Synthesis of α-Tocopherol: Scandium(III) Trifluoromethanesulfonate as an Efficient Catalyst in the Reaction of Hydroquinone with Allylic Alcohol

Makoto Matsui, Norio Karibe,† Kenji Hayashi,† and Hisashi Yamamoto*

School of Engineering, Nagoya University, Furo-cho, Chikusa-ku, Nagoya 464-01

†Eisai Company, Ltd., Tokodai, Tsukuba 300-26

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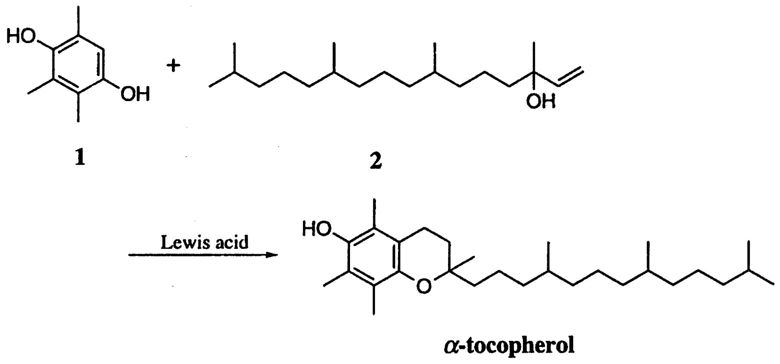
Scandium(III) trifluoromethanesulfonate was found to be an efficient catalyst as a Lewis acid for the condensation reaction of trimethylhydroquinone with isophytol to afford α-tocopherol. The condensation reaction proceeded smoothly using only a 0.001 molar amount of the catalyst. The catalyst was easily recovered from an aqueous layer after the reaction was completed, and could be reused.

The condensation reaction of hydroquinone with allylic alcohol is an important process for the synthesis of α-tocopherol and its related compounds.[1] The rate of the reaction is significantly accelerated in the presence of a Lewis acid catalyst, especially zinc chloride. Unfortunately, the reaction requires one molar amount of catalyst, probably due to a deactivation of the catalyst by water generated during the reaction. Thus, if a Lewis acid with sufficient reactivity in the presence of water is available, the reaction may proceed in the presence of a catalytic amount of such a catalyst. If the reagent can be recovered and reused with the same catalytic activity, such a system would be effective as an industrial process.

Recently, Kobayashi and co- workers reported that rare earth metal(III) trifluoromethanesulfonates (triflates) were excellent catalysts in some fundamental carbon–carbon bond forming reactions.[2] The reactions proceed smoothly, not only in organic solvents, but also in aqueous media, and the catalysts can be easily recovered and reused. We thus decided to study these catalysts for the reaction of hydroquinone and allylic alcohols with the hope of establishing a catalytic system (Scheme 1).

First, various kinds of lanthanide(III) triflates,[3] $Y(OTf)_3$[4] and $Sc(OTf)_3$[5] for condensation reactions of trimethylhydroquinone (**1**) with isophytol (**2**) were examined (Table 1). Catalytic amounts of a Lewis acid in toluene or xylene were exposed to **1** and **2** which was added dropwise under reflux; after the usual workup the crude product was chromatographed on silica gel to yield the condensation product. Among these triflates, $Sc(OTf)_3$ was found to be the most effective, though lanthanide(III) triflate resulted in a relatively lower yield. The reaction proceeded smoothly in the presence of a catalytic amount of $Sc(OTf)_3$ under reflux in xylene; the condensation product, α-tocopherol, was obtained in high yield with satisfactory purity (88% yield and 97% purity; Entry 13).

$Sc(OTf)_3$ is known to be an effective Lewis acid cata-



Scheme 1.

Table 1. Reaction of Trimethylhydroquinone (1) and Isophytol (2) Using Rare Earth Metal (III) Triflate[a)]

Entry	Catalyst (molar amount)	Solvent	Yield (%)[b)]	Purity (%)[c)]
1[d)]	$La(OTf)_3$ (0.2)	Toluene	<1	
2	$Pr(OTf)_3$ (0.1)	Xylene	32[e)]	
3	$Sm(OTf)_3$ (0.1)	Toluene	<1	
4	$Eu(OTf)_3$ (0.2)	Xylene	84	80
5	$Gd(OTf)_3$ (0.1)	Xylene	<1	
6	$Dy(OTf)_3$ (0.1)	Xylene	47	92
7	$Ho(OTf)_3$ (0.1)	Xylene	63	94
8	$Er(OTf)_3$ (0.1)	Xylene	33[e)]	
9	$Tm(OTf)_3$ (0.1)	Toluene	<1	
10	$Yb(OTf)_3$ (0.2)	Xylene	59	91
11	$Lu(OTf)_3$ (0.1)	Xylene	59	92
12	$Y(OTf)_3$ (0.2)	Xylene	42	95
13	$Sc(OTf)_3$ (0.2)	Xylene	88	97

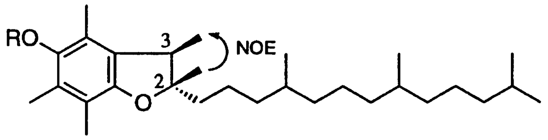
a) Unless otherwise specified, the reaction was carried out in solvent under reflux for 3 h using trimethylhydroquinone, catalyst and isophytol that was added dropwise. b) Isolated yield. c) Determined by GLC analysis. d) It took 6 h for the reaction. e) Determined by GLC analysis.

lyst, even in the presence of water, and can be easily recovered and reused.[2)] Various reaction conditions were examined; the results are given in Table 2. The reaction proceeded smoothly in aromatic solvents to afford α-tocopherol in high yield with high purity (Entries 1, 2, and 3). It should be noted that a quantitative condensation product was obtained using a 0.01 molar amount of the catalyst (Entry 4). Even when a 0.001 molar amount of the catalyst was employed under azeotropic distillation, α-tocopherol was obtained in satisfactory yield and purity (79% yield and 96% purity; Entry 6). Furthermore, the yield and purity of α-tocopherol with the used catalyst, which was recovered from an aqueous layer, were almost the same as that in the first use (91% yield and 94% purity; Entry 5). These results indicate that $Sc(OTf)_3$ is stable and retains its Lewis acidity, even after exposure to water.

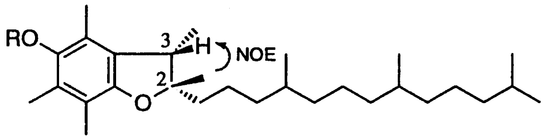
Table 2. Reaction of Trimethylhydroquinone (1) and Isophytol (2) Using Scandium (III) Triflate[a)]

Entry	$Sc(OTf)_3$/ molar amount	Solvent	Time (h)	Yield (%)[b)]	Purity (%)[c)]
1	0.2	Xylene	3	88	97
2	0.2	Toluene	6	98	98
3	0.2	Benzene	6	98	96
4	0.01 (1st use)	Toluene	1	96	95
5	0.01 (2nd use)	Toluene	3	91	94
6[d)]	0.001	Toluene	3	79	96

a) Unless otherwise specified, the reaction was carried out in solvent under reflux using trimethylhydroquinone, catalyst and isophytol that was added dropwise. b) Isolated yield. c) Determined by GLC analysis. d) The reaction was carried out under azeotropic distillation.



3a ; R=Ac, **4a** ; R=H



3b ; R=Ac, **4b** ; R=H

Fig. 1.

In the condensation reaction, a GLC analysis of the products showed two minor peaks accompanied by a major peak, which was α-tocopherol. Isolation of the minor products, which was performed by HPLC after acetylation of condensation mixture, indicated diastereomers of dihydrobenzofuran **3a** and **3b**, which were determined by HRMS and ^{1}H NMR. The relative configuration of C_2 and C_3 methyl groups was confirmed by NOE studies as shown in Fig. 1. Thus, byproducts **4a** and **4b** may be produced through the condensation of hydroquinone **1** with 2-(4,8,12-trimethyltridecyl)-1,3-butadiene, which was generated from the dehydration of isophytol (**2**).

In summary, $Sc(OTf)_3$ is an excellent catalyst in the condensation reaction of hydroquinone with allylic alcohol. The most beneficial features of this catalyst, the necessity to use a very small amount and the possibility of its recovery and reuse, make this system appealing, even at the commercial stage.

Experimental

General. Infrared (IR) spectra were recorded on a Shimadzu FTIR-8100 spectrometer. Analytical gas-liquid-phase chromatography (GLC) was performed on a Gaskuro Kogyo Model 370 instrument with a flame-ionization detector and a capillary column of HP-1 (25 m) using nitrogen as the carrier gas. The ^{1}H NMR spectra were measured on Varian Gemini-200 (200 MHz), Varian Gemini-300 (300 MHz) and JEOL JNM α400 (400 MHz) spectrometers. The chemical shifts of the ^{1}H NMR spectra are reported relative to tetramethylsilane ($\delta=0$) or chloroform ($\delta=7.26$). The splitting patterns are indicated as follows; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. The mass spectra were recorded with Shimadzu QP-5000 and JEOL JMS-SX102A mass spectrometers. High-performance liquid chromatography (HPLC) was performed with a Shimadzu LC 6AD instrument using a 20-mm × 25-cm JASCO Finepak Sil column. All of the experiments were carried out under an atmosphere of dry argon. For a thin-layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica-gel 60 GF_{254}, 0.25 mm) were used. The products were purified by preparative column chromatography on silica gel E. Merck Art. 9385.

In experiments requiring dry solvents, benzene, toluene and xylene (*o*-xylene was used) were dried over sodium metal. All other simple chemicals were purchased and used without further purification.

Typical Procedure for the Condensation Reaction of Trimethylhydroquinone (1) and Isophytol (2) Using Scandium(III) Triflate (Table 2, Entry 4): To a suspension of trimethylhydroquinone (1.0 g, 6.6 mmol) in toluene (2.0 ml) was added scandium(III) trifluoromethanesulfonate (32 mg, 0.066 mmol); the mixture was then heated at reflux for 10 min. After a solution of isophytol (2.0 g, 6.7 mmol) in toluene (2.0 ml) was added dropwise to the suspension over a period of 30 min with refluxing, the mixture was heated at reflux for 3 h. Then, after cooling, the resulting mixture was poured into deionized water (20 ml); the product was subsequently extracted with toluene (10 ml). The combined organic layer was washed twice with deionized water (2×20 ml), dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluent: hexane–AcOEt) to give α-tocopherol as a brown oil (2.8 g, 96% yield, 95% purity). After the combined aqueous washes were concentrated in vacuo, the residue was added toluene (20 ml), and the mixture was refluxed with continuous azeotropic removal of water. Then, after cooling, the resulting precipitate was filtered and reused. Isolation of by products **3a** and **3b** was performed by HPLC (20-mm × 25-cm, JASCO Finepak Sil column). The spectral data are described below:

3a: IR (neat) 2928, 2868, 1763, 1462, 1414, 1368, 1210, 1080, 1042 cm^{-1}; ^{1}H NMR (400 MHz, $\mathrm{CDCl_3}$) δ=0.8—0.9 (m, 12H, 4$\mathrm{CH_3}$), 0.9—1.7 (m, 21H), 1.13 (d, 3H, J=7.1 Hz, $\mathrm{CH_3}$), 1.37 (s, 3H, $\mathrm{CH_3}$), 2.00 (s, 3H, $\mathrm{CH_3}$), 2.04 (s, 3H, $\mathrm{CH_3}$), 2.08 (s, 3H, $\mathrm{CH_3}$), 2.32 (s, 3H, $\mathrm{COCH_3}$), 3.03 (q, 1H, J=7.1 Hz, CH); HRMS (EI, 70 eV) Found: m/z 472.3922. Calcd for [M$^+$]: 472.3916.

3b: IR (neat) 2928, 2870, 1763, 1458, 1412, 1370, 1208, 1080, 1046 cm^{-1}; ^{1}H NMR (400 MHz, $\mathrm{CDCl_3}$) δ=0.8—0.9 (m, 12H, 4$\mathrm{CH_3}$), 0.9—1.7 (m, 21H), 1.10 (d, 3H, J=7.0 Hz, $\mathrm{CH_3}$), 1.26 (s, 3H, $\mathrm{CH_3}$), 2.00 (s, 3H, $\mathrm{CH_3}$), 2.03 (s, 3H, $\mathrm{CH_3}$), 2.08 (s, 3H, $\mathrm{CH_3}$), 2.32 (s, 3H, $\mathrm{COCH_3}$), 2.98 (q, 1H, J=7.0 Hz, CH); HRMS (EI, 70 eV) Found: m/z 472.3905. Calcd for [M$^+$]: 472.3916.

Identification of α-tocopherol was carried out by a comparison of the spectral data (IR, ^{1}H NMR, MS) and a GLC analysis of an authentic sample. The spectral data are described below: IR (neat) 3100—3700, 2926, 1462, 1422, 1377, 1262, 1213, 1086, 918 cm^{-1}; ^{1}H NMR (200 MHz, $\mathrm{CDCl_3}$) δ=0.84 (d, 3H, J=6.3 Hz, $\mathrm{CH_3}$), 0.85 (d, 3H, J=6.3 Hz, $\mathrm{CH_3}$), 0.87 (d, 6H, J=6.5 Hz, 2$\mathrm{CH_3}$), 1.0—1.6 (m, 24H), 1.78 (m, 2H), 2.11 (s, 6H, $\mathrm{CH_3}$), 2.16 (s, 3H, $\mathrm{CH_3}$), 2.60 (t, 2H, J=6.8 Hz), 4.18 (s, 1H, OH); MS (EI, 70 eV) m/z 430 (M$^+$), 205, 165, 121, 83, 69, 57, 43.

Procedure for the Condensation Reaction of Trimethylhydroquinone (1) and Isophytol (2) Using 0.001 Molar Amount of Scandium(III) Triflate (Table 2, Entry 6): To a suspension of trimethylhydroquinone (2.0 g, 13 mmol) in toluene (2.0 ml) was added scandium(III) trifluoromethanesulfonate (6.5 mg, 0.013 mmol); the mixture was then heated at reflux for 10 min. A solution of isophytol (4.1 g, 14 mmol) in toluene (4.0 ml) was added dropwise to the suspension over a period of 10 min with refluxing; the mixture was then refluxed with continuous azeotropic removal of water for 3 h. After cooling, the resulting mixture was poured into deionized water (20 ml), and the product was extracted with diethyl ether (10 ml). The combined organic layer was washed twice with deionized water (2×20 ml), dried over anhydrous magnesium sulfate and concentrated in vacuo. Hexane (10 ml) was added to the crude mixture and the unreacted solid trimethylhydroquinone was filtered out. The residue was purified by column chromatography on silica gel (eluent: hexane–AcOEt) to give α-tocopherol as a brown oil (4.5 g, 79% yield, 96% purity).

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References

1) a) T. Ichikawa and T. Kato, *Bull. Chem. Soc. Jpn.*, **41**, 1224 (1968); b) H. Mayer and O. Isler, "Methods in Enzymology," ed by S. P. Colowick and N. O. Kaplan, Academic Press, New York (1971), Vol. XVIIIC, pp. 241—348; c) P. Schudel, H. Mayer, and O. Isler, "The Vitamins," ed by W. H. Sebrell and R. S. Harris, Academic Press, New York (1972), Vol. V, pp. 168—218; d) F. M. D. Ismail, M. J. Hilton, and M. Stefinovic, *Tetrahedron Lett.*, **33**, 3795 (1992).

2) a) S. Kobayashi, *Chem. Lett.*, **1991**, 2187; b) S. Kobayashi and I. Hachiya, *Tetrahedron Lett.*, **33**, 1625 (1992); c) S. Kobayashi, I. Hachiya, H. Ishitani, and M. Araki, *Tetrahedron Lett.*, **34**, 3755 (1993); d) I. Hachiya and S. Kobayashi, *J. Org. Chem.*, **58**, 6958 (1993); e) S. Kobayashi, I. Hachiya, H. Ishitani, and M. Araki, *Synlett*, **1993**, 472; f) S. Kobayashi, I. Hachiya, and T. Takahori, *Synthesis*, **1993**, 371; g) S. Kobayashi and I. Hachiya, *J. Org. Chem.*, **59**, 3590 (1994); h) S. Kobayashi, I. Hachiya, and Y. Yamanoi, *Bull. Chem. Soc. Jpn.*, **67**, 2342 (1994); i) S. Kobayashi, *Synlett*, **1994**, 689.

3) a) J. H. Forsberg, V. T. Spaziano, T. M. Balasubramanian, G. K. Liu, S. A. Kinsley, C. A. Duckworth, J. J. Poteruca, P. S. Brown, and J. L. Miller, *J. Org. Chem.*, **52**, 1017 (1987); see also b) Ref. 2g.

4) a) K. F. Thom, U. S. Patent 3615169 (1971); *Chem. Abstr.*, **76**, 5436a (1972); b) Refs. 2e and 3a.

5) $\mathrm{Sc(OTf)_3}$ was purchased from Fluka Chemical Co.