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

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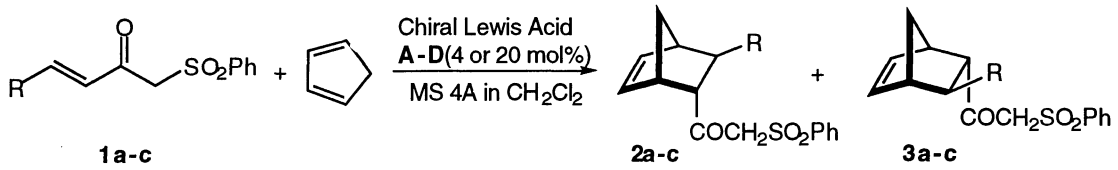
Highly enantio- and *endo*-selective Diels-Alder reactions of (*E*)-1-phenylsulfonyl-3-alken-2-ones, a new type of chelating dienophile, with cyclopentadiene are achieved by the aid of a catalytic amount of chiral titanium catalysts. Mode of enantioselectivities depend upon the size of aryl substituents involved in the chiral ligands; dramatic reversal of selectivities is observed.

Recently, we have found that (*E*)-1-phenylsulfonyl-3-alken-2-ones as sulfonyl-functionalized chelating enones work effectively as hetero 1,3-dienes in chiral Lewis acid-catalyzed hetero Diels-Alder reactions with vinyl ethers. In the presence of a chiral titanium catalyst, high enantioselectivities (> 97% ee) resulted and 4-substituted (2*R*,4*R*)- or (2*R*,4*S*)-2-alkoxy-6-phenylsulfonyl-3,4-dihydro-2*H*-pyrans were produced in high yields and with the exclusive *endo*-selectivities.[1] Noteworthy are enhanced reactivity of the hetero diene/Lewis acid catalyst complexes, satisfactory levels of enantiocontrol, and effective cyclization of the catalyst.

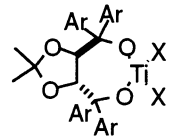
Our continuing interest has been focussed on utilization of these sulfonyl-functionalized chelating enones as prochiral electrophilic substrates in catalyzed asymmetric carbon-carbon bond formations. This led us further to investigate their synthetic potentials as chelating dienophiles in asymmetric Diels-Alder reactions. The most convenient chelating dienophiles ever reported are the α,β-unsaturated amide derivatives of 2-oxazolidinones.[2]



1a-c **2a-c** **3a-c**

1-3
a R = Me
b R = *n*-Pr
c R = Ph

Chiral Lewis Acid **A-D**



A Ar = Ph, X = Br
B Ar = 3,5-Xylyl, X = Br
C Ar = 1-Naphthyl, X = Br
D Ar = 1-Naphthyl, X = Cl

Scheme 1.

We describe here the absolute enantiocontrol of the titanium-catalyzed asymmetric Diels-Alder reactions of (*E*)-1-phenylsulfonyl-3-alken-2-ones **1** to cyclopentadiene (Scheme 1).

Enones **1a-c** were reacted with an excess amount of cyclopentadiene in the presence of a catalytic amount of chiral Lewis acids **A-D** in dichloromethane under the conditions shown in Table 1 and Scheme 1, leading to enantiomeric mixtures of 6-substituted *trans*-5-(phenylsulfonylacetyl)bicyclo[2.2.1]-2-heptenes **2,3**.[3] Chiral titanium catalysts **A-D** were prepared in situ according to the literature procedure from $TiX_2(i\text{-}PrO)_2$ (X = Br, Cl)[4] and various (4*R*,5*R*)-α,α,α',α'-tetraaryl-2,2-dimethyl-1,3-dioxolane-4,5-dimethanol (1.1 equiv) in the presence or absence of molecular sieves 4A.[5] Enantiomeric purities of cycloadducts **2a-c** and **3b,c** were determined by chiral HPLC analysis, while that of **3a** was established by chiral capillary GLC analysis after its conversion to 5,6-*trans*-5-acetyl-6-methylbicyclo[2.2.1]-2-heptene **6** by reductive desulfonylation[6] with tributyltin hydride in the presence of AIBN (Scheme 2). Absolute configurations of the *endo*-isomers **2,3** were confirmed on the basis of their chiral HPLC analysis using the authemtic samples **2a-c** which were prepared by the sulfonylmethylation of 3-(6-substituted bicyclo[2.2.1]-2-heptene-5-carbonyl)-1,3-oxazolidin-2-ones **5**, the known Diels-Alder cycloadducts derived from the α,β-unsaturated amides of 2-oxazolidinones **4a-c** by Narasaka method (Scheme 2).[7]

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

Entry	Enone	Catalyst	Temp	Time	Cycloadduct			
			℃	h	yield/%[b]	*endo:exo*[c]	**2** or **3** (% ee)[d]	Abs. config.[e]
1	**1a**	**A**	−78	18	97	97: 3	**3a** (16)	5*R*,6*S*
2	**1a**	**B**	−78	45	90	97: 3	**2a** (76)	5*S*,6*R*
3	**1a**	**C**	−78	5	90	98: 2	**3a** (100)[f]	5*R*,6*S*
4	**1a**	**D**	−78	5	80	>99: 1	**3a** (100)[f]	5*R*,6*S*
5	**1a**	**D**	rt	5	80	95: 5	**3a** (100)[f]	5*R*,6*S*
6	**1a**	**D**[g]	−78	42	80	>99: 1	**3a** (100)[f]	5*R*,6*S*
7	**1a**	**D**[h]	−78	20	81	98: 2	**3a** (100)[f]	5*R*,6*S*
8	**1a**	**D**[g,h]	rt	18	93	94: 6	**3a** (92)	5*R*,6*S*
9	**1b**	**B**	−78	24	88	>99: 1	**2b** (66)	5*S*,6*R*
10	**1b**	**C**	−78	30	90	>99: 1	**3b** (94)	5*R*,6*S*
11	**1c**	**B**	−78	60	29 (45)	95: 5	**2c** (34)	5*R*,6*R*
12	**1c**	**C**	−78	60	65 (33)	83:17	**3c** (78)	5*S*,6*S*

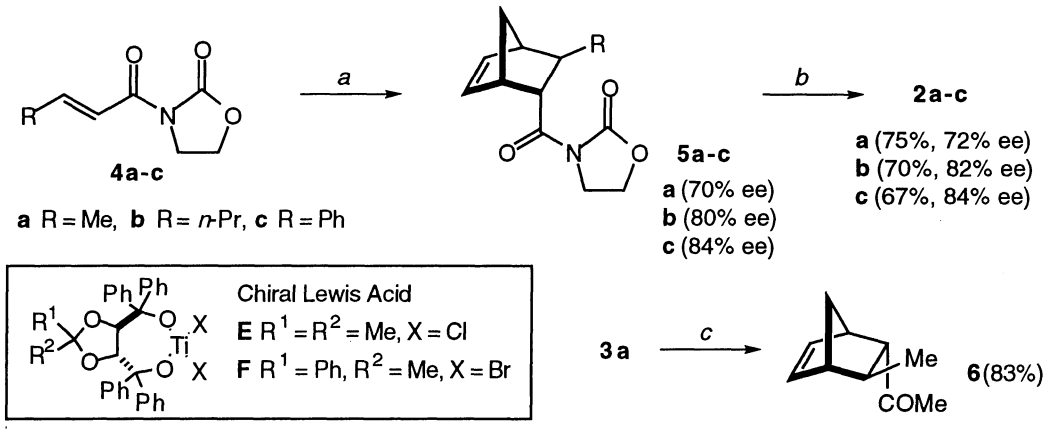
a) Unless otherwise noted, all reactions were performed between enone **1** and cyclopentadiene (10 equiv.) in the presence of catalyst **A-D** (20 mol%) in CH_2Cl_2. b) Yields of isolated cycloadducts as mixture of *endo*- and *exo*-isomers. Yields of the recovered enone **1** are in parenthesis. c) Determined by ^1H NMR and/or ^{13}C NMR spectra. d) Determined by chiral HPLC analysis for **2a-c** and **3b,c**. Cycloadduct **3a** was determined by chiral capillary GLC analysis after its conversion to norbornene **6**, see text and Scheme 2. e) Determined by chiral HPLC analysis using the authentic samples **2**, see text and Scheme 2. f) No enantiomer was detected. g) A smaller amount (4 mol%) of catalyst **D** was used. h) In the absence of molecular sieves 4A.

The methyl-substituted enone **1a** was chosen as dienophile and its titanium-catalyzed Diels-Alder reactions with cyclopentadiene were examined under a variety of reaction conditions. Although the titanium bromide catalyst **A** bearing phenyl substituents as shielding substituents showed excellent *endo*-selectivity (*endo:exo* = 97:3) and chemical yield (97%), only a poor optical yield (*endo*-adduct: 16% ee) was observed (entry 1), the major enantiomer **3a** having the 5*R*, 6*S* configuration. Such a low enantioselectivity makes a

sharp contrast with the high enantioselectivities (>97% ee) observed in the previous hetero Diels-Alder reactions with vinyl ethers.[1] When the catalyst **B** bearing bulkier 3,5-xylyl substituents was used, satisfactory chemical (90%) and *endo*-selectivities (97%) were recorded. Although enantioselectivity was improved (76% ee), the major enantiomer **2a** has the opposite absolute configuration of 5*S*,6*R*. To our delight, the exclusive enantiocontrol was attained in the reaction catalyzed by the catalyst **C** which bears 1-naphthyl shielding substituents (entry 3). The *endo*-selective (98%) cycloadduct **3a** obtained in 90% yield was optically pure (100% ee); its absolute configuration is the same as that of the major enantiomer of the reaction catalyzed by **A**.

Titanium chloride catalysts usually show weaker catalytic activity than bromide catalysts. The reaction catalyzed by the titanium chloride catalyst **D** resulted in a little better *endo*-selectivity (>99%) and the absolute enantioselectivity (100% ee, entry 4). No decrease of enantioselectivity was observed even in the reaction at room temperature (95% *endo*, 100% ee, entry 5) and the amount of catalyst **D** could be reduced to 4 mol% without any decrease of selectivities (entry 6). At –78 °C, a high selectivity was observed without molecular sieves 4A (98% *endo*, 100% ee, entry 7), while, in the absence of molecular sieves 4A at room temperature, catalysis by a small amount (4 mol%) of **D** was not so effective. The enantiomeric purity of **3a** was lowered to 92% ee (entry 8).

The use of the titanium catalysts **C** and **D** bearing 1-naphthyl substituents was essential to attain the absolute enantiocontrol giving cycloadducts **3a** (5*R*,6*S*). With the catalyst **B** bearing 3,5-xylyl substituents, the opposite absolute configuration was induced to give **2a** (5*S*,6*R*) in moderate enantioselectivities. Accordingly, other enones **1b** and **1c** were examined in the reactions in the presence of **B** or **C**. Reaction of enone **1b** catalyzed by **B** or **C** gave **2b** (5*S*,6*R*, 88% yield, >99% *endo*, and 66% ee, entry 9) or **3b** (5*R*,6*S*, 90% yield, >99% *endo*, and 94% ee, entry 10), respectively, and reaction of less reactive **1c** catalyzed by **B** or **C** gave **2c** (5*R*,6*R*, 29% yield, 95% *endo*, and 34% ee, entry 11) or **3c** (5*S*,6*S*, 65% yield, 83% *endo*, and 78% ee, entry 12), respectively.



a) cyclopentadiene, catalyst **E** or **F**, CH_2Cl_2. *b*) $PhSO_2CH_2^-Li^+$, THF, -78 °C.

c) *n*-Bu_3SnH, AIBN, toluene, reflux.

Scheme 2.

In conclusion, (*E*)-1-phenylsulfonyl-3-alken-2-ones **1** can be utilized as effective chelating dienophiles in Lewis acid-catalyzed asymmetric Diels-Alder reactions with cyclopentadiene. Although the mechanism of chiral induction is still ambiguous, the only one of two possible diastereomeric enone/Lewis acid catalyst

complexes was involved in the transition state. It is not certain so far which plays more important role in the determination step of chiral induction, the shielding substituents (Ar) of the chiral ligands or the phenyl substituent on the sulfonyl moiety. There still remains the question of matching/mismatching combination as well as the conformational preference with respect to the sp^2-sp^2 single bond of enones **1**.

Combined with the enhanced reactivity of hetero 1,3-dienes in catalyzed asymmetric hetero Diels-Alder reactions,[1] enones **1** are also useful as dienophiles in catalyzed asymmetric Diels-Alder reactions. In both reactions, excellent enantiocontrols can be achieved. An extension to the reactions using 1,3-dienes other than cyclopentadiene is currently undergoing in our group. Scope and limitation of this type of new chelating enones in the process of catalyzed asymmetric Diels-Alder reaction will be soon reported elsewhere.

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3) Characterization of new compounds discussed in this work was based on the spectral and analytical data. Some typical spectral data are shown as follows: *endo*-(5*R*,6*S*)-**3a** (100% ee): Colorless solid; mp 101-102 °C; $[\alpha]_D^{25}$ 85.0 ° (*c* = 0.86, $CHCl_3$); IR (KBr) 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 1.16 (3H,d, $J_{Me\text{-}6}$ = 6.9 Hz, 6-Me), 1.47 (1H, ddd, J_{gem} = 8.8, *J* = 3.7, and 1.8 Hz, one of H-7), 1.62 (1H, br d, J_{gem} = 8.8 Hz, the other of H-7), 1.80-1.89 (1H, m, H-6), 2.48 (1H, br s, H-1), 2.79 (1H, br t, *J* = 3.8 Hz, H-5), 3.18 (1H, br s, H-4), 4.09, 4.28 (each 1H, each d, J_{gem} = 13.6 Hz, CH_2SO_2), 5.78 (1H, dd, $J_{2\text{-}3}$ = 5.9 and $J_{2\text{-}1}$ = 2.9 Hz, H-3), 6.21 (1H, dd, $J_{3\text{-}2}$ = 5.9 and $J_{3\text{-}4}$ = 3.3 Hz, H-2), 7.50-7.75 (3H, m, Ph), and 7.80-7.90 (2H, m, Ph); ^{13}C NMR ($CDCl_3$) δ = 20.60 (Me), 35.88 (C-6), 46.37 (C-4), 46.44 (C-1), 49.67 (C-7), 62.10 (C-5), 65.70 (CH_2SO_2), 128.40, 129.25, 134.18, 138.92 (each Ph), 131.85, 139.10 (C-2 or C-3), and 198.51 (CO). MS *m/z* (rel intensity, %) 290 (M^+, 2), 225 (100), 141 (21), 77 (34), and 66 (87). Found: C, 66.51; H, 6.23%. Calcd for $C_{16}H_{18}O_3S$: C, 66.21; H, 6.21%.

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7) K. Narasaka, N. Iwasawa, M. Inoue, T. Yamada, M. Nakashima, and J. Sugimori, *J. Am. Chem. Soc.*, **111**, 5340 (1989). The sense of enantioselection observed in the reaction of enone **4a** with cyclopentadiene on the titanium bromide catalyst **A** leading to **5a** was the same to that performed on the titanium chloride catalyst **E** (See above). Therefore, the precursors **5b,c** of authentic samples **2b,c** were prepared from the reactions of **4b,c** in the presence of the titanium bromide catalyst **F** (Scheme 2).

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