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Palladium-Catalyzed Dehydrative Allylation of Hypophosphorous Acid with Allylic Alcohols

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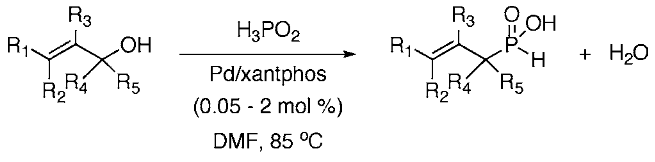
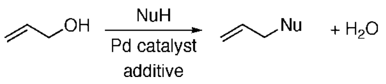
ABSTRACT



20 examples, 43 -100%

A novel palladium-catalyzed allylation of H_3PO_2 with allylic alcohols is described. The phosphorus–carbon bond-forming reaction produces allylic-*H*-phosphinic acids and water, in the absence of additives. Primary *H*-phosphinic acids are obtained in excellent yields, whereas secondary *H*-phosphinic acids react sluggishly. A reusable polymer-supported catalyst is also described. The reaction provides an environmentally sound approach to *H*-phosphinic acids.

Palladium-catalyzed allylations have become well-established and reliable methods for forming C−O, C−N, and C−C bonds but are much less common for C−P bond formation.[1] Commonly used electrophiles are halides or esters (acetate, carbonate, phosphate) derived from an allylic alcohol. More recently, research has focused on the development of catalytic allylations which use allylic alcohols directly.[2,3] The obvious advantages are the ready availability of the starting materials and a more atom-economical and environmentally benign approach because water is the byproduct (eq 1).



(eq 1)

As part of our program to develop phosphorus−carbon bond-forming reactions using hypophosphorous acid (H_3PO_2) and its derivatives,[4] we have reported the palladium-catalyzed cross-coupling of aryl and alkenyl electrophiles[5] and the hydrophosphinylation of alkenes and alkynes.[6] Herein, we report the palladium-catalyzed allylation of H_3PO_2 with

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(1) For metal-catalyzed allylation with P−C bond formation: (a) Lu, X.; Zhu, J. *Synthesis* **1986**, 563. (b) Lu, X.; Zhu, J.; Huang, J.; Tao, X. *J. Mol. Catal.* **1987**, *41*, 235. (c) Lu, X.; Tao, X.; Zhu, J.; Sun, X.; Xu, J. *Synthesis* **1989**, 848. (d) Lu, X.; Zhu, J. *J. Organomet. Chem.* **1986**, *304*, 239.

(2) Reviews: (a) Muzart, J. *Tetrahedron* **2005**, *61*, 4179. (b) Tamaru, Y. *Eur. J. Org. Chem.* **2005**, 2647. For allylation with allylic alcohols in the presence of additives, see, for example: (c) Yang, S.-C.; Hsu, Y.-C.; Gan, K.-H. *Tetrahedron* **2006**, *62*, 3949. (d) Zhu, S.-F.; Yang, Y.; Wang, L.-X.; Liu, B.; Zhou, Q.-L. *Org. Lett.* **2005**, *7*, 2333. (e) Fontana, G.; Lubineau, A.; Scherrmann, M.-C. *Org. Biomol. Chem.* **2005**, *3*, 1375. (f) Manabe, K.; Kobayashi, S. *Org. Lett.* **2003**, *5*, 3241. (g) Ozawa, F.; Okamoto, H.; Kawagishi, S.; Yamamoto, S.; Minami, T.; Yoshifuji, M. *J. Am. Chem. Soc.* **2002**, *124*, 10968. (h) Yang, S.-C.; Tsai, Y.-C. *Organometallics* **2001**, *20*, 763. (i) Chandrasekhar, S.; Jagadeshwar, V.; Saritha, B.; Narsihmulu, C. *J. Org. Chem.* **2005**, *70*, 6506. (j) Takahara, J. P.; Masuyama, Y.; Kurusu, Y. *J. Am. Chem. Soc.* **1992**, *114*, 2577.

(3) Examples of direct allylation without additives: (a) Olsson, V. J.; Sebelius, S.; Selander, N.; Szabo, K. J. *J. Am. Chem. Soc.* **2006**, *128*, 4588. (b) Kayaki, Y.; Koda, T.; Ikariya, T. *Eur. J. Org. Chem.* **2004**, 4989. (c) Kayaki, Y.; Koda, T.; Ikariya, T. *J. Org. Chem.* **2004**, *69*, 2595. (d) Trost, B. M.; Spagnol, M. D. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2083. (e) Vedejs, E.; MacKay, J. A. *Org. Lett.* **2001**, *3*, 535.

(4) Reviews: (a) Montchamp, J.-L. *J. Organomet. Chem.* **2005**, *690*, 2388. (b) Montchamp, J.-L. *Spec. Chem. Mag.* **2006**, *26*, 44.

(5) (a) Bravo-Altamirano, K.; Huang, Z.; Montchamp, J.-L. *Tetrahedron* **2005**, *61*, 6315. (b) Huang, Z.; Bravo-Altamirano, K.; Montchamp, J.-L. *C. R. Chimie* **2004**, *7*, 763. (c) Dumond, Y. R.; Montchamp, J.-L. *J. Organomet. Chem.* **2002**, *653*, 252. (d) Montchamp, J.-L.; Dumond, Y. R. *J. Am. Chem. Soc.* **2001**, *123*, 510.

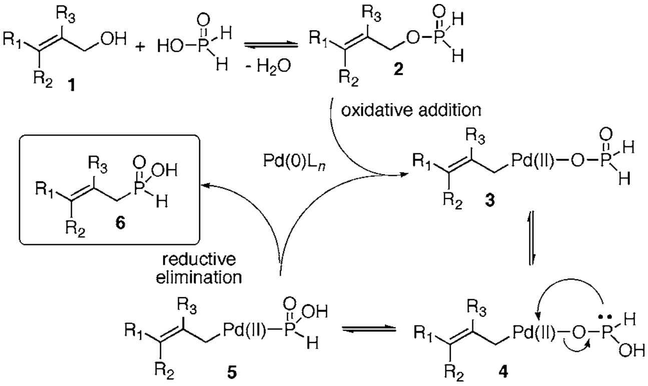
(6) (a) Ribière, P.; Bravo-Altamirano, K.; Antczak, M.; Hawkins, J. D.; Montchamp, J.-L. *J. Org. Chem.* **2005**, *70*, 4064. (b) Deprèle, S.; Montchamp, J.-L. *J. Am. Chem. Soc.* **2002**, *124*, 9386.

10.1021/ol061828e CCC: $33.50

allylic alcohols which proceeds *in the absence of any additives*.[3]

Because allylic acetates and phosphates readily undergo oxidative addition with palladium, it occurred to us that allylic phosphinates should behave similarly. The resulting π-allyl complex may then undergo rearrangement followed by reductive elimination, in a pathway similar to the one we had previously hypothesized during some cross-coupling studies with other allylic derivatives.[5a] If the allyl phosphinate can form through the Fischer-like esterification of H_3PO_2, a catalytic allylation would result. The postulated mechanistic pathway is shown in Scheme 1.

Scheme 1. Postulated Catalytic Mechanism

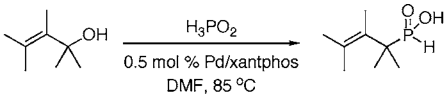


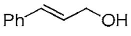
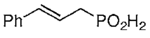
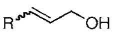
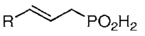
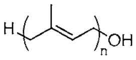
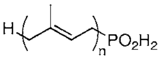
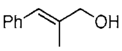
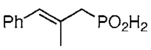
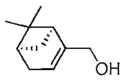
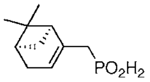
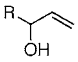
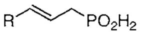
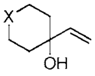
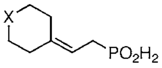
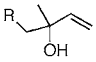
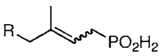
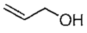
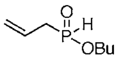
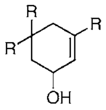
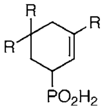
Indeed, when H_3PO_2 was reacted with cinnamyl alcohol (DMF, 85 °C) in the presence of Pd_2dba_3/2xantphos (0.5 mol % of Pd, xantphos = 9,9-dimethyl-4,6-bis(diphenylphosphino)xanthene), the corresponding cinnamyl-*H*-phosphinic acid formed in high yield. No reaction took place in the absence of a catalyst. The reaction proved rather general (Table 1). In most cases, the *H*-phosphinic acid product can be isolated in good purity (>95%) by a simple extractive workup. The reaction generally proceeds in good yield even with equimolar amounts of H_3PO_2 and allylic alcohol (entries 1−4 and 8). Increasing the number of equivalents of H_3PO_2 improves the yield slightly and speeds up the reaction. Disubstituted phosphinic acids do not form under any of the conditions investigated.

Remarkably, the reaction still works well when performed in air and with aqueous H_3PO_2 (2 equiv) in undried, reagent grade DMF (entry 1b), even at room temperature (entry 1c). In experiments conducted in air, 2 equiv of acid appears to be required to prevent oxidation of the products into the corresponding allylic phosphonates.

Low molecular weight *H*-phosphinic acids give lower isolated yields because they are difficult to extract. Addition of $(BuO)_4Si$ to the reaction mixture followed by heating for a few hours provided the butyl esters which were purified by chromatography.[7] For example, butyl allyl-*H*-phosphinate (entry 9) and butyl crotyl-*H*-phosphinate were obtained in 43% and 88% yield, respectively.

Table 1. Scope of the Pd-Catalyzed Allylation[a]



entry	alcohol		H-phosphinic acid	isolated yield (%)[b]
1a				95
1b				100[c]
1c				100[c]
		R =		
2a		*E*-Pr		62
2b		*Z*-Pr		92
2c		Me		50
3a		n = 1		52
3b		n = 2		100
3c		n = 3		86
4				68
5				74
		R =		
6a		Et		92
6b		*p*-FC_6H_4		96
		X =		
7a		CH_2		78
7b		NCO_2Et		73
		R =		
8a		H		82
8b		prenyl		93[d]
8c		geranyl		98[d]
9[e]				43[e,f]
		R =		
10a		H		45[e,f]
10b		Me		52[f]

[a] See Supporting Information for details. Unless otherwise noted, reactions were conducted in dry DMF (0.2 M) at 85 °C, with 0.5 mol % of Pd/xantphos and *n* equiv of H_3PO_2. *n* = 1, entries 1−4 and 8. *n* = 2, entries 5−7. *n* = 3, entries 9 and 10. Reaction times: 2−8 h. [b] Isolated yield after extractive workup. [c] Reaction conducted in air, 2 equiv of aqueous H_3PO_2 (50 wt %), and reagent grade DMF (1b, 85 °C; 1c, rt). [d] 1:1 mixture of isomers. [e] After esterification and chromatographic purification. [f] Conditions: 2 mol % of Pd/xantphos, 3 equiv of H_3PO_2, 85°C, DMF (2 M).

Lowering the amount of catalyst 10-fold, from 0.5 mol % to 0.05 mol %, still provided excellent isolated yields (cinnamyl-*H*-phosphinic acid, 99%, and geranyl-*H*-phosphinic acid, 83%). However, a further decrease in catalyst loading did not give satisfactory results.

The reaction is highly *E*-selective as indicated in entries 1−4 and 6. From the *E*-starting material, the *E*-isomer is obtained exclusively, whereas from the *Z*-starting material, the *E*-isomer forms predominantly (>90:10 *E*/*Z*) or exclusively. When a primary *H*-phosphinic acid can form, rearrangement from secondary and tertiary allylic alcohols takes place. Not surprisingly, when two substituents are in position 3, as with (−)-linalool or nerolidol, a mixture of *E*- and *Z*-isomers is obtained (entries 8b and 8c). Secondary *H*-phosphinates require more concentrated conditions (2 M) and

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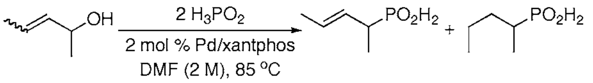
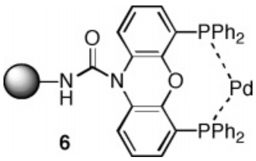
(7) Dumond, Y. R.; Baker, R. L.; Montchamp, J.-L. *Org. Lett.* **2000**, *2*, 3341.

slightly higher catalyst loading for success (entry 10), but *trans*-1,3-diphenyl-2-propen-1-ol fails to give detectable P−C bond formation even under these modified conditions. This could be due to more rapid transfer hydrogenation with this type of substrate. A study conducted with 3,5,5-trimethyl-2-cyclohexen-1-ol (isophorol) using standard conditions showed the formation of reduction and olefin isomerization products which were detected by gas chromatography. With higher concentrations, small amounts of overreduction can be detected. For example, with 3-penten-2-ol (predominantly trans), the expected *E*-(1-methyl-but-2-enyl)-phosphinic acid was obtained as the major product, along with a small amount of the overreduced product (1-methyl-butyl)-phosphinic acid (eq 2, overall isolated yield of 80%, *E*:[H] = 8.5:1).



(eq 2)

Consistent with the mechanism proposed in Scheme 1, preformed[8] primary cinnamyl phosphinate **2** undergoes the palladium-catalyzed P−O to P−C rearrangement (**2** to **6**, Scheme 1) in quantitative yield. The rearrangement even takes place at room temperature. Phosphorous acid (H_3PO_3) fails to undergo the reaction, supporting the postulated importance of the P(V) to P(III) tautomeric equilibrium (**3** to **4**) during rearrangement. The fact that the reaction does not proceed in the absence of catalyst and that primary alcohols give primary *H*-phosphinic products rules out the known thermal [2,3] sigmatropic rearrangement pathway.[9] Allylic acetates also undergo cross-coupling with hypophosphorus compounds, and these results will be reported in the upcoming full paper.[10]



6

The polystyrene-supported catalyst **6** we reported earlier for hydrophosphinylation of unsaturated compounds[11] was also highly effective in this reaction. Cinnamyl alcohol was reacted with H_3PO_2 and **6** (1 mol %), and at the end of the reaction, the polymer catalyst was recovered by filtration and reused directly in four additional runs to provide the corresponding cinnamyl-*H*-phosphinic acid in 92% combined yield (total of five runs). This process constitutes a highly atom-economical and environmentally benign approach to *H*-phosphinic acids from allylic alcohols.

Allylic *H*-phosphinic acids have been prepared previously from the reaction of an allylic halide with $(TMSO)_2PH$.[12] However, this method requires wasteful silylation and a halide-containing electrophile and is difficult to control to avoid symmetrically disubstituted products.[13,14]

In conclusion, we report a novel catalytic phosphorus−carbon bond-forming reaction which proceeds in good yield and does not require any additive, thereby providing a powerful and environmentally sound entry into allylic organophosphorus compounds. The possible extension of the process to phenols is under study.

Acknowledgment. We gratefully acknowledge the National Science Foundation (CHE-0242898) for the financial support of this research.

Supporting Information Available: Representative experimental procedures and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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[8] Deprèle, S.; Montchamp, J.-L. *J. Organomet. Chem.* **2002**, *643/644*, 154.

[9] For example: (a) Mark, V. In *Mechanisms of Molecular Migrations*; Thyagarajan, B. S., Ed.; Interscience: New York, 1969; Vol. 2, pp 319−437. The rearrangement of propargyl phosphinates is well-known: (b) Ionin, B. I.; Petrov, A. A. *Phosphorus, Sulfur Silicon* **1990**, *49/50*, 243. (c) Belakhov, V. V.; Yudelevich, V. I.; Komarov, E. V.; Ionin, B. I.; Komarov, V. Y.; Zakharov, V. I.; Lebedev, V. B.; Petrov, A. A. *J. Gen. Chem. USSR* **1983**, *53*, 1345.

[10] Bravo-Altamirano, K.; Montchamp, J.-L. *Poster 313*, 231st National Meeting of the American Chemical Society, Atlanta, March 26−30, 2006; American Chemical Society: Washington, DC, 2006.

[11] Deprèle, S.; Montchamp, J.-L. *Org. Lett.* **2004**, *6*, 3805.

[12] Boyd, E. A.; Regan, A. C.; James, K. *Tetrahedron Lett.* **1994**, *35*, 4223.

[13] (a) Bujard, M.; Gouverneur, V.; Mioskowski, C. *J. Org. Chem.* **1999**, *64*, 2119. (b) Majewski, P. *Phosphorus, Sulfur Silicon* **1989**, *45*, 151. (c) Kurdyumova, N. R.; Ragulin, V. V.; Tsvetkov, E. N. *Russ. J. Gen. Chem.* **1994**, *64*, 380. (d) Issleib, K.; Mögelin, W.; Balszuweit, A. Z. *Anorg. Allg. Chem.* **1985**, *530*, 16.

[14] For alternative monoallylation approaches using halides, see: (a) Abrunhosa-Thomas, I.; Ribière, P.; Adcock, A. C.; Montchamp, J.-L. *Synthesis* **2006**, *2*, 325. (b) Baylis, E. K. *Tetrahedron Lett.* **1995**, *36*, 9385.