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Catalysis in the industrial preparation of vitamins and nutraceuticals

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Dedicated to Professor W.F. Hölderich on the occasion of his 60th birthday.

Abstract

Representative examples for the application of several new catalytic, especially heterogeneous catalyzed procedures related to nutraceuticals and vitamins are presented. For industrial processes the yield and selectivity of reactions, determining their overall efficiency, are important criteria for successful implementation. The presented results summarize the main achievements in the field of catalysis for life science products.

Keywords: Nutraceuticals; Fine chemicals; Vitamins; Heterogeneous catalysis; Vitamin A; Vitamin E; Vitamin B6; Resveratrol; Ubiquinone-10

1. Introduction

Catalysis is a key methodology for the efficient production of economically important compounds in life science industry [1]. Research and development in companies of this business like DSM Nutritional Products are driven by innovation to secure cost leadership position and develop new products for the market. To achieve these goals the application of new methods in catalysis, especially heterogeneous catalysis, are key technologies and competences.

Here we present selected examples of new catalytic protocols for the synthesis of important products from the classes of vitamins, carotenoids, and nutraceuticals. Furthermore information on the industrial background is given.

2. Background

DSM is committed to develop new processes and products for the business areas performance materials, industrial chemicals, life science products, and nutritional products with the aim to increase leadership position which already covers 75% of the product portfolio. To achieve this target 300 Mio € are spent per year for research and development.

In the product portfolio of DSM Nutritional Products complex molecules from nature, like vitamins, carotenoids, polyunsaturated fatty acids (PUFAs), enzymes, nutraceuticals, eubiotics, and cosmeceuticals are contained (Scheme 1).

Here it must be pointed out that the technology platforms and competences are focused on the business strategy. The key-competences and their roles are shown in Fig. 1.

For the manufacture of vitamins and carotenoids chemical synthesis is a core competence. Typical products, e.g. astaxanthin, tocopherol, calcium pantothenate or biotin are produced by multi step syntheses with high overall yields. Well established capabilities and technologies in synthesis and down-stream processing, broad experience and history in successful development of individual production processes of natural products and a full set of equipment, from laboratory scale to production scale (from tons to several ten thousand tons) are technology competences. The combined capabilities of DSM Nutritional Products and other parts of DSM strengthen our position in synthesis and market introduction.

The competence cluster heterogeneous catalysis is closely linked to our production and is, therefore, a key-competence in DSM. In DSM Nutritional Products more than 50 process steps based on heterogeneous catalysis are implemented on industrial scale. Reaction types with such high commercial interest are hydrogenations, e.g. for the synthesis of Vitamin E and carotenoids, oxidations, e.g. in the field of Vitamins E and C [1,3], esterifications, e.g. for Vitamin C [3], acetalisations, e.g.

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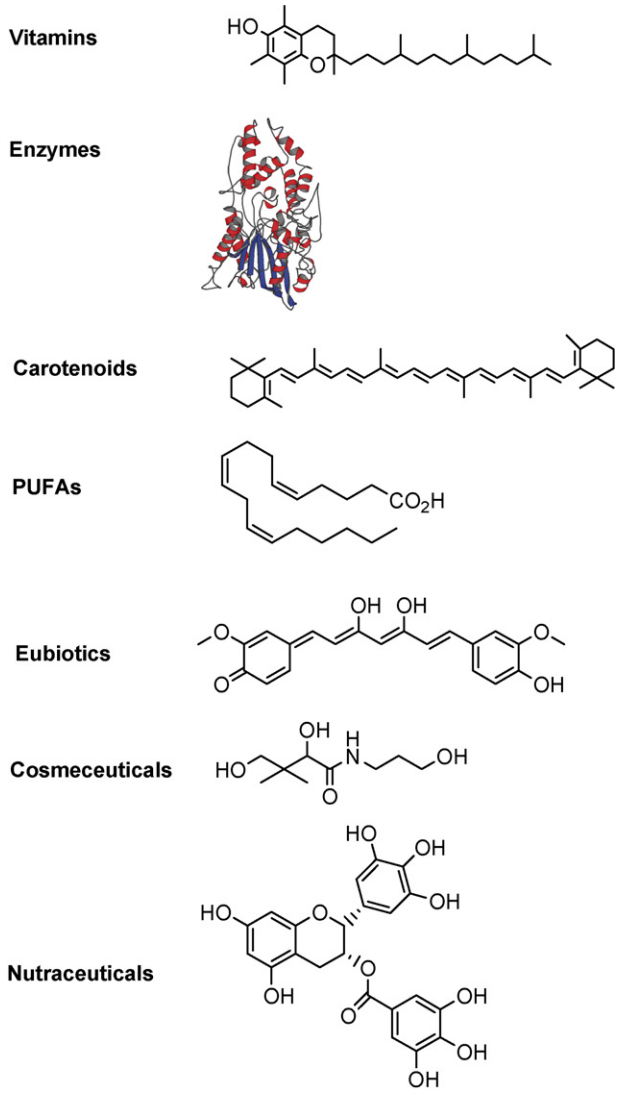


Scheme 1. Typical product classes of DSM Nutritional Products with representative examples.

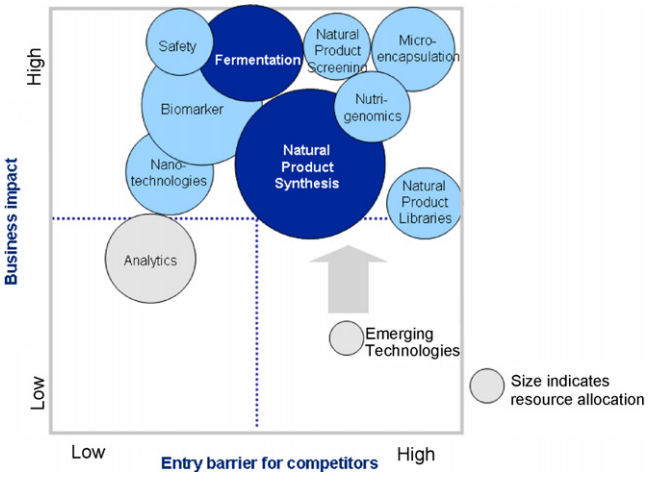
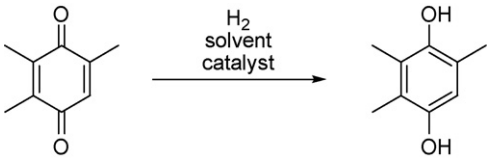


Fig. 1. Business relevant competences within DSM Nutritional Products.



Scheme 2. Hydrogenation of 2,3,5-trimethylquinone.

Fig. 2. Typical laboratory equipment for hydrogenation, oxidation, and formylation reactions.

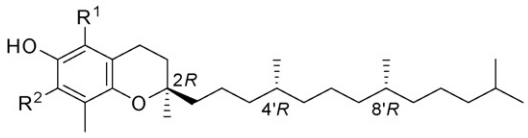
in the production of the key-intermediate isopropenyl methyl ether [1,2], and others.

The need of speed and successful solutions in heterogeneous catalysis, e.g. hydrogenations, ask for high-tech equipment. A typical example is the hydrogenation of 2,3,5-trimethylquinone to 2,3,5-trimethylhydroquinone (Scheme 2). The latter compound is the aromatic building block in Vitamin E production [1,2]. Fig. 2 shows state of the art equipment for the investigation of hydrogenation, oxidation, and formylation reactions on laboratory scale (volume up to 20 l, pressure up to 400 bar).

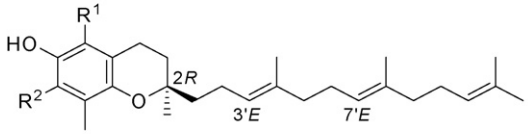
3. Examples

Vitamin E is a class of compounds derived from 6-chromanol. They are divided into the group of tocotrienols (containing a C_{16} side chain unsaturated at positions 3′, 7′, and 11′) and tocopherols (with a saturated C_{16} aliphatic side chain). Furthermore the tocols are distinguished by the number and position of methyl substituents of the phenol part. α-Tocopherol has the highest biological activity of all tocols. Tocopherols possess three stereocenters at positions 2, 4′, and 8′. All naturally occurring tocopherols and tocotrienols are single-isomer compounds with the stereochemistry depicted in Scheme 3. Rich sources of these compounds are edible oils, e.g. from sunflower seeds, corn, or palm fruits (Fig. 3) [4,5].

(All-*rac*)-α-tocopherol is the industrially most important fat soluble antioxidant. Animal feed represents the most valuable market for Vitamin E, which exceeds 30,000 t/year. The main producers are DSM Nutritional Products (Switzerland), BASF



R^1	R^2	
CH_3	CH_3	α-tocopherol
CH_3	H	β-tocopherol
H	CH_3	γ-tocopherol
H	H	δ-tocopherol



R^1	R^2	
CH_3	CH_3	α-tocotrienol
CH_3	H	β-tocotrienol
H	CH_3	γ-tocotrienol
H	H	δ-tocotrienol

Scheme 3. Natural tocols.

Fig. 3. Sources of Vitamin E compounds in nature.

(Germany), and some Chinese producers. The production volume of (all-*rac*)-α-tocopherol was constantly increasing during the last decades (Fig. 4).

The synthesis of Vitamin E (Scheme 4) is divided in the parts:

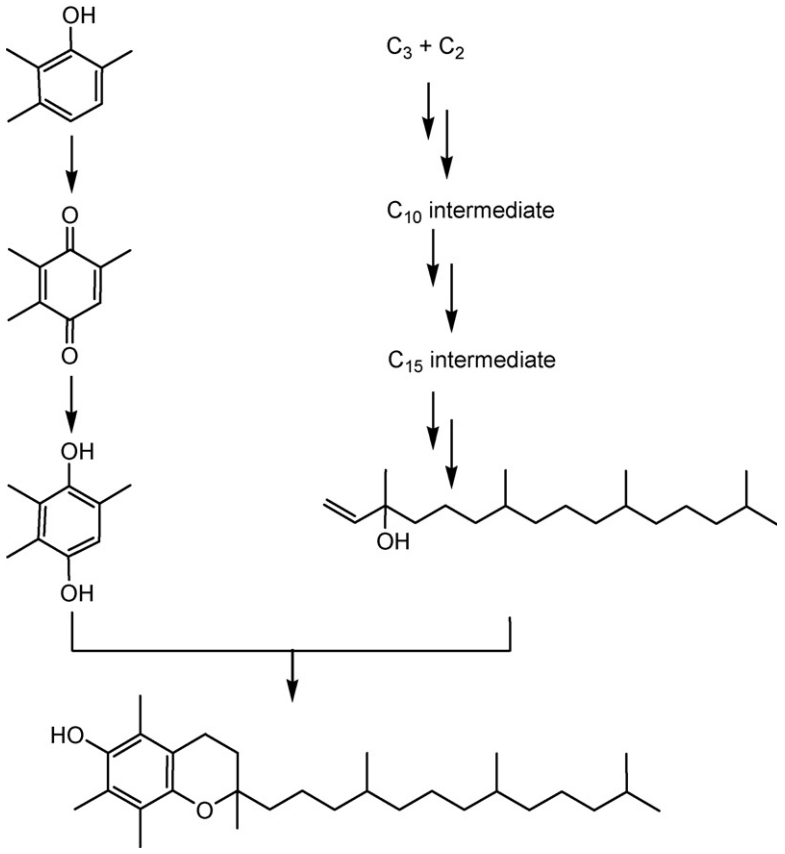
- synthesis of isophytol (IP),
- synthesis of trimethylhydroquinone (TMHQ), and
- condensation reaction of IP and TMHQ.

Here we describe an overview about new achievements and modern trends in Vitamin E chemistry for all parts of the industrial synthesis. The main focus is layed on the synthesis of isophytol and trimethylhydroquinone, whereas important results of the condensation reaction are described in a special overview [6].

The key building block isophytol can be synthesized by using various approaches. The principle of these reaction pathways is a combination of C_3 and C_2 elongation reactions starting from acetone or citral [2]. The rhodium catalyzed geranylacetone synthesis from myrcene and methyl acetoacetate [7] is not discussed here.

Our strategy in the isophytol (isoprenoid side chain) production is built on a multiple usage of key-building blocks and reaction types. Starting materials are acetone, ethyne, and hydrogen. The C_2 extension sequences are carried out by an ethynylation reaction followed by Lindlar-type and total hydrogenation (Scheme 5). For the C_3 extension the Carroll reaction or the Saucy–Marbet reaction are the preferred methods (Scheme 6, [8,9]) which are used by the main producers of Vitamin E.

Several steps of the large-scale isophytol synthesis performed at the DSM facility in Lalden (Rhone Valley, Switzerland, Fig. 5) have been improved by an interdisciplinary team of experts from process research, development, and production [10]. For example the C_3 elongation using isopropenyl methyl ether and an allylic or propargylic alcohol was studied in detail. The process is based on the fundamental work of Saucy and Marbet [9]. This homogeneous reaction is usually acid catalyzed at 370–420 K at a pressure of 8–15 bar. The use of heterogeneous catalysts, e.g. Deloxan ASP®, in a continuous procedure is described in [11]. Processes using $MeSO_3H$ or phosphorous derivatives as catalyst for the preparation of ketones from propargyl alcohols and enol ethers



Scheme 4. Synthesis of Vitamin E from TMHQ and IP.

have the advantages of high yields and short reaction times [12].

The synthesis of methylheptenone (MH) can be achieved from isopropenyl methyl ether (IPM) and methylbutenol (MBE) in 94% yield (Scheme 7). The application of new types of catalysts and modified reaction conditions results in an increased yield (98%), due to the higher selectivity of the reaction [13]. Best results were obtained with hydrogen tris(oxalato)phosphate as catalyst, or with hydrogen bis(oxalato)borate.

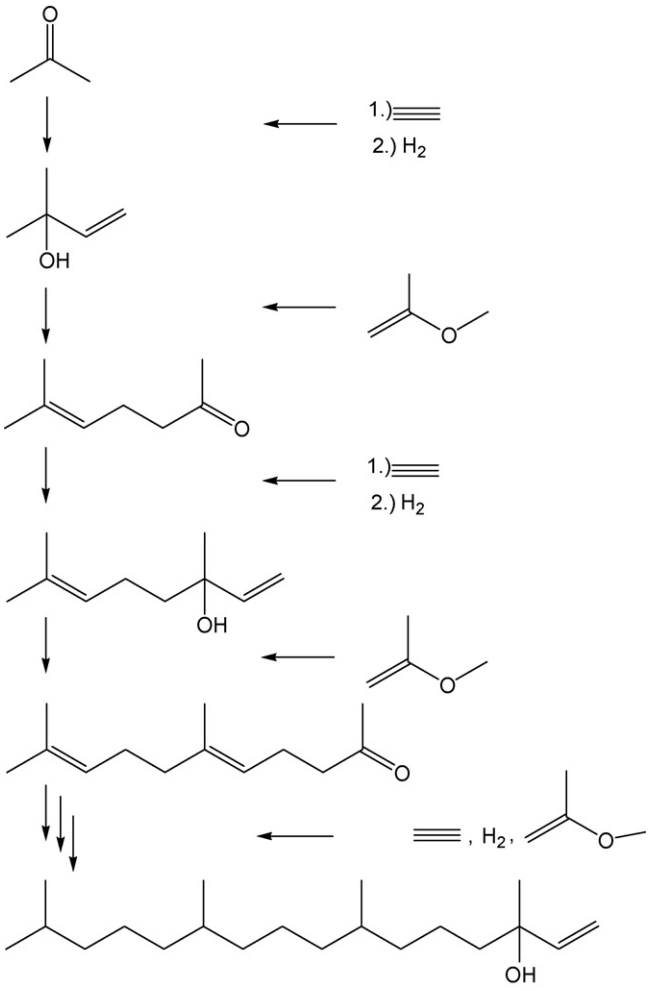
Another important reaction type for the synthesis of carotenoids, fragrances and vitamins, especially Vitamin E (isophytol) is the C_2 elongation by ethynylation. Therefore, the synthesis of α-alkynols by starting from the corresponding ketone (Scheme 8) is of synthetic and industrial importance. The C_2 extension can be carried out using a vinyl Grignard reaction or an ethynylation reaction followed by partial hydrogenation [2]. These methods are well described in literature [14]. In some cases interesting compounds are synthesized from cheap starting materials. The stoichiometric addition of organolithium or organomagnesium reagents, e.g. ethynyl lithium or ethynylmagnesium bromide, to carbonyl compounds, however, create large amounts of waste. A general problem in ethynylation reactions is the formation of so-called diols as by-products (Scheme 8).

Ethynylation reactions using ethine and equimolar amounts of potassium hydroxide are also well known [15]. Carrying out this reaction with catalytic amounts of potassium hydroxide [16] or cesium hydroxide [17] leads to the propargyl alcohol in >90% with the formation of considerably smaller amounts of salt waste. For the application of potassium hydroxide several solvents can be used, e.g. ammonia, dimethylsulfoxide (DMSO), or *N*-methylpyrrolidone (NMP). Reaction temperatures from 273 to 315 K and a pressure range from 10 to 30 bar are preferred.

Another procedure describes the application of quarternary ammonium hydroxide as solid base catalyst for the ethynylation of ketones and aldehydes [18–20]. The ethynylation can be carried out in ammonia or organic solvents, e.g. NMP or DMSO in a temperature range from 293 to 323 K at 25 to 30 bar. Useful catalysts are strong basic resins which are commercially available, e.g. Amberlite IRA 400. Advantages of the described solid fixed-bed procedures are waste minimization and easy recovery of the catalyst.

We found that the potassium hydroxid catalyzed ethynylation can be carried out with a substrate to catalyst ratio s/c of >200 at high temperature [21]. Surprisingly the formation of by-products (‘‘diols’’) could be significantly decreased. Advantages are high yield and selectivity, and especially a high space time yield.

To achieve these goals, in particular for an efficient development, a tool for process optimization was established. The experimental results obtained from calorimetric data on laboratory scale were transferred into a reaction model and compared with plant results. Based on the findings the plant process was modified, and finally a modified process was established. A typical experimental set-up is shown in Fig. 6.



Scheme 5. Synthesis of isophytol.

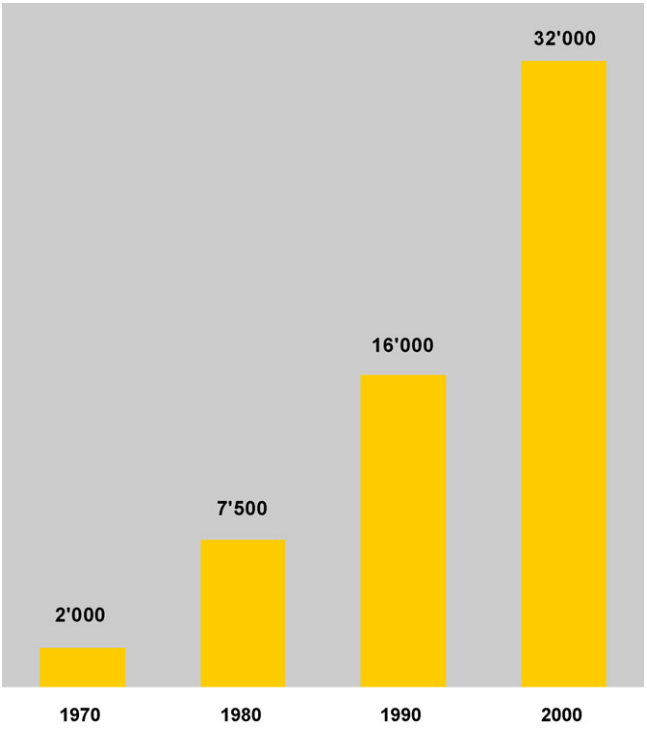


Fig. 4. Increase of the Vitamin E world market (in t/year).

For the industrial synthesis of trimethylhydroquinone (TMHQ), one of the main building blocks in the Vitamin E synthesis (Scheme 4), the main starting material is 2,3,6-trimethylphenol, which is oxidized to trimethylquinone. Several methods are known for this procedure [1,2]. Typical catalysts are copper chloride, especially with co-catalysts [22], cobalt based catalysts [23], mesoporous silica catalysts [24], or heteropoly acids, e.g. of $H_7PMo_8V_4O_{40}$ [25]. Depending on the reaction system, e.g. determined by catalyst, temperature, pressure, batch or continuous mode, yields from 86 to 95% can be achieved. Trimethylquinone can easily be hydrogenated to TMHQ (Scheme 2) in presence of a noble metal catalyst, e.g. Pd on charcoal [1].

Another route to trimethylhydroquinone starts from α-isophorone (trimerisation product of acetone), which can be isomerized to β-isophorone. Allylic oxidation of β-isophorone delivers ketoisophorone (KIP), a key-intermediate in the synthesis of carotenoids [26], e.g. astaxanthin. The acid catalysed Wagner–Meerwein rearrangement of ketoisophorone under acidic conditions results in trimethylhydroquinone diacetate (TMHQ-DA), which can be saponified to trimethylhydroquinone (Scheme 9) [1,2]. For the oxidation of β-isophorone several catalysts are described. Examples are $Pb(OAc)_2$ in pyridine (yield 76% [27]), phospho- and silico-molybdic acid [28],

Fig. 5. Isophytol plant at Lalden (Rhone Valley, Switzerland).

Fig. 6. Typical laboratory system for study of ethynylation reaction parameters.

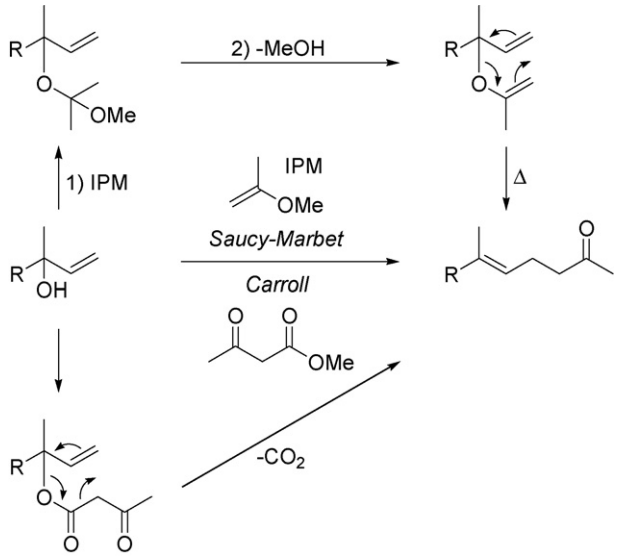
Table 1
In-catalyzed rearrangement of ketoisophorone

Catalyst (s/c)	Reaction time (h)	Conversion (%)	Purity (%)		
			KIP	TMHQ-DA	TMC-DA
$InCl_3$ (100/1)	21	45.5	54.6	37.2	5.8
$In(SO_3CF_3)_3$ (100/1)	5	>99.99	0.0	93.2	6.6
$In(SO_3CF_3)_3$ (1000/1)	10	65.3	34.7	58.5	4.1

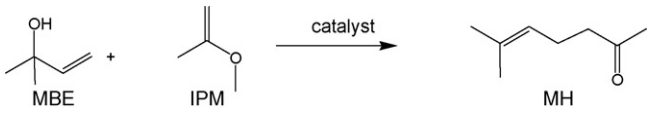
s/c: substrate-catalyst ratio; KIP: ketoisophorone; TMHQ-DA: trimethylhydroquinone; TMC-DA: trimethylcatechol diacetate.

Co-, Cr- or Pb-salts [29], Mn(II)-, or Co(II)-complexes (85% yield [30]), Mn-bis(salicylideneiminato) complexes (>90% yield [31]), Cu-acetylacetonate [32], Mn-complexes [33], or Co-salen complexes [34].

We found that CH- and NH-acids catalyze the Wagner–Meerwein rearrangement of ketoisophorone in a very efficient manner. Using these types of catalysts a yield of



Scheme 6. C_3-elongation by Saucy–Marbet and Carroll reactions.

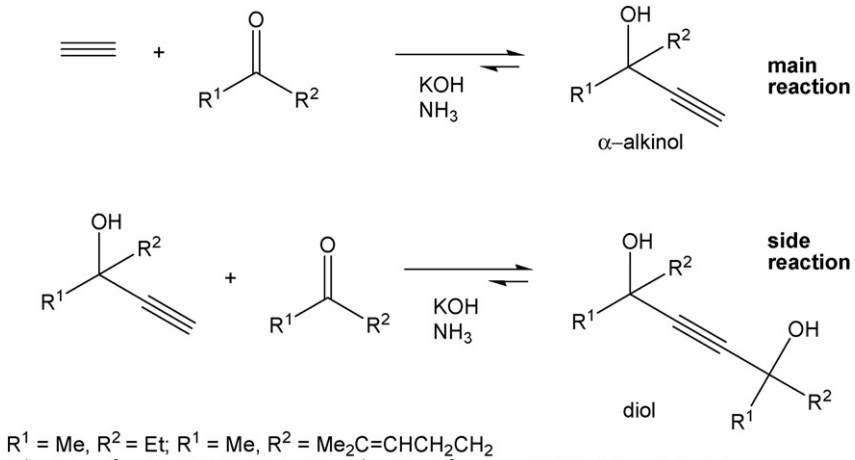


Scheme 7. Synthesis of methylheptenone.

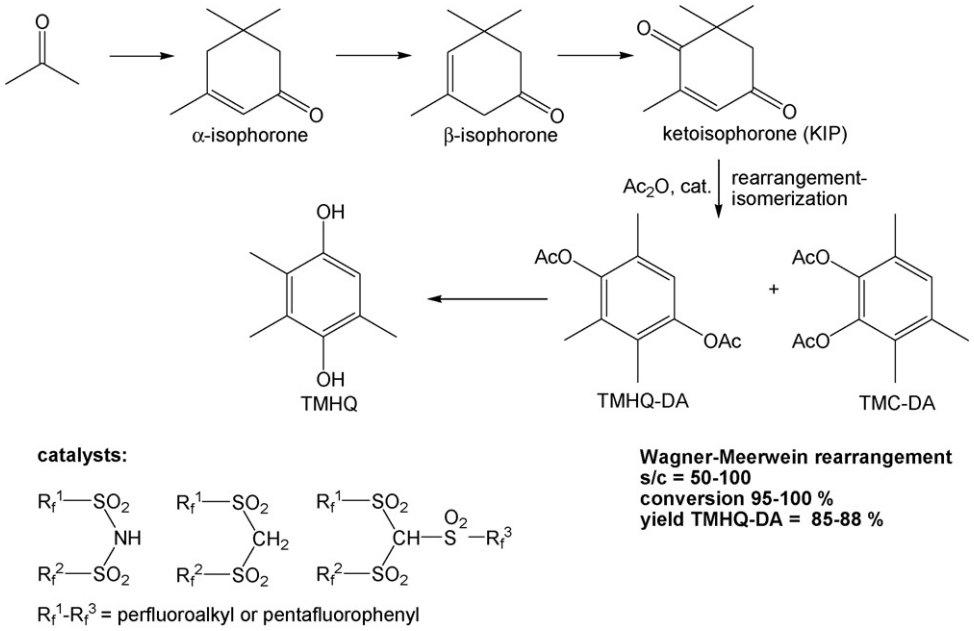
88% could be achieved under total conversion of the starting material [35].

Another type of interesting catalysts for these reactions is based on In-salts, e.g. indium triflate. The application of these catalysts results in an excellent yield (and selectivity). The by-product trimethylcatechol diacetate (TMC-DA) could be minimized in a very efficient manner [36]. The results are summarized in Table 1. Main advantages are the mild reaction conditions, high selectivity, and a high substrate-to-catalyst ratio.

The last step in the industrial synthesis of (all-*rac*)-α-tocopherol (all-racemic Vitamin E, Scheme 10) is based on the reaction of isophytol, phytol or phytyl halides and



Scheme 8. Metal hydroxide catalyzed ethynylation of carbonyl compounds.



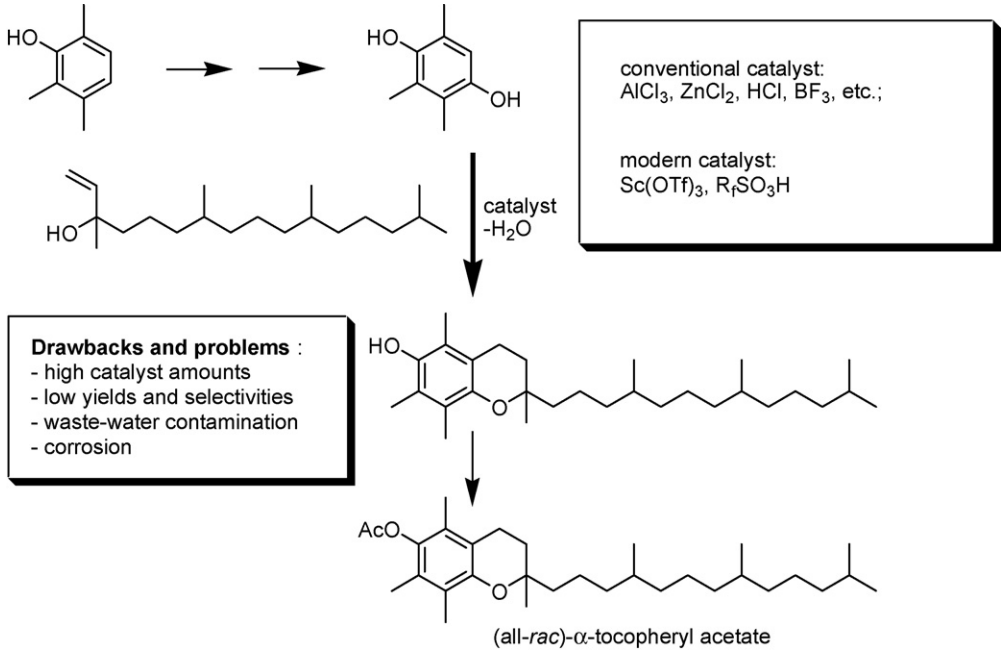
Scheme 9. Synthesis of trimethylhydroquinone diacetate from ketoisophorone.

trimethylhydroquinone [2]. Conventionally this reaction is catalysed by a combination of a Lewis acid, e.g. zinc chloride, and a Brønsted acid, e.g. hydrochloric acid. Main disadvantages are the formation of by-products, waste, and corrosion problems [1,2]. Several approaches to by-pass these problems are based on new catalyst types and new procedures. Most beneficial procedures results from the use of new (e.g. biphasic) solvent systems, or catalysts, e.g. NH- or CH-acidic compounds. A summary of these approaches is given in [1].

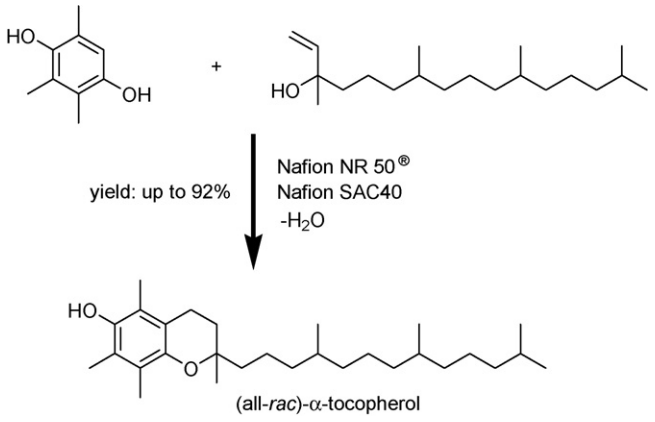
For the application of the new combination of bismuth and other triflates in the synthesis of tocopherol and its derivatives see a separate publication in this issue [6].

Another approach towards catalytic systems for the synthesis of Vitamin E is based on solid acids. These types of catalysts can be used in various solvents. The application of polyfluorinated catalysts based on Nafion® is well known in synthetic organic chemistry, e.g. in the Friedel–Crafts-type reaction of isophytol and trimethylhydroquinone [38].

A new application of Nafion® resin silica composites is beneficial because their stability allows the repeated re-use for several times. Furthermore these catalysts, e.g. Nafion SAC 40, are very selective and allow the synthesis of Vitamin E in high yields (Scheme 11). Compared to other systems their stability is noteworthy, which results in less leaching effects [39].



Scheme 10. Synthesis of (all-rac)-α-tocopherol.

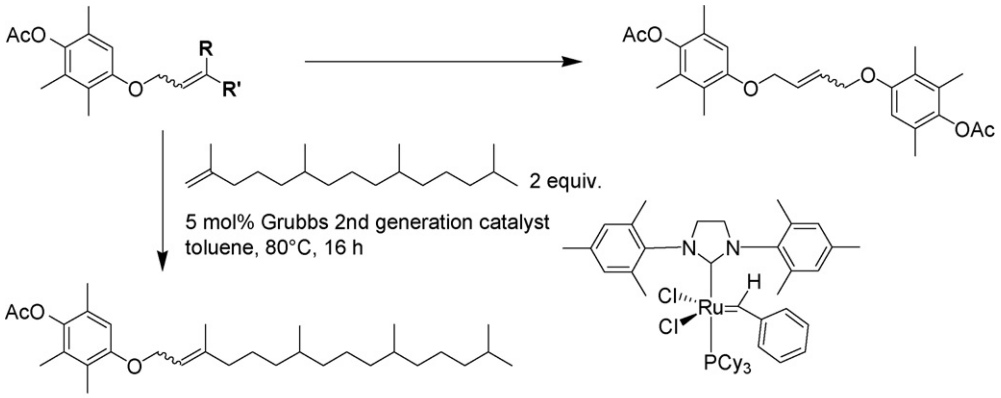


Scheme 11. Nafion/silica composites in the synthesis of Vitamin E [39].

A new synthetic approach to Vitamin E via key-intermediates possessing trisubstituted olefinic double bonds was developed by using metathesis methodology. These results are based on olefin metathesis as a new tool in organic synthesis [40], which is used in

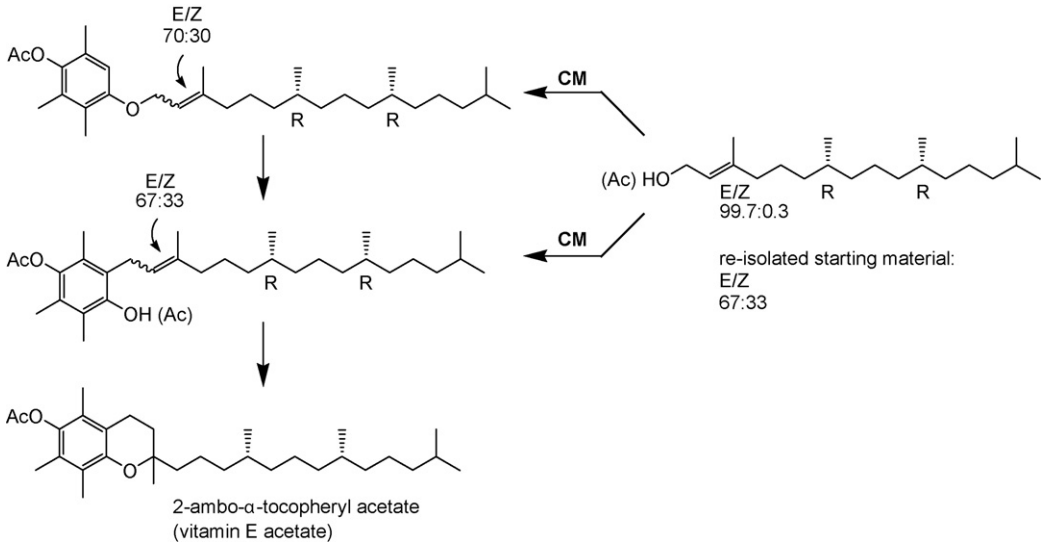
- opening metathesis (ROM),
- closing metathesis (RCM),
- ring opening polymerization metathesis (ROMP), and
- acyclic diene metathesis polymerization (ADMP).

Cross metathesis is applied in industrial processes, e.g. Shell higher olefin process (SHOP) and the FEAST (Further Exploitation of Advanced Shell Technology) process, Phillips Triolefin Process, *but*: "... not yet in such wide-spread laboratory use as the more entropically favorable ring-closing



R	R'	yield CM-product	yield dimer
H	H	29%	33%
CH_3	H	51%	6%
CH_3	CH_3	73%	<1%

Scheme 12. Cross-metathesis reaction in Vitamin E synthesis.



Scheme 13. Synthesis of 2-ambo-tocopherol via olefin cross-metathesis.

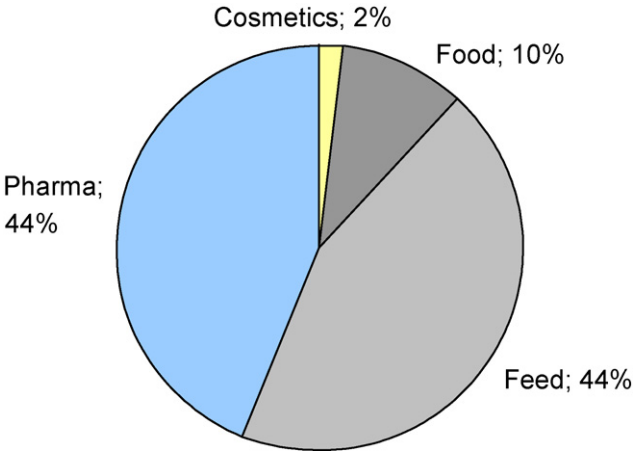
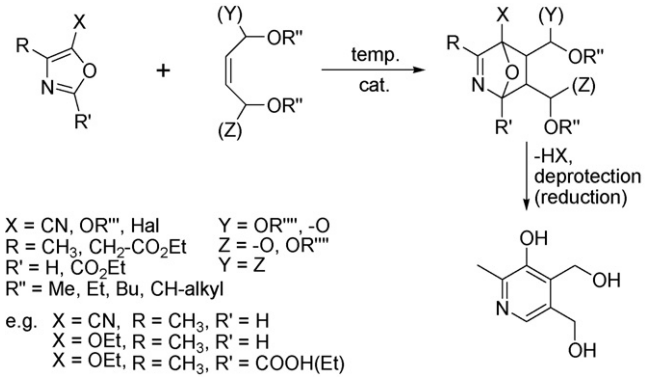


Fig. 7. Application of pyridoxine in various markets.



Scheme 14. Diels–Alder reaction in the synthesis of pyridoxine.

metathesis (RCM)'' [41]. For an actual overview about metathesis see [40–42].

Key finding of our work was the synthesis of trisubstituted olefins in an efficient manner [43]. A representative example is sketched in Scheme 12. Furthermore this new approach to Vitamin E offers the possibility for the synthesis of R-configured stereoisomers, resulting in 2-ambo-α-tocopheryl acetate, possessing an R-configured side chain (Scheme 13). For details, see also the separate publication in this issue.

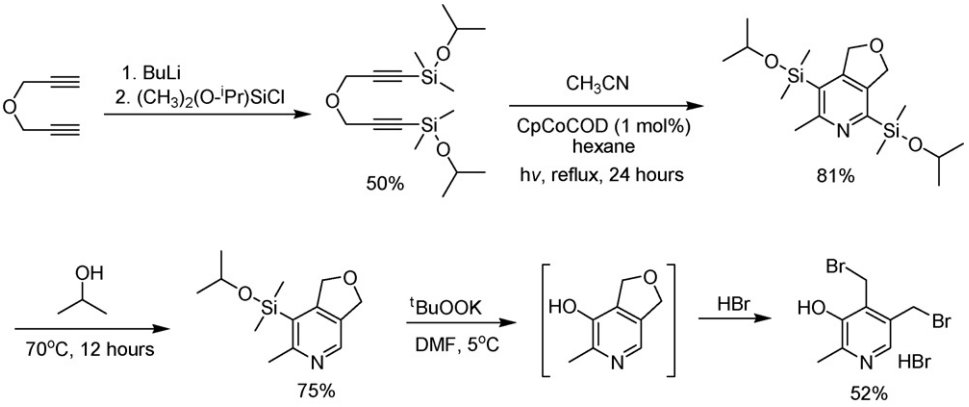
These examples shows that cross metathesis can be used also in the synthesis of vitamins and nutraceuticals. This may be of more general interest for the preparation of other (open-chain) trisubstituted olefinic natural products.

Also in the field of water soluble vitamins it is important to have good procedures for manufacturing in place, due to the highly competitive situation in this field. For example, in Vitamin B_6 DSM is the only western producer. The world market of Vitamin B_6 (pyridoxine) is around 5000 t/a. The product itself is acting as a co-enzyme in transamidase reactions, and is applied in food, feed, pharma, and cosmetics markets (Fig. 7). There are several pathways for the synthesis of pyridoxine known from literature, e.g. the Diels–Alder reaction of an oxazole and a dienophile [44].

For the production of Vitamin B_6 the reaction of an oxazole with a dioxepin derivative is one possibility (Scheme 14). Reaction times of several hours at 388–453 K result, after aromatization and protection, in pyridoxine in an overall yield of >90% (recovery of the protecting reagent isobutyraldehyde). The aromatization reaction is acid catalyzed [1,44]. The diene compounds can be synthesized from diketene or an acid, e.g. propionic acid, alanine or aspartic acid. The dienophile, e.g. an isopropylidenedioxepin derivative, can be produced from 2-butene-1,4-diol and isobutyraldehyde [1,44].

An alternative pathway to Vitamin B_6, based on the cobalt catalyzed [2 + 2 + 2] cycloaddition reaction of acetonitrile with α,ω-diine derivatives yielded Vitamin B_6 in less than 10% [45,46]. Problems of this route are the transformation of a trimethylsilyl ether group into an aromatic OH-group, and formation of carbocyles as by-products. A new approach for the synthesis of pyridoxine intermediates carried out under irradiation (300–800 nm) uses $XCoL_{1,2}$ catalysts (X = phenyl-borino, indenyl, etc., L = ethene, CO, etc.) (Scheme 15 [47]). Advantages of this efficient method are the selectivity and high yield of heterocyclic product, and mild reaction conditions.

Enzyme catalyzed reactions are becoming more and more important in the preparation of pharmaceuticals and fine chemicals. There are enzymatic transformations exhibiting competitive advantages over classical chemical procedures, even for the production of racemic or achiral low-cost fine chemicals like vitamins. High selectivity, avoidance of toxic reagents, and applicability of a continuous mode under mild reaction conditions are key-factors for the development of such



Scheme 15. Pyridoxine by Co-catalyzed [2 + 2 + 2] cycloaddition reaction.

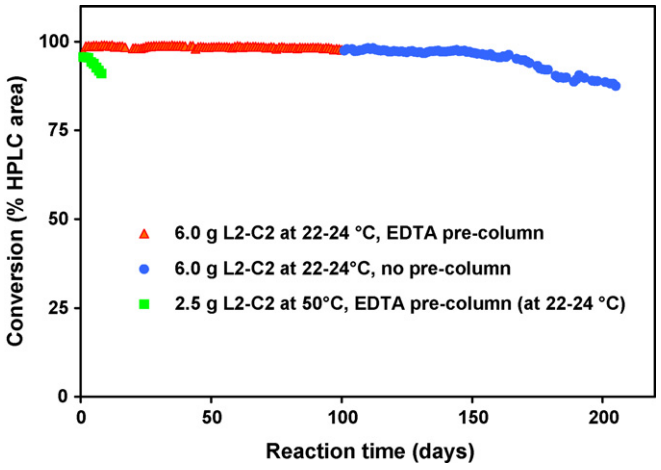
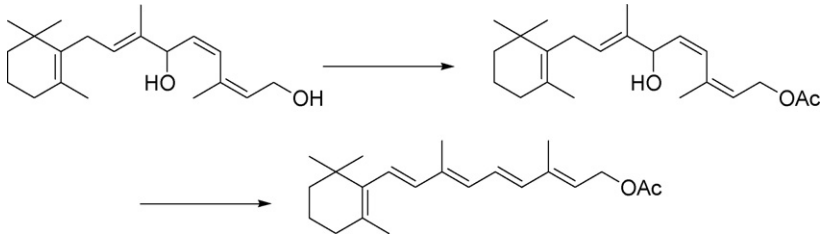


Fig. 8. Enzymatic acylation of a Vitamin A precursor [58].

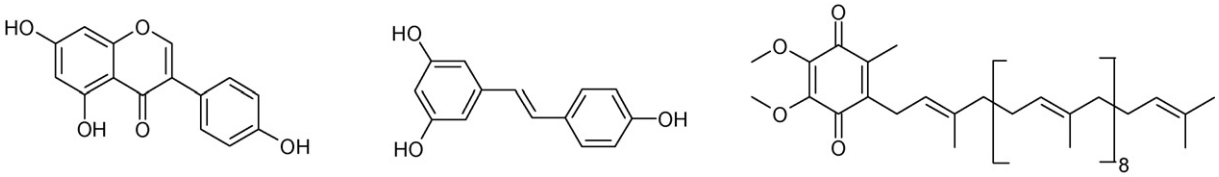
superior processes [48–51]. Lipases accepting a broad range of substrates are particularly useful for catalysis of transesterification reactions [52,53] on a technical scale. The criteria for an industrial competitive process are:

- stability and lifetime of the enzyme,
- purity of staring material, and
- easy work-up in a continuous process (immobilization).

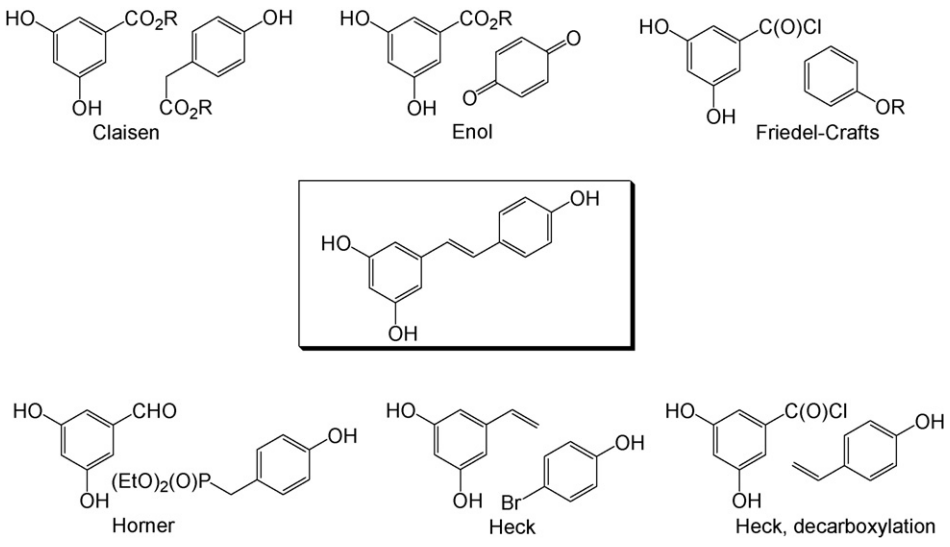
Vitamin A is involved in vision (eye, as dialdehyde), and in the epithelium for cell differentiation [54]. In a DSM Vitamin A synthesis, (all-*E*)-retinyl acetate [55] is obtained from an intermediate diol via partial acetylation (delivering generally mixtures of mono- and diacetylated compounds) and subsequent dehydration/isomerization. The highly regioselective mono-acetylation of a primary-secondary diol by immobilized Chirazyme L-2 delivered the monoacetate with >99% conversion rate and >97% selectivity for the primary hydroxy



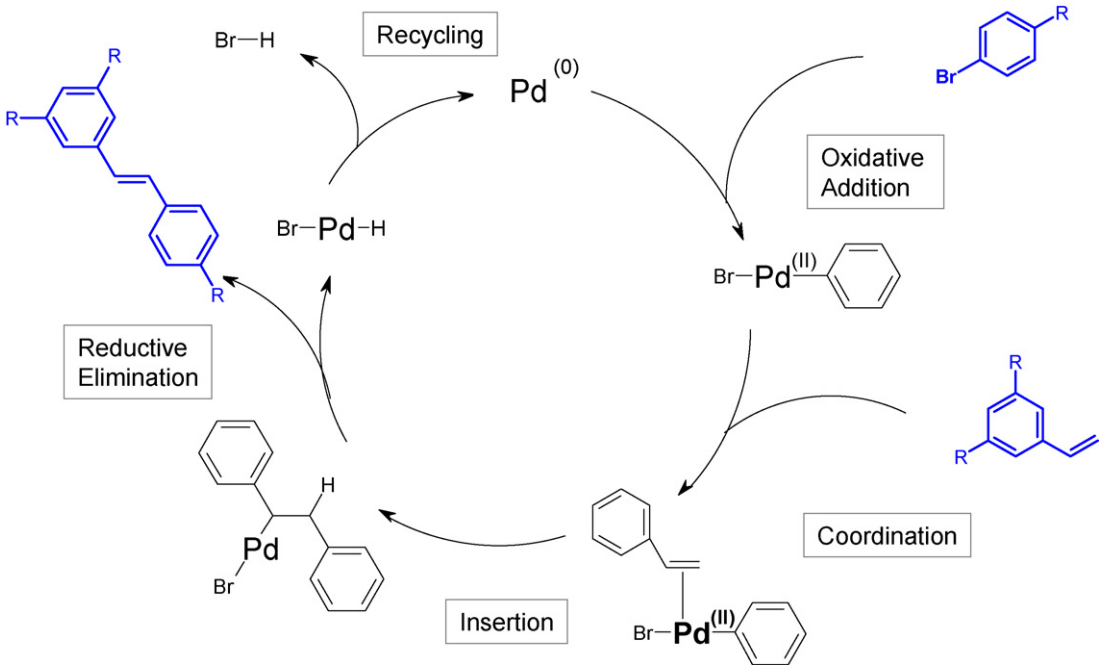
Scheme 16. Enzymatic reaction in the synthesis of a Vitamin A key intermediate.



Scheme 17. Genistein, Resveratrol and Ubiquinone-10.



Scheme 18. Retro-synthetic approach to resveratrol.



Scheme 19. Proposed reaction mechanism in the synthesis of resveratrol.

group (Scheme 16 and Fig. 8). Continuous operation on miniplant-scale using vinyl acetate and a fixed-bed reactor yielded high amounts of the monoacetate [56–58].

For companies active in life science industry it is important to develop a product pipeline with new products in several application fields. In going to these directions chemical synthesis is evaluated in competition to alternative routes, e.g. extraction.

DSM Nutritional Products is active for example in the fields of:

- glucose regulation,
- good modulation,
- joint health, and
- performance enhancers.

Examples of new products established on the market are Genistenin, Resveratrol, and Ubiquinone-10 (coenzyme Q_{10}) (Scheme 17).

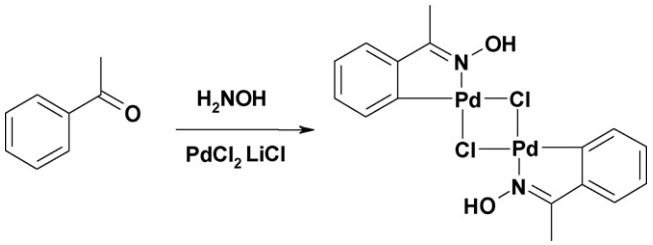
Here we report our results obtained in the synthesis of resveratrol, a new promising candidate for health. Resveratrol is found in wine grapes or a traditional Chinese medical plant (*Polygonum cuspidatum*).

Compared to the chemical approach the isolation of resveratrol from the roots of *Polygonum cuspidatum* is not attractive, due to the low content (0.1%) in roots. Therefore we concentrated on a chemical synthesis. The retro-synthetic approach indicated a ‘‘simple’’ chemical structure, but a challenge in chemical production (Scheme 18).

Based on a detailed study it turned out that the Heck reaction was the most economic approach (Scheme 19). After screening of the reaction parameters and optimization it was found that oxime ligands show the best performance (Scheme 20). Advantages are that these types of ligands are easy to prepare, not expensive, non-toxic, and stable towards air and water. Furthermore this catalysts show a high activity at low concentration [59]. The main achievements are summarized in Table 2.

Further trends in fine chemical industry, especially in the synthesis of fine chemicals and nutraceuticals, are based on the production technology (Fig. 9). Here catalysis, especially heterogeneous catalysis, is the most important technology platform. It can be expected that new competitors enter the market. The raw material (backward integration) and source of carbon are key criteria to approach the market.

In summary, the examples outlined here demonstrate that new catalytic procedures are beneficial, and of high value for life science industry.



Scheme 20. Pd-oxime catalysts for Heck reactions to resveratrol.

Table 2
Results obtained in resveratrol synthesis

Cat. (mol%)	t (h)	Base	Additive	Yield (%)
0.1	3	$^{i}Pr_2EtN$	0.2 equiv. Bu_4NBr	47
0.1	3	$^{i}Pr_2EtN$	–	40
0.1	3	Na_2CO_3	0.2 equiv. Bu_4NBr	91
0.1	3	K_2CO_3	–	98
0.01	18	K_2CO_3	–	86

Fig. 9. Red wine grapes and *Polygonum cuspidatum.*

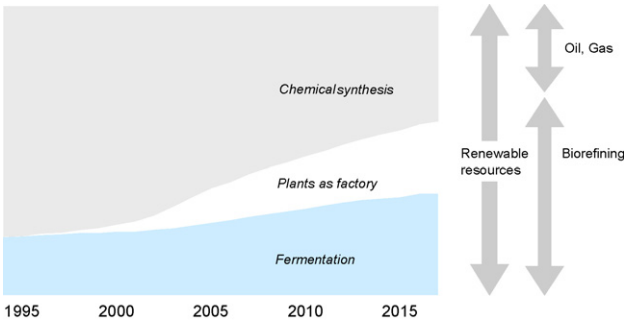


Fig. 10. Future trends in fine chemical synthesis.

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