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Palladium-Catalyzed Arylthiolation of Alkynes Enabled by Surmounting Competitive Dimerization of Alkynes

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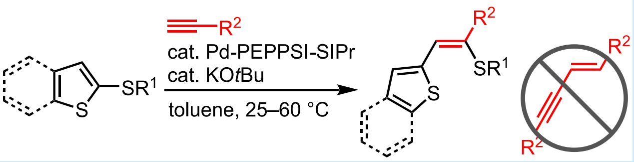
Supporting Information

ABSTRACT: By overcoming the unwanted catalytic dimerization of terminal alkynes, palladium-catalyzed carbothiolation of alkynes with heteroaryl sulfides has been accomplished to provide the corresponding *β*-heteroaryl alkenyl sulfides with high regio- and stereoselectivity. The key for the preferential arylthiolation is the use of arylsulfanyl segments, instead of alkylsulfanyl, for smooth C(heteroaryl)−SR^1 bond cleavage and/or of alkylacetylenes that are reluctant to undergo the dimerization. The reaction proceeds under mild and neutral conditions, with various functionalities being thus tolerated.



Transition-metal-catalyzed addition of organosulfur compounds to alkynes with cleavage of the C−S bonds of the starting molecules is one of the most ideal methods for the synthesis of complex alkenyl sulfides in an atom economical manner.[1] Such transformations, carbothiolation of alkynes, have been achieved mainly with relatively activated organosulfur compounds including thioesters,[2] thioanhydrides,[3] thiocarbonates,[4] thiocarbamates,[5] iminosulfides,[6] thiocyanates,[7] *α*-thioketones,[8] allyl sulfides,[9] alkenyl sulfides,[10] and alkynyl sulfides.[11]

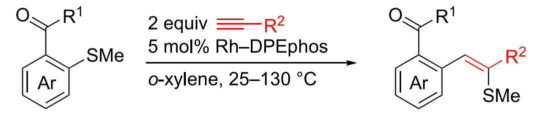
Among these addition reactions, arylthiolation with aryl sulfides can offer simultaneous incorporation of aromatic rings and sulfanyl groups onto alkynes to afford *β*-arylated alkenyl sulfides. However, owing to the lower reactivity of aryl sulfides, there has been only two examples of the arylthiolation of alkynes with aryl sulfides.[12−14] In 2012, Weller and Willis reported rhodium-catalyzed arylthiolation of terminal alkynes with aryl sulfides having carbonyl directing groups at the *ortho* positions (Scheme 1a).[12] Nishihara recently reported directing-group-free arylthiolation of alkynes with a Pd−NHC (N-heterocyclic carbene) catalyst.[13] However, only azolyl sulfides are applicable to Nishihara's arylthiolation, and, for instance, the reaction of 2-benzothienyl methyl sulfide (**1a**) with phenylacetylene (**2a**) gave addition product **3aa** in only 12% yield (Scheme 1b).

We have been interested in catalytic C−S-cleaving transformations of organosulfur compounds.[11b,15−17] For example, we reported the palladium-catalyzed *gem*-arylthiolation of isocyanides with heteroaryl sulfides in which isocyanides insert into the C(heteroaryl)−S bonds of the sulfides.[18] As a part of our interest in development of catalytic transformations of aryl sulfides, we extended the applicability of Nishihara's seminal arylthiolation. Herein, we report palladium-catalyzed arylthiolation of alkynes with a wider variety of heteroaryl sulfides by careful analysis and suppression of unwanted side reactions.

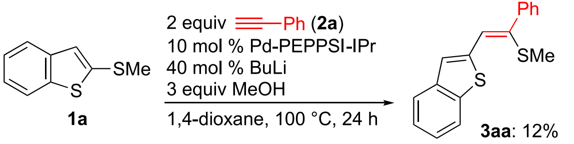
We first attempted the reaction of **1a** with **2a**. According to Nishihara's report,[13] we chose Pd−NHC catalysts to execute smooth C−S bond cleavage. In the presence of 5 mol % of Pd-PEPPSI-SIPr ([1,3-bis(2,6-diisopropylphenyl)imidazolidene](3-chloropyridine)palladium(II) dichloride) and 10 mol % of KO*t*Bu for generation of Pd(0) species, **1a** reacted with 2 equiv of **2a**. As a result, a 41% yield of **3aa** was obtained with a

Scheme 1. Reported and Attempted Arylthiolations of Alkynes with Aryl Sulfides

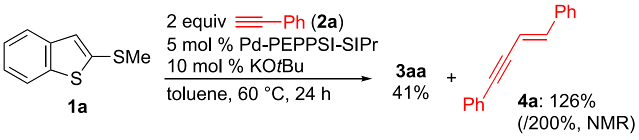
a) Rh-catalyzed reaction reported by Weller and Willis[12]



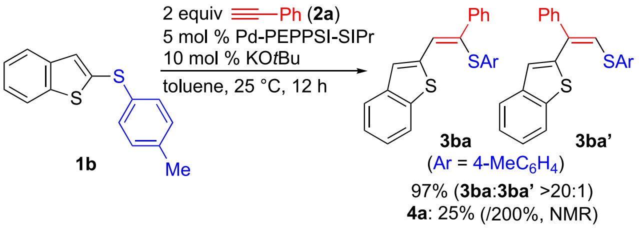
b) Nishihara's result[13]



c) Attempted arylthiolation of **2a** with **1a**



d) Arylthiolation with benzothienyl *p*-tolyl sulfide (**1b**)



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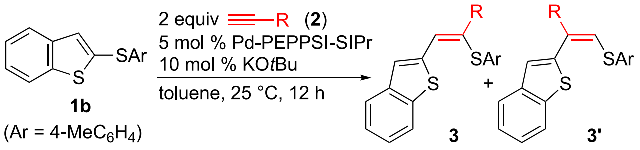
considerable amount of enyne **4a** via palladium-catalyzed dimerization of alkyne[19] (Scheme 1c).

We inferred that the C−S cleavage of **1a** would be much slower than the dimerization resulting in undesirable consumption of **2a**. To facilitate the C−S cleavage for suppression of the undesirable dimerization, we focused on the use of an arylsulfanyl group instead of the methylsulfanyl group. Owing to the lower basicity of the departing arenethiolate anions, the C(benzothienyl)−S bond of aryl 2-benzothienyl sulfides would be cleaved more easily than that of **1a**. Indeed, 2-benzothienyl 4-methylphenyl sulfide (**1b**) smoothly underwent the reaction with **2a**, and the formation of **4a** was fairly suppressed. Of note, the arylthiolation proceeded even at 25 °C, and desired product **3ba** was obtained in 97% yield with a trace amount of regioisomer **3ba′** (Scheme 1d).[20] The structure of major isomer **3ba** was unambiguously determined by X-ray crystallographic analysis.[21,22] Although other benzothienyl sulfides having less basic leaving groups such as $-SCF_3$ and $-SCH_2CF_3$ were tested, no arylthiolation products were obtained and the starting sulfides and alkyne **2a** were recovered. Whereas the C(benzothienyl)−S bonds would easily undergo oxidative addition to Pd(0), the next thiopalladation step (see Scheme 3, *step c*) would not proceed owing to the electron deficiency of the leaving groups.[23]

Based on the encouraging result with **1b**, we then explored the reaction scope with respect to alkynes **2** (Table 1). Electron-rich 4-methoxyphenylacetylene (**2b**) uneventfully participated in the reaction to provide **3bb** in good yield with high regioselectivity (entry 1). On the other hand, the yield of the product decreased in the reaction of electron-deficient 4-(trifluoromethyl)phenylacetylene (**2c**) because of the competing dimerization of **2c** to **4c** (entry 2). Heteroarylacetylenes such as 3-ethynylthiophene and -pyridine also underwent the reaction to afford **3bd** and **3be** in 63 and 61% yields, respectively (entries 3 and 4). On the other hand, the reaction of **1b** with 2-ethynylpyridine (**2f**) afforded the product in very low yield, and a significant amount of the dimerization product of **2f** was observed (entry 5). Alkylacetylenes were found to be suitable for the reaction; 1-hexyne (**2g**) and cyclopropylacetylene (**2h**) provided the corresponding arylthiolation products in high yields with high regioselectivities (entries 6 and 7). Owing to the mild and almost neutral reaction conditions, a series of functionalities such as acetoxy, cyano, malonate ester, and chloro moieties remained intact to yield the corresponding products **3bi−bl** (entries 8−11). Probably due to the bulkiness of the *tert*-butyl group, the reaction of 3,3-dimethyl-1-butyne (**2m**) required an increased reaction temperature as high as 60 °C (entry 12). In contrast, hydroxy-containing **2n** smoothly underwent the reaction even at 25 °C despite the steric congestion (entry 13). The hydroxy group might act as a directing group to facilitate the coordination of **2n** to the palladium center. The use of trimethylsilylacetylene (**2o**) led to reversal of the regioselectivity: arylthiolation product **3bo′** was obtained as a major product in contrast to the reactions of aryl- and alkylacetylenes (entry 14).[21]

Table 1. Reaction Scope with Respect to Alkynes

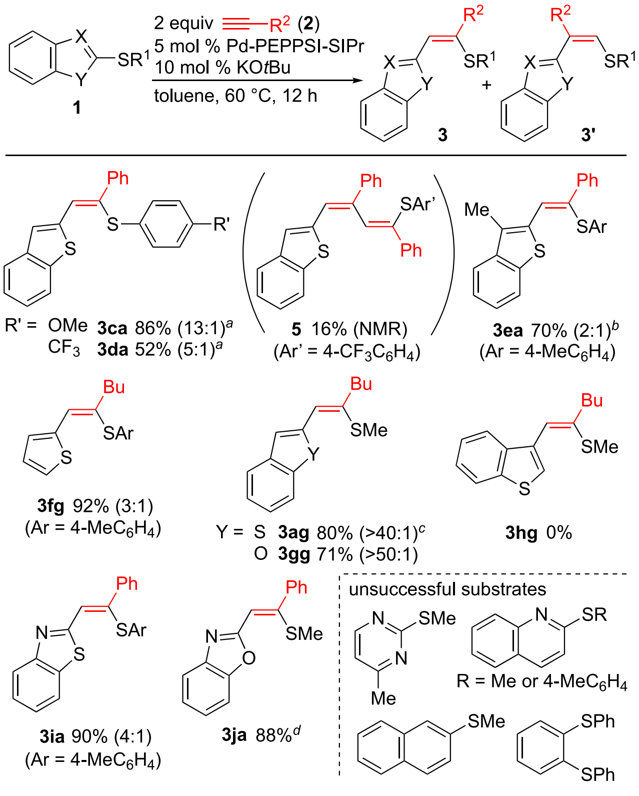


entry	R	2	3	yield, 3:3′
1	4-MeOC$_6$H$_4$	**2b**	**3bb**	81%, 11:1
2	4-CF$_3$C$_6$H$_4$	**2c**	**3bc**	(61%, 9:1)[a] 41%[b]
3	3-thienyl	**2d**	**3bd**	63%[b]
4[c]	3-pyridyl	**2e**	**3be**	61%, 10:1
5	2-pyridyl	**2f**	**3bf**	(<10%)[a]
6[d]	Bu	**2g**	**3bg**	97%, 14:1
7	cyclopropyl	**2h**	**3bh**	78%, >50:1
8	$(CH_2)_3OAc$	**2i**	**3bi**	93%, 8:1
9	$(CH_2)_3CN$	**2j**	**3bj**	92%, 5:1
10	$CH_2CH(CO_2Et)_2$	**2k**	**3bk**	72%, 12:1
11	$(CH_2)_4Cl$	**2l**	**3bl**	97%, 7:1
12[c,d]	*t*Bu	**2m**	**3bm**	87%, 5:1
13[d]	CMe$_2$(OH)	**2n**	**3bn**	(100%, 14:1)[a] 88%[b]
14[c]	SiMe$_3$	**2o**	**3bo**	84%, 1:3

[a] Determined by ^{1}H NMR of a crude mixture. [b] Isolated as a single isomer. [c] At 60 °C. [d] For 24 h.

Next, we investigated the reaction scope with respect to aryl sulfides **1** (Scheme 2). Instead of **1b**, 2-benzothienyl 4-methoxyphenyl sulfide (**1c**) also reacted with **2a** to afford product **3ca** in 86% yield. On the other hand, the reaction of 2-benzothienyl 4-(trifluoromethyl)phenyl sulfide (**1d**) provided a mixture of **3da** and **3da′** in only 52% yield. In addition to **3da** and **3da′**, diene **5** was also generated via a second insertion of alkyne **2a** into the C(alkenyl)−S bond of **3da**. The electron deficiency of the 4-(trifluoromethyl)phenylsulfanyl group would render the C(alkenyl)−S bond of **3da** more reactive. Under the present catalysis, **3da** indeed reacted with **2a** to provide **5**. The

Scheme 2. Reaction Scope with Respect to Heteroaryl Sulfides



[a] At 40 °C. [b] At 25 °C. [c] For 24 h. [d] For 36 h. Obtained as a single isomer.

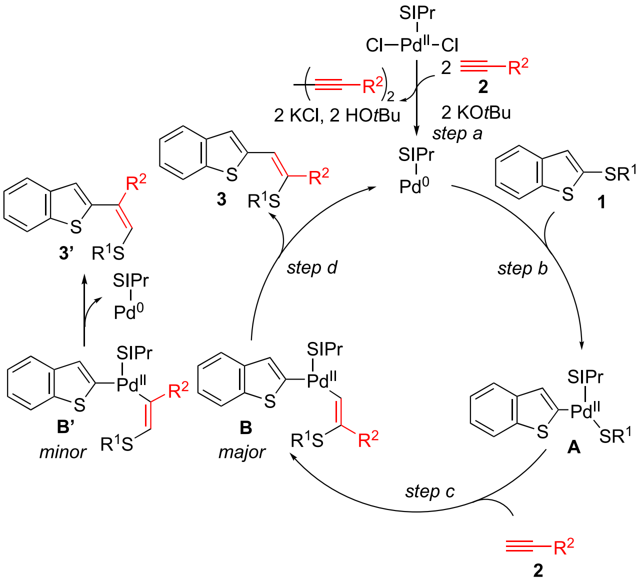
methyl group at the 3 position of benzothienyl sulfide **1e** did not hamper the reaction, whereas the regioselectivity decreased to 2:1. 2-Thienyl sulfide **1f** also took part in the reaction to afford product **3fg** in 92% yield.

During the investigation of the reaction scope, we found that alkylacetylenes are reluctant to undergo the dimerization even at increased reaction temperatures.[19c,e,24] This feature allowed us to react less reactive 2-benzothienyl methyl sulfide (**1a**) at a higher reaction temperature; the reaction of **1a** with 1-hexyne (**2g**) at 60 °C successfully provided desired arylthiolation product **3ag** in 80% yield with exclusive regioselectivity.

In place of benzothienyl sulfides, 2-benzofuryl sulfide **1g** was applicable to the reaction to furnish **3gg** in 71% yield. The position of the C(heteroaryl)−S bond has a great influence; no reaction took place with 3-benzothienyl methyl sulfide (**1h**), resulting in quantitative recovery of **1h**.[25] Azolyl sulfides **1i** and **1j** also reacted with **2a** to afford the corresponding products in high yields under milder reaction conditions compared with those in Nishihara's report.[13] Nevertheless, other heteroaryl sulfides such as methyl 2-pyrimidyl and methyl 2-quinolyl sulfides were not applicable to the reaction with 1-hexyne (**2g**), and the starting sulfides were recovered after the reaction. 4-Methylphenyl 2-quinolyl sulfide, methyl 2-naphthyl sulfide, and 1,2-bis(phenylsulfanyl)benzene also did not undergo the reaction with **2g** even at 130 °C, resulting in the recovery of the starting sulfides.

The present reaction would proceed via a similar mechanism proposed by Nishihara (Scheme 3).[13] With the aid of terminal alkyne **2** and KO*t*Bu, Pd(0) species would be generated from Pd-PEPPSI-SIPr (*step a*). Oxidative addition of **1** to the Pd(0) species would afford arylpalladium thiolate **A** via the cleavage of the C(heteroaryl)−S bond (*step b*). Subsequent *syn*-thiopalladation of alkyne **2** with **A** would generate alkenylarylpalladium(II) **B** (*step c*).[26] Owing to its bulkiness, SIPr-ligated palladium would avoid a steric repulsion with the substituent on alkyne (R^2) to form **B** preferentially.[27] Finally, reductive elimination from **B** would afford product **3** with regeneration of the initial Pd(0) species (*step d*).

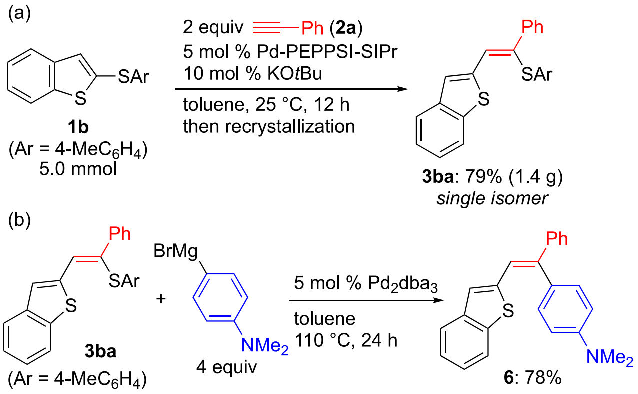
Scheme 3. Plausible Mechanism



Although Pd(0) species potentially promote the dimerization of alkynes,[19] preferential C−S bond cleavage (Scheme 3, *step b*) could be executed by the use of arylsulfanyl group for acceleration of the C−S cleavage and/or by employment of alkylacetylenes that are less prone to undergo the dimerization.

The present arylthiolation was applicable to a gram-scale reaction, and a 79% yield of **3ba** was isolated as a single isomer after the recrystallization process (Scheme 4a). With 5 mol % of Pd_2dba_3 (dba = dibenzylideneacetone) and an excess amount of an arylmagnesium reagent,[28] **3ba** was further converted into the corresponding 1,1,2-triarylethene **6** with retention of the stereochemistry (Scheme 4b).[29]

Scheme 4. Gram-Scale Synthesis and Further Arylation of the C(Alkenyl)−S Bond of 3ba



In conclusion, we have developed regio- and stereoselective palladium-catalyzed arylthiolation of alkynes with heteroaryl sulfides to yield a variety of β-heteroaryl alkenyl sulfides under mild and neutral conditions. Competitive dimerization of alkynes was sufficiently suppressed by the use of arylsulfanyl segments for smooth C(heteroaryl)−SR cleavage and/or of alkylacetylenes that are unwilling to participate in the dimerization. Careful optimization of reaction conditions is necessary for inventing new and/or efficient reactions of catalyst-poisonous organosulfur compounds. Further work is ongoing along this line in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03056.

Experimental procedures, X-ray crystallographic analysis, and spectral data (PDF)

Accession Codes

CCDC 1945583−1945584 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(20) See Table S1 in the Supporting Information for details of the optimization study.

(21) See the Supporting Information for identification of the arylthiolation products **3**.

(22) For XRD analyses, see Figures S1 and S2 in the Supporting Information (CCDC 1945583 and 1945584).

(23) Electron-withdrawing groups on the sulfur atoms of platinum thiolates decrease the rate of insertion of alkynes into the Pt−S bonds. Kuniyasu, H.; Takekawa, K.; Yamashita, F.; Miyafuji, K.; Asano, S.; Takai, Y.; Ohtaka, A.; Tanaka, A.; Sugoh, K.; Kurosawa, H.; Kambe, N. Insertion of Alkynes into an ArS−Pt Bond: Regio- and Stereoselective Thermal Reactions, Facilitation by "*o*-Halogen Effect" and Photoirradiation, Different Alkyne Preferences Depending on the Ancillary Ligand, and Application to a Catalytic Reaction. *Organometallics* **2008**, *27*, 4788−4802.

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(25) We cannot exclude the possibility that the endocyclic sulfur atom of **1b** might serve as a directing group to facilitate the C2−SAr bond cleavage.

(26) Dimethyl acetylenedicarboxylate is known to insert into the S−Pt bond of arylplatinum thiolates to afford alkenylarylplatinums. See the literature in ref 23.

(27) In Table 1, the reaction of **1b** with trimethylsilylacetylene (**2o**) afforded **3bo′** as the major product. We speculate that the α-effect of the silicon atom would stabilize intermediate **B′**, which would reverse the regioselectivity of the thiopalladation process (Scheme 3, *step c*).

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(29) Both of the two C−S bonds of **3ba** were cleaved under the conditions; 4-*N*,*N*-dimethylamino-4′-methylbiphenyl was formed in 72% NMR yield accompanied with **6**. An excess amount of arylmagnesium is thus necessary to obtain **6** in good yield.

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