Palladium-Catalyzed Hydrophosphorylation of Allenes Leading to Regio- and Stereoselective Formation of Allylphosphonates

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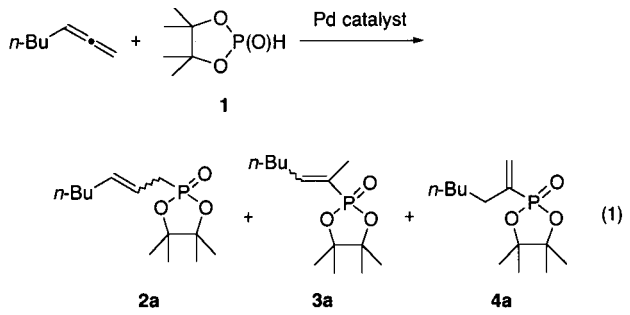
Summary: Palladium 1,1′-bis(diphenylphosphino)ferrocene complex catalysts promote the addition of HP(O)(OCMe$_2$CMe$_2$O) to terminal allenes to afford the corresponding 1,2-adducts regio- and stereoselectively in high yields.

Allylphosphonates are valuable synthetic intermediates. They have been widely used in the preparation of dienes and polyenes, including biologically active species, via the Horner−Emmons olefination reaction with carbonyl compounds.[1] An advantage of allylphosphonates in the olefination over the corresponding phosphonium salts is exemplified by their stereoselectivity and stereospecificity observed in the reactions.[2] The olefinic bonds formed using the ylides derived from (*E*)-allylic phosphonium salts are usually mixtures of *E* and *Z* configurations.[3] Another drawback of the use of allylic ylides lies in the possible loss of the configurational integrity of the olefinic functionality in the allylic moiety.[4] In contrast, the use of (*E*)-allylphosphonates generally allows better stereochemical control over the geometry of the olefinic bond generated. The high enantioselectivity achieved in the asymmetric Michael addition using chiral allylphosphonates is also worth noting.[5] In addition to synthetic applications, the biological activity of allylphosphonates, which have been found in living species, has also attracted attention.[6] Despite these possible utilities of allylphosphonates, however, only a few methods are available for their preparation.[7] The classic Michaelis−Arbuzov reaction[7a] of trialkyl phosphites with allylic halides is still frequently used, although it can involve complicated competing eliminations and the loss of the stereochemical integrity of the double bond. Our continuing effort to manipulate the H−P bonds with metal complexes[8] has revealed that hydrophosphorylation of allenes is efficiently catalyzed by palladium complexes, leading to the regio- and stereoselective formation of allylphosphonates.[9]

Heating a mixture of 1,2-heptadiene (192 mg, 2 mmol), 4,4,5,5-tetramethyl-1,3,2-dioxaphospholane 2-oxide (**1**; 328 mg, 2 mmol), and PdMe$_2$(dppf) (dppf = 1,1′-bis(diphenylphosphino)ferrocene; 69 mg, 5 mol %) in 1,4-dioxane (8 mL) at 100 °C for 2 h under nitrogen resulted in a complete disappearance of the starting materials to predominantly afford the allylic phosphonate **2a** in 98% yield with high stereoselectivity (*E*/*Z* = 92/8) (eq 1). Although the other regioisomers **3a** and **4a** were



formed, their quantities were negligible in this particular reaction (vide infra). Evaporation followed by column chromatography through silica gel with hexane−2-propanol (10/(1−2)) as eluent led to isolation of **2a** as a colorless oil (87% isolated yield).

As was found in the hydrophosphorylation of olefins,[8d] dimethyl and diethyl hydrogen phosphonates were totally unreactive, demonstrating the exceptionally high reactivity of the five-membered cyclic hydrogen phosphonate **1**. Table 1 discloses that the reactivity and the regioselectivity in the addition reaction of 1,2-heptadi-

(1) For example: (a) Kende, A. S.; Blass, B. E.; Henry, J. R. *Tetrahedron Lett.* **1995**, *36*, 4741. (2) Burke, S. D.; Hong, J.; Mongin, A. P. *Tetrahedron Lett.* **1998**, *39*, 2239. (c) Whang, K.; Venkataraman, H.; Kim, Y.; Cha, J. K. *J. Org. Chem.* **1991**, *56*, 7177. (d) Asato, A. E.; Mead, D.; Denny, M.; Bopp, T. T.; Liu, R. S. H. *J. Am. Chem. Soc.* **1982**, *104*, 4979.

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(3) Crombie, L.; Hemesley, P.; Pattenden, J. *J. Chem. Soc. C* **1969**, 1024.

(4) Schweizer, E. E.; Shaffer, E. T.; Hughes, C. T.; Berninger, C. J. *J. Org. Chem.* **1966**, *31*, 2907.

(5) (a) Tanaka, K.; Ohta, Y.; Fuji, K. *J. Org. Chem.* **1995**, *60*, 8036. See also: (b) Hanessian, S.; Gomtsyan, A.; Payne, A.; Hervé, Y.; Beaudoin, S. *J. Org. Chem.* **1993**, *58*, 5032. (c) Hua, D. H.; Chan-Yu-King, R.; McKie, J. A.; Myer, L. *J. Am. Chem. Soc.* **1987**, *109*, 5026.

(6) (a) *The Chemistry of Organophosphorus Compounds*, Vol. 4; Hartley, F. R., Ed.; Wiley: Chichester, U.K., 1996; pp 767−780. (b) Corbridge, D. E. C. *Phosphorus: An Outline of Its Chemistry, Biochemistry and Uses*, 5th ed.; Elsevier: Amsterdam, 1995; pp 1038−1041. (c) Arend, G.; Behrenz, W.; Block H. D. Ger. Offen. 2727479, 1979; *Chem. Abstr.* **1979**, *90*, 138020w.

(7) (a) Bhattacharya, A. K.; Thyagarjan, G. *Chem. Rev.* **1981**, *81*, 415. For other preparations: (b) Kiddle, J. J.; Babler, J. H. *J. Org. Chem.* **1993**, *58*, 3572. (c) Lu, X.; Zhu, J. *J. Organomet. Chem.* **1986**, *304*, 239. (d) Basavaiah, D.; Pandiaraju, S. *Tetrahedron* **1996**, *52*, 2261. (e) Malet, R.; Moreno-Manas, M.; Pleixats, R. *Synth. Commun.* **1992**, *22*, 2219. (f) Janecki, T.; Bodalski, R. *Synthesis* **1990**, 799.

(8) (a) Han, L.-B.; Tanaka. M. *J. Am. Chem. Soc.* **1996**, *118*, 1571. (b) Han, L.-B.; Choi, N.; Tanaka, M. *Organometallics* **1996**, *15*, 3259. (c) Han, L.-B.; Hua, R.; Tanaka, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 94. (d) Han, L.-B.; Mirzaei, F.; Zhao, C.-Q.; Tanaka, M. *J. Am. Chem. Soc.* **2000**, *122*, 5407.

(9) Radical addition of (RO)$_2$P(O)H to allenes gives allylphosphonates, albeit in very low yields. Nifantev, E. E.; Magdeeva, R. K.; Maslennikova, V. I.; Taber, A. M.; Kalechits, I. V. *Zh. Obshch. Khim.* **1982**, *52*, 2459.

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Table 1. Performance of Palladium Complex Catalysts in the Hydrophosphorylation of 1,2-Heptadiene[a]

catalyst	time (h)	yield (%)[b] [**2a**(*E*/*Z*)/**3a**/**4a**]
$Pd(PPh_3)_4$	2	90 [66(86/14)/32[c]/2]
$PdMe_2(PPh_3)_2$	24[d]	91 [76(90/10)/21[c]/3]
$PdMe_2(PPh_2Me)_2$	2	93 [84(90/10)/12/4]
$PdMe_2(PPhMe_2)_2$	12	82 [3/51[e]/46]
$PdMe_2(PMe_3)_2$	12	<5
$PdMe_2$(dppe)	12	<5
$PdMe_2$(dppp)	20	70 [92(90/10)/6/2]
$PdMe_2$(dppb)	2	92 [91(87/13)/7/2]
$PdMe_2$(dppf)	2	>98 [98(92/8)/<1/<1]
	20[f]	75 [94(89/11)/5/1]
$PdMe_2$(binap)	3	87 [87(91/9)/4/9]

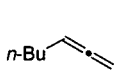
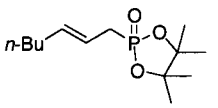
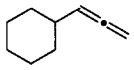
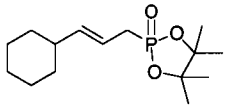
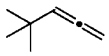
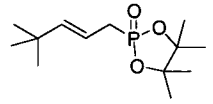
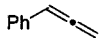
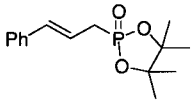
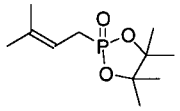
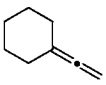
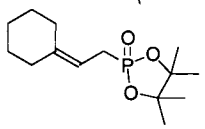
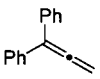
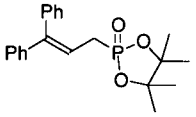
[a] Conditions: 5 mol % catalyst, equimolar **1** and the allene in 1,4-dioxane (0.25 M), 100 °C. [b] Total ^{1}H NMR yields of the isomers. [c] *E*/*Z* > 98/2. [d] Heated at 80 °C. [e] *E*/*Z* = 88/12. [f] Heated at 60 °C.

ene with **1** are significantly influenced by the phosphine ligand used. In general, palladium complexes having less basic ligands such as PPh_3 and PPh_2Me promoted the reaction satisfactorily. The reaction using $PdMe_2(PPhMe_2)_2$ proceeded slowly and the $PdMe_2(PMe_3)_2$-catalyzed reaction was very sluggish (<5%). Bidentate phosphine ligands such as dppb ($Ph_2P(CH_2)_4PPh_2$), dppf, and binap (2,2′-bis(diphenylphosphino)-1,1′-binaphthyl) showed high performance. However, dppp ($Ph_2P(CH_2)_3PPh_2$) was less efficient, and the reaction using dppe (1,2-bis(diphenylphosphino)ethane) was nearly inactive (<5%). As for the products' selectivity, the three regioisomeric adducts **2a**, **3a**, and **4a** are generally formed. Triphenylphosphine complex catalysts such as $Pd(PPh_3)_4$ and $PdMe_2(PPh_3)_2$ gave **2a** and **3a** as the main products (**2a**/**3a** = (66−76)/(21−32)) with a trace amount of **4a**. When alkyldiphenylphosphines such as PPh_2Me, dppp, and dppb were used as the ligand, the formation of **2a** became more favored over **3a** (**2a**/**3a** = (84−92)/(6−12)). However, the use of the $PPhMe_2$ ligand dramatically increased the formation of **4a**, resulting in a **3a**/**4a** ratio of approximately 1/1. The screening of the ligands suggests that dppf is the ligand of choice to synthesize **2a** with high regio- and stereoselectivities.[10]

As demonstrated in Table 2, the Pd-catalyzed hydrophosphorylation reaction is readily applicable to other terminal allenes. Thus, monosubstituted allenes having either an aliphatic or an aromatic substituent reacted efficiently to give the corresponding products with the phosphoryl group bound to the terminal carbon regioselectively. The trans allylic adducts resulted in all cases, although they required addition to the more sterically congested face of the terminal double bond. Note that as the substituent in the monosubstituted allene became sterically more demanding, the stereoselectivity to the trans adduct became even higher. Thus, the *E*/*Z* ratio improved from 92/8 for *n*-butylallene to 94/6 for cyclohexylallene and further to >99/1 for *tert*-butylallene. Similar to the case for the aliphatic allenes, phenylallene also gave the trans adduct exclusively. 3,3-Disubstituted allenes such as 3-methyl-1,2-butadiene and even the easily polymerizable 3,3-diphenyl-1,2-propadiene reacted as efficiently and regioselectively as monosubstituted allenes to produce the corresponding allylphosphonates in good yields.

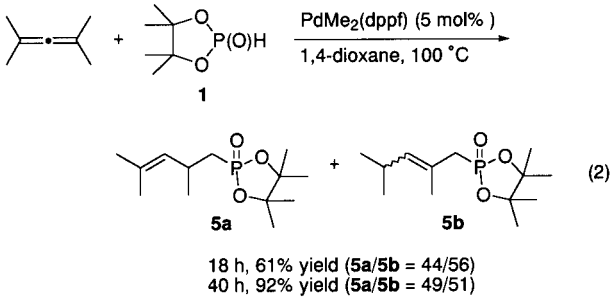
(10) The reaction could be conveniently performed using $Pd_2(dba)_3$/dppf (Pd/P = 1/2) as the catalyst to give **2a** in 91% yield (*E*/*Z* = 93/7).

Table 2. Palladium-Catalyzed Hydrophosphorylation of Terminal Allenes[a]

run	allene	conditions	product	% yield (*E*/*Z*)
1		100 °C, 2 h		87 (92/8)
2		100 °C, 6 h		61 (94/6)
3		100 °C, 4 h		81(> 99/1)
4		100 °C, 1 h		87 (> 99/1)
5[b]		100°C, 4 h		66
6[c]		80 °C, 18 h		89
7[d]		80 °C, 18 h		92

[a] Reaction conditions: equimolar **1** and an allene in 1,4-dioxane (0.2−0.5 M), 3−5 mol % $PdMe_2$(dppf). Yields are isolated yields after column chromatography on silica (hexane/*i*-PrOH = 10/(1−2) and/or preparative HPLC. *E*/*Z* ratios were determined by ^{1}H NMR spectroscopy. [b] Conducted in a sealed glass tube. [c] $PdMe_2[Ph_2P(CH_2)_4PPh_2]$ was used as the catalyst. [d] THF solution of 1,1-diphenylallene (1.5 M) was used.

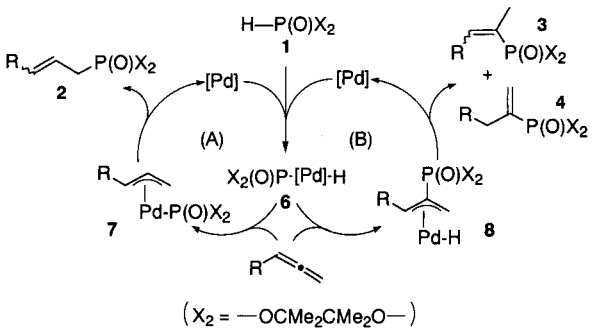
2,4-Dimethyl-2,3-pentadiene, a tetrasubstituted allene, also reacted with **1** smoothly. Very interestingly, however, a nearly 1/1 mixture of **5a** and **5b** resulted in a good yield. The expected product arising from the simple addition to one of the double bonds was not formed at all (eq 2).[11]



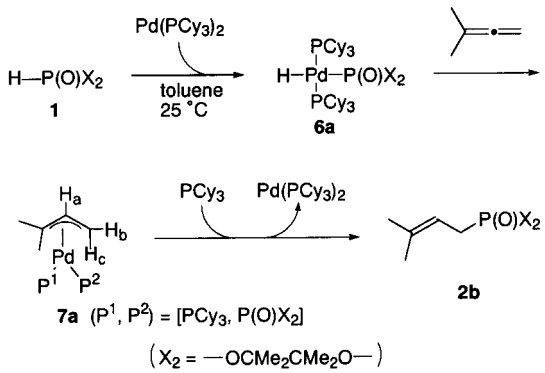
Although the detailed mechanism remains to be clarified, the reaction appears to proceed through the catalytic cycles shown in Scheme 1, in view of the intermediacy of (π-allyl)palladium species (vide infra)

(11) The reaction mechanism for the formation of **5a** and **5b** is not clear at the present time. It may involve an isomerization of the allene by the palladium catalyst via a (π-allyl)palladium species to 2,4-dimethyl-1,3-pendadiene followed by a subsequent addition (also see ref 17).

Scheme 1



Scheme 2



and the mechanism of relevant catalytic reactions.[12] Oxidative addition of the H−P bond to the palladium complex affords a hydridopalladium species (**6**).[8] This species can react with an allene in two alternative pathways to generate either the (π-allyl)palladium compound **7** in cycle A, involving the H−Pd addition (hydropalladation), or another (π-allyl)palladium compound **8** in cycle B, involving the P(O)−Pd addition (phosphorylpalladation).[13] Adduct **2** is formed presumably via cycle A through reductive elimination of **7**, while **3** and **4** are due to cycle B.[14] The results shown in Table 1 appear to suggest that either A or B can be the major pathway, depending on the nature of the phosphine ligand used.

Evidence that substantiates catalytic cycle A was successfully obtained in the following experiments. As reported previously, mixing $Pd(PCy_3)_2$ (0.118 mmol) and **1** (1 equiv) in toluene-d_8 (0.8 mL) at room-temperature resulted in a facile generation of the hydridopalladium complex (**6a**; Scheme 2).[8d] As shown by ^1H and ^{31}P NMR spectroscopy, when 3-methyl-1,2-butadiene (2 equiv) was added, signals assignable to π-allyl complex **7a** emerged rapidly. In the ^1H NMR spectroscopy, the signal for H_a was observed at δ 4.64 (dd, J = 7.9, 13.4 Hz) showing a dd coupling pattern. The signal for H_b, appearing at δ 3.26 with the same intensity as H_a, also displayed a dd coupling pattern due to the coupling with H_a and the phosphorus (P^1) in the trans position. As expected, the anti proton H_c was observed at a higher field of δ 2.39 (t-like, $J_{H_aH_c} = J_{H_cP}$ = 13.4 Hz).[15] The relatively small magnitude of the coupling between H_a and H_b (J = 7.9 Hz) is a strong indication that H_b is the syn proton in the π-allylic system of **7a**.[15] ^{31}P NMR spectroscopy was as informative. Thus, as the reaction proceeded, signals assignable to **7a** (δ 102.3, d, P(O), $J_{P(O)P}$ = 80.2 Hz; δ 43.4, d, PCy_3, $J_{P(O)P}$ = 80.2 Hz) and free PCy_3 (δ 9.8) emerged while signals due to **6a** (δ 95.8, t, P(O), $J_{P(O)P}$ = 39.4 Hz; δ 45.5, d, PCy_3, $J_{P(O)P}$ = 39.4 Hz)[8d] gradually disappeared. As estimated on the basis of the ^1H NMR spectroscopy, approximately 56% of **6a** was consumed in 0.5 h, and it completely disappeared after 2 h at room temperature. It should be noted that the reaction was a clean reaction, with complex **7a** being highly selectively formed, and that signals arising from other possible products were not found.[16] However, reductive elimination of **7a** to form **2b** (δ 36.9) and regenerate $Pd(PCy_3)_2$ (δ 38.7) slowly took place even at room temperature to afford approximately 8% of **2b** after 4 h at 25 °C. When the solution was heated at 80 °C for 1 h, complex **7a** completely disappeared to be converted to **2b** in 92% NMR yield.[17]

In conclusion, the palladium-catalyzed regio- and stereoselective hydrophosphorylation of allenes offers a convenient and clean route to allylphosphonates. Applications are readily expected in view of the well-established utility of the allylphosphonates as versatile intermediates in stereoselective synthesis and their potential in biological activity.

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Supporting Information Available: Text describing experimental details and spectral and/or analytical data of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) For example: (a) Onozawa, S.-y.; Hatanaka, Y.; Tanaka, M. *Chem. Commun.* **1999**, 1863. (b) Ishiyama, T.; Kitano, T.; Miyaura, N. *Tetrahedron Lett.* **1998**, *39*, 2357. (c) Killing, H.; Mitchell, T. N. *Organometallics* **1984**, *3*, 1318. (d) Watanabe, H.; Saito, M.; Sutou, N.; Kishimoto, K.; Inose, J.; Nagai, Y. *J. Organomet. Chem.* **1982**, *225*, 343. (e) Ogawa, A.; Kawakami, J.-I.; Sonoda, N.; Hirao, T. *J. Org. Chem.* **1996**, *61*, 4161. (f) Al-Masum, M.; Meguro, M.; Yamamoto, Y. *Tetrahedron Lett.* **1997**, *38*, 6071. (g) Gevorgyan, V.; Liu, J.-X.; Yamamoto, Y. *J. Org. Chem.* **1997**, *62*, 2963.

(13) Hydropalladation of H−Pd−P(O) species to carbon−carbon double and triple bonds has been confirmed.[8] Although no evidence for phosphorylpalladation of H−Pd−P(O) with carbon−carbon unsaturated bonds is available so far, the Pt-catalyzed Michael addition of PH_3 to acrylonitrile has been proposed to take place via a P−Pt addition rather than a H−Pt addition; see: (a) Wicht, D. K.; Kourkine, I. V.; Lew, B. M.; Nthenge, J. M.; Glueck, D. S. *J. Am. Chem. Soc.* **1997**, *119*, 5039. (b) Pringle, P. G.; Smith, M. B. *J. Chem. Soc., Chem. Commun.* **1990**, 1701.

(14) Products **2**−**4** appear to be stable to the reaction conditions, and **3** and **4** do not appear to have come from isomerization of initially formed **2**. Thus, a $PdMe_2$(dppf)-catalyzed reaction of *tert*-butylallene with **1** was run *in the presence of* ***2a*** under the standard conditions, similarly to run 3, Table 1. Analysis of the resulting mixture by gas chromatography revealed that **2a** remained intact. Another reaction in the presence of 2-(1-octen-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaphospholane 2-oxide, homologous to **4a**, also confirmed its stability and the lack of isomerization.

(15) The correlation of H_a, H_b, and H_c was also unambiguously confirmed by 2D NMR spectroscopy ($^1H-^1H$ and $^1H-^{13}C$ COSY). In the ^{13}C NMR spectrum, carbons in the middle and terminal positions of **7a** appeared at δ 113.2 (dd, J_{CP} = 4.1, 10.3 Hz) and δ 53.1 (d, J_{CP} = 54.8 Hz), respectively. For NMR studies on allylpalladiums, see: (a) Powell, J.; Shaw, B. L. *J. Chem. Soc. A* **1967**, 1839. (b) Vrieze, K.; Praat, A. P.; Cossee, P. *J. Organomet. Chem.* **1968**, *12*, 533.

(16) Since attempted isolation of (π-allyl)palladium complex **7a** has been unsuccessful due partly to its thermal instability, the detailed structure of **7a** is ambiguous at the present time. However, both ^1H and ^{31}P NMR spectroscopy unambiguously indicates that **7a** is the sole (π-allyl)palladium species in the mixture.

(17) The excess 3-methyl-1,2-butadiene recovered after the treatment had isomerized to conjugated 3-methyl-1,3-butadiene (93% NMR yield).