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(Citation)
Synlett,2003(12):1850-1852

(Issue Date)
2003-10

(Resource Type)
journal article

(Version)
Accepted Manuscript

(URL)
https://hdl.handle.net/20.500.14094/90000442

Palladium-Catalyzed Cross-Coupling Reaction of Silicone with Aryl Chlorides

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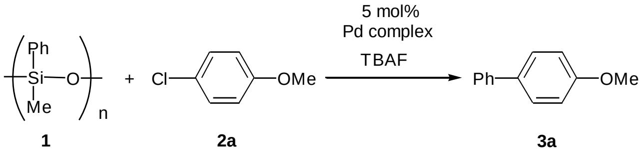
Received July 01, 2003.

Abstract: The palladium-catalyzed cross-coupling reaction of silicone, poly(diorganosiloxane), with aryl chlorides in the presence of K_2CO_3/H_2O as an activator proceeds to afford the biaryl derivatives in moderate to excellent yields. A wide range of aryl chlorides bearing an electron-donating or -withdrawing substituent on the aromatic ring are tolerated. The amount of K_2CO_3 relative to silicone significantly influences the reaction. Treatment of silicone with K_2CO_3/H_2O at room temperature for 1 h prior to the addition of the palladium catalyst and an aryl chloride is necessary.

Key words: palladium, cross coupling, silicone, aqueous potassium carbonate, aryl chlorides

We have recently reported that silicone, poly(diorganosiloxane), participates in the palladium-catalyzed cross-coupling reaction of aryl iodides in the presence of silver(I) oxide (Ag_2O) or tetrabutylammonium fluoride (TBAF) as an activator.[1] This newly developed organosilicon reagent is also available for the rhodium-catalyzed carbon—carbon bond-forming reaction of α,β-unsaturated carbonyl compounds.[2] These results demonstrated the synthetic utility of polysiloxane as a novel organosilicon reagent similar to silanols, silanediols, silanetriols, and other silane reagents.[3] Aryl chlorides are one of the most attractive substrates for the transition metal-catalyzed cross-coupling reaction due to the lower cost compared to aryl bromide or iodide counterparts.[4] Thus, our interest directed to modify the reaction protocol of silicone in order to cross-couple with aryl chlorides. In this paper, we describe a practical palladium-mediated biaryl-forming reaction of siloxane reagents with aryl chlorides.

Initially, we performed the reaction of poly(phenylmethylsiloxane) (**1**)[1b] with 1-chloro-4-methoxybenzene (**2a**) in the presence of 5 mol% of $PdCl_2(PCy_3)_2$,[5] which possessed electron-donating and bulky phosphine ligands and was shown to be effective for several cross-coupling reactions of aryl chlorides, using TBAF[6] as a common activating reagent for organosilicon compounds (Scheme 1). According to the procedure for the previously reported cross-coupling reaction of aryl iodides,[1a] the reaction was carried out using an equimolar amount of TBAF relative to the silicon atom of **1** in toluene at 120 °C for 39 h. However, no coupling product was obtained at all (entry 1). Dramatic improvement was observed by addition of water to afford the desired cross-coupling product **3a** in 65% yield (entry 2). Moreover, it is effective to stir the silicone **1** in the presence of TBAF/H_2O at room temperature for 1 h before the addition of the palladium catalyst and **2a** to accomplish the cross-coupling reaction giving **3a** in 78% yield (entry 3). On the other hand, we detected no coupling product with the palladium catalyst in the absence of a phosphine ligand or $Pd(PPh_3)_4$ (entries 4, 5). These results are explained in terms of the lower reactivity of aryl chlorides compared to that of aryl iodides toward a palladium complex.[7] Ethereal solvent such as 1,4-dioxane was similarly effective for the biaryl formation to furnish the desired coupling product in 81% yield (entry 6). Lowering the temperature to 70 °C also caused cross coupling to give **3a** in 46% yield (entry 7) and increasing the amount of TBAF (2 equiv) resulted in lowering the yield of **3a** (entry 8).



Scheme 1

Table 1 Palladium-catalyzed cross-coupling reaction of 1-chloro-4-methoxybenzene[a]

entry	cat. Pd	solvent	temp./ °C	%yield of **3a**[b]
1[c]	$PdCl_2(PCy_3)_2$	toluene	120	0
2	$PdCl_2(PCy_3)_2$	toluene	120	65
3[c]	$PdCl_2(PCy_3)_2$	toluene	120	78
4[d]	Pd_2dba_3	toluene	120	0
5	$Pd(PPh_3)_4$	toluene	120	0
6	$PdCl_2(PCy_3)_2$	1,4-dioxane	100	81
7	$PdCl_2(PCy_3)_2$	1,4-dioxane	70	46
8[e]	$PdCl_2(PCy_3)_2$	1,4-dioxane	100	61

[a] Unless noted, the reaction was carried out using **1** (1.5 mmol; per unit), **2a** (0.3 mmol), 5 mol% of palladium catalyst, and TBAF (1.5 mmol) in the presence of water (0.5 mL) for 39 h. [b] The yield was determined by ^1H NMR using diphenylmethane as an internal standard. [c] The reaction was performed in the absence of water. [d] Pd_2dba_3 (2.5 mol%) was employed. [e] TBAF (3.0 mmol) was used.

We next investigated the effect of additive and found that fluoride-free cross-coupling reaction was achieved. The results are summarized in Table 2. Cesium carbonate can be employed for this reaction to produce the cross-coupling product in 73% yield (entry 1). It should be noted that use of K_2CO_3 lead to the complete consumption of **2a** giving the 4-methoxybiphenyl (**3a**) in quantitative yield (entry 3).[8] The reaction with K_2CO_3 also proceeded at lower temperature (100 °C) in 1,4-dioxane (entry 5). Another inorganic activator such as NaOH was applicable (entry 6). On the other hand, no coupling product was obtained when Ag_2O was employed (entry 7). This result could be ascribed to the inferior interaction ability between silver and chloride compared with the iodide case.[3c] A decrease in the amount of K_2CO_3 from 2.0 to 1.0 equiv relative to **1** was found to be less effective giving a smaller amount of the cross-coupling product (entry 2). Similarly, the reaction was suppressed to some extent with increasing the amount of K_2CO_3 from 2.0 to 3.0 (entry 4). Consequently, the present reaction was found to be significantly influenced by the amount of activator employed.

Table 2 Effect of additive for the cross coupling of silicone[a]

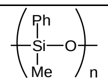
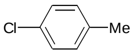
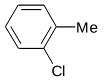
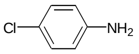
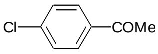
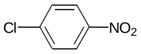
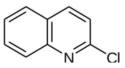
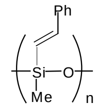
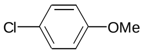
entry	additive	additive/silicone	%yield of **3a**[b]
1	Cs_2CO_3	2	73
2	K_2CO_3	1	65
3	K_2CO_3	2	>99
4	K_2CO_3	3	70
5[c]	K_2CO_3	2	64
6	NaOH	2	>99
7	Ag_2O	1	0

[a] Unless otherwise mentioned, the reaction was carried out in 3 mL of toluene and 0.5 mL of water at 120 °C for 39 h. [b] Estimated by ^1H NMR. [c] The reaction was performed in 1,4-dioxane/H_2O at 100 °C.

During the course of our study on the palladium-mediated cross-coupling reaction of silicone, we suggested that a certain oligomer, which was formed in situ by the activation of silicone with TBAF, might be involved in the cross-coupling reaction.[1] Thus, we examined favorable activating conditions of **1** with K_2CO_3. When **1** was treated with aqueous potassium carbonate at 120 °C for 1 h before addition of palladium catalyst and **2a**, only 25% of the cross-coupling product was obtained. Addition of all reagents in one portion was also ineffective (10% yield). Moreover, the reaction was completely inhibited in the absence of water because of the low solubility of K_2CO_3 in toluene. These results imply that stirring the mixture of silicone and aqueous potassium carbonate at rt for 1 h before addition of the palladium catalyst and an aryl chloride plays an important role in forming the active oligosiloxane to promote the cross-coupling reaction effectively.

Under our optimized reaction conditions, various aryl chlorides were treated with **1** to provide the corresponding coupling products in moderate to excellent yields. As illustrated in Table 3, aryl chlorides bearing an electron-donating or -withdrawing substituent on the aromatic ring underwent the coupling reaction in good yields. Sterically hindered aryl chloride **2c** was also tolerated to produce the corresponding product **3c** in 43% yield (entry 2). A heteroaromatic substrate such as 2-chloroquinoline (**2g**) reacted to afford **3g** in 68% yield (entry 6). Poly[methyl(2-phenylethenyl)siloxane] (**4**), which was prepared by hydrosilylation of poly(methylhydrosiloxane) (PMHS),[1a] served as a substrate for the alkenylation to afford stilbene derivatives in good yields (entries 7,8).

Table 3 Cross-coupling of silicone with aryl chlorides[a]

entry	silicone		aryl chloride		%yield[b]
1		(**1**)		(**2b**)	92
2	**1**			(**2c**)	43
3	**1**			(**2d**)	53
4[c]	**1**			(**2e**)	>99
5	**1**			(**2f**)	77
6	**1**			(**2g**)	68
7		(**4**)		(**2a**)	97
8	**4**		**2f**		70

[a] Unless otherwise specified, the reaction was performed in toluene (3 mL) for 29-48 h at 120 °C using silicone (1.5 mmol), aryl chloride (0.3 mmol), 5 mol% of $PdCl_2(PCy_3)_2$, and 3 mmol of K_2CO_3 in 0.5 mL of H_2O. [b] Determined by ^1H NMR analysis using diphenylmethane as an internal standard. [c] The reaction was carried out using TBAF (1.5 mmol) in 1,4-dioxane at 100 °C.

In general, electron-deficient aryl chlorides are more reactive than electron-rich counterparts because the oxidative addition of the former will occur faster.[7] Nevertheless, the obtained results were rather unusual in that activated aryl chlorides like **2f** or **2g** still remained after 48 h (entries 5, 6) although unactivated chloroarenes such as **2b** was completely consumed within 29 h under analogous conditions to give the coupling product in superior yields (entry 1). Such a phenomenon was also observed when **2a** or **2f** was used as a coupling partner of the cross-coupling reaction with alkenylsiloxane (after stirring for 48 h). These results suggest that rate-determining step of the reaction using K_2CO_3 between silicone and activated chloroarenes may not be oxidative addition of the aryl chloride but transmetalation of the organic group of the silicone reagent.[9]

In conclusion, we have shown that aryl chlorides that are less expensive substrate than aryl iodides or bromides are effective for the cross-coupling reaction of silicone. Aqueous potassium carbonate, which was an inexpensive and weak inorganic base, affected cross coupling of aryl chlorides with silicone. Although the present reaction requires high temperature, silicone would be an attractive reagent due to their ease of handling, low toxicity, and a low cost compared to another main group organometallic reagent such as boron or tin.

Acknowledgement

This work was supported by a Giant-in-aid for Scientific Research (No. 13650915) from Japan Society for the Promotion of Science.

References and Notes

(1) (a) Mori, A.; Suguro, M. *Synlett* **2001**, 845. (b) Average MW of **1** employed is ca. 2500-2700.

(2) Koike, T.; Du, X.; Mori, A.; Osakada, K. *Synlett* **2002**, 301.

(3) (a) Hirabayashi, K.; Kawashima, J.; Nishihara, Y.; Mori, A.; Hiyama, T. *Org. Lett.* **1999**, *1*, 299. (b) Hirabayashi, K.; Kondo, T.; Toriyama, F.; Nishihara Y.; Mori, A. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 985. (c) Hirabayashi, K.; Mori, A.; Kawashima, J.; Suguro, M.; Nishihara, Y.; Ikegashira, K.; Hirabayashi, K.; Ando, J.; Mori, A.; Hiyama, T. *J. Org. Chem.* **2000**, *65*, 1780. (d) Fujii, T.; Koike, T.; Mori, A.; Osakada, K. *Synlett* **2002**, 295. (e) Fujii, T.; Koike, T.; Mori, A.; Osakada, K. *Synlett* **2002**, 298. (f) Mowery, M. E.; DeShong, P. *Org. Lett.* **1999**, *1*, 2137. (g) Mowery, M. E.; DeShong, P. *J. Org. Chem.* **1999**, *64*, 1684. (h) Denmark, S. E.; Wehrli, D. *Org. Lett.* **2003**, *5*, 1357 and reference cited therein. (i) Mori, A.; Danda, Y.; Fujii, T.; Hirabayashi, K.; Osakada, K. *J. Am. Chem. Soc.* **2001**, *123*, 10774. (j) For a review: Organosilicon Compounds in Cross-Coupling Reactions; Hiyama, T. P 421, In Metal-Catalyzed Cross-Coupling Reactions; Diederich, F.; Stang, P. J., Eds.; Wiley-VCH, Weinheim, 1998.

(4) Recent palladium-catalyzed cross-coupling reaction of aryl chlorides using organometallic reagents, see: (a) Old, D. W.; Wolf, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722. (b) Littke, A. F.; Schwarz, L.; Fu, G. C. *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 3387. (c) Zhang, C.; Huang, J.; Trudell, M. L.; Nolan, S. P. *J. Org. Chem.* **1999**, *64*, 3804. (d) Littke, A. F.; Fu, G. C. *Angew. Chem. Int. Ed. Engl.* **1999**, *38*, 2411. (e) Wolfe, J. P.; Buchwald, S. L. *Angew. Chem. Int. Ed. Engl.* **1999**, *38*, 2413. (f) Hagiwara, E.; Gouda, K.; Hatanaka, Y.; Hiyama, T. *Tetrahedron Lett.* **1997**, *38*, 439. (g) Gouda, K.; Hagiwara, E.; Hatanaka, Y.; Hiyama, T. *J. Org. Chem.* **1996**, *61*, 7232.

(5) $PdCl_2(PCy_3)_2$ was prepared according to the literature procedure, see: Grushin, V. V.; Alper, H. *Organometallics* **1993**, *12*, 1890.

(6) Available from Aldrich Chemicals Co. as $TBAF \cdot xH_2O$.

(7) (a) Grushin, V. V.; Alper, H.; *Chem. Rev.* **1994**, *94*, 1047. (b) Littke, A. F.; Fu, G. C. *Angew. Chem. Int. Ed. Engl.* 2002, *41*, 4176.

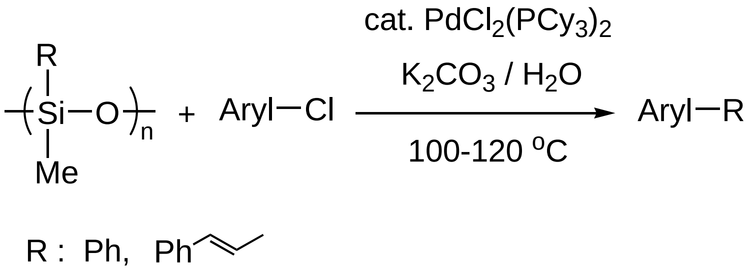
(8) **Typical experimental procedure for the cross-coupling reaction:** To a toluene (3 mL) solution of $[Ph(Me)SiO]_n$ (**1**, 204 mg, 1.5 mmol) was added K_2CO_3 (414 mg, 3.0 mmol) in H_2O (0.5 mL). After stirring at room temperature for 1 h, 1-chloro-4-methoxybenzene (**2a**, 43 mg, 0.3 mmol) and $PdCl_2(PCy_3)_2$ (11 mg, 0.015 mmol) was added and then the resulting yellow mixture was stirred at 120 °C for 39 h. After cooling the mixture to room temperature, the organic layer was separated and aqueous was extracted with diethyl ether (10 mL x 2). The combined organic layer was washed with 1 M HCl (10 mL), saturated aqueous $NaHCO_3$ (10 mL), and brine (10 mL) and then dried over anhydrous magnesium sulfate. Removal of the solvent left a crude oil, which was purified by chromatography on silica gel (reverse phase, $MeOH/H_2O = 3/1$) to yield 52.5 mg of 4-methoxybiphenyl (95%).

(9) The related mechanism has also been proposed in the Stille coupling reaction of chloroarenes: Bedford, R. B.; Cazin, C. S. J.; Hazelwood, S. L. *Chem. Commun.* **2002**, 2608.

Graphical abstract

Palladium-catalyzed cross-coupling reaction of silicone with aryl chlorides

Tooru Koike and Atsunori Mori*



palladium, cross coupling, silicone,
aqueous pottasium carbonate, aryl chlorides