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Lanthanide Trifluoromethanesulfonates as Stable Lewis Acids in Aqueous Media. Yb(OTf)3 Catalyzed Hydroxymethylation Reaction of Silyl Enol Ethers with Commercial Formaldehyde Solution

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Silyl enol ethers smoothly react with commercial formaldehyde solution to give the corresponding hydroxymethylated adducts in high yields by the promotion of a catalytic amount of ytterbium(III) triflate ($Yb(OTf)_3$), which is a stable Lewis acid in aqueous media. Other lanthanide triflates are also found to be effective.

Formaldehyde is a versatile reagent as one of the most highly reactive C1 electrophiles in organic synthesis.[1)] Dry gaseous formaldehyde required for many reactions has some disadvantages because it must be generated before use from solid polymer paraformaldehyde by way of the thermal depolymerization and it is easy to self-polymerize.[2)] On the other hand, commercial formaldehyde solution, which is an aqueous solution containing 37% of formaldehyde and 8-10% of methanol, is cheap, easy to handle, and stable even at room temperature, however the use of this reagent is strongly restricted due to the existence of a large amount of water; for example, common Lewis acids or organometallics, etc. cannot be employed. In this communication, we would like to report the hydroxymethylation reaction of silyl enol ethers with commercial formaldehyde solution as formaldehyde source by using an unprecedented unique catalyst, a lanthanide trifluoromethanesulfonate (lanthanide triflate), especially ytterbium(III) triflate ($Yb(OTf)_3$, $Tf=CF_3SO_2$), which is a stable Lewis acid in aqueous media.

We searched for some Lewis acids which can activate formaldehyde in aqueous solution and found that lanthanide triflates,[3),4)] prepared from the corresponding lanthanide oxides (La_2O_3) and trifluoromethanesulfonic acid,[5)] were quite effective for the hydroxymethylation reaction of silyl enol ethers.[6)] The reaction was most effectively carried out in commercial formaldehyde solution-THF media[7)] under the influence of 5-10 mol% of $Yb(OTf)_3$. Following is a typical experimental procedure; to commercial formaldehyde solution[8)] (1 ml) and THF (3 ml) were successively added $Yb(OTf)_3$ (0.04 mmol, 10 mol%) and a silyl enol ether (0.4 mmol) in THF (1 ml) at rt. The mixture was stirred for 24 h at this temperature and then THF was removed under reduced pressure. Water was added and the product was extracted with dichloromethane. After usual work up, the crude product was chromatographed on silica gel to yield the pure hydroxymethylated adduct. $Yb(OTf)_3$ is almost quantitatively recovered from aqueous layer and can be reused.

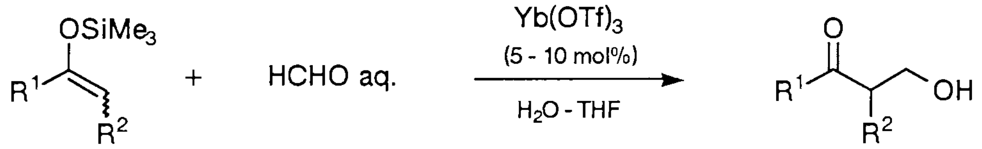
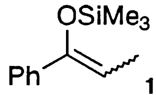
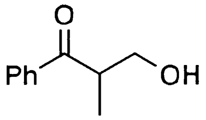
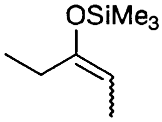
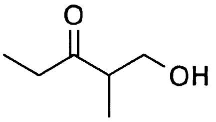
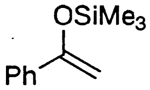
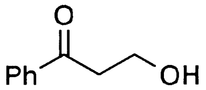
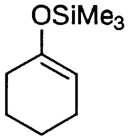
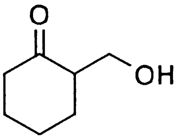
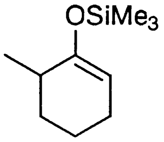
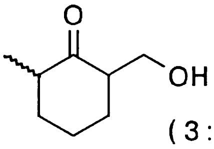
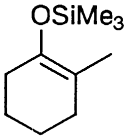
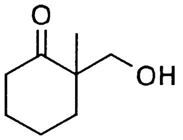
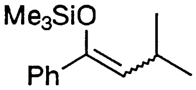
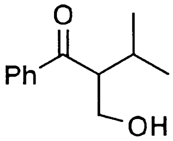
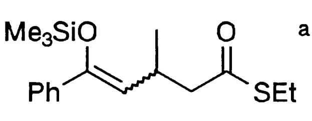
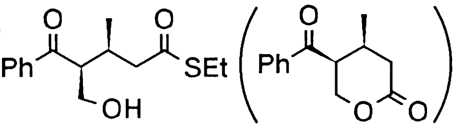
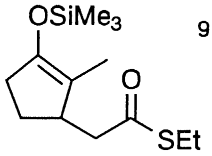
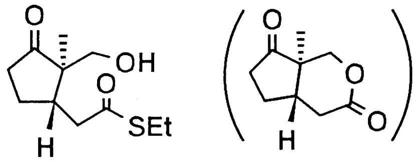
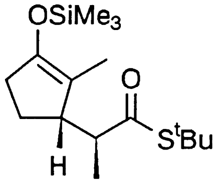
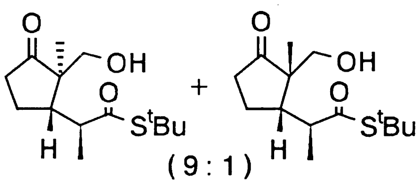


Table 1. Reaction of Silyl Enol Ethers with Commercial Formaldehyde Solution Catalyzed by Yb(OTf)$_3$

Entry	Silyl enol ether	Product	Yield/%
1	 1 a)		94
2	 b)		85
3			77
4			82
5		 (3 : 2)	86
6			92
7	 a)		92
8	 a), 9)	 c)	88
9	 9)	 d)	83
10	 9)	 (9 : 1)	90

a) Z/E=>98/2. b) Z/E=1/4. c) The mixture of the hydroxy thioester and the lactone (2:1) was obtained. d) The mixture of the hydroxy thioester and the lactone (3:1) was obtained. Less than 3% yield of the other diastereoisomers were observed.

Several examples are listed in Table 1, and the following characteristic features of this reaction are noted. (1) In every case, the reactions smoothly proceed under extremely mild conditions (almost neutral) to give the corresponding hydroxymethylated adducts in high yields. Sterically hindered silyl enol ethers (entries 6-10) also work well and the diastereoselectivities are high. (2) Di- and poly-hydroxymethylated products were not observed.[10] (3) The absence of equilibrium (double bond migration) in silyl enol ethers allows for the regiospecific hydroxymethylation reaction (entry 5). (4) Only a catalytic amount of $Yb(OTf)_3$ is required to complete the reaction. The amount of the catalyst was examined by taking the reaction of the silyl enol ether derived from propiophenone (**1**) with commercial formaldehyde solution as a model, and the reaction was found to be catalyzed by even 1 mol% of $Yb(OTf)_3$; 1 mol% (90% yield); 5 mol% (90% yield); 10 mol% (94% yield); 20 mol% (94% yield); 100 mol% (94% yield). (5) Almost 100% of $Yb(OTf)_3$ is quite easily recovered from the aqueous layer after the reaction has completed and it can be reused. 1st use (20 mol%) in the reaction of **1** (94% yield); 2nd use (91% yield); 3rd use (93% yield). (6) Finally, it is noteworthy to refer that the present reaction can be smoothly carried out in aqueous media (water does not interfere with this reaction).

The efficient hydroxymethylation reaction by use of formaldehyde solution[11] described here strongly depends on the unique characters of lanthanide triflates. While most Lewis acids are decomposed or deactivated under the influence of water, lanthanide triflates are stable even in aqueous media and efficiently activate formaldehyde solution as Lewis acids. Effects of some selected lanthanide triflates in the reaction of **1** with commercial formaldehyde solution are shown in Table 2. In most cases, the reactions smoothly proceed to give the corresponding adduct in high yields. Further progress to develop other synthetic reactions utilizing the unique characters of lanthanide triflates is now investigated.

Table 2. Effect of Lanthanide Triflates in the Reaction of **1** with Commercial Formaldehyde Solution

Entry	$Ln(OTf)_3$	Yield/% 100 mol% 24 h	 1 h	 20 mol% 36 h
1	$La(OTf)_3$	90	23	88
2	$Pr(OTf)_3$	92	40	80
3	$Nd(OTf)_3$	74	6	89
4	$Sm(OTf)_3$	92	51	91
5	$Eu(OTf)_3$	92	28	93
6	$Gd(OTf)_3$	92	20	79
7	$Dy(OTf)_3$	89	20	85
8	$Ho(OTf)_3$	91	38	86
9	$Er(OTf)_3$	90	44	83
10	$Yb(OTf)_3$	94	5	94

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