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1,3-Dipolar cycloaddition of α-alkoxycarbonylnitrones with vinyl ethers and allyl alcohols in the presence of Eu(fod)$_3$: selective activation of (*Z*)-isomers of the nitrones

Osamu Tamura,[a,*] Naka Mita,[b] Yasuharu Imai,[a] Takuya Nishimura,[a] Tamiko Kiyotani,[a] Mikio Yamasaki,[c] Motoo Shiro,[c] Nobuyoshi Morita,[a] Iwao Okamoto,[a] Tetsuya Takeya,[a] Hiroyuki Ishibashi[d] and Masanori Sakamoto[b]

[a]*Showa Pharmaceutical University, Machida, Tokyo 194-8543, Japan*
[b]*Meiji Pharmaceutical University, Kiyose, Tokyo 204-8588, Japan*
[c]*Rigaku Corporation, Akishima, Tokyo 196-8666, Japan*
[d]*Division of Pharmaceutical Sciences, Graduate School of Natural Science and Technology, Kanazawa University, Kanazawa 920-1192, Japan*

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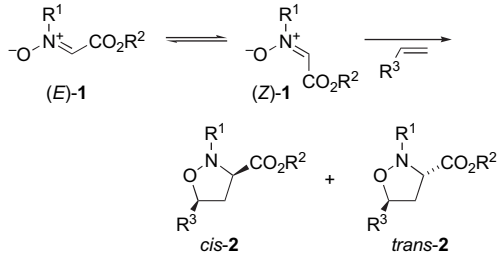
Abstract—Uncatalyzed cycloaddition of α-alkoxycarbonylnitrones **1** with vinyl ethers **7** gave mixtures of *cis*- and *trans*-cycloadducts **8**, whereas Eu(fod)$_3$-catalyzed cycloaddition of **1** with **7** gave the *trans*-cycloadducts *trans*-**8** in a highly stereoselective manner. NMR studies indicated that Eu(fod)$_3$ selectively activated (*Z*)-nitrones (*Z*)-**1** in *E*,*Z*-equilibrium mixtures of nitrones **1**. In contrast, the reaction of **1** with allyl alcohols **12** in the presence of Eu(fod)$_3$ resulted in sequential transesterification and intramolecular cycloaddition to give intramolecular cycloadducts **13**.

1. Introduction

Intermolecular 1,3-dipolar cycloadditions of nitrones are fundamental and very useful for synthesizing various biologically useful compounds, including alkaloids, antibiotics, and amino acids.[1] Cycloaddition of α-alkoxycarbonylnitrone **1** is particularly attractive because of its high reactivity. However, the cycloaddition of **1** with olefins often gives mixtures of *cis*- and *trans*-isoxazolidines *cis*-**2** and *trans*-**2**,[2] probably due to *E*,*Z*-equilibration of **1** in solution even at room temperature (Scheme 1). Although, the geometrical equilibration of **1** was reported in early 1980s,[3] there was little attempt to control the equilibration in the cycloaddition until the middle of the 1990s.

In the course of studies to achieve cycloaddition with controlling the equilibrium, the 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 asymmetric reaction of nitrone **1** with vinyl ethers using a chiral copper catalyst[6] and cyclic nitrones as (*E*)-geometry-fixed equivalents of **1**[7–10] have been reported. Recently, we found that Eu(fod)$_3$ [tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanatedionate) europium(III)] can selectively activate (*Z*)-**1** by forming (*Z*)-**1**–Eu(fod)$_3$ complex, which reacts with vinyl ethers to give the *trans*-isoxazolidine with excellent stereoselectivity.[11] It was also reported that treatment of **1** with allyl alcohols in the presence of Eu(fod)$_3$ induces tandem transesterification and intramolecular cycloaddition, affording bicyclic compounds. We now present a full account of this work, including a consideration of the electronic properties of **1**, NMR studies of **1** in the presence of Eu(fod)$_3$, and cycloaddition of a related cyclic nitrone with vinyl ethers in the presence of Eu(fod)$_3$.



Scheme 1.

Keywords: 1,3-Dipolar cycloaddition; α-Alkoxycarbonylnitrones; Vinyl ethers; Europium; Stereoselective.
* Corresponding author. Tel.: +81 42 721 1578; fax: +81 42 721 1579; e-mail: tamura@ac.shoyaku.ac.jp

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2. Results and discussion

2.1. Electronic properties of α-alkoxycarbonylnitrone 1

We considered that the resonance effect between the nitrone moiety and α-carbonyl group may be the reason for the facile *E*,*Z*-equilibration of **1**; if this is so, the nitrone **1** can be regarded as an isoelectronic structure of a β-diketone anion since both have six π-electrons in a five-membered conjugated system (Fig. 1).

To test this working hypothesis, the bond distances between atoms were calculated at the HF/6-31G* level for the nitrone **3** bearing a ketone group as an electron-withdrawing group, the nitrone **4** without a conjugated system, acetone **5**, and the anion of the β-diketone **6** (Fig. 2).[12] The nitrogen–oxygen single bonds of (*E*)-**3** and (*Z*)-**3** are shorter than that of **4**, and the nitrogen–carbon double bonds of (*E*)-**3** and (*Z*)-**3** are longer than that of **4**. These findings can be interpreted by assuming that the nitrogen–oxygen single bond of **3** has the partial nature of a double bond, and the nitrogen–carbon double bond of **3** has the partial nature of a single bond. In addition, the length of the carbon–oxygen double bond of (*E*)-**3** and (*Z*)-**3** was estimated to be between those in acetone **5** and the anion **6**. All these data strongly suggest that the nitrone **3** exhibits a resonance effect between the nitrone moiety and the α-carbonyl group similar to that of the anion **6**; in other words, the nitrone **3** is isoelectronic with the β-diketone anion.

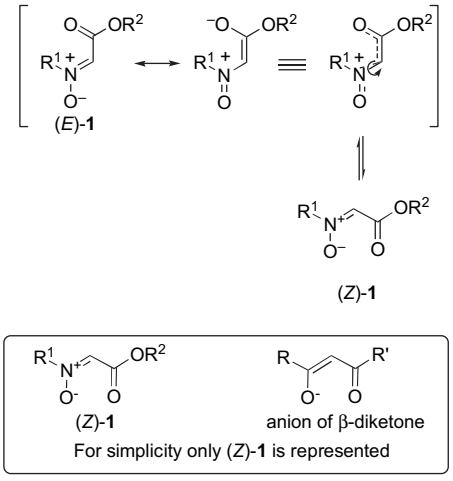


Figure 1.

2.2. Cycloaddition of 1 with vinyl ethers in the presence of Eu(fod)$_3$

A shift reagent for NMR spectra, Eu(fod)$_3$, bears β-diketone anions (fod; 6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato) as ligands (Fig. 3). Therefore, we expected that Eu(fod)$_3$ would selectively activate (*Z*)-**1** in an equilibrium mixture of (*Z*)-**1** and (*E*)-**1** by forming (*Z*)-**1**–Eu(fod)$_3$ complex, which, in turn, could stereoselectively undergo 1,3-dipolar cycloaddition (Scheme 2). Since the Lewis acid should lower the LUMO energy of (*Z*)-**1**,[13] use of dipolarophiles having a high HOMO energy, for example, vinyl ethers, is reasonable.[14–16]

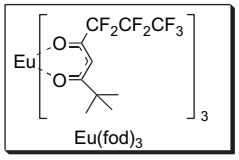
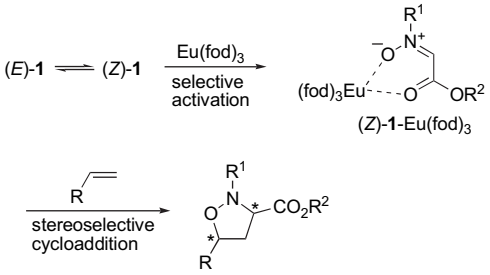


Figure 3.



Scheme 2.

Thus, the reactions of nitrones **1a** and **1b** with several vinyl ethers **7a–d** were first examined as shown in Scheme 3 and Table 1. Reactions of **1** with **7** in the absence of Eu(fod)$_3$ gave mixtures of cycloadducts *trans*-**8** and *cis*-**8** (entries 1, 3, 5, 8, and 10), whereas the reactions of **1** with **7** in the presence of a stoichiometric amount of Eu(fod)$_3$ afforded *trans*-**8** with high selectivity (entries 2, 4, 6, 9, and 11). The effect of Eu(fod)$_3$ in the reactions of **1b** with **7a–d** was remarkably compared with that in the reaction of **1a** with **7a** (entry 2 vs entry 4). Equilibration of **1b** is known to be much faster than that of **1a**,[3a] and hence **1b** would more efficiently form the (*Z*)-**1**–Eu(fod)$_3$ complex. Although, the use of a reduced amount of Eu(fod)$_3$ required a prolonged reaction time, satisfactory *trans*-selectivity was still obtained (entry 7).

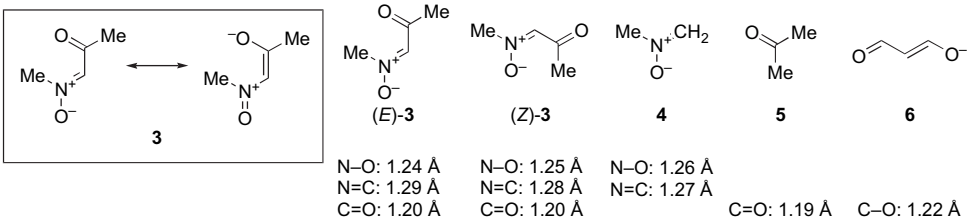
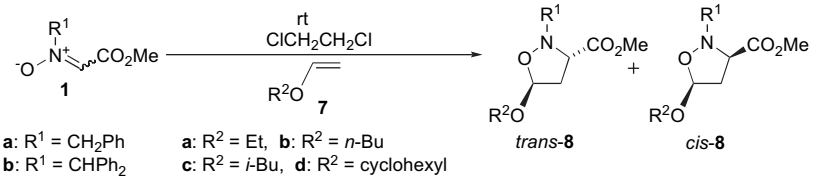


Figure 2. Results of HF/6-31G* calculations for **3**–**6**.

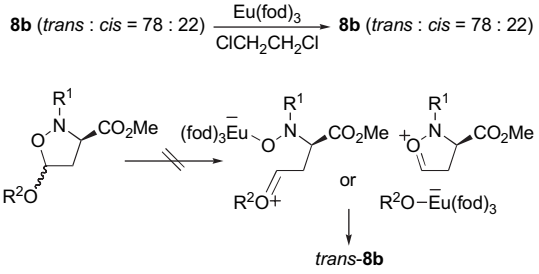


Scheme 3.

Table 1. Reaction of nitrones **1a**,**b** with vinyl ethers **7a–d**

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

As shown in Scheme 4, the treatment of **8b** (*trans*:*cis*=72:28) with Eu(fod)$_3$ resulted in complete recovery of the starting mixture without any change in the ratio.[17] This result strongly suggests that the product *trans*-**8b** obtained by the reaction of **1b** with **7a** in the presence of Eu(fod)$_3$ is a kinetically controlled product. The stereochemical assignments of cycloadducts **8a** and **8b** were made on the basis of comparison of their ^{1}H NMRs with those of known compounds *trans*-**8a**′[6a] and *cis*-**8a**′,[6a] as depicted in Figure 4. Furthermore, the structure of *trans*-**8b** was confirmed by the NOE difference spectra. The stereochemistries of the other products, *trans*-**8c**,**d**, were assigned by comparing their ^{1}H NMR spectra with that of *trans*-**8b**.



Scheme 4.

To examine the coordinating abilities of the nitrones and vinyl ethers, NMR studies of the nitrones **1b** and **9**, and the vinyl ether **7a** in the presence or absence of Eu(fod)$_3$ were conducted (Table 2). In the ^{1}H NMR spectrum ($CDCl_3$) of **1b** in the presence of 0.15 equiv of Eu(fod)$_3$, the signals of the methoxy protons (Ha) and methyne proton (Hb) of the *Z*-isomer were shifted downfield by 1.23 and 0.46 ppm, respectively, whereas the signal of the methoxy protons (Ha) of the *E*-isomer was shifted by only 0.09 ppm. In the case of **9**, the signals of both Ha and Hb were more strongly shifted than that of Ha′. However, in the ^{1}H NMR spectrum

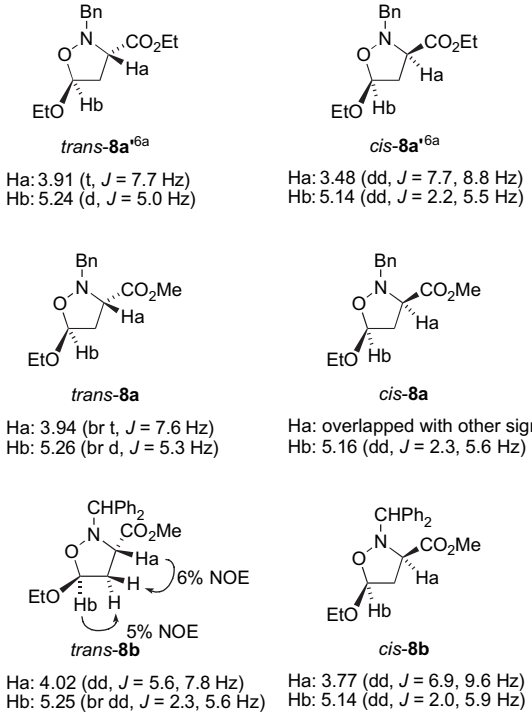
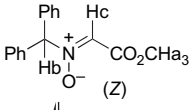
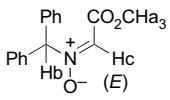
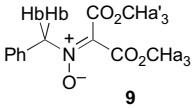
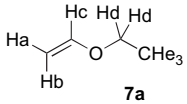


Figure 4.

of **7a**, none of the protons showed a large down-field shift (<0.07 ppm). These results suggested that the nitrones **1b** and **9** formed (*Z*)-**1b**–Eu(fod)$_3$ and **9**–Eu(fod)$_3$ complexes, respectively, and that Eu(fod)$_3$ did not readily coordinate with the vinyl ether **7a** (Fig. 5).

All these results are consistent with the reaction mechanism as shown in Scheme 5. Thus, Eu(fod)$_3$ selectively activates (*Z*)-**1** by forming (*Z*)-**1**–Eu(fod)$_3$ complex, which reacts

Table 2. Chemical shifts of **1b**, **9**, and **7a** in the presence of $Eu(fod)_3$

Compound	No. additive (A) δ (ppm)	+0.15 equiv of $Eu(fod)_3$ (B) δ (ppm)	(B)–(A) $\Delta\delta$ (ppm)
 (*Z*)	Ha: 3.71 Hb: 6.28 Hc: —[a]	Ha: 4.94 Hb: 6.74 Hc: —[a]	Ha: 1.23 Hb: 0.46 Hc: —[a]
 (*E*) **1b**	Ha: 3.71 Hb: —[a] Hc: 8.24	Ha: 3.80 Hb: —[a] Hc: 8.28	Ha: 0.09 Hb: —[a] Hc: 0.04
 **9**	Ha: 3.88 Ha′: 3.84 Hb: 5.73	Ha: 4.31 Ha′: 3.97 Hb: 5.98	Ha: 0.43 Ha′: 0.13 Hb: 0.25
 **7a**	Ha: 3.98 Hb: 4.18 Hc: 6.46 Hd: 3.75 He: 1.29	Ha: 4.02 Hb: 4.23 Hc: 6.53 Hd: 3.81 He: 1.34	Ha: 0.04 Hb: 0.05 Hc: 0.07 Hd: 0.06 He: 0.05

[a] The signal was overlapped with those of aromatic protons.

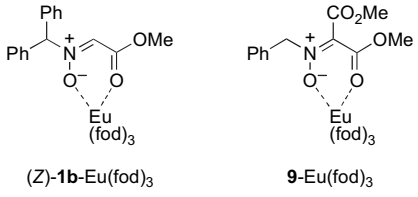
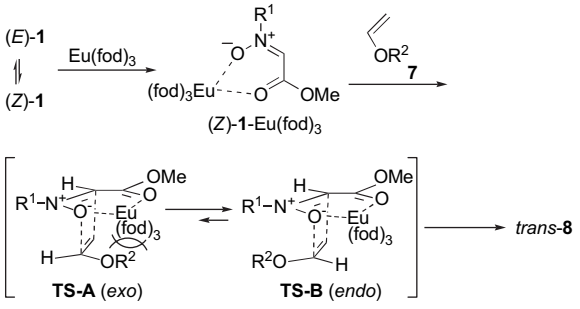


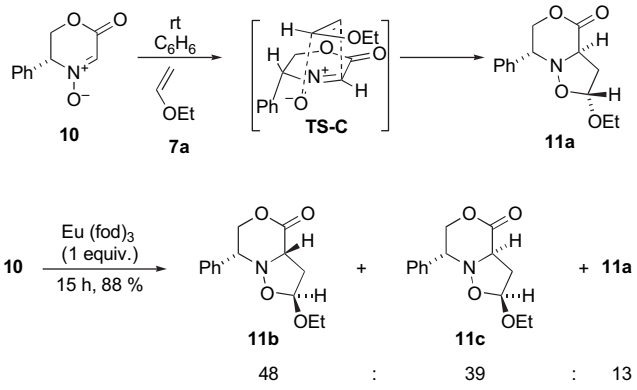
Figure 5.

with the vinyl ether **7** via *endo* transition state **TS-B** to give the cycloadduct *trans*-**8**, because the *exo* transition state **TS-A** would have severe steric interaction between the substituent (R^2O) and the bulky $Eu(fod)_3$.



Scheme 5.

For comparison with the reaction of the *E*,*Z*-equilibrating nitrone **1**, we examined the reaction of the cyclic nitrone **10**[7a–h] with vinyl ether **7a** in the presence of $Eu(fod)_3$ (Scheme 6). Because the nitrone **10** is fixed in *E*-geometry, it cannot act as a bidentate ligand of $Eu(fod)_3$. In the absence of $Eu(fod)_3$, the reaction of **10** with vinyl ether is known to give **11a** as the major cycloadduct via the β-*exo* transition state **TS-C** having the least steric hindrance.[7a,c] In contrast, the reaction of **10** with **7a** in the presence of $Eu(fod)_3$, surprisingly, afforded **11b** as the major isomer. The stereo structure of **11b** was established by X-ray diffraction analysis (Fig. 6)[18] and that of **11c** was tentatively assigned as shown



Scheme 6.

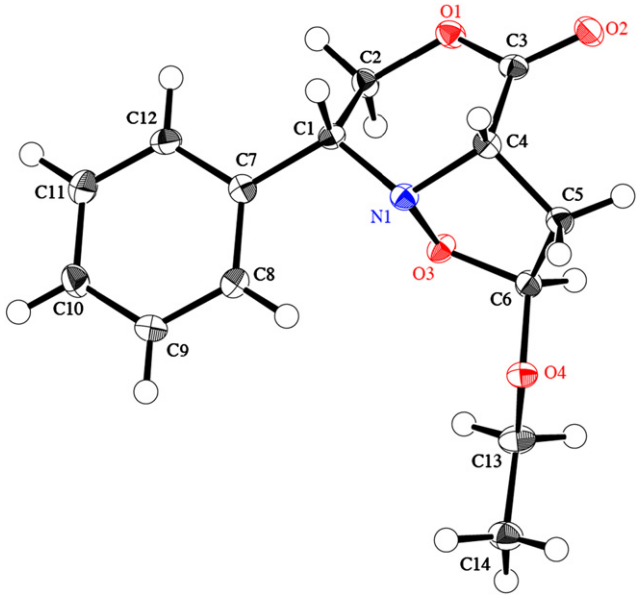
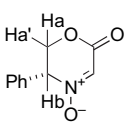
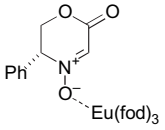
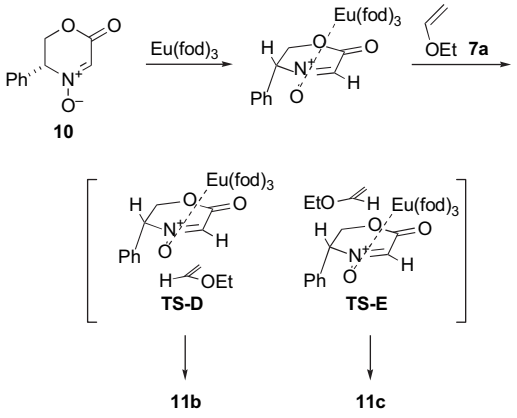


Figure 6. ORTEP drawing of **11b**.

Table 3. Chemical shifts of **10** in the presence of $Eu(fod)_3$

Compound	No. additive (A) δ (ppm)	+0.05 equiv of $Eu(fod)_3$ (B) δ (ppm)	(B)−(A) $\Delta\delta$ (ppm)	
 **10**	Ha: 4.74 Ha′: 4.84 Hb: 5.10	Ha: 4.85 Ha′: 4.94 Hb: 5.40	Ha: 0.11 Ha′: 0.10 Hb: 0.30	 **10**-$Eu(fod)_3$

in Scheme 6. To clarify the reason for the difference, the coordination mode of **10** with $Eu(fod)_3$ was verified again by means of NMR experiments (Table 3). The ^1H NMR spectrum of **10** with 0.05 equiv of $Eu(fod)_3$ showed that the signal of proton Hb was shifted more than those of Ha and Ha′. This suggested that $Eu(fod)_3$ coordinated with the oxygen atom of the nitrone moiety instead of the carbonyl-oxygen atom, forming **10**–$Eu(fod)_3$ complex. The stereochemical course of the reaction of **10** with **7a** in the presence of $Eu(fod)_3$ can be explained by considering the transition states **TS-D** and **TS-E**, as shown in Scheme 7. Thus,



Scheme 7.

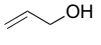
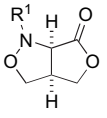
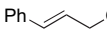
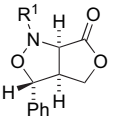
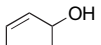
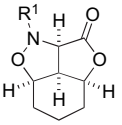
$Eu(fod)_3$ coordinating with the oxygen atom is located on the opposite side of the phenyl group, thereby avoiding steric interaction. As a result, the vinyl ether **7a** approaches from the vacant sites to react via α-*exo* **TS-D** and **TS-E**, affording **11b** and **11c**, respectively.

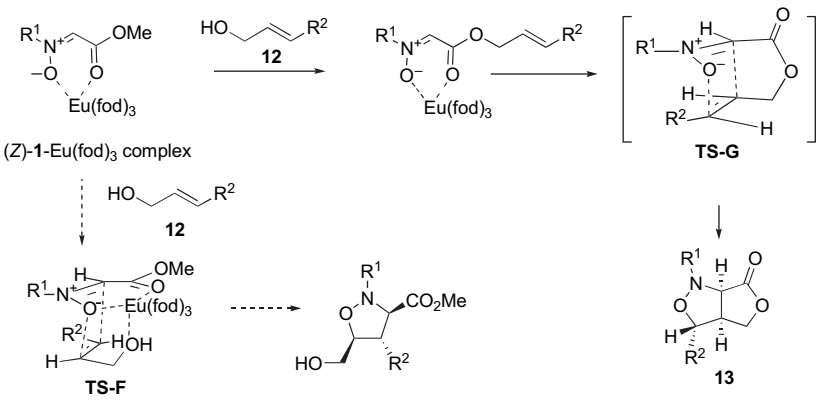
2.3. Reaction of 1 with allyl alcohols in the presence of $Eu(fod)_3$

Next, we turned our attention to the use of allyl alcohols **12** as the dipolarophiles, which might coordinate with the Lewis acid as in the case of the reaction using $MgBr_2$.[4] However, the reaction of allyl alcohols **12** in the presence of $Eu(fod)_3$ gave intramolecular-type bicyclic products **13** (Table 4). Thus, treatment of the nitrone **1b** with large excess of allyl alcohol **12a** and a stoichiometric amount of $Eu(fod)_3$ caused transesterification and intramolecular cycloaddition to give **13a** (entry 1). Use of other allyl alcohols **12b** and **12c** also gave the corresponding intramolecular cycloadducts **13b** and **13c** in moderate yields (entries 2 and 3). As observed in the titanium tetrachloride-catalyzed reaction, the amounts of **12** and $Eu(fod)_3$ could be reduced in the presence of molecular sieves 4 Å (entry 3).[19b]

These results are similar to those of the reactions employing titanium catalyst,[19] and different from those of the reactions using magnesium bromide.[4] In the case of allyl alcohols, transesterification was promoted by $Eu(fod)_3$, and the cycloaddition proceeded not via **TS-F** but via **TS-G** to afford the intramolecular cycloadducts **13** (Scheme 8).

Table 4. Reaction of nitrone **1b** with allyl alcohols **12a–c** in the presence of $Eu(fod)_3$

Entry	Allyl alcohol	Conditions	Yield (%)	Product
1	 **12a** (10 eq.)	1 equiv $Eu(fod)_3$, 4 Å MS, $ClCH_2CH_2Cl$, rt, 14 h	68	 **13a**
2	 **12b** (5 eq.)	1 equiv $Eu(fod)_3$, 4 Å MS, $ClCH_2CH_2Cl$, rt, 5 days	92	 **13b**
3	 **12c** (3 eq.)	0.1 equiv $Eu(fod)_3$, 4 Å MS, $ClCH_2CH_2Cl$, rt then 60 °C, 10 h	71	 **13c**



Scheme 8.

3. Conclusion

We investigated the activation mode of α-alkoxycarbonylnitrone derivatives with $Eu(fod)_3$. $Eu(fod)_3$ selectively activated the *Z*-isomer of nitrones (**1**) existing as *E*,*Z*-equilibrium mixtures by forming the (*Z*)-**1**–$Eu(fod)_3$ complex, which reacts with vinyl ethers to give the *trans*-adducts stereoselectively. In the reaction of *E*-geometry-fixed cyclic nitrone, the major product is different from that of the reaction without $Eu(fod)_3$. In the case of allyl alcohols **12**, $Eu(fod)_3$ promoted the transesterification between the nitrones **1** and allyl alcohols.

4. Experimental

4.1. General

All melting points were determined with a Yanagimoto MP-21 melting point apparatus and were uncorrected. Infrared (IR) spectra were recorded on Hitachi 270-30 and Shimadzu FTIR-8100 spectrometers. ^{1}H NMR spectra were measured with a JEOL JNM-EX270 (270 MHz) or a JEOL-JNM-AL300 (300 MHz) spectrometer. The chemical shifts are expressed in parts per million downfield from tetramethylsilane, using tetramethylsilane (δ=0) and/or residual chloroform (δ=7.25) as an internal standard. Splitting patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad signal. Mass spectra were taken with a JEOL JMS-DX302 mass spectrometer. Unless otherwise noted, all experiments were carried out under an atmosphere of dry argon using anhydrous solvents. For thin layer chromatographic (TLC) analyses, Merck precoated TLC plates (silica gel 60 F_{254}, 0.25 mm, Art 5715) were used.

4.2. Methyl [(phenylmethyl)imino]acetate *N*-oxide (1a)

This was prepared from *N*-benzylhydroxylamine and methyl glyoxylate hemiacetal in refluxing benzene employing a Dean–Stark trap; mp 89–92 °C (hexane–AcOEt) (lit.,[3a] mp 90–92 °C).

4.3. Methyl [(diphenylmethyl)imino]acetate *N*-oxide (1b)

This was prepared from *N*-diphenylmethylhydroxylamine[20] and methyl glyoxylate by the same procedure as that described for **1a**; mp 133.5–134 °C (hexane–AcOEt) (lit.,[3a] mp 131.5–132.5 °C).

4.4. General procedure A: cycloaddition of α-methoxycarbonylnitrones (1a,b) with vinyl ethers (7a–d) in the absence of $Eu(fod)_3$ (Table 1, entries 1, 3, 5, 8, and 10)

To a stirred solution of **1** (1 equiv) in $ClCH_2CH_2Cl$ was added **7** (20 equiv) at room temperature. After completion of the reaction, the mixture was concentrated in vacuo to give a crude product, which was purified by column chromatography on silica gel (hexane/AcOEt=4:1) to afford the cycloadduct **8** as an inseparable mixture of *trans*-**8** and *cis*-**8**.

4.5. General procedure B: cycloaddition of α-methoxycarbonylnitrones (1a,b) with vinyl ethers (7a–d) in the presence of $Eu(fod)_3$ (Table 1, entries 2, 4, 6, 7, 9, and 11)

To a stirred mixture of **1** (1 equiv) and $Eu(fod)_3$ (1 equiv) in $ClCH_2CH_2Cl$ was added **7** (20 equiv) at room temperature. After completion of the reaction, the mixture was diluted with $CHCl_3$ and washed successively with a 10% aqueous solution of tartaric acid and brine. The organic phase was subjected to column chromatography on Al_2O_3 to remove fod. Further purification by column chromatography on silica gel (hexane/AcOEt=4:1) afforded mainly *trans*-**8**.

4.6. Methyl (5-ethoxy-2-phenylmethylisoxazolidine-3-yl)carboxylate (8a) (Table 1, entries 1 and 2)

Following general procedure A, a 78:22 mixture (21.9 mg, 96%) of *trans*-**8a** and *cis*-**8a** was obtained from **1a** (16.7 mg, 87 μmol), **7a** (160 μl, 1.7 mmol), and $ClCH_2CH_2Cl$ (1.5 ml) (Table 1, entry 1). ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.16 (t, 3H×22/100, *J*=7.3 Hz), 1.23 (t, 3H×78/100, *J*=7.3 Hz), 2.59 (ddd, 1H×78/100, *J*=1.7, 7.6, 12.9 Hz), 2.5–2.8 (m, 2H×22/100), 2.76 (ddd, 1H×78/100, *J*=5.3, 7.3, 12.9 Hz), 3.35–3.85 (m, 3H×22/100), 3.48 (qd, 1H×78/100, *J*=7.3, 9.6 Hz), 3.67 (s, 3H×78/100), 3.69 (s, 3H×22/100), 3.80 (qd, 1H×78/100, *J*=7.3, 9.6 Hz), 3.94 (br t, 1H×78/100, *J*=7.6 Hz), 4.05 (d, 1H×22/100, *J*=13.9 Hz), 4.17 (d, 1H×78/100, *J*=12.9 Hz), 4.19 (d, 1H×22/100, *J*=13.9 Hz), 4.35 (d, 1H×78/100, *J*=12.9 Hz), 5.16 (dd, 1H×22/100, *J*=2.3, 5.6 Hz), 5.26 (br d, 1H×78/100, *J*=5.3 Hz), 7.24–7.42 (m, 5H).

Following general procedure B, an 85:15 mixture (18.7 mg, 87%) of *trans*-**8a** and *cis*-**8a** was obtained from **1a** (15.7 mg, 87 μmol), **7a** (160 μl, 1.7 mmol), $Eu(fod)_3$ (90 mg, 87 μmol), and $ClCH_2CH_2Cl$ (1.5 ml) (Table 1, entry 2). IR ($CHCl_3$) 1742 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.16 (t, 3H×15/100, J=7.3 Hz), 1.23 (t, 3H×85/100, J=7.3 Hz), 2.59 (ddd, 1H×85/100, J=1.7, 7.6, 12.9 Hz), 2.5–2.8 (m, 2H×15/100), 2.76 (ddd, 1H×85/100, J=5.3, 7.3, 12.9 Hz), 3.35–3.85 (m, 3H×15/100), 3.48 (qd, 1H×85/100, J=7.3, 9.6 Hz), 3.67 (s, 3H×85/100), 3.69 (s, 3H×15/100), 3.80 (qd, 1H×85/100, J=7.3, 9.6 Hz), 3.94 (br t, 1H×85/100, J=7.6 Hz), 4.05 (d, 1H×15/100, J=13.9 Hz), 4.17 (d, 1H×85/100, J=12.9 Hz), 4.19 (d, 1H×15/100, J=13.9 Hz), 4.35 (d, 1H×85/100, J=12.9 Hz), 5.16 (dd, 1H×15/100, J=2.3, 5.6 Hz), 5.26 (br d, 1H×85/100, J=5.3 Hz), 7.24–7.42 (m, 5H); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 14.9, 15.0, 39.7, 52.4, 63.3, 65.0, 65.4, 103.5, 127.4, 128.3, 129.0, 137.0, 171.5; MS (*m*/*z*) 265 (0.3), 220 (28), 175 (10), 143 (13), 116 (43), 105 (100); HRMS calcd for $C_{14}H_{19}NO_4$: 265.1314, found: 265.1309.

4.7. Methyl (2-diphenylmethyl-5-ethoxyisoxazolidine-3-yl)carboxylate (8b) (Table 1, entries 3 and 4)

Following general procedure A, a 72:28 mixture (31.4 mg, 89%) of *trans*-**8b** and *cis*-**8b** was obtained from **1b** (23.2 mg, 86 μmol), **7a** (160 μl, 1.7 mmol), and $ClCH_2CH_2Cl$ (1.5 ml) (Table 1, entry 3). ^1H NMR (270 MHz, $CDCl_3$) δ 1.14 (t, 3H×72/100, J=7.3 Hz), 1.23 (t, 3H×28/100, J=7.3 Hz), 2.45–2.72 (m, 2H×28/100), 2.60 (ddd, 1H×72/100, J=2.3, 7.9, 13.2 Hz), 2.80 (td, 1H×72/100, J=5.6, 13.2 Hz), 3.25 (qd, 1H×72/100, J=7.3, 9.6 Hz), 3.31–3.44 (m, 2H×28/100), 3.42 (s, 3H×28/100), 3.38 (qd, 1H×72/100, J=7.3, 9.6 Hz), 3.59 (s, 3H×72/100), 3.77 (dd, 1H×28/100, J=6.9, 9.6 Hz), 4.02 (dd, 1H×72/100, J=5.6, 7.8 Hz), 4.91 (br s, 1H×28/100), 5.14 (dd, 1H×28/100, J=2.0, 5.9 Hz), 5.25 (br dd, 1H×72/100, J=2.3, 5.6 Hz), 5.28 (br s, 1H×72/100), 7.10–7.60 (m, 10H).

Following general procedure B, *trans*-**8b** (29.5 mg, quant) was obtained from **1b** (23.3 mg, 87 μmol), **7a** (160 μl, 1.7 mmol), $Eu(fod)_3$ (89.8 mg, 87 μmol), and $ClCH_2CH_2Cl$ (1.5 ml) (Table 1, entry 4). Mp 64–65 °C (MeOH–H_2O); IR ($CHCl_3$) 1743 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.14 (t, 3H, J=7.3 Hz), 2.60 (ddd, 1H, J=2.3, 7.9, 13.2 Hz, spin saturation at δ=4.02 → NOE 6%), 2.80 (td, 1H, J=5.6, 13.2 Hz, spin saturation at δ=5.25 → NOE 6%), 3.25 (qd, 1H, J=7.3, 9.6 Hz), 3.38 (qd, 1H, J=7.3, 9.6 Hz), 3.59 (s, 3H), 4.02 (dd, 1H, J=5.6, 7.8 Hz), 5.25 (br dd, 1H, J=2.3, 5.6 Hz), 5.28 (br s, 1H), 7.10–7.35 (m, 6H), 7.48 (br d, 2H, J=7.9 Hz), 7.57 (br d, 2H, J=7.9 Hz); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 14.8, 39.6, 52.2, 63.7, 64.3, 77.1, 104.3, 126.9, 127.2, 127.8, 128.0, 128.2, 128.7, 141.4, 142.7, 172.2; HRMS calcd for $C_{20}H_{23}NO_4$: 341.1627, found: 341.1616.

4.8. Methyl [5-(*n*-butyloxy)-2-diphenylmethylisoxazolidine-3-yl]carboxylate (8c) (Table 1, entries 5–7)

Following general procedure A, a 75:25 mixture (17.4 mg, 73%) of *trans*-**8c** and *cis*-**8c** was obtained from **1b** (17.2 mg, 64 μmol), **7b** (164 μl, 1.3 mmol), and $ClCH_2CH_2Cl$ (1.5 ml) (Table 1, entry 5). ^1H NMR (270 MHz, $CDCl_3$) δ 0.90 (t, 3H, J=7.3 Hz), 1.2–1.7 (m, 4H), 2.4–2.9 (m, 2H), 3.1–3.8 (m, 2H+25/100H), 3.43 (s, 3H×25/100), 3.57 (s, 3H×75/100), 4.00 (dd, 1H×75/100, J=6.0, 7.3 Hz), 4.91 (s, 1H×25/100), 5.13 (br dd, 1H×25/100, J=2.0, 5.9 Hz), 5.25 (br dd, 1H×75/100, J=2.0, 6.0 Hz), 5.25 (s, 1H×75/100), 7.1–7.6 (m, 10H).

Following general procedure B, compound *trans*-**8c** (26.0 mg, quant) was obtained from **1b** (17.9 mg, 67 μmol), **7a** (160 μl, 1.3 mmol), $Eu(fod)_3$ (66.4 mg, 64 μmol), and $ClCH_2CH_2Cl$ (1.5 ml) (Table 1, entry 6). Furthermore, *trans*-**8c** (19.5 mg, 85%) was also obtained from **1b** (16.7 mg, 60 μmol), **7a** (23 μl, 0.18 mmol), $Eu(fod)_3$ (18.6 mg, 18 μmol), and $ClCH_2CH_2Cl$ (1.5 ml) (Table 1, entry 7). Mp 49–50 °C (MeOH–H_2O); IR ($CHCl_3$) 1740 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.90 (t, 3H, J=7.3 Hz), 1.32 (br sext, 2H, J=7.3 Hz), 1.42–1.58 (m, 2H), 2.59 (ddd, 1H, J=2.0, 7.6, 12.9 Hz), 2.77 (br td, 1H, J=6.0, 12.9 Hz), 3.18 (td, 1H, J=6.9, 9.2 Hz), 3.36 (td, 1H, J=6.9, 9.2 Hz), 3.57 (s, 3H), 4.00 (dd, 1H, J=6.0, 7.3 Hz), 5.23 (dd, 1H, J=2.0, 6.0 Hz), 5.25 (s, 1H), 7.14–7.31 (m, 6H), 7.46 (br d, 2H, J=6.9 Hz), 7.57 (br d, 2H, J=6.9 Hz); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 14.0, 19.3, 31.6, 39.9, 52.3, 64.5, 68.2, 77.2, 104.5, 126.8, 12.2, 127.8, 128.1, 128.2, 128.6, 141.3, 142.7, 172.3; HRMS calcd for $C_{22}H_{27}NO_4$: 369.1940, found: 369.1925.

4.9. Methyl [5-(*iso*-butyloxy)-2-diphenylmethylisoxazolidine-3-yl]carboxylate (8d) (Table 1, entries 8 and 9)

Following general procedure A, a 74:26 mixture (17.5 mg, 76%) of *trans*-**8d** and *cis*-**8d** was obtained from **1b** (16.7 mg, 62 μmol), **7c** (160 μl, 1.2 mmol), and $ClCH_2CH_2Cl$ (1.5 ml) (Table 1, entry 8). ^1H NMR (270 MHz, $CHCl_3$) δ 0.90 (d, 6H×74/100, J=6.6 Hz), 0.92 (d, 6H×26/100, J=6.6 Hz), 1.26 (m, 1H×26/100), 1.82 (sept, 1H×74/100, J=6.6 Hz), 2.4–2.8 (m, 2H), 2.94 (dd, 1H×74/100, J=6.6, 9.2 Hz), 3.08 (dd, 1H×26/100, J=6.9, 9.6 Hz), 3.19 (dd, 1H×74/100, J=6.6, 9.2 Hz), 3.44 (s, 3H×26/100), 3.4–3.7 (m, 2H×26/100), 3.56 (s, 3H×74/100), 4.00 (br t, 1H×74/100, J=7.3 Hz), 4.91 (s, 1H×26/100), 5.11 (dd, 1H×26/100, J=2.3, 5.3 Hz), 5.21 (br dd, 1H×74/100, J=2.0, 5.3 Hz), 5.24 (s, 1H×74/100), 7.1–7.7 (m, 10H).

Following general procedure B, *trans*-**8d** (18.5 mg, 89%) was obtained from **1b** (15.2 mg, 57 μmol), **7c** (160 μl, 1.2 mmol), $Eu(fod)_3$ (59.0 mg, 57 μmol), and $ClCH_2CH_2Cl$ (1.5 ml) (Table 1, entry 9). Mp 53–54 °C; IR ($CHCl_3$) 1740 cm^{-1}; ^1H NMR (270 MHz, $CHCl_3$) δ 0.90 (d, 6H, J=6.6 Hz), 1.82 (sept, 1H, J=6.6 Hz), 2.58 (ddd, 1H, J=2.0, 7.9, 12.9 Hz), 2.24 (ddd, 1H, J=5.3, 6.6, 12.9 Hz), 2.94 (dd, 1H, J=6.6, 9.2 Hz), 3.19 (dd, 1H, J=6.6, 9.2 Hz), 3.56 (s, 3H), 4.00 (br t, 1H, J=7.3 Hz), 5.21 (br dd, 1H, J=2.0, 5.3 Hz), 5.24 (s, 1H), 7.14–7.34 (m, 6H), 7.45 (br d, 2H, J=8.6 Hz), 7.57 (br d, 2H, J=8.6 Hz); MS (*m*/*z*) 369 (11), 296 (4), 167 (100%); HRMS calcd for $C_{22}H_{27}NO_4$: 369.1940, found: 369.1940.

4.10. Methyl [5-cyclohexyloxy-2-diphenylmethylisoxazolidine-3-yl]carboxylate (8e) (Table 1, entries 10 and 11)

Following general procedure A, a 71:29 mixture (25.1 mg, 83%) of *trans*-**8e** and *cis*-**8e** was obtained from **1b**

(17.6 mg, 65 μmol), **7d** (170 μl, 1.2 mmol), and $ClCH_2CH_2Cl$ (1.5 ml) (Table 1, entry 10). ^1H NMR (270 MHz, $CDCl_3$) 1.1–2.0 (m, 10H), 2.4–2.8 (m, 2H), 3.33 (m, 1H×71/100), 3.4–3.9 (m, 2H×29/100), 3.45 (s, 3H×29/100), 3.55 (s, 3H×71/100), 3.99 (dd, 1H×71/100, J=6.6, 7.6 Hz), 4.95 (s, 1H×29/100), 5.26 (s, 1H×71/100), 5.29 (dd, 1H×29/100, J=2.3, 5.6 Hz), 5.42 (dd, 1H×71/100, J=2.0, 5.6 Hz), 7.1–7.6 (m, 10H).

Following general procedure B, *trans*-**8e** (22.2 mg, 92%) was obtained from **1b** (16.5 mg, 61 μmol), **7d** (170 μl, 1.2 mmol), $Eu(fod)_3$ (61.3 mg, 590 μmol) and $ClCH_2CH_2Cl$ (1.5 ml) (Table 1, entry 11). IR ($CHCl_3$) 1740 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) 1.1–1.9 (m, 10H), 2.55 (ddd, 1H, J=2.0, 7.6, 12.9 Hz), 2.73 (ddd, 1H, J=5.6, 6.6, 12.9 Hz), 3.33 (m, 1H), 3.55 (s, 3H), 3.99 (dd, 1H, J=6.6, 7.6 Hz), 5.26 (s, 1H), 5.42 (dd, 1H, J=2.0, 5.6 Hz), 7.1–7.3 (m, 6H), 7.45 (br d, 2H, J=8.3 Hz), 7.57 (br d, 2H, J=8.3 Hz); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 23.8, 24.1, 25.6, 30.9, 33.3, 40.3, 52.1, 64.6, 74.9, 77.2, 101.2, 126.8, 127.1, 127.8, 128.2, 128.6, 141.2, 142.7, 172.4; MS (m/z) 395 (12), 182 (6), 167 (100); HRMS calcd for $C_{24}H_{29}NO_4$: 395.2097, found: 395.2093.

4.11. (1*R*,5*R*,8*R*)-6-Aza-8-ethoxy-3,7-dioxa-5-phenylbicyclo[4.3.0]nonan-2-one (11a), (1*S*,5*R*,8*S*)-isomer (11b), and (1*R*,5*R*,8*S*)-isomer (11c)

A solution of the nitrone **10** (57.3 mg, 0.30 mmol), **7a** (0.08 ml, 0.86 mmol), and $Eu(fod)_3$ (311 mg, 0.30 mmol) in benzene (5 ml) was stirred at room temperature for 15 h. The mixture was diluted with benzene, washed successively with a 10% aqueous solution of tartaric acid and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed on silica gel with hexane–AcOEt (4:1) to give a 48:39:13 mixture of **11b**, **11c**, and **11a** (68.7 mg, 87%). The ratio was estimated on the basis of integrations of the triplets (OCH_2CH_3) in the ^1H NMR spectrum of the mixture. ^1H NMR (300 MHz, $CDCl_3$) δ 1.13 (t, 3H×39/100, J=7.1 Hz, **11c**), 1.19 (t, 3H×13/100, J=7.1 Hz, **11a**), 1.21 (t, 3H×48/100, J=7.1 Hz, **11b**). The mixture was subjected to column chromatography on silica gel with hexane–AcOEt (4:1). The first fraction gave a mixture of **11a** and **11b**, and the second fraction gave **11c**. Further chromatography of the mixture of **11a** and **11b** on silica gel with toluene–ether (20:1) gave **11a** and **11b**. Compound **11a**: ^1H NMR (300 MHz, $CDCl_3$) δ 1.19 (t, 3H, J=7.1 Hz), 2.68 (ddd, 1H, J=1.0, 8.2, 13.2 Hz), 2.79 (ddd, 1H, J=5.0, 8.9, 13.2 Hz), 3.42 (qd, 1H, J=7.1, 9.6 Hz), 3.72 (qd, 1H, J=7.1, 9.6 Hz), 4.12 (dd, 1H, J=3.6, 9.9 Hz), 4.27 (dd, 1H, J=9.9, 11.9 Hz), 4.36 (dd, 1H, J=3.6, 11.9 Hz), 4.49 (br t, 1H, J=8.2 Hz), 5.19 (br d, 1H, J=5.0 Hz), 7.32–7.50 (m, 5H). This spectrum was identical with that of an authentic sample.[7c] Compound **11b**: mp 144–145 °C (hexane–CH_2Cl_2); $[\alpha]_D^{23}$ 2.24 (c 0.151, $CHCl_3$); IR (KBr) 1730 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.21 (t, 3H, J=7.2 Hz), 2.70 (ddd, 1H, J=2.7, 9.0, 14.0 Hz), 2.99 (ddd, 1H, J=1.5, 6.3, 14.0 Hz), 3.51 (ddd, 1H, J=7.2, 9.6, 14.3 Hz), 3.75 (ddd, 1H, J=7.2, 9.6, 14.3 Hz), 4.33 (dd, 1H, J=1.5, 9.0 Hz), 4.57 (dd, 1H, J=4.5, 11.0 Hz), 4.65 (br dd, 1H, J=4.5, 11.0 Hz), 5.11 (t, 1H, J=11.1 Hz), 5.27 (br d, 1H, J=6.3 Hz), 7.31–7.49 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 15.0, 41.1, 59.6, 62.0, 64.2, 67.3, 100.6, 127.4, 128.2, 128.6, 134.9, 170.4; HRMS calcd for $C_{14}H_{17}NO_4$: 263.1158, found: 263.1166.

Compound **11c**: mp 133.5–136.5 °C (hexane–CH_2Cl_2); $[\alpha]_D^{23}$ +38.9 (c 0.196, $CHCl_3$); IR (KBr) 1753 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.13 (t, 3H, J=7.1 Hz), 2.82 (ddd, 1H, J=2.3, 7.3, 13.5 Hz), 3.01 (ddd, 1H, J=5.9, 10.2, 13.5 Hz), 3.32 (qd, 1H, J=7.1, 9.3 Hz), 3.48 (qd, 1H, J=7.1, 9.3 Hz), 4.20 (dd, 1H, J=9.9, 11.5 Hz), 4.26 (dd, 1H, J=3.9, 11.5 Hz), 4.43 (dd, 1H, J=7.5, 10.5 Hz), 4.64 (dd, 1H, J=4.3, 9.9 Hz), 5.19 (dd, 1H, J=2.3, 5.6 Hz), 7.32–7.48 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.8, 41.3, 61.7, 63.9, 64.3, 70.5, 103.2, 127.6, 128.6, 128.8, 135.9, 169.3; HRMS calcd for $C_{14}H_{17}NO_4$: 263.1167, found: 263.1179.

4.12. General procedure C: transesterification and intramolecular cycloaddition of the nitrone 1a with allyl alcohols 12

A suspension of the nitrone **1b**, allyl alcohol **12**, $Eu(fod)_3$, and 4 Å MS in $ClCH_2CH_2Cl$ was stirred at the temperature indicated in Table 4 for a period. After filtration, the filtrate was diluted with CH_2Cl_2, washed successively with 10% aqueous solution of tartaric acid and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed on Al_2O_3 with CH_2Cl_2 to give the crude cycloadduct **13**, which was further chromatographed on silica gel with *n*-hexane–AcOEt to afford **13**.

4.13. (3a*R**,6a*R**)-Tetrahydro-1-diphenylmethyl-1*H*,6*H*-furo[3,4-*c*]isoxazole-6-one (13a)

A crude product was obtained from **1b** (28.9 mg, 0.11 mmol), **12a** (56 μl, 0.82 mmol), $Eu(fod)_3$ (112 mg, 0.11 mmol), and 4 Å MS (300 mg). Purification by preparative TLC on silica gel with CH_2Cl_2 gave **13a** (21.5 mg, 68%). ^1H NMR (270 MHz, $CDCl_3$) δ 3.52 (m, 1H), 3.89 (dd, 1H, J=2.3, 9.2 Hz), 4.13 (d, 1H, J=8.3 Hz), 4.26 (dd, 1H, J=2.6, 9.6 Hz), 4.33 (dd, 1H, J=7.5, 9.0 Hz), 4.43 (dd, 1H, J=7.3, 9.6 Hz), 4.96 (br s, 1H), 7.17–7.37 (m, 6H), 7.5–7.58 (m, 4H). This spectrum was identical with that of an authentic sample.[19a]

4.14. (3*R**,3a*R**,6a*R**)-Tetrahydro-3-phenyl-1-diphenylmethyl-1*H*,6*H*-furo[3,4-*c*]isoxazol-6-one (13b)

A crude product was obtained from **1b** (30.0 mg, 0.112 mmol), **12b** (114 mg, 0.56 mmol), $Eu(fod)_3$ (116 mg, 0.112 mmol), and 4 Å MS (300 mg). Purification by preparative TLC on silica gel with CH_2Cl_2 gave **13a** (37.7 mg, 92%). ^1H NMR (270 MHz, $CDCl_3$) δ 3.37 (dddd, 1H, J=3.0, 5.6, 6.3, 8.6 Hz), 4.16 (d, 1H, J=8.6 Hz), 4.41 (dd, 1H, J=9.9, 5.6 Hz), 4.45 (dd, 1H, J=9.9, 3.0 Hz), 4.97 (d, 1H, J=6.3 Hz), 5.29 (s, 1H), 7.15–7.38 (m, 11H), 7.42–7.60 (m, 4H). This spectrum was identical with that of an authentic sample.[19a]

4.15. (3*R**,3a*S**,4*S**,6a*R**)-Tetrahydro-1-diphenylmethyl-3,4-propano-1*H*,6*H*-furo[3,4-*c*]isoxazol-6-one (13c)

A crude product was obtained from **1b** (30.0 mg, 0.111 mmol), **12c** (34 μl, 0.33 mmol), $Eu(fod)_3$ (11.6 mg,

0.011 mmol), and 4 Å MS (300 mg). Purification by preparative TLC on silica gel with CH_2Cl_2 gave **13c** (26.4 mg, 71%). ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.31–1.70 (m, 4H), 1.90–2.05 (m, 1H), 2.15–2.27 (m, 1H), 3.25 (q, 1H, J=7.6 Hz), 4.28 (d, 1H, J=8.6 Hz), 4.45 (br, 1H), 4.62 (dt, 1H, J=2.6, 6.9 Hz), 5.05 (br s, 1H), 7.17–7.35 (m, 6H), 7.52–7.58 (m, 4H). This spectrum was identical with that of an authentic sample.[19a]

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Supplementary data

Calculated geometries of compounds (*E*)-**3**, (*Z*)-**3**, and **4**–**6**; ^{1}H NMR spectra of diastereomeric mixtures of **8a**–**d**; ^{1}H NMR spectra of *trans*-**8a**–**d**; ^{1}H NMR spectra of **1b**, **9**, **7a**, and **10**; ^{1}H NMR spectra of **1b**, **9**, **7a**, and **10** with Eu(fod)$_3$; ^{1}H NMR spectra of **13a**–**c**. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.10.014.

References and notes

1. For general reviews on cycloadditions of nitrones, see: (a) Confalone, P. N.; Huie, E. M. *Org. React.* **1988**, *36*, 1–173; (b) Frederickson, M. *Tetrahedron* **1997**, *53*, 403–425; (c) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863–909; (d) Osborn, H. M. I.; Gemmell, N.; Harwood, L. M. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2419–2438; (e) Adams, J. P. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2586–2597; (f) Ishikawa, T.; Kudoh, T.; Saito, S. *Yuki Gosei Kagaku Kyokaishi* **2003**, *61*, 1186–1194.
2. For recent examples on cycloadditions of α-alkoxycarbonylnitrones, see: (a) Baumgartner, H.; O'Sullivan, A. C.; Schneider, J. *Heterocycles* **1997**, *45*, 1537–1549; (b) Chiacchio, U.; Rescifina, A.; Iannazzo, D.; Romeo, G. *J. Org. Chem.* **1999**, *64*, 28–36; (c) Ondrus, V.; Orsag, M.; Fisera, L.; Pronayova, N. *Tetrahedron* **1999**, *55*, 10425–10436.
3. (a) Inouye, Y.; Hara, J.; Kakisawa, H. *Chem. Lett.* **1980**, 1407–1410; (b) Inouye, Y. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 244–247; (c) Inouye, Y.; Takaya, K.; Kakisawa, H. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 3541–3542; (d) Aurich, H. G.; Franzke, M.; Kesselheim, H. P. *Tetrahedron* **1992**, *48*, 663–668.
4. Kanemasa, S.; Tsuruoka, T. *Chem. Lett.* **1995**, 49–50.
5. Tokunaga, Y.; Ihara, M.; Fukumoto, K. *Tetrahedron Lett.* **1996**, *37*, 6157–6160.
6. (a) Jensen, K. B.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **1999**, *64*, 2353–2360. See also, (b) Ueda, M.; Miyabe, H.; Teramachi, M.; Miyata, O.; Naito, T. *J. Org. Chem.* **2005**, *70*, 6653–6660.
7. For intermolecular cycloaddition of six-membered ring lactone-type nitrones, see: (a) Tamura, O.; Gotanda, K.; Terashima, R.; Kikuchi, M.; Miyawaki, T.; Sakamoto, M. *Chem. Commun.* **1996**, 1861–1862; (b) Tamura, O.; Kuroki, T.; Sakai, Y.; Takizawa, J.; Yoshino, J.; Morita, Y.; Mita, N.; Gotanda, K.; Sakamoto, M. *Tetrahedron Lett.* **1999**, *40*, 895–898; (c) Tamura, O.; Gotanda, K.; Yoshino, J.; Morita, Y.; Terashima, R.; Kikuchi, M.; Miyawaki, T.; Mita, N.; Yamashita, M.; Ishibashi, H.; Sakamoto, M. *J. Org. Chem.* **2000**, *65*, 8544–8551; (d) Tamura, O.; Yoshida, S.; Sugita, H.; Mita, N.; Uyama, Y.; Morita, N.; Ishiguro, M.; Kawasaki, T.; Ishibashi, H.; Sakamoto, M. *Synlett* **2000**, 1553–1556; (e) Tamura, O.; Shiro, T.; Toyao, A.; Ishibashi, H. *Chem. Commun.* **2003**, 2678–2679; (f) Tamura, O.; Shiro, T.; Ogasawara, M.; Toyao, A.; Ishibashi, H. *J. Org. Chem.* **2005**, *70*, 4569–4577; (g) Baldwin, S. W.; Young, B. G.; McPhail, A. T. *Tetrahedron Lett.* **1998**, *39*, 6819–6822; (h) Long, A.; Baldwin, S. W. *Tetrahedron Lett.* **2001**, *42*, 5343–5345; (i) O'Mahony, C.; Heaney, F. *Chem. Commun.* **1996**, 167–168; (j) Heaney, F.; O'Mahony, C. *J. Chem. Soc., Perkin Trans. 1* **1998**, 341–350; (k) Heaney, F.; Fenlon, J.; O'Mahony, C.; McArdle, P.; Cunningham, D. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3382–3392; (l) Heaney, F.; Fenlon, J.; O'Mahony, C.; McArdle, P.; Cunningham, D. *Org. Biomol. Chem.* **2003**, *1*, 4302–4316. For intramolecular cycloaddition of six-membered ring nitrones, see: (m) Looper, R. E.; Williams, R. M. *Tetrahedron Lett.* **2001**, *42*, 769–771; (n) Looper, R. E.; Williams, R. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2930–2933; (o) Looper, R. E.; Runnegar, M. T. C.; Williams, R. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 3879–3881.
8. For cycloaddition of six-membered ring lactam-type nitrones, see: (a) Bernotas, R. C.; Adams, G. *Tetrahedron Lett.* **1996**, *37*, 7343–7344; (b) Bernotas, R. C.; Adams, G. *Tetrahedron Lett.* **1996**, *37*, 7339–7342; (c) Bernotas, R. C.; Sing, L.; Friedrich, D. *Synthesis* **2005**, 465–469; (d) Heaney, F.; Fenlon, J.; McArdle, P.; Cunningham, D. *Org. Biomol. Chem.* **2003**, *1*, 1122–1132; (e) Wierschem, F.; Rueck-Braun, K. *Eur. J. Org. Chem.* **2004**, 2321–2324.
9. For cycloaddition of five-membered ring lactone-type nitrones, see: (a) Katagiri, N.; Sato, H.; Kurimoto, A.; Okada, M.; Yamada, A.; Kaneko, C. *J. Org. Chem.* **1994**, *59*, 8101–8106; (b) Katagiri, N.; Okada, M.; Kaneko, C.; Furuya, T. *Tetrahedron Lett.* **1996**, *37*, 1801–1804; (c) Katagiri, N.; Okada, M.; Morishita, Y.; Kaneko, C. *Chem. Commun.* **1996**, 2137–2138; (d) Katagiri, N.; Okada, M.; Morishita, Y.; Kaneko, C. *Tetrahedron* **1997**, *53*, 5725–5746.
10. For five-membered ring lactam-type nitrones, see: (a) Westermann, B.; Walter, A.; Florke, U.; Altenbach, H. *Org. Lett.* **2001**, *3*, 1375–1378; (b) Baldwin, S. W.; Long, A. *Org. Lett.* **2004**, *6*, 1653–1656; (c) Cantagrel, F.; Pinet, S.; Gimbert, Y.; Chavant, P. *Eur. J. Org. Chem.* **2005**, 2694–2701.
11. Tamura, O.; Mita, N.; Gotanda, K.; Yamada, K.; Nakano, T.; Katagiri, R.; Sakamoto, M. *Heterocycles* **1997**, *46*, 95–99.
12. The calculations were conducted by using Spartan'04 for Windows.
13. For reviews on Lewis acid catalyzed cycloaddition of nitrones, see: (a) Gothelf, K. V.; Jørgensen, K. A. *Chem. Commun.* **2000**, 1449–1458; (b) Kanemasa, S. *Synlett* **2002**, 1371–1387; (c) Gothelf, K. V. Asymmetric Metal-catalyzed 1,3-Dipolar Cycloaddition Reactions. In *Cycloaddition Reactions in Organic Synthesis*; Kobayashi, S., Jørgensen, K. A., Eds.; Wiley-VCH: Weinheim, 2002; pp 211–247; (d) Ukaji, Y.; Inomata, K. *Synlett* **2003**, 1075–1087.
14. For recent examples on Lewis acid catalyzed cycloaddition of nitrones with vinyl ethers, see: (a) Seerden, J. G.; Boeren, M. M. M.; Scheeren, H. W. *Tetrahedron* **1997**, *53*, 11843–11852; (b) Hori, K.; Ito, J.; Ohta, T.; Furukawa, I.

Tetrahedron **1998**, *54*, 12737–12744; (c) Bayon, P.; De March, P.; Figueredo, M.; Font, J. *Tetrahedron* **1998**, *54*, 15691–15700; (d) Ellis, W. W.; Gavrilova, A.; Liable-Sands, L.; Rheingold, A. L.; Bosnich, B. *Organometallics* **1999**, 332–338; (e) Simonsen, K. B.; Bayon, P.; Hazell, R. G.; Gothelf, K. V.; Jørgensen, K. A. *J. Am. Chem. Soc.* **1999**, *121*, 3845–3853; (f) Domingo, L. R. *Eur. J. Org. Chem.* **2000**, 2265–2272; (g) Sellner, H.; Faber, C.; Rheiner, P. B.; Seebach, D. *Chem.—Eur. J.* **2000**, *6*, 3692–3705; (h) Jensen, K. B.; Roberson, M.; Jørgensen, K. A. *J. Org. Chem.* **2000**, *65*, 9080–9084; (i) Dugovic, B.; Wiesenganger, T.; Fisera, L.; Hametner, C.; Pronayova, N. *Heterocycles* **2005**, *65*, 591–605.

15. Eu-shift reagents are known to catalyse aldol reaction of α-alkoxy aldehydes with ketene silyl acetals by forming chelate complexes, see: (a) Mikami, K.; Terada, M.; Nakai, T. *J. Org. Chem.* **1991**, *56*, 5456–5459; (b) Gu, J. H.; Terada, M.; Mikami, K.; Nakai, T. *Tetrahedron Lett.* **1992**, *33*, 1465–1468; (c) Mikami, K.; Terada, M.; Nakai, T. *J. Chem. Soc., Chem. Commun.* **1993**, 343–345.
16. For Diels–Alder reaction using Eu-shift reagents, see: (a) Molander, G. A. *Chem. Rev.* **1992**, *92*, 29–68; (b) Bednarski, M.; Danishefsky, S. *J. Am. Chem. Soc.* **1983**, *105*, 3716–3717; For recent examples, see: (c) Lowe, R. F.; Stoodley, R. J. *Tetrahedron Lett.* **1994**, *35*, 6351–6354; (d) Marko, I. E.; Evans, G. R.; Declercq, J. *Tetrahedron* **1994**, *50*, 4557–4574; (e) Sha, C.; Shen, C.; Lee, R.; Lee, S.; Wang, S. *Tetrahedron Lett.* **1995**, *36*, 1283–1286; (f) Degnan, A. P.; Kim, C. S.; Stout, C. W.; Kalivretenos, A. G. *J. Org. Chem.* **1995**, *60*, 7724–7725; (g) Wada, E.; Pei, W.; Yasuoka, H.; Chin, U.; Kanemasa, S. *Tetrahedron* **1996**, *52*, 1205–1220; (h) Arai, Y.; Masuda, T.; Masaki, Y.; Shiro, M. *Tetrahedron: Asymmetry* **1996**, *7*, 1199–1204; (i) Helliwell, M.; Phillips, I. M.; Pritchard, R. G.; Stoodley, R. J. *Tetrahedron Lett.* **1999**, *40*, 8651–8655; (j) Dai, W.-M.; Mak, W. L.; Wu, A. *Tetrahedron Lett.* **2000**, *41*, 7101–7105; (k) Dujardin, G.; Leconte, S.; Coutable, L.; Brown, E. *Tetrahedron Lett.* **2001**, *42*, 8849–8852; (l) Gaulon, C.; Dhal, R.; Chapin, T.; Maisonneuve, V.; Dujardin, G. *J. Org. Chem.* **2004**, *69*, 4192–4202.
17. For Eu(fod)$_3$-induced epimerization of an acetal, see Ref. 16c.
18. Crystal data for **11c**: $C_{14}H_{17}NO_4$, M_w=263.29, orthorhombic, $P2_12_12_1$, a=7.28050(10) Å, b=12.9039(2) Å, c=13.6564(3) Å, V=1282.98(4) Å^3, Z=4, Dc=1.363 g/cm^3, F(000)=560, colorless block crystal, dimensions of 0.20×0.18×0.13 mm. The data collection was performed at a temperature of 93(1) K to $2\theta_{max}$=136.5° ($-8\leq h\leq 8$, $-15\leq k\leq 15$, $-15\leq l\leq 16$) using a Rigaku RAXIS RAPID with graphite monochromated Cu Kα radiation. The structure was solved with direct methods 1. The non-hydrogen atoms were refined anisotropically and hydrogen atoms were refined using riding model. The final cycle of full-matrix least-squares refinement on F^2 was based on 1379 observed reflections and 174 variable parameters. $R[F^2>2\sigma(F^2)]$=0.0249, $wR(F^2)$=0.0644. Crystallographic data (excluding structural factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 618991. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (e-mail: deposit@ccdc.cam.ac.uk).
19. (a) Tamura, O.; Okabe, T.; Yamaguchi, T.; Gotanda, K.; Noe, K.; Sakamoto, M. *Tetrahedron* **1995**, *51*, 107–118; (b) Tamura, O.; Okabe, T.; Yamaguchi, T.; Gotanda, K.; Kotani, J.; Sakamoto, M. *Tetrahedron* **1995**, *51*, 119–128; (c) Tamura, O.; Mita, N.; Kusaka, N.; Suzuki, H.; Sakamoto, M. *Tetrahedron Lett.* **1997**, *38*, 429–432; (d) Tamura, O.; Iyama, N.; Ishibashi, H. *J. Org. Chem.* **2004**, *69*, 1475–1480. See also, (e) Chiacchio, U.; Corsaro, A.; Iannazzo, D.; Piperno, A.; Procopio, A.; Rescifina, A.; Romeo, G.; Romeo, R. *J. Org. Chem.* **2002**, *67*, 4380–4383.
20. Exner, O. *Chem. Listy* **1956**, *50*, 779–790.