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# Lewis Acid-Catalyzed Stereoselective Hetero Diels-Alder Reactions of (*E*)-1-Phenylsulfonyl-3-alken-2-ones with Vinyl Ethers — Synthetically Equivalent to Stereoselective Michael Type Conjugate Additions —

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This article summarizes the Lewis acid-catalyzed hetero Diels-Alder reactions of new 1-oxa-1,3-butadienes. (*E*)-1-Phenylsulfonyl-3-alken-2-ones undergo smooth hetero Diels-Alder reactions with vinyl ethers in the presence of Lewis acid. The reactions are absolutely *endo*-selective producing 2,4-*cis*-3,4-dihydro-2*H*-pyrans, the configuration at 3-position depending upon the stereochemistry of the starting vinyl ethers. This reaction can be successfully extended to the catalytic asymmetric version of hetero Diels-Alder reaction by using chiral titanium reagents. The resulting homochiral dihydropyran cycloadducts are transformed to 2-cyclohexen-1-ones which are useful as new chiral building blocks.

## Introduction

Simple  $\alpha,\beta$ -unsaturated aldehyde and ketones are known to act as hetero 1,3-dienes in hetero Diels-Alder reactions with vinyl ethers, but severe reaction conditions are needed, to give mixtures of stereoisomeric dihydropyran derivatives.<sup>1)</sup> Its synthetic importance as a construction method of stereochemically defined heterocycles would be much increased if stereoselectivity of the reaction is improved under mild reaction conditions. Hetero Diels-Alder reactions are also useful synthetic equivalent of Michael type conjugate additions since the resulting heterocycles, 3,4-dihydro-2*H*-pyrans, are readily converted to 1,5-dicarbonyl compounds by simple hydrolytic procedure.<sup>2)</sup> Thus, a new entry to the acyclic stereocontrol methodology based on the stereoselective hetero Diels-Alder reaction would be opened. In this viewpoint, much effort has been devoted to the development of stereoselective hetero Diels-Alder reactions by use of new type of bidentate hetero 1,3-dienes.

We have recently reported the first example of highly stereoselective hetero Diels-Alder reactions of (*E*)-2-oxo-3-alkenylphosphonates with vinyl ethers in the presence of Lewis acid catalyst such as ZnCl<sub>2</sub> or ZnBr<sub>2</sub> under mild reaction conditions.<sup>3)</sup> They can be activated effectively by their chelate formation with a Lewis acid to provide 2-alkoxy-3,4-dihydro-2*H*-pyrans stereoselectively as cycloadducts without serious polymerization of vinyl ethers. However, a stoichiometric amount of Lewis acid was needed in these catalyzed reactions, indicating the poor catalytic cycle.

We describe here our recent results on the Lewis acid-catalyzed hetero Diels-Alder reactions using (*E*)-1-phenylsulfonyl-3-alken-2-ones as new type of hetero 1,3-dienes with

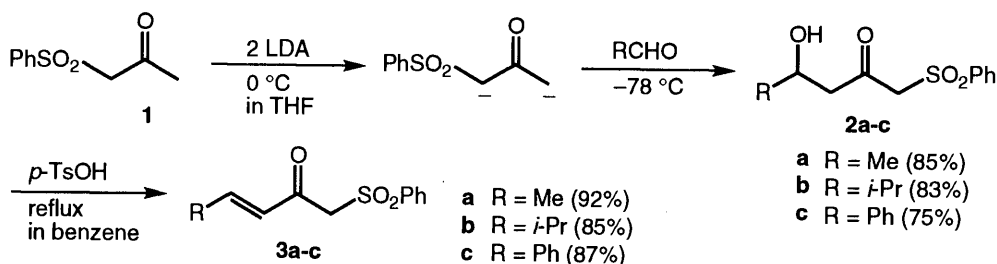
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vinyl ethers and their extensions to catalytic asymmetric reactions. The transformations of the resulting stereochemically defined cycloadducts to 5-substituted 2-cyclohexen-1-ones and 3-substituted cyclohexanones are also presented.

### Synthesis of (*E*)-1-Phenylsulfonyl-3-alken-2-ones

(*E*)-1-Phenylsulfonyl-3-alken-2-ones **3a-c** were prepared by the application of our synthetic method of 2-oxo-3-alkenylphosphonates via dianion intermediates.<sup>4)</sup> According to the literature procedure,<sup>5)</sup> 1-phenylsulfonylpropanone (**1**) was treated with two equimolar amounts of lithium diisopropylamide (LDA) in tetrahydrofuran (THF) at 0 °C for 4 h to give a suspension of the dianion. This suspension was allowed to react with aldehydes such as acetaldehyde, 2-methylpropionaldehyde, and benzaldehyde at -78 °C to give the corresponding aldol adducts **2a-c** in satisfactory yields based on the starting ketone **1**. They were then subjected to dehydration by treatment with catalytic amount of *p*-toluenesulfonic acid under reflux in benzene to produce the desired (*E*)-1-phenylsulfonyl-3-alken-2-ones **3a-c** in high yields.



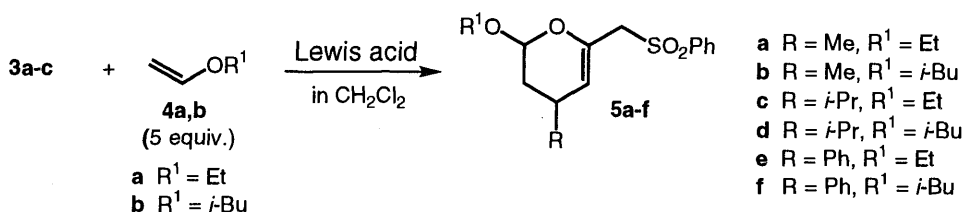
Scheme 1

### Hetero Diels-Alder Reactions of (*E*)-1-Phenylsulfonyl-3-alken-2-ones with Vinyl Ethers

To evaluate the reactivity and stereoselectivity in hetero Diels-Alder reactions, enones **3a-c** were allowed to react with vinyl ethers **4a,b** in the absence or presence of Lewis acid.<sup>6)</sup> Lewis acids such as  $\text{ZnI}_2$ ,  $\text{Eu}(\text{fod})_3$ , and  $\text{TiCl}_2(i\text{-PrO})_2$  were employed (Scheme 2).

The reaction of enone **3a** in the absence of Lewis acid required the use of a large excess of vinyl ether **4b** (20 equiv.) in a sealed tube, and a high reaction temperature and a long reaction time were needed for the completion of reaction (48 h at 130-135 °C). A 34:66 mixture of *cis*- and *trans*-isomers of the cycloadduct **5b**, which correspond to the *endo*- and *exo*-cycloadducts respectively, was obtained on 85% yield. This low reactivity and poor selectivity resemble to the related reactions of simple  $\alpha,\beta$ -unsaturated aldehyde and ketones. However, this reaction was highly accelerated (15 h at -30 °C) in the presence of a catalytic amount of  $\text{TiCl}_2(i\text{-PrO})_2$  (10 mol%) and became exclusively stereoselective to give the *cis*-isomer of **5b** as a single isomer in 91% yield.

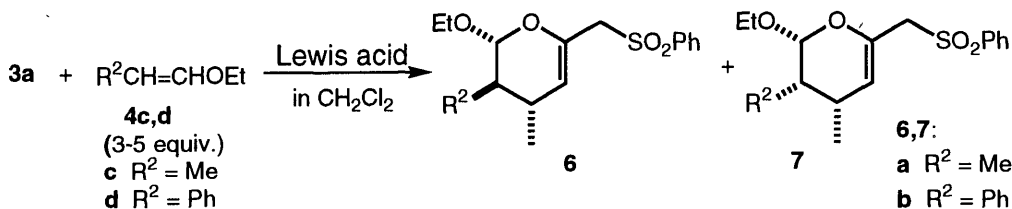
Other Lewis acid catalysts such as  $\text{ZnI}_2$  and  $\text{Eu}(\text{fod})_3$  can be effectively used in a



Reaction conditions	Cycloadducts (yield/%)	<i>cis:trans</i>
no catalyst, 130-135 °C, 86 h	<b>5b</b> (85)	34:66
$\text{ZnI}_2$ (3 mol%), rt, 86 h	<b>5a</b> (92)	92:8
$\text{TiCl}_2(i\text{-PrO})_2$ (10 mol%), -50--30 °C, 15 h	<b>5a</b> (92), <b>5b</b> (91)	<b>5a</b> (98:2), <b>5b</b> ( <i>cis</i> only)
$\text{Eu(fod)}_3$ (0.5-3 mol%), -10-rt, 40-99 h	<b>5a</b> (91-95), <b>5c</b> (80), <b>5d</b> (71), <b>5e</b> (85), <b>5f</b> (89)	<i>cis</i> only

Scheme 2

catalytic amount (0.5-3 mol%). The titanium catalyst (**5a**, *cis/trans*=98/2) was a little better than the zinc catalyst (**5a**, *cis/trans*=92/8) in selectivity. The europium catalyst showed effective catalysis by a catalytic amount for all combinations enones **3a-c** and vinyl ethers **4a,b**, *cis*-isomers of the dihydropyran derivatives **5a,c-f** being exclusively produced in high yields. The high efficiency of catalytic cycle makes a striking contrast with the reactions of 2-oxo-3-alkenylphosphonates.<sup>3)</sup> The remarkable rate accelerations, the high stereoselectivity, and the high efficiency of catalytic cycle, all observed in the Lewis acid-catalyzed hetero Diels-Alder reactions of **3a-c**, are no doubt based on the coordination capability of the sulfonyl moiety to Lewis acid. We further investigated the stereospecificity of the Lewis acid-catalyzed hetero Diels-Alder reactions to  $\beta$ -substituted vinyl ethers **4c,d** (Scheme 3).<sup>7)</sup>



Reaction conditions	Cycloadducts (yield/%)
<i>E/Z</i> - <b>4c</b> (1/1), $\text{Eu(fod)}_3$ (1 mol%), rt, 80 h	<b>6a,7a</b> (65, <b>6a/7a</b> = 1/1)
<i>E/Z</i> - <b>4c</b> (1/19), $\text{Eu(fod)}_3$ (5 mol%), -5 °C, 96 h	<b>6a,7a</b> (95, <b>6a/7a</b> = 1/19)
<i>E</i> - <b>4d</b> , $\text{Eu(fod)}_3$ (3 mol%), rt, 65 h	<b>6b</b> (53)
<i>E</i> - <b>4d</b> , $\text{TiCl}_2(i\text{-PrO})_2$ (10 mol%), -30 °C, 38 h	<b>6b</b> (97)
<i>Z</i> - <b>4d</b> , $\text{TiCl}_2(i\text{-PrO})_2$ (10 mol%), -30 °C, 93 h	<b>7b</b> (97)

Scheme 3

The reaction of enone **3a** with vinyl ether **4c** (*E/Z*-mixture, 5 equiv.) was carried out in the presence of a catalytic amount (1 mol%) of  $\text{Eu}(\text{fod})_3$  at or below room temperature in dichloromethane. A 1:1 mixture of *r*-2-ethoxy-*t*-3,*c*-4-dimethyl-6-(phenylsulfonylmethyl)-3,4-dihydro-2*H*-pyran (**6a**) and *r*-2-ethoxy-*c*-3,*c*-4-dimethyl-6-(phenylsulfonylmethyl)-3,4-dihydro-2*H*-pyran (**7a**) was produced when 1:1 mixture of *E/Z* stereoisomers of vinyl ether **4c** was employed, and 1:19 mixture of **6a** and **7a** from a 1:19 mixture of *E/Z* isomers of **4c**. These results indicate that (1) the reactions are exclusively 2,4-*cis*-selective or *endo*-selective, (2) the  $\text{Eu}(\text{fod})_3$ -catalyzed hetero Diels-Alder reactions of **3a** with **4c** are exclusively stereospecific, and (3) the *E*- and *Z*-isomers of vinyl ether **4c** have comparable reactivities to enone **3a**.

(*E*)-1-Ethoxy-2-phenylethene (**E-4d**)<sup>8)</sup> showed a comparable reactivity to enone **3a** in the reactions catalyzed by  $\text{Eu}(\text{fod})_3$  to give the *endo*-cycloadduct, *r*-2-ethoxy-*c*-4-methyl-*t*-3-phenyl-6-(phenylsulfonylmethyl)-3,4-dihydro-2*H*-pyran (**6b**), as a single stereoisomer. Use of  $\text{TiCl}_2(i\text{-PrO})_2$  was even more effective and a satisfactory rate enhancement was observed. For example, the reaction of **3a** with **E-4d** was completed at -30 °C in the presence of 10 molar percent of  $\text{TiCl}_2(i\text{-PrO})_2$  without polymerization of vinyl ether **4d** to produce **6b**. On the other hand, the reaction with (*Z*)-1-ethoxy-2-phenylethene (**Z-4d**)<sup>9)</sup> provided also the *endo*-cycloadduct, *r*-2-ethoxy-*c*-4-methyl-*c*-3-phenyl-6-(phenylsulfonylmethyl)-3,4-dihydro-2*H*-pyran (**7b**), as a single stereoisomer.

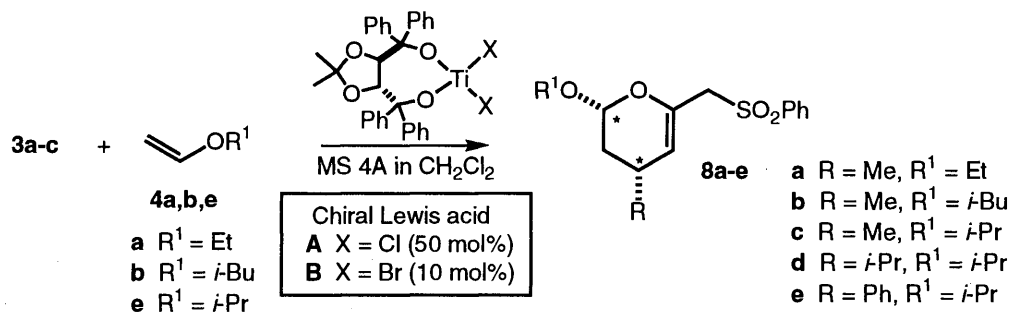
### Chiral Lewis Acid-Catalyzed Asymmetric Hetero Diels-Alder Reactions of (*E*)-1-Phenylsulfonyl-3-alken-2-ones with Vinyl Ethers

The exclusively *endo*-selective Lewis acid-catalyzed hetero Diels-Alder reactions mentioned above is now found to offer a new and powerful strategy for the stereoselective synthesis of 3,4-dihydro-2*H*-pyrans as synthetic equivalent to stereoselective Michael type conjugate additions. To increase their synthetic versatility, we have next challenged to establish the unexplored catalyzed asymmetric reactions of these stereoselective hetero Diels-Alder reactions.

Enones **3a-c** were allowed to react with excess amounts of vinyl ethers **4a,b,e** in the presence of a catalytic amount of chiral Lewis acids **A** and **B** in dichloromethane under a variety of conditions (**Scheme 4**).<sup>10)</sup>

Chiral titanium catalysts **A** and **B** were prepared in situ according to the literature procedure from  $\text{TiX}_2(i\text{-PrO})_2$  ( $\text{X} = \text{Cl}, \text{Br}$ )<sup>11)</sup> and (4*R*,5*R*)- $\alpha,\alpha,\alpha',\alpha'$ -tetraphenyl-2,2-dimethyl-1,3-dioxolane-4,5-dimethanol (1.1 equiv.)<sup>12)</sup> in the presence of molecular sieves 4A.<sup>11)</sup>

Reaction of enone **3a** with a large excess of ethyl vinyl ether (**4a**) was performed in the presence of catalyst **A** (50 mol%), at -78 °C for 9 h and then at -30 °C for 3 h, to give *cis*-isomer **8a** as single isomer in 78% yield (48% ee), while the use of isobutyl vinyl ether (**4b**) resulted slightly better enantioselectivity (62% ee). The titanium bromide catalyst **B** was found to be more effective to improve both the catalytic cycle and rate acceleration. Thus, in the presence of 10 mol% of **B**, reactions of enone **3a** with vinyl ethers **4a,b,e** were completed even at -78 °C to provide *cis*-cycloadduct **8a-c** in excellent yields (91, 92, and 90%) and with moderate to high enantioselectivities (59, 88, and 97% ee). As will be discussed below, the sense of enantioselection was all the same in reactions of enone **3a**



Reaction conditions	Yield/%	Cycloadducts	
		% ee	Abs. config.
Cat. <b>A</b> , -78/-30 °C, 9/3 h	<b>8a</b> (78)	48	2 <i>R</i> ,4 <i>R</i>
Cat. <b>B</b> , -78 °C, 20 h	<b>8a</b> (91)	59	2 <i>R</i> ,4 <i>R</i>
Cat. <b>B</b> , -50 °C, 6 h	<b>8b</b> (96)	74	2 <i>R</i> ,4 <i>R</i>
Cat. <b>B</b> , -78 °C, 6 h	<b>8b</b> (92)	88	2 <i>R</i> ,4 <i>R</i>
Cat. <b>B</b> , -78 °C, 20 h	<b>8c</b> (90)	95-97	2 <i>R</i> ,4 <i>R</i>
Cat. <b>B</b> , -78 °C, 20 h	<b>8d</b> (88)	86	2 <i>R</i> ,4 <i>S</i>
Cat. <b>B</b> , -70 °C, 20 h	<b>8e</b> (77)	97	2 <i>R</i> ,4 <i>R</i>

Scheme 4

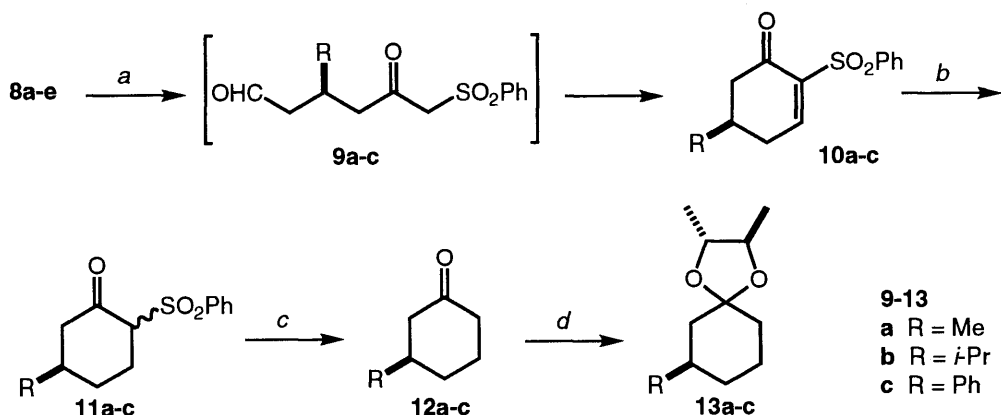
with vinyl ethers **4a,b,e**. In addition, enantioselectivity was effectively enhanced with the increase of bulkiness of the alkoxy substituent R<sup>1</sup> of dienophiles **4a,b,e** (selectivity: **4a** < **4b** < **4e**), and a lower reaction temperature led to a better result. As a result, other enones **3b,c** were allowed to react with isopropyl vinyl ether (**4e**) in the presence of the titanium bromide catalyst **B** under similar conditions to provide **8d** (88% and 86% ee) and **4e** (77% and 97% ee), respectively.

### Transformation of 2-Alkoxy-3,4-dihydro-2*H*-pyran Cycloadducts

To determine the absolute configurations of major enantiomers of dihydropyrans **8a-e** mentioned above (Scheme 4), the cycloadducts **8a-c** were converted to the corresponding 3-substituted cyclohexanone acetals **13a-c** (Scheme 5).<sup>10)</sup> This transformation reactions indicate the synthetic utility of dihydropyran cycloadducts in asymmetric synthesis.

Treatment of cycloadducts **8a-e** with 4*N* hydrochloric acid produced cyclohexenones **10a-c** in high yields via a sequence of the acid-catalyzed hydrolysis forming 1,5-keto aldehyde intermediates **9a-c** which are synthetically equivalent to Michael conjugate adducts, and subsequent intramolecular condensation.

Further transformations of unsaturated ketones **10a-c** to saturated ketones **12a-c** were readily performed as follows: Hydrogenation of **10a** (95% ee), **10b** (86% ee), and **10c** (97% ee) in the presence of 10% Pd-C was followed by the reductive desulfonylation with tributyltin hydride.<sup>13)</sup> Their acetalization with (2*R*,3*R*)-2,3-butanediol gave the corre-



Substrate	Yield/% (5 <i>R</i> )- <b>10</b>	ee%	Total yield/% (3 <i>R</i> )- <b>13</b> (from <b>10</b> )	de%
<b>8c</b>	<b>10a</b> (95)	95	<b>13a</b> (64)	94
<b>8d</b>	<b>10b</b> (91)	86	<b>13b</b> (56)	85
<b>8e</b>	<b>10c</b> (95)	97	<b>13c</b> (65)	97

a) 4N-HCl, THF, rt, 2 h. b) H<sub>2</sub>, 10% Pd-C, THF/EtOH (1/1 v/v). c) *n*-Bu<sub>3</sub>SnH, AIBN, benzene, reflux, 4 h. d) (2*R*,3*R*)-2,3-butanediol, benzene, reflux, 2 h.

**Scheme 5**

spending acetals **13a-c** without epimerization in overall yields of 64% (94% de), 56% (85% de), and 65% (97% de), respectively. The absolute configurations of **13a-c** were determined to be *R* by <sup>13</sup>C NMR spectra.<sup>14)</sup> Thus, the absolute configurations of the major enantiomers of *cis*-dihydropyrans **8** were confirmed as (2*R*,4*R*)-**8a-c**, (2*R*,4*S*)-**8d**, and (2*R*,4*R*)-**8e**.

In conclusion, the absolutely stereoselective formation of 2,4-*cis*-3,4-dihydro-2*H*-pyrans **5**, **6**, and **7** has been achieved by a sequence based on the hetero Diels-Alder reactions of (*E*)-1-phenylsulfonyl-3-alken-2-ones **3** with vinyl ethers **4** in the presence of a catalytic amount of Eu(fod)<sub>3</sub> or TiCl<sub>2</sub>(*i*-PrO)<sub>2</sub>. The sulfonyl moiety is an excellent reactivity-enhancing auxiliary. Furthermore, enones **3** act as marvelous hetero 1,3-dienes of the 1-oxa-1,3-butadiene types in the Lewis acid-catalyzed asymmetric hetero Diels-Alder reactions with vinyl ethers. This asymmetric hetero Diels-Alder methodology offers a very effective synthetic route to the enantiomers of 4-substituted 2,4-*cis*-2-alkoxy-3,4-dihydro-2*H*-pyrans **8**, 5-substituted 2-phenylsulfonyl-2-cyclohexen-1-ones **10**, and 3-substituted cyclohexanones **12**. Lewis acid catalyzed asymmetric hetero Diels-Alder reactions of enones **3** with  $\beta$ -substituted vinyl ethers and the other transformation reactions of the resulting dihydropyran cycloadducts are currently under investigation.

### Acknowledgement

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