Hiyama Cross-Coupling of Chloro-, Fluoro-, and Methoxypyridyltrimethylsilanes: Room-Temperature Novel Access to Functional Bi(het)aryl

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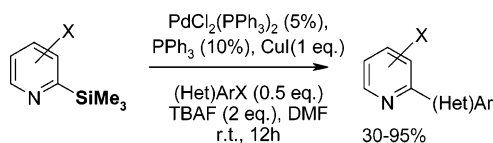
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ABSTRACT

X= Cl, F, OMe; (Het)Ar=aryl, pyridyl, thienyl

The incorporation of chloro, fluoro, or methoxy substituents on the pyridine ring of pyridyltrimethylsilanes allowed us to perform efficient Hiyama cross-coupling with various (het)aryl halides. The reactions proceeded smoothly at room temperature leading to the corresponding functional bis(het)aryl in fair to excellent yields. The presence of pyridine nitrogen α to the trimethylsilyl group was requisite to achieve the cross-coupling.

The Hiyama cross-coupling of organosilanes with organo halides and triflates has proved to be a powerful methodology for preparation of biaryls and alkyl and vinyl aromatics.[1] The organosilanes display many advantages compared to other organometallic precursors: Organoboron reagents are not always easily prepared and stable while organostannanes release toxic tin halides upon coupling process. However, the absence of polarization of the C−Si bond implies the use of activated silicon moieties such as halosilanes,[1b,2] silanols,[3] siloxanes,[4] bis(catechol)silicates,[5] or silacyclobutanes.[1c,6] Although efficient in cross-coupling or aromatics, these

silicon species have been scarcely used in heterocyclic chemistry especially in the important pyridine series for which efficient coupling methodologies are still needed for preparation of new ligands and pharmacophores.

From our knowledge, only two examples of activated pyridylsilanes have been reported. Hiyama[1b] introduced an instable dichloroethylsilyl group at C-2 of picoline which had to be in situ cross-coupled while DeShong prepared a biscatechol derivative from 2-methoxypyridine which was coupled only with aryltriflates (Figure 1).[5]

(1) For reviews, see: (a) Hiyama, T. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Weinheim, Germany, 1998. (b) Hiyama, T. *J. Organomet. Chem.* **2002**, *653*, 58−61. (c) Denmark, S. E.; Sweiss, R. F. *Acc. Chem. Res.,* **2002**, *35*, 835−846. (d) Spivey, A. C.; Gripton, C. J. G.; Hannah, J. P. *Curr. Org. Synth.* **2004**, *1*, 211−226.

(2) (a) Hiyama, T.; Hatanaka, Y. *Pure Appl. Chem.* **1994**, *66*, 1471−1478. (b) Goda, K.-I.; Hagiwara, E.; Hatanaka, Y.; Hiyama, T. *Tetrahedron Lett.* **1997**, *38*, 439−442. (c) Homsi, F.; Hosoi, K.; Nozaki, K.; Hiyama, T. *J. Organomet. Chem.* **2001**, *624*, 208−216.

(3) (a) Hirabayashi, K.; Kawashima, J.; Nishihara, Y.; Mori, A.; Hiyama, T. *Org. Lett.* **1999**, *1*, 299−301. (b) Hirabayashi, K.; Mori, A.; Kawashima, J.; Suguro, M.; Nishihara, Y.; Hiyama, T. *J. Org. Chem.* **2000**, *65*, 5342−5349. (c) Denmark, S. E.; Neuville, L. *Org. Lett.* **2000**, *5*, 3221−3224.

(4) (a) Lee, H.-M.; Nolan, S. P. *Org. Lett.* **2000**, *2*, 2053−2054. (b) McElroy, W. T.; DeShong, P. *Org. Lett.* **2003**, *5*, 4779−4782. (c) Lee, J.-Y.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 5616−5617.

(5) Seganish, W. M.; DeShong, P. *J. Org. Chem.* **2004**, *69*, 1137−1143.

(6) (a) Denmark, S. E.; Choi, J.-Y. *J. Am. Chem. Soc.* **1999**, *121*, 5821−5822. (b) Denmark, S. E.; Wu, Z. *Org. Lett.* **1999**, *1*, 1495−1498. (c) Denmark, S. E.; Wehrli, D.; Choi, J.-Y. *Org. Lett.* **2000**, *2*, 2491−2494.
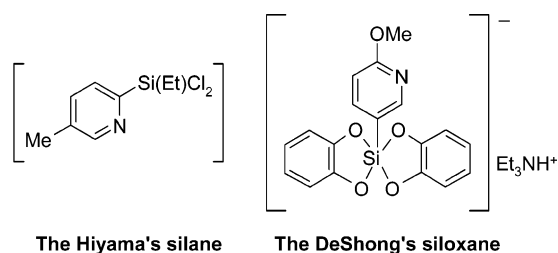
Figure 1. Activated pyridyl silanes of the literature.

So, there was an evident lack of stable and easy to handle pyridylsilanes suitable for the Hiyama coupling and we investigated the reactivity of the trimethylsilyl group in this reaction. Our first attempts to couple 2-trimethylsilylpyridine under classical conditions remained unsuccessful and we turned to chloropyridyltrimethylsilanes. The electron-withdrawing effect of chlorine on pyridine ring was here expected to increase polarization of the C−Si bond thus favoring the formation of the intermediate ate complex by reaction with fluoride ions. Chloropyridyltrimethylsilanes are stable liquids easily prepared from chloropyridines via halogen or hydrogen lithium exchanges and subsequent reaction with chlorotrimethylsilane. Moreover, the C−Cl bond also offers a potential source for further functionalizations.

Herein, we report the first use of chloropyridyltrimethylsilanes as reactive partners in the Hiyama cross-coupling, thus providing an important scope extension for this reaction in heterocyclic chemistry.[7]

An array of chloropyridylsilanes **1**−**6** (Figure 2) was prepared according to literature procedures[8] and involved
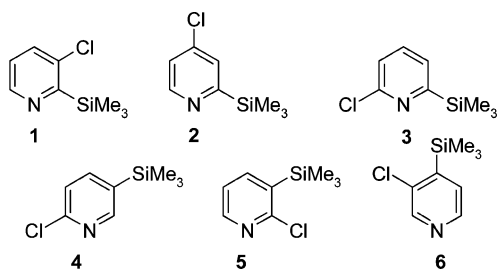

Figure 2. Starting silanes for coupling investigation.

cross-coupling reactions with 4-iodoanisole under various conditions. The investigation of reaction parameters was performed with silane **1** (Table 1).

First attempts using classical coupling conditions of the literature and various palladium catalysts only resulted in homocoupling of 4-iodoanisole (entries 1−3). A significant CuI effect was observed (entry 4) leading to cross-coupling

(7) Trimethylsilylthiazole has been coupled under copper catalysis by Hosomi and co-workers. See: Ito, H.; Sensui, H.-O.; Arimoto, K.; Miura, K.; Hosomi, A. *Chem. Lett.* **1997**, 639−640.

Table 1. Reaction Parameter Screening in Hiyama Coupling of **1**[a]

| entry	ArI (equiv)	catalyst	PR₃	CuI	T (°C)	1a[b] (%)
1	0.8	PdCl₂(PPh₃)₂	PPh₃		120	c
2	0.8	Pd(OAc)₂	PCy₃		120	c
3	0.8	Pd(OAc)₂	PtBu₃		120	c
4	0.8	PdCl₂(PPh₃)₂	PPh₃	1	120	27
5	0.6	PdCl₂(PPh₃)₂	PPh₃	1	120	52
6	0.5	PdCl₂(PPh₃)₂	PPh₃	1	120	80
7	0.5	PdCl₂(PPh₃)₂	PPh₃		20	d
8	0.5	PdCl₂(PPh₃)₂	PPh₃	1	20	82

[a] All reactions performed on 1 mmol of **1**. [b] Isolated yield after column chromatography. [c] GC analysis showed quantitative formation of [4-MeOPh]₂. [d] [4-MeOPh]₂ formed in 50% yield.

product **1a** in 27% yield. The amount of 4-iodoanisole was also a key parameter. The best improvement was obtained by introduction of **1** and ArI in a 2:1 ratio leading to **1a** in excellent yield (80%) while a 1.5:1 ratio led to lower yield and homocoupling or the aryl iodide (entries 5 and 6). Finally, we were pleased to observe that cross-coupling was also efficient at room temperature (entry 8). Note that the role of CuI was also crucial under these conditions since homocoupling of aryl halide was formed in absence of this salt (entry 7). As already observed by Hiyama,[1b] we also found that 2 equiv of TBAF[9] was necessary to achieve the cross-coupling. Couplings were also performed in THF at room temperature but only resulted in poor yields (22%). This coupling of **1** was unprecedented and of particular interest since we had not observed any Stille coupling of the corresponding stannane in our previous works probably due to steric hindrance generated by chlorine at C-3.[10] The above determined best conditions (Table 1, entry 8) were then applied to investigate the cross-coupling of the other chloropyridylsilanes **2**−**6** (Scheme 1). At room temperature, silane **2** gave the cross-coupling product **2a** in high yield while silanes **3**−**6** only gave the desilylated pyridines indicating the formation of unreactive ate complexes under the conditions used. A moderate amount of **4** could therefore be cross-coupled by performing the reaction at 120 °C for 48 h. A reaction with activated 4-iodofluorobenzene was also unsuccessful at room temperature or upon heating where only homocoupling of the halide was obtained. All our attempts

(8) For preparation of **1**−**3** with BuLi−LiDMAE, see: Choppin, S. Gros, Ph. Fort, Y. *Org. Lett.* **2000**, *2*, 803−805. Choppin, S. Gros, Ph. Fort, *Eur. J. Org. Chem.* **2001**, *3*, 603−606. For preparation of **5** and **6** with LDA or LTMP, see: Gribble, G. W. Saulnier, M. G. *Tetrahedron Lett.* **1980**, *21*, 4137−4140. Comins, D. L.; Myoung, Y. *J. Org. Chem.* **1990**, *55*, 292−298. Compound **4** was prepared by reaction of BuLi with 2-chloro-5-bromopyridine in THF at −78 °C and quenching with TMSCl.
(9) Other fluoride sources (TMAF, CsF, polymer-supported fluoride) gave low yields.
(10) Choppin, S. Ph.D. Thesis, Nancy, 2000.

Scheme 1. Attempted Cross-Coupling of Silanes **2–6**[a]
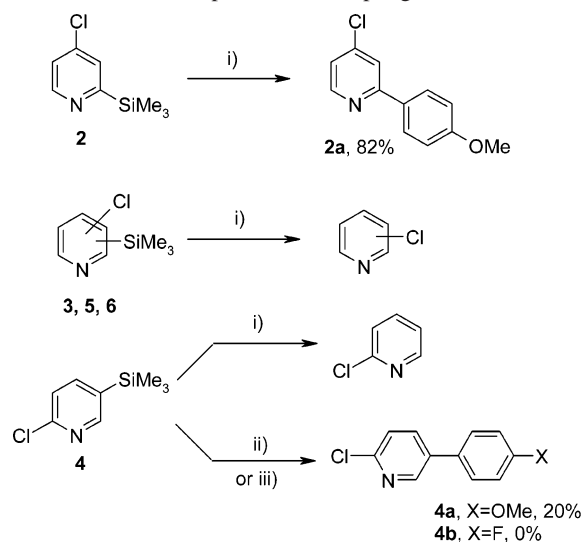
[a] Key: (i) PdCl$_2$(PPh$_3$)$_2$ (5%), PPh$_3$ (10%), CuI (1 equiv), TBAF (2 equiv), 4-iodoanisole (0.5 equiv), DMF, rt, 12 h; (ii) ibid at 120 °C for 48 h; (iii) 4-iodofluorobenzene as electrophile, rt, 24 h or 120 °C, 48 h.

Scheme 2. Proposed Catalytic Cycle for Cross-Coupling of **1** and **2**

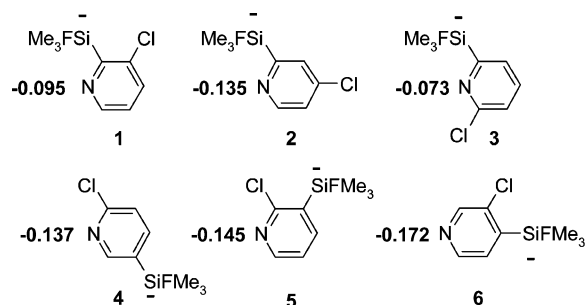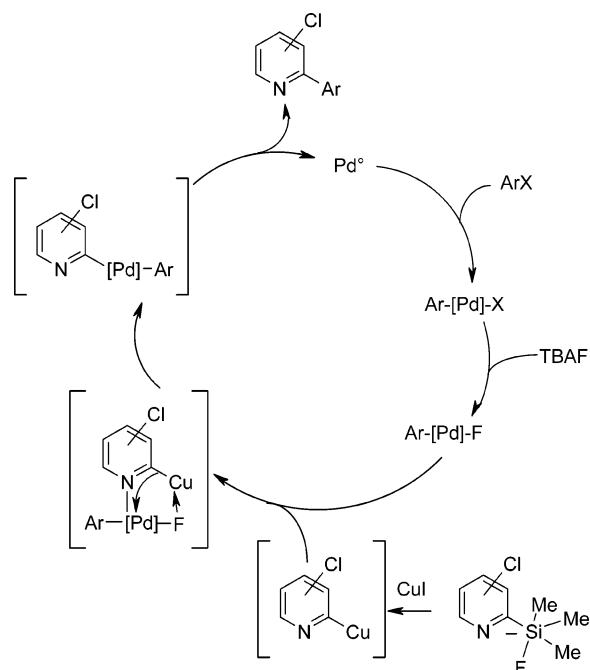**Figure 3.** Calculated charges on nitrogen in ate complexes.

to couple **3**, **5**, or **6** by increasing temperature, reaction time, fluoride, and palladium amount remained unsuccessful.

From a mechanistic angle, the above experiments feature the preeminent role of the pyridine nitrogen in the reaction pathway. Indeed, quantitative cross-coupling was observed only when pyridine nitrogen was present α to the trimethylsilyl group. This suggested the complexation of palladium species by the pyridine nitrogen leading to a complex in which the two partners are ideally placed for achievement of the transmetalation step assisted by fluorine and copper[1b] (Scheme 2). The catalytic cycle also explained that 2 equiv of TBAF was necessary to perform the cross-coupling.

Since the complexation of palladium by pyridine nitrogen should be dependent on electronegativity of this site, the charges on nitrogen in ate complexes were calculated to get a better understanding of the behavior of **1–6** in the reaction (Figure 3).[11]

As shown, the more electronegative nitrogens were found in ate complexes resulting from unreactive **4–6**. So, these substrates were expected to coordinate the palladium species in a greater extent. The lack of a silyl group near the metallic center then did not allow the transmetalation step to proceed. Nitrogen in silane **3** displayed the lowest electronegativity and thus weaker palladium complexation could be expected. However coupling was obtained in 20% yield upon heating (see Scheme 1). So, electronic effects were not the only factor governing the reaction in this case. In contrast, substrates **1** and **2** ideally combined nitrogen electronegativity and a silyl group at C-2 leading to efficient cross-coupling.

We then focused on the reaction of silanes **1** and **2** in cross-coupling reactions with a range of (het)aryl halides.[12] Silane
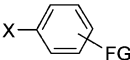
1 reacted smoothly in each case except with 2-iodoanisole may be due to steric hindrance of both the chlorine and methoxy groups. An increase of temperature to 120 °C was necessary to form **1c** in moderate 38% yield (Table 2).

Of particular interest was the efficient cross-coupling of **1** or **2** with 2-bromopyridine providing the corresponding chlorinated 2,2′-bipyridines in good to excellent yields. **1** was also smoothly coupled with the less reactive bromothiophene of 4-bromoacetophenone. In contrast, **2** showed a

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(11) Mulliken charges calculated using semiempirical PM3 method.

(12) **General Procedure for Cross-Coupling of Silanes 1 or 2.** To a stirred mixture of PdCl$_2$(PPh$_3$)$_2$ (35 mg, 0.05 mmol), PPh$_3$ (26 mg, 0.1 mmol), and CuI (188 mg, 1 mmol) in DMF (5 mL) at room temperature were added successively (Het)ArX (0.5 mmol), silane **1** or **2** (185 mg, 1 mmol), and TBAF (2 mL of a 1 M solution in THF, 2 mmol). The reaction medium became instantly dark. After 12 h of stirring at room temperature, the mixture was filtered through a Celite pad. After successive washings with NH$_4$OH, H$_2$O, THF and Et$_2$O, the filtrate was extracted twice with diethyl ether. After drying (MgSO$_4$) of the organic layer, the solvents were evaporated under reduced pressure and the crude product purified by column chromatography.

Table 2. Preparation of Chlorinated Bis(het)aryl Derivatives[a]

HetArX		Silane	Product	Yield%[b]
	X=I, FG=H	1	1b	72
	X=I, FG=2-OMe	1	1c	38[c]
		2	2b	57
	X=I, FG=3-OMe	1	1d	55
		2	2c	77
	X=I, FG=4-F	1	1e	88
		2	2d	95
	X=Br, FG=4-Ac	1	1f	80
		2	2e	42[d]
(2-Br pyridine)		1	1g	65
		2	2f	85
(2-Br thiophene)		1	1h	78
		2	2g	30[e]

[a] All reactions performed on 1 mmol of **1** or **2**. [b] Isolated yield after column chromatography. [c] Reaction performed at 120 °C. [d] 4,4'-Dichloro-2,2'-bipyridine (Cl₂bpy) formed in 40% yield. [e] GC yield. **2g** could not be separated from Cl₂bpy.

strong tendency to homocouple in the presence of these less reactive halides as indicated by formation of 4,4'-dichloro-2,2'-bipyridine in notable amount (typically 40%). Homocoupling of silanes has been reported to be catalyzed by copper halides.[13] The CuI present in our reaction medium was thus assumed to catalyze this reaction via formation of a pyridylcopper intermediate rapidly decomposed into the corresponding bipyridine upon workup.[13,14] With **1**, homocoupling was probably prevented by steric hindrance generated by chlorine at C-3.

Finally, we investigated the reaction with other electron-withdrawing groups on the pyridine ring. We examined the effect of methoxy and fluorine moieties (Scheme 3). The more electronegative and less hindered fluorine atom was convenient to evaluate stereoelectronic effects. We were pleased to observe that methoxy- and fluoropyridines gave

(13) Ikegashira, K.; Nishihara, Y.; Hirabayashi, K.; Mori, A.; Hiyama, T. *Chem. Commun.* **1997**, 1039−1040.

Scheme 3. Cross-Coupling of Methoxy- and Fluoropyridylsilanes[a]

7a, 85%   **8a**, 64%   **9a**, 75%
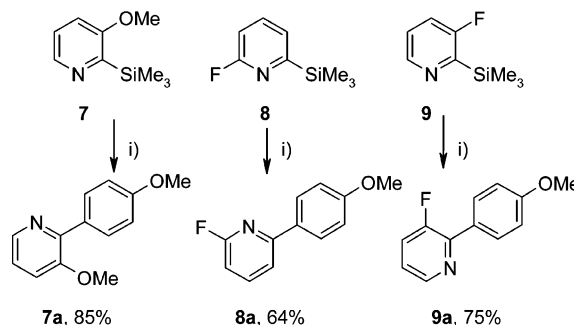
[a] Key: (i) PdCl₂(PPh₃)₂ (5%), PPh₃ (10%), CuI (1 equiv), TBAF (2 equiv), 4-iodoanisole (0.5 equiv), DMF, rt, 12 h.

cleanly the expected products. The replacement of chlorine by fluorine led to impressive improvement of the cross-coupling. Indeed **8** was coupled in 64% yield while we were unable to react **3**. For comparison with reaction of **1**, a coupling was attempted between **9** and 2-iodo-anisole. Unfortunately, the expected coupling product was obtained only in trace amount. Thus, steric effect of the halogen at C-3 in pyridyl silane was not the limiting factor for cross-coupling here.

In summary, we have shown that the introduction of electron-withdrawing substituents on the pyridine ring of 2-trimethylsilylpyridines led to efficient activation of the trimethylsilanes making them useful reactive partners in the Hiyama cross-coupling. The coupling can be performed cleanly at room temperature giving a novel access to functional bi(het)aryl.

Supporting Information Available: Experimental procedure for Hiyama cross-coupling and spectroscopic data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Normant, J. F. *Synthesis* **1972**, 63.