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Chiral Lewis Acid-Catalyzed Asymmetric Hetero Diels-Alder Reaction of (*E*)-2-Oxo-1-phenylsulfonyl-3-alkenes with Vinyl Ethers

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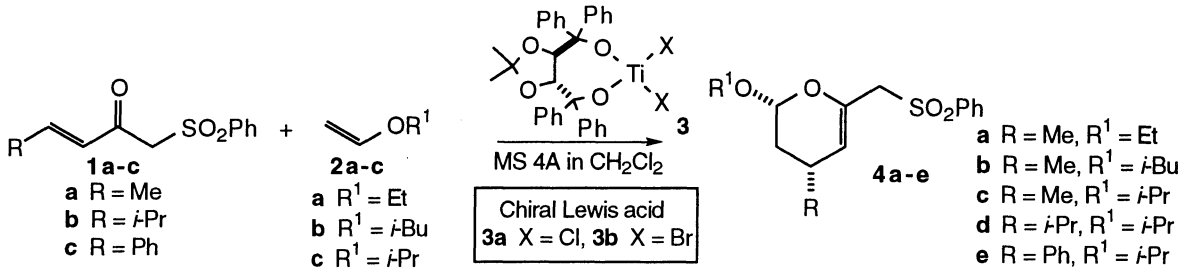
(*E*)-2-Oxo-1-phenylsulfonyl-3-alkenes are effectively activated with the aid of a catalytic amount of chiral titanium reagents in hetero Diels-Alder reactions with vinyl ethers to produce (2*R*,4*R*) or (2*R*,4*S*)-2,4-*cis*-2-alkoxy-4-substituted-3,4-dihydro-2*H*-pyrans in highly *endo*- and enantioselective manners. The resulting cycloadducts are transformed to 5-substituted (5*R*)-2-phenylsulfonyl-2-cyclohexen-1-ones which are useful as new chiral building blocks.

In recent years, impressive progress has been made in the field of asymmetric synthesis, in which catalyzed asymmetric processes for carbon-carbon bond formation are especially interesting.[1] Hetero Diels-Alder reactions of 1-oxa-1,3-butadienes with vinyl ethers, which lead to 3,4-dihydro-2*H*-pyran derivatives, are synthetically equivalent to the Michael type conjugate additions. Although their asymmetric versions should be important as stereoselective carbon-carbon bond forming process, examples of catalyzed asymmetric reactions remain unexplored. One exception includes the chiral titanium-catalyzed intramolecular hetero Diels-Alder reaction of the 1-oxa-1,3-butadiene system, derived from the Knoevenagel condensation of an aromatic aldehyde with *N*,*N*'-dimethylbarbituric acid.[2]

We recently reported that sulfonyl-functionalized α,β-unsaturated ketones work effectively as a new type of hetero 1,3-diene in Lewis acid catalyzed hetero Diels-Alder reactions with vinyl ethers.[3] In the presence of a Lewis acid catalyst (0.5-10 mol%), such as $TiCl_2(i\text{-}PrO)_2$ or $Eu(fod)_3$, high rate acceleration was observed to provide dihydropyrans in excellent yields and with exclusive *endo* selectivities.[4] Such satisfactory results led us to further investigate the Lewis acid catalysis of these hetero Diels-Alder reaction.



Scheme 1.

In this communication, we present the first example of catalyzed asymmetric intermolecular hetero Diels-Alder reactions by the use of (*E*)-2-oxo-1-phenylsulfonyl-3-alkenes **1** and vinyl ethers **2**.

Enones **1a-c** were allowed to react with excess amounts of vinyl ethers **2a-c** in the presence of a catalytic amount of chiral Lewis acids **3a,b** in dichloromethane under the conditions shown in Table 1 (Scheme 1).[5,6]

Chiral titanium catalysts **3a,b** were prepared in situ according to the literature procedure from $TiX_2(i\text{-}PrO)_2$ (X = Cl, Br)[7] and (4*R*,5*R*)-α,α,α',α'-tetraphenyl-2,2-dimethyl-1,3-dioxolane-4,5-dimethanol (1.1 equiv)[8] in the presence of molecular sieves 4A.[7]

Table 1. Chiral Lewis Acid-Catalyzed Asymmetric Hetero Diels-Alder Reactions of Enones **1a-c** with Vinyl Ethers **2a-c**[a]

Entry	Enone	Vinyl ether	Catalyst	Temp	Time	Cycloadduct		
			mol%	℃	h	Yield/%[b]	% ee[c]	Abs. config.[d]
1	**1a**	**2a**	**3a** (50)	-78/-30	9/3	**4a** (78)	48	2*R*,4*R*
2	**1a**	**2a**	**3b** (10)	-78	20	**4a** (91)	59	2*R*,4*R*
3	**1a**	**2b**	**3a** (50)	-30	17	**4b** (85)[e]	62	2*R*,4*R*
4	**1a**	**2b**	**3b** (10)	-50	6	**4b** (96)	74	2*R*,4*R*
5	**1a**	**2b**	**3b** (10)	-78	20	**4b** (92)	88	2*R*,4*R*
6	**1a**	**2c**	**3b** (10)	-78	20	**4c** (90)	97	2*R*,4*R*
7	**1a**	**2c**	**3b** (5)	-78	24	**4c** (90)	95	2*R*,4*R*
8	**1a**	**2c**	**3b** (10)	-78	24	**4c** (92)	95	2*R*,4*R*
9	**1b**	**2c**	**3b** (10)	-78	24	**4d** (88)	86	2*R*,4*S*
10	**1c**	**2c**	**3b** (10)	-70	20	**4e** (77)[f]	97	2*R*,4*R*

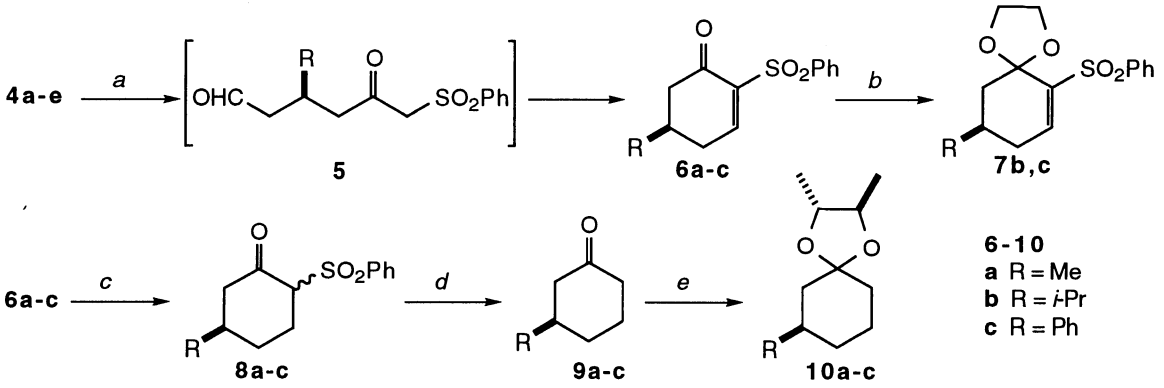
a) Unless otherwise noted, all reactions were performed by using enone **1** and vinyl ether **2** (10 equiv.) in CH_2Cl_2. b) Yield of isolated cycloadducts. c) Determined by HPLC analysis by using chiral column after conversion to cyclohexenone **6a** (entries 1-8) or acetals **7b** (entry 9) and **7c** (entry 10), see Scheme 2 and Table 2. d) Determined by ^{13}C NMR spectra after conversion to acetals **10a-c**, see Scheme 2 and Table 2. e) A small amount (2%) of inseparable *trans*-isomer was contained. f) Enone **1c** was recovered (17%).

Reaction of enone **1a** with a large excess of ethyl vinyl ether **2a** was performed in the presence of catalyst **3a** (50 mol%), at –78 °C for 9 h and then at –30 °C for 3 h, to give *cis*-isomer **4a** as single isomer in 78% yield (48% ee, entry 1), while the use of isobutyl vinyl ether **2b** resulted slightly better enantioselectivity (62% ee) (entry 3). The titanium bromide catalyst **3b** was found to be more effective to improve both the catalytic cycle and rate acceleration. Thus, in the presence of 10 mol% of **3b**, reactions of enone **1a** with vinyl ethers **2a-c** completed even at –78 °C to provide *cis*-cycloadducts **4a-c** in excellent yields (91, 92, and 90%) and with moderate to high enantioselectivities (59, 88, and 97% ee) (entries 2, 5, and 6, respectively). Equally effective results were observed when a less amount (5 mol%) of the catalyst **3b** (90% and 95% ee, entry 7) or less amount of vinyl ether **2c** (5 equiv.) was employed (92% and 95% ee, entry 8).

As discussed below, the sense of enantioselection was all the same in reactions of enone **1a** with vinyl ethers **2a-c**. In addition, enantioselectivity was effectively enhanced with the increase of bulkiness of the alkoxyl substituent R^1 of dienophiles **2a-c** (selectivity: **2a** < **2b** < **2c**), and a lower reaction temperature led to a better result (entry 4 vs entry 5). As a result, other enones **1b,c** were allowed to react with isopropy vinyl ether **2c** in the presence of the titanium bromide catalyst **3b** under similar conditions to provide **4d** (88% and 86% ee) and **4e** (77% and 97% ee), respectively (entries 9 and 10).

To determine the absolute configurations of the major enantiomers of dihydropyrans **4a-e**, the cycloadducts **4a-e** were converted to the corresponding 5-substituted 2-phenylsulfonyl-2-cyclohexen-1-ones **6a-c** or

acetals **7b,c** (Scheme 2). Treatment of cycloadducts **4a-e** with 4N hydrochloric acid produced cyclohexenones **6a-c** in high yields (Table 2) via a sequence of the acid-catalyzed hydrolysis forming 1,5-keto aldehyde **5** and subsequent intramolecular condensation.[9] Further acetalization of **6b,c** gave cyclohexenone acetals **7b,c** in 95% (86% ee) and 95% (97% ee), respectively.



a) 4N-HCl,THF, rt, 2 h. *b*) ethylene glycol, benzene, reflux, 8 h. *c*) H_2, 10% Pd-C, THF/EtOH (1/1 v/v). *d*) *n*-Bu_3SnH, AIBN, benzene, reflux, 4 h. *e*) (2*R*,3*R*)-2,3-butanediol, benzene, reflux, 2 h.

Scheme 2.

Further transformations of unsaturated ketones **6a-c** to saturated ketones **9a-c** were easily performed as follows: Hydrogenation of **6a** (95% ee), **6b** (86% ee), and **6c** (97% ee) in the presence of 10% Pd-C was followed by the reductive desulfonylation with tributyltin hydride.[10] Their acetalization with (2*R*,3*R*)-2,3-butanediol gave the corresponding acetals **10a-c** without epimerization in overall yields of 64% (94% de), 56% (85% de), and 65% (97% de), respectively. The absolute configurations of **10a-c** were determined to be *R* by ^{13}C NMR spectra.[11] Thus, the absolute configurations of the major enantiomers of *cis*-dihydropyrans **4** were confirmed as (2*R*,4*R*)-**4a-c**,[12] (2*R*,4*S*)-**4d**, and (2*R*,4*R*)-**4e**.

Table 2. Transformations of Dihydropyrans **4c-e** to 2-Cyclohexen-1-ones **6a-c**, 2-Cyclohexen-1-one Acetals **7b,c**, and Cyclohexanone Acetals **10a-c**[a]

Entry	Substrate	Yield/%[b] (5*R*)-**6**[c]	ee %[d]	Yield/%[b] (5*R*)-**7**	ee %[d]	Total yield/%[b] (3*R*)-**10**	de %[e]
1[f]	**4c**	**6a** (95)	95	–	–	**10a** (64)	94
2	**4d**	**6b** (91)	–	**7b** (95)	86	**10b** (56)	85
3	**4e**	**6c** (95)	–	**7c** (95)	97	**10c** (65)	97

a) Procedures were described in the text and Scheme 2. b) Isolated yield. c) Optical rotations are as follows: **6a**: $[\alpha]_D^{25}$ –42.8° (*c* = 1.00, $CHCl_3$); **6b**: $[\alpha]_D^{25}$ –6.77° (*c* = 0.93, $CHCl_3$); **6c**: $[\alpha]_D^{25}$ –19.4° (*c* = 1.00, $CHCl_3$). d) Determined by HPLC analysis. **6a**: DAICEL chiral cel OC: *i*-PrOH - hexane = 4:1 v/v. **7b**: DAICEL chiral cel OJ: *i*-PrOH - hexane = 1:2 v/v. **7c**: DAICEL chiral cel OJ: *i*-PrOH - hexane = 1:1 v/v. e) Determined by ^{13}C NMR spectra, see Ref. 11. f) Substrates **4a,b** were also converted to (5*R*)-**6a** in higher than 90% yields.

In conclusion, 1-phenylsulfonyl-2-oxo-3-alkenes **1** act as wonderful hetero 1,3-dienes of the 1-oxa-1,3-diene types in the Lewis acid-catalyzed asymmetric hetero Diels-Alder reactions with vinyl ethers. This hetero Diels-Alder methodology offers a very effective synthetic route for the enantiomers of 4-substituted 2,4-*cis*-2-

alkoxy-3,4-dihydro-2*H*-pyrans, 5-substituted 2-phenylsulfonyl-2-cyclohexen-1-ones, and 3-substituted cyclohexanones.

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4) E. Wada, H. Yasuoka, and S. Kanemasa, *Chem. Lett.*, **1994**, 145 and references cited therein.
5) By use of (+)-Eu(hfc)$_3$ (5 mol%) as catalyst, hetero Diels-Alder reaction of enone **1a** with ethyl vinyl ether **2a** underwent at 0 °C (120 h) to provide *cis*-adduct **4a** in 80% yield, but without any enantioselectivity.
6) All new compounds discussed in the text were fully characterized on the basis of spectra data and analyses. Some typical data are as follows: *cis*-**4c** (95% ee): Colorless solids; mp 52 - 54 °C; $[\alpha]_D^{25}$ –72.27 ° (*c* = 1.01, EtOAc); IR (KBr) 1665 cm^{-1}; ^{1}H NMR (C_6D_6) δ = 0.73 (3H,d, $J_{Me\text{-}4}$ = 7.0 Hz, 4-Me), 0.96, 1.10 (each 3H, each d, $J_{Me\text{-}CH}$ = 6.2 Hz, 2-Me$_2$CHO), 1.28 (1H, ddd, J_{gem} = 13.1, $J_{3\text{-}4}$ = 9.9, and $J_{3\text{-}2}$ = 8.8 Hz, one of H-3), 1.65 (1H, dddd, J_{gem} = 13.1, $J_{3\text{-}4}$ = 5.9, $J_{3\text{-}2}$ = 2.2, and $J_{3\text{-}5}$ = 1.1 Hz, the other of H-3), 1.94 - 2.13 (1H, m, H-4), 3.50, 3.58 (each 1H, each d, J_{gem} = 13.9 Hz, 6-CH$_2$SO$_2$), 3.61 (1H, m, $J_{CH\text{-}Me}$ = 6.2 Hz, 2-Me$_2$CHO), 4.35 (1H, dd, $J_{5\text{-}4}$ = 2.5 and $J_{5\text{-}3}$ = 1.1 Hz, 5-H), 4.62 (1H, dd, $J_{2\text{-}3}$ = 8.8 and 2.2 Hz, 2-H), 6.90 - 7.05 (3H, m, Ph), and 7.80 - 7.90 (2H, m, Ph); ^{13}C NMR (C_6D_6) δ = 20.89, 21.80, 23.76 (each Me), 26.90 (C-3), 36.51 (C-4), 61.47 (6-CH$_2$SO$_2$), 70.18 (2-Me$_2$CHO), 98.61 (C-2), 110.57 (C-5), 128.74, 128.89, 133.00, 140.30 (each Ph), and 141.10 (C-6). Found: C, 62.02; H, 7.17%. Calcd for $C_{16}H_{22}O_4S$; C, 61.91; H, 7.14%.
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11) The completely analogous relationship of the diastereotopic splitting of the ^{13}C NMR signals of the (2*R*,3*R*)-2,3-butanediol acetals of 3-substituted cyclohexanones has been well defined. See, G. L. Lemiere, R. A. Dommisse, J. A. Lepoivre, F. C. Alderweireldt, H. Hiemstra, H. Wynberg, J. B. Jones, and E. J. Toone, *J. Am. Chem. Soc.*, **109**, 1363 (1987); G. H. Posner, L. L. Frye, and M. Hulce, *Tetrahedron*, **40**, 1401 (1984); H. Hiemstra and H. Wynberg, *Tetrahedron Lett.*, **25**, 2183 (1977).
12) The absolute configuration of (3*R*)-**10a** was also confirmed by comparison of the ^{13}C NMR spectrum with that of authentic sample of (3*R*)-**10a** prepared from the commercially available (3*R*)-3-methylcyclohexanone (Aldrich Chemical Co) and (2*R*,3*R*)-2,3-butanediol.

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