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Stereospecific Palladium-Catalyzed Cross-Coupling of (*E*)- and (*Z*)-Alkenylsilanolates with Aryl Chlorides

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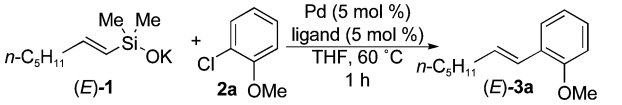
The power and versatility of palladium-catalyzed cross-coupling reactions of organoboranes,[1a] -stannanes,[1b] and -silanes[1c] is attributable in large measure to the wide range of electrophilic coupling partners that participate in the process. In recent years the ability to engage ubiquitous and inexpensive organic chlorides has contributed significantly to the reaction scope. Thanks to advances in ligand design,[2,3] cross-coupling reactions of aryl- and alkenylstannanes,[3a,4] aryl- and alkenylsilanes,[5] and arylboronic acids,[3c,e,6] with aryl chlorides have been reported. However, only limited success has been obtained in the cross-coupling of alkenylboronic acids with aryl chlorides. These substrates suffer from low reactivity and, consequently, double bond isomerization during the cross-coupling reaction.[3e,7] Organosilanol-based cross coupling, developed in these laboratories, has emerged as a useful method because of the high reactivity, ease of preparation, and shelf-stability of the silanols.[8] Furthermore, the use of preformed silanolates precludes addition of an external activator thereby increasing the functional group tolerance and lowering the overall cost of the reaction.[9] Ongoing mechanistic studies have shown that this reaction proceeds through the intermediacy of an organoPd(II) silanolate complex, formed by displacement of an organoPd(II) halide with an organosilanolate.[10] Therefore, the extension of this cross-coupling process to aryl chlorides not only needs to address the issue of oxidative addition, but also the difficulties associated with displacement of the strong Pd−Cl bond by the silanolate to form the organoPd(II) silanolate.[11] Herein, we describe the development of a general, highly stereospecific, high-yielding, palladium-catalyzed cross-coupling of (*E*)- and (*Z*)-alkenyldimethylsilanolates with a wide variety of aryl chlorides.

We began our investigation with the cross-coupling between potassium heptenyldimethylsilanolate, (*E*)-**1**, and 2-chloroanisole, **2a**, using allylpalladium chloride (APC) as the palladium source.[12] A variety of ligands known to be active for cross-coupling of aryl chlorides were screened (Table 1). Disappointingly, bulky trialkylphosphines and an N-heterocyclic carbene palladium precatalyst **6**[7b] were not effective at promoting this cross-coupling reaction (entries 1−4). However, biphenyl-based ligands, developed by Buchwald,[3e] showed promise. In the presence of ligands **4a** and **5b**, the test reaction proceeded to 82% and 60% conversion after 1 h, respectively (entries 6 and 9). Further variation of the phosphine substituent led to poorer results. Although the reaction using **4a** proceeded at room temperature, it stalled before the aryl chloride was completely consumed.

Because of our concern that displacement on the organoPd(II) chloride might be turnover limiting,[10] the influence of the silanolate counterion was studied. A marked difference was observed between the rate of reaction of the sodium and potassium silanolates, but only a negligible difference was observed between the potassium and cesium silanolates (Table 2). Subsequent studies were performed with the potassium silanolate owing to the ease of preparation.

With a reliable cross-coupling method in hand, a variety of aryl chlorides was surveyed to investigate the scope of the reaction.

Table 1. Ligand Survey for the Cross-Coupling of (*E*)-**1** with 2-Chloroanisole



entry	palladium source	ligand	conversion, %[a]
1	APC	Cy_3P	9
2	$(t\text{-}Bu_3P)_2Pd$		0
3	$(t\text{-}Bu_3P)_2Pd$, APC[b]		1
4	**6**	**6**	7
5	APC	$Me(t\text{-}Bu)_2P{\cdot}HBF_4$	4
6	APC	**4a**	82
7	APC	**4b**	8
8	APC	**5a**	39
9	APC	**5b**	60
10	APC	**5c**	10

[a] Determined by GC analysis vs internal standard of tetradecane. [b] $(t\text{-}Bu_3P)_2Pd$ (2.5 mol %), APC (1.25 mol %).

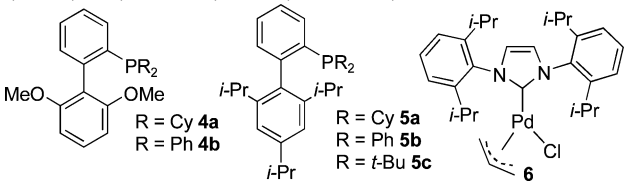
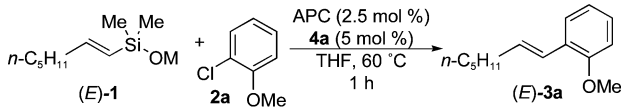


Table 2. Counterion Effects in the Cross-Coupling of (*E*)-**1** with 2-Chloroanisole



entry	M	conversion, %
1	Na	33
2	K	82
3	Cs	83

[a] Determined by GC analysis vs internal standard of tetradecane.

The survey was performed at 60 °C with 1.3 equiv of (*E*)-**1** and these conditions were tolerant of aryl chlorides bearing nitrile, ester, nitro, and ketone substituents (Table 3, entries 1−4). Furthermore, 2 and 3-chloropyridine reacted smoothly (entries 6−7). Mono- and diortho substituted aryl chlorides reacted smoothly thus revealing the limited influence of the increased steric bulk on the aryl chloride (entries 9−11). In general, electron rich aryl chlorides were less reactive as illustrated in the cross-coupling of 2-chloro and 4-chloroanisole (entries 12−13). For these unactivated substrates, additional silanolate (1.5 equiv) and a slightly higher temperatures (66 °C) were required for the aryl chloride to be consumed. Of particular note is the compatibility of the TBS-protected benzyl alcohol (entry 14), which showed that the silanolate-based cross-coupling is compatible with synthetically useful silicon protecting groups. In all cases the coupling was highly stereospecific, but a more compelling test was the extension to the (*Z*)-alkenyl silanolates that are more prone to isomerization. Gratifyingly, the cross-coupling of (*Z*)-heptenylsilanolate, (Z)-**1**, also proceeded with high

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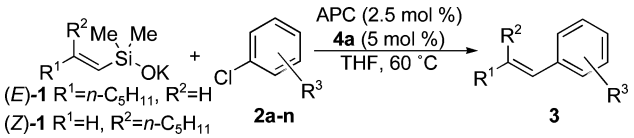
Table 3. Cross-Coupling of (*E*)- and (*Z*)-**1** with Aryl Chlorides



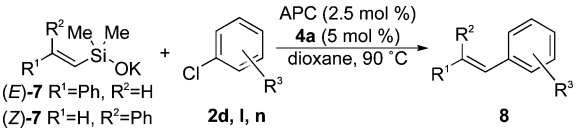
entry	silanol	R^3	time, h	product	yield, %[a]	*E*/*Z*[b]
1	(*E*)-**1**	4-CN	2	(*E*)-**3b**	91	99.2:0.8
2	(*E*)-**1**	4-NO_2	0.33	(*E*)-**3c**	87	99.2:0.8
3	(*E*)-**1**	4-CO_2t-Bu	0.5	(*E*)-**3d**	97	99.6:0.4
4	(*E*)-**1**	4-COPh	0.5	(*E*)-**3e**	98	99.5:0.5
5	(*E*)-**1**	4-CF_3	1	(*E*)-**3f**	91	99.7:0.3
6	(*E*)-**1**	2-pyridyl	3	(*E*)-**3g**	87	99.6:0.4
7	(*E*)-**1**	3-pyridyl	1.5	(*E*)-**3h**	85	99.8:0.2
8	(*E*)-**1**	H	1.5	(*E*)-**3i**	93	99.4:0.6
9	(*E*)-**1**	4-Me	2	(*E*)-**3j**	95	99.6:0.4
10	(*E*)-**1**	2-Me	2	(*E*)-**3k**	95	99.8:0.2
11	(*E*)-**1**	2,6-Me_2	2	(*E*)-**3l**	95	99.7:0.3
12[c]	(*E*)-**1**	4-OMe	3.5	(*E*)-**3m**	89	99.6:0.4
13[c]	(*E*)-**1**	2-OMe	3	(*E*)-**3a**	95	99.5:0.5
14	(*E*)-**1**	4-CH_2OTBS	1.5	(*E*)-**3n**	92	98.8:1.2
15	(*Z*)-**1**	4-CO_2t-Bu	0.33	(*Z*)-**3d**	97	1.2:98.8
16	(*Z*)-**1**	3-pyridine	1.5	(*Z*)-**3h**	91	0.7:99.3
17	(*Z*)-**1**	H	1.5	(*Z*)-**3i**	92	1.4:98.6
18	(*Z*)-**1**	2,6-Me_2	2	(*Z*)-**3l**	87	0.2:99.8
19[c]	(*Z*)-**1**	2-OMe	3	(*Z*)-**3a**	96	0.5:99.5
20	(*Z*)-**1**	4-CH_2OTBS	1.5	(*Z*)-**3n**	98	0.4:99.6

[a] Yield of isolated, analytically pure product. [b] Determined by GC analysis. [c] Used 1.5 equiv of (*E*)-**1** or (*Z*)-**1** at 66 °C.

stereospecificity, functional group compatibility, and yield to afford the (*Z*)-alkenyl products (entries 15−20). The characteristics of the reaction of (*Z*)-**1** in terms of the rate, specificity, and yield were nearly identical to those of (*E*)-**1**.

Because of the problems associated with the coupling of alkenylboronic acids with chlorides, we chose to test the coupling of (*E*)- and (*Z*)-styrylsilanolates ((*E*)-**7** and (*Z*)-**7**) which are much more prone to isomerization. Although the reactions proceeded in DME or toluene at 90 °C, they stalled and reduction products were also detected. Remarkably, switching the solvent to dioxane (at 90 °C) led to complete conversion and very clean products. Even at 90 °C, the reaction proceeded with complete retention of the double-bond geometry. Here again, the TBS-protected benzyl alcohol was compatible under these reaction conditions (Table 4).

Table 4. Cross-Coupling of (*E*)- and (*Z*)-**7** with Aryl Chlorides

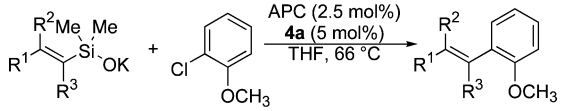


entry	silanol[a]	R^3	time, h	product	yield, %[b]	*E*/*Z*[c]
1	(*E*)-**7**	4-CO_2t-Bu	0.5	(*E*)-**8d**	89	99.9:0.1
2	(*E*)-**7**	2,6-Me_2	1.25	(*E*)-**8l**	91	99.7:0.3
3	(*E*)-**7**	4-CH_2OTBS	1.25	(*E*)-**8n**	94	99.6:0.4
4	(*Z*)-**7**	4-CO_2t-Bu	0.5	(*Z*)-**8d**	94	0.5:99.5
5	(*Z*)-**7**	2,6-Me_2	1.25	(*Z*)-**8l**	90	0.3:99.7
6	(*Z*)-**7**	4-CH_2OTBS	1.25	(*Z*)-**8n**	97	0.5:99.5

[a] Used 1.5 equiv of (*E*)-**7** or (*Z*)-**7**. [b] Yield of isolated, analytically pure product. [c] Determined by GC or SFC analysis.

To further demonstrate the high stereospecificity and scope of this reaction, a series of tri- and tetrasubstituted alkenyl-dimethylsilanols were tested in the cross-coupling reaction with 2-chloroanisole. Trisubstituted alkenylsilanolates (*E*)-**9**, (*Z*)-**9**, and (*E*)-**10** afforded the desired products in high yields with high stereospecificity (Table 5, entries 1−3). Additionally, the tetrasubstiuted alkenylsilanolate (*Z*)-**11** afforded (*Z*)-**14** in a high yield at a comparable rate to the other alkenylsilanolates (Table 5, entry 4). In fact, a substantial decrease in the reaction time was observed for **9**, **10**, and **11** when compared to **1**, illustrating a beneficial influence of the steric bulk of the alkenylsilanolate.

Table 5. Cross-Coupling of Tri- and Tetrasubstituted Silanols with 2-Chloroanisole



(*E*)-**9**: R^1=C_2H_5, R^2=H, R^3=CH_3
(*Z*)-**9**: R^1=H, R^2=C_2H_5, R^3=CH_3
(*E*)-**10**: R^1=C_5H_{11}, R^2=CH_3, R^3=H
(*Z*)-**11**: R^1=CH_3, R^2=C_2H_5, R^3=CH_3

entry	silanol	time, h	product	yield, %[a]	*E*/*Z*[b]
1	(*E*)-**9**[c]	0.5	(*E*)-**12**	97	98.8:1.2
2	(*Z*)-**9**[d]	0.5	(*Z*)-**12**	89	1.4:98.6
3	(*E*)-**10**	1.0	(*E*)-**13**	98	>99:1
4	(*Z*)-**11**	0.75	(*Z*)-**14**	95	<1:99

[a] Yield of isolated, analytically pure product. [b] Determined by GC analysis. [c] (*E*)-**9**/(*Z*)-**9**, 98.9:1.1. [d] (*E*)-**9**/(*Z*)-**9**, 1.5:98.5.

In conclusion, we have demonstrated a stereospecific and high yielding cross-coupling of di-, tri- and tetrasubstituted alkenyldimethylsilanolates with aryl chlorides. This method overcomes the limitations associated with the cross-coupling of alkenylboronic acids with aryl chlorides and thus affords a general synthesis of aryl-substituted alkenes.

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Supporting Information Available: Detailed experimental procedures and full characterization of all products. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Miyaura, N. In *Metal-Catalyzed Cross-Coupling Reactions;* De Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, Germany, 2004; pp 41−123. (b) Mitchell, T. N. In *Metal-Catalyzed Cross-Coupling Reactions;* De Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, Germany, 2004; pp 125−161. (c) Denmark, S. E.; Sweis, R. F. In *Metal-Catalyzed Cross-Coupling Reactions;* De Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, Germany, 2004; pp 163−216.
(2) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176−4211.
(3) (a) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722−9723. (b) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **1999**, *38*, 2411−2413. (c) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020−4028. (d) Gstottmayr, C. W. K.; Bohm, V. P. W.; Herdtweck, E.; Grosche, M.; Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1363−1365. (e) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685−4696. (f) Christmann, U.; Vilar, R. *Angew. Chem., Int. Ed.* **2005**, *44*, 366−374.
(4) (a) Littke, A. F.; Schwarz, L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 6343−6348. (b) Su, W.; Urgaonkar, S.; Verkade, J. G. *Org. Lett.* **2004**, *6*, 1421−1424.
(5) (a) Sahoo, A. K.; Oda, T.; Nakao, Y.; Hiyama, T. *Adv. Synth. Cat.* **2004**, *346*, 1715−1727. (b) Koike, T.; Mori, A. *Synlett* **2003**, 1850−1852. (c) Lee, H. M.; Nolan, S. P. *Org. Lett.* **2000**, *2*, 2053−2055. (d) Gouda, K.-i.; Hagiwara, E.; Hatanaka, Y.; Hiyama, T. *J. Org. Chem.* **1996**, *61*, 7232−7233.
(6) (a) Anderson, K. W.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2005**, *44*, 6173−6177. (b) Dai, Q.; Gao, W.; Liu, D.; Kapes, L. M.; Zhang, X. *J. Org. Chem.* **2006**, *71*, 3928−3934. (c) Kudo, N.; Perseghini, M.; Fu, G. C. *Angew. Chem., Int. Ed.* **2006**, *45*, 1282−1284. (d) Billingsley, K. L.; Anderson, K. W.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 3484−3488. (e) Marion, N.; Navarro, O.; Mei, J.; Stevens, E. D.; Scott, N. M.; Nolan, S. P. *J. Am. Chem. Soc.* **2006**, *128*, 4101−4111.
(7) (a) Song, C.; Ma, Y.; Chai, Q.; Ma, C.; Jiang, W.; Andrus, M. B. *Tetrahedron* **2005**, *61*, 7438−7446. (b) Navarro, O.; Marion, N.; Mei, J.; Nolan, S. P. *Chem.−Eur. J.* **2006**, *12*, 5142−5148.
(8) (a) Denmark, S. E.; Sweis, R. F. *Acc. Chem. Res.* **2002**, *35*, 835−846. (b) Denmark, S. E.; Ober, M. H. *Aldrichimica Acta* **2003**, *36*, 75−85. (c) Denmark, S. E.; Baird, J. D. *Chem.−Eur. J.* **2006**, *12*, 4954−4963.
(9) Denmark, S. E.; Baird, J. D. *Org. Lett.* **2006**, *8*, 793−795.
(10) Denmark, S. E.; Sweis, R. F. *J. Am. Chem. Soc.* **2004**, *126*, 4876−4882.
(11) de Jong, G. T.; Kovacs, A.; Bickelhaupt, F. M. *J. Phys. Chem. A* **2006**, *110*, 7943−7951.
(12) Denmark, S. E.; Smith, R. C. *Synlett* **2006**, 2921−2928.

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