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A Highly Regioselective Cyanothiolation of Alkynes via Oxidative Addition of Thiocyanates to Tetrakis(triphenylphosphine)palladium(0) Catalyst

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Summary: Tetrakis(triphenylphosphine)palladium(0) catalyzes the highly regioselective addition of phenyl thiocyanate (PhSCN) to terminal alkynes, which attains the simultaneous introduction of thio and cyano groups to the internal and terminal positions of alkynes, respectively. This reaction may proceed via the oxidative addition of PhSCN to $Pd(PPh_3)_4$*, which forms* $Pd(SPh)(CN)(PPh_3)_2$ *as the key intermediate.*

Transition-metal-catalyzed reactions of organic silicon, boron, and tin compounds provide very useful methods for selective introductions of heterofunctions as well as carbon−carbon bond forming reactions based on the characteristic features of these heteroatoms.[1] In contrast, the transition-metal-catalyzed reactions of group 16 heteroatom compounds have been largely unexplored, partly because these compounds are believed to be catalyst poisons for transition-metal-catalyzed reactions.[2] In 1991, we disclosed an efficient transition-metal-catalyzed addition of organic disulfides to alkynes,[3] and after this report, several synthetically useful transition-metal-catalyzed addition reactions of organosulfur compounds to unsaturated compounds were developed by us and other groups.[4−6] Herein we report the first example of transition-metal-catalyzed cyanothiolation of terminal alkynes with thiocyanates, which attains simultaneous introduction of both sulfur and cyano groups into carbon−carbon triple bonds with an excellent regioselectivity.

Table 1 indicates the results of catalytic cyanothiolation using several transition metal complexes. Among the complexes examined (entries 1−9), only zerovalent palladium complexes such as $Pd(PPh_3)_4$ indicated a catalytic activity toward the desired cyanothiolation of 1-octyne, and interestingly the corresponding 3-phenylthionon-2-enenitrile was obtained with an excellent regioselectivity (entry 9). To optimize the reaction conditions, the $Pd(PPh_3)_4$-catalyzed cyanothiolation of 1-octyne was examined under several reaction conditions (entries 10−14). The reaction is greatly influenced by the solvent employed. The reaction in CH_3CN resulted in the low yield of the cyanothiolation product (entry 14), whereas the reactions in THF (entry 13) or benzene (entry 11) afforded higher yields. Consequently, upon heating at 120 °C in benzene,[7] the desired product is obtained in good yield with an excellent regioselectivity (entry 11).

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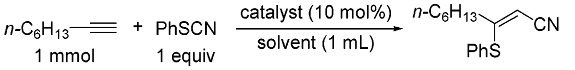
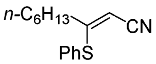
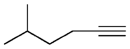
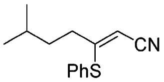
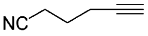
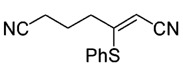
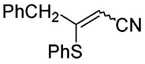
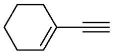
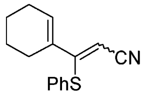
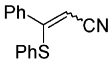
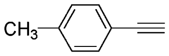
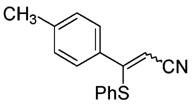
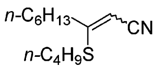
Table 1. Transition-Metal-Catalyzed Cyanothiolation of 1-Octyne[a]



entry	catalyst	solvent	temp, °C	time, h	yield, %[c]
1	$RhH(CO)(PPh_3)_3$	CH_3CN	140	67	0
2[b]		C_6H_6	120	24	0
3	$NiCl_2$	CH_3CN	120	65	0
4[b]		C_6H_6	120	24	0
5[b]	$Pd_2(dba)_3$	C_6H_6	120	24	0
6	$PdCl_2$	C_6H_6	140	62	0
7[b]	$PdCl_2(PPh)_3$	C_6H_6	120	24	0
8[b]	$Pt(PPh_3)_4$	CH_2Cl_2	120	20	0
9	$Pd(PPh_3)_4$	C_6H_6	120	24	12
10	$Pd(PPh_3)_4$	C_6H_6	80	24	9
11	$Pd(PPh_3)_4$	C_6H_6	120	66	61
12	$Pd(PPh_3)_4$	C_6H_6	140	66	49
13	$Pd(PPh_3)_4$	THF	120	66	42
14	$Pd(PPh_3)_4$	CH_3CN	120	66	12

[a] For the detailed procedure of cyanothiolation, see the Supporting Information. [b] Catalyst (3 mol%). [c] Determined by ^{1}H NMR.

Table 2. $Pd(PPh_3)_4$-Catalyzed Cyanothiolation of Terminal Alkynes[a]

entry	alkyne	thiocyanate	product	yield, %[b]	*E/Z*[c]
1	n-C_6H_{13}—≡	PhSCN		61	1/99
2		PhSCN		68[d]	0/100
3		PhSCN		48	0/100
4	$PhCH_2$—≡	PhSCN		48	17/83
5		PhSCN		56	58/42
6	Ph—≡	PhSCN		84	14/86
7[e]		PhSCN		81	12/88
8	n-C_6H_{13}—≡	n-C_4H_9SCN		9	—[f]

[a] Reaction conditions: $Pd(PPh_3)_4$ (10 mol%), alkyne (1.0 mmol), thiocyanate (1.0 mmol), 120 °C, 66 h, benzene (1 mL) (method A: entries 1−3 and 8), without benzene (method B: entries 4−7). [b] Isolated yield. [c] *E*/*Z* ratios were determined by differential NOE mesurements. [d] Determined by ^{1}H NMR. [e] 20 h. [f] Not determined.

Table 2 represents the results of $Pd(PPh_3)_4$-catalyzed cyanothiolation of terminal alkynes under the optimized reaction conditions. This procedure can be applied to both aliphatic and aromatic alkynes. 1-Octyne and 5-methyl-1-hexyne underwent palladium-catalyzed highly regio- and stereoselective cyanothiolation, providing the corresponding (2*E*)-3-phenylthioalk-2-enenitrile in good yields (entries 1 and 2). Functionalities such as cyano and olefinic groups tolerated the reaction conditions (entries 3 and 5). Although the cyanothiolation of phenylacetylene in solvent proceeds very slowly, the reaction in the absence of solvent takes place much more smoothly (84%, entry 6). Similarly, the reaction of 4-ethynyltoluene in the absence of benzene afforded the cyanothiolation product in good yield (81%, entry 7). On the other hand, the addition of aliphatic thiocyanate such as *n*-butyl thiocyanate resulted in a fairly low yield of the cyanothiolation product (entry 8).

To get some information about the real catalyst in this cyanothiolation reaction, an equimolar reaction of $Pd(PPh_3)_4$ with PhSCN in benzene was conducted at room temperature, which provided a yellow solid (complex **A**) [eq 1].

$$\mathrm{Pd(PPh_3)_4} + \underset{\text{1 equiv}}{\mathrm{PhSCN}} \xrightarrow[\text{benzene, rt}]{} \underset{\text{complex }\mathbf{A}}{\mathrm{Pd(SPh)(CN)(PPh_3)_2}} \quad (1)$$

From the IR spectrum of complex **A**, the CN bond absorption was observed clearly and the elemental analysis strongly suggested the formation of $Pd(SPh)(CN)(PPh_3)_2$.[8] These results impelled us to focus on the crystal structure of complex **A**, and we obtained the X-ray crystal structure of complex **A** (Figure 1).[9] This tetracoordinated palladium complex bears −SPh and −CN groups in the trans position in an almost square arrangement. Intramolecular $\pi-\pi$ interaction between two phenyl groups (S−*Ph* and P(2)−*Ph*) was observed. This result indicates the first example where the oxidative addition of PhSCN to $Pd(PPh_3)_4$ proceeds with the cleavage of a sulfur−cyano bond (PhS−CN) not a carbon−sufur bond (Ph−SCN).[10]

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[6] For transition-metal-catalyzed reactions which attain simultaneously introduction of sulfur functions and carbon−carbon bond formation, see: (a) Kuniyasu, H.; Ogawa, A.; Miyazaki, S.; Ryu, I.; Kambe, N.; Sonoda, N. *J. Am. Chem. Soc.* **1991**, *113*, 9796−9893. (b) Ogawa, A.; Takeba, M.; Kawakami, J.; Ryu, I.; Kambe, N.; Sonoda, N. *J. Am. Chem. Soc.* **1995**, *117*, 7564−7565. (c) Ogawa, A.; Kawakami, J.; Mihara, M.; Ikeda, T.; Sonoda, N.; Hirao, T. *J. Am. Chem. Soc.* **1997**, *119*, 12380−12381. (d) Xiao, W.-J.; Vasapollo, G.; Alper, H. *J. Org. Chem.* **1999**, *64*, 9646−9652. (e) Xiao, W.-J.; Vasapollo, G.; Alper, H. *J. Org. Chem.* **2000**, *65*, 4138−4144. (f) Hua, R.; Takeda, H.; Onozawa, S.; Abe, Y.; Tanaka, M. *J. Am. Chem. Soc.* **2001**, *123*, 2899−2900. (g) Sugoh, K.; Kuniyasu, H.; Sugae, T.; Ohtaka, A.; Takai, Y.; Tanaka, A.; Machino, C.; Kambe, N.; Kurosawa, H. *J. Am. Chem. Soc.* **2001**, *123*, 5108−5109. (h) Kawakami, J.; Mihara, M.; Kamiya, I.; Takeba, M.; Ogawa A.; Sonoda, N. *Tetrahedron* **2003**, *59*, 3521−3526. (i) Kawakami, J.; Takeba, M.; Kamiya, I.; Sonoda, N.; Ogawa, A. *Tetrahedron* **2003**, *59*, 6559−6567. (j) Kuniyasu, H.; Kurosawa, H. *Chem. Eur. J.* **2002**, *8*, 2661−2665. (k) Knapton, D. J.; Meyer, T. Y. *Org. Lett.* **2004**, *6*, 687−689. (l) Knapton, D. J.; Meyer, T. Y. *J. Org. Chem.* **2005**, *70*, 785−796. (m) Hirai, T.; Kuniyasu, H.; Kambe, N. *Chem. Lett.* **2004**, *33*, 1148−1150. (n) Hirai, T.; Kuniyasu, H.; Kambe, N. *Tetahedron Lett.* **2005**, *46*, 117−119. (o) Kuniyasu, H.; Kato, T.; Asano, S.; Ye, J. H.; Ohmori, T.; Morita, M.; Hiralke, H.; Fujiwara, S.; Terao, J.; Kurosawa, H.; Kambe, N. *Tetrahedron Lett.* **2006**, *47*, 1141−1144.

[7] See Supporting Information (method A).

[8] For yellow solid: anal. calcd (%) for $C_{43}H_{35}NP_2PdS$: C 67.41, H 4.60, N 1.83; found: C 67.89, H 4.66, N 1.97; IR (KBr) $\nu = 2130$ (CN) cm^{-1}; 79% yield, mp 229−230 °C; ^{31}P NMR (500 MHz, $CDCl_3$) δ 26.2.

[9] Crystallographic data for complex **A**: $Pd(SPh)(CN)(PPh_3)_2\cdot H_2O$, monoclinic, $P2_1/c$ (#14), $a = 18.859(2)$ Å, $b = 9.659(1)$ Å, $c = 21.970(2)$ Å, $\beta = 105.588(5)°$, $V = 3854.8(8)$ Å^3, $Z = 4$, $D_{calc} = 1.351$ g/cm^3. The intensity data were collected at 23 °C on a Rigaku RAXIS imaging plate area detector with graphite-monochromated Mo Kα radiation. The 34 726 independent reflections were measured over a 2θ range of 6.0−55.0°. All non-hydrogen atoms were refined anisotropically. Full matrix least-squares refinement using 4454 reflections converged to final agreement factors R_1-$[I > 3\sigma(I)] = 0.042$, w$R_2[I > 3\sigma(I)] = 0.049$ with GOF = 1.017. The structure was solved by direct methods using SIR92 and refined by full-matrix least squares on *F*. Drawings were generated using ORTEP-III (Burnett & Johnson, 1996). Selected bond lengths (Å): Pd(1)−S(1) 2.338(1), Pd(1)−C(43) 1.980(4), Pd(1)−P(1) 2.339(1), Pd(1)−P(2) 2.327(1); angles (deg): P(1)−Pd(1)−S(1) 92.49(5), P(2)−Pd(1)−S(1) 84.38(5), P(1)−Pd(1)−C(2) 88.0(2), P(2)−Pd(1)−C(2) 95.0(2), P(1)−Pd(1)−P(2) 176.32(4), S(1)−Pd(1)−C(2) 178.5(1).

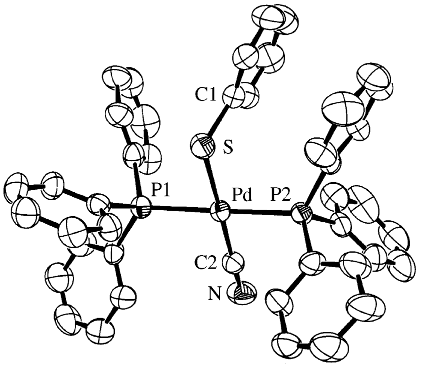
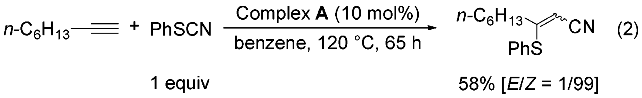


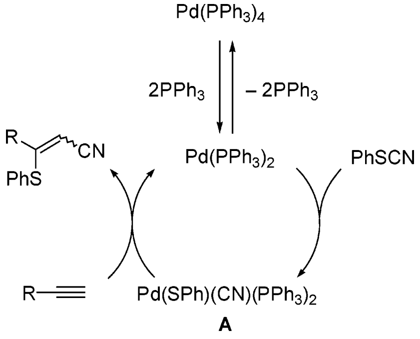
Figure 1. Morecular structure of Pd(SPh)(CN)$(PPh_3)_2$.

Furthermore, the reaction of phenyl thiocyanate with 1-octyne using complex **A** as a catalyst afforded the corresponding cyanothiolation product in 58% yield, regioselectively [eq 2].[11]



These results suggest that complex **A** reacts with alkynes to give the cyanothiolation product probably via either a thiopalladation or a cyanopalladation process, followed by reductive elimination, as shown in Scheme 1.

Scheme 1. A Possible Reaction Pathway for Cyanothiolation



In summary, we have developed the highly selective palladium-catalyzed cyanothiolation of terminal alkynes with thiocyanates. The reaction proceeds via oxidative addition of thiocyanates to palladium(0), which was clearly indicated by the first X-ray crystal structure analysis of the intermediate complex (Pd(SPh)(CN)$(PPh_3)_2$). This process provides a useful method for the catalytic introduction of both thio and cyano groups into the internal and terminal positions of alkynes, respectively, with excellent regioselectivities.

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Supporting Information Available: Experimental procedures and spectral and analytical date. This material is available free of charge via the Internet at http://pubs.acs.org.

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[11] Atempted stoichiometric reaction of complex **A** with 1-octyne did not proceed. This fact suggests that the reductive elimination step may be the rate-determining step, because the presence of excess amounts of PhSCN in this reaction of complex **A** with 1-octyne affords the corresponding cyanothiolation products.