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Palladium-Catalyzed Hydrophosphinylation of Alkenes and Alkynes

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Few catalytic methods have been reported for the addition of phosphorus−hydrogen bonds across unsaturated substrates.[1] During our work on the palladium-catalyzed cross-coupling of hypophosphorous derivatives, we realized that the competing transfer hydrogenation reaction (Scheme 1, path 1) could be minimized or even suppressed.[2] The catalytic transfer hydrogenation of various compounds with hypophosphorous acid or its salts **1** as hydrogen donors has been known for several decades.[3] Early on, its mechanism has been proposed to proceed through insertion of Pd(0) into a P−H bond to form **2b** and then the postulated reactive species palladium hydride **2a** (Scheme 1, path 2). It occurred to us that species **2b** resulting from oxidative addition could be trapped through hydropalladation to form **6a** (or phosphinylpalladation to form **6b**), provided that the decomposition of complex **2a** is comparatively slow (Scheme 1, path 2 versus path 1).

On the basis of this idea, we have now developed a remarkably general catalytic hydrophosphinylation reaction of alkenes and alkynes with hypophosphorous compounds **1** ($ROP(O)H_2$, R = Alk, H, $PhNH_3$) to form H-phosphinic acid derivatives **3**. Products **3** are important biologically active compounds[4] and synthetic intermediates which can be converted into a variety of other organophosphorus compounds using well-established protocols.[5]

In a typical procedure (Table 1), a solution of hypophosphite **1** (5 mmol) in a solvent (10 mL) was heated with 1-octene (2.5 mmol) in the presence of a catalyst (2−3 mol %). In the absence of catalyst, no P−C bond formation occurs. Several catalysts could be employed to achieve hydrophosphinylation with varying degrees of success. However, four systems were found to be particularly useful (Table 1: $Cl_2Pd(PPh_3)_2$/MeLi in toluene, THF, or acetonitrile; Pd_2dba_3/xantphos (or DPEphos, or dppf) in acetonitrile). The reactions were conveniently monitored by a combination of ^{31}P NMR and gas chromatography using an internal standard.[6]

Hydrophosphinylation remained the major pathway, even when excess alcohol or water, which could lead to more pronounced transfer hydrogenation through trapping of **2a** to form **4** (Scheme 1, path 1), were present. The successful reaction of aqueous H_3PO_2 with Pd_2dba_3/xantphos at room temperature (Table 1, entry 16) points to the exquisite selectivity of this system favoring hydrophosphinylation over reduction (transfer hydrogenation).

In Table 2, several representative examples of the hydrophosphinylation are shown. Reactions with Pd_2dba_3/xantphos were conducted with a catalyst loading of 1 mol % or less (as little as 0.02 mol % still delivered a good yield of adduct in 24 h). Various alkenes and alkynes react successfully. The reaction complements our previously reported radical-based methodology.[4] While products derived from di- and trisubstituted alkenes are readily available from the radical reaction,[4] cyclohexene is a poor substrate in the Pd-catalyzed hydrophosphinylation. In contrast, styrene and 5-bromo-1-pentene (Table 2, entries 6−8) are noteworthy because these are poor substrates in our radical reaction.[4] Terminal alkynes give the branched vinylphosphinate exclusively with catalytic $Cl_2Pd(PPh_3)_2$/MeLi (Table 2, entries 11−12), whereas the linear product is the major component with catalytic Pd_2dba_3/xantphos (Table 2, entries 9−10).

Unlike Tanaka's hydrophosphorylation,[7] where alkynes reacted well with various H-phosphonates[7a,c] but alkenes only reacted

Scheme 1. Postulated Mechanistic Pathways in the Palladium-Catalyzed Reaction of Hypophosphorous Derivatives

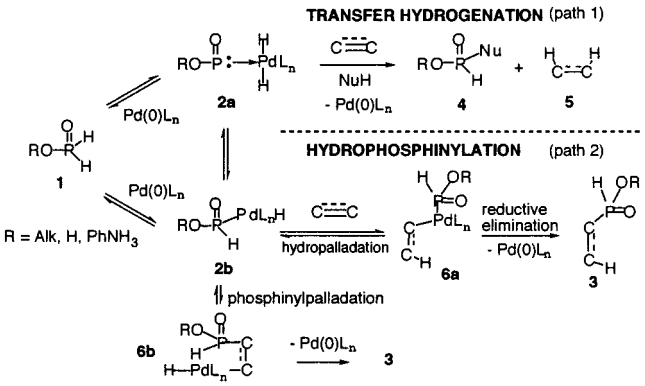
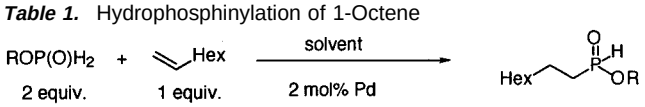


Table 1. Hydrophosphinylation of 1-Octene



entry	R	solvent[a]	catalyst[b]	yield[c]
1	Bu	CH_3CN	$Cl_2Pd(PPh_3)_2$/MeLi	65
2	Bu	THF	$Cl_2Pd(PPh_3)_2$/MeLi	100
3	Bu	toluene	$Cl_2Pd(PPh_3)_2$/MeLi	78
4	Bu	toluene	Cl_2Pd(dppf)/MeLi	86
5	Bu	toluene (rt)	Cl_2Pd(dppf)/MeLi	18
6	Bu	CH_3CN	Pd_2dba_3/dppf	86
7	Bu	CH_3CN	Pd_2dba_3/xantphos	100
8	Bu	CH_3CN (rt)	Pd_2dba_3/xantphos	90
9	Bu	CH_3CN	Pd_2dba_3/DPEphos	100
10	Et	toluene	$Cl_2Pd(PPh_3)_2$/MeLi	86
11	Et	THF	$Cl_2Pd(PPh_3)_2$/MeLi	70
12	Et	CH_3CN	Pd_2dba_3/xantphos	92
13	Me	CH_3CN	Pd_2dba_3/xantphos	100
14	$PhNH_3$	DMF (80 °C)	Pd_2dba_3/xantphos	93
15	H	CH_3CN (rt)	Pd_2dba_3/xantphos	100
16	H	H_2O, CH_3CN (rt)	Pd_2dba_3/xantphos	79

[a] Unless otherwise noted, reactions were conducted at the reflux temperature. rt = room temperature. Reaction times (unoptimized): 12−16 h. For R = Bu, Et, reagent grade solvents were used (ref 8). 1-Octene concentration was 0.2 M. [b] Catalysts: 2 equiv MeLi were used per Pd. dppf = 1,1′-bis(diphenylphosphino)ferrocene. xantphos = 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene. DPEphos = bis(2-diphenylphosphinophenyl)-ether. 1 mol % Pd_2dba_3 + 2.2 mol % bisphosphine ligand. [c] Yields were determined by ^{31}P NMR analysis of the crude reaction mixtures and integration of all the resonances.

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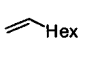
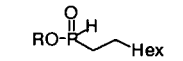
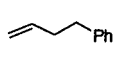
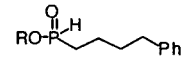
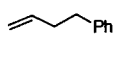
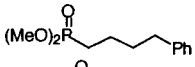
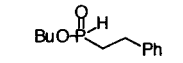
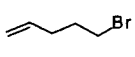
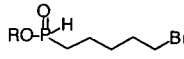
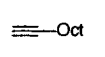
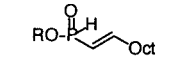
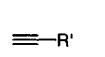
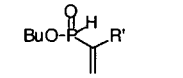
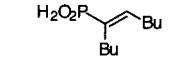
Table 2. Hydrophosphinylation of Various Alkenes and Alkynes[a]

Entry	Substrate	Product	Catalyst[b]		yield[c] %
1			Pd_2dba_3 xantphos	R = Bu	89 (76)
2				R = H	100 (67)
3			Pd_2dba_3 xantphos	R = Et	100 (84)
4				R = H	81 (75)[d]
5			Pd_2dba_3 xantphos		85 (72)[e]
6			Pd_2dba_3 xantphos		100 (69)[f]
7			Pd_2dba_3 xantphos	R = Et	100 (61)
8				R = H	100 (83)
9			Pd_2dba_3 xantphos	R = Et	75 (70)[g]
10				R = Bu	78[h]
11			$Cl_2Pd(PPh_3)_2$ 2 MeLi	R' = Oct	70[i]
12				R' = Ph	85 (50)[i]
13			Pd_2dba_3 xantphos		100 (88)

[a] Reactions were conducted in refluxing CH_3CN, except for entries 2, 4, and 8, which were conducted at room temperature. 1.5 equiv $ROP(O)H_2$ was employed. Alkene/alkyne concentration was 0.3 M. Details are provided in the Supporting Information. [b] Catalyst: 0.05−1.0 mol % Pd. [c] Yields of H-phosphinic acid derivative determined by ^{31}P NMR analysis. The number in parentheses is the isolated yield of the product shown. Isolated yields are unoptimized. [d] Aqueous H_3PO_2 was used directly. [e] The crude reaction mixture was treated with Et_3N, CCl_4, and MeOH. [f] Linear/branched: 4.4:1. [g] Linear/branched: 3.7:1. [h] Linear/branched: 5:1. [i] Branched only. This reaction was run with 3 mol % catalyst in refluxing toluene.

satisfactorily with pinacol H-phosphonate,[7b,d] our reaction works equally well with various hypophosphorous derivatives. Additionally, the H-phosphinic acid or ester products **3** obtained can be elaborated into numerous organophosphorus compounds,[4,5] including simple phosphonates ($R'P(O)(OR)_2$, Table 2, entry 5) which are not accessible using Tanaka's reaction. Good selectivity for the linear product is observed with styrene (entry 6), whereas Tanaka's conditions provide the branched isomer. Hypophosphite esters,[8,4] **1** (R = Alk) are more reactive than their H-phosphonate counterparts. For example, in the reaction of butyl hypophosphite with alkynes, little or no addition product stemmed from the Tanaka-like competing addition[7a] of $(BuO)_2P(O)H$ **4** (a decomposition product always present in the reaction mixture). As expected, **4** is unreactive toward alkenes. Similarly, the products, H-phosphinic esters **3**, are unreactive under the reaction conditions so that formation of symmetrically substituted phosphinic esters $R'_2P(O)(OR)$ is not observed.

In conclusion, we have developed the hydrophosphinylation of alkenes and alkynes as a novel catalytic P−C bond-forming reaction which should find some use for the synthesis of a variety of organophosphorus compounds. The addition of aqueous hypophosphorous acid to alkenes at room temperature constitutes a new environmentally friendly route to H-phosphinic acids. Further studies to explore the scope of the palladium-catalyzed hydrophosphinylation, its application to the synthesis of biologically active compounds, and the development of an asymmetric version will be reported in due course. The prospect of catalytic asymmetric desymmetrization of the phosphinylidene hydrogens in **1** (R = Alk) to form P-chiral compounds is particularly intriguing.[9]

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Supporting Information Available: Representative procedures and spectroscopic data and table (Table 3) summarizing the results obtained with several other catalytic systems (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(5) For example: phosphinic and phosphonic acid derivatives, phosphonochloridates, phosphine oxides, primary phosphines, and dichlorophosphines. See: (a) *Methoden der Organischen Chemie (Houben-Weyl)*; Sasse K., Ed.; Thieme: Stuttgart, 1964; Band XII/1, pp 294−337. (b) *Methoden der Organischen Chemie (Houben-Weyl)*; Regitz M., Ed.; Thieme: Stuttgart, 1982; Vol. E2. (c) Frank, A. W. In *Organic Phosphorus Compounds*; Kosolapoff, G. M., Maier, L., Eds.; Wiley: New York, 1972; Vol. 4, Chapter 10. (d) Quin, L. D. *A Guide to Organophosphorus Chemistry*; Wiley: New York, 2000. (e) Frank, A. W. *Chem. Rev.* **1961**, *61*, 389.

(6) On the basis of experiments with an internal standard, the ^{31}P NMR yields obtained from integration of all resonances, are accurate within 10%, and are reproducible. Surprisingly, little (<5%) or no octane was detected during the hydrophosphinylation of 1-octene with the above catalysts. When octane forms, isomerization products such as *trans*-2-octene are also observed.

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(9) 1-Octene reacted at room temperature with $MenOP(O)H_2$ to afford a 1.4:1 ratio of diastereoisomers in 66% combined yield (1 mol % Pd_2dba_3/xantphos). Albeit modest, this diastereoselectivity is promising, since the chirality is far from the phosphinylidene hydrogens. In the radical reaction, no diastereoselectivity was observed (ref 4).

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