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One-pot Synthesis of β-Amino Esters from Aldehydes Using Lanthanide Triflate as a Catalyst

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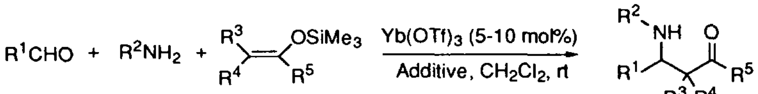
Abstract: One-pot synthesis of a β-amino ester from an aldehyde, an amine, and a silyl enolate has been achieved using a lanthanide triflate as a catalyst. One-pot preparation of a β-lactam from an aldehyde is also described.

The Lewis acid-catalyzed reactions of imines with silyl enolates are one of the most efficient methods for the preparation of β-amino esters.[1] Although the reactions generally require a stoichiometric amount of a Lewis acid such as $TiCl_4$,[2] a small amount of TMSOTf,[3] a diphosphonium salt,[4] FeI_2,[5] a trityl salt,[5] montmorillonite,[6] or $B(C_6F_6)_3$[7] promotes the reactions catalytically. On the other hand, many imines are hygroscopic, unstable at high temperatures, and difficult to purify by distillation or column chromatography. It is desirable from a synthetic point of view that imines, generated *in situ* from aldehydes and amines, immediately react with silyl enolates and provide β-amino esters in a one-pot reaction. However, most Lewis acids can not be used in this reaction because they decompose or deactivate in the presence of the amines and water that exist during imine formation.

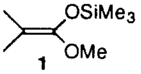
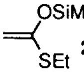
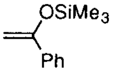
Recently, we found that rare earth metal triflates such as ytterbium triflate ($Yb(OTf)_3$) and scandium triflate ($Sc(OTf)_3$) effectively activate imines.[8] These triflates are stable in water and can be recovered after the reactions are completed and reused.[9] Moreover, they can be used for the activation of nitrogen-containing compounds, which deactivate most Lewis acids.[10] Judging from these unique properties of lanthanide triflates, we planned to use them as catalysts for the above one-pot preparation of β-amino esters from aldehydes.

A general scheme of the one-pot synthesis of β-amino esters from aldehydes is shown in Scheme 1. In the presence of a catalytic amount of ytterbium triflate ($Yb(OTf)_3$, a representative lanthanide triflate) and an additive (a dehydrating reagent such as MS 4A or $MgSO_4$), an aldehyde was treated with an amine and then with a silyl enolate in the same vessel. Several examples are shown in Tables 1 and 2, and the following characteristic features of this reaction are noted. (1) In every case, β-amino esters were obtained in high



Scheme 1.

Table 1. One-pot Synthesis of β-Amino Esters from Aldehydes

Entry	R^1	R^2	Silyl enolate	Additive[a)]	Yield/%
1	Ph	Ph	 **1**	MS4A $MgSO_4$	90 89
2	Ph	Bn	**1**	MS4A	85
3	Ph	p-MeOPh	**1**	$MgSO_4$	91 [b)]
4	Ph	o-MeOPh	**1**	MS4A	96
5	Ph	Ph	 **2**	MS4A	90
6	Ph	Bn	**2**	MS4A	62 [b)]
7	Ph	p-MeOPh	**2**	MS4A	79 84,[b)] 87 [b,c)]
8	Ph	C_4H_9	**1**	MS4A	89
9	PhCO [d)]	Ph	**1**	$MgSO_4$	82
10	PhCO [d)]	Ph		$MgSO_4$	87
11	PhCH=CH	p-MeOPh	**1**	$MgSO_4$	92 [e)]
12	$Ph(CH_2)_2$	Bn	**1**	$MgSO_4$	83 [f)]
13	C_4H_9	Bn	**1**	$MgSO_4$	77 [f)]
14	C_8H_{17}	Bn	**1**	$MgSO_4$	81 [f)]
15	C_8H_{17}	Ph_2CH	**1**	$MgSO_4$	89 [g)]

a) MS4A or $MgSO_4$ was used. Almost comparable yields were obtained in each case. b) CH_3CN was used as a solvent. c) $Sc(OTf)_3$ was used instead of $Yb(OTf)_3$. d) Monohydrate. e) C_2H_5CN, -78 °C. f) -78 °C to 0 °C. g) 0 °C.

yields.[11] Silyl enolates derived from esters as well as thioesters reacted smoothly to give the adducts. No adducts between aldehydes and the silyl enolates were observed in any reaction. (2) A silyl enol ether derived from a ketone also worked well to afford the β-amino ketone in a high yield (Table 1, entry 10). (3) Aliphatic aldehydes reacted with amines and silyl enolates to give the corresponding β-amino esters in high yields. In some reactions of imines, it is known that aliphatic enolizable imines prepared from aliphatic aldehydes gave poor results.[1] (4) Phenylglyoxal monohydrate also worked well in this reaction. The imine derived from phenylglyoxal is unstable and a troublesome treatment is known to be required for its use.[12] (5) The catalyst could be recovered after the reaction was completed and could be reused (1st run, 91%; 2nd run, 92%, in the reaction of benzaldehyde, p-anisidine, and silyl enolate **1** (Table 1, entry 3)). (6) As for the diastereoselectivity of this reaction, good results were obtained after examination of the reaction conditions. While *anti*-adducts were produced preferentially in the reactions of benzaldehyde, *syn*-adducts were obtained with high selectivities in the reactions of aliphatic aldehydes (Table 2). (7) The high yields of the present one-pot reactions depend on the unique properties of lanthanide triflates as the Lewis acid catalysts. Although $TiCl_4$ and TMSOTf are known to be effective for the activation of imines,[2,3] the use of even stoichiometric

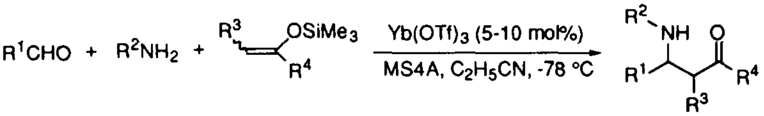
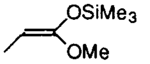
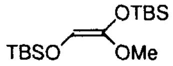
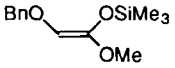
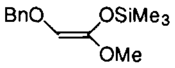
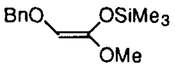


Table 2. Diastereoselective One-pot Synthesis of β-Amino Esters from Aldehydes

Entry	R^1	R^2	Silyl enolate	Yield/%	*syn* / *anti*[a]
1	Ph	Bn		90	1 / 13.3
2	Ph	Bn		78	1 / 9.0
3	$Ph(CH_2)_2$	Ph_2CH		88	8.1 / 1
4	C_4H_9	Ph_2CH		90	8.1 / 1
5	$(CH_3)_2CHCH_2$	Ph_2CH		86	7.3 / 1

a) Determined by ^1H NMR analysis.

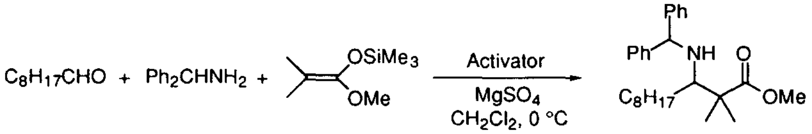
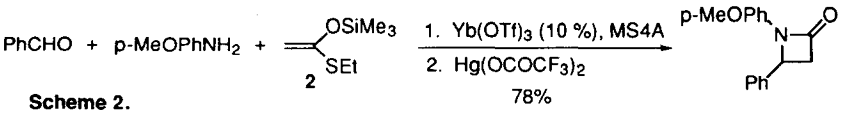


Table 3. Effect of Catalysts

Entry	Activator		Yield (%)
1	$Yb(OTf)_3$	10 mol%	89
2	$TiCl_4$	100 mol%	trace
3	TMSOTf	100 mol%	trace

amounts of $TiCl_4$ and TMSOTf instead of lanthanide triflate in the present one-pot reactions gave only trace amounts of the product in both cases (Table 3). (8) One-pot preparation of a β-lactam from an aldehyde, an amine, and a silyl enolate has been achieved based on the present reaction (Scheme 2). The reaction of the aldehyde, the amine, and 2 was carried out under the standard conditions, and $Hg(OCOCF_3)_2$ was then added to the same pot. The desired β-lactam was isolated in a 78% yield.



Scheme 2.

In summary, the one-pot synthesis of β-amino esters from aldehydes has been achieved by using lanthanide triflate catalysis. The high efficiency using simple starting materials and a catalytic amount of a reusable catalyst is especially noteworthy. Further studies to apply the present method to the synthesis of natural products as well as to develop new synthetic reactions using rare earth metal triflates are now in progress.

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9) Kobayashi, S. *Synlett.* **1994**, 689.
10) Kobayashi, S.; Hachiya, I. *J. Org. Chem.* **1994**, *59*, 3590.
11) A typical experimental procedure is as follows: To a suspension of $Yb(OTf)_3$ (0.04 mmol, 10%) and MS 4A or $MgSO_4$ (125 mg) in CH_2Cl_2 (1 ml) were added an aldehyde (0.4 mmol) in CH_2Cl_2 (0.5 ml) and an amine (0.4 mmol) in CH_2Cl_2 (0.5 ml) at room temperature. The mixture was stirred for 0.5 h and a silyl enolate (0.44 mmol) in CH_2Cl_2 (0.5 ml) was added to the same pot. After the mixture was further stirred for 3 h, water was added and the product was extracted with dichloromethane. After the organic layer was dried and evaporated, the crude product was chromatographed on silica gel to afford the β-amino ester. The catalyst was quantitatively recovered from the aqueous layer and could be reused for further runs. We tested other lanthanide triflates such as $Er(OTf)_3$, $Tm(OTf)_3$, etc. and found that they were also effective.
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