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

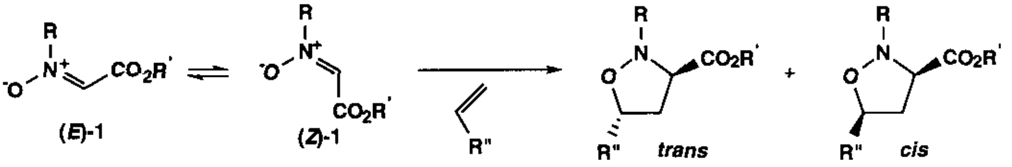
Osamu Tamura,* Naka Mita, Kentoku Gotanda, Ken-ichi Yamada,
Tsuyoshi Nakano, Ruriko Katagiri, and Masanori Sakamoto*

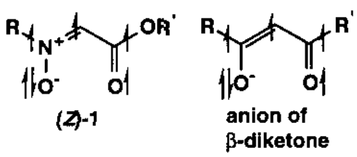
Meiji College of Pharmacy, Nozawa, Setagaya, Tokyo 154 Japan

Abstract - 1,3-Dipolar cycloadditions of α-methoxycarbonylnitrones (**1**) in the presence of $Eu(fod)_3$ were investigated. Treatment of the nitrones (**1**) with vinyl ethers (**2**) in the presence of $Eu(fod)_3$ 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-carboxylnitrone with olefins,[5] and cyclic derivatives of **1**[6,7] have recently been reported. In this communication, we disclose the effects of $Eu(fod)_3$[8] on cycloaddition of **1** with vinyl ethers and allyl alcohols.[8-10]

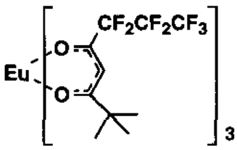
The nitrone (**1**) can be regarded as an isoelectronic structure with an anion of β-diketone since both have



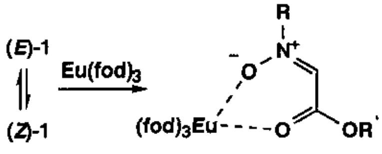


(*Z*)-1 anion of β-diketone

five centers, six π-electrons



$Eu(fod)_3$

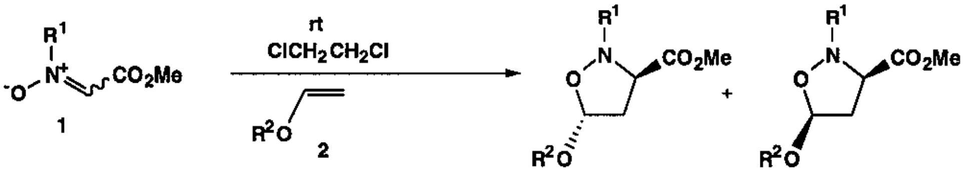


(*Z*)-1-$Eu(fod)_3$ complex

This paper is dedicated to the memory of Dr. Shun-ichi Yamada, Professor Emeritus, Tokyo University.

six π-electrons in five-membered conjugate systems. Therefore, it was expected that Eu(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**-Eu(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 Eu(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 Eu(fod)$_3$ afforded *trans*-**3** with high selectivities (Entries 2,4,6,9,11). Effect of Eu(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 Eu(fod)$_3$ and **2** took longer reaction time, it still gave satisfactory *trans*-selectivity (Entry 7).



a: R^1 = CH$_2$Ph b: R^1 = CHPh$_2$

a: R^2 = Et, b: R^2 = *n*-Bu c: R^2 = *i*-Bu, d: R^2 = cyclohexyl

trans-3 *cis*-3

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

Entry	Nitrone	Eu(fod)$_3$	Conditions	Product	Yield (%)	Ratio *trans*-**3** : *cis*-**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

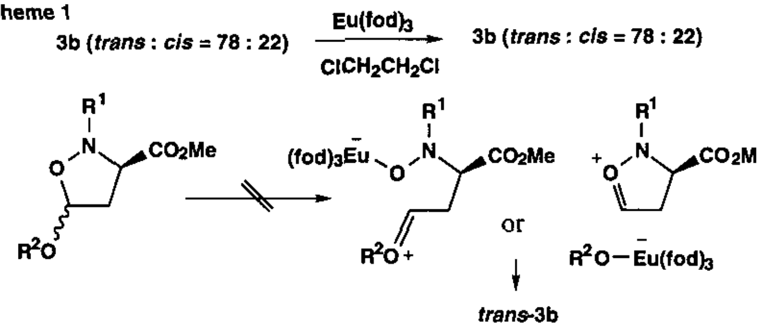
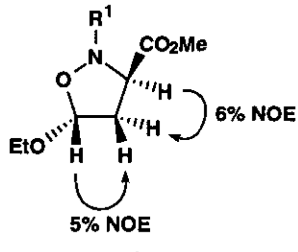


Figure 1



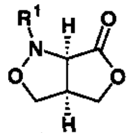
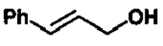
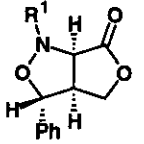
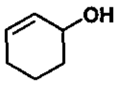
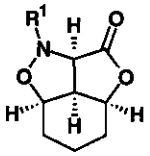
trans-3b: R^1 = $CHPh_2$

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 ^{1}H-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 nitrone (**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).

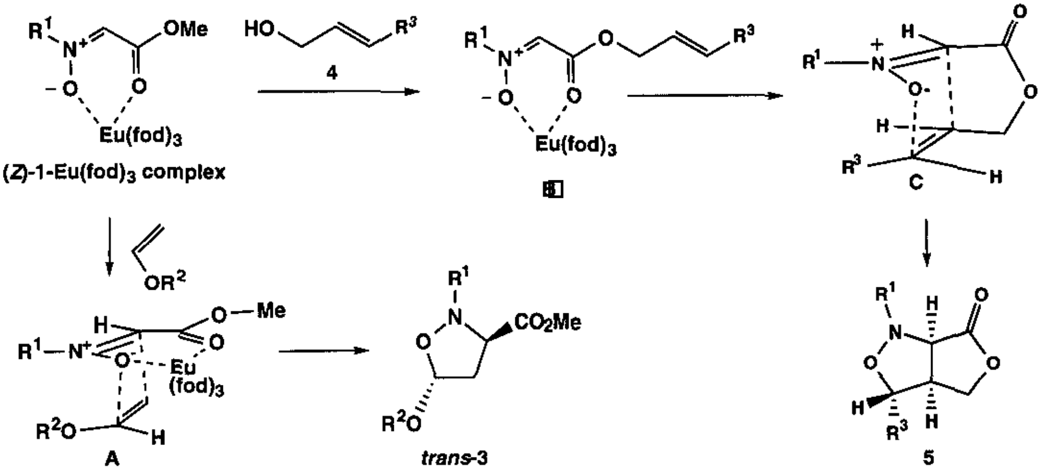
The difference between the reactions in Table 1 and those in Table 2 may be rationalized by considering the common intermediate [(*Z*)-**1**-$Eu(fod)_3$ complex] as shown in Scheme 2. The vinyl ethers (**2**) would react

Table 2. Reaction of the nitrone (**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. $Eu(fod)_3$ $ClCH_2CH_2Cl$ rt, 14 h	68	 **5a**
2	 **4b (5 eq.)**	1 eq. $Eu(fod)_3$ MS 4A, $ClCH_2CH_2Cl$ rt, 5 days	52	 **5b**
3	 **4c (3 eq.)**	0.1 eq. $Eu(fod)_3$ MS 4A, $ClCH_2CH_2Cl$ rt →60 °C, 10 h	71	 **5c**

via the *endo*-transition state (**A**) to avoid severe steric interaction between the substituent (R^{2}O) 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 stereoselectivites. 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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REFERENCES AND NOTES

1. C. Belzecki and I. Panfil, *J. Org. Chem.*, 1979, **44**, 1212; J. Hara, Y. Inouye, and H. Kakisawa *Bull. Chem. Soc. Jpn.*, 1981, **54**, 3871; P. DeShong, C. M. Dicken, R. R. Staib, A. J. Freyer, and S. M. Weinreb *J. Org. Chem.*, 1982, **47**, 4397; K. Kasahara, H. Iida, and C. Kibayashi, *J. Org. Chem.*, 1989, **54**, 2225; M. Burdisso, R. Gandolfi, and P. Grünanger, *J. Org. Chem.*, 1990, **55**, 3427; P. Bravo, L. Bruche, G. Fronza, and G. Zecchi, *Tetrahedron,* 1992, **48**, 9775.
2. M. Frederickson, *Tetrahedron,* 1997, **53**, 403.
3. (a) Y. Inouye, J. Hara, and H. Kakisawa, *Chem. Lett.*, **1980**, 1407. (b) Y. Inouye, *Bull. Chem. Soc. Jpn.*, 1983, **56**, 244. (c) Y. Inouye, K. Takaya, and H. Kakisawa, *Bull. Chem. Soc. Jpn.*, 1983, **56**, 3541. (d) H. G. Aurich, M. Franzke, and H. P. Kesselheim, *Tetrahedron,* 1992, **48**, 663.
4. S. Kanemasa and T. Tsuruoka, *Chem. Lett.*, **1995**, 49.
5. Y. Tokunaga, M. Ihara, and K. Fukumoto, *Tetrahedron Lett.*, 1996, **37**, 6157.
6. (a) N. Katagiri, H. Sato, A. Kurimoto, M. Okada, A. Yamada, and C. Kaneko, *J. Org. Chem.*, 1994, **59**, 8101. (b) N. Katagiri, M. Okada, and C. Kaneko, *Tetrahedron* Lett., 1996, **37**, 1801. (c) N. Katagiri, M. Okada, Y. Morishita, and C. Kaneko, *Chem. Commun.*, **1996**, 2137.

7. O. Tamura, K. Gotanda, R. Terashima, M. Kikuchi, T. Miyawaki, and M. Sakamoto, *Chem. Commun.*, **1996**, 1861.

8. This is an abbreviation for tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanatedionato)-europium(III). For Diels-Alder reactions using Eu(fod)$_3$, see G. A. Molander, *Chem. Rev.*, 1992, **92**, 29; M. Bednarski and S. Danishefsky, *J. Am. Chem. Soc.*, 1983, **105**, 3716; E. Wada, H. Yasuoka, and S. Kanemasa, *Chem. Lett.*, **1994**, 145; I. E. Marko and G. R. Evans, *Tetrahedron Lett.*, 1994, **35**, 2767; G. Dujardin, S. Rossignol, S. Molato, and E. Brown, *Tetrahedron,* 1994, **50**, 9037; R. F. Lowe and R. J. Stoodley, *Tetrahedron Lett.,* 1994, **35**, 6351 and references cited therein.

9. For nitrone cycloadditions in the presence of Lewis acid, see refs.4, 6b, 6c and 10. See also, S. Kanemasa, T. Uemura, and E. Wada, *Tetrahedron Lett.*, 1992, **33**, 7889; S. Kanemasa, T. Tsuruoka, and E. Wada, *Tetrahedron Lett.,* 1993, **34**, 87; S. Kanemasa, T. Tsuruoka, and H. Yamamoto, *Tetrahedron Lett.*, 1995, **36**, 5019; S.-I., Murahashi, Y. Imada, M. Kohno, and T. Kawakami, *Synlett,* **1993**, 395; J.-P. G. Seeden, A. W. A. Scholte op Reimer and H. W. Scheeren, *Tetrahedron Lett.,* 1994, **35**, 4419; J.-P. G. Seerden, M. M. M. Kuypers, and H. W. Scheeren, *Tetrahedron Asymmetry*, 1995, **6**, 1441; K. V. Gothelf and K. A. Jørgensen, *J. Org. Chem.,* 1994, **59**, 5687; K. V. Gothelf, R. G. Hazell, and K. A. Jørgensen, *J. Am. Chem. Soc,* 1995, **117**, 4435; K. V. Gothelf, and K. A. Jørgensen, *J. Org. Chem.*, 1995, **60**, 6847; K. V. Gothelf, I. Thomsen, and K. A. Jørgensen, *J. Am. Chem. Soc.*, 1996, **118**, 59.; K. Hori, H. Kodama, T. Ohta, and I. Furukawa, *Tetrahedron Lett.*, 1996, **37**, 5947.

10. For tandem transesterificaton and intramolecular cycloaddition of the nitrone (**1**) with allyl alcohols in the presence of titanium catalyst, see O. Tamura, T. Yamaguchi, K. Noe, and M. Sakamoto, *Tetrahedron Lett.*, 1993, **34**, 4009; O. Tamura, T. Yamaguchi, T. Okabe, and M. Sakamoto, *Synlett,* **1994**, 620; O. Tamura, T. Okabe, T. Yamaguchi, K. Gotanda, K. Noe, and M. Sakamoto, *Tetrahedron,* 1995, **51**, 107; O. Tamura, T. Okabe, T. Yamaguchi, J. Kotani, K. Gotanda, and M. Sakamoto, *Tetrahedron,* 1995, **51**, 119; O. Tamura, N. Mita, N. Kusaka, H. Suzuki, and M. Sakamoto, *Tetrahedron Lett.,* 1997, **38**, 429.

11. The *E, Z*-ratios of the nitrones (**1a,b**) in CDCl$_3$ 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 ^{1}H-NMR spectrum (CDCl$_3$) 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 ^{1}H-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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