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Palladium-Catalyzed Desulfitative Cross-Coupling of Arylsulfonyl Hydrazides with Terminal Alkynes: A General Approach toward Functionalized Internal Alkynes

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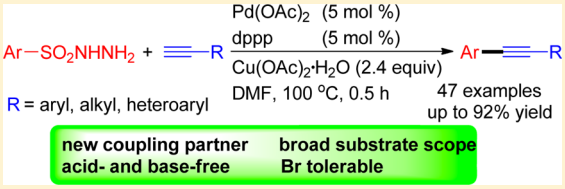
Supporting Information

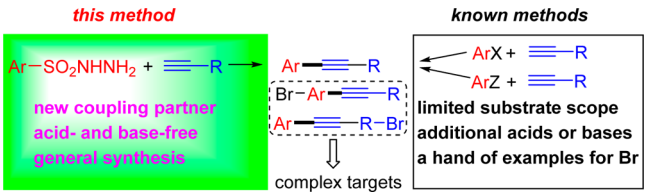
ABSTRACT: A palladium-catalyzed Sonogashira-type coupling between arylsulfonyl hydrazides and terminal alkynes via Ar(C)−S bond cleavage is disclosed, which enables the general synthesis of functionalized internal alkynes, especially the Br-substituted ones, in good to excellent yields under acid- and base-free conditions.



INTRODUCTION

Internal alkynes, especially the functionalized ones, are an important class of unsaturated organic compounds that are ubiquitously found in many natural products and molecular organic materials.[1] They are extremely useful synthons in organic chemistry toward heterocycles, biorelevant compounds, and materials.[1,2] The transition-metal-catalyzed Sonogashira-type cross-coupling reactions that were independently developed by Sonogashira,[3a] Cassar,[3b] and Heck[3c] have emerged as the most powerful tools for the construction of internal alkyne skeletons (Scheme 1).[4] Over the past two

Scheme 1. Synthesis of Internal Alkynes



decades, great efforts have been made in the pursuit of new coupling partners, broader substrate scope, and simpler reaction conditions.[4−13] A number of electrophiles (ArZ) such as iodonium tetrafluoroborate,[6] tetraarylphosphoniums,[7] boronic acids,[8] arenesulfonyl chlorides,[9] tosylates,[10] aryl amines,[11] aryldiazonium salts,[12] and sodium sulfinates[13] have been utilized as coupling partners for the synthesis of internal alkynes. Despite notable achievements, there is a general need of additional bases or acids which might lead to limited functional group tolerance. Therefore, protocols for general and facile syntheses of these compounds are still desired.

As we have continuous interest in selective transformation of terminal alkynes,[14] we aim to develop a general method for the synthesis of functionalized internal alkynes, and it is realized that the use of easily accessible electrophiles under additional acid- and base-free conditions would be a promising choice. Because the readily available and air-stable arylsulfonyl hydrazides are good cross-coupling partners for ready generation of reactive diazo compounds,[15] we envisioned that they might also be good electrophiles in Sonogashira-type cross-coupling reactions to give useful internal alkynes. It is noted that the groups of Tian and Deng have independently employed arylsulfonyl hydrazides as aryl sources in Heck-type[16] and direct C−H bond arylation reactions[17] via desulfitation processes.

Herein, we describe a palladium-catalyzed Sonogashira-type reaction of arylsulfonyl hydrazides with terminal alkynes for the synthesis of 1,2-disubstituted acetylenes under additional acid- or base-free conditions. Both Br-substituted arylsulfonyl hydrazides and terminal alkynes are well-tolerated, providing a general synthesis of Br-functionalized internal alkynes (Scheme 1).

Br-substituted compounds could be ideal precursors for many coupling reactions because of their easy availability and suitable reactivity. However, Br-substituted internal alkynes are difficult to produce from easily available Br-substituted substrates by the traditional Sonogashira-type cross-coupling reactions under alkaline conditions due to their instability under such conditions, consequently limiting the application of the synthesis of more complex targets (Scheme 1). Only a few examples have been reported in alternative reactions.[8b−e,12a−d,13] Very recently, several Br-substituted diarylacetylenes (seven examples) have been successfully prepared from arylhydrazines and aromatic alkynes by Song's group; moderate yields (50−71%) were observed from 3.5 equiv of

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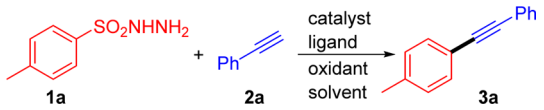
one starting material, but aliphatic alkynes are far from being applicable.[18]

RESULTS AND DISCUSSION

In our initial research, we performed the reaction between 4-methylbenzenesulfonohydrazide (**1a**, 0.2 mmol) and ethynylbenzene (**2a**, 1.0 equiv) in the presence of $Pd(OAc)_2$ (5 mol %), 1,10-phen (5 mol %), and $Cu(OAc)_2{\cdot}H_2O$ (2.0 equiv) in DMF at 100 °C for 0.5 h. The desired desulfitative coupling product 1-methyl-4-(phenylethynyl)benzene (**3a**) was obtained in a 20% yield (Table 1, entry 1). Subsequently, a range of

Table 1. Optimization of Reaction Conditions[a,b]



1a 2a 3a

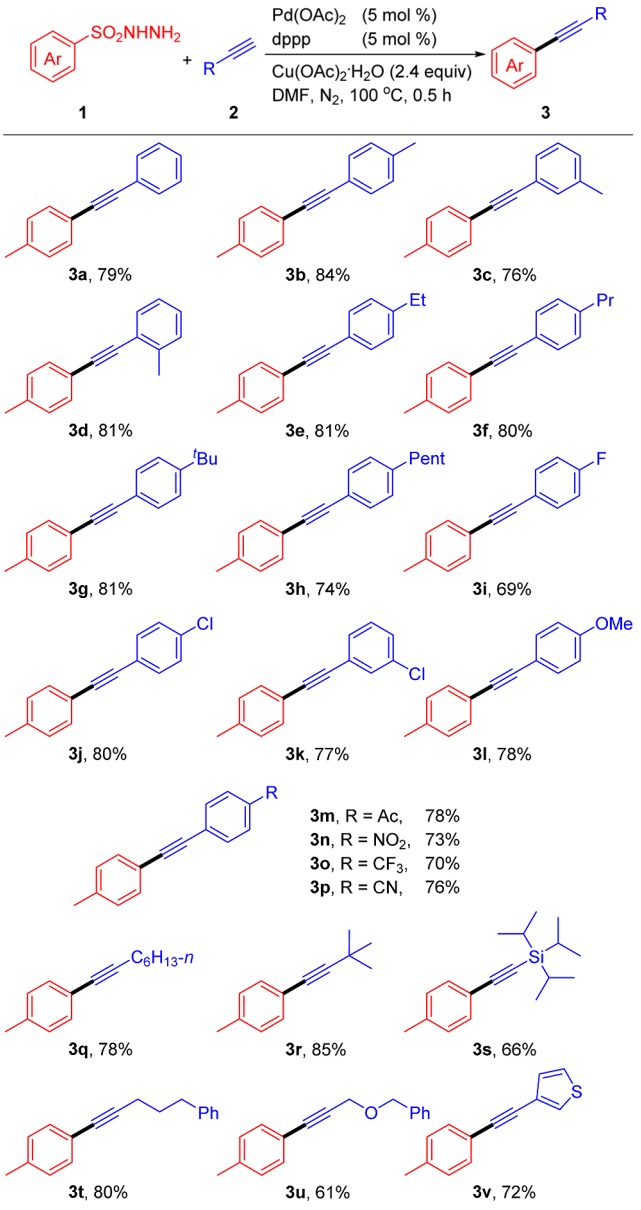
entry	catalyst	ligand	oxidant	solvent	yield (%)
1	$Pd(OAc)_2$	1,10-phen	$Cu(OAc)_2{\cdot}H_2O$	DMF	20
2[c]	$Pd(OAc)_2$	PPh_3	$Cu(OAc)_2{\cdot}H_2O$	DMF	44
3[c]	$Pd(OAc)_2$	PCy_3	$Cu(OAc)_2{\cdot}H_2O$	DMF	43
4	$Pd(OAc)_2$	dppm	$Cu(OAc)_2{\cdot}H_2O$	DMF	41
5	$Pd(OAc)_2$	dppe	$Cu(OAc)_2{\cdot}H_2O$	DMF	61
6	$Pd(OAc)_2$	dppp	$Cu(OAc)_2{\cdot}H_2O$	DMF	78
7	$PdCl_2$	dppp	$Cu(OAc)_2{\cdot}H_2O$	DMF	75
8	$Pd(TFA)_2$	dppp	$Cu(OAc)_2{\cdot}H_2O$	DMF	70
9	$Pd(OH)_2$	dppp	$Cu(OAc)_2{\cdot}H_2O$	DMF	18
10	$Pd_2(dba)_3$	dppp	$Cu(OAc)_2{\cdot}H_2O$	DMF	46
11	$Pd(OAc)_2$	dppp	O_2	DMF	trace
12	$Pd(OAc)_2$	dppp	BQ	DMF	trace
13	$Pd(OAc)_2$	dppp	K_2S_2Og	DMF	trace
14	$Pd(OAc)_2$	dppp	Ag_2CO_3	DMF	trace
15	$Pd(OAc)_2$	dppp	$Cu(OAc)_2{\cdot}H_2O$	DMSO	66
16	$Pd(OAc)_2$	dppp	$Cu(OAc)_2{\cdot}H_2O$	dioxane	12
17	$Pd(OAc)_2$	dppp	$Cu(OAc)_2{\cdot}H_2O$	toluene	33
18	$Pd(OAc)_2$	dppp	$Cu(OAc)_2{\cdot}H_2O$	CH_3CN	25
19[d]	$Pd(OAc)_2$	dppp	$Cu(OAc)_2{\cdot}H_2O$	DMF	84
20[d,e]	$Pd(OAc)_2$	dppp	$Cu(OAc)_2{\cdot}H_2O$	DMF	53
21[d,f]	$Pd(OAc)_2$	dppp	$Cu(OAc)_2{\cdot}H_2O$	DMF	70
22[d,g]	$Pd(OAc)_2$	dppp	$Cu(OAc)_2{\cdot}H_2O$	DMF	45
23[d,h]	$Pd(OAc)_2$	dppp	$Cu(OAc)_2{\cdot}H_2O$	DMF	80
24[d,i]	$Pd(OAc)_2$	dppp	$Cu(OAc)_2{\cdot}H_2O$	DMF	38

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.2 mmol, 1.0 equiv), catalyst (5 mol %), ligand (5 mol %), oxidant (0.4 mmol, 2.0 equiv), DMF (2.0 mL), N_2, 100 °C, 0.5 h. [b]Yields were based on the GC analysis with dodecane as the internal standard. [c]10 mol % of ligand was used. [d]**2a** (1.2 equiv), $Cu(OAc)_2{\cdot}H_2O$ (2.4 equiv). [e]$Pd(OAc)_2$ 1 mol %, dppp 1 mol %. [f]$Pd(OAc)_2$ 3 mol %, dppp 3 mol %. [g]0.25 h. [h]120 °C. [i]80 °C.

ligands such as PPh_3, PCy_3, bis(diphenylphosphino)methane (dppm), 1,2-bis(diphenylphosphino)ethane (dppe), and 1,3-bis(diphenylphosphino)propane (dppp) were examined (Table 1, entries 2–6), and dppp gave the best yield (78%,Table 1, entry 6). For palladium catalysts, $PdCl_2$ and $Pd(TFA)_2$ also showed good efficiency (Table 1, entries 7 and 8), whereas $Pd(OH)_2$ and $Pd_2(dba)_3$ gave low yields of **3a** (Table 1, entries 9 and 10). An assessment of oxidants revealed that $Cu(OAc)_2{\cdot}H_2O$ was optimal for the reaction (Table 1, entry 6); molecular oxygen, benzoquinone (BQ), $K_2S_2O_8$, and Ag_2CO_3 gave only a trace amount of the desired product (Table 1, entries 11–14). Other solvents such as DMSO, dioxane, toluene, and CH_3CN were inferior to DMF (Table 1, entries 15–18). Greater loadings of **2a** and $Cu(OAc)_2{\cdot}H_2O$ further improved the yield of **3a** (84%, Table 1, entry 19). Smaller loading of $Pd(OAc)_2$ (1 and 3 mol %) lowered the product yields (53 and 70%, respectively, entries 20 and 21). When the reaction time was reduced to 0.25 h, the yield of **3a** decreased to 45% (Table 1, entry 22). The reaction was also sensitive to the reaction temperature, and a lower yield of **3a** was observed at temperature higher or lower than 100 °C (Table 1, entries 23 and 24).

With the optimized conditions in hand, we investigated the scope and generality of the reaction. As shown in Table 2, this Sonogashira-type cross-coupling reaction exhibited a wide scope of substrates and an outstanding tolerance toward functional groups, producing various 1,2-disubstituted acetylenes in good to excellent isolated yields. Aromatic alkynes

Table 2. Substrate Scope of Terminal Alkynes[a]



[a]Reaction conditions: **1** (0.2 mmol), **2** (0.24 mmol, 1.2 equiv), $Pd(OAc)_2$ (5 mol %), dppp (5 mol %), $Cu(OAc)_2{\cdot}H_2O$ (0.48 mmol, 2.4 equiv), DMF (2.0 mL), N_2, 100 °C, 0.5 h. Isolated yields.

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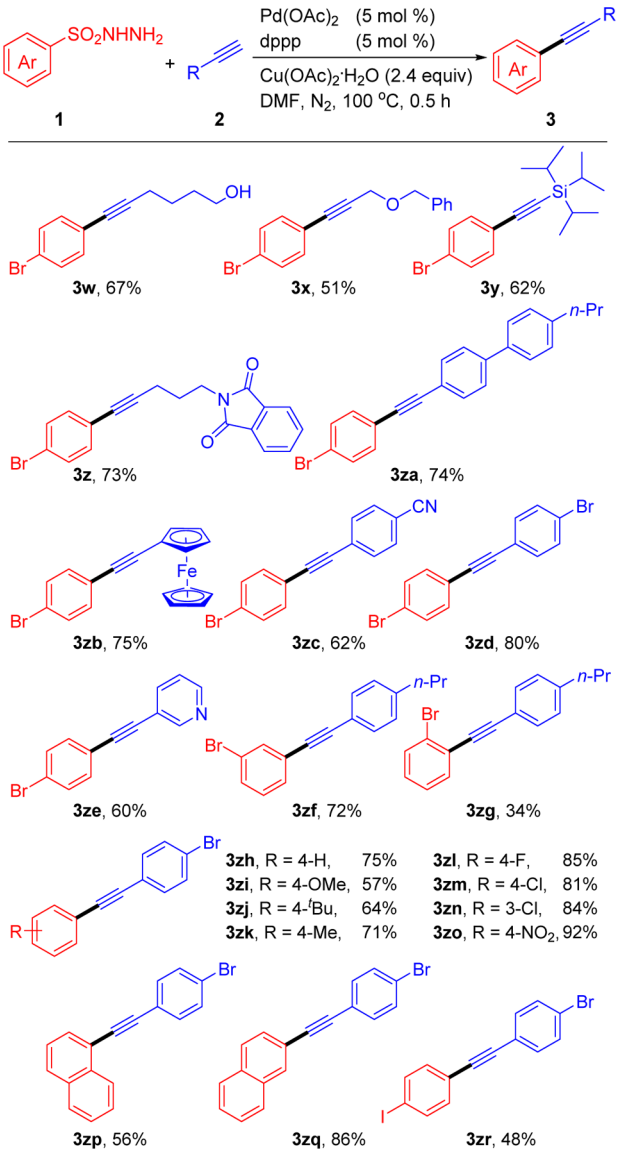
substituted with alkyl (**3b**–**h**), F (**3i**), Cl (**3j** and **3k**), OMe (**3l**), CH_3CO (**3m**), NO_2 (**3n**), CF_3 (**3o**), and CN (**3p**) worked well to give the corresponding internal alkynes in 69–84% yields, regardless of steric hindrance. The attachment of strong electron-withdrawing groups such as F (**3i**), NO_2 (**3n**), and CF_3 (**3o**) resulted in slightly lower yields (69, 73, and 70%, respectively). Aliphatic alkynes were also good substrates, producing the corresponding internal alkynes in 61–85% yields (**3q**–**u**). Heteroaromatic alkyne that contains thiophene reacted efficiently, giving the corresponding product in 72% yield (**3v**).

Gratifyingly, the potentially labile Br that is reactive in many coupling reactions was inert in this reaction system regardless of where it was anchored in arylsulfonyl hydrazides and terminal alkynes (Table 3). A broad range of Br-substituted internal alkynes were produced in good to excellent yields using this strategy (**3w**–**zr**). Functional groups, including primary alcohols (**3w**), ethers (**3x** and **3zi**), silicane (**3y**), amides (**3z**), alkyl (**3za**, **3zj**, and **3zk**), ferrocene (**3zb**), CN (**3zc**), pyridine (**3ze**), F (**3zl**), Cl (**3zm** and **3zn**), and NO_2 (**3zo**), could survive together with Br. Internal alkyne **3zr** halogenated by both Br and I was also achieved, albeit in moderate yield. These clearly demonstrate the great potential of this new methodology for accessing highly functionalized internal alkynes from these Br-substituted alkynes. In contrast, the reaction was sensitive to the steric hindrance in arylsulfonyl hydrazides. 2-Bromobenzenesulfonohydrazide gave only a 34% yield of the desired product (**3zg**). Notably, naphthalene-2-sulfonohydrazide could be employed as the substrate to produce the corresponding product in high yield (86%, **3zq**), whereas a lower yield (56%, **3zp**) was observed in the use of naphthalene-1-sulfonohydrazide, probably due to its steric hindrance.

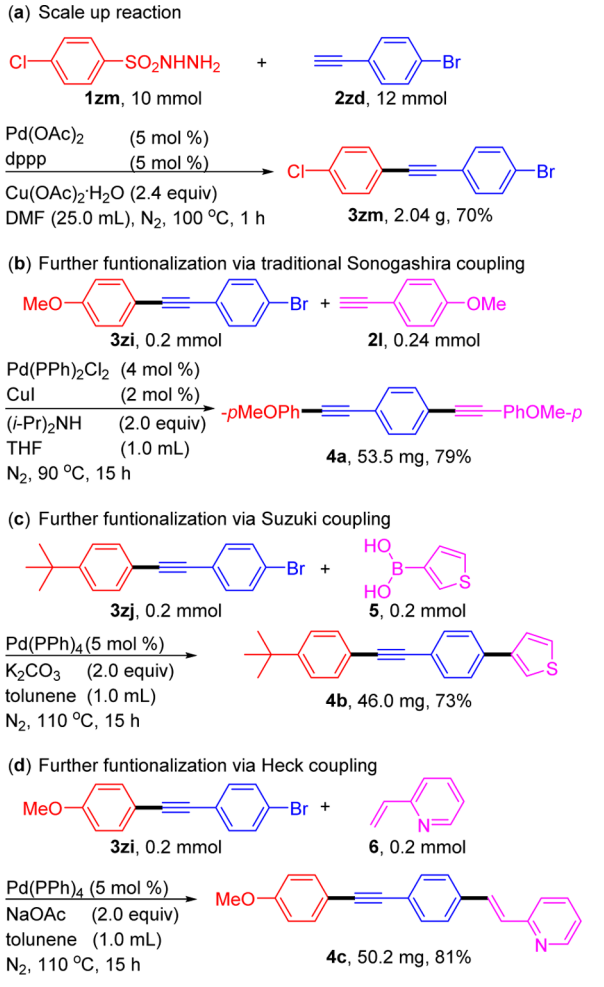
A gram-scale synthesis of **3zm** was successfully achieved under the optimal conditions, giving a 70% isolated yield (Scheme 2a). In addition, the Br-substituted internal alkynes could be further functionalized by means of traditional Sonogashira coupling, Suzuki coupling, and Heck coupling, respectively, and various complex internal alkyne derivatives were successfully synthesized in high yields (Scheme 2b–d). For example, bis(arylethynyl)benzene derivatives **4a** could be achieved in a 79% yield (Scheme 2b) via traditional Sonogashira cross-coupling. This type of conjugated oligophenyleneethynylenes is of potential interest for use as

Table 3. Synthesis of Br-Substituted Internal Alkynes[a]



[a]Reaction conditions: **1** (0.2 mmol), **2** (0.24 mmol, 1.2 equiv), $Pd(OAc)_2$ (5 mol %), dppp (5 mol %), $Cu(OAc)_2·H_2O$ (0.48 mmol, 2.4 equiv), DMF (2.0 mL), N_2, 100 °C, 0.5 h. Isolated yields.

Scheme 2. Scaleup Experiment and Synthetic Utility



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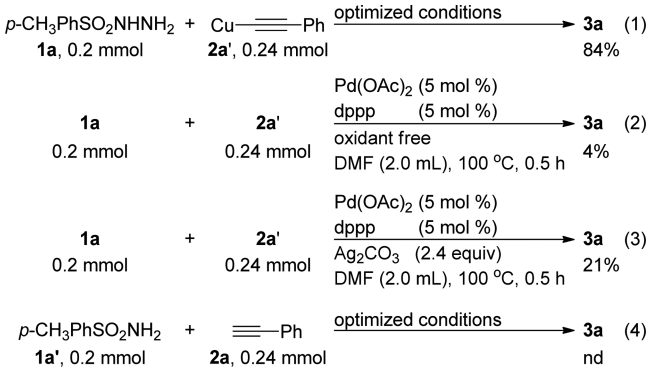
molecular wires[19] or in the preparation of cruciform fluorophores.[20]

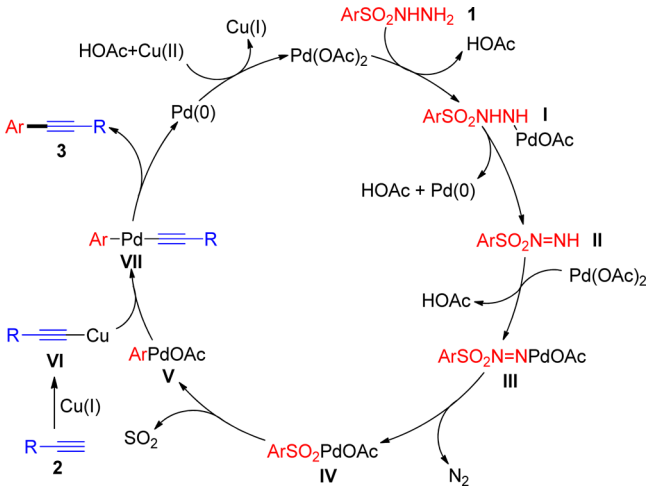
It is generally agreed on that copper(I) phenylacetylide and $ArPd^{II}X$ species are reaction intermediates for Sonogashira-type cross-coupling.[4a,e,21] Indeed, copper(I) phenylacetylide reacted smoothly with **1a** to give **3a** in an 84% yield under the optimized conditions (Scheme 3, eq 1). The oxidants other

Scheme 3. Control Experiments



than $Cu(OAc)_2$ were ineffective for the reaction (Table 1), whereas by replacement of $Cu(OAc)_2$ with Ag_2CO_3, the reaction of copper(I) phenylacetylide with **1a** produced **3a** in a 21% yield. These results suggested that copper(I) acetylides were involved in the catalytic cycle. We supposed that the formation of $ArPd^{II}X$ occurred in the reaction, which was initiated by nitrogen extrusion from arylsulfonyl hydrazides. Thus, stoichiometric reactions of **1a** with 1.0 and 2.0 equiv of $Pd(OAc)_2$ were conducted separately. In ^1H NMR spectra, the signals of the two hydrogen atoms of -$NHNH_2$ disappeared in the presence of 1.0 equiv $Pd(OAc)_2$, which was probably due to the formation of intermediate **II** (Scheme 4), and the signals of

Scheme 4. Proposed Mechanism



all three hydrogen atoms disappeared when 2.0 equiv $Pd(OAc)_2$ was added at room temperature, in which intermediate **III** was probably produced. In the ESI-MS spectra, the peak at m/z 502.8 was assigned to [**III** + DMSO − H]$^-$ (calcd m/z 503.0), which also indicated the formation of intermediate **III** (for details, see the Supporting Information).

Extrusion of N_2 and SO_2 from **III** might give the key intermediate **V**.

On the basis of the study mentioned above and literature reports,[16] a general mechanism is illustrated in Scheme 4. The reaction of $Pd(OAc)_2$ with arylsulfonyl hydrazide gives an $ArPd^{II}OAc$ intermediate (**V**), which is formed via successive deprotonation of the arylsulfonyl hydrazide, β-hydride elimination, and liberation of N_2 and SO_2. Transmetalation of **V** with the copper acetylides species **VI** gives intermediate **VII**, which then undergoes reductive elimination to give the desired cross-coupling product **3**. The Pd^{II} species are then regenerated through the oxidation of the Pd^0 species with $Cu(OAc)_2$.

CONCLUSION

In summary, we developed a Sonogashira-type cross-coupling reaction using readily available arylsulfony hydrazides as arylation reagents under additional acid- and base-free conditions, which shows a wide scope of substrates and excellent functional group tolerance and thus provides a general and facile means for accessing various functionalized 1,2-disubstituted acetylenes. Br-substituted substrates exhibited excellent chemoselectivity; only the coupling reaction involving the sulfonylhydrazide groups occurred, making it an efficient synthesis of Br-functionalized internal alkynes, and more complex target molecules could be prepared from them through the traditional cross-coupling reactions. Further investigations to gain a detailed mechanistic understanding of this reaction are currently underway.

EXPERIMENTAL SECTION

General Information. All reactions were carried out in oven-dried Schlenk tubes under N_2 atmosphere. Solvents were distilled after treatment with calcium hydride. Reagents were used as received unless otherwise noted. Column chromatography was performed using silica gel 60 (particle size 37−54 μm). The pure products were obtained by means of column chromatography (petroleum ether and ethyl acetate were used as the gradient eluting solvents). ^1H NMR, ^{13}C NMR, and ^{19}F NMR data were acquired on a 400 spectrometer (400 MHz for ^1H, 100 MHz for ^{13}C, and 376 MHz for ^{19}F NMR spectroscopy). Chemical shifts for ^1H NMR are referred to internal $CDCl_3$ (7.26 ppm for ^1H NMR and 77.00 ppm for ^{13}C NMR) and reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz), and integration. The ionization method of the HRMS is EI. The type of the mass analyzer is quadrupole.

Synthesis of Starting Materials. Arylsulfonyl hydrazides were prepared according to the literature procedure.[22] Hydrazinemonohydrate (25.0 mmol) was added dropwise to a solution of arylsulfonyl chloride (10.0 mmol) in dry tetrahyrdofuran (15.0 mL) at 0 °C under N_2. During the addition, the mixture became brown, and a white precipitate of hydrazine hydrochloride was deposited. The mixture was stirred at 0 °C for 30 min, ethyl acetate (60.0 mL) was added, and the mixture was washed repeatedly with ice-cold 10% aqueous sodium chloride solution (3 × 20.0 mL). The organic layer was dried over sodium sulfate, filtered, and added slowly to stirred hexane (500.0 mL) over 5 min. After being stirred for 10 min, the mixture was filtered, and the collected solid was dried in vacuum.

General Procedure for the Synthesis of Internal Alkynes. An oven-dried Schlenk tube of 25 mL equipped with a magnetic stir bar was charged with arylsulfonyl hydrazide **1** (0.2 mmol), $Pd(OAc)_2$ (0.01 mmol, 5 mol %), dppp (0.01 mmol, 5 mol %), and $Cu(OAc)_2 \cdot H_2O$ (0.48 mmol, 2.4 equiv); after being charged with nitrogen three times, terminal alkyne **2** (0.24 mmol) and DMF (2.0 mL) were added. The reaction mixture was heated at 100 °C for 0.5 h. After completion of the reaction, the reaction mixture was cooled to room temperature and quenched with H_2O (2 mL). The crude product was extracted with CH_2Cl_2 (5 mL), and the organic layer was dried over anhydrous

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Na_2SO_4 and concentrated under vacuum. The desired product was isolated by column chromatography over silica gel (300−400 mesh) using petroleum ether/ethyl acetate as eluent.

^{1}H and ^{13}C Spectral Data of the Products. *1-Methyl-4-((4-propylphenyl)ethynyl)benzene (**3f**).* White solid; yield: 37.5 mg, 80%; mp 56−57 °C. ^{1}H NMR ($CDCl_3$, 400 M): δ 7.43 (t, J = 7.6 Hz, 4H), 7.15 (d, J = 7.6 Hz, 4H), 2.60 (t, J = 8.0 Hz, 2H), 2.37 (s, 3H), 1.70−1.60 (m, 2H), 0.95 (t, J = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.0, 138.1, 131.4, 129.1, 128.5, 120.6, 120.4, 88.9, 88.8, 37.9, 24.3, 21.5, 13.7. HRMS (EI) m/z: $[M]^+$ calcd for $C_{18}H_{18}$ 234.1409; found 234.1404.

*1-Methyl-4-((4-pentylphenyl)ethynyl)benzene (**3h**).* White solid; yield: 38.8 mg, 74%; mp 46−48 °C. ^{1}H NMR ($CDCl_3$, 400 M): δ 7.43 (t, J = 7.2 Hz, 4H), 7.15 (d, J = 8.0 Hz, 4H), 2.61 (t, J = 7.6 Hz, 2H), 2.37 (s, 3H), 1.65−1.58 (m, 2H), 1.37−1.27 (m, 4H), 0.90 (t, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.2, 138.1, 131.4, 129.1, 128.4, 120.6, 120.4, 88.9, 88.8, 35.9, 31.4, 30.9, 22.5, 21.5, 14.0. HRMS (EI) m/z: $[M]^+$ calcd for $C_{20}H_{22}$ 262.1722; found 262.1716.

*2-(5-(4-Bromophenyl)pent-4-yn-1-yl)isoindoline-1,3-dione (**3z**).* Yellow solid; yield: 53.7 mg, 73%; mp 109−110 °C. ^{1}H NMR ($CDCl_3$, 400 M): δ 7.81−7.79 (m, 2H), 7.67−7.65 (m, 2H), 7.33 (d, J = 8.0 Hz, 2H), 7.11 (d, J = 8.0 Hz, 2H), 3.85 (t, J = 6.8 Hz, 2H), 2.47 (t, J = 7.2 Hz, 2H), 2.04−1.97 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.4, 133.9, 132.9, 132.1, 131.3, 123.2, 122.5, 121.6, 90.0, 80.2, 37.3, 27.1, 17.3. HRMS (EI) m/z: $[M]^+$ calcd for $C_{19}H_{14}BrNO_2$ 367.0208; found 367.0203.

*4-((4-Bromophenyl)ethynyl)-4′-propyl-1,1′-biphenyl (**3za**).* White solid; yield: 55.5 mg, 74%; mp 226−228 °C. ^{1}H NMR ($CDCl_3$, 400 M): δ 7.60−7.55 (m, 4H), 7.53−7.48 (m, 4H), 7.40 (d, J = 8.0 Hz, 2H), 7.26 (d, J = 6.4 Hz, 2H), 2.63 (t, J = 7.6 Hz, 2H), 1.73−1.63 (m, 2H), 0.97 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 142.4, 141.2, 137.6, 133.0, 132.0, 131.6, 129.0, 126.9, 126.8, 122.4, 122.3, 121.4, 90.6, 88.8, 37.7, 24.5, 13.8. HRMS (EI) m/z: $[M]^+$ calcd for $C_{23}H_{19}Br$ 374.0670; found 374.0664.

*1-Bromo-3-((4-propylphenyl)ethynyl)benzene (**3zf**).* White solid; yield: 43.0 mg, 72%; mp 43−44 °C. ^{1}H NMR ($CDCl_3$, 400 M): δ 7.68 (s, 1H), 7.44 (d, J = 8.0 Hz, 4H), 7.22−7.16 (m, 3H), 2.61 (t, J = 7.6 Hz, 2H), 1.70−1.61 (m, 2H), 0.95 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.6, 134.2, 131.5, 131.1, 130.0, 129.7, 128.6, 125.5, 122.1, 119.9, 90.9, 87.2, 38.0, 24.3, 13.7. HRMS (EI) m/z: $[M]^+$ calcd for $C_{17}H_{15}Br$ 298.0357; found 298.0351.

*1-Bromo-2-((4-propylphenyl)ethynyl)benzene (**3zg**).* Colorless liquid; yield: 20.3 mg, 34%. ^{1}H NMR ($CDCl_3$, 400 M): δ 7.59 (d, J = 8.0 Hz, 1H), 7.54−7.47 (m, 3H), 7.28−7.23 (m, 1H), 7.16−7.12 (m, 3H), 2.58 (t, J = 7.6 Hz, 2H), 1.68−1.58 (m, 2H), 0.93 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.6, 133.1, 132.4, 131.6, 129.1, 128.5, 127.0, 125.6, 125.5, 120.0, 94.2, 87.4, 38.0, 24.3, 13.7. HRMS (EI) m/z: $[M]^+$ calcd for $C_{17}H_{15}Br$ 298.0357; found 298.0351.

*1,4-Bis((4-methoxyphenyl)ethynyl)benzene (**4a**).* An oven-dried Schlenk tube of 25 mL equipped with a magnetic stir bar was charged with **3zi** (0.2 mmol), $Pd(PPh_3)_2Cl_2$ (4 mol %), and CuI (2 mol %). After being charged with nitrogen three times, 1-ethynyl-4-methoxybenzene **2l** (0.24 mmol, 1.2 equiv), diisopropylmine (0.4 mmol, 2.0 equiv), and THF (1.0 mL) were added under nitrogen atmosphere, and the mixture was refluxed at 90 °C for 15 h. After cooling to room temperature, the reaction mixture was concentrated in vacuo. The residue was purified by column chromatography on silica gel and eluted with petroleum ether to afford the desired product as a light yellow solid. Yield: 53.5 mg, 79%; mp 214−216 °C. ^{1}H NMR (400 M, $CDCl_3$): δ 7.48−7.46 (m, 8H), 6.88 (d, J = 8.0 Hz, 4H), 3.83 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.8, 133.1, 131.3, 123.1, 115.2, 114.0, 91.1, 87.9, 55.3. HRMS (EI) m/z: $[M]^+$ calcd for $C_{24}H_{18}O_2$ 338.1307; found 338.1301.

*3-(4-((4-(tert-Butyl)phenyl)ethynyl)phenyl)thiophene (**4b**).* An oven-dried Schlenk tube of 25 mL equipped with a magnetic stir bar was charged with **3zj** (0.2 mmol), thiophen-3-ylboronic acid **5** (0.2 mmol), $Pd(PPh)_4$ (5 mol %), and K_2CO_3 (2.0 equiv). After being charged with nitrogen three times, tolunene (1.0 mL) was added under nitrogen atmosphere, and the mixture was refluxed at 110 °C for 15 h. After cooling to room temperature, the reaction mixture was concentrated in vacuo. The residue was purified by column chromatography on silica gel and eluted with ethyl acetate/petroleum ether (1/20) to afford the desired product as a white solid. Yield: 46.0 mg, 73%; mp 189−190 °C. ^{1}H NMR (400 M, $CDCl_3$): δ 7.46−7.43 (m, 5H), 7.38−7.36 (m, 3H), 7.29−7.26 (m, 3H), 1.22 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.5, 141.6, 135.4, 132.0, 131.3, 126.4, 126.2, 126.1, 125.4, 122.1, 120.7, 120.2, 90.2, 88.7, 34.8, 31.2. HRMS (EI) m/z: $[M]^+$ calcd for $C_{22}H_{20}S$ 316.1286; found 316.1280.

*(E)-2-(4-((4-Methoxyphenyl)ethynyl)styryl)pyridine (**4c**).* An oven-dried Schlenk tube of 25 mL equipped with a magnetic stir bar was charged with **3zi** (0.2 mmol), $Pd(PPh_3)_4$ (5 mol %), and NaOAc (2.0 equiv). After being charged with nitrogen three times, 2-vinylpyridine **6** (0.24 mmol, 1.2 equiv) and toluene (1.0 mL) were added under nitrogen atmosphere, and the mixture was refluxed at 110 °C for 15 h. After cooling to room temperature, the reaction mixture was concentrated in vacuo. The residue was purified by column chromatography on silica gel and eluted with ethyl acetate/petroleum ether (1/5) to afford the desired product as a yellow solid. Yield: 50.2 mg, 81%; mp 172−174 °C. ^{1}H NMR (400 M, $CDCl_3$): δ 8.61 (d, J = 4.0 Hz, 1H), 7.68−7.61 (m, 2H), 7.56−7.47 (m, 6H), 7.37 (d, J = 7.6 Hz, 1H), 7.20−7.13 (m, 2H), 6.88 (d, J = 8.4 Hz, 2H), 3.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.6, 155.4, 149.7, 136.6, 136.2, 133.1, 132.0, 131.7, 128.5, 127.0, 123.4, 122.3, 122.2, 115.3, 114.0, 90.7, 88.2, 55.3. HRMS (EI) m/z: $[M]^+$ calcd for $C_{22}H_{17}NO$ 311.1310; found 311.1305.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b00899.

NMR tracing of the reaction, LCMS analysis of the control reaction, general experimental procedure, ^{1}H NMR and ^{13}C NMR spectra data of the known products, and references and copies of ^{1}H, ^{13}C, and ^{19}F NMR charts of products (PDF)

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Notes

The authors declare no competing financial interest.

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