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Green Chemistry and Catalysis



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*Roger Arthur Sheldon,
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**Green Chemistry
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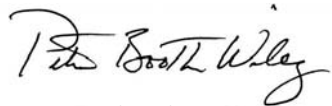
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Green Chemistry and Catalysis



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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

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. $MI = E \text{ factor} + 1$ 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.

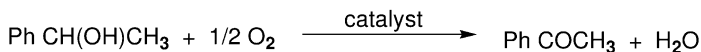
An interesting example, to further illustrate the concepts of E factors and atom efficiency is the manufacture of phloroglucinol [23]. Traditionally, it was produced from 2,4,6-trinitrotoluene (TNT) as shown in Fig. 1.2, a perfect example of nineteenth century organic chemistry.

This process has an atom efficiency of <5% and an E factor of 40, i.e. it generates 40 kg of solid waste, containing $\text{Cr}_2(\text{SO}_4)_3$, 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-



$$\text{atom efficiency} = 360 / 860 = 42 \%$$



$$\text{atom efficiency} = 120 / 138 = 87 \%$$

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

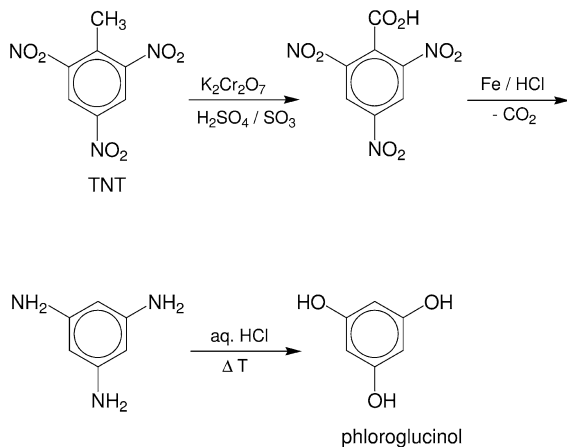


Fig. 1.2 Phloroglucinol from TNT.

fact 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 10000 tons per annum, on the other hand, may already present a disposal problem and would warrant assignment 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 ,

NaBH₄), 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 (H₂SO₄, HF, H₃PO₄) and Lewis acids (AlCl₃, ZnCl₂, BF₃). 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 H₂, O₂, H₂O₂, CO, CO₂ and NH₃ 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 H₂SO₄, 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 (MnSO₄, FeCl₂, NaCl, Na₂SO₄) 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-

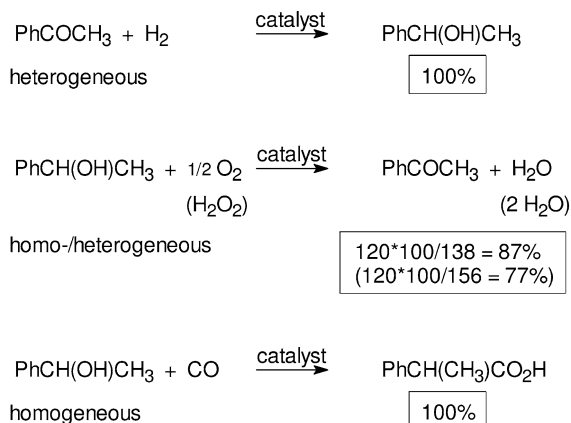


Fig. 1.3 Atom efficient catalytic processes.

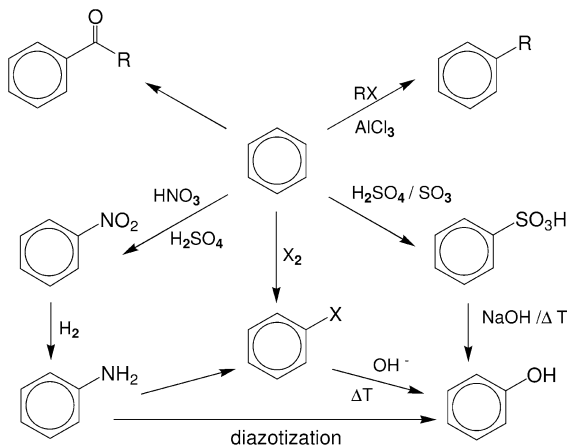


Fig. 1.4 Classical aromatic chemistry.

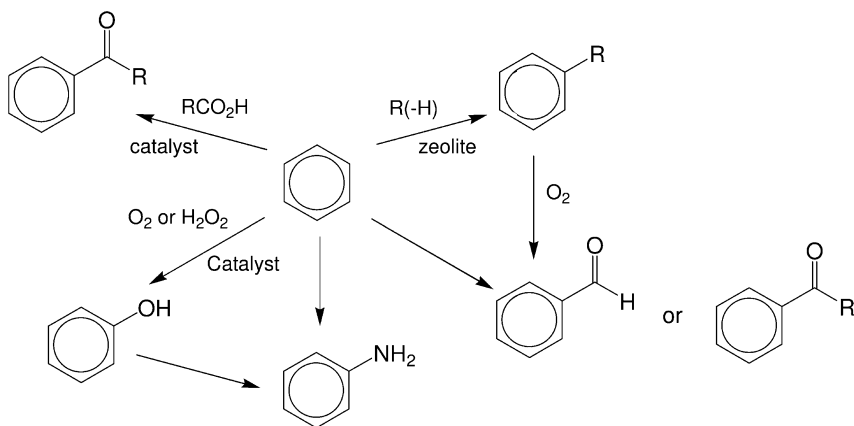


Fig. 1.5 Non-classical aromatic chemistry.

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).

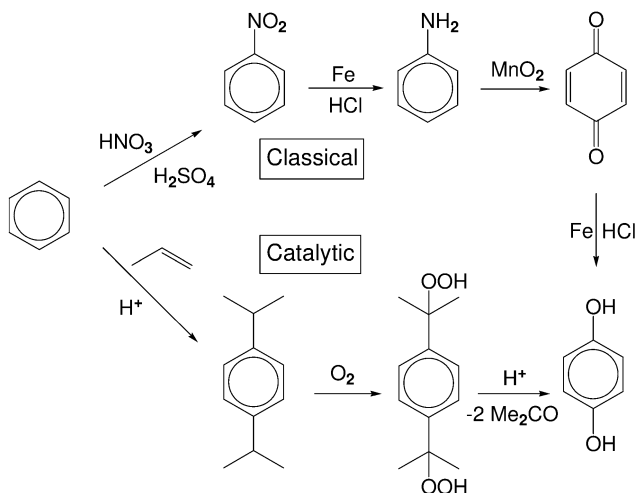


Fig. 1.6 Two routes to hydroquinone.

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

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

1.5

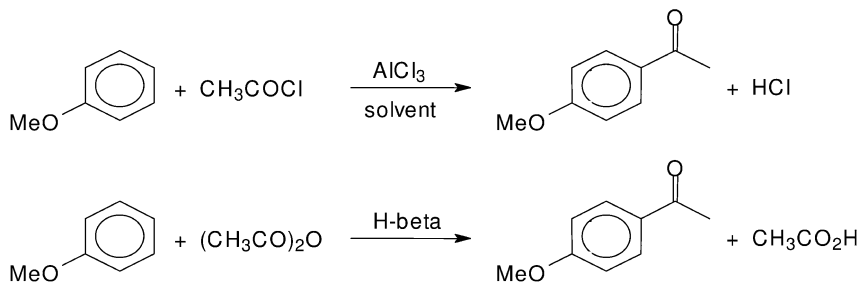
Catalysis by Solid Acids and Bases

As noted above, a major source of waste in the (fine) chemicals industry is derived from the widespread use of liquid mineral acids (HF, H₂SO₄) 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 H₂SO₄ 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, AlCl₃ or BF₃. 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 AlCl₃ in a chlorinated hydrocarbon solvent, and generated 4.5 kg of aqueous effluent, containing AlCl₃, 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**

$\text{AlCl}_3 > 1$ equivalent
 Solvent
 Hydrolysis of products
 Phase separation
 Distillation organic phase
 Solvent recycle
 85-95% yield
 4.5 kg aqueous effluent per kg
 12 unit operations

Heterogeneous

H-beta, catalytic & regenerable
 No solvent
 No water necessary
 -
 Distillation organic phase
 -
 > 95% yield, higher purity
 0.035 kg aqueous effluent per kg
 3 unit operations

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

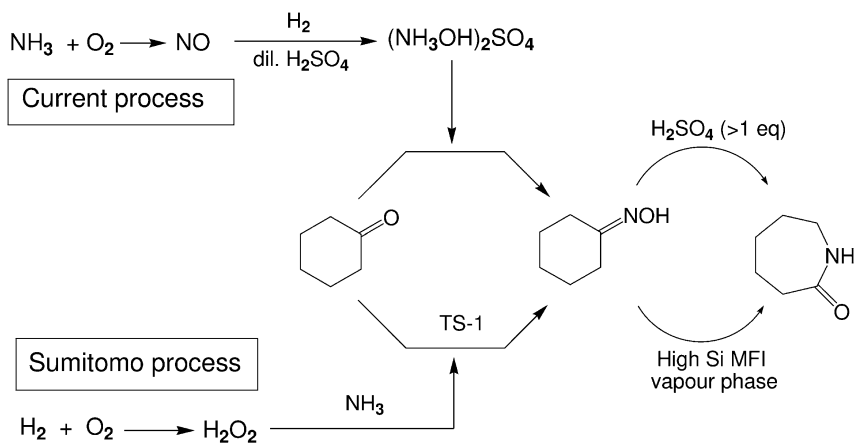


Fig. 1.9 Sumitomo vs. conventional process for caprolactam manufacture.

involves 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 $\text{NH}_3/\text{H}_2\text{O}_2$ 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 $\text{BF}_3 \cdot \text{OEt}_2$ 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-

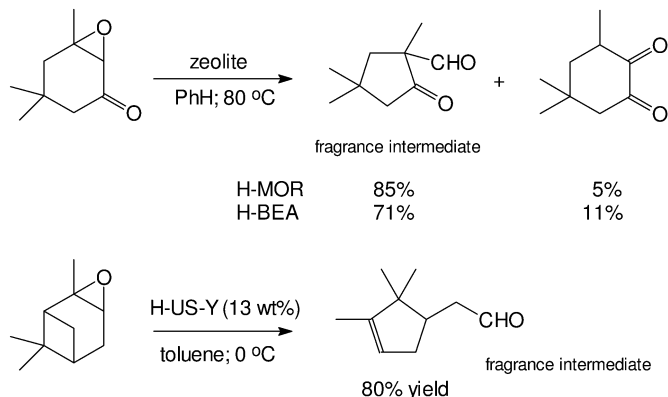
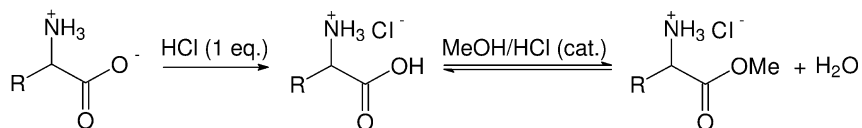


Fig. 1.10 Zeolite-catalysed epoxide rearrangements.

CONVENTIONAL :



ZEOLITE-CATALYZED :

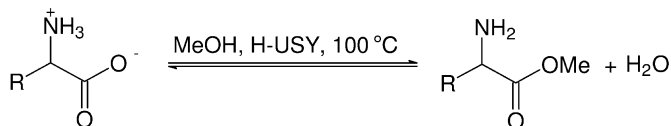


Fig. 1.11 Salt-free esterification of amino acids.

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 $\text{Mg}_{8-x}\text{Al}_x(\text{OH})_{16}(\text{CO}_3)_{x/2} \cdot n\text{H}_2\text{O}$, are hydrated aluminum-magnesium hydroxides possess-

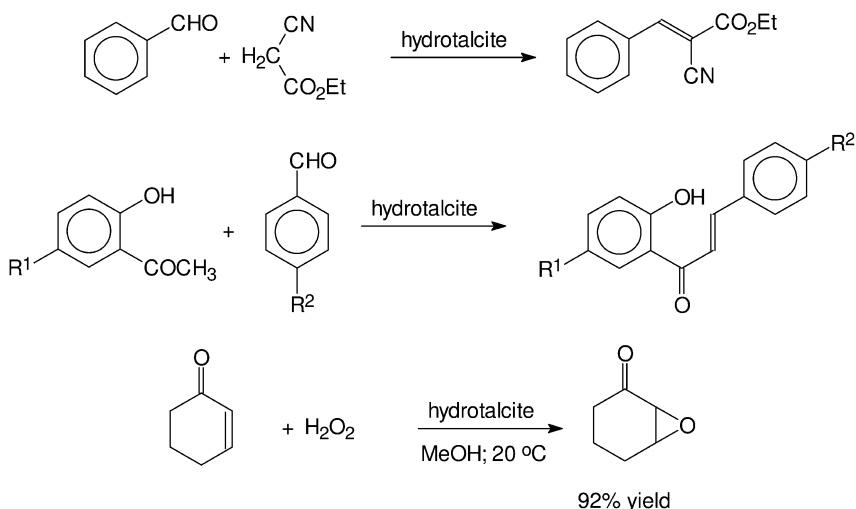


Fig. 1.12 Hydrotalcite-catalysed condensation reactions.

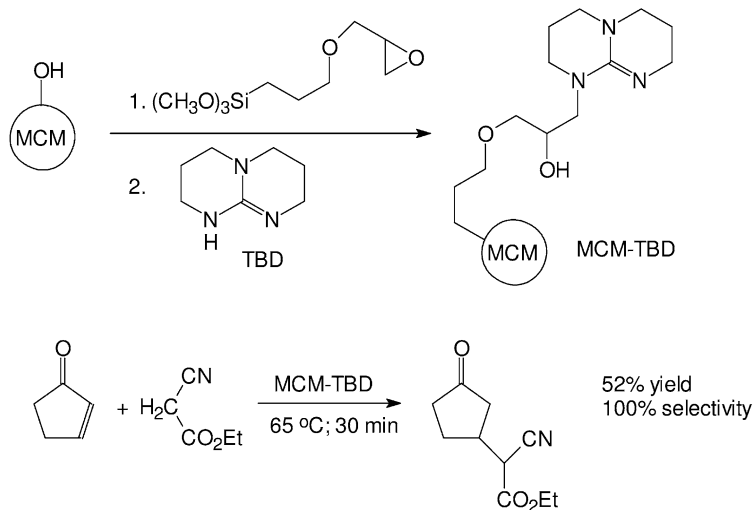


Fig. 1.13 Tethered organic bases as solid base catalysts.

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

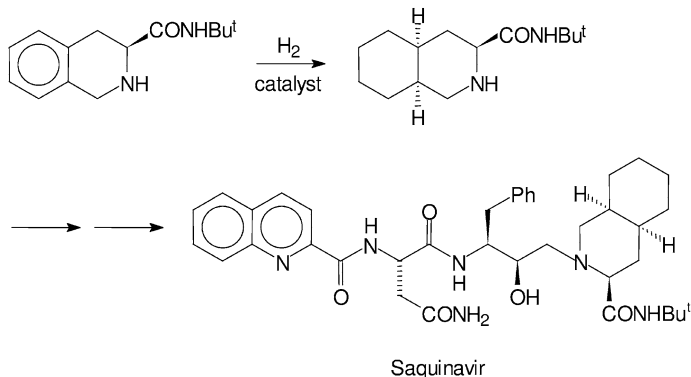


Fig. 1.14 Synthesis of a Saquinavir intermediate.

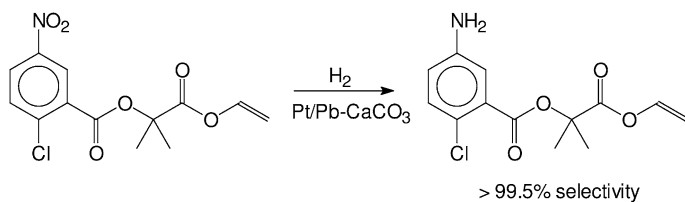


Fig. 1.15 Chemoselective hydrogenation of a nitro group.

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-Ponndorf-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-

Williamson ether synthesis :



Catalytic alternative :

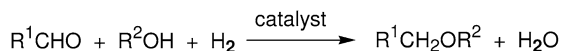


Fig. 1.16 Williamson ether synthesis and a catalytic alternative.

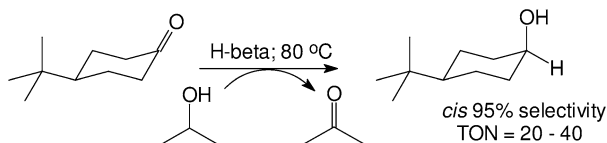


Fig. 1.17 Zeolite beta catalysed MPV reduction.

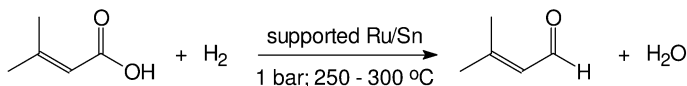


Fig. 1.18 Direct hydrogenation of carboxylic acids to aldehydes.

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/BaSO₄ [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 stigmaterol, 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.

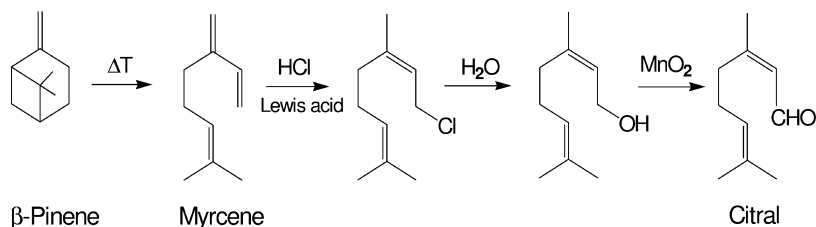
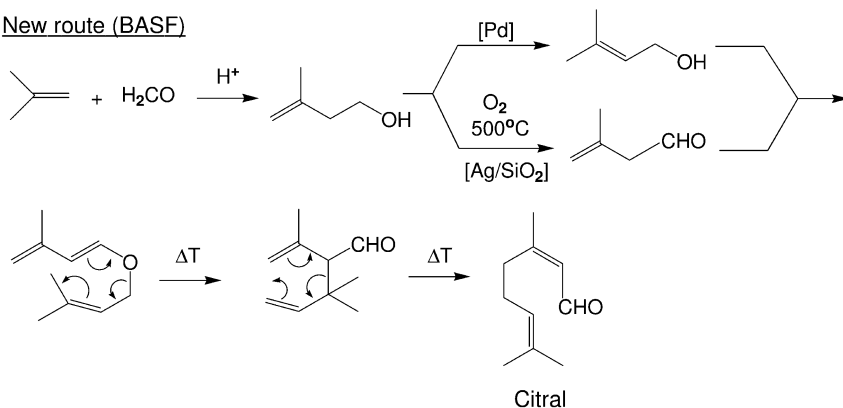
Classical routeNew route (BASF)

Fig. 1.19 Two routes to citral.

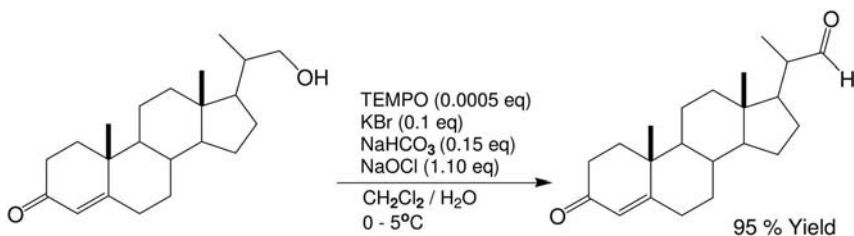


Fig. 1.20 Key step in the production of progesterone from stigmasterol.

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.

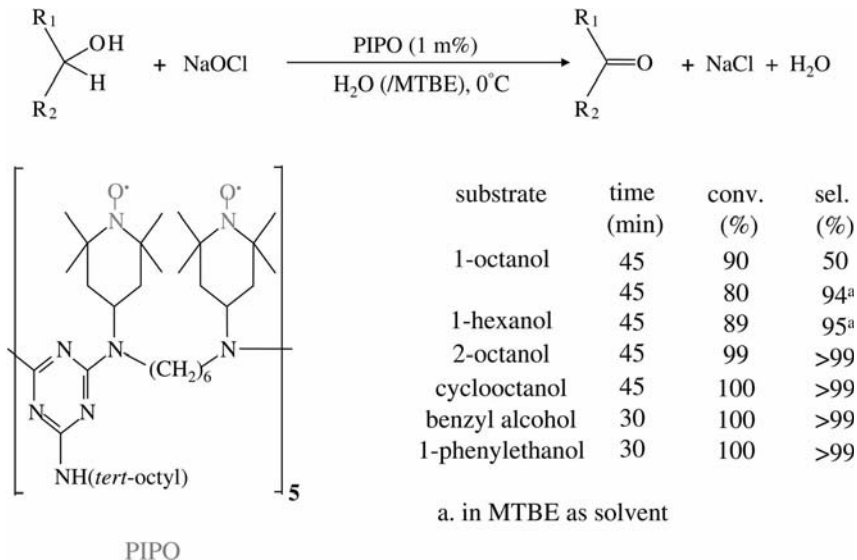


Fig. 1.21 PIPO catalysed oxidation of alcohols with NaOCl.

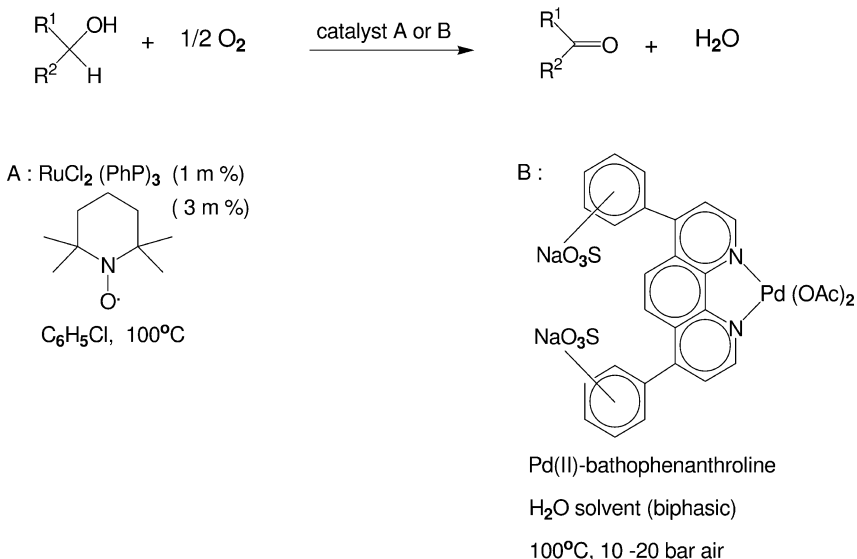


Fig. 1.22 Two methods for aerobic oxidation of alcohols.

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-

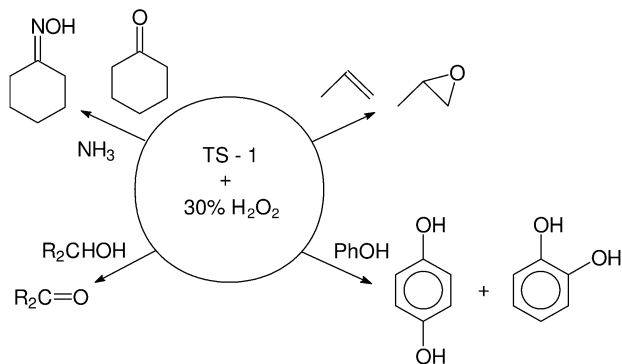


Fig. 1.23 Catalytic oxidations with TS-1/ H_2O_2 .

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 ($5.1 \times 5.5 \text{ \AA}^2$) 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

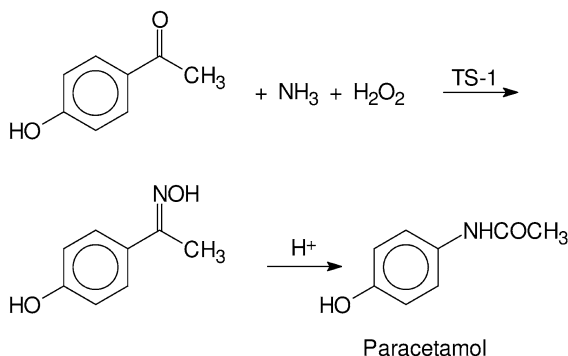


Fig. 1.24 Paracetamol intermediate via ammoximation.

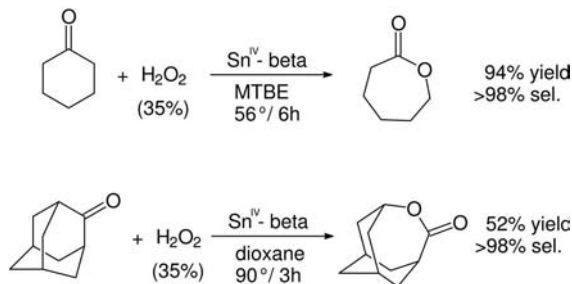


Fig. 1.25 Baeyer-Villiger oxidation with H₂O₂ catalysed by Sn-Beta.

for the Baeyer-Villiger oxidation of ketones and aldehydes [78] with aqueous H₂O₂ (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

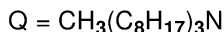
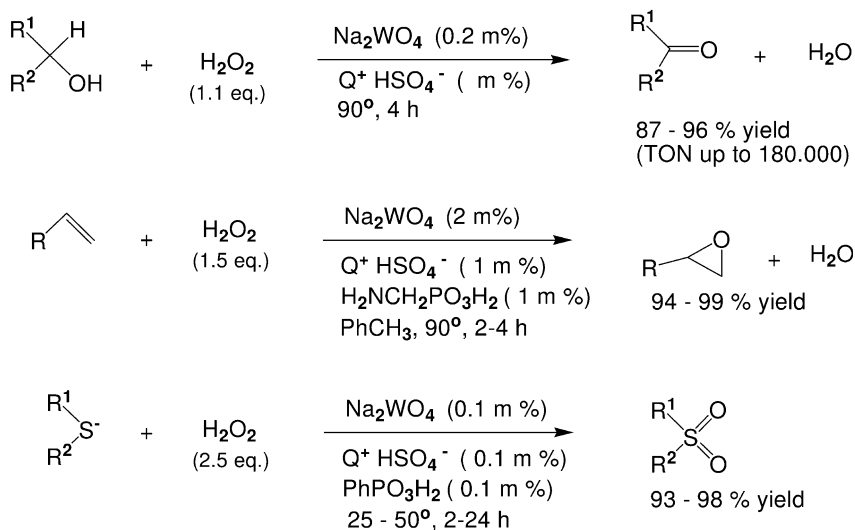


Fig. 1.26 Catalytic oxidations with hydrogen peroxide under phase transfer conditions.

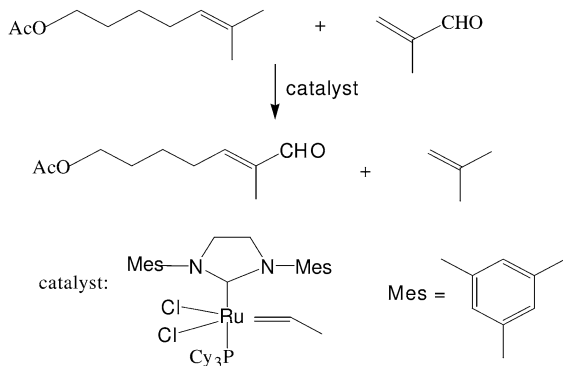


Fig. 1.27 The best oxidation is no oxidation.

aqueous H₂O₂, in an environmentally and economically attractive manner (Fig. 1.26).

Notwithstanding the significant advances in selective catalytic oxidations with O₂ or H₂O₂ 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*-isobutylacetophenone (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-

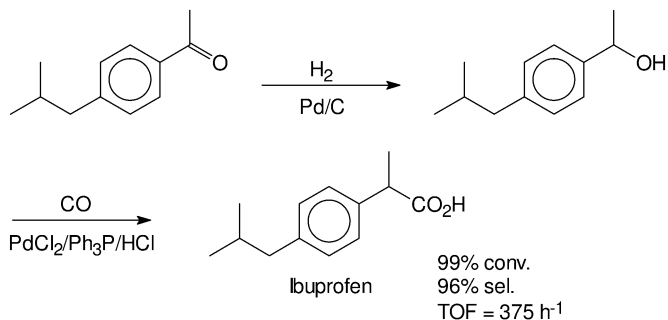


Fig. 1.28 Hoechst-Celanese process for ibuprofen.

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*-methylauramide, 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-

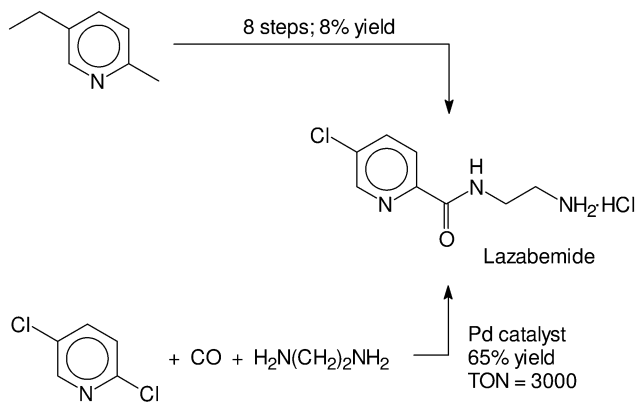


Fig. 1.29 Two routes to lazabemide.

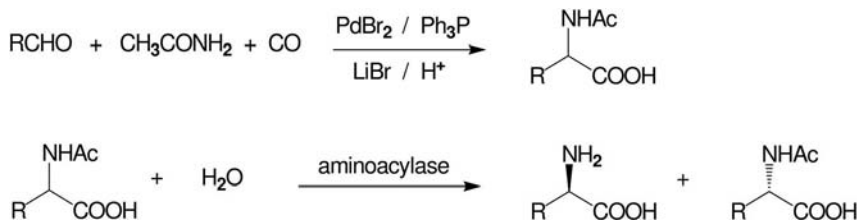


Fig. 1.30 Palladium-catalysed amidocarbonylation.

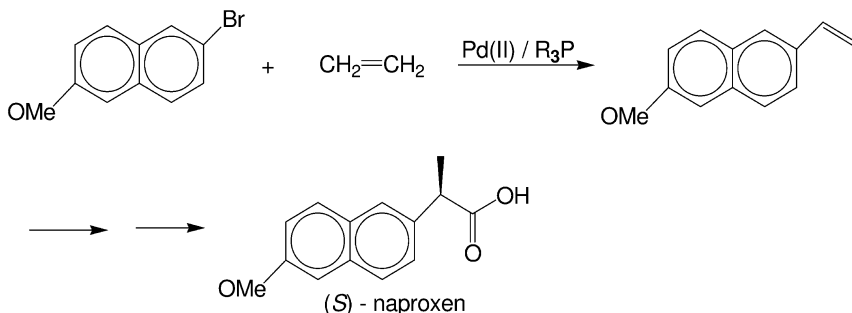


Fig. 1.31 Heck coupling reaction.

inflammatory 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

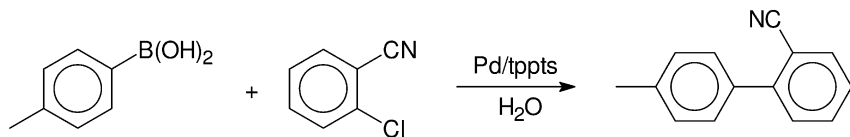
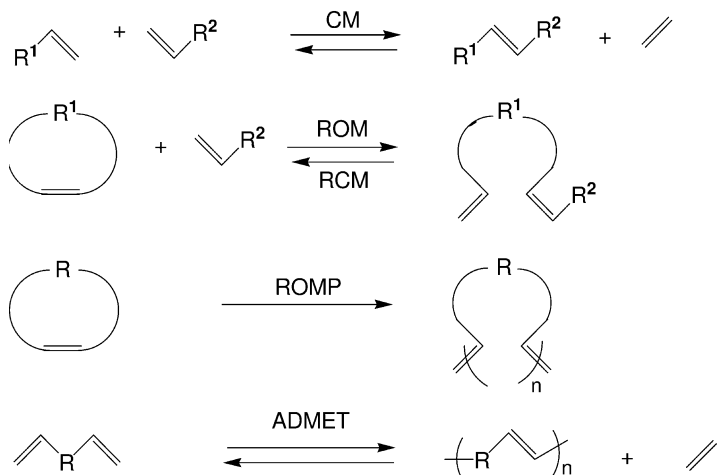


Fig. 1.32 A Suzuki coupling.



CM = Cross metathesis

ROMP = Ring opening metathesis polymerization

ROM = Ring opening metathesis

ADMET = Acyclic diene metathesis

RCM = Ring closing 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/H₂O) in the presence of air.

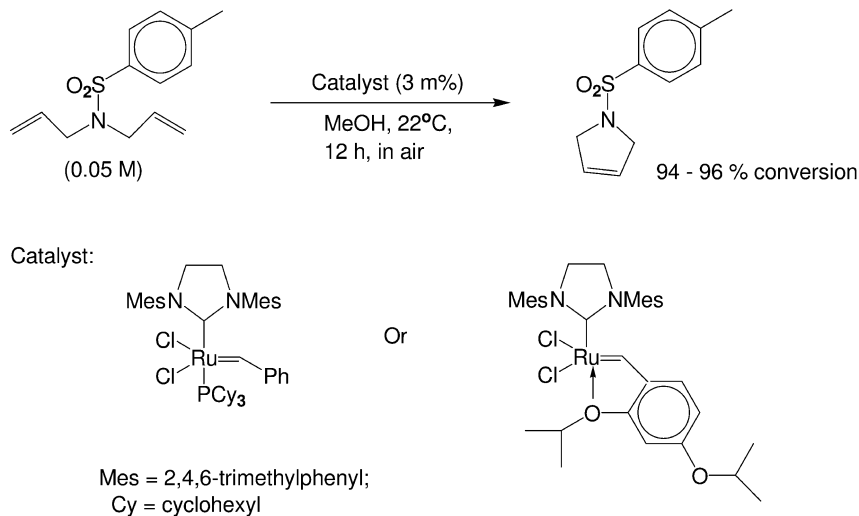


Fig. 1.34 Ru-catalysed ring closing metathesis.

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, distill 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 (ViagraTM) [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 CO₂, for example, has

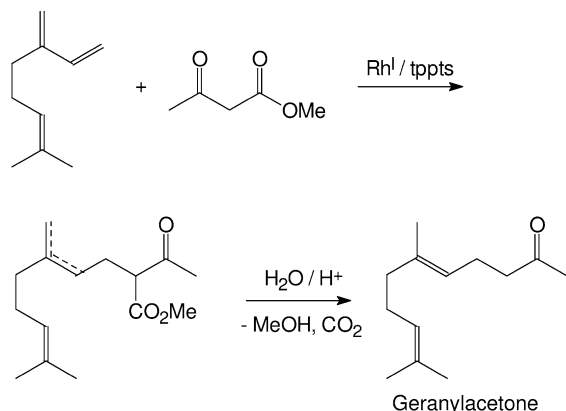
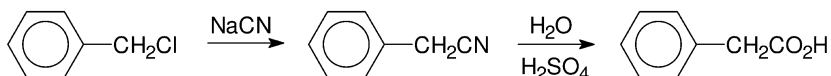
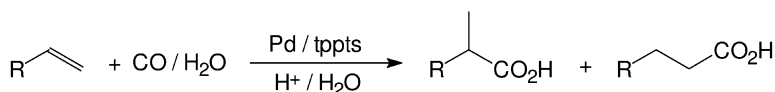
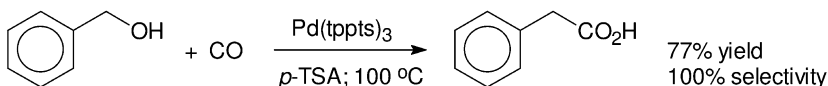
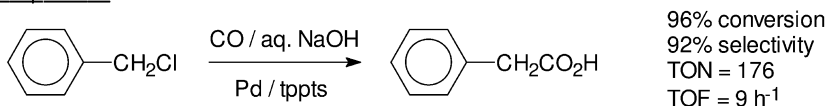


Fig. 1.35 Manufacture of n-butanal and geranylacetone in aqueous biphasic systems.

Old processNew process

R	Selectivity (%)	
	<i>iso</i> -	<i>n</i> -
CH ₃	43	57
C ₆ H ₅	56	33
4- <i>i</i> -BuC ₆ H 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.

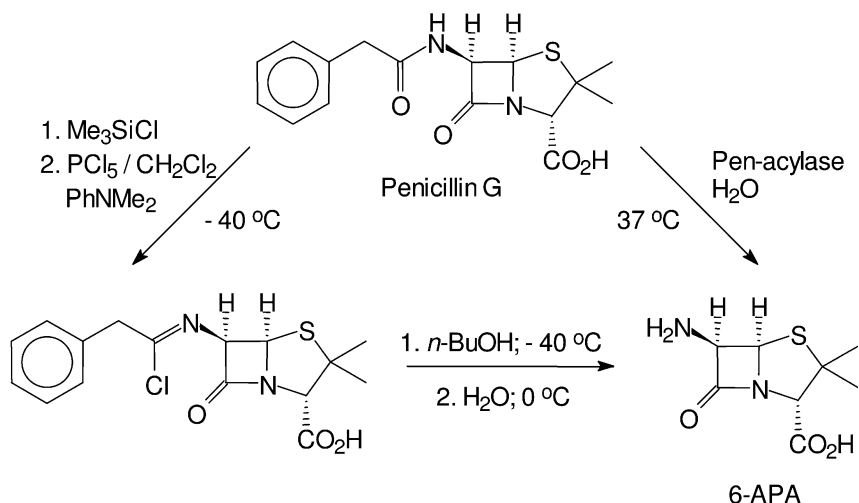


Fig. 1.37 Enzymatic versus chemical deacylation of penicillin G.

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

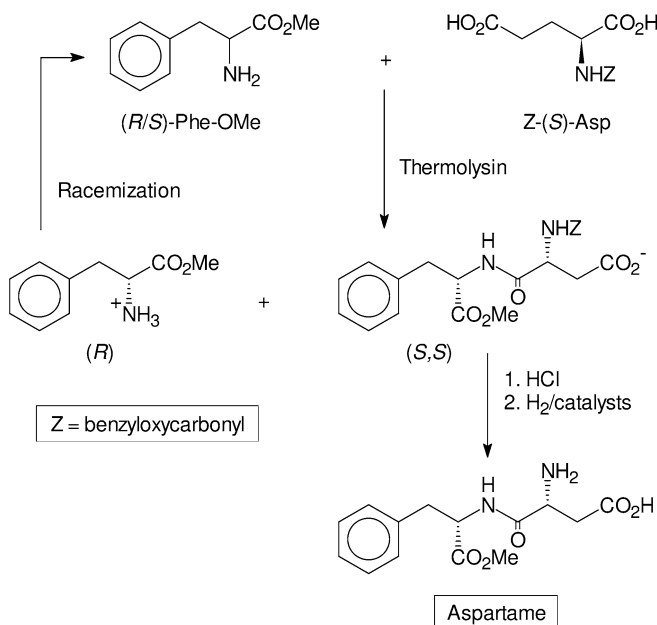


Fig. 1.38 Aspartame via enzymatic coupling.

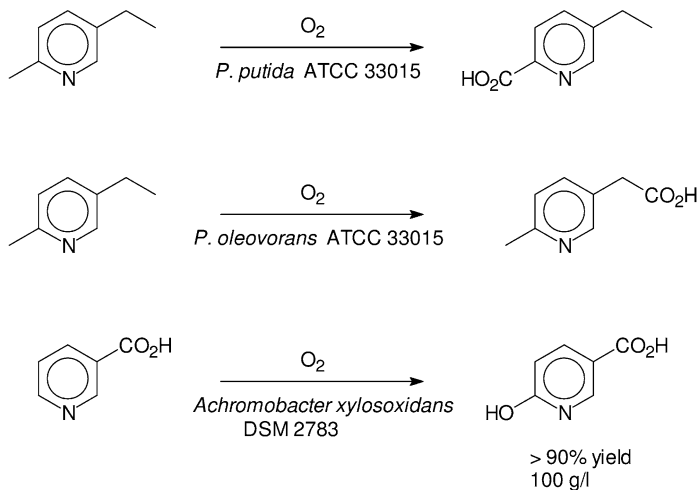


Fig. 1.39 Microbial oxidations of heteroaromatics.

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-

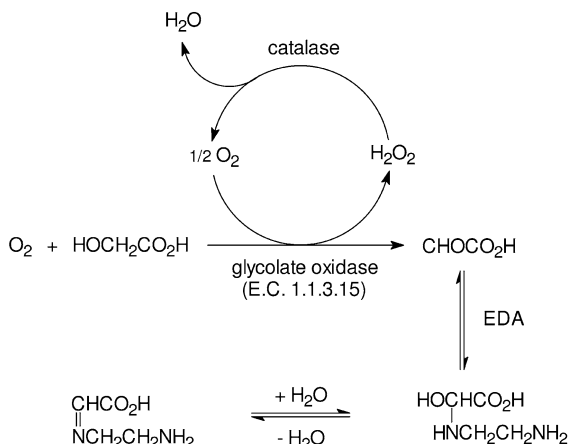


Fig. 1.40 Glyoxylic acid by microbial oxidation.

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 nitroinamide (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.

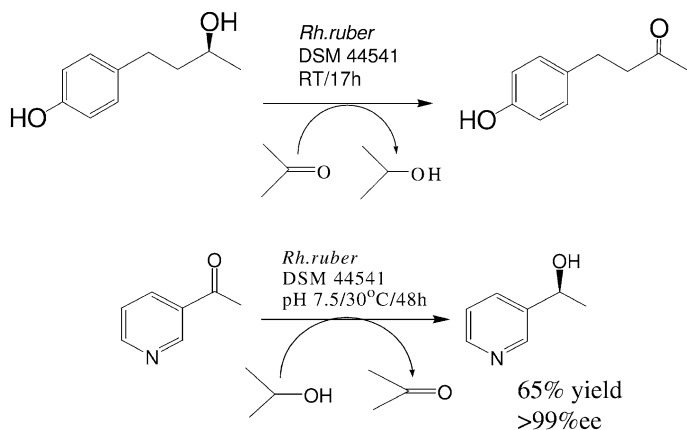


Fig. 1.41 Biocatalytic Oppenauer oxidations and MPV reductions.

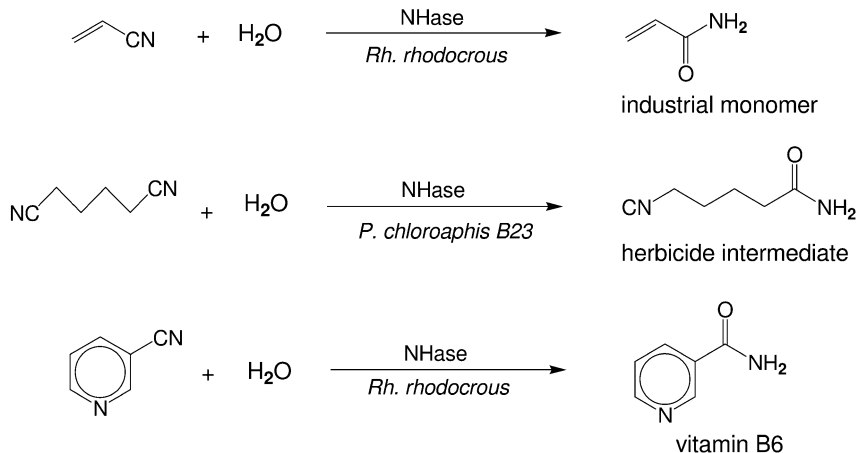


Fig. 1.42 Industrial processes employing a nitrile hydratase.

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

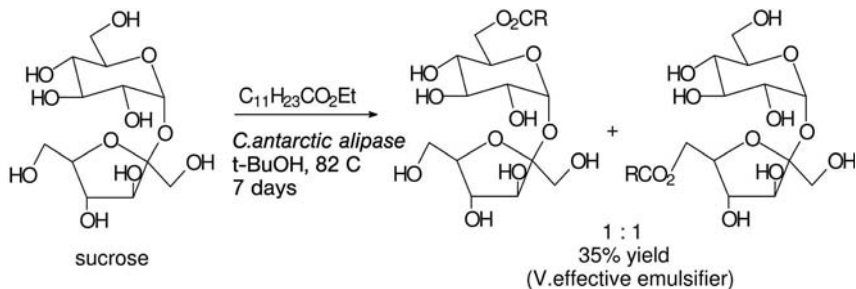


Fig. 1.43 Synthesis of a bioemulsifier from renewable raw materials.

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

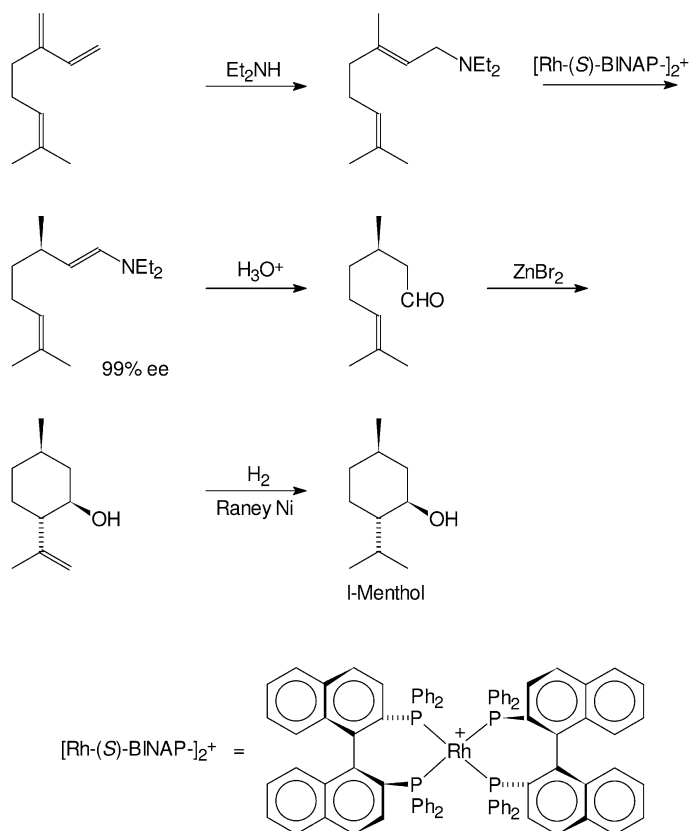


Fig. 1.44 Takasago l-menthol process.

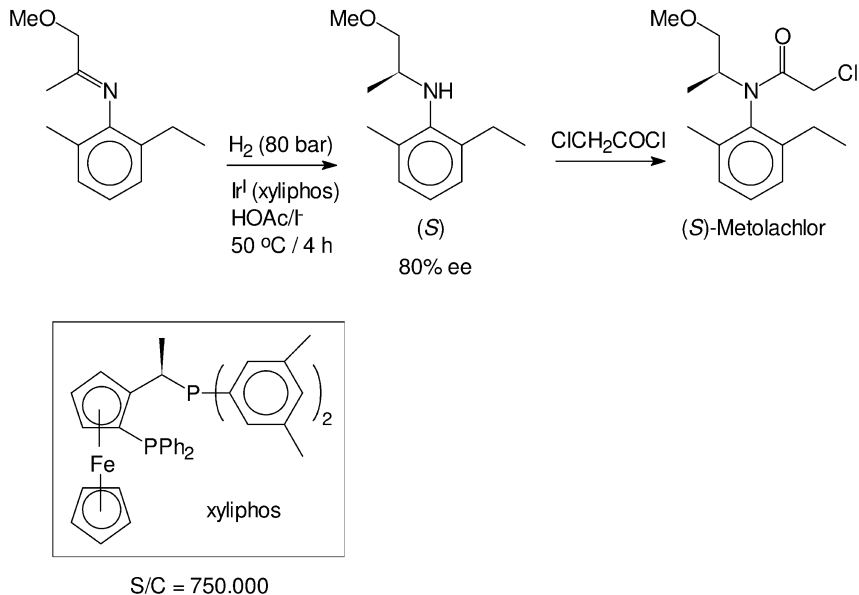


Fig. 1.45 Novartis process for (S)-metolachlor.

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 $1\,800\,000\text{ h}^{-1}$, 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 re-oxidised by dioxygen. Hence, a remarkable feature of the process is that no external catalyst is required; the substrate itself acts as the catalyst.

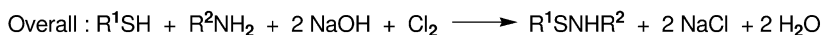
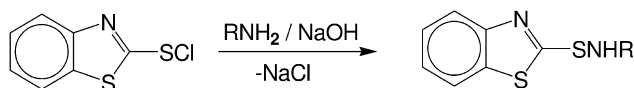
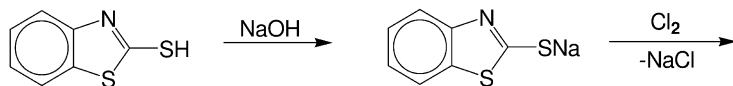
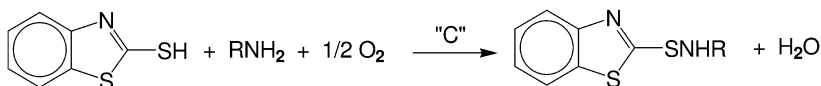
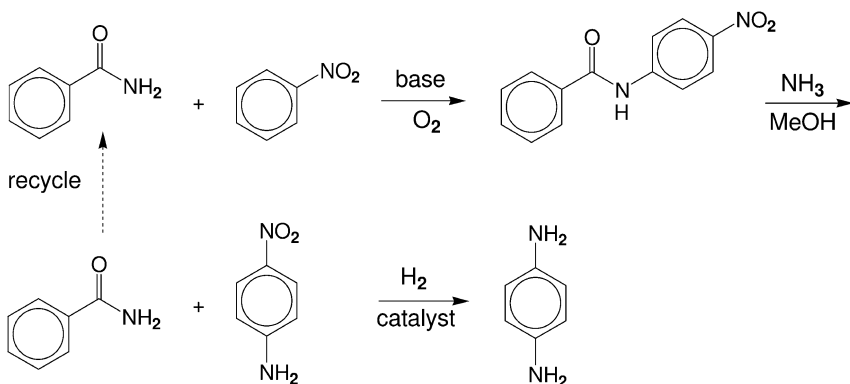
Classical process :Catalytic process :

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 ammoxidation with $\text{NH}_3/\text{H}_2\text{O}_2$ 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-

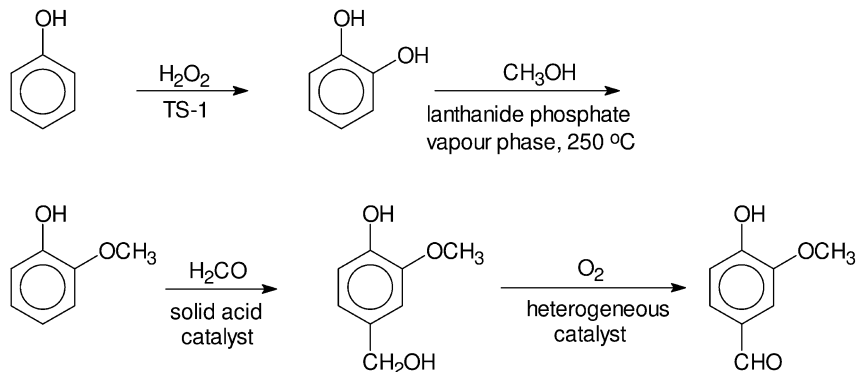


Fig. 1.48 Rhodia vanillin process.

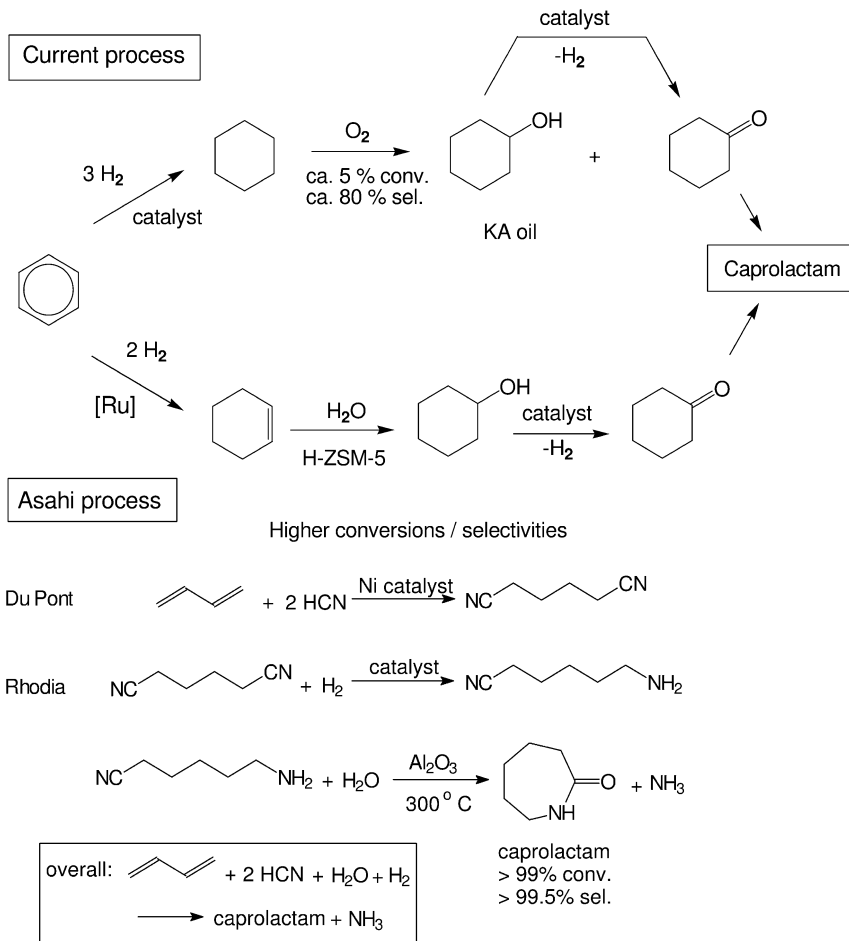


Fig. 1.49 Alternative routes to caprolactam.

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

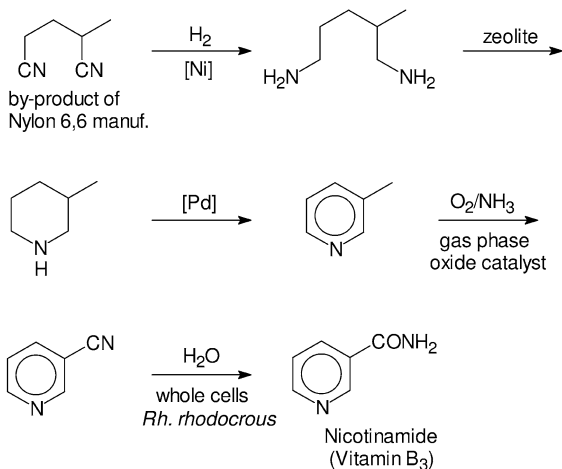


Fig. 1.50 Lonza nicotinamide process.

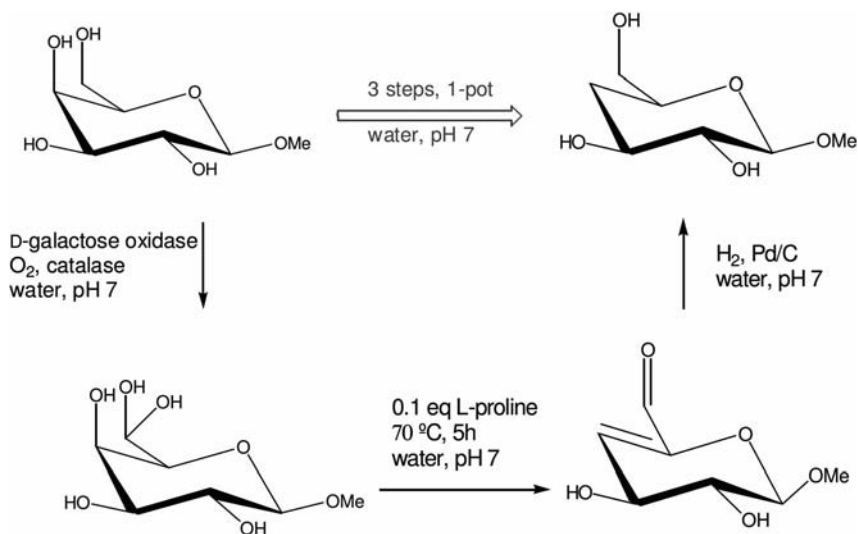


Fig. 1.51 One-pot, three-step synthesis of a deoxy sugar.

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 fermentation 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 ($<1 \text{ g l}^{-1} \text{ h}^{-1}$), but may be further optimised in the future.

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2

Solid Acids and Bases as Catalysts

2.1

Introduction

Processes catalyzed by acids and bases play a key role in the oil refining and petrochemical industries and in the manufacture of a wide variety of specialty chemicals such as pharmaceuticals, agrochemicals and flavors and fragrances. Examples include catalytic cracking and hydrocracking, alkylation, isomerization, oligomerization, hydration/dehydration, esterification and hydrolysis and a variety of condensation reactions, to name but a few [1, 2]. Many of these processes involve the use of traditional Brønsted acids (H_2SO_4 , HF, HCl, *p*-toluenesulfonic acid) or Lewis acids (AlCl_3 , ZnCl_2 , BF_3) in liquid-phase homogeneous systems or on inorganic supports in vapor phase systems. Similarly, typical bases include NaOH, KOH, NaOMe and $\text{KO}^\dagger\text{Bu}$. Their subsequent neutralization leads to the generation of inorganic salts which ultimately end up in aqueous waste streams. Even though only catalytic amounts are generally, but not always, used in the oil refining and petrochemical industries, the absolute quantities of waste generated are considerable owing to the enormous production volumes involved. In contrast, in the fine and specialty chemical industries the production volumes are much smaller but acids and bases are often used in stoichiometric quantities, e.g. in Friedel-Crafts acylations and aldol and related condensations, respectively [3].

An obvious solution to this salt generation problem is the widespread replacement of traditional Brønsted and Lewis acids with recyclable solid acids and bases [3–7]. This will obviate the need for hydrolytic work-up and eliminate the costs and environmental burden associated with the neutralization and disposal of e.g. liquid acids such as H_2SO_4 . The use of solid acids and bases as catalysts provides additional benefits:

- Separation and recycling is facilitated, resulting in a simpler process, which translates to lower production costs.
- Solid acids are safer and easier to handle than their liquid counterparts, e.g. H_2SO_4 , HF, that are highly corrosive and require expensive construction materials.
- Contamination of the product by trace amounts of (neutralized) catalyst is generally avoided when the latter is a solid.

2.2

Solid Acid Catalysis

Acid-catalyzed processes constitute one of the most important areas for the application of heterogeneous catalysis. A wide variety of solid catalysts are used. They include mixed oxides such as silica–alumina and sulfated zirconia, acidic clays [8–10], zeolites [11–14], supported heteropoly acids [15], organic ion exchange resins [16, 17] and hybrid organic–inorganic materials such as mesoporous oxides containing pendant organic sulfonic acid moieties [18, 19]. For the purpose of our further discussion of this topic we can conveniently divide solid acid catalysts into three major categories: amorphous mixed oxides typified by the acidic clays, the crystalline zeolites and related materials (zeotypes), and solid acids containing surface sulfonic acid groups. The latter category embraces organic and inorganic cationic exchange resins and the above-mentioned hybrid organic–inorganic materials. Zeolites definitely occupy center stage, and will be the major focus of our discussion, but the use of (acidic) clays as catalysts is of earlier vintage so we shall begin with this interesting class of materials.

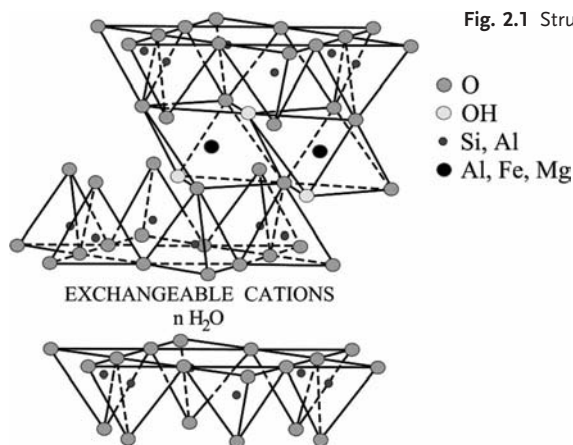
2.2.1

Acidic Clays

Clays are naturally occurring minerals that are produced in enormous quantities and find a wide variety of applications including their use as catalysts [8–10, 20, 21]. They were widely used as solid acid catalysts in oil refining from the 1930s until the mid 1960s when they were replaced by the zeolites which exhibited better activity and selectivity.

Clays are amorphous, layered (alumino)silicates in which the basic building blocks – SiO_4 tetrahedra and MO_6 octahedra ($\text{M}=\text{Al}^{3+}$, Mg^{2+} , Fe^{3+} , Fe^{2+} , etc.) – polymerize to form two-dimensional sheets [8–10, 20]. One of the most commonly used clays is montmorillonite in which each layer is composed of an octahedral sheet sandwiched between two tetrahedral silicate sheets (see Fig. 2.1). Typically, the octahedral sheet comprises oxygens attached to Al^{3+} and some lower valence cations such as Mg^{2+} . The overall layer has a net negative charge which is compensated by hydrated cations occupying the interlamellar spaces. Immersion in water results in a swelling of the clay and exposure of the intercalated cations making them accessible for cation exchange. The interlamellar cations are largely responsible for the clay's Brønsted and/or Lewis acidity. The more electronegative the cation, the stronger the acidity and both the amount and strength of Brønsted and Lewis acid sites can be enhanced by cation exchange or treatment with a mineral acid, e.g. H_2SO_4 .

An Al^{3+} -exchanged montmorillonite, for example, is as active as concentrated sulfuric acid in promoting acid-catalyzed reactions. Sulfuric acid treatment of natural montmorillonite similarly affords the much more active and widely used acid catalyst known as K-10 or KSF (from Sud-Chemie or Fluka, respectively).



For example, K-10 has been successfully used as a Friedel-Crafts alkylation catalyst (see Fig. 2.2) [22].

Clays or acid-treated clays are also effective supports for Lewis acids such as ZnCl₂ or FeCl₃ [23]. Montmorillonite-supported zinc chloride, known as Claycic, has been extensively studied as a catalyst for e.g. Friedel-Crafts alkylations [24, 25] (see Fig. 2.2).

A serious shortcoming of clays, however, is their limited thermal stability. Heating of exchanged clays results in a loss of water, accompanied by collapse of the interlamellar region, thereby dramatically decreasing the effective surface area. This problem was addressed by developing so-called pillared clays (PILCs) [26–28], in which the layered structure is intercalated with pillaring agents which act as ‘molecular propp’. Inorganic polyoxocations such as [Al₁₃O₄(OH)₂₄(H₂O)₁₂]⁷⁺ are popular pillaring agents but a variety of organic and organometallic

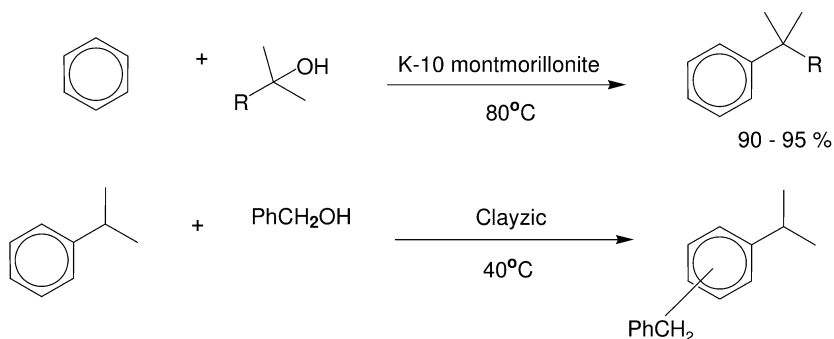


Fig. 2.2 Friedel-Crafts alkylations.

pillaring agents have also been used. Pillaring with Al_2O_3 provides an interlamellar space of ca. 0.8 nm, which remains after drying. The major goal of the pillaring process is to produce novel, inexpensive materials with properties (pore shape and size, acidity, etc.) complementary to zeolites (see next section).

2.2.2

Zeolites and Zeotypes: Synthesis and Structure

Zeolites are crystalline aluminosilicates comprising corner-sharing SiO_4 and AlO_4^- tetrahedra and consisting of a regular system of pores (channels) and cavities (cages) with diameters of molecular dimensions (0.3 to 1.4 nm) [11–14]. A large number of zeolites are known, some of which are naturally occurring, but most of which have been synthesized [29]. Analogous structures containing TO_4 tetrahedra composed of Si, Al or P as well as other main group and transition elements, e.g. B, Ga, Fe, Ge, Ti, V, Cr, Mn and Co, have also been synthesised and are generically referred to as zeotypes. They include, for example, AlPOs, SAPOs and MeAPOs [30]. As with amorphous aluminosilicates, zeolites contain an extraframework cation, usually Na^+ , to maintain electroneutrality with the AlO_4^- moiety. These extraframework cations can be replaced by other cations by ion exchange. Since zeolites react with acids the proton-exchanged species (H-form) is best prepared by ion exchange with an ammonium ion followed by thermal dissociation, affording ammonia and the acid form of the zeolite. The Brønsted acid strength of the latter, which is of the same order as that of concentrated sulfuric acid, is related to the Si/Al ratio. Since an AlO_4^- moiety is unstable when attached to another AlO_4^- unit, it is necessary that they are separated by at least one SiO_4 unit. i.e. the Si/Al ratio cannot be lower than one (the H-form is depicted in Fig. 2.3). The number of proton donor hydroxy groups corresponds to the number of aluminum atoms present in the structure. The more isolated this silanol species, the stronger the acid, i.e. the acid strength increases with decreasing aluminum content or increasing Si/Al ratio (but note that complete replacement of aluminum affords a material with lower acidity).

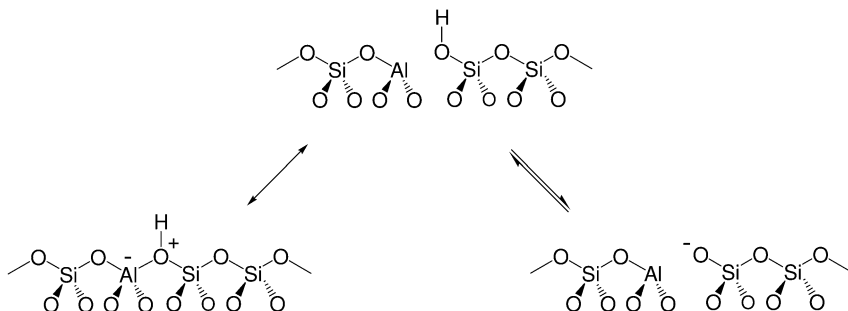


Fig. 2.3 The acid form of zeolites.

Zeolites are prepared by so-called hydrothermal synthesis a simplified scheme of which is shown in Fig. 2.4. The basic ingredients – SiO_2 , Na_2SiO_3 or $\text{Si}(\text{OR})_4$ and Al_2O_3 , NaAlO_2 or $\text{Al}(\text{OR})_3$ – together with a structure directing agent (template), usually an amine or tetraalkylammonium salt, are added to aqueous alkali (pH 8–12). This results in the formation of a sol–gel comprising monomeric and oligomeric silicate species. Gradual heating of this mixture up to ca. 200°C results in dissolution of the gel to form clusters of $\text{SiO}_4/\text{AlO}_4^-$ units which constitute the building blocks for the zeolite structure. In the presence of the template these building blocks undergo polymerization to form the zeolite which crystallizes slowly from the reaction mixture. At this point the zeolite still contains the occluded organic template. This is subsequently removed by calcination, i.e. heating in air at $400\text{--}600^\circ\text{C}$ to burn out the template and evaporate water.

Similarly, zeotype molecular sieves are synthesized by mixing the basic ingredients with the organic template, e.g. aluminophosphates are prepared from alumina and phosphoric acid. Other main group or transition elements can be incorporated into the framework by adding them to the initial sol–gel. Alternatively, different elements can be introduced by post-synthesis modification (see later), e.g. by dealumination followed by insertion of the new elements into the framework position [31].

The most important feature of zeolites (and zeotypes), in the context of catalysis, is not their range of acid–base properties, since that is also available with amorphous aluminosilicates. It is the presence of a regular structure containing

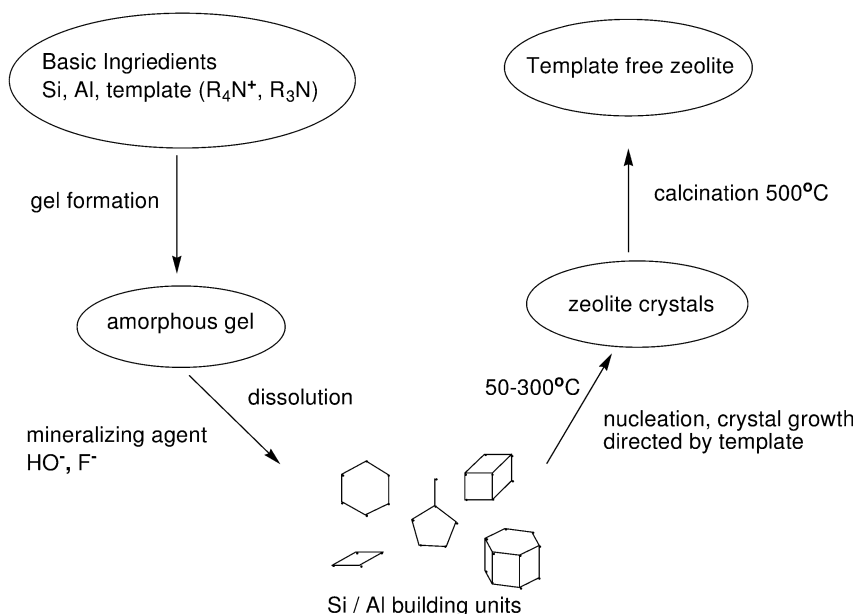


Fig. 2.4 Simplified zeolite synthesis scheme.

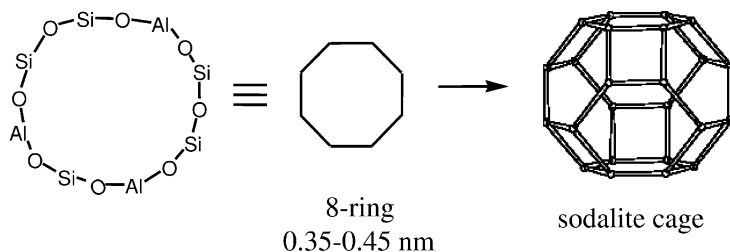


Fig. 2.5 Basic units in zeolites.

molecular sized cavities and channels that make them unique as shape selective catalysts for a wide variety of organic transformations.

Representation of zeolite structures is different to that used by organic chemists. The intersection of lines represents either an SiO_4 or an AlO_4^- tetrahedron and the line itself represents an O atom joining the two tetrahedra. In Fig. 2.5 eight TO_4 octahedra are joined together in a ring, commonly referred to as the 8-ring structure as there are eight oxygen atoms in the ring. These basic ring structures are combined to form three dimensional arrangements which constitute the building blocks for the zeolite. For example, one of these building units is the sodalite cage, a truncated octahedron with four-membered rings made during truncation and six-membered rings as part of the original octahedron.

In zeolites derived from the sodalite unit these cages are joined together through extensions of either the 4-ring or the 6-ring. Zeolite A (see Fig. 2.6) is an example of the former. The center of the structure comprises a supercage, with a diameter of 1.14 nm, surrounded by eight sodalite cages. Access to these cages is via the six mutually perpendicular 8-ring openings having a diameter of 0.42 nm, enabling linear hydrocarbons to enter. The Si/Al ratio is 1–1.2 making zeolite A among the least acidic of all zeolites.

Faujasites are naturally occurring zeolites composed of sodalite cages joined through extensions of their 6-ring faces. An internal supercage of ca. 1.3 nm diameter is accessed by four 12-ring openings with a diameter of 0.74 nm. The latter provide access for relatively large aliphatic and aromatic molecules, e.g. naphthalene. The synthetic zeolites X and Y have the same crystal structure as faujasite but differ in their Si/Al ratios. In zeolites X and Y the Si/Al ratio is 1–1.5 and 1.5–3, respectively, while faujasite has a Si/Al ratio of ca. 2.2.

Mordenite is a naturally occurring zeolite with a Si/Al ratio of ca. 10 and a structure composed of 12-ring and 8-ring tunnels with diameters of 0.39 nm and ca. 0.7 nm, respectively, extending through the entire framework (Fig. 2.7). Every framework atom forms a part of the walls of these tunnels and is accessible to substrate molecules diffusing through them.

The synthetic zeolite, ZSM-5, is a highly siliceous material with a Si/Al ratio from 25 up to 2000 [32]. As shown in Fig. 2.7, it consists of a three-dimensional network of two intersecting 10-ring tunnel systems of 0.55–0.6 nm diameter. One of these resembles the 12-ring tunnels passing through mordenite (see

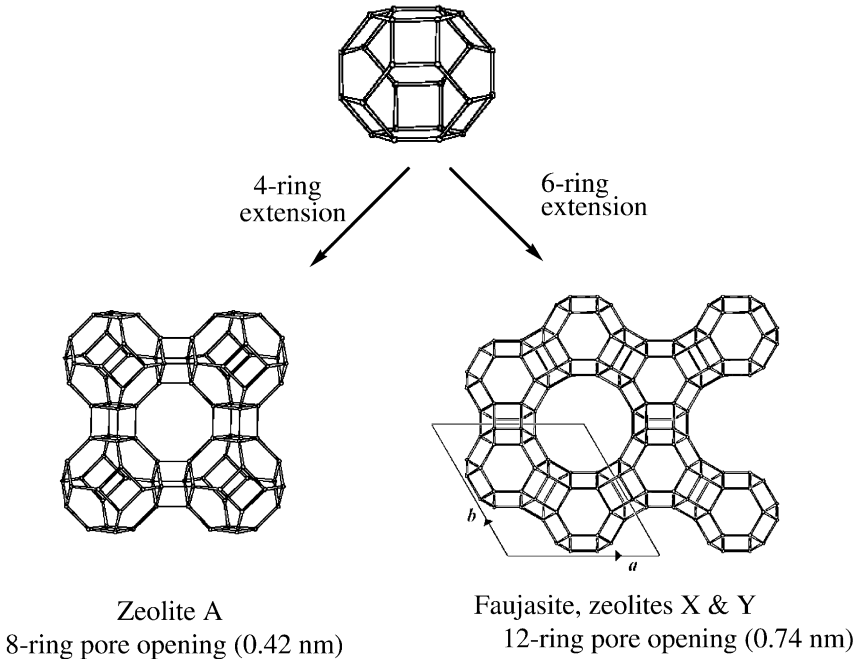


Fig. 2.6 Structures of zeolite A and faujasite.

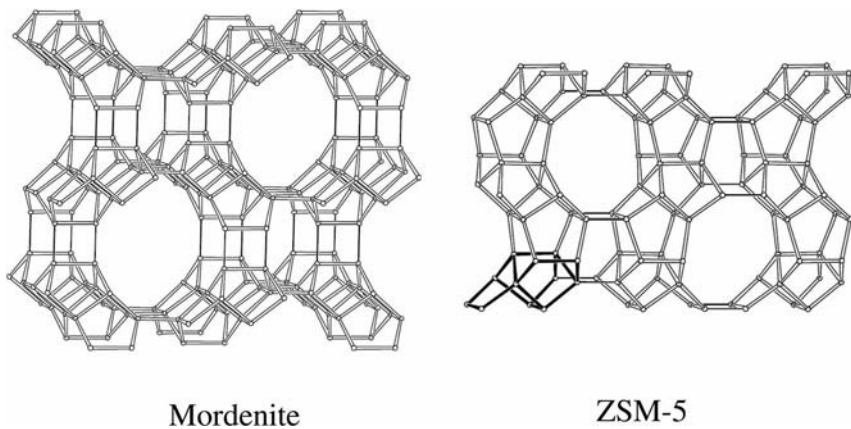


Fig. 2.7 Structures of mordenite and ZSM-5.

above) while the other follows a sinusoidal path perpendicular to, and intersecting with, the first. The basic structural unit of this zeolite is the pentasil unit composed of fused 5-rings (Fig. 2.8).

Zeolites are conveniently divided into groups on the basis of their pore sizes – small, medium, large and ultra large – which are determined by the ring size

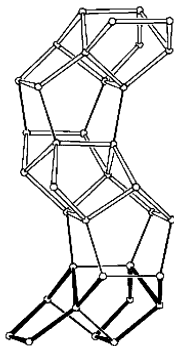


Fig. 2.8 The pentasil unit.

of the pore openings. Examples of commonly used zeolites and zeotypes are collected in Table 2.1.

Obviously the pore size determines which molecules can access the acidic sites inside the zeolite framework (molecular sieving effect) and is responsible for the shape selectivity observed with these materials (see later). The catalytic activity is also influenced by the acid strength of these sites which is determined by the Si/Al ratio (see above). The latter can be increased by post-synthesis removal of Al atoms. Dealumination can be achieved by treatment with a

Table 2.1 Pore dimensions of molecular sieves.

Ring size	Structure type	Isotopic framework structures	Pore size (nm)	Dimensionality
<i>Small pore</i>				
8	LTA	Zeolite A	4.1	3
<i>Medium pore</i>				
10	MFI	ZSM-5 silicalite	5.6×5.3	3
10	MEL	ZSM-11	5.4×5.3	3
10	AEL	AlPO-11 SAPO-11	6.3×3.9	1
<i>Large pore</i>				
12	FAU	X, Y	7.4	3
12	MOR	Mordenite	7.0×6.5	2
12	BEA	Beta	7.5×5.7	3
12	LTL	L	7.1	1
12	AFI	AlPO-5	7.3	1
<i>Extra large pore</i>				
14		AlPO-8	8.7×7.9	1
18	VFI	VPI-5	12.1	1
20		Cloverite	13.2×6.0	3
Unknown	M41S	MCM-41	40–100	1

strong acid or a chelating agent, such as EDTA, or by steaming. It results in the formation of 'silanol nests' with retention of the framework structure (Fig. 2.9).

The wide range of pore sizes available, coupled with their tunable acidity, endows the zeolites with unique properties as tailor-made (acid) catalysts. These important features of zeolites (and zeotypes) may be summarized as follows:

- regular microenvironment and uniform internal structure
- large internal surface area
- pores of molecular dimensions (shape selectivity)
- control of pore size and shape by choice of template and/or post synthesis modification
- control of pore hydrophobicity/hydrophilicity
- control of acidity by adjusting constitution (Si/Al ratio), ion exchange or post-synthesis modification
- framework substitution by transition elements
- the presence of strong electric fields within the confined space of the channels and cavities can serve to activate substrate molecules

The earliest applications of zeolites utilized the molecular sieving properties of small pore zeolites, e.g. zeolite A, in separation and purification processes such as drying and linear/branched alkane separation [33]. In 1962 Mobil Oil introduced the use of synthetic zeolite X, an FCC (fluid catalytic cracking) catalyst in oil refining. In the late sixties the W.R. Grace company introduced the "ultra-

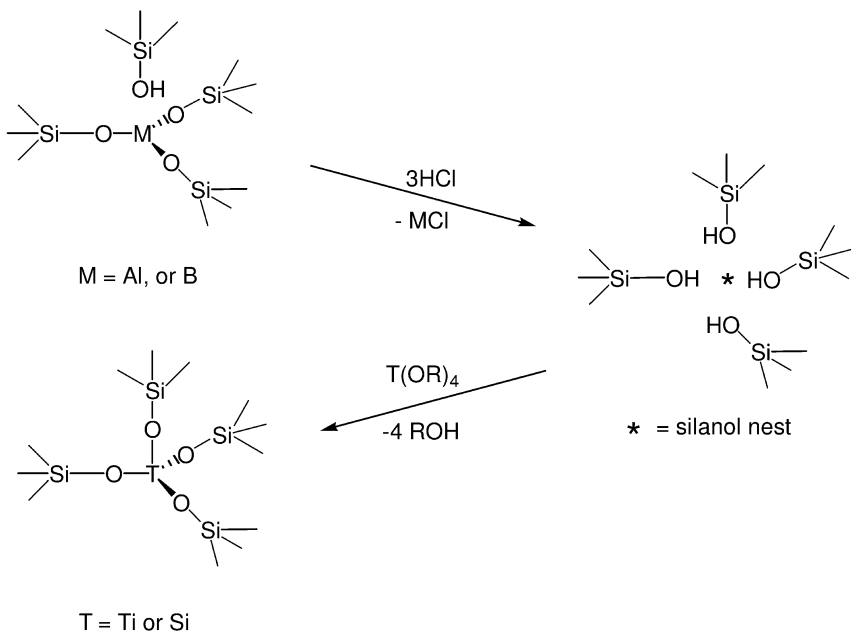


Fig. 2.9 Formation of a silanol nest by dealumination.

stable" zeolite Y (USY) as an FCC catalyst, produced by steaming of zeolite Y, which is still used today. The use of zeolite A as a replacement for phosphates in detergents was first introduced by Henkel in 1974. Although their synthesis had already been reported by Mobil in the late 1960s, extensive studies of catalytic applications of the high-silica zeolites, typified by ZSM-5 and beta, were not conducted until the 1980s and 1990s. ZSM-5 was first applied as an FCC additive to generate high octane gasoline by taking advantage of its shape selectivity in cracking linear rather than branched alkanes. ZSM-5 was subsequently applied as a shape selective acid catalyst in a wide variety of organic transformations (see later).

The 1980s also witnessed the explosive development of a wide variety of zeotypes, notably the aluminophosphate (ALPO) based family of molecular sieves [30]. The early 1990s saw the advent of a new class of mesoporous molecular sieves, the ordered mesoporous (alumino)silicates synthesized with the help of surfactant micelle templates (see Fig. 2.10) [34–37]. Exemplified by the Mobil M415 materials, of which MCM-41 is the most well-known, these micelle-templated silicas contain uniform channels with tunable diameters in the range of 1.5 to 10 nm and a greater uniformity of acid sites than other amorphous materials. According to the IUPAC definition, microporous materials are those having pores <2 nm in diameter and mesoporous solids those with pore diameters in the range 2 to 50 nm.

As noted above, one of the most important characteristics of zeolites is their ability to discriminate between molecules solely on the basis of their size. This feature, which they share with enzymes, is a consequence of them having pore dimensions close to the kinetic diameter of many simple organic molecules. Hence, zeolites and zeotypes have sometimes been referred to as mineral enzymes. This so-called shape selectivity can be conveniently divided into three categories: substrate selectivity, product selectivity and transition state selectivity. Examples of each type are shown in Fig. 2.11.

In *substrate selectivity*, access to the catalytically active site is restricted to one or more substrates present in a mixture, e.g. dehydration of a mixture of n-butanol and isobutanol over the small pore zeolite, CaA, results in dehydration of only the n-butanol [38] while the bulkier isobutanol remains unreacted. *Product*

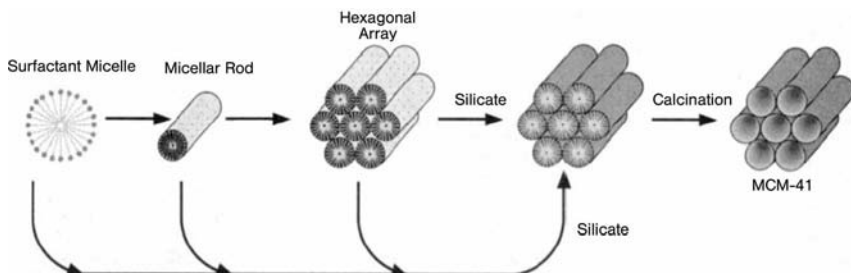


Fig. 2.10 Synthesis of mesoporous, micelle-templated molecular sieves.

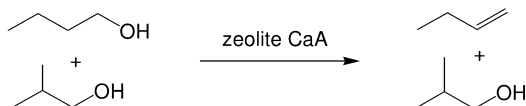
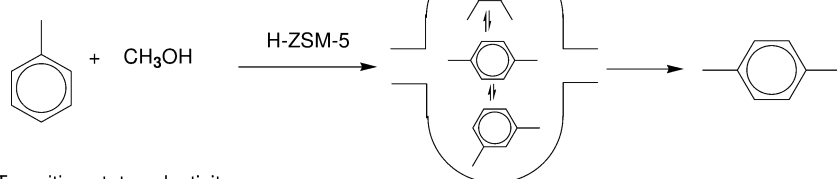
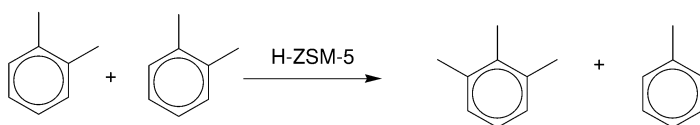
Substrate selectivityProduct selectivityTransition state selectivity

Fig. 2.11 Shape selective catalysis with zeolites.

selectivity is a result of differences in the size of products formed, in a reversible process, inside a molecular sieve. For example, when methanol is allowed to react with toluene over H-ZSM-5, *p*-xylene is formed almost exclusively because this molecule can easily diffuse out of the molecular sieve. The bulkier *o*- and *m*-isomers, in contrast, cannot pass easily through the pores and consequently undergo isomerization, via demethylation, to the *p*-isomer. *Restricted transition state selectivity* is observed when the zeolite discriminates between two different transformations on the basis of the bulk of their transition states. In the example shown, the disproportionation of *o*-xylene to trimethylbenzene and toluene involves a bulky diaryl species in the transition state whereas isomerization to *m*- or *p*-xylene does not. Hence, disproportionation is not observed over H-ZSM-5. Most applications of zeolites as acid catalysts involve one or more of these types of shape selectivity, as we shall see in the following section.

2.2.3

Zeolite-catalyzed Reactions in Organic Synthesis

Pertinent examples of zeolite-catalyzed reactions in organic synthesis include Friedel-Crafts alkylations and acylations and other electrophilic aromatic substitutions, additions and eliminations, cyclizations, rearrangements and isomerizations, and condensations.

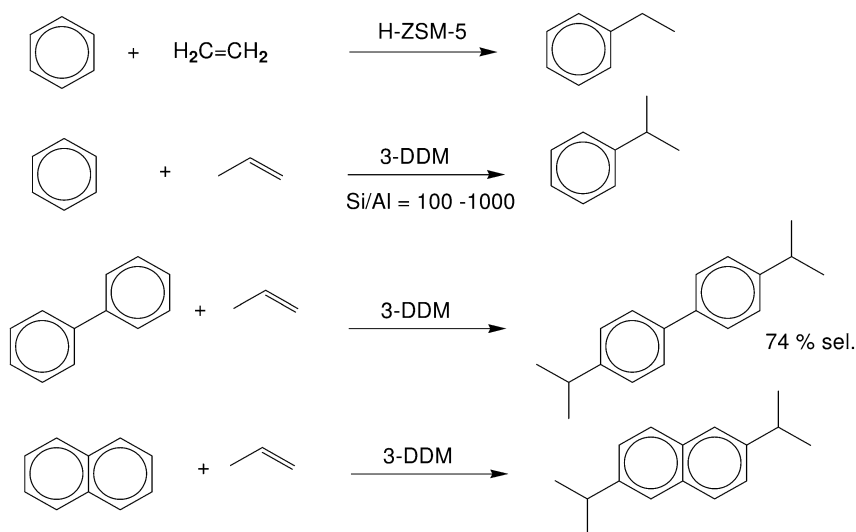
2.2.3.1 Electrophilic Aromatic Substitutions

Friedel-Crafts alkylations are widely used in both the bulk and fine chemical industries. For example, ethylbenzene (the raw material for styrene manufacture) is manufactured by alkylation of benzene with ethylene (Fig. 2.12).

The original process, developed in the 1940s, involved traditional homogeneous catalysis by AlCl_3 . This process was superseded by one employing a heterogeneous catalyst consisting of H_3PO_4 or BF_3 immobilized on a support (UOP process). This system is highly corrosive and, because of the enormous production volumes involved, generates substantial amounts of acidic waste. A major breakthrough in FC alkylation technology was achieved in 1980 with the application of the medium pore zeolite, H-ZSM-5, as a stable recyclable catalyst for ethylbenzene manufacture (Mobil-Badger process). An added benefit of this process is the suppression of polyalkylation owing to the shape selective properties of the catalyst.

This process marked the beginning of an era of intensive research, which continues to this day, on the application of zeolites in the manufacture of petrochemicals and, more recently, fine chemicals.

Zeolite-based processes have gradually displaced conventional ones, involving supported H_3PO_4 or AlCl_3 as catalysts, in the manufacture of cumene, the raw material for phenol production [1, 6, 39]. A three-dimensional dealuminated mordenite (3-DDM) catalyst was developed by Dow Chemical for this purpose [39]. Dealumination, using a combination of acid and thermal treatments, increases the Si/Al ratio from 10–30 up to 100–1000 and, at the same time, changes the total pore volume and pore-size distribution of the mordenite. The



3-DDM = 3-dimensional dealuminated Mordenite (Si/Al = 100 - 1000)

Fig. 2.12 Zeolite-catalyzed Friedel-Crafts alkylations.

3-DDM catalysts have a new pore structure consisting of crystalline domains of 8- and 12-ring pores connected by mesopores (5–10 nm). The presence of the latter enhances accessibility to the micropore regions without seriously compromising the shape-selective character of the catalyst. This combination of changes in acidity and pore structure transforms synthetic mordenites into highly active, stable and selective alkylation catalysts.

Dow Chemical also pioneered the shape-selective dialkylation of polyaromatics, e.g. naphthalene and biphenyl (see Fig. 2.12), using the same type of 3-DDM catalyst [39]. The products are raw materials for the production of the corresponding dicarboxylic acids, which are important industrial monomers for a variety of high performance plastics and fibres.

Zeolites are also finding wide application as catalysts for FC alkylations and related reactions in the production of fine chemicals. For example, a H-MOR type catalyst with a Si/Al ratio of 18 was used for the hydroxyalkylation of guaiacol (Fig. 2.13) to *p*-hydroxymethylguaiacol, the precursor of vanillin [40]. Aromatic hydroxyalkylation with epoxides is of importance in the production of fine chemicals, e.g. the fragrance 2-phenylethanol from benzene and ethylene oxide (Fig. 2.13). Attempts to replace the conventional process, which employs stoichiometric amounts of AlCl_3 , with a zeolite-catalyzed conversion, met with little success [6, 41]. This was largely due to the large polarity difference between the aromatic substrate and the epoxide alkylating agent which leads to unfavorable adsorption ratios between substrate and reagent. This adsorption imbalance is avoided by having the aromatic and epoxide functions in the same molecule, i.e. in an intramolecular hydroxyalkylation. For example, H-MOR and H-Beta were shown to be effective catalysts for the cyclialkylation of 4-phenyl-1-butene oxide (Fig. 2.13) [41].

The Pechmann synthesis of coumarins via condensation of phenols with β -keto esters also involves an intramolecular hydroxyalkylation, following initial

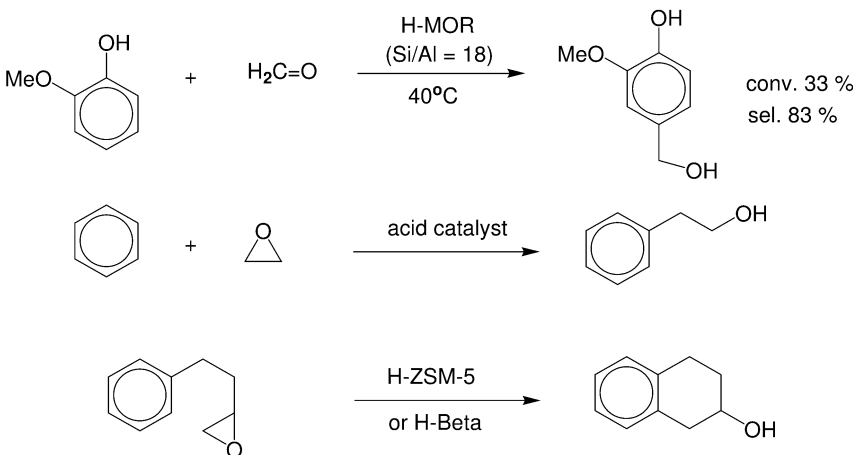


Fig. 2.13 Hydroxyalkylation of aromatics.

transesterification, and subsequent dehydration. It was found that H-Beta could successfully replace the sulfuric acid conventionally used as catalyst. For example, reaction of resorcinol with ethyl acetoacetate afforded methylumbelliferone (Fig. 2.14), a perfumery ingredient and insecticide intermediate [42]. Other examples of the synthesis of coumarin derivatives via zeolite-catalyzed intramolecular alkylations have also been described (Fig. 2.14) [6, 43].

Friedel-Crafts acylation of aromatics generally requires a stoichiometric amount of a Lewis acid such as AlCl_3 . It further shares with hydroxyalkylation the problem of widely differing polarities of the substrate, acylating agent and the product, which makes it difficult to achieve a favorable adsorption ratio of substrate and reagent. Moreover, favored reagents such as the carboxylic acid or anhydride produce water and carboxylic acid, respectively, which may also be preferentially adsorbed. Hence, heterogeneous catalysis of Friedel-Crafts acylation is much more difficult than the related alkylations and poses a formidable challenge. As in the case of hydroxyalkylation, intramolecular processes such as the cyclization of 4-phenylbutyric acid to α -tetralone over a H-Beta catalyst, proved to be more tractable (Fig. 2.15) [44]. As already noted in Chapter 1, the commercialization of the first zeolite-catalyzed FC acylation, by Rhodia, constitutes a benchmark in this area [45, 46]. The process employs H-Beta or HY, in fixed-bed operation, for the acylation of activated aromatics, such as anisole, with acetic anhydride (Fig. 2.15). It avoids the production of HCl from acetyl chloride in the classical process in addition to circumventing the generation of stoichiometric quantities of AlCl_3 waste.

Furthermore, very high *para*-selectivities are observed as a result of the shape-selective properties of the zeolite catalyst.

Similarly, acylation of isobutylbenzene with acetic anhydride over H-Beta at 140°C afforded *p*-acetylisobutylbenzene (Fig. 2.15), an intermediate in the syn-

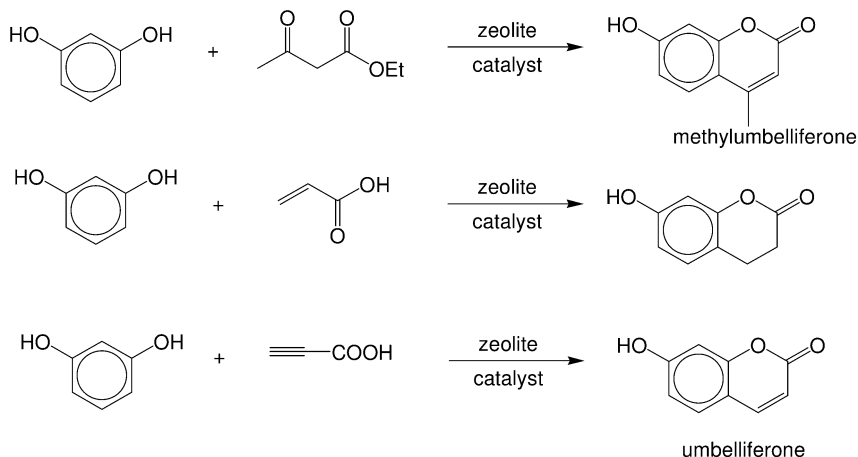


Fig. 2.14 Zeolite-catalyzed synthesis of coumarins.

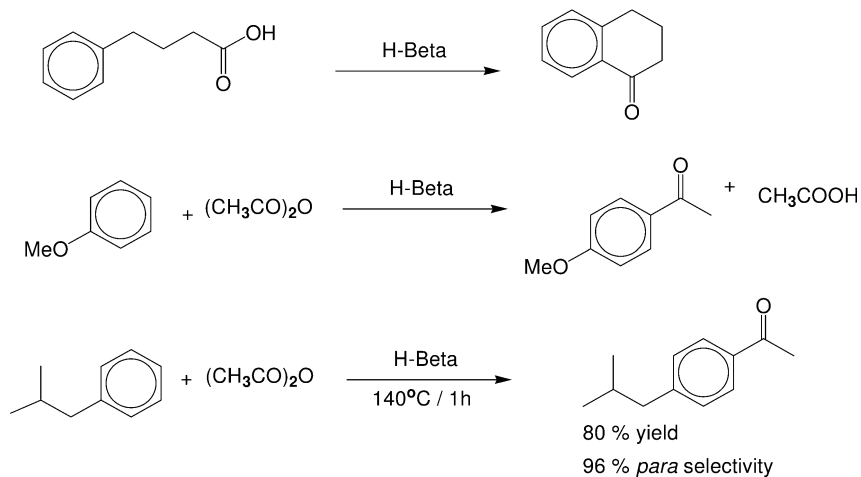
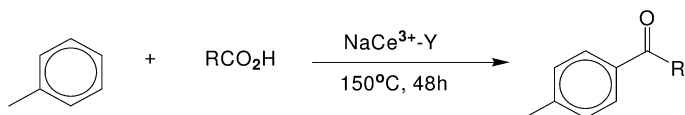


Fig. 2.15 Zeolite-catalyzed Friedel-Crafts acylations.

thesis of the antiinflammatory drug ibuprofen, in 80% yield and 96% *para*-selectivity [47].

Pioneering work in zeolite-catalyzed FC acylations was reported by Geneste and coworkers in 1986 [48]. They showed that a Ce^{3+} -exchanged zeolite Y catalyzed the acylation of toluene and xylenes with carboxylic acids (Fig. 2.16). This demonstrated that relatively mild acidity was sufficient to catalyze the reaction and that the free carboxylic acid could be used as the acylating agent. The reaction exhibited a very high *para*-selectivity. However, only the more lipophilic, higher carboxylic acids were effective, which can be ascribed to differences in preferential adsorption of substrate and acylating agent in the pores of the catalyst, i.e. the adsorption imbalance referred to above.



R	Yield (%)	Selectivity (%)		
		<i>o</i>	<i>m</i>	<i>p</i>
CH ₃	trace			
CH ₃ CH ₂	6	3	2	95
CH ₃ CH ₂ CH ₂	20	3	2	95
CH ₃ (CH ₂) ₄ CH ₂	30	3	3	94
CH ₃ (CH ₂) ₆ CH ₂	75	3	3	94
CH ₃ (CH ₂) ₁₀ CH ₂	96	3	3	94

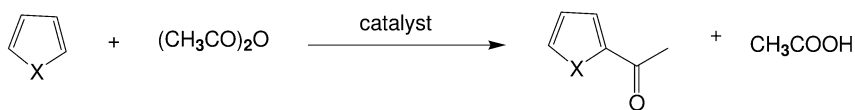
Fig. 2.16 Acylation of toluene over Ce^{3+} -exchanged zeolite Y.

Subsequently, Corma and coworkers [49] reported the acylation of anisole with phenacetyl chloride over H-Beta and H-Y. The FC acylation of electron-rich heteroaromatics, such as thiophene and furan, with acetic anhydride over modified ZSM-5 catalysts (Fig. 2.17) in the gas phase [50] or liquid phase [51] was also reported.

Almost all of the studies of zeolite-catalyzed FC acylations have been conducted with electron-rich substrates. There is clearly a commercial need, therefore, for systems that are effective with electron-poor aromatics. In this context, the reports [52] on the acylation of benzene with acetic acid over H-ZSM-5 in the gas phase are particularly interesting. These results suggest that the adsorption ratios of substrate, acylating agent and product are more favorable in the gas phase than in the liquid phase.

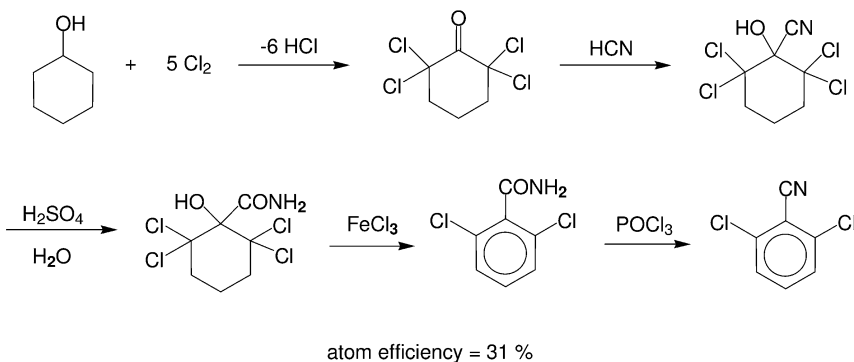
Zeolites have also been investigated as heterogeneous catalysts for other electrophilic aromatic substitutions, e.g. nitration [53] and halogenation [54]. Aromatic nitration, for example, traditionally uses a mixture of sulfuric and nitric acids which leads to the generation of copious quantities of spent acid waste. Dealuminated mordenite (see earlier) is sufficiently robust to function effectively as a catalyst for the vapor phase nitration of benzene with 65% aqueous nitric acid [55]. The advantage of using vapor phase conditions is that the water is continuously removed. Although these results are encouraging, aromatic nitration over solid acid catalysts is still far from commercialization.

An interesting example of aromatic halogenation, in the context of green chemistry, is the production of 2,6-dichlorobenzonitrile, an agrochemical intermediate. The conventional process involves a series of reactions (see Fig. 2.18) with Cl_2 , HCN, and POCl_3 as stoichiometric reagents, having an atom efficiency of 31% and generating substantial amounts of salts as waste. The new process, developed by Toray [56], involves vapor phase chlorination of toluene over a Ag-H-Mordenite catalyst to give a mixture of dichlorotoluene isomers. The required 2,6-isomer is separated by adsorption in faujasite or AlPO-11 and the other isomers are returned to the chlorination reactor where equilibration occurs. The 2,6-dichlorotoluene can be subsequently converted to 2,6-dichlorobenzonitrile by vapour phase ammoxidation over an oxide catalyst.



<u>X</u>	<u>Catalyst</u>	<u>Temp. (°C)</u>	<u>Conv. (%)</u>	<u>Sel. (%)</u>
S	B-ZSM-5	250	24	99
O	Ce-ZSM-5	200	23	99
N	B-Cs-ZSM-5	150	41	98

Fig. 2.17 Acylation of heteroaromatics over zeolite catalysts.

(a) Conventional process

(b)

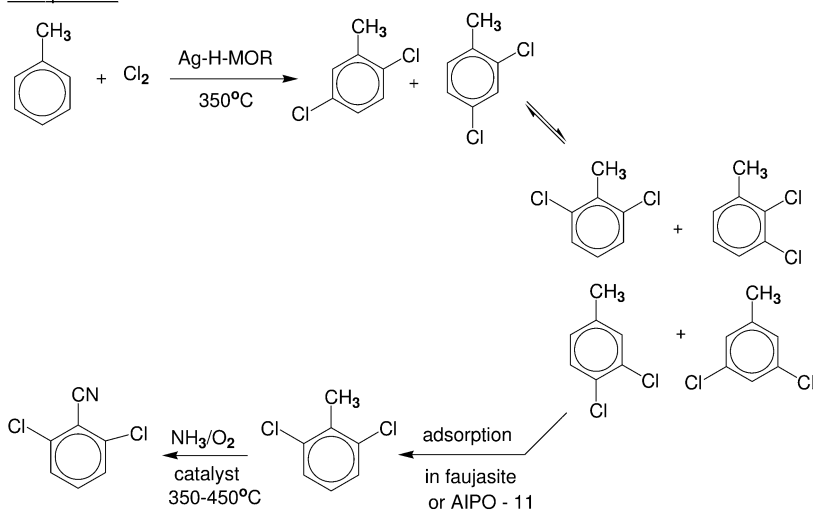
New process

Fig. 2.18 Two processes for 2,6-dichlorobenzonitrile.

2.2.3.2 Additions and Eliminations

Zeolites have been used as (acid) catalysts in hydration/dehydration reactions. A pertinent example is the Asahi process for the hydration/dehydration of cyclohexene to cyclohexanol over a high silica ($\text{Si}/\text{Al} > 20$), H-ZSM-5 type catalyst [57]. This process has been operated successfully on a 60000 tpa scale since 1990, although many problems still remain [57] mainly due to catalyst deactivation. The hydration of cyclohexanone is a key step in an alternative route to cyclohexanol (and phenol) from benzene (see Fig. 2.19). The conventional route involves hydrogenation to cyclohexane followed by autoxidation to a mixture of cyclohexanol and

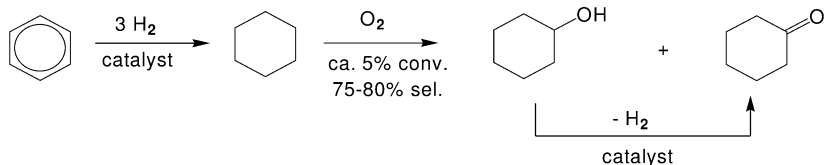
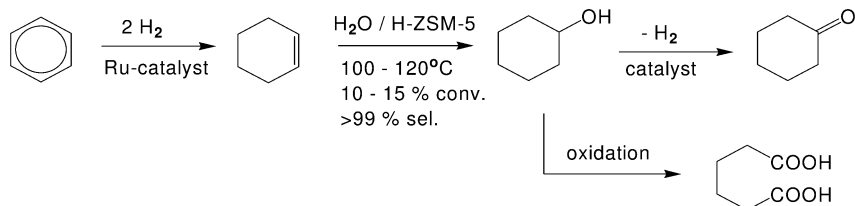
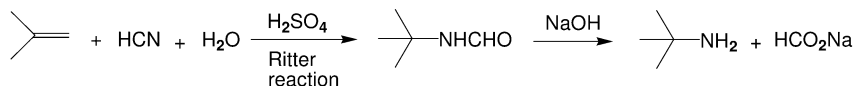
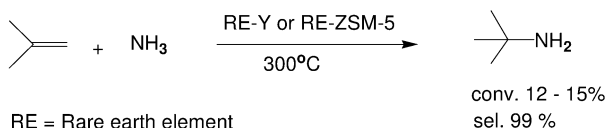
Conventional processAsahi process

Fig. 2.19 Two processes for cyclohexanone.

cyclohexanone and subsequent dehydrogenation of the former. A serious disadvantage of this process is that the autoxidation gives reasonable selectivities (75–80%) only at very low conversions (ca. 5%), thus necessitating the recycle of enormous quantities of cyclohexane. The Asahi process involves initial partial hydrogenation of benzene to cyclohexene over a heterogeneous ruthenium catalyst. The cyclohexane byproduct is recycled by dehydrogenation back to benzene. The cyclohexene hydration proceeds with >99% selectivity at 10–15% conversion. If the ultimate product is adipic acid the cyclohexanone can be by-passed by subjecting cyclohexanol to oxidation (see Fig. 2.19) [57].

Conventional processBASF processFig. 2.20 Two processes for *tert*-butylamine.

Similarly, zeolites can catalyze the addition of ammonia to an olefinic double bond, as is exemplified by the BASF process for the production of *tert*-butylamine by reaction of isobutene with ammonia, in the vapor phase, over a rare earth exchanged ZSM-5 or Y zeolite (Fig. 2.20) [58, 59]. This process has an atom efficiency of 100% and replaced a conventional synthesis via a Ritter reaction, which employs HCN and sulfuric acid and generates formate as a coproduct.

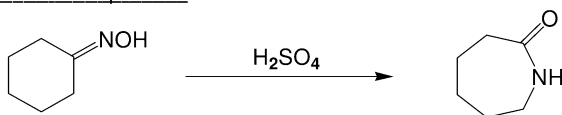
2.2.3.3 Rearrangements and Isomerizations

As already discussed in Chapter 1, the commercialization, by Sumitomo [60–64], of a vapor phase *Beckmann rearrangement* of cyclohexanone oxime to caprolactam over a high-silica MFI (ZSM-5 type) zeolite (Fig. 2.21) is another benchmark in zeolite catalysis. The process, which currently operates on a 90 000 tpa scale, replaces a conventional one employing stoichiometric quantities of sulfuric acid and producing ca. 2 kg of ammonium sulfate per kg of caprolactam.

Interestingly, the activity of the catalyst was proportional to its external surface area. This, together with the fact that caprolactam does not fit easily into the pores of the zeolite, strongly suggests that the reaction takes place on the external surface, possibly at the pore openings. Ichihashi and coworkers [61] proposed that the reaction takes place in a silanol nest resulting from dealumination (see earlier), as was also suggested by Hoelderich and coworkers [65].

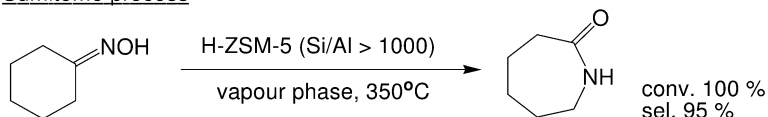
The Friedel-Crafts acylation of phenols proceeds via initial esterification followed by *Fries rearrangement* of the resulting aryl ester to afford the hydroxyaryl

Conventional process



Produces ca. 2 kg $(\text{NH}_4)_2\text{SO}_4$ per kg caprolactam after neutralization

Sumitomo process



catalyst : high-silica ZSM-5 (Si/Al > 1000)
external surface area > $10\text{m}^2\text{g}^{-1}$

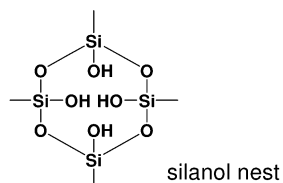


Fig. 2.21 Zeolite-catalyzed Beckmann rearrangement.

ketone. For example, phenylacetate affords a mixture of *o*- and *p*-hydroxyacetophenone (see Fig. 2.22). The latter is a key intermediate in the Hoechst Celanese process for the manufacture of the analgesic, paracetamol.

Traditionally, the Fries rearrangement is conducted with stoichiometric amounts of mineral (H_2SO_4 , HF) or Lewis acids (AlCl_3 , ZnCl_2) and generates large amounts of inorganic salts as by-products, i.e. it suffers from the same disadvantages as standard Friedel-Crafts acylations. Substitution of these corrosive, polluting and non-regenerable catalysts by regenerable solid acid catalysts has obvious environmental benefits. Consequently, a variety of solid acids, particularly zeolites, have been studied as catalysts for the Fries rearrangement, both in the vapor and liquid phases [66]. Most studies were performed with phenyl acetate as the substrate, prepared *ex situ* or formed *in situ* from phenol and acetic anhydride or acetic acid. A variety of zeolites have been used, e.g. H-Y, H-ZSM-5 and H-beta, generally affording *o*-hydroxyacetophenone as the major product, often in very high selectivity [67]. None of these processes has been brought to commercialization, presumably because they produce the commercially less interesting isomer as the product.

Another example of commercial interest is the Fries rearrangement of the benzoate ester of resorcinol to afford 2,4-dihydroxybenzophenone, the precursor of the UV-absorbent 4-*O*-octyl-2-hydroxybenzophenone. Reaction of benzoic acid with one equivalent of resorcinol (see Fig. 2.22), over various solid catalysts, in chlorobenzene as solvent, with continuous removal of water, was investigated by Hoefnagel and van Bekkum [68]. H-Beta was slightly less active than the ion-ex-

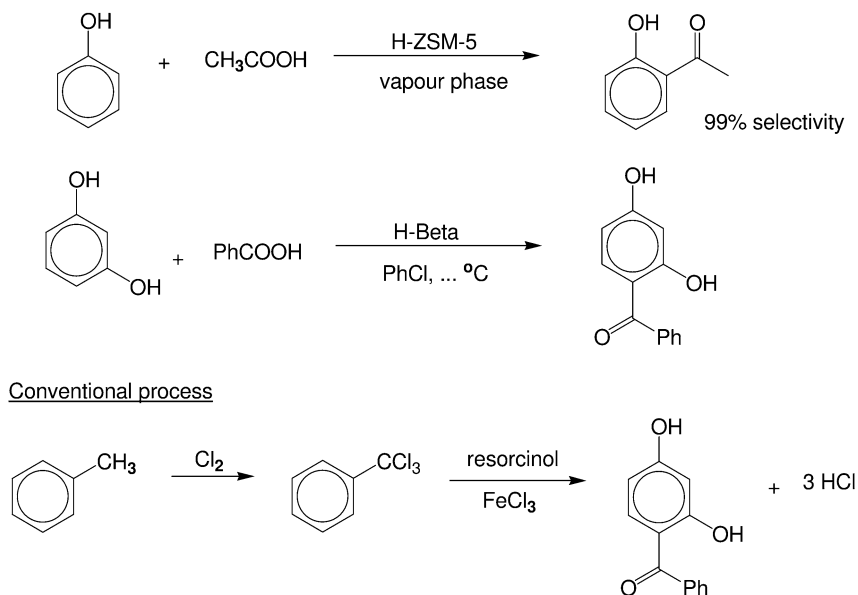


Fig. 2.22 Fries rearrangement over zeolites.

change resin, Amberlyst 15, but gave less by-product formation and has the advantage of being regenerable by simple air burn-off. It would appear to have environmental benefits compared to the existing industrial process which generates substantial amounts of chloride waste (see Fig. 2.22).

Epoxide rearrangements are key steps in the manufacture of numerous synthetic intermediates in the fine chemical industry. They are generally performed with conventional Brønsted or Lewis acids or strong bases as catalysts, often in stoichiometric amounts. Here again, replacement by recyclable solid catalysts has obvious benefits [69].

For example, rearrangement of α -pinene oxide produces, among the ten or so major products, campholenic aldehyde, the precursor of the sandalwood fragrance santalol. The conventional process employs stoichiometric quantities of zinc chloride but excellent results have been obtained with a variety of solid acid catalysts (see Fig. 2.23), including a modified H-USY [70] and the Lewis acid Ti-Beta [71]. The latter afforded campholenic aldehyde in selectivities up to 89% in the liquid phase and 94% in the vapor phase.

Similarly, the rearrangement of substituted styrene oxides to the corresponding phenylacetaldehydes (see Fig. 2.23) affords valuable intermediates for fragrances, pharmaceuticals and agrochemicals. Good results were obtained using zeolites, e.g. H-ZSM-5, in either the liquid or vapor phase [69]. The solid Lewis acid, titanium silicalite-1 (TS-1) also gave excellent results, e.g. styrene oxide was converted to phenylacetaldehyde in 98% selectivity at 100% conversion in 1–2 h at 70 °C in acetone as solvent. Other noteworthy epoxide rearrangements

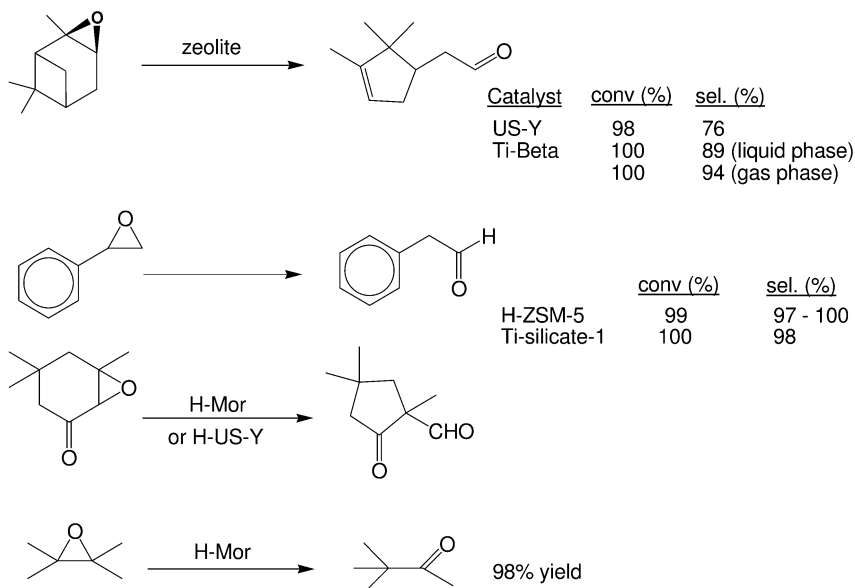


Fig. 2.23 Zeolite-catalyzed epoxide rearrangements.

are the conversion of isophorone oxide to the keto aldehyde (see Fig. 2.23), over H-mordenite [72] or H-US-Y (Si/Al=48) [69], and 2,3-dimethyl-2-butene oxide to pinacolone [73]. The mechanistically related pinacol rearrangement, e.g. of pinacol to pinacolone, has also been conducted over solid acid catalysts including acidic clays and zeolites [74].

2.2.3.4 Cyclizations

Zeolites have also been shown to catalyze a variety of acid-promoted cyclizations. Many of these involve the formation of *N*-heterocycles via intramolecular amination reactions [75–77]. Some examples are shown in Fig. 2.24.

Reaction of ammonia with various combinations of aldehydes, over solid acid catalysts in the vapor phase, is a convenient route for producing pyridines [77]. For example, amination of a formaldehyde/acetaldehyde mixture affords pyridine and 3-picoline (Fig. 2.25). Mobil scientists found that MFI zeolites such as H-ZSM-5 were particularly effective for these reactions.

Alternatively, 3-picoline is produced by vapor phase cyclization of 2-methylpentane-1,5-diamine (Fig. 2.25) over, for example, H-ZSM-5 followed by palladium-catalyzed dehydrogenation [78]. This diamine is a by-product of the manufacture of hexamethylenediamine, the raw material for nylon 6,6, and these two reactions are key steps in the Lonza process for nicotinamide production (see Chapter 1) [79].

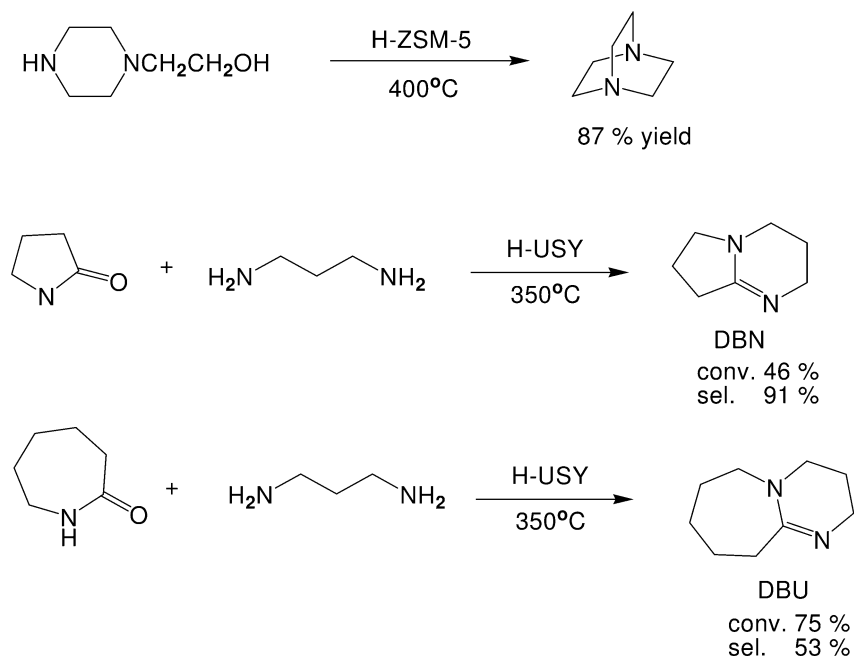


Fig. 2.24 Zeolite-catalyzed cyclizations.

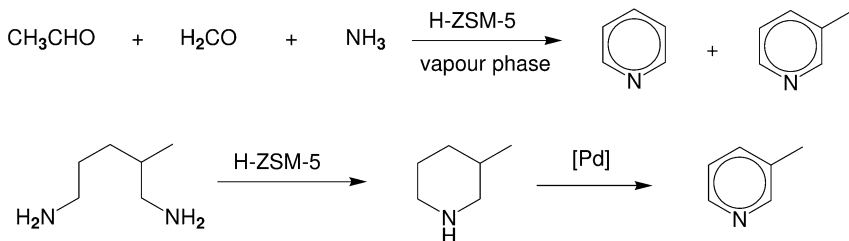


Fig. 2.25 Synthesis of pyridines via zeolite-catalyzed cyclizations.

Other examples of zeolite-catalyzed cyclizations include the Fischer indole synthesis [80] and Diels-Alder reactions [81].

2.2.4

Solid Acids Containing Surface SO_3H Functionality

This category encompasses a variety of solid acids with the common feature of a sulfonic acid moiety attached to the surface, i.e. they are heterogeneous equivalents of the popular homogeneous catalysts, *p*-toluenesulfonic and methanesulfonic acids. The cross-linked polystyrene-based, macroreticular ion exchange resins, such as Amberlyst[®]-15, are probably the most familiar examples of this class. They are the catalysts of choice in many industrial processes and in laboratory scale organic syntheses, e.g. esterifications, etherifications and acetalizations [2, 16, 17]. However, a serious shortcoming of conventional, polystyrene-based resins is their limited thermal stability. Reactions requiring elevated temperatures can be conducted with the more thermally stable Nafion[®] resins, which consist of a perfluorinated, Teflon-like polymeric backbone functionalized with terminal SO_3H groups [2, 82–85]. These materials (see Fig. 2.26 for structure) were originally developed by DuPont for application as membranes in electrochemical processes, based on their inertness to corrosive environments. Nafion is commercially available as Nafion NR50 (DuPont) in the

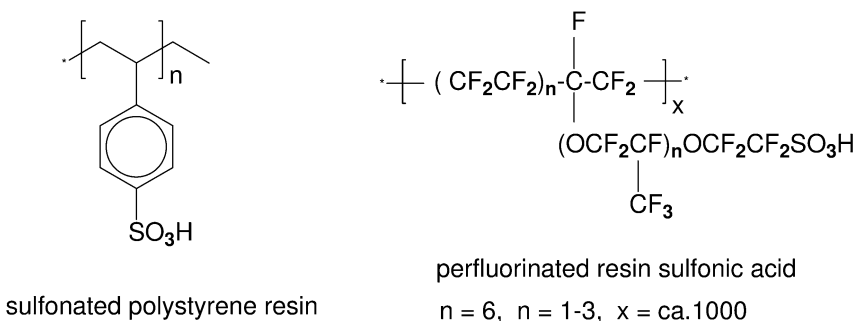


Fig. 2.26 Structures of polystyrene- and perfluorocarbon-based ion exchange resins.

form of relatively large (2–3 mm) beads or as a 5% solution in a mixture of a lower alcohol and water. Other major differences with the polystyrene-based resins are their superior acid strength and higher number of acid sites. As a consequence of their highly electron-withdrawing perfluoroalkyl backbone, Nafion-H has an acidity comparable with that of 100% sulfuric acid, i.e. an acidity function (H_0) of –11 to –13 compared with –2.2 for Amberlyst-15. It also has five times as many acid sites as the latter. This superacidity coupled with thermal stability (up to 280 °C) make Nafion-H an attractive catalyst for a variety of processes [2, 16, 17]. Thus, reactions not requiring especially strong acidity and/or high temperatures are usually conducted with the less expensive polystyrene-based resins while those that require higher acidity and/or temperatures can be performed better with the more robust Nafion-H.

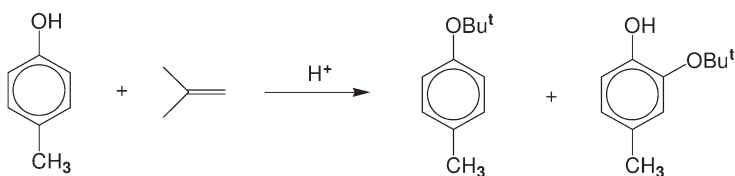
However, Nafion-H NR50 beads have one serious drawback: they have a very low surface area ($<0.02 \text{ m}^2 \text{ g}^{-1}$). To overcome this disadvantage DuPont researchers developed Nafion-silica composites, consisting of small (20–60 nm) Nafion resin particles embedded in a porous silica matrix [86]. The microstructure can be regarded as a porous silica network containing a large number of ‘pockets’ of very strong acid sites (the Nafion polymer) in domains of ca. 10–20 nm. The surface area is increased by several orders of magnitude and the catalytic activity per unit weight is up to 1000 times that of the pure Nafion. They are prepared by a sol–gel technique and are available as SAC 13, which contains 13% (w/w) Nafion. The improved accessibility to the active sites makes this material a particularly attractive solid acid catalyst [2, 84] for a variety of reactions such as Friedel-Crafts alkylations [86, 87] and Friedel-Crafts acylations [2]. The latter are effective only with electron-rich aromatics such as anisole. The Nafion-silica composite was compared with the pure polymer and Amberlyst-15 in the alkylation of *p*-cresol with isobutene [2]. The results are shown in Table 2.2.

Nafion-silica composites were compared with zeolites such as H-Beta, H-USY and H-ZSM-5, in the Fries rearrangement of phenyl acetate (see earlier). The highest conversion was observed with H-Beta [88].

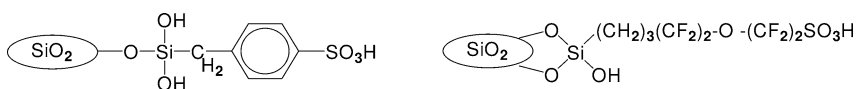
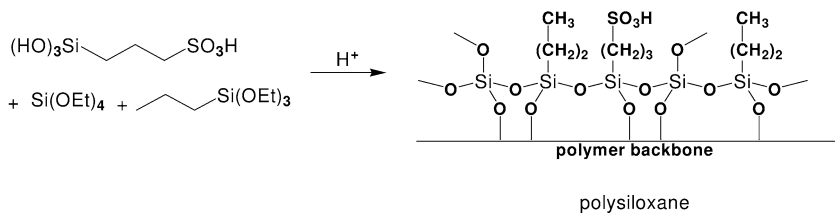
Another class of thermally stable polymers containing surface SO_3H functionalities comprises the sulfonated polysiloxanes (see Fig. 2.27) [89]. They are best prepared by a sol–gel technique involving copolymerization of functionalized and non-functionalized silanes, e.g. 3-(tris-hydroxysilyl)propyl sulfonic acid with tetraethoxysilane. This sol–gel process affords material with a high surface area ($300\text{--}600 \text{ m}^2 \text{ g}^{-1}$), high porosity and large mesopores ($>20 \text{ nm}$). Although they have excellent chemical and thermal stability, and have been marketed under the trade name Deloxan[®], industrial applications have not yet been forthcoming, probably owing to their relatively high price.

Similarly, perfluoroalkylsulfonic acid moieties can be covalently attached to a silica matrix by grafting a silica surface with $(\text{EtO})_3\text{Si}(\text{CH}_2)_3(\text{CF}_2)_2\text{O}(\text{CF}_2)_2\text{SO}_3\text{H}$ (see Fig. 2.27) or by using the latter in a sol–gel synthesis [18, 90].

More recently, attention has shifted to the preparation of hybrid organic–inorganic ordered mesoporous silicas, e.g. of the M41S type (see earlier), bearing pendant alkylsulfonic acid moieties [18, 91–96]. These materials combine a high

Table 2.2 Acid catalyzed alkylation of *p*-cresol.

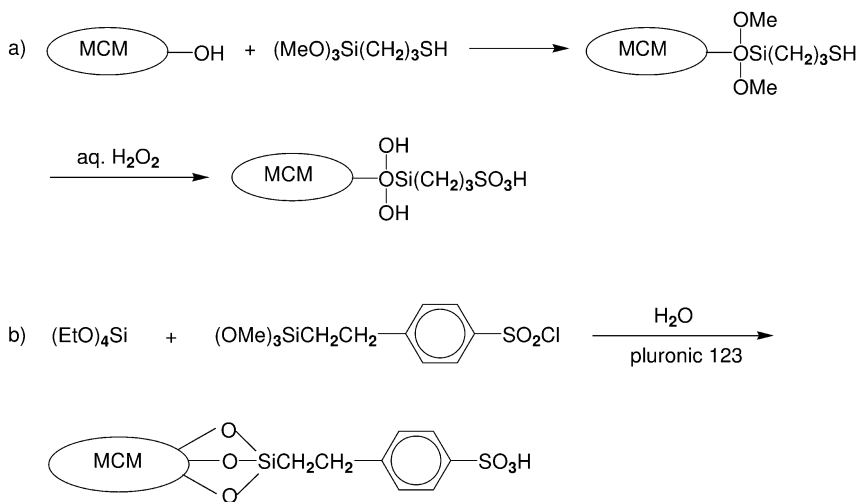
Catalyst	Conv. (%)	Selectivity (%)		Rate (mMg ⁻¹ cat·h ⁻¹)
		Ether	Alkylates	
13% Nafion/SiO ₂	82.6	0.6	99.4	581.0
Nafion NR50	19.5	28.2	71.8	54.8
Amberlyst-15	62.4	14.5	85.5	171.0

surface grafted SO₃H moieties

polysiloxane

Fig. 2.27 Synthesis of SO₃H-functionalized silicas.

surface area, high loading and acid strength with excellent site accessibility and regular mesopores of narrow size distribution. This unique combination of properties makes them ideal solid acid catalysts for, in particular, reactions involving relatively bulky molecules as reactants and/or products. They are prepared by grafting of preformed MCM-41 with, for example, 3-mercaptopropyltrimethoxysilane (MPTS), followed by oxidation of the pendant thiol groups to SO₃H with hydrogen peroxide (Fig. 2.28) [18]. Alternatively, direct co-condensation of tetraethoxysilane (TEOS) with MPTS in the presence of a surfactant templating agent, such as cetyltrimethylammonium bromide or dodecylamine, affords functionalized MCM-41 or HMS (hexagonal mesoporous silica), respectively [18, 91–96]. Non-ionic surfactants, e.g. the poly(ethylene oxide)–poly(propylene oxide) block copolymer, commercially available as Pluronic 123, have



pluronic 123 = ethylene oxide / propylene oxide block copolymer

Fig. 2.28 Synthesis of ordered mesoporous silicas containing pendant SO_3H groups.

been used under acidic conditions [91, 92, 96]. When hydrogen peroxide is added to the sol-gel ingredients the SH groups are oxidized *in situ*, affording the SO_3H -functionalized mesoporous silica in one step [91, 92]. Alternatively, co-condensation of TEOS with 2-(4-chlorosulfonylphenyl)ethyltrimethoxysilane, in the presence of Pluronic 123 as template, afforded a mesoporous material containing pendant arenesulfonic acid moieties (see Fig. 2.28) [91, 92].

These mesoporous SO_3H -functionalized silicas are attractive, recyclable acid catalysts for reactions involving molecules that are too large to access the smaller pores of conventional molecular sieves or those affording bulky products. The additional option of modifying their hydrophobicity/hydrophilicity balance, by introducing varying amounts of alkyltrialkoxysilanes, e.g. $\text{CH}_3\text{CH}_2\text{CH}_2\text{Si}(\text{OEt})_3$, into the sol-gel synthesis provides an opportunity to design tailor-made solid acid catalysts [94]. These organic-inorganic materials have been used as acid catalysts in, for example, esterifications of polyols with fatty acids [18, 94, 95], Friedel-Crafts acylations [97] and bisphenol-A synthesis [93]. The latter is an important raw material for epoxy resins, and is manufactured by reaction of phenol with acetone (see Fig. 2.29) using ion exchange resins such as Amberlyst[®]-15 as catalyst. However, thermal stability and fouling are major problems with these catalysts and there is a definite need for thermally stable, recyclable solid acid catalysts. A sulfonic acid functionalized MCM-41, produced by grafting of preformed MCM-41 with MPTS and subsequent H_2O_2 oxidation, exhibited a superior activity and selectivity compared with various zeolites. Unfortunately, the crucial comparison with Amberlyst-15 was not reported.

Finally, the functionalization of mesoporous silicas with perfluoroalkylsulfonic acid groups, by grafting with 1,2,2-trifluoro-2-hydroxy-1-trifluoromethylethane

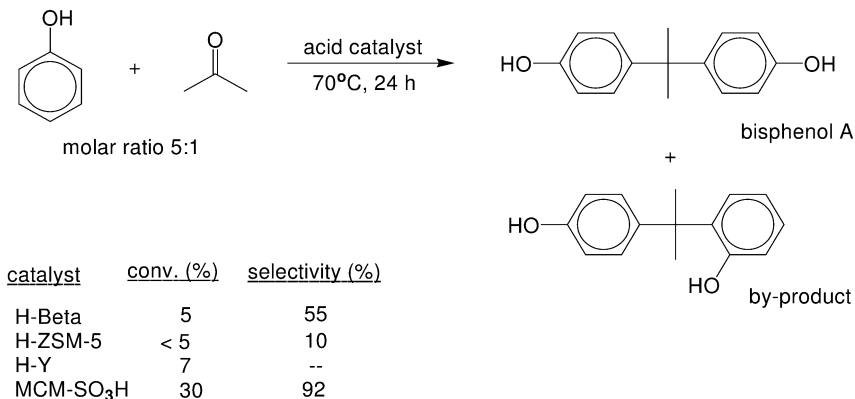


Fig. 2.29 Bisphenol-A synthesis over MCM-SO₃H.

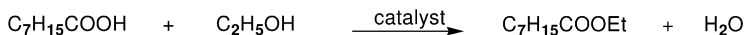
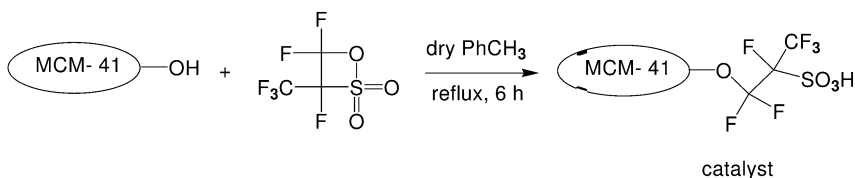


Fig. 2.30 Mesoporous silica grafted with perfluoroalkylsulfonic acid groups.

sulfonic acid β -sultane (see Fig. 2.30) was recently reported [98]. The resulting materials displayed a higher activity than commercial Nafion[®] silica composites (see earlier) in the esterification of ethanol with octanoic acid [98].

2.2.5

Heteropoly Acids

Heteropoly acids (HPAs) are mixed oxides composed of a central ion or 'heteroatom' generally P, As, Si or Ge, bonded to an appropriate number of oxygen atoms and surrounded by a shell of octahedral MO₆ units, usually where M=Mo, W or V. HPAs, having the so-called Keggin structure, are quite common and consist of a central tetrahedron, XO₄ (X=P, As, Si, Ge, etc.) surrounded by 12 MO₆ octahedra (M=Mo, W, V) arranged in four groups of three edge-sharing M₃O₁₃ units (see Fig. 2.31).

Many HPAs exhibit superacidity. For example, H₃PW₁₂O₄₀ has a higher acid strength ($H_0 = -13.16$) than CF₃SO₃H or H₂SO₄. Despite their rather daunting formulae they are easy to prepare, simply by mixing phosphate and tungstate in the required amounts at the appropriate pH [99]. An inherent drawback of

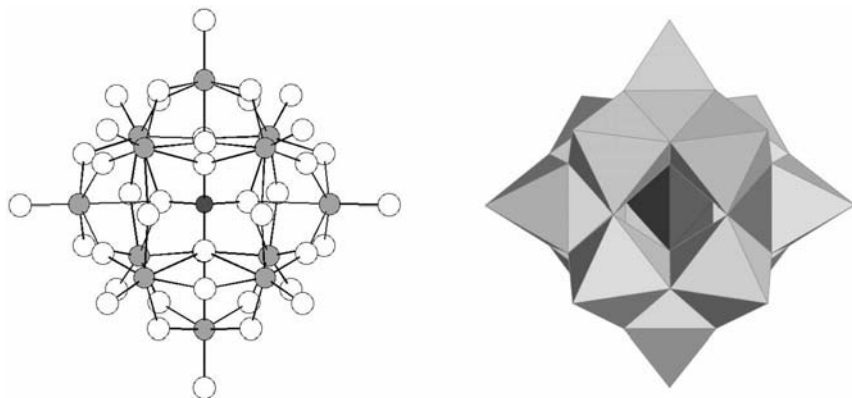


Fig. 2.31 Keggin structure of $[\text{PW}_{12}\text{O}_{40}]^{3-}$
 ● P-atoms; ● W-atoms; ○ O-atoms.

HPAs, however, is their solubility in polar solvents or reactants, such as water or ethanol, which severely limits their application as recyclable solid acid catalysts in the liquid phase. Nonetheless, they exhibit high thermal stability and have been applied in a variety of vapor phase processes for the production of petrochemicals, e.g. olefin hydration and reaction of acetic acid with ethylene [100, 101]. In order to overcome the problem of solubility in polar media, HPAs have been immobilized by occlusion in a silica matrix using the sol-gel technique [101]. For example, silica-occluded $\text{H}_3\text{PW}_{12}\text{O}_{40}$ was used as an insoluble solid acid catalyst in several liquid phase reactions such as ester hydrolysis, esterification, hydration and Friedel-Crafts alkylations [101]. HPAs have also been widely applied as catalysts in organic synthesis [102].

2.3

Solid Base Catalysis

Examples of the application of recyclable solid base catalysts are far fewer than for solid acids [103]. This is probably because acid-catalyzed reactions are much more common in the production of commodity chemicals. The various categories of solid bases that have been reported are analogous to the solid acids described in the preceding sections and include anionic clays, basic zeolites and mesoporous silicas grafted with pendant organic bases.

2.3.1

Anionic Clays: Hydrotalcites

Anionic clays are natural or synthetic lamellar mixed hydroxides with interlayer spaces containing exchangeable anions [10, 104]. The generic terms, layered double hydroxides (LDHs) or hydrotalcites are widely used, the latter because exten-

sive characterization has been performed on hydrotalcite (a Mg/Al hydroxycarbonate) which is both inexpensive and easy to synthesize.

Hydrotalcite is a natural mineral of ideal formula $\text{Mg}_6\text{Al}_2(\text{OH})_{16}\text{CO}_3 \cdot 4\text{H}_2\text{O}$, having a structure similar to brucite, $\text{Mg}(\text{OH})_2$. In hydrotalcite the Mg cations are partially replaced with Al^{3+} and the resulting positive charge is compensated by anions, typically carbonate, in the interlamellar space between the brucite-like sheets. When hydrotalcite is calcined at ca. 500°C it is decarbonated and dehydrated to afford a strongly basic mixed Mg/Al oxide. Rehydration restores the original hydrotalcite structure and creates Brønsted base sites (OH^-) in the interlamellar space.

Activated hydrotalcites prepared in this way have been used as solid base catalysts in, for example, the aldol and related reactions [105]. The aldol condensation is a key step in the production of several commodity chemicals, including the solvent methylisobutylketone (MIBK) and 2-ethylhexanol, the precursor of the PVC plasticizer, dioctylphthalate (see Fig. 2.32). More than 1 million tons of these chemicals are produced worldwide on an annual basis using homogeneous bases such as 30% aqueous caustic (NaOH) [106]. Major problems are associated with the safe handling of the 30% caustic and treatment of caustic contaminated waste streams. About 1 kg of spent catalyst is generated per 10 kg of product and it has been estimated that 30% of the selling price is related to product recovery, purification and waste treatment. Hence, there is a definite incentive to replace these homogeneous bases with recyclable solid bases and hydrotalcites have been used to catalyze the aldol condensation of n-butyraldehyde in the liquid phase and acetone in the vapor phase to give 2-ethylhexenal and mesityl oxide, respectively [105]. Hydrogenation of the aldol condensation products yields 2-ethylhexanol and MIBK, respectively (Fig. 2.32). Impregnation of

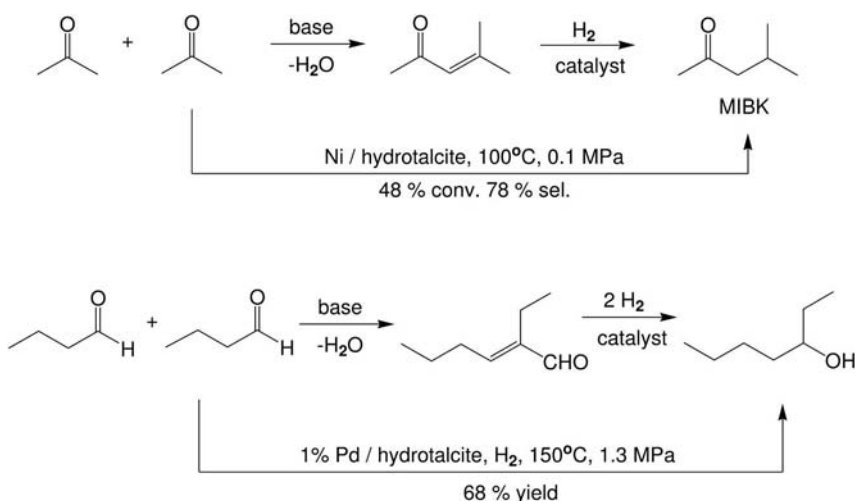
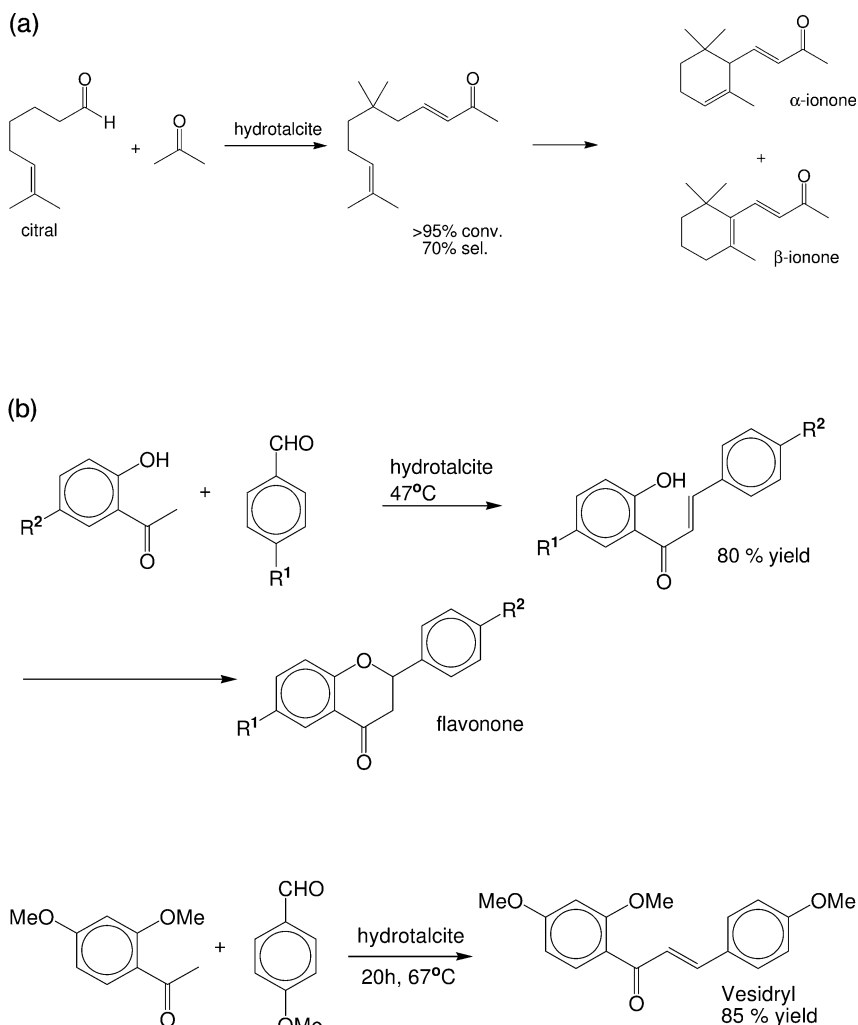


Fig. 2.32 Synthesis of MIBK and 2-ethylhexanol via aldol condensations.

the hydrotalcite with Pd or Ni affords bifunctional catalysts which are able to mediate the one-pot reductive aldol condensation of n-butyraldehyde or acetone to 2-ethylhexanol or MIBK, respectively [105].

Aldol and related condensation reactions such as Knoevenagel and Claisen-Schmidt condensations are also widely used in the fine chemicals and specialty chemicals, e.g. flavors and fragrances, industries. Activated hydrotalcites have been employed as solid bases in many of these syntheses. Pertinent examples include the aldol condensation of acetone and citral [107, 108], the first step in the synthesis of ionones, and the Claisen-Schmidt condensation of substituted benzaldehydes [109], the synthetic



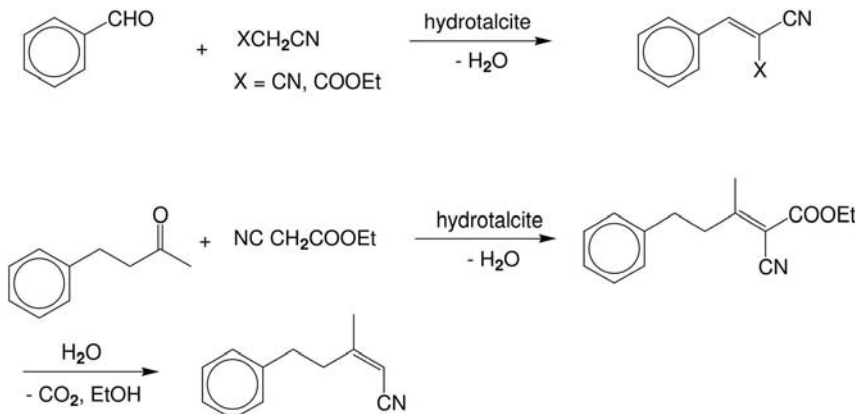


Fig. 2.34 Hydrotalcite-catalyzed Knoevenagel condensations.

route to flavonoids (see Fig. 2.33). The diuretic drug, Vesidryl, was similarly synthesized by condensation of 2,4-dimethoxyacetophenone with *p*-anisaldehyde (see Fig. 2.33) [109].

Excellent results were also obtained using activated hydrotalcite as a solid base catalyst in the Knoevenagel condensation of benzaldehyde with ethylcyanoacetate [110], ethylacetoacetate [111] or malononitrile [112] (see Fig. 2.34). Similarly, citronitrile, a perfumery compound with a citrus-like odor, was synthesized by hydrotalcite-catalyzed condensation of benzylacetone with ethylcyanoacetate, followed by hydrolysis and decarboxylation (Fig. 2.34) [113].

Other reactions which have been shown to be catalyzed by hydrotalcites include Michael additions, cyanoethylations and alkylations of, e.g. 1,3-dicarbonyl

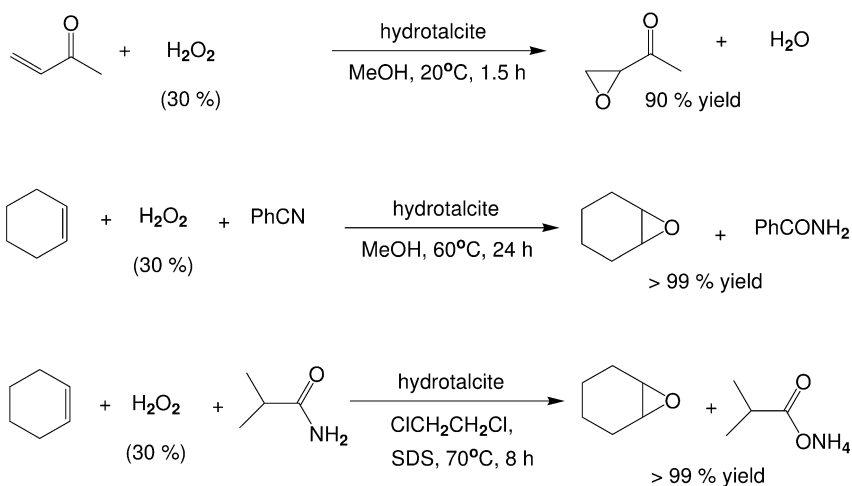


Fig. 2.35 Hydrotalcite-catalyzed oxidations with H_2O_2 .

compounds [105, 114]. Another interesting application is as a solid base catalyst in oxidations (Fig. 2.35) involving the hydroperoxide anion, HO_2^- [115], e.g. the epoxidation of electron deficient olefins with H_2O_2 [116] and the epoxidation of electron-rich olefins with $\text{PhCN}/\text{H}_2\text{O}_2$ [117]. The latter reaction involves the peroxycarboximidate (Payne reagent) as the active oxidant, producing one equivalent of the amide as a co-product. Subsequent studies showed that carboxylic amides also act as catalysts in this reaction (Fig. 2.35), isobutyramide being particularly effective [118]. In this case, one equivalent of the ammonium carboxylate is formed as the co-product.

Interesting recent developments are the use of hydrotalcite supported on carbon nanofibers [119], to facilitate recovery of the catalyst by filtration, and the use of synthetic hydroxyapatite, $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$ as a solid base catalyst in a variety of reactions including Michael additions [120]. The supported hydrotalcite exhibited higher activities and selectivities than the conventional unsupported material in the aldol condensation of citral with acetone [119].

2.3.2

Basic Zeolites

In contrast with the widespread application of zeolites as solid acid catalysts (see earlier), their use as solid base catalysts received scant attention until fairly recently [121]. This is probably because acid-catalyzed processes are much more common in the oil refining and petrochemical industries. Nonetheless, basic zeolites and related mesoporous molecular sieves can catalyze a variety of reactions, such as Knoevenagel condensations and Michael additions, which are key steps in the manufacture of flavors and fragrances, pharmaceuticals and other specialty chemicals [121]. Indeed, the Knoevenagel reaction of benzaldehyde with ethyl cyanoacetate (Fig. 2.36) has become a standard test reaction for solid base catalysts [121].

Two approaches have been used to prepare basic zeolites by post-synthesis modification: (i) ion exchange of protons by alkali metal or rare earth cations and (ii) generation of nanoparticles of alkali metal or alkaline earth metal oxides within the zeolite channels and cavities (see later). In zeolites, Lewis basicity is associated with the negatively charged framework oxygens and, as expected, increases with the size of the counter cation, i.e. $\text{Li} < \text{Na} < \text{K} < \text{Cs}$. Alkali-exchanged zeolites contain a large number of relatively weak basic sites capable of abstracting a proton from molecules having a $\text{p}K_a$ in the range 9–11 and a few more basic ones (up to $\text{p}K_a=13.3$) [121]. This corresponds with the basic

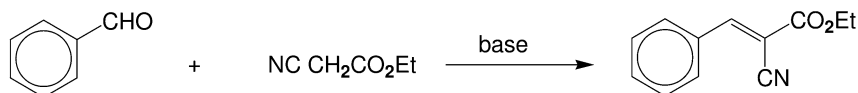


Fig. 2.36 Knoevenagel reaction.

strength required to catalyze many synthetically useful reactions such as the Knoevenagel and Michael reactions referred to above. The use of the ion-exchanged zeolites as base catalysts has the advantage that they are stable towards reaction with moisture and/or carbon dioxide.

Cesium-exchanged zeolite X was used as a solid base catalyst in the Knoevenagel condensation of benzaldehyde or benzyl acetone with ethyl cyanoacetate [121]. The latter reaction is a key step in the synthesis of the fragrance molecule, citronitrile (see Fig. 2.37). However, reactivities were substantially lower than those observed with the more strongly basic hydrotalcite (see earlier). Similarly, Na-Y and Na-Beta catalyzed a variety of Michael additions [122] and K-Y and Cs-X were effective catalysts for the methylation of aniline and phenylacetone with dimethyl carbonate or methanol, respectively (Fig. 2.37) [123]. These procedures constitute interesting green alternatives to classical alkylations using methyl halides or dimethyl sulfate in the presence of stoichiometric quantities of conventional bases such as caustic soda.

Alkali-exchanged mesoporous molecular sieves are suitable solid base catalysts for the conversion of bulky molecules which cannot access the pores of zeolites. For example, Na- and Cs-exchanged MCM-41 were active catalysts for the Knoevenagel condensation of benzaldehyde with ethyl cyanoacetate ($pK_a=10.7$) but low conversions were observed with the less acidic diethyl malonate ($pK_a=13.3$) [123]. Similarly, Na-MCM-41 catalyzed the aldol condensation of several bulky ketones with benzaldehyde, including the example depicted in Fig. 2.38, in which a flavonone is obtained by subsequent intramolecular Michael-type addition [123].

As noted above, the basic sites generated by alkali metal exchange in zeolites are primarily weak to moderate in strength. Alkali and alkaline earth metal oxides, in contrast, are strong bases and they can be generated within the pores and cavities of zeolites by over-exchanging them with an appropriate metal salt, e.g. an acetate, followed by thermal decomposition of the excess metal salt, to afford highly dispersed basic oxides occluded in the pores and cavities. For example, cesium oxide loaded faujasites, exhibiting super-basicities, were prepared by impregnating CsNa-X or CsNa-Y with cesium acetate and subsequent thermal decomposition [124, 125]. They were shown to catalyze, inter alia, Knoevenagel condensations, e.g. of benzaldehyde with ethyl cyanoacetate [126]. A simi-

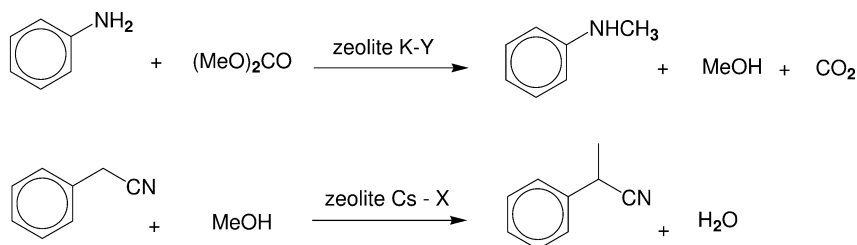


Fig. 2.37 Alkylations catalyzed by basic zeolites.

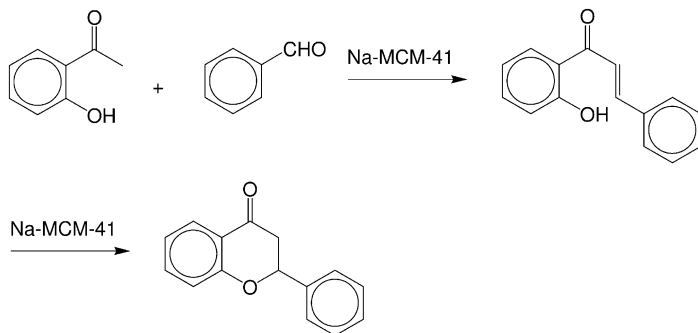


Fig. 2.38 Na-MCM-41 catalyzed flavonone synthesis.

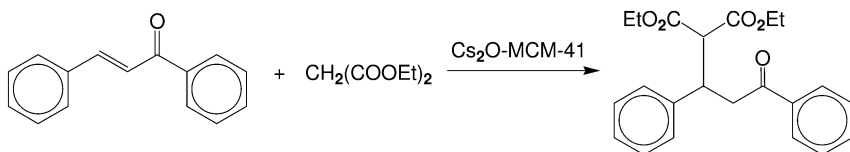


Fig. 2.39 Cesium oxide loaded MCM-41 as a catalyst for the Michael addition.

larly prepared Cs oxide loaded MCM-41 was an active catalyst for the Michael addition of diethylmalonate to chalcone (Fig. 2.39) [127].

A serious drawback of these alkali metal oxide loaded zeolites and mesoporous molecular sieves is their susceptibility towards deactivation by moisture and/or carbon dioxide, which severely limits their range of applications.

2.3.3

Organic Bases Attached to Mesoporous Silicas

Analogous to the attachment of organic alkyl(aryl)sulfonic acid groups to the surface of organic or inorganic polymers (see earlier), recyclable solid base catalysts can be prepared by grafting, e.g. amine moieties, to the same supports. Anion exchange resins, such as Amberlyst, are composed of amine or tetraalkylammonium hydroxide functionalities grafted to cross-linked polystyrene resins and they are widely used as recyclable basic catalysts [128]. As with the cation exchange resins, a serious limitation of these materials is their lack of thermal stability under reaction conditions, in this case a strongly alkaline medium. This problem can be circumvented by grafting basic moieties to inorganic polymers that are thermally stable under reaction conditions.

The use of silica-grafted primary and tertiary amines as solid base catalysts in Knoevenagel condensations was reported already in 1988. Yields were high but activities were rather low, owing to the relatively low loadings ($<1 \text{ mmol g}^{-1}$). A decade later the groups of Brunel [129–131], Macquarrie [132–135] and Jacobs [136] obtained much higher loadings (up to 5 mmol g^{-1}), and activities, by at-

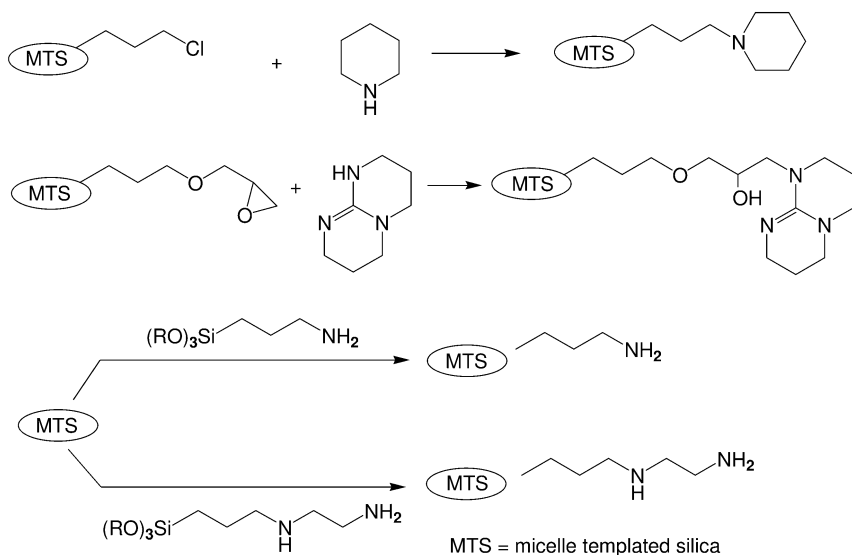


Fig. 2.40 Methods for attachment of organic bases to micelle templated silicas.

taching amine functionalities to mesoporous silicas, thus taking advantage of their high surface areas (ca. $1000 \text{ m}^2 \text{ g}^{-1}$). Two strategies were used for their preparation: (i) grafting of pre-formed micelle templated silicas (MTS) with amine functionalities or with other functionalities, e.g. halide, epoxide, which can be subsequently converted to amines by nucleophilic displacement (see Fig. 2.40) and (ii) direct incorporation by co-condensation of $(\text{EtO})_4\text{Si}$ with an appropriately functionalized silane in a sol-gel synthesis.

For example, Brunel and coworkers [137] anchored primary amine groups to the surface of mesoporous silica by grafting with 3-aminopropyltriethoxysilane. Anchoring of tertiary amine functionality was achieved by grafting with chloro- or iodopropyltriethoxysilane followed by nucleophilic displacement of halide with piperidine. Both materials were active catalysts for the Knoevenagel condensation of benzaldehyde with ethyl cyanoacetate at 80°C in dimethyl sulfoxide. The primary amine was more active, which was explained by invoking a different mechanism: imine formation with the aldehyde group rather than classical base activation of the methylene group in the case of the tertiary amine.

Stronger solid base catalysts can be prepared by grafting guanidine bases to mesoporous silicas. For example, the functionalization of MCM-41 with 1,5,7-triazabicyclo[4,4,0]dec-5-ene (TBD), as shown in Fig. 2.40, afforded a material (MCM-TBD) that was an effective catalyst for Michael additions with ethylcyanoacetate or diethylmalonate (Fig. 2.41) [136].

In a variation on this theme, a bulky guanidine derivative, *N,N,N'*-tricyclohexylguanidine was encapsulated by assembly within the supercages of hydrophobic zeolite Y. The resulting 'ship-in-a-bottle' catalyst was active in the aldol reaction of

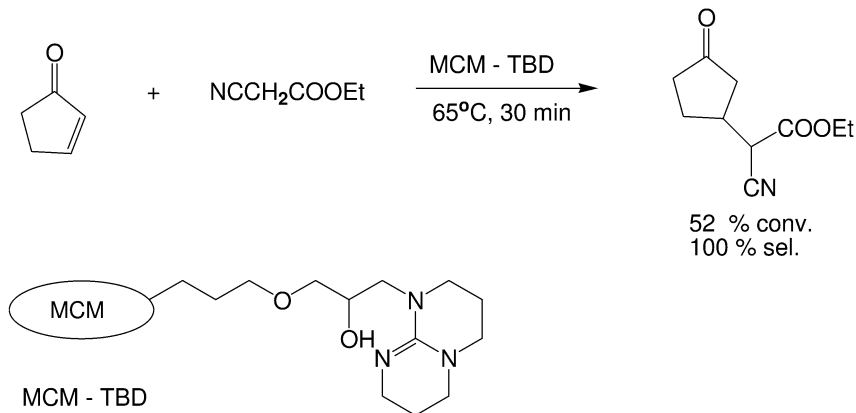


Fig. 2.41 Michael reactions catalyzed by MCM-TBD.

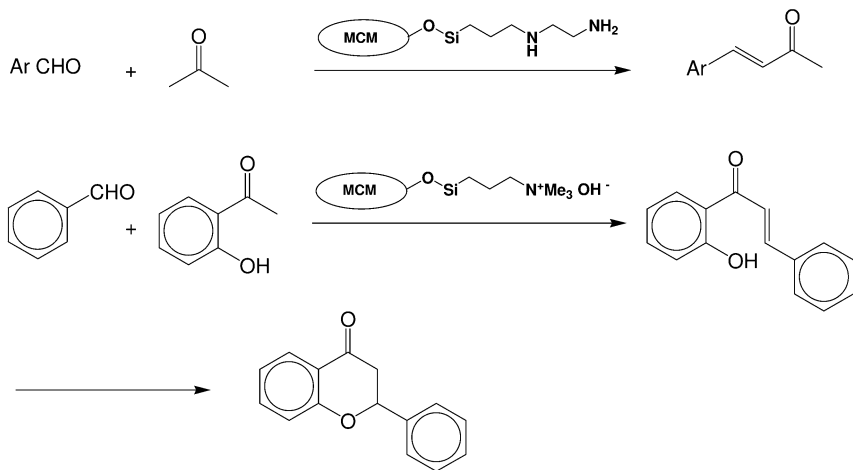


Fig. 2.42 Aldol reactions catalyzed by various solid bases.

acetone with benzaldehyde, giving 4-phenyl-4-hydroxybutan-2-one (Fig. 2.42) [138]. The catalyst was stable and recyclable but activities were relatively low, presumably owing to diffusion restrictions. Grafting of the same guanidine onto MCM-41 afforded a more active catalyst but closer inspection revealed that leaching of the base from the surface occurred. Similarly, diamine functionalized MCM-41 [139] and a tetraalkylammonium hydroxide functionalized MCM-41 [140] were shown to catalyze aldol condensations (Fig. 2.42).

2.4 Other Approaches

In Section 2.1 we discussed the use of solid Brønsted acids as recyclable alternatives to classical homogeneous Brønsted and Lewis acids. In the case of Lewis acids alternative strategies for avoiding the problems associated with their use can be envisaged. The need for greener alternatives for conventional Lewis acids such as AlCl_3 and ZnCl_2 derives from the necessity for decomposing the acid–base adduct formed between the catalyst and the product. This is generally achieved by adding water to the reaction mixture. Unfortunately, this also leads to hydrolysis of the Lewis acid, thus prohibiting its re-use and generating aqueous effluent containing copious amounts of inorganic salts. Since the product is often more basic than the substrate, e.g. in Friedel–Crafts acylations (see earlier), Lewis acid catalyzed processes often require stoichiometric amounts of catalyst.

One approach is to incorporate Lewis acids into, for example, zeolites or mesoporous silicas [141]. For example, incorporation of Sn(IV) into the framework of zeolite beta afforded a heterogeneous water-tolerant Lewis acid [142]. It proved to be an effective catalyst for the intramolecular carbonyl-ene reaction of citronellal to isopulegol [143] (Fig. 2.43) in batch or fixed bed operation. Hydrogenation of the latter affords menthol (Fig. 2.43).

Another approach is to design homogeneous Lewis acids which are water-compatible. For example, triflates of Sc, Y and lanthanides can be prepared in water and are resistant to hydrolysis. Their use as Lewis acid catalysts in aqueous media was pioneered by Kobayashi and coworkers [144–146]. The catalytic activity is dependent on the hydrolysis constant (K_h) and water exchange rate constant (WERC) for substitution of inner sphere water ligands of the metal cation [145]. Active catalysts were found to have $\text{p}K_h$ values in the range 4–10. Cations having a $\text{p}K_h$ of less than 4 are easily hydrolyzed while those with a $\text{p}K_h$ greater than 10 display only weak Lewis acidity.

$\text{Sc}(\text{OTf})_3$ and lanthanide triflates, particularly $\text{Yb}(\text{TOTf})_3$ have been shown to catalyze a variety of reactions in aqueous/organic cosolvent mixtures [145, 146]. For example, they catalyze the nitration of aromatics with 69% aqueous nitric acid, the only by-product being water [147].

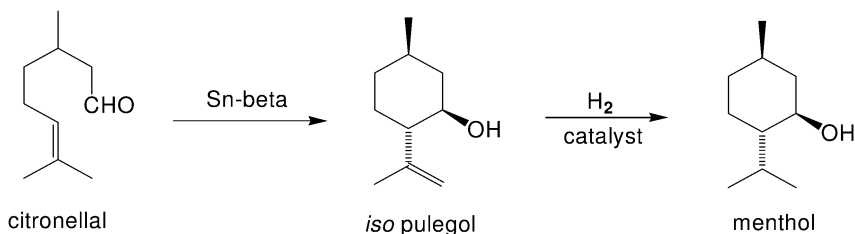


Fig. 2.43 Sn-Beta catalyzed carbonyl-ene reaction.

The lanthanide triflate remains in the aqueous phase and can be re-used after concentration. From a green chemistry viewpoint it would be more attractive to perform the reactions in water as the only solvent. This was achieved by adding the surfactant sodium dodecyl sulfate (SDS; 20 mol%) to the aqueous solution of e.g. $\text{Sc}(\text{OTf})_3$ (10 mol%) [145]. A further extension of this concept resulted in the development of lanthanide salts of dodecyl sulfate, so-called Lewis acid–surfactant combined catalysts (LASC) which combine the Lewis acidity of the cation with the surfactant properties of the anion [148]. These LASCs, e.g. $\text{Sc}(\text{DS})_3$, exhibited much higher activities in water than in organic solvents. They were shown to catalyze a variety of reactions, such as Michael additions and a three component α -aminophosphonate synthesis (see Fig. 2.44) in water [145].

Another variation on this theme is the use of a scandium salt of a hydrophobic polystyrene-supported sulfonic acid (PS- SO_3H) as an effective heterogeneous Lewis acid catalyst in aqueous media [149].

Ishihara and Yamamoto and coworkers [150] reported the use of 1 mol% of $\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$ and $\text{HfOCl}_2 \cdot 8\text{SH}_2\text{O}$ as water-tolerant, reusable homogeneous catalysts for esterification.

Finally, it should be noted that Lewis acids and bases can also be used in other non-conventional media, as described in Chapter 7, e.g. fluorous solvents, supercritical carbon dioxide and ionic liquids by designing the catalyst, e.g. for solubility in a fluorous solvent or an ionic liquid, to facilitate its recovery and reuse. For example, the use of the ionic liquid butylmethylimidazolium hydroxide, $[\text{bmim}][\text{OH}]$, as both a catalyst and reaction medium for Michael additions (Fig. 2.45) has been recently reported [151].

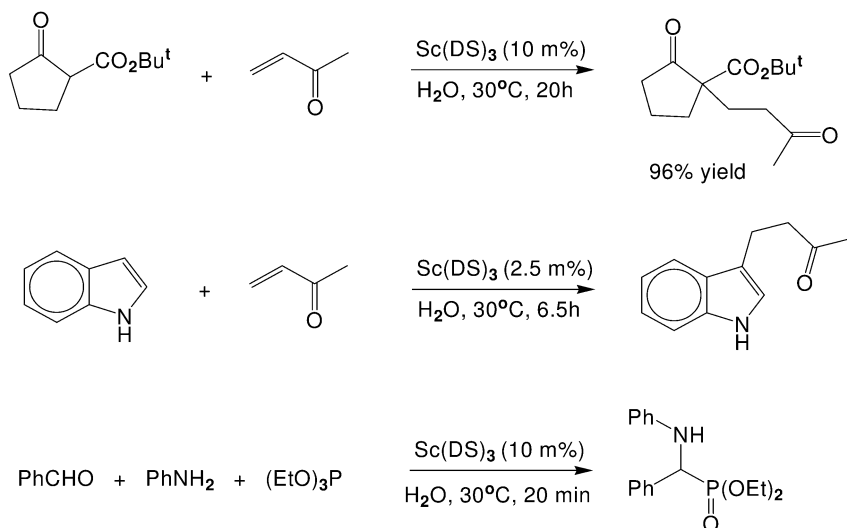


Fig. 2.44 $\text{Sc}(\text{DS})_3$ catalyzed reactions in water.

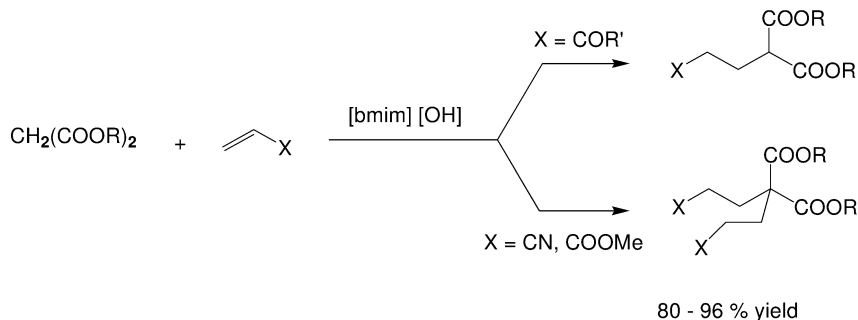


Fig. 2.45 Michael additions catalyzed by [bmim][OH].

It is clear that there are many possibilities for avoiding the use of classical acid and base catalysts in a wide variety of chemical reactions. Their application will result in the development of more sustainable processes with a substantial reduction in the inorganic waste produced by the chemical industry. Particularly noteworthy in this context is the use of chemically modified expanded corn starches, containing pendant SO_3H or NH_2 groups, as solid acid or base catalysts, respectively [152]. In addition to being recyclable these catalysts are biodegradable and derived from renewable raw materials (see Chapter 8).

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3

Catalytic Reductions

3.1

Introduction

Catalytic hydrogenation – using hydrogen gas and heterogeneous catalysts – can be considered as the most important catalytic method in synthetic organic chemistry on both laboratory and production scales. Hydrogen is, without doubt, the cleanest reducing agent and heterogeneous robust catalysts have been routinely employed. Key advantages of this technique are (i) its broad scope, many functional groups can be hydrogenated with high selectivity; (ii) high conversions are usually obtained under relatively mild conditions in the liquid phase; (iii) the large body of experience with this technique makes it possible to predict the catalyst of choice for a particular problem and (iv) the process technology is well established and scale-up is therefore usually straightforward. The field of hydrogenation is also the area where catalysis was first widely applied in the fine chemical industry. Standard hydrogenations of olefins and ketones, and reductive aminations, using heterogeneous catalysts, have been routinely performed for more than two decades [1]. These reactions are usually fast and catalyst separation is easy. Catalysts consist of supported noble metals, Raney nickel, and supported Ni or Cu. However, once enantioselectivity is called for homogeneous catalysis and biocatalysis generally become the methods of choice. The field of homogeneous asymmetric catalysis had a major breakthrough with the discovery of ligands such as BINAP, DIPAMP and DIOP (for structures see later), designed by the pioneers in this field, Noyori, Knowles and Kagan [2–4]. These ligands endow rhodium, ruthenium and iridium with the unique properties which allow us nowadays to perform enantioselective reduction of a large number of compounds using their homogeneous metal complexes. Besides homogeneous and heterogeneous catalysis, the potential of biocatalytic reduction is still growing and has already delivered some interesting applications [5]. Reduction of many secondary carbonyl compounds can be performed using enzymes as catalysts, yielding chiral compounds with high enantioselectivities [6]. Use of new genetic engineering techniques is rapidly expanding the range of substrates to be handled by enzymes. The issue of cofactor-recycling, often denoted as the key problem in the use of biocatalytic reductions, is nowadays mainly a technological issue which can be solved by applying a

substrate or enzyme coupled approach in combination with novel reactor concepts. In this chapter, all three catalytic methods: heterogeneous, homogeneous and biocatalytic reductions, will be separately described and illustrated with industrial examples. Enantioselective hydrogenation applications, which are mainly the domain of homogeneous and enzymatic catalysts, will constitute a main part of this chapter.

3.2

Heterogeneous Reduction Catalysts

3.2.1

General Properties

The classical hydrogenation catalysts for preparative hydrogenation are supported noble metals, Raney nickel and supported Ni and Cu, all of which are able to activate hydrogen under mild conditions [1]. Because only surface atoms are active, the metal is present as very small particles in order to give a high specific surface area. It is generally accepted that the catalytic addition of hydrogen to an $X=Y$ bond does not occur in a concerted manner but stepwise. In other words, the $H-H$ bond has to be cleaved first giving intermediate $M-H$ species, which are then added stepwise to the $X=Y$ bond. This is depicted schematically in Fig. 3.1 for a metallic surface for the hydrogenation of ethylene [7]. The first step is called dissociative adsorption and the newly formed $M-H$ bonds deliver the energetic driving force for the cleavage of the strong $H-H$ bond. The metal surface also forms complexes with the $X=Y$, most probably via a π -bond, thereby activating the second reactant and placing it close to the $M-H$ fragments, allowing the addition to take place. There is consensus that the H is added to the complexed or adsorbed $X=Y$ from the metal side, leading to an overall *cis*-addition [7]. The outcome of a diastereoselective hydrogenation can thus also be rationalized. For substrate coordination to the surface, preferential adsorption of the less hindered face will take place preferentially, due to repulsive interactions. Furthermore if anchoring groups are present in the molecule, such as OH , sulfide or amine, repulsive interactions can be overruled and the opposite stereoisomer will be obtained.

It is important to realize that even today it is not possible to adequately characterize a preparative heterogeneous catalyst on an atomic level. Most research in heterogeneous hydrogenation took place in the 1970s to 1980s, and the results thereof can be found in the pioneering monographs of Rylander [1], Augustine [8], and Smith [9]. Catalysts are still chosen on an empirical basis by trial and error and it is rarely understood why a given catalyst is superior to another one. The factors which influence the reactivity and selectivity are: (i) *Type of metal*: noble metals (Pd, Pt, Rh, Ru) versus base metals (Ni and Cu). Bimetallic catalysts are also applied. (ii) *Type of support*: charcoal, versus aluminas or silicas. (iii) *Type of catalyst*: supported on carrier, fine powders, Ni as Raney nickel

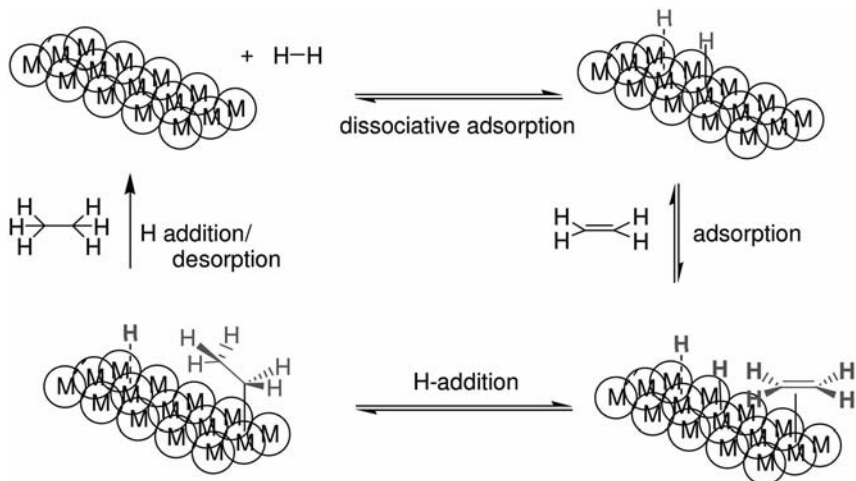


Fig. 3.1 Mechanism of heterogeneous hydrogenation.

and Cu as Cu chromite. (iv) *Metal loading*: In a slurry reactor typically 1–10% loading is employed, while in a fixed-bed reactor, loadings of 0.1–1mol% are used. (v) *Dispersion, crystallite size etc.* (vi) *Modifiers and promoters*: Classical examples are the use of sulfur, phosphorus or nitrogen compounds as partial deactivating agents, e.g. for the selective hydrogenation of halogenated aromatic nitro compounds (see below). (vii) *Solvent*: Commonly employed solvents which have a large impact on the final outcome of the reaction are water, methanol, ethanol, acetic acid, ethyl acetate or methoxyethanol. The preferred catalysts for different conversions are shown in Fig. 3.2. Experimental details for a wide variety of conversions can be found in the monographs [1–3] mentioned earlier. Recent progress is highlighted by Blaser and coworkers [10].

The selective semi-hydrogenation of alkynes is an important reaction in the context of fine chemicals manufacture. The acetylenic group is used for the formation of new carbon–carbon bonds in substitution reactions. Selective hydrogenation to the alkene further enhances its synthetic utility e.g. in the synthesis of insect sex pheromones and vitamins [11–13]. Overall, palladium offers the best combination of activity and selectivity at reasonable cost, and for these reasons has become the basis of the most successful commercial alkyne hydrogenation catalysts to date. Because of their inherently high activity, these catalysts contain typically less than 0.5% of active metal, in order to preserve selectivity at high alkyne conversion. The best known alkyne semi-hydrogenation catalyst is that developed by Lindlar which comprises calcium carbonate-supported palladium, with Pb and quinoline promoters [14]. Selective hydrogenation of 1-bromo-11-hexadecyne has been shown to occur in high yield and without hydrogenolysis of the carbon–bromine bond over Lindlar’s catalyst treated with aromatic amine oxides such as pyridine *N*-oxide [15]. Utilization of lead as

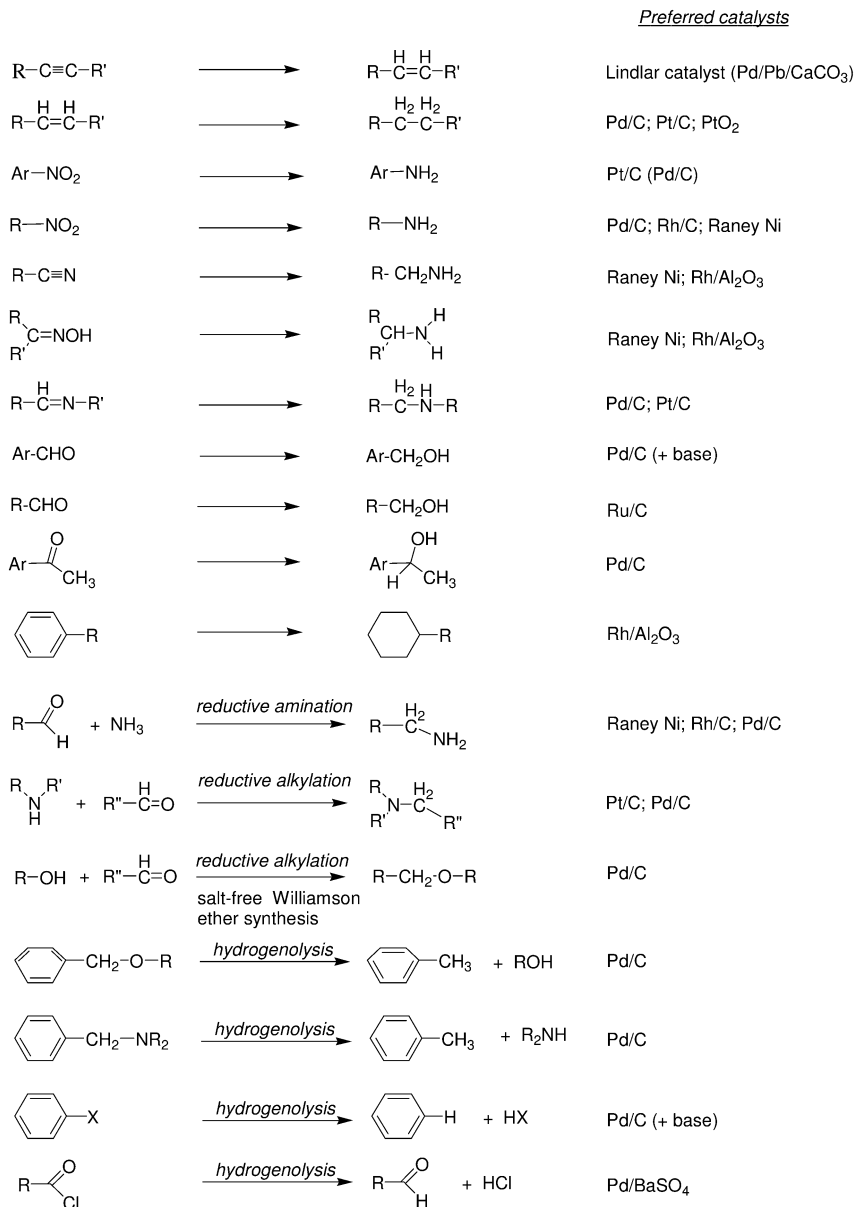


Fig. 3.2 Preferred heterogeneous catalysts for different functional group reductions.

a promoter has been developed further by formulation of true Pd–Pb alloys in the hydrogenation of 11-hexadecynyl acetate, which is an insect pheromone, to the corresponding *cis*-olefin (Fig. 3.3a) [12]. Modification by addition of quinoline is reported to benefit the selective production of *cis*-vitamin D (Fig. 3.3b)

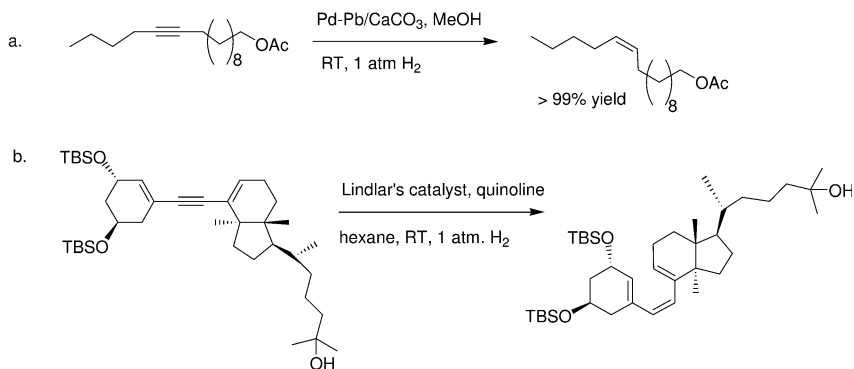


Fig. 3.3 Selective semi-hydrogenation of alkynes to *cis*-olefins.

[16]. More examples can be found in a recent monograph by Bailey and King [17].

The selective hydrogenation of cinnamaldehyde to produce cinnamyl alcohol is an important reaction and it represents an often encountered selectivity problem, namely the selective hydrogenation of aldehydes in the presence of a carbon-carbon double bond. The major application of cinnamyl alcohol is as a base for perfumes, and therefore high selectivities and conversions are vital. Ir and Pt catalysts (Fig. 3.4) seem to give the best results [18,19]. Alternatively a homogeneous catalyst can be applied (see below).

A reaction which deserves extra attention in view of its greenness is the reduction of carboxylic acid derivatives to the corresponding aldehydes in one step. This is quite difficult to achieve with classical hydrogenation catalysts because the product is, in general, more easily hydrogenated than the substrate. On a small scale this conversion can be carried out by the Rosenmund reduction of acid chlorides over a palladium catalyst. However, during high temperature processes using either Ru/Sn catalysts (Rhodia) [20] or ZrO₂ or CrO₃ (Mitsubishi Chemical Corporation) (Fig. 3.5) [21] stable aldehydes can be produced directly from the corresponding acids in good yields. Mitsubishi has successfully commercialized the production of *p*-*tert*-butylbenzaldehyde, *m*-phenoxybenzaldehyde, *p*-methylbenzaldehyde, 10-undecanal, and dodecanal by reduction of the corresponding acids. By use of this technology, ca. 2000 t y⁻¹ of aldehyde have been manufactured since 1988 [22].

Hydrogenation of aromatic nitro compounds with heterogeneous catalysts is often the method of choice for the production of the corresponding anilines. As

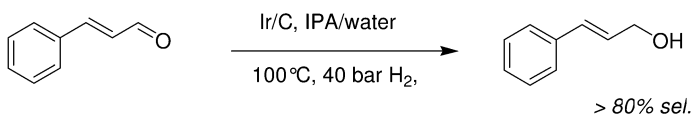


Fig. 3.4 Selective hydrogenation of cinnamal alcohol.

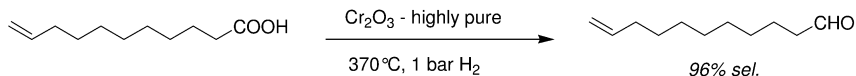


Fig. 3.5 Selective reduction of 10-undecylenic acid to the aldehyde in one step.

a general rule, commercial heterogeneous catalysts are well suited to the reduction of simple nitroarenes. However recent progress has expanded the technology to the technical reduction of functionalized nitroarenes. Until recently, only the Béchamp reduction (stoichiometric Fe) was available for the technical reduction of nitroarenes with additional, easily reducible functional groups (e.g. halide, C=C or C=O). The team of Ciba-Geigy developed two new catalytic systems that can perform the selective reduction of a nitroallyl ester as shown in Fig. 3.6 [23]. In the first process a newly developed Pt–Pb–CaCO₃ catalyst was used. In the second process H₃PO₂ was used as process modifier for a commercial Pt–C catalyst. In the latter system VO(acac)₂ is added to suppress the accumulation of hydroxylamines. Both catalyst systems have a wide scope for related systems. They are able to hydrogenate aromatic nitro compounds containing functional groups such as iodide, C=C, C≡N and even C≡C with high yield and selectivity.

The catalytic hydrogenation of nitriles is one of the basic methods to obtain primary amines. Diamines, especially, are of high industrial importance. Many different catalytic systems have been studied, and two recent reviews give an excellent overview of this rather scattered area [24, 25]. Reactions are often carried out at temperatures up to 100 °C and pressures up to 100 bar with Raney nickel (often in combination with Cr, Fe or Mo) or Raney cobalt as industrially preferred catalysts. Pd and Pt are also suitable catalysts. Besides the usually desired primary amines, condensation of reaction intermediates leads to secondary and tertiary amines. Addition of ammonia or less toxic bases such as NaOH and LiOH [26, 27], can be used to improve the selectivity for primary amines. For fine chemicals applications, functional group tolerance is an important issue. The selective hydrogenation of C≡N groups in the presence of C=C bonds, a particularly difficult task, has recently been studied in the hydrogenation of cinnamitrile, see Fig. 3.7. It is possible to selectively hydrogenate cinnamitrile to 3-phenylallylamine with selectivities up to 80% in the presence of RaNi or RaCo catalysts in methanolic ammonia solution [28].

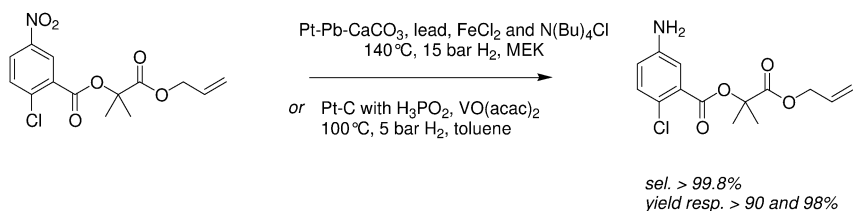


Fig. 3.6 Chemoselective hydrogenation of a nitroallylester.

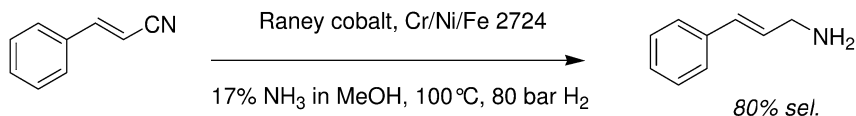


Fig. 3.7 Selective cinnamitrile hydrogenation to 3-phenylallylamine.

The field of arene hydrogenation is almost 100 years old. The initial work of Sabatier on the interaction of finely divided nickel with ethylene and hydrogen gas led to the development of the first active catalyst for the hydrogenation of benzene [29]. In the last two decades, arene hydrogenation has also become important for the area of fine chemistry. Traditionally it is accomplished by use of a Group VIII metal, with the rate of hydrogenation depending on the metal used, i.e. $\text{Rh} > \text{Ru} > \text{Pt} > \text{Ni} > \text{Pd} > \text{Co}$ [1]. Hydrogenation of multiply substituted aromatic rings can lead to the formation of a variety of stereoisomers. Hydrogenation of functionalized arenes usually leads predominantly to the *cis*-substituted product. The nature of carrier, type of metal, solvent, temperature and pressure determine the exact amount of stereochemical induction. In Fig. 3.8, the use of Ru/C enables hydrogenation of tri-substituted benzoic acid into the corresponding *cis*-product with high stereoselectivity [30].

The partial hydrogenation of an arene to its cyclohexene derivative is difficult to achieve, because complete hydrogenation to cyclohexane tends to occur. Often the use of a Ru/C catalyst can solve this problem because Ru is not very effective at hydrogenating olefinic double bonds. Alternatively Pt/C and Rh/C can be used [31]. The Asahi Corporation has developed a benzene-to-cyclohexene process involving a liquid–liquid two-phase system (benzene–water) with a solid ruthenium catalyst dispersed in the aqueous phase. The low solubility of cyclohexene in water promotes rapid transfer towards the organic phase. An 80000 tons/year plant using this process is in operation [32]. Another way to scavenge the intermediate cyclohexene is to support the metal hydrogenation catalysts on an acidic carrier (e.g. silica–alumina). On such a bifunctional catalyst the cyclohexene enters the catalytic alkylation of benzene to yield cyclohexylbenzene [33]. The latter can be converted with high selectivity, by oxidation and rearrangement reactions, into phenol and cyclohexanone [34]. The complete reaction cycle is shown in Fig. 3.9.

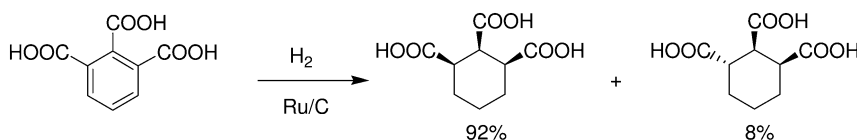


Fig. 3.8 Selective hydrogenation of a tri-substituted aromatic ring.

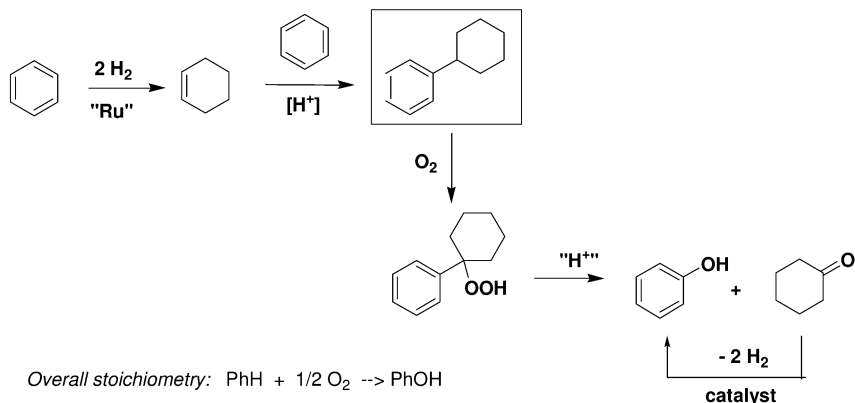


Fig. 3.9 Partial hydrogenation of benzene and production of phenol.

Another example of catalytic hydrogenation, which demonstrates the flexibility of this method, is the hydrogenation of nitrogen-containing aromatic ring systems. For example isoquinoline ring saturation can be directed towards either or both of the two rings (Fig. 3.10). When a platinum catalyst was used in acetic acid, the hydrogenation of isoquinoline results in saturation of the nitrogen-containing aromatic ring. Changing the solvent to methanolic hydrogen chloride results in hydrogenation of the other aromatic ring, and use of ethanol in combination with sulfuric acid results in saturation of both aromatic rings. Under the latter reaction conditions, especially when using Ru catalysts, the *cis*-product is formed preferentially [32].

Additional reactions which need to be highlighted are the reductive alkylation of alcohols and amines with aldehydes leading to the green synthesis of ethers and amines. These reactions are generally catalyzed by palladium [35]. This reaction can replace the classical Williamson's synthesis of ethers which requires an alcohol and an alkyl halide together with a base, and always results in the concomitant production of salt. The choice of Pd/C as catalyst is due to the low efficiency of this metal for the competitive carbonyl reduction. Analysis of the

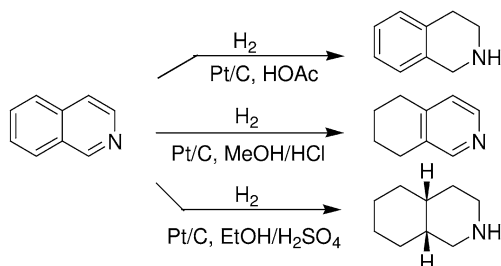


Fig. 3.10 Influence of solvents on the Pt/C catalyzed selective hydrogenation of isoquinoline.

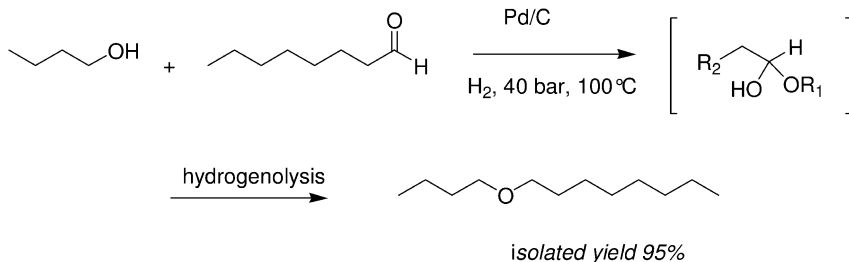


Fig. 3.11 Catalytic alternative to the Williamson's synthesis of ethers.

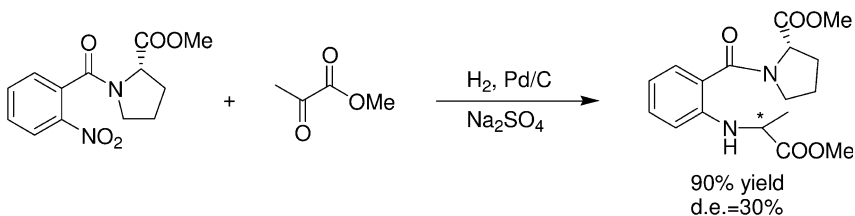


Fig. 3.12 Reductive amination of nitro derivatives leading to non-natural amino acid derivatives.

supposed reaction mechanism indicates that the first step of the reaction is the formation of the hemiketal which is favored by the use of one of the reactants (the alcohol or the aldehyde) as solvent (Fig. 3.11). After hydrogenolysis under H_2 pressure, ethers are produced in high yields after simple filtration of the catalyst and evaporation of the solvent.

In reductive amination, the alkylation is performed under hydrogen in the presence of a catalyst and an aldehyde or ketone as the alkylating agent. The method was developed for anilines and extended to amide *N*-alkylation [36]. A notable example is the use of nitro derivatives as aniline precursors in a one-pot reduction of the nitro group and subsequent reductive alkylation of the resulting aniline (Fig. 3.12).

N- and *O*-benzyl groups are among the most useful protective groups in synthetic organic chemistry and the method of choice for their removal is catalytic hydrogenolysis [37]. Recently the most important reaction conditions were identified [38]: Usually 5–20% Pd/C; the best solvents are alcoholic solvents or acetic acid; acids promote debenzylation, whereas amines can both promote and hinder hydrogenolysis. Chemoselectivity can mainly be influenced by modifying the classical Pd/C catalysts.

3.2.2

Transfer Hydrogenation Using Heterogeneous Catalysts

On a small scale it can be advantageous to perform a transfer hydrogenation, in which an alcohol, such as isopropanol, serves as hydrogen donor. The advantage of this technique is that no pressure equipment is needed to handle hydrogen, and that the reactions can be performed under mild conditions, without the risk of reducing other functional groups. The so-called Meerwein-Ponndorf-Verley (MPV) reduction of aldehydes and ketones, is a hydrogen-transfer reaction using easily oxidizable alcohols as reducing agents. Industrial applications of the MPV-reactions are found in the fragrance and pharmaceutical industries. MPV reactions are usually performed by metal alkoxides such as $\text{Al}(\text{O}-i\text{Pr})_3$. The activity of these catalysts is related to their Lewis-acidic character in combination with ligand exchangeability. Naturally, a heterogeneous catalyst would offer the advantage of easy separation from the liquid reaction mixture. Many examples of heterogeneously catalyzed MPV reactions have now been reported [39]. The catalysts comprise (modified) metal oxides which have either Lewis acid or base properties. The mechanism involves the formation of an alkoxide species in the first step, and in the second step a cyclic six-membered transition state (see Fig. 3.13). Examples are the use of alumina, ZrO_2 and immobilized zirconium complexes, magnesium oxides and phosphates and Mg–Al hydrotalcites.

Especially worth mentioning in a green context is the use of mesoporous materials and zeolites, as stable and recyclable catalysts for MPV reductions. High activity was obtained by using zeolite-beta catalysts. Beta zeolites have a large pore three-dimensional structure with pores of size $7.6 \times 6.4 \text{ \AA}^2$ which makes them suitable for a large range of substrates. Al, Ti- and Sn-beta zeolite have all been used as catalysts for the selective reduction of cyclohexanones [40–42]. The

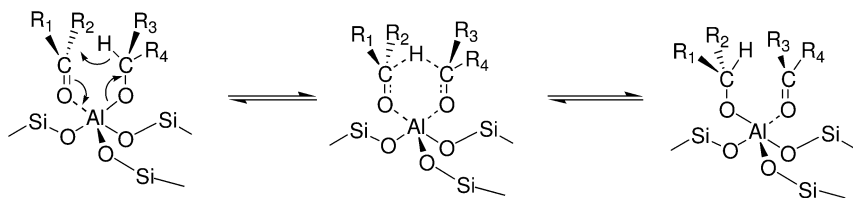


Fig. 3.13 Mechanism of MPV reduction catalyzed by Al-beta zeolite.

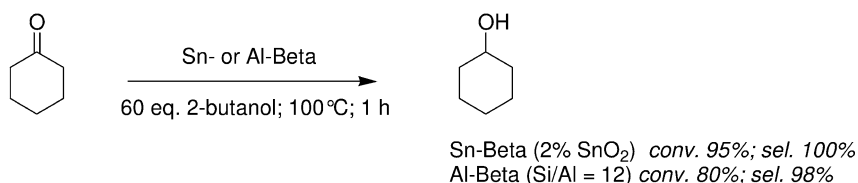


Fig. 3.14 MPV reductions catalyzed by Sn- and Al-zeolite beta.

reaction is shown in Fig. 3.14. In terms of both activity and selectivity Sn-beta (containing 2% SnO₂) seems to be superior. This can be ascribed to the interaction of the carbonyl group with the Sn-center, which is stronger than with Ti and more selective than with Al-centers [42]. Additionally, shape-selectivity effects can be observed for all three zeolites. When using 4-*tert*-butylcyclohexanone as the substrate, the selectivity for the *cis*-isomer easily reaches 99%. This is clear proof that the reaction occurs within the pores of the zeolite and that the active tin centers are not at the external surface of the zeolite or in solution.

3.2.3

Chiral Heterogeneous Reduction Catalysts

Despite the fact that enantioselective hydrogenation is largely the domain of homogeneous catalysts, some classical examples of heterogeneous reduction catalysts need to be mentioned. In this case the metal surface is modified by a (natural) chiral additive. The first successful attempts were published about 60 years ago and despite a large effort in this field, only three examples have shown success: the Raney nickel system for β -functionalized ketones, Pt catalysts modified with cinchona alkaloids for α -functionalized ketones, and Pd catalysts modified with cinchona alkaloids for selected activated C=C bonds [43, 44]. The Raney-Ni-tartaric acid-NaBr catalyst system, known as the Izumi system [45], affords good to high enantioselectivity in the hydrogenation of β -functionalized ketones and reasonable results have also been obtained for unfunctionalized ketones. Besides Raney nickel, Ni powder and supported nickel are almost as good precursors. In the optimized preparation procedure, RaNi undergoes ultrasonication in water followed by modification with tartaric acid and NaBr at 100 °C and pH 3.2. The modification procedure is highly corrosive and produces large amounts of nickel- and bromide-containing waste. This, together with its low activity (typical reaction time is 48 h), hampers its industrial application. Examples are given in Fig. 3.15 [43].

For the hydrogenation of α -functionalized ketones, the Pt on alumina system, modified with cinchonidine or its simple derivative 10,11-dihydro-*O*-methylcinchonidine, is the best catalyst [43, 44, 46]. This so-called Orito system [47] is

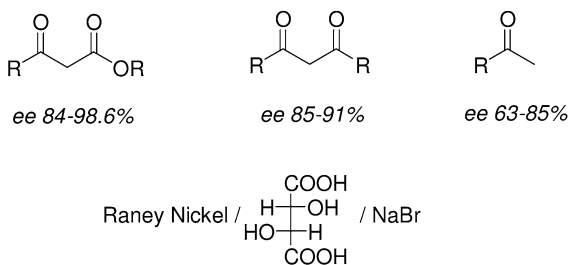


Fig. 3.15 Best results for the enantioselective hydrogenation of β -functionalized ketones and non-functionalized ketones using the Izumi system.

most well known for the hydrogenation of α -ketoesters. Acetic acid or toluene as solvent, close to ambient temperature and medium to high pressure (10–70 bar) are sufficient to ensure high enantioselectivities of 95 to 97.5% (see Fig. 3.16). The highest *ee* has been obtained after reductive heat treatment of Pt/Al₂O₃ and subsequent sonochemical pretreatment at room temperature [48]. In recent years the substrate range of cinchona-modified Pt has been extended to the hydrogenation of selected activated ketones, including ketopantolactone, α -keto acids, linear and cyclic α -keto amides, α -keto acetals and trifluoroacetophenone [43, 44]. Examples are shown in Fig. 3.16.

Up to 72% *ee* has been achieved in the hydrogenation of a diphenyl-substituted reactant, (*trans*)- α -phenylcinnamic acid, with a Pd/TiO₂ catalyst and cinchonidine [49]. For aliphatic α,β -unsaturated acids the enantioselectivities that can be attained are much lower. Therefore, for these type of substrates, homogeneous metal-catalysts are preferred.

Another approach towards asymmetric heterogeneous catalysts is the immobilization of chiral homogeneous complexes via different methods. In this way the advantages of homogeneous catalysts (high activity and selectivity) and heterogeneous catalysts (easy recovery) can be combined. For a complete overview of this active research field the reader is referred to several reviews on this topic [50, 51]. The practical applicability of these catalysts is hampered by the fact that severe demands of recyclability and stability need to be obeyed. In certain cases promising results have been obtained as outlined here.

1. The use of solid and soluble catalysts with covalently attached ligands:

The covalent anchoring of ligands to the surface or to a polymer is a conventional approach which often requires extensive modification of the already expensive ligands. The advantage is that most catalysts can be heterogenized by this approach and various supports can be used. An illustrative example is the use of the BINAP ligand that has been functionalized using several different

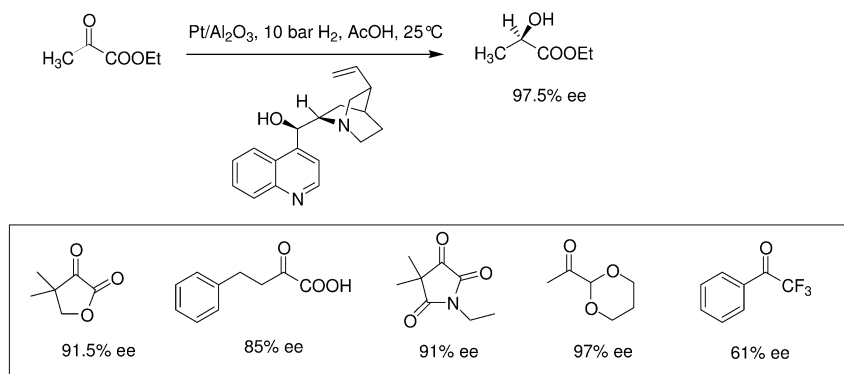
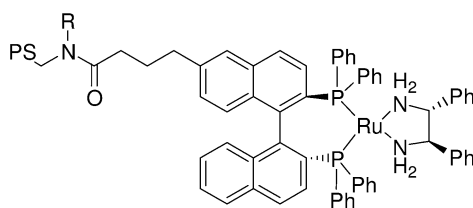


Fig. 3.16 The Pt/cinchona alkaloid system for the enantioselective hydrogenation of α -functionalized ketones.

methods, followed by attachment to supports such as polystyrene (see Fig. 3.17) [52] or polyethyleneglycol [53]. Alternatively it was rendered insoluble by oligomerization [54] or co-polymerized with a chiral monomer [55]. The resulting catalysts have catalytic performances that are comparable to their soluble analogs. The latter soluble catalyst (see Fig. 3.17) achieved even better activities than the parent Ru-BINAP, which was attributed to a cooperative effect of the polymeric backbone. Alternatively, the ligand can be covalently attached to a “smart” polymer which is soluble at the reaction temperature and which precipitates by cooling or heating the reaction mixture (see Chapter 7). In this way the reaction can be conducted homogeneously under optimum mass transport conditions and phase separation can be induced by changing the temperature [56].

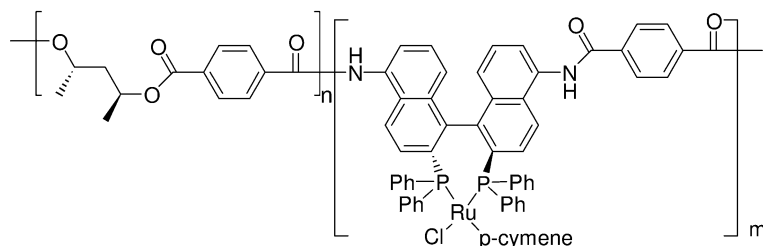
2. Catalysts immobilized on support via ionic interaction:

This is an attractive method since it does not require the functionalization of the ligand. Augustine et al. [57] developed heteropolyacids (HPA), notably phosphotungstates, as a “magic glue” to attach cationic Rh and Ru complexes to various surfaces. The interaction of the heteropolyacid is thought to occur directly



solid catalyst

acetophenone: ee 98%; TOF 390 h⁻¹



soluble polymeric catalyst

cinnamic acid: ee 96%; TOF 50 h⁻¹

Fig. 3.17 Heterogenization of Ru-BINAP catalysts by covalent modification according to Refs. [52, 55].

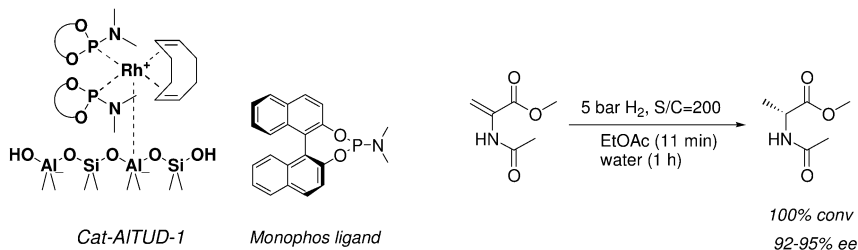


Fig. 3.18 Immobilization through ionic interaction: Rh-Monophos on mesoporous Al-TUD1.

with the metal ion. The most promising catalyst seems to be Rh-DIPAMP (for structure of ligand see Fig. 3.23 below) attached to HPA-clay, due to the high stability of the DIPAMP ligand. This catalyst hydrogenated methyl acetamidoacrylic acid (MAA) with 97% *ee* (TON 270, TOF up to 400 h⁻¹). Recently a mesoporous Al-containing material was used to attach various cationic chiral rhodium complexes to its anionic surface. In this way a stable material was obtained, which showed excellent recyclability over five cycles and which could even be applied in water [58]. Best results were obtained by using Rh-monophos (see Fig. 3.18).

3. Catalysts entrapped or occluded in polymer matrices:

While the entrapment in rigid matrices such as zeolites usually leads to a significant rate decrease, the occlusion in polyvinylalcohol (PVA) or polydimethylsilane (PDMS) looks more promising but is still far from being practically useful. Leaching of the metal complex is often observed in solvents which swell the organic matrix. Rh-DUPHOS (see Fig. 3.23, below) was occluded in PVA or PDMS and was applied for the hydrogenation of methyl acetamidoacrylic acid. Activities and selectivities in this case (TON 140, TOF ca. 15 h⁻¹, *ee* 96%) [59], were significantly lower than for the homogeneous complex (*ee* 99%, TOF 480 h⁻¹).

3.3

Homogeneous Reduction Catalysts

3.3.1

Wilkinson Catalyst

In 1965 Wilkinson invented the rhodium-tris(triphenylphosphine) catalyst as a hydrogenation catalyst [60]. It still forms the basis for many of the chiral hydrogenations performed today. The most effective homogeneous hydrogenation catalysts are complexes consisting of a central metal ion, one or more (chiral) ligands and anions which are able to activate molecular hydrogen and to add the two H atoms to an acceptor substrate. Experience has shown that low-valent Ru,

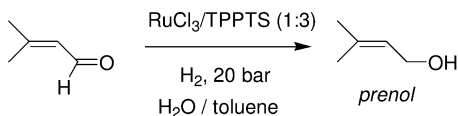


Fig. 3.19 Chemoselective hydrogenation of 3-methyl-2-buten-1-al.

Rh and Ir complexes stabilized by tertiary (chiral) phosphorus ligands are the most active and the most versatile catalysts. Although standard hydrogenations of olefins, ketones and reductive aminations are best performed using heterogeneous catalysts (see above), homogeneous catalysis becomes the method of choice once selectivity is called for. An example is the chemoselective hydrogenation of α, β -unsaturated aldehydes which is a severe test for the selectivity of catalysts.

The use of a tris(triphenyl) ruthenium catalyst resulted in a high selectivity to the desired unsaturated alcohol – prenol – in the hydrogenation of 3-methyl-2-buten-1-al (Fig. 3.19) [61]. Thus the double C=C bond stays intact while the aldehyde group is hydrogenated. The latter product is an intermediate for the production of citral. In this case RuCl_3 was used in combination with water-soluble tris-sulfonated triphenylphosphine (TPPTS) ligands, and in this way the whole reaction could be carried out in a two-phase aqueous/organic system (see Chapter 7). This allowed easy recycling of the catalyst by phase separation [61]. The catalytic cycle for the Wilkinson catalyst according to Halpern is depicted in Fig. 3.20 [62].

The catalytic cycle starts with the dissociation of one ligand P which is replaced e.g. by a solvent molecule. An oxidative addition reaction of dihydrogen

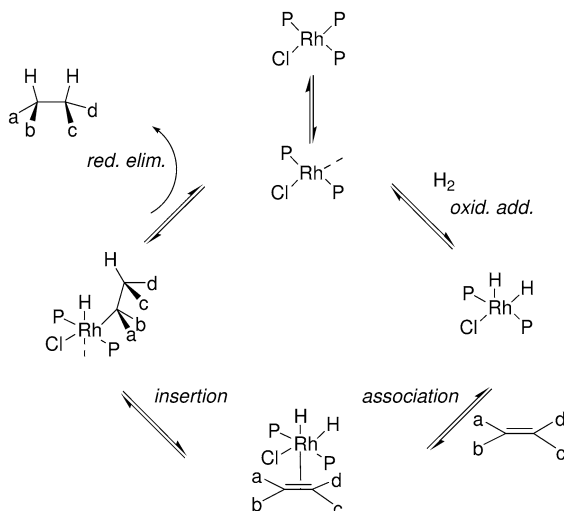


Fig. 3.20 Catalytic cycle of Wilkinson catalyst.

then takes place. This occurs in a *cis* fashion and can be promoted by the substitution of more electron-rich phosphines on the rhodium complex. The next step is the migration of hydride forming the alkyl group. Reductive elimination of alkane completes the cycle. Obviously the rate of this step can be increased by using electron-withdrawing ligands. The function of the ligand, besides influencing the electronic properties of the metal, is to determine the geometry around the metal core. This forms the basis for the enantioselective properties of these catalysts (see below).

3.3.2

Chiral Homogeneous Hydrogenation Catalysts and Reduction of the C=C Double Bond

The foundation for the development of catalysts for asymmetric hydrogenation was the concept of replacing the triphenylphosphane ligand of the Wilkinson catalyst with a chiral ligand. This was demonstrated in the work of the early pioneers Horner [63] and Knowles [64]. With these new catalysts, it turned out to be possible to hydrogenate prochiral olefins. Important breakthroughs were provided by the respective contributions of Kagan and Dang [65], and the Monsanto group headed by Knowles [66]. Chelating chiral phosphorus atoms played a central role in this selectivity, and this culminated in the development of the PAMP and later its corresponding dimer the bidentate DIPAMP ligand [67]. The DIPAMP ligand led to high enantioselectivities in the rhodium catalyzed hydrogenation of protected dehydroaminoacids. On an industrial scale this catalyst is used for the multi-ton scale production of the anti-Parkinson drug L-DOPA [68] (Fig. 3.21).

It must be noted that the enantioselectivity reached by the catalyst does not have to be absolute for industrial production. In this case 100% enantioselectivity of the product was obtained by crystallization. In the past, Selke in the former GDR independently developed a sugar based bis-phosphinite as a ligand which formed the basis for the L-DOPA process by the company VEB-Isis [69,

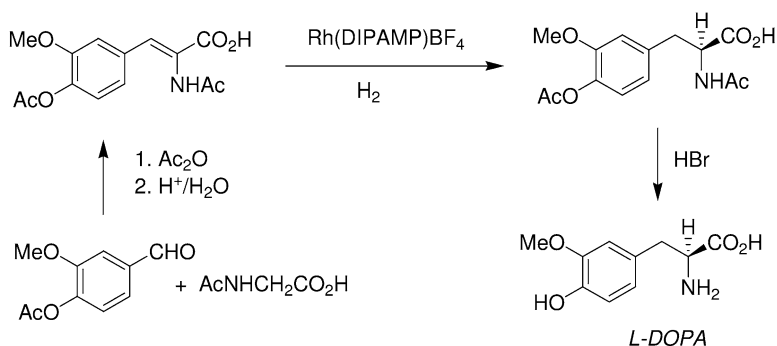


Fig. 3.21 Monsanto's L-DOPA process.

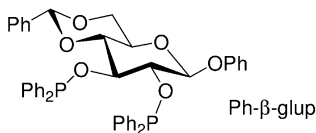


Fig. 3.22 “Selke’s” ligand for the production of L-DOPA.

70], see Fig. 3.22. The process was introduced in 1985 and it ended in 1990, one year after the collapse of the socialist system.

A breakthrough in ligand design was achieved by the work of Kagan, who demonstrated that phosphorus ligands with chirality solely in the backbone, which are much easier to synthesize, led to even better enantioselectivities [4]. This was the beginning in the 1990s of a still-ongoing period in which many new bisphosphines were invented and tested in a variety of enantioselective hydrogenations [71]. Selected examples of chiral bisphosphine ligands have been collected in Fig. 3.23.

Ligands based on ferrocenes have been developed extensively by Hayashi, Togni and the Ciba-Geigy catalysis group (now operating as part of Solvias AG) [72]. An example is found in Lonza’s new biotin process (Fig. 3.24) in which Rh catalyzed hydrogenation of the olefinic double bond of the substrate takes place with 99% *de* [73, 74]. Another example of the use of this class of ferrocene-derived ligands is the use of Josiphos ligand with Ru for the production of (+) *cis*-methyl dihydrojasmonate (Fig. 3.25) [75].

Especially worth mentioning is the use of bis-phospholane DUPHOS as a ligand [76]. A wide variety of substrates, notably enamides, vinylacetic acid derivatives and enol acetates, can be reduced with high enantioselectivities. A recent application is the rhodium catalyzed enantioselective hydrogenation of the α,β -unsaturated carboxylic ester in Fig. 3.26, which is an intermediate for Pfizer’s Candoxatril, a new drug for the treatment of hypertension and congestive heart failure [77]. Other examples are the diastereoselective hydrogenation leading to Pharmacia & Upjohn’s Tipranavir [78] (Fig. 3.27), an HIV protease inhibitor, and the manufacture of α -amino acid derivatives [79]. Both processes were developed by Chirotech (now part of Dow). For the production of α -amino acids, the example of *N*-Boc-(*S*)-3-fluorophenylalanine is given in Fig. 3.28. However, many derivatives have been produced using the same methodology. It is noteworthy that the use of Rh-MeDUPHOS catalysts is accompanied by using a biocatalytic deprotection of the resulting amide using acylase enzymes (see Fig. 3.28).

One of the drawbacks of the use of bisphosphines is the elaborate syntheses necessary for their preparation. Many efforts have been directed towards the development of bis-phosphonites and bis-phosphites. However, surprisingly monodentate phosphinates, phosphates and phosphoramidates recently emerged as effective alternatives for bidentate phosphines (Fig. 3.29). This constitutes an important breakthrough in this area as these can be synthesized in one or two steps, and the cost of these ligands is an order of magnitude lower. Monophos can be made in a single step from BINOL and HMPT.

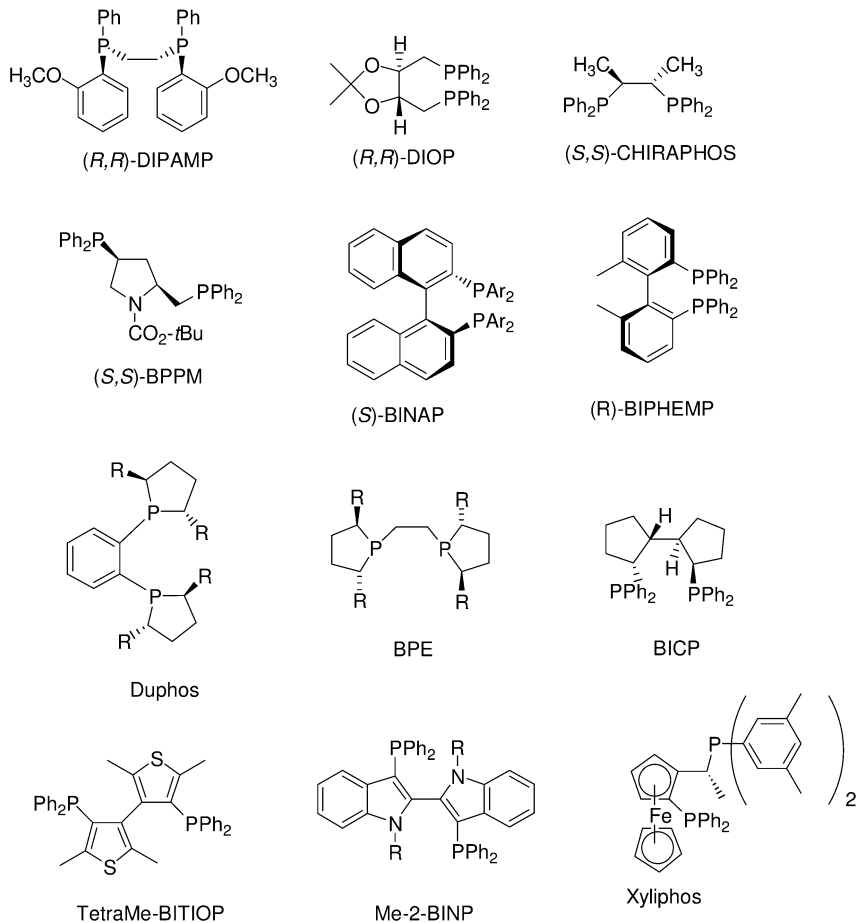


Fig. 3.23 Selected examples of chiral ligands used in homogeneous hydrogenation catalysts.

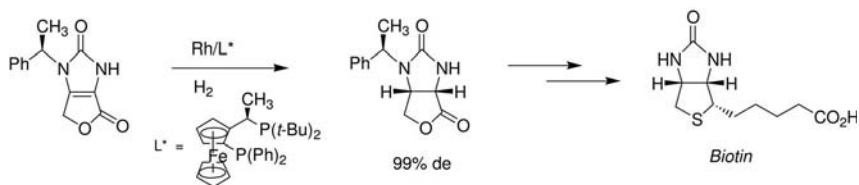


Fig. 3.24 Lonza's biotin process using Rh-Xyliphos-type ligands.

All of the above examples involve an extra coordinating group such as enamide, acid, or ester in the substrate. This is necessary for optimum coordination to the metal. Asymmetric hydrogenation of olefins without functional groups is an emerging area [80].

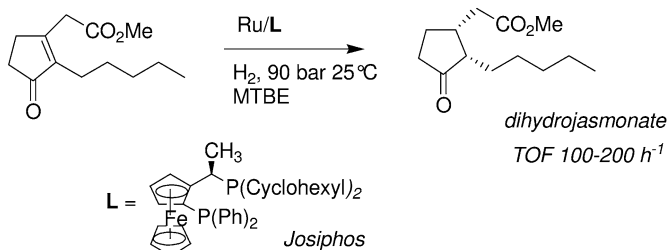


Fig. 3.25 Production of (+) *cis*-methyl dihydrojasmonate using Ru-Josiphos catalyzed hydrogenation.

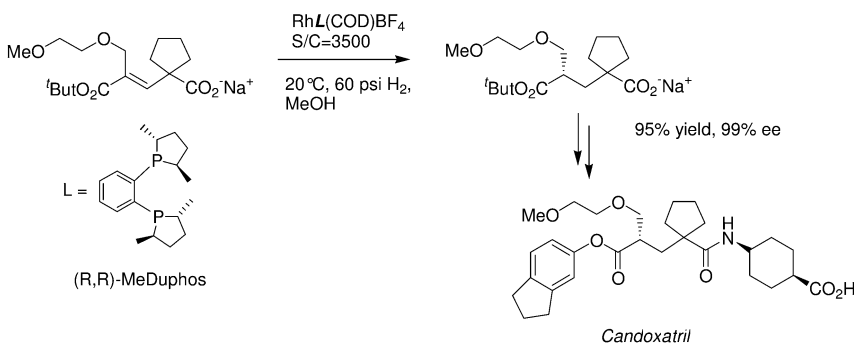


Fig. 3.26 Rh-MeDUPHOS catalyzed hydrogenation in the production of Candoxatril.

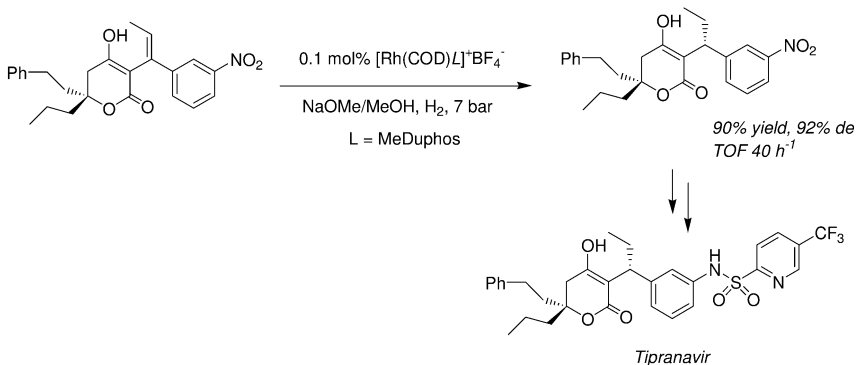


Fig. 3.27 Rh-MeDUPHOS for production of Tipranavir.

According to the mechanism of the enantioselective reduction, a concept has been evolved, termed the “quadrant rule” [81, 82]. This model addresses how the chiral ligand influences the preferential addition of hydrogen either to the *re*- or *si*-face of a C=X bond. As visualized in Fig. 3.30, upon coordination of the ligands to the metal atom, the substituents are oriented in such a way that

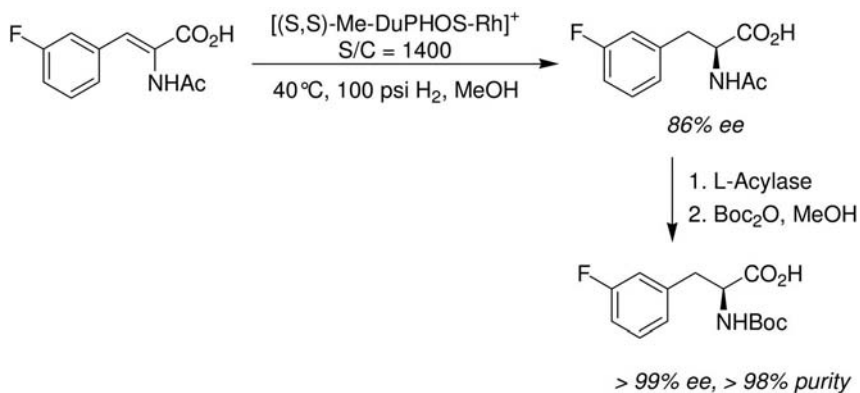


Fig. 3.28 Production of *N*-Boc-(*S*)-3-fluorophenylalanine using Chirotech's Rh-MeDUPHOS technology.

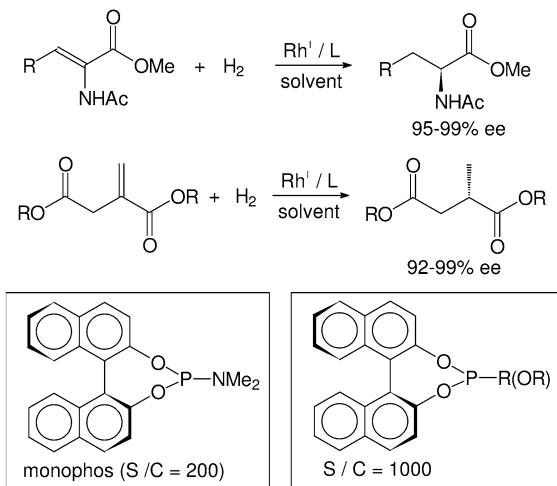


Fig. 3.29 Use of monodentate ligands for the reduction of prochiral olefins.

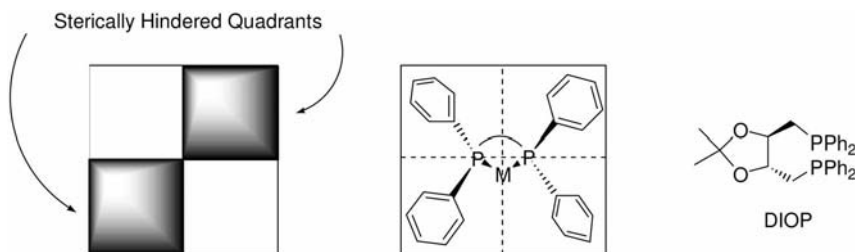


Fig. 3.30 The quadrant model used to predict enantioselectivity in homogeneous hydrogenation.

a chiral array is formed where two diagonal quadrants are blocked by bulky substituents. The situation is visualized for DIOP, a diphosphine with two PAR_2 moieties attached to a flexible chiral backbone. When the substrate coordinates to the metal atom, it will orient in such a way that steric repulsion is minimal. In many cases, this simple model is able to predict the sense of induction. However it will not be able to predict more complex situations [83].

3.3.3

Chiral Homogeneous Catalysts and Ketone Hydrogenation

Enantiopure alcohols can be produced using chiral hydrogenation catalysts for the reduction of ketones. A major breakthrough in this area was achieved in the mid-1980s by Takaya and Noyori, following the initial work of Ikariya's group [84], on the development of the BINAP ligand for Ru-catalyzed hydrogenations [85]. The ruthenium-BINAP ligand is famous for its broad reaction scope: many different classes of ketones can be hydrogenated with very high enantioselectivities. BINAP is a chiral atropisomeric ligand, and its demanding synthesis has been optimized [86]. The Japanese company Takasago has commercialized various Ru-BINAP processes [87]. Drawbacks of the Ru-BINAP procedure are the relatively high pressures and temperatures in combination with long reaction times. This can be circumvented by adding small amounts of strong acids [88] or turning to Rh-DUPHOS type complexes. Furthermore, unlike rhodium complexes, most ruthenium biphosphines have to be preformed for catalysis.

An example of the hydrogenation of a β -ketoester is the dynamic kinetic resolution of racemic 2-substituted acetoacetates [89]. In this process one of the two enantiomeric acetoacetates is hydrogenated with very high diastereoselective preference and in high enantioselectivity. At the same time the undesired acetoacetate undergoes a continuous racemization. This has found application in the hydrogenation of the intermediate for the carbapenem antibiotic intermediate Imipenem on a scale of 120 ton/year [90]. The reaction is shown in Fig. 3.31. Ru-BINAP is also suitable for the enantioselective hydrogenation of α -substituted ketones. In Fig. 3.32, the reduction of acetol leading to the (*R*)-1,2-propane-diol is denoted. This diol is an intermediate for the antibiotic Levofloxacin [87, 90].

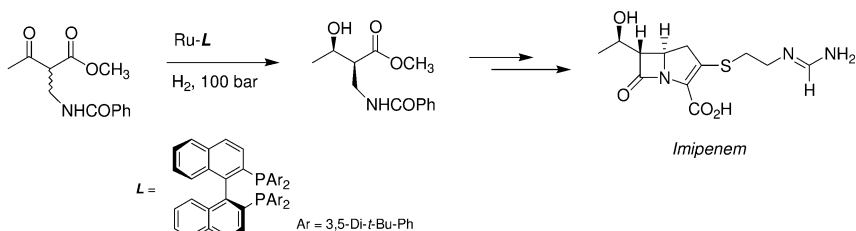


Fig. 3.31 Hydrogenation of a β -ketoester for the production of Imipenem.

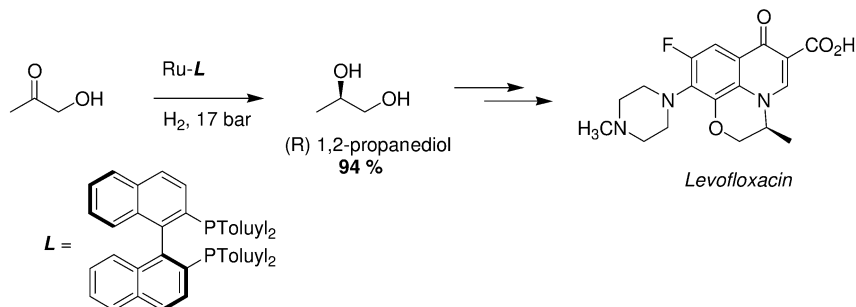


Fig. 3.32 Enantioselective hydrogenation of acetol, intermediate for Levofloxacin.

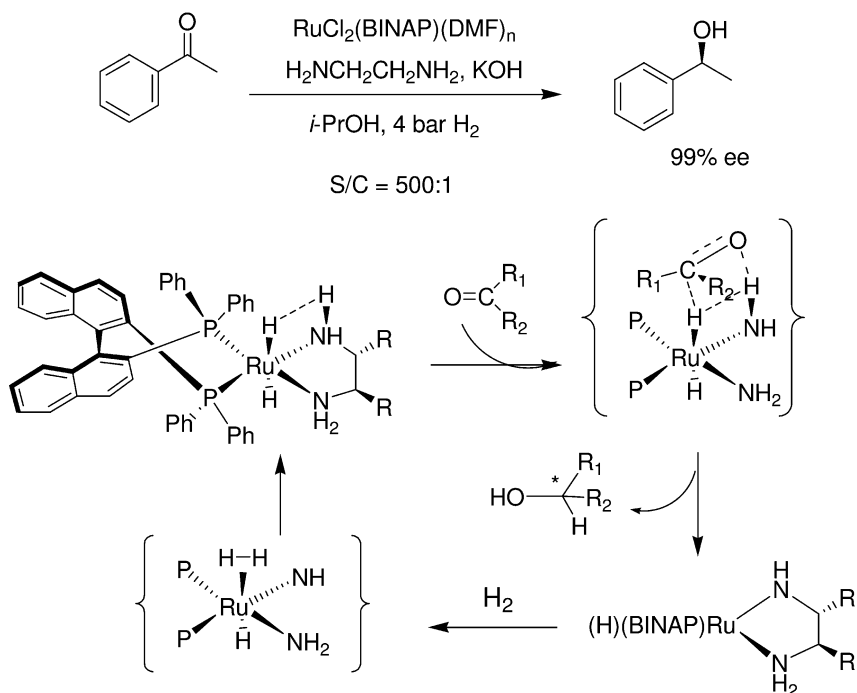


Fig. 3.33 Bifunctional Ru-BINAP(diamine) complexes for enantioselective hydrogenation of simple ketones.

Another breakthrough was made by Noyori for the enantioselective hydrogenation of aromatic ketones by introducing a new class of Ru-BINAP (diamine) complexes [91]. In this case hydrogen transfer is facilitated by ligand assistance. The company Takasago used this catalyst for the production of (*R*)-1-phenylethanol in 99% *ee* using only 4 bar of hydrogen [86] (see Fig. 3.33). (*R*)-1-phenylethanol, as its acetate ester, is sold as a fragrance and has a floral, fresh, green note.

There is consensus that the transfer of the two H atoms occurs in a concerted manner as depicted in Fig. 3.33 [91–94]. This hypothesis explains the need for an N–H moiety in the ligand.

3.3.4

Imine Hydrogenation

The asymmetric hydrogenation of imines is an important application because it gives access to enantiopure amines. For a long period the development of asymmetric imine hydrogenation lagged behind the impressive progress made in asymmetric olefin and ketone hydrogenation [95, 96]. It was difficult to achieve good results both in terms of rate and selectivity. The best results were obtained with rhodium and bisphosphines. However rhodium-based catalysts required 70 bar of hydrogen, which hampered their industrial application. The largest asymmetric catalytic process nowadays, however, involves imine hydrogenation as the key step (see Fig. 3.34). Ciba-Geigy (now Syngenta) produces the herbicide (*S*)-metolachlor on a scale of 10 000 ton/year. The use of iridium, instead of rhodium, finally resulted in the required activity: TOFs with this catalyst are in excess of 100 000 h⁻¹ and TONs of more than 1 × 10⁶ were reached [97]. As a ligand xyliphos, a ferrocenyl-type bisphosphine, was used in combination with iodide and acetic acid as promoters. The enantioselectivity for this process is ca. 80%, which can be easily increased by lowering the substrate/catalyst ratio. However, this is not necessary as 80% *ee* is sufficient. Compared to the first generation process which produced racemic metolachlor, an environmental burden reduction of 89% could be realized.

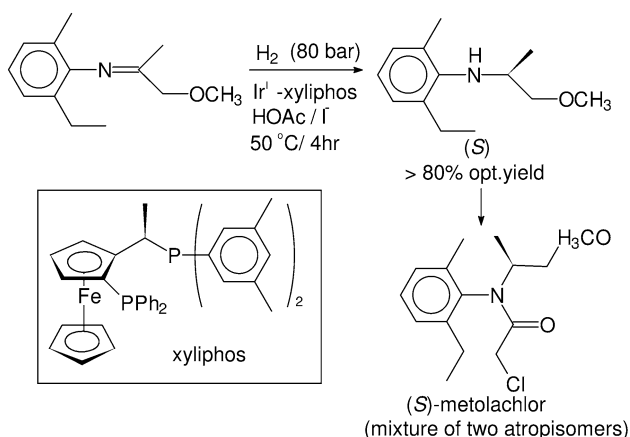


Fig. 3.34 Ir-Xyliphos based process for the production of (*S*)-metolachlor.

3.3.5

Transfer Hydrogenation using Homogeneous Catalysts

For small scale production, the use of hydrogen at elevated pressure imposes practical problems related to reactor design and safety issues. An attractive alternative is the use of alcohols or formate as a reductant (see also below for biocatalytic reductions). The Meerwein–Ponndorf–Verley (MPV) reaction has already been mentioned above and is traditionally performed using stoichiometric amounts of aluminum salts or zeolites [98]. In particular, for enantioselective transformations, a wide variety of Ru-, Rh- and Ir-based homogeneous catalysts are now known and the technique of transfer hydrogenation seems to find application in industry [99–101]. Whereas complexes containing chiral phosphine ligands are the catalysts of choice for hydrogenation reactions with H_2 , Ru, Rh and Ir complexes with chiral NN or NO ligands have been shown to be very effective for asymmetric transfer hydrogenations (Fig. 3.35). These complexes are not able to activate molecular hydrogen. Especially in the case of aryl ketones and ketimines, transfer hydrogenation can be potentially interesting, because the ruthenium hydrogenation technology in this case is limited by medium TONs and TOFs [10].

A plethora of ligands has been reported in the literature but the most effective ones are 1,2-amino alcohols, monotosylated diamines and selected phosphine-oxazoline ligands. The active structures of the complexes reported are half-sand-

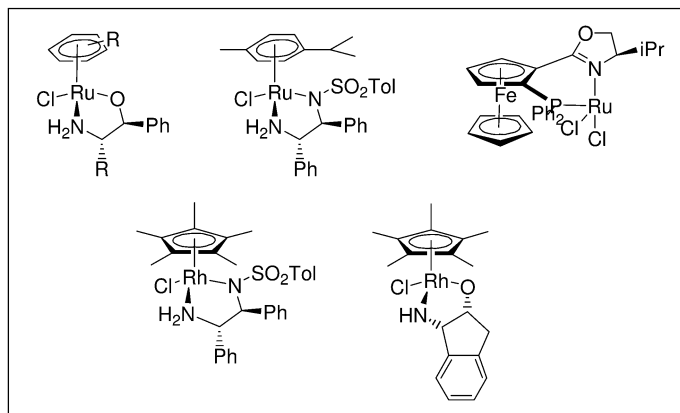
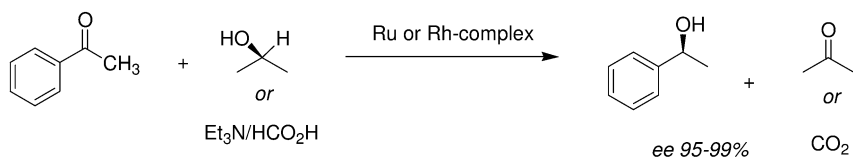


Fig. 3.35 Structure of the most effective Ru and Rh precursors used in transfer hydrogenations.

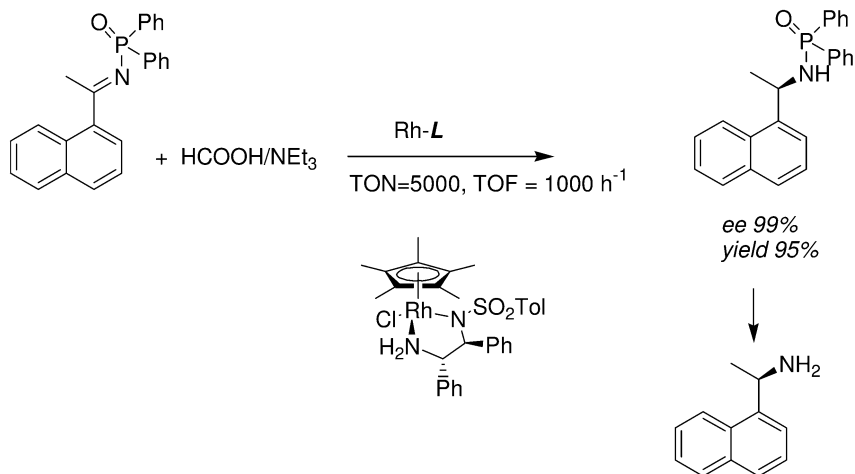


Fig. 3.36 Transfer hydrogenation of imine, as developed by Avecia.

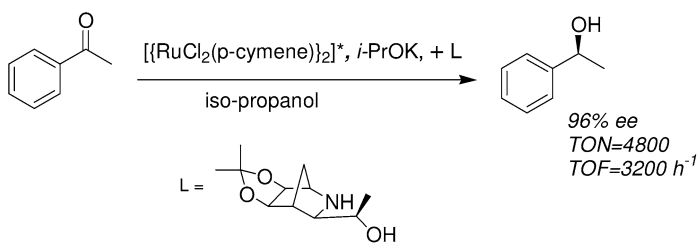


Fig. 3.37 Azanorbornane-based ligands form complexes with Ru, which are the most effective complexes reported today for transfer hydrogenation.

wich π -complexes, Ru-arene and Rh (or Ir)-cyclopentadiene complexes (see Fig. 3.35) [10]. The introduction of these catalysts in 1995 by Noyori [100] was a breakthrough because it led to a great improvement in terms of both reaction rate and enantioselectivity. For a discussion of the bifunctional mechanism operating in this case see the discussion above and Ref. [94]. These catalysts have been developed with acetophenone as model substrate. However many functionalized acetophenones, aryl ketones, acetylenic ketones as well as cyclic aryl ketones give very good results. Imine reduction can also be performed highly efficiently using this technique. An example is shown in Fig. 3.36 where a TOF of 1000 h^{-1} was reached [102].

Furthermore, Avecia has developed the Rh-cyclopentadienyl complexes in Fig. 3.36 for the large scale production of 1-tetralol and substituted 1-phenylethanol [102]. The challenge in this area is to increase the activity of the catalyst. Recently, Andersson and co-workers reported an azanorbornane-based ligand which can reach a TOF up to 3680 h^{-1} for acetophenone hydrogenation (see

Fig. 3.37) [103]. The combined introduction of a dioxolane in the backbone and a methyl group in the α -position to the OH group proved essential to reach this activity. The ligand without these functionalities, resulted in 10 times lower TOFs.

3.4

Biocatalytic Reductions

3.4.1

Introduction

Oxidoreductases play a central role in the metabolism and energy conversion of living cells. About 25% of the presently known enzymes are oxido reductases [104]. The classification of oxidoreductases is presented in Fig. 3.38. The groups of oxidases, monooxygenases and peroxidases – dealing with oxidations – will be described in Chapter 4.

For industrial applications the group of alcohol dehydrogenases, otherwise known as carbonyl-reductases, is of prime interest. The natural substrates of the enzymes are alcohols such as ethanol, lactate, glycerol, etc. and the corresponding carbonyl compounds. However, unnatural ketones can also be reduced enantioselectively. In this way chiral alcohols, hydroxy acids and their esters or amino acids, respectively, can be easily generated. An excellent overview of this field up to 2004 can be found in Refs. [105–108]. The advantages of biocatalytic reductions are that the reactions can be performed under mild conditions leading to excellent enantioselectivities. A vast reservoir of wild-type microorganisms has been screened for new enzymes, and tested with numerous substrates. A number of alcohol dehydrogenases are commercially available. These include baker's yeast and the alcohol dehydrogenases from Baker's yeast, *Thermoanaerobium brockii*, horse liver and the hydroxysteroid dehydrogenase from *Pseudomonas testosterone* and *Bacillus sphaerisus* [105, 106]. Table 3.1 gives a selection of well known alcohol dehydrogenases. Genetic engineering tools can be applied to

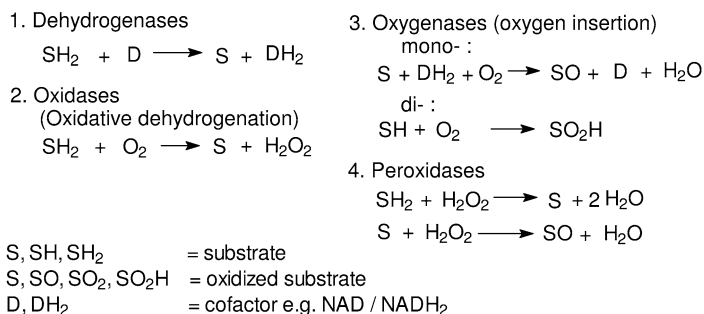


Fig. 3.38 Classification of oxidoreductases.

Table 3.1 Examples of commonly used alcohol dehydrogenases.

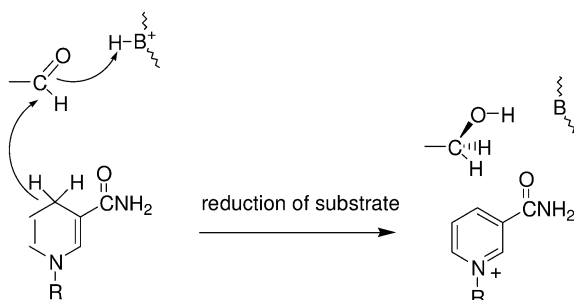
Dehydrogenase	Specificity	Cofactor
Yeast-ADH	Prelog	NADH
Horse liver-ADH	Prelog	NADH
<i>Thermoanaerobium brockii</i> -ADH	Prelog	NADPH
Hydroxysteroid-DH	Prelog	NADH
<i>Candida parapsilosis</i>	Prelog	NADH
<i>Rhodococcus erythropolis</i>	Prelog	NADH
<i>Lactobacillus kefir</i> -ADH	Anti-Prelog	NADPH
<i>Mucor javanicus</i> -ADH ^{a)}	Anti-Prelog	NADPH
<i>Pseudomonas sp.</i> -ADH ^{a)}	Anti-Prelog	NADH

a) Not commercially available.

make enzymes available in larger quantities and at lower costs in recombinant hosts. Furthermore, by directed evolution, tailor-made catalysts can be generated. The scientific knowledge in this field is increasing rapidly and in the future more tailor-made enzymes will be used in industrial processes [109, 110].

The vast majority of alcohol dehydrogenases require nicotinamide cofactors, such as nicotinamide adenine dinucleotide (NADH) and its respective phosphate NADPH. The structure of NAD/NADP is shown in Fig. 3.39. Hydrogen and two electrons are transferred from the reduced nicotinamide to the carbonyl group to effect a reduction of the substrate (see Fig. 3.39).

The mechanism of horse liver dehydrogenase has been described in great detail. In this case the alcohol is coordinated by a Zn ion and Serine. Both the alcohol and the cofactor are held in position via a three-point attachment and efficient hydrogen transfer takes place [111, 112]. The alcohol dehydrogenases can be used to reduce a variety of ketones to alcohols with high enantioselectivity under mild conditions. In Fig. 3.40 a number of examples is shown using *Lactobacillus kefir* [113]. During the course of the reaction, the enzyme delivers the hydride preferentially either from the *si* or the *re*-side of the ketone to give, for

**Fig. 3.39** Mechanism of biocatalytic ketone reduction.

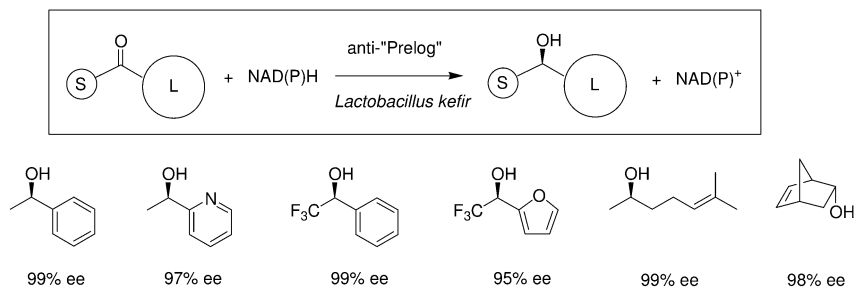


Fig. 3.40 Examples of ketone reduction and the Prelog rule.

simple systems, the (*R*)- or (*S*)-alcohols respectively. For most cases, the stereochemical course of the reaction, which is mainly dependent on the steric requirements of the substrate, may be predicted from a simple model which is generally referred to as the "Prelog" rule [106, 114]. As shown in Fig. 3.40, *Lactobacillus kefir* leads to anti-Prelog selectivity. Obviously the enzymatic reduction is most efficient when the prochiral center is adjoined by small and large groups on either side (Fig. 3.40).

The cofactors are relatively unstable molecules and expensive if used in stoichiometric amounts. In addition, they cannot be substituted by less expensive simple molecules. Since it is only the oxidation state of the cofactor which changes during the reaction it may be regenerated *in situ* by using a second redox reaction to allow it to re-enter the reaction cycle. Thus, the expensive cofactor is needed only in catalytic amounts, leading to a drastic reduction in costs [115]. Much research effort in the field of alcohol dehydrogenases is therefore directed towards cofactor recycling (see below). Cofactor recycling is no problem when whole microbial cells are used as biocatalysts for redox reactions. Many examples have been described using "fermenting yeast" as a reducing agent [116]. In this case cheap sources of redox equivalents, such as carbohydrates, can be used since the microorganism possesses all the enzymes and cofactors which are required for the metabolism. In Fig. 3.41, an example of the production of a pharmaceutically relevant prochiral ketone is given using fermentation technology [117].

However from the standpoint of green chemistry, the use of isolated enzymes (or dead whole cells) is highly preferred because it avoids the generation of copious amounts of biomass. It must be emphasized that the productivity of microbial conversions is usually low, since non-natural substrates are only tolerated at concentrations as low as 0.1–0.3% [106]. The large amount of biomass present in the reaction medium causes low overall yields and makes product recovery troublesome. Therefore the E-factors for whole cell processes can be extremely high. Moreover the use of wild-type cells often causes problems because an array of enzymes is present which can interfere in the reduction of a specific ketone (giving opposite selectivities). The use of recombinant techniques, however, which only express the desired enzyme can overcome this problem [108].

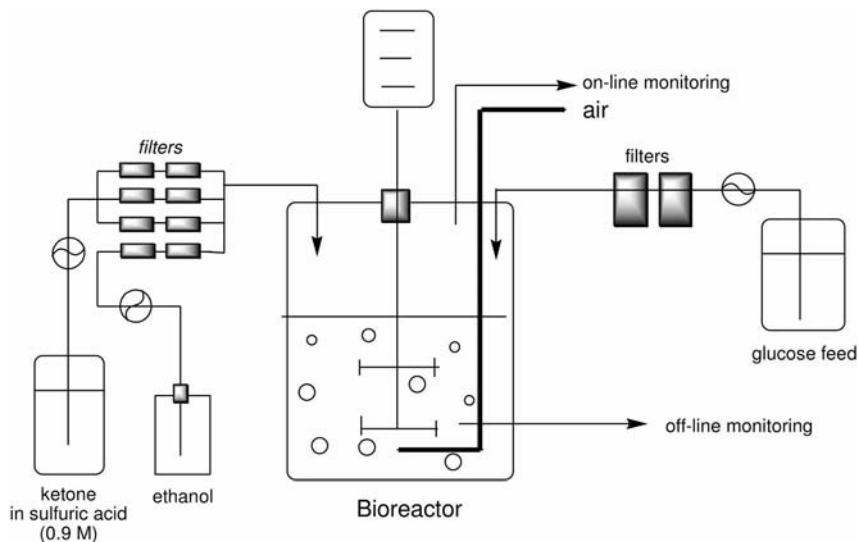


Fig. 3.41 Whole cell technology for biocatalytic reduction, example adapted from Ref. [117].

Much higher productivities can be obtained using isolated enzymes or cell extracts [118]. This approach is therefore highly preferred. Because of the importance of whole cell technology for biocatalytic reduction a few examples will be given. However the main part of this chapter will be devoted to industrial examples of bioreduction involving isolated enzymes and cofactor recycling.

3.4.2

Enzyme Technology in Biocatalytic Reduction

To keep the amount of biomass involved to a minimum, the use of isolated enzymes or cell extracts is highly preferable. In this case, for their efficient recycling, two strategies are feasible [106]. These are depicted in Fig. 3.42. In the first case, the substrate-coupled approach, only one enzyme is needed and additional alcohol is needed to complete the reduction. In terms of overall reaction, these coupled substrate-systems bear a strong resemblance to transition-metal transfer hydrogenation, the so-called Meerwein-Ponndorf-Verley reaction, see above. In the second approach [106–108], a large variety of reducing agents can be used, such as formate, glucose, H_2 or phosphite, in combination with a second enzyme, namely formate dehydrogenase, glucose dehydrogenase, hydrogenase [119] or phosphite dehydrogenase [120], respectively. Industrial processes (see below) commonly use glucose or formate as coreductants.

In the first approach, one enzyme is needed to convert both substrate (ketone) and co-substrate (alcohol). The second alcohol needs to afford a ketone which can be easily removed by distillation, e.g. acetone, to drive the reduction to completion. For most alcohol-dehydrogenases, however, the enzyme can only

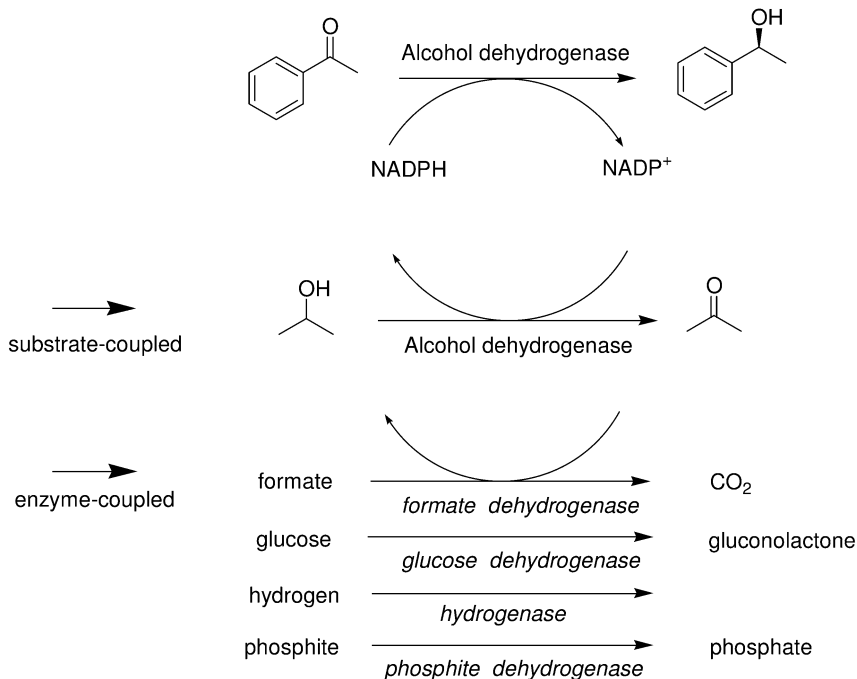


Fig. 3.42 Cofactor recycling during bioreduction processes.

tolerate certain levels of alcohols and aldehydes and therefore these coupled-substrate systems are commonly impeded by cosubstrate-inhibition [121]. Engineering solutions performed by Liese and coworkers were found to address this problem: *in situ* product removal accompanied by constant addition of reducing alcohol can improve the yields using isopropanol as the reductant.

To push the productivity limits of coupled-substrate systems even further, the maximum tolerable concentration of isopropanol applied for cofactor-regeneration with different alcohol dehydrogenases (as isolated enzymes or in preparations) has been constantly increased in the period 2000–2002 by using even more chemostable enzyme preparations [108]. In general, bacterial alcohol dehydrogenases dominate the stability ranking and the best results up till now were reached using *Rhodococcus ruber* DSM 44541 [122]. Elevated concentrations of isopropanol, up to 50% (v/v), using whole cells, not only shift the equilibrium toward the product-side, but also enhance the solubility of lipophilic substrates in the aqueous/organic medium (Fig. 3.43). The alcohol dehydrogenases from *Rhodococcus ruber*, employed as a whole cell preparation, tolerate substrate concentrations of approximately 1–2 M. Using this system a variety of methyl ketones, ethyl ketones and chloromethyl ketones could be reduced with Prelog preference. It is also worth noting that this system has been used in a reduction as well as an oxidation mode (see Chapter 4).

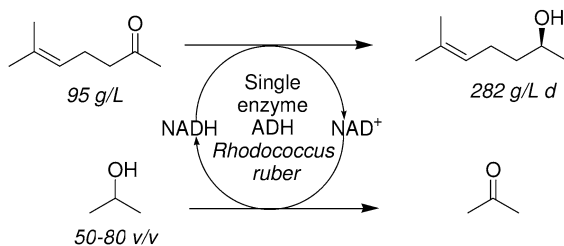


Fig. 3.43 6-Methyl-hept-5-en-2-one reduction and simultaneous NAD^+ regeneration using alcohol dehydrogenase from *Rhodococcus ruber*.

To circumvent the drawback of thermodynamic equilibrium limitations and cosubstrate-inhibition, cofactor recycling can be performed completely independently, by using a second irreversible reaction, and another enzyme. This is the so-called coupled-enzyme approach. In this case a variety of reducing agents has been used. The most advanced regeneration systems make use of innocuous hydrogen as reductant. An example has been demonstrated where hydrogenase from *Pyrococcus furiosus* was used to recycle the NADP^+ cofactor, showing a turnover frequency up to 44 h^{-1} [119, 123]. In nature this enzyme – which operates under thermophilic conditions – is able to reversibly cleave the heterolytic cleavage of molecular hydrogen. It contains both Ni and Fe in the active site. Unfortunately, the enhanced activity of the enzyme at elevated temperature (maximum 80°C) could not be used due to the thermal instability of NADPH and reactions were performed at 40°C . This system, despite the oxygen sensitivity of hydrogenase I, represents an elegant example of green chemistry and bears significant potential (see Fig. 3.44).

One of the prominent industrial bioreduction processes, run by cofactor regeneration, is performed by leucine dehydrogenase. This enzyme can catalyze the reductive amination of trimethylpyruvic acid, using ammonia (see Fig. 3.45). For this process the cofactor regeneration takes place by using formate as the reductant and formate dehydrogenase as the second enzyme. The advantage of

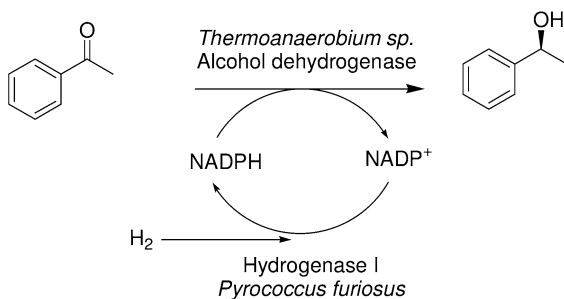


Fig. 3.44 Cofactor recycling using Hydrogenase I from *Pyrococcus furiosus*.

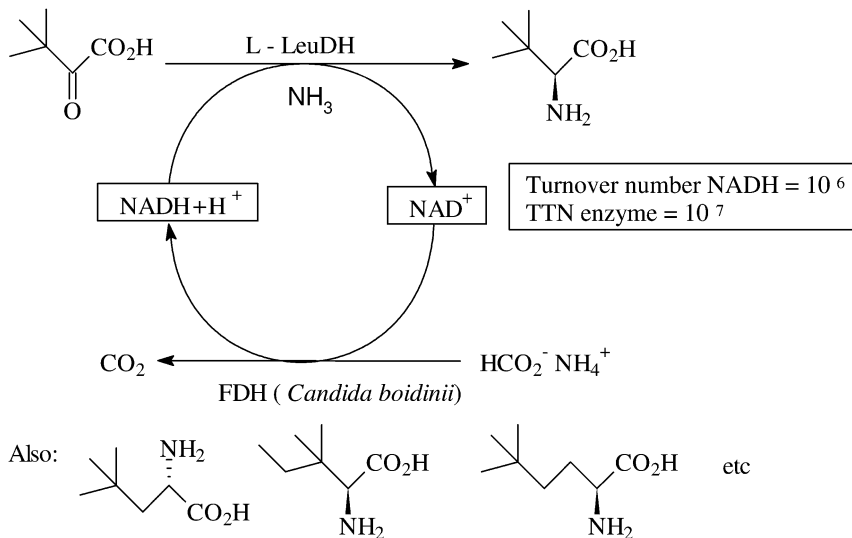


Fig. 3.45 *L*-tert-leucine production by cofactor-dependent reductive amination.

this concept is that the cofactor-regeneration is practically irreversible since carbon dioxide is produced, which can be easily removed. Although the substrate scope of this enzyme is not too good, a number of other substrates have been screened [124, 125].

Another industrial example, albeit on a lower scale, of the use of formate as formal reductant is represented by the synthesis of (*R*)-3-(4-fluorophenyl)-2-hydroxy propionic acid, which is a building block for the synthesis of *Rupintrivir*, a rhinovirus protease inhibitor currently in human clinical trials to treat the common cold [126]. The chiral 2-hydroxy-acid **A** can, in principle, be readily prepared by asymmetric reduction of the α -keto acid salt **B** (see Fig. 3.46) [127]. Chemocatalysts, such as Ru(II)-BINAP and Rh(I)-NORPHOS, gave unsatisfactory results for this substrate. However using *D*-lactate dehydrogenase (*D*-LDH), the keto acid salt **B** could be stereoselectively reduced to the corresponding α -hydroxy acid by NADH with high *ee* and high conversion. For scaling up, an enzyme coupled approach was chosen where formate was used as the stoichiometric reductant. The process is depicted in Fig. 3.46. A relatively simple continuous membrane reactor was found to satisfactorily produce α -hydroxy acid with a productivity of 560 g L⁻¹ d⁻¹. Enzyme deactivation was a key factor in determining the overall cost of the process. In a period of nine days, without adding fresh *D*-LDH and FDH, the rate of reaction decreased slowly and the enzymes lost their activity at a rate of only 1% per day. Therefore the reactor was charged with new enzymes periodically to maintain a high conversion of above 90%.

An example of glucose coupled ketone reduction is the continuous mode reduction using whole (dead) cells of *Lactobacillus kefir* for the enantioselective reduction of 2,5-hexanedione to (2*R*,5*R*)-hexanediol – a popular chiral ligand for

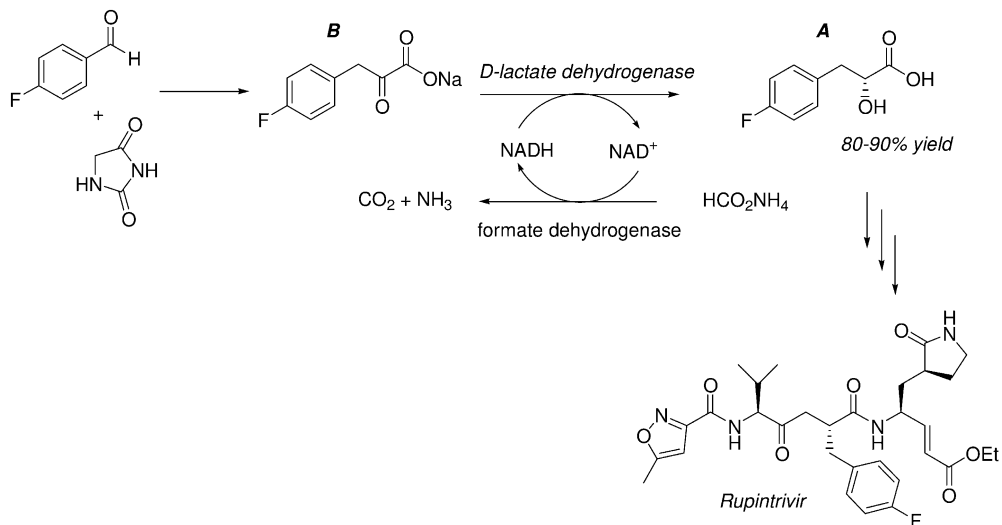


Fig. 3.46 Formate coupled production of chiral α -hydroxy acid.

transition metal catalyzed asymmetric hydrogenations. In this case the biocatalytic process is superior to its chemical counterpart because the $de > 99.5\%$ and $ee > 99.5\%$ are difficult to achieve with chemical catalysts [128]. While substrate and glucose for cofactor regeneration were constantly fed to a stirred tank reactor, the product was removed *in situ*. Using this technique, the productivity could be increased to $64 \text{ g L}^{-1} \text{ d}^{-1}$ (Fig. 3.47) [129].

Another example for biocatalytic reduction using glucose as the reductant, is the production of (*R*)-ethyl-4,4,4-trifluoro-3-hydroxybutanoate by Lonza [130]. It is a building block for pharmaceuticals such as *Befloxatone*, an anti-depressant monoamine oxidase-A inhibitor from Synthelabo. The process uses whole cells of *Escheria coli* that contain two plasmids. One carries an aldehyde reductase

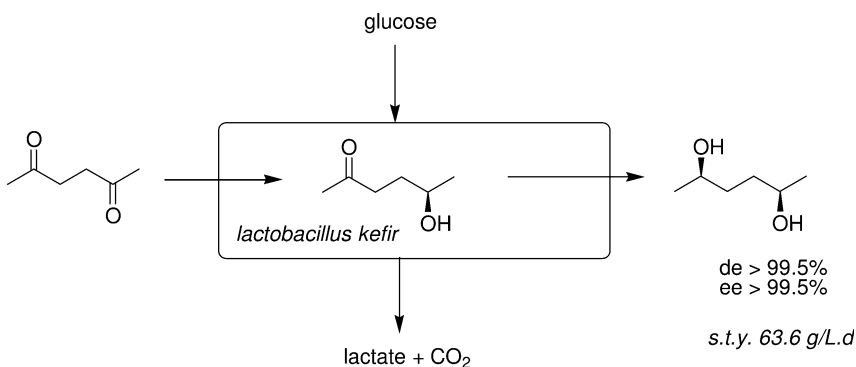


Fig. 3.47 Glucose coupled biocatalytic production of (*2R,5R*)-hexanediol.

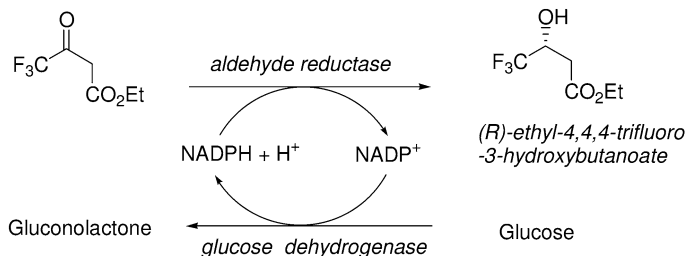


Fig. 3.48 Stereoselective reduction of (R)-ethyl-4,4,4-trifluoroacetoacetate by aldehyde reductase.

gene from the yeast *Sporobolomyces salmonicolor*, which catalyzes the reduction of ethyl-4,4,4-trifluoroacetoacetate, and the second carries a glucose dehydrogenase gene from *Bacillus megaterium* to generate NADPH from NADP⁺ (Fig. 3.48). By this “co-expression” approach the desired enzymes can be produced together in one fermentation. The cells can be stored frozen before use in the biotransformation. The Lonza process is carried out in a water/butyl acetate two-phase system to avoid inhibition of the reductase by the substrate and product. An advantage of the two-phase system is that the cells are permeabilized, allowing the transfer of NADP⁺ and NADPH through the cell wall. This whole-cell biocatalyst was originally constructed for the stereoselective reduction of 4-chloro-3-oxobutanoate (a precursor for L-carnitine), in which case productivities of up to 300 g L⁻¹, and *ee* values of up to 92% were reported [131].

The enantioselective reduction of alkyl-4-chloroacetoacetates is an important area, because it leads to an intermediate for the side chain of statins. Statins are cholesterol-lowering drugs, and the market thereof is the largest in the pharmaceutical sector. In 2003 revenues of US\$ 9.2 billion and US\$ 6.1 billion were recorded for atorvastatin and simvastatin respectively [132]. The established strategy of enantioselective reduction of alkyl-4-chloroacetoacetates has been optimized: Alcohol dehydrogenase from *Candida magnoliae* and glucose dehydrogenase from *Bacillus megaterium* were used in a biphasic organic solvent aqueous buffer system for the production of ethyl (S)-4-chloro-3-hydroxybutano-

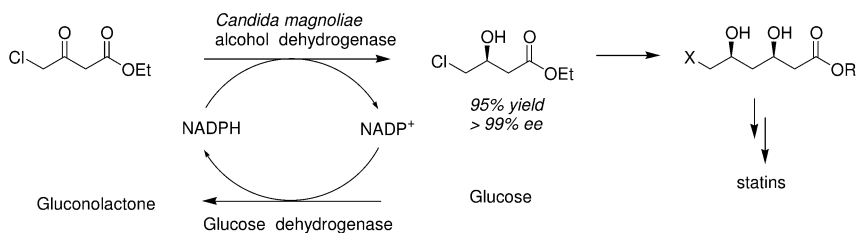


Fig. 3.49 Biocatalytic production of ethyl (S)-4-chloro-3-hydroxybutanoate using alcohol dehydrogenase from *Candida magnoliae*.

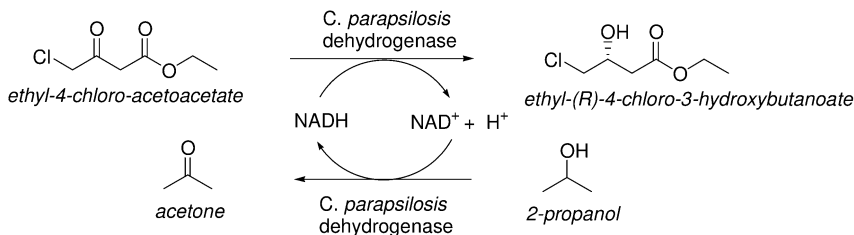


Fig. 3.50 Preparation of ethyl (*R*)-4-chloro-3-hydroxybutanoate by using alcohol dehydrogenase from *Candida parapsilosis*.

ate in enantiopure form (see Fig. 3.49). Product concentrations of 63 g L^{-1} were observed in the organic phase and the product was isolated in 95% yield [133].

When the enantioselective reduction of ethyl 4-chloroacetoacetate was carried out with alcohol dehydrogenase from *Candida parapsilosis*, the other enantiomer was produced: ethyl (*R*)-4-chloro-3-hydroxybutanoate [134]. This product is a key intermediate in a synthesis of (*R*)-carnitine. In this case a substrate coupled approach was chosen. The enzyme also has a strong oxidation activity for 2-propanol, which was therefore selected as the cosubstrate. The situation is depicted in Fig. 3.50. Under optimized conditions, the yield of (*R*)-ethyl-4-chloro-3-hydroxybutanoate reached 36.6 g L^{-1} (>99% *ee*, 95% yield) on a 30 L scale.

3.4.3

Whole Cell Technology for Biocatalytic Reduction

For small-scale reductions on a laboratory scale the use of (dead cells of) baker's yeast is a cheap alternative. It results in Prelog face reduction of a large variety of aliphatic and aromatic ketones to give the (*S*)-alcohols in good optical purities [106]. Examples were given above. On a larger scale the use of fermenting yeast can also be attractive [116]. An example is the production of a natural "green note" flavor compound [104]. Natural flavors have high consumer appeal and are desired in the food industry. Products obtained by fermentation or enzymatic catalysis usually qualify for the label "natural" and can be sold at higher prices than nature identical flavors derived by chemical synthesis. The green notes are a mixture of hexenal, hexan-1-ol, *trans*-2-hexenal, *trans*-2-hexen-1-ol and *cis*-3-hexen-1-ol. The latter dominates the impact of freshness. The flavor company Firmenich SA, Geneva, CH [135], developed a process starting from polyunsaturated fatty acids, which are converted to six-carbon hexenals and hexanal by a combined action of lipoxygenase and hydroperoxide lyase. In the second conversion, the aldehydes were reduced employing a 20% baker's yeast suspension. This process is operated on the ton scale. Separation in this case is relatively facile because the flavor compounds are sufficiently volatile to be isolated by distillation. The yeast is discarded after the biotransformation.

Another example is the microbial reduction of 3,4-methylene-dioxyphenylacetone to the corresponding (*S*) alcohol at Lilly Research Laboratories [136] (see

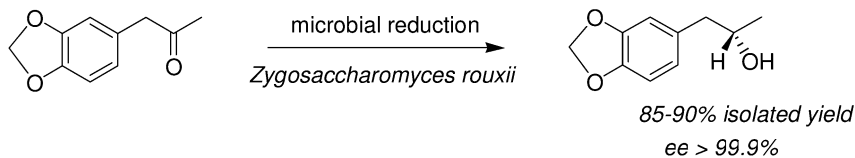


Fig. 3.51 Asymmetric reduction of 3,4-methylene-dioxypheylacetone.

Fig. 3.51). The chiral alcohol is a key intermediate in the synthesis of an anti-convulsant drug. The yeast *Zygosaccharomyces rouxii* employed for this process is hampered by substrate and product toxicity at levels of $>6 \text{ g L}^{-1}$. This was solved by using *in situ* adsorption on Amberlite XAD-7. In this way *in situ* product removal could be achieved. At the end of the process (8–12 h) 75–80 g of the alcohol is found on the resin and about 2 g L^{-1} remains in the aqueous phase. Finally an isolated yield of 85–90% could be obtained with an $ee > 99.9\%$.

Screening for the novel enzyme, although the classical method, is still one of the most powerful tools for finding biocatalytic reduction systems [108]. Enzyme sources used for the screening can be soil samples, commercial enzymes, culture sources, a clone bank, etc. Their origin can be microorganisms, animals or plants. In most of the examples mentioned above, the biocatalyst was chosen after an extensive screening program. A third example of a fermenting process, which illustrates the importance of screening, is shown in Fig. 3.52. The key intermediate in the synthesis of Montelukast, an anti-asthma drug, was prepared from the corresponding ketone by microbial transformation [137]. After screening 80 microorganisms, the biotransforming organism *Microbacterium campoquemoensis* (MB5614) was identified, which was capable of reducing the complex ketone to the (S) alcohol.

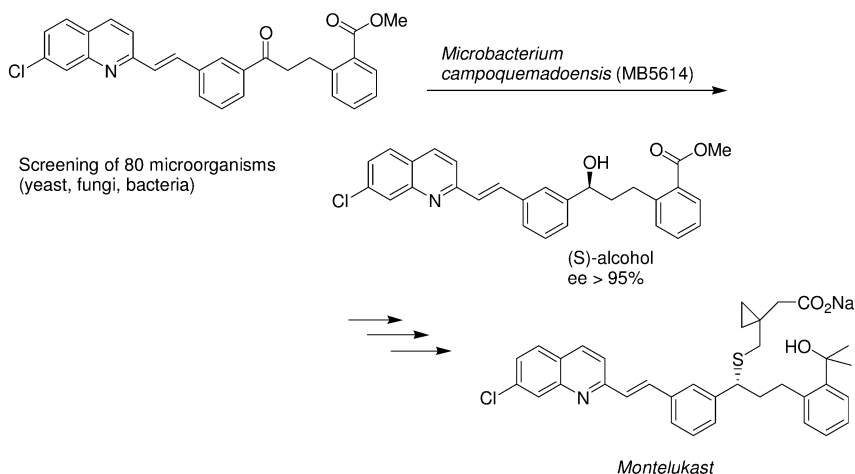


Fig. 3.52 Fermenting process for the production of Montelukast.

3.5

Conclusions

Summarizing, it is evident that catalytic reduction is an important technology that is widely applied for the production of fine chemicals. It is a key example of green technology, due to the low amounts of catalysts required, in combination with the use of hydrogen (100% atom efficient!) as the reductant. In general, if chirality is not required, heterogeneous supported catalysts can be used in combination with hydrogen. Apart from the standard reductions, such as ketone and nitro reductions, reductive aminations etc., the Pd-catalyzed reductive alkylation of alcohols and amines with aldehydes, leading to the green synthesis of ethers and amines, needs to be mentioned. Once selectivity and chirality is called for, homogeneous catalysts and biocatalysts are required. The use and application of chiral Ru, Rh and Ir catalysts has become a mature technology. It allows a large variety of transformations: imines and functionalized ketones and alkenes can be converted with high selectivity in most cases. The enantioselective reduction of non-functionalized and non-aromatic alkenes is still an area of development.

Biocatalysis is developing rapidly. Especially in the area of ketone reduction, biocatalytic reduction is often the method of choice, due to the high purities of product that can be achieved (>99%). In these cases alcohol, formate or glucose are used as the reductants. Significant progress can be expected in this area due to the advancement in enzyme production technologies and the possibility of tailor-made enzymes. In the future more applications of catalytic reduction will certainly come forward, for new chemical entities as well as for the replacement of current less-green technologies.

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4

Catalytic Oxidations

4.1

Introduction

The controlled partial oxidation of hydrocarbons, comprising alkanes, alkenes and (alkyl)aromatics, is the single most important technology for the conversion of oil- and natural gas-based feedstocks to industrial organic chemicals [1–3]. For economic reasons, these processes predominantly involve the use of molecular oxygen (dioxygen) as the primary oxidant. Their success depends largely on the use of metal catalysts to promote both the rate of reaction and the selectivity to partial oxidation products. Both gas phase and liquid phase oxidations, employing heterogeneous and homogeneous catalysts, respectively, are used industrially, in a ca. 50/50 ratio (see Table 4.1).

The pressure of increasingly stringent environmental regulation is also providing a stimulus for the deployment of catalytic oxidations in the manufacture of fine chemicals. Traditionally, the production of many fine chemicals involved oxidations with stoichiometric quantities of, for example, permanganate or dichromate, resulting in the concomitant generation of copious amounts of inorganic salt-containing effluent. Currently, there is considerable pressure, therefore, to replace these antiquated technologies with cleaner, catalytic alternatives [3, 4]. In practice this implies an implementation of catalytic technologies which allow the use of oxygen and hydrogen peroxide (which produces water as the side product) as stoichiometric oxidants. Therefore this chapter will focus on catalysts which use either O_2 or H_2O_2 as oxidants. In some cases, e.g. in the case of stereoselective conversion where a highly added benefit of the product prevails, the use of other oxidants will be considered as well.

In principle, homogeneous as well as heterogeneous and bio-catalysts can be deployed in liquid phase oxidations but, in practice, the overwhelming majority of processes are homogeneous, i.e. they involve the use of soluble metal salts or complexes as the catalyst. Pivotal examples of the potential of selective catalyzed oxidations have already been mentioned in Chapter 1. For example, in the oxidation of alcohols and epoxidation of olefins enormous progress has been achieved over the last decade towards green methods, notably using homogeneous metal complexes. However also in the field of biocatalytic transformations, industrial applications start to appear, notably in the field of aromatic side

Table 4.1 Bulk chemicals via catalytic oxidation.

Product	Feedstock	Oxidant/Process ^{a)}
Styrene	Benzene/ethene	None/G (O ₂ /L) ^{b)}
Terephthalic acid	<i>p</i> -Xylene	O ₂ /L
Formaldehyde	Methanol	O ₂ /G
Ethene oxide	Ethene	O ₂ /G
Phenol	a. Benzene/propene b. Toluene	O ₂ /L
Acetic acid	a. n-Butane b. Ethene	O ₂ /L
Propene oxide	Propene	RO ₂ H/L
Acrylonitrile	Propene	O ₂ /G
Vinyl acetate	Ethene	O ₂ /L; G
Benzoic acid	Toluene	O ₂ /L
Adipic acid	Benzene	O ₂ /L
ϵ -Caprolactam	Benzene	O ₂ /L
Phthalic anhydride	<i>o</i> -Xylene	O ₂ /G
Acrylic acid	Propene	O ₂ /G
Methyl methacrylate	Isobutene	O ₂ /G
Maleic anhydride	n-Butane	O ₂ /G

a) L=liquid phase; G=gas phase.

b) Styrene from propene epoxidation with EBHP.

chain oxidation of heteroaromatics [5]. In the next section, the basics of mechanisms in metal-catalyzed oxidations – homolytic versus heterolytic – will be presented. The fundamentals of redox catalysis by enzymes will also be given. The green methodologies for converting different classes of substrates will then be treated consecutively.

4.2

Mechanisms of Metal-catalyzed Oxidations: General Considerations

The ground state of dioxygen is a triplet containing two unpaired electrons with parallel spins. The direct reaction of ³O₂ with singlet organic molecules to give singlet products is a spin forbidden process with a very low rate. Fortunately, this precludes the spontaneous combustion of living matter, a thermodynamically very favorable process.

One way of circumventing this activation energy barrier involves a free radical pathway in which a singlet molecule reacts with ³O₂ to form two doublets (free radicals) in a spin-allowed process (Fig. 4.1, Reaction (1)). This process is, however, highly endothermic (up to 50 kcal mol⁻¹) and is observed at moderate temperatures only with very reactive molecules that afford resonance stabilized radicals, e.g. reduced flavins (Fig. 4.1, Reaction (2)). It is no coincidence, therefore,

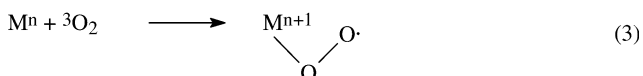
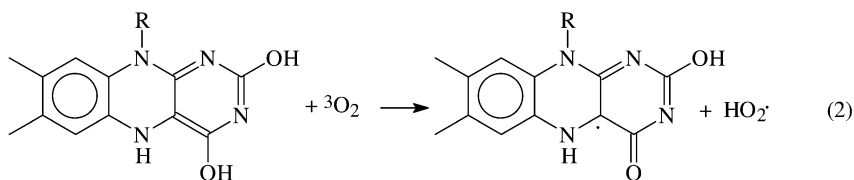
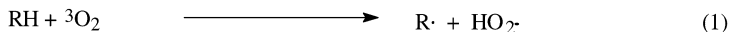


Fig. 4.1 Reactions of triplet oxygen.

that this is the key step in the activation of dioxygen by flavin-dependent oxygenases.

A second way to overcome this spin conservation obstacle is via reaction of ${}^3\text{O}_2$ with a paramagnetic (transition) metal ion, affording a superoxometal complex (Fig. 4.1, Reaction (3)). Subsequent inter- or intramolecular electron-transfer processes can lead to the formation of a variety of metal–oxygen species (Fig. 4.2) which may play a role in the oxidation of organic substrates.

Basically, all (catalytic) oxidations, with dioxygen or peroxide reagents, either under homogeneous or heterogeneous conditions, can be divided into two types on the basis of their mechanism: homolytic and heterolytic. The former involve free radicals as reactive intermediates. Such reactions can occur with most organic substrates and dioxygen, in the presence or absence of metal catalysts. This ubiquity of free radical processes in dioxygen chemistry renders mechanistic interpretation more difficult than in the case of hydrogenations or carbonylations where there is no reaction in the absence of the catalyst.

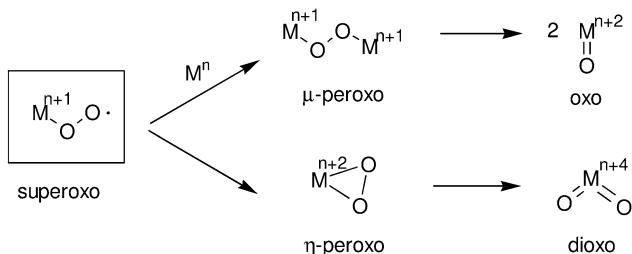


Fig. 4.2 Metal–oxygen species.

Heterolytic oxidations generally involve the (metal-mediated) oxidation of a substrate by an active oxygen compound, e.g. H_2O_2 or RO_2H . Alternatively, stoichiometric oxidation of a substrate by a metal ion or complex is coupled with the reoxidation of the reduced metal species by the primary oxidant (e.g. O_2 or H_2O_2).

4.2.1

Homolytic Mechanisms

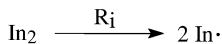
As noted above, dioxygen reacts with organic molecules, e.g. hydrocarbons, via a free radical pathway. The corresponding hydroperoxide is formed in a free radical chain process (Fig. 4.3). The reaction is autocatalytic, i.e. the alkyl hydroperoxide accelerates the reaction by undergoing homolysis to chain initiating radicals, and such processes are referred to as autoxidations [1].

The susceptibility of any particular substrate to autoxidation is determined by the ratio $k_p/(2k_t)^{1/2}$, which is usually referred to as its oxidizability [6]. The oxidizabilities of some typical organic substrates are collected in Table 4.2.

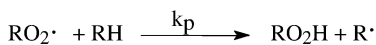
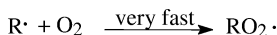
The reaction can be started by adding an initiator which undergoes homolytic thermolysis at the reaction temperature to produce chain-initiating radicals. The initiator could be the alkyl hydroperoxide product although relatively high temperatures ($>100^\circ\text{C}$) are required for thermolysis of hydroperoxides. Alternatively, chain-initiating radicals can be generated by the reaction of trace amounts of hydroperoxides with variable valence metals, e.g. cobalt, manganese, iron, cerium etc. The corresponding alkoxy and alkylperoxy radicals are produced in one-electron transfer processes (Fig. 4.4).

In such processes the metal ion acts (in combination with ROOH) as an initiator rather than a catalyst. It is important to note that homolytic decomposition of alkyl hydroperoxides via one-electron transfer processes is generally a com-

Initiation:



Propagation:



Termination:



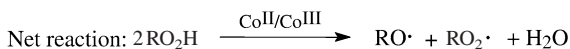
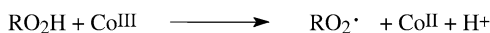
Fig. 4.3 Mechanism of autoxidation.

Table 4.2 Oxidizabilities of organic compounds at 30 °C^{a)}.

Substrate	$k_p/(2k_t)^{1/2} \times 10^3 \text{ (M}^{-1/2} \text{ s}^{-1/2}\text{)}$
Indene	28.4
Cyclohexene	2.3
1-Octene	0.06
Cumene	1.5
Ethylbenzene	0.21
Toluene	0.01
<i>p</i> -Xylene	0.05
Benzaldehyde ^{b)}	290
Benzyl alcohol	0.85
Dibenzyl ether	7.1

a) Data taken from Ref. [6].

b) At 0 °C.

**Fig. 4.4** Metal initiated and mediated autoxidation.

peting process even with metal ions that catalyze heterolytic processes with hydroperoxides (see above). Since dioxygen can be regenerated via subsequent chain decomposition of the alkyl hydroperoxide this can lead to competing free radical autoxidation of the substrate. Generally speaking, this has not been recognized by many authors and can lead to a misinterpretation of results.

4.2.1.1 Direct Homolytic Oxidation of Organic Substrates

Another class of metal catalyzed autoxidations involves the direct one-electron oxidation of the substrate by the oxidized form of the metal catalyst. For example, the autoxidation of alkylaromatics in acetic acid in the presence of relatively high concentrations (~0.1 M) of cobalt(III) acetate involves rate-limiting one electron transfer oxidation of the alkylbenzene to the corresponding cation radical (Fig. 4.5). This is followed by elimination of a proton to afford the corresponding benzylic radical, which subsequently forms a benzylperoxy radical by reaction with dioxygen. The primary products from substituted toluenes are the corresponding aldehydes, formed by reaction of benzylperoxy radicals with cobalt(II) (which simultaneously regenerates the cobalt(III) oxidant). The usual reaction of alkylperoxy radicals with the toluene substrate (see Fig. 4.3) is largely

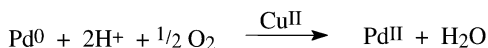


Fig. 4.6 Wacker oxidation and oxidative dehydrogenation of alcohols.

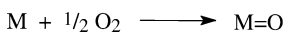
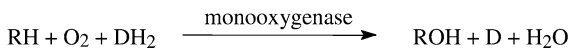


Fig. 4.7 Mars-van Krevelen mechanism.



$\text{D}/\text{DH}_2 = \text{cofactor}$

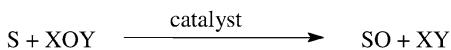
Fig. 4.8 Stoichiometry in oxidations mediated by monooxygenases.

ganic substrates, such as alkenes and alkanes [12]. This would obviate the need for a stoichiometric cofactor as a sacrificial reductant, i.e. it would amount to a Mars-van Krevelen mechanism in the liquid phase.

4.2.2.1 Catalytic Oxygen Transfer

Another way to avoid the need for a sacrificial reductant is to use a reduced form of dioxygen, e.g. H_2O_2 or RO_2H , as a single oxygen donor. Such a reaction is referred to as a catalytic oxygen transfer and can be described by the general equation shown in Fig. 4.9.

Catalytic oxygen transfer processes are widely applicable in organic synthesis. Virtually all of the transition metals and several main group elements are known to catalyze oxygen transfer processes [13]. A variety of single oxygen donors can be used (Table 4.3) in addition to H_2O_2 or RO_2H . Next to price and



S = substrate; SO = oxidized substrate

XOY = H_2O_2 , RO_2H , R_3NO , NaOCl , KHSO_5 , etc.

Fig. 4.9 Catalytic oxygen transfer.

Table 4.3 Oxygen donors.

Donor	% Active Oxygen	Coproduct
H ₂ O ₂	47.0 (14.1) ^{a)}	H ₂ O
N ₂ O	36.4	N ₂
O ₃	33.3	O ₂
CH ₃ CO ₃ H	21.1	CH ₃ CO ₂ H
<i>tert</i> -BuO ₂ H	17.8	<i>tert</i> -BuOH
HNO ₃	25.4	NO _x
NaOCl	21.6	NaCl
NaO ₂ Cl	35.6	NaCl
NaOBr	13.4	NaBr
C ₅ H ₁₁ NO ₂ ^{b)}	13.7	C ₅ H ₁₁ NO
KHSO ₅	10.5	KHSO ₄
NaIO ₄	7.5	NaIO ₃
PhIO	7.3	PhI

a) Figure in parentheses refers to 30% aq. H₂O₂.

b) *N*-Methylmorpholine-*N*-oxide (NMO).

ease of handling, two important considerations which influence the choice of oxygen donor are the nature of the co-product and the weight percentage of available oxygen. The former is important in the context of environmental acceptability and the latter bears directly on the volumetric productivity (kg product per unit reactor volume per unit time). With these criteria in mind it is readily apparent that hydrogen peroxide, which affords water as the co-product, is generally the preferred oxidant. The co-product from organic oxidants, such as RO₂H and amine oxides, can be recycled via reaction with H₂O₂. The overall process produces water as the co-product but requires one extra step compared to the corresponding reaction with H₂O₂. With inorganic oxygen donors environmental considerations are relative. Sodium chloride and potassium bisulfate are obviously preferable to the heavy metal salts (Cr, Mn, etc.) produced in classical stoichiometric oxidations. Generally speaking, inorganic oxidants are more difficult to recycle, in an economic manner, than organic ones. Indeed, the ease of recycling may govern the choice of oxidant, e.g. NaOBr may be preferred over NaOCl because NaBr can, in principle, be re-oxidized with H₂O₂. As noted earlier, a disadvantage of H₂O₂ and RO₂H as oxygen donors is possible competition from metal-catalyzed homolytic decomposition leading to free radical oxidation pathways and/or low selectivities based on the oxidant.

Heterolytic oxygen transfer processes can be divided into two categories based on the nature of the active oxidant: an oxometal or a peroxometal species (Fig. 4.10). Catalysis by early transition metals (Mo, W, Re, V, Ti, Zr) generally involves high-valent peroxometal complexes whereas later transition metals (Ru, Os), particularly first row elements (Cr, Mn, Fe) mediate oxygen transfer via oxometal species. Some elements, e.g. vanadium, can operate via either mechanism, depending on the substrate. Although the pathways outlined in Fig. 4.10

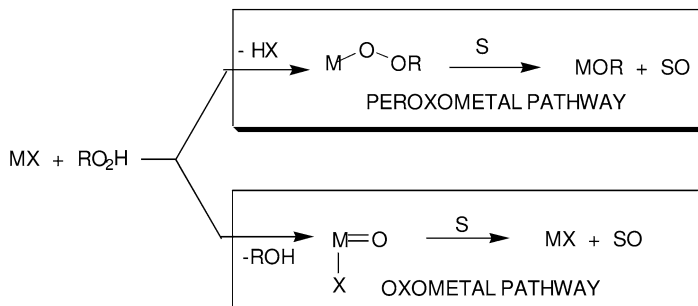


Fig. 4.10 Peroxometal versus oxometal pathways.

pertain to peroxidic reagents analogous schemes involving $\text{M}=\text{O}$ or MOX ($\text{X}=\text{ClO}$, IO_4 , HSO_5 , R_3NO etc.) as the active oxidant, can be envisaged for other oxygen donors. Reactions that typically involve peroxometal pathways are alkene epoxidations, alcohol oxidations and heteroatom (N and S) oxidations. Oxometal species, on the other hand, are intermediates in the oxidation of alkane, benzylic and allylic C–H bonds and the dihydroxylation and oxidative cleavage of olefins, in addition to the above-mentioned transformations.

For the sake of completeness we also note that oxygen transfer processes can be mediated by organic catalysts which can be categorized on the same basis as metal catalysts. For example, ketones catalyze a variety of oxidations with monoperoxydisulfate (KHSO_5) [14]. The active oxidant is the corresponding dioxirane and, hence, the reaction can be construed as involving a ‘peroxometal’ pathway. Similarly, TEMPO-catalyzed oxidations of alcohols with hypochlorite [15, 16] involve an oxoammonium salt as the active oxidant, i.e. an ‘oxometal’ pathway.

4.2.3

Ligand Design in Oxidation Catalysis

In the majority of catalytic oxidations simple metal salts are used as the catalysts. In contrast, oxidations mediated by redox enzymes involve metal ions coordinated to complex ligands: amino acid residues in a protein or a prosthetic group, e.g. a porphyrin ligand in heme-dependent enzymes. Indeed, many of the major challenges in oxidation chemistry involve demanding oxidations, such as the selective oxidation of unactivated C–H bonds, which require powerful oxidants. This presents a dilemma: if an oxidant is powerful enough to oxidize an unactivated C–H bond then, by the same token, it will readily oxidize most ligands, which contain C–H bonds that are more active than the C–H bonds of the substrate. The low operational stability of, for example, heme-dependent enzymes is a direct consequence of the facile oxidative destruction of the porphyrin ring. Nature solves this problem *in vivo* by synthesizing fresh enzyme to replace that destroyed. *In vitro* this is not a viable option. In this context it is worth bearing in mind that many simple metal complexes that are used as cata-

lysts in oxidation reactions contain ligands, e.g. acetylacetonate, that are rapidly destroyed under oxidizing conditions. This fact is often not sufficiently recognized by authors of publications on catalytic oxidations.

Collins [17] has addressed the problem of ligand design in oxidation catalysis in some detail and developed guidelines for the rational design of oxidatively robust ligands. Although progress has been achieved in understanding ligand sensitivity to oxidation the ultimate goal of designing metal complexes that are both stable and exhibit the desired catalytic properties remains largely elusive. We note, in this context, that an additional requirement has to be fulfilled: the desired catalytic pathway should compete effectively with the ubiquitous free radical autoxidation pathways.

One category of oxidations deserves special mention in the context of ligand design: enantioselective oxidations. It is difficult to imagine enantioselective oxidations without the requirement for (chiral) organic ligands. Here again, the task is to design ligands that endow the catalyst with the desired activity and (enantio-)selectivity and, at the same time, are (reasonably) stable.

In the following sections oxidative transformations of a variety of functional groups will be discussed from both a mechanistic and a synthetic viewpoint.

4.2.4

Enzyme Catalyzed Oxidations

Oxidations by enzymes are performed by the group of oxidoreductases. An overview of the classification of oxidoreductases is given in Fig. 4.11.

The alcohol *dehydrogenases* were already described in Chapter 3. These enzymes are cofactor dependent and in the active site hydrogen transfer takes place from NADH or NADPH. In the reverse way they can, however, be applied for the oxidation of alcohols in some cases (see below). *Oxidases* are very appealing for biocatalytic purposes, because they use oxygen as the only oxidant without the need for a cofactor. Oxidases usually have flavins (glucose oxidase, alcohol oxidase) or copper (examples; galactose oxidase, laccase and tyrosinase) in the active site [18]. The mechanism for glucose oxidase (GOD) is denoted in

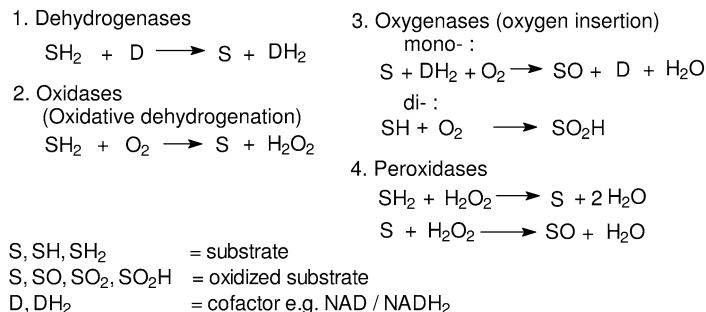


Fig. 4.11 Classes of oxidoreductases.

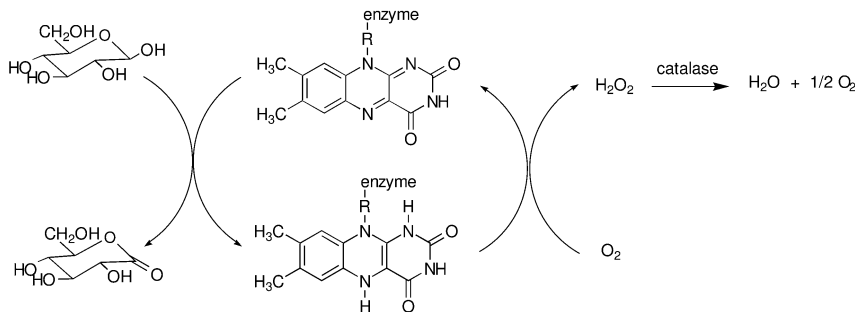


Fig. 4.12 Aerobic oxidation of D-glucose catalyzed by flavin-dependent glucose oxidase.

Fig. 4.12. GOD oxidases the oxidation of β -D-glucose to D-gluconolactone, a reaction which has attracted the attention of generations of analytical scientists due to its possible applicability in glucose sensors for diabetes control.

Galactose oxidase exhibits a mononuclear copper-active site, which is flanked by a tyrosinyl radical. In a single step, a two-electron oxidation of alcohols can be performed by this enzyme, where one electron is extracted by copper and the other by the tyrosine residue [19].

In the case of oxygenases, catalytic oxygen transfer has to take place, and many of the principles described above are operative here as well. A combination of oxygen and NADH or NADPH is supplied to the active site which results in net transfer of "O" and H_2O as the by-product. Thus NAD(P)H is required as sacrificial reductant and only one of the two oxygen atoms in oxygen ends up in the product. An exception is the dioxygenases where both oxygen atoms can end up in the product. *Oxygenases* can be classified, depending on their redox-active cofactor (Table 4.4). The active site commonly contains either a heme-iron, non-heme-iron, flavin or copper (mono- or binuclear) as redox-active group.

Table 4.4 Classification of oxygenases.

Type	Examples	Substrates
Heme-iron aromatics	Cytochrome-P450	alkanes, alkenes
Non-heme-iron	Methane monooxygenase	alkanes, alkenes
	Rieske dioxygenases	aromatics, alkenes
	Lipoxygenase	alkenes
Flavin	Hydroxybiphenyl monooxygenase	aromatics
	Styrene monooxygenase	styrenes
	Cyclohexane monooxygenase	Baeyer-Villiger
Copper	Tyrosinase	phenolic
	Dopamine β -monooxygenase	benzylic C-H

A pivotal class of oxygenases are the so-called iron heme-proteins from the Cytochrome P450 family, in which the iron is ligated by a porphyrin moiety [11, 20, 21]. In the first case, an oxometal-type mechanism is operative, where a putative $P^+Fe(IV)=O$ (P =porphyrin) species transfers oxygen directly to the substrate (see Fig. 4.13). The exact identity is still a matter of controversy. Generally, a $Fe(IV)=O$ species stabilized by a cationic radical porphyrin moiety seems to be favored instead of a formally $Fe(V)=O$ species. Especially intriguing is the potential of these types of enzymes to perform a stereoselective hydroxylation of non-activated alkanes – a reaction which is still very rare in the case of metal-catalysed oxidations. A so-called rebound mechanism has been proposed in this case which involves a $[Fe-OH R^*]$ transient species (see Fig. 4.14). Iron-heme-type enzymes are the enzymes which have the broadest substrate spectrum. They are capable of performing oxygenation on a wide range of compounds, from alkanes and fatty acids, to alkenes and alcohols. Due to the instability of the heme group, and the requirement for a cofactor, these enzymes are commonly employed under microbial whole cell conditions [22].

Another important class of oxygenases are the flavin-dependent oxygenases, notably in Baeyer-Villiger oxidation and epoxidation [23, 24]. The mechanism for Baeyer-Villiger conversion of cyclic ketones into esters by the enzyme cyclohexane monooxygenase is shown in Fig. 4.15 [25]. The prosthetic group FAD, which is tightly bound to the active site of the enzyme, is reduced to $FADH_2$ by NADPH. Rapid reaction between $FADH_2$ and molecular oxygen (see Fig. 4.1, Reaction (2)) affords 4*a*-hydroperoxyflavin which is a potent oxidizing agent. Addition of 4*a*-hydroperoxyflavin to the carbonyl group of cyclohexanone creates a tetrahedral intermediate, which rearranges to give $FAD-4a-OH$ and ϵ -caprolactone. Finally a water molecule is eliminated from $FAD-4a-OH$ to regenerate

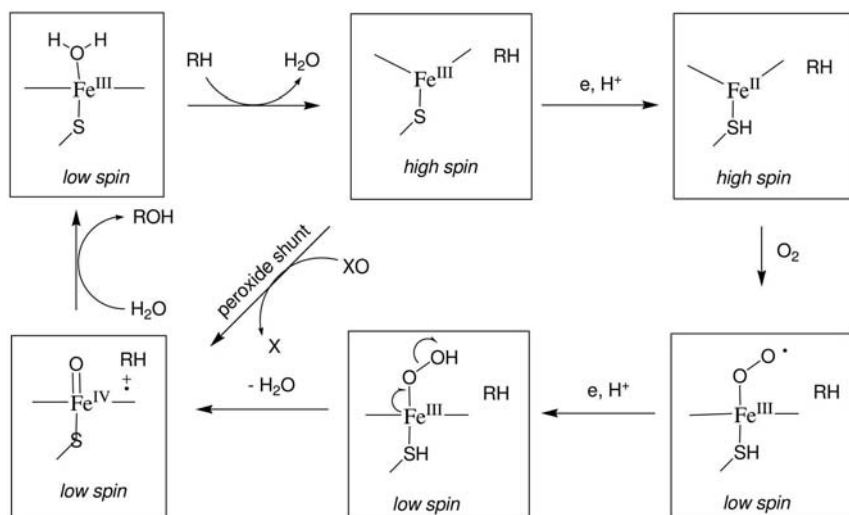


Fig. 4.13 Fe-porphyrins and the peroxide shunt pathway.

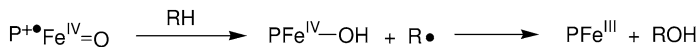


Fig. 4.14 Fe-porphyrins and the oxygen-rebound mechanism.

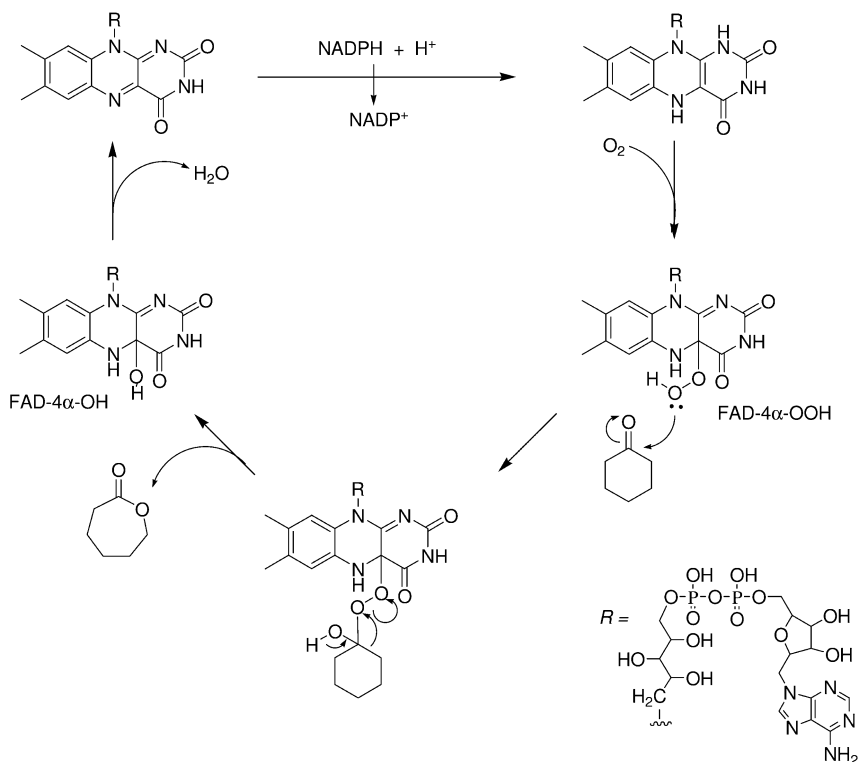


Fig. 4.15 Mechanism of the Baeyer-Villiger oxidation of cyclohexanone using flavin-dependent monooxygenase.

FAD ready for a subsequent catalytic cycle. This enzyme catalyzed Baeyer-Villiger oxidation bears great resemblance to the analogous chemical reaction performed by peroxides or peracids, which act as nucleophiles. Globally these flavin-enzymes can perform the same reactions as peracids, i.e. epoxidations, Baeyer-Villiger-reactions and nucleophilic heteroatom oxidation [26–28].

Within the group of non-heme-iron monooxygenases, two notable classes can be identified: The binuclear non-heme monooxygenases and the mononuclear dioxxygenases [29, 30]. The most important example of the first group, methane monooxygenase, is capable of mediating the oxidation of a broad range of substrates including methane, at ambient temperature [31]. In this enzyme a non-heme di-iron core is present in which the two-irons are connected through two carboxylate bridges, and coordinated by histidine residues (see Fig. 4.16) [32]. Also in this case Fe(IV)=O species have been proposed as the active intermediates.

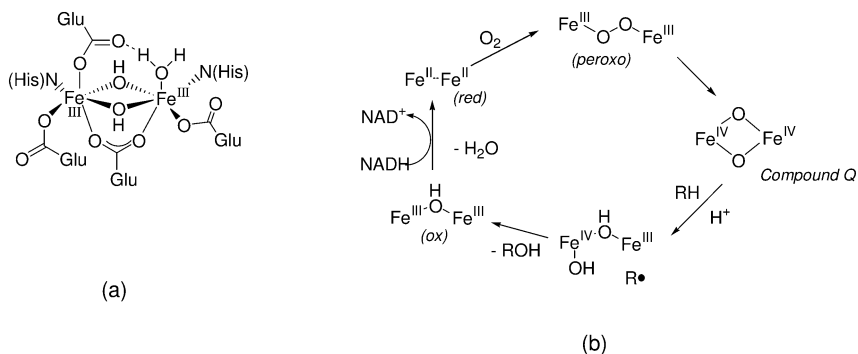


Fig. 4.16 Structure of the MMO-iron site and its catalytic cycle.

The class of mononuclear dioxygenases [30] can e.g. perform hydroperoxidation of lipids, the cleavage of catechol and dihydroxylation of aromatics. A prominent example is naphthalene dioxygenase, which was the first identified by its crystal structure. It contains iron and a Rieske ($2\text{Fe}-2\text{S}$) cluster and is commonly referred to as a Rieske-type dioxygenase [33]. The iron in this case is flanked by two histidines and one aspartic acid residue. Among the mononuclear iron enzymes, the 2-His-1-carboxylate is a common motif, which flanks one-side of the iron in a triangle and plays an important role in dioxygen activation [34] (Fig. 4.17).

Alternatively copper is capable of H-atom abstraction leading to aliphatic hydroxylation. The enzyme dopamine β -monoxygenase is an example thereof and the reaction is exemplified in Fig. 4.18 [35]. Recently, it has been disclosed that the two copper centers in the enzyme are far apart and not coupled by any magnetic interaction [36]. The binding and activation of dioxygen thus takes place at a single Cu-center, which can provide one electron to generate a superoxo $\text{Cu}^{\text{II}}-\text{O}_2^-$ intermediate. This superoxo intermediate is supposed to be capable of H-atom abstraction.

All the above examples of monooxygenases are dependent on cofactors. The enzymes are usually composed of several subunits which, in a series of cascades, provide the reducing equivalents to the iron-active site. The need for a co-

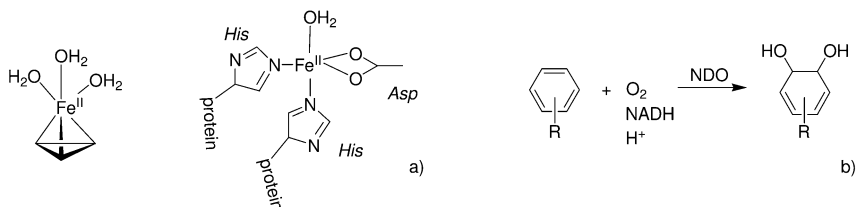


Fig. 4.17 (a) The 2-His-1-carboxylate facial triad in naphthalene dioxygenase (NDO). (b) Reaction catalyzed by NDO.

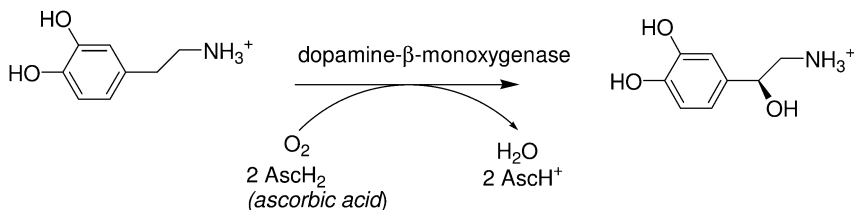


Fig. 4.18 Hydroxylation of dopamine by the non-coupled binuclear copper center in dopamine- β -monooxygenase.

factor is circumvented in the case of *peroxidases* where H_2O_2 acts as the oxidant. In this case the addition of hydrogen peroxide results in a shunt pathway, which directly recovers the $[\text{Fe(IV)=O}][\text{P}^{+\bullet}]$ species from Fe(III) (see Fig. 4.13). Besides iron-heme-dependent peroxidases [37], vanadate-dependent peroxidases are also known which can catalyze sulfide oxidations and which exhibit much higher stabilities [38].

4.3 Alkenes

Various combinations of metal catalyst and single oxygen donor have been used to effect different oxidative transformations of olefins: epoxidation, dihydroxylation, oxidative cleavage, ketonization and allylic oxidation. The most extensively studied example is undoubtedly olefin epoxidation [39].

4.3.1 Epoxidation

The epoxidation of propene with *tert*-butylhydroperoxide (TBHP) or ethylbenzene hydroperoxide (EBHP), for example, accounts for more than one million tons of propene oxide production on an annual basis (Fig. 4.19).

The reaction in Fig. 4.19 is catalyzed by compounds of high-valent, early transition metals such as Mo(VI), W(VI), V(V) and Ti(IV). Molybdenum compounds are particularly effective homogeneous catalysts and are used in the ARCO process in combination with TBHP or EBHP. In the Shell process, on the other hand, a heterogeneous Ti(IV)/ SiO_2 catalyst is used with EBHP in a continuous,

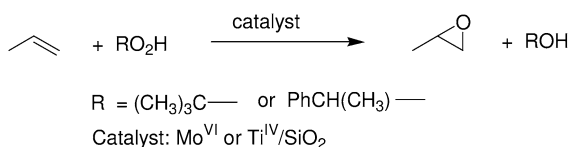


Fig. 4.19 Epoxidation of propylene using RO_2H as oxidant.

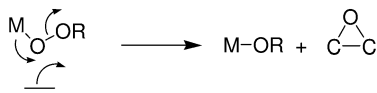


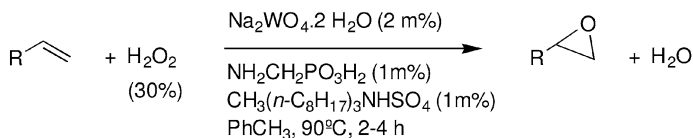
Fig. 4.20 Peroxometal mechanism in the epoxidation.

fixed-bed operation. Alkyl hydroperoxides in combination with homogeneous (Mo, W, V, Ti) or heterogeneous (Ti(IV)/SiO₂) catalysts can be used for the selective epoxidation of a wide variety of olefins [40]. Chiral titanium complexes are used as catalysts for enantioselective epoxidations with alkyl hydroperoxides (see below).

The epoxidation of olefins with RO₂H or H₂O₂ (see above) catalyzed by early transition elements involves, as would be expected, a peroxometal mechanism in which the rate-limiting step is oxygen transfer from an electrophilic (alkyl) peroxometal species to the nucleophilic olefin (Fig. 4.20). The metal center does not undergo any change in oxidation state during the catalytic cycle. It functions as a Lewis acid by withdrawing electrons from the O–O bond and thus increased the electrophilic character of the coordinated peroxide. Active catalysts are metals that are strong Lewis acids and relatively weak oxidants (to avoid one electron oxidation of the peroxide) in their highest oxidation state.

Neither the homogeneous Mo nor the heterogeneous Ti(IV)/SiO₂ catalysts are effective with hydrogen peroxide as the oxygen donor. Indeed, they are severely inhibited by strongly coordinating molecules such as alcohols, and particularly water. Because of the strong interest in the use of H₂O₂ as the primary oxidant, particularly in the context of fine chemicals production, much effort has been devoted to developing epoxidation catalysts that are effective with aqueous hydrogen peroxide.

In the mid-1980s two approaches were followed to achieve this goal. Enichem scientists developed a titanium(IV)-silicalite catalyst (TS-1) that is extremely effective for a variety of synthetically useful oxidations, including epoxidation with



Olefin	Conv (%)	Yield (%)
1-octene	96	94
1-decene	99	99
1-dodecene	98	97
2-octene	99	99
styrene	52	3

Fig. 4.21 Epoxidation catalyzed by TS-1.

30% aqueous H_2O_2 (Fig. 4.21) [41]. The unique activity of TS-1 derives from the fact that silicalite is a hydrophobic molecular sieve, in contrast to Ti(IV)/SiO_2 which is hydrophilic. Consequently, hydrophobic substrates are preferentially adsorbed by TS-1 thus precluding the strong inhibition by water observed with Ti(IV)/SiO_2 . However, a serious limitation of TS-1 in organic synthesis is that its scope is restricted to relatively small molecules, e.g. linear olefins, which are able to access the micropores ($5.3 \times 5.5 \text{ \AA}^2$). This provoked a flurry of activity aimed at developing titanium-substituted molecular sieves with larger pores which, as yet, has not produced catalysts with comparable activity to TS-1 [42].

4.3.1.1 Tungsten Catalysts

At the same time Venturello and coworkers [43] followed a different approach. They showed that a mixture of tungstate and phosphate in the presence of a tetraalkylammonium salt as a phase transfer agent catalyzed epoxidations with H_2O_2 in a two-phase dichloroethane/water medium. Since its discovery in 1983 this system has been extensively studied [44, 45] in particular with regard to the exact nature of the active phosphotungstate catalyst [46]. More recently, Noyori and coworkers reported [47] a significant improvement of the original system. An appropriate choice of phase transfer catalyst, containing a sufficiently lipophilic tetraalkylammonium cation and a bisulfate (HSO_4^-) anion, in combination with catalytic amounts of $\text{H}_2\text{NCH}_2\text{PO}_3\text{H}_2$ and sodium tungstate produced an effective system for the epoxidation of olefins with H_2O_2 in toluene/water or in the absence of an organic solvent (Fig. 4.22). The type of ammonium salt used with phosphate/tungstic acid catalyst is important. For example *n*-octylammonium hydrogen sulfate is critical in Noyori's work; chloride causes deactivation and other ammonium hydrogen sulfates produce catalysts that are not as effective or are even completely inactive.

Subsequently, the Noyori-system was shown [48] to be an effective system for the oxidative cleavage of cyclic olefins to dicarboxylic acids (Fig. 4.23) using ≥ 4 equivalents of H_2O_2 , via the intermediate formation of the epoxide. For example, cyclohexene afforded adipic acid in 93% isolated yield, thus providing a 'green route' to adipic acid. Although the economics may be prohibitive for adipic acid manufacture, owing to the consumption of 4 equivalents of H_2O_2 , the method has general utility for the selective conversion of a variety of cyclic olefins to the corresponding dicarboxylic or keto-carboxylic acids.

The success of tungstate as catalyst has stimulated a wealth of research in this area. Recently it was shown that a silicotungstate compound, synthesized

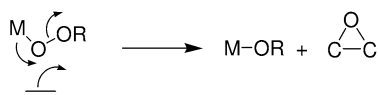


Fig. 4.22 Halide- and halogenated solvent-free biphasic epoxidation with 30% aqueous H_2O_2 using tungstate catalysts.

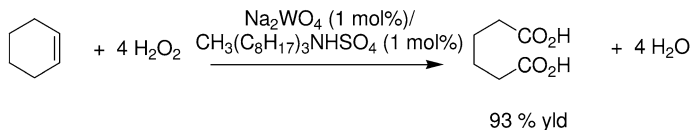


Fig. 4.23 Oxidative cleavage of cyclohexene using tungstate catalyst.

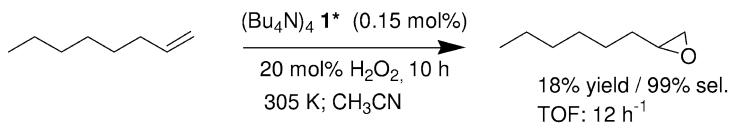


Fig. 4.24 Silicotungstate as recyclable catalyst for epoxidation.

by protonation of a divalent, lacunary Keggin-type compound, exhibits high catalytic performance for epoxidations with H₂O₂. For example, propene could be oxidized to propylene oxide with >99% selectivity at 305 K in acetonitrile using 0.15 mol% catalyst (1.5 mol% W) in 10 h (Fig. 4.24) [49]. This catalyst could be recovered and reused at least five times.

“Green” versions of the Venturello system have been developed: A smart recoverable phosphate/tungstic acid was obtained by using tributylphosphate as a cosolvent, in combination with a quaternary ammonium cetylpyridinium cation: $\pi\text{-}[\text{C}_5\text{H}_5\text{NC}_{16}\text{H}_{33}]_3[\text{PO}_4(\text{WO}_3)_4]$ [50]. This soluble material oxidizes propene with 30% H₂O₂ at 35 °C, and the reduced catalyst precipitates out once hydrogen peroxide is consumed. Heterogeneous versions of the Venturello-catalyst [51] have been obtained by direct support on ion-exchange resins [52]. Another approach is to heterogenize the quaternary ammonium functions that charge-balance the anionic W-catalysts as in PW₄-amberlite [52]. Other peroxotungstates can also be immobilized: cetylpyridium-dodecatungstates were immobilized on fluoroapatite and employed under anhydrous solvent-free conditions [53]. Furthermore peroxotungstate was immobilized on ionic liquid-modified silica and used as a catalyst in acetonitrile [54]. In general these catalysts are subject to low productivities. A much more active heterogeneous W-system was obtained by combining a [WO₄]²⁻-exchanged LDH catalyst with NH₄Br [55]. In this case W catalyzes the oxidation of the bromide ions. The thus formed bromohydrin is converted into the epoxide. Interesting activities could be observed for e.g. *α*-methylstyrene with H₂O₂ in the presence of NH₄Br at 40 °C, which produces almost 50 g of epoxide per g [WO₄]²⁻-LDH catalyst within 5 h with 95% epoxide selectivity [55].

4.3.1.2 Rhenium Catalysts

In the early 1990s Herrmann and coworkers [56] reported the use of methyltrioxorhenium (MTO) as a catalyst for epoxidation with anhydrous H₂O₂ in *tert*-butanol. In the initial publication cyclohexene oxide was obtained in 90% yield using 1 mol% MTO at 10 °C for 5 h. At elevated temperatures (82 °C) the corre-

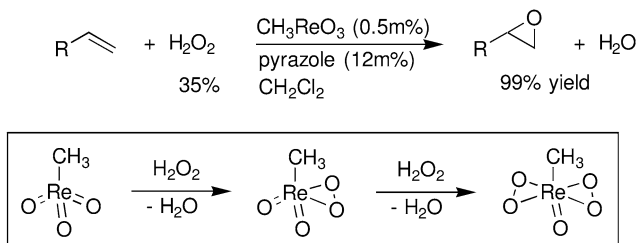


Fig. 4.25 MTO-Catalyzed epoxidations with H_2O_2 .

sponding *trans*-diol was obtained (97% yield) owing to the acidity of the system promoting ring opening of the epoxide. Subsequently, the groups of Herrmann [57] and Sharpless [58] significantly improved the synthetic utility of MTO by performing reactions in the presence of 10–12 mol% of heterocyclic bases, e.g. pyridine [58], 3-cyanopyridine [58] and pyrazole [57] in a dichloromethane/water mixture. For example, using the MTO-pyrazole system high activities and epoxide selectivities were obtained [57] with a variety of olefins using 35% aqueous H_2O_2 and 0.5 mol% MTO. The use of 2,2,2-trifluoroethanol further enhances the catalytic performance of the MTO/base/hydrogen peroxide system by a three- to ten-fold increase in TOF [59, 60]: In the epoxidation of cyclohexene turnover numbers of over 10000 could be achieved by slow addition of the substrate. Notably, the use of perfluorinated alcohols in the absence of catalysts already leads to significant epoxidation [60, 61]. This observation, that fluorinated alcohols are able to activate hydrogen peroxide, is tentatively attributed to the characteristic feature of highly fluorinated alcohols: owing to the strong electron-withdrawing effect of the perfluoroalkyl groups the hydroxy group is very electron poor and unable to accept a hydrogen bond but, at the same time, easily donates a hydrogen bond. In this way the perfluorinated alcohol acts as a Lewis acid and increases the electrophilicity of the hydrogen peroxide.

MTO-catalyzed epoxidations proceed via a peroxometal pathway involving a diperoxorhenium(VII) complex as the active oxidant (see Fig. 4.25). Major disadvantages of MTO are its limited stability under basic H_2O_2 conditions [62] and its rather difficult and, hence, expensive synthesis.

4.3.1.3 Ruthenium Catalysts

The systems described above all involve peroxometal species as the active oxidant. In contrast, ruthenium catalysts involve a ruthenium-oxo complex as the active oxidant [1]. Until recently, no Ru-catalysts were known that were able to activate H_2O_2 rather than to decompose it. However in 2005 Beller and co-workers recognized the potential of the Ru(terpyridine)(2,6-pyridinedicarboxylate) catalyst [63] for the epoxidation of olefins with H_2O_2 [64]. The result is a very efficient method for the epoxidation of a wide range of alkyl substituted or allylic alkenes using as little as 0.5 mol% Ru. In Fig. 4.26 details are given. Terminal

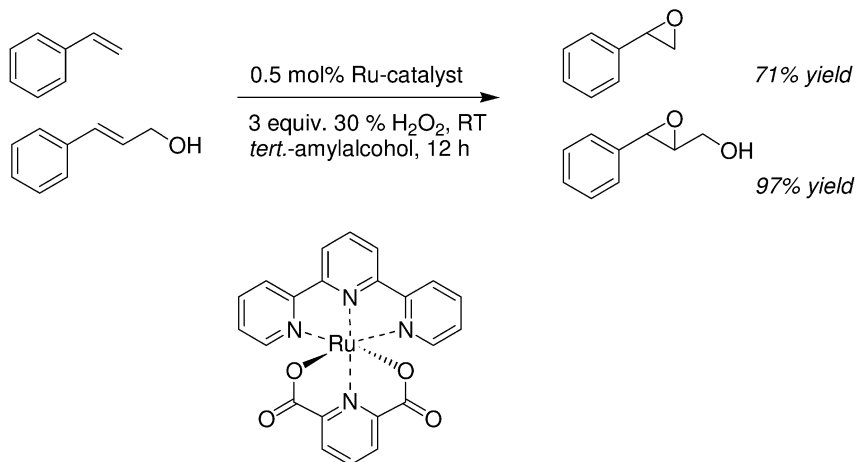


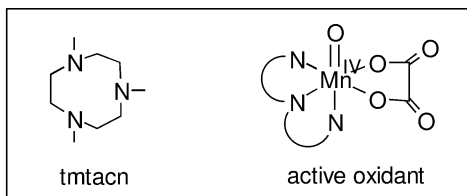
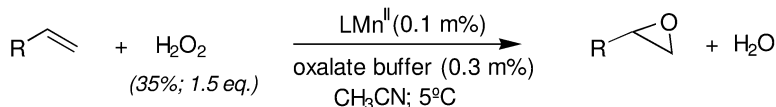
Fig. 4.26 Ru(terpyridine)(2,6-pyridinedicarboxylate) catalysed epoxidations.

olefins are not very active under these conditions. This system can be operated under neutral conditions, which makes it suitable for the synthesis of acid-sensitive epoxides as well.

4.3.1.4 Manganese Catalysts

Manganese-based catalysts probably involve an oxomanganese(V) complex as the active oxidant. Montanari and coworkers [65] described the use of a manganese(III) complex of a halogenated porphyrin, in the presence of hexylimidazole and benzoic acid, for epoxidations with 30% H₂O₂ in dichloromethane–water. More recently, Hage and coworkers [66] showed that a manganese(II) complex of trimethyl-1,4,7-triazacyclononane (tmtacn), originally developed as a bleach activator for application in detergents, is a highly active catalyst for epoxidations with H₂O₂ in aqueous methanol. In the original publication a vast excess of H₂O₂ was needed owing to competing manganese-catalyzed decomposition of the H₂O₂. Subsequent detailed investigations of this system by Jacobs and De Vos and coworkers [67] culminated in the development of an optimized system, comprising Mn(II)-tmtacn (0.1 mol%) in the presence of oxalate buffer (0.3 mol%) with 35% H₂O₂ (1.5 eq.) in acetonitrile at 5 °C. This system is an extremely active catalyst for the epoxidation of even relatively unreactive olefins. Mechanistic details are uncertain but it would seem likely that the active oxidant is an oxomanganese(IV) or (V) [68] complex containing one tmtacn and one oxalate ligand (see Fig. 4.27).

Recently it has been shown that simple manganese sulfate in the presence of sodium bicarbonate is reasonably effective in promoting the epoxidation of alkenes with aqueous H₂O₂ using DMF or *t*-BuOH as solvents [69]. In this system peroxo-carbonate is formed *in situ*, thus minimizing the catalase activity of the Mn salt. Following this discovery, Chan and coworkers introduced an imidazole-based ionic



Olefin				
Time (h)	0.3	0.3	1	2
Yield (%)	>99	>99	92	66

Fig. 4.27 Mn-tmtacn catalyzed epoxidation with H₂O₂.

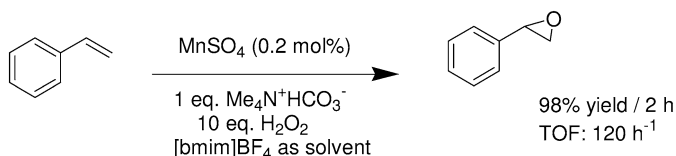


Fig. 4.28 Mn/bicarbonate system for epoxidation in ionic liquid.

liquid in the Mn/bicarbonate system in order to overcome the requirements of volatile organic cosolvents (see Fig. 4.28) [70]. A major disadvantage of these Mn salt systems is that 10 equivalents of H₂O₂ are still required to reach substantial conversions. Moreover simple terminal olefins cannot be oxidized in this way.

In addition, recently it was found that by using peracetic acid as the oxidant Mn^{II}(bipy)₂ becomes an extremely active catalyst. A turnover frequency over 200 000 h⁻¹ was found for 1-octene using 2 equivalents of peracetic acid in acetonitrile [71]. In spite of this high activity, the system above with Mn-tacn and H₂O₂ would be preferred because of the safety issues associated with peracetic acid and the production of acetic acid.

4.3.1.5 Iron Catalysts

Mechanistically related to Mn, is the use of Fe as an epoxidation catalyst. Recently, iron complexes with a tetradentate amine core were reported, that were capable of activating H₂O₂ without the involvement of hydroxyl radicals [72]. For a variety of substituted as well as terminal alkenes, effective epoxidation

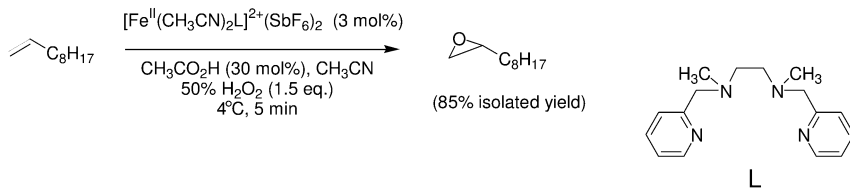


Fig. 4.29 Fe-tetradentate amine complexes as catalysts in epoxidation with H_2O_2 /acetic acid.

was described using 3 mol% of Fe, ≤ 30 mol% acetic acid and 1.5 eq. of 50% H_2O_2 (see Fig. 4.29) [73]. For a variety of substituted as well as terminal alkenes, complete conversion of the alkene was obtained leading to 77–85% isolated yields. Acetic acid was essential to obtain high epoxide yields. Investigations showed that under reaction conditions with the acid, peracetic acid is formed and that the iron(II) complex self-assembled into a μ -oxo, carboxylate bridged diiron(III) complex resembling the diiron(III) core found in the active site of the oxidized enzyme methane monooxygenase (MMO). The results obtained by Jacobsen are amongst the best obtained so far in epoxidation using iron catalysts and hydrogen peroxide. At the same time, Que showed that analogs of this iron complex led to asymmetric cis-dihydroxylation of olefins (see below) [74]. In addition it was found that, *in situ* prepared iron catalysts from ferric perchlorate or ferric nitrate and phenanthroline ligands, are very active catalysts with peracetic acid as the oxidant and acetonitrile as solvent [75]. TOFs of the order of 5000 h^{-1} were obtained for a variety of terminal and internal olefins. A major disadvantage is of course the requirement for peracetic acid (see above for Mn).

4.3.1.6 Selenium and Organocatalysts

Finally, organic compounds and arylseleninic acids have been described as catalysts for epoxidations with H_2O_2 . Perfluoroheptadecan-9-one was shown [76] to be a recyclable catalyst for the epoxidation of relatively reactive olefins with 60% aqueous H_2O_2 in 2,2,2-trifluoroethanol. The discovery that hydrogen peroxide can be used in conjunction with catalytic amounts of peroxyseleninic acids, dates from 1978 [77]. Recently 3,5-bis(trifluoromethyl)benzeneseleninic acid was used as the catalyst, and even sensitive epoxides could be formed in nearly quantitative yields, using S/C ratios as high as 200 (see Fig. 4.30 and Table 4.5) [78]. In these reactions bis(3,5-bis(trifluoromethyl)phenyl)-diselenide is the starting compound, which under reaction conditions gives the seleninic acid (see Fig. 4.30). Under these optimised conditions turnover frequencies of over 1000 h^{-1} were observed at room temperature.

It is clear from the preceding discussion that several systems are now available for epoxidations with aqueous H_2O_2 . The key features are compared in Table 4.5 for epoxidation of cyclohexene and a terminal olefin. They all have their limitations regarding substrate scope, e.g. TS-1 is restricted to linear olefins and

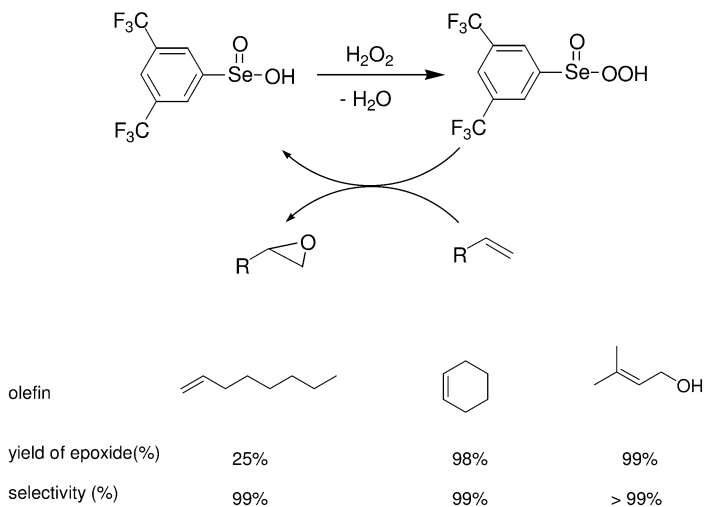


Fig. 4.30 Aromatic seleninic acids as catalysts for epoxidation.

Table 4.5 Catalytic epoxidation with H_2O_2 : state of the art.

Catalyst	Mn ^{a)}	W ^{b)}	Re ^{c)}	Re ^{d)}	Se ^{e)}	Ru ^{f)}	Ti ^{g)}
Ref.	67	48	57	59	78	64	41
S/C	666	50	200	1000	200	200	100
Solvent	CH_3CN	PhCH_3	CH_2Cl_2	$\text{CF}_3\text{CH}_2\text{OH}$	$\text{CF}_3\text{CH}_2\text{OH}$	TAA ^{h)}	CH_3OH
Temp. ($^\circ\text{C}$)	5	90	25	25	20	25	25
1-Alkene							
Yield (%)	99	81	99	99	25	–	74
TOF (h^{-1}) ⁱ⁾	2000	12	14	48	13	–	108
Cyclohexene							
Yield (%)	83	i)	99	99	98	84 ^{k)}	1
TOF (h^{-1}) ⁱ⁾	550	i)	198	2000	1000	14	1

a) Mn(tmtacn)/oxalate buffer.

b) $\text{WO}_4^{2-}/\text{H}_2\text{NCH}_2\text{PO}_3\text{H}_2/(\text{C}_8\text{H}_{17})_3\text{MeN}^+\text{HSO}_4^-$.

c) $\text{CH}_3\text{ReO}_3/\text{pyrazole}$ (12 mol%).

d) $\text{CH}_3\text{ReO}_3/\text{pyrazole}$ (10 mol%).

e) 0.25 mol% bis(3,5-bis(trifluoromethyl) phenyl)diselenide.

f) Ru(terpyridine)(pyridinedicarboxylate).

g) TS-1 (=titanosilicalite).

h) TAA = *tert.*-amylalcohol.

i) mol product/mol cat/h.

j) Gives adipic acid via ring opening.

k) Activity for 1-methyl-cyclohexene. This substrate is more nucleophilic, and therefore more reactive [1]. Essentially no reaction.

W gives ring opening with acid-sensitive epoxides, or the solvent required for good results, e.g. dichloromethane (MTO) and acetonitrile (Mn-tmtacn). Hence, the quest for even better systems continues.

4.3.1.7 Hydrotalcite and Alumina Systems

Relatively simple solid materials like hydrotalcites and clays can also act as catalysts for epoxidation in the presence of H_2O_2 . In the case of anionic clays like $\text{Mg}_{10}\text{Al}_2(\text{OH})_{24}\text{CO}_3$, these materials are basic enough to promote nucleophilic epoxidations [79]. For “normal” electrophilic epoxidation nitrile and amide additives are required [80]. It must, however, be recognized that these materials are polynuclear-alumina clays and simple alumina will also catalyze these reactions without additives [81]. A variety of alumina-materials can absorb hydrogen peroxide onto that surface forming an active oxidant (alumina-OOH). Reactions could be carried out using ethylacetate as the solvent, which is a cheap and environmentally attractive solvent. The major limitation of this system is the low tolerance towards water and to overcome this problem, reactions need to be carried out under Dean-Stark conditions. Furthermore selectivities are usually in the 70–90% range. Notably, the epoxide of α -pinene, which is very unstable, was also obtained in a reasonable 69% yield [81].

4.3.1.8 Biocatalytic Systems

A variety of monooxygenases (see above) can perform epoxidations. Some biocatalytic methods come into sight, which will become attractive for industrial use. In these cases chiral epoxides are the targeted products, and therefore this subject will be dealt with in Section 4.6.

4.3.2

Vicinal Dihydroxylation

The osmium-catalyzed vicinal dihydroxylation of olefins with single oxygen donors, typically TBHP or *N*-methylmorpholine-*N*-oxide (NMO), has been known for more than two decades [82] and forms the basis for the Sharpless asymmetric dihydroxylation of olefins (see below). The reaction involves an oxometal mechanism in which it is generally accepted that oxoosmium(VIII) undergoes an initial 2+2 cycloaddition to the olefin to give an oxametallocycle which subsequently rearranges to an osmium(VI)-diol complex (Fig. 4.31) [83]. This is followed by rate-limiting reaction with the oxidant to afford the diol product with concomitant regeneration of osmium tetroxide. Recently, the scope of this method was extended to electron-deficient olefins such as α,β -unsaturated amides by performing the reaction at acidic pH. Citric acid (25 mol%) was identified as the additive of choice and 1.1 equivalent of NMO was required as oxidant [84].

Beller and coworkers [85] showed that osmium-catalyzed dihydroxylations can be performed successfully with dioxygen as the primary oxidant (Fig. 4.32).

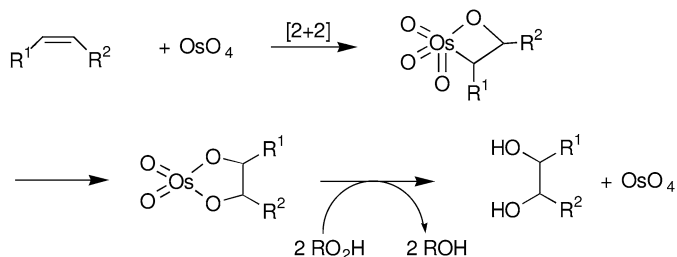
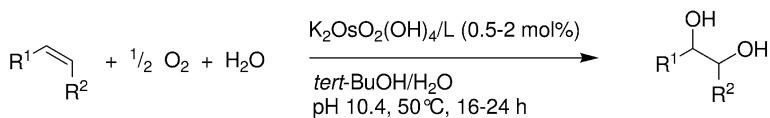


Fig. 4.31 Mechanism of osmium-catalyzed vicinal dihydroxylation of olefins.



L = quinuclidine, DABCO

Olefin				
Conv. (%)	99	66	100	90
Sel. (%)	96	77	97	75

Fig. 4.32 Osmium-catalyzed dihydroxylation using air as the oxidant.

Using potassium osmate (0.5–2 mol%) in the presence of an organic base, e.g. quinuclidine, in aqueous *tert*-butanol at pH 10.4, a variety of olefins was converted to the corresponding *vic*-diols in high yield. Apparently reoxidation of osmium(VI) to osmium(VIII) with dioxygen is possible under alkaline conditions. When chiral bases were used asymmetric dihydroxylation was observed (see Section 4.7) albeit with moderate enantioselectivities.

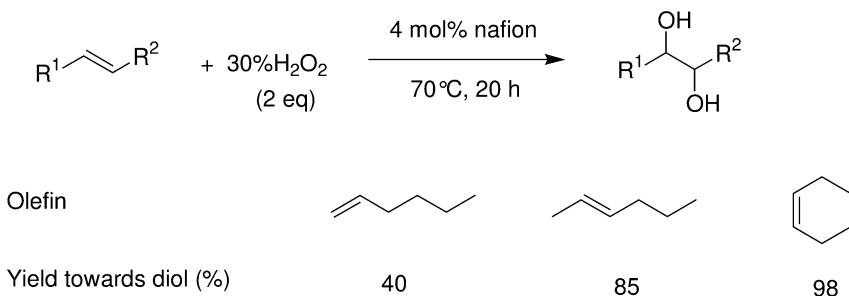


Fig. 4.33 Heterogeneous acid-catalyzed dihydroxylation of olefins.

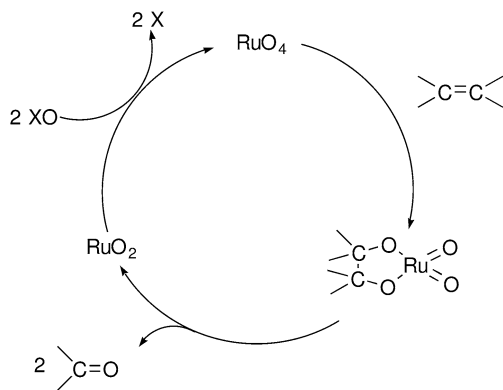
Osmium is unrivalled as catalyst for the asymmetric cis-dihydroxylation of olefins. However, Sato and coworkers reported that the perfluorosulfonic acid resin, Nafion[®] (see Chapter 2) is an effective catalyst for the trans-dihydroxylation of olefins with H₂O₂ [86]. The method is organic solvent-free and the catalyst can be easily recycled (see Fig. 4.33). The first step of this reaction is epoxidation which is probably carried out by resin-supported peroxysulfonic acid formed *in situ*. This is followed by acid-catalyzed epoxide-ring opening.

4.3.3

Oxidative Cleavage of Olefins

It has long been known that oxidative cleavage of olefinic double bonds occurs with stoichiometric amounts of the powerful oxidant rutheniumtetroxide [87]. Ruthenium-catalyzed oxidative cleavage has been described with various oxygen donors, e.g. NaIO₄ [88, 89] and NaOCl [90] as the primary oxidant. The presumed catalytic cycle, in which RuO₄ is the active oxidant, is shown in Fig. 4.34. Various attempts have been made to introduce a green element in this reaction, i.e. recyclable heterogenous Ru-nanoparticles [91], and environmentally acceptable solvents [92], but the main problem of the oxidant has not been solved.

From an economic viewpoint it would obviously be advantageous if hydrogen peroxide or even dioxygen could be used as the primary oxidant. Unfortunately, ruthenium compounds generally catalyze rapid, non-productive decomposition of hydrogen peroxide [93]. However, a bimetallic system, comprising MoO₃/RuCl₃, for the oxidative cleavage of olefins with H₂O₂ in *tert*-butanol has been described [94]. For optimum performance a small amount of a carboxylic acid, which could be the product of the oxidative cleavage, was added. Presumably, the reaction involves initial molybdenum-catalyzed conversion to the *vic*-diol via the epoxide, followed by ruthenium-catalyzed oxidative cleavage of the diol.



XO = NaOCl, NaIO₄, RCO₃H etc.

Fig. 4.34 A catalytic cycle for ruthenium-catalyzed oxidative cleavage of olefins.

Methodologies for the oxidative cleavage of olefins still, in our opinion, leave something to be desired. Bearing in mind the osmium-catalyzed aerobic dihydroxylation of olefins (see Section 4.3.2) and the ruthenium-catalyzed aerobic oxidations of alcohols and cleavage of diols (see below) one cannot help wondering if conditions cannot be designed for the ruthenium-catalyzed aerobic oxidative cleavage of olefins. Indeed for compounds like styrene and stilbene up to 80% yield can be obtained for oxidative cleavage at 130 °C using 0.004 mol% of a RuCl_2 -PNNP complex [95]. Alternatively, a combination of osmium and ruthenium might be expected to have this capability.

Another possibility is the use of tungsten, which has led to excellent results for the conversion of cyclohexene to adipic acid (see Fig. 4.23) [48]. For linear olefins using the Venturello-system, oxidative cleavage products can be obtained in around 80% yield [96].

4.3.4

Oxidative Ketonization

The selective aerobic oxidations of ethene to acetaldehyde and terminal alkenes to the corresponding methyl ketones, in the presence of a $\text{PdCl}_2/\text{CuCl}_2$ catalyst are collectively referred to as Wacker oxidations [97]. The reaction involves hydroxypalladation of the olefin, via nucleophilic attack of coordinating hydroxide on a palladium-olefin π complex followed by a β -hydride shift to give the acetaldehyde (or methyl ketone) product and palladium(0) (Fig. 4.35). The latter undergoes copper-catalyzed reoxidation with dioxygen. The presence of chloride ions at acidic pH is necessary for a reasonable rate of reoxidation and to prevent the formation of palladium clusters.

A major disadvantage of the Wacker system is the extremely corrosive nature of (acidic) aqueous solutions of PdCl_2 and CuCl_2 , which necessitates the use of costly titanium alloys as materials of construction. With higher olefins oxidation rates are lower and complex mixtures are often formed as a result of competing palladium-catalyzed isomerization of the olefin. Research has been focused on developing acid-free $\text{PdCl}_2/\text{CuCl}_2$ catalyzed Wacker oxidations using ionic liquid [98], ionic liquid/ ScCO_2 [99], and heterogeneous Pd montmorillonite [100].

However, all these systems suffer from high concentrations of chloride ion, so that substantial amounts of chlorinated by-products are formed. For these reasons there is a definite need for chloride- and copper-free systems for Wacker oxidations. One such system has been recently described, viz., the aerobic oxidation of terminal olefins in an aqueous biphasic system (no additional solvent)

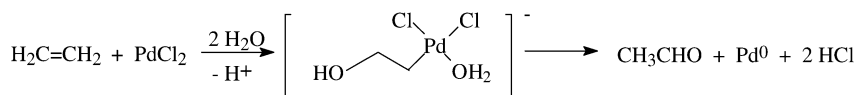


Fig. 4.35 $\text{PdCl}_2/\text{CuCl}_2$ catalyzed Wacker oxidation.

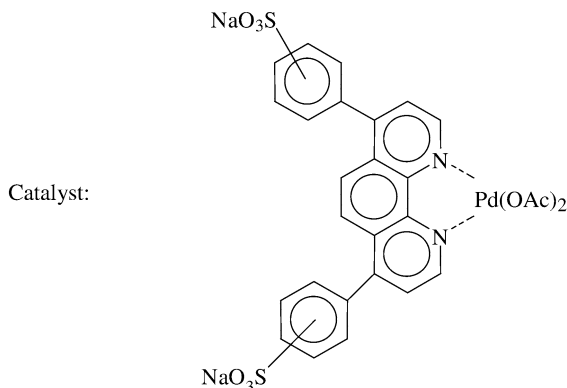
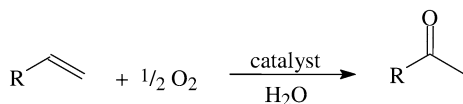


Fig. 4.36 Water-soluble palladium complexes for Wacker oxidation.

catalyzed by water-soluble palladium complexes of bidentate amines such as sulfonated bathophenanthroline (see Fig. 4.36) [101].

Moreover, it was disclosed that PdCl_2 in combination with *N,N*-dimethylacetamide (DMA) solvent could offer a simple and efficient catalyst system for acid- and Cu-free Wacker oxidation [102]. The reaction is illustrated in Fig. 4.37. A wide range of terminal olefins could be oxidized to form the corresponding methyl ketones in high yields, reaching a TOF up to 17 h^{-1} . The Pd-DMA catalyst layer could be recycled. Furthermore this system is also capable of per-

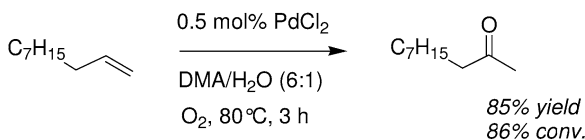
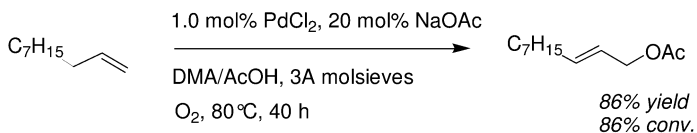


Fig. 4.37 PdCl_2 /*N,N*-dimethylacetamide system for Wacker oxidation of olefins.



ratio linear:branched = 13:1

Fig. 4.38 PdCl_2 /*N,N*-dimethylacetamide system for regioselective acetoxylation of terminal olefins.

forming regioselective acetoxylation of terminal olefins to linear allylic acetates (see Fig. 4.38). This system shows a strong resemblance to the Bäckvall system (see below and Fig. 4.41) [103].

In this context it is also worth mentioning that Showa Denko has developed a new process for the direct oxidation of ethene to acetic acid using a combination of palladium(II) and a heteropoly acid [104]. However, the reaction probably involves heteropoly acid-catalyzed hydration followed by palladium-catalyzed aerobic oxidation of ethanol to acetic acid rather than a classical Wacker mechanism.

4.3.5

Allylic Oxidations

Classical (metal-catalyzed) autoxidation of olefins is facile but not synthetically useful owing to competing oxidation of allylic C–H bonds and the olefinic double bond, leading to complex product mixtures [105]. Nonetheless, the synthetic chemist has a number of different tools for the allylic oxidation of olefins available.

Stoichiometric oxidation with SeO_2 became more attractive after Sharpless showed that the reaction could be carried out with catalytic amounts of SeO_2 and TBHP as the (re)oxidant [106]. The reaction involves an oxometal mechanism (see Fig. 4.39). The use of fluoroseleninic acids with iodoxybenzene as oxidant introduces the possibility of recycling the catalyst [107].

Allylic oxidation (acyloxylation) can also be achieved with copper catalysts and stoichiometric amounts of peresters or an alkylhydroperoxide in a carboxylic acid as solvent [108], via a free radical mechanism (Fig. 4.40). The use of water-soluble ligands [109] or fluoros solvents [110] allows recycling of the copper catalyst. In view of the oxidants required, this reaction is economically viable only when valuable (chiral) products are obtained using asymmetric copper catalysts [111–113]. The scope of the reaction is rather limited however.

Arguably the best, or at least the most versatile, allylic oxidation method is based on Pd [114]. Since the intermediates are palladium-allyl complexes rather than free radicals the number of by-products is limited compared to the preceding examples (Fig. 4.41). Furthermore, a large number of nucleophiles (amines, alcohols, stabilized carbanions, carboxylates or halides) may attack the palladium-allyl complex, giving a wide variety of products.

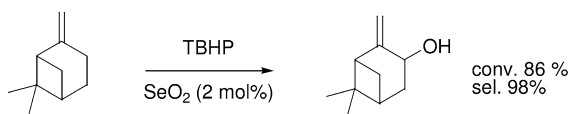


Fig. 4.39 Selenium-catalyzed allylic oxidation of olefins.

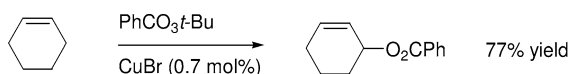


Fig. 4.40 The Kharasch–Sosnovsky reaction for allylic oxidation of olefins.

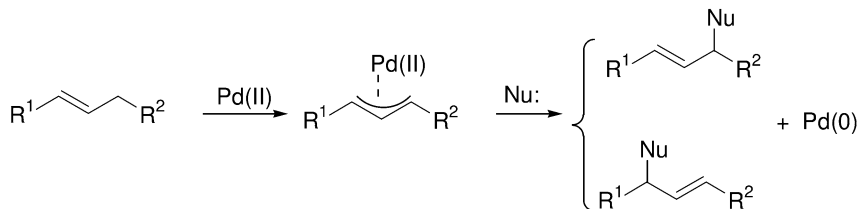


Fig. 4.41 Pd-catalyzed allylic oxidation of olefins.

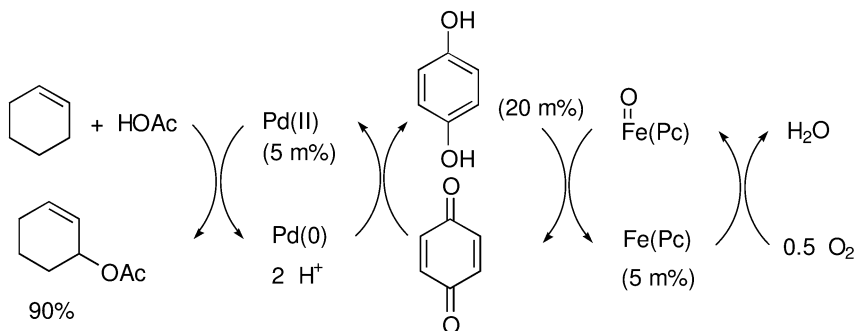


Fig. 4.42 The Pd/mediator approach for allylic oxidation of olefins.

In the group of Bäckvall a method was developed involving palladium and benzoquinone as cocatalyst (Fig. 4.42) [103]. The difficulty of the catalytic reaction lies in the problematic reoxidation of Pd(0) which cannot be achieved by dioxygen directly (see also Wacker process). To overcome this a number of electron mediators have been developed, such as benzoquinone in combination with metal macrocycles, heteropolyacids or other metal salts (see Fig. 4.42). Alternatively a bimetallic palladium(II) air oxidation system, involving bridging phosphines, can be used which does not require additional mediators [115]. This approach would also allow the development of asymmetric Pd-catalyzed allylic oxidation.

4.4

Alkanes and Alkylaromatics

One of the remaining “holy grails” in catalysis is undoubtedly the selective oxidation of unfunctionalized hydrocarbons, such as alkanes [116]. Generally speaking the difficulty lies in the activation of the poorly reactive C–H bonds and stabilization of a product which is often more reactive than the starting material. There are few notable exceptions e.g. the gas phase oxidation of butane to maleic anhydride (a highly stable product) and isobutane to *tert*-butylhydroperoxide (a highly reactive tertiary C–H bond). The aerobic oxidation of cyclo-

hexane to cyclohexanol/cyclohexanone – the starting material for adipic acid used on a million tonnes scale for the manufacture of nylon-6,6 – is more challenging [117]. Since the substrate lacks reactive C–H bonds and the product cannot be stabilized, the reaction is stopped at <10% conversion to prevent further oxidation, affording a roughly 1:1 mixture of cyclohexanol/cyclohexanone in ca. 80% selectivity.

As noted in Section 4.2 the selective oxidation of unreactive C–H bonds with dioxygen is fraught with many problems, e.g. the oxidative destruction of organic ligands and competition with free radical oxidation pathways. For this reason most biomimetic systems employ sacrificial reductants or a reduced form of dioxygen, e.g. H_2O_2 [118]. One extensively studied class of biomimetic catalysts comprises the so-called Gif-systems [119], which were believed to involve direct insertion of high-valent oxoiron(V) species into C–H bonds. However, more recent results suggest that classical free radical mechanisms may be involved [120].

4.4.1

Oxidation of Alkanes

Classical autoxidation of tertiary C–H bonds in alkanes can afford the corresponding hydroperoxides in high selectivities. This is applied industrially in the conversion of pinane to the corresponding hydroperoxide, an intermediate in the manufacture of pinanol (Fig. 4.43).

More reactive hydroperoxides can be converted selectively to alcohols via the method of Bashkirov (Fig. 4.44), where a boric acid ester protects the product from further oxidation and thus increases the selectivity [121]. The method is used to convert C_{10} – C_{20} paraffins to alcohols which are used as detergents and surfactants, for the oxidation of cyclohexane (see elsewhere) and cyclododecane to cyclododecanol (cyclododecanone) for the manufacture of nylon-12.

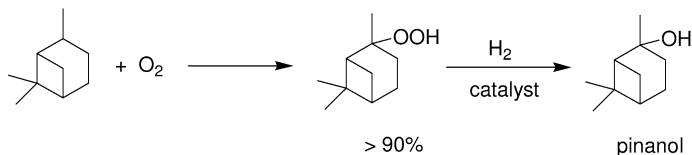


Fig. 4.43 Selective oxidation of pinane.

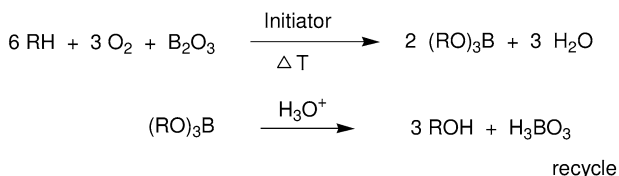


Fig. 4.44 Bashkirov method for conversion of alkanes to alcohols.

For less reactive hydrocarbons more drastic measures are required. High valent metal compounds, especially ruthenium compounds [122], can react with hydrocarbons but usually more than stoichiometric amounts of peracids or peroxides are required to reach the high oxidation state of the metal (e.g. Ru^{VI}). One of the very few examples in which a clean oxidant (H₂O₂ or O₂) is used, was reported by Drago et al. using a *cis*-dioxoruthenium complex (Fig. 4.45 a). In both cases a free radical mechanism could not be excluded, however [123]. In a variation on this theme Catalytica researchers described the direct oxidation of methane to methanol, using a platinum-bipyrimidine complex in concentrated sulfuric acid (Fig. 4.45 b) [124]. Analogous to the Bashkirov method the sulfuric acid protects the methanol, via esterification, from overoxidation to (eventually) CO₂ and H₂O, which is a highly thermodynamically favorable process.

Recently the Co/Mn/*N*-hydroxyphthalimide (NHPI) systems of Ishii have been added to the list of aerobic oxidations of hydrocarbons, including both aromatic side chains and alkanes. For example, toluene was oxidized to benzoic acid at 25 °C [125] and cyclohexane afforded adipic acid in 73% selectivity at 73% conversion [126], see Fig. 4.46. A related system, employing *N*-hydroxysaccharine, instead of NHPI was reported for the selective oxidation of large ring cycloalkanes [127].

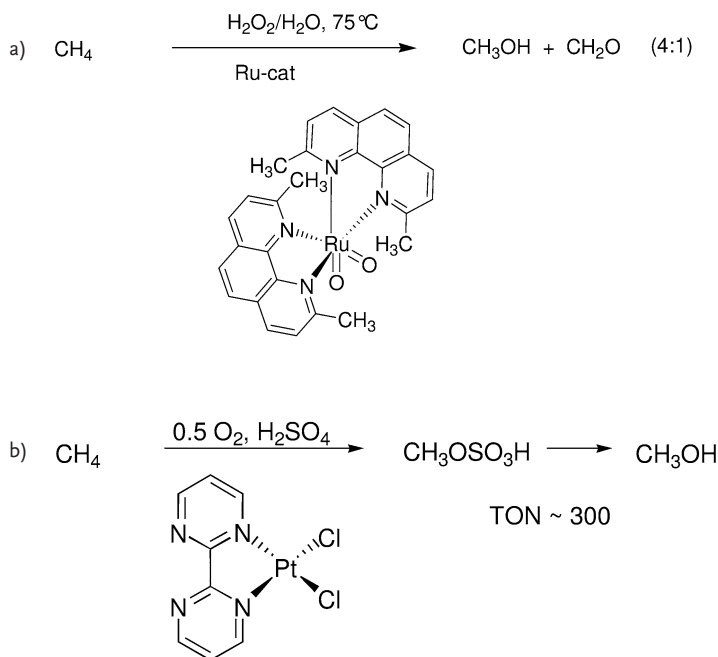


Fig. 4.45 Approaches for selective conversion of methane to methanol using O₂ or H₂O₂ as oxidants.

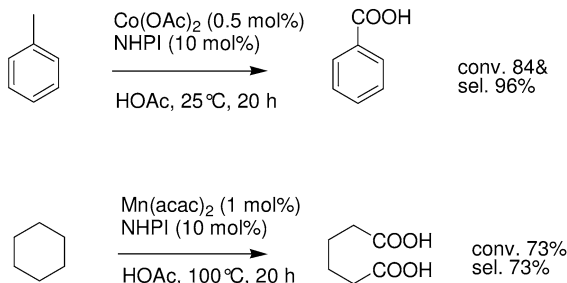


Fig. 4.46 NHPI as cocatalyst for aerobic oxidation of toluene and cyclohexane.

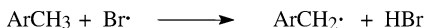


Fig. 4.47 Synergistic effect of bromide ions and NHPI compared.

The role of NHPI seems to be analogous to that of bromide ions during autoxidation processes: Bromide ion has a pronounced synergistic effect on metal-catalyzed autoxidations [128–130]. This results from a change in the chain-propagation step from hydrogen abstraction by alkylperoxy radicals to the energetically more favorable hydrogen abstraction by bromine atoms (Fig. 4.47). The bromine atoms are formed by one-electron oxidation of bromide ions by, for example, cobalt(III) or manganese(III), generally a more favorable process than one-electron oxidation of the hydrocarbon substrate.

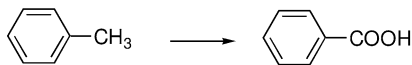
4.4.2

Oxidation of Aromatic Side Chains

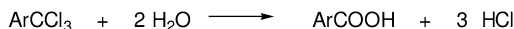
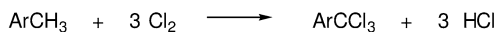
The power of ‘green chemistry’ is nicely illustrated by reference to the production of aromatic acids. Classical methods using chlorine or nitric acid have been largely displaced by catalytic oxidations with dioxygen (see Fig. 4.48). This leads to high atom utilization, low-salt technology, no chloro- or nitro-compounds as by-products and the use of a very cheap oxidant.

Oxidation of hydrocarbons with dioxygen is more facile when the C–H bond is activated through aromatic or vinylic groups adjacent to it. The homolytic C–H bond dissociation energy decreases from ca. $100 \text{ kcal mol}^{-1}$ (alkyl C–H) to ca. 85 kcal mol^{-1} (allylic and benzylic C–H), which makes a number of autoxidation processes feasible. The relative oxidizability is further increased by the presence of alkyl substituents on the benzylic carbon (see Table 4.6). The autoxidation of isopropylbenzene (Hock process, Fig. 4.49) accounts for the majority of the world production of phenol [131]:

In the Amoco/MC process terephthalic acid (TPA) is produced by aerobic oxidation of *p*-xylene. This bulk chemical ($>10 \times 10^6 \text{ t a}^{-1}$) is chiefly used for poly-



1) CHLORINATION + HYDROLYSIS, atom utilization = 36%



2) NITRIC ACID OXIDATION, atom utilization = 56%



3) CATALYTIC AEROBIC OXIDATION, atom utilization = 87%



Fig. 4.48 Classical versus 'green' aromatic side-chain oxidation.

Table 4.6 Relative oxidizability of aromatic side-chains.

Substrate	Rel. Oxidizability
PhCH ₃	1.0
PhCH ₂ CH ₃	15
PhCH(CH ₃) ₂	107

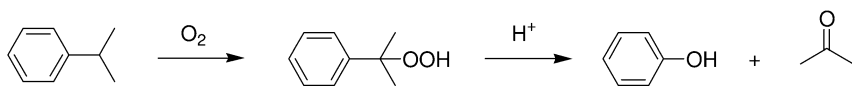


Fig. 4.49 Hock process for production of phenol.

etheneterephthalate (PET, a polymer used in e.g. plastic bottles). The solvent of choice is acetic acid, which shows a high solubility for substrates and low for products, is safe, recyclable (up to 40 times), has a wide temperature range and is relatively inert [132], although some solvent is "burnt" into CO₂ and H₂O (Fig. 4.50).

The rather drastic conditions are required because in this particular case the COOH group deactivates the intermediate *p*-toluic acid towards further oxidation, and some *p*-carboxybenzaldehyde is found as a side-product, which is hydrogenated back to *p*-toluic acid. Other than that, a large number of functional groups are tolerated (see Table 4.7) [129]. The combination of cobalt, manganese and bromide ions is essential for optimum performance. The benzylic radicals are best generated with bromine atoms (see above) which in turn are more easily produced

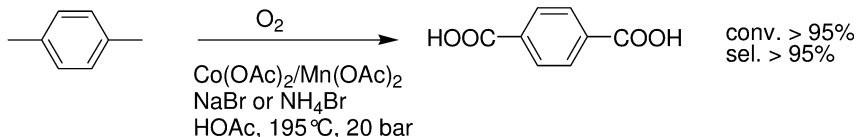


Fig. 4.50 Amoco/MC process for the production of terephthalic acid.

Table 4.7 Tolerance of functional groups in Co/Mn/Br-catalyzed aerobic oxidation of substituted toluenes.^{a)}

Complete conversion 90–98% yield	Side reactions 30–70% yield	Total radical consumption no yield
F, Cl, Br (o,m,p)	OAc (m,p)	I (o,m,p)
OCH ₃ (p)	OCH ₃ (o,m)	OH (o,m,p)
OPh (m,p)	NHAc (m,p)	NH ₂ (o,m,p)
COOH (m,p)	COOH (o)	OPh (o)
NO ₂ (m,p)	Ph (o)	NO ₂ (o)
Ph (m,p)	SO ₂ NH ₂ (o)	
COPh (o,m,p)		
SO ₂ NH ₂ (m,p)		
SO ₂ R (m,p)		
POR ₂ (o,m,p)		

a) Taken from Ref. [129].

by reaction of bromide with Mn^{III} rather than Co^{III} (see Fig. 4.51). The resulting peracid, however, is more easily reduced by Co^{II} than by Mn^{II}. In the Eastman Kodak and related processes fairly large amounts of e.g. acetaldehyde (0.21 t/t) are used as additives instead of bromide, leading to less corrosion.

The use of manganese catalysts maintains a low concentration of Co(III), which is important since the latter promotes extensive decarboxylation of acetic acid at $T > 130^\circ\text{C}$. A somewhat similar process which operates under biphasic conditions rather than in acetic acid also gives high conversions and selectivities [133].

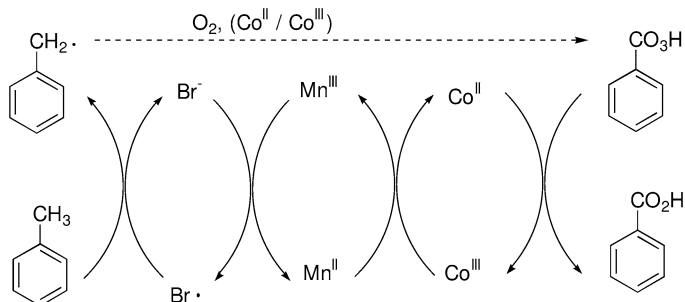


Fig. 4.51 Mechanism for the aerobic oxidation of aromatic side-chains.

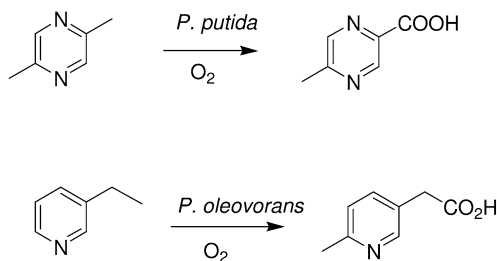


Fig. 4.52 Biocatalytic oxidation of alkyl groups on aromatic heterocycles.

Lonza has successfully developed a biocatalytic method for the oxidation of alkyl groups on aromatic heterocycles [5]. The oxidation is carried out in a fermenter using *Pseudomonas putida* grown on xylenes as the microorganism. Product concentrations of up to 24 g L^{-1} could be reached. Another microorganism *Pseudomonas oleovorans* grown on n-octane could be used for the terminal oxidation of ethyl groups (see Fig. 4.52). These are important examples of industrial biocatalytic applications where the high selectivity and activity demonstrated by enzymes for these difficult alkane transformations has a clear advantage. The reactions need to be carried out with living cells, because the monooxygenase enzymes, which carry out these transformations are cofactor-dependent (see Chapter 1, Section 1.2). The success of this methodology is related to the relatively high water-solubility of these heterocycles, which makes them more amenable to oxidation by enzymes.

Another example of industrially viable biooxidation of *N*-heterocycles side chain oxidation is the oxidation of 2-methylquinoxaline to 2-quinoxalinecarboxylic acid by Pfizer [134].

4.4.3

Aromatic Ring Oxidation

Oxidation of aromatic rings is quite complicated for a number of reasons. Firstly, radical intermediates preferentially abstract hydrogen atoms from the aromatic side chain, rather than the nucleus (the dissociation energies of the Ar-H bond and the ArCR₂-H bond are $\sim 110 \text{ kcal mol}^{-1}$ and $\sim 83 \text{ kcal mol}^{-1}$, respectively). Secondly, the phenol products are much more reactive towards oxidation than the hydrocarbon substrates. Recently a solution was found to the problem of over-oxidation by using aqueous-organic solvent mixtures. The optimum conditions are represented in Fig. 4.53. As catalyst, FeSO₄, which is a conventional Fenton catalyst, was applied in the presence of 5-carboxy-2-methylpyridazine *N*-oxide as ligand and trifluoroacetic acid as cocatalyst [135]. The choice of the N,O ligand turned out to be crucial. Using 10-fold excess of benzene to hydrogen peroxide, 97% selectivity of phenol (relative to benzene) could be achieved at almost full conversion of H₂O₂. Similar results could be obtained by using aqueous-ionic liquid biphasic mixtures and iron-dodecanesulfonate salts as catalyst [136].

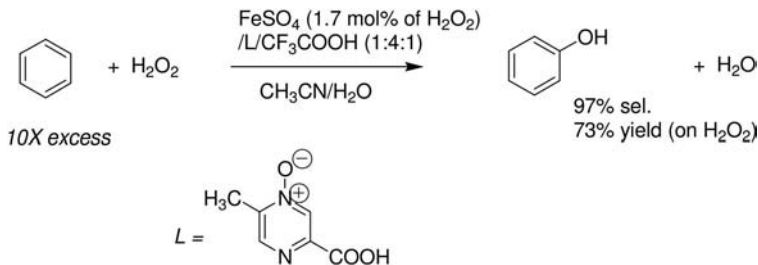


Fig. 4.53 Direct oxidation of benzene to phenol using H₂O₂.

This technology could also be applied for the oxidation of methane (70 °C, 5 Mpa) to formic acid (46% selectivity based on hydrogen peroxide). Another catalyst which can be applied for the direct oxidation of benzene with H₂O₂ is the TS-1 catalyst, as described above for propylene epoxidation [41]. Conversion is generally kept low, because introduction of a hydroxy group activates the aromatic nucleus for further oxidation to hydroquinone, catechol and eventually to tarry products [137].

Arguably the best technology – due to its simplicity – for directly converting benzene to phenol is represented by the Fe-ZSM-5/N₂O gas phase technology as developed by Panov and coworkers [138]. Nitrous oxide is the terminal oxidant, and MFI-type zeolite-containing low amounts (<1.0 wt%) of iron acts as the catalyst. The use of N₂O instead of oxygen circumvents the occurrence of free radical reactions. In this way highly selective conversion to phenol (>95%) could be reached at 350 °C (Fig. 4.54). The technology was adopted by Monsanto, but no chemical plant was built. Oxidation of other aromatics and alkenes using this technology generally leads to low selectivities.

For the direct hydroxylation of *N*-heterocycles a microbial oxidation is most suitable. Lonza developed a process to produce 6-hydroxynicotinic acid on a 10 tonnes scale [5]. The enzymatic production is carried out in two-steps. Firstly, *Achromobacter xylosoxydans* LK1 biomass is produced, which possesses a highly

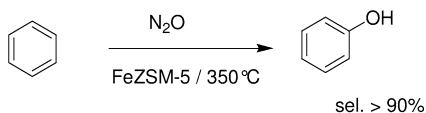


Fig. 4.54 Direct oxidation of benzene to phenol using N₂O as the terminal oxidant.

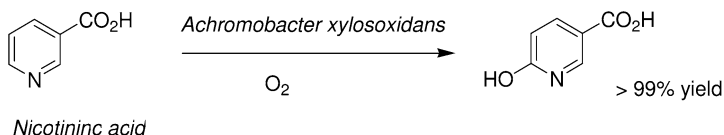


Fig. 4.55 Hydroxylation of nicotinic acid.

active nicotinic acid hydroxylase. In the second step the biomass is used for the hydroxylation (Fig. 4.55). The impressive yield of >99% is due to the selectivity of the enzyme involved.

4.5

Oxygen-containing Compounds

4.5.1

Oxidation of Alcohols

The oxidation of primary and secondary alcohols into the corresponding carbonyl compounds plays a central role in organic synthesis [1, 139, 140]. Traditional methods for performing such transformations generally involve the use of stoichiometric quantities of inorganic oxidants, notably chromium(VI) reagents [141]. However, from both an economic and environmental viewpoint, atom efficient, catalytic methods that employ clean oxidants such as O_2 and H_2O_2 are more desirable.

The catalytic oxidation of alcohols is a heavily studied field, where many metals can be applied. New developments in the 21st century can be discerned, such as the use of nanocatalysts (notably Pd and Au) which combine high stability with a high activity. Furthermore catalysis in water, and the use of non-noble metals such as copper are important green developments. Thus both homogeneous and heterogeneous catalysts are employed. In addition, biocatalysis is on the rise. In combination with a mediator, the copper-dependent oxidase, laccase is very promising for alcohol oxidation. Furthermore, alcohol dehydrogenases can also be employed for (asymmetric) alcohol oxidation, by using acetone as a cosubstrate. It should be noted that hydrogen peroxide is not really needed for alcohol conversion, compared to the use of oxygen it has little advantage. The focus in this section will therefore be on molecular oxygen. For a complete overview in this field the reader is referred to reviews on this topic [142–144]. We will start with some mechanistic aspects and a separate section highlighting the green aspects of using industrially important oxoammonium ions as catalyst. The latter methodology is widely used in industrial batch processes.

As discussed above, metal-catalyzed oxidations with hydrogen peroxide or alkyl hydroperoxide can be conveniently divided into two categories, involving peroxometal and oxometal species, respectively, as the active oxidant [13]. This is illustrated for alcohol oxidations in Fig. 4.56 [4]. In the peroxometal pathway the metal ion does not undergo any change in oxidation state during the catalytic cycle and no stoichiometric oxidation is observed in the absence of H_2O_2 . In contrast, oxometal pathways involve a two-electron change in oxidation state of the metal ion and a stoichiometric oxidation is observed, with the oxidized state of the catalyst, in the absence of H_2O_2 . Indeed, this is a test for distinguishing between the two pathways.

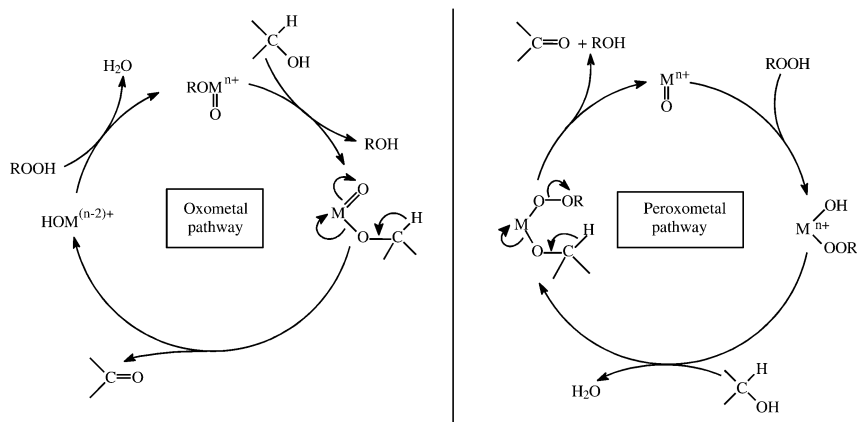


Fig. 4.56 Oxometal versus peroxometal pathways for alcohol oxidation.

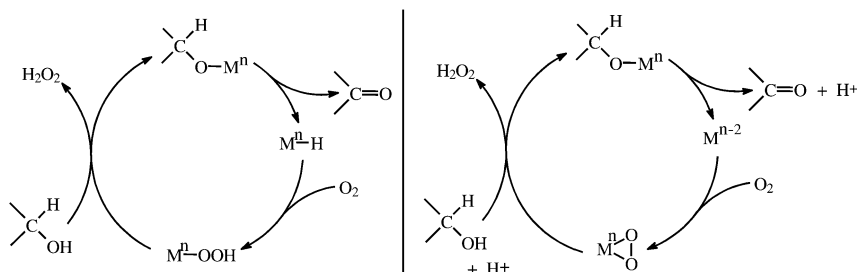


Fig. 4.57 Mechanism for metal catalyzed aerobic oxidation of alcohols.

In aerobic oxidations of alcohols a third pathway is possible with late transition metal ions, particularly those of Group VIII elements. The key step involves dehydrogenation of the alcohol, via β -hydride elimination from the metal alkoxide to form a metal hydride (see Fig. 4.57). This constitutes a commonly employed method for the synthesis of such metal hydrides. The reaction is often base-catalyzed which explains the use of bases as cocatalysts in these systems. In the catalytic cycle the hydridometal species is reoxidized by O_2 , possibly via insertion into the M-H bond and formation of H_2O_2 . Alternatively, an alkoxy metal species can afford a proton and the reduced form of the catalyst, either directly or via the intermediacy of a hydridometal species (see Fig. 4.57). Examples of metal ions that operate via this pathway are $\text{Pd}(\text{II})$, $\text{Ru}(\text{III})$ and $\text{Rh}(\text{III})$. We note the close similarity of the β -hydride elimination step in this pathway to the analogous step in the oxometal pathway (see Fig. 4.56). Some metals, e.g. ruthenium, can operate via both pathways and it is often difficult to distinguish between the two.

4.5.1.1 Ruthenium Catalysts

Ruthenium compounds have been extensively studied as catalysts for the aerobic oxidation of alcohols [142]. They operate under mild conditions and offer possibilities for both homogeneous and heterogeneous catalysts. The activity of common ruthenium precursors such as $\text{RuCl}_2\text{PPh}_3$, can be increased by the use of ionic liquids as solvents (Fig. 4.58). Tetramethylammoniumhydroxide and aliquat[®] 336 (tricaprylmethylammonium chloride) were used as solvent and rapid conversion of benzyl alcohol was observed [145]. Moreover the tetramethylammonium hydroxide/ $\text{RuCl}_2(\text{PPh}_3)_3$ could be reused after extraction of the product.

Ruthenium compounds are widely used as catalysts for hydrogen transfer reactions. These systems can be readily adapted to the aerobic oxidation of alcohols by employing dioxygen, in combination with a hydrogen acceptor as a cocatalyst, in a multistep process. These systems demonstrate high activity. For example, Bäckvall and coworkers [146] used low-valent ruthenium complexes in combination with a benzoquinone and a cobalt-Schiff's base complex. Optimization of the electron-rich quinone, combined with the so-called "Shvo" Ru-catalyst, led to one of the fastest catalytic systems reported for the oxidation of secondary alcohols (Fig. 4.59).

The regeneration of the benzoquinone can also be achieved with dioxygen in the absence of the cobalt cocatalyst. Thus, Ishii and coworkers [147] showed that a combination of $\text{RuCl}_2(\text{Ph}_3\text{P})_3$, hydroquinone and dioxygen, in PhCF_3 as solvent, oxidized primary aliphatic, allylic and benzylic alcohols to the corresponding aldehydes in quantitative yields.

Another example of a low-valent ruthenium complex, is the combination of $\text{RuCl}_2(\text{Ph}_3\text{P})_3$ and the stable nitroxyl radical, 2,2',6,6'-tetramethylpiperidine-*N*-oxyl (TEMPO). This system is a remarkably effective catalyst for the aerobic oxidation of a variety of primary and secondary alcohols, giving the corresponding aldehydes and ketones, respectively, in >99% selectivity [148]. The best results were obtained using 1 mol% of $\text{RuCl}_2(\text{Ph}_3\text{P})_3$ and 3 mol% of TEMPO (Fig. 4.60). Primary alcohols give the corresponding aldehydes in high selectivity, e.g. 1-octanol affords 1-octanal in >99% selectivity. Over-oxidation to the corresponding carboxylic acid, normally a rather facile process, is completely suppressed in the presence of a catalytic amount of TEMPO. TEMPO suppresses the autoxidation of aldehydes by efficiently scavenging free radical intermediates

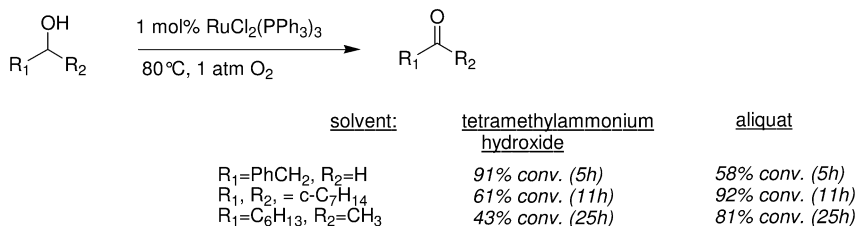


Fig. 4.58 Ruthenium salts in ionic liquids as catalysts for oxidation of alcohols.

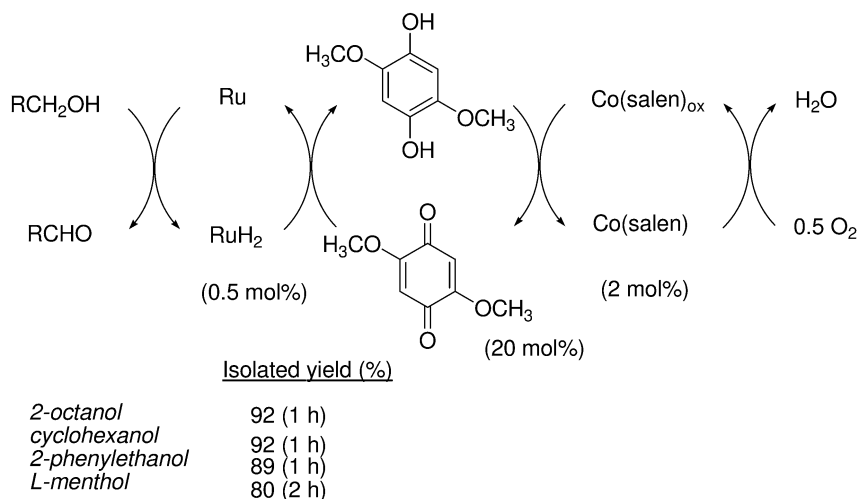


Fig. 4.59 Low-valent ruthenium complexes in combination with benzoquinone.

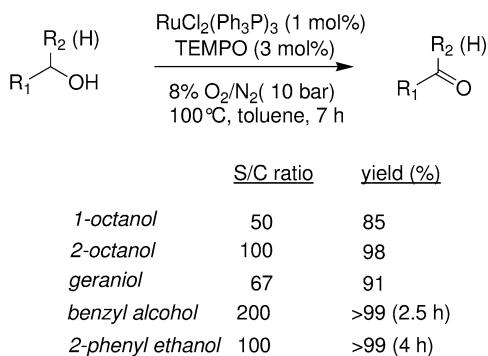
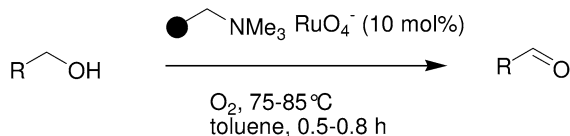


Fig. 4.60 Ruthenium/TEMPO catalyzed oxidation of alcohols.

resulting in the termination of free radical chains, i.e. it acts as an antioxidant. Allylic alcohols were selectively converted to the corresponding unsaturated aldehydes in high yields.

Perruthenate catalysts, i.e. TPAP, are superior Ru-catalysts, which are air-stable, non-volatile and soluble in a wide range of organic solvents. It was shown that TPAP is an excellent catalyst for the selective oxidation of a wide variety of alcohols using *N*-methylmorpholine-*N*-oxide (NMO) or oxygen as the stoichiometric oxidant [139, 149–151]. In particular, polymer-supported perruthenate (PSP), prepared by anion exchange of KRuO_4 with a basic anion exchange resin (Amberlyst A-26), has emerged as a versatile catalyst for the aerobic oxidation (Fig. 4.61) of alcohols [152]. However the activity was ca. 4 times lower than homogeneous TPAP, and this catalyst could not be recycled, which was attrib-



yield

1-octanol 91% (8h)

benzyl alcohol >95% (0.5 h)

cinnamyl alcohol >95% (1 h)

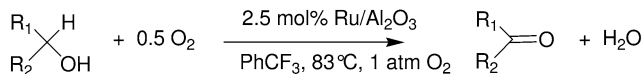
Fig. 4.61 TPAP catalyzed oxidation of alcohols.

uted to oxidative degradation of the polystyrene support. PSP displays a marked preference for primary versus secondary alcohol functionalities [152]. The problem of deactivation was also prominent for the homogeneous TPAP oxidation, which explains the high (10 mol%) loading of catalyst required.

Recently two heterogeneous TPAP-catalysts were developed, which could be recycled successfully and displayed no leaching: In the first example the tetraalkylammonium perruthenate was tethered to the internal surface of mesoporous silica (MCM-41) and was shown [153] to catalyze the selective aerobic oxidation of primary and secondary allylic and benzylic alcohols. Surprisingly, both cyclohexanol and cyclohexenol were unreactive although these substrates can easily be accommodated in the pores of MCM-41. The second example involves straightforward doping of methyl modified silica, denoted as ormosil, with tetrapropylammonium perruthenate via the sol-gel process [154]. A serious disadvantage of this system is the low-turnover frequency (1.0 and 1.8 h⁻¹) observed for primary aliphatic alcohol and allylic alcohol respectively.

Many examples of heterogeneous ruthenium systems are available. One of the more promising seems to be ruthenium on alumina, which is an active and recyclable catalyst [155]. This system displayed a large substrate scope (see Fig. 4.62) and tolerates the presence of sulfur and nitrogen groups. Only primary aliphatic alcohols required the addition of hydroquinone. Turnover frequencies in the range of 4 h⁻¹ (for secondary allylic alcohols) to 18 h⁻¹ (for 2-octanol) were obtained in trifluorotoluene, while in the solvent-free oxidation at 150 °C a TOF of 300 h⁻¹ was observed for 2-octanol.

Ruthenium-exchanged hydrotalcites were shown by Kaneda and coworkers [156], to be heterogeneous catalysts for the aerobic oxidation of reactive allylic and benzylic alcohols. Ruthenium could be introduced in the Brucite layer by ion exchange [156]. The activity of the ruthenium-hydrotalcite was significantly enhanced by the introduction of cobalt(II) in addition to ruthenium(III), in the Brucite layer [157]. For example, cinnamyl alcohol underwent complete conversion in 40 min in toluene at 60 °C, in the presence of Ru/Co-HT, compared with 31% conversion under the same conditions with Ru-HT. A secondary aliphatic



yield

<i>1-octanol*</i>	91% (2 h)
<i>2-octanol</i>	85% (4 h)
<i>benzyl alcohol</i>	> 99% (1 h)
<i>2-phenyl ethanol</i>	> 99% (1 h)
<i>geraniol</i>	86% (6 h)

* 5 mol% Ru/Al₂O₃ and 5 mol% hydroquinone needed

Fig. 4.62 Ru on alumina for aerobic alcohol oxidation.

alcohol, 2-octanol, was smoothly converted into the corresponding ketone but primary aliphatic alcohols, e.g. 1-octanol, exhibited extremely low activity. The results obtained in the oxidation of representative alcohols with Ru-HT and Ru/Co-HT are compared in Table 4.8.

Other examples of heterogeneous ruthenium catalysts are a ruthenium-based hydroxyapatite catalyst [158], a ferrite spinel-based catalyst MnFe_{1.5}Ru_{0.35}Cu_{0.15}O₄ [159], and Ru supported on CeO₂ [160], which all gave lower activities.

Another class of ruthenium catalysts, which has attracted considerable interest due to their inherent stability under oxidative conditions, are the polyoxometalates [161]. Recently, Mizuno et al. [162] reported that a mono-ruthenium-substituted silicotungstate, synthesized by the reaction of the lacunary polyoxometalate [SiW₁₁O₃₉]⁸⁻ with Ru³⁺ in an organic solvent, acts as an efficient heterogeneous catalyst with high turnover frequencies for the aerobic oxidation of alcohols (see Fig. 4.63). Among the solvents used 2-butyl acetate was the most

Table 4.8 Oxidation of various alcohols to their corresponding aldehydes or ketones with Ru-hydroxalcalites using molecular oxygen.^{a)}

Substrate	Ru-Mg-Al-CO ₃ -HT ^{b)}		Ru-Co-Al-CO ₃ -HT ^{c)}	
	Time/h	Yield (%)	Time/h	Yield (%)
PhCH=CHCH ₂ OH	8	95	0.67	94
PhCH ₂ OH	8	95	1	96
PhCH(CH ₃)OH	18	100	1.5	100
n-C ₆ H ₁₃ CH(CH ₃)OH			2	97

a) 2 mmol substrate, 0.3 g hydroxalcalite (~14 mol%), in toluene, 60 °C, 1 bar O₂.

b) Ref. [156].

c) Ref. [157].

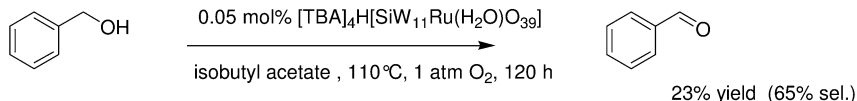


Fig. 4.63 Ru-HPA catalyzed oxidation of alcohols.

effective and this Ru-heteropolyanion could be recycled. The low loading used resulted in very long reaction times of >2 days and low selectivities.

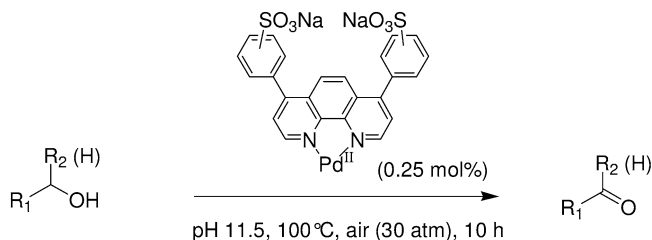
4.5.1.2 Palladium-catalyzed Oxidations with O₂

Much effort has been devoted to finding synthetically useful methods for the palladium-catalyzed aerobic oxidation of alcohols. For a detailed overview the reader is referred to several excellent reviews [163]. The first synthetically useful system was reported in 1998, when Peterson and Larock showed that simple Pd(OAc)₂ in combination with NaHCO₃ as a base in DMSO as solvent catalyzed the aerobic oxidation of primary and secondary allylic and benzylic alcohols to the corresponding aldehydes and ketones, respectively, in fairly good yields [164, 165]. Recently, it was shown that replacing the non-green DMSO by an ionic liquid (imidazole-type) resulted in a three times higher activity of the Pd-catalyst [166].

Uemura and coworkers [167, 168] reported an improved procedure involving the use of Pd(OAc)₂ (5 mol%) in combination with pyridine (20 mol%) and 3 Å molecular sieves in toluene at 80 °C. This system smoothly catalyzed the aerobic oxidation of primary and secondary aliphatic alcohols to the corresponding aldehydes and ketones, respectively, in addition to benzylic and allylic alcohols. Although this methodology constitutes an improvement on those previously reported, turnover frequencies were still generally <10 h⁻¹ and, hence, there is considerable room for further improvement. Recent attempts to replace either pyridine by triethylamine [169], or Pd(OAc)₂ by palladacycles [170] all resulted in lower activities. Notably, the replacement of pyridine by pyridine derivatives having a 2,3,4,5 tetraphenyl substituent completely suppressed the Pd black formation using only 1 atm air [171]. However the reaction times in this case were rather long (3–4 days).

A much more active catalyst is constituted by a water-soluble palladium(II) complex of sulfonated bathophenanthroline as a stable, recyclable catalyst for the aerobic oxidation of alcohols in a two-phase aqueous-organic medium, e.g. in Fig. 4.64 [16, 172, 173]. Reactions were generally complete in 5 h at 100 °C/30 bar air with as little as 0.25 mol% catalyst. No organic solvent is required (unless the substrate is a solid) and the product ketone is easily recovered by phase separation. The catalyst is stable and remains in the aqueous phase which can be recycled to the next batch.

A wide range of alcohols were oxidized with TOFs ranging from 10 h⁻¹ to 100 h⁻¹, depending on the solubility of the alcohol in water (since the reaction occurs in the aqueous phase the alcohol must be at least sparingly soluble in water). Representative examples of primary and secondary alcohols that were



Substrate	Time	Isolated Yield (%)
2-pentanol	5 h	90
2-phenyl ethanol	10 h	85
3-penten-2-ol	10 h	79
1-pentanol ^{a,b}	15 h	90
Benzyl alcohol ^a	10 h	93

a) 0.5 mol% Pd^{II}-catalyst; b) 2 mol% TEMPO added.

Fig. 4.64 Pd-bathophenanthroline as catalyst for alcohol oxidation in water.

smoothly oxidized using this system are collected in Fig. 4.64. The corresponding ketones were obtained in >99% selectivity in virtually all cases.

Primary alcohols afforded the corresponding carboxylic acids via further oxidation of the aldehyde intermediate, e.g. 1-hexanol afforded 1-hexanoic acid in 95% yield. It is important to note, however, that this was achieved without the requirement of one equivalent of base to neutralize the carboxylic acid product (which is the case with supported noble metal catalysts). In contrast, when 1 mol% TEMPO (4 equivalents per Pd) was added, the aldehyde was obtained in high yield, e.g. 1-hexanol afforded 1-hexanal in 97% yield. Under cosolvent conditions using water/ethylene carbonate, Pd-neocuproine was found to be even more active (Fig. 4.65) [174]. This system is exceptional because of its activity (TOF $\gg 500 \text{ h}^{-1}$ could be reached for 2-octanol) and functional group tolerance, such as C=C bonds, C \equiv C bonds, halides, α -carbonyls, ethers, amines etc. Thereby this system is expected to have a broad synthetic utility.

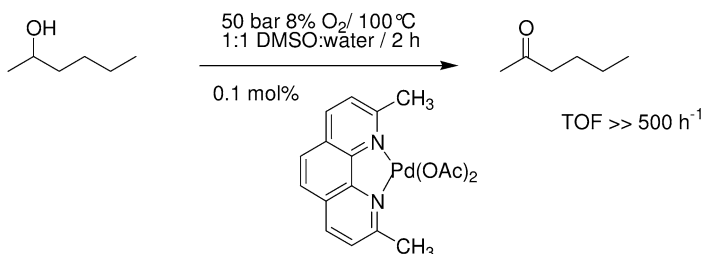


Fig. 4.65 Pd-neocuproine as catalyst for alcohol oxidation in water/cosolvent mixtures.

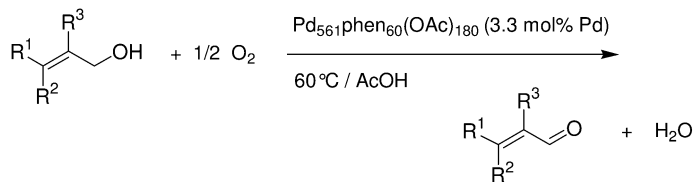


Fig. 4.66 Alcohol oxidation by giant palladium clusters.

In the context of heterogeneous palladium catalysts, Pd/C catalysts are commonly used for water-soluble substrates, i.e. carbohydrates [175]. Palladium can also be introduced in the brucite-layer of the hydrocalcite [176]. As with Ru/Co-hydrocalcite (see above), besides benzylic and allylic also aliphatic and cyclic alcohols are smoothly oxidized using this palladium-hydrocalcite. However a major shortcoming is the necessity of at least 5 mol% catalyst and the co-addition of 20–100 mol% pyridine. A seemingly very active heterogeneous catalyst is $\text{PdCl}_2(\text{PhCN})_2$ on hydroxyapatite [177]. Using trifluorotoluene as the solvent, very high TONs (>20 000) could be obtained for benzyl alcohol. However for aliphatic alcohols long reaction times were needed (24 h).

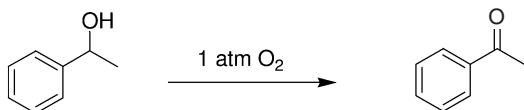
Major trends can be discerned for Pd-catalysts, aimed at increasing the stability and activity. First is the use of palladium-carbene complexes [178]. Although activities are still modest, much can be expected in this area. Second is the synthesis and use of palladium nanoparticles. For example, the giant palladium cluster, $\text{Pd}_{561}\text{phen}_{60}(\text{OAc})_{180}$ [179], was shown to catalyze the aerobic oxidation of primary allylic alcohols to the corresponding α,β -unsaturated aldehydes (Fig. 4.66) [180].

Some other recent examples are the use of palladium nanoparticles entrapped in aluminum hydroxide [181], resin-dispersed Pd nanoparticles [182], and poly(ethylene glycol)-stabilized palladium nanoparticles in scCO_2 [183]. Although in some cases the activities for activated alcohols obtained with these Pd-nanoparticles are impressive, the conversion of aliphatic alcohols is still rather slow.

4.5.1.3 Gold Catalysts

Recently, gold has emerged as one of the most active catalysts for alcohol oxidation and is especially selective for poly alcohols. In 2005, Corma [184] and Tsukuda [185], independently demonstrated the potential of gold nanoparticles for the oxidation of aliphatic alcohols. For example, in the case of gold nanoparticles deposited on nanocrystalline cerium oxide [184], a TOF of $12\,500 \text{ h}^{-1}$ was obtained for the conversion of 1-phenylethanol into acetophenone at 160°C (Fig. 4.67). Moreover this catalyst is fully recyclable. Another example of a gold catalyst with exceptional activity is a 2.5% Au–2.5% Pd/ TiO_2 as catalyst [186]. In this case for 1-octanol a TOF of 2000 h^{-1} was observed at 160°C (reaction without solvent, Fig. 4.67).

As reported below, Au is now considered as the catalyst of choice for carbohydrate oxidation. Similarly, glycerol can be oxidized to glyceric acid with 100% se-



<i>Au on nanocrystalline CeO₂:</i>	solvent-free	80 °C	TOF 74 h ⁻¹ (90% yld)
	solvent-free	160 °C	TOF 12500 h ⁻¹ (99% sel.)
<i>2.5% Au-Pd-alloys on TiO₂:</i>	solvent-free	160 °C	TOF 269000 h ⁻¹

Fig. 4.67 Au nanoparticles for alcohol oxidation.

lectivity using either 1% Au/charcoal or 1% Au/graphite catalyst under mild reaction conditions (60 °C, 3 h, water as solvent) [187].

4.5.1.4 Copper Catalysts

Copper would seem to be an appropriate choice of metal for the catalytic oxidation of alcohols with dioxygen since it comprises the catalytic centre in a variety of enzymes, e.g. galactose oxidase, which catalyze this conversion *in vivo* [188, 189]. Several catalytically active biomimetic models for these enzymes have been designed which are seminal examples in this area [190–193]. A complete overview of this field can be found in a review [194].

Marko and coworkers [195, 196] reported that a combination of Cu₂Cl₂ (5 mol%), phenanthroline (5 mol%) and di-*tert*-butylazodicarboxylate, DBAD (5 mol%), in the presence of 2 equivalents of K₂CO₃, catalyzes the aerobic oxidation of allylic and benzylic alcohols (Fig. 4.68). Primary aliphatic alcohols, e.g. 1-decanol, could be oxidized but required 10 mol% catalyst for smooth conversion.

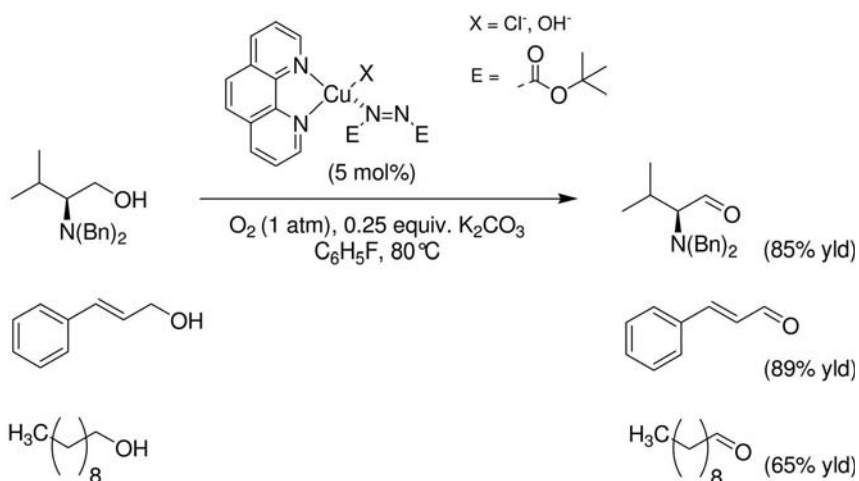


Fig. 4.68 Cu-phenanthroline-DBAD catalyzed aerobic oxidation of alcohols.

An advantage of the system is that it tolerates a variety of functional groups. Serious drawbacks of the system are the low activity, the need for two equivalents of K_2CO_3 (relative to substrate) and the expensive DBAD as a cocatalyst. According to a later report [197] the amount of K_2CO_3 can be reduced to 0.25 equivalents by changing the solvent to fluorobenzene. The active catalyst is heterogeneous, being adsorbed on the insoluble K_2CO_3 (filtration gave a filtrate devoid of activity). Besides fulfilling a role as a catalyst support the K_2CO_3 acts as a base and as a water scavenger. In 2001, Marko et al. reported a neutral variant of their $Cu^I Cl(phen)-DBADH_2$ -base system [198]. Furthermore, it was found that 1-methylimidazole as additive in the basic system dramatically enhanced the activity [199].

The use of Cu in combination with TEMPO also affords an attractive catalyst [200, 201]. The original system however operates in DMF as solvent and is only active for activated alcohols. Knochel et al. [202] showed that $CuBr.Me_2S$ with perfluoroalkyl substituted bipyridine as the ligand and TEMPO as cocatalyst was capable of oxidizing a large variety of primary and secondary alcohols in a fluoruous biphasic system of chlorobenzene and perfluorooctane (see Fig. 4.69). In the second example Ansari and Gree [203] showed that the combination of $CuCl$ and TEMPO can be used as a catalyst in 1-butyl-3-methylimidazolium hexafluorophosphate, an ionic liquid, as the solvent. However in this case turnover frequencies were still rather low even for benzylic alcohol (around $1.3 h^{-1}$).

Recently, an alternative to the catalytic system described above was reported [204]. The new catalytic procedure for the selective aerobic oxidation of primary alcohols to aldehydes was based on a $Cu^{II}Br_2(Bpy)-TEMPO$ system (Bpy=2,2'-bipyridine). The reactions were carried out under air at room temperature and were catalyzed by a [copper^{II}(bipyridine ligand)] complex and TEMPO and base (KOTBu) as co-catalysts (Fig. 4.70).

Several primary benzylic, allylic and aliphatic alcohols were successfully oxidized with excellent conversions (61–100%) and high selectivities. The system displays a remarkable selectivity towards primary alcohols. This selectivity for

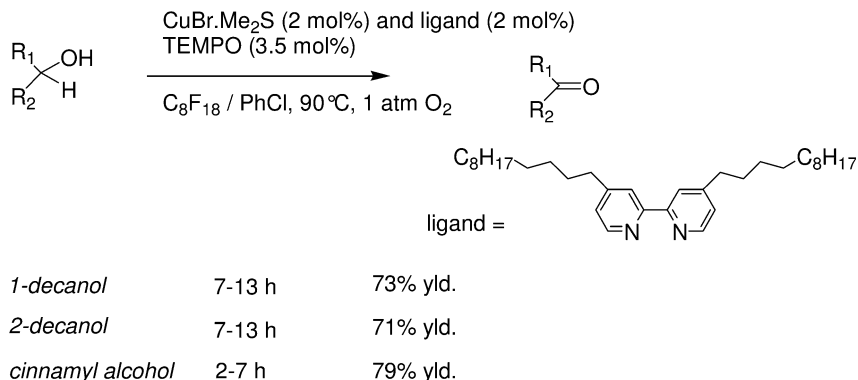
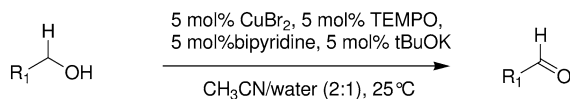


Fig. 4.69 Fluorous $CuBr_2$ -bipy-TEMPO system for alcohol oxidation.



<i>benzyl alcohol</i>	2.5 h	100% yld
<i>2-phenyl ethanol</i>	5 h	no reaction
<i>1-octanol</i>	24 h	61% yld
<i>geraniol</i>	5 h	100% yld

Fig. 4.70 $\text{CuBr}_2(\text{bipy})$ -TEMPO catalyzed oxidation of alcohols

the oxidation of primary alcohols resembles that encountered for certain copper-dependent enzymes. In the mechanism proposed, TEMPO coordinates side-on to the copper during the catalytic cycle.

4.5.1.5 Other Metals as Catalysts for Oxidation with O_2

$\text{Co}(\text{acac})_3$ in combination with *N*-hydroxyphthalimide (NHPI) as cocatalyst mediates the aerobic oxidation of primary and secondary alcohols, to the corresponding carboxylic acids and ketones, respectively, e.g. Fig. 4.71 [205]. By analogy with other oxidations mediated by the Co/NHPI catalyst studied by Ishii and coworkers [206, 207], Fig. 4.71 probably involves a free radical mechanism. We attribute the promoting effect of NHPI to its ability to efficiently scavenge alkylperoxy radicals, suppressing the rate of termination by combination of alkylperoxy radicals (see above for alkane oxidation).

After their leading publication on the osmium-catalyzed dihydroxylation of olefins in the presence of dioxygen [208], Beller et al. [209] recently reported that alcohol oxidations could also be performed using the same conditions. The reactions were carried out in a buffered two-phase system with a constant pH of 10.4. Under these conditions a remarkable catalyst productivity (TON up to 16 600 for acetophenone) was observed. The pH value is critical in order to ensure the reoxidation of $\text{Os}(\text{VI})$ to $\text{Os}(\text{VIII})$. The scope of this system seems to be limited to benzylic and secondary alcohols.

As heterogeneous oxidation catalyst, 5% Pt, 1% Bi/C has been identified as an efficient catalyst for the conversion of 2-octanol to 2-octanone and 1-octanol to octanoic acid (see Fig. 4.72) [210]. Also manganese-substituted octahedral mo-

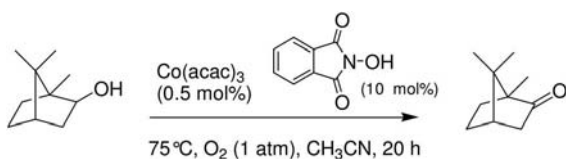


Fig. 4.71 Co/NHPI catalyzed oxidation of alcohols.

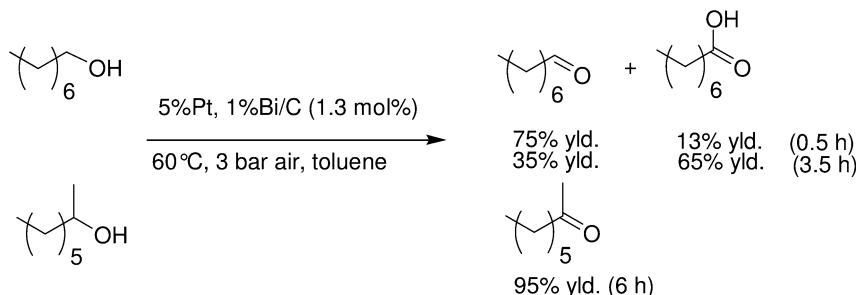


Fig. 4.72 Pt/Bi on carbon as effective catalyst for alcohol oxidation.

lecular sieves have been reported [211]. In this case benzylic and allylic alcohols could be converted within 4 h. However 50 mol% of catalyst was needed to achieve this.

Scant attention has been paid to vanadium-catalyzed oxidation of alcohols, despite its ability to act according to the oxometal mechanism. Punniamurthy recently reported that indeed vanadium turns out to be a remarkably simple and selective catalyst with a wide substrate scope, which requires few additives [212], albeit, the activities are still rather low.

4.5.1.6 Catalytic Oxidation of Alcohols with Hydrogen Peroxide

The use of tungsten affords a highly active catalytic system for the oxidation of alcohols. Noyori and coworkers [213, 214] have achieved substantial improvements in the sodium tungstate-based, biphasic system by employing a phase transfer agent containing a lipophilic cation and bisulfate as the anion, e.g. $\text{CH}_3(\text{n-C}_8\text{H}_{17})_3\text{NHSO}_4$. This system requires 1.1 equivalents of 30% aq. H_2O_2 in a solvent-free system. For example, 1-phenylethanol was converted to acetophenone with turnover numbers up to 180000. As with all Mo- and W-based systems, the Noyori system shows a marked preference for secondary alcohols, e.g. Fig. 4.73.

Titanium silicalite (TS-1), an isomorphously substituted molecular sieve [215], is a truly heterogeneous catalyst for oxidations with 30% aq. H_2O_2 , including the oxidation of alcohols [216].

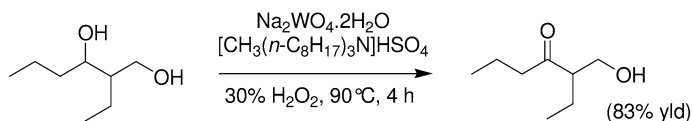


Fig. 4.73 Tungsten catalyzed alcohol oxidation with hydrogen peroxide.

4.5.1.7 Oxoammonium Ions in Alcohol Oxidation

In addition a very useful and frequently applied method in the fine chemical industry to convert alcohols into the corresponding carbonyl compounds is the use of oxoammonium salts as oxidants [15]. These are very selective oxidants for alcohols, which operate under mild conditions and tolerate a large variety of functional groups.

The oxoammonium is generated *in situ* from its precursor, TEMPO (or derivatives thereof), which is used in catalytic quantities, see Fig. 4.74. Various oxidants can be applied as the final oxidant. In particular, the TEMPO-bleach protocol using bromide as cocatalyst introduced by Anelli et al. is finding wide application in organic synthesis [217]. TEMPO is used in concentrations, as low as, 1 mol% relative to substrate and full conversion of substrates can commonly be achieved within 30 min. The major drawbacks of this method are the use of NaOCl as the oxidant, the need for addition of bromine ions and the necessity to use chlorinated solvents. Recently a great deal of effort has been devoted towards a greener oxoammonium-based method, by e.g. replacing TEMPO by heterogeneous variations or replacing NaOCl with a combination of metal as cocatalyst and molecular oxygen as oxidant. Examples of heterogeneous variants of TEMPO are anchoring TEMPO to solid supports such as silica [218, 219] and the mesoporous silica, MCM-41 [220] or by entrapping TEMPO in sol-gel [221]. Alternatively, an oligomeric TEMPO can be used [222].

Alternatively TEMPO can be reoxidized by metal salts or enzyme. In one approach a heteropolyacid, which is a known redox catalyst, was able to generate oxoammonium ions *in situ* with 2 atm of molecular oxygen at 100 °C [223]. In the other approach, a combination of manganese and cobalt (5 mol%) was able to generate oxoammonium ions under acidic conditions at 40 °C [224]. Results for both methods are compared in Table 4.9. Although these conditions are still open to improvement both processes use molecular oxygen as the ultimate oxidant, are chlorine free and therefore valuable examples of progress in this area. Alternative Ru and Cu/TEMPO systems, where the mechanism is me-

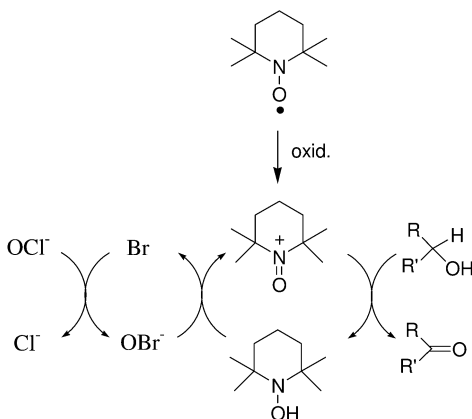


Fig. 4.74 Oxoammonium salts as active intermediates in alcohol oxidation.

Table 4.9 Aerobic oxoammonium-based oxidation of alcohols.

Substrate	Aldehyde or ketone yield ^{a)}		
	2 mol% Mn(NO ₃) ₂ 2 mol% Co(NO ₃) ₂ 10 mol% TEMPO acetic acid, 40 °C 1 atm O ₂ ^{b)}	1 mol% H ₅ PMo ₁₀ V ₂ O ₄₀ 3 mol% TEMPO acetone, 100 °C 2 atm O ₂ ^{c)}	Laccase (3 U/ml) Water pH 4.5 30 mol% TEMPO 25 °C, 1 atm O ₂ ^{d)}
n-C ₆ H ₁₃ -CH ₂ OH	97% (6 h)		
n-C ₇ H ₁₅ -CH ₂ OH		98% (18 h)	
n-C ₉ H ₁₉ -CH ₂ OH			15% (24 h)
n-C ₇ H ₁₅ -CH(CH ₃)OH	100% (5 h)		
n-C ₆ H ₁₃ -CH(CH ₃)OH		96% (18 h)	
PhCH ₂ OH	98% (10 h) ^{e)}	100% (6 h)	92% (24 h)
PhCH(CH ₃)OH	98% (6 h) ^{e)}		
<i>cis</i> -C ₃ H ₇ -CH=CH-CH ₂ OH		100% (10 h)	
Ph-CH=CH-CH ₂ OH	99% (3 h)		94% (24 h)

a) GLC yields.

b) Minisci et al. Ref. [224].

c) Neumann et al. Ref. [223].

d) Fabbrini et al. Ref. [225].

e) Reaction performed at 20 °C with air.

tal-based rather than oxoammonium based, and which display higher activity, will be discussed below. Another approach to generate oxoammonium ions *in situ* is an enzymatic one. Laccase, that is an abundant highly potent redox enzyme, is capable of oxidizing TEMPO to the oxoammonium ion (Table 4.9) [225]. A recent report shows that 15 mol% TEMPO and 5 h reaction time can lead to similar results using laccase from *Trametes versicolor* [226].

4.5.1.8 Biocatalytic Oxidation of Alcohols

Enzymatic methods for the oxidation of alcohols are becoming more important. An excellent overview of biocatalytic alcohol oxidation is given in a review [227]. Besides the already mentioned oxidases (laccase, see above and e.g. glucose oxidase), the enzymes widespread in nature for (asymmetric) alcohol dehydrogenation are the alcohol dehydrogenases. However, their large scale application has predominantly been impeded by the requirement for cofactor-recycling. The vast majority of dehydrogenases which oxidize alcohols require NAD(P)⁺ as cofactor, are relatively unstable and too expensive when used in molar amounts. Recently, a stable NAD⁺-dependent alcohol dehydrogenase from *Rhodococcus ruber* was reported, which accepts acetone as co-substrate for NAD⁺ regeneration and at the same time performs the desired alcohol oxidation (Fig. 4.75). Alcohol concentrations up to 50%v/v could be applied [228]. However it must be realized that this oxidation generally results in kinetic resolution: Only one of the enan-

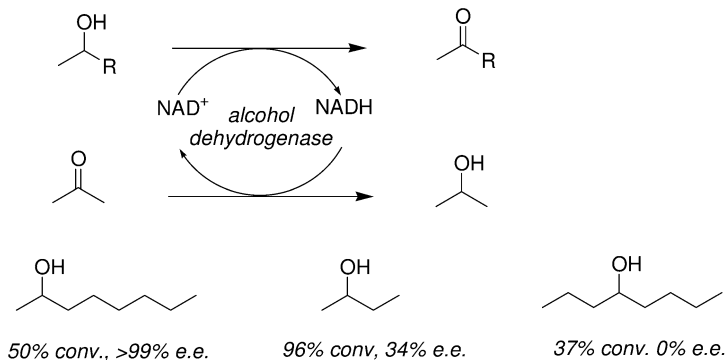


Fig. 4.75 Biocatalytic oxidation of alcohol using acetone for cofactor recycling.

tiomers is converted. For example, for 2-octanol, maximum 50% conversion is obtained and the residual alcohol has an *ee* of >99%. On the other hand for 2-butanol, no chiral discrimination occurs, and 96% conversion was observed. Also steric requirements exist: while cyclohexanol is not oxidized, cyclopentanol is a good substrate.

4.5.2

Oxidative Cleavage of 1,2-Diols

The oxidation of *vic*-diols is often accompanied by cleavage of the C–C bond to yield ketones and/or aldehydes. Especially the clean conversion of (cyclohexene to) 1,2-cyclohexanediol to adipic acid (Fig. 4.76) has received tremendous interest [229].

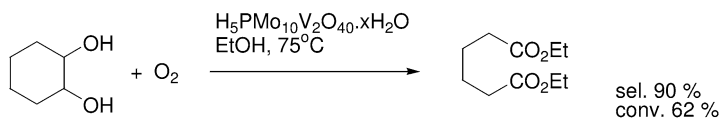


Fig. 4.76 Formation of adipic acid via 1,2-cyclohexanediol cleavage.

4.5.3

Carbohydrate Oxidation

Carbohydrate oxidations are generally performed with dioxygen in the presence of heterogeneous catalysts, such as Pd/C or Pt/C [230]. An example of homogeneous catalysis is the ruthenium-catalyzed oxidative cleavage of protected manitol with hypochlorite (Fig. 4.77) [231].

Glucose oxidation to gluconate, is carried out using glucose oxidase from *Aspergillus niger* mould [232]. Very recently it was found that unsupported gold particles in aqueous solution with an average diameter of 3–5 nm, show a sur-

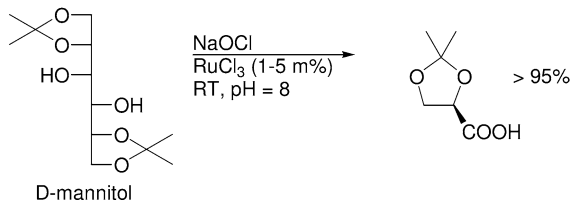


Fig. 4.77 Ruthenium/hypochlorite for oxidation of protected mannitol.

prisingly high activity in the aerobic oxidation of glucose, not far from that of an enzymatic system [233]. Both gold and glucose oxidase share the common stoichiometric reaction producing gluconate and hydrogen peroxide: $C_6H_{12}O_6 + O_2 + H_2O \rightarrow C_6H_{12}O_7 + H_2O_2$. In both cases the hydrogen peroxide is decomposed, either through alkali-promoted decomposition, or catalase-promoted decomposition.

4.5.4

Oxidation of Aldehydes and Ketones

Aldehydes undergo facile autoxidation (see Fig. 4.78), which is frequently used to form peracids *in situ*. The peracid itself will react with aldehydes in a Baeyer-Villiger (BV) reaction to form carboxylic acids [6].

The reaction is used commercially in the oxidation of acetaldehyde to peracetic acid [234], acetic anhydride [235] and acetic acid [236], respectively (Fig. 4.79). In the production of acetic anhydride, copper(II) salt competes with dioxygen for the intermediate acyl radical affording acetic anhydride via the acyl cation.

Also heterogeneous catalysts can be employed, such as Pd or Pt on carbon [237]. Recently, it was found that gold supported on a mesoporous CeO_2 matrix

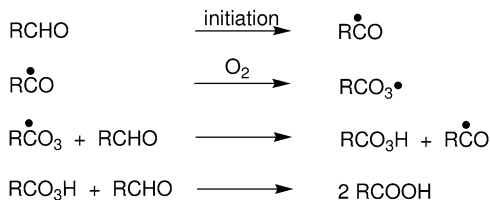


Fig. 4.78 Autoxidation of aldehydes.

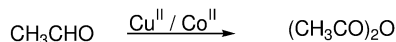
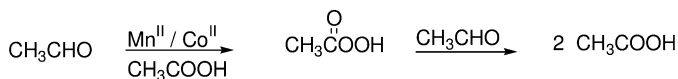


Fig. 4.79 Production of acetic acid and acetic anhydride starting from acetaldehyde.