processes leading to key APIs. This subject matter is discussed in Section 1.2.

Organocatalysis is an old field that was revived about 18 years ago and deserves special mention here. It was in fact Justus von Liebig in 1859, who accidentally (again) discovered that dicyan can be transformed to oxamide using an aqueous solution of acetaldehyde [39]. Nicotine and quinine were used in the early twentieth century by Bredig and coworker for the thermal decarboxylation of optically pure camphorcarboxylic acid [40, 41]. Bredig and Fiske later conducted a groundbreaking synthesis of mandelonitrile with HCN using quinine and quinidine as the catalysts [42]. Then in the 1970s, two independent teams from Hoffmann-La Roche [43] (led by Hajos) and from Schering AG led by Rudolf Wiechert [44] showed that it was possible to conduct a highly enantioselective Robinson annulation reaction using L-proline. The group of Wiechert obtained an enantioselectivity of 71% ee, while the team of Hajos, using slightly different conditions, achieved a superior enantioselectivity of 93% ee. This was a remarkable

achievement for that time. Despite this, this field remained dormant for several years until, in the year 2000, List et al. reported the direct asymmetric aldol reaction between acetone and simple aldehydes using L-proline (this result was a consequence of studies reinvestigating the Hajos–Parrish–Eder–Sauer–Wiechert reaction) [45] and McMillian and coworkers reported an organocatalyzed Diels–Alder reaction catalyzed by an imidazolidinone. The reaction was highly successful, affording the aldol product with an enantioselectivity of 96% ee [46]. After these landmark publications, many other big groups entered the field, working on other common benchmark reactions like the Michael addition, the Henry reaction, and the Mannich reaction, to name a few.

As of yet, the number of industrial examples of the industrial application of organocatalysts is very limited; there is no flagship reaction yet identified that shows organocatalysis to be a truly industrial player. However, there are good omens that this situation will change in the near future, particularly as there has in recent years been progress in increasing the reaction TOFs, which historically have been much lower than those obtained with metal-based catalysts. Innovations in the area of photochemically organocatalyzed reactions are also making these reactions more efficient (see subsequent text). Throughout the book we give examples of their application. The reader is also encouraged to consult the excellent recent review by Sun [47] on this subject.

In the context of biocatalysis, which is currently a very important industry, and currently a tremendous tool for producing APIs, we can go back to the early work of Eduard Buchner more than 100 years ago. In 1897, Buchner made some significant developments with the use of enzyme catalysts for biochemical processes. He extracted enzymes which he called zymases from yeast-cell-free extracts, and which were responsible for the fermentation of sucrose. He showed that these substances were responsible for fermenting sugars. He eventually won the Nobel Prize in Chemistry in 1907 for this pioneering work (Table 1.1). In fact, in 1877, Wilhelm Kühne first used the term *enzyme*, which comes from Greek "leavened," to describe this process (Source: https://en.wikipedia.org/wiki/Enzyme). The word *enzyme* was used later to refer to pepsin, and the word *ferment,* originally introduced by Louis Pasteur to describe the active juices secreted by yeast cells, was used to refer to chemical activity produced by living organisms [9]. Major advances came in 1926, when James Sumner crystallized urease, and showed that it was a protein, and in 1937, did the same for catalase [9, 12]. Richard Willstätter had previously shown that enzymes known as catalases and peroxidases could catalyze the decomposition of hydrogen peroxide to oxygen and water [9]. Then later, James Northrop and Wendell Stanley isolated pepsin, chymotrypsin, and trypsin and showed that enzymes could be pure proteins [9]. These efforts paved the way for the modern field of biocatalysis as we know it today. Sidney Altman and Thomas Cech would later show that not only proteins can behave as enzymes, but, as demonstrated, RNA acts as a biological catalyst (Table 1.1). In 1985, Kary B. Mullis reported the polymerase chain reaction (PCR), which allowed for the replication of DNA millions of times using a polymerase enzyme. For his efforts he was awarded the Nobel Prize in Chemistry in 1993 (Table 1.1).

1.3 Key Historical Developments in Catalysis for API Synthesis: Including Catalytic Asymmetric Synthesis

Developments in the application of catalysis for the production of APIs stemmed from the enormous advances in the development of the field of catalysis during the past century. Since a large proportion of APIs are in fact single enantiomer chiral molecules, the area of asymmetric catalysis has been of more interest to the pharmaceutical industry. Progress in the synthesis and production of enantiopure APIs only began to take shape in the 1960s and 1970s [48]. In 1987, approximately 87% of the newly introduced drugs were racemic [49]. This was perhaps due to two main reasons: (i) APIs are, in general, complex molecules containing multifunctional groups and stereocenters, and as such the knowhow for controlling these aspects only came about through the pioneering groundbreaking work that was contributed by the masters of organic synthesis, like Woodward, Sheehan, Johnson, Stork, and others in the 1950s and 1960s; and (ii) since most APIs are chiral with one enantiopode in the active form, it was essential to develop asymmetric synthetic methods to access them. However, since asymmetric catalytic methods only started to become useful and reliable from the 1970s on, as such very few chiral non-racemic APIs were produced via catalytic asymmetric methods before the 1980s.

From the inspiring developments in catalysis during the 1950s and 1960s in the field of metallocene chemistry came new developments in the field of catalytic asymmetric cyclopropanation via metal-stabilized carbene intermediates [50]. The cyclopropane unit has been a desirable target for the pharmaceutical industry considering the plethora of biologically active molecules that contain this unit, such as *Cyclizidine*, which is an indolizidine antibiotic (Figure 1.2) [49], and *cilastatin*, a dehydropeptidase, that works as an antibiotic [51], as well as carbocylic nucleosides [52]. In fact, *Cilastatin* is produced via the Merck-Sumitomo process that uses a copper(II) catalyst containing a salicylaldimine ligand (Scheme 1.1), which was originally developed in the laboratory of Aratani [53] (more specific details on the development of the cyclopropantion reaction are discussed in Chapter 9). It should also be noted that the first homogeneous chiral catalyst invented was by Nozaki et al. and used in asymmetric cyclopropanation reactions [54].

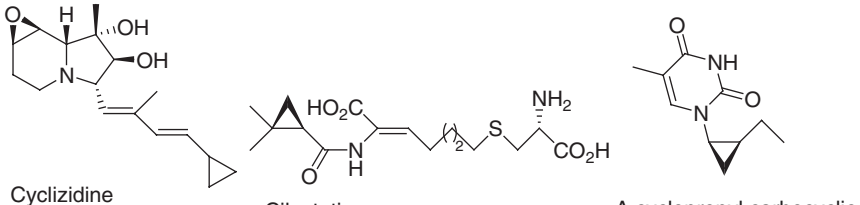
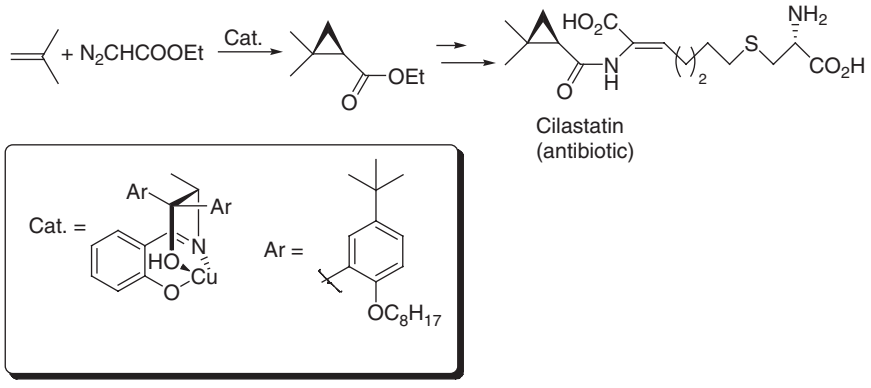
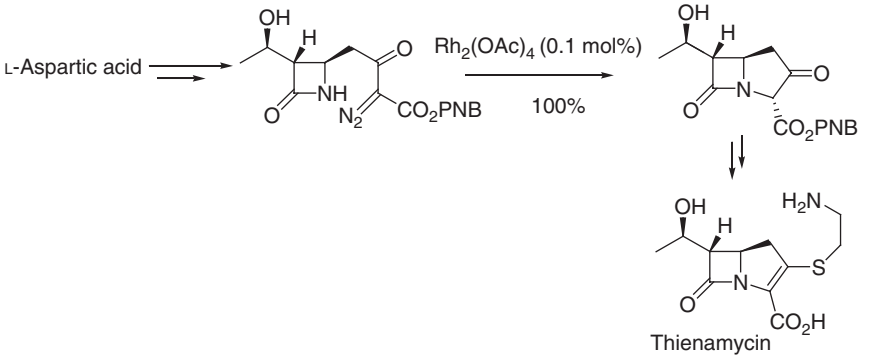


Figure 1.2 Some key biologically active compounds containing a cyclopropyl ring.



Scheme 1.1 Industrial synthesis of *Cilastatin*, employing the catalytic asymmetric cyclopropanation as the key step.

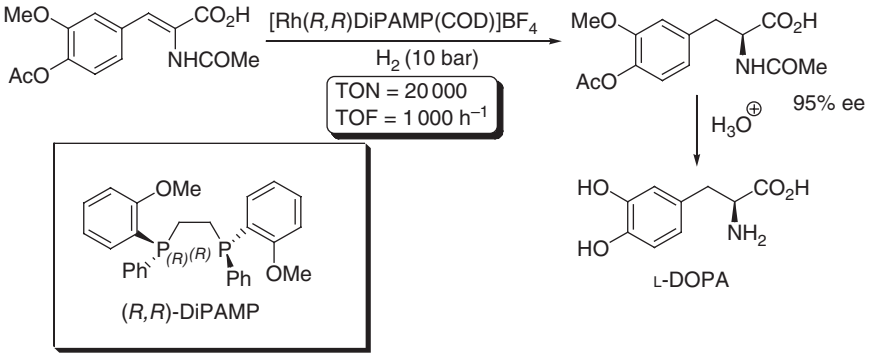
Also in connection to metallocarbenes was the synthesis of the potent antibiotic *thienamycin* by Merck in 1980. This was a landmark synthesis for its time, and the key step was an N—H insertion of a carbene unit to form the carbapenem ring system (Scheme 1.2) [55–57] (see Chapter 10 for insertion reactions). This method has been considered one of the most efficient methods as of yet devised for the synthesis of bicyclic β-lactams from 2-azetidinones [49]. The reaction was highly effective, affording a quantitative yield of the cyclized product with a $Rh_2(OAc)_4$ catalyst loading of 0.1 mol%.



Scheme 1.2 Merck's synthesis of *Thienamycin*, employing a Rh-catalyzed activated carbene insertion within an N—H bond.

Inspired by the pioneering work of Wilkinson in the 1960s and 1970s on homogeneous catalytic hydrogenation, workers such as Knowles, Horner, Kagan, and Morrison looked at new chiral non-racemic phosphines for asymmetric alkene hydrogenation [58]. The results in the beginning were poor, but then Henri Kagan made an important breakthrough in the asymmetric hydrogenation of α-(acylamino)acrylic acids using the DIOP (2,3-*O*-Isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane) ligand (a privileged ligand). The highest enantioselectivity of 85% ee was achieved [59].

Soon afterwards, Knowles and coworkers reported the use of the chiragenic diphosphine (1,2-Bis[(2-methoxyphenyl)(phenylphosphino)]ethane) DIPAMP [60], which was then used as a key step in the synthesis of the drug *L-DOPA* for Parkinson's disease (Scheme 1.3)[2] [61]. Usual conditions are substrate/catalyst >10 000 and about 3 atm pressure at 50 °C and 1 h reaction time. An ee of 95% was obtained and the turnover number (TON) and turnover frequency (TOF) were very high. As a rule of thumb for catalytic reactions that use expensive metal complexes, and that are competing with other viable routes, the TONs should be >1 000–10 000 [62]. This API was produced on a ton scale annually for several years [63]. Knowles received one-quarter of the chemistry Nobel Prize in 2001 for these efforts.



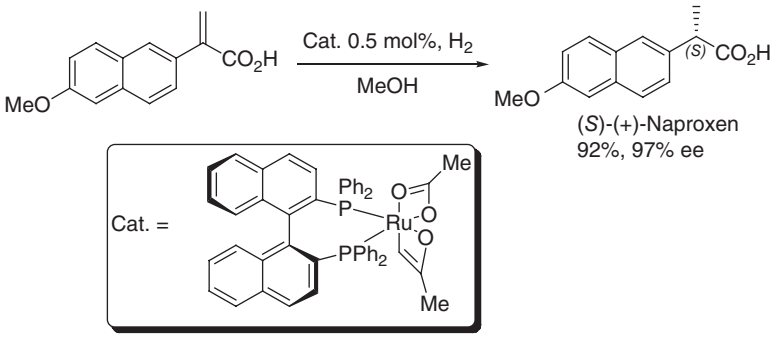
Scheme 1.3 Industrial synthesis of *L-DOPA*, employing a catalytic asymmetric hydrogenation as the key step.

Ru catalysts have also been used for API production. Noyori and coworkers developed the famous BINAP (1,1′-Binaphthalene-2,2′-diyl)bis(diphenylphosphine)) ligand that when complexed with certain Ru pre-catalysts forms very active asymmetric hydrogenation catalysts [64]. Noyori and coworkers then applied this catalyst successfully in the synthesis of the nonsteroidal anti-inflammatory compound *Naproxen*, which is a very large-selling prescription drug (Scheme 1.4). (This API also features in Chapter 12.) [65, 66] *(S)-Ibuprofen* was also obtained using this catalytic method with the catalyst $Ru(OAc)_2$[(*S*)-H_8-BINAP] applying a high hydrogen pressure of 135 atm, giving the product in 100% yield with an ee of 97% [65].

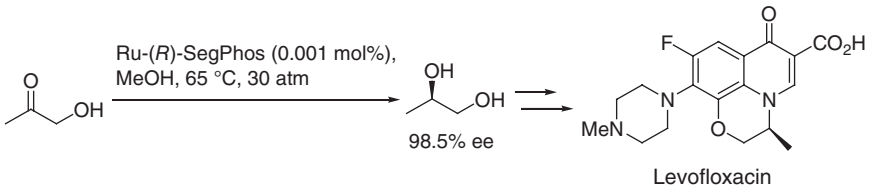
The catalytic asymmetric reduction of carbonyl groups has also given some important APIs.

A Ru(I)-SegPhos catalyst was used to make (2*R*)-1,2-propanediol from hydroxyacetone, the former being a building block for the antibiotic *Levofloxacin* (Levaquin®;

[2] This drug appears in the book *Awakening*s (1973) by Oliver Sacks and the film (1990, Columbia pictures) with the same name starring the late and brilliant Robin Williams and the equally great Robert DeNiro. Sacks recounts his experience treating patients at the Beth Abraham Hospital in New York with encephalitis lethargica with the new drug L-DOPA. The scene in the film between the industrial chemist and the main protagonist, representing Oliver Sacks and portrayed by Robin Williams is quite interesting.



Scheme 1.4 Key catalytic step in the asymmetric hydrogenation reaction to give *Naproxen*.



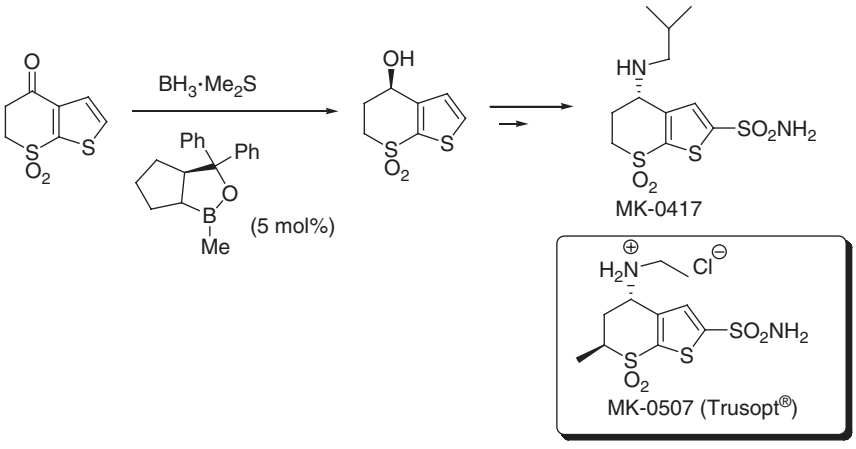
Scheme 1.5 Key catalytic step in the asymmetric hydrogenation of hydroxyacetone leading to *Levofloxacin*.

Scheme 1.5) [65]. The product is obtained with an ee of 98.5% and a catalyst loading of only 0.01 mol%, which was remarkable.

It was also used to make (*S*)-*Propranolol* using $[Rh(cod)Cl]_2$ as the pre-catalyst and (2*S*,4*S*)-MCCPM as the chiral ligand with an ee of 90.8%, which can also be obtained using the Sharpless–Katsuki Ti-catalyzed epoxidation (see subsequent text) [67]. ((*S*)-*Propranolol* also features in Chapter 12, where a key enzymatic step is used in its synthesis.)

Since then, numerous other APIs have been synthesized using this catalytic methodology (see Chapter 4). This is a superb manufacturing technology for the chiral intermediates used for API production.

In 1981, Hirao et al. studied the application of chiral alkoxy-amine-borane complexes for the enantioselective reduction of ketones [68]. Based on these pioneering studies in 1987, Corey et al., together with his coworkers Bakshi and Shibata, introduced the highly successful oxazaborolidine family of catalysts that have now been used so successfully in the industrial sphere (the reaction is known as the Corey–Bakshi–Shibata reduction or CBS reduction) [69]. At the 1991 annual chemical congress of the RSC to mark its 150th anniversary, Corey in his talk considered these molecules analogous to "Molecular robots" (actually this was the title of his wonderful talk) in their form and function. The CBS reduction has been used with great effect by Merck to produce MK-0417 which was a predecessor of the anti-glaucoma drug *dorzolamide* (MK-0507, Trusopt®; Scheme 1.6) [70]. Currently the key reduction step to give Trusopt is conducted via a whole-cell-based biotransformation [71]. There have been many other commercial applications of this catalytic



Scheme 1.6 Key catalytic CBS reduction in the synthesis of MK-0417, a *Dorzolamide* (MK-0507, Trusopt) forerunner.

process, and the reader is encouraged to read the review by Caille et al. [72]This catalyst is discussed in Chapter 4.

The key catalytic oxidation steps for API synthesis have generally been asymmetric. After much initial experimentation by pioneers like Mimoun, Kagan, Schurig [73], and Henbest and coworkers in the mid-1960s who developed the first optically active peracid [74], Sharpless and coworkers and the late Tsutomu Katsuki in 1980 revolutionized the field when they showed that allylic alcohols could be epoxidized with *tert*-butylhydrogen peroxide and a bimetallic catalyst that consisted of Ti and a tartrate ester with exceptional enantioselectivities and high yields [75–78]. This might be considered one of the key motivators that heralded in the modern era of catalytic asymmetric synthesis, putting it firmly on the map. The importance of this discovery was recognized by the award of the Nobel Prize in Chemistry to Sharpless in 2001. (In a way, we can use the attribution of the Nobel Prize as a type of barometer for measuring the advances in catalysis and chemistry in general.) Commercial applications have been found and operation on the large scale have proved to be reliable and successful [65]. One of the principal commercial applications was the use of this technology by the chemical company Arco for the single enantiomer glycidol derivatives and their application in the synthesis of APIs (Figure 1.3) [79]. This was then licensed to PPG-Sipsy, and produced on a multiton scale per year, but this process has been discontinued by PPG-Sipsy.

The Jacobsen–Katsuki epoxidation was independently discovered by Jacobsen and Katsuki in 1990 [80]. This is a very useful catalytic reaction for the epoxidation of unfunctionalized olefins. The active catalysts are obtained by activation of Mn-salen complexes with an oxidant, like bleach. Very high enantioselectivities can be obtained for the epoxidation of conjugated olefins. In fact, this reaction is one of the most efficient processes for the execution of chiral kinetic resolutions so far known (see Chapter 4).

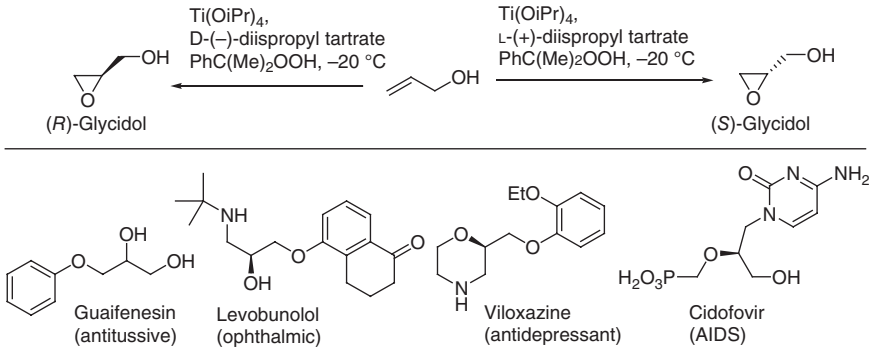
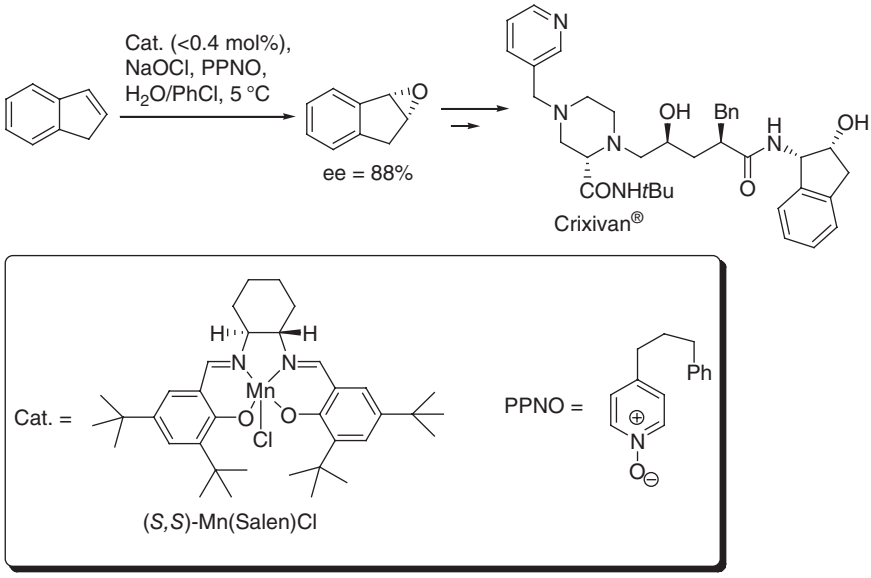


Figure 1.3 The application of the Sharpless–Katsuki epoxidation for the synthesis of single enantiomer glycidol: APIs obtained from glycidol.

This reaction has been successfully embraced by the pharmaceutical industry for the production of Merck and Co.'s HIV protease inhibitor *Indinavir* (Crixivan®). (This catalyst is also discussed in Chapter 12.) [65, 73] This reaction was developed by Merck and ChiRex (Sepracor) for the enantioselective epoxidation of indene (Scheme 1.7) with a TON of greater than 250 and a TOF of 250 h^{-1}. The TOF is not fantastic, and this might explain why the reaction is carried out on a small scale by these companies [65].

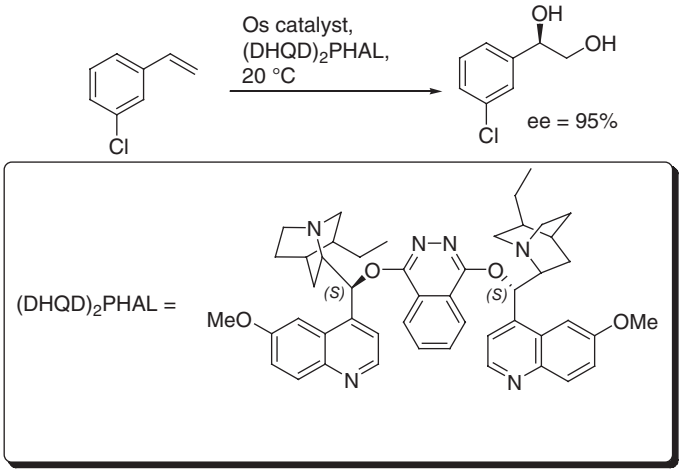


Scheme 1.7 Asymmetric catalytic epoxidation of indene, a key step in the manufacture of *cis*-1-amino-2-indanol for *Indinavir* production by Merck and Co.

In 1987, Sharpless' group reported the catalytic asymmetric *cis*-dihydroxylation using chiral osmium catalysts [81]. This was a major breakthrough in the

field of asymmetric catalysis, as the process is highly efficient and affords enantiopure chiral *vic*-diols. Since this time the reaction was greatly optimized, with a commercial readymade mixture already on the market (commercialized by Millipore-Sigma – formerly Sigma-Aldrich – that contains all the essential ingredients (Osmium catalyst, chiral cinchona ligand, base, and reoxidant, i.e. AD mix α and β [82]).

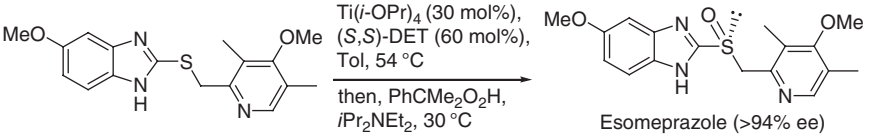
Enantiomerically pure *m*-chlorostyrene diol – which is a useful building block for API synthesis – is manufactured on a scale of hundreds of kilos by Rhodia (now part of Solvay; Scheme 1.8) [46]. The reaction ocurred with a TON of 500 and a TOF of 50 to 100 h^{-1}.



Scheme 1.8 Large-scale asymmetric catalytic osmium dihydroxylation of *m*-chlorostyrene diol by Solvay-Rhodia.

The advances made with the epoxidation of allylic alcohols led to development of the asymmetric sulfoxidation of sulfides independently by Kagan and Modena in 1984 [83]. Kagan found that using the Sharpless–Katsuki system with 1 equiv. of water it was possible to obtain sulfoxides with very high enantioselectivities. Modena used a larger excess of the tartrate ligand. The catalytic version of this reaction was later developed [84]. A number of industrial applications of this key process for the production of APIs ensued [85]. The most notable application was for the manufacture of *Esomeprazole* (discussed also in Chapter 4) by AstraZeneca, which was approved by the FDA in 2001 [84]. The racemic version known as *Omeprazole* (discussed also in Chapter 4) was originally launched in 1988: however, due to competition from generic companies after the patent expired in 2001, AstraZeneca proceeded with the chiral switch to the (*S*)-enantiomer, that is known essentially as *Esomeprazole* (Nexium®) and thus became their big-selling ulcer drug to replace *Omeprazole*. This oxidation is carried out on a scale of 100 t yr^{-1} [65, 66, 86]. The key step in the synthesis of *Esomeprazole* is an asymmetric Kagan–Modena sulfide oxidation, which afforded the sulfoxide with an enantioselectivity of 94% ee (Scheme 1.9) [87]. The enantiopurity could be pushed

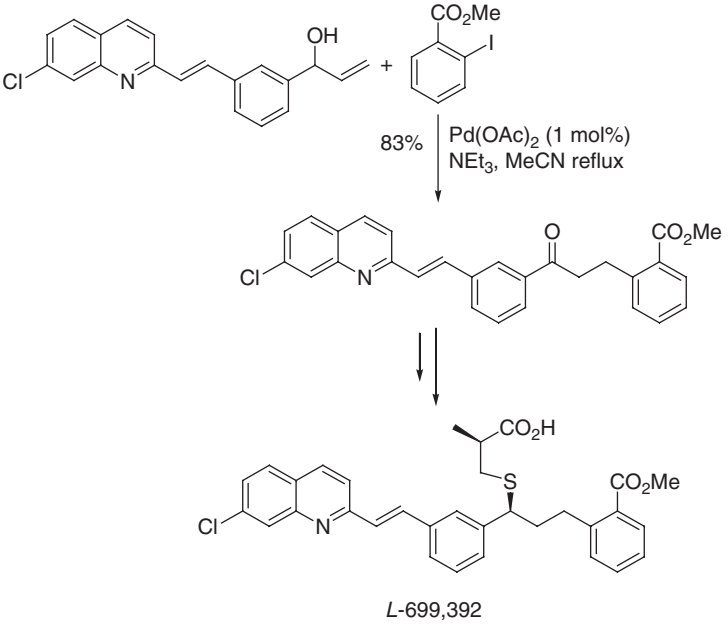
up to >99.5% ee by converting the product to its sodium salt and crystallizing from methyl isobutyl ketone (MIBK) and MeCN. This process can be run on a multi-kilo scale. The TON and TOF were not very high, and are in the range, 4–16 and 3–12 h^{-1}, respectively [88].



Scheme 1.9 The key sulfide asymmetric oxidation step using the Kagan/Modena procedure for the large-scale manufacture of *Esomeprazole* by AstraZeneca.

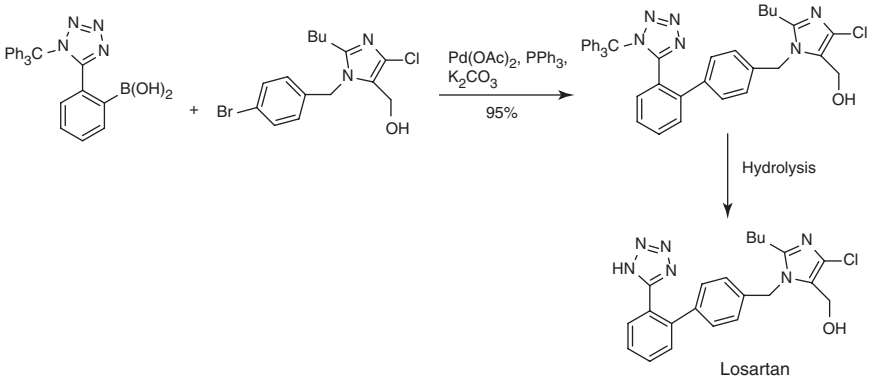
In the case of cross-coupling reactions involving the creation of C—C bonds, the Mizoroki–Heck (MH), the SM reaction and the Negishi coupling reaction have all been very successfully applied to the manufacture of APIs.

In the case of the MH reaction, numerous industrial applications exist, such as in the production of the anti-inflammatory drug *Naproxen* (discussed in Chapter 6) that is produced by Albemarle (formerly Hoechst AG) and the asthma drug *Monteculast* (Singulair®) produced by Merck [2, 51]. It is also used by Merck for the production of the leukotriene antagonist *L-699,392* (discussed in Chapter 6; Scheme 1.10) [89]. An allylic alcohol was reacted with methyl iodobenzoate using 1 mol% palladium acetate in the presence of triethylamine in refluxing acetonitrile, giving the product in 83% yield.



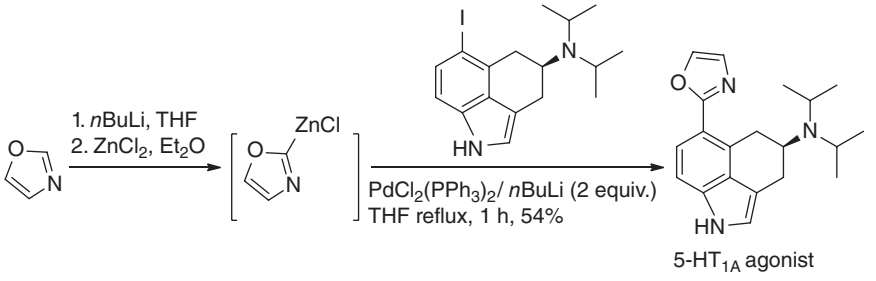
Scheme 1.10 The Mizoroki–Heck coupling reaction in the manufacturing process to *L-699,392* developed by Merck & Co.

As mentioned, catalyzed C—C coupling reactions are currently key tools in the synthetic/medicinal/process chemists' tool box. In 1995, the versatile SM reaction was exploited by Merck as a key step in the synthesis of the angiotensin II receptor antagonist, *Losartan* (see also Chapter 6, for further details; Scheme 1.11) [86].



Scheme 1.11 The SM coupling reaction in the manufacturing process to *Losartan* developed by Merck.

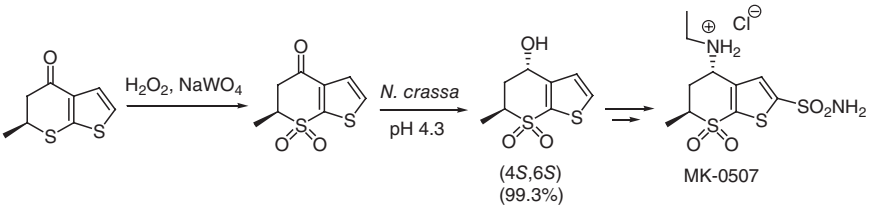
The Negishi reaction is not used to the same extent by the pharmaceutical industry as the SM reaction [90], it is used by Lilly for the production of a 5-HT1A agonist (Scheme 1.12) [91].



Scheme 1.12 The key Negishi-coupling step in the production of a 5-HT_{1A} agonist by Lilly.

Enzymes are excellent catalysts for API synthesis, since they can afford products with enantiomeric excesses of >99%. With the current advances in biotechnological tools, enzymes can be produced from microbes in the quantities required by industry [92]. No protection/deprotection steps are required, and the reactions can be run in water. Enantiomeric reduction, hydroxylation, oxidation, hydrolysis, etc., can be carried out with specialized commercial enzymes [93]. Valued high-profile drugs such as Januvia®, Crestor®, Lipitor®, and Singulair® are produced using biocatalysis. However, enzymes are expensive, and one way of overcoming this disadvantage is by enzyme immobilization to solid supports for recycling. (This topic is discussed in Chapter 12.)

In the biocatalysis arena, biotransformation for the asymmetric reduction of ketones is well documented; and many processes are known, one of which was used by Merck and Zeneca for the production of *Dorzolamide* (MK-0507, Trusopt, a carbonic anhydrase inhibitor used in the treatment of glaucoma (see also Chapter 4) [94]. After many studies and optimizations, the target MK-0507 was obtained via enzymatic reduction of the corresponding sulfone intermediate using the fungus *Neurosporo crassa* (Scheme 1.13). The key hydroxysulfone compound – which was then converted to the MK-0507 target via a multistep route – was obtained in an isolated yield of over 80% with >99% purity and as a mixture of the main (4*S*,6*S*)-diastereomer (>98%) and the minor (4*R*,6*S*)-diastereomer (0.5%). It is believed that a highly stereospecific dehydrogenase found in the cytoplasmic fraction of the organism is responsible for this reduction; it is nicotinamide adenine dinucleotide phosphate (NADPH) specific.



Scheme 1.13 The key biotransformation with *N. crassa* for the manufacture of *MK-0507* by Zeneca-Merck.

Many other examples are discussed in Chapter 12.

These are just some key examples of the application of catalysis for API manufacture in the pharmaceutical industry; throughout the rest of the book, we have many more. A number of excellent reviews abound in the literature, like, for example, the very informative reviews of Magano and Dunetz [90], Farina et al. [3], Busacca et al. [2], and Torborg and Beller [62], just to name a few.

1.4 Catalytic Synthesis of APIs in the Twenty-First Century: New Developments, Paradigm Shifts, and Future Challenges

To finalize this chapter, we take a quick look at key developments that have taken place over the past years that allow the manufacture of APIs in a more sustainable and process-intensive manner. We also consider other issues such as the perennial question of catalytic enantioselective methods for single-enantiomer API manufacturing.

Starting with the latter question, Hans-Ulrich Blaser, Benoît Pugin, and Martin Studer who are well-known experts from Solvias AG, are of the opinion that the relatively slow progress in the field of asymmetric catalysis in the pharmaceutical industrial context is probably due to the very high attrition rates for new chemical entities (around 90% in all therapeutic areas) and the relatively low number of

new drugs that have been introduced in the past 15 years [65]. To get an idea of the importance of chemocatalytic methods for providing single-enantiomer compounds (not just APIs, but agrochemicals and other molecules, as this precise information was not available), in 2004, it was estimated that 35% of the worldwide revenues (in excess of $7 billion) were obtained via the usage of chemocatalysis (about 50% would come from the chiral pool and chiral resolution, and 15% from biocatalysis) [93]. The other reason given was the fact that the development of new chiral technologies requires greater investment in both time and money than do classical organic transformations. They have also correctly observed that in some cases the catalysts are not available on a large scale, they are difficult to prepare, and there might be some intellectual property (IP) issues. Hawkins and Watson have also pointed out that the cost of an asymmetric catalyst can be broken into three components: (i) the chiral ligand, (ii) the metal if present, and (iii) any royalties (he noted that as far back as 1997, there has been an increased tendency to patent synthetic methodology with the result that it creates "a complex legal maze for the chemical industry") [95]. They have also drawn attention to the variable prices of metals, which generally are dependent on "geopolitical events well beyond the chemists' control." Despite these difficulties, these authors believe that the future is still bright, and the application of such technologies will accelerate. This, they believe, will be because of the number of small and medium-sized companies that provide exciting new chemical technologies and services, so that these activities are no longer needed to be conducted in-house by Big Pharma. They can also offer their catalyst platforms in the required quantities for large-scale production.

Two of the authors of this book (AJB and GJH), who are involved in the commercialization of chiral molecules by the chiral technology (in the context of involvement with the chiral technology specialist company Chiratecnics (www.chiratecnics.com)), hold a similar view, and have noted very slow assimilation of new chiral catalyst entities by the pharmaceutical industry during the past 10 years.

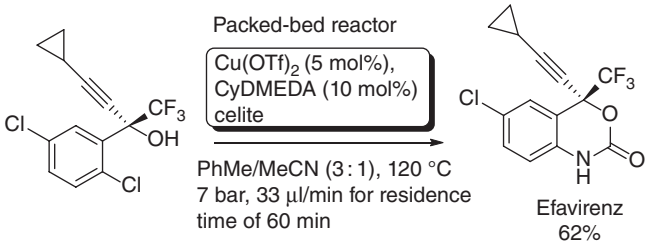
Other key factors that contribute to the difficulty in the adoption of new catalytic systems by the pharmaceutical industry is the prerequisite of having high catalytic efficiencies in terms of TON and TOF on a large scale. This is a key issue when the chiral catalyst contains either very expensive and rare metal catalysts or ligands or both.

A number of new enabling technologies are increasingly being implemented in the industrial arena; one major new technology is continuous-flow synthesis, which is at the forefront of the so-called continuous manufacturing concept [96]. Continuous-flow procedures coupled with catalysis is a very powerful approach to produce APIs in a sustainable and process-intensive manner. Continuous-flow procedures offer many advantages over traditional batch methods, which include controlled heat transfer, controlled mixing (both fast and slow), increased photoflux in photochemical reactions – these are becoming increasingly important (see subsequent text) – increased electrode surface-to-reactor volume ratio (electrochemistry), safer reactions and controlled manipulation of highly reactive/toxic materials, and, very importantly in the context of sustainable manufacturing processes in the pharmaceutical industry, increased capacity to run serial

reactions [97]. Scale-up can be achieved by increasing the number of reactors or the reactor dimensions. Ultimately, the aim for the pharmaceutical industry is to manufacture the drug product from raw materials (ideally biomass based) in a single end-to-end process. This can be a solution to the common problems of production via batch methods, which include long production times and vulnerability to supply chain disruptions, so batch processes are generally incompatible with process intensification and scale-up. Although other industries, like the oil industry, have made the transition from batch to continuous manufacturing allowing for significant process intensification, batch or fed-batch methods are still the norm in the pharmaceutical and biotech industries.

The academic groups of Peter Seeberger, Steven Ley, Ian Baxendale, Timothy Jamison, Klavs Jensen, Andreas Kirschning, and others have made enormous advances in the development of sequential continuous flow systems, generally employing flow-chemistry catalytic reaction steps.

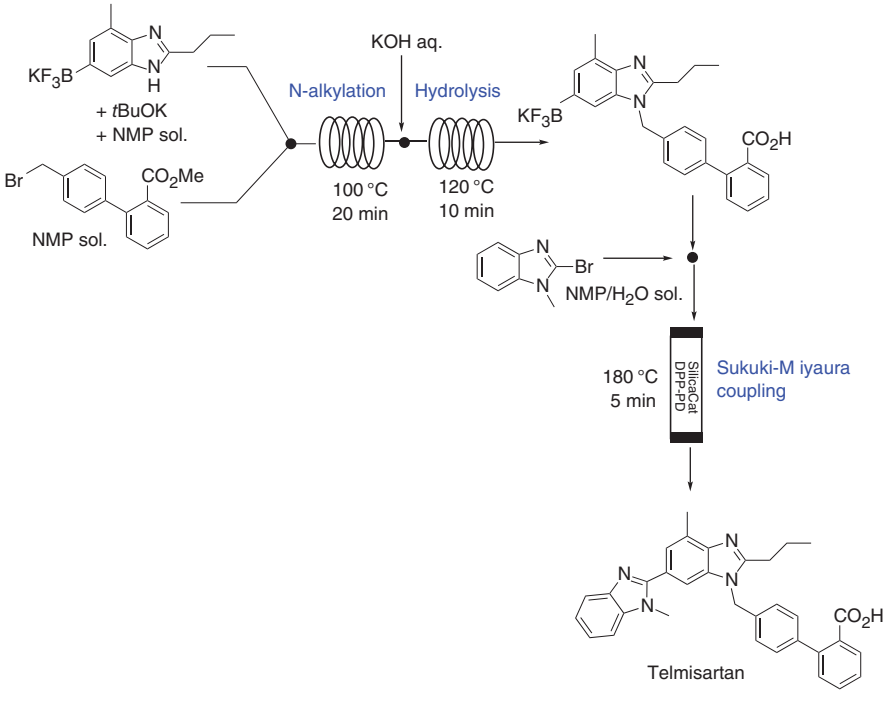
Seeberger's group reported an efficient proof-of-concept semicontinuous flow synthesis of the HIV combination therapy drug *Efavirenz* (Sustiva®) [98]. *Efavirenz* was discovered at Merck Research Laboratories in 1993; however, their production method did not involve any catalytic steps (the key step being the stoichiometric asymmetric addition of an acetylide to a ketimine intermediate) [99]. The last step in their synthesis was a Cu-catalyzed synthesis of a *N*-aryl carbamate which they conducted under continuous-flow conditions (CFCs), with the Cu catalyst immobilized in a packed-bed reactor with Celite – this option was taken due to the poor solubility of the NaOCN in the reaction solvent – (Scheme 1.14). Using $Cu(OTf)_2$ (in the packed-bed reactor with the NaOCN) and CyDMEDA as ligand with a temperature of 120 °C and pressure of 7 bar, they obtained *rac-Efavirenz* in 62% isolated yield.



Scheme 1.14 The key catalytic step in the route to the anti-HIV drug *Efavirenz* performed under CRC described by Seeberger and coworkers. (For an excellent overall scheme showing the whole process see Benaglia's and Puglisi's review Ref. [5].)

Multistep continuous-flow processes are very desirable. In 2013, Ley's group reported the synthesis of Novartis' tyrosine kinase inhibitor *Imatinib* (Gleevac®) – a drug used to treat chronic myeloid leukemia and gastrointestinal stromal tumors, using a three-step all-in-one sequential flow process [100]. The key step included a successful Buchwald–Hartwig catalysis. Minimal manual intervention was required.

Back-to-back fully automated sequential flow chemistry was also developed by Gupton and coworkers for the synthesis of *Telmisartan* (Micardis®), an angiotensin receptor antagonist used in the treatment of hypertension (Scheme 1.15) [101].



Scheme 1.15 Gupton and coworkers' fully automatic flow-synthesis of *Telmisartan*.

The key step was a SM coupling reaction using a Pd catalyst (in a SilicaCat DPP-Pd cartridge) at 180 °C. The reaction was complete in only 5 min. This process provided *Telmisartan* in an overall yield of 81% at a production rate of 1 mg min^{-1}.

Organocatalysts have also been used frequently under CFCs; Benaglia and Puglisi's review (Ref. [5]) is replete with good examples.

To show the enormous potential of this approach for the manufacture of APIs, Jamison and coworker reported in 2015 the three-minute synthesis and purification of *Ibuprofen* – although no catalysts were involved, the main reaction was a Friedel–Crafts acylation, which could be rendered catalytic in the future [102]. Even more impressive examples were (i) Jensen's and Jamison's multistep synthesis and workup sequence for the renin inhibitor *Aliskiren* hemi-fumarate (Tekturna® and Rasilez®) [103] (which also features in Chapter 3) and (ii) for the streamlined continuous back-to-back synthesis of diphenylhydramine hydrochloride, *Lidocaine hydrochloride*, *Diazepam* and *Fluoxetine hydrochloride* [104]. In the former, no catalysts were used, but what is impressive is the requirement of a reaction time of only 1 h as compared to 48 h in batch mode and this is under solvent-free conditions. With only a volume of 0.7 l, 0.8 tons of *Aliskiren* hemi-fumarate can be produced per annum. In the case of the latter, this also did not include any catalytic reaction steps in any of the synthesis, but it was a thoroughly integrated process, from synthesis, to purification to reaction monitoring (Fourier-transform infrared (FTIR) was integrated for real-time reaction monitoring of the formed API).

With these developments, we are becoming closer to obtaining real plug-and-play systems that can conduct sustainable catalytic synthesis.

The benefits of coupling continuous-flow procedures with catalysis is that, in many cases, the catalyst can be immobilized within the system, usually in an associated tube and used with considerable effect [5].

Continuous-flow chemistry coupled to photochemistry (or photo-flow chemistry) is a very new powerful adaptation of continuous-flow procedures [105]. Lévesque and Seeberger have already shown the usefulness of this technique for the production of the antimalaria drug *Artemisinin* [106].

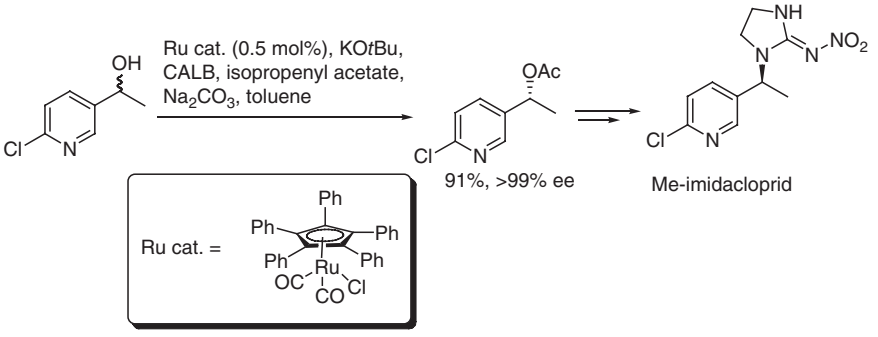
Continuous biocatalytic processing is also a powerful route to API synthesis, and in fact many biotech companies are studying the technological and economic feasibility of continuous manufacturing [107]. Continuous processing with soluble and immobilized enzymes is possible using suitable reactor design [108]. Traditionally, continuous operation has been conducted at the upstream side, whereas downstream processing has been carried out in a batch-wise manner. Integration of the downstream process with the upstream process remains a challenge [108]. There are numerous examples of continuous enzymatic processes on a large scale. The glucose-isomerase-catalyzed conversion of glucose (derived from starch) into high-fructose syrups is the most important industrial biocatalytic process which is operated continuously. The isomerase enzyme is immobilized [108]. Immobilized enzymes generally show enhanced stability as compared to soluble enzymes.

Sequential catalytic reactions as a route to API synthesis also have much potential, in terms of sustainability and economics. This strategy has already been used with effect for the synthesis of complex synthetic targets; however, as of yet this approach still needs to be embraced by the pharmaceutical industry for API manufacture. There are a number of excellent reviews on this topic [109].

Dual catalysis is another emerging approach to APIs; this is in fact a tandem process as opposed to a sequential catalytic process which involves more than one transformation. In this case, there are two separate catalysts operating in tandem in the same transformation. Dual catalysis comes in many disguises, for instance, with two different metal-based catalysts, or a combination of a metal catalyst with an enzyme [2] or the more recent approach that involves the combination of metal or organocatalyst catalysis/photoredox catalysis [108]. A very recent example of the first type was reported by Buchwald's group, where they used both a Cu and a Pd catalyst for the asymmetric catalytic synthesis of 1,1-diarylalkanes, which are present as a motif in a number of APIs, via the hydroarylation of vinylarenes [110]. Both catalysts worked synergistically; a copper hydride was used to transform the vinylarene to the stereodefined Cu(I) intermediate, which then underwent transmetallation with the Pd(0) catalyst to the Pd(II) intermediate that underwent reductive elimination to form the diaryl product.

The second variant is a powerful procedure for carrying out efficient dynamic kinetic asymmetric transformations (DYKATs), like, for instance, the resolution of racemic alcohols. The enzyme can catalyze the enantioselective acylation, to give an enantiomerically pure ester product and alcohol starting material, while the role of the metal catalyst, like a Ru complex, would be the racemization of the

enantiomerically pure alcohol. This will allow the formation of only enantiomerically pure ester at the end [2]. This strategy has been used with great effect in the manufacture of the pesticide *Neonicotinoide* by Bäckvall and coworkers [111]. *Candida Antarctica* lipase B (CALB) was used in conjunction with a RuCp* catalyst to give the key acetate intermediate in 91% yield and > 99% ee (Scheme 1.16).



Scheme 1.16 The key dual catalytic DYKAT in the synthesis of the insecticide *Me-imidacloprid* developed by Bäckvall and coworkers.

In the last strategy, which is another technique that should offer much for sustainable API manufacture, an organic dye or an inorganic semiconductor that functions as the photocatalyst is used. Upon irradiation with visible light, it undergoes excitation to give a long-lived triplet-excited photocatalyst, which is both a stronger oxidant and reductant than the ground state complex. This is followed by either electron transfer from the excited photocatalyst to the substrate (oxidative quenching) or electron transfer from the substrate to the photocatalyst (reductive quenching). The upshot of this is that a radical anion or cation is formed under very mild conditions [111]. These radicals are capable of engaging in organo- or transition-metal catalytic cycles in novel manners that complement the common reactivity of these catalysts [111]. Many interesting examples are given in the review from Frank Glorius' group [111], one of which was MacMillan's asymmetric catalytic α-alkylation of aldehydes with alkyl bromides [112]. This transformation was unattainable up to MacMillian's report in 2008.

Catalyst immobilization, which has been around for some time and we have already mentioned it in the context of biocatalysis, is another strategy to improve the sustainability of the catalytic procedure on the large scale [113], although there have been some concerns that maybe this strategy brings few advantages [114].

The use of nanoparticle catalysis for API synthesis also has significant potential [115]. The advantages of using nanoparticle catalysts include their remarkable catalytic activities and selectivities, which can be tuned via careful modification by controlling their size and shape, and also by changing the support materials and capping agents. They can be potentially recycled via immobilization techniques and applied with effect in continuous-flow systems, thus offering green and cost-effective alternatives. Unfortunately, as of yet, nanoparticle catalysis has not found broad application in complex molecule synthesis, as they have been limited to cross-couplings and oxidation/reduction reactions [115].

1.5 Conclusions

In this chapter we took a brief glimpse at the development of the modern science of catalysis from its humble origins at the turn of the last century. We saw the impact of a number of key developments on its evolution, and its transformation into a key industrial tool. From these origins and developments we learned how novel catalytic processes have been used effectively to provide key APIs, most of which are single enantiomers.

We have also addressed some of the major challenges that are facing the pharmaceutical industry with regard to API production, and looked at some of the new innovations, principally that of process intensification through continuous manufacturing, sustainability, and other issues that impact the economics of API production.

In the next chapter the reader will learn more about the major technical and other issues that are taken into account by the pharmaceutical industry in taking an API from the laboratory bench to the market.

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