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Allylic Phosphinates via Palladium-Catalyzed Allylation of *H*-Phosphinic Acids with Allylic Alcohols

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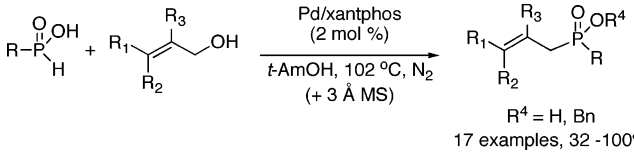
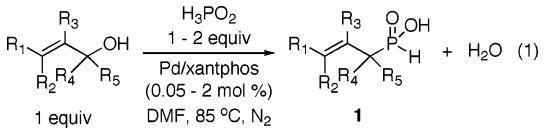
ABSTRACT



Abstract A novel catalytic allylation of *H*-phosphinic acids is described. Using Pd/xantphos (2 mol %), *H*-phosphinic acids react directly with allylic alcohols to produce P-allylated disubstituted phosphinic acids.

H-Phosphinic acids are increasingly available building blocks which have been used extensively in the synthesis of a variety of functionalized organophosphorus compounds.[1] The functionalization of *H*-phosphinic acids by standard methods (such as base-promoted alkylation,[2] palladium-catalyzed cross-coupling with aryl halides,[3] and radical addition to alkenes[4]) is relatively well-developed. However, there is a lack of methods which are general, are atom-economical, are catalytic, and take place under mild conditions. Possible exceptions are the recent work by Tanaka, Han, and Zhao on the reaction of phenyl-*H*-phosphinate esters with alkynes using palladium, nickel, or copper catalysts, and Stockland with Michael acceptors using microwave irradiation without any catalyst.[5] However, this reaction appears limited to phenyl-containing phosphinates, which behave quite differently from other *H*-phosphinates. In fact, we previously observed the reactivity of phenyl-*H*-phosphinate esters in radical reactions and their propensity for formation of a second P−C bond.[6]



We recently reported the palladium-catalyzed dehydrative allylation of hypophosphorous acid with allylic alcohols (eq

(1) (a) Montchamp, J.-L. *Specialty Chem. Mag.* **2006**, *26*, 44. (b) Montchamp, J.-L. *J. Organomet. Chem.* **2005**, *690*, 2388.

(2) Abrunhosa-Thomas, I.; Sellers, C. E.; Montchamp, J.-L. *J. Org. Chem.* **2007**, *72*, 2851, and references cited therein.

(3) (a) Xu, Y.; Zhang, J. *Synthesis* **1984**, 778. (b) Xu, Y.; Li, Z.; Xia, J.; Guo, H.; Huang, Y. *Synthesis* **1983**, 377. (c) Xu, Y.; Li, Z. *Synthesis* **1986**, 240. (d) Xu, Y.; Zhang, J. *J. Chem. Soc.. Chem. Commun.* **1986**, 1606. (e) Xu, Y.; Wej, H.; Zhang, J.; Huang, G. *Tetrahedron Lett.* **1989**, *30*, 949. (f) Huang, C.; Tang, X.; Fu, H.; Jiang, Y.; Zhao, Y. *J. Org. Chem.* **2006**, *71*, 5020. (g) Rao, H.; Jin, Y.; Fu, H.; Jiang, Y.; Zhao, Y. *Chem.−Eur. J.* **2006**, *12*, 3636. (h) Lei, H.; Stoakes, M. S.; Schwabacher, A. W. *Synthesis* **1992**, 1255.

(4) (a) Hirai, T.; Han, L.-B. *Org. Lett.* **2007**, *9*, 53. (b) Piettre, S. R. *Tetrahedron Lett.* **1996**, *37*, 2233. (c) Zeiss, H.-J. *Tetrahedron Lett.* **1992**, *38*, 8263. (d) Dingwall, J. G.; Tuck, B. *J. Chem. Soc., Perkin Trans. 1* **1986**, 2081. (e) Pudovik, A. N.; Konovalova, I. V.; Guryleva, A. A. *J. Gen. Chem. USSR* **1963**, *33*, 2850. (f) Finke, M.; Kleiner, H.-J. *Liebigs Ann. Chem.* **1974**, 741.

(5) (a) Nune, S. K.; Tanaka, M. *Chem. Commun.* **2007**, 2858. (b) Han, L.-B.; Zhao, C.-Q.; Onozawa, S.-y.; Goto, M.; Tanaka, M. *J. Am. Chem. Soc.* **2002**, *124*, 3842. (c) Han, L.-B.; Zhang, C.; Yazawa, H.; Shimada, S. *J. Am. Chem. Soc.* **2004**, *126*, 5080. (d) Niu, M.; Fu, H.; Jiang, Y.; Zhao, Y. *Chem. Commun.* **2007**, 272. (e) Stockland, R. A. Jr. Taylor, R. I.; Thompson, L. E.; Patel, P. B. *Org. Lett.* **2005**, *7*, 851.

(6) Deprèle, S.; Montchamp, J.-L. *J. Org. Chem.* **2001**, *66*, 6745.

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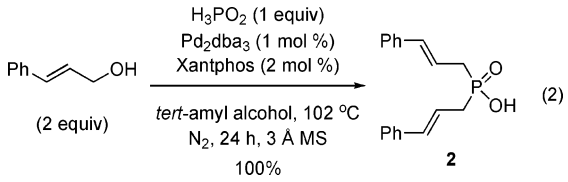
1), which leads to allylic *H*-phosphinic acids (RPO_2H_2 **1**).[7] In this reaction, further allylation of the products **1** is not observed, as H_3PO_2 is much more reactive. Mechanistically there is no reason why an analogous reaction could not also generally take place with **1**, since the required tautomeric equilibrium between the P(V) phosphinic and the P(III) phosphonous forms is still available. One expected competing side-reaction is the oxidation of **1** into the corresponding phosphonic acid[8] at the higher temperature that might be required. Thus, more strict anhydrous and anaerobic conditions are necessary than in eq 1.

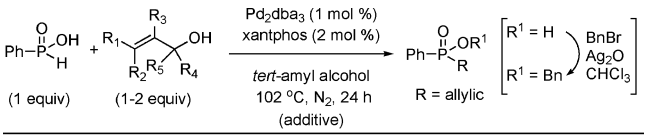
Herein, we report the development and preliminary scope of this novel reaction. In the case of the allylation of H_3PO_2, we found DMF to be the optimum solvent.[7] Seeking a solvent which might catalyze the tautomeric equilibrium, we reasoned that a hydrogen-bonding alcoholic medium might be superior, but a further requirement is to prevent direct esterification of **1** with the solvent which would compete with the allylic alcohol. This led to the identification of a tertiary alcohol. Further temperature (and cost) considerations narrowed the choice to *tert*-amyl alcohol. To test this hypothesis, H_3PO_2 was initially tested in this reaction. Gratifyingly, it was found that *tert*-amyl alcohol could be employed, even as a cosolvent, and good yields of cinnamyl-*H*-phosphinic acid were obtained. In fact, when H_3PO_2 (1 equiv) was reacted with cinnamyl alcohol (2 equiv), in the presence of 2 mol % Pd/xantphos (xantphos = 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene), in anhydrous *tert*-amyl alcohol (3 Å MS, reflux, N_2), the disubstituted phosphinic acid **2** was obtained in quantitative isolated yield (eq 2). In the absence of sieves, the yield is significantly decreased (76%).

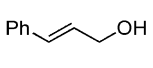
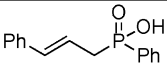
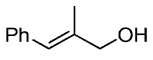
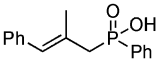
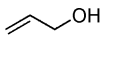
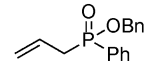
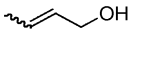
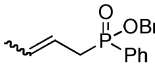
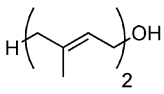
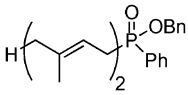
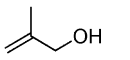
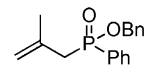
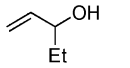
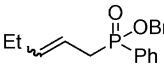


This result provided the basis for the study of the allylation of phenyl-*H*-phosphinic acids with various allylic alcohols (Table 1). In most cases, the products were isolated after in-situ esterification of the phosphinic acid. As expected, when the reaction is not nearly quantitative, a significant amount of the phosphonic acid (resulting from the oxidation of the *H*-phosphinic acid starting material)[8] constitutes the balance of the product. This impurity is also esterified to the phosphonate dibenzyl ester, which is separated during the purification process, but typically lowers the overall isolated yield of pure disubstituted phosphinic benzyl ester.

Unlike the reaction with H_3PO_2, which proceeds with high *E*-selectivity,[7] the present reaction is poorly selective (entries 4 and 7), possibly because of the more forcing reaction conditions. In most cases, powdered 3 Å molecular sieves must be added to obtain good yields and minimize formation of $PhPO_3H_2$.[8] Although the yields are moderate to good, the catalytic allylation clearly takes place with a variety of allylic alcohols. Of course, the reaction does not take place in the absence of the palladium catalyst. The role of catalyst loading was briefly investigated (entry 1), and as little as 0.25 mol % Pd still resulted in a quantitative isolated yield (entry 1b).

Table 1. Palladium-Catalyzed Allylation of Phenyl-*H*-Phosphinic Acid[a]



entry	alcohol	product	^{31}P-NMR yield (%)[b]	isolated yield (%)[c]
1a			100	98
1b			100	100[d]
2			92	80
3			92	69[e]
4			92	56 (*E*/*Z* 77:23)
5			70	44 single isomer
6			49	32[e]
7			81	62[e] (*E*/*Z* 81:19)

[a] See Supporting Information for experimental details. Freshly distilled *tert*-AmOH was used ($PhPO_2H_2$ 0.3−0.5 M). Entries 2−4 and 6−7: powdered 3 Å sieves (1 g/mmol) added. [b] ^{31}P NMR yields were determined on the crude mixture of phosphinic acids. [c] Isolated yield. Benzyl esters were purified by chromatography on silica gel, and the numbers represent the overall yield of the allylation-esterification sequence. [d] Conducted with 0.25 mol % Pd/xantphos. [e] Reaction conducted in a sealed pressure tube with 2 equiv of allylic alcohol.

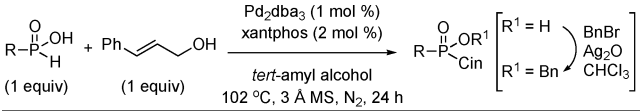
With these results in hand, we set out to explore the scope of the reaction using various *H*-phosphinic acid starting materials since this could constitute a general route to useful allylic derivatives. A range of *H*-phosphinic acids[9] bearing several functional groups reacted uneventfully with an equimolar amount of cinnamyl alcohol (Table 2). As in Table 1, the majority of the disubstituted phosphinic acids was isolated after esterification and chromatographic purification. In the case of entry 6, using 2 equiv of cinnamyl alcohol did not increase the yield.

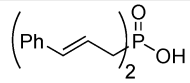
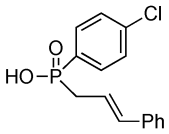
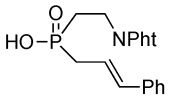
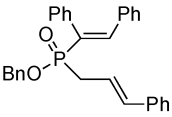
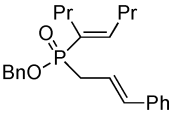
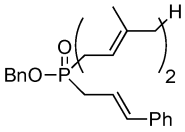
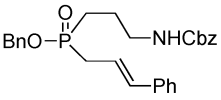
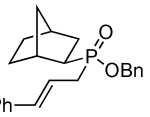
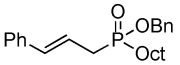
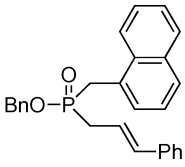
A possible mechanism for the allylation of *H*-phosphinic acids is shown in Scheme 1.[10] Fischer-like esterification of

(7) Bravo-Altamirano, K.; Montchamp, J.-L. *Org. Lett.* **2006**, *8*, 4169.
(8) Bravo-Altamirano, K.; Montchamp, J.-L. *Tetrahedron Lett.* **2007**, *48*, 5755.

(9) See Supporting Information for details. The starting *H*-phosphinic acids are available through methods we have developed. (a) Montchamp, J.-L.; Dumond, Y. R. *J. Am. Chem. Soc.* **2001**, *123*, 510. (b) Deprèle, S.; Montchamp, J.-L. *J. Am. Chem. Soc.* **2002**, *124*, 9386. (c) Deprèle, S.; Montchamp, J.-L. *Org. Lett.* **2004**, *6*, 3805. (d) See also refs 1, 6, 7.

Table 2. Allylation of *H*-Phosphinic Acids with Cinnamyl Alcohol[a]

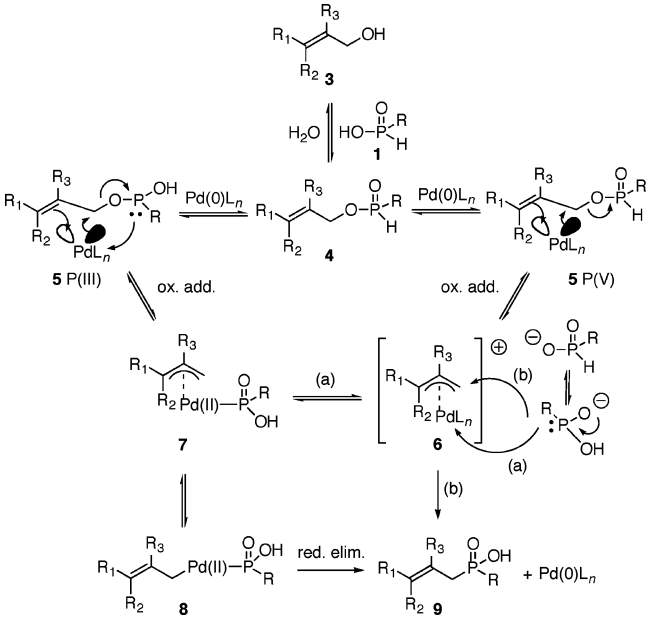


entry	*H*-phosphinic acid **1** R =	product	^{31}P-NMR yield (%)[b]	isolated yield (%)[c]
1	Ph		95	98
2	*p*-ClC$_6$H$_4$		100	83
3[d]	PhtN		100	73
4	Ph		71	67
5	Pr		57	34
6	geranyl		86	58
7	NHCbz		88	49
8			65	38
9	*n*-octyl		91	91
10			93	74[e]

[a] See Supporting Information for experimental details. Freshly distilled *tert*-AmOH with powdered 3 Å sieves (1 g/mmol of **1**) added. [b] ^{31}P NMR yields were determined on the crude reaction mixture of phosphinic acids. [c] Isolated yield. Benzyl esters were purified by chromatography on silica gel, and the numbers represent the overall yield of the allylation-esterification sequence. [d] Pht = phthalimide. [e] Molecular sieves were not used.

1 with alcohol **3** provides allyl phosphinate **4**. From there, oxidative addition takes place via **5** (*H*-phosphinates are better leaving groups than carboxylates)[11] to provide a

Scheme 1. Postulated Reaction Mechanism



π-allylpalladium intermediate, which collapses to intermediate **8** via **7**, followed by reductive elimination to phosphinic acid **9**. An alternative pathway involves ion-pair **6**, and the attack of the P(III) phosphinate anion on the carbon atom of the π-allylpalladium cation (path a) to produce directly product **9**. Attack at Pd in **6**[12] produces **7**, path b. Distinguishing between the two paths is rather difficult, and both might be operative. However, the overall mechanism requires a tautomeric equilibrium between P(V) and P(III) forms, and therefore a phosphinylidene-containing unit [P(═O)H]. Preliminary mechanistic experiments with preformed **4** indicate that a species similar to **5** P(III) is likely involved since catalyzed isomerization of silylated **4** (BSA as an additive) is taking place rather efficiently.[13] Similarly, various acidic or basic additives also promote the rearrangement of preformed **4**.[13] The use of *tert*-AmOH as a solvent likely promotes the tautomeric equilibrium, and the addition of a drying agent removes the water in the esterification process and reduces the competing oxidation of **1**.

Next, the synthetic utility of the reaction was briefly investigated. Allylation is particularly useful because it provides a handle for further synthetic elaboration. For example, bis(cinammyl)phosphinic acid **2** (eq 2) was converted into the rare [1,4]azaphosphinane-4-oxide ring system[14] through esterification, ozonolysis, and reductive amination (Scheme 2). A similar sequence leads to the formation

(10) The mechanism is analogous to what we have proposed with H_3PO_2, see ref 7 and Bravo-Altamirano, K.; Abrunhosa-Thomas, I.; Montchamp, J.-L. *J. Org. Chem.* **2008**, *73*, 2292.

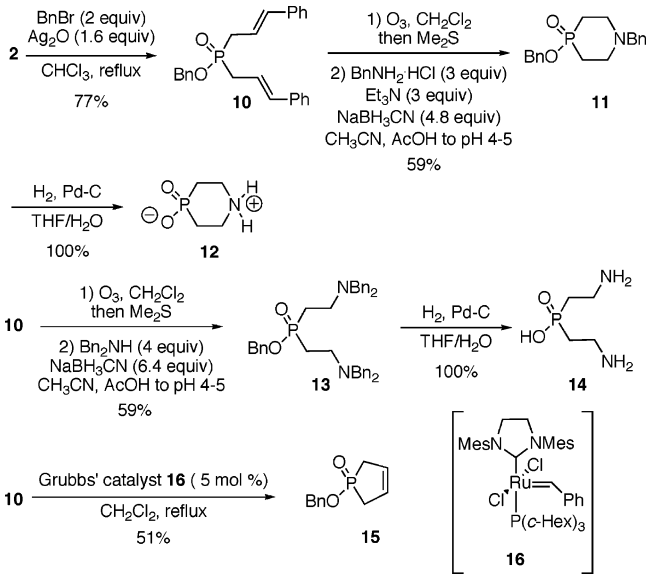
(11) p*K*a H_3PO_2 1.3, Khan, T. A.; Tripoli, R.; Crawford, J. J.; Martin, C. G.; Murphy, J. A. *Org. Lett.* **2003**, *5*, 2971 (values around 2.0 can also be found in the literature). pK_a AcOH 4.76.

(12) Trost, B. M. *Chem. Rev.* **1996**, *96*, 395.

(13) Unpublished results. Bravo-Altamirano, K. Ph.D. dissertation, Texas Christian University, May 2007.

(14) (a) Reznik, V. S.; Levin, Y. A.; Akamsin, V. D.; Galyametdinova, I. V.; Pyrkin, R. I. *Russ. Chem. Bull.* **2000**, *49*, 495. (b) Levin, Y. A.; Pyrkin, R. I.; Galyametdinova, I. Patent, U.S.S.R. 1974, SU 414264. (c) Manthey, M. K.; Huang, D. T. C.; Bubb, W. A.; Christopherson, R. I. *J. Med. Chem.* **1998**, *41*, 4550.

Scheme 2. Synthesis of the [1,4]Azaphosphinane-4-oxide Heterocycle, Double Reductive Amination, and Ring-Closing Metathesis of **3**



of diamine **13** via double reductive-amination. Hydrogenolysis produces bis(2-aminoethyl)phosphinic acid **14**.[15]

Another application of intermediate **10** is the ring closing metathesis to phospholene **15** (Scheme 2). Although the formation of phospholenes via RCM is well-precedented,[16] the precursors are always terminal alkenes. In the case of **10**, ring closing metathesis takes place smoothly but slowly (~71% conversion in 48 h). Nonetheless, phospholene **15** was obtained in acceptable yield.

Unfortunately, attempts at inducing the phospho-Cope rearrangement[17] of the product from Table 2, entry 4, both under the literature conditions (NaOH, H_2O, 195 °C) or using microwave heating, were unsuccessful.

In conclusion, we have developed the direct Pd-catalyzed allylation of H-phosphinic acids with allylic alcohols. Because of the flexibility provided by the allylic functionality, the resulting disubstituted phosphinic acids are potentially important intermediates in the synthesis of more functionalized compounds. Applications to the synthesis of phosphinopeptides and other biologically active compounds are currently being pursued. Coupled with our previously reported methods for the catalytic synthesis of *H*-phosphinic acids, this reaction provides a general and environmentally benign entry into symmetrically and differentially substituted allylic phosphinic acids.

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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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