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Preparation of a New Asymmetric Lanthanoid Complex Catalyst for the Mukaiyama Aldol Reaction

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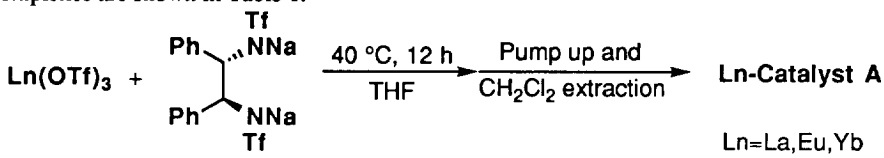
Abstract: Several chiral Lewis acid catalysts were prepared from lanthanoid trifluoromethanesulfonate (triflate) and a chiral sulfonamide ligand, and were applied to the Mukaiyama aldol reaction. The reaction proceeded in a catalytic manner with moderate enantiomeric excess.

Lanthanoid reagents are attracting much attention recently because of their potential ability in organic synthesis.[1] Especially of interest is their use in catalytic asymmetric reactions. Although many asymmetric catalysts of various metal species have been developed, there are only a few reports on successful catalytic asymmetric C-C bond forming reactions catalyzed by a lanthanoid complex. We have developed so far catalytic asymmetric nitroaldol[2] and Michael reactions[3] utilizing the basic character of lanthanoid complexes. From the course of our investigations on lanthanoid chemistry, herein we describe our preliminary results on the development of a Lewis acid chiral lanthanoid complex applicable to the Mukaiyama aldol reaction.

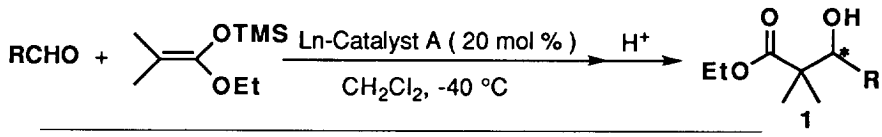
It is known that lanthanoid reagents can be used as a Lewis acid catalyst and in some cases chiral complexes such as NMR chiral shift reagent Eu(hfc)3, Eu(fod)3[4,5] and samarium(II) menthoxide[6] have been applied. But with the exception of Kobayashi's recent report on asymmetric Diels-Alder reaction catalyzed by a chiral ytterbium complex,[7] high enantiomeric excess have not been obtained and there is no report on successful asymmetric Mukaiyama aldol reaction[8] catalyzed by a lanthanoid complex. Moreover the structure of the complexes is generally uncertain. We feel that the development of more efficient Lewis acid lanthanoid catalysts and further studies to fully understand lanthanoid chemistry are necessary.

A chiral lanthanoid catalyst was prepared by reacting equimolar amounts of lanthanum triflate[9] and a chiral bidentate ligand bistriflamide of (1*S*, 2*S*)-1, 2-diphenylethylenediamine[10, 11] (deprotonated with excess of NaH) in THF for 12 h (Scheme 1). This catalyst was first applied to the reaction between benzaldehyde and ketene silyl acetal derived from ethyl isobutyrate. In THF, this complex did not exhibit any catalytic activity for the reaction. After investigating some other solvents for the reaction, dichloromethane proved to be most satisfactory. Hence the catalyst-THF solution was evaporated *in vacuo*, and the residue was extracted with dichloromethane. In this dichloromethane solution, the aldol reaction proceeded in a catalytic manner using 20 mol % catalyst.[12] Eu and Yb catalyst were also prepared by this method from Eu(OTf)3 and Yb(OTf)3, respectively. Results of the reactions between some aldehydes and ketene silyl acetal catalyzed by these complexes are shown in Table 1.



Scheme 1

Table 1. Mukaiyama aldol reaction catalyzed by lanthanoid complexes



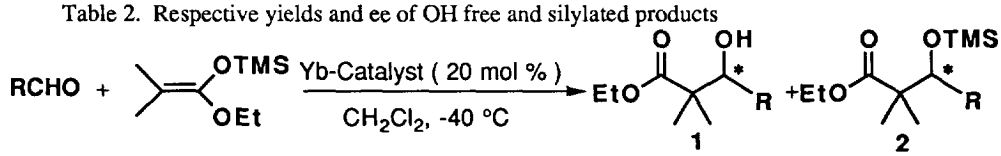
	Ln-Catalyst A		
	La	Eu	Yb
RCHO	Yield % (ee)	Yield % (ee)	Yield % (ee)
PhCHO	42 (47)	59 (40)	71 (33)
p-NO_2PhCHO	86 (41)	92 (40)	98 (44)
$PhCH_2CH_2CHO$	19 (39)	34 (39)	55 (40)

All the La, Eu and Yb catalysts gave the products in about 40% ee. However the reactivity was dependent on the lanthanoid metal species employed. In general, yields decreased from Yb, Eu to La. Especially in the reaction of hydrocinnamaldehyde with ketene silyl acetal catalyzed by La complex, only OH free product was observed and no silylated product was observed on TLC. In every other case both OH free aldol adduct and silylated adduct were observed. To accomplish a catalytic cycle, it is necessary that the intermediate lanthanoid alkoxide should be silylated and the silylated product should be formed. Thus the difference in the reactivity among La, Eu and Yb complexes may reflect the reactivity of the corresponding metal alkoxide intermediate towards silylation.

Further studies were carried out using the Yb catalyst which originally gave the best yields. In this catalyst system, it is possible that trimethylsilyl triflate is formed during the reaction and it actually catalyzes the reaction.[13] Since trimethylsilyl triflate catalyzed reaction gives the product predominantly in silylated form, silylated product may show lower ee than OH free product when achiral trimethylsilyl triflate catalyzed reaction coexists. To investigate this possibility, OH free product **1** and silylated product **2** were separated by silica gel column chromatography before desilylation and ees of the both products were determined respectively (Table 2). In the case of benzaldehyde, silylated product **2** exhibited a lower ee than the OH free product **1** (Entry 1). This result suggests that the trimethylsilyl triflate catalyzed reaction exists in this case. To minimize the decrease of the silylated product's ee, slow addition of substrate (ketene silyl acetal) using a syringe pump technique was carried out. By this procedure, the ee was improved to 49% ee, with both silylated product and OH free product having comparable ee (Entry 2). In contrast with *p*-nitrobenzaldehyde as substrate, OH free product and silylated product showed the same level of ee without use of syringe pump technique (Entry 3) and hence ee was not affected by slow addition procedure (Entry 4). *p*-Methoxybenzaldehyde exhibited different results. The silylated product was almost racemic whereas the OH free product had 29% ee. The syringe pump technique was not so effective as in the case of benzaldehyde. Thus whether the trimethylsilyl triflate catalyzed reaction exists or not seems to depend on the substrate employed.[14]

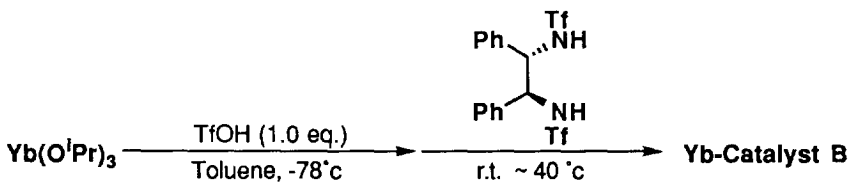
Finally, another approach to the preparation of catalyst was investigated (Scheme 2). To a toluene solution of $Yb(O^iPr)_3$[15] was added 1 equiv. of trifluoromethanesulfonic acid (TfOH) at -78 °C followed by 1 equiv. of ligand at room temperature. This solution was further stirred for 12 h at 40 °C. After removal of the solvent under reduced pressure, dichloromethane was added and the supernatant was used for the reaction (Table 2, Entry 7, 8). This catalyst gave comparable results to those obtained from reactions catalyzed by $Yb(OTf)_3$ derived complex. Although structure of the complexes are unknown, we postulate that the same type of complexes are formed from each catalyst preparation method.

Table 2. Respective yields and ee of OH free and silylated products



Entry	RCHO	Catalyst[a)]	OH free product 1 Yield % (ee)	Silylated product 2 Yield % (ee)	Total Yield % (ee)
1	PhCHO	A	16 (41)	55 (31)	71 (33)
2	PhCHO[b)]	A	41 (51)	43 (48)	84 (49)
3	*p*-NO_2PhCHO	A	5 (42)	93 (44)	98 (44)
4	*p*-NO_2PhCHO[b)]	A	35 (41)	58 (41)	93 (41)
5	*p*-MeOPhCHO	A	16 (29)	39 (1)	55 (9)
6	*p*-MeOPhCHO[b)]	A	20 (42)	16 (8)	36 (27)
7	PhCHO	B	27 (44)	55 (17)	82 (26)
8	PhCHO[b)]	B	36 (44)	36 (32)	72 (38)

a) Catalyst A: $Yb(OTf)_3$ derived complex. Catalyst B: $Yb(O^iPr)_3$ derived complex.
b) Ketene silyl acetal was added over 6.5 h using syringe pump technique.



Scheme 2

A typical experimental procedure is described for ytterbium complex catalyzed reaction of benzaldehyde with ketene silyl acetal derived from ethyl isobutyrate; Bistriflamide of (1*S*,2*S*)-1,2-diphenylethylenediamine (0.06 mmol) was reacted with excess of NaH (0.24 mmol) in 1.2 ml of THF at 0 °C for 30 min. and 1.0 ml of supernatant solution was added to $Yb(OTf)_3$ (0.05 mmol) in THF (1.0 ml). The reaction mixture was stirred at 40 °C for 12 h and solvent was removed under reduced pressure. Dichloromethane (1.0 ml) was added to the residue and the supernatant solution was used as catalyst solution. The catalyst solution was cooled to -40 °C and benzaldehyde (0.25 mmol) was added to the solution. Ketene silyl acetal (0.30 mmol) was then added over 6.5 h using syringe pump technique and stirred for a further 5.5 h. After usual work up, crude product was purified by silica gel column chromatography to yield silylated product (43%) and OH free product (41%). Silylated product was desilylated with 1N HCl / THF and ee of the both products were determined by HPLC analysis using DAICEL CHIRALCEL OD. The product's absolute configuration was determined to be *S* according to the literature procedure.[16)]

Further studies for structure determination and improvement of the catalyst are now in progress.

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