

Palladium-Catalyzed Asymmetric Alkylation of 2,3-Alkadienyl Phosphates. Synthesis of Optically Active 2-(2,3-Alkadienyl)malonates

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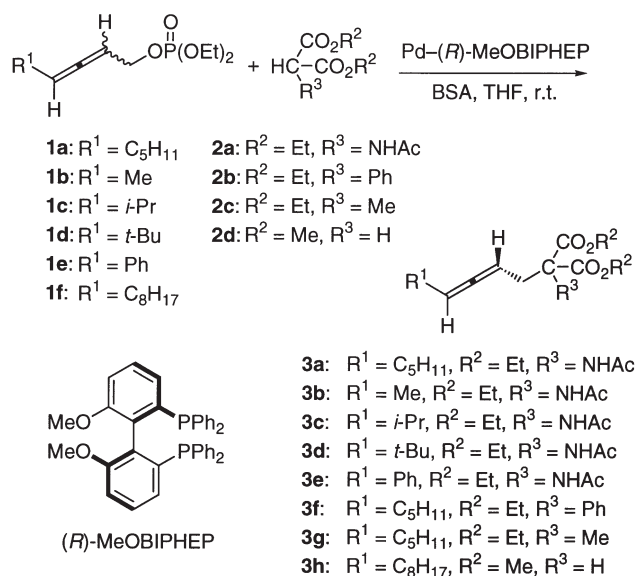
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Asymmetric alkylation of 2,3-alkadienyl phosphates with soft carbon nucleophiles proceeds efficiently in the presence of palladium complex catalyst bearing MeOBIPHEP or BINAP ligand to give optically active functionalized allenes up to 90% ee.

Optically active allenes bearing axial chirality are important synthetic intermediates for various naturally occurring biologically active compounds.¹ Therefore, much attention has been paid to the asymmetric synthesis of this class of compounds. Optically active allenes have been prepared by either optical resolution of racemic allenes¹ or chirality transfer reactions of optically active precursors.^{2,3} Preparation of optically active allenes using chiral catalyst is an attractive method; however, the reported methods give moderate enantioselectivity (20–60% ee)⁴ except kinetic resolution by asymmetric oxidative degradation of allenes.⁵ Recently, Hayashi *et al.* reported that palladium-catalyzed reaction of 2-bromo-1,3-butadienes gives optically active allenes with enantioselectivity up to 89% ee.⁶ We wish to report that palladium-catalyzed asymmetric reaction of racemic 2,3-alkadienyl phosphates **1** with soft carbon nucleophiles **2** gives optically active functionalized allenes **3** (Scheme 1).⁷ This is based on the non-asymmetric reaction reported by Gore *et al.*⁸

Alkylations of 2,3-alkadienyl phosphates **1** with soft carbon nucleophiles **2** were examined in the presence of *N,O*-bis(trimethylsilyl)acetamide (BSA) and the palladium catalyst prepared from Pd₂(dba)₃•CHCl₃ and MeOBIPHEP⁹ or BINAP¹⁰ in THF at room temperature (Scheme 1). The representative results of the reactions are summarized in Table 1.



Scheme 1.

Table 1. Asymmetric alkylation of diethyl 2,3-alkadienyl phosphates **1** with malonates **2**^a

Entry	Phosphate	Malonate	Time/h	Product	Yield/% ^b	Ee/% ^c
1	1a	2a	8	3a	76	73
2	1b	2a	6	3b	72	77
3	1c	2a	6	3c	89	81
4	1d	2a	12	3d	69	90
5	1e	2a	8	3e	80	60
6	1a	2b	2	3f	85	76
7	1a	2c	3	3g	74	69
8	1f	2d	8	3h	90	70

^aAll reactions were carried out in THF (0.1 M) at room temperature. The ratio of 1/2/BSA/Pd₂(dba)₃•CHCl₃/(*R*)-MeOBIPHEP was 100/110/120/1/4. ^bIsolated yield based on **1**. ^cDetermined by HPLC analysis with chiral stationary phase column.

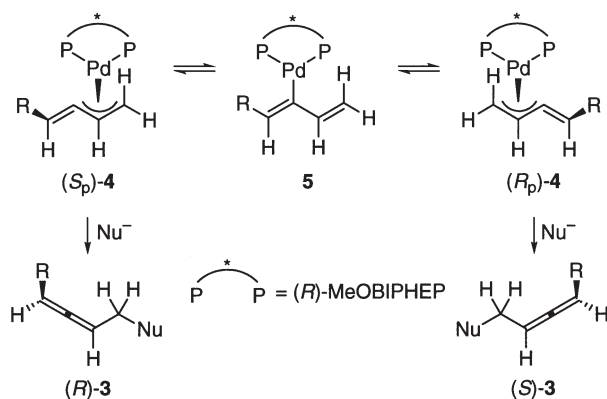
The palladium-catalyzed reactions of phosphates **1a–e** with diethyl 2-acetamidomalonate (**2a**) give the corresponding functionalized allenes **3a–e** with 60–90% ee in good yields (entries 1–5). The catalytic reactions of the phosphate **1a** with diethyl 2-phenylmalonate (**2b**) and diethyl 2-methylmalonate (**2c**) gave **3f** and **3g**, respectively, with similar enantioselectivities (entries 6 and 7), indicating that the acetamido group is not essential for getting high level of enantioselectivity. Noteworthy is that the reaction of the phosphate **1f** with dimethyl malonate (**2d**) afforded monosubstituted malonate **3h** as a sole product. Disubstituted malonate could not be detected among the products (entry 8).

Typically, asymmetric reaction of diethyl 5,5-dimethyl-2,3-hexadienyl phosphate (**1d**) with acetamidomalonate **2a** was carried out in THF at room temperature for 12 h in the presence of BSA and the palladium catalyst prepared *in situ* from Pd₂(dba)₃•CHCl₃ (0.01 equiv) and (*R*)-MeOBIPHEP (0.04 equiv). Ethyl 2-acetamido-2-ethoxycarbonyl-7,7-dimethyl-4,5-octadienoate [(–)-**3d**] was obtained with 90% ee in 69% isolated yield. The absolute configuration of (–)-**3d** was determined to be (*R*) on the basis of the Lowe's rule.¹¹

A survey of chiral bidentate phosphine ligands revealed that the C₂ ligands bearing binaphthyl and biphenyl backbone, such as MeOBIPHEP and BINAP are effective.

The palladium-catalyzed reaction of 2,3-alkadienyl phosphates **1** with soft carbon nucleophiles⁸ can be rationalized by assuming the mechanism shown in Scheme 2. The first step is facile formation of 1–3-η³-1,3-alkadienylpalladium **4** from allyl esters bearing highly reactive leaving group OP(O)(OEt)₂.¹² Soft carbon nucleophiles attack at the less hindered α-position of the palladium complex **4**. It is in contrast to the γ-attack of hard carbon nucleophiles,^{8,13} such as organozinc and Grignard reagents, and carbon monoxide¹⁴ via η¹-1,3-alkadien-3-yl-palladium **5** to give conjugated dienes.

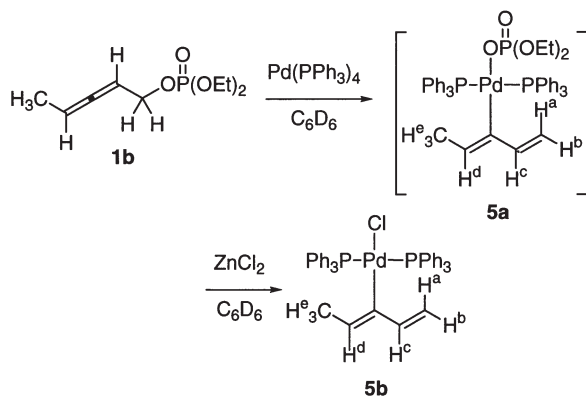
An equilibrium is present between two diastereomeric η³-alkadienylpalladium complexes (*S_p*)-**4** and (*R_p*)-**4** through η¹-alkadienylpalladium complex **5**. Preferential nucleophilic attack of malonate anion to (*S_p*)-**4** at the less hindered allylic terminus from the opposite side to the palladium would give the optically active



functionalized allene (*R*)-3.

Fast equilibrium between two diastereomeric η^3 -alkadienylpalladium complexes (*S_p*)-4 and (*R_p*)-4 was confirmed by the following control experiment. When enantiomerically pure (*S*)-1a¹⁵ was allowed to react with malonate 2a in the presence of BSA and the palladium catalyst, prepared from Pd₂(dba)₃•CHCl₃ and 1,4-bisdiphenylphosphinobutane, in THF at room temperature for 2 h, the racemic allene 3a was obtained in 76% yield.

The participation of η^1 -alkadienylpalladium complex 5 was confirmed from the reaction of phosphate 1b with Pd(PPh₃)₄. The ¹H and ³¹P NMR spectra of the product derived from the reaction of the phosphate 1b with an equivalent of Pd(PPh₃)₄ in C₆D₆ in an NMR tube showed a facile, exclusive formation of η^1 -pentadienylpalladium 5a.¹⁶ The chloro complex 5b was obtained by ligand exchange reaction upon treatment with zinc chloride as shown in Scheme 3. The structure of 5b was confirmed by single-crystal X-ray analysis.¹⁷



In summary, we succeeded in asymmetric synthesis of functionalized allenes 3 with high enantioselectivity by the palladium-catalyzed asymmetric alkylation of racemic 2,3-alkadienyl phosphates 1 using palladium-MeOBIPHEP catalyst. Further mechanistic study and application are in progress.

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This paper is dedicated to Prof. Teruaki Mukaiyama on the occasion of his 75th birthday.

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- Enantiomerically pure (*S*)-1a {[α]_D 48.1° (c 1.1, CHCl₃)} was obtained by the optical resolution of racemic 1a by HPLC with a chiral stationary phase (Chiralcel OD).
- 5a: ¹H NMR (500 MHz, C₆D₆, selected data) δ 0.60 (t, *J* = 7 Hz, 6 H), 1.57 (d, *J* = 7 Hz, 3 H, H^c), 3.25 (dq, *J* = 7, 7 Hz, 4 H), 4.51 (br, 1 H, H^d), 4.60 (d, *J* = 10 Hz, H^b), 5.27 (dd, *J* = 10, 17 Hz, H^c), 6.13 (d, *J* = 17 Hz, H^a). 5b: ¹H NMR (500 MHz, C₆D₆, selected data) δ 1.72 (d, *J* = 7 Hz, 3 H, H^c), 4.71 (dd, *J* = 2, 11 Hz, H^b), 4.97 (br, 1 H, H^d), 5.68 (ddd, *J* = 2, 10, 16 Hz, H^c), 6.07 (dd, *J* = 2, 16 Hz, H^a), ³¹P{¹H} NMR (202 MHz, C₆D₆) δ 25.73. For related (η^1 -1,3-butadien-2-yl)palladium complexes generated from Pd(PPh₃)₄ and 2,3-butadienyl chlorides, see: S. A. Benyunes, L. Brandt, A. Fries, M. Green, M. F. Mahon, and T. M. T. Papworth, *J. Chem. Soc., Dalton Trans.*, **1993**, 3785.
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