tive intermolecular ene reactions with an alkene as the enophile have been described yet, with only two reports on the intramolecular reaction by Narasaka et al. (including one of the present authors)[3] and Desimoni et al.[4]

On the other hand, the scope of organocatalysis-mediated reactions is expanding very rapidly, and many new chiral organocatalysts have been developed in recent years.[5] Jørgensen and co-workers[6] and our group[7] both independently developed a diarylprolinol silyl ether as an effective organocatalyst.[8] During our application of this catalyst to the asymmetric Diels–Alder reaction, which is known to be mediated by organocatalysis,[9] we found that the reaction of cyclopentadiene and α,β-enals afforded not the Diels–Alder product, but rather the ene product with high enantioselectivity, as described herein. This behavior appears to be highly unusual. Since the discovery of the mechanistically related Diels–Alder reaction in 1928,[10] cyclopentadiene has often been employed as one of the most versatile dienes.[11] However, as far as we are aware there have been no reports of it acting as the ene component in an ene reaction, though the reaction of cyclopentadiene with benzalacetone or benzalacetophenone to give 1,2-dihydropentalenes, in which a Michael-type adduct is postulated as an intermediate, has been reported.[12]

The reaction of cyclopentadiene and cinnamaldehyde was selected as a model and various organocatalysts were examined (Table 1).[13] When diphenylprolinol (**1**) was

Table 1: Effect of catalyst on the ene reaction of cyclopentadiene.[a]
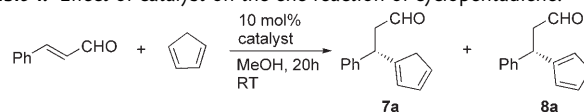
Entry	Catalyst	Yield [%][b]	7a/8a[c]	ee [%][d]
1	**1**	0	–	–
2	**2**	83	56:44	83
3	**3**	67	59:41	85
4	**4**	68	54:46	91
5	**5**	63	65:35	85
6	**6**	0	–	–
7[e]	**4**	0	–	–
8[f]	**4**	84	70:30	92

[a] Unless otherwise shown, the reaction was conducted with 0.07 mmol of catalyst, 0.7 mmol of cinnamaldehyde, and 2.1 mmol of cyclopentadiene at room temperature. [b] Yield of the isolated products **7a** and **8a**. [c] Determined by ^{1}H NMR spectroscopic analysis. [d] The ee value of a mixture of **7a** and **8a** (see the text and Supporting Information). [e] CF$_3$CO$_2$H (20 mol%) was used as an additive. [f] p-Nitrophenol (20 mol%) was used as an additive.

Enantioselective Ene Reaction of Cyclopentadiene and α,β-Enals Catalyzed by a Diphenylprolinol Silyl Ether**

*Hiroaki Gotoh, Ryouhei Masui, Hiroshi Ogino, Mitsuru Shoji, and Yujiro Hayashi**

The ene reaction is a useful carbon–carbon bond-forming reaction.[1] Although several excellent asymmetric carbonyl ene reactions have been reported,[2] no highly enantioselec-

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employed, no reaction proceeded. On the other hand, its trimethylsilyl (TMS) ether **2** is an effective catalyst and ene products **7a** and **8a** were generated in good yield. As there is isomerization between **7a** and **8a**, the ratio of **7a** and **8a** changed according to the reaction conditions and time. The optical purity of the products was determined for the mixture of **7a** and **8a** by chiral HPLC analysis, after reduction with NaBH$_4$ and hydrogenation, and showed that high enantioselectivity (83% ee) had been achieved. Modification of the

catalyst was investigated to improve this result further. The silyl moiety affected the enantioselectivity, and the presence of the bulkier *tert*-butyldimethylsilyl (TBS) ether in catalyst **4** led to higher enantioselectivity with a decrease in reactivity. Changing the phenyl group to the 3,5-dimethylphenyl group in catalyst **5** had little effect, but the 3,5-bis(trifluoromethyl)-phenyl-containing catalyst **6** was completely inactive in the

Catalyst	R¹	R²
1	H	H
2	TMS	H
3	TES	H
4	TBS	H
5	TMS	Me
6	TMS	CF₃
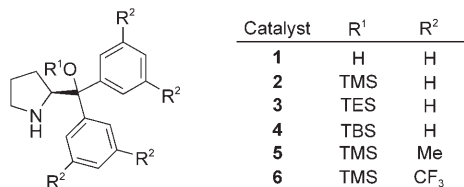
present reaction, which is in marked contrast to the asymmetric reactions reported by Jørgensen and co-workers.[6] The additive is also important: The strong acid (CF₃CO₂H) does not promote the reaction and only affords the dimethyl acetal of cinnamaldehyde instead. When 20 mol% of *p*-nitrophenol was employed in combination with the TBS ether **4**, the reaction rate increased and a good yield (84%) was obtained without compromising the enantioselectivity (92% *ee*). When the MacMillan catalyst[9a] was employed with *p*-nitrophenol under our optimal reaction conditions, no reaction was observed. The reaction scarcely proceeded when our catalyst **4** was employed as its HCl salt under the MacMillan Diels–Alder reaction conditions (MeOH/H₂O),[9a] thus affording the Diels–Alder adduct in 12% yield after 20 h without formation of the ene product. The ene reaction also proceeded with the same efficiency on a larger scale (4.0 mmol).

The generality of the reaction was next examined (Table 2). Not only the phenyl group but also a naphthyl substituent can be successfully employed as a β-substituent of

the acrylaldehyde, thus affording the ene adduct with excellent enantioselectivity. The reaction rate is slow for electron-deficient substituents, such as *p*-nitro- and *p*-bromophenyl groups, for which 20 mol% of the catalyst was employed to provide good yield with excellent enantioselectivity. In the former reaction, a small amount of the Diels–Alder products was obtained. For electron-rich rings, such as *p*-methoxy- or 3,4-methylenedioxyphenyl, the reaction rate is increased with excellent enantioselectivity. A heteroaromatic substituent at the β-position of the acrylaldehyde is also suitable, and although enantioselectivity was 77% in the case of thienyl, 91% *ee* was obtained when furyl was employed. When the β-substituent is an alkyl group, as in 3-cyclohexylpropenal and hept-2-enal, a complex mixture was obtained.

The absolute configuration was determined as follows: The mixture of **7a** and **8a** was treated with NaBH₄ to afford an alcohol, which was converted into its TBS ether **9** (see Scheme 1). Ozonolysis followed by reduction with NaBH₄
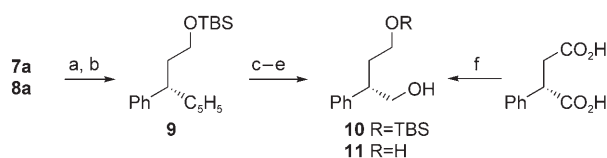
Scheme 1. Determination of the absolute configuration. Reagents: a) NaBH₄; b) TBSCl, imidazole (79%, 2 steps); c) 1. O₃; 2. NaBH₄; d) 1. NaIO₄; 2. NaBH₄; 3. separation of alcohol (11%) and diol (16%; for 4 steps); e) TBAF (quant.); f) LiAlH₄, 75%. TBAF = tetrabutylammonium fluoride.
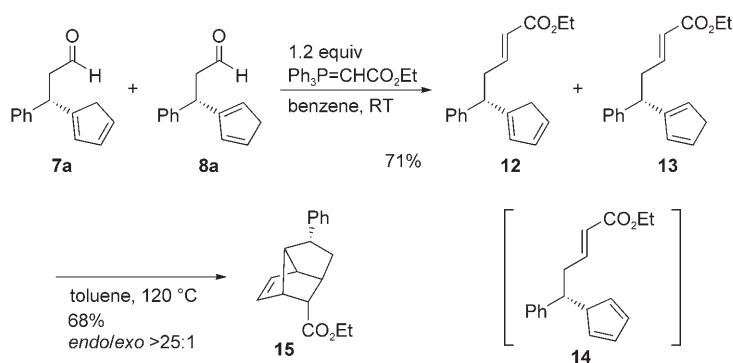
afforded an alcohol, which on oxidation with NaIO₄ and reduction with NaBH₄ gave **10** in 11% over four steps. Removal of the TBS group provided diol **11**, which is in good agreement, as determined by chiral HPLC analysis, with an authentic sample prepared by the reduction of (*S*)-phenylsuccinic acid.

The reaction would proceed as follows: Catalyst **4** and α,β-enal combine to give an iminium ion, which reacts with cyclopentadiene, as described in Scheme 2, to avoid the steric repulsion caused by the bulky diphenyl silyl ether group. The 5-substituted 1,3-cyclopentadiene unit would be formed by this mechanism and then readily isomerize to the more stable 1- and 2-substituted isomers.[14,15]
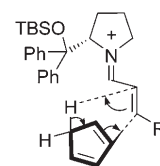
Scheme 2. Transition-state model.

An intramolecular Diels–Alder reaction was investigated as a synthetic application of these ene products.[16] Cyclopentadiene derivatives **7a** and **8a** were treated with a Wittig reagent to afford *trans* α,β-unsaturated esters **12** and **13**, respectively, in good yield. Although the 1- and 2-substituted cyclopenta-1,3-dienes **12** and **13** were formed and isolated, the 5-substituted isomer **14** was not detected,[14] but the Diels–Alder reaction proceeded via the latter in toluene at 120 °C to afford tricyclic compound **15** stereoselectively in 68% yield (Scheme 3). As the Diels–Alder reaction proceeded from the most reactive

Table 2: Asymmetric ene reaction of cyclopentadiene catalyzed by **4**.[a]

Entry	R	t [h]	Yield [%][b]	7/8[c]	ee [%][d]
1	phenyl	20	84	70:30	92
2[e]	2-naphthyl	3	70	57:43	93
3[e]	*p*-nitrophenyl	3	60[f]	43:57	90
4[e]	*p*-bromophenyl	6	79	67:33	95
5	*p*-methoxyphenyl	8	82	57:43	93
6	3,4-methylenedioxyphenyl	5	78	60:40	93
7[e]	2-furyl	2	80	63:37	91
8	2-thienyl	3	82	40:60	77
9[e]	*o*-methoxyphenyl	3	80	82:18	95

[a] The reaction was conducted with 0.07 mmol of catalyst **4**, 0.14 mmol of *p*-nitrophenol, 0.7 mmol of aldehyde, and 2.1 mmol of cyclopentadiene in MeOH (1.4 mL) at room temperature. [b] Yield of the isolated products **7a** and **8a**. [c] Determined by ¹H NMR spectroscopic analysis. [d] Determined by chiral HPLC analysis after reduction and hydrogenation. [e] 20 mol% of catalyst was employed. [f] Diels–Alder products were obtained in 11% yield.

Scheme 3. Synthesis of a chiral tricyclic compound.

isomer **14**, separation of the regioisomers is not necessary for obtaining the Diels–Alder adduct.

In summary, we have discovered the first enantioselective intermolecular ene reaction that uses α,β-enals as the enophile, is catalyzed by diphenylprolinol silyl ether, and affords chiral cyclopentadienes as versatile synthetic intermediates. This reaction is also the first in which cyclopentadiene acts as the ene component in an ene reaction with α,β-enals despite the numerous reports of it acting as a diene in the Diels–Alder reaction.

Experimental Section

(*E*)-Cinnamaldehyde (500 μL, 4.0 mmol) was added to a solution of catalyst **4** (146.3 mg, 0.40 mmol) and *p*-nitrophenol (110.7 mg, 0.80 mmol) in MeOH (8.0 mL) at room temperature. The solution was stirred for 1 min and then cyclopentadiene (0.98 mL, 12 mmol) was added. The reaction mixture was stirred for 20 h at room temperature, and then excess cyclopentadiene was azeotropically removed with benzene. The residue was purified by column chromatography on silica gel (AcOEt/hexane, 1:20) to afford ene products **7a** and **8a** (667.2 mg, 84%). The ratio of **7a** and **8a** was determined by ^{1}H NMR (400 MHz) spectroscopic analysis. As the isomers **7a** and **8a** were separated by HPLC with an OJ-H column (254 nm, 2-propanol/hexane (1:200), 1.0 mL min^{-1}; **7a** $t_R = 15.7$ min, **8a** $t_R = 18.0$ min), a small amount of **7a** and **8a** was isolated and analyzed.

NaBH$_4$ (7.3 mg, 0.194 mmol) was added to a solution of **7a** and **8a** (12.8 mg, 0.065 mmol) in MeOH (0.65 mL) at 0 °C. The reaction mixture was stirred for 20 min at this temperature, then the reaction was quenched with phosphate buffer solution (pH 7.0). The organic materials were extracted with AcOEt, were dried over anhydrous Na$_2$SO$_4$, concentrated under reduced pressure, and the residue was used in the next reaction without further purification.

Pd/C (10 mol%, 3.2 mg) was added to a solution of this crude mixture in AcOEt (0.65 mL) at room temperature, and the reaction mixture was stirred overnight under a H$_2$ atmosphere. The reaction mixture was filtered through a pad of celite and concentrated in vacuo. The residue was purified by preparative TLC (AcOEt/hexane, 1:3) to afford (*R*)-3-cyclopentyl-3-phenylpropan-1-ol (13.2 mg, quant.). The enantiomeric excess was determined by HPLC using an AS-H column at 254 nm (2-propanol/hexane (1:200), 1.0 mL min^{-1}; major enantiomer $t_R = 13.4$ min, minor enantiomer $t_R = 11.5$ min).

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