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Nickel-Catalyzed Addition of P(O)−H Bonds to Propargyl Alcohols: One-Pot Generation of Phosphinoyl 1,3-Butadienes

Li-Biao Han,* Yutaka Ono, and Hideaki Yazawa

National Institute of Advanced Industrial Science and Technology,
Tsukuba, Ibaraki 305-8565, Japan
libiao-han@aist.go.jp

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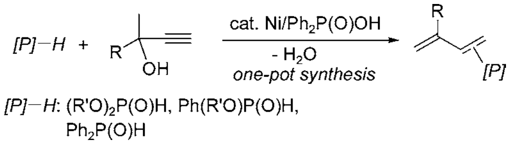
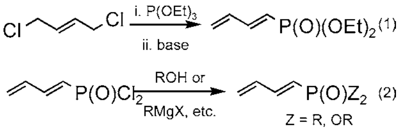
ABSTRACT



Diphenylphosphine oxide and related P(O)H compounds react with propargyl alcohols at room temperature in the presence of a catalytic amount of Ni(0) complex and Ph$_2$P(O)OH to produce high yields of phosphinoyl 1,3-dienes though an efficient in situ dehydration process.

Phosphinoyl 1,3-dienes, as exemplified by **2** in eq 3, are known as one of the functionalized phosphorus compounds which can be transformed to other valuable compounds.[1] For example, 1,3-butadienylphosphonates (**2**, [P] = P(O)(OR)$_2$) undergo Michael addition with a variety of nucleophiles including enolates of ketones and aldehydes to give new allylic phosphonates.[2a−c] They also react with dienophiles to give the corresponding Diels−Alder reaction products.[2d] Cycloaddition of 1,3-butadienylphosphonates with enamines proceeds readily to yield novel cyclohexadienylphosphonates.[2e] However, methods for the preparation of **2** are quite limited. Thus, although the simplest phosphinoyl 1,3-diene (**2**, R = H) could be prepared by a reaction of P(OEt)$_3$ with 1,4-dichloro-2-butene (eq 1) or by a substitution reaction of 1,3-butadienylphosphonic dichloride with nucleophiles (eq 2), substituted phosphinoyl 1,3-dienes are generally not readily prepared.[3]



Recently, we have revealed an efficient nickel-catalyzed addition of P(O)H compounds to alkynes which produces high yields of alkenylphosphorus compounds regio- and stereoselectively.[4a] We considered that a two-step reaction sequence, consisting of the metal-catalyzed addition of P(O)H compounds to the readily available propargyl alcohols and an acid-catalyzed dehydration of the resulting alkenylphosphorus compounds **1**, might give substituted phosphinoyl 1,3-dienes **2** (path a, eq 3). As described below, this strategy

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(1) Edmundson, R. S. In *The Chemistry of Organophosphorus Compounds;* Hartley, F. R., Ed.; John Wiley & Sons: Chichester, 1996; Vol. 4, pp 495−652.

(2) (a) Pudovik, A. N.; Konovalova, I. V.; Ishmaeva, E. A. *Zh. Obshch. Khim.* **1962**, *32*, 237. (b) Darling, S. D.; Muralidharan, F. N.; Muralidharan, V. B. *Tetrahedron Lett.* **1979**, *30*, 2757. (c) Darling, S. D.; Muralidharan, F. N.; Muralidharan, V. B. *Tetrahedron Lett.* **1979**, *30*, 2761. (d) Griffin, C. E.; Daniewski, W. M. *J. Org. Chem.* **1970**, *35*, 1691. (e) Darling, S. D.; Subramanian, N. *J. Org. Chem.* **1975**, *40*, 2851.

(3) For the preparation of phosphinoyl 1,3-dienes: (a) Kuzina, N. G.; Mashlyakovskii, L. N.; Simanovich, M. B.; Ionin, B. I. *J. Gen. Chem. USSR (Engl. Transl.)* **1977**, *47*, 1537. (b) Mashlyakovskii, L. N. *J. Gen. Chem. USSR (Engl. Transl.)* **1970**, *40*, 780. (c) Mashlyakovskii, L. N.; Ionin, B. I. *J. Gen. Chem. USSR (Engl. Transl.)* **1965**, *35*, 1582. (d) Kosolapoff, G. M. (Monsanto Chem. Co.) U.S. Patent 2,389,576, 1943. (e) Ojea, V.; Fernandez, M. C.; Ruiz, M.; Quintela, J. M. *Tetrahedron Lett.* **1996**, *37*, 5801. (f) Akermark, B.; Nystroem, J.-E.; Rein, T.; Baeckvall, J.-E.; Helquist, P.; Aslanian, R. *Tetrahedron Lett.* **1984**, *50*, 5719. (g) Zyablikova, T. A.; Il′yasov, A. V.; Mukhametzyanova, E. K.; Shermergorn, I. M. *J. Gen. Chem. USSR (Engl. Transl.)* **1982**, *52*, 249. (h) Darcel, C.; Bruneau, C.; Dixneaf, P. H. *Synthesis* **1996**, 711. (i) Ryabov, B. V.; Ionin, B. I.; Petrov, A. A. *J. Gen. Chem. USSR (Engl. Transl.)* **1988**, *58*, 859. (j) Brel′, V. K.; Abamkin, E. V.; Martynov, I. V.; Ionin, B. I. *J. Gen. Chem. USSR (Engl. Transl.)* **1989**, *59*, 2142.

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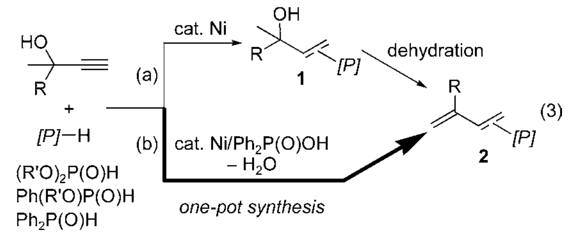
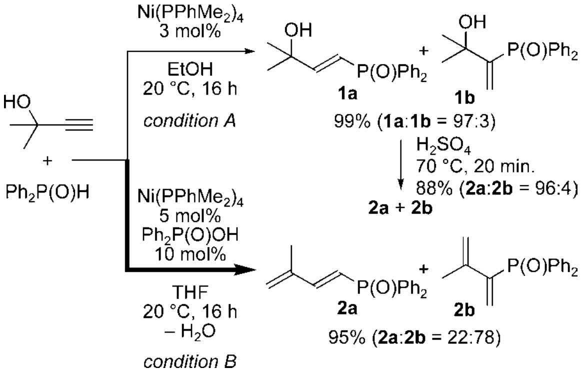
does work well; however, unexpectedly, we found that under certain reaction conditions, *the reaction of P(O)H compounds with propargyl alcohols can directly afford high yields of **2** via an in situ dehydration process (path b), which reveals an unprecedented one-pot synthetic route to **2** from these readily available starting* materials.[5] We discuss the details below.



As reported previously, the Ni-catalyzed addition of P(O)H compounds to simple terminal alkynes in a protic solvent such as EtOH produced the *anti*-Markovnikov *trans*-alkenylphopshorus compounds while a similar addition carried out in an aprotic solvent using Ni/$Ph_2P(O)OH$ as catalyst gave the Markovnikov vinylphosphorus adducts.[4] As shown in Scheme 1, the reaction of 2-methyl-3-butyn-2-ol with $Ph_2P(O)H$ in the presence of 3 mol % Ni($PPhMe_2$)$_4$ in EtOH (condition A) did follow this rule to produce the corresponding *trans*-alkenylphosphine oxide **1a** highly selectively (99% combined NMR yield; **1a**/**1b** = 97:3). Subsequent dehydration of the adducts easily took place upon heating the reaction mixture with an acid to afford phosphinoyl 1,3-butadienes (vide infra) in high yields. Surprisingly, however, when a similar addition reaction was carried out in THF using Ni/$Ph_2P(O)OH$ as catalyst (condition B) at room temperature, the expected addition products **1a** and **1b** could not be detected at all; instead, phosphinoyl butadienes **2a** and **2b**, *formally formed via the dehydration of **1a** and **1b***, respectively, were obtained in 95% combined yield (**2a**/**2b** = 22:78).

Scheme 1



The distribution of the products (**1a**,**b** and **2a**,**b**) of this Ni-catalyzed reaction of 2-methyl-3-butyn-2-ol with $Ph_2P(O)H$ was significantly affected by both the solvent and the additive $Ph_2P(O)OH$ employed (Table 1). When alcoholic solvent was used, the reaction gave the *anti*-Markovnikov adduct **1a** predominantly with or without the addition of $Ph_2P(O)OH$ (runs 1−4). Thus, as shown by run 3, in EtOH the addition of $Ph_2P(O)OH$ only results in a little increase in the formation of the dehydration product **2a**. The effect of $Ph_2P(O)OH$ was significantly observed, however, in an aprotic solvent. Thus, in the absence of $Ph_2P(O)OH$, only low yields of **2a**,**b** were obtained in THF (run 5), which was in sharp contrast to the results of a similar reaction carried out in the presence of a catalytic amount of $Ph_2P(O)OH$ which gave predominantly dehydration products **2a**,**b** (Scheme 1). Similar results were obtained from other solvents such as DMF and benzene (runs 6 and 7). As to the Ni catalyst, it is noted that Ni(PPh_2Me)$_4$ did not catalyze the reaction as efficiently as Ni($PPhMe_2$)$_4$, and a complicated result was obtained with or without $Ph_2P(O)OH$ (runs 8 and 9).[5]

Table 1. Effects of Solvent and Additive on the Addition[a]

run	catalyst	solvent	product ratio[b] (**1a**/**1b**/**2a**/**2b**)	yield[b] (%)
1	Ni($PPhMe_2$)$_4$	MeOH	91:9:0:0	92
2	Ni($PPhMe_2$)$_4$	EtOH	96:4:0:0	99
3	Ni($PPhMe_2$)$_4$[c]	EtOH	78:11:11:0	96
4	Ni($PPhMe_2$)$_4$	^{i}PrOH	92:4:4:0	95
5	Ni($PPhMe_2$)$_4$	THF	46:19:11:24	89
6	Ni($PPhMe_2$)$_4$	DMF	72:19:9:0	83
7	Ni($PPhMe_2$)$_4$[c]	PhH	0:0:22:78	91
8	Ni(PPh_2Me)$_4$	THF	d	*d*
9	Ni(PPh_2Me)$_4$[c]	THF	e	*e*
10	Ni(cod)$_2$[c]	THF	-	0
11	Ni(cod)$_2$/1.0 $PPhMe_2$[c]	THF	0:0:17:83	83
12	Ni(cod)$_2$/2.0 $PPhMe_2$[c]	THF	0:0:31:69	92
13	Ni(cod)$_2$/4.0 $PPhMe_2$[c]	THF	0:0:31:69	91
14	Ni(cod)$_2$/1.0 PMe_3[c]	THF	0:0:9:91	79

[a] Conditions: 2-methyl-3-butyn-2-ol (1.0 mmol), $Ph_2P(O)H$ (1.0 mmol), Ni complex (5 mol %) in 2 mL of solvent, room temperature, 16 h. [b] Determined by ^{1}H NMR. [c] $Ph_2P(O)OH$ (10 mol %) was added. [d] Starting materials were consumed to give a complicated mixture of products. [e] Starting materials remained (ca. 45%). A complicated mixture of products was obtained.

The reaction could be more conveniently conducted by using an in situ generated catalyst from the readily available Ni(cod)$_2$ and phosphines (note that Ni(cod)$_2$ alone (run 10)

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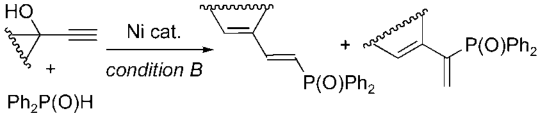
(4) (a) Han, L.-B.; Zhang, C.; Yazawa, H.; Shimada, S. *J. Am. Chem. Soc.* **2004**, *126*, 5080. For related examples: (b) Sadow, A. D.; Haller, I.; Fadini, L.; Togni, A. *J. Am. Chem. Soc.* **2004**, *126*, 14704. (b) Ribière, P.; Bravo-Altamirano, K.; Antczak, M. I.; Hawkins, J. D.; Montchamp, J.-L. *J. Org. Chem.* **2005**, *70*, 4064.

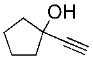
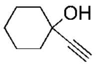
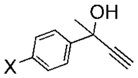
(5) It is interesting to note that such an in situ dehydration did not take place when $Me_2Pd(PPhMe_2)_2$/$Ph_2P(O)OH$ was used as the catalyst. (a) Han, L.-B.; Zhao, C.-Q.; Onozawa, S.-y.; Goto, M.; Tanaka, M. *J. Am. Chem. Soc.* **2002**, *124*, 3842. (b) Han, L.-B.; Mirzaei, F.; Zhao, C.-Q.; Tanaka, M. *J. Am. Chem.* Soc. **2000**, *122*, 5407. (c) Zhao, C.-Q.; Han, L.-B.; Goto, M.; Tanaka, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 1929. (d) Han, L.-B.; Zhao, C.-Q.; Tanaka, M. *J. Org. Chem.* **2001**, *66*, 5929. For comparisons, also see the following. (e) Ru-catalyzed addition of Ph_2PH to propargyl alcohols: Jérôme, F.; Monnier, F.; Lawicka, H.; Dérien, S.; Dixneuf, P. H. *Chem. Commun.* **2003**, 696. (f) Ru-catalyzed double phosphinylation of propargyl alcohols: Milton, M. D.; Onodera, G.; Nishibayashi, Y.; Uemura, S. *Org. Lett.* **2004**, *6*, 3993.

does not catalyze the reaction at all). It is interestingly noted that the reaction is not only strongly affected by the phosphine used but also affected by the ratios of phosphine to Ni(cod)$_2$. Thus, while the catalyst of Ni(cod)$_2$/1.0 PPhMe$_2$ gave **2a** and **2b** in 83% combined yield with a regioisomer ratio of **2a**/**2b** = 17/83, catalysts Ni(cod)$_2$/2.0 PPhMe$_2$ and Ni(cod)$_2$/4.0 PPhMe$_2$ afforded **2a**,**b** in better yields with less formation of **2b**. When the small PMe$_3$ was used as the ligand, the ratio of **2a**/**2b** could be even improved to 9/91. However, the reaction did not proceed satisfactorily when bulky phosphines such as PPh$_2$Me, PEt$_3$, PBu$_3$, PPhEt$_2$, and PPh(cyclohexyl)$_2$ were employed as ligands.

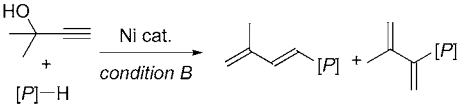
The reaction can be applied to other tertiary propargyl alcohols. Thus, *under condition B*, 1-ethynylcyclopentanol and 1-ethynylcyclohexanol reacted with Ph$_2$P(O)H as efficiently as 2-methyl-3-butyn-2-ol to give the phosphinoyl 1,3-butadienes in high yields (Table 2).[6] 2-Phenyl-3-butyn-2-ol also gave the dehydration product in a moderate yield (run 3). It is interesting to note that an electronic factor strongly affects this reaction. Thus, the yield of the dehydration products increased when an electron-donating methyl group was introduced to the benzene ring (run 4), and an exclusive formation of the dehydration products was obtained when stronger electron-donating MeO and Me$_2$N groups were introduced (runs 5 and 6).[6]

Table 2. One-Pot Generation of Phosphinoyl Butadienes by the Nickel-Catalyzed Addition of Ph$_2$P(O)H to Propargyl Alcohols



run	propargyl alcohol	yield (%)[a] [ratio][b]
1		91 (83) [25:75]
2		92 (78) [44:56]
		
3	X = H	57 (55) [0:100]
4	X = Me	68 (66) [3:97]
5	X = MeO	99 (97) [13:87]
6	X = Me$_2$N	99 (97) [2:98]

[a] Determined by NMR. Isolated yields are shown in parentheses. [b] *Trans*/*gem* isomer ratio.



(4)

[P]—H = (MeO)$_2$P(O)H 68% (23:77)
[P]—H = Ph(EtO)P(O)H 77% (32:68)

In addition to Ph$_2$P(O)H, other P(O)H compounds can also be used as the substrates. For example, reactions of (MeO)$_2$P(O)H and Ph(EtO)P(O)H with 2-methyl-3-butyn-1-ol gave the corresponding in situ dehydration phosphinoyl butadienes in 68% and 77% combined yields, respectively (eq 4).

The reaction mechanism of this Ni-catalyzed in situ dehydration reaction is not fully understood at this stage. However, the possibility that the addition of Ph$_2$P(O)H to give adducts **1** followed by a subsequent dehydration to produce **2** is readily ruled out because no dehydration of **1** was observed under the following conditions: (a) Ph$_2$P(O)OH (10 mol %), (b) Ni(PPhMe$_2$)$_4$ (5 mol %), (c) Ni(PPhMe$_2$)$_4$ (5 mol %)/Ph$_2$P(O)OH (10 mol %), or (d) Ni(PPhMe$_2$)$_4$ (5 mol %)/Ph$_2$P(O)OH (10 mol %)/Ph$_2$P(O)H (20 mol %). Furthermore, no dehydration of **1** took place either when it was added to the reaction mixture of Scheme 1 (condition B). Thus, it is clear that **1**, once formed, does not lose water to give **2** under the present reaction conditions.[8]

In summary, a new convenient method for the preparation of phosphinoyl 1,3-butadiens from the readily accessible propargyl alcohols and P(O)-H compounds was developed. Studies on the reaction mechanism and applications to other heteroatom compound additions are now in progress.

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Supporting Information Available: Experimental procedure and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) Surprisingly, a similar in situ dehydration did not take place with a secondary propargyl alcohol 3-butyn-2-ol.

(7) An electron-withdrawing group CF$_3$ completely retarded the formation of the corresponding dehydration products.

(8) The reaction of 2-methyl-1-buten-3-yne with Ph$_2$P(O)H under condition B (Scheme 1) gave a mixture of **2a** and **2b** in 95% combined yield with a ratio of 27:73. This result may indicate that the one-pot generation of phosphinoyl 1,3-butadienes proceeds via a stepwise pathway starting from the dehydration of the propargyl alcohol forming an enyne compound which then reacts with Ph$_2$P(O)H to give the adducts.