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# Copper-free Sonogashira Coupling Reaction Using a *trans*-Spanning 1,2-Bis(2-thienylethynyl)benzene Ligand

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Novel copper-free Sonogashira coupling reaction of aryl halides with terminal acetylenes proceeded in the presence of 1,2-bis(2-thienylethynyl)benzene (**1**) as a *trans*-bidentatable ligand.

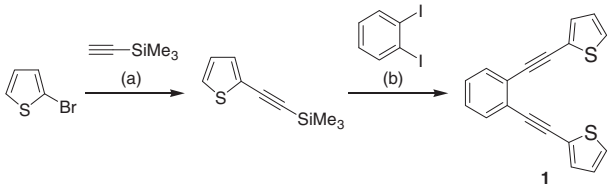
A carbon–carbon triple bond is often found as a useful moiety in natural products, bioactive compounds, and functional materials, and the development of the synthetic methods of acetylenes is an important research project in organic chemistry.[1] From the organometallic approach, the Sonogashira coupling reaction using a Pd/Cu system[2] is one of the most convenient methods for the synthesis of acetylenes. In this method, however, the reaction has often suffered from an oxidative coupling reaction of acetylene induced by $Cu/O_2$ to afford diyne. For the purpose of avoiding this problem, copper-free Sonogashira coupling reactions have been developed for highly selective reaction systems in the past decade by the use of, for example, ionic liquid as a solvent,[3] *N*-heterocyclic carbene ligands,[4] and heterogeneous palladium complexes.[5,6]

We are interested in transition-metal-catalyzed reactions using bidentate ligands, which coordinate at *trans*-positions of the metal center, known as *trans*-spanning ligands.[7] Despite the unique coordination structure, *trans*-spanning ligands have been rarely employed for transition-metal-catalyzed reactions, because those ligands often inhibit oxidative addition or reductive elimination.[8] Nonetheless, Ueda et al. reported that the Mizoroki–Heck reaction took place in the presence of a rigid *trans*-spanning ligand.[9a] Furthermore, Gelman suggested that *trans*-spanning ligands have the tendency to form cationic palladium species which facilitates olefin insertion.[7b] From these viewpoints, *trans*-spanning ligands are expected to have a potential to strongly affect the reactivity and/or the selectivity of transition-metal-catalyzed reactions. Herein, we report a Cu-free Sonogashira coupling reaction using a *trans*-spanning ligand.

To begin with, 1,2-bis(2-thienylethynyl)benzene (**1**) was designed as a *trans*-spanning ligand. Both sulfur atoms of the thiophene rings are coordinatable[10,11] at *trans*-positions of the metal because of the relatively rigid structure of **1**. Indeed, pyridine analogs, bearing two pyridine rings instead of thiophene rings, were reported as examples of the *trans*-spanning ligands.[9] Diethynylbenzene **1** was synthesized easily by repetitive Sonogashira coupling reactions from 2-bromothiophene in 3 steps (Scheme 1).

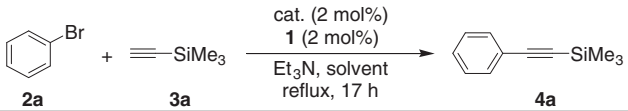
Now, we have examined Cu-free Sonogashira coupling reaction using **1** (Table 1). A mixture of bromobenzene (**2a**) (0.5 mmol), trimethylsilylacetylene (**3a**) (0.75 mmol), palladium catalyst (0.01 mmol), **1** (0.01 mmol), triethylamine (1.7 mmol), and a solvent (1.5 mL) was refluxed for 17 h. When triethylamine (1.5 mL) was used as a solvent in the presence of $[Pd(PPh_3)_4]$ catalyst, the corresponding coupling product **4a** was obtained in 40% yield as shown in Table 1 (Entry 1). The use of acetonitrile as the solvent was specifically suitable to give **4a** in good yield, though THF and toluene were ineffective (Entries 2, 3, and 4). When $[PdCl_2(PPh_3)_2]$ was employed, an enhancement of the reactivity was observed (Entry 5), whereas $[PdCl_2(PhCN)_2]$, $[PdCl_2(cod)]$, and $[Pd(OAc)_2]$ were not effective (Entries 6, 7, and 8). The yield of **4a** was considerably diminished by employment of 6 mol% of **1** (Entry 9) or in the absence of **1** (Entry 10).

Cu-free Sonogashira coupling reactions of various acetylenes with aryl halides were examined under the optimized reaction conditions (Entry 5 in Table 1), and the results are shown in Table 2. The reaction of phenylacetylene (**3b**) with iodobenzene (**2b**) gave the corresponding coupling product **4b** in




**Scheme 1.** Preparation of **1**. Reagents and conditions: (a) $[Pd(PPh_3)_4]$, CuI, $Et_3N$, 82%; (b) i) KOH, MeOH, ii) $[Pd(PPh_3)_4]$, CuI, $Et_3N$, 27%.

**Table 1.** Cu-free Sonogashira coupling reaction using **1**[a]

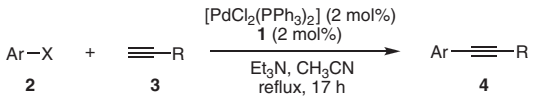


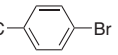
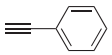
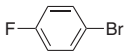
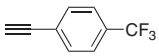
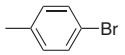
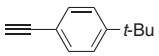
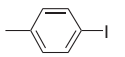
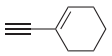
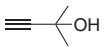

**2a** **3a** **4a**

| Entry | Catalyst | Solvent | Yield[b]/% |
|---|---|---|---|
| 1 | $[Pd(PPh_3)_4]$ | $Et_3N$ | 40 |
| 2 | $[Pd(PPh_3)_4]$ | THF | 5 |
| 3 | $[Pd(PPh_3)_4]$ | toluene | 11 |
| 4 | $[Pd(PPh_3)_4]$ | $CH_3CN$ | 74 |
| 5 | $[PdCl_2(PPh_3)_2]$ | $CH_3CN$ | 90 |
| 6 | $[PdCl_2(PhCN)_2]$ | $CH_3CN$ | <5 |
| 7 | $[PdCl_2(cod)]$ | $CH_3CN$ | <5 |
| 8 | $[Pd(OAc)_2]$ | $CH_3CN$ | <5 |
| 9[c] | $[PdCl_2(PPh_3)_2]$ | $CH_3CN$ | 35 |
| 10[d] | $[PdCl_2(PPh_3)_2]$ | $CH_3CN$ | 22 |

[a]Reagents and conditions: A mixture of **2a** (0.5 mmol), **3a** (0.75 mmol), $Et_3N$ (1.7 mmol), catalyst (0.01 mmol), **1** (0.01 mmol), and solvent (1.5 mL) was refluxed for 17 h under $N_2$ atmosphere. [b]GC yield. [c]**1** (6 mol%). [d]Without **1**.

**Table 2.** Cu-free Sonogashira coupling reaction of various aryl halides with acetylenes[a]

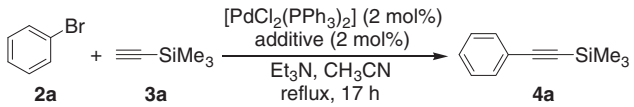


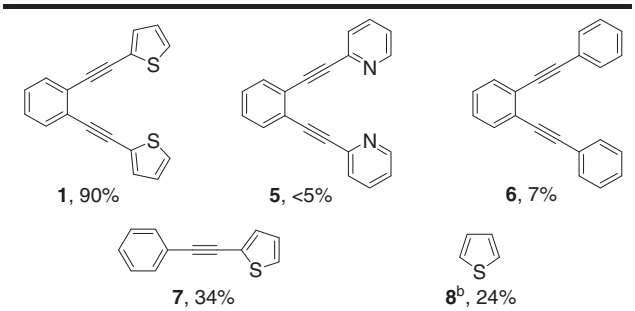

| Entry | Ar–X | | R | | Yield[b]/% | Entry | Ar–X | | R | | Yield[b]/% |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 |  | **2a** | SiMe$_3$ | **3a** | **4a** 81 | 10[f] |  | **2c** | **3a** | | **4j** 82 |
| 2[c,d] |  | **2b** |  | **3b** | **4b** 84 | 11 |  | **2d** | **3a** | | **4k** 74 |
| 3 | | **2b** |  | **3c** | **4c** 98 | 12 |  | **2e** | **3a** | | **4l** 47 |
| 4 | | **2b** |  | **3d** | **4d** 82 | 13 |  | **2f** | **3a** | | **4l** 83 |
| 5 | | **2b** |  | **3e** | **4e** 95 | 14[c] |  | **2g** | **3a** | | **4m** 90 |
| 6 | | **2b** |  | **3f** | **4f** 82 | 15 |  | **2h** | **3a** | | **4n** 21 |
| 7[c] | | **2b** | *n*-Hex | **3g** | **4g** 38 | 16 |  | **2i** | **3a** | | **4o** 17 |
| 8[e] | | **2b** | (CH$_2$)$_4$OH | **3h** | **4h** 29 | 17 |  | **2j** | **3a** | | **4p** 99 |
| 9[e] | | **2b** | (CH$_2$)$_3$CN | **3i** | **4i** 70 | | | | | | |

[a]Reagents and conditions: A mixture of **2** (0.5 mmol), **3** (0.75 mmol), Et$_3$N (1.7 mmol), catalyst (0.01 mmol), **1** (0.01 mmol), and acetonitrile (1.5 mL) was refluxed for 17 h under $N_2$ atmosphere. [b]Isolated yield. [c]At 60 °C. [d]Diyne from **3b** was detected in 7% yield (based on **3b**). [e]At ambient temperature. [f]Reaction time: 3 h.

84% yield (Entry 2).[12] 4-Substituted aromatic acetylenes such as **3c** and **3d** and conjugate enyne **3e** also gave the corresponding products in good to excellent yields (Entries 3, 4, and 5). An aliphatic acetylene, 2-methyl-3-butyn-2-ol (**3f**), was applicable to this coupling reaction (Entry 6). The reactions of **3g**, **3h**, and **3i**, having hydrogen atoms at the propargylic position, also proceeded selectively at lower temperature to yield the corresponding products (Entries 7, 8, and 9). Next, the reactions of electron-deficient aryl bromides such as **2c** and **2d**, gave the desired products **4j** and **4k** in 82% and 74% yields, respectively (Entries 10 and 11). In the case of 4-methyl-substituted aryl halide, the use of iodide **2f** instead of bromide **2e** increased the reactivity greatly to afford the corresponding product **4l** in good yield (Entries 12 and 13). The reaction of 1-bromo-2-iodobenzene (**2g**), having two different halides, proceeded efficiently at 60 °C on the more reactive iodo position selectively to give 1-bromo-2-(trimethylsilylethynyl)benzene (**4m**) in 90% yield (Entry 14). The result of the reaction of 1-bromonaphthalene (**2h**) gave a low yield of **4n** due to steric factors (Entry 15). In this catalytic reaction, heteroaromatic halides were also employable. 2-Bromopyridine (**2i**) reacted with **3a** to give the corresponding product **4o**, though the reaction suffered from unfavorable coordination of a nitrogen atom of **2i** (Entry 16). In contrast, 2-bromothiophene (**2j**) was converted to give the desired product **4p** quantitatively (Entry 17). In most cases, trace amounts of diynes were detected by GC/MS analysis, but the diynes could be removed from the Sonogashira coupling products by purification using column chromatography.

**Table 3.** Cu-free Sonogashira coupling reaction using various additives[a]




[a]GC yield. [b]4 mol%.

In order to confirm the effect of the *trans*-spanning ligand **1**, the catalytic reaction was conducted in the presence of several diethynylbenzene derivatives and related compounds (Table 3). The use of **5** seemed to be unfavorable because two pyridine moieties would coordinate strongly to the palladium. A diethynylbenzene **6**, which has no heteroatom as a coordination site, was also unfavorable in this reaction. The use of 2 mol% of 2-thienylethynylbenzene (**7**) or 4 mol% of thiophene (**8**), giving **4a** in 34% or 24% yield, respectively, resulted in similar reactivity as observed in the case that no additive is employed

(Entry 10 in Table 1). These results imply that rigid and *trans*-coordinatable diethynylbenzene, bearing relatively weak coordination sites such as thiophene,[13] would be effective for this catalytic reaction. Additionally, unfavorable effect of *trans*-coordination on the catalytic process could be mitigated due to the weak coordination of thiophene groups, though pyridine analog **5** clearly decreased the reactivity. The fundamental effect of **1** in Cu-free Sonogashira reaction[14] is unclear. However, according to the fact that the reaction was promoted by ligand **1**, *trans*-Pd complex with **1** may have an important role in this system.[15–17]

In summary, we have developed Cu-free Sonogashira coupling reaction using the *trans*-spanning ligand **1**. The sulfur atom of thiophene, which coordinates weakly to the metal, would be suitable for this reaction. Further studies on the mechanistic insight are now in progress.

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13 Although attempts to obtain X-ray quality crystals of transition-metal complex of **1** have been unsuccessful because of its relatively weak binding ability of **1**,[11] the formation of the *trans*-bidentate complex of **1**, as well as **5**,[9] was conceivable according to the DFT calculation.

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18 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.


  