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

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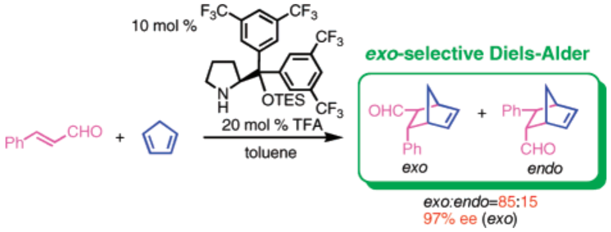
ABSTRACT



In combined use with CF_3CO_2H, 2-[bis(3,5-bis-trifluoromethylphenyl) triethylsiloxymethyl]pyrrolidine was found to be an effective organocatalyst of an *exo*-selective, enantioselective Diels–Alder reaction of α,*β*-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's[4] and

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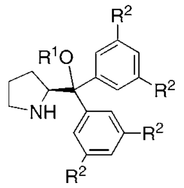
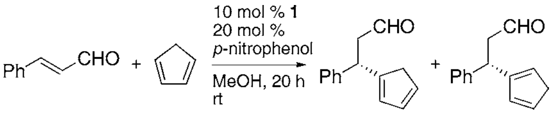


catalyst	R1	R2
1	TBS	H
2	TMS	CF_3
3	TES	CF_3

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

our[5] 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.

Scheme 1. Asymmetric Ene Reaction



4a 4b

84%, 92% ee, 70:30

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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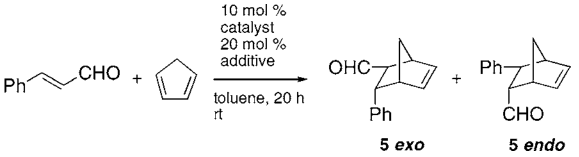
Table 1. Effect of the Catalyst in the Reaction of Cinnamaldehyde and Cyclopentadiene Catalyzed by Organocatalysts[a]



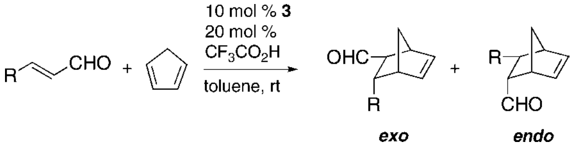
entry	catalyst	additive	yield [%][b]	*exo*/*endo*[c]	ee (*exo*) [%][d]	ee (*endo*) [%][d]
1	**1**	CF_3CO_2H	10	79:21	79	88
2	**2**	none	0			
3	**2**	CH_3CO_2H	0			
4	**2**	CCl_3CO_2H	69	87:13	95	79
5	**2**	CF_3CO_2H	86	84:16	95	83
6	**2**	CSA	10	57:43	69	5
7	**2**	$TsOH·H_2O$	13	88:12	45	0
8	**2**	TfOH	0			
9	**3**	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 ^{1}H 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 CH_3CO_2H, CCl_3CO_2H, CF_3CO_2H, camphorsulfonic acid, $TsOH·H_2O$, and TfOH. The reaction did not proceed in the presence of a weak acid such as CH_3CO_2H nor a strong acid such as TfOH, and of these, CF_3CO_2H was found to be most effective (entry 5). In marked contrast, no reaction proceeded in the presence of CH_3CO_2H (entry 3). Screening of the solvent indicated that toluene is suitable. The effect of the silyl 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 excellent 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).

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 (2*S*)[e]	88 (2*S*)[e]
2	2-Np	28	94	86:14	96	82
3	*o*-MeOPh	78	71	78:22	96	96
4	*p*-BrPh	24	quant	86:14	96	84
5	*p*-NO_2Ph	6	93	87:13	96	82
6[f]	2-furyl	100	67	80:20	94 (2*S*)[e]	78 (2*S*)[e]
7	cyclohexyl	17	78	85:15	97	93
8	*n*-Bu	3	65	78:22	94	91
9[g]	CO_2Et	17	92	70:30	84	64
10[h]	*p*-NO_2Ph	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 CF_3CO_2H, 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 ^{1}H 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 CF_3CO_2H (40 mol %) were used. [g] The reaction was performed at 4 °C. [h] Catalyst **3** (2 mol %) and CF_3CO_2H (4 mol %) were used.

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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(11) The regiochemistry was determined by 2D-^{1}H-NMR.

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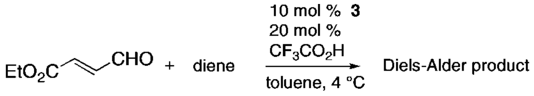
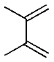
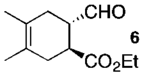
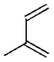
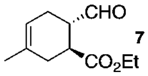
Table 3. Enantioselective Diels−Alder Reaction between β-Ethoxycarbonylacrolein and Dienes Catalyzed by Diarylprolinol Silyl Ether **3**[a]



entry	diene	product	time [h]	yield [%][b]	ee [%][c]
1		 **6**	16	93	82
2		 **7**	16	86	92

[a] Unless otherwise shown, the reaction was conducted with 0.07 mmol of catalyst **3**, 0.14 mmol of CF_3CO_2H, 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 ^{1}H-, ^{13}C 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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