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Glyoxylate-Ene Reaction Catalyzed by $Ln(OTf)_3$

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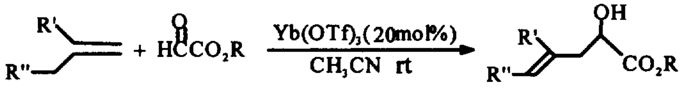
Abstract: $Yb(OTf)_3$ can catalyze the glyoxylate-ene reaction effectively as a water-stable and reusable catalyst. Moreover, the selectivity of DA product or ene product can be adjusted by solvents in the reaction of glyoxylates with a diene (isoprene). In the presence of chiral ytterbium complexes generated in situ from $Yb(OTf)_3$ and optical 6,6'-disubstituted binaphthols, methyl glyoxylate smoothly reacts with α-methyl styrene to afford α-hydroxyl esters in modest optical yields. © 1997 Elsevier Science Ltd.

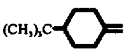
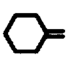
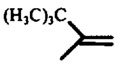
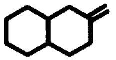
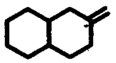
Glyoxylate-ene reactions produce α-hydroxyl esters which are a class of compounds of synthetic and biological importance. The reactions take place at high temperature or are catalyzed by Lewis acids[1] . Several Lewis acid catalysts such as $TiCl_4$ and $SnCl_4$[2] have been developed. Nevertheless, these catalysts are somewhat sensitive to air and moisture, and therefore require careful handling, preparation and /or storage. Furthermore, they can not be recovered after the reaction is completed. Recently impressive progress has been made in the application of lanthanide reagents to organic synthesis[3]. It was reported that lanthanide trifluoro- methanesulfonates(lanthanide triflates) were quite effective as water-stable catalysts in many fundamental reactions including Diels-Alder[4] , Michael Addition[5] , methanolysis of methoxyacetates[6] , ring opening of epoxides[7] and Friedel-Crafts acylations[8] . However, the Glyoxylate-Ene reaction catalyzed by $Ln(OTf)_3$.has so far not been reported in the literature to our knowledge. This paper describes the ene reaction of glyoxylates with alkenes catalyzed by lanthanide triflates.

Lanthanide triflates were found to act quite well as reusable catalysts in the ene reaction of glyoxylates with alkenes in the mild conditions[9] . Screening of a series of lanthanide(III) triflate catalysts for the model reaction of ethyl glyoxylate with α-methyl styrene revealed that some heavy and light -lanthanide(III) triflates such as $La(OTf)_3$, $Yb(OTf)_3$ and $Y(OTf)_3$ were superior to middle-lanthanide(III) triflates. In addition, lanthanide trichlorides and lanthanide(III) alkoxides could not promote the reaction. We selected $Yb(OTf)_3$ as an economical catalyst and examined the effect of the solvents on the yield of product in the model reaction. Among the solvents examined, polar solvents such as tetrahydrofuran, dichloromethane and acetonitrile are more beneficial to promote the reaction than nonpolar solvents such as toluene. Acetonitrile is the best appropriate solvent.

Table1. Preparation of α-Hydroxyl Esters by the Reaction of Glyoxylates with Alkenes Catalyzed by Yb(OTf)$_3$



1 2 3

Entry	Alkene	R	Reaction Time(h)	Product	Yield(%)[a]
1	α-methyl styrene	Me	5h	3a	86
2	α-methyl styrene	Et	5h	3b	85(83[c])
3	α-methyl styrene	Pr^i	5h	3c	85
4	α-methyl styrene	Bu	5h	3e	80
5		Et	12h	3d	72
6		Et	12h	3f	63
7		Et	12h	3g	65
8	α-ethyl styrene	Et	6h	3h(E/Z=84/16)[b]	91
9		Et	20h	3i(69/31)[b]	72
10		Me	20h	3j(64/36)[b]	69

(a). Isolated yield (b). The ratio was determined by ^{1}HNMR (c). 2nd use = 83% yield

Several examples of the ene reactions of glyoxylates with various alkenes are listed in **Table 1**. In every case, the reactions smoothly proceeded in the presence of a catalytic amount of ytterbium triflate(20mol%) under extremely mild conditions to give the corresponding α-hydroxyl esters in good yields after usual work up. Yb(OTf)$_3$ could be recovered and reused. It is noteworthy to refer that the yield of 2nd run of catalyst was almost comparable to that of 1st run (**entry 2 in Table1**). To our knowledge, the present reaction is a first example of the lanthanide-catalyzed ene reaction of glyoxylates with alkenes.

The reaction between a diene, such as isoprene, and a glyoxylate can lead to the formation of both the hetero DA product and the ene product. To our knowledge, the reaction always mainly produces ene products under the influence of traditional Lewis acids such as TiCl$_4$ and SnCl$_4$ [10] , furthermore, in the literature no catalyst has yet been able to change the reaction course to improve the amount of hetero DA product relative to the ene product formed. So the chemoselectivity of the reaction of glyoxylates with a diene in the presence of Yb(OTf)$_3$ is very interesting. The reaction results are shown in **Table 2**. Both Ene product and DA product were obtained at the same time, moreover, the ratio of ene and DA products strongly depended on the used solvents. Acetonitrile led to a high degree of DA selectivity. In sharp contrast, dichloromethane brought about a great degree of ene selectivity. Here, it seems that a high degree of DA selectivity was first realised in the reaction of glyoxylates with isoprene by using Yb(OTf)$_3$ catalyst in acetonitrile. In the meantime ene products could also been obtained mainly in dichloromethane.

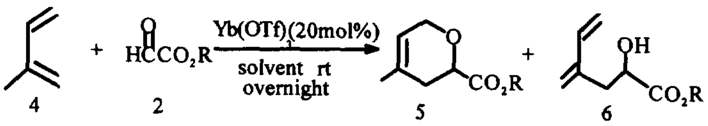
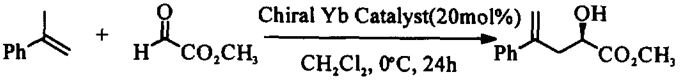


Table2. Reaction Results of Glyoxylates and Isoprene

R	Solvent	Product Ratio	Yield(%)	R	Solvent	Product Ratio	Yield(%)
Me	CH_2Cl_2	5a/6a 30/70	69	Pr^i	CH_2Cl_2	5c/6c 25/75	81
Me	CH_3CN	5a/6a 65/35	73	Pr^i	CH_3CN	5c/6c 69/31	88
Et	CH_2Cl_2	5b/6b 33/67	78	Bu^n	CH_2Cl_2	5d/6d 31/69	75
Et	CH_3CN	5b/6b 71/29	85	Bu^n	CH_3CN	5d/6d 78/22	87

Finally we still wish to describe an initial attempt of the asymmetric glyoxylate-ene reaction catalyzed by the chiral ytterbium complexes prepared in situ from $Yb(OTf)_3$ and optically pure binaphthol or its derivatives in dichloromethane[11] as exemplified in eq 1 (**Table 3**).



(eq1)

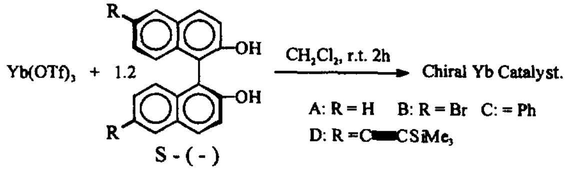


Table 3 Asymmetric Glyoxylate-Ene Reaction Catalyzed by Chiral Yb triflate.

Catalyst	Yield (%)[a]	O.P % (config.)[b]	Catalyst	Yield(%)[a]	O.P % (config)[b]
A	82	12 (S)	C	87	25 (S)
B	78	38 (S)	D	83	29(S)

a Isolated yield. b Optical yields and absolute configurations determined by the comparison of the specific rotation value, see ref 12.

Initial results reveal that asymmetric synthesis has been achieved by the four chiral ytterbium catalysts. 6,6'-Substituents of optically pure binaphthols had obvious effect on the enantioselectivity. Bromo groups led to the highest enantioselectivity excess (38% ee) which was 26% more than that (12%ee) produced by simple optically pure binaphthol. Further investigation on the catalytic asymmetric glyoxylate-ene reaction is now in progress.

In summary, we find $Yb(OTf)_3$ is an excellent catalyst for the reaction of glyoxylates with alkenes under mild conditions, which provides α-hydroxyl esters of synthetic and biological importance in good to excellent yields after chromatographic purification. A real advantage of the procedure is the simplicity and robustness of the reaction: the catalyst is air stable, recoverable and reusable with no loss of yield. For the reaction of glyoxylates with isoprene, CH_2Cl_2 benefits to enhance ene selectivity and CH_3CN is superior to DA selectivity. Chiral ytterbium complex generated from Yb(OTf)$_3$ and (S)-6,6'-dibromo-binaphthol produces a modest asymmetric induction in the ene reaction of methyl glyoxylate with α-methyl styrene.

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9. A typical experimental procedure is the following: To a solution of Yb(OTf)$_3$ (0.2mmol) in CH$_3$CN (4 mL) were added the glyoxylate (1mmol) and alkene (1.2mmol) at room temperature. The mixture was stirred at room temp. for some hours then water was added and the product was extracted with diethyl ether. The organic phase was collected, dried and evaporated to afford the crude product purified by silica gel chromatography. Yb(OTf)$_3$ can be almost quantitatively recovered from the aqueous layer and can be reused.
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11. The following simple procedure illustrates the chiral ytterbium complex catalyzed glyoxylate-ene reaction: To Yb(OTf)$_3$ (0.2mmol) and (S)-6,6'-dibromo-binaphthol (0.24mmol) was added dichloromethane (2ml) at 0°C and the mixture was stirred for 0.5h at the same temperature. Methyl glyoxylate (1mmol) and α-methyl styrene (1.2mmol) were successively added at 0°C , and the mixture was stirred for 24h. Water was then added to quench the reaction . After usual work up, the crude product was puried by silica gel column chromatography to afford the desired ene adduct (78% yield, 38%ee).
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