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A Synthetic Method for Palladium-Catalyzed Stannylation at the 5- and 6-Benzo Positions of Indoles

Emily B. Corcoran, Anna B. Williams, and Robert N. Hanson*

Department of Chemistry and Chemical Biology, Northeastern University, Boston, Massachusetts 02115, United States

r.hanson@neu.edu

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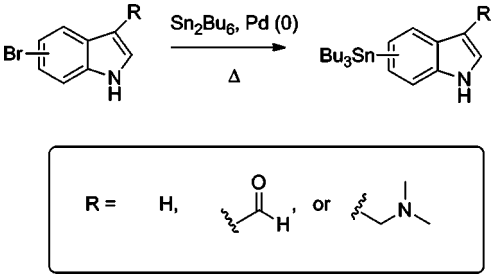
ABSTRACT



The stannylation of indole derivatives proceeds in good yields under palladium catalysis (5 mol %) without protection of the indolic nitrogen. The general utility of both $PdCl_2(PhCN)_2/PCy_3$ and Pd_2dba_3/PCy_3 as catalytic systems for the stannylation of three indole derivatives, with varying degrees of electron density, is presented.

The indole scaffold is ubiquitous in nature and performs diverse biological roles, such as signal transduction, plant hormones, and amino acids, as well as being present in many natural products of pharmacological interest. In our ongoing program to design and prepare PET and SPECT radiotracers as probes of biological systems, we undertook the preparation and evaluation of radiohalogenated indole derivatives featuring an iodine-123 or fluorine-18 radionuclide at the benzo positions of the indole ring system. We focused on the radiohalogenation of benzo positions, particularly C5 and C6, of the indole scaffold as modification of the C2 or C3 substituents may jeopardize biological activity.

The benzo positions, unlike the C2 and C3 positions, are not preferred positions for electrophilic substitution. Nonradioactive halogens can be introduced into these benzo positions through use of either haloaniline or halophenylhydrazine precursors (via palladium-catalyzed cyclization or Fischer indole synthesis) or alternatively diazonium salts. These strategies, however, are incompatible with radiohalogens which possess short half-lives and for which high specific activity is necessary. The criteria associated with synthesis of radiotracers for SPECT and PET focused our efforts on the development of new methods for labeling this important class of compounds.

The radiohalogenation of indoles at the benzo positions is typically achieved by the following methods: (1) acid- or copper-catalyzed halogen−radiohalogen exchange,[1−3] (2) decomposition of diazonium fluoroborates,[4] or (3) halodemetalation reactions in which electrophilic halogen displaces an alkylmetal moiety.[5−8] Of these methods, the indirect halogen−radiohalogen exchange via halodestannylation is preferable as its mild reaction conditions provide radiohalogenated products that are readily separable from their metalated precursors in high specific activity (Scheme 1). Although these reactions proceed

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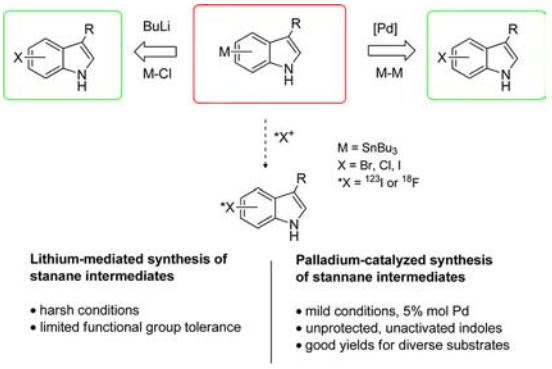
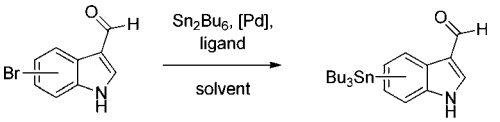
with ease, challenges in the preparation of the stannylated intermediates often preclude the use of this technology with unactivated, electron-rich substrates. The most common method for preparation of benzo-stannylated indoles entails a preliminary hydrogen or halogen−lithium exchange and subsequent transmetalation with trialkylstannyl chloride.[5,9] While effective for simple indoles, these reactions have very limited functional group tolerance and more complex derivatives require milder conditions, such as those associated with palladium catalysis. Palladium-catalyzed stannylation of the indolic benzo positions, unless the substrate is otherwise activated,[10] has posed a difficult synthetic challenge with most reactions suffering from low yields (less than 50%) and high catalyst loading (10 mol %).[11]

Scheme 1. Indirect Halogen−Radiohalogen Exchange at the Benzo Positions of Indole Derivatives



Herein we describe a general method for efficient palladium-catalyzed C5-/C6-stannylation of indole derivatives which features lower palladium loadings (5 mol %) and obviates protection of the indolic nitrogen. Our investigation focused on the preparation of the 5- and 6-tributylstannyl derivatives of three indole scaffolds featuring electronically diverse C3 substituents: 1*H*-indole, indole-3-carbaldehyde, and gramine. The initial steps of this project pertained to the stannylation of the 5-/6-bromo-1*H*-indole-3-carbaldehyde derivatives **1** and **2**. Common transmetalation conditions (Table 1, entry 1), in which **1** was refluxed in toluene with hexabutylditin in the presence of tetrakis(triphenylphosphine), showed no evidence of any reaction progress over a period of 24 h. Similar results were obtained with $PdCl_2$dppf in toluene; however, the same conditions in dioxane gave the desired product **3** in a 24% isolated yield (Table 1, entry 3). Use of more basic ligands, PCy_3 and dppe, with $PdCl_2(PhCN)_2$ as the precatalyst (Table 1, entries 4 and 5) gave **3** in increased

Table 1. Selected Optimization Reactions toward the Synthesis of the 5-/6-Tributylstannyl-1*H*-indol-3-carbaldehydes[a]



1: 6-bromo
2: 5-bromo
3: 6-tributylstannyl
4: 5-tributylstannyl

entry	ArX	catalyst	ligand	solvent	yield[b] (%)
1	1	$Pd(PPh_3)_4$	none	toluene	0
2	1	$PdCl_2$dppf	none	toluene	0
3	1	$PdCl_2$dppf	none	dioxane	24
4	1	$PdCl_2(PhCN)_2$	PCy_3	dioxane	82
5	1	$PdCl_2(PhCN)_2$	dppe	dioxane	79
6	2	$PdCl_2(PhCN)_2$	PCy_3	dioxane	22
7	2	$PdCl_2(PhCN)_2$	$P(^tBu)_3$	dioxane	0
8	2	$PdCl_2(PhCN)_2$	dppe	dioxane	60
9	2	$PdCl_2(PhCN)_2$	PCy_2bph	dioxane	79

[a] Unless otherwise noted, reactions were carried out using **1** or **2** (1 equiv), [Pd] (0.05 equiv), ligand (0.1 equiv), and hexa-*n*-butylditin (3 equiv) at 110−120 °C under an atmosphere of argon for 12−24 h. [b] Isolated yields reported as an average of two runs.

yields of 82% and 79%, respectively. Unlike **1**, compound **2** failed to react favorably with the $PdCl_2(PhCN)_2/PCy_3$ catalytic system, giving **4** in only 22% yield (Table 1, entry 6). Increasing the basicity of the ligand by use of $P(tBu)_3$ (Table 1, entry 7) did not promote any formation of **4**, while the use of less basic ligands dppe and PCy_2bph (Table 1, entries 8 and 9) gave **4** in moderate to good yields (60% and 79%, respectively).

We were pleased to discover that PCy_3, in conjunction with either $PdCl_2(PhCN)_2$ or Pd_2dba_3, was capable of promoting the stannylation of the unsubstituted indoles **5** and **6** to form **7** and **8** in good yields, ranging from 90 to 97%, after only 3 h (Table 2, entries 1, 4, 5, and 8). Less basic ligands, such as PCy_2bph and dppe, gave only moderate yields after 12 h for both **7** and **8**, ranging from 29 to 58% (Table 2, entries 2, 3, 6, and 7). Unlike the 3-carbaldehyde derivatives, the C3 unsubstituted indole derivatives demonstrated no appreciable differences between the C5 and C6 positions with regard to optimal reaction conditions. Although the preparation of **7** and **8** was accomplished easily under these conditions, the isolation of these compounds posed a challenge because of the extremely acid-sensitive nature of these compounds. Use of silica chromatography, despite pretreatment with 5% triethylamine in hexanes, resulted in substantial hydrodestannylation of **7** and **8** to form unsubstituted 1*H*-indole. Similar results were observed using basic alumina chromatography. Minimal loss of product during isolation was achieved by reversed-phase chromatography using an isocratic acetonitrile mobile phase; use of water during the reversed-phase purification process also led to significant formation of the destannylated byproduct.

Lastly, we undertook the stannylation of the electron-rich gramine derivatives **9** and **10**. To the best of our

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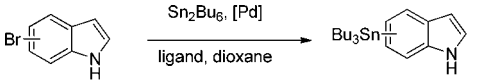
Table 2. Optimization of the Stannylation of C3-Unsubstituted Indoles[a]



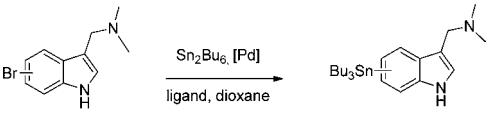
5: 5-bromo
6: 6-bromo

7: 5-tributylstannyl
8: 6-tributylstannyl

entry	ArX	catalyst	ligand	yield[b] (%)
1[c]	5	$PdCl_2(PhCN)_2$	PCy_3	92
2	5	$PdCl_2(PhCN)_2$	dppe	57
3	5	Pd_2dba_3	dppe	29
4[c]	5	Pd_2dba_3	PCy_3	90
5[c]	6	$PdCl_2(PhCN)_2$	PCy_3	90
6	6	$PdCl_2(PhCN)_2$	dppe	58
7	6	Pd_2dba_3	dppe	43
8[c]	6	Pd_2dba_3	PCy_3	97

[a] Unless otherwise noted, reactions were carried out using **5** or **6** (1 equiv), [Pd] (0.05 equiv), ligand (0.1 equiv), and hexa-*n*-butylditin (3 equiv) at 110−120 °C under an atmosphere of argon for 12 h. [b] Isolated yields reported as an average of two runs. [c] Reaction heated at 110 °C for 3 h.

Table 3. Optimization of the Stannylation of Gramine Derivatives[a]



9: 5-bromo
10: 6-bromo

11: 5-tributylstannyl
12: 6-tributylstannyl

entry	Ar-X	catalyst	ligand	yield[b] (%)
1	9	$PdCl_2(PhCN)_2$	PCy_3	82
2	9	Pd_2dba_3	PCy_3	28
3	9	$PdCl_2(PhCN)_2$	dppe	11
4	9	Pd_2dba_3	PCy_2bph	5
5	10	$PdCl_2(PhCN)_2$	PCy_3	70
6	10	Pd_2dba_3	PCy_3	15
7	10	$PdCl_2(PhCN)_2$	dppe	33
8	10	Pd_2dba_3	PCy_2bph	13

[a] Unless otherwise noted, reactions were carried out using **9** or **10** (1 equiv), [Pd] (0.05 equiv), ligand (0.1 equiv), and hexa-*n*-butylditin (3 equiv) at 110−120 °C under an atmosphere of argon for 12 h. [b] Isolated yields reported as an average of two runs.

knowledge, this constitutes the first application of palladium catalysis toward the metalation of the benzo positions of the gramine scaffold. The only reported stannylation of gramine was accomplished at the C4 position through lithium−hydrogen exchange and subsequent reaction with $Sn(^nBu)_3Cl$.[12] The stannylation of these substrates proved more challenging than the other indole derivatives. Although the $PdCl_2(PhCN)_2/PCy_3$ catalytic system (Table 3, entries 1 and 5) was effective at promoting the stannylation of the gramine derivatives in moderately good yields (70−82%), other catalytic systems which were effective for other substrates gave only minimal product formation. Most notably, Pd_2dba_3, in combination with the PCy_3 ligand, failed to catalyze the stannylation of gramines in decent yields. Indeed, all other ligands screened resulted in minimal product formation (Table 3, entries 2−4 and 6−8). We are uncertain as to the source of this discrepancy between the unsubstituted indoles and the gramines, as reported NMR chemical shifts for these compounds demonstrate that these two classes of substrates are electronically equivalent at the C5 and C6 positions.[13] One possible explanation is that the presence of the tertiary amine is poisoning the catalyst, leaving a large portion of the bromogramine starting material unconsumed. As our goal of using low (5 mol %) catalyst loading to effect these stannylations was met using $PdCl_2(PhCN)_2$ with PCy_3, further optimization using other catalytic systems at higher loadings was not pursued. Similar to **7** and **8**, compounds **11** and **12** were successfully isolated in good yields solely with reversed-phase chromatography using an isocratic acetonitrile mobile phase. Contact with acid, even one as weak as water, led to significant destannylation.

Throughout our investigations, the $PdCl_2(PhCN)_2/PCy_3$ catalytic system demonstrated a general utility in promoting the stannylation of the C5 and C6 positions of each indole derivative, with the only exception of **2**, for which less basic ligands were significantly more effective. For the carbaldehyde and unsubstituted indoles, Pd_2dba_3 and $PdCl_2(PhCN)_2$ performed comparably well, but isolation of product was accomplished more easily from reaction mixtures containing $PdCl_2(PhCN)_2$ as Pd_2dba_3 often coeluted with the product during chromatography.

In conclusion, we have reported a general method for the efficient preparation of C5- and C6-stannylated indole derivatives. In contrast to previous methods, this method eliminates the need for high catalyst loadings and protection of the indolic nitrogen. Additionally, it tolerates diverse functional groups unlike the common lithium-mediated procedures for the preparation of electron-rich stannanes. This synthetic methodology provides access to a variety of previously inaccessible stannylated indole derivatives, the preparation of which has been a bottleneck in the production of biologically relevant radiohalogenated indole derivatives for use in medical imaging as well as other applications. This work is also applicable to the preparation of electron-rich stannanes for use in Stille cross-coupling reactions. To date, access to diverse stannylated indole derivatives has been extremely challenging, thus limiting the role of indoles to that of the aryl halide rather than the metalated species, in Stille reactions.[14] The focus of further work will be the extension of this methodology toward the preparation of C4- and C7-stannylated indole derivatives as well as the stannylation of indole derivatives featuring more complex substitution patterns. Additional studies into the use of the reported stannylated

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indole intermediates for the development of radiotracers are underway.

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Supporting Information Available. Experimental procedures and spectral data for unknown compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.