Metal-Catalyzed Addition of Phosphine and Methanesulfonic Acid to Alkyne

Mieko Arisawa and Masahiko Yamaguchi*

Department of Organic Chemistry
Graduate School of Pharmaceutical Sciences
Tohoku University, Aoba, Sendai 980-8578, Japan

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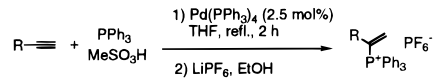
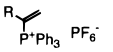
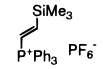
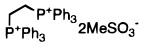
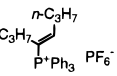
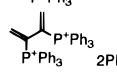
The Wittig reaction is a powerful method of synthesizing olefinic compounds by combining a carbonyl compound and phosphorous ylide.[1] Phosphonium salt, the precursor of the ylide, is generally synthesized by the substitution of an organohalogen compound with triphenylphosphine. If the salt, however, can be prepared by the addition to an unsaturated compound, the scope of the methodology may be considerably broadened. Unsaturated compounds are readily available and are generally inert under the conditions for various organic transformations in which halogen compounds might be affected. We found an unprecedented addition reaction of tertiary phosphine to unactivated alkyne catalyzed by transition metal complexes.[2] The regiochemistry and stereochemistry can be controlled by the judicious choice of the metal catalyst. Alkenylphosphonium salts have various applications in synthetic chemistry,[3] and several methods were developed for their preparation: (1) stepwise dehydrogenation of saturated phosphonium salt,[4] (2) substitution of vinyl halide or triflate with phosphine,[5] and (3) electrochemical oxidation of alkene and phosphine.[6] The present method provides extremely easy access to important organophosphorus compounds using readily available starting materials and catalysts. It may also be worth noting that phosphine, which is generally used as a ligand in the transition-metal-catalyzed reaction, can form P−C bonds with substrates.

1-Hexyne was treated with an equimolar amount of triphenylphosphine and methanesulfonic acid in the presence of Pd(PPh_3)$_4$ (2.5 mol %) in refluxing THF for 2 h. The counteranion was exchanged with PF_6, and recrystallization gave (1-hexen-2-yl)phosphonium salt in a quantitative yield (Table 1, entry 1). The phosphine attacks the internal carbon atom of 1-hexyne regioselectively (Markovnikov mode), and no trace of its isomer is detected by NMR analysis of the crude product. Methanesulfonic acid and the palladium catalyst are essential for the addition reaction, and no reaction occurs in their absence. With this catalyst, the product/catalyst ratio of 500 can be attained in a larger scale reaction (entry 2). The effect of the acid structure is small, and benzenesulfonic acid, *p*-toluenesulfonic acid, *p*-chlorobenzenesulfonic acid, trifluoromethanesulfonic acid, camphorsulfonic acid, and even sulfuric acid can be used equally as well. The catalytic activities of several palladium complexes are compared: Pd(PPh_3)$_4$ (99%), $Pd_2(dba)_3$·$CHCl_3$ (99%), and Pd(OAc)$_2$ (84%) are active, while $PdCl_2(PPh_3)_2$ is inactive. This observation may reflect the ability to form a Pd(0) complex under the reaction conditions. While triphenylphosphine effectively reacts with alkynes, diphenylmethylphosphine and tributylphosphine are inert. Various terminal alkynes react with triphenylphosphine to give the corresponding adducts in high yields with high regioselectivities (entries 1−8). Hydroxy, ester, and nitrile groups are unaffected (entries 6,7, and 8). Trimethylsilylethyne is converted to β-trimethylsilylethenylphosphonium salt in 86% yield (entry 9). Phosphine attacks the terminal carbon atom in this case. When ethyne is used, 1,2-bis(triphenylphosphino)ethane is obtained (entry 10), which may be formed by the conjugate addition of phosphine to the initially generated ethenylphosphonium salt. The internal acetylene, 4-octyne, also reacts with phosphine giving the (*E*)-adduct (entry 11), $^3J_{H-P} = 23.6$ Hz. The introduction of two triphenylphosphine molecules occurs when 1,4-bis(trimethylsilyl)-1,3-butadiyne is reacted with 2.0 equiv of triphenylphosphine (entry 12). Here, the silyl groups are expelled during the reaction.

When a rhodium catalyst [RhCl(cod)]$_2$ (cod = 1,5-cyclooctadiene) or $RhCl(PPh_3)_3$ is used, the observed regioselectivity of the reaction is opposite to that of the palladium-catalyzed reaction (*anti*-Markovnikov mode), as shown in Table 2 (entries 1−4). Treatment of an equimolar mixture of 4-phenyl-1-butyne, triphenylphosphine, and methanesulfonic acid with [RhCl(cod)]$_2$ (1.5

Table 1. Palladium-Catalyzed Addition of PPh_3 and $MeSO_3H$ to Alkyne[a]



Entry	Alkyne	Product	Yield %
	R−≡−H		
1	R = *n*-C_4H_9		96 [b]
2			95
3	R = *n*-C_6H_{13}		92
4	R = $PhCH_2$		91
5	R = $Ph(CH_2)_2$		95
6	R = $HO(CH_2)_2$		91
7	R = *t*-$BuCO_2(CH_2)_2$		89
8	R = $NC(CH_2)_3$		81
9	Me_3Si−≡−H		86
10	H−≡−H		75
11	*n*-C_3H_7−≡−*n*-C_3H_7		92
12	Me_3Si−≡≡−$SiMe_3$		71

[a] See the typical conditions for the reaction. [b] The reaction was conducted in 50 mmol scale using 0.1 mol % of Pd(PPh_3)$_4$, and the product was isolated as $MeSO_3^-$ salt.

(1) Reviews: Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863. Kelly, S. E. Alkene Synthesis. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Chapter 3.1, Vol. 1, p 729.

(2) An uncatalyzed reaction of phosphine and unactivated alkyne giving alkenylphosphine is reported: Barsegyan, S. K.; Gasparyan, G. Ts.; Ovakimyan, M. Zh.; Indzhikyan, M. G. *J. Gen. Chem. USSR* **1990**, *60*, 859. Metal-catalyzed addition reaction of phosphorous compounds possessing P−H bonds: Han, L.-B.; Hua, R.; Tanaka, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 94. Addition of phosphine to activated alkynes: Nozaki, K.; Sato, N.; Ikeda, K. Takaya, H. *J. Org. Chem.* **1996**, *61*, 4516 and references therein.

(3) For recent examples, see: Posner, G. H.; Lu, S.-B. *J. Am. Chem. Soc.* **1985**, *107*, 1424. Okada, Y.; Minami, T.; Yahiro, S.; Akinaga, K. *J. Org. Chem.* **1989**, *54*, 974. Lee, P. H.; Kim, J. S.; Kim, Y. C.; Kim, S. *Tetrahedron Lett.* **1993**, *34*, 7583. Byrley, I. Hewson, A. T. *Tetrahedron Lett.* **1994**, *35*, 7099. Clerici, F.; Gelmi, M. L.; Pocar, D.; Rondena, R. *Tetrahedron* **1995**, *51*, 9985. Bitterer, F.; Kucken, S.; Stelzer, O. *Chem. Ber.* **1995**, *128*, 275. Okuma, K.; Ikari, K.; Ono, M.; Sato, Y.; Kuge, S.; Ohta, H.; Machiguchi, T. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 2313. Shen, Y.; Yao, J. *J. Org. Chem.* **1996**, *61*, 8659. Miedaner, A.; Noll, B. C.; DuBois, D. L. *Organometallics* **1997**, *16*, 5779. Hanamoto, T.; Kiguchi, Y.; Shindo, K.; Matsuoka, M.; Kondo, M. *J. Chem. Soc., Chem. Commun.* **1999**, 151.

(4) Schweizer, E. E.; Bach, R. D. *J. Org. Chem.* **1964**, *29*, 1746. Schweizer, E. E.; Wehman, A. T. *J. Chem. Soc. (C)* **1971**, 343. Saleh, G.; Minami, T.; Ohshiro, Y.; Agawa, T. *Chem. Ber.* **1979**, *112*, 355. Okuma, K.; Ono, M.; Ohta, H. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 1308.

(5) Schweizer, E. E.; Wehman, A. T.; Nycz, D. M. *J. Org. Chem.* **1973**, *38*, 1583. Hinkle, R. J.; Stung, P. J.; Kowalski, M. H. *J. Org. Chem.* **1990**, *55*, 5033. Huang, C.-C.; Duan, J.-P.; Wu, M.-Y.; Liao, F.-L.; Wang, S.-L.; Cheng, C.-H. *Organometallics* **1998**, *17*, 676.

(6) Ohmori, H.; Takanami, T.; Masui, M. *Tetrahedron Lett.* **1985**, *26*, 2199. Ohmori, H.; Takanami, T.; Masui, M. *Chem. Pharm. Bull.* **1987**, *35*, 4960.

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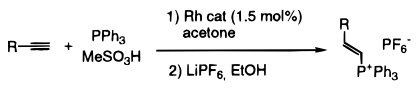
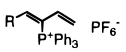
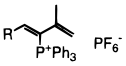
Table 2. Rhodium-Catalyzed Addition of PPh_3 and $MeSO_3H$ to Alkyne



Entry	Alkyne	Conditions[a]	Product	Yield %
	R—≡—H			
1	R = $Ph(CH_2)_2$	A		79
2	R = $PhCH_2$	A		74
3	R = PhMeCH	A		58
4	R = $PhCO_2(CH_2)_2$	A		79
5	R = Ph	B		84
6	R = *p*-ClC_6H_4	B		93
7	R = *m*-ClC_6H_4	B		92
8	R = *p*-MeC_6H_4	B		81
				
9	R = *n*-C_8H_{17}	B		89
10	R = Ph	B		86
				
11	R = *n*-C_8H_{15}	B		93
12	R = Ph	B		94
13		B		91[b]
14		B		76[c]

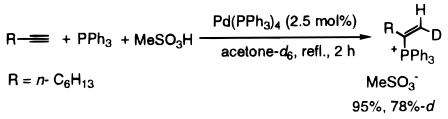
[a] Conditions A: $[RhCl(cod)]_2$, acetone, rt, 12 h. Conditions B: $RhH(PPh_3)_4$, acetone, refl., 12 h. [b] P(*p*-tol)$_3$ was used. [c] P(*p*-ClC_6H_4)$_3$ was used.

mol %) in acetone at room temperature for 12 h yields (*E*)-(4-phenyl-1-butenyl)phosphonium salt predominantly with a small amount of the regiosiomer in a ratio of 10:1. The isomerically pure (*E*)-product is obtained by recrystallization of the PF_6 salt in 79% yield, $^3J_{H-H} = 16.8$ Hz. Under the same conditions $RhH(CO)(PPh_3)_3$ gave only the internal adduct (37% yield). A 1:1 mixture of the regioisomers was obtained with $RhH(PPh_3)_4$ (53% yield). Use of the rhodium chloride complex appears to be critical for the synthesis of the *anti*-Markovnikov product. The reaction at room temperature is also essential to obtain the terminal adduct predominantly, and considerable amounts of the internal adduct are formed at higher temperatures. The regioselectivity may be under kinetic control: An isolated terminal phosphonium salt, (4-phenyl-1-butenyl) triphenylphosphonium salt, does not isomerize to the internal derivative when treated with methanesulfonic acid in the presence of either $[RhCl(cod)]_2$ under acetone reflux or $Pd(PPh_3)_4$ under THF reflux. An internal phosphonium salt, (4-phenyl-1-buten-2-yl)triphenylphosphonium salt, also does not isomerize to the terminal compound in the presence of $[RhCl(cod)]_2$ under acetone reflux.

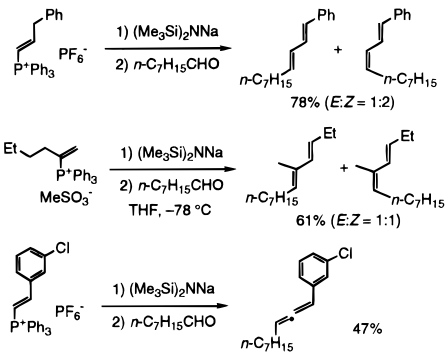
The behavior of the conjugated alkyne slightly differs from that of the aliphatic 1-alkyne. The addition of triphenylphosphine to arylacetylene is effectively catalyzed by $RhH(PPh_3)_4$ (Table 2, entries 5−8), whereas $Pd(PPh_3)_4$ and $[RhCl(cod)]_2$ are not effective at all. The reaction is applicable to phenylacetylenes possessing either electron-donating or electron-withdrawing groups giving the *anti*-Markovnikov products. $RhH(PPh_3)_4$ catalyzes the addition to conjugated enyne compound, yielding (1,3-alkadien-3-yl)phosphonium salt in the Markovnikov mode (entries 9−14). The (*Z*)-stereochemistry indicates the *trans*-addition of proton and phosphine. Tris(*p*-tolyl)phosphine and tris(*p*-chlorophenyl)phosphine also yield the corresponding alkenylphosphonium salts (entries 13 and 14).

The addition of a proton and phosphine generally proceeds via *cis*-addition with the exception of enynes. Accordingly, when 1-octyne was treated with methanesulfonic acid and triphenylphosphine in the presence of $Pd(PPh_3)_4$ in acetone-d_6, the product was obtained in 95% yield with 78% deuteration at the *cis*-vinyl proton of the triphenylphosphinyl group, $^3J_{H-P} = 48.8$ Hz (Scheme 1). H−D exchange probably takes place between the sulfonic acid and the deuterated solvent, generating deuterated sulfonic acid, which transferred D^+ to the alkyne. Two mechanisms are conceivable for the present addition reaction. One involves the oxidative addition of the sulfonic acid to Pd(0) to form a palladium hydride complex, which adds to the carbon−carbon triple bonds. The reductive elimination then takes place, resulting in the alkenylphosphonium salt.[5] Alternatively, phosphinopalladation reaction at 1-alkyne occurs followed by protodepalladation.[7]

Scheme 1



Scheme 2



Applications of the alkenylphosphonium salts in the Wittig synthesis are shown in Scheme 2. The reaction of (3-phenyl-1-propenyl)phosphonium salt with sodium hexamethyldisilazide produced an ylide, and treatment with an aldehyde gave a conjugated diene. Similarly, reaction of (1-hexen-2-yl)phosphonium salt yielded an unsaturated ylide via double bond migration, which reacted with an aldehyde producing methyl-1,3-diene. An allene was obtained from a (2-arylethenyl)phosphonium salt.

Typical procedures for the Markovnikov addition reaction are as follows: Under an argon atmosphere, a mixture of $Pd(PPh_3)_4$ (2.5 mol %, 29 mg), triphenylphosphine (1 mmol, 262 mg), 1-hexyne (1 mmol, 0.12 mL), and methanesulfonic acid (1 mmol, 96 mg) in THF (2 mL) was heated at reflux for 2 h. Then, the solvent was removed under reduced pressure, and the residue was washed with ether. After the crude product was dissolved in ethanol (2 mL), lithium hexafluorophosphate (1.5 mmol, 228 mg) was added, and the mixture was stirred at room temperature for 1 h. The precipitated solid was collected by filtration, and the solid was dissolved in $CHCl_3$ followed by filtration. The solution was concentrated, and the residue was recrystallized from $CHCl_3$ and ether (3:1), yielding (1-hexen-2-yl)triphenylphosphonium hexafluorophosphate (468 mg, 96%) as a colorless solid.

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

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(7) Allen, A., Jr.; Lin, W. *Organometallics* **1999**, *18*, 2922.