An europium(III) complex as an efficient catalyst for the Michael reaction of α,β-enones with ketene silyl acetals: LIS-NMR analysis for the transition state through complexation between europium(III) catalyst and enones

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(Received February 28, 1994)

Abstract

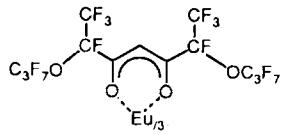
The europium(III) complex, $Eu(dppm)_3$, is found to be an efficient catalyst for the Michael reactions of α,β-enones with ketene silyl acetals. The high level of *erythro* selectivity obtained in the reaction of tert-butyl (*E*)-propenyl ketones (**2c**) with (*E*)-1-tert-butoxy-1-[(trimethylsilyl)oxy]propene (**3d**) is rationalized on the basis of the LIS-NMR analysis of the europium(III) catalyst/enone **2c** complex.

Key words: Catalysis; Michael reaction; Lanthanide shift reagent; Europium complexes

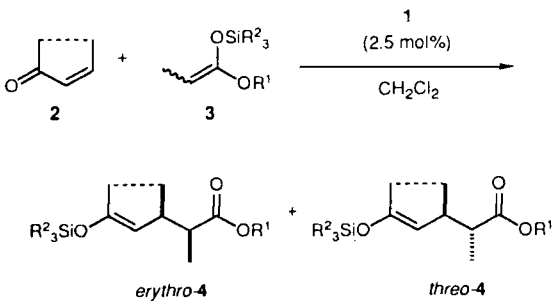
Introduction

Lanthanide complexes have been widely used as NMR shift reagents for structural and conformational analysis of the substrate complexed therewith [1]. However, limited cases have been reported in their use as a catalyst for organic synthesis [2], in spite of the high Lewis acidity of the lanthanide nucleus. Therefore, the development of lanthanide complexes as efficient Lewis acid catalysts for carbon–carbon bond formation, in particular, is an attractive and important challenge [3].

Recently, we have found that lanthanide shift reagent, $Eu(dppm)_3$ (**1**)** [4] exhibits an important catalytic activity for aldol reactions of ketene silyl acetals (KSA) [5]†. Herein, we wish to report the Michael reaction of cyclic and acyclic α,β-enones (**2**) with ketene silyl acetals (KSA) (**3**) catalyzed by the Eu(III) complex (**1**) (eqn. (1)). Lanthanide-induced shift LIS-NMR analysis affords information on the transition state of the present catalytic Michael reactions through complexation of the Eu(III) catalyst/enone (**2**).



$Eu(dppm)_3$ (1)



(1)

Experimental

General

(−)-$Eu(dppm)_3$ (30 wt./vol.% CCl_2FCClF_2 solution) was purchased from Daiichi Kagaku Yakuhin Co. Dichloromethane was freshly distilled from CaH_2. ^1H NMR and ^{13}C NMR were measured on a Varian EM 390 or JEOL EX-90Q spectrometer. IR spectra were recorded on a JASCO A-102 spectrometer.

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**Tris[di(perfluoro-2-propoxypropionyl)methanato]europium-(III).
†In our initial study of Eu(III)-catalyzed reactions with α,β-unsaturated aldehydes, competitive aldol versus Michael reactions were observed [5a].

SSDI 0020-1693(94)03929-I

Catalytic Michael reaction

To a solution of enone (**2**) (1.0 mmol) and KSA (**3**) (1.5 mmol) in CH_2Cl_2 (3 ml) was added a solution of Eu(dppm)$_3$ (**1**) in CCl_2FCClF_2 (30 wt./vol.% solution, 0.025 mmol). After stirring for several hours at the indicated temperature, the reaction mixture was quenched with 1% $NaHCO_3$ solution. The usual work-up followed by short-path column chromatography gave the corresponding Michael product (**4**) as the enol silyl ether form. The resultant silyl enol ether was treated with 1 N HCl / methanol (1:2) mixture to give δ-keto esters.

LIS-NMR analysis

An NMR tube (5 φ) replaced with N_2 was charged with a freshly distilled enone (**2**) (0.15–0.16 mmol), $CDCl_3$ (dried over MS 4 Å, 0.6 ml), and tetramethylsilane (0.1%) as an internal standard. The analytically prepared solution of enone was titrated with a solution of (−)-Eu(dppm)$_3$ in CCl_2FCClF_2 (30 wt./vol.% solution) (ranging from 2.5 to 7.5 mol%) via a Hamilton microliter syringe. The sample was allowed to equilibrate for 10–15 min before measurement.

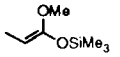
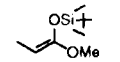
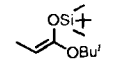
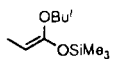
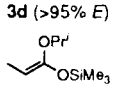
Results and discussion

The Eu(III) complex **1** is thus found to be effective for the Michael reaction involving either cyclic or acyclic enones (**2**). The representative results are summarized in Table 1. (Only a low level of asymmetric induction (up to 6% e.e., Table 1, run 8) was observed in the present catalytic Michael reactions.) The cyclic enones (**2a,b**) are relatively more reactive than the acyclic enones (**2c,d**) in affording the products as the enol silyl ether form [6]* in excellent yield even at lower reaction temperature (runs 1–5 versus 6–10). The Eu(III) catalyst exhibits a moderate-to-high level of *erythro* selectivity**, except for the enone **2d**. It should be noted that the major isomer is always *erythro*, whether the geometry of the KSA is *Z* or *E*. Of particular interest is the extremely high level of *erythro* selectivity observed with tert-butyl (*E*)-propenyl ketone (**2c**), when a sterically bulky KSA (**3d**) (R^1 = tert-butyl) was employed (run 7).

In order to analyze the transition state of the catalytic Michael reactions through complexation of the Eu(III) catalyst with enones **2**, we undertook the LIS-NMR analysis of enones **2**. The results of the LIS-NMR analysis of enones **2b**, **2c** and **2d** are listed in Table 2. The change in chemical shift (Δδ) for each increment was calculated to give a slope (*S*) which provides information on the complexation of the Eu(III) catalyst with enones **2**. For enone **2c**, the larger LIS of the β-proton (S_β) compared to that of the α-proton (S_α) indicates that the enone **2c** exists in the s-*cis* form [8, 9]. Furthermore, the greater LIS of the β-proton (S_β) than that of the β′-proton ($S_{\beta'}$) suggests that the Eu(III) catalyst would complex to the enone **2c** in *syn*-fashon (**A**) (Fig. 1), wherein repulsive interaction between sterically demanding Eu(III) and the bulky tert-butyl moiety would be avoided.

The Eu(III)/**2c** complex and the KSA **3d** would thus adopt an open chain transition state T_1 [10, 6], free from an unfavorable interaction between Eu(III) and both the methyl and alkoxy (OR^1) moieties of the KSA (**3a**, **3d** and **3e**) (Fig. 2). The increase of *erythro* selectivity from **3a** (R^1 = Me) to **3d** (R^1 = t-Bu) via **3e** (R^1 = i-Pr)

TABLE 1. Eu(III)-catalyzed Michael reactions of enones (**2**) with KSA (**3**)[a]

Run	2	3	Conditions	Yield[b] (%)	*erythro/threo*[c]
1	 **2a**	 **3a** (85% *E*)	−40 °C, 3 h	100	57:43
2	**2a**	 **3b** (70% *Z*)	−40 °C, 3 h	77	62:38
3	**2a**	 **3c** (>95% *Z*)	−40 °C, 3 h	85	65:35
4	 **2b**	**3b**	−40 °C, 3 h	100	59:41
5	**2b**	**3c**	−40 °C, 3 h	85	57:43
6	 **2c**	**3a**	r.t., 1 day	58	66:34
7	**2c**	 **3d** (>95% *E*)	r.t., 1 day	48	95:5
8	**2c**	 **3e** (86% *E*)	r.t., 1 day	74	87:13
9	 **2d**	**3a**	r.t., 1 day	52	50:50
10	**2d**	**3d**	r.t., 1 day	40	50:50

[a]All reactions were carried out in 1.0 mmol of **2**, 1.5 mmol of **3**, and 0.025 mmol of Eu(dppm)$_3$ (**1**) in CH_2Cl_2 (3 ml). [b]Isolated yield of the δ-keto esters obtained via desilylation of the silyl enol ether products. [c]Diastereomeric ratio was determined by ^{1}H NMR analysis.

*The stereochemistry of **4** was assigned after desilylation to δ-keto esters through comparison with the literature value [7].

**To avoid the confusion in discussing diastereoselectivity and complexation, we have decided to employ the Heathcock's '*erythro/threo*' convention to define the configuration of diastereomers.

TABLE 2. Slope $(S)^d$ of the observed LIS versus Eu(dppm)$_3$/enone **2b**, **c** and **d**

S^a (Proton)	**2b**	**2c**	**2d**
S_α (H_α)	2.07×10^{-1}	1.18×10^{-1}	1.39×10^{-1}
S_β (H_β)	5.17×10^{-2}	1.64×10^{-1}	1.81×10^{-1}
S_γ (H_γ)	7.71×10^{-2}	3.47×10^{-2}	4.31×10^{-2}
$S_{\alpha'}$ ($H_{\alpha'}$)	2.22×10^{-1}		
$S_{\beta'}$ ($H_{\beta'}$)	7.72×10^{-2}	1.01×10^{-1}	1.42×10^{-1}

[a]Values are derived from the best fit (linear regression) line for a set of data. Units are ppm mol% of Eu(dppm)$_3^{-1}$.

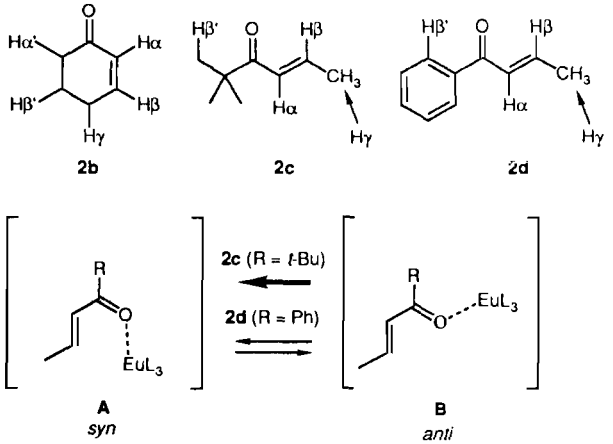


Fig. 1. *syn* and *anti* complexation of the Eu(III) catalyst with enones **2**.

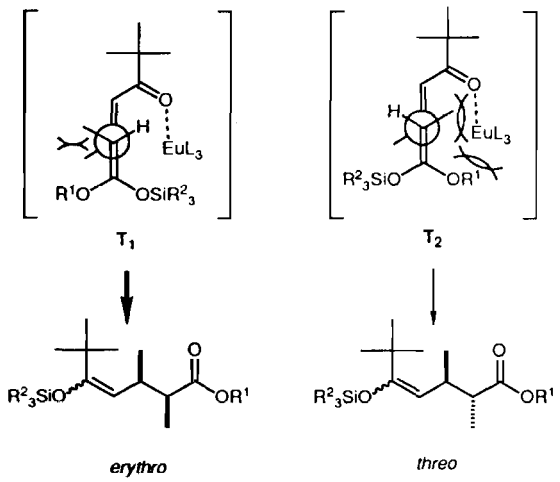
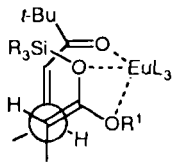


Fig. 2. Transition states in the Michael reaction of **2c** with KSA (**3**).

(Table 1, run 6 versus runs 7 and 8) has some implications for the feasibility of the extended transition states and is well explained by the increased repulsion using the more bulky alkoxy group in T_2. A Seebach-like synclinal model for *erythro* selectivity has been suggested (see ref. 11). However, this model is inconsistent with the increased *erythro* selectivity with increase in the steric bulkiness of OR^1 which should lead to less coordination with Eu(III) because of the steric repulsion of OR^1.



Heathcock and Otera have independently studied diastereoselectivity in the Michael reactions induced by an equimolar amount of Lewis acids such as $TiCl_4$ [7]. They have also reported that *erythro* selectivity is increased by introduction of bulky substituents such as a tert-butyl group on the oxygen or silicon atom of the KSA, particularly in the case using tert-butyl ketone **2c**.

In sharp contrast, the relatively smaller difference between S_β and $S_{\beta'}$ of enone **2d** ($S_\beta/S_{\beta'}=1.27$) as compared to the larger value of $S_\beta/S_{\beta'}$ (1.63) of enone **2c** implies its rapid equilibrium between *syn* (**A**) and *anti* (**B**) complexation (Fig. 1). For the Eu(III) catalyst/enone **2d** complex, linear complexation (C=O–Eu bond angle; 180°) is also conceivable [12]. Actually low diastereoselectivity was observed in the Michael reaction with enone **2d** (Table 1, runs 9 and 10). The cyclic enone **2b** with a small difference between S_α and $S_{\alpha'}$, wherein the *s-cis*, *syn* complexation is impossible, reacts with poor diastereoselectivity, as actually observed.

In summary, we have reported that the Eu(III) complex, Eu(dppm)$_3$, can act as an efficient catalyst for the Michael reaction of a KSA showing a similar trend in diastereoselectivity to that obtained in a similar reaction promoted by $TiCl_4$. We have also rationalized the *erythro* diastereoselectivity on the basis of the LIS-NMR analysis of the Eu(III) catalyst/enone complex.

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