

1,3-DIPOLAR CYCLOADDITIONS OF α -METHOXYCARBONYL-NITRONES IN THE PRESENCE OF $\text{Eu}(\text{fod})_3$

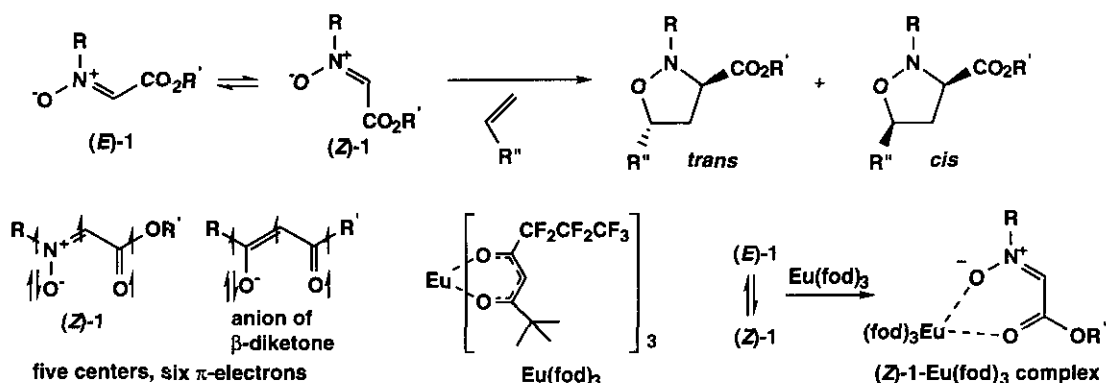
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Abstract - 1,3-Dipolar cycloadditions of α -methoxycarbonylnitrones (**1**) in the presence of $\text{Eu}(\text{fod})_3$ were investigated. Treatment of the nitrones (**1**) with vinyl ethers (**2**) in the presence of $\text{Eu}(\text{fod})_3$ caused intermolecular cycloaddition to give stereoselectively *trans*-adducts (*trans*-**3**). In contrast, the reactions of the nitrones (**1**) with allyl alcohols (**4**) under similar conditions induced transesterification and intramolecular cycloaddition to afford polycyclic products (**5**).

Intermolecular 1,3-dipolar cycloaddition of α -alkoxycarbonylnitrones (**1**) is very attractive for construction of various nitrogen containing carbon frameworks because of the high reactivity of **1**.¹ Facile reductive cleavage of the nitrogen-oxygen bond in the products leads to γ -hydroxy- α -amino acid derivatives, which are useful for nitrogen containing compounds of biological interest.^{1,2} However, the cycloaddition of **1** with olefins often gives mixtures of *trans*- and *cis*-isoxazolidines. One of the main reasons for this drawback would be equilibration between (*E*)-form [(*E*)-**1**] and (*Z*)-form [(*Z*)-**1**].^{1,3} To overcome this problem, reaction of **1** with allyl alcohols in the presence of magnesium bromide,⁴ salt effects on 1,3-dipolar cycloaddition of α -carboxylnitronone with olefins,⁵ and cyclic derivatives of **16**,⁷ have recently been reported. In this communication, we disclose the effects of $\text{Eu}(\text{fod})_3$ ⁸ on cycloaddition of **1** with vinyl ethers and allyl alcohols.⁸⁻¹⁰

The nitronone (**1**) can be regarded as an isoelectronic structure with an anion of β -diketone since both have



six π -electrons in five-membered conjugate systems. Therefore, it was expected that $\text{Eu}(\text{fod})_3$ bearing β -diketone anions as the ligands could selectively activate (*Z*)-**1** of an equilibrating mixture of (*Z*)-**1** and (*E*)-**1** by forming (*Z*)-**1**- $\text{Eu}(\text{fod})_3$ complex, and that the resulting reaction would proceed stereoselectively.

Since the Lewis acid should lower the LUMO energy of **1**, use of dipolarophile having high HOMO energy would be reasonable. Thus, the reactions of **1a,b**¹¹ with several vinyl ethers (**2a-d**) were first examined as shown in Table 1. While reactions of **1** with **2** in the absence of $\text{Eu}(\text{fod})_3$ gave mixtures of *trans*- and *cis*-cycloadducts (*trans*-**3** and *cis*-**3**) (Entries 1,3,5,8,10), the reactions of **1** with **2** in the presence of equimolar amounts of $\text{Eu}(\text{fod})_3$ afforded *trans*-**3** with high selectivities (Entries 2,4,6,9,11). Effect of $\text{Eu}(\text{fod})_3$ in the reaction of **1b** with **2** was remarkable compared with that in reaction of **1a** with **2** (Entry 2 vs Entry 4). This difference would be due to the difference between **1a** and **1b** in the rate of the *E,Z*-equilibrium.¹² Although use of reduced amounts of $\text{Eu}(\text{fod})_3$ and **2** took longer reaction time, it still gave satisfactory *trans*-selectivity (Entry 7).

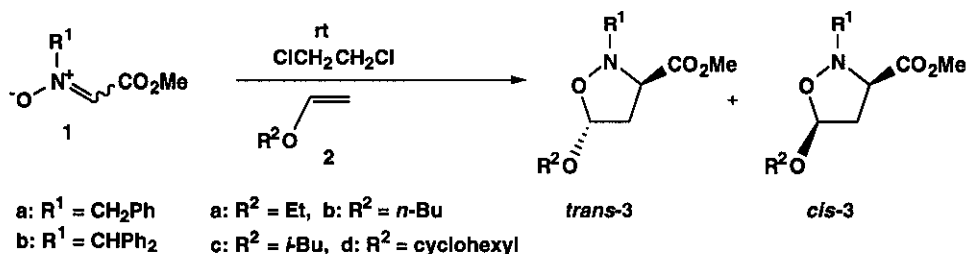


Table 1. Reaction of nitrones (**1a,b**) with vinyl ethers (**2a-d**).

Entry	Nitrone	$\text{Eu}(\text{fod})_3$	Conditions	Product	Yield (%)	Ratio <i>trans</i> - 3 : <i>cis</i> - 3
1	1a	none	2a (20 eq.), 36 h	3a	86	78 : 22
2		1 eq.	2a (20 eq.), 7 h		87	85 : 15
3	1b	none	2a (20 eq.), 36 h	3b	89	72 : 28
4		1 eq.	2a (20 eq.), 5 h		quant	>98 : 2<
5	1b	none	2b (20 eq.), 36 h	3c	73	75 : 25
6		1 eq.	2b (20 eq.), 6 h		quant	>98 : 2<
7		0.3 eq.	2b (3 eq.), 48 h		85	>98 : 2<
8	1b	none	2c (20 eq.), 36 h	3d	76	74 : 26
9		1 eq.	2c (20 eq.), 7 h		89	95 : 5
10	1b	none	2d (20 eq.), 36 h	3e	82	71 : 29
11		1 eq.	2d (20 eq.), 7 h		92	>98 : 2<

Scheme 1

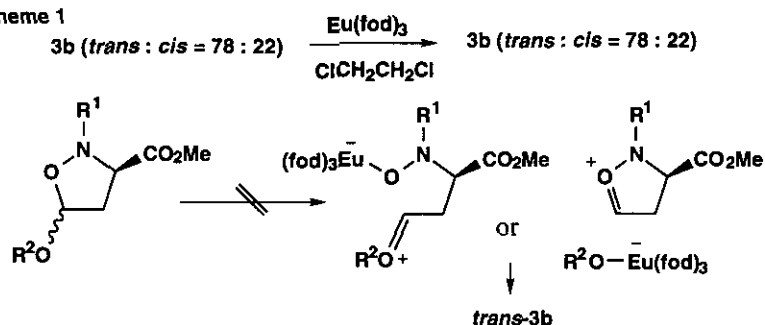
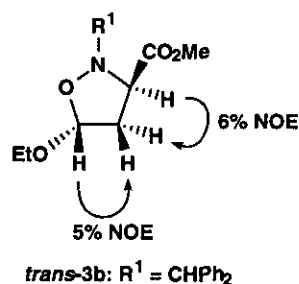


Figure 1



As shown in Scheme 1, treatment of the 3b (*cis* : *trans* = 72 : 28) with Eu(fod)₃ resulted in the complete recovery of the starting mixture without any change of the ratio. This result strongly suggests that the *trans*-3 obtained from the reactions in the presence of Eu(fod)₃ would be kinetic controlled products, since stereochemical isomerization did not take place with the Lewis acid.¹³ The stereochemical assignment of *trans*-3b was made based on the NOE difference spectra as depicted in Figure 1. The stereochemistries of the other products (*trans*-3a,c,d) were assigned by comparing their ¹H-NMR spectra with that of *trans*-3b.

Next, our attention turned to use of allyl alcohols as the dipolarophiles, which might be coordinate to the Lewis acid (Table 2). Treatment of the nitron (1b) with large excess of allyl alcohol (4a) and an equimolar amount of Eu(fod)₃ caused transesterification and intramolecular cycloaddition to give 5a (Entry 1). This result is similar to that in the case employing titanium catalyst,¹⁰ and different from that using magnesium bromide.⁴ Use of other allyl alcohols (4b,c) also gave the corresponding intramolecular cycloadducts (5b,c) in moderate yields (Entries 2,3). As observed in titanium tetrachloride catalyzing reaction,¹⁰ equivalents of 4 and Eu(fod)₃ could be reduced by using molecular sieves 4A (Entry 3).

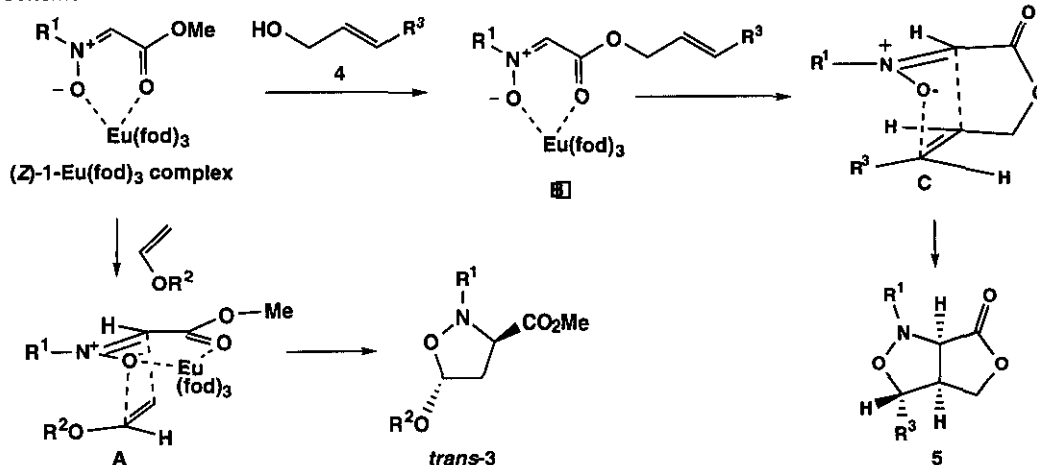
The difference between the reactions in Table 1 and those in Table 2 may be rationalized by considering the common intermediate [(*Z*)-1-Eu(fod)₃ complex] as shown in Scheme 2. The vinyl ethers (2) would react

Table 2. Reaction of the nitron (1b) with allyl alcohols (4a-c) in the presence of Eu(fod)₃.

Entry	Allyl Alcohol	Conditions	Yield (%)	Product
1	4a (10 eq.)	1 eq. Eu(fod) ₃ ClCH ₂ CH ₂ Cl rt, 14 h	68	5a
2	4b (5 eq.)	1 eq. Eu(fod) ₃ MS 4A, ClCH ₂ CH ₂ Cl rt, 5 days	52	5b
3	4c (3 eq.)	0.1 eq. Eu(fod) ₃ MS 4A, ClCH ₂ CH ₂ Cl rt → 60 °C, 10 h	71	5c

via the *endo*-transition state (A) to avoid severe steric interaction between the substituent (R^2O) and the bulky Lewis acid $[Eu(fod)_3]$.¹⁴ Accordingly, the reaction of **1** with **2** in the presence of $Eu(fod)_3$ would give *trans*-**3** with high stereoselectivities. While details of mechanism of the transesterification by employing allyl alcohols (**4**) remains unknown, (*Z*)-**1**- $Eu(fod)_3$ complex may give the allyloxycarbonylnitrone intermediate (B), which would cycloadd intramolecularly to afford **5** via the transition state (C).

Scheme 2



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11. The *E*, *Z*-ratios of the nitrones (**1a,b**) in CDCl₃ are as follows: **1a** (1.6 : 1), **1b** (1.1 : 1).^{3a}
12. Since it is known that the equilibration of **1b** is much faster than that of **1a**,^{3a} **1b** would more efficiently form (*Z*)-**1**-Eu(fod)₃ complex than **1a**.
13. Epimerization of an acetal moiety can be induced by Eu(fod)₃.^{9e}
14. In ¹H-NMR spectrum (CDCl₃) of **1b** in the presence of 0.15 eq of Eu(fod)₃, the methoxy-protons and methine-proton of (*Z*)-**1b** went to down-field by 1.23 and 0.46 ppm, respectively, while methoxy-protons of (*E*)-**1b** shifted only by 0.09 ppm. In ¹H-NMR spectrum of **2a** with 0.15 eq of Eu(fod)₃, none of the protons gave large down-field shift (< 0.07 ppm). These results suggest the formation of (*Z*)-**1**-Eu(fod)₃ complex and almost no coordination of **2** with Eu(fod)₃.

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