Chapter 3

Hydrogenation in the Vitamins and Fine Chemicals Industry – An Overview

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Additional information is available at the end of the chapter

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1. Introduction

In the pharmaceutical and partly also in the fine chemicals industry many chemical conversions require stoichiometric amounts of reagents, and thus generate large amounts of waste [1, 2]. This is in contrast to the production of bulk chemicals which mostly relies on catalysis. This difference can be explained by the higher complexity of pharmaceuticals and fine chemicals which makes catalysis more demanding and process development more expensive.

According to Sheldon's classification [3], most vitamins are typical fine chemicals with production volumes of about 100 to 10'000 tons per year. Some vitamins can be placed in the class of bulk chemicals. Typically these compounds have been produced industrially for decades in multi-step syntheses with high overall yields. The application of catalytic methods in the highly competitive field of vitamins has increased significantly in recent years because of price pressure on these products. Research and development is thus driven by the necessity to reduce waste, use less toxic reagents and solvents, improve energy efficiency, recycle catalysts and reagents, and combine unit operations to reduce costs and achieve more sustainable processes. These goals are mostly in accordance with the twelve principles of "green chemistry"[4,5,6].

Catalytic hydrogenation is certainly the most widely applicable method for the reduction of organic compounds and belongs to the most important transformations in chemical industry. Catalytic hydrogenations in the fine chemicals industry are usually carried out with heterogeneous catalysts. Homogeneous catalysts are typically applied for highly

selective transformations, particularly enantioselective reductions. In the case of full recycling of heterogeneous or homogeneous catalysts, hydrogenation with molecular hydrogen is an atom economic transformation and undoubtedly the cleanest possible method for reducing a compound. Alternatively, hydrogen donors such as isopropanol or formic acid can be applied in transfer hydrogenations. In the field of catalytic hydrogenation reactions several significant inventions have been reported in the last 150 years. Sabatier and co-worker investigated the application of highly dispersed metals, e.g. nickel, in the hydrogenation of organic compounds [7,8]. The elective semi-hydrogenation of C≡C-bonds in presence of lead-doped palladium on calcium carbonate catalysts found by Lindlar was a further milestone in the field of catalytic hydrogenation reactions [9-11]. During the last decades asymmetric hydrogenations, pioneered by W.S. Knowles and R. Noyori, were a further highlight in the field of hydrogenation applied in organic synthesis [12,13].

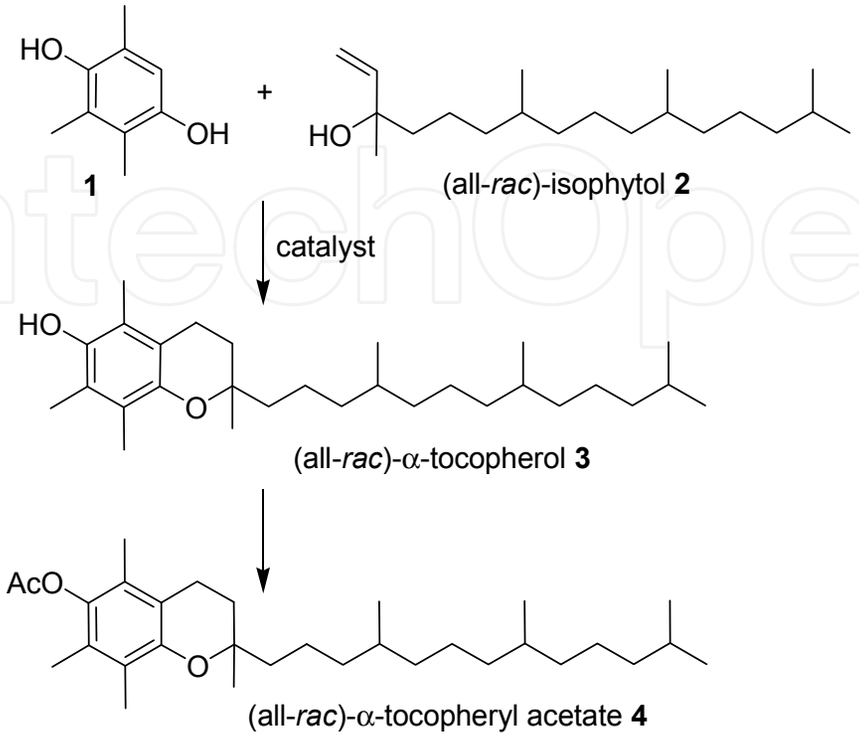
Catalytic hydrogenations can be carried out in a variety of ways, either in the liquid or gas phase and in batch-wise or continuous mode. In continuous processes usually fixed-bed reactors or fluidized-bed reactors are used. The suitable choice of a reactor system depends on various factors such as, in particular, the choice of catalyst, the reaction conditions, heat formation, space-time-yield, residence time, hydrogen pressure, mass-transport phenomena, temperature, solvent and economic reasons.

In this contribution we will focus on industrially important catalytic hydrogenation reactions which are of interest for DSM Nutritional Products concerning the manufacture of vitamins, carotenoids and nutraceuticals. The various hydrogenations are organized by reaction types, rather than by the products prepared: hydrogenations of C=C double bonds, selective semi-hydrogenations of C≡C triple bonds, hydrogenations of C=X/C≡X multiple bonds (X = oxygen or nitrogen), and stereoselective hydrogenations.

2. Hydrogenation of C=C double bonds

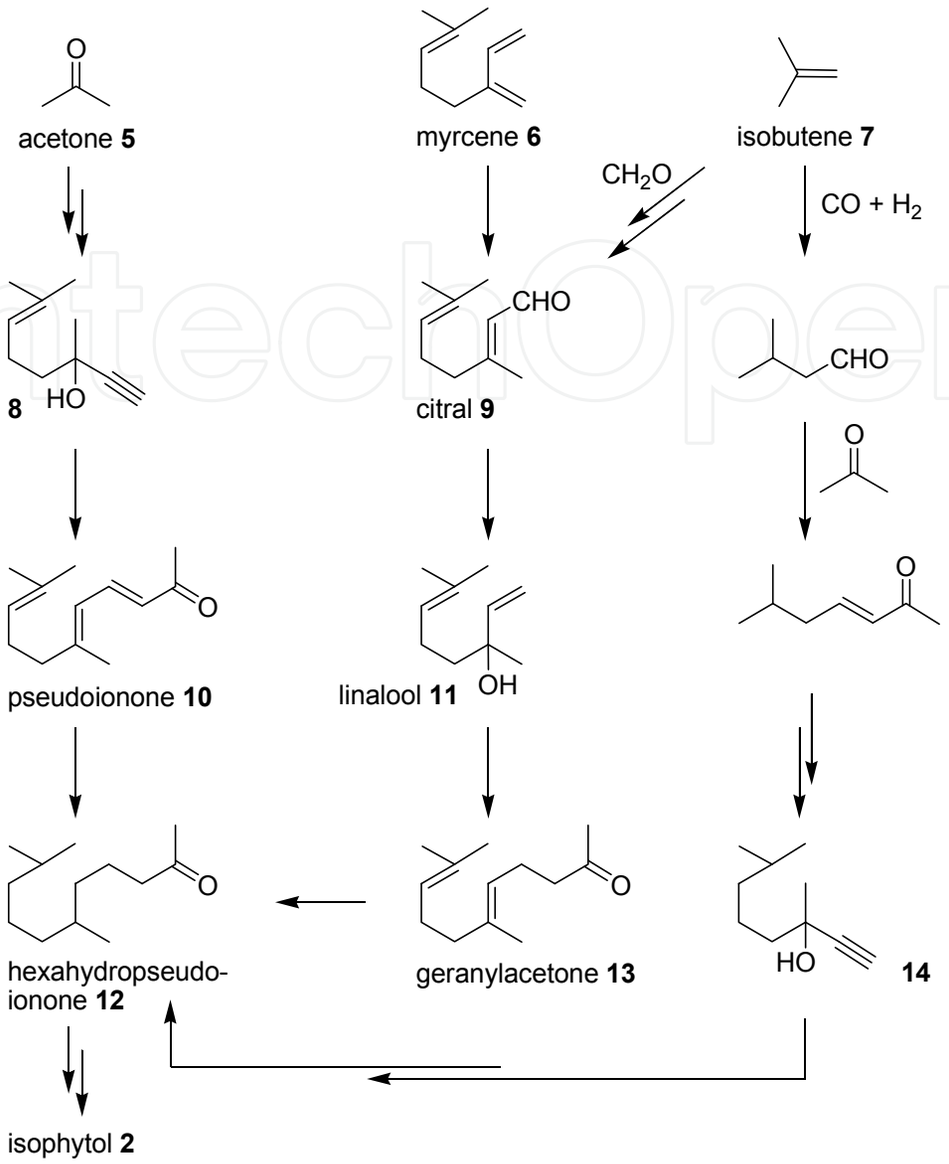
Probably the most common hydrogenation reaction performed in industry is the hydrogenation of carbon-carbon double bonds. A wide variety of catalysts are available from commercial suppliers and this transformation is considered a robust and atom-economical reaction. Even so, careful optimisation of the reaction conditions can be required to obtain full conversion and reduce or eliminate by-products. This is also important in the synthesis of vitamins and fine chemicals.

(all-*rac*)-α-Tocopherol (**3**) is the economically most important member of the group of vitamin E compounds, due to its biological and antioxidant properties. This fat-soluble vitamin is produced on a scale of >30'000 tonnes per year (mostly in form of its acetate derivative **4**) for applications in human and animal nutrition. One of the key building blocks for the chemical production of synthetic vitamin E is trimethylhydroquinone (TMHQ, **1**), which is converted into (all-*rac*)-α-tocopherol (**3**) by condensation with (all-*rac*)-isophytol (**2**, Scheme 1) [14-16].



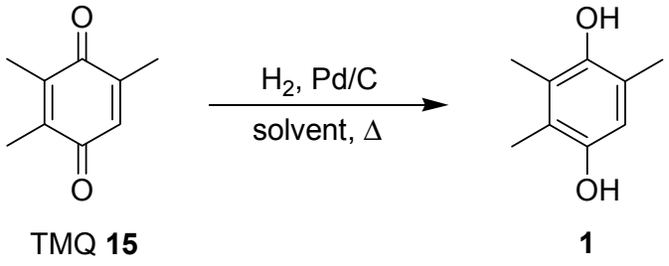
Scheme 1. Final steps of the chemical production of vitamin E.

The synthesis of isophytol can be carried out starting from acetone (**5**) and building up the isoprenoic side chain by a sequence of C_2 and C_3 elongations (*via* **8** and **10**, Scheme 2). Another approach starts from citral (**9**) followed by reaction to linalool (**11**) and elongation to geranylacetone (**13**) [14,15]. Routes to **9** based on prenyl chloride and myrcene (**6**) are described in literature but are not competitive. The use of cheap isobutene (**7**) is preferred which represents also an access to other isoprenoic building blocks, e.g. **14**. The C_3-elongation can be carried out by Saucy-Marbet or Carroll reactions and the C_2 elongation by ethynylation or vinylation reactions (vinyl Grignard addition) [1]. In such reaction sequences several hydrogenations of C=C bonds are necessary. A key intermediate in the synthesis of isophytol (**2**) is hexahydropseudoionone (**12**), which can be produced from pseudoionone (**10**) or geranylacetone (**13**). In the past the hydrogenation reactions were carried out batch-wise in presence of a Pd/C catalyst below 80 °C and <10 bar pressure [17]. This hydrogenation was also investigated using Pd- or Rh-containing polymers on Al_2O_3 [18]. The liquid phase hydrogenation of pseudoionone (**10**), geranylacetone (**13**) or dihydrogeranylacetone in presence of a suspended catalyst in a special reactor which allows an easy hold-up of the catalyst has been described in [19]. The synthesis of these saturated ketones in a continuous fixed-bed mode applying a Pd catalyst supported on SiO_2 results in excellent yield under nearly full conversion [20].



Scheme 2. Synthesis of isophytol (*E*/*Z* isomerism of olefins is omitted here).

The other key intermediate for the synthesis of vitamin E, TMHQ (**1**), is accessible *via* catalytic hydrogenation of trimethylbenzoquinone (TMQ, **15**) using a palladium on carbon catalyst (Scheme 3).

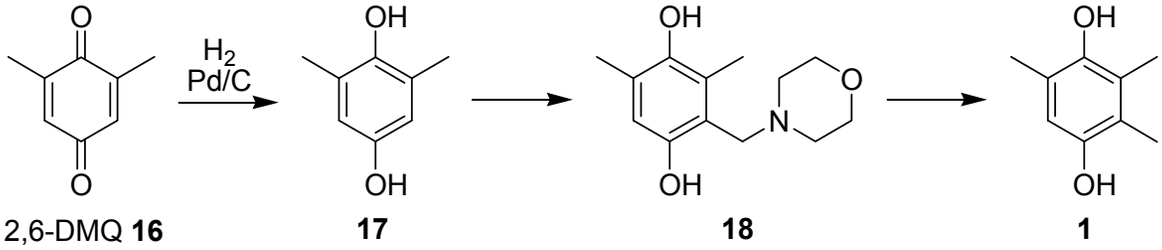


Scheme 3. Catalytic hydrogenation of TMQ to TMHQ.

The hydrogenation is usually carried out in a continuous mode at medium to low pressure and elevated temperature to prevent crystallization of the product from the reaction mixture. Yields are generally quantitative.

Alternatively, a range of different Pd-catalyzed hydrogenation conditions can be found in the literature, e.g. using Pd/C in solvents like carboxylic esters [21] or acetone [22], or palladium on acidic [23,24] or basic oxides [25] in lower alcohols. Also a Pt-catalyzed hydrogenation has been described using platinum nitrate and aluminium oxide in *i*-butanol [25].

An alternative access to TMHQ (**1**) starts from less methylated 1,4-benzoquinones, e.g. 2,6-dimethylbenzoquinone (2,6-DMQ, **16**), which is first hydrogenated to 2,6-dimethylhydroquinone (**17**) and methylated later, e.g. by aminomethylation *via* **18** followed by hydrogenolysis to TMHQ (**1**) (Scheme 4) [26].



Scheme 4. Synthesis of TMHQ from 2,6-DMQ.

The K-vitamins are a group of substituted 2-methyl-1,4-naphthoquinones with (or without) a prenyl chain of different length in C-3 position (Figure 1). The core unit of all K-vitamins is menadione (vitamin K_3, **21**) [27,28]. The standard synthesis of vitamins K_1 and K_2 (**19**,**20**) is the coupling of the aromatic unit with the (poly)prenyl side chain, similar to vitamin E. The direct coupling of the side chain to menadione (**21**) is not possible; therefore a key step is the hydrogenation of menadione to menadiol (**22**) so that alkylation can take place. The hydrogenation is usually carried out batch-wise using a palladium on carbon catalyst.

After esterification, condensation with isophytol (**2**) according to the methods of the group of Isler [29,30] or Hirschmann *et al.* [31], and subsequent saponification the hydroquinone is then re-oxidized to the corresponding naphthoquinone, e.g. in the industrial preparation of synthetic vitamin K_1 (phylloquinone, Konakion®, **23**) (Scheme 5).

A remarkable stereoselective hydrogenation of a trisubstituted olefinic C=C double bond was used in several total synthesis routes to the water-soluble vitamin (+)-biotin (**26**, Scheme 6) [32]. This product is produced on a scale of about 100 tonnes per year, and only the (3a*S*,4*S*,6a*R*)-stereoisomer exhibits full biological activity. Stereocenter C-4 of the thiophane ring can be introduced by catalytic hydrogenation of the exocyclic olefin **24** with undefined double-bond stereochemistry on Pd/C or other heterogeneous catalysts, yielding **25** with the desired all-*cis* relative configuration at centers C-4, C-3a, and C-6a. The N-benzyl protecting groups are stable under those conditions. This strategy, originally developed by Goldberg and Sternbach [33,34], was later on used by other groups in various syntheses of racemic and optically active intermediates [32].

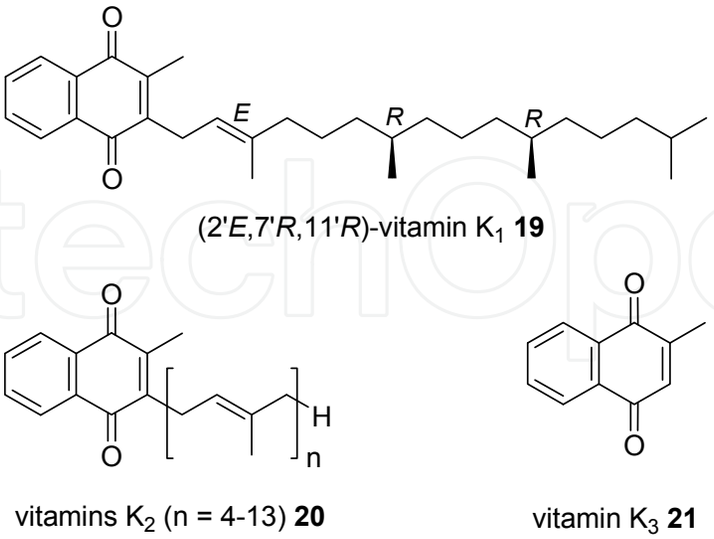
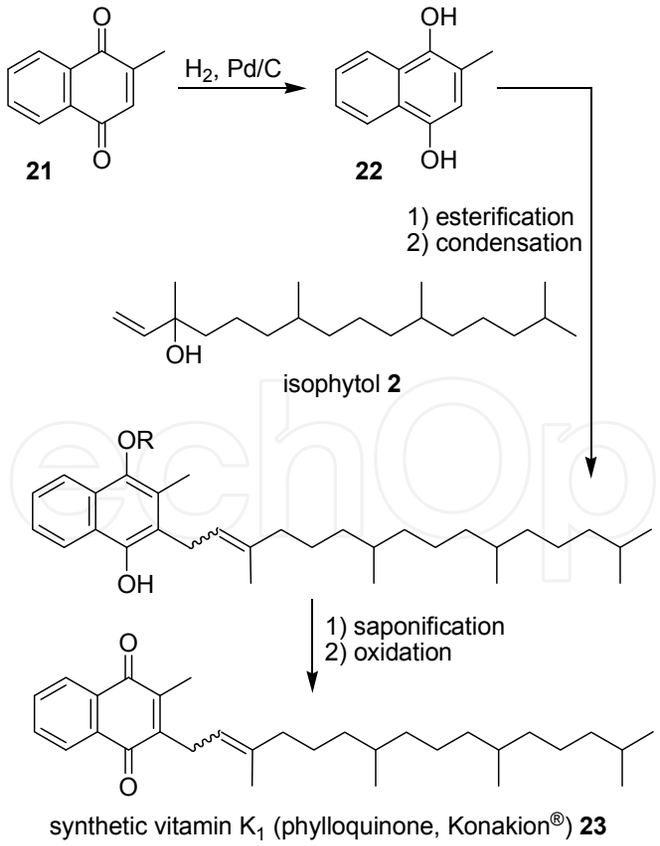
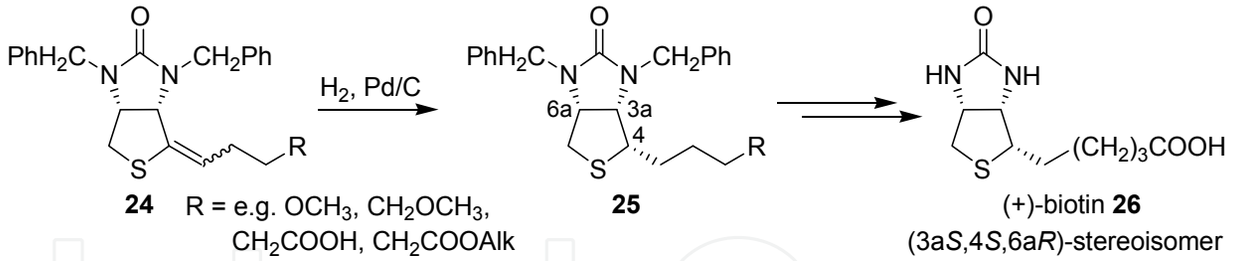


Figure 1. Molecular structures of the different K vitamins.



Scheme 5. Chemical production of vitamin K1.



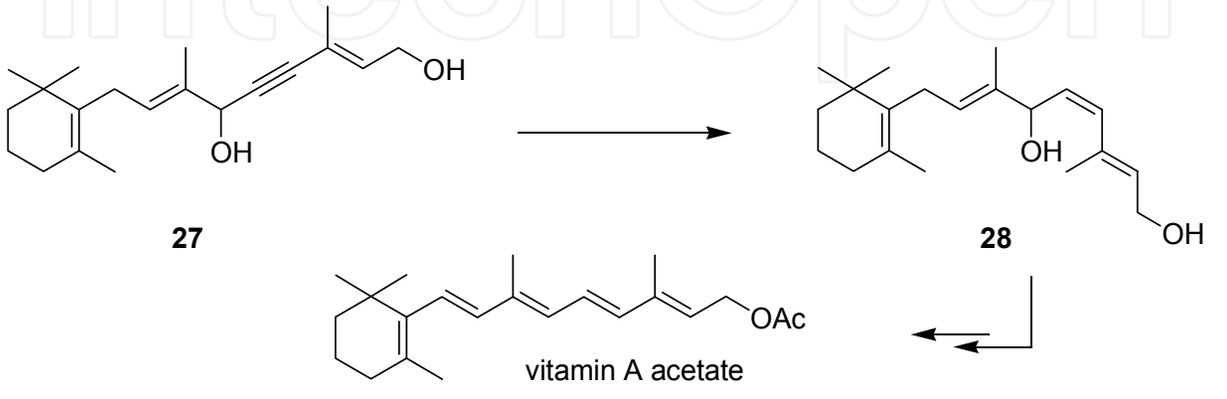
Scheme 6. Stereoselective heterogeneous hydrogenation in routes towards (+)-biotin.

3. Semi-hydrogenation of C≡C triple bonds (Lindlar type)

The semi-hydrogenation of carbon-carbon triple bonds to alkenes is one of the most useful hydrogenations for the production of vitamins, however careful choice of catalyst and reaction conditions are required to obtain high selectivity. In general, hydrogenation of acetylenes with a metal catalyst results in the formation of the fully saturated alkane product, since the second hydrogenation (alkene to alkane) is generally faster than the first (alkyne to alkene). However, as long as some of the starting alkyne remains in the reaction mixture, selectivity can be high since the alkynes bind more strongly to the metal surface. The selectivity can be enhanced by the use of suitable catalyst poisons which modify the activity of the metal catalyst.

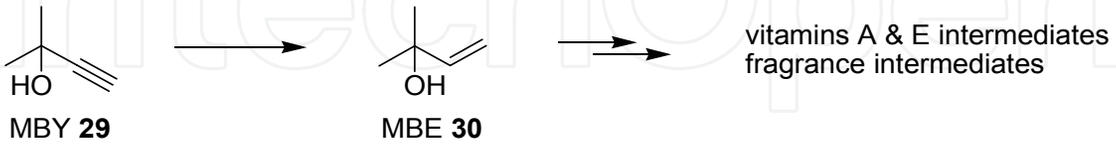
One of the most widely used and most selective catalysts is the one originally developed by Lindlar [9,11]. With this catalyst, the palladium supported on calcium carbonate is doped with a lead acetate solution during manufacture. This catalyst can then be used either directly in the hydrogenation or modified further by an organic compound such as an amine. Since the hydrogen is delivered from the metal surface to the alkyne, usually high selectivity is obtained for the *Z*-(*cis*)-alkene product. "Lindlar catalysts" generally have 5% palladium loading and 2-5% lead loading, depending on the application.

One of the earliest uses of the catalyst developed by Lindlar was the semi-hydrogenation of a vitamin A key intermediate (**27**, Scheme 7) to give tetraene **28**. Whilst this could be achieved with poisoned palladium on charcoal or palladium on calcium carbonate [35], selectivities were significantly higher with the lead-doped catalyst and the reaction could easily be stopped after the uptake of just one equivalent of hydrogen gas.



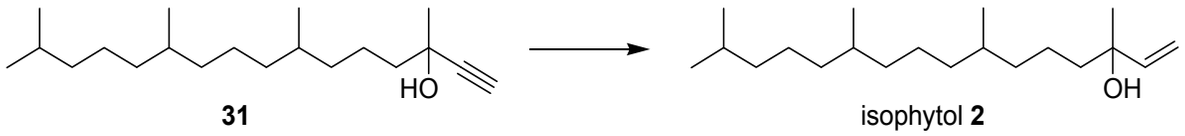
Scheme 7. Semi-hydrogenation of a vitamin A intermediate.

Since this early success the "Lindlar catalyst" (as it has become known) has been used in many different production processes. It is of particular importance in the synthesis of vitamins A & E and also intermediates for the fragrance industry. An important starting material in DSM Nutritional Products's production of such compounds is methylbutenol (MBE, **30**, Scheme 8). MBE is synthesised by the partial hydrogenation of the corresponding alkyne MBY (**29**) in a batch-wise process. Selectivity is very high (>98%) and the catalyst can be recycled multiple times.



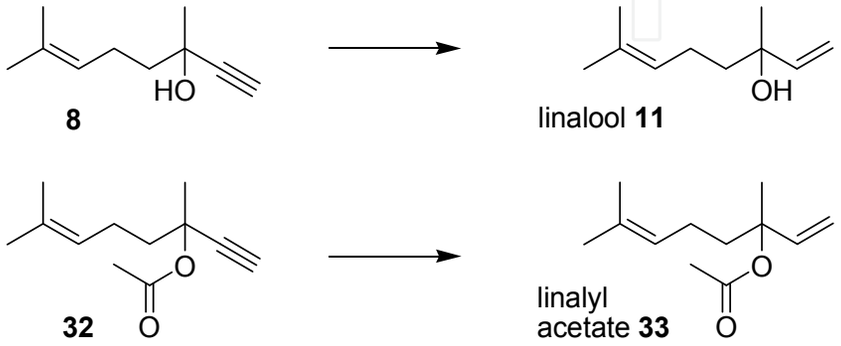
Scheme 8. Semi-hydrogenation of MBY.

From MBE, the chain is extended in a sequential manner to obtain dehydroisophytol (**31**, Scheme 9). This is then reduced in another semi-hydrogenation to give isophytol (**2**, cf. Scheme 2) [15]. Isophytol can then be coupled with TMHQ (**1**), as described previously, to form α-tocopherol (cf. Scheme 1). As with MBY-MBE, the hydrogenation is carried out in a batch-wise process at 2-5 bar hydrogen pressure.



Scheme 9. Preparation of isophytol by semi-hydrogenation.

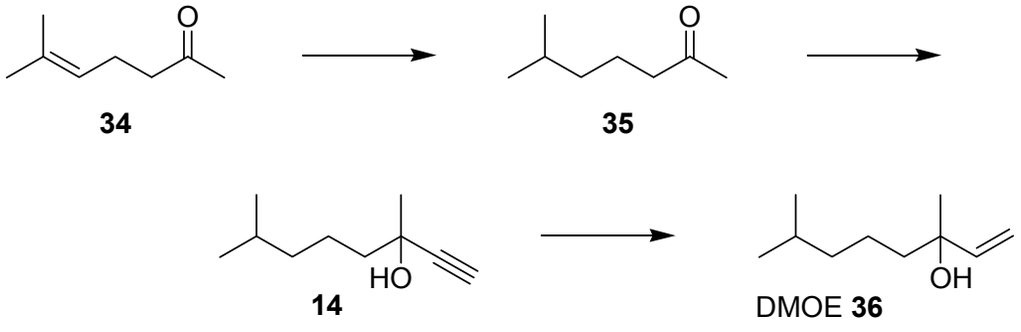
Two compounds of interest to the fragrance industry are linalool (**11**) and linalyl acetate (**33**, Scheme 10). Both have pleasant floral and spicy odours and are found in a wide range of natural flowers and spice plants. Their main uses are as perfume components in soaps, shampoos and lotions. They can both be synthesised by semi-hydrogenation of **8** and **32** using Lindlar catalysts, however the reaction conditions had to be optimised independently since even minor changes to the substrate structure can significantly affect the hydrogenation selectivity.



Scheme 10. Production of linalool and linalyl acetate by semi-hydrogenation.

As an extension to the work above, another fragrance compound, dimethyloctenol (DMOE, **36**), can be prepared by the combination of a hydrogenation of a C=C double bond and a selective semi-hydrogenation of a C≡C triple bond (Scheme 11). Methylheptenone (**34**) can be hydrogenated with a range of Pd/C or Pd/Al_2O_3 catalysts to give methylheptanone (**35**). The reaction was run without solvent at a range of temperatures (30-80 °C) and pressures (1-10 bar hydrogen). The latter compound was ethynylated to give the alkyne **14**, which can undergo semi-hydrogenation with high selectivity (up to 95%) to give the desired tertiary allyl alcohol **36**. Lindlar catalysts with varying amounts of lead-doping were successful at moderate temperatures (20-40 °C) and pressures (1-10 bar hydrogen) [36].

New approaches for the application of Lindlar-type catalysts are the use of supported palladium nanoparticles. By carefully controlling their preparation, a narrow range of diameters can be obtained and deposited on a carbon support [37,38]. These catalysts allow the hydrogenation of C≡C bonds with low metal loadings and in several cases with a high selectivity, e.g. hex-3-yne can be hydrogenated to hex-3-ene in high selectivity at full conversion, however to the best of our knowledge, these have not yet been applied on an industrial scale for the production of vitamins and fine chemicals.



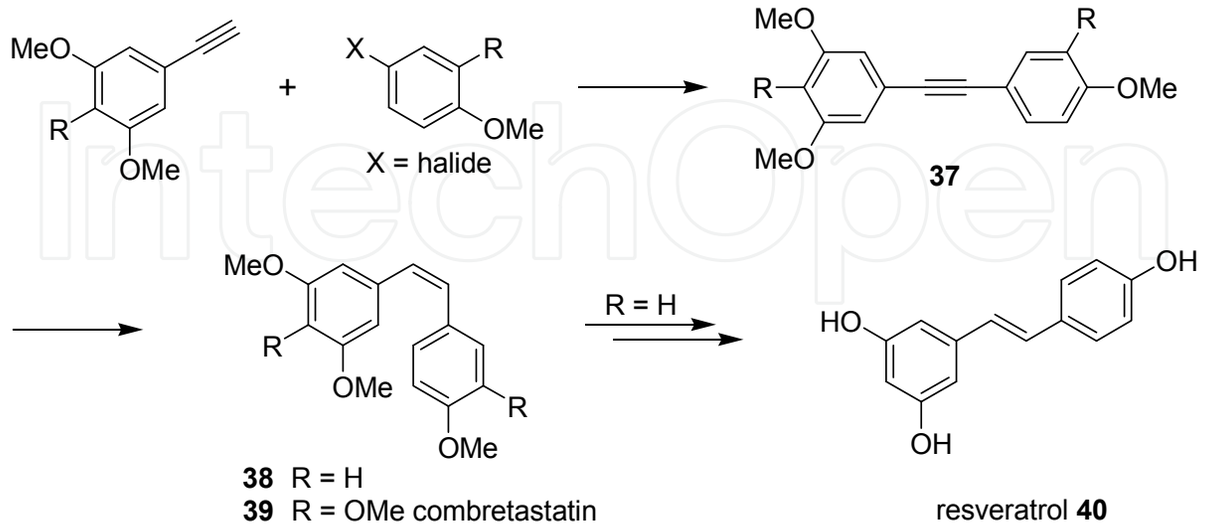
Scheme 11. Synthesis of DMOE by combination of two different kinds of hydrogenation.

Further trends in the research on Lindlar hydrogenations are focusing on the addition of $FeCl_2$ and tetramethylammonium chloride to the catalyst, and the use of palladium on metal sintered fibers. This allows the hydrogenation of triple bonds in a continuous reaction mode, also with low Pd loadings, in which Pb doping is not necessary [39-42].

Resveratrol (**40**, Scheme 12) is a polyphenol that can be isolated from natural sources such as red grapes or giant knotweed. It has attracted significant attention due to its possible health benefits in areas such as anti-cancer, anti-aging, anti-inflammatory and cardiovascular protection. The synthesis of resveratrol has been reported a number of times and can be industrially performed using Mizoroki-Heck coupling of 3,5-diacetoxy-styrene and 4-acetoxybromobenzene as key step [43,44].

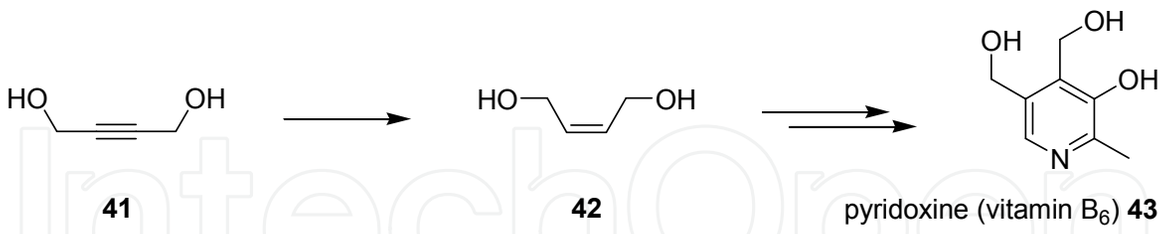
An alternative approach to resveratrol uses the selective hydrogenation of tolan derivatives **37** in presence of a Lindlar-type catalyst to form intermediate **38** [45]. The precursor **37** can be synthesized by Sonogashira coupling (Scheme 12). In general this procedure can be

applied to the synthesis of electron-rich stilbene derivatives as in the preparation of natural compounds like combretastatin (**39**) [46].



Scheme 12. Synthesis of combretastatin and resveratrol via Sonagashira coupling and semi-hydrogenation.

Z-Butene-1,4-diol (**42**) is an intermediate in the synthesis of vitamin B_6 (**43**), and is synthesized by selective hydrogenation of butynediol (**41**) in presence of a $Pd/CaCO_3$ catalyst (Scheme 13) [47,48]. The hydrogenation also proceeds well in water. The application of Pd/C or Pd/Al_2O_3 has been described under similar conditions [49]. The hydrogenation can also be carried out in a monolith bubble column reactor. Full conversion and high selectivity can be achieved in presence of a Pd-catalyst [50].



Scheme 13. Semi-hydrogenation of butynediol for vitamin B_6.

As described above, Lindlar hydrogenations are usually carried out in a batch-wise mode in presence of a Pb-doped Pd catalyst on a calcium carbonate carrier. However, new trends in the selective semi-hydrogenation of C≡C bonds are continuous processing and the application of environmentally friendly solvents. The application of supercritical fluids (sc-fluids) in fine chemical processes, e.g. extractions or as process solvent is well documented [51].

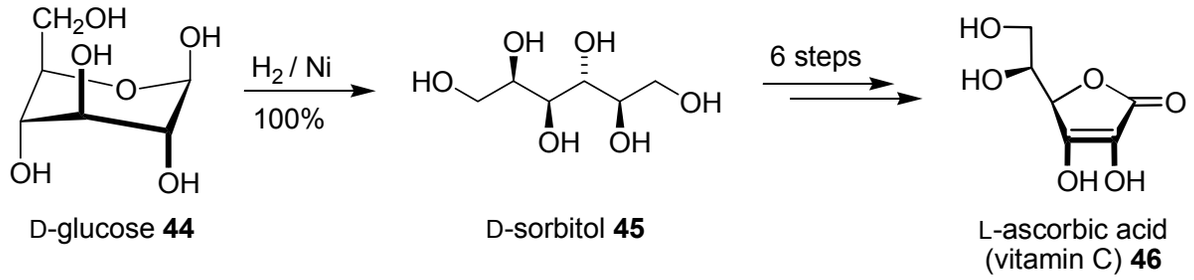
Lindlar-type hydrogenations in supercritical fluids, e.g. sc-CO_2, can be carried out in a continuous manner applying a plug-flow reactor set-up. The set-up allows the usage of a new type of Pd-catalyst, amorphous $Pd_{81}Si_{19}$ in a Pb-free system [52].

4. Hydrogenation of C=O and C≡N functional groups

As well as the hydrogenation of C-C multiple bonds, the hydrogenation of C-X multiple bonds is used extensively in the production of vitamins and fine chemicals.

L-Ascorbic acid (vitamin C, **46**) is the vitamin that is produced on the largest volume worldwide (approximately 100,000 tonnes per year). The most important method for its industrial manufacture is the Reichstein process [53], which transforms D-glucose (**44**) into L-ascorbic acid *via* a mixed series of high-yielding chemical and microbiological steps. In the first step of the synthesis sequence D-glucose is hydrogenated to D-sorbitol (**45**) in presence of a Ni-alloy catalyst (Scheme 14). The reaction is usually carried out at high pressure and elevated temperature in a batch-mode or continuous process. Under these conditions the product is obtained in high selectivity and almost quantitative yield with only minor amounts of D-mannitol and L-iditol as by-products.

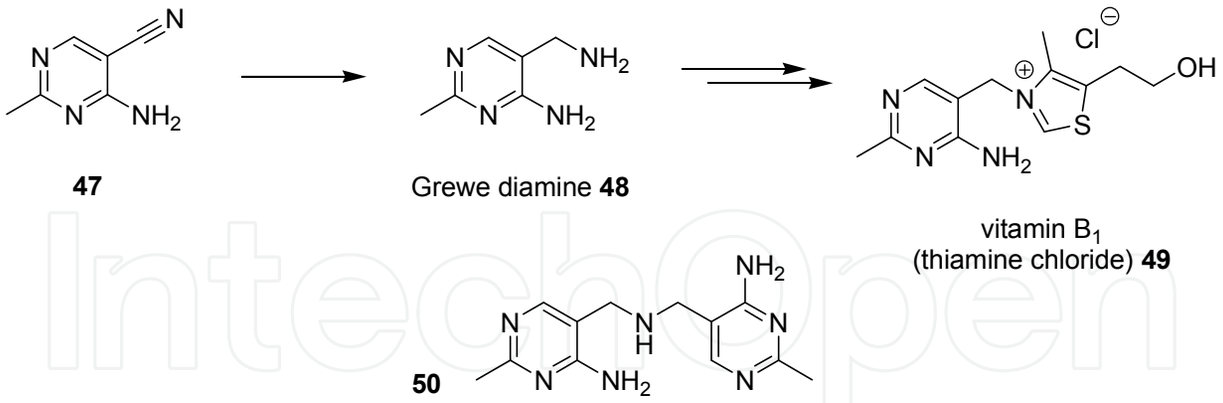
Alternatively to the catalytic hydrogenation, microbiological [54] and electrochemical [55] methods also are known for the reduction of D-glucose to D-sorbitol.



Scheme 14. Reduction of D-glucose to D-sorbitol in the Reichstein process for the synthesis of vitamin C.

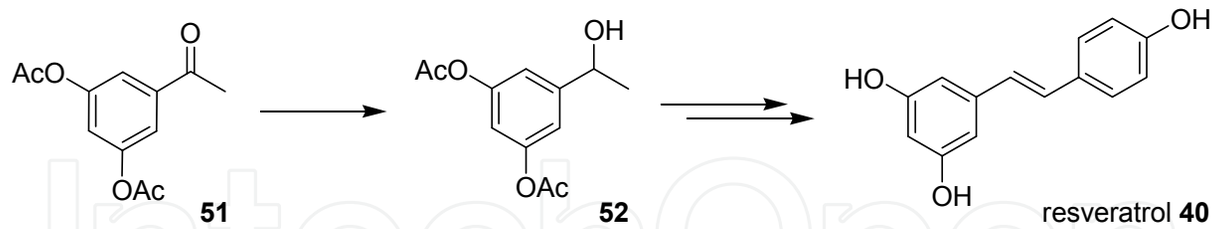
Vitamin B_1 (thiamine chloride, **49**, Scheme 15) contains two heterocyclic rings linked by a methylene unit. In all industrial syntheses, the key intermediate is Grewe diamine (**48**), onto which the thiazole ring is constructed. In general, the diamine is prepared by hydrogenation of a pyrimidino nitrile (**47**) using a nickel-alloy catalyst. This was first reported in 1944 by Huber [56] who found that the use of palladium and platinum supported catalysts gave significant amounts of secondary amine **50** as by-product. The use of nickel catalysts also gave significant quantities of secondary amines, but these could be reduced to less than 5% by the addition of ammonia to the reaction mixture.

Modern industrial syntheses still use the same basic process, although optimisation has improved the reaction significantly, further reducing the unwanted by-products. Reactions proceed in a batch-wise process with a solvent saturated with ammonia at moderate (>10 bar) hydrogen pressure to ensure high activity and throughput. The catalyst can be recycled multiple times and usually remains in the reaction after batch. The choice of nickel catalyst is also important and recently nickel-alloy catalysts (Centoprime®) have been developed that reduce amine by-products further [57-60].



Scheme 15. Production of Grewe diamine for vitamin B1.

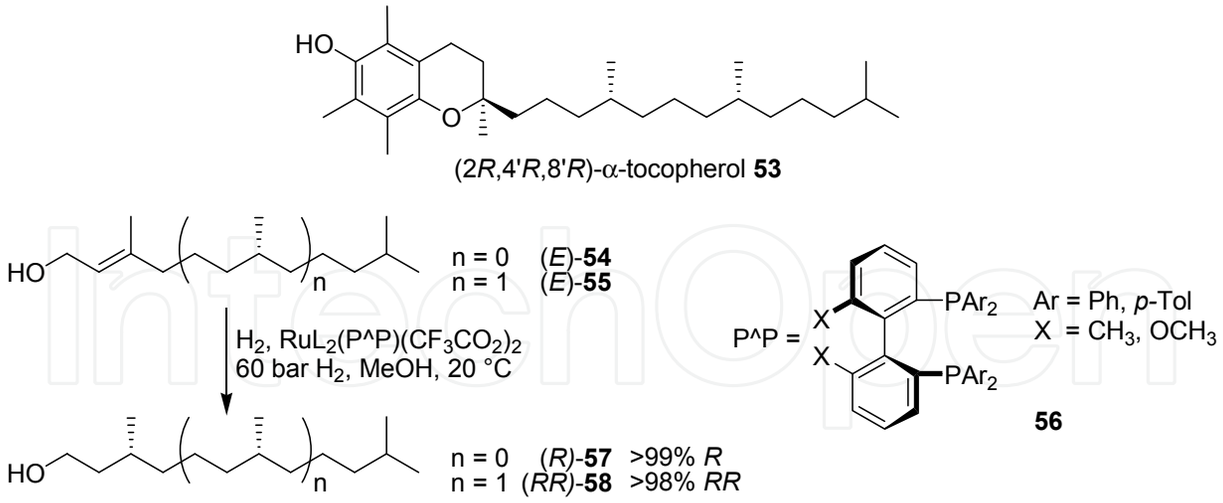
Resveratrol (**40**) can be produced industrially by an alternative route to that described earlier (cf. Scheme 12). A key intermediate in this production is the benzylic alcohol **52** [43]. This is prepared by the hydrogenation of acetophenone derivative **51** using a transition metal catalyst [61]. A number of catalysts can successfully perform this transformation, but the suppression of by-products is essential. Use of palladium or platinum on carbon resulted in yields of up to 90% (depending on the solvent); however levels of critical by-products were too high to be applied on large scale. The problems were solved by the use of nickel-alloy catalysts. Using these catalysts in ethyl acetate (2-10 bar hydrogen) allowed the production of the required alcohol **52** in greater than 95% yield. In addition the catalyst can remain in the reactor and be recycled multiple times resulting in a cost effective process.



Scheme 16. Hydrogenation of a ketone for the synthesis of resveratrol.

5. Stereoselective hydrogenation of C=C double bonds

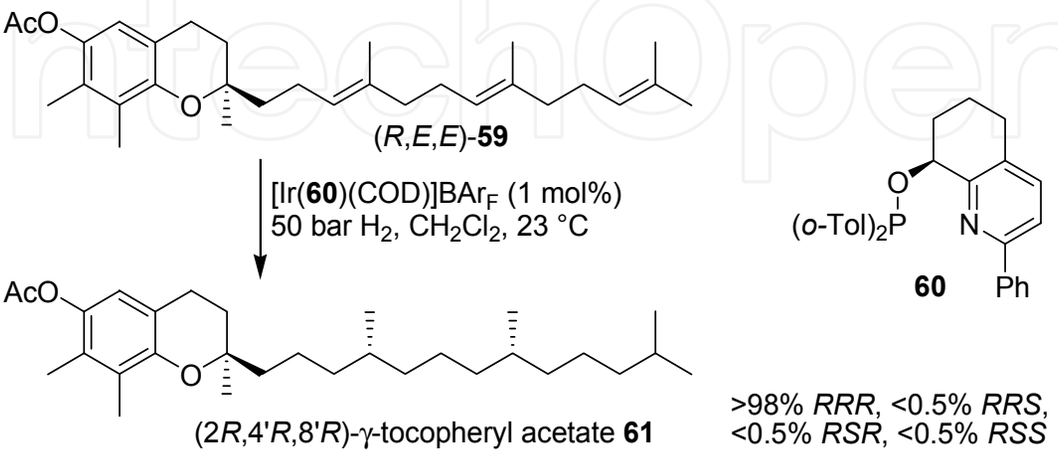
Stereoselective processes, in particular the asymmetric hydrogenation of C=C double bonds, play an increasingly important role in the total synthesis of isomerically pure biologically active products. The naturally occurring fat soluble antioxidant (2*R*,4′*R*,8′*R*)-*α*-tocopherol (**53**, Scheme 17) is not available in sufficient amounts from natural source starting material. In the course of the considerable efforts towards an economic total synthesis of **53** during the last decades [16], exceptionally efficient new asymmetric hydrogenation processes were developed for the introduction of chirality to the aliphatic tocopherol side chain.



Scheme 17. Asymmetric hydrogenation reactions of allylic alcohols in isoprenoid chemistry.

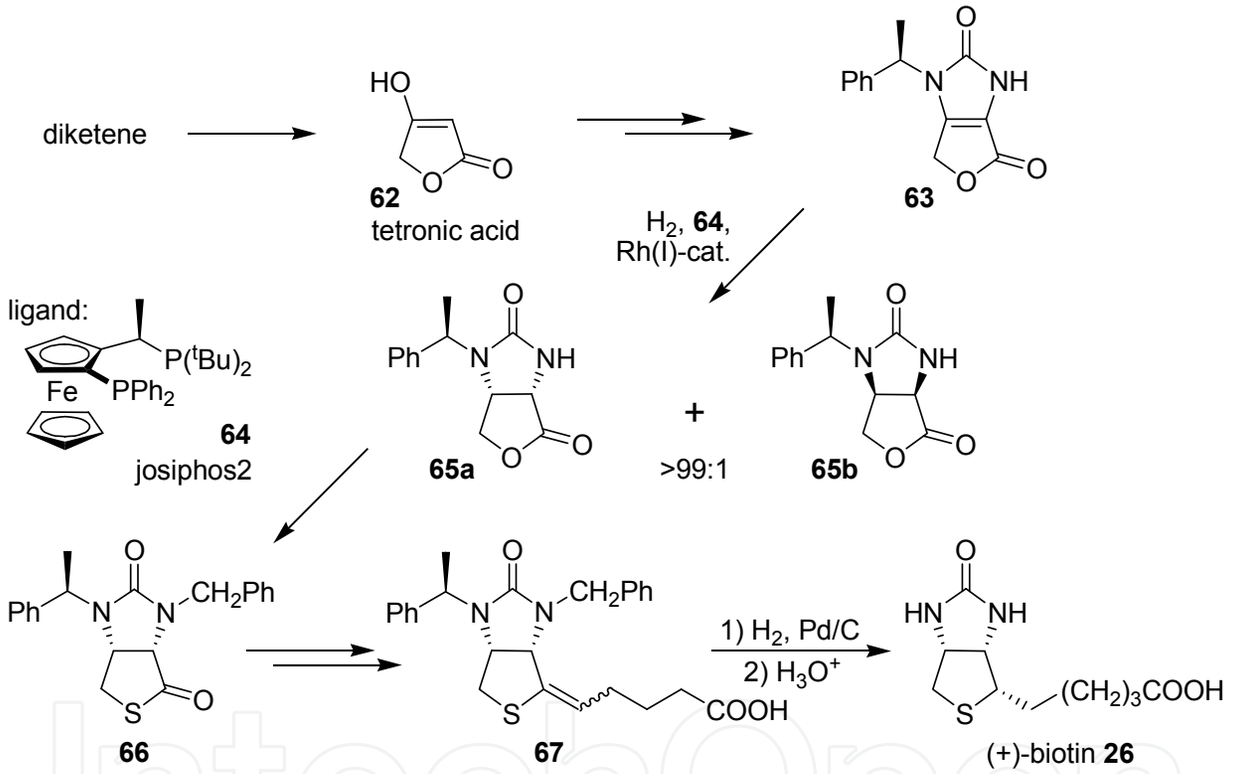
The homogeneous asymmetric hydrogenation of allylic alcohols catalyzed by ruthenium complexes could be performed on pilot scale with substrate-to-catalyst ratios of up to 150'000 (Scheme 17). The C_{10}-building block (*E*)-**54** was transformed into (*R*)-**57** with >99% selectivity by using (*S*)-MeOBIPHEP (**56**, Ar = *p*-Tol, X = OCH_3) as ligand. Under similar conditions, hydrogenation of (*E*)-**55** gave (*R,R*)-**58** (>98% *RR*) with the catalyst derived from (*S*)-*p*-Tol-BIPHEMP (**56**, Ar = *p*-Tol, X = CH_3) [62].

Even two chiral centers can be introduced by the one-pot reduction of unfunctionalized trialkyl substituted olefins in the presence of Ir-BAr_F complexes containing chiral P,N-ligands (Scheme 18). By applying this novel retrosynthetic concept, an (all-*R*)-tocopherol derivative could be obtained for the first time from the corresponding (all-*E*)-tocotrienol derivative in a collaboration of the Pfaltz group with DSM Nutritional Products. Asymmetric hydrogenation of γ-tocotrienyl acetate (*R,E,E*)-**59** with pyridyl phosphinite **60** yielded acetate **61** with complete conversion and excellent stereoselectivity (>98% *R,R,R*) [63,64].



Scheme 18. Asymmetric hydrogenation reactions of unfunctionalized trisubstituted olefinic double bonds.

A Rh(I)-catalysed highly diastereoselective hydrogenation is the basis for a very short synthesis of (+)-biotin (**26**) developed by Lonza and applied on a technical scale (Scheme 19). The hydrogenative key transformation was the result of a cooperation with the catalysis group of former Ciba-Geigy [65]. After ligand screening and optimisation, the conversion of substrate **63**, easily accessible from diketene *via* cheap tetronic acid (**62**), could be improved to high selectivity (**65a**:**65b** >99:1) with ferrocene derived josiphos2 (**64**) as ligand. Although the synthesis *via* thiolactone **66** and subsequent stereoselective heterogeneous hydrogenation of olefin **67** (cf. Chapt. 2, Scheme 6, **23**→**24**) was operated on tonne scale, production had to be terminated due to high production costs. The final debenzylation step to yield **26** led to destruction of the chirality in the expensive (*R*)-methylbenzylamine auxiliary used for introduction of one of the two nitrogen functionalities.



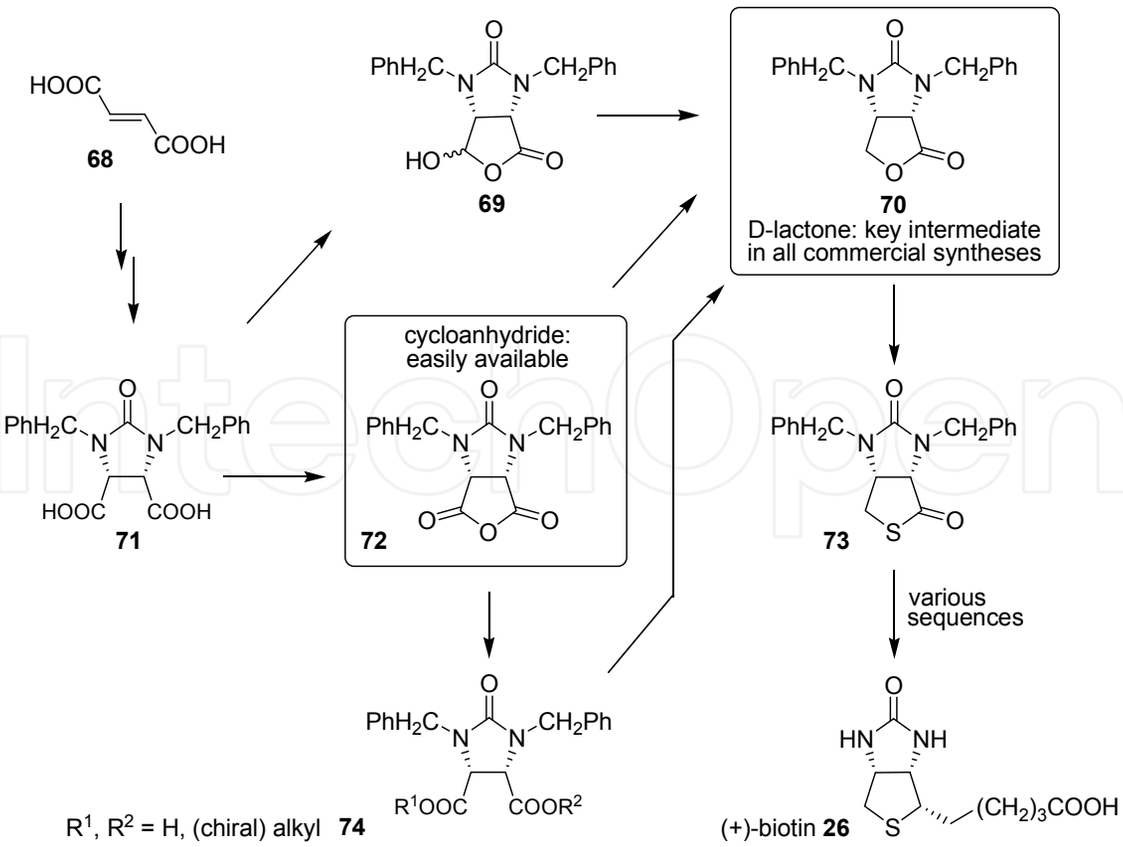
Scheme 19. Diastereoselective hydrogenation in the Lonza procedure to (+)-biotin.

The chiral D-lactone **70** is the key intermediate in all other commercially interesting biotin syntheses (Scheme 20) [66,67]. In former times, diastereomeric acetals derived from hydroxylactone **69** were used. *Meso*-compound **72** (obtained from fumaric acid **68** *via* diacid **71**) was recognised as an easily available starting material for introduction of the optical activity. Classical optical resolution to form diastereomeric imides or ammonium salts, diastereoselective ring opening with chiral alcohols (e.g. → **74**), as well as enzyme catalyzed transesterification reactions were used. All those processes, however, are elaborative and need chiral auxiliaries in stoichiometric amounts which have to be recycled. Often, additional protective group transformations are necessary. Until 2006, the direct

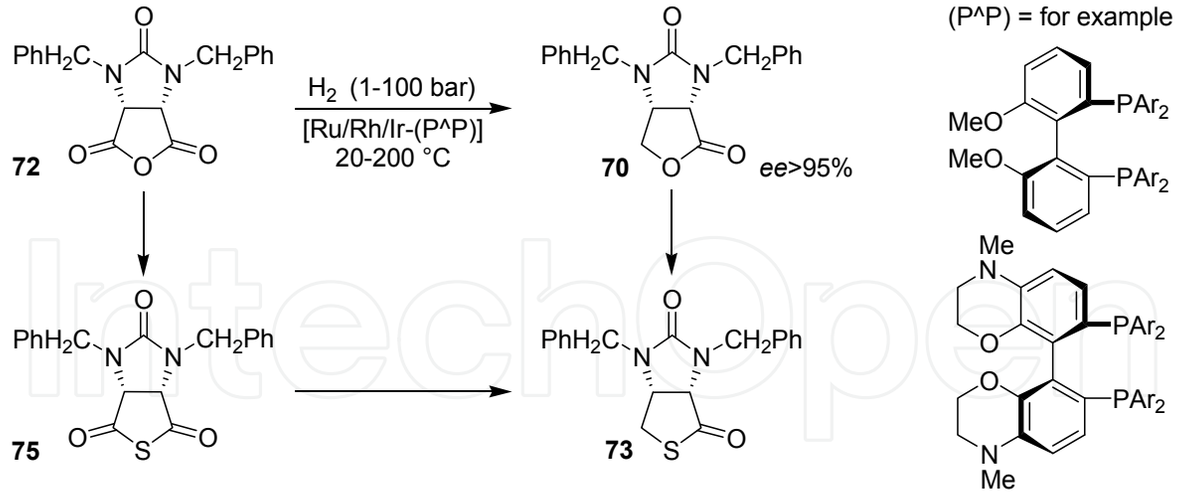
desymmetrisation of anhydride **72** to D-lactone **70** and further elaboration to thiolactone **73** was only possible by reduction with expensive (*R*)-BINAL-H in over-stoichiometric amounts under low-temperature conditions [68], which is not applicable on larger scale.

A breakthrough was achieved in an inter-company cooperation, between DSM Nutritional Products and the catalysis group of Solvias [66,67]. The asymmetric hydrogenation of anhydride **72** to D-lactone **70** with Ir- and Rh-complexes with atropisomeric ligands [69] yielded best results. After a short series of screening and optimisation experiments, full conversion and *ee* values of >95% could be reached, resulting in successful production trials on tonne scale (Scheme 21). The transformation of thioanhydride **75** to thiolactone **73** needed some more drastic reaction conditions, delivering lower selectivities and moderate yield

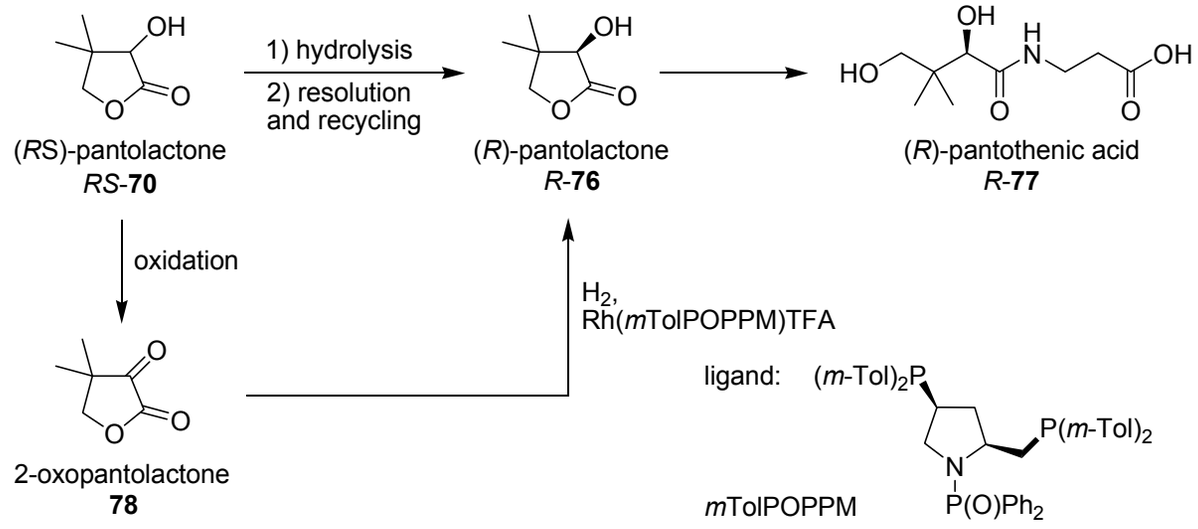
(*R*)-Pantothenic acid (*R*-**77**) is naturally occurring as a component of coenzyme A and is essential for various biochemical processes. *R*-**77** and its commercial form calcium (*R*)-pantothenate are industrially produced by optical resolution from racemic pantolactone (*RS*-**76**, Scheme 22) as the key intermediate. The latter is prepared from isobutyraldehyde, formaldehyde, and hydrogen cyanide, and subsequent acidic hydrolysis [70]. Alternative processes rely on the enantioselective hydrogenation of 2-oxopantolactone (**78)** [71]. With a rhodium catalyst containing *m*TolPOPPM as a ligand, high turn-over numbers (TON) of 200'000 and high optical purity (91% *ee*) could be obtained. The heterogeneous version of this transformation using a Pt/alumina catalyst in the presence of a chiral modifier, e.g. cinchonidine, delivered very similar *ee* values [72].



Scheme 20. Synthetic strategies for the introduction of optical activity into (+)-biotin.



Scheme 21. Preparation of an optically active lactone by catalytic asymmetric hydrogenation.

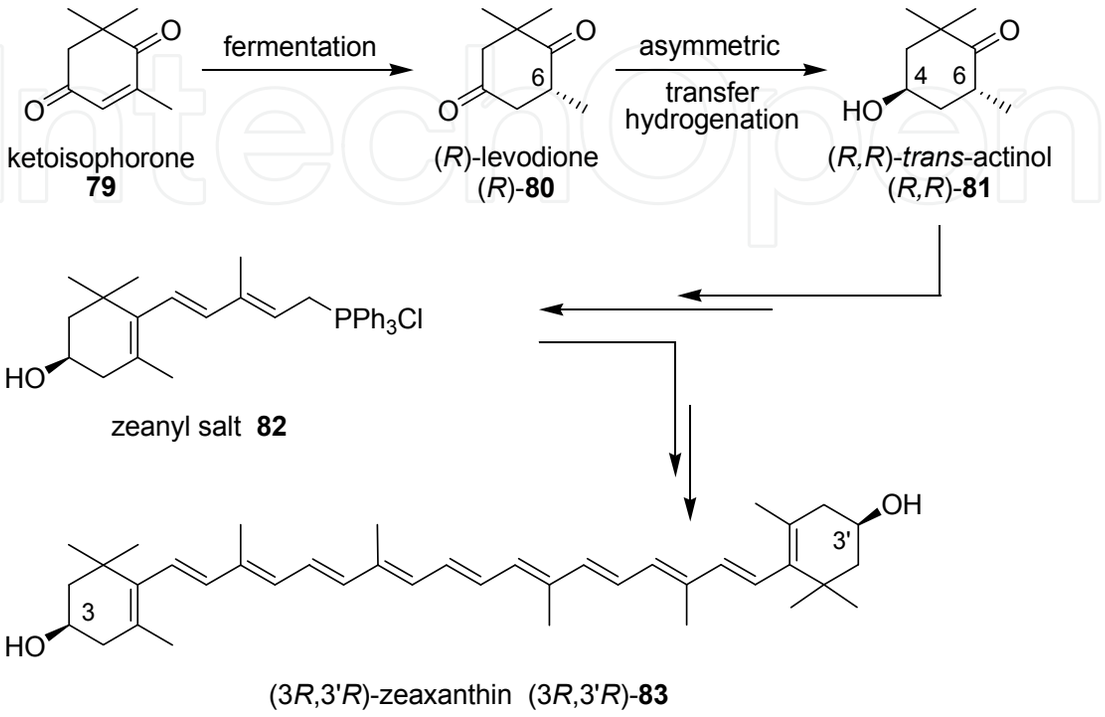


Scheme 22. Enantioselective hydrogenation of 2-oxopantolactone in the synthesis of pantothenic acid.

(3*R*,3'*R*)-Zeaxanthin [(3*R*,3'*R*)-**83**] is found in the human eye and is of interest for the treatment of age-related macular degeneration (AMD) [73] which is a major cause of blindness in the Western World. (3*R*,3'*R*)-**83** occurs in nature in corn (maize) and egg yolk. Its total synthesis starts from ketoisophorone (**79**, Scheme 23) which is efficiently transformed by yeast fermentation into the chiral intermediate (*R*)-levodione [(*R*)-**80**]. The overall reaction scheme consists of various reaction steps (*via* (*R,R*)-**81**, **82**). Stereoselective hydrogenation of (*R*)-levodione [(*R*)-**80**] to *trans*-actinol, however, was difficult to achieve [74].

While the heterogeneous nickel catalyzed hydrogenation of (*R*)-**80** yielded a 80:20 mixture of (*R,R*)-*trans*-actinol [(*R,R*)-**81**] and the corresponding (4*S*,6*R*)-isomer, the homogeneous Ru-BINAP catalyzed asymmetric hydrogenation gave only poor chemo- and enantioselectivities. The breakthrough could be achieved by a ruthenium catalyzed asymmetric transfer hydrogenation with isopropanol using a dianion complex [Ru(N-*p*Ts-ethylenediamine){-2H}(η^6-arene)] [75]. At a substrate-to-catalyst ratio of around 1000,

high *de* values were obtained when performing the reaction at room temperature and reaction times below 24 h. This was the basis for up-scaling and transfer to technical implementation.



Scheme 23. Asymmetric transfer hydrogenation of (*R*)-levodione in the synthesis of (3*R*,3'*R*)-zeaxanthin.

6. Conclusions

Various types of hydrogenation reactions are indispensable parts of economically and ecologically beneficial manufacturing processes towards valuable products in the vitamins and fine chemicals industry. The increasing importance of environmentally benign production methods is addressed by developing concepts for improving the efficiency of transformations, continuous processing and recycling, and achieving high chemo- and stereoselectivities, thus avoiding laborious separation protocols and waste formation. The examples presented and discussed in detail show many achievements in this field during recent decades, but also the necessity to further search for alternative solutions.

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