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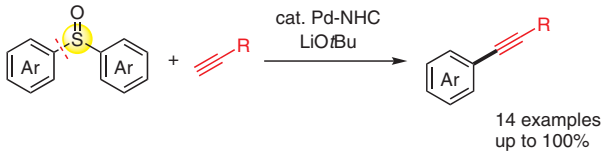
C–S Bond Alkynylation of Diaryl Sulfoxides with Terminal Alkynes by Means of a Palladium–NHC Catalyst

Yuto Yoshida
Keisuke Nogi
Hideki Yorimitsu*

Department of Chemistry, Graduate School of Science, Kyoto University, Sakyo-ku, Kyoto 606-8502, Japan
yori@kuchem.kyoto-u.ac.jp



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Abstract Sonogashira–Hagihara-type alkynylation of diaryl sulfoxides with unactivated terminal alkynes has been developed. With a combination of a palladium–NHC catalyst and LiO*t*Bu as a base, a series of diaryl sulfoxides were converted into the alkynylated products via C–S bond cleavage.

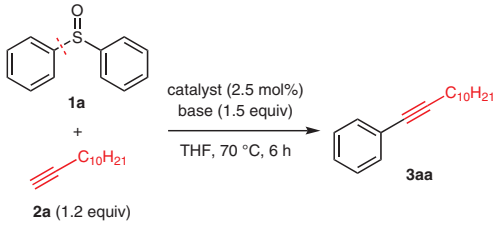
Key words C–S bond alkynylation, palladium catalyst, aryl sulfoxide, alkyne

Arylalkynes are important structural motifs in organic chemistry owing to the unique properties of C–C triple bonds. Collective efforts have been directed toward development of efficient and versatile protocols for the synthesis of arylalkynes.[1] Sonogashira–Hagihara-type alkynylation[1,2] is considered as a prevailing synthetic route to arylalkynes from aryl electrophiles and terminal alkynes. In analogy with other cross-coupling reactions, the scope of usable aryl electrophiles has been expanding beyond reactive aryl iodides and bromides. Indeed, alkynylation of aryl tosylates,[3] mesylates,[4] and fluorides,[5] and decarbonylative alkynylation of aryl esters[6] have been recently reported.

On the other hand, Sonogashira–Hagihara-type alkynylation of C–S bonds has been only sporadically investigated due to the robustness of the C–S bonds. Therefore, usable substrates are limited to activated organosulfur compounds such as azaaryl sulfides[7] and mercaptoazaarenes.[8] Very recently, we reported alkynylation of common aryl sulfides such as methyl phenyl sulfide with the aid of an electron-rich palladium–NHC (*N*-heterocyclic carbene) catalyst.[9] However, highly reactive alkynylmagnesium reagents were indispensable as the alkynylating reagents.

To accomplish Sonogashira–Hagihara-type alkynylation with more general organosulfur compounds, we focused on aryl sulfoxides as electrophilic substrates. Owing to the electron deficiency of the sulfoxide unit, their C–S(=O) bonds should be more readily cleavable than those of aryl sulfides. Inspired by our recent borylation[10] and arylation[11] of aryl sulfoxides, we have addressed alkynylation of aryl sulfoxides with unactivated terminal alkynes.

Table 1 Optimization of reaction conditions



Entry	Catalyst	Base	NMR yield of **3aa** (%)
1	SPhos Pd G2	NaO*t*Bu	0
2	XPhos Pd G2	NaO*t*Bu	0
3	$Pd(PPh_3)_4$	NaO*t*Bu	0
4	$PdCl_2(dppf)$	NaO*t*Bu	0
5	Pd-PEPPSI-IPr	NaO*t*Bu	51
6	SingaCycle-A1	NaO*t*Bu	39
7	SingaCycle-A3	NaO*t*Bu	61
8	Pd–PEPPSI–SIPr	NaO*t*Bu	90
9	Pd–PEPPSI–SIPr	LiO*t*Bu	99
10	Pd–PEPPSI–SIPr	KO*t*Bu	1
11	Pd–PEPPSI–SIPr	Li_2CO_3	0
12	Pd–PEPPSI–SIPr	Li_3PO_4	0
13	Pd–PEPPSI–SIPr	$LiN(SiMe_3)_2$	0
14[a]	Pd–PEPPSI–SIPr	NEt_3	0

[a]5 mol% CuI was added.

Our study began with alkynylation of diphenyl sulfoxide (**1a**) with 1-dodecyne (**2a**) as a model reaction. In the presence of NaO*t*Bu as a base, an array of palladium catalysts were screened (Table 1). SPhos Pd G2[12] (Figure 1), which showed good catalytic activity for our previous borylation

of diaryl sulfoxides,[10] did not afford the desired coupling product **3aa** at all (Table 1, entry 1). Other phosphine-ligated palladium complexes were also ineffective (Table 1, entries 2–4). To our delight, IPr (1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene)-ligated Pd–PEPPSI–IPr[13] gave **3aa** in 51% yield (Table 1, entry 5). After further screening of palladium–NHC complexes, we found Pd–PEPPSI–SIPr (SIPr = 1,3-bis(2,6-diisopropylphenyl)imidazolidin-2-ylidene) to be optimal, and **3aa** was obtained in 90% yield (Table 1, entry 8). The alkynylation heavily depends on the base, and the product was obtained quantitatively with Li-O*t*Bu (Table 1, entry 9). In sharp contrast, the yield of **3aa** was dramatically decreased with KO*t*Bu (Table 1, entry 10). In that case, isomerization of 1-dodecyne (**2a**) to 2-dodecyne occurred,[14] which would be one reason for the very low yield of **3aa**. Other lithium bases were totally ineffective (Table 1, entries 11–13). Triethylamine, a typical base for Sonogashira–Hagihara-type alkynylation, also did not afford **3aa** even in the presence of a copper co-catalyst (Table 1, entry 14).

Having identified optimal reaction conditions (Table 1, entry 9), we then investigated the scope of aryl sulfoxides and terminal alkynes (Scheme 1).[15] Trifluoromethyl-substituted electron-deficient aryl sulfoxide **1b** smoothly reacted with 1-octyne (**2b**) to afford **3bb** in 88% yield. In contrast, electron-rich aryl sulfoxide **1c** furnished **3cb** only in 14% NMR yield. We infer that the electron-donating MeO group would suppress the oxidative addition of the C–S(=O) bond. Steric congestion also hampered the coupling reaction; di-*o*-tolyl sulfoxide (**1d**) was reluctant to undergo the coupling. As a heteroaryl sulfoxide, di-2-benzofuryl sulfoxide (**1f**) coupled with methyl propargyl ether (**1c**) albeit the yield of the product **3fc** was low. Notably, our alkynylation selectively proceeded at C–S(=O) bonds, and potentially reactive C–SMe and C–Cl bonds were compatible to afford **3gc**, **3hc**, and **3id** in 67%, 64%, and 70% yields, respectively. Cyano and *tert*-butoxycarbonyl units on **3ae** and **3if** remained intact. Instead of alkylacetylene, trimethylsilylacetylene (**2g**) furnished alkyne **3ig** in moderate yield. Probably due to the weaker basicity of the corresponding acetylide anion, *tert*-butyl propiolate (**2h**) did not afford the product **3ah** at all.

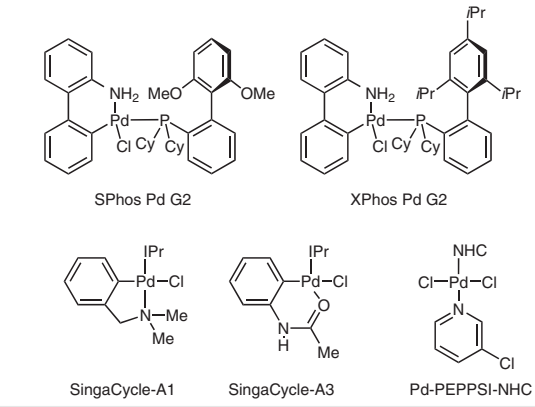
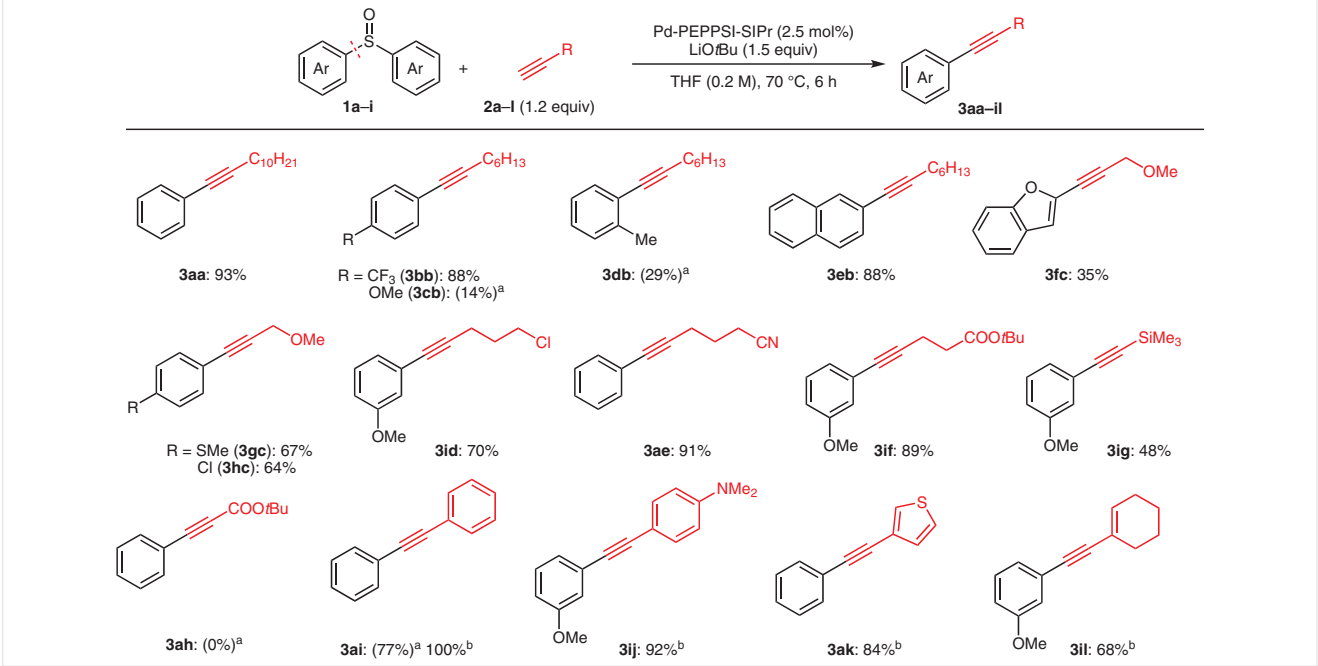


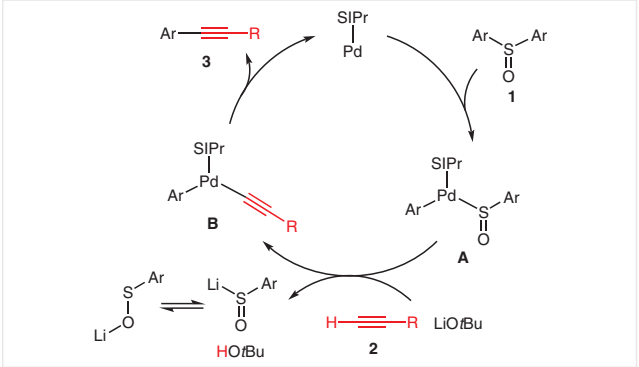
Figure 1 Palladium precatalysts used in Table 1; IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene, SIPr = 1,3-bis(2,6-diisopropylphenyl)imidazolidin-2-ylidene, Cy = cyclohexyl



Scheme 1 Scope of substrates. [a] NMR yield. [b] 2 equiv of **2**, THF (0.05 M), 80 °C, 12 h.

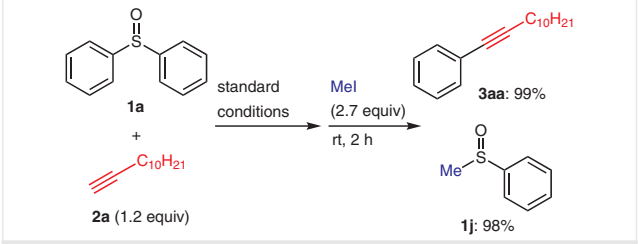
Alkynylation of **1a** with phenylacetylene (**2i**) furnished diphenylacetylene (**3ai**) in 77% NMR yield under the standard conditions. Eventually, **3ai** was obtained quantitatively when the reaction was conducted with two equivalents of **2i** at 80 °C for 12 h under more diluted conditions. By means of the modified reaction conditions, diarylalkynes **3ij** and **3ak** were obtained in good yields. Enyne **2l** also participated to provide desired coupling product **3il** in 68% yield.

A plausible reaction mechanism is shown in Scheme 2. Diaryl sulfoxide **1** would undergo oxidative addition to low-valent palladium to generate oxidative adduct **A**.[10] The arenesulfenate anion on **A** would be replaced with the acetylide anion derived from alkyne **2** with the aid of LiO*t*-Bu, which results in the formation of palladium species **B**. Finally, reductive elimination from **B** would afford the alkynylated product **3**.



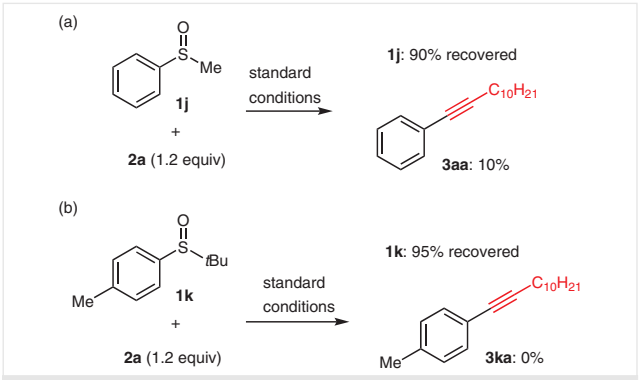
Scheme 2 Plausible reaction mechanism

To confirm the formation of the arenesulfenate anion as a leaving group, we tried to trap it with an electrophile (Scheme 3). After the alkynylation of **1a** with **2a**, the reaction mixture was treated with an excess amount of iodomethane. As a consequence, the expected methylated byproduct, methyl phenyl sulfoxide (**1j**), was obtained in 98% yield along with a 99% yield of the alkyne **3aa**. This indicates that arenesulfenate anions would be generated and stay intact in the reaction flask.



Scheme 3 Electrophilic trap of arenesulfenate anion

Finally, we examined the alkynylation with alkyl aryl sulfoxides instead of diaryl sulfoxides. However, methyl phenyl sulfoxide (**1j**) furnished only a 10% yield of the alkynylated product **3aa** along with the 90% recovery of **1j** (Scheme 4, a). *tert*-Butyl *p*-tolyl sulfoxide (**1k**) did not react at all; **1k** was recovered quantitatively (Scheme 4, b). The C(sp^2)–S(=O) bonds of alkyl aryl sulfoxides would be more electron-rich than those of diaryl sulfoxides, and the former would be less reactive toward electron-rich Pd(0) species. Moreover, alkanesulfenate anions generated during the reaction would be unstable and catalyst poisonous species to impede the catalyst turnover.[11,16] To overcome these problems, further investigations should be necessary.



Scheme 4 Alkynylation of alkyl aryl sulfoxides

In conclusion, we have developed Sonogashira–Hagihara-type alkynylation of diaryl sulfoxides by means of Pd–PEPPSI–SIPr catalyst and LiO*t*Bu as a base. A series of diaryl sulfoxides and terminal alkynes could be converted into the products.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1591676.

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(15) **Alkynylation of 1a with 2a – Representative Procedure**
An oven-dried Schlenk tube was charged with diphenyl sulfoxide (**1a**, 61 mg, 0.30 mmol), 1-dodecyne (**2a**, 60 mg, 0.36 mmol), Pd–PEPPSI–SIPr (5.1 mg, 0.0075 mmol), LiO*t*Bu (36 mg, 0.45 mmol), and THF (1.5 mL). The resulting mixture was stirred at 70 °C for 6 h. The reaction was quenched with sat. aq NH_4Cl (0.10 mL), and the resulting mixture was passed through pads of anhydrous Na_2SO_4, activated alumina, and silica gel with Et_2O as an eluent. The ethereal solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography with an eluent (hexane/toluene = 25:1) to provide **3aa** as a colorless oil (68 mg, 0.28 mmol, 93% yield). All the resonances in ^1H NMR and ^{13}C NMR spectra were consistent with reported values. See: Yasukawa, T.; Miyamura, H.; Kobayashi, S. *Org. Biomol. Chem.* **2011**, *9*, 6208.

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