Highly Efficient Carbopalladation Across Vinylsilane: Dual Role of the 2-PyMe$_2$Si Group as a Directing Group and as a Phase Tag

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Carbopalladation, the insertion of unsaturated molecules into carbon−palladium bonds, is a critically important step in many palladium-catalyzed carbon−carbon bond-forming processes[1] such as the Mizoroki−Heck reaction,[2] cyclic cascade reaction,[1d] cyclooligomerization, and polymerization. We have recently been engaged in the development of removable directing groups,[3] which control the metal-mediated and -catalyzed processes by complex induced proximity effect (CIPE).[4] For example, expeditious hydrosilylation was achieved by utilizing a 2-pyridyldimethylsilyl (2-PyMe$_2$Si) group as a directing group.[3a] The removal of the 2-PyMe$_2$Si group was achieved by H_2O_2 oxidation.[3a,d] Moreover, the phase tag property of this group enables easy product purification (acid−base extraction).[3] In ongoing efforts to exploit the utility of this removable directing group, investigation of carbopalladation across the vinylsilane bearing 2-PyMe$_2$Si group was undertaken (Scheme 1).[5]

It already has been known that there are several difficulties upon carbopalladation across vinylsilane. For example, the treatment of vinylsilane with aryl iodide under the typical Heck reaction conditions affords exclusively styrene derivative as a result of carbon−silicon bond cleavage.[6,7] The only procedure realizing the vinylsilane carbopalladation (Heck-type reaction) to some extent is the use of an equimolar amount of silver nitrate, which is not very useful from the practical point of view.[8] By taking advantage of efficacious CIPE through the coordination of the pyridyl group to the catalyst palladium, we expected the occurrence of the Heck-type reaction without the need of silver salt. In this communication, we describe the "proof-of-principle" of our strategy and the dual role of the 2-PyMe$_2$Si group as a directing group and as a phase tag.

In early experiments we established that iodobenzene and 2-pyridyldimethyl(vinyl)silane (**1**) are cross-coupled in the presence of 2.5 mol % of [$Pd_2(dba)_3$·$CHCl_3$], 10 mol % of PPh_3, and 1.2 equiv of Et_3N (THF, 50 °C; 58% yield after 6 h; Table 1, entry 1). Noteworthy is that the formation of styrene (carbon−silicon bond cleavage) was completely suppressed even in the absence of silver salt. On the basis of this auspicious preliminary result, we have set out to investigate the effect of added ligand (Table 1). Chelating diphosphine enormously shut down the reaction presumably due to the occupation of the coordination site for **1** (entry 2).[2b] Electronic tuning of PPh_3 was found to be very informative. Whereas the use of electron-donating $P(C_6H_4\text{-}OCH_3\text{-}4)_3$ gave rise to the detrimental effect on rate, electron-withdrawing $P(C_6H_4CF_3\text{-}4)_3$ greatly accelerated the reaction (entries 3 and 4). Substantial rate enhancements over PPh_3 were also observed with $AsPh_3$, $P(OPh)_3$, and tri-2-furylphosphine (TFP). Particularly, the use of TFP gave rise to an extremely high yield of **2a** (97%, entry 7). Remarkably, this Pd/TFP catalyst system permits the coupling at low catalyst loading (0.1 mol %) without significant loss of catalytic activity (entry 8).

Scheme 1

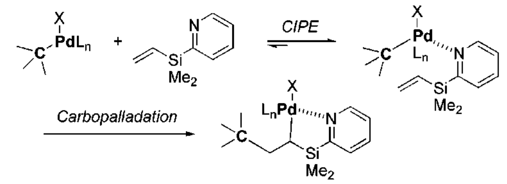
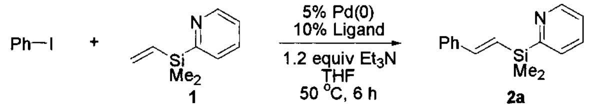


Table 1. Effect of the Ligand on the Rate of the Palladium-Catalyzed Heck Coupling of **1** and Iodobenzene[a]



entry	ligand	conversion (%)[b]	yield (%)[b]
1	PPh_3	63	58
2	$Ph_2PCH_2CH_2PPh_2$	6	5[c]
3	$P(C_6H_4OCH_3\text{-}4)_3$	24	15
4	$P(C_6H_4CF_3\text{-}4)_3$	100	90
5	$AsPh_3$	91	80
6	$P(OPh)_3$	100	85
7	TFP	100	97[d]
8	TFP	100	78[e]

[a] Unless otherwise noted, all reactions were performed at 50 °C for 6 h using **1** (0.5 mmol), PhI (1.1 equiv), Et_3N (1.2 equiv), $Pd_2(dba)_3$·$CHCl_3$ (2.5 mol %), and ligand (10 mol %) in THF (1.5 mL). [b] Determined by GC analysis. [c] 5 mol % of ligand was employed. [d] The reaction completed within 2 h. [e] The mixture was stirred for 38 h using 0.1 mol % of catalyst.

To evaluate the carbopalladation aptitude of vinylsilane **1**, competitive reaction was carried out with methyl acrylate and styrene, the most commonly used reactive substrates in the Heck chemistry (eq 1).[2] To our surprise, the only product detected in the reaction mixture was **2a** (89% yield), which clearly signifies the high reactivity of **1** toward the Heck reaction.[8e] It is reasonable to assume that the coordination of the pyridyl group to palladium might render the carbopalladation event kinetically

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(1) For excellent reviews, see: (a) Hegedus, L. S. *Transition Metals in the Synthesis of Complex Organic Molecules*, 2nd ed.; University Science Books: Sausalito, CA, 1999. (b) Diederich, F.; Stang, P. J., Eds. *Metal-Catalyzed Cross-Coupling Reactions*; Wiley-VCH: Weinheim, 1998. (c) Tsuji, J. *Palladium Reagents and Catalysts*; John Wiley: Chiester, 1995. (d) Negishi, E.; Copéret, C.; Ma, S.; Liou, S.-Y.; Liu, F. *Chem. Rev.* **1996**, *96*, 365.

(2) (a) Bräse, S.; de Meijere, A. In ref 1b, Chapter 3. (b) Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2. (c) de Meijere, A.; Meyer, F. E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2379. (d) Heck, R. F. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: New York, 1991; Vol. 4, Chapter 4.3.

(3) (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.; Mitsudo, K.; Yoshida, J. *J. Org. Chem.* **1999**, *64*, 8709. (e) Itami, K.; Nokami, T.; Yoshida, J. *Org. Lett.* **2000**, *2*, 1299.

(4) (a) Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, *19*, 356. (b) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879. (c) Beak, P.; Basu, A.; Gallagher, D. J.; Park, Y. S.; Thayumanavan, S. *Acc. Chem. Res.* **1996**, *29*, 552. See also: (d) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307.

(5) For chelation-controlled Heck arylation, see: (a) Andersson, C.-M.; Larsson, J.; Hallberg, A. *J. Org. Chem.* **1990**, *55*, 5757. (b) Nilsson, K.; Hallberg, A. *J. Org. Chem.* **1992**, *57*, 4015. (c) Buezo, N. D.; Alonso, I.; Carretero, J. C. *J. Am. Chem. Soc.* **1998**, *120*, 7129 and references therein. See also ref 2b.

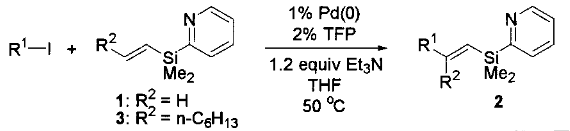
(6) (a) Hallberg, A.; Westerlund, C. *Chem. Lett.* **1982**, 1993. (b) Karabelas, K.; Hallberg, A. *J. Org. Chem.* **1989**, *54*, 1773.

(7) (a) Akhrem, I. S.; Chistovalova, N. M.; Mysov, E. I.; Vol'pin, M. E. *J. Organomet. Chem.* **1974**, *72*, 163. (b) Yoshida, J.; Tamao, K.; Yamamoto, H.; Kakui, T.; Uchida, T.; Kumada, M. *Organometallics* **1982**, *1*, 542. (c) Hatanaka, Y.; Hiyama, T. *J. Org. Chem.* **1988**, *53*, 920. For a review on the Pd-catalyzed C−C coupling reactions involving C−Si bond cleavage (Hiyama coupling), see: (d) Hiyama, T. In ref 1b, Chapter 10.

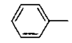
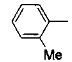
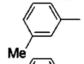
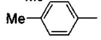
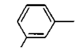
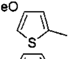
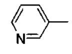
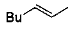
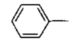
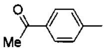
(8) (a) Karabelas, K.; Westerlund, C.; Hallberg, A. *J. Org. Chem.* **1985**, *50*, 3896. (b) Karabelas, K.; Hallberg, A. *Tetrahedron Lett.* **1985**, *26*, 3131. (c) Karabelas, K.; Hallberg, A. *J. Org. Chem.* **1986**, *51*, 5286. (d) Karabelas, K.; Hallberg, A. *J. Org. Chem.* **1988**, *53*, 4909. (e) Voigt, K.; von Zezschwitz, P.; Rosauer, K.; Lansky, A.; Adams, A.; Reiser, O.; de Meijere, A. *Eur. J. Org. Chem.* **1998**, 1521. See also: (f) Yamashita, H.; Roan, B. L.; Tanaka, M. *Chem. Lett.* **1990**, 2175.

10.1021/ja002582q CCC: $19.00

Table 2. Palladium-Catalyzed Heck-type Coupling of Pyridyl-Substituted Vinylsilane with Aryl, Heteroaryl, and Alkenyl Iodides[a]

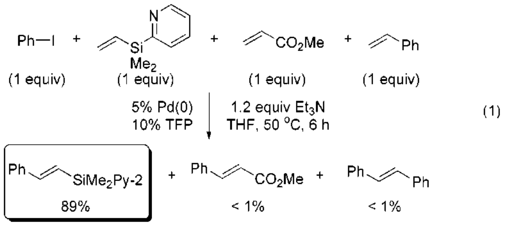


1: $R^2 = H$
3: $R^2 = n\text{-}C_6H_{13}$

entry	R^1	R^2	yield (%)[b]	stereo-selectivity[c]
1		H	93 (**2a**)	>99% *E*
2		H	94 (**2b**)	>99% *E*
3		H	91 (**2c**)	>99% *E*
4		H	95 (**2d**)	>99% *E*
5		H	92 (**2e**)[d]	>99% *E*
6		H	92 (**2f**)	>99% *E*
7		H	95 (**2g**)	>99% *E*
8		H	90 (**2h**)[e]	>99% *E*
9		n-C_6H_{13}	94 (**2i**)	>99% *E*
10		n-C_6H_{13}	90 (**2j**)	>99% *E*

[a] Unless otherwise noted, all reactions were performed at 50 °C using vinylsilane (0.5 mmol), organic iodide (1.1 equiv), Et_3N (1.2 equiv), $Pd_2(dba)_3{\cdot}CHCl_3$ (0.5 mol %), and TFP (2 mol %) in THF (1.5 mL). [b] Isolated yields. [c] Determined by GC and NMR analysis. [d] 2 mol % of catalyst was used. [e] Reaction was performed at 90 °C in toluene.

and/or thermodynamically favorable.



(1)

Under the standard set of reaction conditions (0.5 mol % of $[Pd_2(dba)_3{\cdot}CHCl_3]$, 2 mol % of TFP, and 1.2 equiv of Et_3N at 50 °C in THF), pyridyl-substituted vinylsilanes (**1** and **3**) cross-coupled with a wide array of electronically and structurally diverse aryl, heteroaryl, and alkenyl iodides[9] in high yield (Table 2).[10] In all cases, virtually complete stereoselectivities (>99% *E*) were observed. Quite interestingly, the regio- and stereoselective Heck reaction proceeded even with β-substituted vinylsilane **3**, providing compelling evidence for the enhanced reactivity of pyridyl-substituted vinylsilane (entries 9 and 10). In light of the prevailing dogma that the intermolecular Heck reaction is sensitive to the substitution pattern on the alkene scaffold, the regio- and stereocontrolled carbopalladation across the acyclic 1,2-disubstituted alkene **3** is extremely appealing.[2,11]

As we recently reported, the additional benefit of using the 2-$PyMe_2Si$ group is that it can also be utilized as a phase tag,[3a] which enables easy purification.[12] By taking advantage of this phase tag property of the 2-$PyMe_2Si$ group, all products listed in Table 2 were isolated only by simple acid−base extraction (Scheme 2). Acid extraction (1 N HCl, 6 times) of the reaction mixture transfers the product and base (Et_3N) to the aqueous phase, while the catalyst and excess aryl iodide remain in the organic phase. Neutralization of the aqueous phase and subsequent extraction with organic solvent re-transfer the product to the organic phase. Finally, the evaporation of organic solvent affords the product **2**. The yield of **2** using this acid−base extraction is generally higher (~5%) than that using silica gel chromatography and is slightly lower (~3%) than that determined by GC analysis of the reaction mixture. Importantly, the purities of the products are over 95% in all cases as judged by NMR and GC analysis. This easy separation/purification protocol without using any chromatographic isolation technique is notable.[13]

Scheme 2

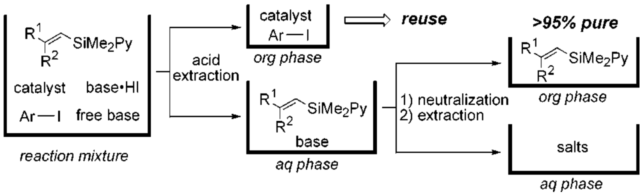


Table 3. Reuse of Palladium Catalyst in the Heck Coupling of **1** and Iodobenzene[a]

entry	time, h	yield (**2a**), %	purity, %	stereoselectivity, % *E*
1[a]	2	93	>95	>99
2[b]	5	90	>95	>99
3[b]	6	89	>95	>99
4[b]	6	91	>95	>99

[a] Reaction was performed at 50 °C using **1** (0.5 mmol), iodobenzene (1.1 equiv), Et_3N (1.2 equiv), $Pd_2(dba)_3{\cdot}CHCl_3$ (2.5 mol %), and TFP (10 mol %) in THF (1.5 mL). [b] Reactions were performed at 50 °C using **1** (0.5 mmol), iodobenzene (1.0 equiv), Et_3N (1.2 equiv), and recovered palladium catalyst in THF (1.5 mL).

One important corollary of these findings is that the palladium catalyst may possibly be recovered from the initial organic phase in the acid−base extraction purification process (Scheme 2), leading to the consecutive use for the next run. In practice, thus recovered palladium catalyst can be used in the second, third, and forth runs without eroding the catalytic activity (Table 3).[14] Importantly, the purities of the isolated **2a** (by acid−base extraction) were over 95% in every run as in the case in Table 2.

In summary, we have developed a new strategy for the carbopalladation across vinylsilane by exploiting the 2-$PyMe_2Si$ group as a directing group. In addition, easy product purification, catalyst recovery, and catalyst reuse are now viable by taking advantage of the phase tag property of 2-$PyMe_2Si$ group.

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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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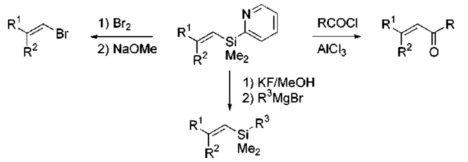
(9) Under the identical reaction conditions, cross coupling did not take place when aryl bromides were used instead of aryl iodides.

(10) Pyridyl-substituted vinylsilane can be converted to other vinylsilanes via pyridyl−silyl bond cleavage (ref 3e), or can be directly subjected to the reactions with various electrophiles. See Supporting Information for details.



(11) For the stereoselective synthesis of trisubstituted alkene by the Heck reaction of 1,2-disubstituted alkene, see: (a) Moreno-Mañas, M.; Pleixats, R.; Roglans, A. *Synlett* **1997**, 1157. (b) Blettner, C. G.; König, W. A.; Stenzel, W.; Schotten, T. *Tetrahedron Lett.* **1999**, *40*, 2101. (c) Gürtler, C.; Buchwald, S. L. *Chem. Eur. J.* **1999**, *5*, 3107 and references therein.

(12) For an excellent review on the strategic separations in organic synthesis, see: Curran, D. P. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1174.

(13) *Green Chemistry: Frontiers in Benign Chemical Synthesis and Processes*; Anastas, P. T., Williamson, T. C., Eds.; Oxford University Press: New York, 1998.

(14) See Supporting Information for details.