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Rhodium(I)-catalyzed addition of phenols to dienes. A new convergent synthesis of vitamin E

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Abstract

A highly convergent and atom-economical synthesis of (*dl*)-[α]-tocopherol (vitamin E) is proposed, the realization of which was made possible by the discovery of the regioselective Rh(I)-catalyzed arylation of β-springene with trimethylhydroquinone. Other phenolic compounds and 2-substituted-1,3-dienes were shown to undergo this transformation.

Keywords: vitamin E; homogeneous catalysis; rhodium; *C*-alkylation; phenol.

With a worldwide annual production over 10 000 tons, vitamin E [(*dl*)-[α]-tocopherol] is one of the most important food and feed additives.[1] Obviously, any shorter or more convergent synthesis of this natural anti-oxidant is of great economical significance.

Industrial syntheses of this vitamin rely on a logical $C^{20}+C^{9}$ disconnection between the hydroquinone ring and the phytyl side-chain: tocopherol is formed by the acid-catalyzed Friedel–Crafts alkylation of trimethylhydroquinone (TMHQ) with isophytol, followed by the chromane ring closure (Scheme 1, route a).[2]

If this disconnection remains unavoidable on chemical grounds, much can be done to improve the phytyl side-chain synthesis, and thus to increase the overall economy of the process. For instance, the common industrial phytyl side-chain synthon, isophytol, is prepared from petroleum bulk chemicals (acetone, acetylene etc.), but in linear lengthy syntheses (6–9 steps).[2] Our analysis of this problem led us to consider β-springene as a viable alternative: not only this C^{20} fragment is easily prepared from the convergent coupling of two myrcene units, but the direct addition between a 2-substituted diene and TMHQ highlights one of the most important aspect of industrial synthesis: atom economy.[3] Myrcene itself originates from the thermal cracking of β-pinene, a cheap commodity from timber industry (Scheme 1, route b).[4] However this choice was not devoid of chemical challenges, the most obvious being the chemo- and regioselective coupling between TMHQ and β-springene.

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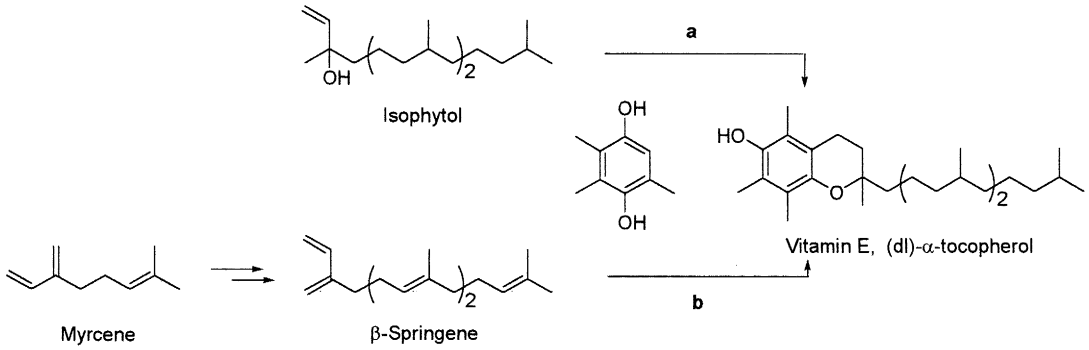


Scheme 1. Routes to vitamin E

In this communication we disclose how a new rhodium(I)-catalyzed arylation of non-activated dienes with phenols allowed us to perform one of the most efficient syntheses of vitamin E.[5]

As a prelude to our study, many Brönsted and/or Lewis acid catalysts were evaluated in an attempt to promote the chemo- and regioselective Friedel–Crafts addition of β-springene to trimethylhydroquinone. As anticipated, this seemingly simple transformation was hampered with several problems: protonation of the weakly dissymmetric diene resulted in the formation of a mixture of benzopyran and benzofuran isomers. Furthermore, trisubstituted olefins in the chain were often competitively protonated, resulting in unwanted polycylic adducts.[6]

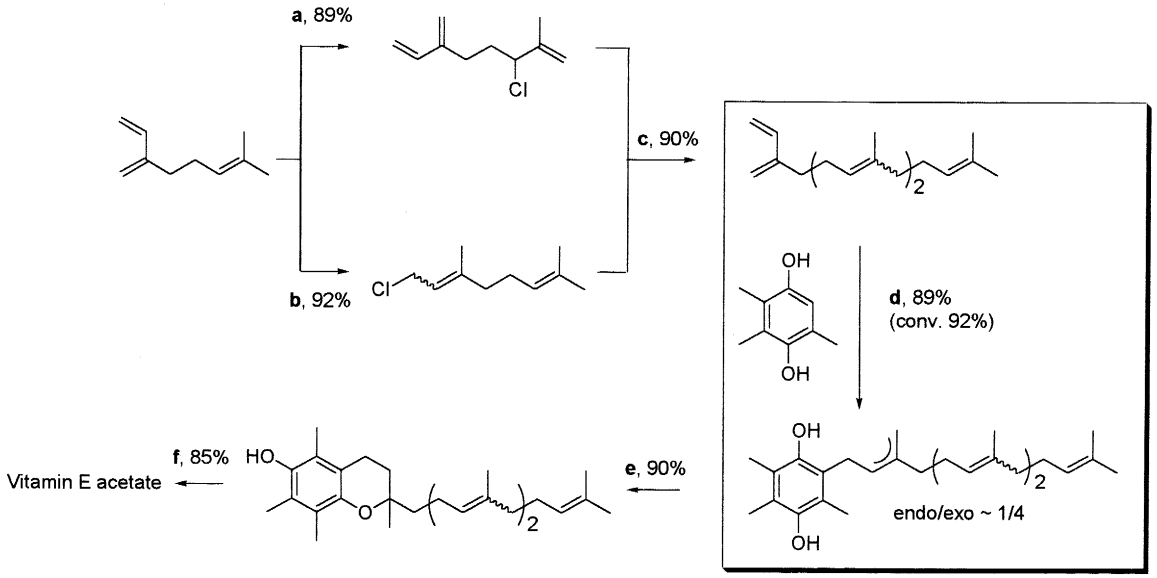
Direct functionalization of aromatics by transition metal catalysts through C–H bond activation was recently shown to be a powerful tool for substitution under mild conditions.[7] Though most examples are reported with electron-poor (hetero)aromatics possessing *ortho*-directing groups (aromatic ketones, pyridines, imidazoles etc.), we decided to investigate whether electron-rich phenols could be alkylated in a similar fashion.[8]

Amongst numerous metal/ligand couples tested, we found that a combination of a catalytic amount of a Rh(I) salt, a phosphine ligand and a base resulted in a high yielding, entirely regiocontrolled, arylation of β-springene (or myrcene) with TMHQ under mild conditions (Scheme 2, step d).[9]

For the success of this transformation, bidentate diphosphine ligands were found superior, diphenylphosphinobutane (dppb) being the best. As Rh(I) source, the cyclooctadienyl rhodium chloride dimer [$RhCl(COD)_2$] (0.5–1 mol%, Rh/P=1/3) was found convenient to use, though other weakly coordinated rhodium salts were also efficient. In sharp contrast to Friedel–Crafts alkylation conditions, a weak catalytic base was found necessary here: either potassium (sodium) phosphate, carbonate or bicarbonate (suspended in the reaction medium).

The resulting vitamin E synthesis is shown in Scheme 2. The ene-type chlorination of myrcene resulted in chloro-3-myrcene,[10] whereas its hydrochlorination in the presence of copper(I) chloride gave a mixture of geranyl/neryl chloride,[11] both in excellent yields. Reductive coupling of both halves was realized by successive Grignard formation on the latter followed by copper(I) chloride-mediated coupling with the former. β-Springene thus formed can be condensed with TMHQ under Rh(I) catalysis in high yield and selectivity (vide supra). The oxygen-sensitive adduct was directly cyclized to tocotrienol.

The chromane ring formation of tocotrienol rests on a non-trivial chemoselective acid-catalyzed protonation of the proximal olefin in the phytyl chain, followed by nucleophilic attack of the hydroquinone alcohol function (step e). Working with a Brönsted or a Lewis acid catalyst ($MeAlCl_2$) in an apolar aprotic solvent (hexane), resulted in the generation of protons in the vicinity of the hydroquinone



Scheme 2. A convergent vitamin E synthesis.[a] [a]Reagents and conditions: (a) Cl_2 (g), pentane, reflux; (b) CuCl (5 mol%), HCl (g), CH_2Cl_2, 0°C; (c) Mg°, THF, −20°C then CuCl (5 mol%); (d) $[RhCl(COD)]_2$ (0.5 mol%), dppb (0.7 mol%), K_2CO_3 (20 mol%), toluene, 110°C; (e) $MeAlCl_2$ or *p*TSA (5 mol%), hexane, 100°C; (f) H_2 (20 atm.), Pd/C (2 mol%), EtOH then Ac_2O (1.2 equiv.), Et_3N (1.5 equiv.), 25°C

nucleus and thus ensured an entropically-favored proximal olefin protonation.[12] Further hydrogenation and acetylation was carried out under standard conditions, to give (*dl*)-[α]-tocopherol acetate.

Thus, high purity vitamin E could be obtained in six convergent steps with an overall 50% yield from cheap industrially available starting materials. Key to the success of this synthesis is the new high yielding Rh(I)-catalyzed addition of phenols to dienes. The potential of this method was thus rapidly explored with other phenolic compounds (Table 1).

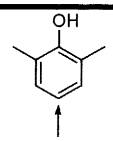
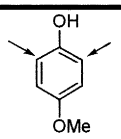
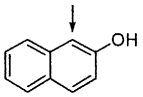
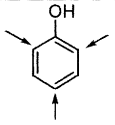
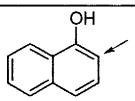
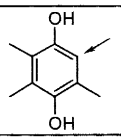
For instance, myrcene was condensed with electron-rich phenols in good yields, though regioselectivity with phenols possessing more than one *ortho*/*para* free position was not always high (however, *meta* addition was never observed). In all cases, myrcene was functionalized on its terminal carbon atom only, a behavior which is reminiscent of other Rh(I)-catalyzed hetero- and carbonucleophile additions to this diene.[13] Adducts with *exo* olefin configuration were formed predominantly (with *exo*/*endo* ratios ranging from 75/25 to 98/2). Electron-poor phenols (*m*- and *p*-cyanophenol, hydroxy-4-pyridine) and aniline did not react under these conditions.

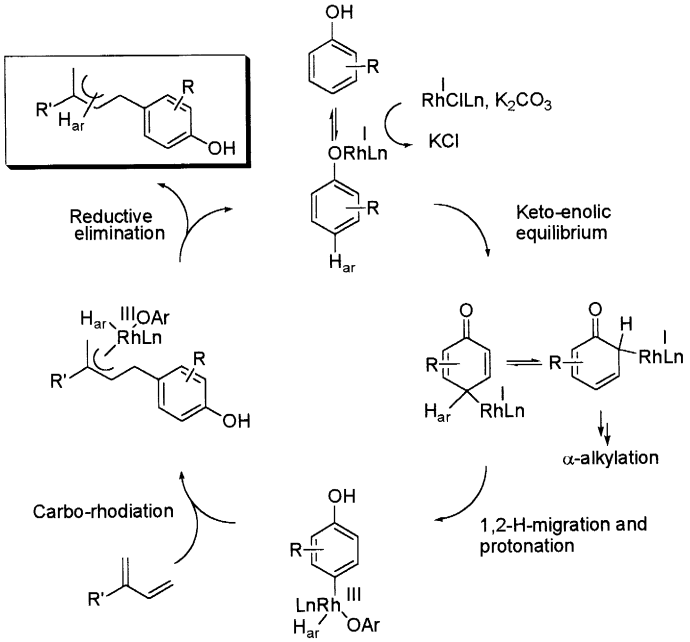
Various dienes were also evaluated (cyclohexadiene, dimethyl-2,3-butadiene, 1-substituted butadienes etc.) but only 2-substituted butadienes gave the expected adducts under these conditions.

Proposed mechanism: when the condensation of *O*-deuterated dimethyl-2,6-phenol with myrcene (in a mixture of toluene/D_2O to ensure the complete replacement of exchangeable protons by deuterium) was carried out, no deuterium was incorporated in the adduct. Thus, it appears that it is the aromatic hydrogen atom which is transferred to the myrcenyl chain, since no other hydrogen atoms are available. This observation, when taken together with most of the experimental observations (e.g. regioselectivity) argues for the putative mechanism depicted in Scheme 3.

First, because of the competitive *para*-substitution of unsubstituted phenols, a direct hydroxyl-directed insertion of Rh(I) in the *ortho* C–H bond can be ruled out. Rather, in the presence of a base, a rhodium(I) phenoxide is formed upon displacement of the weakly coordinated chloride ligand (KCl precipitates

Table 1
Condensation of myrcene with various phenols.[a] [a]Reagents and conditions: $[RhCl(COD)]_2$ (1 mol%), dppb (3 mol%), K_2CO_3 (1 equiv.), toluene, 110°C, 24 h. [b]Unoptimized yields, isolated products. [c]Mono- and bis-addition observed. [d]*ortho*/*para*/bis addition ratio=59/23/18, determined by ^1H NMR. [e]Determined by ^1H NMR

Phenol (regioselectivity)	Yield (%)[b]	exo/endo ratio[d]	Phenol (regioselectivity)	Yield (%)[b]	exo/endo ratio[e]
	77	98/2		70[c]	n.d.
	82	75/25		72[d]	n.d.
	56	90/10		95	80/20



Scheme 3. A possible mechanistic rationale

and can be recovered for quantitation by filtration). A keto–enolic equilibrium causes the rhodium nucleus to migrate in the *ortho*/*para* positions, if available. Rearrangement of this intermediate with 1,2-H migration yields an aryl–hydrido–Rh(III) complex (which retains the aromatic proton). A simple keto–enolic equilibrium at this stage would result in hydrogen scrambling, and is thus unlikely.

A perfectly regioselective carbo-rhodiation of the diene, followed by reductive elimination of the

resulting hydrido–π-allyl rhodium(III) complex delivers the alkylated phenol as an *endo*/*exo* mixture, and regenerates the Rh(I) phenoxide catalyst. We feel that the exact mechanism cannot be unambiguously settled at this stage.

In conclusion, the vitamin E synthesis presented here was made possible by the use of a highly efficient atom-economical transition metal-catalyzed addition. Such transformation, when selective, may be of great value to improve existing multi-ton processes.

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