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# Palladium-Catalyzed Alkynylthiolation of Alkynes with Triisopropylsilylethynyl Sulfide

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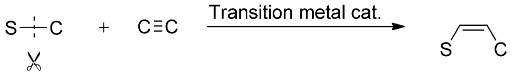
Addition of a carbon–sulfur σ bond to alkynes, carbothiolation of alkynes, under transition metal catalysis is among the most useful methods for the synthesis of organosulfur compounds as the reaction can directly provide various alkenyl sulfides of some complexity (Scheme 1).[1] Recently, several groups have reported various types of carbothiolation, such as arylthiolation,[2] alkenylthiolation,[3] allylthiolation,[4] and acylthiolation.[5,6] However, the addition of alkynyl sulfides to alkynes has not been well documented[7,8] although alkynylthiolation is expected to be a straightforward route to 1-thio-1,3-enynes, which are potentially valuable and versatile yet difficult-to-synthesize intermediates.

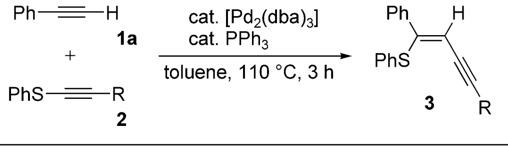


Scheme 1. Carbothiolation of alkynes by cleavage of carbon–sulfur bond.

Very recently, our group and Jiang's group have independently reported haloalkynylation reactions of alkynes with 1-halo-1-alkyne under palladium catalysis to obtain ($Z$)-1-halo-1,3-enyne.[9] Along this line, we report herein addition of silyl-substituted alkynyl sulfides to alkynes under palladium catalysis. This new addition reaction has a broader scope of acceptor alkynes, including aryl-, alkenyl-, and alkyl-substituted terminal alkynes and internal alkynes. The resulting alkenyl sulfides are expected to undergo reactions characteristic of organosulfur compounds, thus providing more complex skeletons such as multisubstituted olefins and thiophenes.[1,10]

Treatment of phenylacetylene (**1a**) with triisopropylsilylethynyl phenyl sulfide (**2a**, 1.2 equiv) in the presence of catalytic amounts of $[Pd_2(dba)_3]$ (dba = dibenzylideneacetone) and triphenylphosphine in toluene at 110 °C for 3 hours afforded the corresponding ($Z$)-1-phenylthio-1,3-enyne **3aa** in 63 % yield (Table 1, entry 1). The reaction proceeded with perfect regio- and stereoselectivities, which were clarified by X-ray crystallographic analysis (vide infra). Polar solvents, such as $N,N$-dimethylformamide (DMF), decreased the yields, and most of the starting materials were recovered un-

Table 1. Palladium-catalyzed addition of alkynyl sulfides to phenylacetylene (**1a**).[a]



| Entry | 2 | R | 3 | Yield [%] |
|---|---|---|---|---|
| 1 | **2a** | $SiiPr_3$ | **3aa** | 63 |
| 2 | **2b** | $SiEt_3$ | **3ab** | 27 |
| 3 | **2c** | $SitBuMe_2$ | **3ac** | 22 |
| 4 | **2d** | Mes | **3ad** | 57 |
| 5 | **2e** | *t*Bu | **3ae** | 27 |
| 6 | **2f** | Ph | **3af** | < 10 |
| 7 | **2g** | *n*Hex | **3ag** | < 10 |

[a] Conditions: **1a** (0.50 mmol), **2** (0.60 mmol), $[Pd_2(dba)_3]$ (0.0125 mmol), $PPh_3$ (0.050 mmol), toluene (2 mL).

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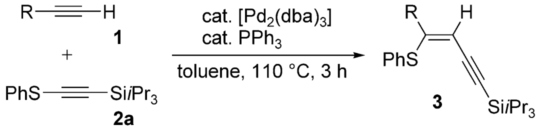
changed. The molar ratio of palladium/phosphine had a significant influence on yield, and a ratio of 1:2 was the best.[11] [$Pd_2(dba)_3$] was the best precursor, and palladium(II) complexes, such as $Pd(OAc)_2$, were much less active.

In analogy with our previous report,[9a] the triisopropylsilyl group of **2a** was essential to attain satisfactory yields. The reactions of the triethylsilyl analog **2b** and the *tert*-butyldimethylsilyl analog **2c** furnished the corresponding products **3ab** and **3ac** in lower yields (Table 1, entries 2 and 3). We assume that the fairly large triisopropylsilyl group would play an important role to sterically prevent the C–C triple bond of **2** from undergoing undesired side reactions. Similar trends were observed in the reactions of alkyl- and aryl-substituted **2** (**2d** vs. **2f** and **2e** vs. **2g**). In particular, the mesityl-substituted alkynyl sulfide **2d** was converted into the corresponding adduct in good yield (Table 1, entry 4). The mesityl group would more effectively shield the adjacent triple bond than the *tert*-butyl, phenyl, and hexyl groups. Triisopropylsilyl protection is necessary for **2** as the silyl group can be subjected to a wide range of useful transformations, whereas the mesityl group is virtually useless.

A variety of terminal alkynes efficiently underwent the palladium-catalyzed addition reaction (Table 2). The electron-deficient arylacetylenes underwent the addition to yield product **3ba** in 56% yield (Table 2, entry 1). Exceptionally, tricyclohexylphosphine ($PCy_3$) proved to be the best ligand for the reactions of phenylacetylene **1a** and *para*-trifluoromethylphenylacetylene **1b** (Table 2, entries 2 and 3).[11] The reaction of *para*-chlorophenylacetylene **1c** provided the corresponding adduct in good yield, thus leaving the chloro moiety intact (Table 2, entry 4). The acceptor acetylenes are not limited to arylacetylenes. 1,3-Enyne **1e** also underwent the reaction to yield the corresponding 3,5-dien-1-yne **3ea** (Table 2, entry 6). Although aliphatic alkynes such as 1-octyne (**1f**) participated in this reaction (Table 2, entry 7), *tert*-butylacetylene (**1g**) was less reactive probably owing to its steric bulkiness (Table 2, entry 8). Notably, an unprotected hydroxy group was tolerated under the reaction conditions (Table 2, entry 9).

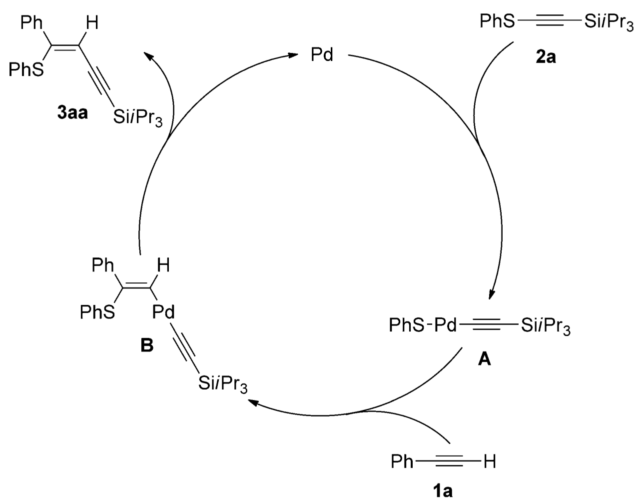
Table 2. Palladium-catalyzed addition of triisopropylsilylethynyl phenyl sulfide (**2a**) to terminal alkynes.[a]



| Entry | 1 | R | 3 | Yield [%] |
|---|---|---|---|---|
| 1 | **1b** | $p$-$CF_3$-$C_6H_4$ | **3ba** | 56 |
| 2[b] | **1a** | Ph | **3aa** | 88 |
| 3[b] | **1b** | $p$-$CF_3$-$C_6H_4$ | **3ba** | 89 |
| 4 | **1c** | $p$-Cl-$C_6H_4$ | **3ca** | 62 |
| 5 | **1d** | 2-Naphthyl | **3da** | 81 |
| 6 | **1e** | $CH_2$=CMe | **3ea** | 69 |
| 7 | **1f** | *n*Hex | **3fa** | 88 |
| 8 | **1g** | *t*Bu | **3ga** | 41 |
| 9 | **1h** | $HO(CH_2)_9$ | **3ha** | 84 |

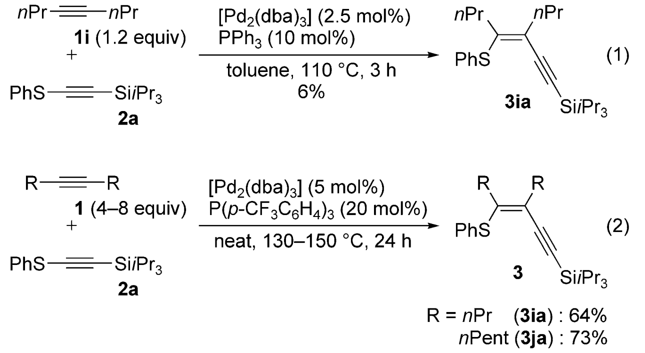
[a] Conditions: **1** (0.50 mmol), **2a** (0.60 mmol), [$Pd_2(dba)_3$] (0.0125 mmol), $PPh_3$ (0.050 mmol), toluene (2 mL). [b] $PCy_3$ (0.050 mmol) was used.

A proposed mechanism for the palladium-catalyzed addition of **2a** to alkynes **1a** is illustrated in Scheme 2. Oxidative addition of **2a** onto zero-valent palladium would afford alkynylpalladium phenylthiolate **A** by selective cleavage of the C(sp)–S bond.[12] The selective cleavage would result from the favorable coordination of the alkyne moiety of **2a** to the palladium center prior to the oxidative addition.[13] Subsequent regio- and stereoselective insertion of alkyne **1a** into the Pd–S bond would occur to yield alkenylalkynylpalladium **B. B** would be selectively formed by the migration of the phenylthio group onto the alkyne with the triphenylphosphine-coordinated bulkier palladium bound at the sterically less hindered terminal carbon. Reported stoichiometric investigations of the insertion of alkynes into a sulfur–metal bond[14] are suggestive of this mechanism although the pathway through alkynylpalladation of alkyne instead of the thiopalladation would be also conceivable.[15] Finally, reductive elimination proceeds to furnish the alkynylthiolation product and generates the initial palladium complex.



Scheme 2. A proposed mechanism.

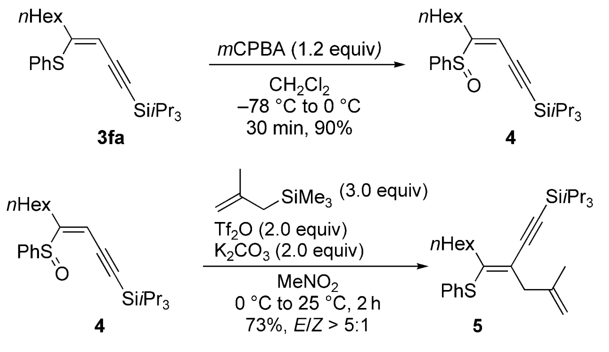
Attempted alkynylthiolation of an internal alkyne, instead of terminal alkynes, resulted in very low yield [Scheme 3, Eq. (1)]. The sterically hindered C–C triple bond of an internal alkyne would hamper the insertion step. In order to accelerate the slow, presumably rate-determining, bimolecular elementary reaction, the same reaction was investigated at higher temperatures in higher concentrations of alkyne. After extensive screening of reaction conditions, we were glad to find that treatment of **2a** with 4-octyne (**1i**, 8 equiv) at 130 °C for 24 hours without using any solvents afforded the corresponding (*Z*)-1-phenylthio-1,3-enyne **3ia** in 64% yield [Scheme 3, Eq. (2)]. When less volatile 6-dodecyne (**1j**, 4 equiv) was used at 150 °C, the target adduct **3ja** was obtained in a higher yield of 73%. It is of note that the reac-



Scheme 3. Palladium-catalyzed addition of triisopropylsilylethynyl phenyl sulfide (**2a**) to internal alkynes.

tion of terminal alkynes under the solvent-free conditions resulted in the formation of oligomers of starting alkynes.

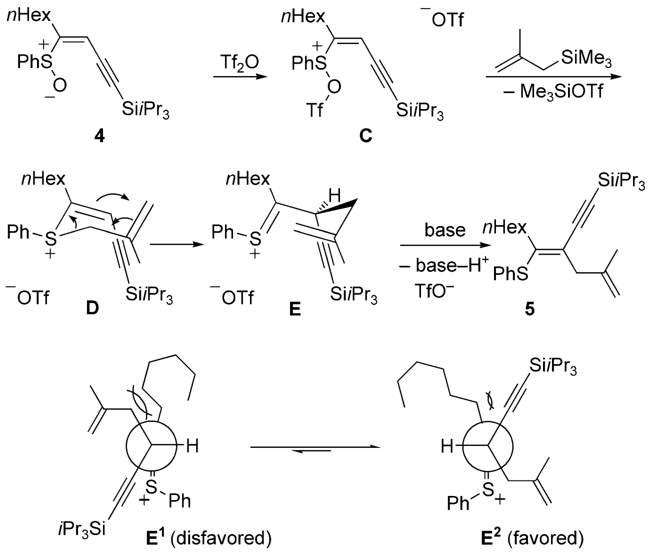
Vinylic sulfur compounds **3** are useful synthetic intermediates, and Scheme 4 demonstrates an example of the utility that we have developed. After monoxidation of **3 fa** with



Scheme 4. Transformations of **3 fa**.

*meta*-chloroperoxybenzoic acid (*m*CPBA), a Pummerer-type reaction[16] of the alkenyl sulfoxide **4** was performed by using allylic silane. Treatment of **4** with methallyltrimethylsilane, trifluoromethanesulfonic anhydride, and potassium carbonate in nitromethane afforded allylated product **5** in good yield. Notably, the reaction proceeded largely with inversion of configuration and the formation of the *E* isomer predominated, which was determined by NOE analysis.[17]

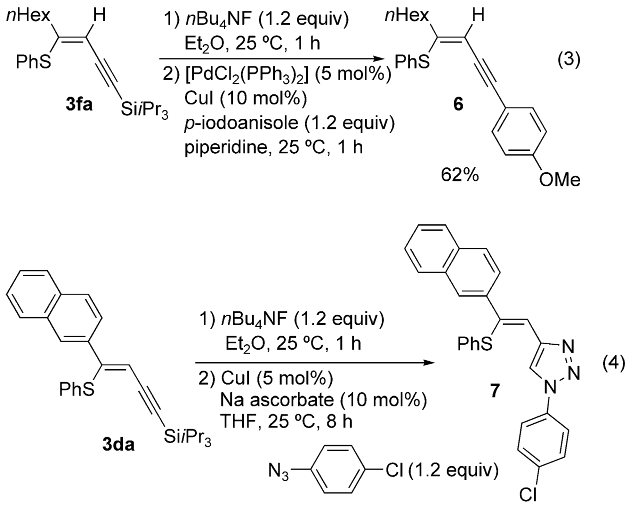
Scheme 5 rationalizes the stereoselectivity of the reaction. Treatment of **4** with trifluoromethanesulfonic anhydride should give sulfonium salt **C**.[16,18] Methallylsilane would then attack the cationic sulfur along with liberation of trimethylsilyl triflate to afford sulfonium salt **D**.[18c,19] Sulfonium salt **D** would then undergo [3,3]-sigmatropic rearrangement via a chairlike transition state, followed by deprotonation, to afford **5**.[19c,20] During the deprotonation from intermediate **E**, two possible conformations, **E**$^1$ and **E**$^2$, should be considered from a stereoelectronic viewpoint, in which the cleaving carbon–hydrogen bond and the carbon–sulfur double bond are perpendicular. The steric repulsion between the hexyl group and methallyl group in **E**$^1$ would be larger than



Scheme 5. Mechanism of allylation.

that between the hexyl and the alkynyl groups in **E**$^2$. The following deprotonation would occur preferably from **E**$^2$ to yield the *E* isomer selectively. The methallylation represents the first general intermolecular vinylogous Pummerer reaction of alkenyl sulfoxide,[21,22] which is a useful method for constructing highly substituted alkenes.

As the stereochemistry of product **3** was ambiguously determined by the NOE analysis of **3 fa**,[17] we tried to confirm the precise configuration by X-ray crystallographic analysis. First, desilylation of product **3 fa** followed by Sonogashira coupling afforded **6** in good yield [Scheme 6, Eq. (3)]. Unfortunately, attempts to obtain single crystals of **6**[23] resulted in failure. Next, the desilylated product of **3 da** was subjected to a cycloaddition reaction with aryl azide[24] to give triazole **7** [Scheme 6, Eq. (4)]. Triazole **7** eventually formed crystals for crystallographic analysis,[25] and these crystals



Scheme 6. Reactions performed for unambiguous determination of the configuration of **3**.

provide clear evidence of the *syn*-alkynylthiolation process (Figure 1).

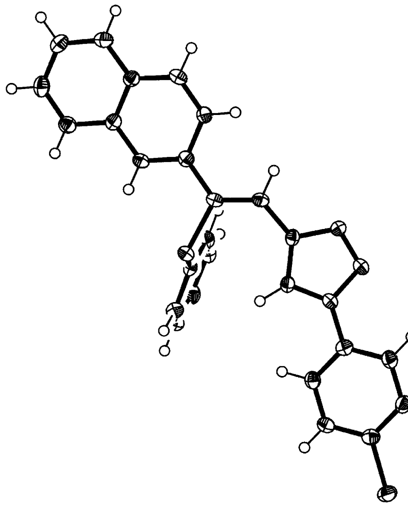


Figure 1. ORTEP diagram of **7**.

We have developed the *syn*-addition reaction of the carbon–sulfur bond of alkynyl sulfide to alkynes under palladium catalysis. The products, (*Z*)-1-thio-1,3-enynes, are demonstrated to be useful building blocks for the synthesis of polysubstituted 1,3-enynes, especially by monoxidation followed by an unusual allylation reaction with allylic silane. Studies on the application of this reaction to the synthesis of complex molecules such as multisubstituted thiophenes[6] are under investigation.

## Experimental Section

*Typical procedure for palladium-catalyzed addition of silyl-substituted alkynyl sulfides to terminal alkynes*

[$Pd_2(dba)_3$] (11 mg, 0.0125 mmol) was placed in a 20 mL reaction flask under nitrogen. Tricyclohexylphosphine (1.0 M in toluene, 50 μL, 0.050 mmol) and toluene (1.0 mL) were added, and the mixture was stirred for 15 min. Phenylacetylene (**1a**, 51 mg, 0.50 mmol), triisopropylsilylethynyl phenyl sulfide (**2a**, 170 mg, 0.60 mmol), and toluene (1.0 mL) were sequentially added, and the resulting mixture was heated at 110 °C for 3 h. After the reaction mixture was cooled to room temperature, the reaction was quenched with water. The product was extracted with hexane (10 mL) three times. The combined organic layers were dried over anhydrous sodium sulfate and concentrated in vacuo. Purification on silica gel (eluted with hexane) provided **3aa** (170 mg, 0.44 mmol) in 88 % yield as a yellow oil.

*Typical procedure for palladium-catalyzed addition of silyl-substituted alkynyl sulfides to internal alkynes*

[$Pd_2(dba)_3$] (23 mg, 0.025 mmol) and tris(*p*-trifluoromethylphenyl)phosphine (47 mg, 0.10 mmol) were placed in a 20 mL reaction flask under nitrogen. 6-Dodecyne (**1j**, 83 mg, 0.50 mmol) and triisopropylsilylethynyl phenyl sulfide (**2a**, 580 mg, 2.0 mmol) were sequentially added, and the resulting mixture was heated at 150 °C for 24 h. After cooling, purification on silica gel (eluted with hexane) provided **3ja** (170 mg, 0.37 mmol) in 73 % yield as an oil.

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**Keywords:** addition · alkynyl sulfide · alkynylthiolation · enyne · palladium

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[25] Crystallographic data for **7**: $C_{26}H_{18}ClN_3S$, $M=439.94$, monoclinic, $P2_1/c$ (No. 14), $a=15.6272(8)$ Å, $b=6.1312(2)$ Å, $c=22.6906(11)$ Å, $\beta=110.847(3)°$, $V=2031.73(16)$ Å$^3$, $Z=4$, $T=93$ K, $\rho_{calcd}=1.438$ g cm$^{-3}$, $R_1=0.0642$ ($I>2\sigma(I)$), $wR_2=0.1397$ (all data), GOF = 1.090. CCDC 805498 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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