Bull. Chem. Soc. Jpn. Vol. 79, No. 3, 492–494 (2006)

# Functional Group Compatible Palladium-Catalyzed Cross-Coupling Reactions between Aryllithium and Aryl Halide Mediated by a Five-Membered Cyclic Silyl Ether

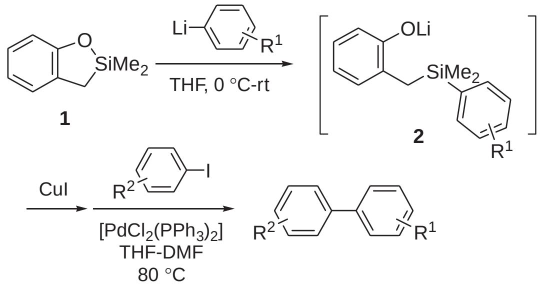
**Eun-Cheol Son, Hayato Tsuji, Tomoyuki Saeki, and Kohei Tamao***†

International Research Center for Elements Science
(IRCELS), Institute for Chemical Research,
Kyoto University, Uji, Kyoto 611-0011

Received October 5, 2005; E-mail: tamao@riken.jp

A functional group compatible palladium-catalyzed cross-coupling reaction between aryllithiums and aryl halides mediated by a five-membered cyclic silyl ether as a precursor for an activated arylsilane has been developed. The reaction proceeds under mild conditions without the addition of a fluoride salt or a base to activate the silyl reagent.

The transition metal-catalyzed cross-coupling reactions between organometallic reagents and organic halides or pseudohalides have been extensively studied because of their versatility for carbon–carbon bond formation.[1] Among these organometallic nucleophiles, organosilicon compounds are some of the most useful reagents in the palladium-catalyzed cross-coupling reactions[2–4] as long as the proper activation of the silicon carbon bond is achieved; the silicon-based cross-coupling reactions require the formation of hypercoordinate silicon species to promote the transmetallation of the organic group from the silicon to the transition-metal center. For this purpose, a fluoride or a strong base[5] has been used for the activation. Many attempts have recently been made to achieve milder reaction conditions such as fluoride-free or a strong base-free silicon-based cross-coupling reactions.[6,7] Since the silicon center of the substrates must have at least one electronegative atom or group such as F, Cl, or OR for the effective formation of the hypercoordinate silicon species, less reactive tetraorganosilicon compounds have been rarely employed in the transition metal-catalyzed coupling reactions except for a few reactions,[8–10] despite their high stability and high compatibility with other chemical species, as well as their negligible toxicity. We now report the biaryl synthesis between aryllithiums and aryl halides mediated by a five-membered cyclic silyl ether, 2,2-dimethyl-1-oxa-2-silaindan, as a precursor for the activated tetraorganosilicon nucleophiles shown in Scheme 1.[11] The present method allows aryl halides to possess various functional groups.



Scheme 1.

Table 1. Effects of Solvent and Copper Reagent[a)]

| Entry | Solvent | Copper reagent (mol amount)[c)] | Yield of biaryl /%[b)] |
|---|---|---|---|
| 1 | THF | CuI (1) | 25 |
| 2 | THF/MeCN | CuI (1) | 60 |
| 3 | THF/DMSO | CuI (1) | 80 |
| 4 | THF/DMF | CuI (1) | 87[e)] |
| 5 | THF/DMF | CuI (0.5) | 72[f)] |
| 6 | THF/DMF | None | 0 |
| 7[d)] | THF/DMF | CuI (1) | trace |
| 8 | THF/DMF | CuCl (1) | 10 |
| 9 | THF/DMF | CuBr (1) | 52 |
| 10 | THF/DMF | CuCN (1) | trace |

a) $R^1 = H$, $R^2 = 4\text{-}NO_2$. Reaction time = 3 h unless otherwise noted. b) GC yield. c) Mol amount of the copper reagent is based on the cyclic ether **1**. d) Without Pd catalyst. e) Reaction time = 2 h. f) Isolated yield.

As shown in Scheme 1, the arylsilane nucleophile **2** was generated in situ from **1** and an aryllithium ($R^1$-$C_6H_4Li$), to which copper(I) iodide and an aryl iodide ($R^2$-$C_6H_4I$) together with DMF and a 0.02 molar amount of $[PdCl_2(PPh_3)_2]$ were successively added. Upon heating at 80 °C for 2–24 h, the corresponding cross-coupled biaryl compounds were obtained in good yield.[12] It should be noted that the reaction smoothly proceeds without the addition of an external fluoride or even a weak base as an activator.

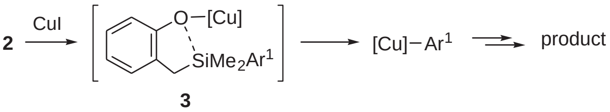
The effects of the solvent and copper reagent are listed in Table 1. Solvent effect (Entries 1–4): The coupling reaction is promoted by the addition of a polar co-solvent. Dimethylformamide (DMF) afforded the best result. Copper(I) reagent effect (Entries 4–10): A stoichiometric amount of CuI is necessary for the effective cross-coupling reactions.

Based on these results, we have postulated a mechanism for the reaction (Scheme 2). The lithium phenoxide species **2** is converted to the copper phenoxide **3**, which subsequently undergoes an intramolecular transmetallation of the aryl group ($Ar^1$) from silicon to copper. This transmetallation is supposed to be promoted by the intramolecular coordination of oxygen to the silicon center by placing these atoms in close proximity. In addition, this step would require a highly polar solvent as reported by Hosomi et al.[9a,b] Indeed, the reaction in THF (Table 1, Entry 1) afforded a large amount of the phenol derivative generated by hydrolysis of the unreacted intermediate **2** or **3**, together with a small amount of the cross-coupled product.

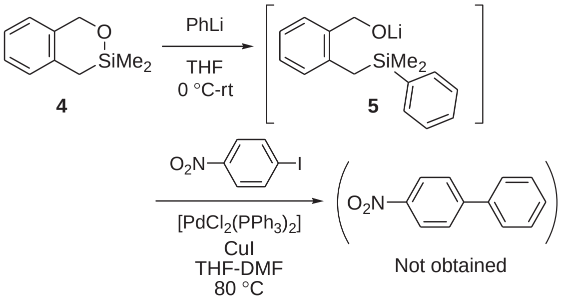
---

† Present address: RIKEN Frontier Research System, 2-1 Hirosawa, Wako, Saitama 351-0198

Published on the web March 8, 2006; DOI 10.1246/bcsj.79.492



Scheme 2.



Scheme 3.

To confirm the significance of such an intramolecular activation, we have tested two types of other silyl substrates. First, trimethylsilylbenzene was used as a silyl nucleophile to attempt an intermolecular activation using a mixture of lithium phenoxide and CuI. This reaction did not afford the desired biaryl compound under similar reaction conditions.[13] Second, a six-membered cyclic silyl ether **4** was used as a precursor of the arylsilane nucleophile **5** (Scheme 3). This reaction affords not the desired cross-coupled product, but the benzyl alcohol derivative due to hydrolysis of the unreacted intermediate **5**. These results clearly demonstrate the advantage of the five-membered cyclic silyl ether **1** suitable for the intramolecular activation in the intermediate **3**.

The cross-coupling reactions of the aryllithium with various functionalized aryl iodides in the presence of **1** have been examined, and the results are summarized in Table 2. As expected, aryl iodides with a nitro, cyano group, ester, and acyl group afforded the corresponding cross-coupled product in high yield (Entries 1 and 3–5). Aryl iodides with an electron-donating group and an aryl bromide require a somewhat longer reaction time (Entries 2, 7, and 8). Sterically hindered aryl iodides resulted in lower yields (Entries 9 and 10). Aryllithiums with electron-donating and electron-withdrawing groups as well as thienyllithium also afford the corresponding biaryl compounds in moderate yields (Entries 11–13).

In summary, we have developed a functional group compatible palladium-catalyzed cross-coupling reaction between aryllithium and aryl halide using 2,2-dimethyl-1-oxa-2-silaindan (**1**) as a precursor for an activated arylsilane. The reactions proceed well in the presence of CuI under mild conditions without the addition of an external fluoride or even a weak base to activate the silyl reagent.

## Experimental

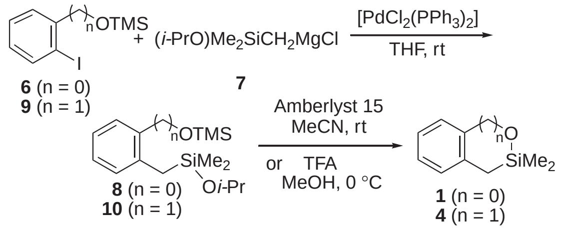
**General.** All reactions were performed under argon. $^1$H (300 MHz) and $^{13}$C (67.9 MHz) NMR spectra were recorded on a Varian Mercury 300 and a JEOL EX-270 spectrometer, respectively. $^1$H and $^{13}$C chemical shifts are referenced to internal benzene-$d_6$ ($^1$H, $\delta$ 7.20 and $^{13}$C, $\delta$ 128.0 ppm). Column chromatography was performed using Kieselgel (70–230 mesh, Merck). THF and DMF were purchased as dried solvents, and other chemicals were used as received.

Table 2. Reactions with Functionalized Aryl Iodides

| Entry | $R^1$ | $R^2$ | Time/h | Yield of biaryl/%$^{a)}$ |
|---|---|---|---|---|
| 1 | H | 4-$NO_2$ | 2 | 87 |
| 2 | H | 4-$NO_2$$^{b)}$ | 6 | 52 |
| 3 | H | 4-CN | 3 | 87 |
| 4 | H | 4-COMe | 3 | 94 |
| 5 | H | 4-$CO_2Et$ | 3 | 81 |
| 6 | H | 4-F | 3 | 89 |
| 7 | H | 4-Me | 3 | 71 |
| 8 | H | 4-OMe | 5 | 77 |
| 9 | H | 2-OMe | 5 | 56 |
| 10 | H | 2,4,6-$Me_3$ | 5 | 44 |
| 11 | OMe | 4-$NO_2$ | 12 | 67 |
| 12 | $CF_3$ | 4-$NO_2$ | 24 | 65 |
| 13 | —$^{c)}$ | 4-$NO_2$ | 17 | 52 |

a) Isolated yield. b) The aryl bromide was used. c) 2-Thienyllithium was used instead of phenyllithium.

**Preparation of 2,2-Dimethyl-1-oxa-2-silaindan (1).** The cyclic ether **1** is a known compound.[14] We have developed our own preparative procedure as shown in the following scheme.



(1)

**1-[(Isopropoxy)dimethylsilyl]methyl-2-trimethylsiloxybenzene (8):** To a solution of 1-iodo-2-trimethylsiloxybenzene (**6**) (33.5 g, 115 mmol) and [$PdCl_2(PPh_3)_2$] (2.42 g, 3.4 mmol) in THF (50 mL) was added the Grignard reagent **7**,[15] which was prepared from the corresponding halide (23 mL, 124 mmol), magnesium (3.35 g, 138 mmol), and THF (100 mL) at room temperature, and the mixture was stirred for 10 h. After quenching with water, the mixture was extracted with $Et_2O$. The combined organic layer was washed with brine and dried over $MgSO_4$. After filtration and evaporation of the solvent, the residue was subjected to vacuum distillation to afford **8** (32.5 g, 110 mmol; 95% yield) as colorless oil; bp 78–80 °C/53 Pa. $^1$H NMR ($C_6D_6$) $\delta$ 0.22 (s, 6H), 0.23 (s, 9H), 1.17 (d, $J = 6.0$ Hz, 6H), 2.35 (s, 2H), 3.97 (sept, $J = 6.0$ Hz, 1H), 6.82 (d, $J = 7.5$ Hz, 1H), 6.91 (dd, $J = 7.5, 7.2$ Hz, 1H), 6.99 (dd, $J = 7.5, 7.2$ Hz, 1H), 7.16 (d, $J = 7.5$ Hz, 1H). $^{13}$C NMR ($C_6D_6$) $\delta$ −0.9, 0.7, 21.6, 26.3, 65.3, 118.6, 121.7, 125.6, 127.9, 130.6, 152.9. $^{29}$Si NMR $\delta$ 12.0, 17.7. MS (EI, 70 eV) $m/z$ (%) 296 ($M^+$, 51), 253 (100). Anal. Calcd for $C_{15}H_{28}O_2Si_2$: C, 60.75; H, 9.52%. Found: C, 60.60; H, 9.73%.

**2,2-Dimethyl-1-oxa-2-silaindan (1):** To a suspension of Amberlyst 15 (0.10 g) in MeCN (10 mL) was added **8** (1.48 g, 5.0 mmol) at room temperature, and the resulting mixture was stirred for 2 h. Amberlyst was removed by decantation and rinsed with THF. The combined organic phase was concentrated under reduced pressure, and subjected to bulb-to-bulb distillation to afford **1** (0.52 g, 3.2 mmol; 63% yield) as colorless oil; bp 105 °C/160 Pa. $^1$H NMR ($C_6D_6$) $\delta$ 0.10 (s, 6H), 1.80 (s, 2H), 6.87 (dd, $J = 6.9, 7.2$ Hz, 1H), 7.07 (dd, $J = 7.2, 7.2$ Hz, 1H), 7.11 (d, $J = 6.9$ Hz, 1H), 7.23 (d, $J = 7.2$ Hz, 1H).

**Preparation of 3,3-Dimethyl-2-oxa-3-sila-1,2,3,4-tetrahydronaphthalene (4).** The cyclic ether **4**[16] was prepared in a similar manner to that described for **1**.

**1-[(Isopropoxy)dimethylsilyl]methyl-2-trimethylsiloxymethylbenzene (10):** To a solution of 1-iodo-2-trimethylsiloxymethylbenzene (**9**) (5.17 g, 16.9 mmol) and $[PdCl_2(PPh_3)_2]$ (0.35 g, 0.5 mmol) in THF (10 mL) was added the Grignard reagent **7**, which was prepared from the corresponding halide (3.5 mL, 19.2 mmol), magnesium (0.49 g), and THF (20 mL), at room temperature, and stirred for 4 h. After quenching with water, the mixture was extracted with $Et_2O$ three times, and the combined organic layer was washed with brine and dried over $MgSO_4$. The remaining crude product was purified by silica gel column chromatography (hexane/AcOEt $= 4/1$ as an eluent) to afford the title compound (5.06 g, 16.3 mmol; 96% yield) as a colorless oil. $^1H$ NMR ($C_6D_6$) $\delta$ 0.11 (s, 6H), 0.20 (s, 9H), 1.08 (d, $J = 6.0$ Hz, 6H), 2.78 (s, 2H), 3.82 (sept, $J = 6.0$ Hz, 1H), 4.85 (s, 2H), 7.06–7.18 (m, 3H), 7.61 (m, 1H). $^{13}C$ NMR ($C_6D_6$) $\delta$ $-0.9$, $-0.1$, 23.8, 26.2, 63.8, 65.5, 124.8, 127.3, 128.0, 129.5, 137.3, 138.1. $^{29}Si$ NMR ($C_6D_6$) $\delta$ 11.6, 17.7. MS (EI, 70 eV) $m/z$ (%) 310 ($M^+$, 0.2), 267 (0.1), 237 (12), 75 (100). Anal. Calcd for $C_{16}H_{30}O_2Si_2$: C, 61.88; H, 9.74%. Found: C, 61.69; H, 9.80%.

**3,3-Dimethyl-2-oxa-3-sila-1,2,3,4-tetrahydronaphthalene (4):** To a solution of **10** (4.2 g, 13.5 mmol) in MeOH (45 mL) was added trifluoroacetic acid (0.01 mL, 0.14 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 0.5 h and at room temperature for 1 h. The mixture was concentrated under reduced pressure and purified by vacuum distillation to afford the title compound (1.92 g, 10.7 mmol; 80% yield) as colorless oil; bp 120 °C/60 Pa. $^1H$ NMR ($C_6D_6$) $\delta$ 0.08 (s, 6H), 1.86 (s, 2H), 4.76 (s, 2H), 6.91 (d, $J = 7.2$ Hz, 1H), 7.02 (dd, $J = 7.2, 7.2$ Hz, 1H), 7.07 (d, $J = 7.2$ Hz, 1H), 7.14 (dd, $J = 7.2, 7.2$ Hz, 1H).

**A Typical Procedure for Biaryl Synthesis.** To a solution of **1** (918 mg, 5.6 mmol) in THF (9.0 mL) was added a dibutyl ether solution of phenyllithium (2.04 mol L$^{-1}$, 2.75 mL, 5.6 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 10 min and at room temperature for 20 min. To the resulting silicon reagent **2** was added CuI (1.07 g, 5.6 mmol) in one portion, and the resulting dark brown mixture was stirred at room temperature for 10 min. To the mixture were added $[PdCl_2(PPh_3)_2]$ (78 mg, 0.11 mmol), 4-iodonitrobenzene (1.27 g, 5.1 mmol), and DMF (3.0 mL). The resulting mixture was stirred at 80 °C for 2 h. After quenching with water, the mixture was filtered and the filtrate was extracted with $Et_2O$ three times. The combined organic layer was washed with brine and dried over $MgSO_4$. After filtration and evaporation of the solvent, the residue was subjected to silica gel column chromatography (hexane/AcOEt $= 4/1$ as an eluent) to afford 4-nitrobiphenyl (880 mg, 4.4 mmol, 87% yield based on 4-iodonitrobenzene) as a yellow solid.

This work was supported by Grants-in-Aid for "Joint Project of Chemical Synthesis Core Research Institutions" and COE Research on "Elements Science" No. 12CE2005 from Ministry of Education, Culture, Sports, Science and Technology, Japan. We also thank Prof. F. Ozawa for valuable discussions.

## References

1 a) *Metal-Catalyzed Cross-Coupling Reactions*, ed. by F. Diederich, P. J. Stang, Wiley-VCH, Weinheim, **1998**. b) N. Miyaura, *Top. Curr. Chem.* **2002**, *219*, 11. c) 30 Years of Cross-Coupling Reaction, in *J. Organomet. Chem. (Special Issue)*, ed. by K. Tamao, T. Hiyama, E. Negishi, **2002**, Vol. 653. d) Cross-Coupling, Synlett Cluster Papers, in *Synlett*, ed. by H. Yamamoto, **2005**, pp. 1763–1804.

2 For reviews, see: a) Y. Hatanaka, T. Hiyama, *Synlett* **1991**, 845. b) S. E. Denmark, R. F. Sweis, *Acc. Chem. Res.* **2002**, *35*, 835.

3 J. Yoshida, K. Tamao, H. Yamamoto, T. Kakui, T. Uchida, M. Kumada, *Organometallics* **1982**, *1*, 542.

4 a) Y. Hatanaka, T. Hiyama, *J. Org. Chem.* **1988**, *53*, 918. b) K. Tamao, K. Kobayashi, Y. Ito, *Tetrahedron Lett.* **1989**, *30*, 6051.

5 a) E. Hagiwara, K. Gouda, Y. Hatanaka, T. Hiyama, *Tetrahedron Lett.* **1997**, *38*, 439. b) S. E. Denmark, R. F. Sweis, *J. Am. Chem. Soc.* **2001**, *123*, 6439.

6 The $Ag_2O$ promoted silicon-based cross-coupling reaction is an example: K. Hirabayashi, J. Kawashima, Y. Nishihara, A. Mori, T. Hiyama, *Org. Lett.* **1999**, *2*, 299.

7 Intramolecular coordination-assisted activation: M. Shindo, K. Matsumoto, K. Shishido, *Synlett* **2005**, 176.

8 For example: K. Itami, T. Nokami, J. Yoshida, *J. Am. Chem. Soc.* **2001**, *123*, 5600.

9 a) H. Ito, H. Sensui, K. Arimoto, K. Miura, A. Hosomi, *Chem. Lett.* **1997**, 639. b) H. Ito, A. Hosomi, *J. Synth. Org. Chem., Jpn.* **2000**, *58*, 274. c) H. Taguchi, K. Ghoroku, M. Tadaki, A. Tsubouchi, T. Takeda, *Org. Lett.* **2001**, *3*, 3811.

10 A. K. Sahoo, T. Oda, Y. Nakao, T. Hiyama, *Adv. Synth. Catal.* **2004**, *346*, 1715, and references cited therein.

11 While developing the present work in our laboratory, Nakao, Hiyama, and their co-workers have reported tetraorganosilicon-based cross-coupling reactions using a similar five-membered cyclic silyl ether: Y. Nakao, H. Imanaka, A. K. Sahoo, A. Yada, T. Hiyama, *J. Am. Chem. Soc.* **2005**, *127*, 6952.

12 The cyclic silyl ether **1** could not be recovered as a pure component after the reaction.

13 Hosomi et al. also reported that a reaction of trimethylsilylbenzene and 4-iodotoluene in the presence of CuI did not afford the cross-coupled product. See Ref. 9a.

14 A. J. Stern, J. S. Swenton, *J. Org. Chem.* **1989**, *54*, 2953.

15 K. Tamao, N. Ishida, Y. Ito, M. Kumada, *Org. Synth.* **1990**, *69*, 96.

16 E. Baciocchi, R. Bernini, O. Lanzalunga, *J. Chem. Soc., Chem. Commun.* **1993**, *22*, 1691.