

Lanthanide-Catalyzed endo-Selective Hetero Diels-Alder Reactions of 4-Substituted Methyl (E)-2-Oxo-3-butenates with Vinyl Ethers

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<https://doi.org/10.15017/7885>

出版情報：九州大学機能物質科学研究所報告. 11 (2), pp.181-184, 1997-12-15. Institute of
Advanced Material Study Kyushu University

バージョン：

権利関係：



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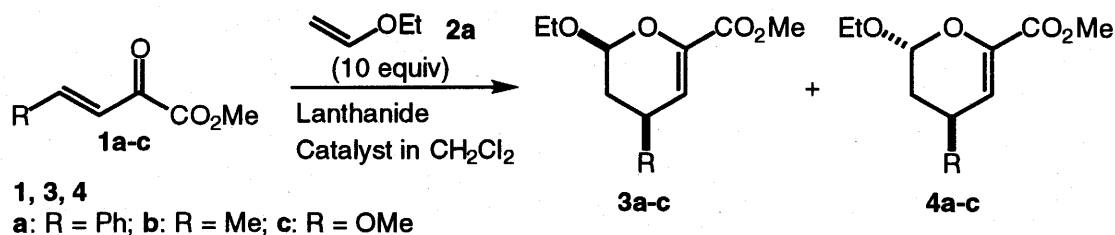
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Methyl (*E*)-2-oxo-4-phenyl-, -4-methyl-, and -4-methoxy-3-butenates as hetero 1,3-dienes undergo smooth hetero Diels-Alder reactions with vinyl ethers in the presence of a catalytic amount of lanthanide catalysts. The reactions are highly *endo*-selective producing 2,4-*cis*-3,4-dihydro-2*H*-pyrans in moderate to high yields, the configuration at 3-position depending on the stereochemistry of the starting vinyl ethers. Catalytic asymmetric version of this reaction was also examined by using chiral lanthanide catalysts, but enantioselectivity was not satisfactory.

The inverse electron demand hetero Diels-Alder reaction of 1-oxa-1,3-butadienes with vinyl ethers has proved to be a powerful method for the construction of dihydropyrans.¹⁾ Hetero Diels-Alder reactions are also useful for stereo controlled construction of acyclic framework through simple hydrolytic and reductive ring cleavage reactions of the resulting heterocycles.^{2,3)} Their synthetic importance as a construction method of stereochemically defined heterocycles and acyclic framework would be much increased if stereoselectivity of the reaction is improved. Thus, a several kinds of improvement for the construction of stereochemically defined heterocycles have been studied by modification of hetero 1,3-dienes and development of milder reaction conditions.³⁻⁶⁾ In addition, a few examples of asymmetric induction based on the Lewis acid-catalyzed diastereofacially selective reactions by using chiral 1-oxa-1,3-butadienes or chiral vinyl ethers have been described.⁷⁻¹²⁾ Recently, we have shown the first successful examples of chiral Lewis acid-catalyzed

intermolecular asymmetric hetero Diels-Alder reactions, in which 1-phenylsulfonyl-3-alken-2-ones as a new type of hetero 1,3-dienes and vinyl ethers are used in the presence of chiral titanium reagents.¹³⁾ In the course of our investigation along these catalyzed hetero Diels-Alder reactions, we came across the exclusive *endo*-selective cycloadditions in the presence of Eu(fod)₃.^{3,5a)} These results let us to investigate the applicability of lanthanide catalyst to *endo*-selective reactions of 4-substituted methyl (*E*)-2-oxo-3-butenates with vinyl ethers because problems of low *endo/exo* selectivity were reported in the reactions in the presence of Lewis acids such as TiCl₄ and EtAlCl₂.⁷⁾

In this communication we would like to present the reactions of methyl (*E*)-2-oxo-4-phenyl-, methyl-, and methoxy-3-butenates with vinyl ethers such as ethyl vinyl ether and (*E,Z*)-ethoxypropene in the presence of lanthanide catalysts. Some extensions to catalytic asymmetric reactions is also described.¹⁴⁾



Scheme 1

Received September 29, 1997

Dedicated to Professor Masashi Tashiro on the occasion of his retirement

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Table 1. Lanthanide-Catalyzed Hetero Diels-Alder Reactions of 4-Substituted Methyl (*E*)-2-Oxo-3-butenates 1a-c with Ethyl Vinyl Ether 2a^a

Entry	Enone	Catalyst (mol %)	Reaction conditions		Product (yield/%) ^b		
			Temp/°C	Time/h	ratio ^c	3 (% ee) ^d	
1	1a	Eu(fod) ₃ (2)	rt	12	3a,4a (71)	97: 3	–
2	1a	Yb(fod) ₃ (2)	rt	12	3a,4a (71)	97: 3	–
3	1a	Eu(fod) ₃ (10)	-45	40	3a,4a (73)	99: 1	–
4	1a	Yb(fod) ₃ (10)	-45	40	3a,4a (73)	99: 1	–
5	1a	Yb(OTf) ₃ (10)	-78	14	– ^e	–	–
6	1b	Eu(fod) ₃ (10)	-45	40	3b,4b (80)	98: 2	–
7	1c	Eu(fod) ₃ (2)	rt	48	3c,4c (76)	92: 8	–
8	1c	Eu(fod) ₃ (10)	-40	48	3c,4c (86)	95: 5	–
9	1a	(+)-Eu(hfc) ₃ (2)	rt	9	3a,4a (78)	99: 1	3a (16)
10	1a	(+)-Eu(hfc) ₃ (10)	-45	40	3a,4a (85)	99: 1	3a (31)
11	1a	(+)-Yb(hfc) ₃ (10)	-45	40	3a,4a (72)	99: 1	3a (7)
12	1b	(+)-Eu(hfc) ₃ (10)	-78	60	3b,4b (32)	99: 1	3b (39)
13	1c	(+)-Eu(hfc) ₃ (2)	rt	120	3c,4c (39)	84:16	3c (–) ^f

^aAll reactions were performed with 10 equivalents of ethyl vinyl ether 2a in CH₂Cl₂. ^bYields of isolated cycloadducts. ^cDetermined by ¹H NMR and/or ¹³C NMR. ^dDetermined by HPLC analysis using Daicel chiralcel OD-H. ^ePolymerization of vinyl ether was observed. Enone was recovered (97%). ^fEe% was not determined.

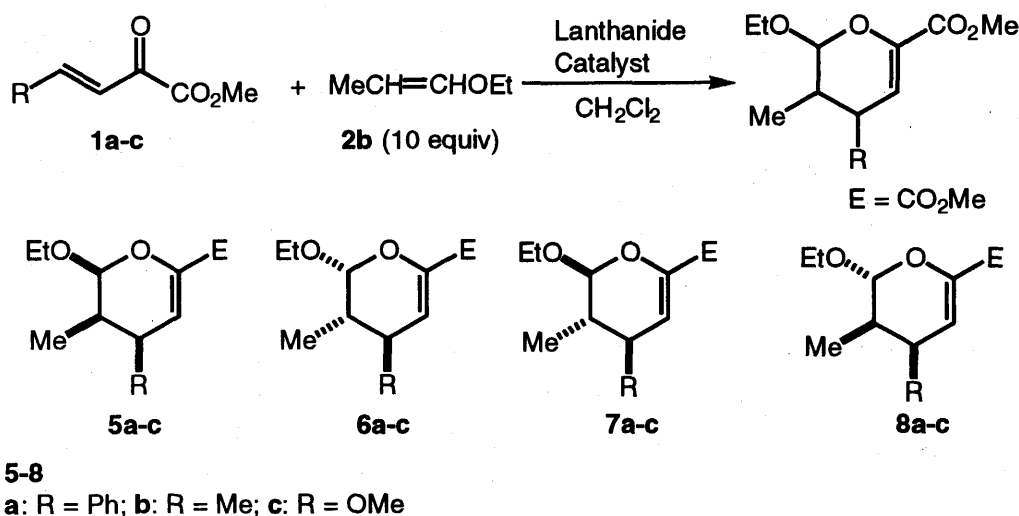
Methyl (*E*)-2-oxo-4-phenyl-3-butenate (1a),¹⁵ methyl (*E*)-2-oxo-3-pentenoate (1b),¹⁶ and methyl 2-oxo-4-methoxy-3-butenate (1c)¹⁷ were prepared according to the literature procedures.

To evaluate the effect of lanthanide catalysts on reactivity and stereoselectivity in hetero Diels-Alder reactions of enones 1a-c and ethyl vinyl ether (2a) (10 equiv) were reacted in the presence of Eu(fod)₃, Yb(fod)₃, and Yb(OTf)₃ in dichloromethane (Scheme 1 and Table 1). The diastereomer ratios (*endo/exo* = 3/4) of the resulting cycloadducts were determined on the basis of ¹H and/or ¹³C NMR spectra.

The reaction with enone 1a at room temperature for 12 h in the presence of 2 molar percent of Eu(fod)₃ gave two diastereomeric cycloadducts, methyl *cis*-2-ethoxy-4-phenyl-3,4-dihydro-2*H*-6-carboxylate (3a) and methyl *trans*-2-ethoxy-4-phenyl-3,4-dihydro-2*H*-6-carboxylate (4a) (97/3), in 71% yield (entry 1). With 10 molar percent of Eu(fod)₃, the same reaction was completed at -45 °C in 40 h to provide cycloadducts in 73% yield with high *endo*-selectivity (3a/4a = 99/1) (entry 3). Equally effective results in yields (71 and 73%) and stereoselectivities (3a/4a = 97/3 and 3a/4a = 99/1) were observed in reactions at room temperature and -45 °C, respectively, when Yb(fod)₃ catalyst was employed (entries 2 and 4). With Yb(OTf)₃ catalyst, undesirable polymerization of 2a was observed even at

-78 °C and enone 1a (97%) was recovered unreacted (entry 5). Thus, in the presence of 10 molar percent of Eu(fod)₃, reactions with enones 1b,c were carried out at low temperature (-45 or -40 °C) to provide cycloadducts 3 and 4 in good yields (80 and 86%) with high *endo*-selectivities (3b/4b = 98/2 and 3c/4c = 95/5), respectively (entries 6 and 8). The reaction with 1c at room temperature slightly decreased *endo*-selectivity (3c/4c = 92/8) (entry 7).

Next, catalytic asymmetric version of these reactions was investigated with 10 molar percent of (+)-Eu(hfc)₃ and (+)-Yb(hfc)₃ as chiral catalysts (Table 1). The ratios of enantiomeric excess (ee%) of cycloadducts were determined by chiral HPLC analysis.¹⁸ The reaction with 1a was completed at room temperature in 9 h to provide 3a in 78% yield with high diastereoselectivity (98% de), but its enantioselectivity was low (16% ee) (entry 9). The same reaction at -45 °C led to a slightly better enantioselectivity (31% ee, entry 10). Use of (+)-Yb(hfc)₃ catalyst resulted in rather decreased enantioselectivity (7% ee) even at -45 °C (entry 11). The reaction with 1b was performed at -78 °C for 60 h to provide 3b in 32% yield with 98% de and 39% ee (entry 12). The reaction with 1c was carried out at room temperature for 120 h in the presence of 2 molar percent of (+)-Eu(hfc)₃ to provide 3c and 4c in 39% yield (entry 13). Both reactivity and



Scheme 2

Table 2. Europium-Catalyzed Hetero Diels-Alder Reactions of 4-Substituted Methyl (*E*)-2-Oxo-3-butenates 1a-c with *E*- and *Z*-Isomers of Ethoxypropene 2b^a

Entry	Substrates (ratio of <i>E/Z</i>)	Catalyst	Reaction conditions		Product (yield/%) ^b		
			Temp/°C	Time/h	ratio ^c 5,7	(% ee) ^d	
1	1a + Z-2b	Eu(fod) ₃	-45	40	5a,6a (73)	99: 1	—
2	1b + Z-2b	Eu(fod) ₃	-45	48	5b,6b (84)	99: 1	—
3	1c + Z-2b	Eu(fod) ₃ ^e	rt	48	5c,6c (88)	98: 2	—
4	1a + 2b (37/63)	Eu(fod) ₃	-40	24	5a,6a 7a,8a (69) ^f	99: 1 ^g 94: 6 ^h	—
5	1a + Z-2b	(+)-Eu(hfc) ₃	-45	40	5a,6a (27) ⁱ	99: 1	5a (23)
6	1b + Z-2b	(+)-Eu(hfc) ₃	-45	48	5b,6b (56) ⁱ	99: 1	5b (4)
7	1a + 2b (37/63)	(+)-Eu(hfc) ₃	-40	24	5a,6a 7a,8a (66) ^f	99: 1 ^g 99: 1 ^h	7a (—) ^j

^aUnless otherwise noted, all reactions were performed by using 10 equivalents of vinyl ether **2b** in the presence of 10 mol% of catalyst in CH₂Cl₂. ^bYields of isolated cycloadducts. ^cDetermined by ¹H NMR and/or ¹³C NMR. ^dDetermined by HPLC analysis by using Daicel chiralcel OD-H. ^eTwo mol% of catalyst was used. ^fYield as a mixture of **5a-8a**. Isomer ratio of cycloadduct was as follows; **5a,6a:7a,8a** = 21:79 (entry 4) and 16:84 (entry 7). ^gIsomer ratio of cycloadduct **5a** and **6a** obtained from *Z*-ethoxypropene. ^hIsomer ratio of cycloadduct **7a** and **8a** obtained from *E*-ethoxypropene. ⁱEnone **1a** (68%) or **1b** (30%) was recovered in each case. ^jEe % was not determined.

diastereoselectivity (**3c/4c** = 84/16) were rather decreased than those of the reaction with Eu(fod)₃ as catalyst (vs entry 7). The ratio of enantiomeric excess of cycloadducts **3c** and **4c** could not be determined.

We further investigated the stereospecificity of the hetero Diels-Alder reactions of enones **1a-c** by using *E* and *Z* isomers of ethoxypropene (**2b**) in the presence of

catalytic amount of europium catalysts in dichloromethane (Scheme 2 and Table 2).

With Eu(fod)₃ (10 mol%), the reactions of **1a,b** with *Z*-**2b** gave stereospecific cycloadducts, methyl *r*-2-ethoxy-*c*-3-methyl-*c*-4-phenyl-6-carboxylate (**5a**) (98% de) and methyl *r*-2-ethoxy-*c*-3,*c*-4-dimethyl-3,4-dihydro-2*H*-pyran-6-carboxylate (**5b**) (98% de), in 73 and

84% yields, respectively (entries 1 and 2). Methyl *r*-2-ethoxy-*c*-3-methyl-*c*-4-methoxy-3,4-dihydro-2*H*-pyran-6-carboxylate (**5c**) (98% de) was produced stereospecifically from the reaction of **1c** with **Z-2b** even at room temperature in the presence of 2 mol percent of Eu(fod)₃ (entry 3). Further, a stereoisomeric mixture of **5a,6a**, methyl *r*-2-ethoxy-*t*-3-methyl-*c*-4-phenyl-3,4-di-hydro-2*H*-6-carboxylate (**7a**), and methyl *r*-2-ethoxy-*t*-3-methyl-*t*-4-phenyl-3,4-dihydro-2*H*-6-carboxylate (**8a**) was obtained in 69% yield from the reaction of **1a** and a 37:63 mixture of *E/Z* stereoisomers **2b** (entry 4). The isomer ratio of cycloadducts **5a,6a** (**5a/6a** = 99/1) and **7a,8a** (**7a/8a** = 94/6), which were obtained stereospecifically from **Z-2b** and *E*-**2b**, respectively, was 21:79.¹⁹ These results indicate that (1) the reactions are highly 2,4-*cis*-selective and *endo*-selective, (2) the reactions are exclusively stereospecific, and (3) the reactivity of *E*-**2b** was about 8 times rather than that of **Z-2b** toward to enone **1a**. Thus the catalytic asymmetric reactions of enones **1a** with **Z-2b**, **1b** with **Z-2b**, and **1a** with a *E/Z* (37/63) mixture of **2b** were carried out in the presence of (+)-Eu(hfc)₃ (10 mol%) (entries 5-7). All reactions underwent *endo*-selectively (98% de) and stereospecifically to produce corresponding cycloadducts **5a** (23% ee), **5b** (4% ee), and **7a** with low enantioselectivities.¹⁸

In conclusion, the highly stereoselective formation of methyl 2,4-*cis*-3,4-dihydro-2*H*-pyran-6-carboxylates **3,5**, and **7** has been achieved by a sequence based on the hetero Diels-Alder reactions of 4-substituted methyl 2-oxo-3-butenates **1** with vinyl ethers **2** in the presence of a catalytic amount of Eu(fod)₃ or Yb(fod)₃. However, the enantioselectivities of these reactions by using (+)-Eu(hfc)₃ or (+)-Yb(hfc)₃ were not satisfactory. The work concerning catalytic asymmetric induction of these reactions is now in progress, and the details of results will be reported elsewhere.

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- The absolute configurations of cycloadducts were not determined yet.
- No isomerization of **Z-2b** to *E*-**2b** and no epimerization at 2-position of cycloadducts **5a-8a** were observed under similar reaction conditions.