Super Lewis Acid Catalyst

Trimethylsilyl Pentafluorophenylbis(trifluoromethanesulfonyl)methide as a Super Lewis Acid Catalyst for the Condensation of Trimethylhydroquinone with Isophytol**

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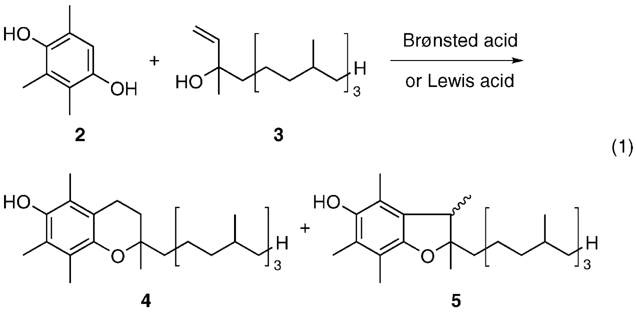
Recently, Ghosez and co-workers demonstrated that a surprising reversal of relative acidity on going from Brønsted acids to trimethylsilyl derivatives thereof could result from the difference in size between the trifluoromethanesulfonate anion (TfO^-) and the trifluoromethanesulfonimide anion (Tf_2N^-).[1] The order of Brønsted acidity is HOTf ($pK_a = -0.96$ in HOAc (Ac = acetyl)[2,3]) > $HNTf_2$ ($pK_a = 0.67$ in HOAc [2,3]),[4] whereas the order of Lewis acidity is $Me_3SiNTf_2 > Me_3SiOTf$. Me_3SiNTf_2 is a highly efficient Lewis acid catalyst for various carbon–carbon bond-forming reactions.[1,5] Our interest in a genuine silyl cation, such as Me_3SiNTf_2, prompted us to study the physical properties and catalytic efficiency of a new silicon super Lewis acid, namely, trimethylsilyl pentafluorophenylbis(trifluoromethanesulfonyl)methide $Me_3Si[C_6F_5CTf_2]$ (**1**), since the pK_a value of $C_6F_5CHTf_2$ ($pK_a = 1.5$ in HOAc[2]) is higher than that of $HNTf_2$.[6] Herein we report that **1**, which is a stronger Lewis acid than Me_3SiNTf_2, is an extremely active and highly effective catalyst for the regioselective condensation of trimethylhydroquinone (**2**) with isophytol (**3**) to afford (±)-α-tocopherol (**4**, vitamin E) [Eq. (1)].[7] The use of **1** limited the yield of byproducts (two diastereomers of dihydrobenzofuran **5**) to less than 2%. In addition, we demonstrate that the reusable super Brønsted acids polystyrene-bound 2,3,5,6-tetrafluorophenylbis(trifluoromethanesulfonyl)methane (**6**)[6a,b] and 4-(1*H*,1*H*-perfluorotetradecanoxy)-2,3,5,6-tetrafluorophenylbis(trifluoromethanesulfonyl)methane (**7**),[6c] and their trimethylsilyl derivatives are also effective for the regioselective synthesis of **4**.



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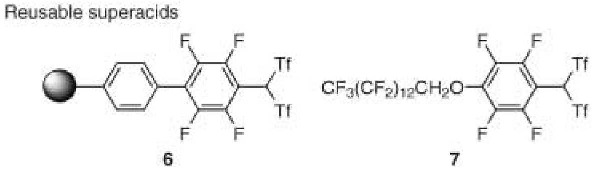

6 **7**

The new silicon superacid **1** was prepared by the protodesilylation of allyltrimethylsilane (2 equiv) with $C_6F_5CHTf_2$ (1 equiv)[8] in the absence of solvent, analogous to Me_3SiNTf_2.[1] The reaction was fast at room temperature and yielded **1** in essentially quantitative yield (0 °C to RT, 1 h). This compound could be isolated as a white solid by distillation (8 Pa, 120 °C).

Following the report of Ghosez and co-workers,[1] we used the NMR method of Childs et al.[9] to assess the Lewis acidity of **1**. This involves measuring the variation of the chemical shift of the proton in the 3-position of an α,β-unsaturated carbonyl compound on complexation with a Lewis acid. A prerequisite for this study is knowledge of the stoichiometry of the complex. Therefore, we monitored the change in the ^1H NMR spectrum of a solution of crotonaldehyde in $CDCl_3$ on successive addition of small amounts of **1**. This spectrometric titration showed a homogeneous variation in chemical shift for all of the protons up to a saturation level of slightly above 1 equivalent of **1**. Hence, the complex has 1:1 stoichiometry.

The effects of Lewis and Brønsted acids on the chemical shift of H^3 of crotonaldehyde are summarized in Table 1. The largest value of $\Delta\delta(H^3)$ for **1** shows that it is very effective in complexing crotonaldehyde. In contrast, $C_6F_5CHTf_2$ has a small value of $\Delta\delta(H^3)$. Thus, **1** is clearly a much stronger Lewis acid than Me_3SiNTf_2 and Me_3SiOTf. This is consistent with predictions based on the ^{29}Si chemical shifts of the three silicon Lewis acids. Therefore, the order of Lewis acidity is **1** > $Me_3SiNTf_2 > Me_3SiOTf$. However, the order of Brønsted acidity is $HOTf > HNTf_2 > C_6F_5CHTf_2$, as judged on the basis not only of pK_a values but also $\Delta\delta(H^3)$ values. This reversal of the acidity sequence on going from a Brønsted acid to a trimethylsilyl derivative can be easily understood by means of the hypothesis of Ghosez and co-workers.[1]

The difference in Lewis acidity between **1** and Me_3SiOTf was dramatically illustrated by their effect on the rate of cycloaddition of methyl acrylate with 1-phenyl-3-(trimethylsilyloxy)buta-1,3-diene in the presence of 2,6-di-*tert*-butyl-4-

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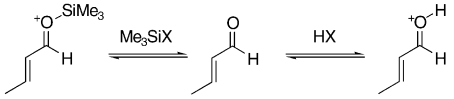
Table 1: Effect of Lewis and Brønsted acids on the chemical shifts of the H^3 proton of crotonaldehyde.[a]



HX	$\Delta\delta(H^3)$[b]	Me_3SiX [$\delta(^{29}Si)$][d]	$\Delta\delta(H^3)$[b]
$C_6F_5CHTf_2$	0.086	**1** (58.5)	1.99
$HNTf_2$	0.76 (0.46[c])	Me_3SiNTf_2 (55.9)[e]	1.74 (1.74[c])
HOTf	1.27 (1.28[c])	Me_3SiOTf (43.5)[f]	0.003 (ca. 0[c])

[a] NMR samples were prepared by mixing crotonaldehyde (0.4 mmol) and HX or Me_3SiX (0.6 mmol) in $CDCl_3$ (0.6 mL) at RT. [b] ^1H NMR shift differences of crotonaldehyde owing to its coordination to acids were downfield shifts in all cases. [c] Data from ref. [1]. [d] ^{29}Si chemical shift of Me_3SiX in $CDCl_3$ in the absence of crotonaldehyde. [e] Ref. [15]. [f] Ref. [16].

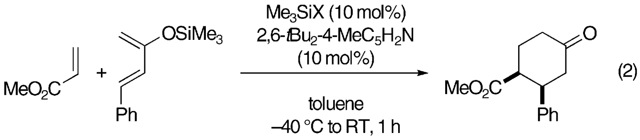
Table 2: Condensation of **2** with **3** catalyzed by silicon Lewis or Brønsted acids.[a]

$$\mathbf{2}+\mathbf{3}\xrightarrow[\text{heptane, azeotropic reflux}]{\text{HX or } Me_3SiX \text{ (10 mol\%)}}\mathbf{4}$$

HX	**4**		Me_3SiX	**4**
	Yield [%][b]	Purity [%][c]	Yield [%][b]	Purity [%][c]
$C_6F_5CHTf_2$	95	90.0	**1**[e]	97	99.2
$HNTf_2$	95	90.8	Me_3SiNTf_2[f]	94	92.5
HOTf[d]	92[d]	89[d]	Me_3SiOTf	> 79	85.9

[a] A solution of **3** (3.1 mmol) in heptane (1.0 mL) was added by syringe drive (1.3 $mL\,h^{-1}$) to a solution of a catalyst (10 mol%) and **2** (3.0 mmol) in heptane (1.5 mL) under azeotropic reflux with removal of water (bath temperature 115 °C). The reaction mixture was then stirred for an additional 2 h under the same conditions. [b] Yield of product isolated by column chromatography on silica gel. [c] Determined by GLC analysis of the isolated products. [d] Data from ref. [7c]. [e] 2,6-Di-*tert*-butylpyridine (5 mol%) was added. [f] 2,6-Di-*tert*-butylpyridine (10 mol%) was added.

methylpyridine[10] [Eq. (2)]. According to Ghosez and co-workers, Me_3SiOTf is unable to catalyze this Diels–Alder reaction, whereas Me_3SiNTf_2 acts as an excellent Lewis acid catalyst.[1] Both **1** and Me_3SiCTf_3 are highly active catalysts. Me_3SiCTf_3 was prepared from $HCTf_3$ and allyltrimethylsilane in situ, but could not be isolated by distillation since it was too unstable. Although $HCTf_3$ and Me_3SiCTf_3 are also very attractive superacids, since their counteranion is much larger than the OTf^- and NTf_2^- ions,[11] we could not assess their acidities because of their low solubility in HOAc and $CDCl_3$.[4]



1, Me_3SiCTf_3, or Me_3SiNTf_2[1]: 85~90% yield; Me_3SiOTf: 0% yield[1]

Vitamin E is the most important fat-soluble antioxidant in biological systems.[12] The most economically valuable form of vitamin E is synthetic (all-*rac*)-α-tocopherol (**4**) an equimolar mixture of all eight stereoisomers, mainly applied as its acetate derivative.[12,13] The world market for vitamin E is about 25000 t/a and is constantly growing.[14] Most industrial syntheses of **4** are based on the reaction of **2** with **3** in the presence of Brønsted or Lewis acids [Eq. (1)].

From the perspective of green and sustainable chemistry, most of these methods suffer from three major disadvantages: low catalytic activities, formation of byproduct **5**, and/or the difficulty of reusing catalysts. In particular, it is important to develop a highly regioselective condensation to give **4** in high purity, because it is difficult to separate **5** from the desired product **4**. To overcome these disadvantages, based on our earlier experimental results,[7] we examined several superacids as catalysts for the condensation of **2** with **3** under azeotropic reflux with removal of water in heptane. Representative results are shown in Table 2. All the reactions were carried out in the presence of 10 mol% of catalyst under a nitrogen atmosphere and in the dark to prevent loss of yield of **4** by oxidation of **2**. Silicon Lewis acids were used for condensation in the presence of 2,6-di-*tert*-butylpyridine instead of 2,6-di-*tert*-butyl-4-methylpyridine, because the former is a weaker Lewis base.[10] As expected, the use of **1** afforded **4** in high yield, as did Me_3SiNTf_2. Similar catalytic activity was observed with the corresponding Brønsted acids. It is noteworthy that **4** was obtained in 99.2% purity only in the condensation catalyzed by **1**. In contrast, the purity of **4** was about 90% in other cases.

To optimize the reaction conditions, catalysts and additives were investigated in more detail (Table 3). In the presence of 2,6-di-*tert*-butylpyridine, decreasing the amount of **1** to less than 10 mol% dramatically lowered the yield of **4**, but its purity remained above 98%. However, the condensation proceeded smoothly with 0.5 mol% of **1** in the presence of 2 mol% of methallyltrimethylsilane instead of a hindered base, and gave **4** in 89% yield and 98.1% purity. Methallyltrimethylsilane was added to transform residual $C_6F_5CHTf_2$ into **1**. Surprisingly, the use of a combination of $HCTf_3$ and methallyltrimethylsilane was slightly superior to **1**.

Table 3: Effects of additives on the condensation of **2** with **3** catalyzed by silicon Lewis or Brønsted acids.[a]

$$\mathbf{2}+\mathbf{3}\xrightarrow[\text{heptane, azeotropic reflux}]{Me_3SiX + \text{additive}}\mathbf{4}$$

		4	
Me_3SiX or HX (mol%)	Additive (mol%)	Yield [%]	Purity[b] [%]
1 (1)	2,6-$tBu_2C_5H_3N$ (1)	58	98.3
1 (0.5)	$CH_2{=}CMeCH_2SiMe_3$ (2)	89	98.1
1 (0.5)	none	81	98.0
$HCTf_3$ (0.5)	$CH_2{=}CMeCH_2SiMe_3$ (2.5)	98	98.7
$HCTf_3$ (0.5)	none	93	98.2

[a] Unless otherwise noted, the reaction (6 mmol scale) was carried out by the same procedure as in Table 2. [b] Determined by GLC analysis of the isolated products.

Finally, we examined reusable superacids **6** (1.01 mmol $Tf_2CHC_6F_4$ units per gram of polystyrene resin) and **7** for the condensation of **2** with **3** (Table 4). Both superacids were effective for the condensation, and their regioselectivities were slightly improved by adding methallyltrimethylsilane. Solid catalyst **6** was easily recovered in quantitative yield by filtration after the reaction, and there was no decrease in yield

Table 4: Condensation of **2** with **3** catalyzed by reusable super Brønsted or Lewis acids.[a]

$$\mathbf{2}+\mathbf{3}\xrightarrow[\text{heptane, azeotropic reflux}]{\text{HX (5 mol\%) CH}_2\text{=CMeCH}_2\text{SiMe}_3}\mathbf{4}$$

Entry	HX	Methallyltrimethylsilane [mol %]	**4**		Recovery [%] of HX
			Yield [%]	Purity [%][b]	
1[c]	**6**	25	81	97.6	> 95
2 (1st run)	**6**	0	82	96.5	> 95
3 (2nd run)[d]	**6**	0	83	96.0	> 95
4	**7**	25	86	98.2	77

[a] Unless otherwise noted, the reaction (3 mmol scale) was carried out by the same procedure as in Table 2. [b] Determined by GLC analysis of the isolated products. [c] The mixture of HX and methallyltrimethylsilane was stirred at 40°C for 1 h to prepare Me_3SiX in situ before adding heptane, **2**, and **3**. [d] The reaction was carried out with **6** recovered from the first run (entry 2).

in consecutive reaction cycles with recovered catalyst **6** (entries 2 and 3). Fluorous catalyst **7** prompted the condensation and subsequent acetylation to give the acetate of **4** and was recovered in 77 % yield by extraction with perfluoromethylcyclohexane. The polymer-bound catalyst **6** gave higher regioselectivity in the condensation than $C_6F_5CHTf_2$, probably because the polymeric anion is much bulkier than $C_6F_5C^-Tf_2$.

In conclusion, trimethylsilyl super Lewis acids are superior to the corresponding super Brønsted acids with respect to both catalytic activity and regioselectivity in the condensation of **2** with **3**. In particular, bulkier anions in superacids greatly contributed to improved regioselectivity: hindered anions such as $C_6F_5C^-Tf_2$ and $^-CTf_3$ were more effective than $^-NTf_2$ and ^-OTf. Furthermore, high catalytic activities, high regioselectivity, and recycling of catalysts by using reusable superacids, such as **6** and **7**, were achieved.

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