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Palladium/copper-catalyzed sila-Sonogashira reactions of aryl iodides with alkynylsilanes via a direct C–Si bond activation

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ABSTRACT

The palladium-catalyzed cross-coupling reactions of aryl iodides with alkynylsilanes in the presence of a substoichiometric amount (50 mol %) of copper(I) chloride as an activator in DMF under strictly non-basic reaction conditions afford the corresponding unsymmetrical diarylethynes in moderate to excellent yields. A wide range of substrates bearing an electron-donating or an electron-withdrawing substituent on the aromatic ring are compatible.

The palladium-catalyzed cross-coupling reaction of aryl halides or pseudo-halides with terminal alkynes in the presence of a base (Sonogashira reaction)[1–4] has been proven to be a most efficient method for the synthesis of unsymmetrical diarylethynes, and besides the original protocol using the palladium/copper(I) system,[5] copper-free[6] or silver-cocatalyzed[7] method to retard the formation of undesired conjugate diynes from terminal alkynes,[8] has been developed.[9]

Numerous reports describe the coupling of trimethylsilylacetylene with aryl halides in Sonogashira-type reactions.[10,11] The C(*sp*)–Si bond is generally not affected by these reaction conditions. The silyl group can, therefore, if desired, subsequently be removed to furnish a structurally modified terminal alkyne. The trimethylsilyl group is thereby used as a protective group.

In a sharp contrast, we have reported 'sila'-Sonogashira reaction, in which aryl triflates[12] or chlorides[13] can be coupled directly with alkynylsilanes via the Si–C bond activation by using the Pd/Cu co-catalyst system, in DMF as solvent to yield unsymmetrical diarylethynes in good to high yields. This process avoids totally the formation of the alkyne homocoupling Glaser-type product.[14,15] In these reactions, the transmetalation from silicon to copper has been proposed when copper(I) co-catalyst was used.[12] This process has been applied more recently to the copper-free sila-Sonogashira-type cross-coupling of electron-poor aryl and heteroaryl bromides or iodides, with 1-aryl-2-(trimethylsilyl)acetylenes, giving the cross-coupled product in the presence of tetra-*n*-butylammonium chloride, with use of microwave.[16] However, in the aforementioned reactions, the yields of the desired products from electron-rich aryl iodides are rather lower and they required the addition of a base to activate the carbon–silicon bond, indeed resulting to protodesilylation to yield the terminal alkynes that are often employed for the typical Sonogashira reactions.

To the best of our knowledge, there are no general methods to synthesize unsymmetrical diarylethynes by the coupling of stable, functionally rich alkynylsilanes with aryl iodides under *neutral* conditions. We herein describe the Pd-catalyzed 'sila'-Sonogashira-type cross-coupling reaction of unactivated aryl iodides with alkynylsilanes, which proceeds in the presence of CuCl under strictly non-basic reaction conditions, leading to various unsymmetrical diarylethynes.

We first carried out the sila-Sonogashira coupling reaction of trimethyl(phenylethynyl)silane (**1a**, 0.3 mmol) with an electron-rich 4-methoxyphenyl iodide (**2a**, 0.2 mmol). The results are summarized in Table 1. In the presence of CuCl (150 mol %) as an activator and 5 mol % of $Pd(PPh_3)_4$ as the catalyst in DMF (1 mL), which is the best solvent for the homocoupling of alkynylsilanes,[17] the desired cross-coupled product **3a** was obtained in 90% yield, based on **2a** (run 1). However, the reaction mixture contained 1,4-diphenyl-1,3-butadiyne (**4**; 7%, based on **1a**), presumably derived from homocoupling of **1a** (confirmed by GC and NMR). Thus, we screened other catalysts for the reactions of **1a** with **2a** and found that the catalysts employed had a considerable influence on the yield of **3a**. The reason why $Pd(PPh_3)_4$ was so effective may be due to stabilization of the catalyst by coordination of excess PPh_3 ligands. Among transition metal catalysts examined in the coupling of **1a** with **2a**, $PdCl_2(PPh_3)_2$ combined with PPh_3 (P/Pd = 2.0; 5 mol %) gave a 71% yield of **3a** (run 2). Other catalytic systems with $Pd(OAc)_2$ or $Pd(dba)_2$ gave poor results (runs 5–8). In addition, $Ni(cod)_2$ was completely ineffective as the catalyst (run 10). Deletion of $Pd(PPh_3)_4$ yielded no product, confirming the requirement for a palladium catalyst. Increasing the **1a**:**2a** ratio had a significant effect on yield of **3a**; 94% (2:1), 90% (1.5:1), and 60% (1:1) yield, respectively.

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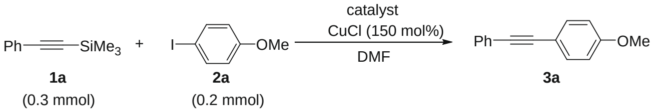
Table 1
CuCl-mediated cross-coupling of **1a** with **2a** using various catalysts[a]



Run	Catalyst	Yield (%)	
		3a	**4**[b]
1	$Pd(PPh_3)_4$	90	7
2	$PdCl_2(PPh_3)_2/2PPh_3$	71	11
3	$PdCl_2(PPh_3)_2$	19	6
4	$PdCl_2(NCPh)_2$	<1	<1
5	$Pd(OAc)_2/2PPh_3$	12	5
6	$Pd(OAc)_2$	<1	<1
7	$Pd(dba)_2/2PPh_3$	10	2
8	$Pd(dba)_2$	8	<1
9	$PdCl_2(dppf)$[c]	46	10
10	$Ni(cod)_2$	0	0

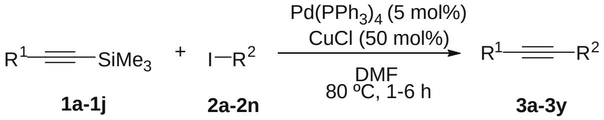
[a] Reaction conditions: DMF (1 mL), **1a** (0.3 mmol), **2a** (0.2 mmol), catalyst (5 mol %), and CuCl (0.3 mmol) at 80 °C. Reaction time is 12 h.
[b] Yields of 1,4-diphenyl-1,3-butadiyne (**4**) were based on **1a**.
[c] dppf = 1,1′-bis(diphenylphosphino)ferrocene.

Counter ions of a halogenated copper salt dramatically affected the yield of **3a**. CuCl, which is the effective copper salt for the cross-coupling of alkynylsilanes with aryl triflates[12] and aryl chlorides,[13] was also suitable for the present reaction. Whereas CuI that was reportedly effective for coupling reactions using organoboron[18] and organotin[19] reagents hardly accelerated the present reaction. It is noteworthy that the present reaction does not require any activator such as a fluoride ion[20,21] or an added base, which is normally required for activation of alkynylsilicon compounds in Hiyama cross-coupling reaction.

With the optimized 2:1 ratio of **1a**:**2a** for the cross-coupling in hand, we next screened the amount of CuCl in the reactions of **2a** with **1a**. The results are summarized in Table 2.[22] Although the use of a stoichiometric amount (100 mol %) of CuCl afforded **3a** in 99% GC yield (run 1), the use of a catalytic amount was found to retard the reaction progress (run 2). Searching the decreased amounts of CuCl (runs 3–5), we employed a substoichiometric amount (50 mol %) of CuCl as the optimal condition.[20a]

The generality of the reaction of alkynylsilanes **1a–j** with aryl iodides **2a–n** was studied under the optimum conditions, that is, 50 mol % of CuCl and 5 mol % of $Pd(PPh_3)_4$. The results are also summarized in Table 2. The reactions of various aryl iodides **2** bearing the substituents in the para-position with **1a** proceeded to give the corresponding unsymmetrical diarylethynes **3b–g** in good to excellent yields (runs 6–11). However, a sterically hindered aryl iodides **2h–k** partially retarded reaction of **1a** and gave the lower yield of the desired products (runs 12–15). Reaction of iodides **2l** and **2m** having heteroaromatics such as 2-pyridyl and 2-thienyl groups also afforded the corresponding cross-coupled products **3l** and **3m** in 69% and 68% isolated yields, respectively (runs 16 and 17). On the other hand, the reactions of alkynylsilanes 1b–h bearing various functional groups similarly underwent the

Table 2
Cross-coupling reaction of alkynylsilanes **1** with aryl iodides **2**[a]



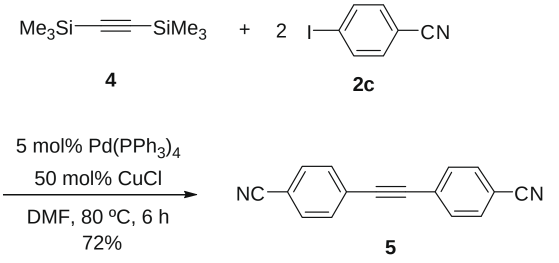
Run	Alkynylsilane **1**, R^1=	Halide **2**, R^2=	Time (h)	CuCl (mol %)	Products	Yield[b] (%)
1	C_6H_5–(**1a**)	4-MeO–C_6H_4 (**2a**)	3	100	**3a**	(99)
2	**1a**		3	10		(>1)
3	**1a**		3	200		(90)
4	**1a**		3	150		(96)
5	**1a**		3	50		(94) 84
6	**1a**	4-Me–C_6H_4 (**2b**)	3	50	**3b**	75
7	**1a**	4-NC–C_6H_4 (**2c**)	1		**3c**	89
8	**1a**	4-MeCO–C_6H_4 (**2d**)	1		**3d**	90
9	**1a**	4-O_2N–C_6H_4 (**2e**)	3		**3e**	92
10	**1a**	4-Cl–C_6H_4 (**2f**)	1		**3f**	92
11	**1a**	4-EtO_2C–C_6H_4 (**2g**)	1		**3g**	93
12	**1a**	2-MeO–C_6H_4 (**2h**)	3		**3h**	49
13	**1a**	2-Me–C_6H_4 (**2i**)	6		**3i**	66
14	**1a**	2-MeCO–C_6H_4 (**2j**)	3		**3j**	77
15	**1a**	2,4,6-Me_3–C_6H_2 (**2k**)	6		**3k**	36
16	**1a**	2-Pyridyl (**2l**)	3		**3l**	69
17	**1a**	2-Thienyl (**2m**)	3		**3m**	68
18	4-MeO–C_6H_4–(**1b**)	**2b**	6		**3n**	73
19	**1b**	**2d**	1		**3o**	89
20	**1b**	**2c**	1		**3p**	78
21	4-NC–C_6H_4 (**1c**)	**2a**	6		**3q**	71
22	4-MeCO–C_6H_4 (**1d**)	C_6H_5 (**2n**)	6		**3r**	88
23	**1d**	**2a**	6		**3s**	83
24	4-O_2N–C_6H_4 (**1e**)	**2a**	6		**3t**	59
25	4-CF_3–C_6H_4 (**1f**)	**2n**	3		**3u**	77
26	2-Pyridyl (**1g**)	**2a**	3		**3v**	47
27	2-Thienyl (**1h**)	**2a**	6		**3w**	75
28	4-${}^tBuMe_2SiO$–C_6H_4 (**1i**)	**2n**	1		**3x**	48
29	n-C_6H_{13} (**1j**)	**2n**	1		**3y**	49

[a] Conditions: **1** (2.0 mmol); **2** (1.0 mmol); CuCl (50 mol %); $Pd(PPh_3)_4$ (5 mol %); DMF (5 mL) unless otherwise noted.
[b] Isolated yields based on aryl iodides **2** and GC yields were shown in parentheses.

cross-coupling reactions and gave the corresponding unsymmetrical diarylethynes **3n**–**w** in up to 89% yield (runs 18–27). The present reaction is applied to the coupling reaction of alkynylsilane **1i** having *t*-butyldimethylsilyl (TBDMS) group as a protecting group. Indeed, **1i** selectively coupled with **2n** to give **3x** with the TBDMS group remaining intact (run 28). Alkyl-substituted alkynylsilane **1j** underwent the reaction to give **3y** in 49% yield (run 29).

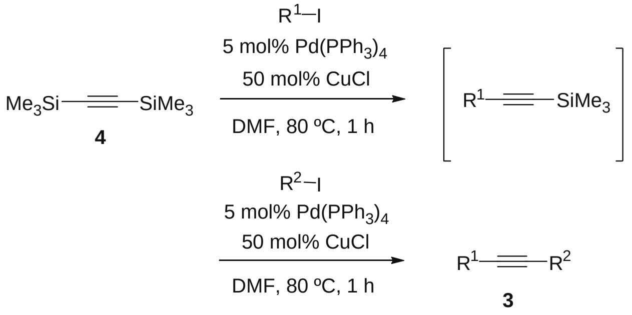
Noteworthy is that this reaction using aryl iodides **2** considerably surpasses those of aryl triflates and bromides, probably owing to the efficiency of oxidative addition of Pd(0) to the C–I bond of **2**. For instance, the reactions of **1c** with **2a, 1d** with **2n**, and **1d** with **2a** furnished cross-coupled products **3q**, **3r**, and **3s** in 71%, 88%, and 83% yields, respectively, whereas the corresponding substrates of aryl triflates and bromides decreased the yields (27, 30, and 19% for triflates,[12] and 8%, 17%, and 10% for bromides, respectively). Therefore, the use of aryl iodides **2** is important for the synthesis of **3** from alkynylsilanes **1** in higher yields.

Because these reactions disclosed the direct transmetalation of an alkynyl group from silicon to copper, bis(trimethylsilyl)ethyne (**4**) can be used as an alternative to acetylene. Indeed, the reaction of **4** with 4-cyanophenyl iodide (**2c**, 2 mol equiv) furnished 1,2-bis(4-cyanophenyl)ethyne (**5**) in 72% yield (Eq. 1). This method for the synthesis of symmetrical diarylethynes is also useful because precise control of the amount of acetylene is considerably difficult due to its gaseous form although acetylene is usually used for the synthesis of symmetrical diarylethynes through Sonogashira reaction.



(1)

In addition, the utility of the cross-coupling reaction with alkynylsilanes is demonstrated by a one-pot synthesis of unsymmetrical diarylethynes **3**, starting from **4**. The one-pot double sila-Sonogashira reactions of **4** with R^1-I and another aryl iodide R^2–I allow the synthesis of unsymmetrical diarylethynes **3** as shown in Scheme 1. Subsequent addition of two kinds of aryl iodides resulted in three-component coupling of bis(trimethylsilyl)ethyne (**4**), R^1–I, and R^2–I to give R^1–C≡C–R^2 **3p** and **3z** in 49% and 93% yields, respectively.



R^1–I	R^2–I	GC Yield
R^1 = 4-NCC$_6$H$_4$-(**2c**)	R^2 = 4-MeOC$_6$H$_4$- (**2a**)	**3p**: 49%
R^1 = 4-NCC$_6$H$_4$- (**2c**)	R^2 = 4-ClC$_6$H$_4$- (**2f**)	**3z**: 93%

Scheme 1.

In conclusion, we have successfully developed a preparative process for the generation of unsymmetrical diarylethynes from the cross-coupling reactions of aryl iodides with alkynylsilanes in the presence of CuCl in DMF. Because the presented method is carried out using the alkynes protected with the silicon moiety, side reactions leading to the butadiynes by the Pd-catalyzed homocoupling reactions of terminal alkynes can be avoided. This reaction is synthetically useful in the sense of being straightforward carbon–carbon bond formation via a direct activation of carbon–silicon bond using a stable, nontoxic, and functional group tolerant organosilicon compound. It is a highly applicable novel transformation that occurs in the absence of a fluoride ion and a base as an activator.

Further studies on application of the present system to other base-free carbon–carbon bond forming reactions of organosilicon compounds toward new organic molecules bearing a carbon–carbon triple bond are currently ongoing and will be published in due course.

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22. *Typical procedure for sila-Sonogashira reactions of aryl iodides 2 with alkynylsilanes 1 (*Table 2, *run* **19**)*:* To a solution of Pd(PPh$_3$)$_4$ (58 mg, 0.05 mmol, 5 mol %) and CuCl (50 mg, 0.5 mmol, 50 mol %) in dry DMF (5 mL) were added 1-(4-methoxypheny)-2-trimethylsilylethyne (**1b**) (432 µL, 2.0 mmol) and 4-acetylphenyl iodide (**2d**) (246 mg, 1.0 mmol) at room temperature. The dark yellow suspension was heated for 1 h at 80 °C and monitored by GC and TLC. After completion of the reaction, the reaction mixture was quenched with 1 M HCl and extracted with diethyl ether (20 mL, 3 times). The combined organics were washed with brine and dried over anhydrous MgSO$_4$. Filtration and concentration with a rotary evaporator gave a viscous oil. The residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate = 9:1, $R_f = 0.21$), **3o** (224 mg, 0.89 mmol, 89%) was obtained as a white solid. ^{1}H NMR (300 MHz, CDCl$_3$): δ 2.61 (s, 3H), 3.84 (s, 3H), 6.88–6.91 (m, 2H), 7.48–7.50 (m, 2H), 7.57–7.60 (m, 2H), 7.92–7.94 (m, 2H).