ORGANIC LETTERS

2007
Vol. 9, No. 7
1383−1385

Palladium-Catalyzed *anti*-Hydrothiolation of 1-Alkynylphosphines

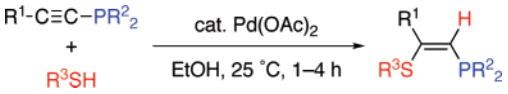
Azusa Kondoh, Hideki Yorimitsu,* and Koichiro Oshima*

Department of Material Chemistry, Graduate School of Engineering, Kyoto University, Kyoto-daigaku Katsura, Nishikyo-ku, Kyoto 615-8510, Japan

yori@orgrxn.mbox.media.kyoto-u.ac.jp; oshima@orgrxn.mbox.media.kyoto-u.ac.jp

Received February 4, 2007

ABSTRACT



Treatment of 1-alkynylphosphine with thiol in the presence of a catalytic amount of palladium acetate results in regio- and stereoselective *anti*-hydrothiolation, yielding the corresponding (*Z*)-1-phosphino-2-thio-1-alkene.

Metal-catalyzed addition of thiols to alkynes (hydrothiolation) is an important reaction for synthesizing 1-alkenyl sulfides under mild conditions.[1,2] In the course of our studies on the use of 1-alkynylphosphines as key starting material for the synthesis of new phosphine ligands,[3] we now report that hydrothiolation of 1-alkynylphosphines proceeds smoothly under palladium catalysis. In general, transition-metal-catalyzed hydrothiolation proceeds in a *syn* fashion.[1,2f,4] In contrast, the present reaction represents a rare example of highly selective *anti*-hydrothiolation.[2d,g,5] The products, (*Z*)-1-phosphino-2-thio-1-alkenes, are a new class of heteroatom-containing compounds and can potentially serve as useful ligands of transition-metal complexes.[6]

Treatment of 1-octynyldiphenylphosphine (**1a**) with dodecanethiol[7] (**2a**) in the presence of a catalytic amount of palladium acetate in ethanol for 1 h at 25 °C provided (*Z*)-1-diphenylphosphino-2-dodecylthio-1-octene (**3aa**) in 87% isolated yield and in 90% NMR yield (Table 1, entry 1).[8,9] Other palladium complexes such as $PdCl_2$ and $Pd_2(dba)_3$ also showed catalytic activity (entries 2 and 3). Nickel chloride and platinum chloride were inferior to palladium chloride (entries 4 and 5). Copper(II) chloride was ineffective (entry 6). The effect of solvent on the reaction was not significant (entries 7−11). The reactions proceeded in nonpolar solvents such as toluene and dichloromethane (entries 8 and 9) as well as in polar DMF (entry 10). It is worth noting that the reaction in water resulted in the highest yield of **3aa** (entry 11), although the reaction was heterogeneous.[10] To guarantee

(1) (a) Ogawa, A. *J. Organomet. Chem.* **2000**, *611*, 463−474. (b) Kondo, T.; Mitsudo, T. *Chem. Rev.* **2000**, *100*, 3205−3220. (c) Kuniyasu, H. In *Catalytic Heterofunctionalization*; Togni, A., Grützmacher, H., Eds.; Wiley-VCH: Weinheim, 2001; Chapter 7. (d) Beller, M.; Seayad, J.; Tillack, A.; Jiao, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 3368−3398. (e) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079−3159.

(2) Very recent examples: (a) Ananikov, V. P.; Malyshev, D. A.; Beletskaya, I. P.; Aleksandrov, G. G.; Eremenko, I. L. *Adv. Synth. Catal.* **2005**, *347*, 1993−2001. (b) Cao, C.; Fraser, L. R.; Love, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 17614−17615. (c) Han, L.-B.; Zhang, C.; Yazawa, H.; Shimada, S. *J. Am. Chem. Soc.* **2004**, *126*, 5080−5081. (d) Burling, S.; Field, L. D.; Messerle, B. A.; Vuong, K. Q.; Turner, P. *Dalton Trans.* **2003**, 4181−4191. (e) Malyshev, D. A.; Scott, N. M.; Marion, N.; Stevens, E. D.; Ananikov, V. P.; Beletskaya, I. P.; Nolan, S. P. *Organometallics* **2006**, *25*, 4462−4470. (f) Ananikov, V. P.; Orlov, N. V.; Beletskaya, I. P. *Organometallics* **2006**, *25*, 1970−1977. (g) Misumi, Y.; Seino, H.; Mizobe, Y. *J. Organomet. Chem.* **2006**, *691*, 3157−3164.

(3) Kondoh, A.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2007**, *129*, doi:10.1021/ja070048d.

(4) (a) Kuniyasu, H.; Ogawa, A.; Sato, K.; Ryu, I.; Kambe, N.; Sonoda, N. *J. Am. Chem. Soc.* **1992**, *114*, 5902−5903. (b) Ogawa, A.; Ikeda, T.; Kimura, K.; Hirao, T. *J. Am. Chem. Soc.* **1999**, *121*, 5108−5114.

(5) Gabriele, B.; Salerno, G.; Fazio, A. *Org. Lett.* **2000**, *2*, 351−352.

(6) Structurally analogous [(*o*-alkylthio)aryl]diphenylphosphines are useful in organometallic chemistry: (a) Kim, J. S.; Reibenspies, J. H.; Darensbourg, M. Y. *J. Am. Chem. Soc.* **1996**, *118*, 4115−4123. (b) Casey, M.; Lawless, J.; Shirran, C. *Polyhedron* **2000**, *19*, 517−520. (c) Reinius, H. K.; Krause, A. O. I. *J. Mol. Catal., A* **2000**, *158*, 499−508. (d) Kongprakaiwoot, N.; Luck, R. L.; Urnezius, E. *J. Organomet. Chem.* **2006**, *691*, 5024−5029.

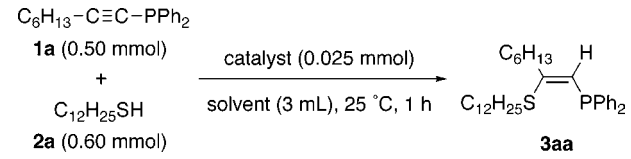
(7) (a) Nishide, K.; Node, M. *J. Synth. Org. Chem., Jpn.* **2004**, *62*, 895−910. (b) Node, M.; Kumar, K.; Nishide, K.; Ohsugi, S.; Miyamoto, T. *Tetrahedron Lett.* **2001**, *42*, 9207−9210.

(8) **Experimental procedure:** Palladium acetate (6 mg, 0.025 mmol) was placed in a 20 mL reaction flask under argon. A solution of **1a** (0.15 g, 0.50 mmol) in ethanol (3.0 mL) was added to the flask. Dodecanethiol (**2a**, 0.12 g, 0.60 mmol) was added, and the resulting solution was stirred for 1 h at 25 °C. The solvent was evaporated under reduced pressure, and the crude product obtained was chromatographed on silica gel to afford **3aa** (0.22 g, 0.44 mmol, 87%).

(9) The perfect *Z* stereoselectivity was observed at the initial stage of the reaction.

10.1021/ol0702876 CCC: $37.00
Published on Web 03/06/2007

Table 1. Hydrothiolation of 1-Octynyldiphenylphosphine (**1a**) with Dodecanethiol (**2a**)



entry	catalyst	solvent	yield (%)[a]
1	$Pd(OAc)_2$	ethanol	90 (87)
2	$PdCl_2$	ethanol	86
3	$Pd_2(dba)_3$[b]	ethanol	85
4	$PtCl_2$	ethanol	78
5	$NiCl_2$	ethanol	58
6	$CuCl_2$	ethanol	17
7	$Pd(OAc)_2$	THF	86
8	$Pd(OAc)_2$	1,2-dichloroethane	89
9	$Pd(OAc)_2$	toluene	89
10	$Pd(OAc)_2$	DMF	79
11	$Pd(OAc)_2$	water	92

[a] Based on ^{31}P NMR analysis. An isolated yield is in parentheses. [b] 0.0125 mmol of $Pd_2(dba)_3$ was used.

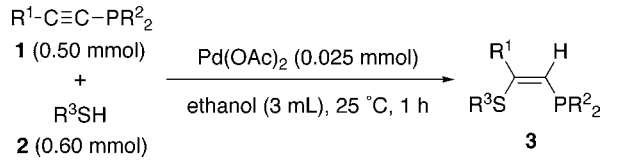
a wide scope of substrates, ethanol was selected as the best solvent.[11]

A variety of 1-alkynylphosphines underwent the hydrothiolation reactions (Table 2). Sterically demanding 1-alkynylphosphines including **1b** and **1c** underwent the hydrothiolation smoothly (entries 1 and 2). Phenylethynylphosphine **1d** as well as terminal ethynylphosphine **1e** afforded the corresponding *anti*-adducts in good yields (entries 3 and 4). A variety of functional groups such as keto and hydroxy groups were compatible under the reaction conditions (entries 5−7). Pyridine-containing **3ia** (entry 8) can be useful for constructing supramolecular architectures. The addition of **2a** to bis(diphenylphosphino)ethyne (**1j**) took place to yield the corresponding *anti*-adduct **3ja** in 55% yield (entry 9). Alkynyldicyclohexylphosphine **1k** also underwent the hydrothiolation, although a longer reaction time was required to complete the reaction (entry 10).

The scope of thiol **2** was satisfactory (entries 11−18). Not only bulky thiol **2b** but also thiols having an additional functionality such as **2e**−**i** added to **1a** under the palladium catalysis. The successful hydrothiolation with protected cysteine **2h** implies that the reaction would be applicable to modification of proteins and peptides (entry 17). The X-ray crystallographic analysis of **3ki** verified the *Z* stereochemistry of the products.[12]

The reaction was efficient enough to allow for multiple hydrothiolations (Scheme 1). Treatment of biphenyl-based

Table 2. Palladium-Catalyzed Hydrothiolation of 1-Alkynylphosphines **1** with Thiols **2**



entry	**1**	R^1	R^2	**2**	R^3	yield (%)[a]
1	**1b**	*t*-Bu	Ph	**2a**	$C_{12}H_{25}$	93 (**3ba**)
2	**1c**	*i*-Pr	Ph	**2a**	$C_{12}H_{25}$	83 (**3ca**)
3	**1d**	Ph	Ph	**2a**	$C_{12}H_{25}$	81 (**3da**)
4	**1e**	H	Ph	**2a**	$C_{12}H_{25}$	78 (**3ea**)
5	**1f**	$EtOOC(CH_2)_6$	Ph	**2a**	$C_{12}H_{25}$	77 (**3fa**)
6[b]	**1g**	*p*-Ac-C_6H_4	Ph	**2a**	$C_{12}H_{25}$	75 (**3ga**)
7	**1h**	PhCH(OH)	Ph	**2a**	$C_{12}H_{25}$	72 (**3ha**)
8	**1i**	3-pyridyl	Ph	**2a**	$C_{12}H_{25}$	78 (**3ia**)
9[c]	**1j**	Ph_2P	Ph	**2a**	$C_{12}H_{25}$	55 (**3ja**)
10[d]	**1k**	Ph	*c*-C_6H_{11}	**2a**	$C_{12}H_{25}$	82 (**3ka**)
11	**1a**	C_6H_{13}	Ph	**2b**	*t*-Bu	62 (**3ab**)
12	**1a**	C_6H_{13}	Ph	**2c**	Ph	82 (**3ac**)
13	**1a**	C_6H_{13}	Ph	**2d**	2-furfuryl	75 (**3ad**)
14	**1a**	C_6H_{13}	Ph	**2e**	cinnamyl	60 (**3ae**)
15	**1a**	C_6H_{13}	Ph	**2f**	*p*-Br-C_6H_4	80 (**3af**)
16	**1a**	C_6H_{13}	Ph	**2g**	$HO(CH_2)_3$	74 (**3ag**)
17	**1a**	C_6H_{13}	Ph	**2h**	*N*-acetylCys[e]	66 (**3ah**)
18[d]	**1k**	Ph	*c*-C_6H_{11}	**2i**	*p*-MeO-C_6H_4	70 (**3ki**)

[a] Isolated yields. [b] 1,2-Dichloroethane was used as a solvent. [c] The reaction was performed with $Pd(OAc)_2$ (0.050 mmol) in ethanol/dichloromethane (2 mL:1 mL) for 16 h. [d] The reaction was performed for 4 h. [e] *N*-Acetyl-L-cysteine was used.

di(alkynylphosphine) **1l** with **2a** in the presence of a catalytic amount of $Pd(OAc)_2$ in 1,2-dichloroethane provided the corresponding bifunctional diphosphine **3la** in good yield. Di(phenylethynyl)phenylphosphine (**1m**) underwent hydrothiolation twice to yield **3ma**. However, attempted 3-fold hydrothiolation of tri(phenylethynyl)phosphine resulted in the formation of mixtures of the corresponding mono-, di-, and triadducts. 1,3-Propanedithiol (**2j**) reacted with **1a** to afford an 81% yield of **3aj**. Such products having multicoordination sites can be useful building blocks for supramolecular architecture.

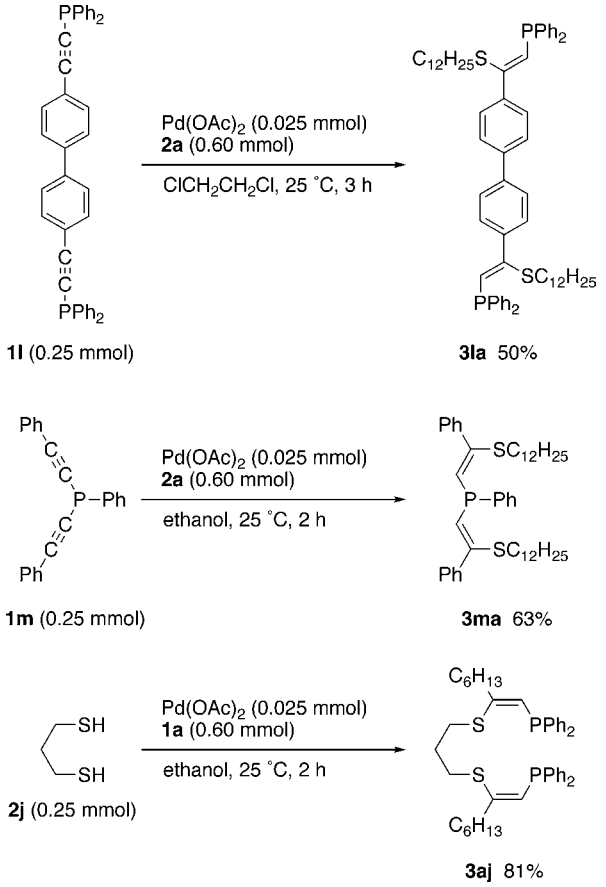
Judging from the regio- and stereoselectivity of the reaction, we are tempted to assume the reaction mechanism as follows (Scheme 2). A palladium salt initially reacts with **1** to generate a palladium(1-alkynylphosphine) complex **4**. Thiol **2** attacks the carbon−carbon triple bond that is activated by the coordination to form intermediate **6**. Protonolysis of **6** affords **3** and regenerates the initial palladium species. The stereochemistry of the products suggests that the reaction should not proceed via oxidative addition of the thiol to a palladium complex followed by thiopalladation or hydropalladation[1,4] but via the coordination-assisted activation of the triple bond. The regioselectivity in the reaction **1g** strongly supports our plausible mechanism that involves the transition state **5**. Without the coordination of the phosphorus center of **1g** to the palladium, the regioselectivity of the reaction of **1g** could be opposite

(10) Some intermolecular addition reactions proceed more efficiently in water even though the substrates are virtually insoluble in water: (a) Kinoshita, H.; Nakamura, T.; Kakiya, H.; Shinokubo, H.; Matsubara, S.; Oshima, K. *Org. Lett.* **2001**, *3*, 2521−2524. (b) Kurahashi, T.; Shinokubo, H.; Osuka, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 6336−6338 and refs cited therein.

(11) No reactions took place in the absence of the catalyst in ethanol or in water.

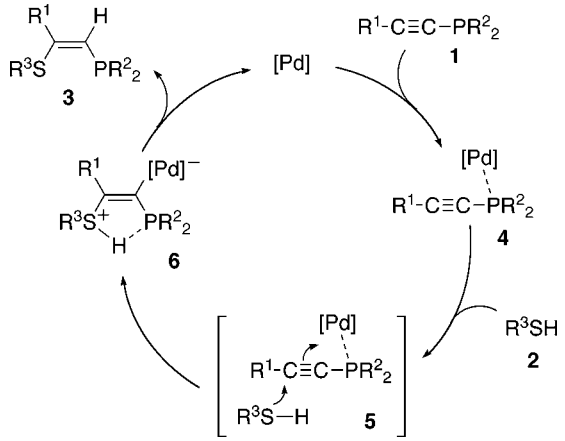
(12) See Supporting Information.

Scheme 1



because of the strong electron-withdrawing nature of the acetyl group. It is also worth noting that the corresponding phosphine oxide of **1a** completely resisted the reaction.

Scheme 2



In summary, we have found a concise method for the synthesis of an array of (*Z*)-1-phosphino-2-thio-1-alkenes through the hydrothiolation of 1-alkynylphosphines. The method will create a new type of heteroatom-containing molecules which find applications in various fields of chemical science.

Acknowledgment. This work was supported by Grants-in-Aid for Scientific Research and COE Research from the Ministry of Education, Culture, Sports, Science, and Technology, Japan. We thank Prof. Masaki Shimizu in the same department for allowing us to use an X-ray diffractometer.

Supporting Information Available: Characterization data of compounds (pdf) and crystallographic data of **3ki** (cif). This material is available free of charge via the Internet at http://pubs.acs.org.

OL0702876