1
Introduction: Green Chemistry and Catalysis

1.1
Introduction

It is widely acknowledged that there is a growing need for more environmentally acceptable processes in the chemical industry. This trend towards what has become known as 'Green Chemistry' [1–9] or 'Sustainable Technology' necessitates a paradigm shift from traditional concepts of process efficiency, that focus largely on chemical yield, to one that assigns economic value to eliminating waste at source and avoiding the use of toxic and/or hazardous substances.

The term 'Green Chemistry' was coined by Anastas [3] of the US Environmental Protection Agency (EPA). In 1993 the EPA officially adopted the name 'US Green Chemistry Program' which has served as a focal point for activities within the United States, such as the Presidential Green Chemistry Challenge Awards and the annual Green Chemistry and Engineering Conference. This does not mean that research on green chemistry did not exist before the early 1990s, merely that it did not have the name. Since the early 1990s both Italy and the United Kingdom have launched major initiatives in green chemistry and, more recently, the Green and Sustainable Chemistry Network was initiated in Japan. The inaugural edition of the journal Green Chemistry, sponsored by the Royal Society of Chemistry, appeared in 1999. Hence, we may conclude that Green Chemistry is here to stay.

A reasonable working definition of green chemistry can be formulated as follows [10]: *Green chemistry efficiently utilizes (preferably renewable) raw materials, eliminates waste and avoids the use of toxic and/or hazardous reagents and solvents in the manufacture and application of chemical products.*

As Anastas has pointed out, the guiding principle is the *design* of environmentally benign products and processes (benign by design) [4]. This concept is embodied in the 12 Principles of Green Chemistry [1, 4] which can be paraphrased as:

1. Waste prevention instead of remediation
2. Atom efficiency
3. Less hazardous/toxic chemicals
4. Safer products by design
5. Innocuous solvents and auxiliaries

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6. Energy efficient by design
7. Preferably renewable raw materials
8. Shorter syntheses (avoid derivatization)
9. Catalytic rather than stoichiometric reagents
10. Design products for degradation
11. Analytical methodologies for pollution prevention
12. Inherently safer processes

Green chemistry addresses the environmental impact of both chemical products and the processes by which they are produced. In this book we shall be concerned only with the latter, i.e. the product is a given and the goal is to design a green process for its production. Green chemistry eliminates waste at source, i.e. it is primary pollution prevention rather than waste remediation (end-of-pipe solutions). Prevention is better than cure (the first principle of green chemistry, outlined above).

An alternative term, that is currently favored by the chemical industry, is Sustainable Technologies. Sustainable development has been defined as [11]: *Meeting the needs of the present generation without compromising the ability of future generations to meet their own needs.*

One could say that Sustainability is the goal and Green Chemistry is the means to achieve it.

1.2. E Factors and Atom Efficiency

Two useful measures of the potential environmental acceptability of chemical processes are the E factor [12–18], defined as the mass ratio of waste to desired product and the atom efficiency, calculated by dividing the molecular weight of the desired product by the sum of the molecular weights of all substances produced in the stoichiometric equation. The sheer magnitude of the waste problem in chemicals manufacture is readily apparent from a consideration of typical E factors in various segments of the chemical industry (Table 1.1).

The E factor is the actual amount of waste produced in the process, defined as everything but the desired product. It takes the chemical yield into account and includes reagents, solvents losses, all process aids and, in principle, even fuel (although this is often difficult to quantify). There is one exception: water is generally not included in the E factor. For example, when considering an aqueous waste stream only the inorganic salts and organic compounds contained in the water are counted; the water is excluded. Otherwise, this would lead to exceptionally high E factors which are not useful for comparing processes [8].

A higher E factor means more waste and, consequently, greater negative environmental impact. The ideal E factor is zero. Put quite simply, it is kilograms (of raw materials) in, minus kilograms of desired product, divided by kilograms

Table 1.1 The E factor.

Industry segment	Product tonnage [a)]	kg waste [b)]/kg product
Oil refining	10^6–10^8	<0.1
Bulk chemicals	10^4–10^6	<1–5
Fine chemicals	10^2–10^4	5–>50
Pharmaceuticals	10–10^3	25–>100

a) Typically represents annual production volume of a product at one site (lower end of range) or world-wide (upper end of range).

b) Defined as everything produced except the desired product (including all inorganic salts, solvent losses, etc.).

of product out. It can be easily calculated from a knowledge of the number of tons of raw materials purchased and the number of tons of product sold, for a particular product or a production site or even a whole company. It is perhaps surprising, therefore, that many companies are not aware of the E factors of their processes. We hasten to point out, however, that this situation is rapidly changing and the E factor, or an equivalent thereof (see later), is being widely adopted in the fine chemicals and pharmaceutical industries (where the need is greater). We also note that this method of calculation will automatically exclude water used in the process but not water formed.

Other metrics have also been proposed for measuring the environmental acceptability of processes. Hudlicky and coworkers [19], for example, proposed the effective mass yield (EMY), which is defined as the percentage of product of all the materials used in its preparation. As proposed, it does not include so-called environmentally benign compounds, such as NaCl, acetic acid, etc. As we shall see later, this is questionable as the environmental impact of such substances is very volume-dependent. Constable and coworkers of GlaxoSmithKline [20] proposed the use of mass intensity (MI), defined as the total mass used in a process divided by the mass of product, i.e. MI = E factor + 1 and the ideal MI is 1 compared with zero for the E factor. These authors also suggest the use of so-called mass productivity which is the reciprocal of the MI and, hence, is effectively the same as EMY.

In our opinion none of these alternative metrics appears to offer any particular advantage over the E factor for giving a mental picture of how wasteful a process is. Hence, we will use the E factor in further discussions.

As is clear from Table 1.1, enormous amounts of waste, comprising primarily inorganic salts, such as sodium chloride, sodium sulfate and ammonium sulfate, are formed in the reaction or in subsequent neutralization steps. The E factor increases dramatically on going downstream from bulk to fine chemicals and pharmaceuticals, partly because production of the latter involves multi-step syntheses but also owing to the use of stoichiometric reagents rather than catalysts (see later).

The atom utilization [13–18], atom efficiency or atom economy concept, first introduced by Trost [21, 22], is an extremely useful tool for rapid evaluation of the amounts of waste that will be generated by alternative processes. It is calculated by dividing the molecular weight of the product by the sum total of the molecular weights of all substances formed in the stoichiometric equation for the reaction involved. For example, the atom efficiencies of stoichiometric (CrO_3) vs. catalytic (O_2) oxidation of a secondary alcohol to the corresponding ketone are compared in Fig. 1.1.

In contrast to the E factor, it is a theoretical number, i.e. it assumes a yield of 100% and exactly stoichiometric amounts and disregards substances which do not appear in the stoichiometric equation. A theoretical E factor can be derived from the atom efficiency, e.g. an atom efficiency of 40% corresponds to an E factor of 1.5 (60/40). In practice, however, the E factor will generally be much higher since the yield is not 100% and an excess of reagent(s) is used and solvent losses and salt generation during work-up have to be taken into account.

An interesting example, to further illustrate the concepts of E factors and atom efficiency is the manufacture of phloroglucinol [23]. Traditionally, it was produced from 2,4,6-trinitrotoluene (TNT) as shown in Fig. 1.2, a perfect example of nineteenth century organic chemistry.

This process has an atom efficiency of <5% and an E factor of 40, i.e. it generates 40 kg of solid waste, containing $Cr_2(SO_4)_3$, NH_4Cl, $FeCl_2$ and $KHSO_4$ per kg of phloroglucinol (note that water is not included), and obviously belongs in a museum of industrial archeology.

All of the metrics discussed above take only the mass of waste generated into account. However, what is important is the environmental impact of this waste, not just its amount, i.e. the nature of the waste must be considered. One kg of sodium chloride is obviously not equivalent to one kg of a chromium salt. Hence, the term 'environmental quotient', EQ, obtained by multiplying the E factor with an arbitrarily assigned unfriendliness quotient, Q, was introduced [15]. For example, one could arbitrarily assign a Q value of 1 to NaCl and, say, 100–1000 to a heavy metal salt, such as chromium, depending on its toxicity, ease of recycling, etc. The magnitude of Q is obviously debatable and difficult to quantify but, importantly, 'quantitative assessment' of the environmental im-

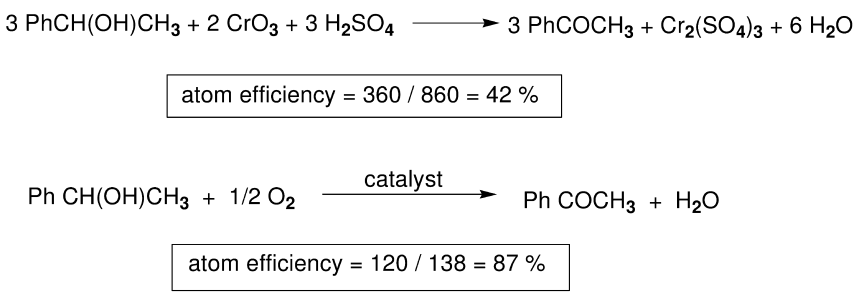


Fig. 1.1 Atom efficiency of stoichiometric vs. catalytic oxidation of an alcohol.

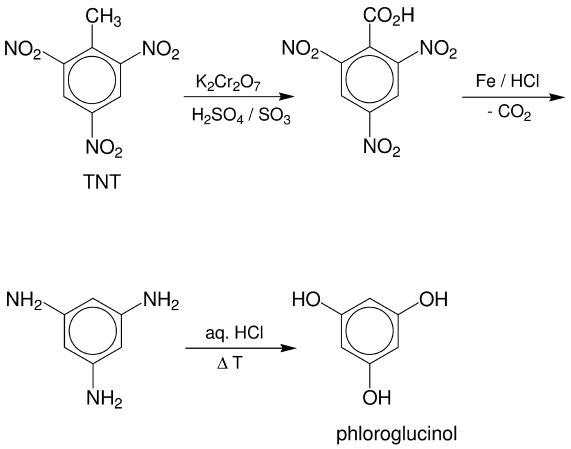


Fig. 1.2 Phloroglucinol from TNT.

pact of chemical processes is, in principle, possible. It is also worth noting that Q for a particular substance can be both volume-dependent and influenced by the location of the production facilities. For example, the generation of 100–1000 tons per annum of sodium chloride is unlikely to present a waste problem, and could be given a Q of zero. The generation of 10 000 tons per annum, on the other hand, may already present a disposal problem and would warrant assignation of a Q value greater than zero. Ironically, when very large quantities of sodium chloride are generated the Q value could decrease again as recycling by electrolysis becomes a viable proposition, e.g. in propylene oxide manufacture via the chlorohydrin route. Thus, generally speaking the Q value of a particular waste will be determined by its ease of disposal or recycling. Hydrogen bromide, for example, could warrant a lower Q value than hydrogen chloride as recycling, via oxidation to bromine, is easier. In some cases, the waste product may even have economic value. For example, ammonium sulfate, produced as waste in the manufacture of caprolactam, can be sold as fertilizer. It is worth noting, however, that the market could change in the future, thus creating a waste problem for the manufacturer.

1.3 The Role of Catalysis

As noted above, the waste generated in the manufacture of organic compounds consists primarily of inorganic salts. This is a direct consequence of the use of stoichiometric inorganic reagents in organic synthesis. In particular, fine chemicals and pharmaceuticals manufacture is rampant with antiquated 'stoichiometric' technologies. Examples, which readily come to mind are stoichiometric reductions with metals (Na, Mg, Zn, Fe) and metal hydride reagents ($LiAlH_4$,

$NaBH_4$), oxidations with permanganate, manganese dioxide and chromium(VI) reagents and a wide variety of reactions, e.g. sulfonations, nitrations, halogenations, diazotizations and Friedel-Crafts acylations, employing stoichiometric amounts of mineral acids (H_2SO_4, HF, H_3PO_4) and Lewis acids ($AlCl_3$, $ZnCl_2$, BF_3). The solution is evident: substitution of classical stoichiometric methodologies with cleaner catalytic alternatives. Indeed, a major challenge in (fine) chemicals manufacture is to develop processes based on H_2, O_2, H_2O_2, CO, CO_2 and NH_3 as the direct source of H, O, C and N. Catalytic hydrogenation, oxidation and carbonylation (Fig. 1.3) are good examples of highly atom efficient, low-salt processes.

The generation of copious amounts of inorganic salts can similarly be largely circumvented by replacing stoichiometric mineral acids, such as H_2SO_4, and Lewis acids and stoichiometric bases, such as NaOH, KOH, with recyclable solid acids and bases, preferably in catalytic amounts (see later).

For example, the technologies used for the production of many substituted aromatic compounds (Fig. 1.4) have not changed in more than a century and are, therefore, ripe for substitution by catalytic, low-salt alternatives (Fig. 1.5).

An instructive example is provided by the manufacture of hydroquinone (Fig. 1.6) [24]. Traditionally it was produced by oxidation of aniline with stoichiometric amounts of manganese dioxide to give benzoquinone, followed by reduction with iron and hydrochloric acid (Béchamp reduction). The aniline was derived from benzene via nitration and Béchamp reduction. The overall process generated more than 10 kg of inorganic salts ($MnSO_4$, $FeCl_2$, NaCl, Na_2SO_4) per kg of hydroquinone. This antiquated process has now been replaced by a more modern route involving autoxidation of *p*-diisopropylbenzene (produced by Friedel-Crafts alkylation of benzene), followed by acid-catalysed rearrangement of the bis-hydroperoxide, producing <1 kg of inorganic salts per kg of hydroquinone. Alternatively, hydroquinone is produced (together with catechol) by tita-

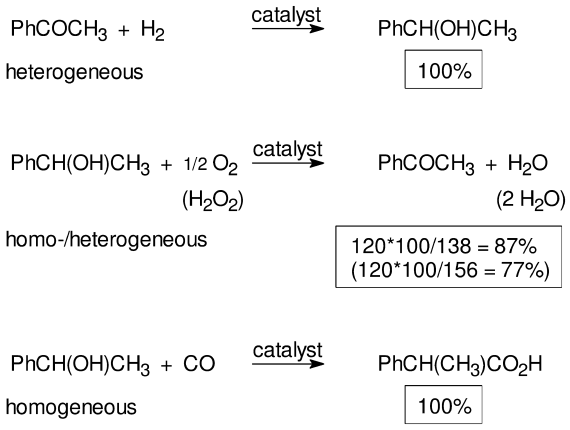


Fig. 1.3 Atom efficient catalytic processes.

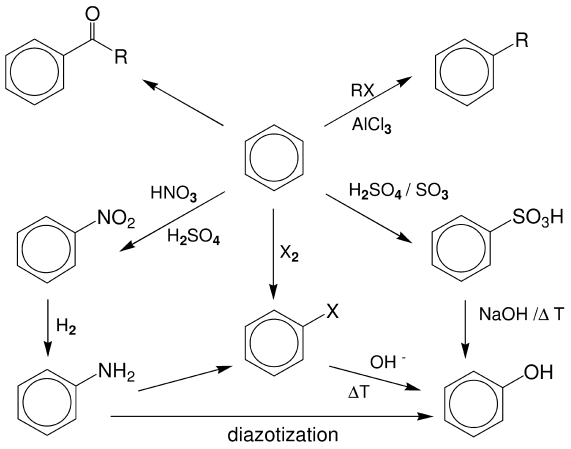


Fig. 1.4 Classical aromatic chemistry.

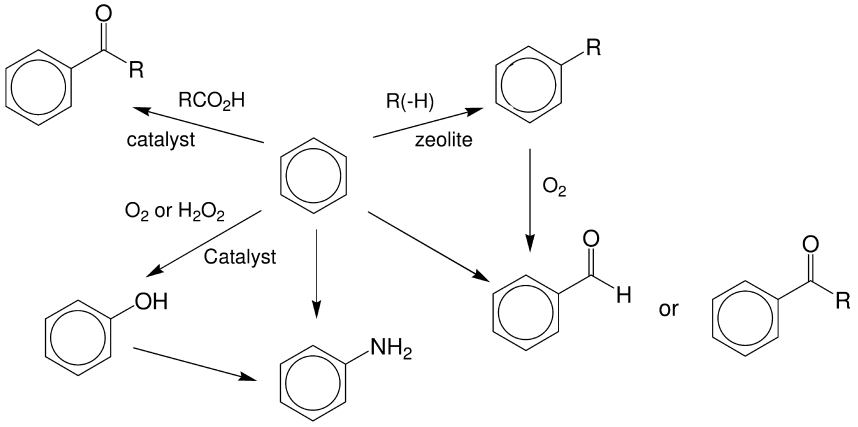


Fig. 1.5 Non-classical aromatic chemistry.

nium silicalite (TS-1)-catalysed hydroxylation of phenol with aqueous hydrogen peroxide (see later).

Biocatalysis has many advantages in the context of green chemistry, e.g. mild reaction conditions and often fewer steps than conventional chemical procedures because protection and deprotection of functional groups are often not required. Consequently, classical chemical procedures are increasingly being replaced by cleaner biocatalytic alternatives in the fine chemicals industry (see later).

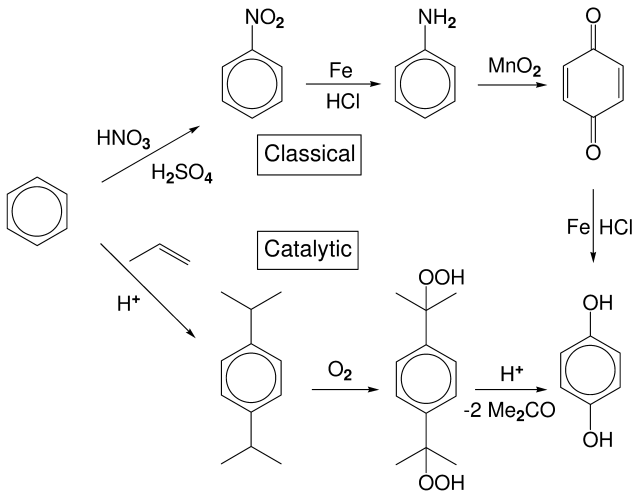


Fig. 1.6 Two routes to hydroquinone.

1.4
The Development of Organic Synthesis

If the solution to the waste problem in the fine chemicals industry is so obvious – replacement of classical stoichiometric reagents with cleaner, catalytic alternatives – why was it not applied in the past? We suggest that there are several reasons for this. First, because of the smaller quantities compared with bulk chemicals, the need for waste reduction in fine chemicals was not widely appreciated.

A second, underlying, reason is the more or less separate evolution of organic chemistry and catalysis (Fig. 1.7) since the time of Berzelius, who coined both terms, in 1807 and 1835, respectively [25]. Catalysis subsequently developed as a subdiscipline of physical chemistry, and is still often taught as such in university undergraduate courses. With the advent of the petrochemicals industry in the 1930s, catalysis was widely applied in oil refining and bulk chemicals manufacture. However, the scientists responsible for these developments, which largely involved heterogeneous catalysts in vapor phase reactions, were generally not organic chemists.

Organic synthesis followed a different line of evolution. A landmark was Perkin's serendipitous synthesis of mauveine (aniline purple) in 1856 [26] which marked the advent of the synthetic dyestuffs industry, based on coal tar as the raw material. The present day fine chemicals and pharmaceutical industries evolved largely as spin-offs of this activity. Coincidentally, Perkin was trying to synthesise the anti-malarial drug, quinine, by oxidation of a coal tar-based raw material, allyl toluidine, using stoichiometric amounts of potassium dichromate. Fine chemicals and pharmaceuticals have remained primarily the domain of

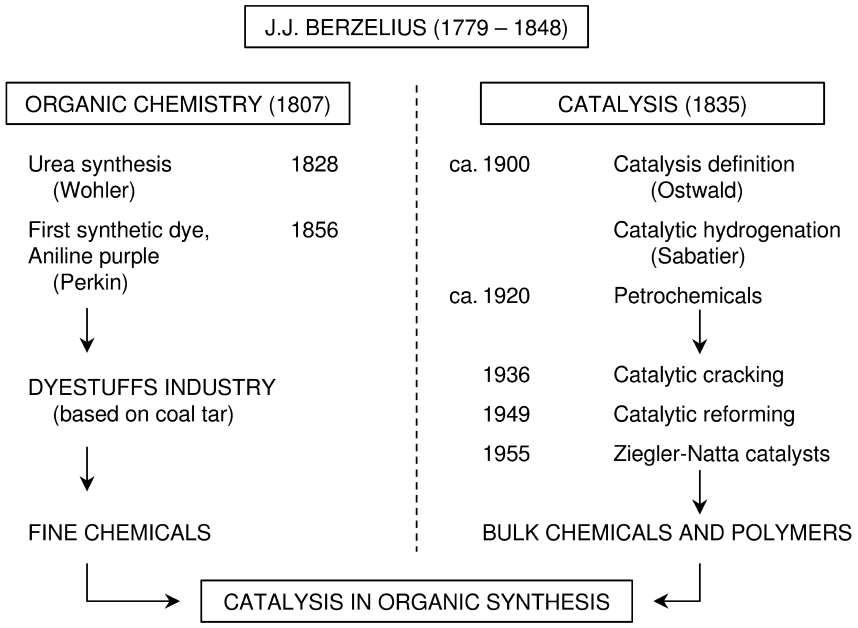


Fig. 1.7 Development of catalysis and organic synthesis.

synthetic organic chemists who, generally speaking, have clung to the use of classical "stoichiometric" methodologies and have been reluctant to apply catalytic alternatives.

A third reason, which partly explains the reluctance, is the pressure of time. Fine chemicals generally have a much shorter lifecycle than bulk chemicals and, especially in pharmaceuticals, 'time to market' is crucial. An advantage of many time-honored classical technologies is that they are well-tried and broadly applicable and, hence, can be implemented rather quickly. In contrast, the development of a cleaner, catalytic alternative could be more time consuming. Consequently, environmentally (and economically) inferior technologies are often used to meet market deadlines. Moreover, in pharmaceuticals, subsequent process changes are difficult to realise owing to problems associated with FDA approval.

There is no doubt that, in the twentieth century, organic synthesis has achieved a high level of sophistication with almost no molecule beyond its capabilities, with regard to chemo-, regio- and stereoselectivity, for example. However, little attention was focused on atom selectivity and catalysis was only sporadically applied. Hence, what we now see is a paradigm change: under the mounting pressure of environmental legislation, organic synthesis and catalysis, after 150 years in splendid isolation, have come together again. The key to waste minimisation is precision in organic synthesis, where every atom counts. In this chapter we shall briefly review the various categories of catalytic pro-

cesses, with emphasis on fine chemicals but examples of bulk chemicals will also be discussed where relevant.

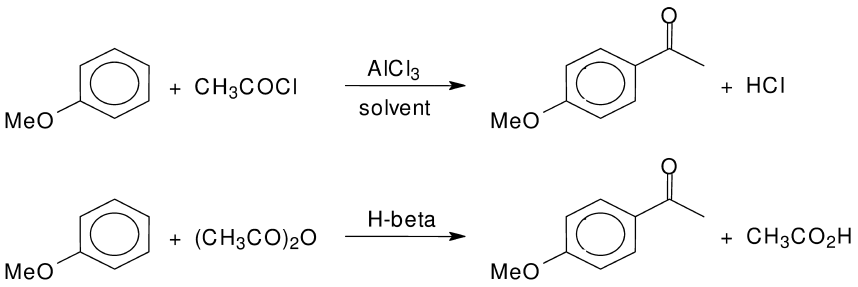
1.5 Catalysis by Solid Acids and Bases

As noted above, a major source of waste in the (fine) chemicals industry is derived from the widespread use of liquid mineral acids (HF, H_2SO_4) and a variety of Lewis acids. They cannot easily be recycled and generally end up, via a hydrolytic work-up, as waste streams containing large amounts of inorganic salts. Their widespread replacement by recyclable solid acids would afford a dramatic reduction in waste. Solid acids, such as zeolites, acidic clays and related materials, have many advantages in this respect [27–29]. They are often truly catalytic and can easily be separated from liquid reaction mixtures, obviating the need for hydrolytic work-up, and recycled. Moreover, solid acids are non-corrosive and easier (safer) to handle than mineral acids such as H_2SO_4 or HF.

Solid acid catalysts are, in principle, applicable to a plethora of acid-promoted processes in organic synthesis [27–29]. These include various electrophilic aromatic substitutions, e.g. nitrations, and Friedel-Crafts alkylations and acylations, and numerous rearrangement reactions such as the Beckmann and Fries rearrangements.

A prominent example is Friedel-Crafts acylation, a widely applied reaction in the fine chemicals industry. In contrast to the corresponding alkylations, which are truly catalytic processes, Friedel-Crafts acylations generally require more than one equivalent of, for example, $AlCl_3$ or BF_3. This is due to the strong complexation of the Lewis acid by the ketone product. The commercialisation of the first zeolite-catalysed Friedel-Crafts acylation by Rhône-Poulenc (now Rhodia) may be considered as a benchmark in this area [30, 31]. Zeolite beta is employed as a catalyst, in fixed-bed operation, for the acetylation of anisole with acetic anhydride, to give *p*-methoxyacetophenone (Fig. 1.8). The original process used acetyl chloride in combination with 1.1 equivalents of $AlCl_3$ in a chlorinated hydrocarbon solvent, and generated 4.5 kg of aqueous effluent, containing $AlCl_3$, HCl, solvent residues and acetic acid, per kg of product. The catalytic alternative, in stark contrast, avoids the production of HCl in both the acylation and in the synthesis of acetyl chloride. It generates 0.035 kg of aqueous effluent, i.e. more than 100 times less, consisting of 99% water, 0.8% acetic acid and <0.2% other organics, and requires no solvent. Furthermore, a product of higher purity is obtained, in higher yield (>95% vs. 85–95%), the catalyst is recyclable and the number of unit operations is reduced from twelve to two. Hence, the Rhodia process is not only environmentally superior to the traditional process, it has more favorable economics. This is an important conclusion; green, catalytic chemistry, in addition to having obvious environmental benefits, is also economically more attractive.

Another case in point pertains to the manufacture of the bulk chemical, caprolactam, the raw material for Nylon 6. The conventional process (Fig. 1.9) in-



Homogeneous	Heterogeneous
$AlCl_3$ > 1 equivalent	H-beta, catalytic & regenerable
Solvent	No solvent
Hydrolysis of products	No water necessary
Phase separation	-
Distillation organic phase	Distillation organic phase
Solvent recycle	-
85-95% yield	> 95% yield, higher purity
4.5 kg aqueous effluent per kg	0.035 kg aqueous effluent per kg
12 unit operations	3 unit operations

Fig. 1.8 Zeolite-catalysed vs. classical Friedel-Crafts acylation.

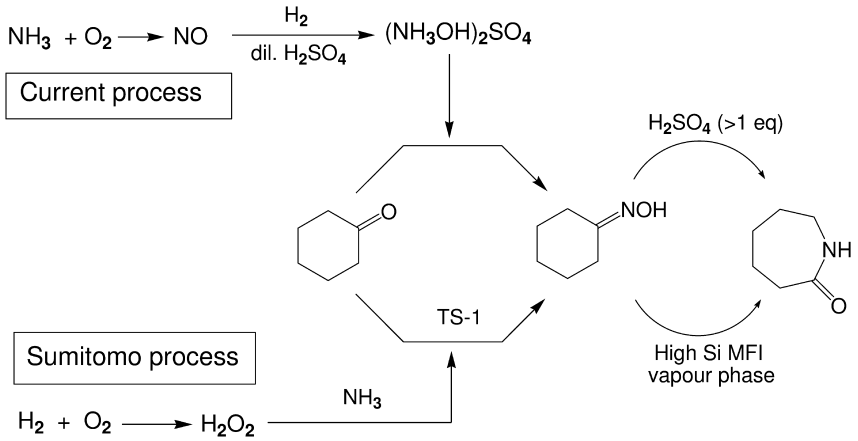


Fig. 1.9 Sumitomo vs. conventional process for caprolactam manufacture.

volves the reaction of cyclohexanone with hydroxylamine sulfate (or another salt), producing cyclohexanone oxime which is subjected to the Beckmann rearrangement in the presence of stoichiometric amounts of sulfuric acid or oleum. The overall process generates ca. 4.5 kg of ammonium sulfate per kg of caprolactam, divided roughly equally over the two steps.

Ichihashi and coworkers at Sumitomo [32, 33] developed a catalytic vapor phase Beckmann rearrangement over a high-silica MFI zeolite. When this is combined with the technology, developed by Enichem [34], for the ammoximation of cyclohexanone with NH_3/H_2O_2 over the titanium silicalite catalyst (TS-1) described earlier, this affords caprolactam in >98% yield (based on cyclohexanone; 93% based on H_2O_2). The overall process generates caprolactam and two molecules of water from cyclohexanone, NH_3 and H_2O_2, and is essentially salt-free. This process is currently being commercialised by Sumitomo in Japan.

Another widely used reaction in fine chemicals manufacture is the acid-catalysed rearrangement of epoxides to carbonyl compounds. Lewis acids such as $ZnCl_2$ or $BF_3 \cdot OEt_2$ are generally used, often in stoichiometric amounts, to perform such reactions. Here again, zeolites can be used as solid, recyclable catalysts. Two commercially relevant examples are the rearrangements of α-pinene oxide [35, 36] and isophorone oxide [37] shown in Fig. 1.10. The products of these rearrangements are fragrance intermediates. The rearrangement of α-pinene oxide to campholenic aldehyde was catalysed by H-USY zeolite [35] and titanium-substituted zeolite beta [36]. With the latter, selectivities up to 89% in the liquid phase and 94% in the vapor phase were obtained, exceeding the best results obtained with homogeneous Lewis acids.

As any organic chemist will tell you, the conversion of an amino acid to the corresponding ester also requires more than one equivalent of a Brønsted acid. This is because an amino acid is a zwitterion and, in order to undergo acid catalysed esterification, the carboxylate anion needs to be protonated with one equivalent of acid. However, it was shown [38] that amino acids undergo esterification in the presence of a catalytic amount of zeolite H-USY, the very same catalyst that is used in naphtha cracking, thus affording a salt-free route to amino acid esters (Fig. 1.11). This is a truly remarkable reaction in that a basic compound (the amino ester) is formed in the presence of an acid catalyst. Esterification of optically active amino acids under these conditions (MeOH, 100 °C) un-

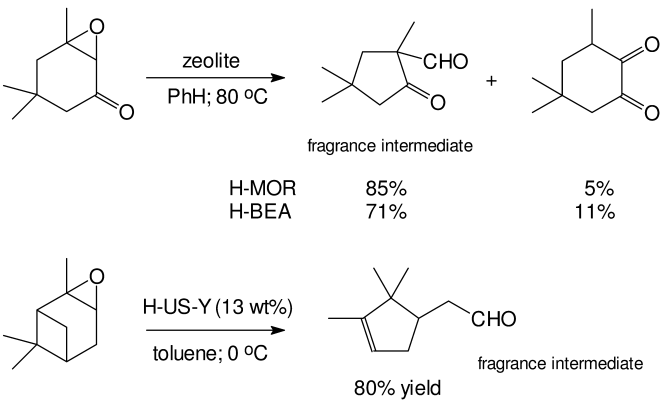


Fig. 1.10 Zeolite-catalysed epoxide rearrangements.

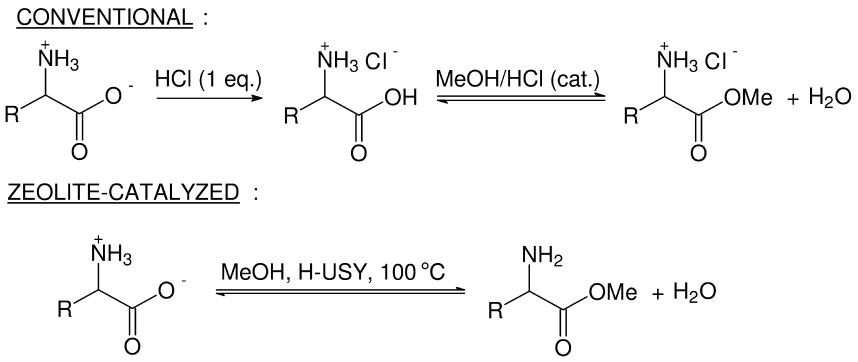


Fig. 1.11 Salt-free esterification of amino acids.

fortunately led to (partial) racemisation. The reaction could be of interest for the synthesis of racemic phenylalanine methyl ester, the raw material in the DSM-Tosoh process for the artificial sweetener, aspartame.

In the context of replacing conventional Lewis acids in organic synthesis it is also worth pointing out that an alternative approach is to use lanthanide salts [39] that are both water soluble and stable towards hydrolysis and exhibit a variety of interesting activities as Lewis acids (see later).

The replacement of conventional bases, such as NaOH, KOH and NaOMe, by recyclable solid bases, in a variety of organic reactions, is also a focus of recent attention [27, 40]. For example, synthetic hydrotalcite clays, otherwise known as layered double hydroxides (LDHs) and having the general formula $Mg_{8-x}Al_x(OH)_{16}(CO_3)_{x/2} \cdot nH_2O$, are hydrated aluminum-magnesium hydroxides possess-

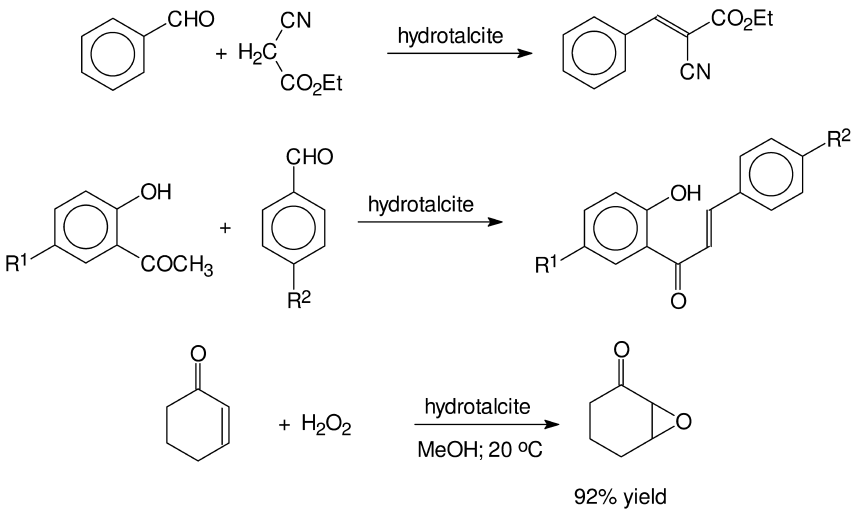


Fig. 1.12 Hydrotalcite-catalysed condensation reactions.

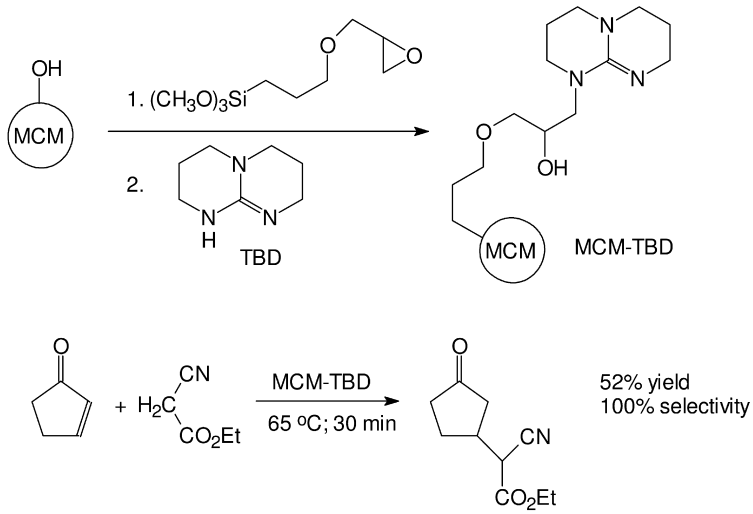


Fig. 1.13 Tethered organic bases as solid base catalysts.

ing a lamellar structure in which the excess positive charge is compensated by carbonate anions in the interlamellar space [41, 42]. Calcination transforms hydrotalcites, via dehydroxylation and decarbonation, into strongly basic mixed magnesium-aluminum oxides, that are useful recyclable catalysts for, inter alia, aldol [43], Knoevenagel [44, 45] and Claisen-Schmidt [45] condensations. Some examples are shown in Fig. 1.12.

Another approach to designing recyclable solid bases is to attach organic bases to the surface of, e.g. mesoporous silicas (Fig. 1.13) [46–48]. For example, aminopropyl-silica, resulting from reaction of 3-aminopropyl(trimethoxy)silane with pendant silanol groups, was an active catalyst for Knoevenagel condensations [49]. A stronger solid base was obtained by functionalisation of mesoporous MCM-41 with the guanidine base, 1,5,7-triazabicyclo-[4,4,0]dec-5-ene (TBD), using a surface glycidylation technique followed by reaction with TBD (Fig. 1.13). The resulting material was an active catalyst for Knoevenagel condensations, Michael additions and Robinson annulations [50].

1.6 Catalytic Reduction

Catalytic hydrogenation perfectly embodies the concept of precision in organic synthesis. Molecular hydrogen is a clean and abundant raw material and catalytic hydrogenations are generally 100% atom efficient, with the exception of a few examples, e.g. nitro group reduction, in which water is formed as a coproduct. They have a tremendously broad scope and exhibit high degrees of che-

mo-, regio-, diastereo and enantioselectivity [51, 52]. The synthetic prowess of catalytic hydrogenation is admirably rendered in the words of Rylander [51]:

"Catalytic hydrogenation is one of the most useful and versatile tools available to the organic chemist. The scope of the reaction is very broad; most functional groups can be made to undergo reduction, frequently in high yield, to any of several products. Multifunctional molecules can often be reduced selectively at any of several functions. A high degree of stereochemical control is possible with considerable predictability, and products free of contaminating reagents are obtained easily. Scale up of laboratory experiments to industrial processes presents little difficulty."
Paul Rylander (1979)

Catalytic hydrogenation is unquestionably the workhorse of catalytic organic synthesis, with a long tradition dating back to the days of Sabatier [53] who received the 1912 Nobel Prize in Chemistry for his pioneering work in this area. It is widely used in the manufacture of fine and specialty chemicals and a special issue of the journal Advanced Synthesis and Catalysis was recently devoted to this important topic [54]. According to Roessler [55], 10–20% of all the reaction steps in the synthesis of vitamins (even 30% for vitamin E) at Hoffmann-La Roche (in 1996) are catalytic hydrogenations.

Most of the above comments apply to heterogeneous catalytic hydrogenations over supported Group VIII metals (Ni, Pd, Pt, etc.). They are equally true, however, for homogeneous catalysts where spectacular progress has been made in the last three decades, culminating in the award of the 2001 Nobel Prize in Chemistry to W.S. Knowles and R. Noyori for their development of catalytic asymmetric hydrogenation (and to K.B. Sharpless for asymmetric oxidation catalysis) [56]. Recent trends in the application of catalytic hydrogenation in fine chemicals production, with emphasis on chemo-, regio- and stereoselectivity using both heterogeneous and homogeneous catalysts, is the subject of an excellent review by Blaser and coworkers [57].

A major trend in fine chemicals and pharmaceuticals is towards increasingly complex molecules, which translates to a need for high degrees of chemo-, regio- and stereoselectivity. An illustrative example is the synthesis of an intermediate for the Roche HIV protease inhibitor, Saquinavir (Fig. 1.14) [55]. It involves a chemo- and diastereoselective hydrogenation of an aromatic while avoiding racemisation at the stereogenic centre present in the substrate.

The chemoselective hydrogenation of one functional group in the presence of other reactive groups is a frequently encountered problem in fine chemicals manufacture. An elegant example of the degree of precision that can be achieved is the chemoselective hydrogenation of an aromatic nitro group in the presence of both an olefinic double bond and a chlorine substituent in the aromatic ring (Fig. 1.15) [58].

Although catalytic hydrogenation is a mature technology that is widely applied in industrial organic synthesis, new applications continue to appear, sometimes in unexpected places. For example, a time-honored reaction in organic

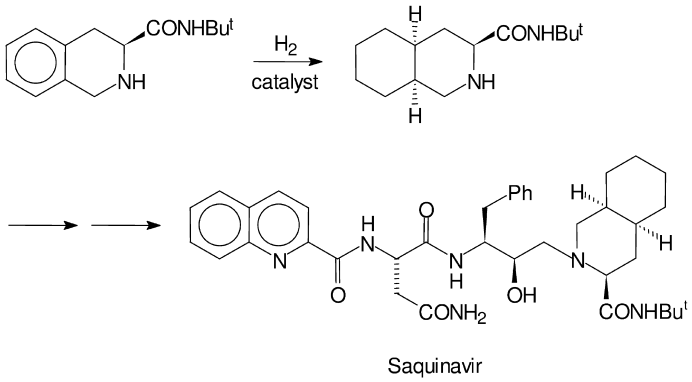


Fig. 1.14 Synthesis of a Saquinavir intermediate.

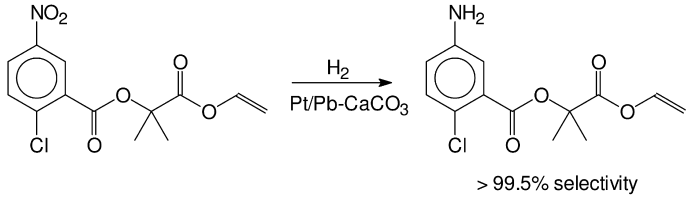


Fig. 1.15 Chemoselective hydrogenation of a nitro group.

synthesis is the Williamson synthesis of ethers, first described in 1852 [59]. A low-salt, catalytic alternative to the Williamson synthesis, involving reductive alkylation of an aldehyde (Fig. 1.16) has been reported [60]. This avoids the coproduction of NaCl, which may or may not be a problem, depending on the production volume (see earlier). Furthermore, the aldehyde may, in some cases, be more readily available than the corresponding alkyl chloride.

The Meerwein-Pondorff-Verley (MPV) reduction of aldehydes and ketones to the corresponding alcohols [61] is another example of a long-standing technology. The reaction mechanism involves coordination of the alcohol reagent, usually isopropanol, and the ketone substrate to the aluminum center, followed by hydride transfer from the alcohol to the carbonyl group. In principle, the re-

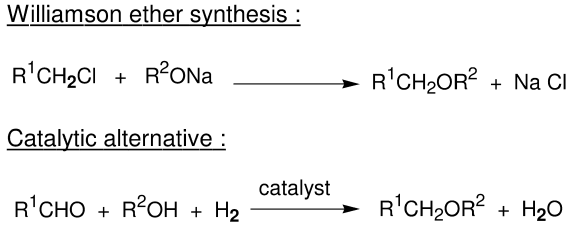


Fig. 1.16 Williamson ether synthesis and a catalytic alternative.

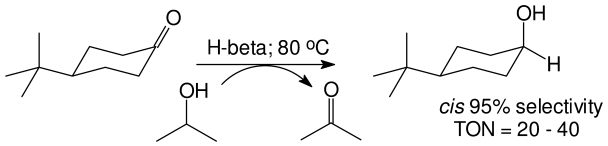


Fig. 1.17 Zeolite beta catalysed MPV reduction.

Fig. 1.18 Direct hydrogenation of carboxylic acids to aldehydes.

action is catalytic in aluminum alkoxide but, in practice, it generally requires stoichiometric amounts owing to the slow rate of exchange of the alkoxy group in aluminum alkoxides. Recently, van Bekkum and coworkers [62, 63] showed that Al- and Ti-Beta zeolites are able to catalyse MPV reductions. The reaction is truly catalytic and the solid catalyst can be readily separated, by simple filtration, and recycled. An additional benefit is that confinement of the substrate in the zeolite pores can afford interesting shape selectivities. For example, reduction of 4-*tert*-butylcyclohexanone led to the formation of the thermodynamically less stable *cis*-alcohol, an important fragrance intermediate, in high (>95%) selectivity (Fig. 1.17). In contrast, conventional MPV reduction gives the thermodynamically more stable, but less valuable, *trans*-isomer. Preferential formation of the *cis*-isomer was attributed to transition state selectivity imposed by confinement in the zeolite pores.

More recently, Corma and coworkers [64] have shown that Sn-substituted zeolite beta is a more active heterogeneous catalyst for MPV reductions, also showing high *cis*-selectivity (99–100%) in the reduction of 4-alkylcyclohexanones. The higher activity was attributed to the higher electronegativity of Sn compared to Ti.

The scope of catalytic hydrogenations continues to be extended to more difficult reductions. For example, a notoriously difficult reduction in organic synthesis is the direct conversion of carboxylic acids to the corresponding aldehydes. It is usually performed indirectly via conversion to the corresponding acid chloride and Rosenmund reduction of the latter over $Pd/BaSO_4$ [65]. Rhône-Poulenc [30] and Mitsubishi [66] have developed methods for the direct hydrogenation of aromatic, aliphatic and unsaturated carboxylic acids to the corresponding aldehydes, over a Ru/Sn alloy and zirconia or chromia catalysts, respectively, in the vapor phase (Fig. 1.18).

Finally, it is worth noting that significant advances have been made in the utilisation of biocatalytic methodologies for the (asymmetric) reduction of, for example, ketones to the corresponding alcohols (see later).

1.7 Catalytic Oxidation

It is probably true to say that nowhere is there a greater need for green catalytic alternatives in fine chemicals manufacture than in oxidation reactions. In contrast to reductions, oxidations are still largely carried out with stoichiometric inorganic (or organic) oxidants such as chromium(VI) reagents, permanganate, manganese dioxide and periodate. There is clearly a definite need for catalytic alternatives employing clean primary oxidants such as oxygen or hydrogen peroxide. Catalytic oxidation with O_2 is widely used in the manufacture of bulk petrochemicals [67]. Application to fine chemicals is generally more difficult, however, owing to the multifunctional nature of the molecules of interest. Nonetheless, in some cases such technologies have been successfully applied to the manufacture of fine chemicals. An elegant example is the BASF process [68] for the synthesis of citral (Fig. 1.19), a key intermediate for fragrances and vitamins A and E. The key step is a catalytic vapor phase oxidation over a supported silver catalyst, essentially the same as that used for the manufacture of formaldehyde from methanol.

This atom efficient, low-salt process has displaced the traditional route, starting from *β*-pinene, which involved, inter alia, a stoichiometric oxidation with MnO_2 (Fig. 1.19).

The selective oxidation of alcohols to the corresponding carbonyl compounds is a pivotal transformation in organic synthesis. As noted above, there is an urgent need for greener methodologies for these conversions, preferably employing O_2 or H_2O_2 as clean oxidants and effective with a broad range of substrates. One method which is finding increasing application in the fine chemicals industry employs the stable free radical, TEMPO 2,2′,6,6′-tetramethylpiperidine-*N*-oxyl) as a catalyst and NaOCl (household bleach) as the oxidant [69]. For example, this methodology was used, with 4-hydroxy TEMPO as the catalyst, as the key step in a new process for the production of progesterone from stigmasterol, a soy sterol (Fig. 1.20) [70].

This methodology still suffers from the shortcomings of salt formation and the use of bromide (10 mol%) as a cocatalyst and dichloromethane as solvent. Recently, a recyclable oligomeric TEMPO derivative, PIPO, derived from a commercially available polymer additive (Chimasorb 944) was shown to be an effective catalyst for the oxidation of alcohols with NaOCl in the absence of bromide ion using neat substrate or in e.g. methyl *tert*-butyl ether (MTBE) as solvent (Fig. 1.21) [71].

Another improvement is the use of a Ru/TEMPO catalyst combination for the selective aerobic oxidations of primary and secondary alcohols to the corresponding aldehydes and ketones, respectively (Fig. 1.22) [72]. The method is effective (>99% selectivity) with a broad range of primary and secondary aliphatic, allylic and benzylic alcohols. The overoxidation of aldehydes to the corresponding carboxylic acids is suppressed by the TEMPO which acts as a radical scavenger in preventing autoxidation.

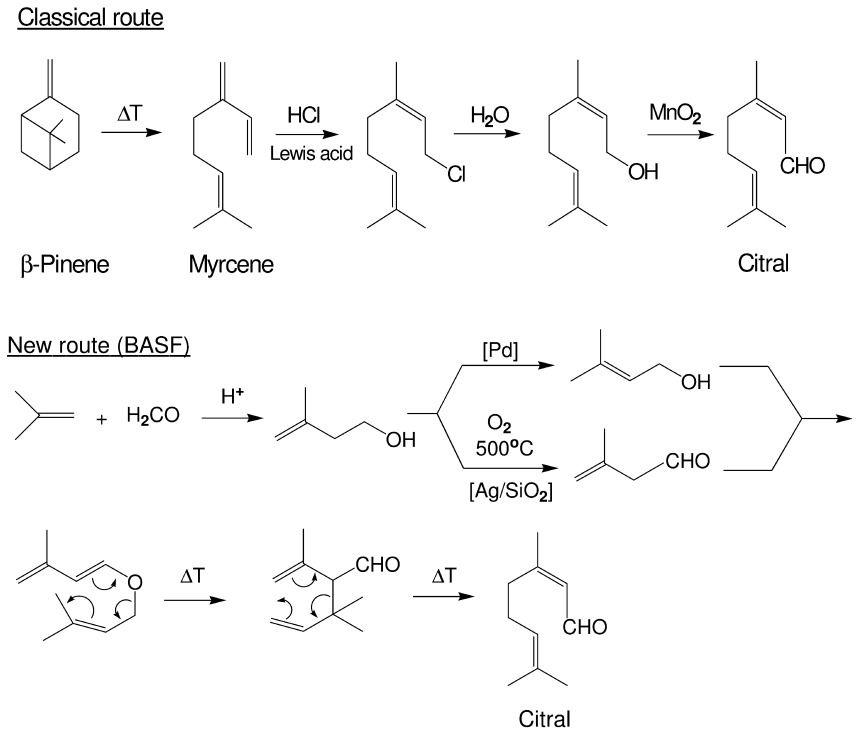


Fig. 1.19 Two routes to citral.

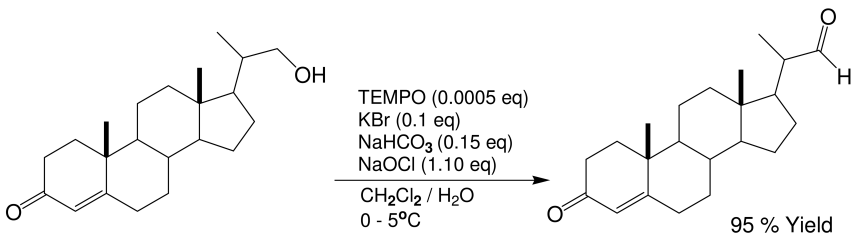
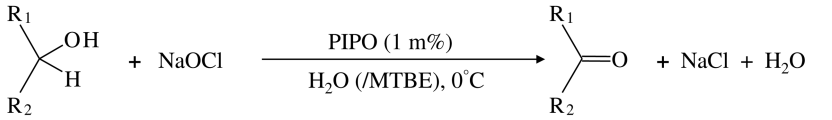
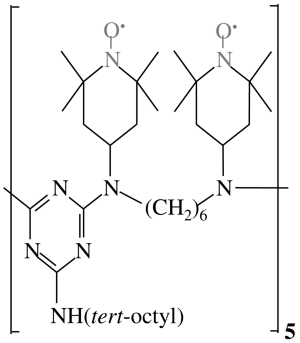


Fig. 1.20 Key step in the production of progesterone from stigmasterol.

Another recent development is the use of water soluble palladium complexes as recyclable catalysts for the aerobic oxidation of alcohols in aqueous/organic biphasic media (Fig. 1.22) [73].

In the fine chemicals industry, H_2O_2 is often the oxidant of choice because it is a liquid and processes can be readily implemented in standard batch equipment. To be really useful catalysts should be, for safety reasons, effective with 30% aqueous hydrogen peroxide and many systems described in the literature do not fulfill this requirement.



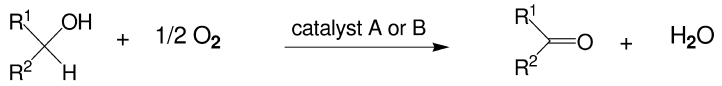


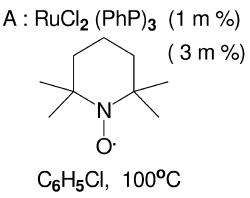
PIPO

substrate	time (min)	conv. (%)	sel. (%)
1-octanol	45	90	50
	45	80	94[a]
1-hexanol	45	89	95[a]
2-octanol	45	99	>99
cyclooctanol	45	100	>99
benzyl alcohol	30	100	>99
1-phenylethanol	30	100	>99

a. in MTBE as solvent

Fig. 1.21 PIPO catalysed oxidation of alcohols with NaOCl.





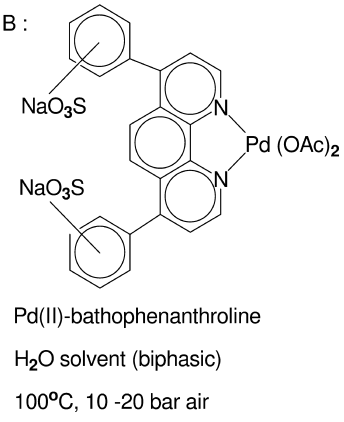


Fig. 1.22 Two methods for aerobic oxidation of alcohols.

In this context, the development of the heterogeneous titanium silicalite (TS-1) catalyst, by Enichem in the mid-1980s was an important milestone in oxidation catalysis. TS-1 is an extremely effective and versatile catalyst for a variety of synthe-

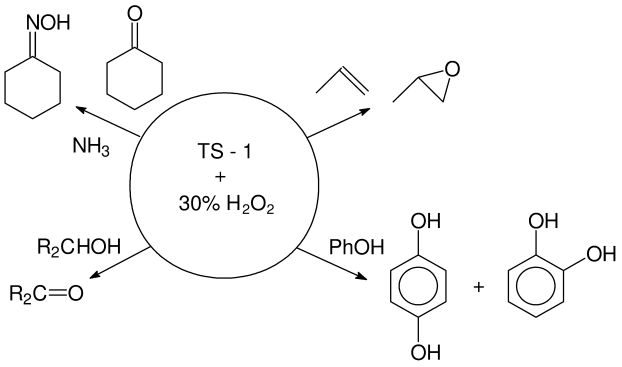


Fig. 1.23 Catalytic oxidations with TS-1/H_2O_2.

tically useful oxidations with 30% H_2O_2, e.g. olefin epoxidation, alcohol oxidation, phenol hydroxylation and ketone ammoximation (Fig. 1.23) [74].

A serious shortcoming of TS-1, in the context of fine chemicals manufacture, is the restriction to substrates that can be accommodated in the relatively small (5.1×5.5 Å^2) pores of this molecular sieve, e.g. cyclohexene is not epoxidised. This is not the case, however, with ketone ammoximation which involves *in situ* formation of hydroxylamine by titanium-catalysed oxidation of NH_3 with H_2O_2. The NH_2OH then reacts with the ketone in the bulk solution, which means that the reaction is, in principle, applicable to any ketone (or aldehyde). Indeed it was applied to the synthesis of the oxime of *p*-hydroxyacetophenone, which is converted, via Beckmann rearrangement, to the analgesic, paracetamol (Fig. 1.24) [75].

TS-1 was the prototype of a new generation of solid, recyclable catalysts for selective liquid phase oxidations, which we called "redox molecular sieves" [76]. A more recent example is the tin(IV)-substituted zeolite beta, developed by Corma and coworkers [77], which was shown to be an effective, recyclable catalyst

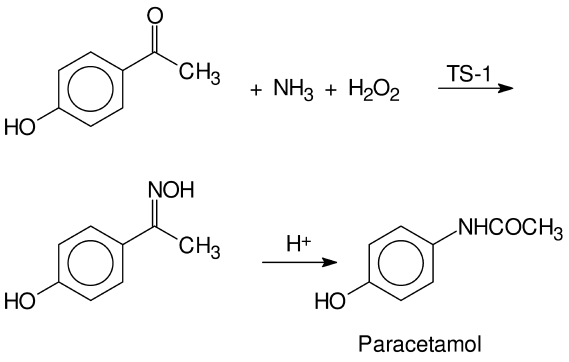


Fig. 1.24 Paracetamol intermediate via ammoximation.

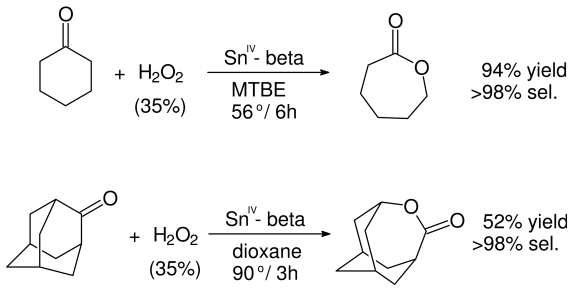


Fig. 1.25 Baeyer-Villiger oxidation with H_2O_2 catalysed by Sn-Beta.

for the Baeyer-Villiger oxidation of ketones and aldehydes [78] with aqueous H_2O_2 (Fig. 1.25).

At about the same time that TS-1 was developed by Enichem, Venturello and coworkers [79] developed another approach to catalysing oxidations with aqueous hydrogen peroxide: the use of tungsten-based catalysts under phase transfer conditions in biphasic aqueous/organic media. In the original method a tetraalkylammonium chloride or bromide salt was used as the phase transfer agent and a chlorinated hydrocarbon as the solvent [79]. More recently, Noyori and coworkers [80] have optimised this methodology and obtained excellent results using tungstate in combination with a quaternary ammonium hydrogen sulfate as the phase transfer catalyst. This system is a very effective catalyst for the organic solvent- and halide-free oxidation of alcohols, olefins and sulfides with

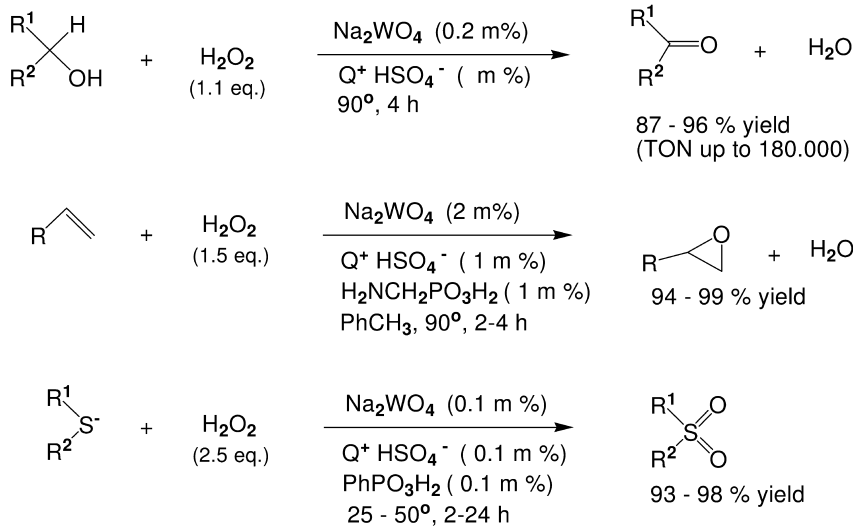


Fig. 1.26 Catalytic oxidations with hydrogen peroxide under phase transfer conditions.

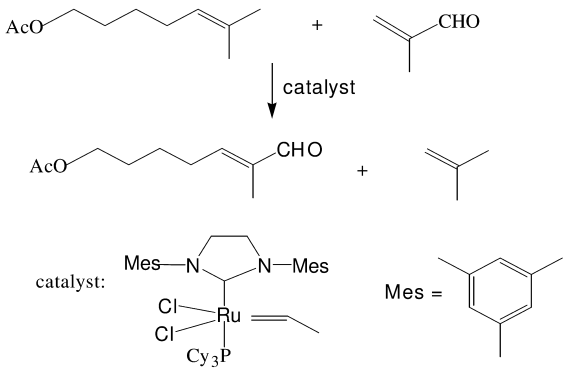


Fig. 1.27 The best oxidation is no oxidation.

aqueous H_2O_2, in an environmentally and economically attractive manner (Fig. 1.26).

Notwithstanding the significant advances in selective catalytic oxidations with O_2 or H_2O_2 that have been achieved in recent years, selective oxidation, especially of multifunctional organic molecules, remains a difficult catalytic transformation that most organic chemists prefer to avoid altogether. In other words, the best oxidation is no oxidation and most organic chemists would prefer to start at a higher oxidation state and perform a reduction or, better still, avoid changing the oxidation state. An elegant example of the latter is the use of olefin metathesis to affect what is formally an allylic oxidation which would be nigh impossible to achieve via catalytic oxidation (Fig. 1.27) [81].

1.8 Catalytic C–C Bond Formation

Another key transformation in organic synthesis is C–C bond formation and an important catalytic methodology for generating C–C bonds is carbonylation. In the bulk chemicals arena it is used, for example, for the production of acetic acid by rhodium-catalysed carbonylation of methanol [82]. Since such reactions are 100% atom efficient they are increasingly being applied to fine chemicals manufacture [83, 84]. An elegant example of this is the Hoechst-Celanese process for the manufacture of the analgesic, ibuprofen, with an annual production of several thousands tons. In this process ibuprofen is produced in two catalytic steps (hydrogenation and carbonylation) from *p*-isobutylactophenone (Fig. 1.28) with 100% atom efficiency [83]. This process replaced a more classical route which involved more steps and a much higher E factor.

In a process developed by Hoffmann-La Roche [55] for the anti-Parkinsonian drug, lazabemide, palladium-catalysed amidocarbonylation of 2,5-dichloropyridine replaced an original synthesis that involved eight steps, starting from 2-

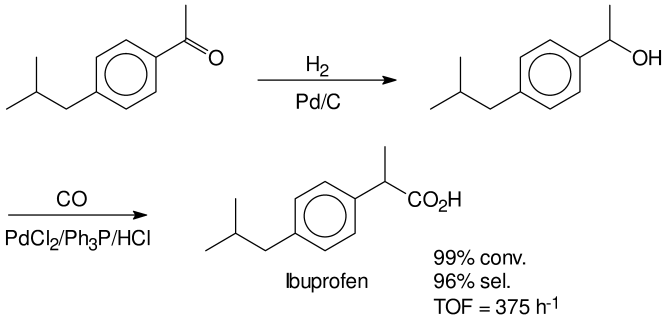


Fig. 1.28 Hoechst-Celanese process for ibuprofen.

methyl-5-ethylpyridine, and had an overall yield of 8%. The amidocarbonylation route affords lazabemide hydrochloride in 65% yield in one step, with 100% atom efficiency (Fig. 1.29).

Another elegant example, of palladium-catalysed amidocarbonylation this time, is the one-step, 100% atom efficient synthesis of α-amino acid derivatives from an aldehyde, CO and an amide (Fig. 1.30) [85]. The reaction is used, for example in the synthesis of the surfactant, *N*-lauroylsarcosine, from formaldehyde, CO and *N*-methyllauramide, replacing a classical route that generated copious amounts of salts.

Another catalytic methodology that is widely used for C–C bond formation is the Heck and related coupling reactions [86, 87]. The Heck reaction [88] involves the palladium-catalysed arylation of olefinic double bonds (Fig. 1.31) and provides an alternative to Friedel-Crafts alkylations or acylations for attaching carbon fragments to aromatic rings. The reaction has broad scope and is currently being widely applied in the pharmaceutical and fine chemical industries. For example, Albemarle has developed a new process for the synthesis of the anti-in-

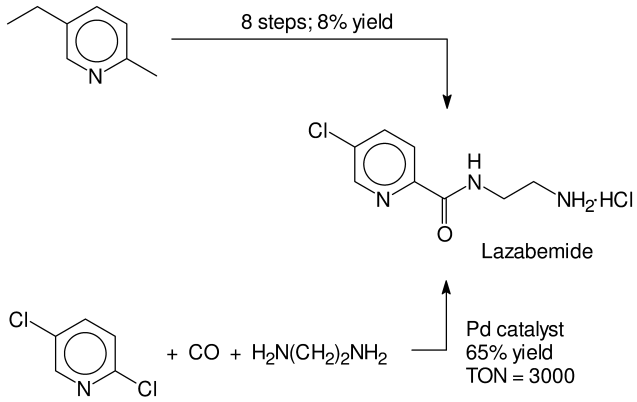


Fig. 1.29 Two routes to lazabemide.

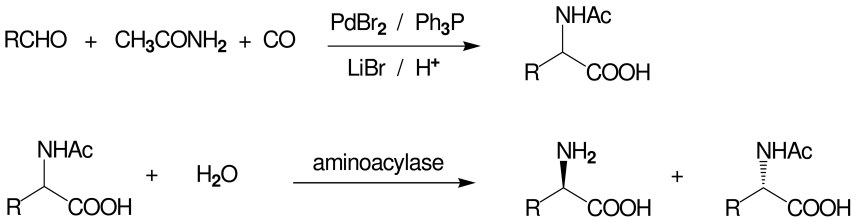


Fig. 1.30 Palladium-catalysed amidocarbonylation.

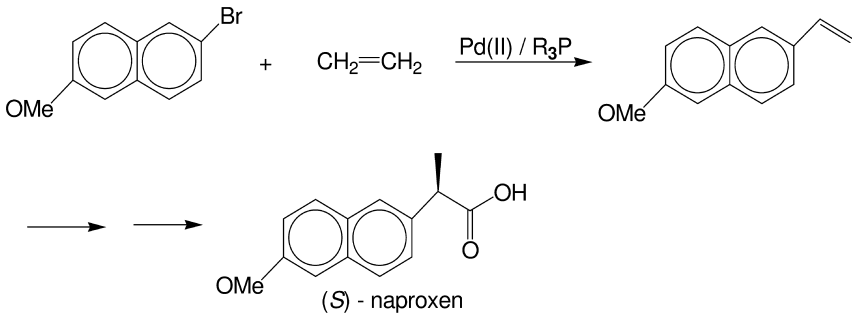


Fig. 1.31 Heck coupling reaction.

flammatory drug, naproxen, in which a key step is the Heck reaction shown in Fig. 1.31 [86].

The scope of the Heck and related coupling reactions was substantially broadened by the development, in the last few years, of palladium/ligand combinations which are effective with the cheap and readily available but less reactive aryl chlorides [86, 87] rather than the corresponding bromides or iodides. The process still generates one equivalent of chloride, however. Of interest in this context, therefore, is the report of a halide-free Heck reaction which employs an aromatic carboxylic anhydride as the arylating agent and requires no base or phosphine ligands [89].

A closely related reaction, that is currently finding wide application in the pharmaceutical industry, is the Suzuki coupling of arylboronic acids with aryl halides [90]. For example this technology was applied by Clariant scientists to the production of *o*-tolyl benzonitrile, an intermediate in the synthesis of angiotensin II antagonists, a novel class of antihypertensive drugs (Fig. 1.32) [91]. Interestingly, the reaction is performed in an aqueous biphasic system using a water soluble palladium catalyst, which forms the subject of the next section: the question of reaction media in the context of green chemistry and catalysis.

However, no section on catalytic C–C bond formation would be complete without a mention of olefin metathesis [92, 93]. It is, in many respects, the epitome of green chemistry, involving the exchange of substituents around the double bonds in the presence of certain transition metal catalysts (Mo, W, Re and Ru) as shown in Fig. 1.33. Several outcomes are possible: straight swapping

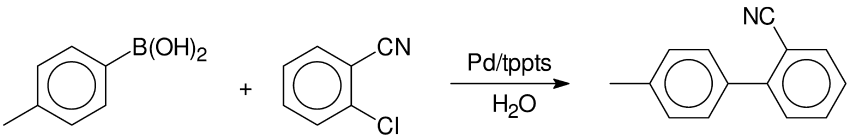
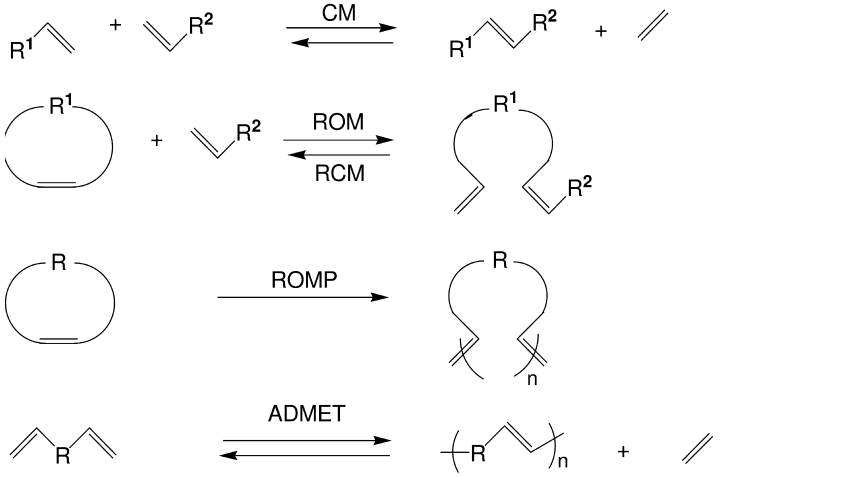


Fig. 1.32 A Suzuki coupling.



CM = Cross metathesis
ROM = Ring opening metathesis
RCM = Ring closing methatnesis
ROMP = Ring opening metathesis polymerization
ADMET = Acyclic diene metathesis

Catalysts = Mo, W, Re and Ru complexes

Fig. 1.33 Olefin metathesis reactions.

of groups between two acyclic olefins (cross metathesis, CM), closure of large rings (ring closing metathesis, RCM), diene formation from reaction of a cyclic olefin with an acyclic one (ring opening metathesis, ROM), polymerization of cyclic olefins (ring opening metathesis polymerization, ROMP) and polymerization of acyclic dienes (acyclic diene metathesis polymerisation, ADMET).

Following its discovery in the 1960s olefin metathesis was applied to bulk chemicals manufacture, a prominent example being the Shell Higher Olefins Process (SHOP) [94]. In the succeeding decades the development of catalysts, in particular the ruthenium-based ones, that function in the presence of most functional groups, paved the way for widespread application of olefin metathesis in the synthesis of complex organic molecules [92, 93]. Indeed, olefin metathesis has evolved into a pre-eminent methodology for the formation of C–C bonds under mild conditions. An illustrative example is the RCM reaction shown in Fig. 1.34 [95]. The ruthenium carbene complex catalyst functioned in undistilled protic solvents ($MeOH/H_2O$) in the presence of air.

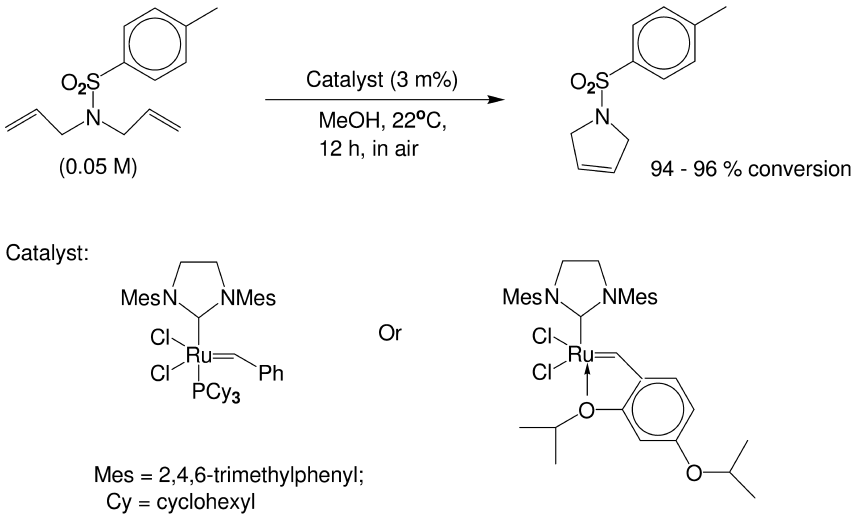


Fig. 1.34 Ru-catalysed ring closing metathesis.

1.9
The Question of Solvents: Alternative Reaction Media

Another important issue in green chemistry is the use of organic solvents. The use of chlorinated hydrocarbon solvents, traditionally the solvent of choice for a wide variety of organic reactions, has been severely curtailed. Indeed, so many of the solvents that are favored by organic chemists have been blacklisted that the whole question of solvent use requires rethinking and has become a primary focus, especially in the fine chemicals industry [96]. It has been estimated by GSK workers [97] that ca. 85% of the total mass of chemicals involved in pharmaceutical manufacture comprises solvents and recovery efficiencies are typically 50–80% [97]. It is also worth noting that in the redesign of the sertraline manufacturing process [98], for which Pfizer received a Presidential Green Chemistry Challenge Award in 2002, among other improvements a three-step sequence was streamlined by employing ethanol as the sole solvent. This eliminated the need to use, distil and recover four solvents (methylene chloride, tetrahydrofuran, toluene and hexane) employed in the original process. Similarly, impressive improvements were achieved in a redesign of the manufacturing process for sildenafil (Viagra™) [99].

The best solvent is no solvent and if a solvent (diluent) is needed then water is preferred [100]. Water is non-toxic, non-inflammable, abundantly available and inexpensive. Moreover, owing to its highly polar character one can expect novel reactivities and selectivities for organometallic catalysis in water. Furthermore, this provides an opportunity to overcome a serious shortcoming of homogeneous catalysts, namely the cumbersome recovery and recycling of the catalyst. Thus, performing the reaction in an aqueous biphasic system, whereby the

catalyst resides in the water phase and the product is dissolved in the organic phase [101, 102], allows recovery and recycling of the catalyst by simple phase separation.

An example of a large scale application of this concept is the Ruhrchemie/Rhône Poulenc process for the hydroformylation of propylene to n-butanal, which employs a water-soluble rhodium(I) complex of trisulfonated triphenylphosphine (tppts) as the catalyst [103]. The same complex also functions as the catalyst in the Rhône Poulenc process for the manufacture of the vitamin A intermediate, geranylacetone, via reaction of myrcene with methyl acetoacetate in an aqueous biphasic system (Fig. 1.35) [104].

Similarly, Pd/tppts was used by Hoechst [105] as the catalyst in the synthesis of phenylacetic acid by biphasic carbonylation of benzyl chloride (Fig. 1.36) as an alternative to the classical synthesis via reaction with sodium cyanide. Although the new process still produces one equivalent of sodium chloride, this is substantially less salt generation than in the original process. Moreover, sodium cyanide is about seven times more expensive per kg than carbon monoxide.

The salt production can be circumvented by performing the selective Pd/tppts-catalysed carbonylation of benzyl alcohol in an acidic aqueous biphasic system (Fig. 1.36) [106]. This methodology was also applied to the synthesis of ibuprofen (see earlier) by biphasic carbonylation of 1-(4-isobutylphenyl)ethanol [107] and to the biphasic hydrocarboxylation of olefins [108].

As mentioned earlier (Section 1.5) another example of novel catalysis in an aqueous medium is the use of lanthanide triflates as water-tolerant Lewis acid catalysts for a variety of organic transformations in water [39].

Other non-classical reaction media [96] have, in recent years, attracted increasing attention from the viewpoint of avoiding environmentally unattractive solvents and/or facilitating catalyst recovery and recycling. Two examples, which readily come to mind, are supercritical carbon dioxide and room temperature ionic liquids. Catalytic hydrogenation in supercritical CO_2, for example, has

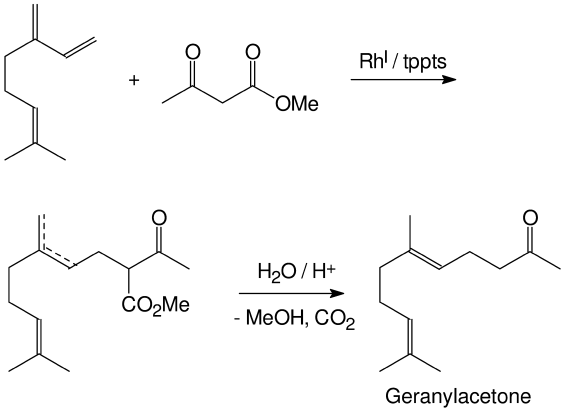
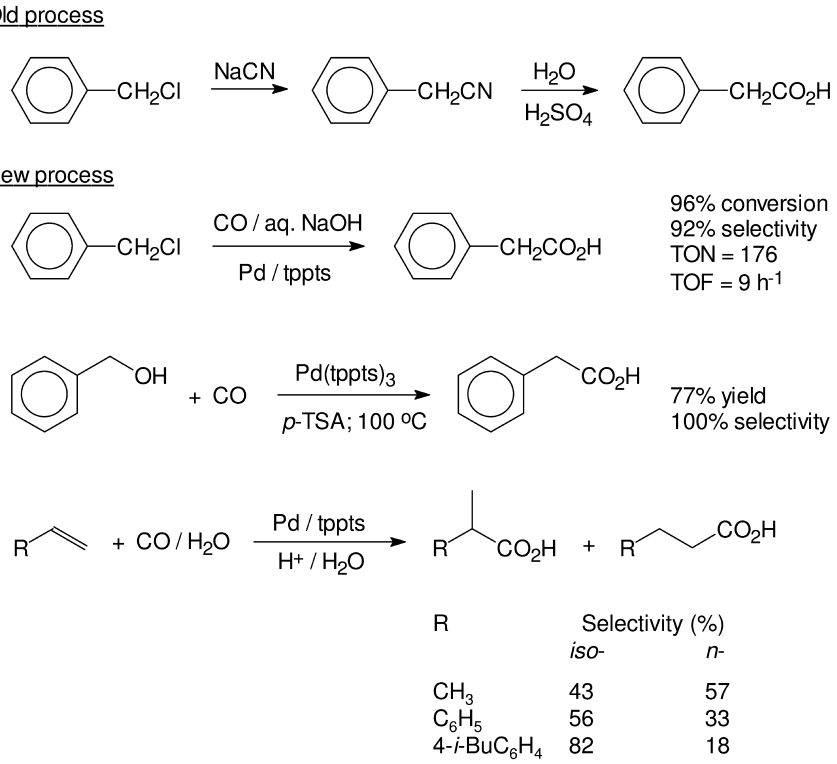


Fig. 1.35 Manufacture of n-butanal and geranylacetone in aqueous biphasic systems.



R	Selectivity (%)	
	iso-	*n-*
CH_3	43	57
C_6H_5	56	33
4-*i*-BuC_6H_4	82	18

Fig. 1.36 Aqueous biphasic carbonylations.

been commercialised by Thomas Swan and Co. [109]. Ionic liquids are similarly being touted as green reaction media for organic synthesis in general and catalytic reactions in particular [110–112]. They exhibit many properties which make them potentially attractive reaction media, e.g. they have essentially no vapor pressure and cannot, therefore, cause emissions to the atmosphere. These non-conventional reaction media will be treated in depth in Chapter 7.

1.10 Biocatalysis

Biocatalysis has many attractive features in the context of green chemistry: mild reaction conditions (physiological pH and temperature), an environmentally compatible catalyst (an enzyme) and solvent (often water) combined with high activities and chemo-, regio- and stereoselectivities in multifunctional molecules. Furthermore, the use of enzymes generally circumvents the need for functional group activation and avoids protection and deprotection steps required in traditional organic syntheses. This affords processes which are shorter, generate less

waste and are, therefore, both environmentally and economically more attractive than conventional routes.

The time is ripe for the widespread application of biocatalysis in industrial organic synthesis and according to a recent estimate [113] more than 130 processes have been commercialised. Advances in recombinant DNA techniques have made it, in principle, possible to produce virtually any enzyme for a commercially acceptable price. Advances in protein engineering have made it possible, using techniques such as site directed mutagenesis and *in vitro* evolution, to manipulate enzymes such that they exhibit the desired substrate specificity, activity, stability, pH profile, etc. [114]. Furthermore, the development of effective immobilisation techniques has paved the way for optimising the performance and recovery and recycling of enzymes.

An illustrative example of the benefits to be gained by replacing conventional chemistry by biocatalysis is provided by the manufacture of 6-aminopenicillanic acid (6-APA), a key raw material for semi-synthetic penicillin and cephalosporin antibiotics, by hydrolysis of penicillin G [115]. Up until the mid-1980s a chemical procedure was used for this hydrolysis (Fig. 1.37). It involved the use of environmentally unattractive reagents, a chlorinated hydrocarbon solvent (CH_2Cl_2) and a reaction temperature of –40 °C. Thus, 0.6 kg Me_3SiCl, 1.2 kg PCl_5, 1.6 kg $PhNMe_2$, 0.2 kg NH_3, 8.41 kg of n-BuOH and 8.41 kg of CH_2Cl_2 were required to produce 1 kg of 6-APA [116].

In contrast, enzymatic cleavage of penicillin G (Fig. 1.37) is performed in water at 37 °C and the only reagent used is NH_3 (0.9 kg per kg of 6-APA), to adjust the pH. The enzymatic process currently accounts for the majority of the several thousand tons of 6-APA produced annually on a world-wide basis.

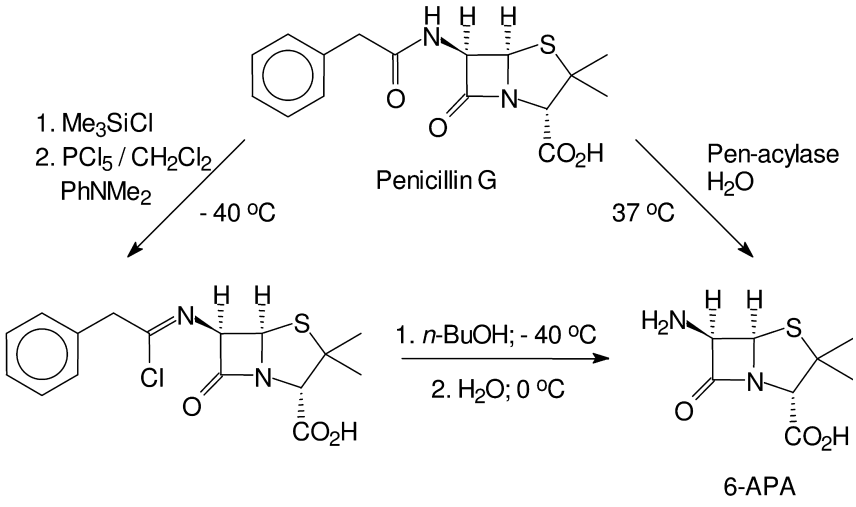


Fig. 1.37 Enzymatic versus chemical deacylation of penicillin G.

Another advantage of biocatalysis is the high degree of chemo-, regio- and stereoselectivities which are difficult or impossible to achieve by chemical means. A pertinent example is the production of the artificial sweetener, aspartame. The enzymatic process, operated by the Holland Sweetener Company (a joint venture of DSM and Tosoh) is completely regio- and enantiospecific (Fig. 1.38) [117].

The above-mentioned processes employ isolated enzymes – penicillin G acylase and thermolysin – and the key to their success was an efficient production of the enzyme. As with chemical catalysts, another key to success in biocatalytic processes is an effective method for immobilisation, providing for efficient recovery and re-use.

In some cases it is more attractive to use whole microbial cells, rather than isolated enzymes, as biocatalysts. This is the case in many oxidative biotransformations where cofactor regeneration is required and/or the enzyme has limited stability outside the cell. By performing the reaction with growing microbial cells, i.e. as a fermentation, the cofactor is continuously regenerated from an energy source, e.g. glucose. Lonza, for example, has commercialised processes for the highly chemo- and regioselective microbial ring hydroxylation and side-chain oxidation of heteroaromatics (see Fig. 1.39 for examples) [118]. Such conversions would clearly not be feasible by conventional chemical means.

DuPont has developed a process for the manufacture of glyoxylic acid, a large volume fine chemical, by aerobic oxidation of glycolic acid, mediated by resting

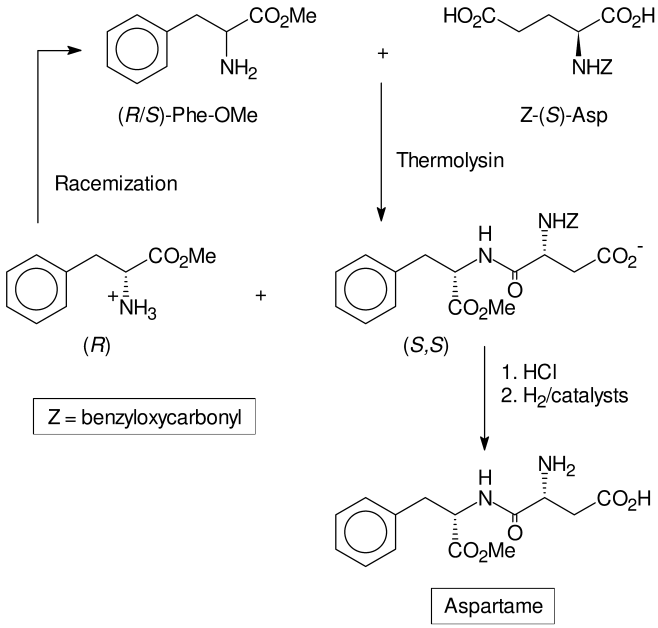


Fig. 1.38 Aspartame via enzymatic coupling.

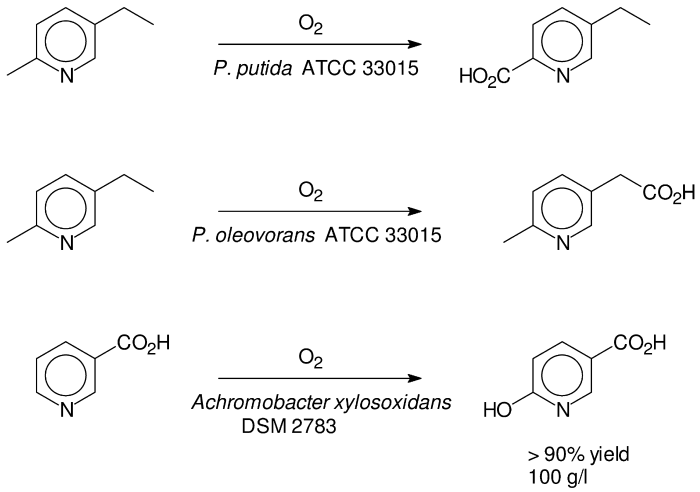


Fig. 1.39 Microbial oxidations of heteroaromatics.

whole cells of a recombinant methylotrophic yeast (Fig. 1.40) [119]. The glycolic acid is readily available from acid-catalysed carbonylation of formaldehyde. Traditionally, glyoxylic acid was produced by nitric acid oxidation of acetaldehyde or glyoxal, processes with high E factors, and more recently by ozonolysis of maleic anhydride.

The key enzyme in the above process is an oxidase which utilises dioxygen as the oxidant, producing one equivalent of hydrogen peroxide, without the need for cofactor regeneration. Another class of enzymes which catalyse the oxidation of alcohols comprises the alcohol dehydrogenases. However, in this case cofactor regeneration is required, which is an impediment to commercialisation. Re-

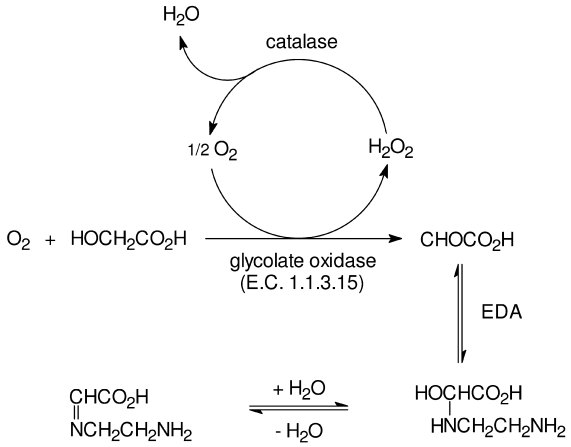


Fig. 1.40 Glyoxylic acid by microbial oxidation.

cently, a highly enantioselective alcohol dehydrogenase, showing broad substrate specificity and exceptionally high tolerance for organic solvents, was isolated from *Rhodococcus ruber* DSM 4451 [120]. The enzyme maintains a high activity at concentrations of up to 20% (v/v) acetone and 50% (v/v) 2-propanol. This enables the use of the enzyme, conveniently as whole microbial cells, as a catalyst for (enantioselective) Oppenauer oxidation of a broad range of alcohols, using acetone (20% v/v in phosphate buffer at pH 8) as the oxidant (Fig. 1.41), with substrate concentrations up to 1.8 mol l^{-1} (237 g l^{-1} for octan-2-ol).

Alternatively, the reaction could be performed in a reduction mode, using the ketone as substrate and up to 50% v/v isopropanol as the reductant, affording the corresponding (*S*)-alcohol in 99% ee at conversions ranging from 65 to 92%.

Another example in which a biocatalytic transformation has replaced a chemocatalytic one, in a very simple reaction, is the Mitsubishi Rayon process for the production of acrylamide by hydration of acrylonitrile (Fig. 1.42). Whole cells of *Rhodococcus rhodocrous*, containing a nitrile hydratase, produced acrylamide in >99.9% purity at >99.9% conversion, and in high volumetric and space time yields [121]. The process (Fig. 1.42) currently accounts for more than 100 000 tons annual production of acrylamide and replaced an existing process which employed a copper catalyst. A major advantage of the biocatalytic process is the high product purity, which is important for the main application of acrylamide as a specialty monomer.

Similarly, DuPont employs a nitrile hydratase (as whole cells of *P. chlororaphis* B23) to convert adiponitrile to 5-cyanovaleramide, a herbicide intermediate [122]. In the Lonza nitrotinamide (vitamin B6) process [123] the final step (Fig. 1.42) involves the nitrile hydratase (whole cells of *Rh. rhodocrous*) catalysed hydration of 3-cyanopyridine. Here again the very high product purity is a major advantage as conventional chemical hydrolysis affords a product contaminated with nicotinic acid, which requires expensive purification to meet the specifications of this vitamin.

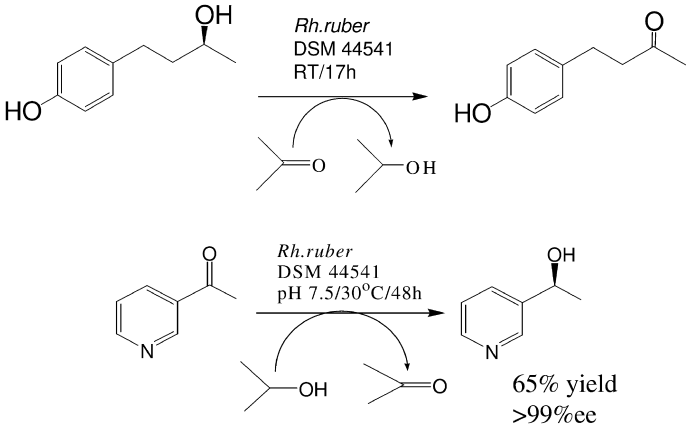


Fig. 1.41 Biocatalytic Oppenauer oxidations and MPV reductions.

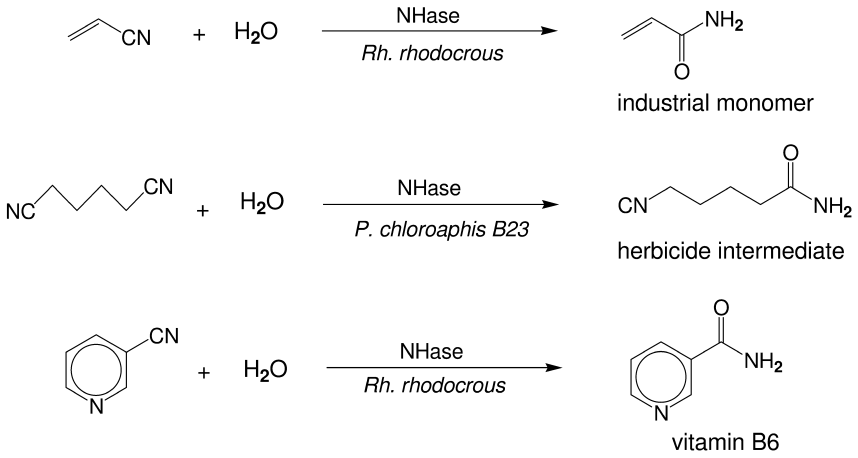


Fig. 1.42 Industrial processes employing a nitrile hydratase.

1.11
Renewable Raw Materials and White Biotechnology

Another important goal of green chemistry is the utilisation of renewable raw materials, i.e. derived from biomass, rather than crude oil. Here again, the processes used for the conversion of renewable feedstocks – mainly carbohydrates but also triglycerides and terpenes – should produce minimal waste, i.e. they should preferably be catalytic.

In the processes described in the preceding section a biocatalyst – whole microbial cells or an isolated enzyme – is used to catalyse a transformation (usually one step) of a particular substrate. When growing microbial cells are used this is referred to as a precursor fermentation. Alternatively, one can employ *de novo* fermentation to produce chemicals directly from biomass. This has become known as white biotechnology, as opposed to red biotechnology (biopharmaceuticals) and green biotechnology (genetically modified crops). White biotechnology is currently the focus of considerable attention and is perceived as the key to developing a sustainable chemical industry [124].

Metabolic pathway engineering [125] is used to optimise the production of the required product based on the amount of substrate (usually biomass-derived) consumed. A so-called biobased economy is envisaged in which commodity chemicals (including biofuels), specialty chemicals such as vitamins, flavors and fragrances and industrial monomers will be produced in biorefineries (see Chapter 8 for a more detailed discussion).

De novo fermentation has long been the method of choice for the manufacture of many natural L-amino acids, such as glutamic acid and lysine, and hydroxy acids such as lactic and citric acids. More recently, *de novo* fermentation is displacing existing multistep chemical syntheses, for example in the manufacture of vitamin B2 (riboflavin) and vitamin C. Other recent successes of white

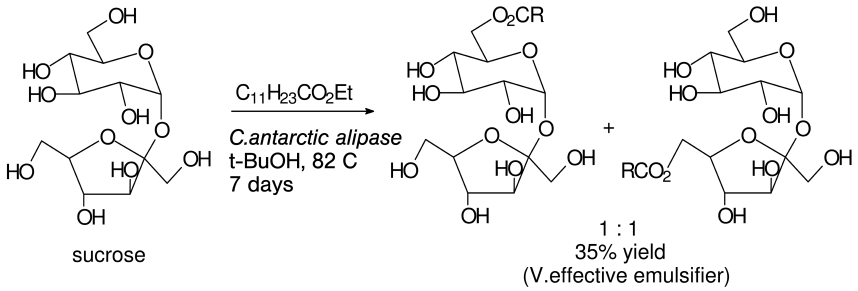


Fig. 1.43 Synthesis of a bioemulsifier from renewable raw materials.

biotechnology include the biodegradable plastic, polylactate, produced by Cargill-Dow and 1,3-propanediol, a raw material for the new polyester fibre, Sorona (poly-trimethylene terephthalate) developed by DuPont/Genencor. The latter process has become a benchmark in metabolic pathway engineering [125]. Both of these processes employ corn-derived glucose as the feedstock.

Finally, an elegant example of a product derived from renewable raw materials is the bioemulsifier, marketed by Mitsubishi, which consists of a mixture of sucrose fatty acid esters. The product is prepared from two renewable raw materials – sucrose and a fatty acid – and is biodegradable. In the current process the reaction is catalysed by a mineral acid, which leads to a rather complex mixture of mono- and di-esters. Hence, a more selective enzymatic esterification (Fig. 1.43) would have obvious benefits. Lipase-catalysed acylation is possible [126] but reaction rates are very low. This is mainly owing to the fact that the reaction, for thermodynamic reasons, cannot be performed in water. On the other hand, sucrose is sparingly soluble in most organic solvents, thus necessitating a slurry process.

1.12
Enantioselective Catalysis

Another major trend in performance chemicals is towards the development of products – pharmaceuticals, pesticides and food additives, etc. – that are more targeted in their action with less undesirable side-effects. This is also an issue which is addressed by green chemistry. In the case of chiral molecules that exhibit biological activity the desired effect almost always resides in only one of the enantiomers. The other enantiomer constitutes isomeric ballast that does not contribute to the desired activity and may even exhibit undesirable side-effects. Consequently, in the last two decades there has been a marked trend towards the marketing of chiral pharmaceuticals and pesticides as enantiomerically pure compounds. This generated a demand for economical methods for the synthesis of pure enantiomers [127].

The same reasoning applies to the synthesis of pure enantiomers as to organic synthesis in general: for economic and environmental viability, processes should

be atom efficient and have low E factors, that is, they should employ catalytic methodologies. This is reflected in the increasing focus of attention on enantioselective catalysis, using either enzymes or chiral metal complexes. Its importance was acknowledged by the award of the 2001 Nobel Prize in Chemistry to Knowles, Noyori and Sharpless for their contributions to asymmetric catalysis.

An elegant example of a highly efficient catalytic asymmetric synthesis is the Takasago process [128] for the manufacture of 1-menthol, an important flavour and fragrance product. The key step is an enantioselective catalytic isomerisation of a prochiral enamine to a chiral imine (Fig. 1.44). The catalyst is a Rh-Binap complex (see Fig. 1.44) and the product is obtained in 99% ee using a substrate/catalyst ratio of 8000; recycling of the catalyst affords total turnover numbers of up to 300 000. The Takasago process is used to produce several thousand tons of 1-menthol on an annual basis.

An even more impressive example of catalytic efficiency is the manufacture of the optically active herbicide, (*S*)-metolachlor. The process, developed by Novartis [129], involves asymmetric hydrogenation of a prochiral imine, catalysed

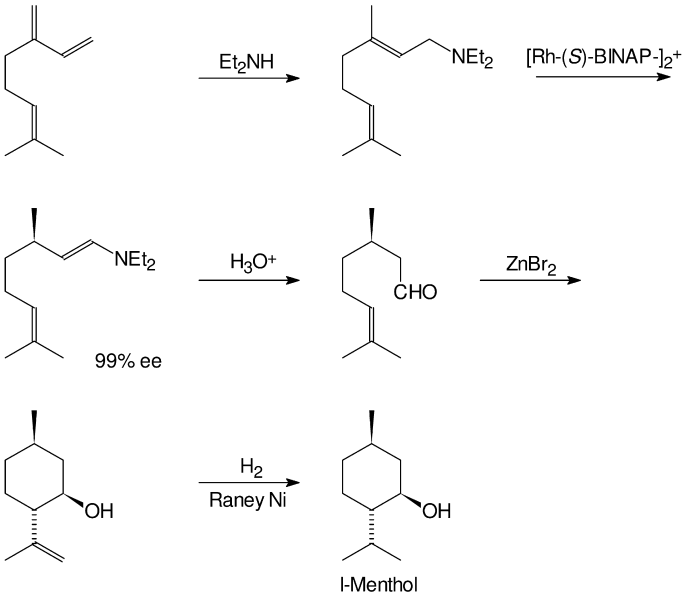


Fig. 1.44 Takasago l-menthol process.

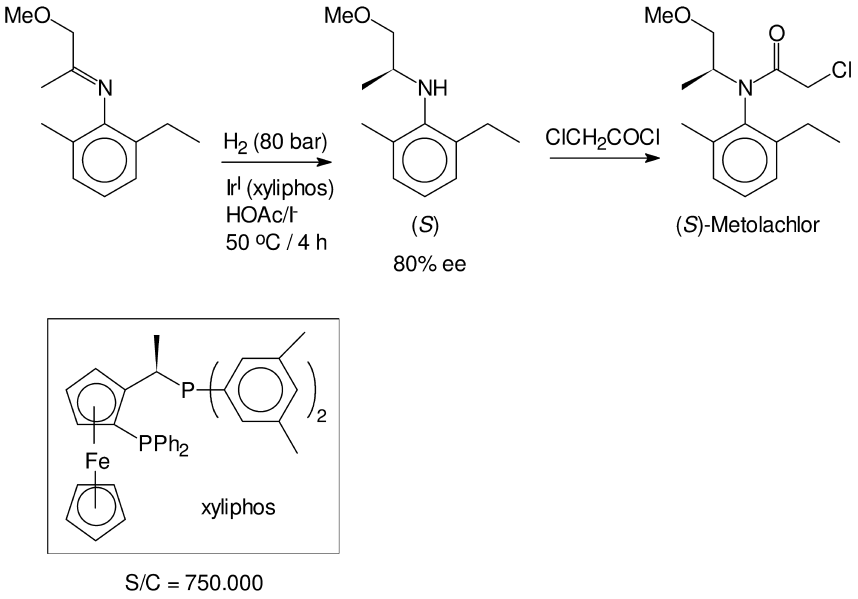


Fig. 1.45 Novartis process for (*S*)-metalachlor.

by an iridium complex of a chiral ferrocenyldiphosphine (Fig. 1.45). Complete conversion is achieved within 4 h at a substrate/catalyst ratio of >1 000 000 and an initial TOF exceeding 1 800 000 h^{-1}, giving a product with an ee of 80%. A higher ee can be obtained, at lower substrate/catalyst ratios, but is not actually necessary for this product. The process is used to produce several thousand tons of this optically active herbicide.

The widespread application of enantioselective catalysis, be it with chiral metal complexes or enzymes, raises another issue. These catalysts are often very expensive. Chiral metal complexes generally comprise expensive noble metals in combination with even more expensive chiral ligands. A key issue is, therefore, to minimise the cost contribution of the catalyst to the total cost price of the product; a rule of thumb is that it should not be more than ca. 5%. This can be achieved either by developing an extremely productive catalyst, as in the metachlor example, or by efficient recovery and recycling of the catalyst. Hence, much attention has been devoted in recent years to the development of effective methods for the immobilisation of metal complexes [130, 131] and enzymes [132]. This is discussed in more detail in Chapter 9.

1.13 Risky Reagents

In addition to the increasingly stringent environmental regulations with regard to the disposal of aqueous effluent and solid waste, tightened safety regulations are making the transport, storage and, hence, use of many hazardous and toxic chemicals prohibitive. The ever increasing list includes, phosgene, dimethyl sulfate, formaldehyde/hydrogen chloride (for chloromethylations), sodium azide, hydrogen fluoride, and even chlorine and bromine.

Although it will not be possible to dispense with some of these reagents entirely, their industrial use is likely to be confined to a small group of experts who are properly equipped to handle and contain these materials. In some cases, catalytic alternatives may provide an answer, such as the use of catalytic carbonylation instead of phosgene and solid acids as substitutes for hydrogen fluoride.

Chlorine-based chemistry is a case in point. In addition to the problem of salt generation, the transport of chlorine is being severely restricted. Moreover, chlorine-based routes often generate aqueous effluent containing trace levels of chlorinated organics that present a disposal problem.

Obviously, when the desired product contains a chlorine atom, the use of chlorine can be avoided only by replacing the product. However, in many cases chlorine is a reagent that does not appear in the product, and its use can be circumvented. How remarkably simple the solution can be, once the problem has been identified, is illustrated by the manufacture of a family of sulfenamides that are used as rubber additives.

Traditionally, these products were produced using a three-step, chlorine-based, oxidative coupling process (Fig. 1.46). In contrast, Monsanto scientists [133] developed a process involving one step, under mild conditions (< 1 h at 70 °C). It uses molecular oxygen as the oxidant and activated charcoal as the catalyst (Fig. 1.46). The alkylaminomercaptobenzothiazole product is formed in essentially quantitative yield, and water is the coproduct. We note that activated charcoal contains various trace metals which may be the actual catalyst.

Another elegant example, also developed by Monsanto scientists [134], is the synthesis of *p*-phenylene diamine, a key raw material for aramid fibres. The traditional process involves nitration of chlorobenzene followed by reaction of the resulting *p*-nitrochlorobenzene with ammonia to give *p*-nitroaniline, which is hydrogenated to *p*-phenylenediamine. Monsanto scientists found that benzamide reacts with nitrobenzene, in the presence of a base and dioxygen, to afford 4-nitrobenzanilide. Reaction of the latter with methanolic ammonia generates *p*-nitroaniline and benzamide, which can be recycled to the first step (Fig. 1.47), resulting in an overall reaction of nitrobenzene with ammonia and dioxygen to give *p*-nitroaniline and a molecule of water. The key step in the process is the oxidation of the intermediate Meisenheimer complex by the nitrobenzene substrate, resulting in an overall oxidative nucleophilic substitution. The nitrosobenzene coproduct is reoxidised by dioxygen. Hence, a remarkable feature of the process is that no external catalyst is required; the substrate itself acts as the catalyst.

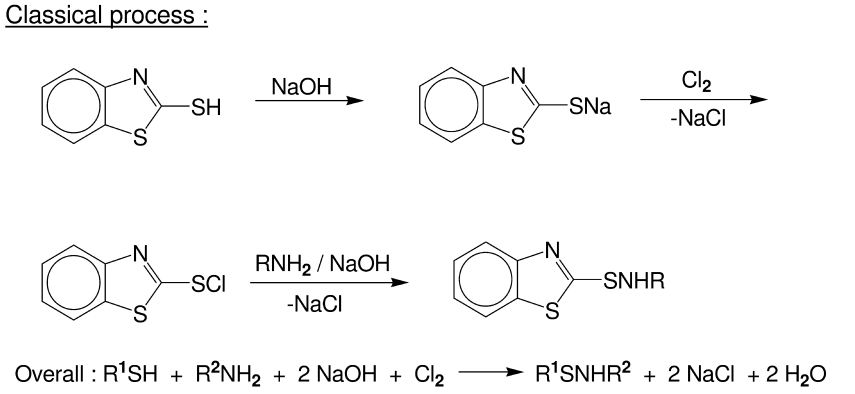


Fig. 1.46 Two routes to alkylaminomercaptobenzothiazoles.

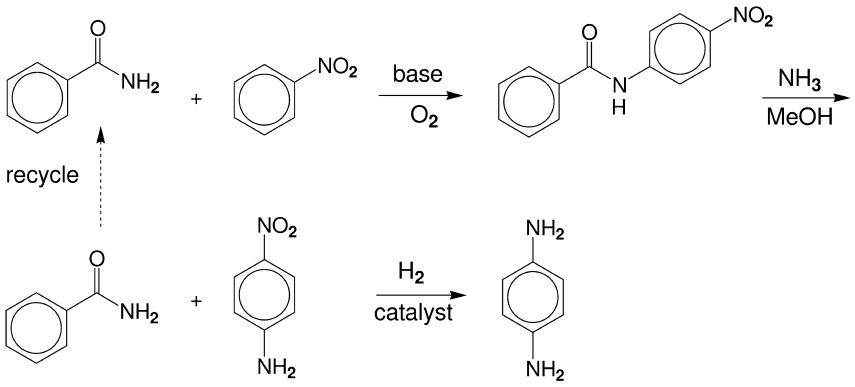


Fig. 1.47 Monsanto process for *p*-phenylenediamine.

1.14
Process Integration and Catalytic Cascades

The widespread application of chemo- and biocatalytic methodologies in the manufacture of fine chemicals is resulting in a gradual disappearance of the traditional barriers between the subdisciplines of homogeneous and heterogeneous catalysis and biocatalysis. An effective integration of these catalytic technologies in organic synthesis is truly the key to success.

An elegant example is the Rhodia process for the manufacture of the flavor ingredient, vanillin [30]. The process involves four steps, all performed with a heterogeneous catalyst, starting from phenol (Fig. 1.48). Overall, one equivalent of phenol, H_2O_2, CH_3OH, H_2CO and O_2 are converted to one equivalent of vanillin and three equivalents of water.

Another pertinent example is provided by the manufacture of caprolactam [135]. Current processes are based on toluene or benzene as feedstock, which can be converted to cyclohexanone via cyclohexane or phenol. More recently, Asahi Chemical [136] developed a new process via ruthenium-catalysed selective hydrogenation to cyclohexene, followed by zeolite-catalysed hydration to cyclohexanol and dehydrogenation (Fig. 1.49). The cyclohexanone is then converted to caprolactam via ammoximation with NH_3/H_2O_2 and zeolite-catalysed Beckmann rearrangement as developed by Sumitomo (see earlier).

Alternatively, caprolactam can be produced from butadiene, via homogeneous nickel-catalysed addition of HCN (DuPont process) followed by selective catalytic hydrogenation of the adiponitrile product to the amino nitrile and vapor phase hydration over an alumina catalyst (Rhodia process) as shown in Fig. 1.49 [137].

Interestingly, the by-product in the above-described hydrocyanation of butadiene, 2-methylglutaronitrile, forms the raw material for the Lonza process for nicotinamide (see earlier) [123]. Four heterogeneous catalytic steps (hydrogenation, cyclisation, dehydrogenation and ammoxidation) are followed by an enzymatic hydration of a nitrile to an amide (Fig. 1.50).

The ultimate in integration is to combine several catalytic steps into a one-pot, multi-step catalytic cascade process [138]. This is truly emulating Nature where metabolic pathways conducted in living cells involve an elegant orchestration of a series of biocatalytic steps into an exquisite multicatalyst cascade, without the need for separation of intermediates.

An example of a one-pot, three-step catalytic cascade is shown in Fig. 1.51 [139]. In the first step galactose oxidase catalyses the selective oxidation of the primary alcohol group of galactose to the corresponding aldehyde. This is fol-

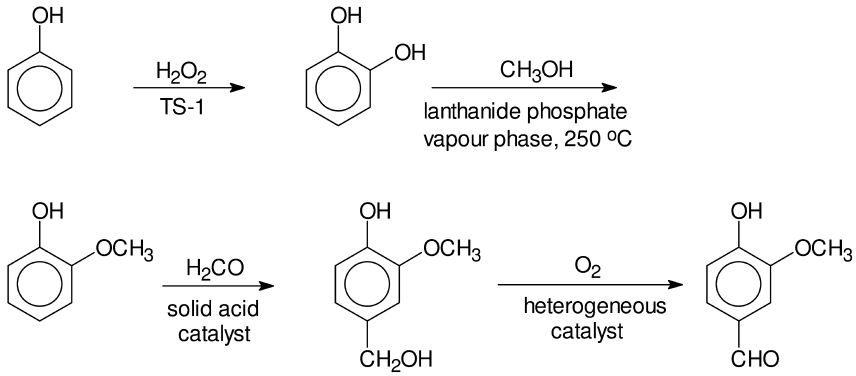


Fig. 1.48 Rhodia vanillin process.

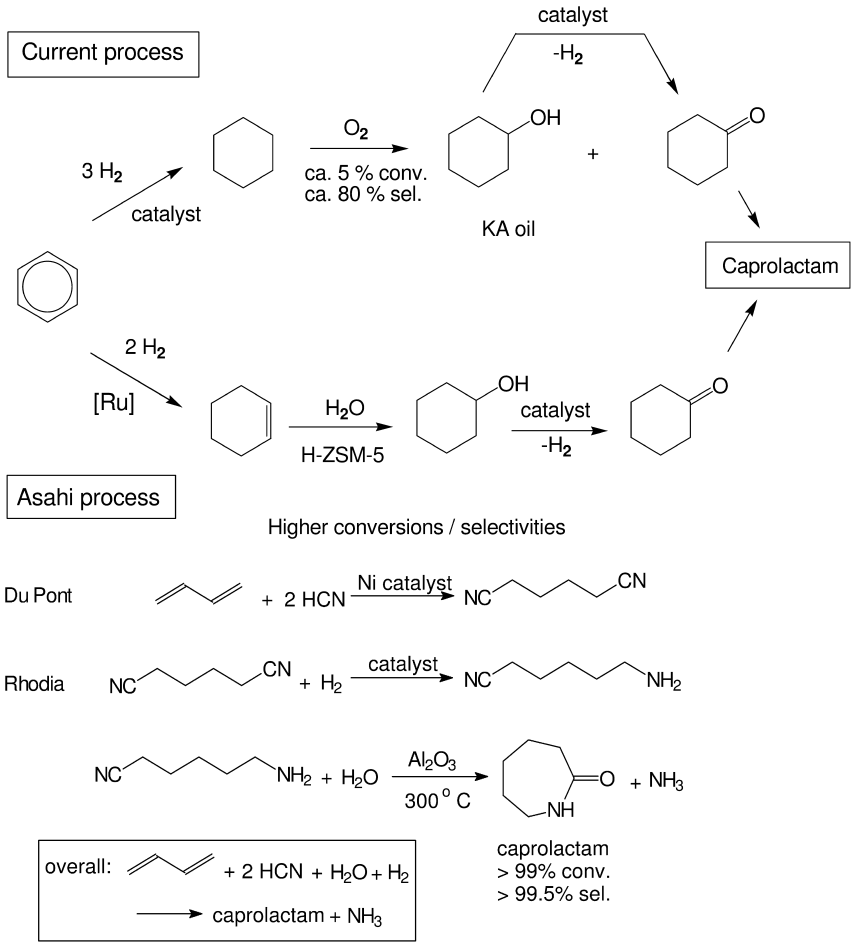


Fig. 1.49 Alternative routes to caprolactam.

lowed by L-proline catalysed elimination of water and catalytic hydrogenation, affording the corresponding deoxy sugar.

In some cases the answer may not be to emulate Nature's catalytic cascades but rather to streamline them through metabolic pathway engineering (see earlier). The elegant processes for vanillin, caprolactam and nicotinamide described above may, in the longer term, be superseded by alternative routes based on *de novo* fermentation of biomass. For many naturally occurring compounds this will represent a closing of the circle that began, more than a century ago, with the synthesis of natural products, such as dyestuffs, from raw materials derived from coal tar. It is perhaps appropriate, therefore, to close this chapter with a mention of the dyestuff indigo. Its first commercial synthesis, in the nineteenth century [140] involved classical organic chemistry and has hardly changed since

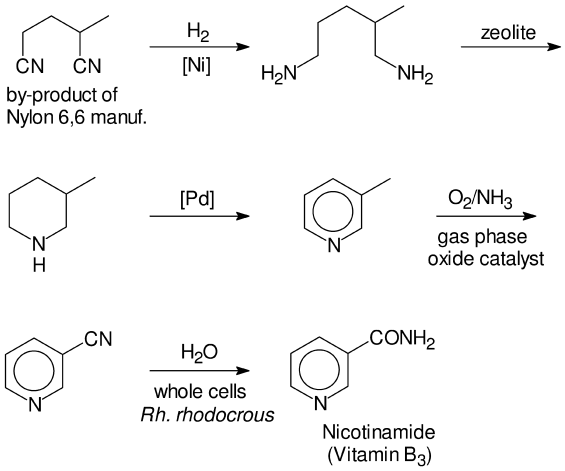


Fig. 1.50 Lonza nicotinamide process.

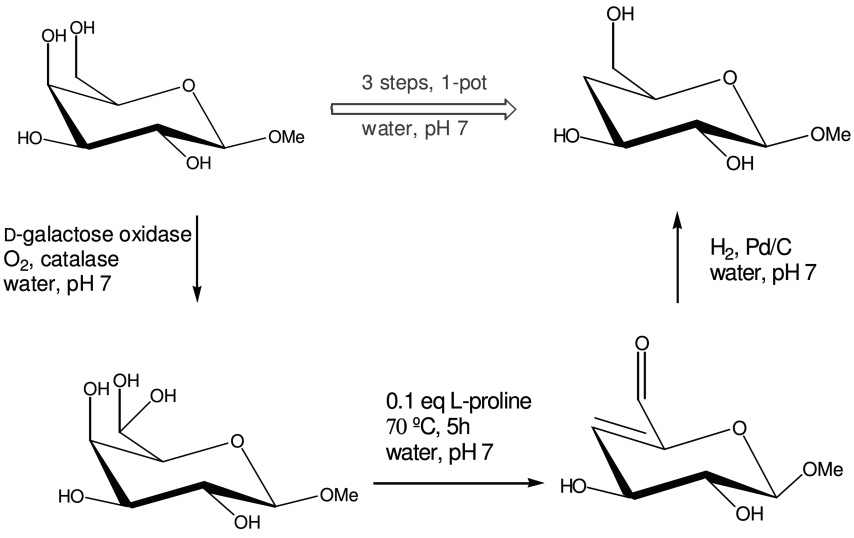


Fig. 1.51 One-pot, three-step synthesis of a deoxy sugar.

that time. Mitsui Toatsu reported [141] an alternative conversion of aniline to indigo in two catalytic steps. However, in the future indigo may be produced by an even greener route. Genencor [142] has developed a one-step fermenatation of glucose to indigo using a recombinant *E. coli* strain in which the tryptophan pathway has been engineered, to produce high levels of indole, and genes encoding for naphthalene dioxygenase have been incorporated. The latter enzyme catalyses the aerobic oxidation of indole to indigo. The process (see Chapter for a more detailed discussion) is not yet commercially viable, probably because of

relatively low volumetric (18 g l^{-1}) and space–time yields (<1 g l^{-1} h^{-1}), but may be further optimised in the future.

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