CHEMISTRY LETTERS, pp. 145-148, 1994.

(*E*)-2-Oxo-1-sulfonyl-3-alkenes as Reactive Hetero 1,3-Dienes. Absolutely *endo*-Selective Hetero Diels-Alder Reactions with Vinyl Ethers in the Presence of a Lewis Acid Catalyst

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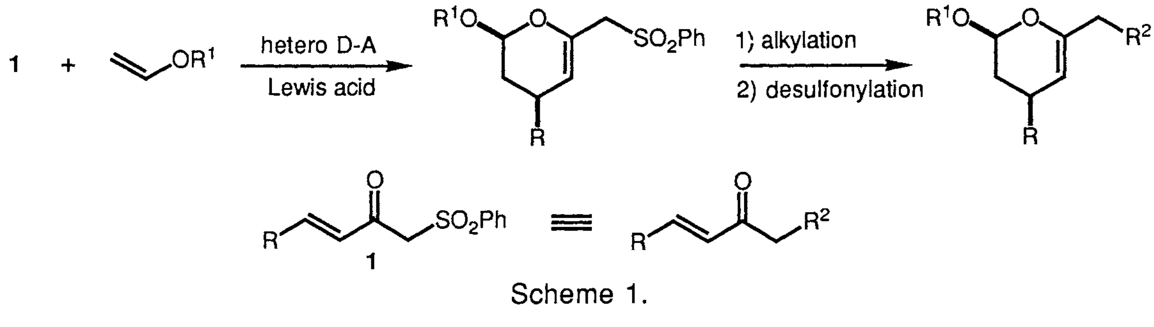
(*E*)-2-Oxo-1-sulfonyl-3-alkenes as new hetero 1,3-dienes undergo smooth hetero Diels-Alder reactions with vinyl ethers in the presence of Eu(fod)$_3$ or TiCl$_2$(*i*-PrO)$_2$. The reactions are absolutely *endo*-selective producing 2,4-*cis*-3,4-dihydro-2*H*-pyrans in excellent yields, sufficient catalytic cycles being attained. The sulfonyl-stabilized carbanions derived from the cycloadducts are alkylated followed by reductive desulfonylation.

Simple α,β-unsaturated aldehydes and ketones are known to act as hetero 1,3-dienes in hetero Diels-Alder reactions with vinyl ethers, but under severe reaction conditions, to give mixtures of stereoisomeric dihydropyran derivatives.1) Their 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. Limited numbers of derivatives have been proposed for highly reactive 1-oxa-1,3-butadienes,2,3) most cases are based on the molecular design which involves the introduction of an additional electron withdrawing substituent to the unsaturated system.

We have recently reported the first example of highly stereoselective hetero Diels-Alder reactions of 2-oxo-3-alkenylphosphonates with vinyl ethers in the presence of a Lewis acid catalyst such as ZnCl$_2$ or ZnBr$_2$ under mild reaction conditions.4) This success of catalyzed hetero Diels-Alder reactions should be emphasized since vinyl ethers are so labile to Lewis acid that they undergo ready polymerization, and this is a serious problem often encountered in the Lewis acid-catalyzed reactions using simple α,β-unsaturated aldehydes and ketones. We have been interested since then in exploring a new hetero 1,3-diene system which enables highly stereoselective hetero Diels-Alder reactions by the aid of a catalytic amount of Lewis acid.

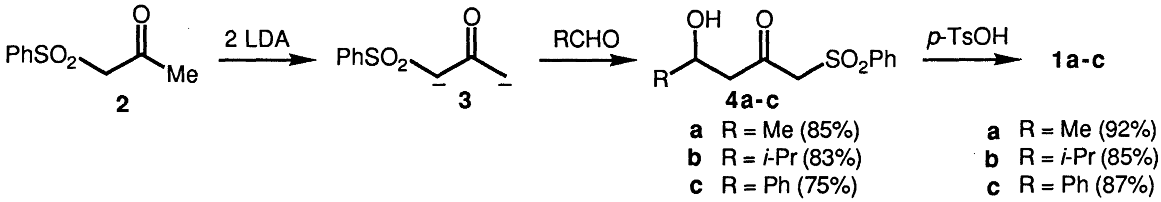


Scheme 1.

In this communication, we would like to report the Lewis acid-catalyzed hetero Diels-Alder reactions of

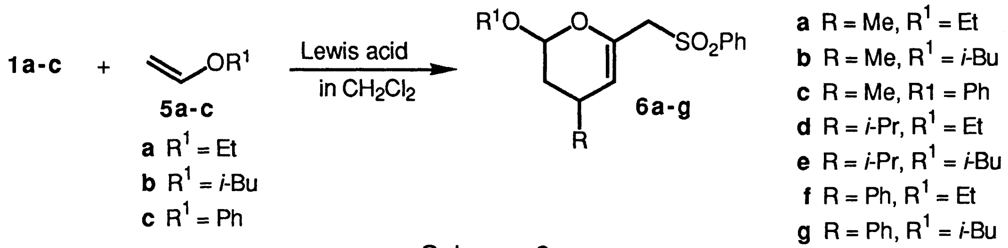
(E)-2-oxo-1-phenylsulfonyl-3-alkenes **1** with vinyl ethers. The sulfonyl group accelerates not only the cycloaddition but also the introduction of a substituent via an anion intermediate and can be finally removed by reduction, indicating that heterodienes **1** are reactive synthetic equivalents of simple α,β-unsaturated ketones (Scheme 1).

Sulfonyl-substituted enones **1a-c** were readily synthesized by the application of our synthetic method of 2-oxo-3-alkenylphosphonates via dianion intermediates.5) According to the Belletire's method, 1-phenylsulfonyl-2-propanone (**2**) was converted to dianion **3** by treatment with lithium diisopropylamide (LDA, 2 equiv.) at 0 °C for 4 h.6) Aldol reactions of dianion **3** with aldehydes, such as acetaldehyde, 2-methylpropionaldehyde, and benzaldehyde, at the same temperature for 1 h gave β-hydroxy α'-phenylsulfonyl ketones **4a-c** in satisfactory yields (Scheme 2). Acid-catalyzed dehydration of **4a-c** was performed in the presence of a catalytic amount of *p*-toluenesulfonic acid under reflux in benzene to produce the corresponding *trans*-enones **1a-c** in good yields.



Scheme 2.

To evaluate the reactivity and stereoselectivity in hetero Diels-Alder reactions, enones **1a-c** were allowed to react with vinyl ethers **5a-c** in the absence or presence of Lewis acid. Lewis acids such as ZnI_2, $Eu(fod)_3$, and $TiCl_2(i\text{-}PrO)_2$ were employed (Scheme 3 and Table 1),7) and diastereomer ratios of the resulting cycloadducts were determined on the basis of ^1H and/or ^{13}C NMR spectra.



Scheme 3.

The reaction of enone **1a** in the absence of Lewis acid required the use of a large excess of vinyl ether **5b** (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 **6b**, which correspond to the *endo*- and *exo*-cycloadducts respectively, was obtained in 85% yield (entry 3). This low reactivity and poor selectivity resemble to the related reactions of simple α,β-unsaturated aldehydes and ketones. However, this reaction was highly accelerated (15 h at –30 °C) in the presence of a catalytic amount of $TiCl_2(i\text{-}PrO)_2$ (10 mol%) and became exclusively stereoselective to give the *cis*-isomer of **6b** as a single isomer in 91% yield (entry 4).3) The reaction of enone **1a** with vinyl ether **5c** also proceeded stereoselectively in the presence of $TiCl_2(i\text{-}PrO)_2$ to give the *cis*-isomer **6c** as a single isomer in 97% yield (entry 5).

Other Lewis acid catalysts such as ZnI_2 and $Eu(fod)_3$ can be effectively used in a catalytic amount (0.5-3 mol%). The titanium catalyst was a little better than the zinc catalyst in selectivity (entry 1 *vs* entry 2). The europium catalyst showed effective catalysis by a catalytic amount for all combinations of enones **1a-c** and vinyl ethers **5a,b**, *cis*-isomers of the dihydropyran derivatives **6a,d-g** being exclusively produced in excellent yields (entries 6-11). This high efficiency of catalytic cycle makes a striking contrast with the reactions of 2-oxo-3-alkenylphosphonates.[4] Although we employed excess (5 equiv.) of vinyl ethers **5a-c** in fear of their partial loss by Lewis acid-catalyzed polymerization, less amounts are probably enough, especially in the reactions performed at low temperatures (entries 2 and 4-7).

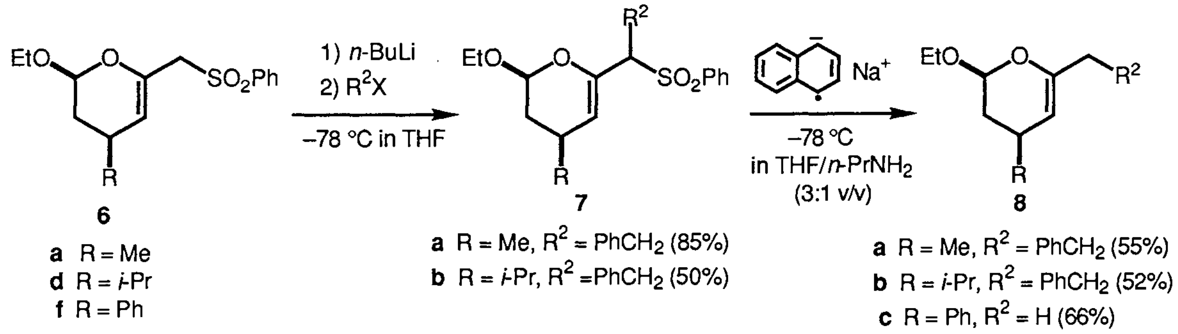
The remarkable rate acceleration, the high stereoselectivity, and the high efficiency of catalytic cycle, all observed in the Lewis acid-catalyzed hetero Diels-Alder reactions of **1a-c**, are no doubt based on the capability of the sulfonyl moiety for the coordination to Lewis acid. The sulfonyl moiety of **6a-g** has a synthetic advantage since it facilitates the generation of an anionic center at α-position which would be utilized for the introduction of a substituent by alkylation.

Table 1. Lewis Acid-Catalyzed Hetero Diels-Alder Reactions of Enones **1a-c** with Vinyl Ethers **5a-c**[a]

Entry	Enone	Vinyl Ether equiv.	Lewis Acid equiv.	Temp °C	Time h	Cycloadduct yield/%[b]	*cis* : *trans*[c]
1	**1a**	**5a** (5)	ZnI_2 (0.03)	rt	86	**6a** (92)	92 : 8
2	**1a**	**5a** (5)	$TiCl_2(i\text{-}PrO)_2$ (0.1)	–50	15	**6a** (90)	98 : 2
3[d]	**1a**	**5b** (20)	–	130-135	48	**6b** (85)	34 : 66
4	**1a**	**5b** (5)	$TiCl_2(i\text{-}PrO)_2$ (0.1)	–30	15	**6b** (91)	*cis* only
5	**1a**	**5c** (5)	$TiCl_2(i\text{-}PrO)_2$ (0.1)	–50	90	**6c** (97)	*cis* only
6	**1a**	**5a** (5)	$Eu(fod)_3$ (0.01)	–5	40	**6a** (95)	*cis* only
7	**1a**	**5a** (5)	$Eu(fod)_3$ (0.005)	–10	72	**6a** (91)	*cis* only
8	**1b**	**5a** (5)	$Eu(fod)_3$ (0.03)	rt	90	**6d** (80)	*cis* only
9	**1b**	**5b** (5)	$Eu(fod)_3$ (0.03)	rt	99	**6e** (71)	*cis* only
10	**1c**	**5a** (5)	$Eu(fod)_3$ (0.03)	rt	43	**6f** (85)	*cis* only
11	**1c**	**5b** (5)	$Eu(fod)_3$ (0.03)	rt	92	**6g** (89)	*cis* only

a) All reactions were carried out in CH_2Cl_2. b) Yield of isolated cycloadducts. c) Determined by ^1H NMR and/or ^{13}C NMR. d) In a sealed tube in benzene.

The sulfonyl-stabilized carbanion of dihydropyran **6a** was generated by treatment with butyllithium at –78 °C and reacted with benzyl bromide at the same temperature to provide benzylated product **7a** (96% de) in 85% yield (Scheme 4). Similar benzylation of **6d** gave **7b** (90% de) in 50% yield. The phenylsulfonyl group in the alkylated **7a,b** and unalkylated **6f** were successfully removed by reduction. Treatment with sodium naphthalenide (4 equiv.), generated from naphthalene and metal sodium under ultrasonic conditions in THF,[8] at –78 °C in THF/*n*-$PrNH_2$ (3:1 v/v) gave the desulfonylated products **8a-c** in 55, 52, and 68% yields, respectively.



Scheme 4.

In conclusion, the absolutely stereoselective formation of 2,4-*cis*-3,4-dihydro-2*H*-pyrans **6** and **8** has been achieved by a sequence based on the hetero Diels-Alder reactions of (*E*)-2-oxo-1-phenylsulfonyl-3-alkenes **1** with vinyl ethers in the presence of a catalytic amount of $Eu(fod)_3$ or $TiCl_2(i\text{-}PrO)_2$. The sulfonyl moiety of enones **1** is an excellent reactivity-enhancing auxiliary.

Partial finantial support to this work by Grant-in-Aid for Scientific Research (No. 03640457) from the Ministry of Education, Science and Culture is acknowledged.

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7) All new compounds discussed in the text were fully characterized on the basis of spectral data and analyses. Some typical spectral data are as follows: *cis*-**6a**: Colorless prisms; mp 88-89 °C; IR (KBr) 1665 cm^{-1}; ^1H NMR (C_6D_6) $\delta = 0.73$ (3H, d, $J_{Me\text{-}4} = 7.3$ Hz, 4-Me), 1.03 (3H, t, $J = 7.0$ Hz, EtO), 1.29 (1H, ddd, $J_{gem} = 13.2$, $J_{3\text{-}4} = 9.5$, and $J_{3\text{-}2} = 8.1$ Hz, one of H-3), 1.64 (1H, dddd, $J_{gem} = 13.2$, $J_{3\text{-}4} = 6.0$, $J_{3\text{-}2} = 2.2$, and $J_{3\text{-}5} = 1.1$ Hz, the other of H-3), 1.92-2.18 (1H, m, H-4), 3.12 (1H, dq, $J_{gem} = 9.5$ and $J = 7.0$ Hz, one of 2-EtO), 3.48 (1H, dd, $J_{gem} = 13.2$ and $J_{CH2\text{-}5} = 1.1$ Hz, one of 6-CH_2SO_2), 3.55 (1H, dd, $J_{gem} = 13.2$ and $J_{CH2\text{-}5} = 0.7$ Hz, the other of 6-CH_2SO_2), 3.60 (1H, dq, $J_{gem} = 9.5$ and $J = 7.0$ Hz, the other of 2-EtO), 4.35 (1H, br. d, $J_{5\text{-}4} = 2.6$ Hz, H-5), 4.49 (1H, dd, $J_{2\text{-}3} = 8.1$ and 2.2 Hz, H-2), 6.88-7.03 (3H, m, Ph), and 7.78-7.88 (2H, m, Ph); ^{13}C NMR (C_6D_6) $\delta = 15.29$ (EtO), 20.88 (4-Me), 26.62 (C-3), 35.85 (C-4), 61.40 (6-CH_2SO_2), 64.26 (2-EtO), 100.15 (C-2), 110.65 (C-5), 128,74, 128.95, 133.01, 140.15 (each Ph), and 140.96 (C-6); MS *m*/*z* (rel intensity, %) 296 (M^+, 10), 155 (97), 154 (47), 111 (23), 107 (63), and 72 (100).

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(Received September 30, 1993)