

The Aldol Reaction of Silyl Enol Ethers with Aldehydes in Aqueous Media

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Abstract: The aldol reaction of silyl enol ethers with aldehydes is successfully carried out in aqueous media by using a lanthanide trifluoromethanesulfonate as a catalyst. Water soluble aldehydes are applicable and the catalyst can be recovered and reused in this reaction.

The titanium tetrachloride-mediated aldol reaction of silyl enol ethers with aldehydes was first reported in 1973.¹⁾ The reaction is notably distinguished from the conventional aldol reactions carried out under basic conditions; it proceeds in a highly regioselective manner to afford cross aldols in high yields.²⁾ Since this pioneering effort, several efficient activators such as trityl salts,³⁾ Cray montmorillonite,⁴⁾ fluoride anions,⁵⁾ etc. have been developed to realize high yields and selectivities, and now the reaction is considered as one of the most important carbon-carbon bond forming reactions in organic synthesis.

These reactions are usually carried out under strictly nonaqueous conditions. The presence of even a small amount of water causes lower yields probably due to the rapid decomposition or deactivation of the promoters and the hydrolysis of the silyl enol ethers. Only one exception is the water-promoted aldol reaction of silyl enol ethers with aldehydes reported by Lubineau and Meyer,⁶⁾ however, the yields and the substrate scope were not yet satisfactory.

Recently we have found that lanthanide trifluoromethanesulfonates (lanthanide triflates) are stable Lewis acids in water. The reaction of silyl enol ethers with commercial formaldehyde solution smoothly proceeds in aqueous media by using a catalytic amount of lanthanide triflate, especially ytterbium(III) triflate ($\text{Yb}(\text{OTf})_3$), to give the corresponding hydroxymethylation adducts in high yields.⁷⁾ In the course of our investigations to explore the unique character of lanthanide triflates, we found that they also effectively activated a wide variety of aldehydes other than formaldehyde. In this communication, we would like to report the aldol reaction of silyl enol ethers with aldehydes in aqueous media using a lanthanide triflate as a catalyst.⁸⁾

Effect of solvents in the model reaction of 1-trimethylsilyloxycyclohexene with benzaldehyde under the influence of a catalytic amount of $\text{Yb}(\text{OTf})_3$ (10 mol%) are shown in Table 1. Under these conditions, the reaction proceeded faster in aqueous media than in organic solvents such as dichloromethane, acetonitrile, THF. Among several lanthanide triflates screened, neodymium triflate ($\text{Nd}(\text{OTf})_3$), gadolinium triflate ($\text{Gd}(\text{OTf})_3$), $\text{Yb}(\text{OTf})_3$, or lutetium triflate ($\text{Lu}(\text{OTf})_3$) was quite effective, while the yield of the desired aldol adduct was lower in the presence of lanthanum triflate ($\text{La}(\text{OTf})_3$), praseodymium triflate ($\text{Pr}(\text{OTf})_3$) or thulium triflate ($\text{Tm}(\text{OTf})_3$).

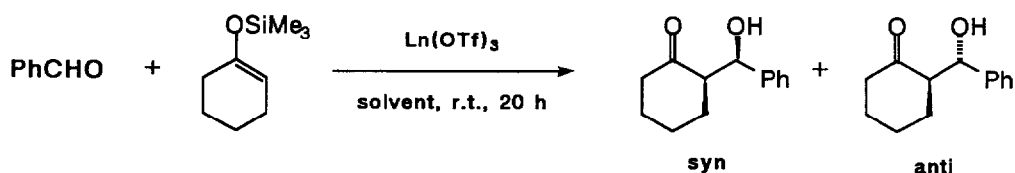


Table 1. Effect of Solvent ($\text{Ln}(\text{OTf})_3$: $\text{Yb}(\text{OTf})_3$)

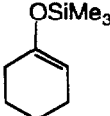
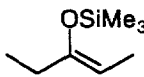
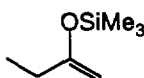
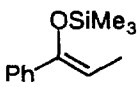
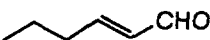


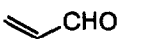
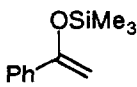
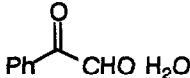
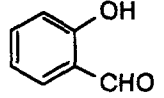
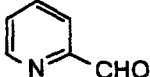
| Solvent | Yield / % | syn/anti |
|---|-----------|----------|
| CH_2Cl_2 | 10 | — |
| THF | 10 | — |
| CH_3CN | 5 | — |
| DMF | 56 | 73 / 27 |
| $\text{H}_2\text{O} - \text{THF} (1:4)$ | 91 | 73 / 27 |

Table 2. Effect of Lanthanide Triflate (solvent: $\text{H}_2\text{O} - \text{THF} (1:4)$)

| $\text{Ln}(\text{OTf})_3$ | Yield/% | syn/anti | $\text{Ln}(\text{OTf})_3$ | Yield/% | syn/anti |
|---------------------------|---------|----------|---------------------------|---------|----------|
| $\text{La}(\text{OTf})_3$ | 8 | — | $\text{Dy}(\text{OTf})_3$ | 73 | 68 / 32 |
| $\text{Pr}(\text{OTf})_3$ | 28 | 72 / 28 | $\text{Ho}(\text{OTf})_3$ | 47 | 72 / 28 |
| $\text{Nd}(\text{OTf})_3$ | 83 | 68 / 32 | $\text{Er}(\text{OTf})_3$ | 52 | 62 / 38 |
| $\text{Sm}(\text{OTf})_3$ | 46 | 74 / 26 | $\text{Tm}(\text{OTf})_3$ | 20 | 75 / 25 |
| $\text{Eu}(\text{OTf})_3$ | 34 | 64 / 36 | $\text{Yb}(\text{OTf})_3$ | 91 | 73 / 27 |
| $\text{Gd}(\text{OTf})_3$ | 89 | 77 / 23 | $\text{Lu}(\text{OTf})_3$ | 88 | 78 / 22 |

Several examples of the present aldol reaction of silyl enol ethers with aldehydes are listed in Table 3. In every case, the aldol adducts are obtained in high yields in the presence of a catalytic amount of $\text{Yb}(\text{OTf})_3$, $\text{Gd}(\text{OTf})_3$, or $\text{Lu}(\text{OTf})_3$. Diastereoselectivities are generally moderate. One of the most characteristic points in the present reaction is that water soluble aldehydes, for instance, acetaldehyde, acrolein, chloroacetaldehyde can

Table 3. Lanthanide Triflate Catalyzed Aldol Reaction

| Entry | Aldehyde | Silyl Enol Ether | Catalyst | Yield/% | syn/anti ^{a)} |
|-------|--|--|----------------------|---------|------------------------|
| 1 | PhCHO |  1 | Yb(OTf) ₃ | 91 | 73 / 27 |
| 2 | PhCHO |  2Z | Yb(OTf) ₃ | 89 | 63 / 27 |
| 3 | PhCHO |  2E | Yb(OTf) ₃ | 93 | 71 / 29 |
| 4 | PhCHO |  3 | Yb(OTf) ₃ | 81 | 53 / 47 |
| 5 | p-Cl PhCHO | 1 | Yb(OTf) ₃ | 89 | 65 / 35 |
| 6 | p-MeO PhCHO | 1 | Yb(OTf) ₃ | 77 | 61 / 39 |
| 7 |  CHO | 1 | Yb(OTf) ₃ | 90 | 55 / 45 |
| 8 |  CHO | 2Z | Yb(OTf) ₃ | 79 | 65 / 35 |
| 9 |  CHO | 2E | Yb(OTf) ₃ | 72 | 68 / 32 |
| 10 | CH ₃ CHO | 3 | Gd(OTf) ₃ | 93 | 46 / 54 |
| 11 |  CHO | 3 | Gd(OTf) ₃ | 82 | 60 / 40 |
| 12 | Cl-CH ₂ CHO | 3 | Yb(OTf) ₃ | 95 | 45 / 55 |
| 13 | Cl-CH ₂ CHO |  | Yb(OTf) ₃ | 67 | — |
| 14 |  CHO H ₂ O | 3 | Yb(OTf) ₃ | 67 | 27 / 73 |
| 15 |  CHO | 3 | Lu(OTf) ₃ | 81 | 55 / 45 |
| 16 |  CHO | 3 | Lu(OTf) ₃ | 87 | 42 / 58 |

a) Determined by ¹H NMR.

be allowed to react with silyl enol ethers to afford the corresponding cross aldol adducts in high yields (entries 10-13). Some of these aldehydes are commercially supplied as water solutions and are appropriate for direct use. Phenylglyoxal monohydrate also works well (entry 14). It is known that water often interferes with the aldol reaction of metal enolates with aldehydes and that in the cases where such water soluble aldehydes are employed, some troublesome purifications including dehydration are necessary. Furthermore, salicylaldehyde (entry 15) and 2-pyridinecarboxaldehyde (entry 16) can be successfully employed. The former has a free hydroxy group which is incompatible with metal enolates or Lewis acids, and the latter is generally difficult to use under the influence of Lewis acids because of the coordination of the nitrogen atom to the Lewis acids resulting in the deactivation of the acids.

Another important feature of this reaction is that the catalyst can be easily recovered from the aqueous layer after the reaction is completed and can be reused (see, the following experimental procedure).

A typical experimental procedure is described for the reaction of the silyl enol ether of propiophenone 3 with benzaldehyde; to a Yb(OTf)₃ (0.04 mmol, 10 mol%) solution (THF:H₂O=2:1, 1.5 ml) was added a mixture of 3 (0.44 mmol) and the aldehyde (0.4 mmol) in THF (1 ml) at r.t. The mixture was stirred for 20 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 aldol adduct (81%, syn/anti=53/47). Yb(OTf)₃ can be almost quantitatively recovered from the aqueous layer⁹) and can be reused (2nd use; 83%, syn/anti=53/47).

Further investigations to develop new synthetic reactions using lanthanide triflates as catalysts are now in progress.

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- 9) No hydrolysis of Ln(OTf)₃ was observed under the present reaction conditions. It was also confirmed that trifluoromethanesulfonic acid (TfOH) could not promote the aldol reaction of silyl enol ethers with aldehydes in aqueous media. Only hydrolysis of the silyl enol ethers occurred and no product was obtained after examinations of several concentrations of TfOH.

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