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

Yasushi Imada,* Katsuya Ueno, Koji Kutsuwa, and Shun-Ichi Murahashi*
Department of Chemistry, Graduate School of Engineering Science, Osaka University, 1-3 Machikaneyama, Toyonaka, Osaka 560-8531
Department of Chemistry, Faculty of Engineering Okayama University of Science, 1-1 Ridaicho, Okayama 700-0005

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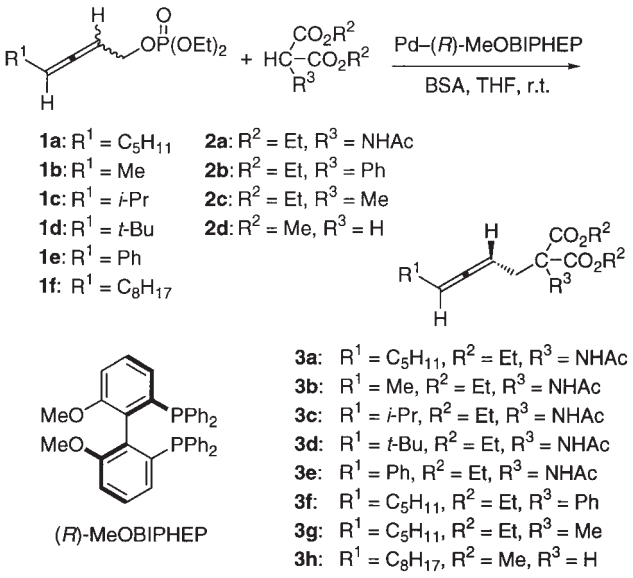
Asymmetric alkylation of 2,3-alkadienyl phosphates with soft carbon nucleophiles proceeds efficiently in the presence of palladium complex catalyst bearing MeOBIPHEP or BINAP ligand to give optically active functionalized allenes up to 90% ee.

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 allenes[1] 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 $Pd_2(dba)_3$•$CHCl_3$ and MeOBIPHEP[9] or BINAP[10] 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

[a]All reactions were carried out in THF (0.1 M) at room temperature. The ratio of **1/2**/BSA/$Pd_2(dba)_3$•$CHCl_3$/(R)-MeOBIPHEP was 100/110/120/1/4. [b]Isolated yield based on **1**. [c]Determined by HPLC analysis with chiral stationary phase column.

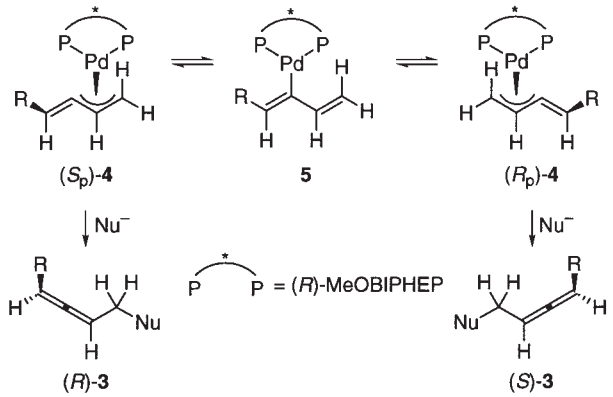
The palladium-catalyzed reactions of phosphates **1a–e** with diethyl 2-acetamidomalonate (**2a**) give the corresponding functionalized allenes **3a–e** with 60–90% ee in good yields (entries 1–5). The catalytic reactions of the phosphate **1a** with diethyl 2-phenylmalonate (**2b**) and diethyl 2-methylmalonate (**2c**) gave **3f** and **3g**, respectively, with similar enantio-selectivities (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 $Pd_2(dba)_3$•$CHCl_3$ (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 C_2 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 nucleophiles[8] can be rationalized by assuming the mechanism shown in Scheme 2. The first step is facile formation of 1–3-η^3-1,3-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 monoxide[14] via η^1-1,3-alkadien-3-yl-palladium **5** to give conjugated dienes.

An equilibrium is present between two diastereomeric η^3-alkadienylpalladium complexes (S_p)-**4** and (R_p)-**4** through η^1-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

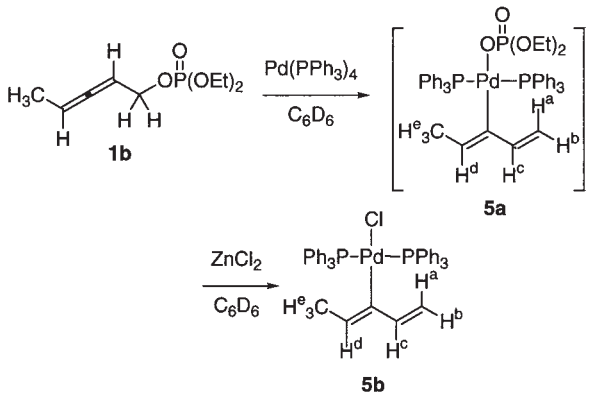


Scheme 2.

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*)-**1a**[15] was allowed to react with malonate **2a** in the presence of BSA and the palladium catalyst, prepared from $Pd_2(dba)_3$•$CHCl_3$ 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 $Pd(PPh_3)_4$. The ^1H and ^{31}P NMR spectra of the product derived from the reaction of the phosphate **1b** with an equivalent of $Pd(PPh_3)_4$ in C_6D_6 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]



Scheme 3.

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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15 Enantiomerically pure (*S*)-**1a** {$[\alpha]_D$ 48.1° (*c* 1.1, $CHCl_3$)} was obtained by the optical resolution of racemic **1a** by HPLC with a chiral stationary phase (Chiralcel OD).

16 **5a**: ^1H NMR (500 MHz, C_6D_6, selected data) δ 0.60 (t, $J = 7$ Hz, 6 H), 1.57 (d, $J = 7$ Hz, 3 H, H^e), 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, C_6D_6, selected data) δ 1.72 (d, $J = 7$ Hz, 3 H, H^e), 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), $^{31}P\{^1H\}$ NMR (202 MHz, C_6D_6) δ 25.73. For related (η^1-1,3-butadien-2-yl)palladium complexes generated from $Pd(PPh_3)_4$ 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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