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Rate acceleration of phosphoric acid-catalyzed Diels-Alder reaction by internal hydrogen-bonding of adjacent hydroxy group

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Abstract

The Brønsted acid-catalyzed Diels-Alder reaction was examined. Phosphoric acids were effective Brønsted acids for the Diels-Alder reaction of cyclohexadienones and activated by the internal hydrogen-bonding of the adjacent hydroxy group.

Keywords: Diels-Alder reaction; Brønsted acid catalyst; Rate acceleration

1. Introduction

Brønsted acids, such as diol, urea, thiourea, guanidine, and phosphoric acid, have been recently received much attention as organocatalysts [1]. Chiral Brønsted acids have been applied to a wide range of reactions [2–9]. These reports suggest that a suitable nucleophilic substrate, such as imine, is necessary for the effective rate acceleration of the reaction by a Brønsted acid. Because of low nucleophilicity and/or polymerization of dienophiles such as α,β-unsaturated aldehydes and ketones, the Brønsted acid-catalyzed Diels-Alder reaction has not received much attention for a long time [10]. Rawal and co-workers have developed reactive aminosiloxydiene [11] and reported the enantioselective TADDOL-catalyzed Diels-Alder reaction [12] of methacrolein with dienes. Nakashima and Yamamoto have designed a highly reactive and acidic chiral Brønsted acid, chiral *N*-triflyl phosphoramide, and developed a highly enantioselective Diels-Alder reaction of α,β-unsaturated ketone with silyloxydiene using the chiral phosphoramide [13].

We have reported π-facially selective Diels-Alder reactions of cross-conjugated cyclohexadienones with cyclopentadiene [14]. The Diels-Alder reaction was accelerated in CF_3CH_2OH, although the reaction rate was slow in CH_2Cl_2 and CH_3CN. We considered that the rate acceleration was attributed to hydrogen-bonding between cross-conjugated cyclohexadienone and CF_3CH_2OH and examined the Diels-Alder reaction catalyzed by some Brønsted acids. We found rate acceleration of phosphoric acid-catalyzed Diels-Alder reaction by internal hydrogen-bonding of the adjacent hydroxy group.

2. Experimental

2.1. General

All reactions involving air- and moisture-sensitive reagent were carried out under N_2. Tetrahydrofuran (THF) was distilled after refluxing over Na–benzophenone before use. Merck silica gel $60F_{254}$ TLC aluminum sheets were used for routine monitoring of reaction. Column chromatography was performed on Merck silica gel 60 (70–230 mesh, ASTM). Merck silica gel $60F_{254}$ was used for preparative thin-layer chromatography. Os IC-I was purchased from Wako Pure Chemical Industries, Ltd.

Melting points were taken on a Yanagimoto melting-point apparatus. NMR spectra were recorded on a JEOL JNM-LA500 instrument. Internal references for ^{1}H NMR spectra were Me_4Si (TMS) for $CDCl_3$ (0.0 ppm) and C_5D_5N (7.55 ppm). Chemical shifts for ^{13}C NMR spectra were referenced to $CDCl_3$ (77.0 ppm) and C_5D_5N (135.5 ppm). MS were recorded on a JEOL JMS-SX102A instrument under electron ionization (EI) conditions (70 eV). Elemental analyses were carried out on a Perkin-Elmer 2400II analyzer.

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2.2. General procedure for the Diels-Alder reaction

Freshly distilled cyclopentadiene (10 eq) and additive were added to a 0.3 M solution of dienophile in CH_2Cl_2 at room temperature. The reaction mixture was shielded from the light and stirred at room temperature. After 48 h, the solvent was removed in vacuo. The residue was purified by preparative TLC (silica gel, hexane/EtOAc 2:1).

2.3. Preparation of compound (**4**)

Lithium (1.00 g, 144 mmol) was added in small portions at −78 °C to a solution of benzoic acid (5.06 g, 41.9 mmol) in THF (40 ml) and liquid ammonia (300 ml) until a blue color persisted. After stirred for 30 min at −78 °C, 2-(2-bromoethyl)-1,3-dioxolane (12.4 ml, 106 mmol) was slowly added. The resulting yellow solution was stirred for 3 h at −78 °C. After addition of NH_4Cl (6.74 g, 126 mmol), the mixture was warmed slowly to room temperature while ammonia was removed. The residue was dissolved in water (90 ml) and extracted with CH_2Cl_2. To the aqueous layer at 0 °C was added conc. HCl to give pH 1–2. The solution was extracted with CH_2Cl_2. The combined organic layer was washed with H_2O and brine, dried over Na_2SO_4, and filtered. After evaporation, 1,4-diene was obtained (9.48 g) as a yellow oil. The crude product was used for the next reaction without further purification: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.96–5.90 (m, 2H), 5.74–5.69 (m, 2H), 4.85 (t, J = 4.6 Hz, 1H), 3.99–3.91 (m, 2H), 3.87–3.80 (m, 2H), 2.72–2.57 (m, 2H), 1.85–1.81 (m, 2H), 1.63–1.59 (m, 2H).

To a mixture of the 1,4-diene (9.48 g, 42.3 mmol) and K_2CO_3 (17.5 g, 127 mmol) in DMF (140 ml) was added MeI (13.2 ml, 212 mmol) at 0 °C and the resulting mixture was stirred for 3 h at room temperature. The reaction mixture was poured into water and extracted with Et_2O. The combined organic phase was washed with water and brine, dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography (silica gel, hexane/EtOAc 4:1) to give methyl ester (8.77 g, 89% from benzoic acid) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.93–5.88 (m, 2H), 5.72 (dt, J = 10.4, 2.1 Hz, 2H), 4.84 (t, J = 4.6 Hz, 1H), 3.98–3.91 (m, 2H), 3.87–3.80 (m, 2H), 3.69 (s, 3H), 2.70–2.57 (m, 2H), 1.82–1.79 (m, 2H), 1.61–1.57 (m, 2H); HR-EIMS *m/z*: calcd for $C_{13}H_{18}O_4$ [M^+] 238.1205, Found 238.1211.

To a suspension of CrO_3 (158 mg, 1.04 mmol) in CH_2Cl_2 was added 3,5-dimethylpyrazole (DMP) (152 mg, 1.58 mmol) at −20 °C. After stirring for 20 min, a solution of the methyl ester (74.8 mg, 314 μmol) in CH_2Cl_2 (1.5 ml) was added to the reaction mixture. The reaction mixture was stirred at −20 °C for 1 h, diluted with Et_2O, passed through a pad of Celite. The filtrate was washed with sat. $Na_2S_2O_3$ and brine. The organic layer was dried over Na_2SO_4 and evaporated. The residue was purified by column chromatography (silica gel, hexane/EtOAc 2:1) to give **4** (44.1 mg, 56%) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.03 (d, J = 10.4 Hz, 2H), 6.36 (d, J = 10.4 Hz, 2H), 4.84 (t, J = 4.3 Hz, 1H), 3.98–3.90 (m, 2H), 3.88–3.82 (m, 2H), 3.76 (s, 3H), 2.16–2.10 (m, 2H), 1.56 (dt, J = 12.5, 4.3 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.8, 170.5, 147.5 (x2), 130.4 (x2), 103.1, 64.9 (x2), 53.0, 51.5, 31.7, 28.2; HR-EIMS *m/z*: calcd. for $C_{13}H_{16}O_5$ [M^+] 252.0998. Found 252.0991. Anal. Calcd. for $C_{13}H_{16}O_5$: C, 61.90; H, 6.39. Found C, 62.08; H, 6.39.

2.4. Compound (**5**)

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.91 (dd, J = 10.4, 1.5 Hz, 1H), 5.93 (d, J = 10.4 Hz, 1H), 5.92 (dd, J = 5.8, 2.7 Hz, 1H), 5.80 (dd, J = 5.8, 2.8 Hz, 1H), 4.77 (t, J = 4.6 Hz, 1H), 3.93–3.90 (m, 2H), 3.83–3.79 (m, 2H), 3.83 (s, 3H), 3.35 (m, 1H), 3.07 (dd, J = 8.8, 4.6 Hz, 1H), 2.87 (m, 1H), 2.71 (ddd, J = 8.5, 3.1, 1.5 Hz, 1H), 2.08 (td, J = 12.8, 4.3 Hz, 1H), 1.78 (td, J = 12.8, 4.3 Hz, 1H), 1.66–1.59 (m, 1H), 1.49–1.43 (m, 1H), 1.41 (dt, J = 7.9, 1.8 Hz, 1H), 1.34 (d, J = 7.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.4, 174.2, 148.7, 135.6, 134.0, 130.5, 103.6, 64.9 (x2), 52.1, 50.6, 49.5, 48.6, 48.0, 47.8, 45.6, 39.8, 29.0; HR-EIMS *m/z*: calcd. for $C_{18}H_{22}O_5$ [M^+] 318.1467. Found 318.1466; Anal. Calcd. for $C_{18}H_{22}O_5$: C, 67.91; H, 6.97. Found C, 67.65; H, 7.20.

2.5. Preparation of compound (**6**)

To a stirred solution of LDA, prepared from *i*-Pr_2NH (0.66 ml, 5.05 mmol) and *n*-BuLi (1.10 M in THF, 3.40 ml, 3.74 mmol) in THF (1.0 ml) at 0 °C, was added a solution of **5** (795 mg, 2.50 mmol) in THF (8.0 ml) at −78 °C. After 20 min, MeI (1.50 ml, 24.1 mmol) was added and the mixture was stirred overnight at −78 to −50 °C. The reaction mixture was quenched with sat. NH_4Cl and extracted with Et_2O. The combined organic layer was washed with H_2O and brine, dried over Na_2SO_4, and evaporated. The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc 4:1) to give methyl derivative (450.5 mg, 54%) as a white solid, and recovered **5** (162.4 mg, 20%): m.p. (benzene) 111–113 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.92 (dd, J = 10.4, 1.5 Hz, 1H), 5.90 (dd, J = 5.0, 2.7 Hz, 1H), 5.89 (d, J = 10.7 Hz, 1H), 5.82 (dd, J = 5.5, 2.7 Hz, 1H), 4.76 (t, J = 4.6 Hz, 1H), 3.94–3.89 (m, 2H), 3.83–3.78 (m, 2H), 3.81 (s, 3H), 2.84 (bs, 1H), 2.73 (bs, 1H), 2.42 (dd, J = 2.7, 1.5 Hz, 1H), 2.22 (td, J = 12.8, 4.3 Hz, 1H), 1.71–1.61 (m, 2H), 1.59 (d, J = 8.8 Hz, 1H), 1.54 (s, 3H), 1.50–1.42 (m, 1H), 1.39 (dt, J = 8.8, 1.6 Hz, 1H): ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.5, 174.0, 148.2, 136.7, 134.6, 130.7, 103.9, 65.1 (x2), 57.3, 54.0, 52.3, 51.2, 49.8, 48.8, 47.8, 41.2, 29.6, 26.9; HR-EIMS *m/z*: calcd. for $C_{19}H_{24}O_5$ [M^+] 332.1624. Found 332.1638; Anal. Calcd. for $C_{19}H_{24}O_5$: C, 68.66; H, 7.28. Found C, 68.58; H, 7.40.

To a solution of the methyl derivative (30.6 mg, 92.1 μmol) in CH_3CN/acetone/H_2O (1:1:1, 0.3 ml) was added *N*-methylmorpholine-*N*-oxide (NMO) (16.9 mg, 144 μmol) and Os IC-I (abt. 7%, 12.7 mg, 4.66 μmol) at 0 °C. After stirring for 2 days at 0 °C to room temperature, the reaction mixture was filtered. The filtrate was dried over Na_2SO_4 and concentrated. The crude product was purified with column chromatography (silica gel, CH_2Cl_2/MeOH 30:1) to give diol (32.1 mg, 95%) as a white solid: m.p. (benzene) 153–155 °C; ^{1}H NMR (500 MHz, C_5D_5N) δ 7.43 (dd, J = 10.4, 1.8 Hz, 1H), 6.09 (d, J = 10.4 Hz, 1H), 4.79 (t, J = 4.3 Hz, 1H), 4.30 (d, J = 5.2 Hz, 1H), 4.01 (d, J = 5.2 Hz, 1H), 3.84–3.79 (m, 2H), 3.70–3.65 (m, 2H), 3.67 (s, 3H), 2.47

(bs, 1H), 2.41–2.34 (m, 2H), 2.27–2.23 (m, 2H), 1.85–1.73 (m, 2H), 1.69–1.60 (m, 1H), 1.50 (d, J = 10.4 Hz, 1H), 1.41 (s, 3H); ^{13}C NMR (125 MHz, C_5D_5N) δ 202.9, 173.7, 150.2, 128.7, 103.8, 70.1, 69.0, 65.1, 65.0, 59.7, 53.6, 52.1, 50.7, 48.8, 48.3, 41.6, 31.6, 29.9, 27.0; Anal. Calcd. for $C_{19}H_{26}O_7$: C, 62.28; H,7.15. Found C, 62.17; H, 6.89.

To a solution of the diol (105 mg, 0.29 mmol) in THF (1.0 ml) and acetone (1.5 ml) was added acetone dimethyl acetal (88 μl, 0.72 mmol) and TsOH·H_2O (1.21 mg, 0.58 μmol) at room temperature. The resulting mixture was stirred for 16 h and quenched with water. The mixture was extracted with EtOAc. The combined organic phase was washed with H_2O and brine, dried over Na_2SO_4, concentrated under reduced pressure. The residue was purified by preparative TLC (silica gel, hexane/EtOAc 2:1 x3) to give acetal (103 mg, 88%) as a white solid: m.p. (benzene) 166–158 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (dd, J = 10.4, 1.2 Hz, 1H), 6.06 (d, J = 10.4 Hz, 1H), 4.74 (t, J = 4.6, 1H), 4.14 (dd, J = 5.2, 1.8 Hz, 1H), 3.92–3.89 (m, 3H), 3.82 (s, 3H), 3.81–3.79 (m, 2H), 2.32 (bs, 1H), 2.22 (bs, 2H), 2.18–2.13 (m, 1H), 1.82 (d, J = 10.7 Hz, 1H), 1.67–1.56 (m, 2H), 1.50–1.45 (m, 1H), 1.45–1.41 (m, 1H), 1.40 (s, 3H), 1.38 (s, 3H), 1.18 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.4, 173.1, 149.6, 128.6, 108.7, 103.4, 78.1, 77,2, 64.9 (x2), 55.4, 52.4, 52.1, 48.2, 47.3, 46.6, 41.0, 30.8, 29.4, 26.7, 25.2, 24.0; HR-EIMS *m/z*: calcd. for $C_{22}H_{30}O_7$ [M^+] 406.1992. Found 406.1983; Anal. Calcd. for $C_{22}H_{30}O_7$: C, 65.01; H, 7.44. Found C, 64.99; H, 7.54.

$NaBH_4$ (85.3 mg, 2.25 mmol) was added to a solution of the acetal (91.6 mg, 0.23 mmol) in MeOH (2.25 ml) at 0 °C. The reaction mixture was stirred at 0 °C for 20 min. After quenched with sat. NH_4Cl, the mixture was extracted with EtOAc. The combined organic layer was washed with water and brine, dried over Na_2SO_4, evaporated. The crude product was purified by column chromatography (silica gel, CH_2Cl_2/MeOH 20:1) to give **6** (84.0 mg, 91%) as a white solid: m.p. (benzene) 215–218 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.23 (ddd, J = 10.4, 3.4, 0.9 Hz, 1H), 5.81 (dd, J = 10.4, 1.8 Hz, 1H), 4.74 (t, J = 4.6 Hz, 1H), 4.27 (bs, 1H), 4.26 (dd, J = 5.2, 0.9 Hz, 1H), 4.15 (d, J = 4.9 Hz, 1H), 3.95–3.87 (m, 2H), 3.84–3.79 (m, 2H), 3.76 (s, 3H), 2.06–2.05 (m, 3H), 1.97 (d, J = 4.0 Hz, 1H), 1.83 (td, J = 13.1, 4.3 Hz, 1H), 1.78 (d, J = 10.7 Hz, 1H), 1.61–1.51 (m, 2H), 1.43–1.36 (m, 2H), 1.39 (s, 3H), 1.33 (s, 3H), 1.21 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.4, 132.3, 128.1, 108.1, 103.9, 78.5, 77.5, 72.6, 64.9 (x2), 52.8, 52.1, 49.7, 48.9, 45.9, 44.0, 33.1, 32.2, 30.8, 30.1, 25.2, 24.2; HR-EIMS *m/z*: calcd. for $C_{22}H_{32}O_7$ [M^+] 408.2148. Found 408.2128; Anal. Calcd. for $C_{22}H_{32}O_7$: C, 64.69; H, 7.90. Found C, 64.77; H, 7.70.

2.6. Compound (*10*)

a colorless yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.81 (dd, J = 5.2, 3.1 Hz, 1H), 6.77 (dd, J = 5.2, 3.1 Hz, 1H), 6.66 (d, J = 8.2 Hz, 1H), 6.39 (d, J = 8.2 Hz, 1H), 4.58 (bs, 1H), 4.08 (bs, 1H), 4.03 (bs, 1H), 3.65 (t, J = 6.4 Hz, 2H), 2.74–2.61 (m, 2H), 2.26 (dt, J = 7.0, 1.5 Hz, 1H), 2.17 (dt, J = 7.0, 1.5 Hz, 1H), 1.88–1.74 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.2, 152.0, 142.7, 142.5, 128.0, 126.2, 126.0, 112.9, 69.2, 62.3, 48.5, 46.0, 34.5, 28.5; HR-EIMS *m/z*: calcd. for $C_{14}H_{16}O_2$ [M^+] 216.1150. Found 216.1148; Anal. Calcd. for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found C, 77.49; H, 7.76.

2.7. X-Ray structure determination

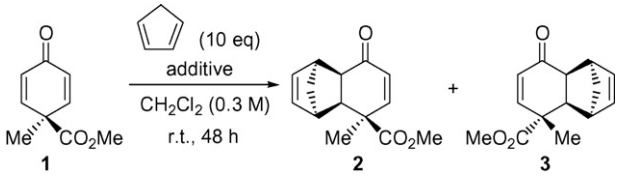
A crystal suitable for X-ray structure determination was mount on a Mac science DIP2030 imaging plate equipped with graphite-monochromated Mo Ka radiation (λ = 0.71069 Å). Unit-cell parameters were determined by autoindexing several images in each data set separately with the DENZO program [15]. For each data set, rotation images were collected in 3° increments with a total rotation of 180° about φ (60 frames). Data were processed by using the SCALEPACK program [15]. The structure were solved by a direct method and refined by full-matrix least-squares methods with the TeXsan (Rigaku) program [16].

3. Results and discussion

The Diels-Alder reaction of cyclohexadienone **1** with cyclopentadiene in CH_2Cl_2 was selected as a probe for the Brønsted acid-catalyzed reaction (Scheme 1). Because the Diels-Alder reaction of **1** with cyclopentadiene in CH_2Cl_2 at room temperature gave only trace amount of cycloadducts **2** and **3** and the uncatalyzed reaction can be ignored [14b]. First, the Diels-Alder reaction in the presence of CF_3CH_2OH (10 eq), 3,3′-bis(trifluoromethyl)urea (0.2 eq), and 3,3′-bis(trifluoromethyl)thiourea (0.2 eq) as a Brønsted acid was examined. However, they were not efficient for catalyst [17].

The Diels-Alder reaction of **1** with cyclopentadiene in the presence of phenols (1.0 eq) as a Brønsted acid was examined (Table 1). Phenols accelerated the Diels-Alder reaction more than CF_3CH_2OH. According to the acidity of the phenols, the conversion yield was improved. Treatment of **1** with cyclopentadiene in the presence of *p*-NO_2–C_6H_4OH (1.0 eq) gave the cycloadducts **2** and **3** (37% conversion yield). When Phenol (10 eq) was used as a Brønsted acid, the conversion yield of **1** was 80%. These results indicated that the acidity of Brønsted acid was important for rate acceleration of the Diels-Alder reaction.

Based on the rate acceleration by phenols, we examined the Diels-Alder reaction in the presence of biphenols (1.0 eq) (Table 2). The Diels-Alder reaction in the presence of biphenol was accelerated compared with phenol (Table 2, entry 1). However, the mono-methyl ether of biphenol did not act as the catalyst of the Diels-Alder reaction (Table 2, entry 2). The inactivation of the mono-methyl ether will be caused by the intramolecular hydrogen-bonding between the hydroxy group



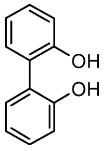
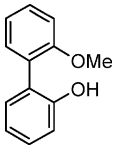
Scheme 1. Diels-Alder reaction of **1** with cyclopentadiene.

Table 1
Diels-Alder reaction of **1** with cyclopentadiene in the presence of phenols *p*-R-C_6H_4OH (1.0 eq)

Entry	Phenol (*R* =)	Conversion (%)[a]	**2**:**3**[b]
1	–	4	90:10
2	OMe	11	95:5
3[c]	H	19	93:7
4	Cl	21	95:5
5	CF_3	26	96:4
6	CN	28	95:5
7	NO_2	37	94:6

The reaction was carried out at room temperature for 48 h.
[a] The yield was determined by ^{1}H NMR of the crude product.
[b] The ratio was determined by ^{1}H NMR of the crude product.
[c] When phenol (10 eq) was used as an additive, the adducts **2** and **3** were obtained in 80% conversion yield (**2**:**3** = 94:6).

Table 2
Diels-Alder reaction of **1** with cyclopentadiene in the presence of biphenols (1.0 eq)

Entry	Diphenol	Conversion (%)[a]	**2**:**3**[b]
1		33	94:6
2		2	91:9

The reaction was carried out at room temperature for 48 h.
[a] The yield was determined by ^{1}H NMR of the crude product.
[b] The ratio was determined by ^{1}H NMR of the crude product.

and the oxygen of the ether. In the phenol-catalyzed Diels-Alder reaction of cyclohexadiene **1**, the π-face selectivity was increased.

Next, the Diels-Alder reaction of **1** with cyclopentadiene in the presence of acids are summarized in Table 3. Acetic acid (1.0 eq) accelerated Diels-Alder reaction as much as PhOH. (Table 3, entry 1). When phosphoric acid was used as a Brønsted acid, the Diels-Alder reaction was efficiently accelerated even if the amount of 0.1 eq (Table 3, entry 2). The addition of more acidic CF_3CO_2H and H_2SO_4 (0.1 eq) was also examined (Table 3, entries 3 and 4). When H_2SO_4 was used as a

Table 3
Diels-Alder reaction of **1** with cyclopentadiene in the presence of acids

Entry	Acid	Conversion (%)[a]	**2**:**3**[b]
1	CH_3CO_2H(1.0 eq)	11	94:6
2	H_3PO_4 (0.1 eq)	>99	96:4
3	CF_3CO_2H (0.1 eq)	32	97:3
4	H_2SO_4 (0.1 eq)	96[c]	95:5

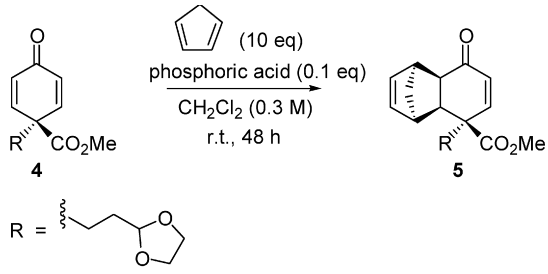
The reaction was carried out at room temperature for 48 h.
[a] The yield was determined by ^{1}H NMR of the crude product.
[b] The ratio was determined by ^{1}H NMR of the crude product.
[c] The isolated yield was 75%.

Table 4
Diels-Alder reaction of **1** with cyclopentadiene in the presence of phosphoric acids (0.1 eq)

Entry	Phosphoric acid	Conversion (%)[a]	**2**:**3**[b]
1	H3PO4	96	96:4
2	$(PhO)P(O)(OH)_2$	28	97:3
3	$(PhO)_2P(O)OH$	14	93:7

The reaction was carried out at room temperature for 15 min.
[a] The yield was determined by ^{1}H NMR of the crude product.
[b] The ratio was determined by ^{1}H NMR of the crude product.

Table 5
Diels-Alder reaction of **4** with cyclopentadiene in the presence of phosphoric acid (0.1 eq)



Entry	Phosphoric acid	Yield (%)[a]
1	–	No reaction
2	H_3PO_4	41
3	$(PhO)P(O)(OH)_2$	91
4	$(PhO)_2P(O)OH$	79

The reaction was carried out at room temperature for 48 h.
[a] Isolated yield.

Brønsted acid, cyclohexadienone **1** and/or cycloadducts **2** and **3** were decomposed by the acid and the isolated yield of the products was decreased. The low activity of AcOH and CF_3CO_2H may be attributed to the dimerization in CH_2Cl_2.

The acceleration effect by the addition of phosphoric acids H_3PO_4, $(PhO)P(O)(OH)_2$, and $(PhO)_2P(O)OH$ was compared (Table 4). When the reaction mixture was stirred for 24 h, cyclohexadienone **1** was quantitatively converted to the product irrespective of the phosphoric acid used. To compare the ability of the phosphoric acids, the reaction was quenched at 15 min. The most effective Brønsted acid was H_3PO_4 and the order of the rate acceleration profile was in the order $H_3PO_4 \gg (PhO)P(O)(OH)_2 > (PhO)_2P(O)OH$. As same as the phenol-catalyzed Diels-Alder reaction, the π-face selectivity was increased.

The phosphoric acid-catalyzed Diels-Alder reaction of **4,** bearing an acetal group, with cyclopentadiene was examined

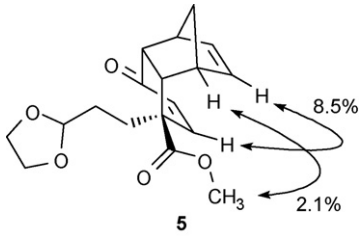
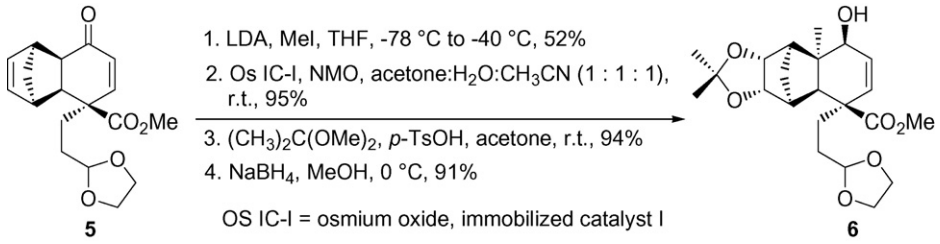


Fig. 1. NOE experiments on **5**.



Scheme 2. Conversion of **5** to **6**.

(Table 5). Cyclohexadienone **4** was treated with cyclopentadiene in the presence of phosphoric acid at room temperature. After 48 h, cyclohexadienone **4** was consumed and cycloadduct **5** was obtained as a single isomer. The stereochemistry of **5** was determined by ^{1}H NMR dif-NOE experiments (Fig. 1) and confirmed by X-ray structural analysis [18] of **6**, which was generated from **5** over 4 steps (Scheme 2 and Fig. 2). Cyclohexadienone **4** and/or cycloadduct **5** were decomposed by H_3PO_4 and $(PhO)_2P(O)OH$ and the isolated yield of **5** was decreased (41% and 79%, respectively, Table 5, entries 2 and 4). When $(PhO)P(O)(OH)_2$ was used as a Brønsted acid, cycloadduct **5** was obtained in 91% isolated yield (Table 2, entry 3).

Cyclohexadienone **7**, bearing the spiro-ether, was used as a dienophile of the phosphoric acid-catalyzed Diels-Alder reaction (Table 6). When cyclohexadienone **7** was treated with cyclopentadiene in the presence of $(PhO)_2P(O)OH$ for 48 h, a mixture of diastereomers **8** and **9** was obtained along with the by-product **10**, which was generated by $(PhO)_2P(O)_2OH$-catalyzed tautomerization of **8** and/or **9**. (Table 6, entry 2). The $(PhO)_2P(O)_2OH$-catalyzed tautomerization was prevented by the addition of PhNHMe (Table 6, entry 3) [19].

The phosphoric acid-catalyzed Diels-Alder reaction of other dienophiles was also examined (Tables 7 and 8). The Diels-Alder reaction of cinnamaladehyde [20] was three to six times accelerated by the phosphoric acids (Table 7). The most efficient Brønsted acid was $(PhO)P(O)(OH)_2$, not H_3PO_4. The *endo*-selectivity was increased in the phosphoric acid-catalyzed Diels-Alder reaction. 2,6-Dimethylbenzoquinone [21] readily reacted with cyclopentadiene without Brønsted acid at room temperature and the phosphoric acid-catalyzed Diels-Alder reaction was quenched at 2 h (Table 8). The Diels-Alder reaction was accelerated in the order $(PhO)P(O)(OH)_2 > H_3PO_4 > (PhO)_2P(O)OH$, which indicated that the catalytic ability of H_3PO_4 depends on the dienophile. This may be attributed to the association of phos-

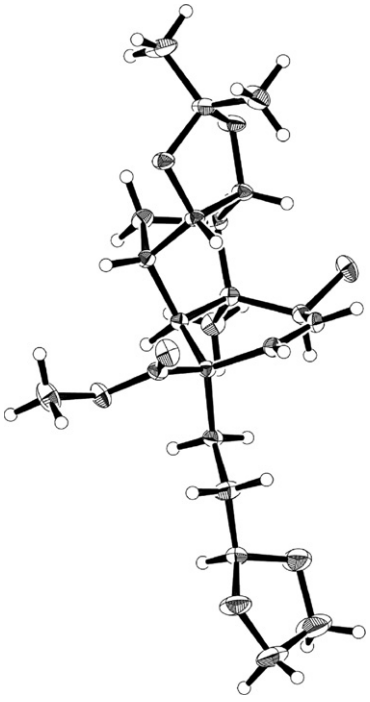
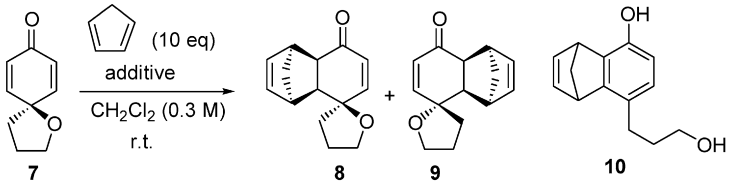


Fig. 2. ORTEP drawing of **6** showing the thermal ellipsoids at the 30% probability level.

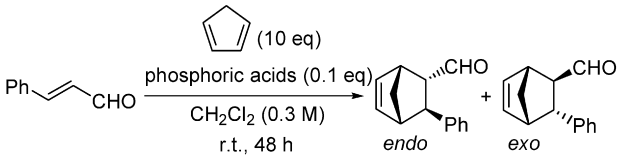
Table 6
The $(PhO)_2P(O)OH$-catalyzed Diels-Alder reaction of **7** with cyclopentadiene



Entry	Additive	Time (h)	Conversion (%)[a]	**8**:**9**
1	–	24	14	96:4
2	$(PhO)_2P(O)OH$ (0.1 eq)	48	51[b]	>99:<1
3	$(PhO)_2P(O)OH$ (0.1 eq) PhNHMe (0.1 eq)	24	61	99:1

The reaction was carried out at room temperature.
[a] The yield was determined by ^{1}H NMR of the crude product.
[b] The $(PhO)P(O)(OH)_2$-catalyzed tautomerization product **10** was obtained in 26% yield.

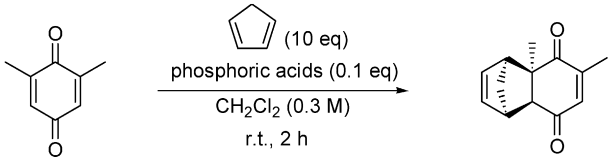
Table 7
Diels-Alder reaction of cinnamaldehyde with cyclopentadiene in the presence of phosphoric acid



Entry	Phosphoric acid	Conversion (%)[a]	*endo*:*exo*[b]
1	–	5	52:48
2	H_3PO_4	17	77:23
3	$(PhO)P(O)(OH)_2$	33	82:18
4	$(PhO)_2P(O)OH$	25	82:18

The reaction was carried out at room temperature for 48 h.
[a] The yield was determined by ^1H NMR of the crude product.
[b] The ratio was determined by ^1H NMR of the crude product.

Table 8
Diels-Alder reaction of 2,6-dimethylbenzoquinone with cyclopentadiene in the presence of phosphoric acid



Entry	Phosphoric acid	Conversion (%)[a]
1	–	19
2	H_3PO_4	40
3	$(PhO)P(O)(OH)_2$	74
4	$(PhO)_2P(O)OH$	28

The reaction was carried out at room temperature for 2 h.
[a] The yield was determined by ^1H NMR of the crude product.

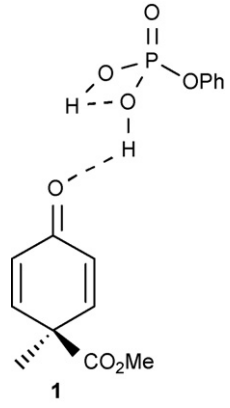


Fig. 3. Speculated hydrogen-bonding between **1** and $(PhO)P(O)(OH)_2$.

phoric acid in CH_2Cl_2. Generally, $(PhO)P(O)(OH)_2$ catalyzed the Diels-Alder reaction more than $(PhO)_2P(O)OH$ and H_3PO_4.

4. Conclusion

The Brønsted acid-catalyzed Diels-Alder reaction was examined. Phosphoric acids were effective Brønsted acids for the Diels-Alder reaction of cyclohexadienones, although the activity of phosphoric acids was moderate for the other dienophiles (cinnamaldehyde and benzoquinone). This can be understandable by the terms of the Lewis basisity of the dienophiles [22]. In the Brønsted acid-catalyzed Diels-Alder reaction, the diastereoselectivity was also improved. When the acid-labile substrate was used, the acidity of the phosphoric acid was controlled by the combination with base [2d,4d,4g]. Although the activity of H_3PO_4 depended on the substrate, $(PhO)P(O)(OH)_2$ accelerated the Diels-Alder reaction more than $(PhO)_2POH$. The activation of the Diels-Alder reaction by the internal hydrogen-bonding of the biaryl diol [2b,12], the bis-ammonium salts of mono-*N*-alkylated 1,2-diamino-1,2-ethane [23a,b], and α-hydroxyenone [23c] have been reported. This report also suggest that $(PhO)P(O)(OH)_2$ is activated by the internal hydrogen-bonding of the adjacent hydroxy group (Fig. 3).

Acknowledgements

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[17] CF_3CH_2OH (10 eq): 40% conversion yield, **2**:**3** = 94:6; 3,3′-bis(trifluoromethyl)urea (0.2 eq; not completely dissolved in CH_2Cl_2): 9% conversion yield, **2**:**3** = 92:8; 3,3′-bis(trifluoromethyl)thiourea (0.2 eq; not completely dissolved in CH_2Cl_2): 14% conversion yield, **2**:**3** = 93:7.

[18] Crystallographic data of **6** have been deposited with the Cambridge crystallographic Data Center: CCDC-656085. monoclinic system, space group P21/c (#14), $a = 13.8630(3)$ Å, $b = 10.4920(2)$ Å, $c = 14.6750(3)$ Å, $V = 2129.98(8)$ Å^3, $Z = 4$, $P_{calc} = 1.274\,g\,cm^{-3}$, $F(000) = 880.000$, $R = 0.116$ ($R_w = 0.243$) for 4333 reflections out of 4901 collected (262 parameters) with $I > 3(I)$. Goodness of fit = 1.11.

[19] Although Diels-Alder reaction of cinnamaldehyde with cyclopentadiene catalyzed by $(PhO)_2P(O)OH$-PhNHMe was also examined [cf. T. Kano, Y. Tanaka, K. Maruoka, Org. Lett. 8 (2006) 2687.], $(PhO)_2P(O)OH$-PhNHMe was not effective for the Diels-Alder reaction as an amine-salt catalyst.

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