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Total Synthesis of (*R,R,R*)-γ-Tocopherol through Cu-Catalyzed Asymmetric 1,2-Addition

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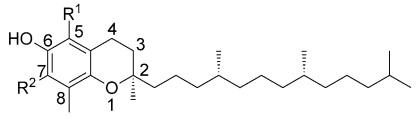
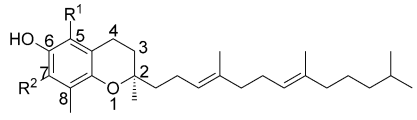
Abstract: Based on the asymmetric copper-catalyzed 1,2-addition of Grignard reagents to ketones, (*R,R,R*)-γ-tocopherol has been synthesized in 36% yield over 12 steps (longest linear sequence). The chiral center in the chroman ring was constructed with 73% *ee* by the 1,2-addition of a phytol-derived Grignard reagent to an α-bromo enone prepared from 2,3-dimethylquinone.

Vitamins are essential food ingredients for humans and in feed for animal husbandry. The most important fat-soluble antioxidant, vitamin E, was first reported about one century ago,[1] and is of particular industrial interest as a food and feed additive.[2] Although formally vitamin E comprises a family of tocopherols and tocotrienols with a chroman core (Figure 1), in practice the term is synonymous with α-tocopherol or its acetate as it is by far the most dominant member.[2a,3] *All-rac*-α-tocopherol is produced on a scale of more than 30000 ton per year.[4] To meet this huge demand for vitamin E, the industrial synthesis is accomplished by the condensation of trimethylhydroquinone (**9**) and chemically produced isophytol **10** (Scheme 1).[5]



R^1	R^2	Tocopherol
-Me	-Me	α- (**1**)
-Me	-H	β- (**2**)
-H	-Me	γ- (**3**)
-H	-H	δ- (**4**)



R^1	R^2	Tocotrienol
-Me	-Me	α- (**5**)
-Me	-H	β- (**6**)
-H	-Me	γ- (**7**)
-H	-H	δ- (**8**)

Figure 1. Vitamin E.

The naturally occurring (*R,R,R*)-tocopherols are biologically the most active,[3,6] and in particular the stereochemistry at C2 is important.[7] Consequently, the asymmetric synthesis of **1**, and especially the stereoselective synthesis of the chroman core,[8] has been the topic of intense research, which has been discussed in several reviews.[9] A selection of the more recent approaches in asymmetric catalysis is depicted in Scheme 2.[10] A very recent shoot of this tree is the application of the Ni-catalyzed conjugate addition of methyl organometallics to a 2-alkyl-4-chromenone core. Although providing racemic product, given the rapid developments in asymmetric conjugate addition, enantioselectivity seems to be a matter of time and effort.[11]

γ-Tocopherol is another major member of the vitamin E family and the main vitamin E in US diet. Although α-tocopherol has the highest vitamin E activity,[7] γ-tocopherol has an unsubstituted aromatic position and therefore can trap electrophilic mutagens, such as nitronium ions,[12] more efficiently.[13] This has elicited further research focused on γ-tocopherol.[14]

Compared to α-tocopherol, synthesis efforts on (*R,R,R*)-γ-tocopherol **3** have been particularly scarce, and the first total synthesis of γ-tocopherol was reported in 1994 with a copper-mediated coupling methodology.[9a,d,16] In 1997, Habicher et al. prepared γ-tocopherol by photodecarboxylation of γ-tocopherol-5-carboxylic acid, in turn derived from α-tocopherol.[17] Based on this aryl demethylation approach of α-tocopherol, Salvadori et al. reported the preparation of labeled and unlabeled (*R,R,R*)-γ-tocopherol **3**.[18] No catalytic asymmetric synthesis of **3** has been reported.

In 2012, we reported the enantioselective 1,2-addition of Grignard reagents to α,β-unsaturated ketones applying a copper/Josiphos-type catalyst (Scheme 3).[19] This leads to chiral enantioenriched tertiary allylic alcohols, and in a subsequent study we established their absolute configuration.[20]

We realized that this catalytic asymmetric 1,2-addition could function as a cornerstone for a novel, relatively straightforward approach to tocopherols and tocotrienols (Scheme 4) provided the subsequent ring closure to the chroman nucleus would be racemization-free. This requires either a strictly S_N2-type nucleophilic substitution of the tertiary alcohol by the aromatic hydroxyl group, or an aromatic alkoxylation reaction. The latter, proceeding via an oxidation–reduction pathway of the hydroquinone, had been discovered and studied in depth already by Cohen et al. and does not lead to erosion of *ee*,[21] as confirmed by subsequent studies.[10c,22] Based on these two key steps,

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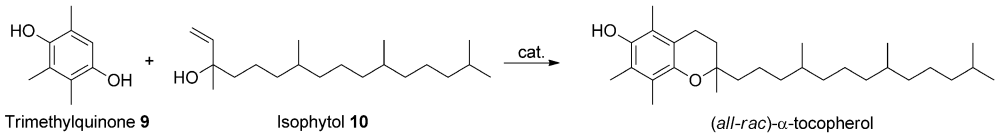
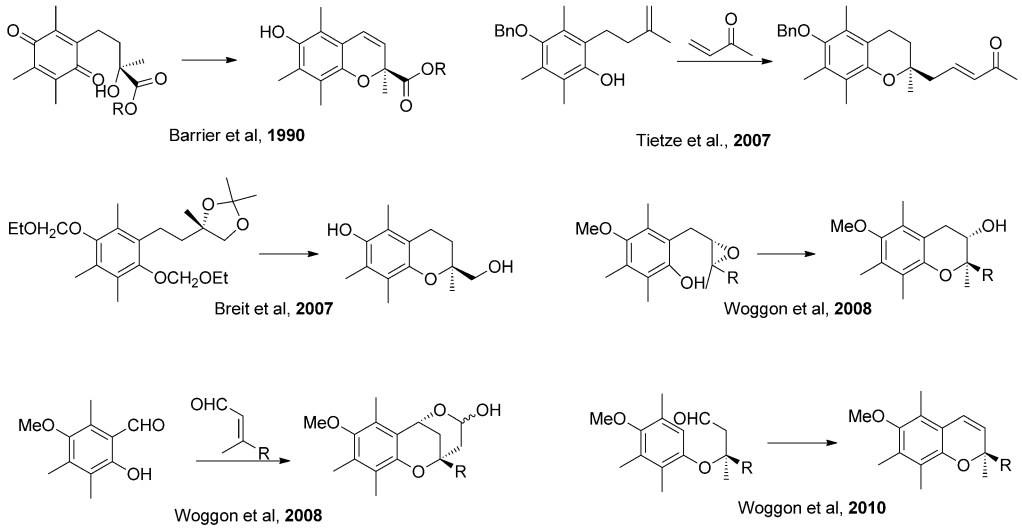
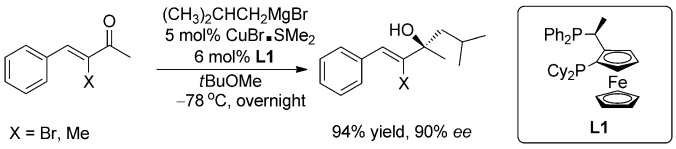


Scheme 1. Synthesis of *all-rac*-α-tocopherol.



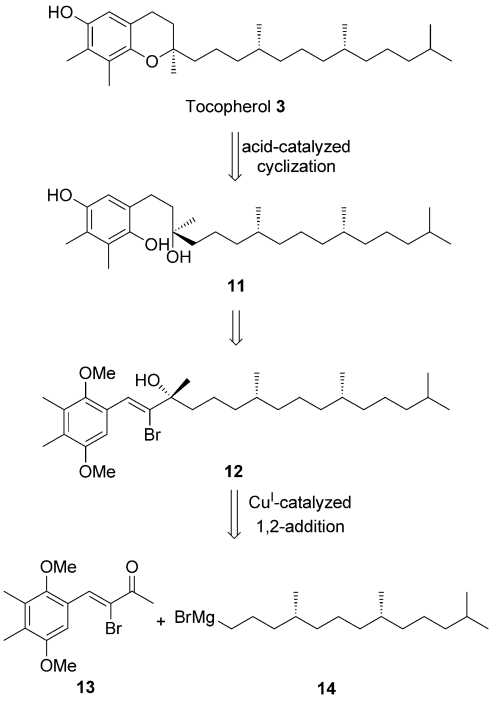
Scheme 2. Recently reported strategies on the stereoselective construction of the 2*R*-chroman core in the synthesis of **1**.[15]



Scheme 3. An example of the asymmetric Cu-catalyzed 1,2-addition of Grignard reagents.

a retrosynthesis was designed allowing full freedom both in the substitution pattern (α, β, γ, δ)- of the aromatic ring and in the chain leading to tocopherols and tocotrienols.

Aiming at γ-tocopherol, in the synthesis direction ketone **13** should be accessible from commercially available 2,3-dimethyl hydroquinone **15**. As the copper-catalyzed asymmetric Grignard addition requires both an unsaturation and an α-substituent flanking the carbonyl group, subsequent steps should lead to **12**. (Scheme 4) We showed already that after the 1,2-addition, the auxiliary Br is readily removed via Li–halogen exchange followed by protonation. Also reduction of the alkene was not expected to be complicated provided hydrogenolysis of the hydroxyl group could be suppressed. For the actual copper-catalyzed asymmetric 1,2-addition, the current method would have to be advanced. Substrates containing heavily substituted phenyl groups had not been studied in this reaction and therefore the influence of these substitutions on the chemo-, regio-, and enantioselectivity was not known. Moreover, the required Grignard reagent **14** is a long chain with the

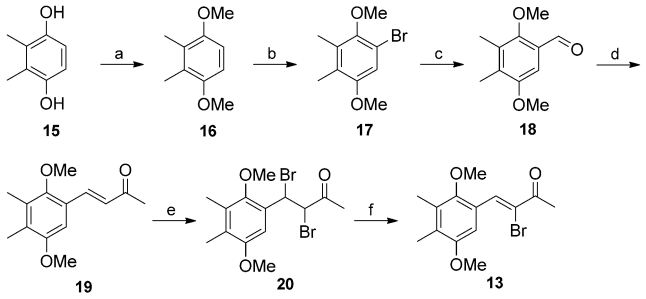


Scheme 4. Retrosynthesis of (*R*,*R*,*R*)-γ-tocopherol **3**.

nearest branch at the δ-position, whereas in the current catalyst system high *ee* values were obtained solely with β-branched Grignard reagents such as isobutylmagnesium bro-

mide (see Scheme 3). Although efficient catalytic strategies have been developed both by Pfaltz et al.[23] and by us,[24] for the asymmetric synthesis of so-called saturated polyisoprenoids, readily available (*R,R*)-phytol was chosen in this case as the precursor of the chain.[25]

The synthesis of **13** is summarized in Scheme 5. An attempted formylation of **15** according to Skattebøl et al. (with paraformaldehyde, $MgCl_2$ and triethylamine)[26] did not provide aldehyde **18**, not unexpected as this reaction has not been reported with hydroquinones as substrate. Therefore, **16** was prepared in quantitative yield.[27] A direct formylation of **16** turned out to be very difficult as well. Duff reaction (hexamine and TFA) with **16** has been reported[28] to afford **18** in 44% yield, a result that was reproduced but not improved. Vilsmeier–Haack reaction (phosphoryl chloride and DMF),[29] Rieche formylation (titanium tetrachloride and dichloromethyl methyl ether),[30] and also ortholithiation with *n*BuLi/TMEDA followed by reaction with DMF[31] did not provide significant amounts of **18**. In an alternative approach, using the conditions reported by Fukuyama et al., **16** was first brominated,[32] followed by bromo–lithium exchange and reaction with DMF.[33] This led after optimization to **18** in an excellent yield from **16**. Then, **18** was transformed into enone **19** by aldol condensation with acetone in 96% yield.[34] Subsequent dibromination/HBr elimination furnished α-enone **13** in 80% yield over two steps.[20,35]

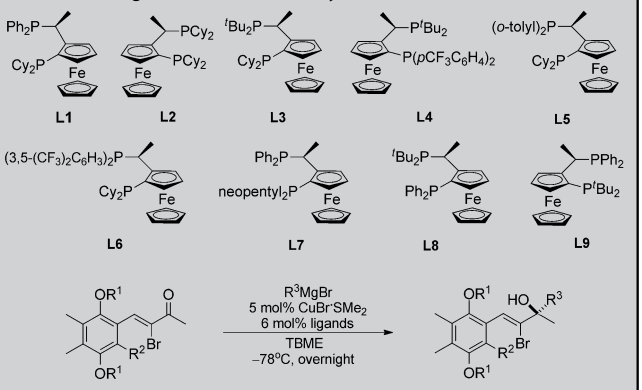


Scheme 5. Synthesis of **13**: a) MeI, NaH, DMF, 0 °C to r.t., 3 h; b) NBS, CH_2Cl_2, reflux, overnight, 93% over two steps; c) *n*BuLi, DMF, THF, −78 °C, 0.5 h, 92%; d) acetone, NaOH, EtOH, r.t., 10 min, 96%; e) NaBr, oxone, CH_2Cl_2/H_2O, 0 °C to r.t., overnight; f) Et_3N, THF, reflux, overnight, 80% over two steps. NBS = *N*-bromosuccinimide.

The preparation of Grignard reagent **14** started from phytol **21** which already contains two chiral centers with the desired absolute configuration (Scheme 6). Ozonolysis of phytol led to ketone **22**,[36] which was followed by Baeyer–Villiger oxidation according to the procedure of Pratt and Porter et al. to give **23**.[37] After hydrolysis of the acetate, **24** was isolated in 92% yield over three steps. Bromination gave the desired **25** in 76% yield from **24**.[38] This bromide was converted into its corresponding Grignard reagent **14** as an ≈ 1.5 M solution in diethyl ether.

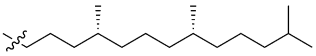
With both **13** and **14** in hand, the copper-catalyzed asymmetric 1,2-addition was studied. Applying the established conditions (Scheme 3) and Grignard reagent **14**, tertiary alcohol **26** was obtained in very good yield. The diastereoselectivity, however, was only 42% (Table 1, entry 1). Screening various solvents, for example, diethyl ether, diisopropyl ether, 1,2-dimethoxyethane, and cyclopentyl methyl ether, as well as applying a prolonged addition time, or portion-wise addition of **13** and **14** did not improve this result. To benchmark the obtained 42% *de*, the asymmetric addition of isobutylmagnesium bromide to **13** was carried out as well, which provided **27** in a re-

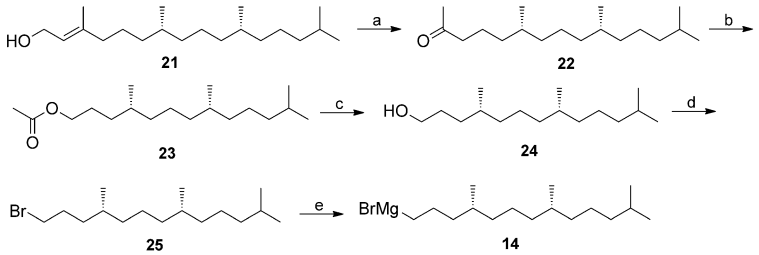
Table 1. Investigations on the Cu-catalyzed 1,2-addition.



Entry	Ketone	R^1	R^2	R^3	Ligands	1,2-Adduct	*de/ee*[a]
1	**13**	Me	H	$C_{16}H_{33}$* [b]	**L1**	**26**	42
2	**13**	Me	H	$(CH_3)_2CHCH_2$	**L1**	**27**	87
3	**28**	TBS	H	$C_{16}H_{33}$*	**L1**	–	–
4	**29**	Me	Me	$C_{16}H_{33}$*	**L1**	**30**	7
5	**13**	Me	H	$C_{16}H_{33}$*	**L2**	**26**	36
6	**13**	Me	H	$C_{16}H_{33}$*	**L3**	**26**	7
7	**13**	Me	H	$C_{16}H_{33}$*	**L4**	**26**	12
8	**13**	Me	H	$C_{16}H_{33}$*	**L5**	**26**	racemic
9	**13**	Me	H	$C_{16}H_{33}$*	**L6**	**26**	racemic
10	**13**	Me	H	$C_{16}H_{33}$*	**L7**	**26**	26
11	**13**	Me	H	$C_{16}H_{33}$*	**L8**	**26**	43
12	**13**	Me	H	$C_{16}H_{33}$*	**L9**	**26**	73

[a] *de/ee* is not related to the absolute configuration of the 1,2-addition products. [b] $C_{16}H_{33}$* =





Scheme 6. Synthesis of **14**: a) ozone, CH_2Cl_2/MeOH, −78 °C; b) $(CF_3CO)_2O$, $Na_2CO_3 \cdot 1.5H_2O_2$, CH_2Cl_2, r.t., 2 days; c) LiOH, THF/MeOH/H_2O, r.t., 2 h; 92% over three steps; d) NBS, PPh_3, 0 °C, 2 h, 76%; e) Mg, Et_2O.

warding 87% *ee* (entry 2). This strongly suggested that the moderate *de* in the case of **26** is not due to the substitution pattern of the phenyl ring but due to the structure of the Grignard reagent **14**. That there are boundaries at the substitution pattern on the aromatic ring became clear in a parallel study. When the methyl protecting groups in **13** were replaced by *tert*-butyldimethylsilyl groups leading to enone **28**, this substrate did not react under standard 1,2-addition conditions (entry 3). Also **29** was prepared as the precursor for (*R,R,R*)-α-tocopherol **1**, but the product of the addition of **14**, **30**, was almost racemic (entry 4).

These studies forced a re-evaluation of the applied chiral ligand, rev-Josiphos **L1**. In the development of the catalytic asymmetric 1,2-addition of Grignard reagents we had already experienced that **L1** was unique in its chiral induction. Both closely related ligands such as the parent Josiphos, and unrelated ligands such as BINAP, and phosphoramidites performed badly. These studies were carried out with isobutylmagnesium bromide as the nucleophile.

We therefore studied various chiral ligands, including the commercial ligands **L2**–**L4** and **L8** and **L9** and the ligands **L5**–**L7** prepared for this purpose,[39,40] in combination with Grignard reagent **14**. Most ligands performed less well compared to rev-Josiphos **L1** (entries 5–10). Josiphos-type ligand **L8**, being an exception, afforded a virtually identical *de* as **L1** (entry 11). Ligand **L8** bears a sterically demanding di-*tert*-butyl phosphine group in combination with the Josiphos-like arrangement of a dialkyl phosphine on the ethyl branch and a diaryl phosphine on the ferrocene ring. In our experience, the enantioselectivity of the copper-catalyzed 1,2-addition profits from rev-Josiphos type ligands, that is, a dialkyl phosphine on the ferrocene and a diaryl phosphine ethyl branch. Following this idea, we studied commercial ligand **L9**. To our delight, a significant improvement of the diastereoselectivity to 73% was observed in the 1,2-addition of Grignard reagent **14** to **13** (entry 12). So, the three rev-Josiphos-type ligands **L7**, **L1**, and **L8**, gave us a clear hint to increase the *de* in the 1,2-addition of **14** to **13**, by increasing the steric bulk at the ferrocene phosphorus substituent of rev-Josiphos type ligands. This lured us into an attempt to prepare several new rev-Josiphos type ligands with sterically very hindered phosphorus substituents on position 2 of the ferrocenyl ring (Figure 2). A considerable effort was invested in the preparation of **L1**-type ligands with R = $EtMe_2C$, Et_3C, $iPrMe_2C$, and adamantyl according to literature procedures for related ligands.[41] However, the coupling of the R_2PCl reagent with the *ortho*-lithiated ferrocene invariably failed, probably due to this (desired) steric hindrance. Ligand **L7** was accessible by this method but afforded a low *de* in the subsequent 1,2-addition, probably because the steric bulk was not directly positioned at the phosphorus center. Therefore we had to conclude that 73% *de* was the maximum achievable stereoselectivity at present.

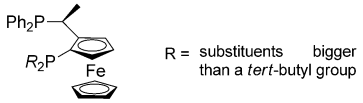
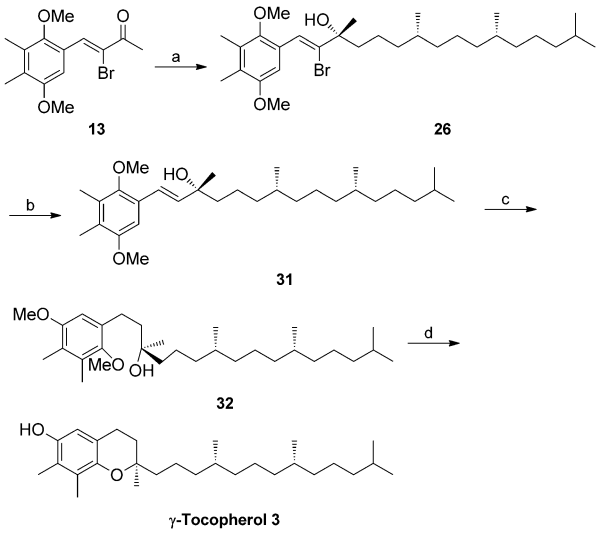


Figure 2. Designed rev-Josiphos type Ligands.

With the most optimal ligand **L9**, we produced the key chiral tertiary alcohol **26** in 73% *de* and 93% yield. Straightforward debromination of **26** with *t*BuLi at −78 °C for 0.5 h afforded **31** in 91% yield (Scheme 7).[42] Reduction of the double bond in **31** turned out to be a showcase for flavine-catalyzed diimide reduction.[43] Heterogeneous transition metal catalysts, for example, Pd/C,[44] Pt/C, PtO_2,[45] and Pd/C/NaOAc,[10c] in combination with H_2 invariably provided the hydrogenolysis product and also the recently disclosed diimide reduction with $FeCl_3$ as the catalyst suffered from hydrogenolysis.[46] Flavine-catalyzed double bond reduction of **31** afforded **32** as the only product in 90% yield.[47] To prepare for the ring-closing step, **32** was oxidized to the corresponding quinone by treatment with cerium(IV) ammonium nitrate, followed by subsequent reduction to afford hydroquinone **11**. Finally, acid-catalyzed and oxygen-induced cyclization of **11** provided the desired (*R,R,R*)-γ-tocopherol **3** in 72% yield over three steps.[22b,c] The synthetic material was identical in all aspects (^1H and ^{13}C NMR, mass analysis) with the reported data.[48]



Scheme 7. Synthesis of (*R,R,R*)-γ-tocopherol. a) **14**, CuBr·SMe_2, **L9**, TBME, −78 °C, overnight, 93%; b) *t*BuLi, Et_2O, −78 °C, 0.5 h, 91%; c) flavin catalyst, O_2, $N_2H_4{\cdot}H_2O$, EtOH, r.t., overnight; 90%; d) i. $Ce(NH_4)_2(NO_3)_6$, THF/H_2O, 0 °C, 0.5 h; ii. $Na_2S_2O_4$, acetone/H_2O, r.t., 0.5 h; iii. *p*-TSA, toluene, 60 °C, 5 min, 72% over three steps. *p*-TSA = *p*-toluenesulfonic acid.

In summary, we developed an efficient synthesis of (*R,R,R*)-γ-tocopherol based on copper-catalyzed asymmetric 1,2-addition. Starting from commercially available 2,3-dimethyl hydroquinone and phytol, (*R,R,R*)-γ-tocopherol was prepared in 12 steps (longest linear sequence), 36% overall yield and 73% *de* at the C2 chiral center. The synthesis is not misplaced in the current collection of catalytic asymmetric approaches to the tocopherols, as the route is straightforward, in particular in its introduction of chirality at C2, and its use of readily available

building blocks. An important finding is that the catalyst system used for the asymmetric addition of a complex Grignard reagent could be considerably optimized in terms of stereoselectivity. This means that the scope of Grignard reagents suitable for this reaction has been enlarged and offers further opportunities for study. Inherently the method is very versatile as Grignard reagents are readily prepared from alkyl bromides.

Acknowledgements

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Keywords: (*R,R,R*)-γ-tocopherol · 1,2-addition · asymmetric catalysis · natural product synthesis · vitamin E

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