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Palladium-Catalyzed Dehydrogenative Cis Double Phosphorylation of Alkynes with *H*-Phosphonate Leading to (*Z*)-Bisphosphoryl-1-alkenes

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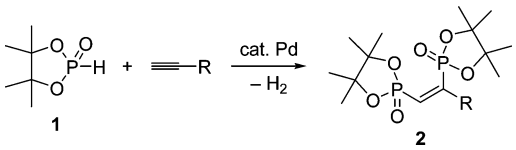
We disclose a palladium-catalyzed dehydrogenative cis double phosphorylation of terminal alkynes with *H*-phosphonate **1** affording (*Z*)-bisphosphoryl-1-alkenes **2** (eq 1).[1] Metal-mediated additions of hydrogen phosphonates $(RO)_2P(O)H$ to carbon−carbon unsaturated bonds, so far reported, all are hydrophosphorylation reactions (i.e., the addition of the P(O)−H bond).[2] A dehydrogenative cis double phosphorylation reaction has never been recognized.[3] Although, synthetic and biological applications of (*Z*)-bisphosphoryl-1-alkenes **2** as precursors for bidentate ligands and antibiotics[4] are readily expected, there is no general method for their preparation and only a very limited number of these compounds are known.[5]



(1)

We accidentally found this reaction during an ongoing study on the palladium-catalyzed hydrophosphorylation of alkynes.[6] As previously reported, when $PdCl_2$ was employed as a catalyst, no addition took place with a mixture of $(MeO)_2P(O)H$ and 1-octyne in toluene at 100 °C for 16 h. Remarkably, however, under similar reaction conditions an addition did proceed when the more reactive five member *H*-phosphonate **1**[6b] was employed to give, to our surprise, not the expected hydrophosphorylation product **3a** but a cis double phosphorylation product bis(phosphinoyl)alkene **2a** as the main product, stereoselectively (eq 2).[7] The formation of a 1,2-bis(phosphoryl)alkane **4a** was also detected with a ratio of **2a**/**3a**(regioisomer ratio α/β)/**4a** = 49:28(14/11):13 (entry 1, Table 1).[8]

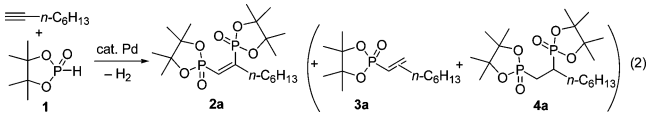
As shown in Table 1, this double phosphorylation can be catalyzed by divalent palladium(II) complexes, especially the chloropalladium(II) complexes, but is poorly catalyzed by zerovalent palladium(0) complexes which predominantly produces the hydrophosphorylation adduct **3a** rather than the double phosphorylation product **2a**. Thus, $Pd(PPh_3)_4$ afforded **3a** in 48% yield, and produced only trace amount of **2a**. As expected palladium(II) complexes that are easily reducible to zerovalent palladium species are not good catalysts for this double phosphorylation either. Thus, $Pd(OAc)_2$ only gave **2a** in 21% yield (entry 2). The addition of Ph_3P also dramatically suppressed the formation of **2a** (entry 3). On the other hand, other divalent phosphine-free chloropalladium complexes such as $PdCl_2(PhCN)_2$, $PdCl_2(COD)$, and $(\eta^3\text{-allylPdCl})_2$ could catalyze the dehydrogenative double phosphorylation as efficiently as $PdCl_2$, giving **2a** in good yields.

Since the formation of **4a** may be due to the reduction of **2a** with an hydrogen in situ generated,[8] we assumed that its formation should be suppressed by the addition of an olefin serving as an hydrogen scavenger to favor the formation of **2a**. This did work well. Thus, the yield of **2a** increased to 69% when the same reaction of **1** with 1-octyne catalyzed by $(\eta^3\text{-allylPdCl})_2$ was carried out in the presence of 3 equiv of styrene (entry 8). Interestingly, not only the formation of **4a** but also the formation of **3a** was significantly suppressed by the addition of styrene. While the sterically crowed methyl methacrylate worked less effectively (entry 12), other electron-deficient olefins such as acrylonitrile and methyl acrylate can further improve the yield of **2a** to 72% and 77%, respectively (entries 9 and 11).

Table 1. Pd-Catalyzed Dehydrogenative Double Phosphorylation of *H*-Phosphonate **1** with 1-Octyne[a]

			% yield[b]		
entry	catalyst	olefin (equiv)	**2a**	**3a**[c]	**4a**
1	$PdCl_2$	none	49	28	13
2	$Pd(OAc)_2$	none	21	55	4
3	$PdCl_2$/4.0 Ph_3P	none	7	59	0
4	$PdCl_2(PhCN)_2$	none	53	30	7
5	$PdCl_2(COD)$	none	56	27	8
6	$Pd(PPh_3)_4$	none	10	48	1
7	$(\eta^3\text{-allylPdCl})_2$	none	51	30	7
8		$CH_2{=}CHPh$ (3)	69	10	2
9		$CH_2{=}CHCN$ (3)	72	14	1
10		$CH_2{=}CHCO_2Me$ (3)	74	12	1
11		$CH_2{=}CHCO_2Me$ (1)	77(75)[d]	13	2
12		$CH_2{=}CMeCO_2Me$ (3)	67	15	9

[a] Reaction conditions: **1** (0.25 mmol), 1-octyne (0.25 mmol), $(\eta^3\text{-allylPdCl})_2$ (3 mol % based on Pd), olefin, toluene (1 mL), 100 °C, 16−22 h. [b] Determined by ^{31}P NMR. Yields are based on *H*-phosphonae **1** used. [c] Total yields of the α and β regioisomers. [d] Yield in parentheses is an isolated yield.



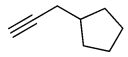
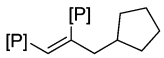
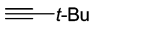
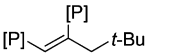
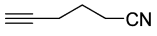
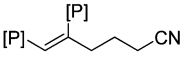
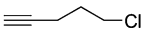
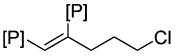
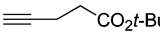
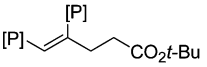
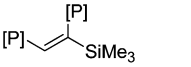
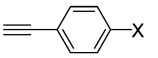
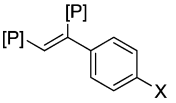
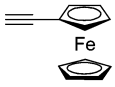
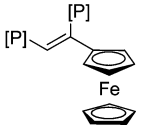
(2)

By employing a similar reaction condition used for the reaction of **1** with 1-octyne (entry 11, Table 1), the palladium catalyzed dehydrogenative double phosphorylation of **1** with other alkynes was investigated thoroughly (Table 2). Like 1-octyne, other aliphatic terminal alkynes including the bulky *t*-butylacetylene (entries 1 and 2) could undergo the dehydrogenative double phosphorylation to give the corresponding bis(phosphinoyl)alkenes. In addition, functionalized alkynes with cyano, chloro, carboxyl, and silyl groups all could be used as the substrates in the reaction to generate the corresponding products. Terminal aromatic alkynes also gave good yields of the corresponding dehydrogenative double phosphorylation products (entries 8−11). Both arylacetylenes having an electron-donating (entries 9 and 10) and an electron-withdrawing (entry 11) group gave similar results to phenylacetylene, which may indicate that an electronic effect of a substituent is small in this reaction. Ferrocenylacetylene also produced the corresponding double phosphorylation adduct in a moderate yield.

Compound **1** readily reacted with $(\eta^3\text{-allylPdCl})_2$ (**1**:Pd = 2:1, THF, 25 °C, 0.5 h) to give **5** in 95% isolated yield (Scheme 1). Furthermore, a stoichiometric reaction of **5** with 1-octyne (**5**:1-

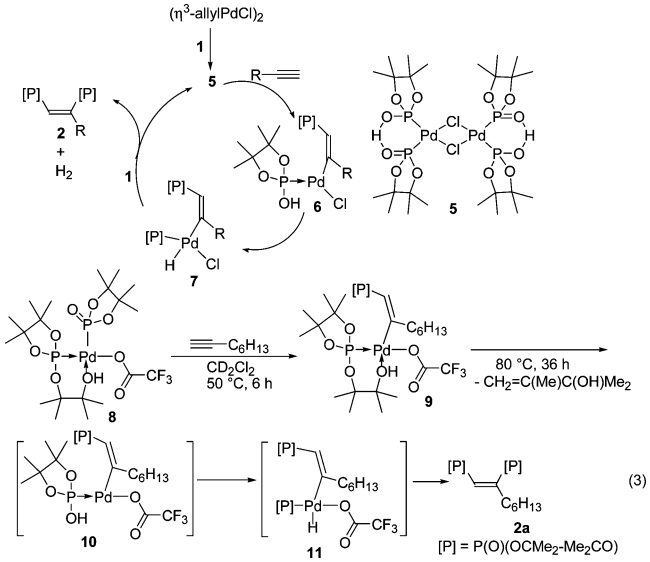
10.1021/ja7108272 CCC: $40.75

Table 2. Palladium-Catalyzed Dehydrogenative Cis Double Phosphorylation of Alkynes with *H*-Phosphonate **1**[a]

entry	alkyne	product[b]	% isolated yield
1			53
2			58
3			75
4			71
5			46
6			62
7			
8		X = H	71
9		X = Me	68
10		X = OMe	67
11		X = F	69
12			56

[a] Reaction conditions: **1** (1 mmol), alkyne (1 mmol), $CH_2{=}CHCO_2Me$ (1 mmol), $(\eta^3\text{-allylPdCl})_2$ (3 mol % as Pd), toluene (4 mL), 100 °C, 16 h. Yields based on **1** used. [b] [P] = P(O)($OCMe_2{-}Me_2CO$).

Scheme 1. A Simplified Sketch for the Dehydrogenative Double Phosphorylation of Alkynes with **1** ([P] = P(O)($OCMe_2{-}Me_2CO$), for Clarity, Ligands on Palladium were Omitted).



(3)

octyne = 1:2, toluene, 50 °C, 16 h) gave 76% yield of **2a**. Moreover, **5** catalyzed the dehydrogenative double phosphorylation of **1** with 1-octyne, as efficiently as $(\eta^3\text{-allylPdCl})_2$, to give **2a** in 75% yield.

Although a detailed reaction mechanism remains to be clarified, we feel that a Pd(II)/Pd(IV) catalytic cycle, rather than a conventional Pd(0)/Pd(II) catalytic cycle,[3] as shown in Scheme 1 should be suitable for explaining the reaction. Thus first, **5** reacted with an alkyne to give **6** via a selective cis addition of the P(O)−Pd bond to the carbon−carbon triple bond. Intramolecularly and/or intermolecularly via a reaction with **1**, complex **6** gave a hydridopalladium complex **7**, which reacts with **1** to release hydrogen, produce **2**, and regenerate the palladium(II) species. Although, currently a firm evidence for the generation of the hydrogen is not available, the formation of **6** from **5** as well as **2** from **6** were strongly evidenced by related reactions found accidently during the course of other studies (eq 3).[9] Thus, complex **8** (an analogue of **5**) reacted with 1-octyne (**8**:1-octyne = 1:2.5) in CD_2Cl_2 in a sealed tube at 50 °C to give quantitatively a new complex **9** (an analogue of **6**) via a cis insertion of the Pd−P(O) bond of **8** to 1-octyne with P(O) bonding to the terminal carbon and Pd bonding to the internal carbon. Furthermore heating **9** at 80 °C resulted in the formation of **2a** in 75% yield, which may be rationalized to take place via intermediates **10** and **11**.[10]

In summary, we have successfully revealed the first dehydrogenative cis double phosphorylation of *H*-phosphonate with alkynes forming (*Z*)-bisphosphoryl-1-alkenes. Further studies on the reaction mechanism and applications to other *H*-phosphorus compounds are now in progress.

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Supporting Information Available: Characterization data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(1) Part of this work was presented at the 87th Spring Meeting of the Chemical Society of Japan, 3D3−13, March 2007.
(2) Han, L.-B.; Zhang, C.; Yazawa, H.; Shimada, S. *J. Am. Chem. Soc.* **2004**, *126*, 5080, and references cited therein.
(3) For an analogy, the dehydrogenative double silylation is well recognized. (a) Tamao, K.; Miyake, N.; Kiso, Y.; Kumada, M. *J. Am. Chem. Soc.* **1975**, *97*, 5603. A related metal-mediated dehydrogenative coupling of phosphines: (b) Han, L.-B.; Tilley, T.D. *J. Am. Chem. Soc.* **2006**, *128*, 13698. Although in a preliminary mechanistic study, we found the formation of (*E*)-[$(MeO)_2P(O)$]CH=CPh[$P(O)(OMe)_2$] by the reaction of phenylacetylene with [$(MeO)_2P(O)$]$_2$Pd(PPh_2Me)$_2$. However, it should be noted that this compound was not generated via a similar dehydrogenative double phospholylation but via the normal hydrophosphorylation of PhC≡CP(O)$(OMe)_2$ with $(MeO)_2P(O)H$. (c) Han, L.-B.; Tanaka, M. *Chem. Commun.* **1999**, 395. (d) Han, L.-B.; Tanaka, M. *Shokubai* **1999**, *41*, 577.
(4) (a) Green, J. R. *J. Organomet. Chem.* **2005**, *690*, 2439. (b) Blackburn, G. M.; Forster, A. R.; Guo, M.-J.; Taylor, G. E. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2867. (c) Christensen, B. G.; Beattie, T. R.; Graham, D. W. French Patent 2034480; CAN 75:88759.
(5) Only the simplest (*Z*)-[$(RO)_2P(O)$] $R^1C{=}CR^2[P(O)(OR)_2]$ ($R^1 = R^2 =$ H) and a limited number of others having functionalities [R^1 (R^2) = CN, F, or CHE_2 (E = CO_2R, CN)] are known. Compounds such as **2** where R^1 (R^2) is a simple alkyl (aryl) group are not known. (a) Timofeeva, T. N.; Ignat'ev, V. M.; Ionin, B. I.; Petrov, A. A. *Doklady Akade. Nauk SSSR* **1969**, *189*, 1052; CAN 72:67041. (b) Honig, M. L.; Martin, D. J. *Phosphorus Relat. Group V Elem.* **1974**, *4*, 63−4. (c) Kadyrov, A. A.; Rokhlin, E. M.; Galakhov, M. V. *Izv. Akadi Nauk SSSR, Ser. Khim.* **1988**, 1885; CAN 110:231729. (d) Bal'on, Ya. G.; Kozhushko, B. N.; Paliichuk, Yu. A.; Shokol, V. A. *Zh. Obshch. Khim.* **1992**, *62*, 2530; CAN 119: 72703. (e) Shekhadeh, A.; Didkovskii, N. G.; Dogadina, A. V.; Ionin, B. I. *J. Gen. Chem. USSR* **2005**, *75*, 9.
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(7) The trans isomer of **2a** could not be detected by ^{31}P NMR spectroscopy of the crude reaction mixture. The structure of **2a** was readily determined on the bases of its ^1H and ^{31}P NMR spectra (see Supporting Information for details).
(8) Two ways for the formation of **4a** are possible: reduction of **2a** by hydrogen and hydrophosphorylation of **3a** with **1**. Allen, A., Jr.; Manke, D. R.; Lin, W. *Tetrahedron Lett.* **2000**, *41*, 151.
(9) Structures of complexes **8** and **9** were all unambiguously determined by X-ray crystallography (see Supporting Information for detailed data).
(10) The formation of 2,3-dimethyl-3-buten-2-ol (81% yield) was detected by ^1H NMR spectroscopy.

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