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Palladium-Catalyzed Cross-Coupling Reactions of 2-Indolyldimethylsilanols with Substituted Aryl Halides

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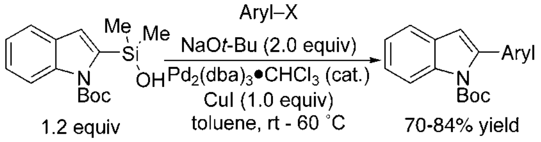
ABSTRACT



A mild and general cross-coupling reaction of 2-indolylsilanols has been developed. The experimental variables that lead to successful coupling are (1) the use of sodium *tert*-butoxide as the activator, (2) the use of copper(I) iodide in stoichiometric quantities, and (3) the use of $Pd_2(dba)_3 \cdot CHCl_3$ as the catalyst. Under these conditions *N*-(Boc)-2-indolyldimethylsilanol reacts with a variety of aromatic iodides to afford the coupling products in good yield (70–84%).

The palladium-catalyzed cross-coupling of silicon compounds[1] is gaining acceptance as a practical alternative to the more commonly known cross-coupling reactions of tin- or boron-based reagents.[2] Organosilicon functions are easily introduced, nontoxic, and synthetically useful nucleophiles for cross-coupling reactions with alkenyl and aryl halides. These reagents eliminate the toxicity associated with stannanes as well as avoid the problems of the handling and sensitivity of organoboron compounds.

A significant advance in the organosilicon cross-coupling process is the development of nonfluoride activators that are compatible with silicon-based protecting groups.[3] Recent reports from these laboratories described the use of mild bases such as KOTMS or Cs_2CO_3 for the cross-coupling reactions of alkenyl- and arylsilanols with good scope and reactivity.[3,4] Although successful cross-coupling reactions have been developed for simple arylsilanols, little work has been done to explore the use of heterocyclic silanols as coupling partners.[5]

Indoles are among the most common heterocycles in nature, and the biological activity of indoles has been an active area of medicinal research.[6] Among the many synthetic strategies used to prepare 2-substituted indoles,[7] cross-coupling reactions allow for their direct construction based on a preexisting indole nucleus. However, mild and general methods for the cross-coupling of 2-indolyl nucleophiles are lacking.[8,9] Particularly challenging are coupling reactions of indoles that are protected as their *N*-butoxycarbonyl (Boc) derivatives, which decreases the nucleophilicity at C(2), thus decelerating the key transmetalation step in the coupling. Typical procedures employ harsh conditions (Stille coupling[9]) or afford the desired products in low yields (Suzuki

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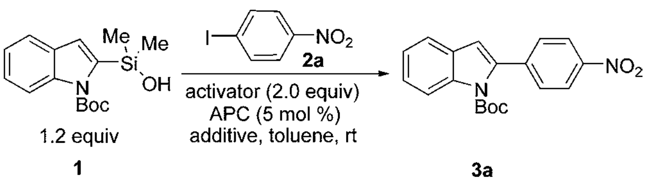
coupling[8,10]). We report herein mild and high-yielding cross-coupling reactions of indolyl-2-silanols with aryl iodides and bromides that proceed with both *N*-Boc and *N*-methylindole precursors.

For initial studies on the cross-coupling, *N*-Boc(2-indolyl)-dimethylsilanol (**1**) was selected, because of the general utility of the Boc protecting group.[11,12] In contrast to the corresponding *N*-Boc(2-indolyl)boronic acid or -stannane, **1** is easily prepared, chromatographically stable, and can be stored for extended periods at −20 °C. To develop a method for the cross-coupling of **1**, a set of conditions was developed employing 4-nitroiodobenzene, allylpalladium chloride dimer ($[allylPdCl]_2$), and KH as the activator in toluene at room temperature.[13] Under these conditions, only *N*-Boc-indole, the product of protiodesilylation, was observed and none of the desired cross-coupling product was obtained.

To overcome the problem of low reactivity and the formation of undesired side-products, we next examined the effect of copper salts that have a beneficial effect on the rate of cross-coupling of stannanes[14] and silanes[15] and may also inhibit protiodesilylation.[5] The tetrameric copper trimethylsilanolate[16] afforded a small amount of the desired product, whereas among other copper sources ($CuCl_2$, CuBr, CuCN) only copper(I) iodide showed any salutary effect (30% conversion after 24 h) and thus was chosen for subsequent optimization studies.

To find an optimal activator for this reaction, several inorganic bases were surveyed in combination with copper(I) iodide (Table 1). Although KH and NaH effected the cross-coupling reaction (entries 1 and 2), they are too harsh and would preclude the use of substrates bearing sensitive functional groups. However, a dramatic cation dependence was observed for the *tert*-butoxide bases where NaO*t*-Bu was found to be optimal (entries 3−5). This behavior may result from the greater solubility of the sodium silanolate.[17]

Table 1. Activator Optimization in the Cross-Coupling of **1** with **2a**



entry[a]	activator	product,[b] % after 24 h
1	NaH	47
2	KH	30
3	LiO*t*-Bu	0
4	NaO*t*-Bu	46
5	KO*t*-Bu	3

[a] Conditions: 1.2 equiv of **1**, 2.0 equiv of activator, 1.0 equiv of CuI, 0.05 equiv of APC, 0.5 M in **2a** in toluene at room temperature. [b] Determined by HPLC analysis with an internal standard.

Next, the influence of palladium source was surveyed (Table 2). The use of $PdCl_2$, $PdCl_2(PPh_3)_2$, and $Pd(OAc)_2$ showed little product formation, (Table 3, entries 1−3). Whereas $PdBr_2$ and $(CH_3CN)_2PdCl_2$ were more active catalysts compared to $[allylPdCl]_2$, they were still inferior to the chloroform solvate of $Pd_2(dba)_3$ (entry 7). Although this reaction reached completion within 12 h at room temperature, **2a** is a very reactive electrophile, and other less reactive aryl halides might require more forcing conditions. Simply doubling the concentration from 0.5 to 1.0 M in **2a** resulted in complete conversion of the iodide to the desired product in 6 h in 92% yield (HPLC) along with only 3% of the halide-homocoupling side product.

Table 2. Catalyst Optimization of the Cross-Coupling of **1** with **2a**[a]

		product (%)[b]	
entry	Pd source	12 h	24 h
1	$PdCl_2$	0	3
2	$PdCl_2(PPh_3)_2$	0	15
3	$Pd(OAc)_2$	0	17
4	$[allylPdCl]_2$	22	46
5	$PdBr_2$	55	94
6	$(CH_3CN)_2PdCl_2$	57	98
7	$Pd_2(dba)_3 \cdot CHCl_3$	87	>99

[a] Conditions: 1.2 equiv of **1**, 2.0 equiv of NaO*t*-Bu, 1.0 equiv of CuI, 0.1 equiv Pd, 0.5 M in **2a** in toluene at room temperature. [b] Determined by HPLC analysis with an internal standard.

Because $Pd_2(dba)_3 \cdot CHCl_3$ was superior to the other catalysts surveyed, $Pd_2(dba)_3$ was also examined as a catalyst for this reaction (Table 3, entry 2). Surprisingly, $Pd_2(dba)_3 \cdot CHCl_3$ was more active than $Pd_2(dba)_3$ under these conditions (compare entries 1 and 2). To determine if the chloroform

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[10] (a) *N*-Boc(2-indolyl)boronic acid reacts poorly with iodobenzene under typical Suzuki conditions; see: Johnson, C. N.; Stemp, G.; Anand, N.; Stephen, S. C.; Gallagher, T. *Synlett* **1998**, 1025−1027. (b) Ishikura and co-workers have demonstrated the cross-coupling of an in-situ-generated *N*-Boc(2-indolyl)boronate with aryl bromides from a 2-lithated indolyl species and triethylborane; see: Ishikura, M.; Agata, I.; Katagiri, N. *J. Heterocycl. Chem.* **1999**, *36*, 873−879.

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[13] Preliminary experiments with KOTMS as the activator gave protiodesilylation as the major product, so we surmised that using KH as an activator would quickly and irreversibly deprotonate the silanol and remove the only available proton source as H_2.

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[17] Solubility in toluene (wt %) at 25 °C: NaO*t*-Bu, 6%; KO*t*-Bu, 2.3%. LiO*t*-Bu is more soluble but less nucleophilic.

must be present as the solvate of the palladium species for the enhanced reactivity, $Pd_2(dba)_3$ was employed with 5 mol % chloroform as an additive (entry 3), and the activity was restored. To probe if the reactivity is simply a result of enhanced solubility of the palladium species, CH_2Cl_2 was also employed as an additive (at 5 and 100 mol % wrt **2a**) but was inferior to chloroform (entry 4).[18]

Table 3. Effect of Additive and Palladium Source on the Cross-Coupling of **1** with **2a**[a]

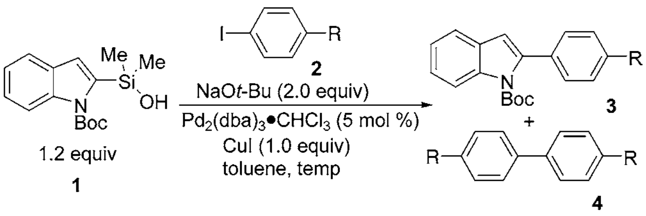
entry	catalyst	copper iodide (equiv)	additive (equiv)	product (%)[b] at 6 h
1	$Pd_2(dba)_3{\cdot}CHCl_3$	1.0		92[c]
2	$Pd_2(dba)_3$	1.0		44
3	$Pd_2(dba)_3$	1.0	$CHCl_3$ (0.05)	96[d]
4	$Pd_2(dba)_3$	1.0	CH_2Cl_2 (0.05)	64
5	$Pd_2(dba)_3$	1.0	CH_2Cl_2 (1.00)	45
6	$Pd_2(dba)_3{\cdot}CHCl_3$	0.0		48
7	$Pd_2(dba)_3{\cdot}CHCl_3$	0.5		76
8	$Pd_2(dba)_3{\cdot}CHCl_3$	1.0		92

[a] Conditions: 1.2 equiv of **1**, 2.0 equiv of NaO*t*-Bu, 0.1 equiv of Pd, 0.5 M in **2** in toluene at room temperature. [b] Determined by HPLC using a response factor to biphenyl at 6 h. [c] Halide-homocoupling product (3%) was observed. [d] Halide-homocoupling product (4%) was observed.

With a highly evolved procedure in hand that employs a different base and palladium source than was initially tested, we briefly reexamined the role of copper iodide (Table 3, entries 6−8). Interestingly, in the absence of CuI, the reaction proceeds to 48% conversion after 6 h but stalls (52% after 24 h). With 0.5 equiv of CuI, the reaction does go to completion after 12 h (95%). From these studies, the combination of NaO*t*-Bu (2.0 equiv), CuI (1.0 equiv), and $Pd_2(dba)_3{\cdot}CHCl_3$ (0.05 equiv) was used to survey the scope of the halide partner in this cross-coupling reaction.

The results of cross-coupling of **1** with a variety of electrophiles are collected in Table 4. In general, electron-deficient aromatic iodides coupled smoothly at room temperature in good yields (entries 1−4). Electron-rich and sterically encumbered substrates required mild heating to reach completion (entries 6−9). Generally, less reactive aryl iodides showed more of the halide-homocoupling side product **4** than electron-deficient aryl iodides. Although the cross-coupling of aryl iodides proceeded well, initial attempts at the cross-coupling of aryl-bromides with **1** were unsuccessful.[19]

Table 4. Cross-Coupling of **1** with Substituted Aryl Iodides

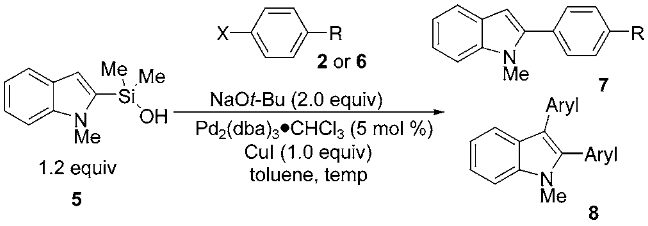


entry	R	temp (°C)	time (h)	product	yield (%) 3[a]	yield (%) 4[b]
1	4-NO_2	rt	6	**3a**	84	6
2	4-CF_3	rt	22	**3b**	82	3
3	4-$CO_2C(CH_3)_3$	rt	24	**3c**	84	trace
4	3-NO_2	40	12	**3d**	72	14
5	H	40	12	**3e**	70	12
6	2-Me	50	24	**3f**	73	14
7	4-OMe	50	24	**3g**	72	14
8	2-OMe	50	24	**3h**	75	15
9	1-naphthyl	60	24	**3i**	75	13

[a] Yield of analytically pure products. [b] Determined by ^1H NMR analysis of crude reaction mixtures.

To probe the use of other nitrogen substituents, the *N*-methyl(2-indolyl)dimethylsilanol **5** was prepared and subjected to these reaction conditions with several aryl iodides (Table 5). In general, a similar trend was observed with respect to the electrophile as with the *N*-Boc case where electron-deficient aryl iodides reacted faster (entries 1 and 2) than electron-rich substrates (entries 3−5). Although the reactions proceeded to completion at room temperature, for cases with electron-withdrawing substituents the isolated yields of the desired cross-coupling products were lower (entries 1 and 2). In these cases, the 2,3-disubstituted indole **8** was formed as a minor byproduct. Presumably, the silanol is sufficiently activated to undergo an electrophilic aromatic substitution that is competitive with the desired cross-coupling pathway. We surmised that switching from an aryl iodide to an aryl bromide would slow this side process and favor cross-coupling. Indeed, employing 1,4-bis(diphenylphosphino)butane (dppb) and heating these reactions to 55 °C furnished the desired products in good yields (entries 6 and 7).

Table 5. Cross-Coupling of **5** with Substituted Aryl Halides **2** and **6**



entry	X	R	temp (°C)	time (h)	product	yield (%) 7[a]	yield (%) 8[b]
1	I	4-NO_2	rt	3	**7a**	62	16
2	I	4-CN	rt	3	**7b**	62	30
3	I	H	rt	3	**7c**	82	
4	I	2-thienyl	rt	6	**7d**	73	
5	I	4-OMe	rt	3	**7e**	80	
6	Br	4-NO_2	55	20	**7a**	84[c]	5
7	Br	4-CN	55	20	**7b**	80[c]	5

[a] Yield of analytically pure products. [b] Determined by ^1H NMR analysis of crude reaction mixtures. [c] Addition of 0.2 equiv of dppb was required.

In conclusion, we have developed a successful cross-coupling of (2-indolyl)dimethylsilanols. The reactivity of the

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(18) Role of chloroform is currently unclear.

(19) Use of electron-rich phosphine ligands typically employed for the cross-coupling of aryl bromides failed with **1**.

2-indolyl moiety toward cross-coupling is strongly influenced by the substituent on the indole nitrogen. Current studies employing these conditions for the cross-coupling of other heteroaromatic silanols is underway along with mechanistic studies on the role of copper.

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Supporting Information Available: Details of the preparation and full characterization of **1**, **5**, and all cross-coupling products. This material is available free of charge via the Internet at http://pubs.acs.org.

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