Diarylprolinol Silyl Ether as Catalyst of an *exo*-Selective, Enantioselective Diels–Alder Reaction

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ABSTRACT



In combined use with CF₃CO₂H, 2-[bis(3,5-bis-trifluoromethylphenyl) triethylsiloxymethyl]pyrrolidine was found to be an effective organocatalyst of an *exo*-selective, enantioselective Diels–Alder reaction of $\alpha_{,\beta}$ -unsaturated aldehydes.

Diarylprolinols are a class of small, chiral organic molecules that have proven to be particularly useful in asymmetric synthesis. Diphenylprolinol reacts with a boron reagent to generate chiral oxazaborolidine, which has been widely utilized in the Corey–Bakshi–Shibata (CBS) reduction developed by Corey.¹ His group also discovered that chiral oxazaborolidinium ions prepared from diarylprolinols are versatile chiral Lewis acid catalysts, promoting the Diels– Alder reaction and the cyanation reaction of aldehydes.² Enantioselective reactions catalyzed by organocatalyst have received a great deal of attention in recent years,³ and silyl ethers of diarylprolinols ^{4,5,6} have been found to act as effective organocatalysts of various enantioselective transformations, as independently developed by Jørgensen's⁴ and

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Figure 1. The diphenylprolinol-organocatalysts examined in this study.

our⁵ groups. We have found that they promote the enantioselective Michael reaction of nitroalkene and aldehyde to afford the adduct with excellent diastereo- and enantioselectivities.^{5a}Enders and co-workers elegantly applied this reaction to a triple-cascade organocatalytic reaction for the synthesis of chiral cyclohexanecarbaldehydes.⁶ⁱ Recently we reported that diphenylprolinol silyl ether catalyzes the enantioselective ene reaction of an α , β -unsaturated aldehyde with cyclopentadiene to afford substituted cyclopentadienes with excellent enantioselectivity (Scheme 1).^{5b} In the course



of developing this reaction further, we happened to find that an *exo*- and enantioselective Diels—Alder reaction proceeds on changing the reaction conditions. That is, in the presence of an acid catalyst, the Diels—Alder reaction becomes the principle pathway, affording the *exo*-isomer with high diastereo- and excellent enantioselectivities.

The Diels-Alder reaction is a synthetically powerful method for the construction of regio and stereochemically defined cyclohexane frameworks, key components of a wide variety of natural products.⁷ The selective formation of the exo-isomer has long proven to be difficult.⁸ For instance, the Diels-Alder reactions of cyclopentadiene with acrolein, methyl acrylate, and methyl vinyl ketone all afford predominantly the endo-isomer. This endo-selectivity is enhanced by Lewis acid.9 Even in the recently developed Diels-Alder reaction catalyzed by organocatalyst,¹⁰ selective formation of the exo-isomer can be a challenging problem; MacMillan reported the first asymmetric Diels-Alder reaction catalyzed by organocatalyst of cyclopentadiene and α,β -unsaturated aldehydes which proceeded with excellent enantioselectivity in spite of low diastereoselectivity.^{10a} On the other hand, Maruoka and co-workers reported an elegant exo- and enantioselective Diels-Alder reaction catalyzed by binaphthyl-based diamine salts.^{10h} While excellent exo- and enantioselectivities were achieved, the scope was limited to cyclopentadiene and three α,β -unsaturated aldehydes. Development of an exo-selective and enantioselective Diels-Alder reaction of wider generality is desirable. In this paper, we will disclose such a reaction using the catalyst diarylprolinol silyl ether.

As a model we studied the reaction of cinnamaldehyde and cyclopentadiene in the presence of several diarylprolinol silyl ethers (results summarized in Table 1). As we have reported, in the presence of *p*-nitrophenol the *tert*-butyldimethylsilyl ether of diphenylprolinol (1) is an effective catalyst of an enantioselective ene reaction, affording the cyclopentadiene derivative **4** with excellent enantioselectivity (Scheme 1).^{5b}

However when the reaction was performed under acidic conditions, its course changed dramatically. When cinnamaldehyde and cyclopentadiene were treated with catalyst 1 in the presence of CF_3CO_2H in toluene, the cyclopentadiene derivative 4 was not formed but rather Diels—Alder adduct

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 Table 1. Effect of the Catalyst in the Reaction of

 Cinnamaldehyde and Cyclopentadiene Catalyzed by

 Organocatalysts^a



entry	catalyst	additive	yield [%] ^b	exolendo ^c	ee (exo) [%] ^d	ee (endo) [%] ^d
1	1	CE CO II	10	70.01	70	00
1	1	CF ₃ CO ₂ H	10	79:21	19	00
2	2	none	0			
3	2	CH_3CO_2H	0			
4	2	$\rm CCl_3CO_2H$	69	87:13	95	79
5	2	CF_3CO_2H	86	84:16	95	83
6	2	CSA	10	57:43	69	5
7	2	$TsOH \cdot H_2O$	13	88:12	45	0
8	2	TfOH	0			
9	3	$\rm CF_3CO_2H$	80	85:15	97	88

^{*a*} Unless otherwise shown, the reaction was conducted with 0.07 mmol of catalyst, 0.14 mmol of additive, 0.7 mmol of cinnamaldehyde, and 2.1 mmol of cyclopentadiene at rt. ^{*b*} Isolated yield of a mixture of *5-exo* and *5-endo*. ^{*c*} Determined by ¹H NMR. ^{*d*} Determined by chiral HPLC analysis.

5 was obtained in good optical purity in spite of the low yield (Table 1, entry 1). Moreover, the exo-isomer was obtained predominantly. Catalyst, solvent, and additive were screened: 3,5-bis(trifluoromethyl)phenyl-substituted catalyst 2 was found to be a superior Diels-Alder reaction catalyst to diphenyl analogue 1. Several acids were investigated as additives including CH₃CO₂H, CCl₃CO₂H, CF₃CO₂H, camphorsulfonic acid, TsOH·H₂O, and TfOH. The reaction did not proceed in the presence of a weak acid such as CH₃-CO₂H nor a strong acid such as TfOH, and of these, CF₃-CO₂H was found to be most effective (entry 5). In marked contrast, no reaction proceeded in the presence of CH₃CO₂H (entry 3). Screening of the solvent indicated that toluene is suitable. The effect of the silvl group substituent was also investigated. Triethylsilyl derivative 3 gave higher enantioselectivity than the corresponding trimethylsilyl derivative 2. Results under the best reaction conditions are as follows: When a mixture of cinnamaldehyde and cyclopentadiene was treated with triethylsilyl ether **3** in the presence of CF_3CO_2H in toluene, the Diels-Alder product 5 was obtained in 80% yield with high *exo*-selectivity (exo/endo = 85:15) and excellent enantioselectivity (exo 97% ee, endo 88% ee, entry 9).

As the best conditions for the Diels—Alder reaction had been found, the generality of the reaction was investigated (results summarized in Table 2). Not only phenyl, but also a 2-naphthyl-substituted acrolein derivative gave an excellent result (entry 2). Although the reaction is slow for acrolein derivatives possessing electron-rich aromatic substituents such as *o*-methoxyphenyl, a good yield was obtained by prolonging the reaction time, high *exo*-selectivity and excel**Table 2.** Enantioselective Diels-Alder Reaction between Cyclopentadiene and α , β -Unsaturated Aldehydes Catalyzed by Diarylprolinol Silyl Ether **3**^{*a*}



entry	R	time [h]	yield [%] ^b	exo/endo ^c	ee (exo) [%] ^d	ee (endo) [%] ^d
1	Ph	26	quant	85:15	$97~(2S)^{e}$	$88 (2S)^{e}$
2	2-Np	28	94	86:14	96	82
3	$o ext{-MeOPh}$	78	71	78:22	96	96
4	p-BrPh	24	quant	86:14	96	84
5	p-NO ₂ Ph	6	93	87:13	96	82
6 ^f	2-furyl	100	67	80:20	$94(2S)^{e}$	$78~(2S)^{e}$
7	cyclohexyl	17	78	85:15	97	93
8	<i>n</i> -Bu	3	65	78:22	94	91
9^g	$\mathrm{CO}_2\mathrm{Et}$	17	92	70:30	84	64
10^h	p -NO $_2$ Ph	17	quant	86:14	94	73

^{*a*} Unless otherwise shown, the reaction was conducted with 0.07 mmol of catalyst **3**, 0.14 mmol of CF₃CO₂H, 0.7 mmol of cinnamaldehyde, and 2.1 mmol of cyclopentadiene at rt in toluene. ^{*b*} Isolated yield of a mixture of *exo* and *endo* isomers. ^{*c*} Determined by ¹H NMR (400-MHz). ^{*d*} The ee was determined by chiral HPLC or GC analysis. ^{*e*} Absolute configuration, see reference 10a. ^{*f*} Catalyst **3** (20 mol %) and CF₃CO₂H (40 mol %) were used. ^{*s*} The reaction was performed at 4 °C. ^{*h*} Catalyst **3** (2 mol %) and CF₃CO₂H (4 mol %) were used.

lent enantioselectivity were realized (entry 3). When the substituent is electron-deficient, such as *p*-bromophenyl and *p*-nitrophenyl, the reaction is fast, with high diastereo- and excellent enantioselectivities (entries 4, 5). Not only aromatic groups, but also heteroaromatic groups such as furyl are suitable substituents (entry 6). Alkyl group-substituted acrolein also gave good results, and steric size does not compromise the enantioselectivity (entries 7, 8). 3-Ethoxycarbonylpropenal is also a suitable α,β -unsaturated aldehyde, affording high selectivity (entry 9). Though we have used 10 mol % of the catalyst in the above reactions, loading can be reduced to 2 mol %. That is, in the presence of 2 mol % of **3** and 4 mol % of CF_3CO_2H , the reaction proceeds efficiently, affording the Diels-Alder product in 99% yield with excellent enantioselectivity (exo 94% ee, endo 73% ee, entry 10).

Other dienes can also be employed successfully. Acyclic dienes such as 2,3-dimethyl-1,3-butadiene and isoprene are suitable dienes, producing the Diels–Alder products, also with excellent enantioselectivity as shown in Table 3. In the reaction of isoprene, there is the possibility that regio-isomers will be formed, but only a single isomer **7** was observed.¹¹ The absolute configuration of **6** was determined by transformation to the known (1*S*, 6*S*)-(3,4-dimethyl-(6-hydroxymethyl)cyclohex-3-enyl)methanol.¹²

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Table 3. Enantioselective Diels–Alder Reaction between β -Ethoxycarbonylacrolein and Dienes Catalyzed by Diarylprolinol Silyl Ether **3**^{*a*}

	EtO ₂ C ¹	CHO + diene	10 mol % 3 20 mol % CF_3CO_2H toluene, 4 °C	Diels-Alder p	roduct
entry	diene	product	time [h]	yield [%] ^b	ee [%] ^c
1 2		CO ₂ Et	16 16	93 86	82 92

 a Unless otherwise shown, the reaction was conducted with 0.07 mmol of catalyst **3**, 0.14 mmol of CF₃CO₂H, 0.7 mmol of cinnamaldehyde, and 2.1 mmol of diene at 4 °C. b Isolated yield. c The ee was determined by chiral HPLC analysis.

In summary, we have developed an *exo*-selective Diels– Alder reaction of α,β -unsaturated aldehdyes catalyzed by diarylprolinol silyl ether **3** under acidic conditions. As it is known that chiral oxazaborolidinium ions prepared from diarylprolinol are versatile enantioselective Diels–Alder catalysts,² it is interesting to note that after appropriate modification the same small molecule, diarylprolinol, can act both as part of a Lewis acid catalyst and as an organocatalyst in the asymmetric Diels–Alder reaction.

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Supporting Information Available: Detailed experimental procedures, full characterization, copies of ¹H-, ¹³C NMR and IR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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