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New application of indium catalysts: A novel and green concept in the fine chemicals industry*

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Abstract: New industrially important catalytic processes for application in the fine chemicals industry (e.g., synthesis of vitamins and key-intermediates) are presented. Protocols with indium catalysts provide the advantages of high selectivity and low catalyst loading for Friedel–Crafts-type alkylation, Wagner–Meerwein rearrangement, and acylation reactions. The transformations discussed could be carried out in a continuous manner.

Keywords: fine chemicals; catalysis; indium; green chemistry; tocopherol; acylation; vitamins; Friedel–Crafts reaction; rearrangements.

INTRODUCTION

The development and application of catalytic reactions is one of the fundamental issues for the fine chemicals industry where many transformations are still based on stoichiometric reactions from the area of organic chemistry, and often large amounts of waste are formed. Processes can be classified by production volume as well as extent of atom economy (i.e., number of atoms of all starting materials which end up in the product) [1]. From an industrial point of view, an additional aspect has to be considered, which includes the loss of solvents, the type of waste, and the energy balance. The E-factor, introduced by Sheldon [2] and defined as kg by-product per kg product, gives typical numbers, and is a first orientation to characterize a process or synthetic procedure. There is a need for more selective, especially catalytic processes in the fine chemicals industry. The key factors in industrial process research and development are environmental aspects, raw material costs, technology, and selectivity of a reaction.

Vitamins are organic compounds, which are essential for animal and human organisms, because they are not synthesized or formed only in insufficient amounts in the body [3]. According to Sheldon's classification [2], most vitamins are typical fine chemicals with prices above 10 US $ per kg and production volumes of about 1 000–10 000 tons per annum. During our investigations, we found that In catalysts can be used for rearrangement, alkylation, ring closure, and acylation reactions. Indium is applied in mobile phones (InSn-oxides), and the recycling of In is an established technology.

Several transformations like the Mukaiyama–Aldol-type reaction, acylation reaction, and Diels–Alder reaction can be catalyzed by In salts [4–9]. For example, anisole can be transferred into 1-(4-methoxy-phenyl)-hexan-1-one in 61 % yield in the presence of 10 mol % $InCl_3$ (Scheme 1).

Here we describe new applications of In catalysts in several reaction types, i.e., Wagner–Meerwein rearrangement, Friedel–Crafts alkylation, and acylation reaction.

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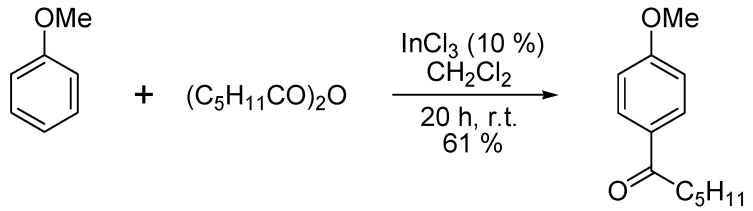
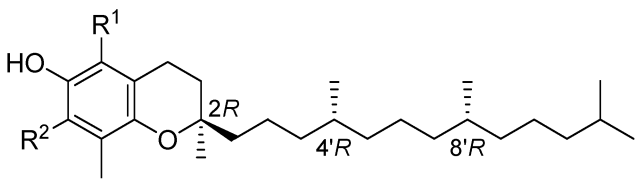


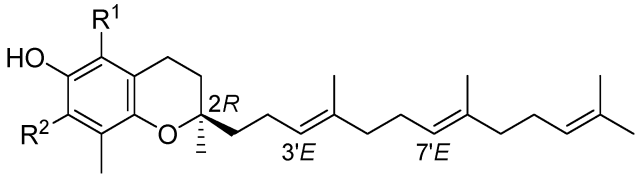
Scheme 1 Friedel–Crafts acylation of anisole.

TOCOPHEROL AND TOCOPHERYL ACETATE

The term "vitamin E" covers a group of substances derived from 6-chromanol, exhibiting vitamin E activity. The eight naturally occurring compounds are divided into two groups, the tocopherols, which have a saturated C_{16} isoprenoid side chain, and the tocotrienols, which have a triply unsaturated C_{16} side chain (Scheme 2) [10,11].



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

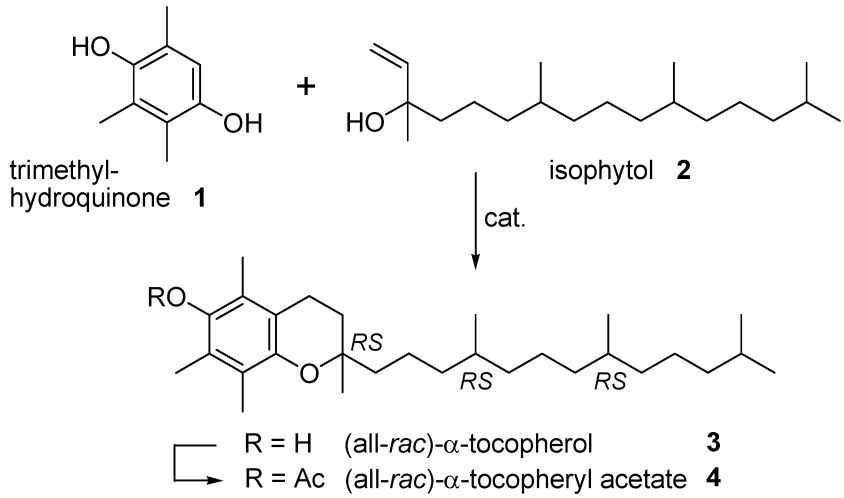


R^1	R^2	
CH_3	CH_3	α-tocotrienol
CH_3	H	β-tocotrienol
H	CH_3	γ-tocotrienol
H	H	δ-tocotrienol

Scheme 2 Naturally occurring compounds with vitamin E activity.

The industrial total synthesis of (all-*rac*)-α-tocopherol (**3**), the compound of highest commercial interest due to its biological and antioxidant properties, with a world market of 35 000 t/a, is based on the reaction of trimethylhydroquinone (**1**) with isophytol (**2**) (Scheme 3).

(all-*rac*)-α-Tocopherol is transferred into its acetate derivative **4**, the predominant commercial form. Several classical Lewis and Brønsted acids, or combinations thereof, work well in the reaction of **1** with **2**. Typical examples are $ZnCl_2$/HCl, BF_3, or $AlCl_3$, applied in various organic solvents. For an overview of vitamin E chemistry, see [12–14]. For large-scale production, however, corrosion problems and contamination of waste water, in particular with zinc and halide ions, are major drawbacks of such procedures. Also, the amounts of catalysts necessary for obtaining satisfying results are often substoichiometric rather than really catalytic. This may be due to the fact that one mole of water is formed during this condensation reaction, which may contribute to the inactivation of the catalyst. In addition, the purity of the product depends strongly on the catalyst and conditions used. And, in many cases, an excess of (iso)phytol has to be used in order to obtain good yields, since (tertiary) allyl alcohols typically tend to dehydrate under strongly acidic reaction conditions. The majority of work in this area in recent years has, therefore, concentrated on the development of more efficient catalytic systems. An actual overview of new types of catalysts useful in this area is given in [15].

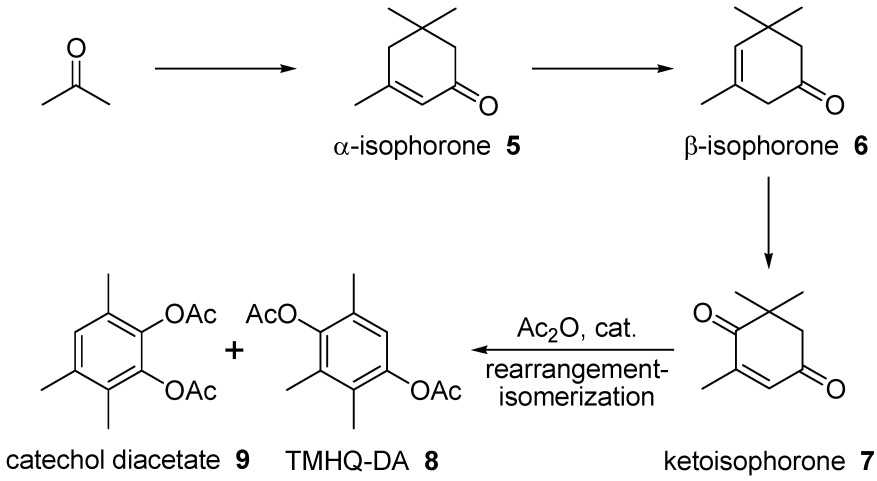


Scheme 3 Industrial synthesis of (all-*rac*)-α-tocopherol.

Here we describe recent achievements in the field of vitamin E chemistry, especially the synthesis of **1** or a derivative thereof, the Friedel–Crafts reaction of **1** with **2**, and the acylation of **3**, and of propargylic alcohols.

WAGNER–MEERWEIN REARRANGEMENT

The synthesis of **1** can be achieved by direct oxidation of 2,3,6-trimethylphenol followed by reduction using Pd-catalyzed hydrogenation [11,15]. Another method for the preparation of **1** starts from α-isophorone (**5**), the inexpensive trimerization product of acetone, which can be isomerized to β-isophorone (**6**). Allylic oxidation of **6** delivers ketoisophorone (**7**), a key-intermediate in the synthesis of carotenoids (e.g., astaxanthin). **7** is transferred by acid catalysis to trimethylhydroquinone diacetate (TMHQ-DA, **8**), which can be saponified to **1** (Scheme 4) [11,15].



Scheme 4 Wagner–Meerwein rearrangement for the synthesis of diacetate **8**.

New types of catalysts for the Wagner–Meerwein rearrangement of **7** are Nafion supported on silica [16,17], or NH- and CH-acids [18]. Total conversion of **7** could be obtained with a substrate-to-catalyst ratio (s/c) of 100, yielding **8** in 85 to 88 %.

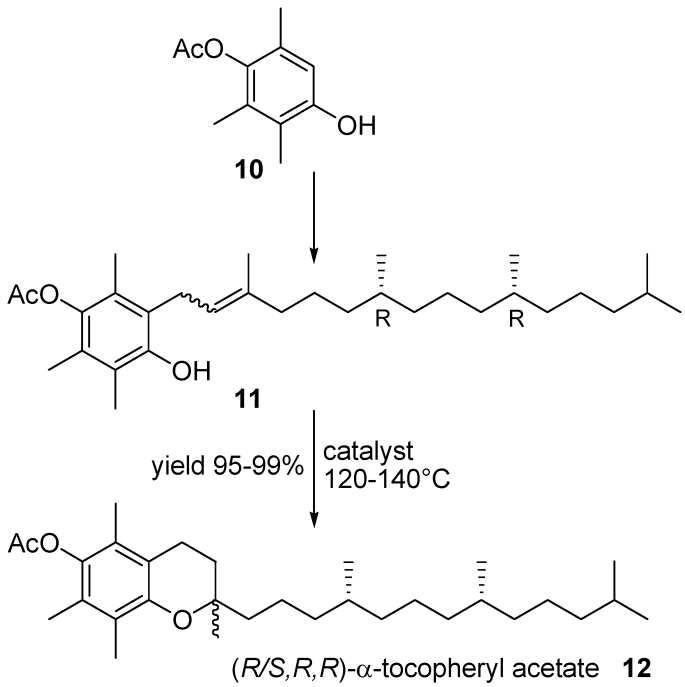
Further investigations resulted in the application of In catalysts in the synthesis of **8**. It was found that surprisingly excellent yields and selectivity could be achieved under mild reaction conditions with low catalyst loadings. The main advantage is the high regioselectivity, the unwanted by-product catechol diacetate (**9**) being formed in minor amounts (4–6 %) only [19]. The results are summarized in Table 1. In a preferred manner, the reaction is carried out in a semi-batch reaction mode.

Table 1 Synthesis of **8** using In catalysts.

Catalyst	s/c	Reaction time (h)	Conversion (%)	Yield (%)
$InCl_3$	100	21	45	37
$In(SO_3CF_3)_3$	100	5	100	93
$In(SO_3CF_3)_3$	1000	10	65	59

All reactions were carried out at 323 K, at a **7**/Ac_2O-ratio of 1/3.

The application of trimethylhydroquinone-1-monoacetate (TMHQ-1-MA, **10**, Scheme 5) as an alternative aromatic starting material for the synthesis of tocopheryl acetate (**4**) was an additional advantage of our approach. **10** can be prepared efficiently by highly selective enzyme-catalyzed saponification of trimethylhydroquinone diacetate **8** [20]. The condensation reaction starting from TMHQ-1-MA (**10**) and **2** is described below.



Scheme 5 Ring closure of phytyltrimethylhydroquinone acetate to (*R/S*,*R*,*R*)-α-tocopheryl acetate.

FRIEDEL–CRAFTS-TYPE ALKYLATION REACTION FOR THE SYNTHESIS OF TOCOPHEROL

As mentioned, the Friedel–Crafts reaction of **1** and **2** is a key step in the synthesis of vitamin E. During the last decades, a large number of catalytic procedures have been developed for this reaction [15]. Regarding an environmentally friendly recycling of catalyst and easy recovery of the product, supercritical fluids [21,22] and multiphase solvent systems were applied as alternative reaction media. The use of polar aprotic solvents and, in particular, two-phase solvent systems (e.g., consisting of ethylene or propylene carbonate and a hydrocarbon like heptane) was found to yield excellent results, even with "traditional" catalysts like $ZnCl_2$/HCl. Examples of such catalysts are rare earth metal triflates, e.g., $Sc(OTf)_3$ [23], heteropolytungsten acids [24], polyfluorinated compounds [25–27], and tris(oxalato)phosphorus acid [28]. Remarkable findings are not only the high chemical yield, but in particular the extremely high selectivity of the overall condensation reaction. The formation of isomeric products, e.g., benzofuran compounds, is considerably reduced.

We found that **1** or its mono-acetate derivative (**10**) can be easily transferred into tocopherol (**3**) or tocopheryl acetate (**4**) in a yield of 95 % using rare earth metal triflates, e.g., $Gd(OTf)_3$ in bi-phasic solvent systems, especially systems based on ethylene or propylene carbonate and hexane, heptane, or octane [29]. The benefit from this catalyst system is the high selectivity at low catalyst loading (s/c 1000).

Under similar conditions, $Bi(OTf)_3$ is also a very efficient catalyst. Even at a s/c ratio of 5000, a 98 % yield of product was obtained after distillation [30]. Another advantage of these catalysts is their independence from the reaction mode. Several feed modes can be used, e.g., continuous feed of the allyl alcohol or its derivatives to a mixture of the catalyst and the aromatic starting material in the solvent (or solvent mixture).

Furthermore, we found that $Hf(OTf)_4$ or $Sc(OTf)_3$ catalyzes the reaction of **2** with **1** or **10** very efficiently. The chroman compounds **3** and **4** can be isolated in >92 % yield at a s/c ratio of 10 000. The main advantage of these catalysts is the selectivity achieved, because the saponification of the ester derivatives (starting material) under the reaction conditions is not observed (less than 0.3 %) [31].

Indium catalysts are very efficient in the synthesis of **3** and **4**, for example, the application of $InCl_3$ results in yields higher than 98 % especially in bi-phasic solvent systems (e.g., ethylene carbonate/heptane) [32]. A further advantage is that the reactions can be carried out in various singular solvents, e.g., cyclohexane, hexane, or octane. The reactions also proceed well in the presence of indium triflate ($In(OTf)_3$). The main advantages of the application of In catalysts is the low catalyst loading (s/c 1000 to 10 000) and the high selectivity. Here, it must also be pointed out that the saponification of the ester derivatives is not observed (less than 0.2 %).

Additionally, it was found that the synthesis of **3** or **4** also can be performed by using isophytol derivatives, e.g., benzoyl or acetyl derivatives. At a s/c ratio of >1000, excellent selectivity could be achieved at 80 to 150 °C reaction temperature in various solvent systems (yield >95 %). These reactions could be carried out in several variations of the feed-mode, e.g., continuous feed of the allyl alcohol (or its derivative) to a mixture of catalyst and phenol compound in the solvent.

In a detailed study, we investigated the influence of the catalyst-solvent system on the stereochemical outcome of the reaction when starting from optically active phytyltrimethylhydroquinone acetate. Starting from natural phytol ((*R*,*R*)-configuration) and TMHQ-1-MA (**10**), we synthesized (4'*R*,8'*R*)-phytyltrimethylhydroquinone acetate (**11**) and studied the ring closure reaction to **12** (Scheme 5).

This transformation delivered excellent selectivity and yield in the presence of In salts under various conditions, independent from the solvent used. Useful solvents are bi-phasic solvent mixtures consisting of dialkyl carbonates and alkanes, or esters (e.g., ethyl acetate or butyl acetate) and nonpolar solvents like alkanes, cycloalkanes or aromatic solvents like toluene or xylene. With s/c ratios of 2 000 to

10 000, no epimerization in 4' or 8' position was observed. (2*RS*,4'*R*,8'*R*)-α-tocopheryl acetate (2-*ambo*-tocopheryl acetate, **12**) could be synthesized in excellent yield.

ACYLATION REACTION OF TOCOPHEROL

The study of acylation reactions in order to find ecologically friendly methods, means reactions with high selectivity and less excess of acylation agents, is of interest in the development of modern synthetic methods [33–36].

The tocopherol **3** synthesized by the presented methods can easily be transferred into tocopheryl acetate (**4**) using a continuous acylation reaction [15]. We investigated the application of In catalysts in the acylation of tocopherol and found that these catalysts were very efficient in this reaction. At 323 K, a total conversion of **3** could be obtained under solvent-free reaction conditions in 15 to 90 min reaction time. The results obtained are summarized in Table 2. The acylation could be carried out in continuous or semi-batch reaction mode.

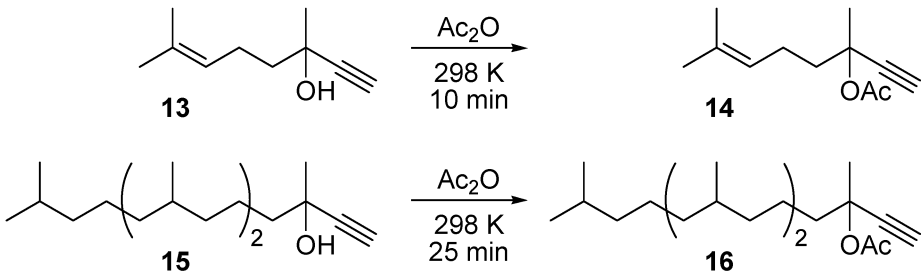
Table 2 Acylation of **3** in the presence of In catalysts.

Catalyst	s/c	Reaction time (min)	Conversion (%)	Yield (%)[a]
$InCl_3$	1 000	60	>99.9	>97
$InCl_3$	10 000	90	>99.9	>97
$In(SO_3CF_3)_3$	1 000	15	>99.9	>97
$In(SO_3CF_3)_3$	10 000	15	>99.9	>97

All reactions were carried out at 323 K, at a **3**/Ac_2O-ratio of 1/3.
[a]Isolated after bulb-to-bulb distillation, 150 mmol scale.

ACYLATION REACTION OF PROPARGYLIC ALCOHOLS

The acylation of propargylic alcohols **13** and **15** with acetic anhydride was studied under solvent-free conditions (Scheme 6). The application of In catalyst, $InCl_3$, or $In(OTf)_3$ resulted in excellent yields after work-up. S/c ratios of 1 000 to 10 000 were beneficial, and the acetates of tertiary alcohols (**14**, **16**) could be obtained in >95 % yield.



Scheme 6 Acylation of propargylic alcohols.

This method can be used for acylation reactions under mild reaction conditions. The benefits include the reduced amount of acylation agent (Ac_2O, excess 20 %), the high selectivity (no elimination products were detected), and the solvent-free conditions, which allow an easy work-up. The reactions can be performed batch-wise or continuously.

CONCLUSION

New industrially important catalytic processes for the application in the synthesis of vitamins and key-intermediates are presented. Compared to experimental protocols so far described in the literature, several advantages were demonstrated. The high selectivity at full conversion in acylation and Friedel–Crafts alkylation reaction is especially remarkable. Usually, in those reactions high amounts of catalysts (often over stoichiometric) have to be applied, and unsatisfactory yields are obtained. Known O-acylation reactions were carried out with high excess of alcohol or acylation agent. Recovery of starting material is often energy-intensive, and the downstream processing less efficient. The Wagner–Meerwein rearrangement needs high amounts of strong (often corrosive) acid. The yields obtained following these protocols are often too low for industrial application with respect to selectivity problems. The presented results by-pass all these problems and fulfill the criteria of green chemistry [37]. In particular, the principles 1 (prevent waste), 2 (atom economy), 5 (auxiliary, solvents), 6 (energy minimization), and 9 (catalytic procedures) are accomplished by using In catalysts.

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