

# Perfluorinated Brønsted ‘Superacids’: Powerful Catalysts for the Preparation of Vitamin E

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**Abstract:** The key-step in the industrial synthesis of (all-*rac*)- $\alpha$ -tocopherol (synthetic vitamin E) is the condensation reaction of trimethylhydroquinone with the C<sub>20</sub> building block isophytol. For this Friedel-Crafts-type reaction, perfluorinated NH- and CH-acidic compounds (perfluoroalkyl(aryl)sulfonyl imides and methides) have been applied as excellent catalysts, preferably in biphasic solvent systems.

**Keywords:** Biphasic catalysis · Friedel-Crafts alkylation · Perfluorinated NH-acidic imides ·  $\alpha$ -Tocopherol · Tris(perfluoroalkylsulfonyl) methanes

## Introduction

Vitamin E is the biologically most important fat-soluble antioxidant. The form of highest commercial value is synthetic (all-*rac*)- $\alpha$ -tocopherol (**3**), which is produced in a scale of over 25'000 tons per year worldwide.

All industrial syntheses of (all-*rac*)- $\alpha$ -tocopherol (**3**) use the reaction of trimethylhydroquinone (**1**) with (all-*rac*)-isophytol (**2**) or a C<sub>20</sub> equivalent thereof (Scheme 1). Several classical *Lewis* and *Brønsted* acids have been applied as catalysts in this reaction. Typical examples are zinc chloride and a mineral acid, BF<sub>3</sub>, AlCl<sub>3</sub>, Fe/HCl, or the combination of boric acid and carboxylic acids [1]. Such known catalysts, however, cause often serious corrosion and wastewater problems in large-scale production.

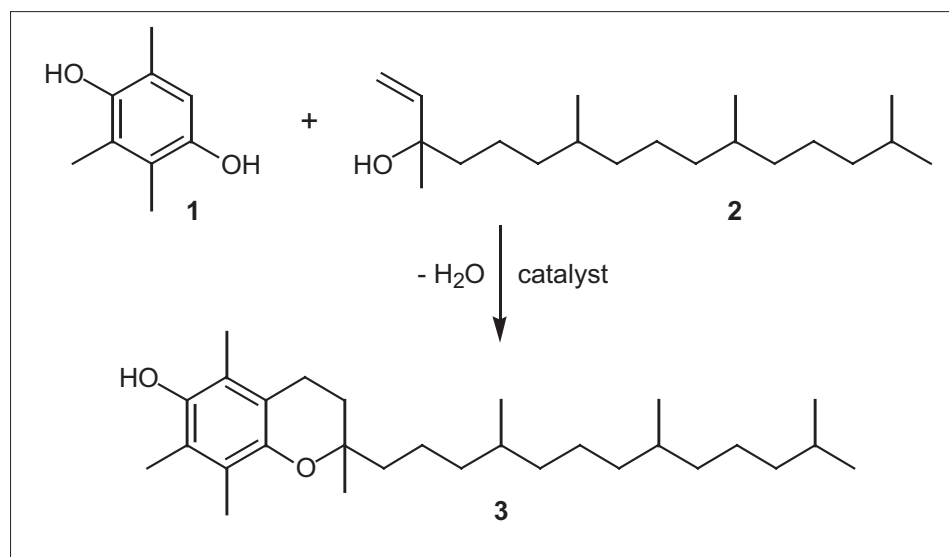
In order to avoid the disadvantages of the known syntheses of (all-*rac*)- $\alpha$ -tocopherol (**3**), we focused our research on the

development of more selective and environmentally friendly processes [2]. Polyfluorinated compounds were already involved in various approaches to accomplish this Friedel-Crafts-type alkylation reaction. Examples are scandium triflate [3] and the imide (CF<sub>3</sub>SO<sub>2</sub>)<sub>2</sub>NH [4], as well as heterogeneous solid perfluoro-alkanesulfonic acids (*i.e.* their ‘microencapsulated’ variants and Nafion NR 50) [5].

## Synthesis of Catalysts

In this communication we describe our findings when using fluorinated NH-acidic

catalysts of type **4** and CH-acidic compounds **5** for the efficient synthesis of **3** from **1** and **2**. Starting from commercially available sulfonyl halides (accessible by electrochemical fluorination), the highly air-sensitive bis[perfluoroalkyl(aryl)sulfonyl] imides **4** have been obtained *via* the sulfonamides and silyl derivatives (Scheme 2). Literature procedures [6–8] had to be adapted slightly to the individual compounds. The products were usually obtained after high-vacuum sublimation or short-path distillation from conc. H<sub>2</sub>SO<sub>4</sub>, or were isolated (*e.g.* aryl derivative **4g**) from the water-insoluble ammonium salt after use of cation exchange resin. Some of the



Scheme 1. Industrial synthesis of (all-*rac*)- $\alpha$ -tocopherol (**3**)

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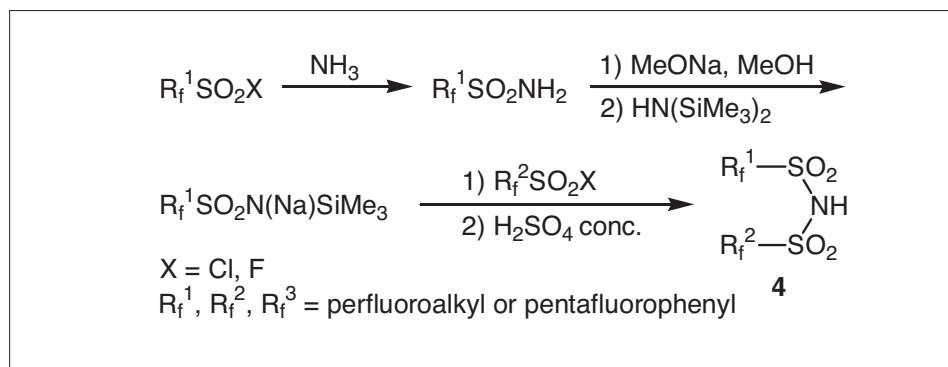
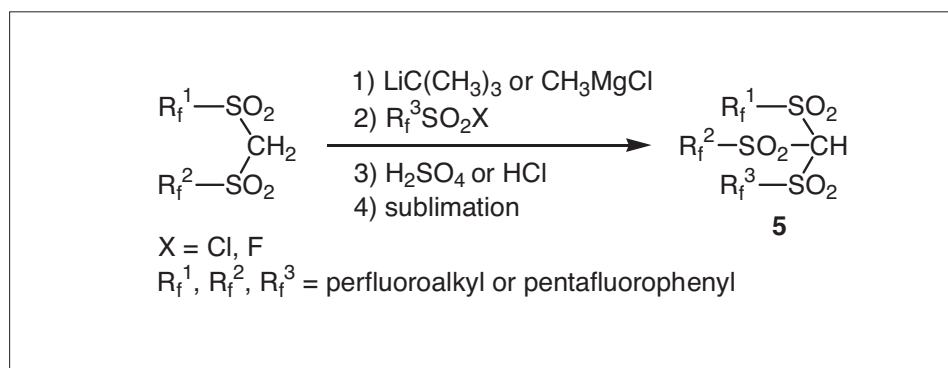

 Scheme 2. Preparation of perfluorinated imide catalysts **4**

 Scheme 3. Preparation of perfluorinated methide catalysts **5**

 Table. Results of the condensation reaction of **1** and **2** in various solvents using NH-acidic compounds of the type  $(\text{R}_f^1\text{SO}_2)(\text{R}_f^2\text{SO}_2)\text{NH}$  (**4**)

| <b>4</b> | $\text{R}_f^1$                                 | $\text{R}_f^2$                                 | Solvent system <sup>a</sup> | Crude yield <b>3</b> [%] <sup>b</sup> |
|----------|--|--|-----------------------------|---------------------------------------|
| <b>a</b> | $\text{CF}_3$                                  | $\text{CF}_3$                                  | A                           | 89.5                                  |
|          |  |  | B                           | 91.0                                  |
| <b>b</b> | $\text{CF}_3$                                  | $\text{C}_4\text{F}_9$                         | A                           | 89.6                                  |
|          |  |  | B                           | 94.0                                  |
| <b>c</b> | $\text{C}_2\text{F}_5$                         | $\text{C}_4\text{F}_9$                         | A                           | 90.2                                  |
| <b>d</b> | $\text{CF}_3$                                  | $\text{C}_6\text{F}_5$                         | C                           | 83.8                                  |
|          |  |  | D                           | 87.4                                  |
|          |  |  | E                           | 92.6                                  |
| <b>e</b> | $\text{C}_2\text{F}_5$                         | $\text{C}_2\text{F}_5$                         | B                           | 93.6                                  |
| <b>f</b> | <i>n</i> / <i>iso</i> - $\text{C}_3\text{F}_7$ | <i>n</i> / <i>iso</i> - $\text{C}_3\text{F}_7$ | B                           | 94.5                                  |
| <b>g</b> | $\text{C}_6\text{F}_5$                         | $\text{C}_6\text{F}_5$                         | B                           | 87.2                                  |
|          |  |  | E                           | 84.9                                  |
| <b>h</b> | $\text{CF}_2\text{CF}_2\text{CF}_2$            |  | B                           | 94.5                                  |
| <b>i</b> | $\text{C}_4\text{F}_9$                         | $\text{C}_4\text{F}_9$                         | E                           | 94.0                                  |
| <b>k</b> | $\text{C}_4\text{F}_9$                         | $\text{C}_6\text{F}_5$                         | E                           | 93.3                                  |
| <b>m</b> | $\text{CF}_3$                                  | $\text{C}_8\text{F}_{17}$                      | E                           | 86.4                                  |
| <b>n</b> | $\text{C}_8\text{F}_{17}$                      | $\text{C}_8\text{F}_{17}$                      | E                           | 85.6                                  |
| <b>o</b> | $\text{C}_4\text{F}_9$                         | $\text{C}_8\text{F}_{17}$                      | E                           | 91.1                                  |

<sup>a</sup>A = toluene; B = ethylene carbonate/heptane (4:5 v/v); C = diethyl ketone; D =  $\gamma$ -butyrolactone; E = propylene carbonate/heptane (4:5 v/v). <sup>b</sup>Yields based on **2** (GC analysis of crude product with internal standard). Conditions: 50 mmol **1**, 0.1 mol% **4** (based on **2**), 50 ml (one-phase) or 40 + 50 ml (two-phase) solvent, addition of 33 mmol **2** during 20 min, 100 °C, additional heating for 30 min [2].

imides **4** were commercially available [2]. Sulfonylation of bis(perfluoroalkylsulfonyl) methanes (Scheme 3) delivered the strongly acidic methides [tris(perfluoroalkylsulfonyl) methanes] **5** [9].

## Results of the Condensation Reactions

Imides **4** as well as methides **5**, used in really low catalyst amounts, yielded highly satisfying results in the condensation reaction. This applied to mildness of conditions, selectivity, and yield, which is remarkable when considering the mechanistic pathway of this transformation. In the preparation of  $\alpha$ -tocopherol (**3**) from **1** and **2** according to Scheme 1, the Friedel-Crafts alkylation reaction is followed by the chroman ring-closure step. It is of common knowledge that tertiary allylic alcohols like **2** easily dehydrate in the presence of acids [10] to form highly reactive carbocations. Therefore, the formation of considerable amounts of olefinic by-products is unavoidable in such reactions.

We were, however, pleased to find only small amounts (generally less than 4%) of phytadienes (several  $\text{C}_{20}$ -dienes) when **2** was reacted with **1** in the presence of catalytic amounts of perfluoroalkyl/aryl substituted imides **4** (0.1 mol% based on **2**). The conversion of **2** was around 99%, and yields of up to 94% (all-*rac*)- $\alpha$ -tocopherol (**3**) were obtained (Table) [2][11]. Trissulfonyl methides **5** or selected metal salts thereof gave **3** in up to 96% yield [12]. In general, two-phase solvent systems like

ethylene carbonate/heptane proved to be most effective.

In conclusion, perfluorinated NH-acidic imides **4** and CH-acidic methides **5** are excellent catalysts for the synthesis of (all-*rac*)- $\alpha$ -tocopherol (**3**) from trimethylhydroquinone (**1**) and isophytol (**2**). Best results were achieved by the application of biphasic solvent systems, *i.e.* combining the activity and selectivity of homogeneous catalysts with heterogeneous reaction media.

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