

Palladium-Catalyzed Cross-Coupling Reactions of (2-Pyridyl)allyldimethylsilanes with Aryl Iodides

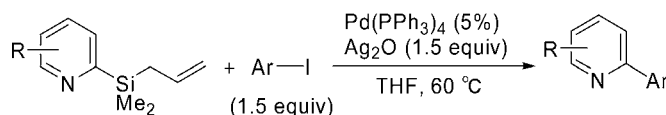
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ABSTRACT



(2-Pyridyl)allyldimethylsilanes were found to be novel pyridyl transfer reagents in palladium-catalyzed cross-coupling reactions of various aryl iodides in the presence of silver(I) oxide as an activator.

2-Substituted pyridines constitute an important class of compounds, which are ubiquitous in biologically active molecules, π -conjugated systems, and ligands for metal-catalyzed reactions. Although various methods for the synthesis of 2-substituted pyridines have been developed so far,¹ a new method, which enables the introduction of 2-pyridyl groups to organic structures under milder conditions, is still needed. Palladium-catalyzed cross-coupling reactions serve as a powerful method for carbon–carbon bond formation, and various aryl and heteroarylmotifs have been used for such cross-coupling reactions.² Only a few

examples of the use of 2-pyridylmetals, however, have been reported in the literature, presumably because 2-pyridylmetal reagents are often unstable.³

Recently, Gros and co-workers reported a palladium-catalyzed cross-coupling reaction using 2-pyridyltrimethylsilanes.⁴ They revealed that copper iodide and Bu₄NF activate the pyridyl carbon–silicon bond. Although some activating substituents such as chlorine should be present on the pyridine ring, this reaction is quite useful from a synthetic point of view.⁵ We envisioned that pyridylsilanes having no activating substituents on the pyridine ring can be utilized

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(1) Recent reviews for pyridine syntheses: (a) Henry, G. D. *Tetrahedron* **2004**, *60*, 6043. (b) Tyrrell, E.; Brookes, P. *Synthesis* **2004**, 469. For recent metal-catalyzed reactions to synthesize pyridine derivatives, see: (c) Godula, K.; Sezen, B.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 3648. (d) Jordan, R. F.; Taylor, D. F. *J. Am. Chem. Soc.* **1989**, *111*, 778. (e) Moore, E. J.; Pretzer, W. R.; O'Connell, T. J.; Harris, J.; LaBounty, L.; Chou, L.; Grimmer, S. S. *J. Am. Chem. Soc.* **1992**, *114*, 5888. (f) Murakami, M.; Hori, S. *J. Am. Chem. Soc.* **2003**, *125*, 4720 and references therein.

(2) (a) *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, Germany, 2004. Recent reviews for cross-coupling reactions using organosilicon compounds: (b) Hiyama, T.; Shirakawa, E. *Top. Curr. Chem.* **2002**, *219*, 61. (c) Hiyama, T. *J. Organomet. Chem.* **2002**, *653*, 58. (d) Denmark, S. E.; Sweis, R. F. *Chem. Pharm. Bull.* **2002**, *50*, 1531.

(3) (Trialkylstannyl)pyridines are commercially available; see also ref 2a. In situ generation of (2-pyridyl)dichlorosilanes has been reported: (a) Hagiwara, E.; Kusumoto, T.; Hiyama, T. 76th National Meeting of the Chemical Society of Japan, Yokohama, 1999. 2-Pyridylboron reagents have been reported: (b) Hodgson, P. B.; Salingue, F. H. *Tetrahedron Lett.* **2004**, *45*, 685. See also ref 1b.

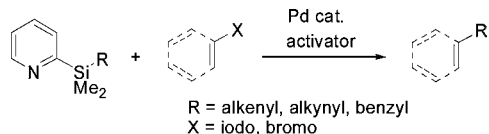
(4) Pierrat, P.; Gros, P.; Fort, Y. *Org. Lett.* **2005**, *7*, 697.

(5) Biaryl syntheses using arylsilanes and pyridyl halides have been reported: (a) Hatanaka, Y.; Gouda, K.-i.; Okahara, Y.; Hiyama, T. *Tetrahedron* **1994**, *50*, 8301. (b) Hagiwara, E.; Gouda, K.-i.; Hatanaka, Y.; Hiyama, T. *Tetrahedron Lett.* **1997**, *38*, 439. (c) Mowery, M. E.; Deshong, P. *Org. Lett.* **1999**, *1*, 2137. (d) Lee, H. M.; Nolan, S. P. *Org. Lett.* **2000**, *2*, 2053. (e) Sahoo, A. K.; Nakao, Y.; Hiyama, T. *Chem. Lett.* **2004**, *33*, 632. (f) Sahoo, A. K.; Oda, T.; Nakao, Y.; Hiyama, T. *Adv. Synth. Catal.* **2004**, *346*, 1715. (g) Wolf, C.; Lerebours, R. *Org. Lett.* **2004**, *6*, 1147.

in the cross-coupling reactions by introducing an appropriate substituent on silicon.⁶ Herein, we report that the cross-coupling reaction of the 2-pyridyl group does take place effectively using (2-pyridyl)allyldimethylsilanes as coupling reagents in the presence of Ag₂O as an activator.

Recently, we have developed 2-pyridylsilanes as novel transfer reagents of alkenyl,⁷ alkynyl,⁸ and benzyl groups⁹ in palladium-catalyzed cross-coupling reactions (Scheme 1).

Scheme 1. Cross-Coupling Reactions Using 2-Pyridylsilanes

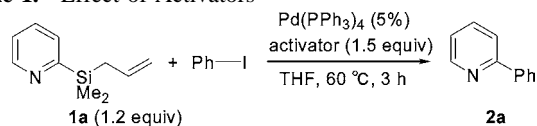


In these cases, the 2-pyridylsilyl group works as an activating group of the silicon atom, and cross-coupling products of the 2-pyridyl group were hardly observed.

During the course of our study, we found that cross-coupling products involving the 2-pyridyl group were obtained when 2-pyridyl(benzyl)silanes or 2-pyridyl(allyl)silanes were used in the presence of silver salts. Although the reaction of 2-pyridyl(benzyl)silanes with aryl iodides gave both diarylmethanes and 2-pyridylbenzenes, 2-pyridyl(allyl)silanes gave only 2-pyridylbenzenes.

Thus, we searched for a suitable activator for the reaction of (2-pyridyl)allyldimethylsilane **1a** with iodobenzene to obtain 2-pyridylbenzene **2a** in the presence of Pd(PPh₃)₄ (Table 1). The reaction did not take place in the absence of

Table 1. Effect of Activators



entry	activator	yield ^a (%)
1	Bu ₄ NF	0
2	CuI	0
3	CuI/Bu ₄ NF	8
4	AgF	21
5	Ag ₂ O	35
6 ^b	Ag ₂ O	60
7 ^{b,c}	Ag ₂ O	78

^a GC yield. ^b 10 h. ^c 1.5 equiv based on **1a** of PhI was used.

an activator. The use of Bu₄NF as an activator was unsuccessful (entry 1).¹⁰ Although the use of CuI¹¹ gave rise

(6) Silicates can transfer the activated pyridyl group in excellent yields: (a) Seganish, W. M.; Deshong, P. *J. Org. Chem.* **2004**, *69*, 1137. Recently, the (2-hydroxymethyl)phenyl group was developed as a reusable activating group of the silicon atom and can transfer 2-pyridyl group: (b) Nakao, Y.; Imanaka, H.; Sahoo, A. K.; Yada, A.; Hiyama, T. *J. Am. Chem. Soc.* **2005**, *127*, 6952. See also ref 3a.

to the decomposition of **1a**, (entry 2),¹² the combined activator CuI/Bu₄NF afforded **2a** in low yield (entry 3). Silver salts were more effective as activators (entries 4 and 5).¹³ In the case of Ag₂O, a large amount of **1a** remained unchanged. Thus, by elongation of the reaction time, the yield was increased to 60% (entry 6). Since the homocoupling reaction of iodobenzene also took place, the use of an excess amount (1.5 equiv) of iodobenzene gave the best yield (78% yield) (entry 7).

Using the Pd(PPh₃)₄/Ag₂O system, we examined several (2-pyridyl)silanes having different substituents on silicon (Figure 1).¹⁴ As mentioned previously, the reaction of **1a**

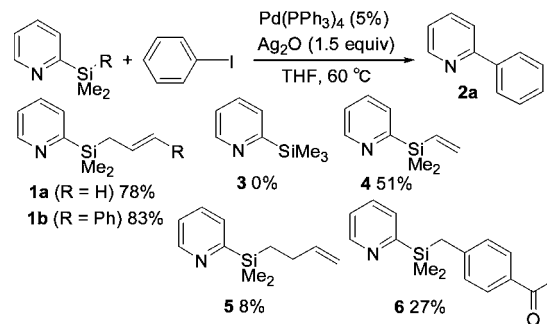


Figure 1. Effect of substituents on silicon atom.

gave **2a** in 78% yield and no allyl transfer product, allylbenzene, was formed. The use of 2-pyridyl(cinnamyl)silane **1b**, however, resulted in the formation of the homocoupling product of the cinnamyl group (38%) and 1,3-diphenylpropene (21%) together with the desired **2a** (83%). Although 2-pyridyltrimethylsilane **3** did not give **2a**, 2-pyridyl(vinyl)silane **4**¹⁵ and 2-pyridyl(3-butenyl)silane **5** afforded **2a**. 2-Pyridyl(benzyl)silane **6** also gave **2a**, but benzyl coupling occurred predominantly.⁹ Based on these results, we assume that the coordination of the carbon-carbon double bond to silver assists the attack of oxygen on silicon (vide infra), although isolation of silver-coordinated complex was unsuccessful.¹⁶

(7) (a) Itami, K.; Nokami, T.; Yoshida, J. *J. Am. Chem. Soc.* **2001**, *123*, 5600. (b) Itami, K.; Nokami, T.; Ishimura, Y.; Mitsudo, K.; Kamei, T.; Yoshida, J. *J. Am. Chem. Soc.* **2001**, *123*, 11577.

(8) Itami, K.; Kamei, T.; Yoshida, J. Unpublished results.

(9) Itami, K.; Mineno, M.; Kamei, T.; Yoshida, J. *Org. Lett.* **2002**, *4*, 3635.

(10) Bu₄NF has been the most versatile fluoride ion source in cross-coupling reactions since Hiyama revealed its efficiency: Hatanaka, Y.; Hiyama, T. *J. Org. Chem.* **1988**, *54*, 268. See also ref 2.

(11) Palladium-catalyzed cross-coupling reactions using alkenyl- or arylsilanes in the presence of copper salts: (a) Sugimoto, M.; Kinugasa, H.; Ito, Y. *Tetrahedron Lett.* **1994**, *35*, 8635. (b) Taguchi, H.; Ghoroku, K.; Tadaki, M.; Tsubouchi, A.; Takeda, T. *J. Org. Chem.* **2002**, *67*, 8450. (c) Denmark, S. E.; Kobayashi, T. *J. Org. Chem.* **2003**, *68*, 5153. (d) Denmark, S. E.; Baird, J. D. *Org. Lett.* **2004**, *6*, 3649. See also ref 6b.

(12) Under the conditions reported by Gros, 2-pyridyltrimethylsilane did not give 2-pyridylbenzene either.

(13) Palladium-catalyzed cross-coupling reactions using aryl- or alkynylsilanes in the presence of silver salts: (a) Hirabayashi, K.; Kawashima, J.; Nishihara, Y.; Mori, A.; Hiyama, T. *Org. Lett.* **1999**, *1*, 299. (b) Hirabayashi, K.; Mori, A.; Kawashima, J.; Suguro, M.; Nishihara, Y.; Hiyama, T. *J. Org. Chem.* **2000**, *65*, 5342. (c) Koseki, Y.; Omino, K.; Anzai, S.; Nagasaka, T. *Tetrahedron Lett.* **2000**, *41*, 2377.

The successful cross-coupling reaction of (2-pyridyl)-allyldimethylsilane **1a** prompted us to examine the reactions of related organosilicon compounds (Figure 2). The introduc-

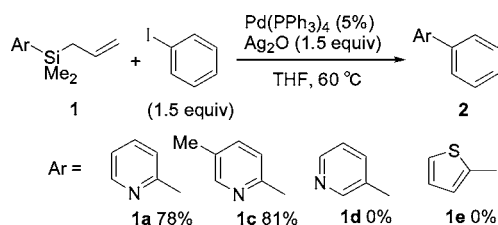
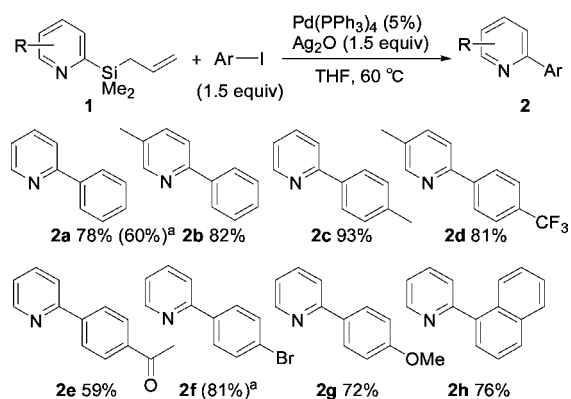


Figure 2. Effect of aryl group on silicon atom.

tion of a methyl group on the pyridine ring did not interfere with the coupling reaction. On the other hand, (3-pyridyl)-allyldimethylsilane **1d** and (2-thienyl)allyldimethylsilane **1e** did not give the corresponding coupling product, and the starting organosilicon compounds were recovered unchanged. These results indicate that the presence of a nitrogen atom β to the silicon atom seems to be crucial for the reaction.

Various aryl iodides can be used for the present reaction, and the corresponding cross-coupling products were obtained as shown in Figure 3. The nature of substituents of aryl



*Yields were based on aryl iodides and 1.5 equiv of **1** was used.

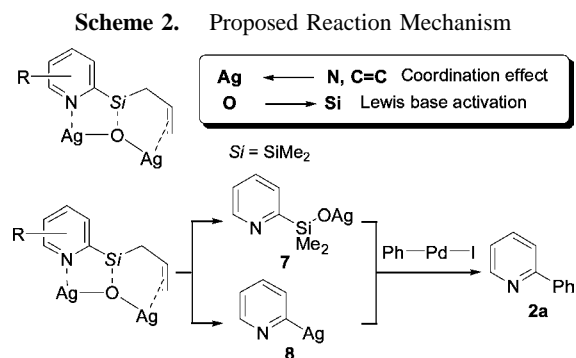
Figure 3. Scope and limitation of aryl halides.

iodides did not affect yields significantly. The reaction is compatible with electron-donating groups on the aryl group

(14) Various substituents have been reported as potentially activating groups of silicon atom. (a) Denmark, S. E.; Choi, J. Y. *J. Am. Chem. Soc.* **1999**, *121*, 5821. (b) Hosoi, K.; Nozaki, K.; Hiyama, T. *Chem. Lett.* **2002**, 138. (c) Trost, B. M.; Machacek, M. R.; Ball, Z. T. *Org. Lett.* **2003**, *5*, 1895. (d) Anderson, J. C.; Munday, R. H. *J. Org. Chem.* **2004**, *69*, 8971. See also refs 5e,f and 7.

such as methyl and methoxy groups and electron-withdrawing groups such as the trifluoromethyl group.

The following mechanistic discussion seems to be reasonable, although there is no definite evidence (Scheme 2). The



initial step involves the coordination of the allyl group and the pyridyl nitrogen to silver followed by the Lewis basic activation of the silicon by oxygen.⁹ This process leads to either allyl carbon–silicon bond cleavage or pyridyl carbon–silicon bond cleavage.¹⁷ The former mode of cleavage may give the siloxysilver species **7**, which seems to be active in palladium-catalyzed cross-coupling reactions. The second mode of cleavage leads to the formation of 2-pyridylsilver intermediate **8**. The transmetalation from silver to palladium followed by the coupling gives **2a**. It is difficult to distinguish these two possibilities, and more information should be accumulated in order to reveal the mechanistic details.

In summary, we have developed a palladium-catalyzed cross-coupling reaction using (2-pyridyl)allyldimethylsilanes as pyridyl transfer reagents. Ag_2O was found to be quite effective as an activator. Further work aimed at elucidating the detailed mechanism and the applications to the synthesis of various 2-pyridyl group containing compounds are currently in progress.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(15) Styrene, which is the cross-coupling product between the vinyl group and iodobenzene, was observed as a byproduct.

(16) We reported syntheses and crystal structures of copper–(2-pyridyl)-vinyl dimethylsilane and copper–(2-pyridyl)allyl dimethylsilane complexes: (a) Itami, K.; Ushioji, Y.; Nokami, T.; Ohashi, Y.; Yoshida, J. *Org. Lett.* **2004**, *6*, 3695. (b) Kamei, T.; Fujita, K.; Itami, K.; Yoshida, J. *Org. Lett.* **2005**, *7*, 4725.

(17) Itami, K.; Kamei, T.; Mineno, M.; Yoshida, J. *Chem. Lett.* **2002**, 1084.