High Reactivity of a Five-Membered Cyclic Hydrogen Phosphonate Leading to Development of Facile Palladium-Catalyzed Hydrophosphorylation of Alkenes

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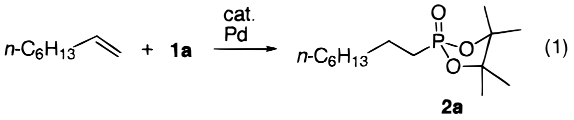
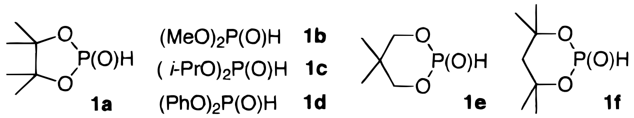
Transition metal-catalyzed addition reactions of heteroatom compounds across unsaturated carbon linkages are emerging rapidly as one of the most powerful tools for constructing carbon−heteroatom bonds.[1] However, methodologies for phosphorus compounds are still limited.[1e] Organophosphonates $RP(O)(OR')_2$, a useful class of compounds in synthetic applications and biological activity, are traditionally prepared via the classic Arbuzov reaction of $P(OR')_3$ with organic halides RX with the concomitant elimination of an equivalent quantity of R′X.[2] A more attractive, versatile, and clean alternative of high atom economy for their preparation would be the addition of $HP(O)(OR')_2$ to alkenes catalyzed by metal complexes.[3] Despite extensive screening of catalysts, such reactions have never been realized, although the corresponding Pd-catalyzed hydrophosphorylation of alkynes takes place efficiently.[4,5] Very surprisingly, however, when *a five-membered cyclic hydrogen phosphonate, 4,4,5,5-tetramethyl-1,3,2-dioxaphospholane 2-oxide (**1a**),*[6] was employed as the reactant, metal-catalyzed additions to alkenes proceeded smoothly to afford the adducts in high yields (eq 1). Herein are preliminarily disclosed the synthetic and mechanistic aspects of this unprecedented phenomenon.[7]



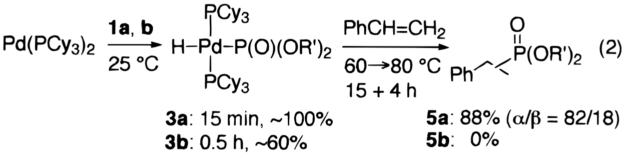
A mixture of **1a** (1 mmol) and 1-octene (1 mmol) in toluene (2 mL), when heated in the presence of *cis*-$PdMe_2(PPh_2Me)_2$ (5 mol %) at 110 °C for 3 h, developed a pale yellow solution, in which adduct **2a** was found by gas chromatography to be formed in 63% yield.[8] Surprisingly similar treatments using noncyclic and six-membered cyclic hydrogen phosphonates **1b**−**f** did not form corresponding adducts at all. The reaction of 1-octene with **1a** was significantly influenced by the nature of the ligand, alkyldiphenylphosphine like PPh_2Me being of choice under similar conditions. Besides palladium complexes, $Ni(PPh_3)_4$ (26% yield, 10 mol % catalyst) and $RhCl(PPh_3)_3$ (49% yield) were also moderately active under similar conditions. However, $Pt(CH_2{=}CH_2)(PPh_3)_2$ was nearly inactive.

Chart 1



Preliminary screening of palladium catalysts revealed that the procedure using $Ph_2P(CH_2)_4PPh_2$ complexes in 1,4-dioxane also worked efficiently. For instance, heating an equimolar mixture of **1a** and 1-octene at 100 °C in the presence of $PdMe_2[Ph_2P(CH_2)_4PPh_2]$ (5 mol %) in dioxane afforded a 93% GC yield of **2a** (reaction time = 15 h).[9] Table 1 summarizes the catalytic reactions run mostly by this procedure, which can be readily applied to both aliphatic and aromatic alkenes. Thus, ethene and propene gave near quantitative yields of the adducts. The addition to 3,3-dimethyl-1-butene, a bulky alkene, also worked well, ending up with the selective terminal attachment of phosphorus to the double bond. In contrast, styrene formed a mixture of regioisomers (α-adduct/β-adduct = 45/55, 95% total yield). However, the selectivity for the α-isomer could be markedly improved to 95% when $PdMe_2(PPh_2Cy)_2$ was used as the catalyst. Acyclic internal alkenes were nearly inert under similar conditions. However, 2-norbornene reacted as efficiently as terminal alkenes. Less strained cyclopentene reacted somewhat slowly and the reactivity of cyclohexene was even lower.

The hydrophosphorylation is best explained by Scheme 1, which involves (i) oxidative addition of the H−P bond, (ii) addition of the H−Pd bond of **3** (hydropalladation) to an alkene molecule, and (iii) reductive elimination of adduct **2** from **4**. The following observations substantiate these elemental steps. First, the oxidative addition of **1a** with $Pd(PCy_3)_2$ readily proceeded at room temperature to generate **3a** as the sole product in 15 min (eq 2). Phosphonate **1b** behaved similarly, but more slowly; the conversion of **1b** to **3b** was 60% after 30 min. Second, the resulting hydridopalladium species **3a** readily reacted with styrene



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[1] Recent reviews: (a) Horn, K. A. *Chem. Rev.* **1995**, *95*, 1317. (b) Sharma, H. K.; Pannell, K. H. *Chem. Rev.* **1995**, *95*, 1351. (c) Burgess, K.; Ohlmeyer, M. J. *Chem. Rev.* **1991**, *91*, 1179. (d) Beletskaya, I.; Pelter, A. *Tetrahedron* **1997**, *53*, 4957. (e) Han, L.-B.; Tanaka, M. *Chem. Commun.* **1999**, 395.

[2] (a) *Organic Phosphorus Compounds*; Kosolapoff, G. M., Maier, L., Eds.; Wiley-Interscience: New York, 1972. (b) *Handbook of Organophosphorus Chemistry*; Engel, R., Ed.; Marcel Dekker: New York, 1992. (c) Corbridge, D. E. C. *Phosphorus: An Outline of Its Chemistry, Biochemistry and Uses*, 5th ed., Elsevier: Amsterdam, 1995.

[3] Radical additions of $HP(O)(OR)_2$ to alkenes are well-known (ref 2). For recent examples, see: (a) Nifant'ev, E. E.; Magdeeva, R. K.; Dolidze, A. V.; Ingorokva, K. V.; Vasyanina, L. K. *Russ. J. Gen. Chem.* **1993**, *63*, 1201. (b) Nifant'ev, E. E.; Magdeeva, R. K.; Dolidze, A. V.; Ingorokva, K. V.; Samkharadze, L. O.; Vasyanina, L. K.; Bekker, A. R. *Zh. Obshch. Khim.* **1991**, *61*, 96. (c) Nifant'ev, E. E.; Magdeeva, R. K.; Shchepet'eva, N. P. *Zh. Obshch. Khim.* **1980**, *50*, 1744.

[4] Metal-catalyzed addition to alkenes usually is more difficult to achieve than the corresponding addition to alkynes. (a) Baker, R. T.; Nguyen, P.; Marder, T. B.; Westcott, S. A. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1336. (b) Iverson, C. N.; Smith, M. R., III *Organometallics* **1997**, *16*, 2757. (c) Ishiyama, T.; Yamamoto, M.; Miyaura, N. *Chem. Commun.* **1997**, 689. (d) Suginome, M.; Nakamura, H.; Ito, Y. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2516. (e) Kondo, T.; Uenoyama, S.-y.; Fujita, K.-i.; Mitsudo, T.-a. *J. Am. Chem. Soc.* **1999**, *121*, 482.

[5] Han, L.-B.; Tanaka, M. *J. Am. Chem. Soc.* **1996**, *118*, 1571.

[6] Compound **1a** is a white solid easily prepared from PCl_3 or H_3PO_3 and pinacol. (a) Zwierrzak, A. *Can. J. Chem.* **1967**, *45*, 2501. (b) Munoz, A.; Hubert, C.; Luche, J.-L. *J. Org. Chem.* **1996**, *61*, 6015. Very little is known about its reactivity. The O−P−O angle in the ring was estimated at ca. 99°, 5° smaller than the normal angle for the acyclic analogues, resulting in a ring-strain energy of ca. 5−6 kcal/mol, which makes **1a** more acidic. (c) Ovchinnikov, V. V.; Galkin, V. I.; Yarkova, E. G.; Markova, L. E.; Cherkasov, R. A.; Pudovik, A. N. *Zh. Obshch. Khim.* **1978**, *48*, 2424. (d) Newton, M. G.; Campbell, B. S. *J. Am. Chem. Soc.* **1974**, *96*, 7790. (e) Ovchinnikov, V. V.; Lapteva, L. I.; Sagadeev, E. V.; Konovalov, A. I. *Thermochim. Acta* **1996**, *288*, 105. (f) Ovchinnikov, V. V.; Cherezov, S. V.; Cherkasov, R. A.; Pudovik, A. N. *Zh. Obshch. Khim.* **1985**, *55*, 1244.

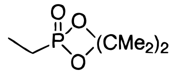
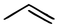
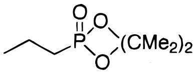
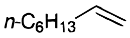
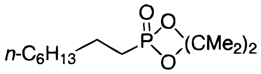
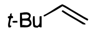
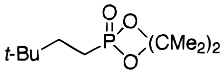
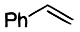
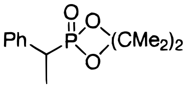
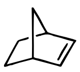
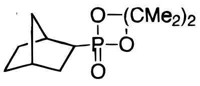
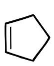
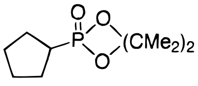
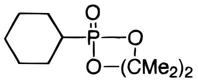
[7] Great ring-size effect on the hydrolysis of phosphates $(RO)_3P(O)$ is well-established. (a) Hudson, R. F.; Brown, C. *Acc. Chem. Res.* **1972**, *5*, 204. (b) Westheimer, F. H. *Acc. Chem. Res.* **1968**, *1*, 70.

[8] 33% of **1a** remained unchanged. 2-Octenes (31%, *cis*/*trans* = 36/64), which was inert toward the hydrophosphorylation under present conditions, was also formed.

[9] The reaction can also be conveniently conducted with $Pd_2(dba)_3/PPh_2(CH_2)_4PPh_2$ (Pd/P = 1/2) as the catalyst (82% isolated yield of **2a**).

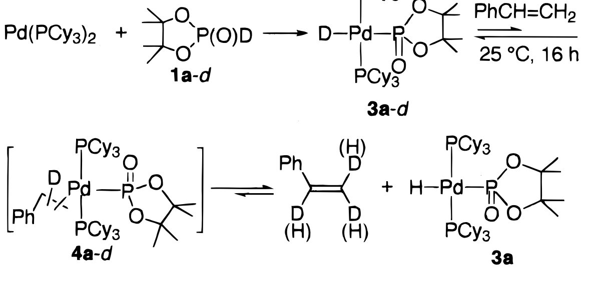
10.1021/ja000444v CCC: $19.00

Table 1. Hydrophosphorylation of Alkenes[a]

entry	alkene	adduct	% yield[b]
1[c]			quant.
2[c]			quant.
3			quant. (89)
4			quant.
5			quant.[d]
6			83[e]
7			87[f]
8			37[g]

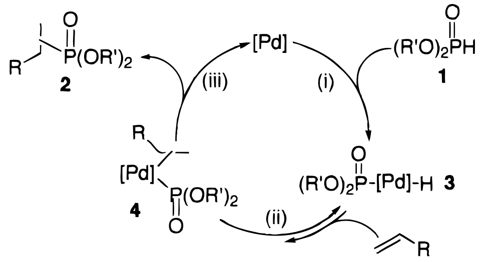
[a] Reaction conditions: an equimolar **1a** and an alkene in 1,4-dioxane (0.5−1 M), 3−5 mol % $PdMe_2[Ph_2P(CH_2)_4PPh_2]_2$, 100 °C, 15 h. Unless otherwise noted, only one adduct shown in the table was formed. [b] GC yield. The figure in parentheses is the isolated yield after column chromatography on silica (hexane/*i*-PrOH = 10/1 ∼ 2). [c] Run under 5 atm of pressure of the alkene. [d] Catalyst: $PdMe_2(PPh_2Cy)_2$. Regioselectivity of the α-adduct >95%. [e] 100% *exo*. [f] After 44 h of heating. [g] After 48 h of heating.

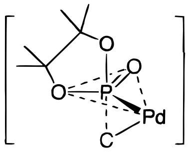
(2 equiv) upon heating at 60 °C for 15 h and at 80 °C for an additional 4 h to give isomeric adducts **5a** (88% yield based on **1a**, α/β = 82/18). In contrast, **3b** did not form the corresponding adducts at all in a similar reaction with styrene. Third, the extensive H−D exchange between **3a**-*d* and styrene strongly supports involvement of hydropalladation.[10] Thus, styrene (0.2 mmol) was added at room temperature to **3a**-*d*, cleanly generated in situ by the reaction of $Pd(PCy_3)_2$ (0.1 mmol) with **1a**-*d* (0.1 mmol) in toluene-d_8. ^1H NMR spectroscopy revealed the formation of ca. 0.04 mmol of **3a** in 2 h (eq 3). Upon further stirring, the quantity of **3a** reached an equilibrium value (ca. 0.08 mmol) after 16 h. At the same time, deuterated styrenes were observed (ca. 0.1 mmol in total, α/β-*cis*/β-*trans* = 26/36/38). Note that the deuterium incorporation ratio at the α- and β-carbons of styrene is 26/74, which is in fairly good agreement with the regioisomeric ratio of **5a** (α/β = 82/18) observed in the foregoing reaction of **3a** with styrene (eq 2). Although complex **4a** has not been unambiguously identified, ^{31}P NMR analysis of the mixture of **3a** and styrene displayed weak signals in a 93−100 ppm region, assignable to Pd-bound P(O) species in **4a**. On the other hand, no species arising from the addition of the P(O)−Pd bond to styrene was detected. The H−D exchange experiment verifies that the hydropalladation is a facile process and that the reductive elimination of **2** from **4** is slow as compared with the backward reaction to **3** via β-hydrogen elimination. This suggests, fourth, that the reductive elimination step is rate-determining in the catalysis. The high reactivity of **1a** as compared with the other hydrogen phosphonates is associated most likely with the reductive elimination process. Indeed, heating a benzene-d_6 solution of *trans*-$PdMe[P(O)(OR')_2](PEt_3)_2$ [**6a**, $(OR')_2$ = pinacolato] at 70 °C for 1 h resulted in the formation of $MeP(O)(OR')_2$ in 92% NMR yield, while its analogue **6b** (OR′ = OMe) remained unchanged in a similar treatment. The origin of the accelerating effect of the five-membered ring in the reductive elimination is ambiguous at this stage. It may be tentatively assumed that a trigonal bipyramidal transition state (**7**) is involved, similarly to the hydrolysis of phosphates;[7] during the course of reductive elimination from **4**, which has the strained five-membered ring, the ring oxygens occupy apical and equatorial positions with a cyclic O−P−O angle of 90°, the strain-free apical/equatorial angle for a dsp^3-hybridized hypervalent phosphorus.



(3)

Scheme 1





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In conclusion, Pd-catalyzed hydrophosphorylation of terminal and some cyclic alkenes has been made possible by taking advantage of the exceptionally high reactivity of a five-membered cyclic hydrogen phosphonate. Further synthetic applications of this finding and extensions to other heteroatom compounds are now in progress.

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

JA000444V

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[10] Pt−P rather than Pt−H addition was proposed for the Pt-catalyzed addition of PH_3 to acrylonitrile. (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.