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New Trends in (heterogeneous) Catalysis for the Fine Chemicals Industry

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Abstract: New catalytic methods and modern trends for the synthesis of fine chemicals, especially vitamins, carotenoids, flavoring and fragrance compounds are presented. In particular the application of heterogeneous catalysis in the formation and production on industrial scale of these classes of organic compounds will be highlighted and its use in the replacement of former stoichiometric processes.

Keywords: Carotenoids · Catalysis · Fine chemicals · Flavoring compounds · Fragrance compounds · Vitamins

Werner Bonrath studied chemistry in Bonn and Münster (Germany) and then moved to the MPI (Mülheim, Germany) to complete his PhD with Günther Wilke. He joined Hoffmann-La Roche in 1989 working in the area of catalysis for vitamins, carotenoids and fine chemicals. He completed his habilitation at the University of Jena (Germany) in 2007 and is currently a lecturer there and at the University of Basel. Since the merger with DSM, he is Competence Manager Heterogeneous Catalysis. In 2013 he received the Senior Industrial Investigator Award of the Swiss Chemical Society.

1. Introduction

Catalysis is a key technology for the synthesis, development and production of chemicals. There is a need for the implementation of new catalytic methods with the aim to replace stoichiometric ones. One starting point was the replacement of Brønsted acids such as sulfuric acid by heterogenic (solid) acids and during the 1980s several new heterogeneous catalytic processes were implemented.[1] R. Sheldon pointed out in the 1990s that in the fine chemicals industry (bio)chemical transformations are often based on stoichiometric organic reactions, and significant amounts of by-products and waste are formed.[2,3] In order to improve the effectiveness of our processes, we established a competence platform to boost the development and application of efficient catalytic methods.[4,5] These activities have the main focus on sustainable chemistry, reduction of waste, combination of unit operations, and, as a consequence, the reduction of production costs. The concept of the twelve principles of 'green chemistry'[6–8] and atom economy[9] are included.

In this review new applications of catalytic methods on processes towards selected fine chemicals of economic importance, namely the classes of vitamins, carotenoids, flavoring and fragrances are summarized. The examples are grouped into the key competences developed at DSM Nutritional Products (Fig. 1). An overview presenting the achievements in the research and development of vitamins and bioactive ingredients has been previously published.[10,11]

The term 'vitamin' itself was introduced into the scientific world by C. Funk and originates from the combination of the words 'vital' and 'amine'.[12] The class of vitamins covers a group of 13 different compounds, which must be consumed in the diet of humans and animals to ensure they remain healthy. For an overview about history of vitamins, their chemistry and physiology, see refs [10, 13–15]. The lipid-soluble vitamins, as well as carotenoids, have as a characteristic feature a isoprenoic C_5-unit. The industrially most relevant representative of the group of vitamin E compounds is (all-*rac*)-α-tocopherol (**1**), is produced in over 35'000 tons per annum, and mainly used in animal nutrition (feed) applications.[4,5,10]

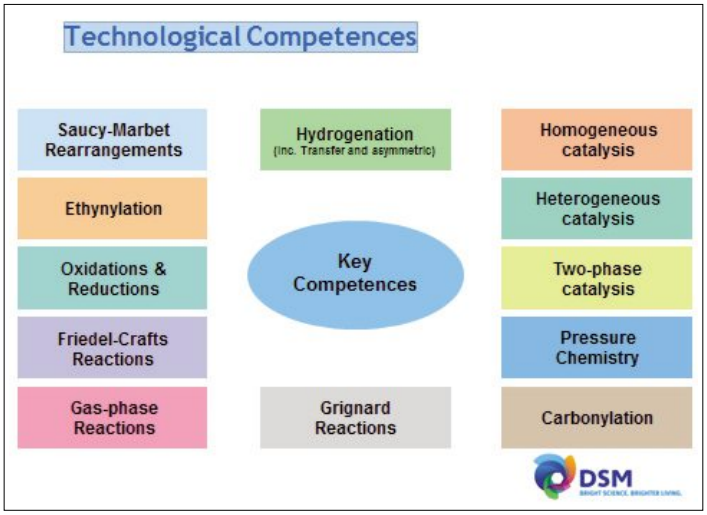

Fig 1. Technology (key) competences at DSM Nutritional Products.

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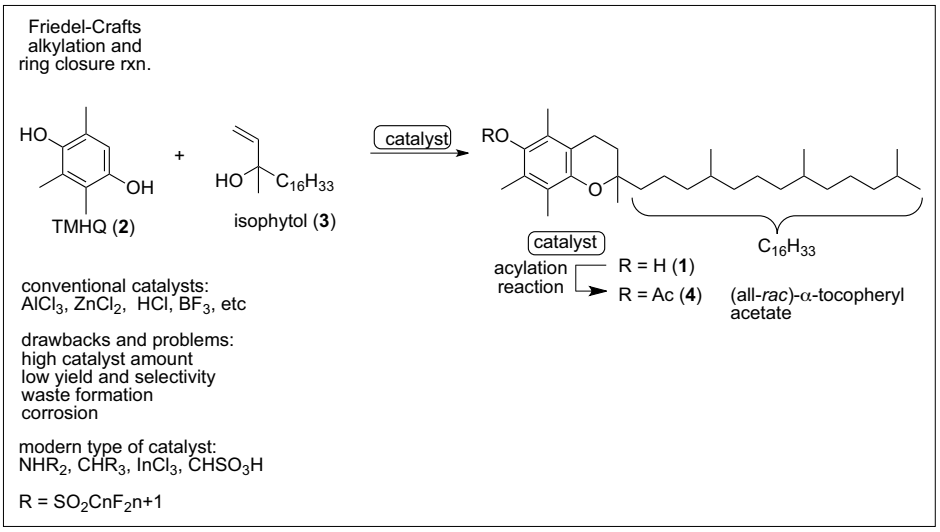
2. Friedel-Crafts Reaction

We started our investigations into the Friedel-Crafts-type reaction for the synthesis of vitamin E (α-tocopherol). A key step of the manufacture of (all-*rac*)-α-tocopherol (**1**), is the Friedel-Crafts condensation reaction of trimethylhydroquinone (**2**) with isophytol (**3**) (Scheme 1). In the past a catalyst system based on a Brønsted/Lewis acid combination like $ZnCl_2$ with mineral acids, BF_3, Fe/HCl, $AlCl_3$, or other reagents has been applied. We found that in a two-phase liquid–liquid solvent system Lewis or Brønsted acids alone are efficient catalysts which perform in a higher yield (>95%) and selectivity. Metal triflates[16] and halides,[17] perfluoro substituted imides,[18] methides,[19] and tris(oxalato)phosphorus acid[20] are efficient catalysts for the reaction at a substrate to catalyst ratio of 1000 to 10000 depending on reaction conditions.

The discovery of alternative and more efficient Brønsted acids for the synthesis of (all-*rac*)-α-tocopherol not only improved the condensation reaction considerably, but also had a strong impact on other key steps in vitamin production, as outlined in Scheme 1.



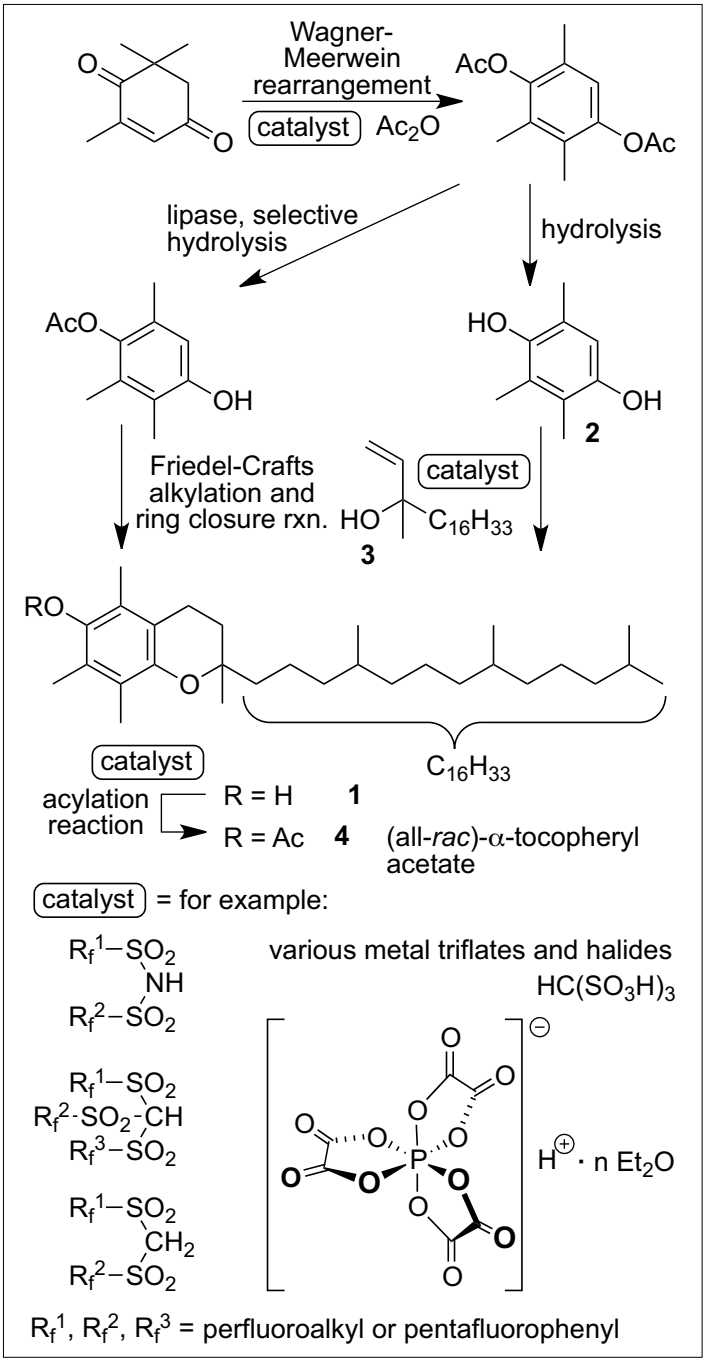
Scheme 1. Friedel-Crafts catalysts.

3. The One-catalyst Several Reaction Approach

The idea to establish efficient catalytic systems results in the idea to develop a catalyst which can be used in different reaction types. We wished to replace a number of different Brønsted acids in multiple reaction steps with a single acid catalyst to reduce salt waste formation and to increase selectivity and yield for such reactions. A successful example fulfilling the idea of this concept was the application of methane trisulfonic acid in sub-stoichiometric amounts, which catalyzes the three different types of reactions: Wagner-Meerwein rearrangement, Friedel-Crafts condensation and acylation in the synthetic route to (all-*rac*)-α-tocopheryl acetate (**4**) outlined in Scheme 2.[21]

4. Catalysis in Multi-phase Systems

Retinol (vitamin A) is a lipid-soluble diterpene that, for stability reasons, is applied as vitamin A acetate. Kuhn and Morris in 1937 published the first synthesis of vitamin A.[22] From an industrial view three chemical syntheses of vitamin A are of commercial interest, and all use β-ionone (**5**) as the key intermediate. Hoffmann-La Roche developed the first of these in 1947.[23] Otto Isler developed the first industrial vitamin A synthesis starting

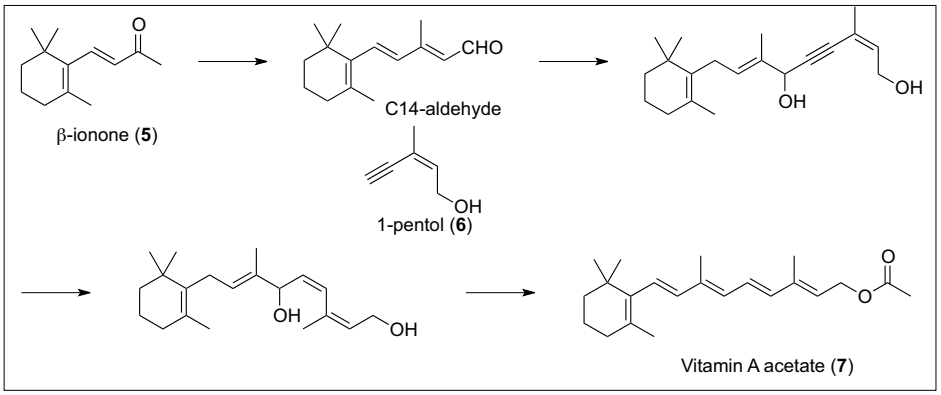


Scheme 2. Brønsted acid catalysis in the synthesis of vitamin E.

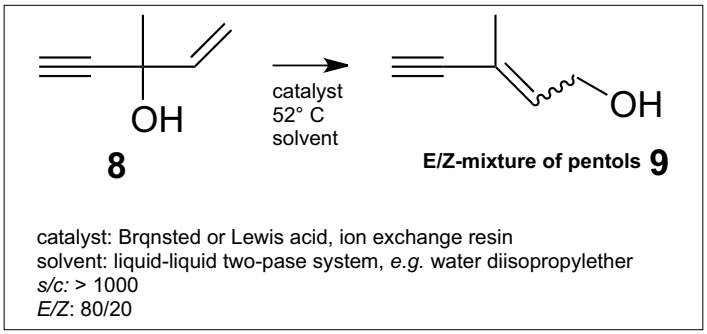
from β-ionone and a one-carbon extension to form 'C14-aldehyde' (Darzen reaction, Scheme 3). The C_{14}-unit was coupled with the acetylenic Grignard reagent of '1-pentol' (1-hydroxy-3-methylpent-2-en-4-in, **6**) followed by Lindlar-type hydrogenation,[24] mono-acetylation and elimination of the secondary alcohol to give crystalline vitamin A acetate (**7**).

The other two commercialized routes were developed by BASF using Wittig chemistry and Rhône-Poulenc using the Julia olefination. In both routes, β-ionone is initially converted to vinyl-β-ionol.[25]

We were interested in a new process for the '1-pentol' manufacture. This enyn-ol can be synthesized from 3-hydroxy-3-methyl-pent-4-en-1-in (**8**) by acid-catalyzed allylic rearrangement in dichloromethane (Scheme 4).[26] Replacement of the chlorinated solvent by a liquid–liquid two-phase solvent system, such as diisopropyl ether–water or another water–immiscible ether combination, results in an increased yield.[27] Usually Brønsted acids, *e.g.* sulfuric acid are used for the allylic rearrangement. A further improvement was the application of a solid acid, *e.g.* an ion-exchange resin, like Amberlyst-type resins, which have been commercially available for decades. Following this more 'green' approach the waste streams could be reduced and an increased selectivity was obtained.[28]



Scheme 3. O. Isler's route to vitamin A.



Scheme 4. Allylic rearrangement in multi-phase systems.

5. Saucy-Marbet Reaction

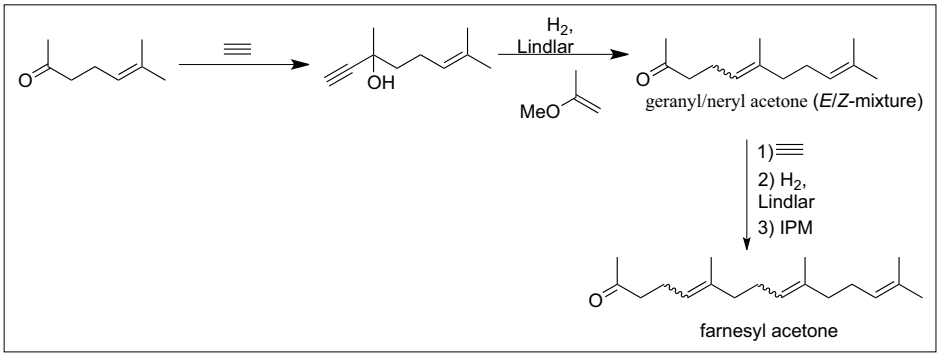
The isoprenoid units (C_5) are found in all lipid-soluble vitamins, carotenoids and many fragrance compounds. The isoprenoids are chemically formed by sequential C_2- (base-catalyzed) ethynylation[10,11], for example in the transformation of acetone to methylbutynol, and C_3-elongation reactions (acid-catalyzed Saucy-Marbet[29] or Carroll reactions). In some applications, an aldol condensation with acetone is used for C_3-elongation, for example in the preparation of ψ-ionone from citral. The formation of significant amounts of by-products (self-condensation of starting materials) are, however, often observed when using such procedures.

The most efficient C_3-elongation process is based on the Saucy-Marbet reaction, which is usually carried out under acid catalysis. By using the activated acetone equivalent isopropenyl methyl ether as a C_3-building block, the corresponding ketones can be obtained in high selectivity and yields. Modern trends in acid-catalyzed reactions aim for the replacement of regular Brønsted acids by solid acids, for example ion-exchange resins or zeolites. This technology allows continuous processing and benefits from waste reduction, since an often required neutralization step can be avoided, and hence eliminating the formation of additional salts. Multi-phase catalysis is another valuable concept towards the elaboration of efficient (continuous) processes. Furthermore we developed a new catalytic system for Saucy-Marbet reaction and found that ammonium salts catalyze this reaction in an very effective manner.[30] In particular the fragrance compounds geranyl acetone (starting from linalool) and farnesyl acetone (starting from nerolidol) could be manufactured in an efficient manner (Scheme 5).

6. Hydrogenation Reactions

Catalytic hydrogenation is the most applicable method for the reduction of organic compounds and one of the most important transformations in chemical industry. Catalytic hydrogenations in fine chemical industry are usually carried out using heterogeneous catalysts. Nowadays catalyst screening (the search for the most efficient catalyst) and the process optimization would not be possible without the use of parallel experimentation. DSM Nutritional Products (formerly Roche Vitamins) has decades of experience in hydrogenation reactions and parallel experimentation was started before commercial parallel equipment became mainstream. Today a modern set-up of equipment is installed which allows a fast development and implementation of catalytic hydrogenation on industrial scale.[31]

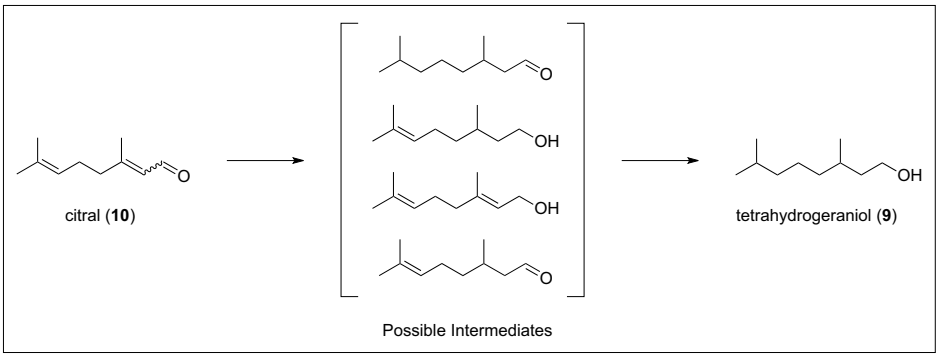
Since the time of Sabatier and coworkers the field of catalytic hydrogenation reactions has seen several significant inventions.[32,33] A milestone in the field of catalytic hydrogenation reactions was the selective hydrogenation of C≡C-bonds in presence of lead-doped palladium on calcium carbonate catalysts found by



Scheme 5. Synthesis of geranyl/neral acetone and farnesyl acetone applying the Saucy-Marbet reaction.

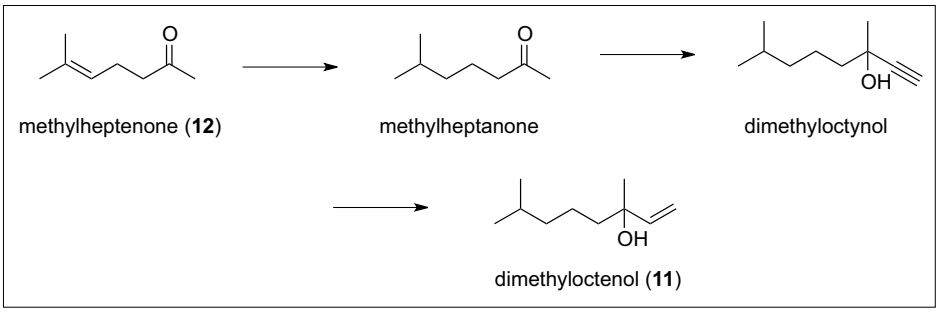
Lindlar.[34–36] A next highlight was the asymmetric hydrogenations, pioneered by W. S. Knowles and R. Noyori.[37,38] The role of homogeneous and heterogeneous catalytic hydrogenation reactions in processes for the production of vitamins, carotenoids, fragrance compounds and nutraceuticals has been discussed in ref. [39].

We were interested in preparing tetrahydrogeraniol (**9**), a fragrance compound (fresh and floral, rose and geranium aroma) that has many applications in detergents, shampoos and baked goods and chewing gum. Starting from citral (**10**) we found the use of nickel-alloy catalysts resulted in the desired product tetrahydrogeraniol with only small amounts of (the intermediate) by-products resulting in a process which gives full conversion, >95% yield, and also allowed the catalyst to be reused multiple times (Scheme 6).[40]



Scheme 6. Synthesis of tetrahydrogeraniol.

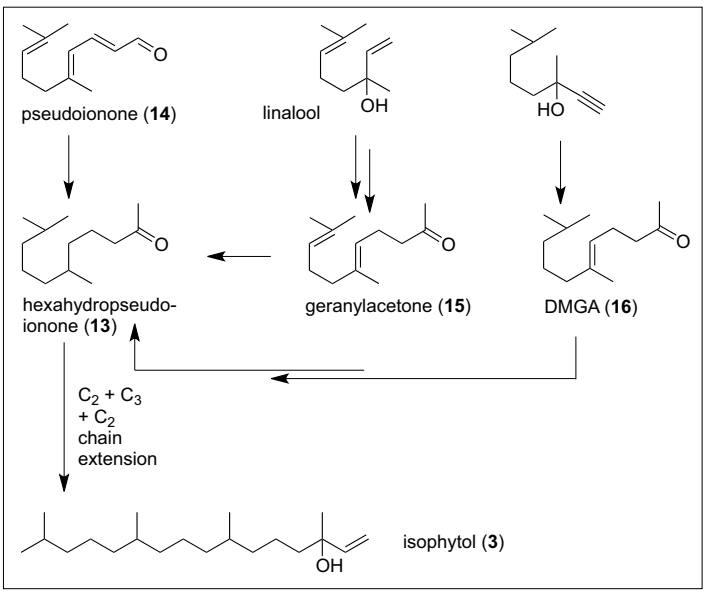
Compounds with rose-like odors are of interest for the flavor and fragrance industry. An aroma compound like dimethyloctenol/dihydrolinalool (**11**) is used as a substitute for linalool and can be prepared starting from methylheptenone (**12**) by a hydrogenation of the C=C double bond, ethynylation, and a selective semi-hydrogenation of the resulting C≡C triple bond (Scheme 7).[41]



Scheme 7. Synthesis of dimethyloctenol.

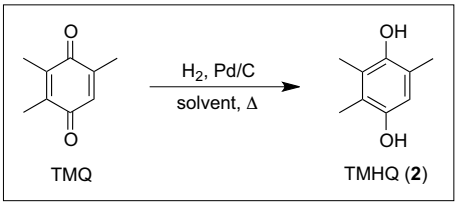
Here it has to be pointed out that the Lindlar-type hydrogenation was carried out by monitoring of the reaction to avoid over-hydrogenation to the fully saturated by-product. Following this approach a yield of >95 % can be achieved and an efficient process established.

As pointed out in Section 4, the isoprenoids can be produced in a sequence of C_3 and C_2 elongation reactions. In such reaction sequences several hydrogenations of C=C bonds are necessary. Hexahydropseudoionone (**13**) is one of the key intermediates in the synthesis of isophytol (**3**), and can be produced from ψ–ionone (**14**) or geranyl acetone (**15**) (Scheme 8). In the past the hydrogenation reactions were carried out batch-wise in presence of a Pd/C or a Pd or Rh on Al_2O_3 catalyst below 80 °C and <10 bar pressure.[41,42] The liquid-phase hydrogenation of **14**, **15** or dihydrogeranyl acetone (**16**) in presence of a suspended catalyst in a special reactor set-up which allows an easy hold-up of the catalyst has been described.[43] The synthesis of these saturated ketones in a continuous fixed-bed mode applying a Pd/SiO_2 catalyst results in excellent yield under nearly full conversion.[44]



Scheme 8. Synthesis of isoproind building blocks by hydrogenation.

Trimethylhydroquinone (TMHQ, **2**) is a key intermediate for the synthesis of vitamin E, and is accessible *via* catalytic hydrogenation of trimethyl-1,4-benzoquinone (TMQ) using a palladium on carbon catalyst (Scheme 9).



Scheme 9. Catalytic hydrogenation of TMQ to TMHQ.

The hydrogenation is carried out at medium to low pressure in a continuous mode at elevated temperature to prevent crystallization of TMHQ (**2**) and results in nearly quantitative yield. However, improved and cheaper routes to TMQ/TMHQ are still needed. We developed an alternative access to TMHQ starting from 1,4-benzoquinones, *e.g.* 2,6-dimethylbenzoquinone (2,6-DMQ, **17**). Hydrogenation results in 2,6-dimethyl-hydroquinone (**18**) which then needs to be methylated to give the desired product. One of the most efficient methods that we developed was the aminomethylation which initially gives the benzylic amine (**19**). This can undergo hydrogenolysis with a palladium on carbon catalyst to give **2** in good yield (Scheme 10).[45]

As pointed out in the synthesis of dihydrolinalool, new developments of Lindlar catalysts are important to establish new procedures for selective hydrogenation of C≡C bonds into the corresponding (*Z*-configured) C=C bonds. H. Lindlar developed a catalyst for the semi-hydro-

genation of a vitamin A key intermediate (Scheme 12). This catalyst was a lead-doped palladium on calcium carbonate[46], which gave significantly higher selectivities and yields than existing catalysts and the reaction could easily be stopped after the uptake of just one equivalent of hydrogen gas.

Nowadays, the Lindlar catalyst is of high importance in the synthesis of vitamins A, E, carotenoids, and also intermediates for the fragrance industry. The starting material for such compounds is methylbutenol (MBE, **20**, Scheme 11). MBE is synthesized by the partial hydrogenation of the corresponding alkyne MBY (**21**) in a batch-wise process. Selectivity is very high (>98%) and the catalyst can be recycled multiple times.

From MBE, the chain is extended by C_3 and C_2 elongation reactions in a sequential manner to obtain dehydroisophytol (Scheme 13) which is reduced in a batch-wise process at 2-5 bar hydrogen pressure in another semi-hydrogenation to give isophytol (Scheme 13).[46]

Linalool (**22**) and linalyl acetate (**23,** Fig. 2) are found in a wide range of natural flowers and spice plants and are of interest to the fragrance industry. Their main applications are as perfume components in soaps, shampoos and lotions. Both compounds can be synthesized by semi-hydrogenation of dehydrolinalool or dehydrolinalyl acetate by Lindlar hydrogenation; however the reaction conditions had to be optimized independently since even minor changes to the substrate structure can have significant effects on the hydrogenation selectivity. Lindlar catalysts with varying amounts of lead-doping were successful at moderate temperatures (20–40 °C) and pressures (1–10 bar hydrogen).[47]

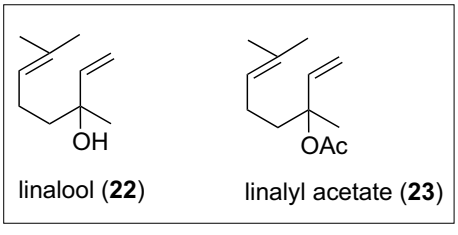
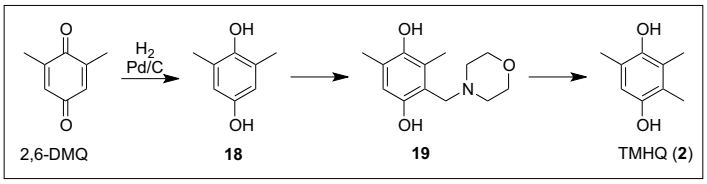


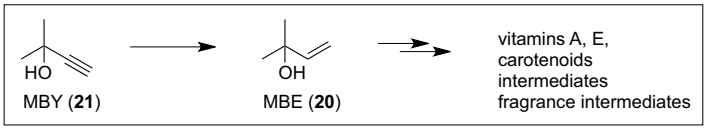
Fig 2. Linalool and linalyl acetate.

In the past, Lindlar hydrogenations have been carried out batch-wise in slurry type reactions.[48] The development of new types of catalysts (Pd-nanoparticles on an oxide sinter metal fiber) allows immobilization and thus continuous processing in a fixed bed reactor.[49]

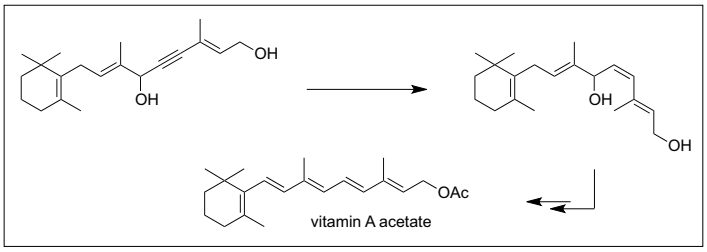
Supported palladium nanoparticles with a narrow range of diameters are new approaches for the application of Lindlar-type catalysts.[50,51] In several cases application of these catalysts high selectivity can be observed, *e.g.* hex-3-yne can be hydrogenated to hex-3-ene at full conversion. However, these catalysts have not yet been applied on an industrial scale for the production of vitamins and fine chemicals.



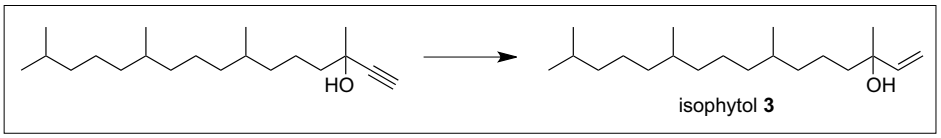
Scheme 10. Synthesis of TMHQ from 2,6-DMQ.



Scheme 11. Semi-hydrogenation of MBY.



Scheme 12. Semi-hydrogenation of a vitamin A intermediate.



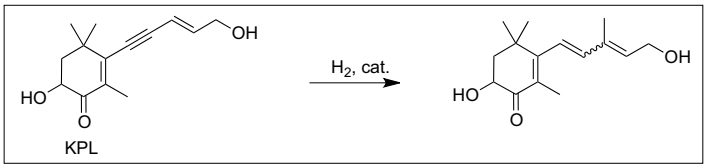
Scheme 13. Preparation of isophytol by semi-hydrogenation.

Another focus on Lindlar hydrogenations catalysts is the research on the addition of $FeCl_2$ and tetramethylammonium chloride as catalyst on carbon, and the use of palladium on metal sintered fibers. This allows hydrogenation of triple bonds in a continuous reaction mode, also with low Pd loadings, in which Pb doping is not necessary.[49–53]

The search for new Lindlar catalysts with excellent performance also includes the application of new carrier material. It was found that SiO_2 can be applied in form of small particles with pore diameter of 100–200 mm.[54] Modification of this Pb-free catalyst, by Cu doping, results in a highly selective catalyst for the isophytol synthesis.[55]

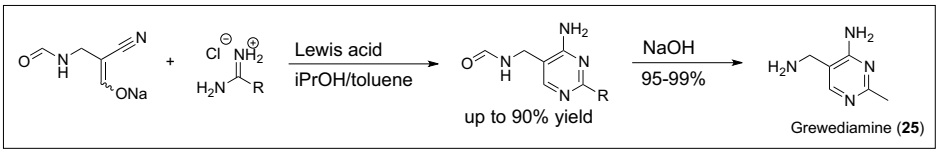
Another approach for the development of new Lindlar-type catalysts is the establishment of a Pb-free catalyst with high mechanical stability and easy and efficient heat transfer to avoid hot-spots, especially in a continuous hydrogenation set-up. Such catalysts were found and applied to the selective hydrogenation of α-alkynols using a metal alloy carrier, coated with an oxide layer and Pd as active metal.[56–58] The carrier material comprises Cr, Mo, or Fe, Ni, Co, Mo in various amounts. This catalyst shows a high performance and good selectivity, 96–99.5% depending on the substrate, and has an excellent life time.

In the field of alkyne hydrogenation the selective hydrogenation of polyene-yne systems, especially for carotenoid intermediates, is an interesting and ambitious topic, because such hydrogenation needs high performing systems to avoid over-hydrogenation or formation of by-products. Often the reduction of internal C≡C bonds in such compounds is carried out using stoichiometric reagents such as Zn and acetic acid or Zn and an ammonium salt.[59–61] We found that by detailed investigation of the Lindlar catalyst synthesis, significant improvements in the semi-hydrogenation could be made with these challenging substrates. Use of a well-defined calcium carbonate poisoned with lead and careful control of the process parameters during the metal deposition resulted in a high-performing catalyst, with increased selectivity and activity (Scheme 14).[62] The Astaxanthin intermediate ketoylpentynol (KPL, **25**) can be reduced in excellent yield



Scheme 14. New type of powder Lindlar-catalyst for carotenoid intermediates.

up to 95%. The research and development of this breakthrough Lindlar catalyst was done from laboratory scale up to successful plant trials.



Scheme 15. Synthesis of Grewe diamine.

7. Synthesis of Heterocyclic Compounds

As outlined in the introduction, the principles of 'green chemistry' are an important trend in industrial chemistry. The principle of replacement of stoichiometric reactions by catalytic ones is a main activity in this field. Aminopyrimidines are industrially relevant compounds, *e.g.* intermediates in the vitamin B1 synthesis[63] and all industrial relevant vitamin B1 processes use Grewediamine (**25**) as a key building block.[64] This 4-aminopyrimidine derivative can be synthesized from acrylonitrile in a three-step procedure using an acid-sensitive sodium enolate. We wished to improve the synthesis of this key building block and found that Lewis acid-catalyzed direct coupling of the sodium enolate and acetamidine hydrochloride gave higher yields. It also has the advantage of avoiding toxic reagents and salt formation based on the acetamidine hydrochloride neutralization, which was applied in the non-catalyzed reaction (Scheme 15).[65] Following this approach N-formyl-Grewediamine can be synthesized in up to 90% yield applying aminophilic Lewis acids such as Zn or Cu catalysts. The reaction product can be transformed in base-catalyzed hydrolysis in a two-phase solvent system (another example of beneficial two-phase solvent systems).[64] The hydrolysis can be performed at full conversion and 99% selectivity. Here it can be pointed out that this approach can also be used as a general method for the synthesis of aminopyrimidines.

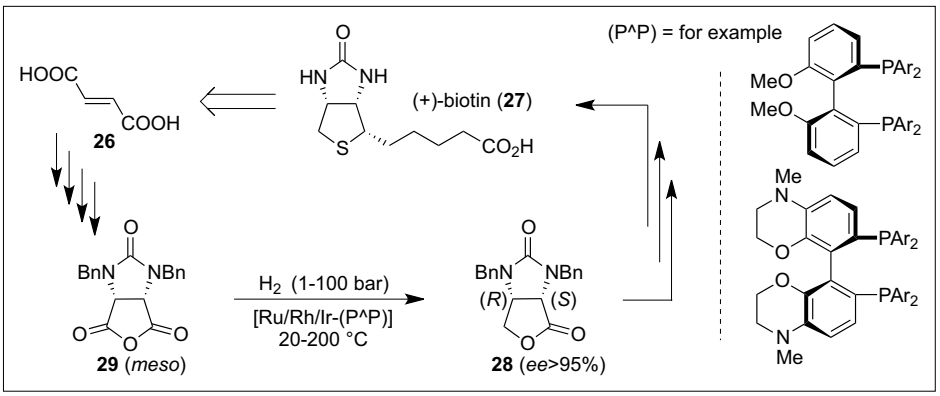
8. Asymmetric Synthesis

In addition to the developments described above, asymmetric synthesis is gaining in importance, even for relatively low cost molecules such as vitamins and fragrance compounds. This offers up the possibility of either avoiding a time-consuming and waste-generating resolution step, or the preparation of an enantiomerically enriched version of a compound that is currently produced as a mixture of stereoisomers.

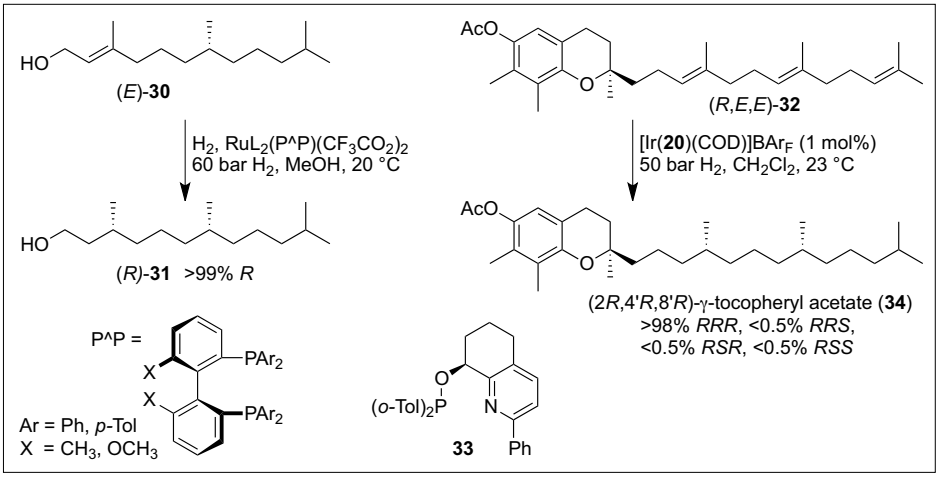
The main industrial synthesis of (+)-biotin (**27**), an important water-soluble B-vitamin uses *N*-benzyl-protected key building blocks, in particular D-lactone **28**, that are easily accessible from fumaric acid (**26**). However, the preparation of the chiral lactone is usually performed by resolution using stoichiometric amounts of a chiral alcohol. Asymmetric synthesis is possible, but requires the use of expensive reagents in multi-step procedures. An ideal alternative would be the selective reduction of the *meso*-anhydride **29**. Until recently only low selectivities have been obtained and enantioselective hydrogenation would be a more cost effective alternative. A range of homogeneous catalysts based on Ru, Rh and Ir were screened with bisphosphine ligands and several 'hits' were identified. Further optimization resulted in a process that proceeded with high optical induction and excellent yield. This direct desymmetrization yields D-lactone **28** with an *ee* of >95%, which can be upgraded to >99% by simple recrystallization (Scheme 16).[66]

Another example for the development of stereoselective processes concerns the preparation of the single-isomer product (2*R*,4'*R*,8'*R*)-α-tocopherol (2*R*,4'*R*,8'*R*-**1**),[67] which is so far only available in limited amounts by partial synthesis. Mixtures of mainly lower homologues of the biologically most active α-tocopherol (so-called mixed tocopherols) are isolated from a side stream of soybean processing, and chemically upgraded. Significant efforts have been directed towards an economical total synthesis of this natural product during the last decades, with the aim to overcome the problem of shortage of the natural source starting material.

Although an economic total synthesis of (2*R*,4'*R*,8'*R*-**1**) could not be accomplished to date, considerable progress has been made in the synthesis of the chiral sidechain by the use of exceptionally efficient asymmetric hydrogenation technologies. Based on the seminal work of Noyori and colleagues in the 1980s, the ruthenium-catalyzed asymmetric hydrogenation of allylic alcohols was performed on pilot scale with substrate-to-catalyst ratios of up to 150'000 (Scheme 17). Using (*S*)-*p*-Tol-BIPHEMP (Ar = *p*-Tol, X = CH_3) as ligand,



Scheme 16. Catalytic asymmetric hydrogenation of a (+)-biotin intermediate.



Scheme 17. Asymmetric hydrogenation towards (2*R*,4'*R*,8'*R*)-tocopherols.

C_{15}-building block (*E*)-**30** was transformed into (*R*)-**31** with >99% selectivity.[68]

Although the asymmetric hydrogenation is incredibly efficient, the total number of chemical steps made this route too expensive. An improved retrosynthetic concept would be the concomitant introduction of the two chiral centers by the reduction of two unfunctionalized trialkyl-substituted olefins in one molecule. In the past, asymmetric hydrogenations required a coordinating group close to the alkene to obtain high selectivity. However, the pioneering work of Pfaltz showed that the selective hydrogenation of unfunctionalized C=C could be achieved using iridium complexes with P,N-ligands.[69] In a collaboration between the Pfaltz group and DSM Nutritional Products it was found that the γ-tocotrienol derivative (*R*,*E*,*E*)-**32** could be successfully hydrogenated with an iridium catalyst containing the pyridyl phosphinite ligand **33**. This furnished (all-*R*)-γ-tocopheryl acetate **34** with excellent stereoselectivity and contained less than 0.5% of each of the other stereoisomers.[70]

9. Conclusions

Although considerable progress has been made, modern industrial fine chemistry needs the continuing development and application of new (heterogeneous) catalysts. These catalysts have to be efficient to allow the implementation of sustainable and low-cost processes. Fundamental research on catalysts themselves and their analysis combined with process and chemical engineering will result in the next generation processes required to reach challenging environmental and financial targets for the large-scale synthesis of fine chemicals. In addition to the industrial cross-functional technical teams necessary to achieve this, collaboration with academic groups all over the world will speed-up the time for implementation of new processes.

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