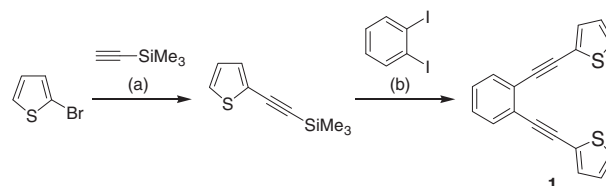


## Copper-free Sonogashira Coupling Reaction Using a *trans*-Spanning 1,2-Bis(2-thienylethynyl)benzene Ligand

Shingo Atobe, Motohiro Sonoda,\* Yuki Suzuki, Hiroyuki Shinohara, Takuya Yamamoto, and Akiya Ogawa\*  
Department of Applied Chemistry, Graduate School of Engineering, Osaka Prefecture University,  
1-1 Gakuen-cho, Naka-ku, Sakai, Osaka 599-8531

(Received March 24, 2011; CL-110250; E-mail: ogawa@chem.osakafu-u.ac.jp)

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*-bidentate ligand.



**Scheme 1.** Preparation of **1**. Reagents and conditions: (a) [Pd(PPh<sub>3</sub>)<sub>4</sub>], CuI, Et<sub>3</sub>N, 82%; (b) i) KOH, MeOH, ii) [Pd(PPh<sub>3</sub>)<sub>4</sub>], CuI, Et<sub>3</sub>N, 27%.

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.<sup>1</sup> From the organometallic approach, the Sonogashira coupling reaction using a Pd/Cu system<sup>2</sup> 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<sub>2</sub> 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,<sup>3</sup> *N*-heterocyclic carbene ligands,<sup>4</sup> and heterogeneous palladium complexes.<sup>5,6</sup>

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.<sup>7</sup> 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.<sup>8</sup> Nonetheless, Ueda et al. reported that the Mizoroki–Heck reaction took place in the presence of a rigid *trans*-spanning ligand.<sup>9a</sup> Furthermore, Gelman suggested that *trans*-spanning ligands have the tendency to form cationic palladium species which facilitates olefin insertion.<sup>7b</sup> 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<sup>10,11</sup> 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.<sup>9</sup> 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 triethyl-

**Table 1.** Cu-free Sonogashira coupling reaction using **1**<sup>a</sup>

Entry	Catalyst	Solvent	Yield <sup>b</sup> /%
1	[Pd(PPh <sub>3</sub> ) <sub>4</sub> ]	Et <sub>3</sub> N	40
2	[Pd(PPh <sub>3</sub> ) <sub>4</sub> ]	THF	5
3	[Pd(PPh <sub>3</sub> ) <sub>4</sub> ]	toluene	11
4	[Pd(PPh <sub>3</sub> ) <sub>4</sub> ]	CH <sub>3</sub> CN	74
5	[PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub> ]	CH <sub>3</sub> CN	90
6	[PdCl <sub>2</sub> (PhCN) <sub>2</sub> ]	CH <sub>3</sub> CN	<5
7	[PdCl <sub>2</sub> (cod)]	CH <sub>3</sub> CN	<5
8	[Pd(OAc) <sub>2</sub> ]	CH <sub>3</sub> CN	<5
9 <sup>c</sup>	[PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub> ]	CH <sub>3</sub> CN	35
10 <sup>d</sup>	[PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub> ]	CH <sub>3</sub> CN	22

<sup>a</sup>Reagents and conditions: A mixture of **2a** (0.5 mmol), **3a** (0.75 mmol), Et<sub>3</sub>N (1.7 mmol), catalyst (0.01 mmol), **1** (0.01 mmol), and solvent (1.5 mL) was refluxed for 17 h under N<sub>2</sub> atmosphere. <sup>b</sup>GC yield. <sup>c</sup>**1** (6 mol%). <sup>d</sup>Without **1**.

amine (1.5 mL) was used as a solvent in the presence of [Pd(PPh<sub>3</sub>)<sub>4</sub>] 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<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>] was employed, an enhancement of the reactivity was observed (Entry 5), whereas [PdCl<sub>2</sub>(PhCN)<sub>2</sub>], [PdCl<sub>2</sub>(cod)], and [Pd(OAc)<sub>2</sub>] 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).

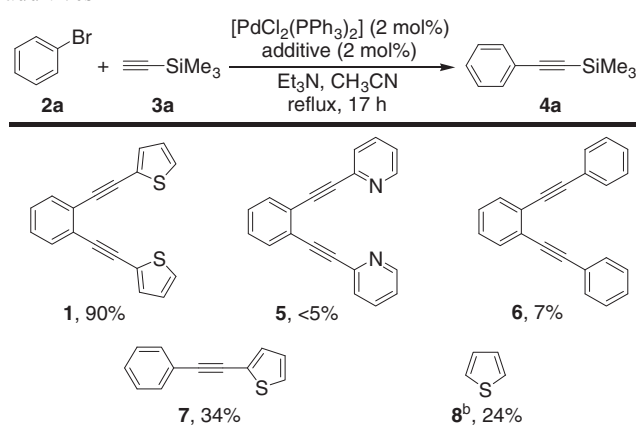
Cu-free Sonogashira coupling reactions of various acetylenes with aryl halides were examined under the optimized reaction conditions (Entry 5 in Table 1), and the results are shown in Table 2. The reaction of phenylacetylene (**3b**) with iodobenzene (**2b**) gave the corresponding coupling product **4b**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

**Table 2.** Cu-free Sonogashira coupling reaction of various aryl halides with acetylenes<sup>a</sup>

		$\text{Ar-X} + \text{R-C}\equiv\text{C} \xrightarrow[\text{Et}_3\text{N, CH}_3\text{CN, reflux, 17 h}]{[\text{PdCl}_2(\text{PPh}_3)_2] (2 \text{ mol}\%), \mathbf{1} (2 \text{ mol}\%)}$				$\text{Ar-C}\equiv\text{C-R}$	
Entry	Ar-X	$\text{R-C}\equiv\text{C}$	Yield <sup>b</sup> /%	Entry	Ar-X	$\text{R-C}\equiv\text{C}$	Yield <sup>b</sup> /%
1		$\text{SiMe}_3$	<b>4a</b> 81	10 <sup>f</sup>		<b>3a</b>	<b>4j</b> 82
2 <sup>c,d</sup>			<b>4b</b> 84	11		<b>3a</b>	<b>4k</b> 74
3	<b>2b</b>		<b>4c</b> 98	12		<b>3a</b>	<b>4l</b> 47
4	<b>2b</b>		<b>4d</b> 82	13		<b>3a</b>	<b>4l</b> 83
5	<b>2b</b>		<b>4e</b> 95	14 <sup>c</sup>		<b>3a</b>	<b>4m</b> 90
6	<b>2b</b>		<b>4f</b> 82	15		<b>3a</b>	<b>4n</b> 21
7 <sup>c</sup>	<b>2b</b>	$n\text{-Hex}$	<b>4g</b> 38	16		<b>3a</b>	<b>4o</b> 17
8 <sup>e</sup>	<b>2b</b>	$(\text{CH}_2)_4\text{OH}$	<b>4h</b> 29	17		<b>3a</b>	<b>4p</b> 99
9 <sup>e</sup>	<b>2b</b>	$(\text{CH}_2)_3\text{CN}$	<b>4i</b> 70				

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

84% yield (Entry 2).<sup>12</sup> 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-(trimethylsilyl)ethynylbenzene (**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<sup>a</sup>

<sup>a</sup>GC yield. <sup>b</sup>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,<sup>13</sup> 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<sup>14</sup> 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.<sup>15–17</sup>

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.

This work was supported in part by the Grant-in-Aid for Young Scientists (B) from The Ministry of Education, Culture, Sports, Science and Technology (MEXT) of Japan (No. 19750082), and by a Shionogi Pharmaceuticals Inc. Award in Synthetic Organic Chemistry, Japan, through The Society of Synthetic Organic Chemistry, Japan, granted to M.S.

This paper is in celebration of the 2010 Nobel Prize awarded to Professors Richard F. Heck, Akira Suzuki, and Ei-ichi Negishi.

#### References and Notes

- 1 *Acetylene Chemistry: Chemistry, Biology, and Material Science*, ed. by F. Diederich, P. J. Stang, R. R. Tykwinski, Wiley-VCH, Weinheim, **2005**.
- 2 a) K. Sonogashira, Y. Tohda, N. Hagihara, *Tetrahedron Lett.* **1975**, *16*, 4467. b) S. Takahashi, Y. Kuroyama, K. Sonogashira, N. Hagihara, *Synthesis* **1980**, 627. For recent reviews, see: c) R. Chinchilla, C. Nájera, *Chem. Rev.* **2007**, *107*, 874. d) H. Doucet, J.-C. Hierso, *Angew. Chem., Int. Ed.* **2007**, *46*, 834.
- 3 T. Fukuyama, M. Shinmen, S. Nishitani, M. Sato, I. Ryu, *Org. Lett.* **2002**, *4*, 1691.
- 4 a) A. John, M. M. Shaikh, P. Ghosh, *Dalton Trans.* **2009**, 10581. b) A. Zanardi, J. A. Mata, E. Peris, *Organometallics* **2009**, *28*, 4335. c) S. Roy, H. Plenio, *Adv. Synth. Catal.* **2010**, *352*, 1014.
- 5 a) S. M. Islam, P. Mondal, A. S. Roy, S. Mondal, D. Hossain, *Tetrahedron Lett.* **2010**, *51*, 2067. b) M. Bakherad, A. H. Amin, A. Keivanloo, B. Bahramian, M. Raeissi, *Tetrahedron Lett.* **2010**, *51*, 5653. c) T. Suzuka, Y. Okada, K. Ooshiro, Y. Uozumi, *Tetrahedron* **2010**, *66*, 1064.
- 6 For recent copper-free Sonogashira reactions, see: a) C. Yi, R. Hua, *J. Org. Chem.* **2006**, *71*, 2535. b) M. Bakherad, A. Keivanloo, B. Bahramian, M. Hashemi, *Tetrahedron Lett.* **2009**, *50*, 1557. c) S. Gu, W. Chen, *Organometallics* **2009**, *28*, 909. d) A. Chandra, B. Singh, R. S. Khanna, R. M. Singh, *J. Org. Chem.* **2009**, *74*, 5664. e) Y. Luo, J. Wu, *Tetrahedron* **2009**, *65*, 6810. f) R. Thorwirth, A. Stolle, B. Ondruschka, *Green Chem.* **2010**, *12*, 985. g) S. J. Shirbin, B. A. Boughton, S. C. Zammit, S. D. Zanatta, S. M. Marcuccio, C. A. Hutton, S. J. Williams, *Tetrahedron Lett.* **2010**, *51*, 2971. h) H. Firouzabadi, N. Iranpoor, M. Gholinejad, *J. Mol. Catal. A: Chem.* **2010**, *321*, 110.
- 7 a) C. A. Bessel, P. Aggarwal, A. C. Marschilok, K. J. Takeuchi, *Chem. Rev.* **2001**, *101*, 1031. b) L. Kaganovsky, K.-B. Cho, D. Gelman, *Organometallics* **2008**, *27*, 5139. c) P. Štěpnička, M. Krupa, M. Lamač, I. Čiřáková, *J. Organomet. Chem.* **2009**, *694*, 2987.
- 8 To the best of our knowledge, no report clearly mentions that *trans*-coordination inhibits oxidative addition, but it is considered that the inhibition exists in the same theory as reductive elimination. For the inhibition of reductive elimination, see: A. Gillie, J. K. Stille, *J. Am. Chem. Soc.* **1980**, *102*, 4933.
- 9 a) T. Kawano, T. Shinomaru, I. Ueda, *Org. Lett.* **2002**, *4*, 2545. b) Y.-Z. Hu, C. Chamchoumis, J. S. Grebowicz, R. P. Thummel, *Inorg. Chem.* **2002**, *41*, 2296. c) T. Kawano, J. Kuwana, I. Ueda, *Bull. Chem. Soc. Jpn.* **2003**, *76*, 789. d) E. Bosch, C. L. Barnes, N. L. Brennan, G. L. Eakins, B. E. Breyfogle, *J. Org. Chem.* **2008**, *73*, 3931.
- 10 S. M. A. Rahman, M. Sonoda, M. Ono, K. Miki, Y. Tobe, *Org. Lett.* **2006**, *8*, 1197.
- 11 For  $\eta^1$ -S-bound coordination, see: a) L. Antolini, G. Minghetti, A. Mucci, F. Parenti, L. Pigani, G. Sanna, R. Seeber, C. Zanardi, *Inorg. Chim. Acta* **2005**, *358*, 3033. b) X. Fang, J. G. Watkin, B. L. Scott, G. J. Kubas, *Organometallics* **2001**, *20*, 3351. c) E. C. Constable, R. P. G. Henney, D. A. Tocher, *J. Chem. Soc., Dalton Trans.* **1992**, 2467. For a general review, see: d) S. Harris, *Organometallics* **1994**, *13*, 2628.
- 12 When bromobenzene (**2a**) was used instead of iodobenzene (**2b**), some by-products having enyne structures from phenylacetylene (**3b**) were formed together with the corresponding product **4b**.
- 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**,<sup>11</sup> the formation of the *trans*-bidentate complex of **1**, as well as **5**,<sup>9</sup> was conceivable according to the DFT calculation.
- 14 There are a few reports mentioned about the reaction pathways of Cu-free Sonogashira reactions, see: a) V. Grosshenny, F. M. Romero, R. Ziessel, *J. Org. Chem.* **1997**, *62*, 1491. b) J. Cheng, Y. Sun, F. Wang, M. Guo, J.-H. Xu, Y. Pan, Z. Zhang, *J. Org. Chem.* **2004**, *69*, 5428. c) Y. Liang, Y.-X. Xie, J.-H. Li, *J. Org. Chem.* **2006**, *71*, 379. d) T. Ljungdahl, T. Bennur, A. Dallas, H. Emtenäs, J. Mårtensson, *Organometallics* **2008**, *27*, 2490. e) S. S. Palimkar, V. S. More, K. V. Srinivasan, *Ultrason. Sonochem.* **2008**, *15*, 853.
- 15 *trans*-Form of [Pd(Ar)(X)L<sub>2</sub>] complex was relatively stable to its *cis*-form, and therefore the isomerization could be considerable. a) G. Calvin, G. E. Coates, *J. Chem. Soc.* **1960**, 2008. b) P. Fitton, M. P. Johnson, J. E. McKeon, *Chem. Commun. (London)* **1968**, 6. c) K. Osakada, R. Sakata, T. Yamamoto, *Organometallics* **1997**, *16*, 5354. d) F. Kessler, B. Weibert, H. Fischer, *Organometallics* **2010**, *29*, 5154.
- 16 In our system, *trans*-[Pd(Ar)(X)(**1**)] complex was likely to generate after an oxidative addition of aryl halide, though our experimental efforts for detection of the complex were unsuccessful.
- 17 In some Pd-catalyzed reactions, *trans*-[Pd(Ar)(X)L<sub>2</sub>] complexes are considered as key intermediates in a transmetalation step, see: a) V. Farina, B. Krishnan, *J. Am. Chem. Soc.* **1991**, *113*, 9585. b) C. Amatore, A. Jutand, A. Suarez, *J. Am. Chem. Soc.* **1993**, *115*, 9531. c) S. Tollis, V. Narducci, P. Cianfriglia, C. L. Sterzo, E. Viola, *Organometallics* **1998**, *17*, 2388. d) A. Ricci, F. Angelucci, M. Bassetti, C. L. Sterzo, *J. Am. Chem. Soc.* **2002**, *124*, 1060.
- 18 Supporting Information is available electronically on the CSJ-Journal Web site, <http://www.csj.jp/journals/chem-lett/index.html>.