Palladium-Catalyzed Cross-Coupling Reaction of Alkenyldimethyl(2-pyridyl)silanes with Organic Halides: Complete Switch from the Carbometalation Pathway to the Transmetalation Pathway

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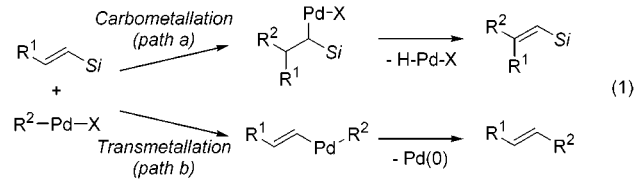
The transition metal-catalyzed cross-coupling reactions constitute one of the most versatile and efficacious carbon−carbon bond formations, and the development of improved catalysts and reagents continues to evolve at a rapid pace.[1] Although there are a number of reaction types known to date, integration of these reaction types by utilizing a multifunctional substrate lags far behind presumably due to the difficulty in controlling those individual reaction pathways. It would be of great importance in organic synthesis if such plural reaction pathways were perfectly controlled, ideally with slight changes of additive or reaction conditions, and integrated into sequential and/or one-pot reactions. During the course of our investigations in this area, we became interested in the multiform reactivities of vinylsilanes, which can potentially react with organic halides and palladium catalyst in two mechanistically different modes, namely carbometalation pathway (path a, eq 1)[2,3] and transmetalation pathway (path b, eq 1).[4] Although both of these reaction pathways have been extensively utilized in organic synthesis, their integration has not been examined to date.

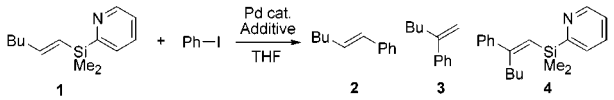


(1)

Recently we reported that the palladium-catalyzed cross-coupling reaction of vinyl(2-pyridyl)silanes with organic halides occurs in the carbometalation pathway (path a) to give the substituted vinyl(2-pyridyl)silanes in extremely high yields.[3,5] The realization of the previously difficult Heck-type reaction of vinylsilane may be due to the strong coordination effect of the pyridyl group on silicon. In this communication, we establish that (1) this carbometalation pathway (path a) can be completely switched to the transmetalation pathway (path b) by the Pd/TBAF system and (2) these two distinct reaction pathways can be integrated into the one-pot sequential reactions which have never been accomplished to date.

As we already established,[3] the Mizoroki−Heck-type reaction[6] occurs with dimethylhexenyl(2-pyridyl)silane (**1**) and iodobenzene in the presence of palladium catalyst [$Pd_2(dba)_3$·$CHCl_3$ + tri-2-furylphosphine (TFP)] (Table 1, entry 1). Although various Pd catalysts were examined, the only product detected was the carbometalation product **4**. This may be due to the strong directing effect of the pyridyl group and the poor transmetalation ability of silicon. Thus we followed the lead of Hiyama,[4] who has established that the transmetalation from silicon to palladium can be accelerated by adding a fluoride ion.[7] We subjected **1** and iodobenzene to the action of palladium catalyst and fluoride source at 60 °C in THF. By adding tetrabutylammonium fluoride (TBAF) to the Pd/TFP catalyst, the course of the reaction changed to the transmetalation pathway and the carbometalation pathway was completely suppressed (entry 2). Moreover, we found that phosphine-free Pd complexes were more active catalysts giving the transmetalation product **2** in extremely high yields (entries 3−6). The observed excellent **2**/**3** ratio (99/1) is noteworthy since the production of cine substitution product (**3**) is the plague in this chemistry for some instances.[4]

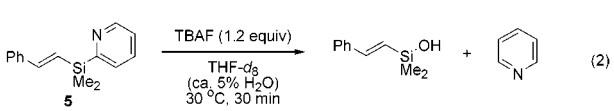
Table 1. Effect of Catalyst and Additive in the Palladium-Catalyzed Cross-Coupling Reaction of **1** and Iodobenzene[a]



entry	Pd catalyst	additive	yield (%)	**2**/**3**/**4**[c]
1[a]	$Pd_2(dba)_3$/TFP	Et_3N	94	0/0/100
2[b]	$Pd_2(dba)_3$/TFP	TBAF	59	97/3/0
3[b]	$Pd(OAc)_2$	TBAF	93	98/2/0
4[b]	$[allylPdCl]_2$	TBAF	95	98/2/0
5[b]	$PdCl_2(CH_3CN)_2$	TBAF	96	99/1/0
6[b]	$PdCl_2(PhCN)_2$	TBAF	99	99/1/0

[a] Reaction was performed at 50 °C for 2 h using **1** (0.5 mmol), PhI (0.55 mmol), $Pd_2(dba)_3$·$CHCl_3$ (0.5 mol %), tri-2-furylphosphine (TFP) (2 mol %), and Et_3N (0.6 mmol) in THF. [b] Reactions were performed at 60 °C for 1.5 h using **1** (0.3 mmol), PhI (0.2 mmol), Pd catalyst (5 mol %), and TBAF (0.3 mmol) in THF. [c] Determined by GC and NMR analysis.

We were pleased to find that the potentially transferable pyridyl group is not transferred into the product and ends up in the quantitative formation of pyridine.[8] These facts led us to investigate the reaction mechanism in more detail. First, styryldimethyl(2-pyridyl)silane (**5**) was allowed to react with 1.0 equiv of $PdCl_2(CH_3CN)_2$ in the presence of TBAF (1.2 equiv) and (*E*,*E*)-1,4-diphenylbutadiene was isolated in 72% yield. This result unambiguously supports the occurrence of the transmetalation pathway. Again, the pyridyl group transferred products (2,2′-bipyridyl and styrylpyridine) were not observed at all.



(2)

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(5) For other related chemistry of 2-pyridylsilanes, see: (a) Yoshida, J.; Itami, K.; Mitsudo, K.; Suga, S. *Tetrahedron Lett.* **1999**, *40*, 3403. (b) Itami, K.; Mitsudo, K.; Yoshida, J. *Tetrahedron Lett.* **1999**, *40*, 5533. (c) Itami, K.; Mitsudo, K.; Yoshida, J. *Tetrahedron Lett.* **1999**, *40*, 5537. (d) Itami, K.; Nokami, T.; Yoshida, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 1074.

(6) (a) Bräse, S.; de Meijere, A. In ref 1, Chapter 3. (b) Heck, R. F. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: New York, 1991; Vol. 4, Chapter 4.3.

(7) Pd-catalyzed cross-coupling reaction utilizing fluorosilicates; see: (a) Yoshida, J.; Tamao, K.; Takahashi, M.; Kumada, M. *Tetrahedron Lett.* **1978**, 2161. (b) Yoshida, J.; Tamao, K.; Yamamoto, H.; Kakui, T.; Uchida, T.; Kumada, M. *Organometallics* **1982**, *1*, 542.

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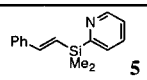
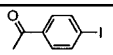
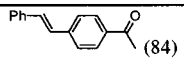
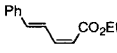
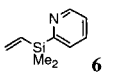
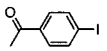
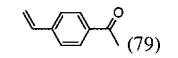
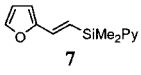
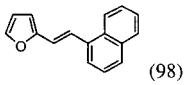
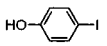
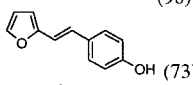
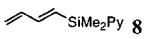
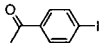
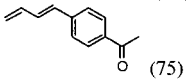
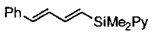
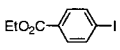
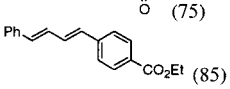
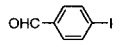
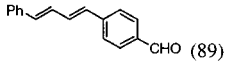
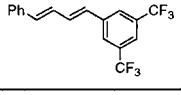
Table 2. Palladium-Catalyzed Cross-Coupling Reaction of Alkenyldimethyl(2-pyridyl)silanes and Various Organic Halides[a]

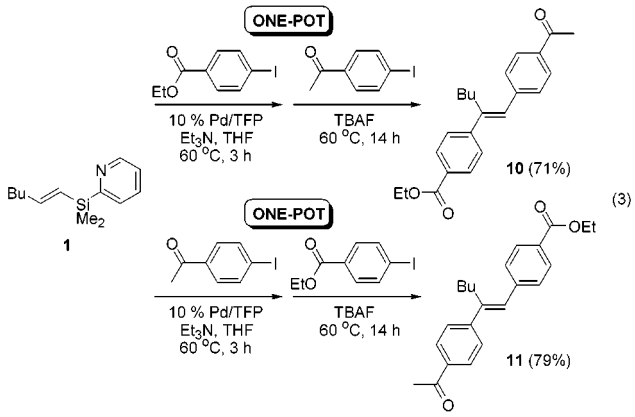
entry	silane	halide	product (isolated yield, %)
1	 **5**		 (84)
2	**5**		 (91)
3	**5**		 (91)
4	**5**		 (59)
5	 **6**		 (79)
6	 **7**		 (98)
7	**7**		 (73)
8	 **8**		 (75)
9	 **9**		 (85)
10	**9**		 (89)
11	**9**		 (73)

[a] All reactions were performed at 60 °C for 2−5 h using alkenyldimethylpyridylsilane (0.3 mmol), organic halide (0.2 mmol), TBAF (0.3 mmol), and $PdCl_2(PhCN)_2$ (5 mol %) in THF.

Next, we monitored the reaction of **5** and TBAF in THF-d_8 by ^{1}H NMR and found that **5** is converted into styryldimethylsilanol and pyridine within 30 min at 30 °C (eq 2).[9] The small amount of water (ca. 5%) present in the commercially available THF solution of TBAF seemed to be the reactant in this case. Indeed, silanol was not formed with anhydrous TASF instead. This 2-Py−Si bond cleavage is reminiscent to that attained by the KF-promoted methanolysis of 2-pyridylsilanes.[10] Very recently, Mori[11] and Denmark[12] have reported that silanols can be cross-coupled with organic halides in the presence of Pd catalyst and we assume that our cross coupling using 2-pyridylsilanes is mechanistically similar to theirs.[13] After all, it seems plausible to deduce that the perfect switch of the reaction pathway stems from *the selective removal of the carbometalation-directing pyridyl group and the introduction of an electronegative group that activates silicon as a leaving group*.

With the feasibility of the selective transmetalation pathway established, a survey of the substrate scope was undertaken (Table 2). Various electronically and structurally diverse aryl and alkenyl halides were found to cross-couple with 2-pyridyl-substituted vinylsilanes in good to excellent yields. The advantage of using 2-pyridyl-substituted vinylsilanes as coupling components is apparent, as they are readily available in stereoisomerically pure form by the Peterson-type reaction of carbonyl compounds with $(2\text{-PyMe}_2\text{Si})_2\text{CHLi}$.[14] Thus, the overall process can be regarded as a novel carbonyl olefination reaction.

In light of the ability of 2-pyridyl-substituted vinylsilane to cross-couple with organic halide in two mechanistically different modes (Table 1), we next embarked on the one-pot sequential cross coupling, in which the carbometalation-oriented cross coupling (path a, eq 1) occurs first and the transmetalation-oriented cross coupling (path b, eq 1) takes place thereafter. The β-substituted vinylsilane **1** was initially cross-coupled with 4-iodobenzoic acid ethyl ester in the presence of Pd/TFP catalyst. After the initial reaction was completed, 4-iodoacetophenone and TBAF were added to the mixture. The sequential cross-coupling product **10** was obtained in 71% yield (eq 3).[15] Interestingly, the regioisomer **11** can be obtained in 79% yield by simply changing the order of addition (eq 3). In both cases, the reaction proceeded in virtually complete regio- and stereoselective fashion. This procedure provides an extremely facile entry into a diverse range of stereodefined polysubstituted olefins, the synthesis of which has been a central issue in organic synthesis.[16]



(3)

In summary, a highly efficient palladium-catalyzed cross-coupling reaction of alkenyldimethyl(2-pyridyl)silanes with organic halides has been developed. The potentially occurring two reaction pathways (carbometalation and transmetalation pathways) were perfectly controlled by simply changing the additives, and integrated into the one-pot sequential cross-coupling reaction. Although both of these reaction pathways are the types that are already known, the integration of two mechanistically distinct reactions clearly opens up new possibilities in the catalytic cross-coupling chemistry.

Acknowledgment. This research was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture, Japan. This paper is dedicated to our mentor Professor Yoshihiko Ito.

Supporting Information Available: Experimental procedures and analytical and spectroscopic data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) The transfer of the substituted pyridyl group from Si to Pd in the presence of KF has been reported. Hagiwara, E.; Kusumoto, T.; Hiyama, T. 76th National Meeting of the Chemical Society of Japan, Yokohama, 1999.

(9) Protodesilylation of styryldimethylsilanol was found to take place upon letting the mixture stand for several hours to afford styrene quantitatively.

(10) Itami, K.; Mitsudo, K.; Yoshida, J. *J. Org. Chem.* **1999**, *64*, 8709.

(11) (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.

(12) Denmark, S. E.; Wehrli, D. *Org. Lett.* **2000**, *2*, 565.

(13) Indeed, the cross coupling of styryldimethylsilanol with iodobenzene did occur under our reaction conditions (Table 1, entry 6) giving stilbene in 98% yield.

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(15) Substituted stilbenes are known to display interesting pharmacological and physical properties. For examples, see: (a) Young, W. R.; Aviram, A.; Cox, R. J. *J. Am. Chem. Soc.* **1972**, *94*, 3976. (b) Kagechika, H.; Himi, T.; Namikawa, K.; Kawachi, E.; Hashimoto, Y.; Shudo, K. *J. Med. Chem.* **1989**, *32*, 1098. (c) Meier, H. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1399.

(16) Organ, M. G.; Cooper, J. T.; Rogers, L. R.; Soleymanzadeh, F.; Paul, T. *J. Org. Chem.* **2000**, *65*, 7959 and references therein.