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Palladium-Catalyzed Cross-Coupling Reactions of Heterocyclic Silanolates with Substituted Aryl Iodides and Bromides

Scott E. Denmark* and John D. Baird

Roger Adams Laboratory, Department of Chemistry, University of Illinois, Urbana, Illinois 61801

denmark@scs.uiuc.edu.

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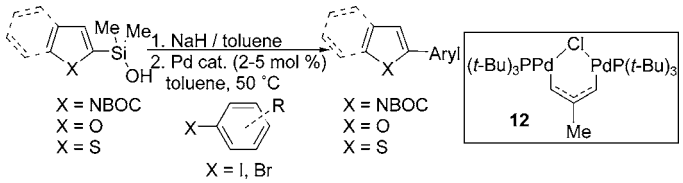
ABSTRACT



Sodium silanolates derived from a number of heterocyclic silanols undergo cross-coupling with a variety of aromatic iodides and bromides under mild conditions. In situ deprotonation of the silanols with an equivalent amount of sodium hydride in toluene generates the sodium salt that couples with iodides under the action of $Pd_2(dba)_3 \cdot CHCl_3$ in good yield at room temperature to 50 °C. The aromatic bromides also couple with these salts under the action of the Pd(I) catalyst 12.

The Pd-catalyzed cross-coupling of organometallic donors including organostannane,[1] -borane,[2] and -zinc[3] reagents is among the most important modern synthetic methods for the formation of carbon−carbon bonds.[4] In recent years, we have developed organosilanols as a new class of donors for a myriad of cross-coupling processes.[5] In addition to the many advantages of organosilanols, we have demonstrated two mechanistically distinct modes of activation: the classic fluoride-induced couplings[6a] and the couplings promoted by various Bronsted bases ($KOSiMe_3$, Cs_2CO_3, NaO^{t}Bu, NaH).[6b] The unique advantages of the latter mode are the avoidance of corrosive fluoride sources which are incompatible with silicon protecting groups. More importantly, fluoride-activated coupling is often plagued by protiodemetalation which is a particularly difficult problem for electron-rich heterocyclic coupling partners.

Heterocyclic compounds are of prime importance in pharmaceutical, natural products, and materials chemistry. Unfortunately, the cross-coupling of heterocyclic donors is of only limited utility for many classes of heterocyclic systems.[7] The cross-coupling of electron-rich heterocyclic stannanes typically requires rather forcing conditions, and their inherent toxicity poses a serious drawback.[8] Although

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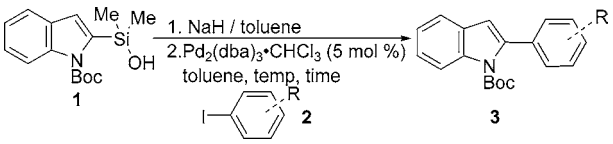
the cross-coupling of arylboronic acids has enjoyed great success, many heterocyclic boronic acids remain problematic as they are unstable to long-term storage and suffer rapid protiodeborylation under reaction conditions.[9] We have recently reported the cross-coupling of *N*-Boc(2-indolyl)-dimethylsilanol (**1**) with aryl iodides under mild conditions in good yields.[10a] The silanol is a robust, shelf-stable reagent that is ideally suited for the synthesis of 2-substituted indoles. In our hands, the corresponding boronic acid decomposed within days.

The original procedure for the cross-coupling of **1** with iodides required the use of CuI (1.0 equiv) and NaO^{t}Bu (2 equiv) along with $Pd_2(dba)_3$•$CHCl_3$ (5 mol %).[10a] Under Bronsted base activation, we propose that the cross-coupling proceeds through a key silicon−oxygen−palladium intermediate prior to the transmetalation step.[6b] The activator serves to generate a metal silanolate which then forms a palladium−silanolate complex. The role of CuI in the reaction remains unclear. We hypothesized that if the sodium silanolate was generated by deprotonation with NaH the requisite sodium silanolate would be formed quantitatively without a conjugate acid in the medium.

We were delighted to find that the sodium silanolates generated in situ from NaH were active in the cross-coupling reaction *and that these reactions proceeded smoothly in the absence of CuI.* In the cross-coupling of 4-iodoanisole (**2a**), the previous conditions required heating the reaction at 50 °C for 24 h to furnish the product in 72% yield. Using the in situ formed silanolate, this product is generated in a comparable 68% yield in just 3 h at 80 °C without CuI (Table 1, entry 1).

Table 1. Formation of Sodium Silanolate Na^+**1**$^-$ in Situ and Cross-Coupling with Aryl Iodides



entry	R	temp, °C	time, h	product	yield,[a] %
1	4-OMe	80	3	**3a**	68
2	4-CO_2Et	rt	3	**3b**	82
3	4-CN	rt	3	**3c**	81

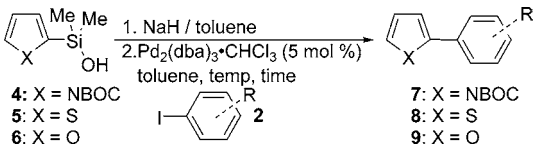
[a] Yield of chromatographed, recrystallized products.

Because NaO^{t}Bu can induce transesterification, we surmised that the milder silanolate base would be compatible with ester groups. Indeed, the in situ prepared Na^+**1**$^-$ afforded smooth conversion to the desired product **3b** in 82% yield in 3 h at room temperature (entry 2). Further, the in situ method was compatible with aryl iodides bearing nitrile groups, which were previously problematic when using NaO^{t}Bu, to furnish **3c** in 81% yield (entry 3).[10a]

A series of electron-rich heterocyclic 2-silanols were prepared including pyrrolyl (**4**), thienyl (**5**), and furyl (**6**).[11] These silanols were all easily obtained by metalation and trapping with either hexamethylcyclotrisiloxane or trapping with dimethyldichlorosilane followed by aqueous hydrolysis. The *N*-Boc (2-pyrrolyl)dimethylsilanol **4** was chosen for ease of removal of the Boc protecting group.[12,13]

Following the conditions outlined above, **4** coupled smoothly with ethyl 4-iodobenzoate (**2b**) and 2-iodotoluene (**2d**) but required mild heating to effect the cross-coupling of **2a** (Table 2, entries 1−3). Other in situ generated heterocyclic silanolates were also tested. For example, Na^+**5**$^-$ provided the desired cross-coupling products from **2b** and **2d** in 3 h at room temperature; however, **2a** required heating to effect complete conversion (entry 4). Furylsilanol **6** exhibited enhanced reactivity with **2b**, furnishing the desired product in 1 h in 82% yield. Tolyl derivate **2d** reacted with Na^+**6**$^-$ in a manner similar to that of Na^+**4**$^-$ and afforded **9d** in 61% yield in 3 h. Surprisingly, the cross-coupling of **2a** with Na^+**6**$^-$ proved challenging and required a catalytic amount of $(2\text{-furyl})_3$As to reach completion (entry 7).

Table 2. Cross-Coupling of Heterocyclic Silanols with Aryl Iodides



entry	X	R	temp, °C	time, h	product	yield,[a] %
1	*N*-Boc	4-OMe	50	36	**7a**	72
2	*N*-Boc	4-CO_2Et	rt	3	**7b**	76
3	*N*-Boc	2-Me	rt	3	**7d**	80
4	S	4-OMe	80	24	**8a**	72
5	S	4-CO_2Et	rt	3	**8b**	78
6	S	2-Me	rt	3	**8d**	79
7[b]	O	4-OMe	50	24	**9a**	71
8	O	4-CO_2Et	rt	1	**9b**	82
9	O	2-Me	rt	3	**9d**	61

[a] Yield of chromatographed products purified by recrystallization or sublimation. [b] Required the use of 0.2 equiv of $(2\text{-furyl})_3$As for complete conversion.

The positive results with aryl iodides encouraged us to investigate the cross-coupling of aryl bromides with in situ

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(11) The synthesis of 2-substituted thiophenes can be achieved from silanes. Nakao, Y.; Imanaka, H.; Sahoo, A. K.; Yada, A.; Hiyama, T. *J. Am. Chem. Soc.* **2005**, *127*, 6952−6953.

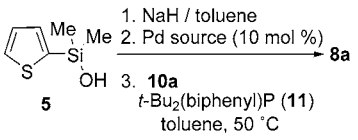
(12) The corresponding *N*-Boc(2-pyrrolyl)boronic acid is a poor substrate for cross-coupling reactions as it suffers from rapid protiodeborylation and also undergoes a competing homodimerization. Johnson, C. N.; Stemp, G.; Anand, N.; Stephen, S. C.; Gallagher, T. *Synlett* **1998**, 1025−1027.

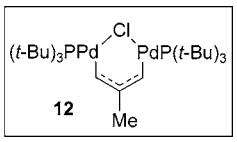
(13) Cross-coupling reactions of 2-thienyl- and 2-furylboronic acids typically employ 2.0 equiv of the boronic acids. Kondolff, I.; Doucet, H.; Santelli, M. *Synlett* **2005**, 2057−2061.

generated sodium silanolates. For optimization studies, we chose $Na^+\mathbf{5}^-$ and 4-bromoanisole (**10a**) as the electrophile. Initial conditions using $Pd_2(dba)_3{\cdot}CHCl_3$ (5 mol %) were unsuccessful, so we surveyed several Pd sources with 1,1-di-*tert*-butylphosphinobiphenyl **11** at 50 °C which has been successfully employed with aryl bromides in other cross-coupling studies within our group.[14]

Disappointingly, $PdCl_2$ and $PdBr_2$ did not catalyze the cross-coupling of **6** with **10a** in the presence of **11** (Table 3, entries 1−3). The use of an allylpalladium chloride dimer in conjunction with **11** brought about complete conversion in 3 h, although the desired arene **8a** was accompanied with 11% of the homocoupling product (entry 4). The Pd(I) catalyst **12**, which has been shown to be a highly active Pd source for the cross-coupling of arylboronic acids, afforded clean conversion to **8a** within 3 h without the formation of the homocoupling side product (entry 5).[15] Furthermore, the loading of **12** can be decreased to 2.5 mol % with no loss in activity.

Table 3. Catalyst and Ligand Optimization for the Cross-Coupling of Aryl Bromide **10a** with $Na^+\mathbf{5}^-$





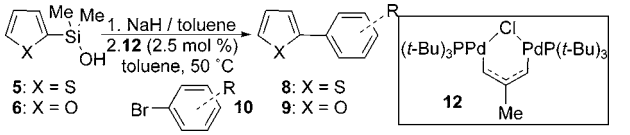
entry	Pd source	ligand,[a] mol %	time, h	conversion, %[b]
1	$PdCl_2$	10	12	trace
2	$PdBr_2$	10	12	4
3	$PdBr_2$	20	24	trace
4	$[allylPdCl]_2$	20	3	100[c]
5	Pd(I) catalyst	0	3	100

[a] Employed 1,1-di-*tert*-butylphosphinobiphenyl as an additive. [b] Area % by GC analysis. [c] Accompanied with 11% of the product of aryl bromide homocoupling, as determined by ^1H NMR analysis.

The cross-coupling of $Na^+\mathbf{5}^-$ and $Na^+\mathbf{6}^-$ proceeded smoothly with a range of aryl bromides providing the desired products in moderate to good yields (Table 4). Most reactions were complete within 3 h, although the cross-coupling of 1-bromonaphthalene was slower requiring 7 and 6 h to reach completion for $Na^+\mathbf{5}^-$ and $Na^+\mathbf{6}^-$, respectively. However, the cross-coupling of $Na^+\mathbf{6}^-$ with **10a** stalled at 78% conversion to give the product in 66% yield (entry 7).[16]

To corroborate our hypothesis that the sodium silanolate is the active silicon intermediate, we prepared $Na^+\mathbf{1}^-$ and tested its competence under the reaction conditions. Adding a hexane solution of **1** to a stirred suspension of 1.0 equiv of NaH in toluene afforded a white precipitate whose identity was confirmed by NMR and HRMS as $Na^+\mathbf{1}^-$. The salt was a stable, free-flowing white powder. We were pleased to find that this reagent possessed reactivity similar to that for the in situ prepared silanolate in reaction with **2b** and $Pd_2(dba)_3{\cdot}CHCl_3$ to afford **3b** in 76% yield. The other silanolates, $Na^+\mathbf{5}^-$ and $Na^+\mathbf{6}^-$, were prepared analogously but were formed as stable waxes which were nonetheless still easily manipulated. The cross-coupling of $Na^+\mathbf{5}^-$ and $Na^+\mathbf{6}^-$ with **2b** and $Pd_2(dba)_3{\cdot}CHCl_3$ gave the desired products in 87% and 79% yields, respectively. Storing the active silicon species as the sodium salt provides two advantages. First, the reaction procedure is simplified by only having to charge the active silanolate into the reaction vessel instead of adding both the silanol and the activator. Second, the dimerization of silanols to their corresponding disiloxanes[17] is prevented by storing the sodium salts.

Table 4. Cross-Coupling of Silanolates with Substituted Aryl Bromides



entry	X	R	time, h	product	yield,[a] %
1	S	4-OMe	3	**8a**	71
2	S	4-CO_2Et	3	**8b**	67
3	S	4-CN	3	**8c**	78
4	S	2-Me	3	**8d**	77
5	S	4-CF_3	3	**8e**	86
6	S	[b]	7	**8f**	74
7[c]	O	4-OMe	6	**9a**	66
8	O	4-CO_2Et	3	**9b**	60
9	O	4-CN	3	**9c**	73
10	O	2-Me	3	**9d**	71
11	O	4-CF_3	3	**9e**	71
12	O	[b]	6	**9f**	69

[a] Yield of chromatographed products purified by sublimation. [b] 1-Bromonaphthalene. [c] Reaction stalled at 78% conversion.

In conclusion, we have developed a simplified and general procedure for the cross-coupling of in situ generated and isolated heterocyclic silanolates with aryl iodides and bromides. Extension to more complex heterocycles is in progress.

Acknowledgment. We are appreciative for generous financial support from the National Institutes of Health (R01GM61738). J. D. B. acknowledges the University of Illinois for a graduate fellowship.

Supporting Information Available: Preparation of $Na^+\mathbf{1}^-$ and all sodium silanolates, detailed experimental procedures, and full characterization of all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) The cross-coupling of the *N*-Boc-(2-indolyl)- and (2-pyrrolyl)-dimethylsilanols with arylbromides was unsuccessful. Significant amounts of phenol were observed when the reactions were run at 80 °C. We believe the phenol is derived from a competing reductive elimination to form a dimethylsilyl ether that is hydrolyzed upon aqueous workup.

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