Published in final edited form as:

J Org Chem. 2008 February 15; 73(4): 1440–1455. doi:10.1021/jo7023784.

Palladium Catalyzed Cross-Coupling of Five-Membered Heterocyclic Silanolates

Scott E. Denmark^{*}, John D. Baird, and Christopher S. Regens

Department of Chemistry, University of Illinois Urbana-Champaign, Urbana, Illinois 61801

Abstract

The preparation of π -rich 2-aryl heterocycles by palladium-catalyzed cross-coupling of sodium heteroarylsilanolates with aryl iodides, bromides and chlorides is described. The cross-coupling process was developed through extensive optimization of the follow key variables: (1) identification of stable, isolable alkali metal silanolates, (2) identification of conditions for preformation and isolation of silanolate salts, (3) judicious choice in the palladium catalyst/ligand combination, and (4) selection of the protecting group on the nitrogen of indole. It was found that the alkali metal silanolates, either isolated or formed *in situ*, offered a significant rate enhancement and broader substrate scope over the use of silanols activated by Brønsted bases such as NaOt-Bu. In addition, the optimized conditions for the cross-coupling of 2-indolylsilanolates were readily applied to the cross-coupling of 2-pyrrolyl-, 2-furyl-, and 2-thienylsilanolates.

Introduction

The synthetic challenges associated with the construction and manipulation of heterocyclic compounds has remained at the forefront of organic chemistry for over a century. These challenges have stimulated the development of milder and more efficient methods for the synthesis of heterocyclic compounds. Pyrroles and indoles are among the most important and are ubiquitous in nature. Indole-containing compounds are found in pigments (Tyrian purple, **1**) as well as compounds with neurological (serotonin, **2**) and psychomimetic (psilocybin, **3**) properties (Chart 1). Given their prevalence in nature and physiological properties, these compounds have found widespread application in the pharmaceutical industry.¹ For instance, Lipitor® **4**, a tetrasubstituted *N*-alkylpyrrole, is the highest grossing drug.² Moreover, 2-substituted indoles are an important class of therapeutic agents with a broad range of biological activity,³ for example, **5** is a potent KDR kinase inhibitor⁴ containing a hydroxy quinoline at C(2), and gonadotropin releasing hormone antagonist⁵ **6** features a 3,4,5-trimethylphenyl group.

Since the first synthesis of indole in the mid 1800's,⁶ a myriad of methods for the construction of the indole nucleus have been developed.^{1,7} Some of the more venerable methods include sigmatropic rearrangements of phenyl hydrazones⁸ or [2,3]-sigmatropic rearrangements of

e-mail: denmark@scs.uiuc.edu.

sulfonium ylides.⁹ The former method, known as the Fisher indole synthesis, has been used extensively in both industrial and academic settings as a means to access a wide range of indoles and their derivatives in a one-pot synthesis.¹⁰ Other notable constructions of 2-aryl indoles include: nucleophilic (Madelung-Houlihan¹¹ and Nenitzescu¹² synthesis), electrophilic (Bischler-Möhlau¹³), reductive (Reissert¹⁴ synthesis) and radical cyclizations.¹⁵ Although these classic methods have been used to synthesize a variety of indoles, there are disadvantages to the above methods limiting their compatibility with a wide range of functional groups.¹⁶ For instance, the Fisher procedure usually requires strongly acidic media at elevated temperatures. The Madelung-Houlihan and Reissert protocols usually require super stoichiometric amounts of a strong base.

Recent advances in transition-metal catalysis have provided new and milder methods for the construction of the indole skeleton. By far, palladium is the most widely used transition metal for this purpose.¹⁷ Some representative transformations include: oxidative-cyclization of *ortho*-aminophenethyl alcohols,¹⁸ Hegedus-Mori-Heck indole synthesis¹⁹ and heteroannulation of 2-haloanilines.²⁰

Because of the wide variety of methods for construction of the indole skeleton, reactions that functionalize a preexisting indole nucleus have received less attention.²¹ One such important example involves palladium-catalyzed, direct arylation or alkenylation of a simple indole skeleton at the C(2) position. Fagnou, Sanford, Sames, and others have recently reported significant advances in the synthesis of C(2)- and C(3)-functionalized indoles by these direct functionalizations.²² Although these methods provide for a very efficient synthesis of substituted heterocycles, they require forcing conditions i.e., long reaction times (>12 h) and elevated temperatures (>100 °C). In addition, the scope of the C-arylation is limited by lower functional group compatibility and moderate regioselectivity.

On the other hand, palladium-catalyzed, cross-coupling provides an alternative access to substituted indoles from a preexisting core. Palladium-catalyzed cross-coupling reactions of organometallic donors (B, Sn, Zn, Mg) and organic acceptors (halide, triflate) have revolutionized construction of carbon-carbon bonds because of their functional group tolerance, increasing commercial availability of reagents, and ease of execution (Equation 1).

Equation 1

Whereas the cross-coupling of stannanes or boronic acids typically proceeds smoothly for simple aryl donors (**7**), the cross-coupling of *heteroaryl* donors can be much more challenging.²³ Not only does the heteroatom alter the structural and electronic properties of the ring, but it can also decrease turnover through unproductive binding of the catalyst. For example, the cross-coupling of 2-indolylstannanes typically requires elevated temperatures for extended periods of time (>24 h) and always generates toxic tin byproducts.²⁴ The corresponding 2-indolylzinc reagents are known, but their preparation is cumbersome, and they must be used immediately.²⁵ The cross-coupling of 2-indolylboronic acids suffers from protideborylation under conventional Suzuki cross-coupling conditions.²⁶ Protideborylation can be overcome by preparing the boronic acid or boronate *in situ*, but this solution limits reaction flexibility and complicates handling.²⁷ Nonetheless, several procedures have been reported for the cross-coupling of nitrogen heterocycles with aryl chlorides.²⁸ An additional complication for the

cross-coupling of 2-indolyl reagents is that they are strongly influenced by the group on the nitrogen atom. For example, an electron-withdrawing group on the nitrogen atom such as the *N*-butoxycarbonyl (Boc) group decreases the nucleophilicity at the C(2) position and consequently hinders the cross-coupling reaction.²⁴ Despite the tremendous advances in both palladium-catalyzed direct arylation and cross-coupling reactions of other heterocyclic donors, mild, simple, and successful methods for the preparation of 2-substituted indoles are still currently lacking.

Although less prevalent than boranes and stannanes, organosilanes are a promising class of cross-coupling reagents that possess many desirable characteristics including their inherent low-toxicity,²⁹ ease of manipulation, ability to be prepared *via* a variety of different methods, low-molecular weight, and formation of non-toxic reaction byproducts.³⁰ Recent reports from these laboratories have shown that the palladium-catalyzed cross-coupling of organosilanols proceeds *via* two distinct pathways; a fluoride-promoted and a Brønsted base promoted pathway.³¹ With Brønsted bases, the active species in these reactions is a palladium silanolate intermediate (Scheme 1).^{31b} The base forms an alkali metal silanolate that attacks the R^2PdXL_n species, displacing X and generates a palladium-silanolate complex *iii*. Following transmetalation, and reductive elimination a carbon-carbon bond is formed and the Pd(0) catalyst is regenerated.

The Brønsted base promoted cross-coupling of several classes of silanols (alkenylsilanols,³² arylsilanols,³³ and heteroarylsilanols³⁴) has been successfully developed with a number of bases including potassium trimethylsilanolate (KOSiMe₃), Cs₂CO₃, and NaOt-Bu. Although these Brønsted bases afford the desired coupling products in satisfactory yields, they are incompatible with base sensitive substrates such as those bearing enolizable carbonyl groups, and it has been proposed that the activator can slow the rate of cross-coupling by serving as a competitive inhibitor with silanolate for palladium.³² More recent studies in the cross-coupling of heteroarylsilanols have demonstrated that the use of metal silanolates directly, either isolated or preformed by stoichiometric deprotonation, are a superior alternatives.³⁵

Given the importance of 2-substituted indoles, and in light of the current limitations described above, we set as our goals the development and optimization of a cross-coupling reaction of a 2-indolylsilanol derivative that would (i) employ a silanol that is stable and capable of storage for extended periods of time, (ii) couple smoothly with a range of aryl halides, and (iii) afford the products in good yields under mild conditions. The course of this study involved the preparation of the requisite silanols, and the optimization of the reaction parameters including scope of activator, palladium source, solvent, and temperature. Additionally, the effect of the nitrogen substituent on the cross-coupling reaction was probed by preparing several *N*-substituted dimethyl(2-indolyl)silanols, such as *N*-Boc, *N*-SEM and *N*-methyl. This survey allowed for the synthesis of 2-arylindoles with cleavable protecting groups as well as the cross-coupling of 2-indolylsilanols with aryl chlorides. In addition, to explore the scope of the indole substrate, a range of 5-substituted 2-indolylsilanols were also prepared bearing bromo, methoxy, methyl and cyano groups at the C(5)-position of indole. Application of this technology to other heterocycles enabled the cross-coupling of *N*-Boc-2-pyrrolyl, 2-furyl, and 2-thienylsilanols.³⁶

Results

1. Synthesis of Heterocyclic Dimethylsilanols and Silanolates

1.1. Preparation of Dimethyl(2-indolyl)silanols—To evaluate the stability of the 2-indolylsilanols, it was first necessary to prepare a variety of *N*-protected 2-indolylsilanols, namely: the *N*-*tert*-butoxycarbonyl (Boc),³⁷ *N*-2-(trimethylsilyl)ethoxymethyl (SEM),³⁸ and *N*-methyl derivatives.³⁹ Second, the applicability of these reagents in cross-coupling with a

broad range of aromatic halides (iodides, bromides and chlorides) would be examined. The investigation began with the preparation of *N*-Boc-dimethyl(2-indolyl)silanol **11**. This substrate was selected in early studies because of its ease of deprotection, resistance to protidesilylation, and ease of introduction of the dimethylsilanol unit through facile metalation at the C(2) position of the indole ring. Despite the advantages of the *N*-Boc protecting group, the electron-withdrawing propensity of the protecting group could diminish the nucleophilicity of the indole, thus providing for a more difficult cross-coupling reaction.

In contrast to the *N*-Boc derivative **11**, the *N*-SEM derivative **13** is more electron-rich and the protecting group is stable to a range of reaction conditions.⁴⁰ The 2-(trimethylsilyl)ethoxymethyl group also has the added advantage of undergoing facile deprotection with a variety of fluoride sources (TBAF,⁴¹ HF•pyridine,^{41b} etc.).

Finally, the electron-rich *N*-methyl derivative **15** was chosen for reactivity comparison studies to **11**, as well as 2-indolylstannanes.²⁴ In addition, **15** would obviously provide access to 2-substituted *N*-methylindole containing natural products and pharmaceutical agents.^{7c}

The *N*-Boc, *N*-SEM, and *N*-methyl protected dimethyl(2-indolyl)silanol were easily prepared by metalation at the C(2) position and trapping with a silicon electrophile (Scheme 2). *N*-Boc-dimethyl-2-indolylsilanol (**11**) was prepared following the procedure of Davies and coworkers.⁴² The procedure utilized non-cryogenic lithiation of *N*-Boc-indole **10** with LDA and trapping with dimethyldichlorosilane to afford **11** in 71% yield, which could be carried out reproducibly on > 50 mmol scale (Scheme 2, eq. 1).⁴³ The silanol was stable to silica gel chromatography and could be stored for several months at room temperature without diminished reactivity or purity.

The *N*-SEM derivative **13** was prepared by metalation of *N*-SEM-indole **12**⁴⁴ at the C(2) position with *tert*-butyllithium at 0 °C followed by trapping with hexamethylcyclotrisiloxane (D₃)⁴⁵ at -70 °C to provide **13** in satisfactory yield (62%) (Scheme 2, eq 2). This silanol could be purified by chromatography and was a shelf-stable reagent. Attempts to develop milder conditions to install the silanol moiety were unsuccessful.

The *N*-methyl-dimethyl(2-indolyl)silanol (**15**) was easily prepared in a similar manner as the *N*-SEM derivative. In this case metalation was achieved with *n*-butyllithium at 50 °C for 5 h and the resulting lithio species was trapped with D₃ at 0 °C to afford **15** in 57% yield (Scheme 2, eq. 3).

1.2. Preparation of 5-Substituted Dimethyl(2-indolyl)silanol—To evaluate the scope of the cross-coupling reaction it was of interest to examine the effects of substitution on the C(5) position of the indole ring. Therefore, a range of electron-withdrawing and electron-donating functional groups at the C(5) position of indole were targeted. The investigation started by preparing 5-methoxy-(**20**), 5-cyano- (**21**), 5-methyl- (**22**), and *N*-Boc-dimethyl[(5-bromo)-2-indolyl]silanol (**23**). These substrates were easily prepared in good yield (73–88%) following the procedure of Davies and co-workers (Equation 2).⁴²

^aConditions: (a) Me_2SiCl_2 (1.50 equiv), LDA (1.25 equiv), 0 °C, CH_2Cl_2 , 18h. (b) sat. (aq) NaHCO_3 , 0 °C, 0.5 h.

Equation 2^a

1.3. Preparation of Alkali Metal Dimethyl(2-indolyl)silanolates—These studies focused on three different protocols for the preparation of alkali metal silanolates: (1) equilibrative deprotonation (typically with an alkoxide base) involves formation of the silanolate during the cross-coupling reaction (2) irreversible preformation of the silanolate (by a strong Brønsted base) which is directly used in the cross-coupling reaction, and (3) irreversible deprotonation of the silanol and isolation of the metal silanolate salt.

1.3.1. Alkali Metal Silanolates Generated by Equilibrative Deprotonation: During the course of the optimization studies on the cross-coupling reaction of dimethyl(2-indolyl)silanols it was discovered that the indolylsilanol could be activated by simple deprotonation to form an alkali metal silanolate.³⁵ The sodium *N*-Boc-dimethyl(2-indolyl)silanolate ($\text{Na}^+\mathbf{11}^-$) and sodium *N*-methyl-dimethyl(2-indolyl)silanolate ($\text{Na}^+\mathbf{15}^-$) could be prepared by equilibrative deprotonation with sodium *tert*-butoxide (NaOt-Bu), in the presence of palladium and an aryl iodide in toluene. Although this procedure provided the desired metal silanolates, a minor amount of the protodesilylated product was observed, especially in the cross-coupling of **11** with aryl iodides.

To better understand the origin of the protodesilylation the following control experiment was conducted to determine whether protodesilylation was occurring over time or immediately upon treatment with NaOt-Bu . A solution of **11** was added to a suspension of NaOt-Bu in toluene. Aliquots were removed at various time intervals and were quenched into a 1.0 M pH 5.0 aqueous acetate buffer solution. The quenched aliquots were examined by HPLC analysis to determine the ratio of **11/10** (Table 1).⁴⁶ This experiment showed that protodesilylation was occurring at the onset of the reaction, affording a 21% yield of **10** at 0.25 h and did not increase in 1 h (Table 1, entries 1–2). However, when the experiment was conducted with a weaker base, potassium trimethylsilanolate (KOSiMe_3), a greater amount of protodesilylation (57%) was observed after 1 h, and complete protodesilylation was seen at 6 h (Table 1, entries 3–4).

Interestingly, when a stronger base was used, lithium hexamethyldisilazide (LiHMDS), protodesilylation was suppressed. More importantly, the ratio remained constant over 6 h, although a very minor component (3%) believed to be disiloxane **24** was observed (Table 1, entries 5–6). These experiments suggested that, to achieve efficient formation of the silanolate, the deprotonation needed to be rapid, quantitative, and irreversible.

1.3.2. Preformation of Alkali Metal Silanolates: To independently generate the dimethyl(2-indolyl)silanolate $\text{Na}^+\mathbf{11}^-$ in solution, which could be used in the subsequent cross-coupling reaction, sodium hydride (NaH) was selected as the base for rapid and efficient deprotonation of **10**. Indeed, with NaH, protodesilylation was completely suppressed to provide $\text{Na}^+\mathbf{11}^-$ cleanly by the preformation protocol. Unfortunately, generation the potassium silanolate $\text{K}^+\mathbf{11}^-$ from the preformation of **11** with potassium hydride (KH) led to the formation of *N*-Boc-indole **10** after standing as a solution in toluene.

1.3.3. Isolation of Alkali Metal Silanolates: To test the stability and streamline the manipulation of the sodium dimethyl(2-indolyl)silanolates the isolation of the salt was evaluated. Upon removal of the solvent from the preformation protocol above, sodium silanolate $\text{Na}^+\mathbf{11}^-$ was isolated in 86% yield and was found to be a stable, free-flowing white solid. The salt was stable upon storage at room temperature for several weeks and was much easier to handle and manipulate than **11**. More importantly $\text{Na}^+\mathbf{11}^-$ was a productive reagent for the cross-coupling reaction. Sodium *N*-SEM-dimethyl(2-indolyl)silanolate ($\text{Na}^+\mathbf{13}^-$) could also be easily prepared and isolated using a stoichiometric amount of 95% NaH to afford the silanolate as a stable white solid in 99% yield. In addition, the sodium silanolate of *N*-Boc-dimethyl[(5-bromo)-2-indolyl]silanol (**23**) could be isolated in near quantitative yield.

1.3.3.1. Isolation of Other Heterocyclic Silanols and Sodium Silanolates: Because we were interested in exploring the potential for cross-coupling of other π -excessive heterocyclic silanols, the corresponding *N*-Boc-2-pyrrolyl, 2-furyl, and 2-thienylsilanols were prepared. The *N*-Boc-dimethyl(2-pyrrolyl)silanol **25** (Scheme 3, eq 1) could be prepared following the non-cryogenic lithiation procedure as described above for *N*-Boc-indole, Scheme 4. The preparation of the dimethyl(2-furyl)silanol **26** and dimethyl(2-thienyl)silanol **27** silanols (Scheme 3, eq. 2 and eq. 3) proceeded by standard literature procedures for metalation at the C(2) position using *n*-BuLi at -70°C followed by trapping with D_3 . The sodium silanolates of **25**, **26**, and **27** were generated by the preformation protocol with NaH and used directly in the cross-coupling reactions. However, the sodium salts of **26** and **27** could also be prepared and isolated using 1.0 equiv of NaH (Scheme 3). These salts were stable, storable white solids and were competent in the cross coupling reactions as well.

2. Cross-Coupling of Silanols and Silanolates

2.1. Cross-Coupling of (2-Indolyl)silanols and Silanolates

2.1.1. Reaction Optimization of *N*-Boc-dimethyl(2-indolyl)silanols: Our point of entry to examine these reagents as donors in the cross-coupling process was the reaction of *N*-Boc-dimethyl(2-indolyl)silanol (**11**) with 4-iodonitrobenzene. The preliminary results were not as promising as originally anticipated. The cross-coupling of these reactants in the presence of 5 mol % of allylpalladium chloride dimer ($[\text{allylPdCl}]_2$), and 2.0 equiv of KH in toluene produced only *N*-Boc-indole. Clearly the reaction conditions needed to be modified to suppress the interfering protodesilylation. The beneficial effect of copper additives in cross-coupling reactions is well-documented.⁴⁷ Therefore, a selection of copper salts were screened (*inter alia*, CuI, CuBr, CuCl_2 , CuCN) using $[\text{allylPdCl}]_2$ (APC) as the catalyst, and 2.0 equiv KH as the activator.⁴⁸ This study revealed that only CuI afforded any improvement over the ‘copper-free’ conditions (30% conversion after 24 h).

Because copper additives provided no significant improvement with KH, other activators were tested in conjunction with CuI. Although NaH was superior to KH only 47% conversion was observed after 24h. It was thought that NaH was too harsh and may limit generality with some sensitive substrates. Cesium hydroxide (CsOH), potassium *tert*-pentoxide, or lithium *tert*-butoxide (LiOt-Bu) did not effect any cross-coupling of **11**. The counter ion of the *tert*-butoxide bases had a pronounced effect on the cross-coupling reaction. Improved conversion (46%) was observed using NaOt-Bu, in the cross-coupling of **11** with 4-iodonitrobenzene; however, potassium *tert*-butoxide (KOt-Bu) provided only a 3% yield of the desired cross-coupling product

With a successful activator in hand, palladium sources were then surveyed (Table 2). Whereas some palladium(II) salts (PdCl₂, PdCl₂(PPh₃)₂, and Pd(OAc)₂) provided only trace amounts of product (Table 2, entries 1–3), others such as, PdBr₂ and (CH₃CN)₂PdCl₂ allowed the reaction to reach completion within 24 h. Allylpalladium chloride dimer ([allylPdCl]₂) led to an incomplete reaction (Table 2, entry 4). Interestingly, it was found that the palladium(0) source Pd₂(dba)₃•CHCl₃ was superior to the palladium(II) sources surveyed. With 5 mol % of Pd₂(dba)₃•CHCl₃ the cross-coupling reaction of **11** gave complete (99%) conversion to the product (Table 2, entry 7).. Interestingly reaction times were much longer using Pd₂(dba)₃•CHCl₃, in comparison to Pd₂(dba)₃; however, the simple addition of 0.05 equiv of CHCl₃ to the reaction mixture containing Pd₂(dba)₃ provided comparable results to the chloroform solvate. In addition, the reaction time could be reduced to 6 h by increasing the concentration to 1.2 M (Table 2, entry 8).

The remaining experiments evaluated the impact of varying the loading of CuI. A control experiment using 1.2 equiv **11**, 1.0 equiv 4-iodonitrobenzene, 2.0 equiv NaOt-Bu and 5 mol% Pd₂(dba)₃•CHCl₃ in the absence of CuI afforded 48% of **28a** after 6h. The beneficial effect of increasing the amount of CuI was revealed as 1.0 equiv nearly doubled the yield of **28a** to 92% after 6h.. Although the effect of copper was interesting, the origin of the observed increase in yield was unclear and warranted further investigation.

2.1.1. Copper Iodide Effects on the Cross-Coupling Reaction: Of the many conceivable roles that CuI could play, one of the simplest would involve the *in-situ*-generation of a copper silanolate. Unfortunately, attempts to independently isolate and characterize the copper *N*-Boc-dimethyl(2-indolyl)silanolate from mesitylcopper were unsuccessful.⁴⁹

Another possibility is that the indolylsilanolate is undergoing a direct transmetalation from silicon to generate an indolylcopper species. This copper species should give **10** upon protic quench and the **10/11** ratio should increase over time and with added amounts of copper. To test this hypothesis, a series of experiments was preformed in which the amount of CuI was varied (0.0 equiv to 2.0 equiv), with 1.0 equiv of **11**, 2.0 equiv NaOt-Bu, excluding the palladium catalyst and an aryl iodide. Aliquots were removed and quenched into a 1.0 M pH 5.0 acetate buffer. The formation of **10** was monitored by HPLC analysis over the course of 6 h. These experiments revealed that the CuI loading did not have an effect on the formation of either *N*-Boc-indole **10**, or disiloxane **24**.⁵⁰ Upon quench, the silanol was observed in 75% yield after stirring for 6 h, where the remainder of mass was attributed to minor amounts of protodesilylation (7%) and disiloxane (5%), invariant over the CuI loading. These results demonstrate that transmetalation from silicon to copper, in the presence of CuI, was not operative.

2.1.2. Preparative Cross-Coupling Reactions of *N*-Boc-Dimethyl(2-indolyl)Silanols with Aromatic Iodides: To test the generality of these copper-mediated, palladium-catalyzed cross-coupling conditions under the equilibrative deprotonation protocol, a series of aryl iodides, representing a range of electronic and steric influences, were surveyed (Table 3). Aryl iodides

bearing electron-withdrawing groups in the *para*-position underwent smooth cross-coupling to afford the corresponding 2-aryl indole in 82–84% yield at room temperature (Table 3, entries 1–3).

Electron-rich aryl iodides (those bearing methoxy substituents) worked well (72–75% yields) at slightly elevated temperatures (50 °C, Table 3, entries 7–8). Similarly, electronically neutral substrates (1-iodonaphthalene and iodobenzene) provided good yields (75 and 70% yield, resp.) albeit with a slightly greater amount of halide homocoupling byproduct (Table 3, entries 5,9).

Although the cross-coupling **11** with aryl iodides was successful under the equilibrative deprotonation protocol, it was of interest to compare these results with those in which silanolate $\text{Na}^+ \text{11}^-$ is prepared by the preformation protocol. Thus, silanol **11** was deprotonated with NaH (1.0 equiv) in toluene and when a clear and colorless solution was observed, it was added to a mixture of $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ and the aryl iodide in toluene. Using this '*in situ*' activation of **11** obviated the use of a copper additive and provided good to excellent yield of the desired cross-coupling products (Table 4). The rate of cross-coupling was significantly faster than the copper mediated process (3 h compared to 6–24 h). Also, the use of the preformed silanolate $\text{Na}^+ \text{11}^-$ enabled successful cross-coupling of substrates (ethyl 4-iodobenzoate and 4-iodobenzonitrile) that were problematic in the copper mediated cross-coupling reaction⁵¹ in excellent yield (82 and 81%, resp., Table 4, entries 2–3).

2.2. Cross-Coupling of *N*-Boc-C(5)-Substituted Dimethyl(2-indolyl)silanols and Silanolates

2.2.1. Reaction Optimization: Initially, this study focused on the cross-coupling of *N*-Boc-dimethyl[(5-methoxy)-2-indolyl]silanol **20** with aryl iodides in the presence of copper additives under the equilibrative deprotonation protocol because the superior performance using the preformation protocol was not known at the time. The conditions for copper-mediated reactions of **11** with aryl iodides were extended to the cross-coupling of **20** with 4-iodonitrobenzene (i.e. $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ as the catalyst, and NaOt-Bu as the activator). However, in these cases a stoichiometric or substoichiometric amount of a copper(II) additive was used because copper(II) additives provided a significant rate enhancement compared to copper(I) additives in other cross-coupling reactions of heterocyclic silanols.⁵²

When the reaction was run at room temperature only a modest yield of the product was observed (Table 5, entry 1). Furthermore, a 2,3-disubstituted indole byproduct **31**, was isolated in this case (Table 5, entry 1). Using 1.0 equiv of copper(II) acetate solved the problem of poor reactivity but presented another complication, namely, homocoupling of the 2-indolylsilanol **20** to give bisindole **32** (Table 5, entry 2). When the reaction was run in the absence of $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ and aryl iodide, a 22% yield of **32** was obtained within 1 h (Table 5, entry 3). This suggests that the formation of **32** was due to $\text{Cu}(\text{OAc})_2$ and not the palladium catalyst. Fortunately, the formation of **32** could be suppressed by decreasing the amount of $\text{Cu}(\text{OAc})_2$ to 0.25 equiv (Table 5, entry 4). Finally, on a 1.0 mmol scale the desired cross-coupling product **30a** could be isolated in 72% yield, along with only 3% of the byproduct **31a** (Table 5, entry 6).

To determine if the formation of the 2,3-disubstituted indole byproduct was unique to the cross-coupling with 4-iodonitrobenzene, a different electron-deficient aryl iodide, 4-iodobenzotrifluoride, was tested. After 4 h, an 82% yield of the desired 2-arylated indole **30b** was isolated, with no detectable amount of 2,3-disubstituted indole. This demonstrated that arylation at the C(3) position was limited to the most electron-deficient aryl iodides (Equation 3).

Equation 3^a

From our experience with preformation and coupling of the parent silanolate $\text{Na}^+\mathbf{11}^-$, we choose to evaluate the copper-free cross-coupling with preformation of $\text{Na}^+\mathbf{20}^-$, with a series of electron-deficient and electron-rich aryl iodides (Table 6). Silanolate $\text{Na}^+\mathbf{20}^-$ was prepared with 1.0 equiv of NaH ; however, ~20% protodesilylation was observed. To accommodate this loss, 1.2 equiv of **20** was used for the cross-coupling reaction. In general, electron-deficient aryl iodides reacted smoothly without the formation of the byproducts observed in the copper-mediated reactions (i.e. 2,3-disubstituted indoles, homocoupling of **20**, etc.) (Table 6, entries 1–3). Unfortunately, the cross-coupling reaction with 4-iodoanisole only provided a 52% yield of (Table 6, entry 5).⁵³

Clearly, protodesilylation needed to be suppressed to facilitate a successful cross-coupling reaction of **20** with electron-rich aryl iodides. It was found that a soluble base such as NaHMDS provided a rapid and quantitative deprotonation of **20**, thus solving the problem of protodesilylation for the preformation of $\text{Na}^+\mathbf{20}^-$. Therefore, extending this form of activation to the cross-coupling reaction of **20** with 4-iodoanisole was of interest. However, it was not clear whether the byproduct from the deprotonation, hexamethyldisilazane (HMDS), would interfere with cross-coupling reaction. To test this issue, *N*-Boc-dimethyl(2-indolyl)silanol **11** was allowed to react with 4-nitroiodobenzene and 4-iodoanisole using NaHMDS for the preformation of $\text{Na}^+\mathbf{11}^-$. The cross-coupled product was isolated in 93% yield after 12 h at room temperature (Equation 4). Similarly, the cross-coupling of 4-iodoanisole, with **11** afforded a 62% yield of along with 4% of **10** after 24 h, thus HMDS was not deleterious to the cross-coupling reaction.

These conditions were then employed in the cross-coupling of substituted indole derivative **20** with 4-iodoanisole. Gratifyingly, using NaHMDS , as the activator, the reaction afforded an 82% yield of **30g** after 12 h at 40 °C (Equation 5).

Equation 4

Equation 5

2.2.2. Scope in Aryl Iodide for Cross-Coupling with N-Boc-C(5)-Substituted Dimethyl(2-indolyl)silanols: To test the generality in both components, a series of 2-indolylsilanols and aryl iodides were surveyed. 2-Indolylsilanols bearing methyl, bromo and cyano substituents at the 5-position were evaluated together with a variety of electron-rich and electron-deficient aromatic iodides (Table 7). The sodium silanolate of N-Boc-dimethyl[(5-cyano)-2-indolyl]silanol (**21**) N-Boc-dimethyl[(5-methyl)-2-indolyl]silanol (**22**) were generated by the preformation protocol using 1.0 equiv of NaHMDS. In the presence of $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ in toluene, $\text{Na}^+ \mathbf{21}^-$ reacted with 4-iodoanisole at room temperature to afford a 70% yield of **33g** after 24 h (Table 7, entry 1). The silanolate of **22** reacted smoothly with ethyl 4-iodobenzoate to afford an 82% yield of **34j** after 3 h (Table 7, entry 2). Electron-rich and sterically hindered aryl iodides required heating to 50 °C and provided good yields (65–76%) of the corresponding products (Table 7, entries 3–5). Finally, the sodium silanolate of N-Boc-dimethyl[(5-bromo)-2-indolyl]silanol (**23**) was isolated and used in the cross-coupling reactions.⁵⁴ Combining the salt $\text{Na}^+ \mathbf{23}^-$ in toluene with $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ (5 mol%) as the catalyst afforded good to excellent yields (56–85%) of cross-coupling products (**35**) with electron-deficient, electron-rich and sterically demanding substrates (Table 7, entries 6–9).

2.3. Cross-Coupling of 2-Dimethyl(2-indolyl)silanols and Silanolates with Aromatic Bromides and Chlorides—Although the cross-coupling of dimethyl(2-indolyl)silanols demonstrated generality for a range of aryl iodides bearing electron-donating and electron-withdrawing groups, aryl iodides possess many disadvantages including their light sensitivity, higher cost, and greater molecular weight compared to the corresponding aryl bromides and chlorides. One of the major challenges in the cross-coupling of aryl bromides and chlorides is the oxidative addition to palladium of the much stronger C–Br (BDE for C₆H₅–Br, 81 kcal/mol) or C–Cl bonds (BDE for C₆H₅–Cl, 96 kcal/mol).⁵⁵ Over the past several years, advances in the cross-coupling of aryl bromides and aryl chlorides have been made possible by the development of ligands that facilitate the oxidative addition of the organic halide to palladium(0) catalysts.⁵⁶

Enabling the cross-coupling of other aryl electrophiles would further expand the scope and utility of this reaction. However, because the cross-coupling of silanolates likely proceeds through a palladium silanolate intermediate, the successful cross-coupling of aryl bromides and chlorides would require not only overcoming the difficult oxidative addition, but also displacement of the halide on the palladium of the oxidative addition product. To begin the optimization, the more reactive aryl bromides were surveyed with $\text{Na}^+ \mathbf{11}^-$. Unfortunately, a survey of phosphine ligands together with $[\text{allylPdCl}]_2$ (including di(*tert*-butyl)biphenylphosphine, bisdiphenylphosphinobutane, and tri-(*tert*-butyl)phosphine) failed to effect the cross-coupling of $\text{Na}^+ \mathbf{11}^-$ with aryl bromides.⁵⁷ Even palladacycle catalyst **37**,⁵⁸ which was successful for the cross-coupling of sodium 2-furyl and 2-thienylsilanolates with aryl bromides (*vide infra*), afforded only a trace of the cross-coupling product with 4-bromobenzotrifluoride. These failures suggested the poor reactivity may be attributed to the electron-withdrawing N-Boc group.

2.3.1. Optimization of the Cross-Coupling of *N*-SEM-dimethyl(2-indolyl)silanol with Aromatic Bromides and Chlorides: The successful cross-coupling of aryl bromides and chlorides with indoles would likely require a more nucleophilic partner.⁵⁹ Manipulation of the *N*-substituent provides a convenient modification of the nucleophilicity of the indole. With this in mind, the more electron-donating *N*-SEM group would serve as a suitable replacement for NBoc. Indeed, Labadie and co-workers have shown that *N*-SEM-2-indolylstannanes are significantly more reactive than *N*-Boc-2-indolylstannanes in cross-coupling with aryl iodides.²⁴ We were delighted to find by simply stirring a solution of Na⁺13[−] in toluene, with an aryl bromide and 2.5 mol% of **37** at 50 °C afforded excellent yields of the desired cross-coupling products (Table 8). To investigate the scope of this reaction, Na⁺13[−] was combined with range electron-deficient, electron-rich and 2-substituted aryl bromides.

Both electron-rich and electron-deficient aryl bromides worked well to afford the desired 2-arylindole in 93% yield (Table 8, entries 1 and 4). Similarly, electron neutral and sterically encumbered substrates also provided excellent yields of the desired cross-coupled product (Table 8, entries 2–3). Also, it is worth noting that cross-coupling Na⁺13[−] with 3-bromo-TBS-protected benzyl alcohol also proceeded smoothly demonstrating that the silanolate is compatible with common silicon protecting groups (Table 8, entry 3). With these very promising results we were encouraged to examine the more challenging aryl chlorides with Na⁺13[−].

The cross-coupling of aryl chlorides with alkali (*E*)- and (*Z*)-alkenylsilanolates has been communicated recently from these laboratories.⁶⁰ A variety of substituted (*E*)- and (*Z*)-alkenylsilanolates underwent cross-coupling with substituted aryl chlorides in THF or dioxane in the presence of 2.5 mol % of [allylPdCl]₂, and 5 mol %, of the substituted biphenyl-based ligand, S-Phos (**38**).⁶¹

Initial optimization studies with Na⁺13[−], 4-chloroanisole was selected as the electrophile. Combination of these reactants with 2.5 mol % of [allylPdCl]₂ and 5 mol % of S-Phos in dioxane afforded the desired cross-coupling products (92% conversion, after 24 h by ¹H NMR analysis). However, in toluene the reaction was complete within 3 h. When the reaction was scaled to 1.0 mmol, the desired product was isolated in excellent yield (94%) after 3 h at 70 °C (Equation 6).

Equation 6

Thus, the experimental parameters for rapid, high yielding cross-coupling were easily identified for Na⁺13[−], and the stage was set for evaluating the reaction scope with other aryl chlorides. High yields of substituted indole products were obtained under these reaction conditions for a range of aryl chlorides (Table 9). The cross-coupling of Na⁺13[−] proceeded smoothly with aryl chlorides bearing cyano, ketone, and trifluoromethyl substituents (Table 9, entries 1–3). Sterically encumbered substrates such 2,6-dimethylchlorobenzene also reacted smoothly to furnish the product in 88% (Table 9, entry 5). Aromatic chlorides bearing methoxy

groups at either the 2- or 4-position reacted readily to afford the coupling products in excellent yield (Table 9, entries 4 and 6). Smooth cross-coupling was also observed for 3-chloropyridine (Table 9, entry 7). In contrast, 2-chloropyridine proved to be a more difficult substrate as the reaction was sluggish at 70 °C, but increasing the temperature to 90 °C provided the desired product in 3 h (Table 9, entry 8). The cross-coupling of 8-chlorocaffeine proceeded efficiently to give the substituted xanthine in 86% (Table 9, entry 9).

2.3 Cross-Coupling of *N*-Methyl-dimethyl(2-indolyl)silanols—To complete the study on the effect of the nitrogen substituent on reactivity, the *N*-Me derivative **15** was examined. Because of the inductively donating alkyl group, **15** should be more reactive than the corresponding *N*-Boc derivative **11**. We were delighted to find that under the conditions developed for **15** using NaOt-Bu, smooth cross-coupling could be achieved for a variety of aryl iodides.

For those aryl iodides bearing electron-withdrawing groups, the reactions were complete within 3 h, but the yields of the desired cross-coupling products were low (Table 10, entries 1–2). In addition to the desired product, the 2,3-disubstituted indoles were isolated as the major side product in these cases. For electron-neutral, or electron-rich aryl iodides, the reactions proceeded to completion in 3–6 h, and none of the 2,3-disubstituted indoles were observed in these cases (Table 10, entries 3–5). The 2,3-disubstituted indoles could arise from a competitive carbopalladation at the C(3) position of indole ring. A control experiment in which the nitrosubstituted product **39a** was re-subjected to the reaction conditions did not provide any of the 2,3-disubstituted indole **40a**. Thus, the silanol moiety in **15** is involved in the formation of this side product.⁶² It was found that the use of the less reactive aryl bromides obviated this side reaction. Heating the reactions to 55 °C with an aryl bromide in the presence of 1,4-bis(diphenylphosphino)butane (dppb) provided the desired cross-coupling products in good yields (Table 10, entries 6–7).

2.4. Cross-Coupling of 2-Furyl, 2-Thienyl, and *N*-Boc-Dimethyl(2-pyrrolyl)silanolates—The application of silicon-based cross-coupling reaction to other π -rich heterocycles (pyrrole, furan, and thiophene) with aryl iodides and bromides was investigated. These reactions would take advantage of the insight gained from the optimization and cross-coupling of preformed and isolated 2-indolylsilanols. Thus, the preformed (NaH) sodium-*N*-Boc-dimethyl(2-pyrrolyl)silanolate cross-coupled smoothly with electron-deficient aryl iodides as well as 2-substituted aryl iodides using 5 mol% of Pd₂(dba)₃•CHCl₃ in toluene at room temperature (Table 11, entries 1 and 2) whereas the electron-rich aryl iodides required mild heating (Table 11, entry 3). The cross-coupling of sodium 2-furylsilanolate proceeded similarly with electron-deficient and 2-substituted aryl iodides (Table 11, entries 4, 6) and again, reaction with 4-iodoanisole required mild heating and 0.2 equiv of (2-furyl)₃As to achieve complete conversion (Table 11, entry 7). The isolated salt Na⁺**26**[−] gave nearly identical results with ethyl 4-iodobenzoate (Table 11, entry 5). The sodium 2-thienylsilanolate (both preformed and isolated) behaved in a completely analogous fashion with electron-deficient, 2-substituted aryl iodides and electron-rich aryl iodides (Table 11, entries 14–17).

At this point it was of interest to extend these heterocyclic silanols for the cross-coupling of aryl bromides. Thus, a short survey of palladium sources in conjunction with 1,1-di-(*tert*-butyl)phosphinobiphenyl at 50 °C, which has been successful for the cross-coupling of other silanols with aryl bromides,⁶³ was undertaken. Neither PdCl₂ nor PdBr₂ effected successful cross-coupling. Allylpalladium chloride dimer enabled complete conversion of the bromide, but the reaction was accompanied by small amounts (11%) of the halide homocoupling product (Table 12, entries 1–4). However, the Pd (I) catalyst **37** provided clean conversion to the desired product in 3 h without the formation of the halide homocoupling product. With these

encouraging results, we investigated the cross-coupling of these heterocyclic silanolates with a range of aryl bromides.

Preformation of the sodium heterocyclic silanolates (2-furyl-, and 2-thienyl-) in toluene followed by addition of the aryl bromide and 2.5 mol % of **37** at 50 °C provided the cross-coupling products in good to excellent yields for electron-rich, electron-deficient and sterically encumbered aryl bromides (Table 11). The cross-coupling of sodium dimethyl(2-furyl) silanolate proceeded smoothly with a range of aryl bromides (Table 11, entries 8–13). Cross-coupling with aryl bromides were less dependant on the nature of the substituent. Whereas those reactions of bromides bearing either electron withdrawing groups or ortho methyl groups reached completion in 3 h, electron-rich and naphthyl bromides required a slightly longer reaction time of 6 h. The cross-coupling of dimethyl(2-thienyl) silanolate with aryl bromides behaved similarly to dimethyl(2-furyl)silanolate, providing comparable reaction times and yields (Table 11, entries 18–23). The exception was 1-bromonaphthalene, which required 7 h to reach completion (Table 11, entry 23). Finally, attempts to use preformed sodium *N*-Boc-dimethyl(2-pyrrolyl)silanolate with aryl bromides failed, as was also the case with *N*-Boc-dimethyl(2-indolyl)silanols.

Discussion

The development of stable and easily prepared 2-indolylsilanol reagents for cross-coupling that overcome the limitations associated with the tin and boron congeners was one of the major aims of this study. This goal was accomplished by the introduction of the corresponding silanols as stable reagents that could be stored on the bench for extended periods of time. The utilization of these compounds in cross-coupling reactions was facilitated by the discovery that preformed alkali metal silanolates can be used without an additional activator.

1. Formation of Alkali Metal Dimethyl-2-Indolylsilanolates

To effect clean and stoichiometric deprotonation of *N*-Boc-dimethyl(2-indolyl)silanol, a strong and kinetically fast base was required. With NaOt-Bu, as the base, approximately 20% protidesilylation to the parent indole was observed. This outcome was also observed when NaH was used for the preparation of sodium *N*-Boc-dimethyl[(5-methoxy)-2-indolyl]silanolate ($\text{Na}^+\mathbf{20}^-$). In contrast, when NaHMDS was employed as the base, $\text{Na}^+\mathbf{20}^-$ was formed cleanly. These observations suggest that once the sodium silanolate was formed, it was stable in solution. Thus, the protidesilylation process occurred upon initial mixing of the silanol and the base because the amount of protidesilylated product did not increase with time (e.g. for *N*-Boc-2-indolylsilanol and NaOt-Bu 21% of **10** at 15 min and 18% of **10** at 1 h). To reconcile this behavior, we propose that protidesilylation occurs from the mutual coexistence of both silanol and silanolate, where the silanol provides the proton for desilylation. A reasonable mechanism for this process involves the protonation of the indole at the 2-position by the silanol to give a β -silyl cation intermediate **vi** (Scheme 4). Fragmentation of **vi** would provide the protidesilylated product **10** and polysiloxanes.

During the optimization studies for the formation of $\text{Na}^+\mathbf{11}^-$ the effect of the counter cation was investigated. When silanol **11** was mixed with LiHMDS, $\text{Li}^+\mathbf{11}^-$ was prepared cleanly. Quenching $\text{Li}^+\mathbf{11}^-$ with acetate buffer revealed protidesilylated product **10** was not formed at early time points (1 h) and did not appear over a 6 h time course. This observation shows that the lithium silanolate was also stable in solution, and that LiHMDS effected a clean kinetic deprotonation devoid of side processes. Preparing $\text{K}^+\mathbf{11}^-$ provided valuable insight with respect to both the nature of the counter cation as well as the effect of a weaker base. When silanol **11** was treated with KOSiMe₃ a significant amount of desilylation was observed. In this case, the conjugate acid, HOSiMe₃, is pK_a matched to silanol **11**, and provides a proton source in Scheme 4. An experiment that prepared the potassium dimethyl(2-indolyl)silanolate

using KH revealed that the potassium silanolate decomposes in toluene over time, which also may serve to explain the observed desilylation with KOSiMe_3 . From these experiments we deduced that an ideal base would effect a kinetically fast and irreversible deprotonation of the silanol to give a metal silanolate directly in the absence of a conjugate acid. However, the base must also provide a metal silanolate that is both active in the cross-coupling reaction and stable under the reaction conditions. Fortunately, the sodium silanulates of **11** and the 5-substituted silanulates $\text{Na}^+\text{20}^-$, $\text{Na}^+\text{21}^-$ and $\text{Na}^+\text{22}^-$ were easily prepared by the preformation protocol using a stoichiometric amount of NaH or NaHMDS respectively. In addition, it was found that $\text{Na}^+\text{11}^-$, $\text{Na}^+\text{13}^-$ and 5-bromo substituted $\text{Na}^+\text{23}^-$ could be isolated as stable salts.

Detailed kinetic studies on the Brønsted base activation of alkenylsilanols have shown that the active species in the cross-coupling reaction is a palladium silanolate complex formed by attack of a metal silanolate onto the Pd center of an aryl palladium(II) halide.^{31b} Formation of the metal silanolate is an important prerequisite to generate the key Si-O-Pd linkage. The metal silanolate has traditionally been prepared by equilibrium deprotonation wherein the silanol was treated with a Brønsted base such as KOSiMe_3 . However, to achieve successful cross-coupling with 2-indolylsilanols, a base several orders of magnitude stronger than a silanolate is required to avoid desilylation. Although satisfactory results can be obtained by forming the silanolate *in situ*, employing a preformed metal silanolate has additional advantages. First, because silanols have been shown to dimerize to the corresponding disiloxanes in the presence of acids or bases,⁶⁴ storing the metal salt prevents this process. Second, using the isolated preformed silanolate in the reaction not only simplifies the experimental procedure (adding one reagent as opposed to the silanol and base), but also ensures that the cross-coupling partner is always present in its active form. Moreover, a metal silanolate can be generated cleanly from a stoichiometric quantity of metal hydride, without the need for an excess of activator.

The use of an excess of the activator can be problematic in the cross-coupling reaction for several reasons. Surplus activator (i.e. KOt-Bu , KOSiMe_3) can compete with silanolate for the Pd center of the aryl Pd halide. As a competitive inhibitor, the activator can form an inactive species **vii** in the cross-coupling reaction where it serves as a ligand on the Pd(II) aryl complex (Scheme 5, eq 1).³² This process sequesters palladium in an inactive form, and subsequently slows the cross-coupling reaction. Silanolate must displace the activator to allow the Pd to reenter the catalytic cycle as the palladium silanolate **viii** (Scheme 5, eq 2).

An excess of the activator can also limit functional group compatibility. For example, when NaOt-Bu was employed with substrates bearing ethyl esters, a competing transesterification reaction took place. Furthermore, excess amounts of hydride reagents have been reported to give reduction side products,³² and are incompatible with substrates bearing sensitive functional groups. The direct introduction of the silanolate avoids these problems.

2. Optimization of the Cross-Coupling Reaction

2.1. Role of the Activator—Optimization studies of the cross-coupling of sodium *N*-Boc-dimethyl(2-indolyl)silanulates provided valuable insight into use of metal silanulates for the cross-coupling reaction. In the case of hydride activators, the success of NaH (47% product) compared to KH (30%) is likely due to the greater stability of the sodium compared to the potassium derivative. Interestingly, using *tert*-butoxide bases as activators offered insight into the effect of silanolate counter ion. Whereas the lithium silanolate from LiOt-Bu can be formed as a stable species, this salt is less nucleophilic, and likely suffers from slow displacement of the palladium halide.⁶⁰ In contrast, when NaOt-Bu was used, the more nucleophilic and stable sodium silanolate gave modest yields (46%). The use of KOt-Bu proved less successful, and can be understood by the observed instability of the potassium silanolate. While the effect of the counter ion on the reaction can be understood in terms of silanolate stability and nucleophilicity, the effect of the Brønsted base on the reaction can be rationalized in terms of

kinetic basicity. Successful activators were able to carry out a kinetically fast and irreversible deprotonation, such that the conjugate acid formed cannot serve as a proton source for $\text{Na}^+\mathbf{11}^-$. The superiority of NaHMDS compared to NaOt-Bu for C(5)-substituted 2-indolylsilanols may be a function of the increased solubility of NaHMDS.

2.2. Role of Palladium Catalysts—Early optimization studies demonstrated that Pd(0) sources gave the best results. In particular, the chloroform solvate of Pd_2dba_3 proved superior to either Pd_2dba_3 alone or Pd_2dba_3 in conjunction with CH_2Cl_2 . Halogenated solvents can provide unexpected rate effects with palladium catalysts,⁶⁵ but methylene chloride did not afford a similar enhancement as chloroform. That chloroform was responsible for enhanced reactivity was demonstrated by using Pd_2dba_3 and adding 5 mol % of CHCl_3 to the reaction. This combination provided the cross-coupling product in comparable yield to using $\text{Pd}_2\text{dba}_3 \cdot \text{CHCl}_3$. The role of the chloroform in the reaction still remains unclear. Solubility studies have concluded that $\text{Pd}_2\text{dba}_3 \cdot \text{CHCl}_3$ is less soluble in toluene at room temperature than Pd_2dba_3 ($1.5 \times 10^{-3}\text{M}$ vs. 3.0×10^{-3} , resp). This data suggests that solubility of the precatalyst in toluene is not influencing the rate enhancement. The chloroform is likely being deprotonated under the reaction conditions, and the deprotonated haloform may serve as an alternate base in the reaction or could form a dichlorocarbene that somehow affects the palladium catalyst.⁶⁶

The cross-coupling of heterocyclic silanolates with aryl bromides and chlorides required a phosphine ligand to facilitate the oxidative addition step. The cross-coupling of 2-furyl and 2-thienylsilanolates were successful using the palladacycle catalyst **37**.⁵⁸ Although the origin of the high reactivity of this catalyst remains unknown, recent reports in the literature have suggested that palladacycle catalysts may function by a slow release of palladium nanoparticles into solution.⁶⁷

2.3. Role of Copper Salts—The use of copper salts, in particular CuI and $\text{Cu}(\text{OAc})_2$, had a beneficial effect on the rate of the cross-coupling reaction. The beneficial effect of added copper salts in palladium-catalyzed cross-coupling reactions of stannanes⁴⁷ and boranes,⁴⁷ is well documented. Their role can be either to act as a phosphine scavenger,⁴⁷ or to facilitate preliminary transmetalation from the donor (organostannane) to copper before a transmetalation to palladium.⁴⁷

Although it was shown that copper had no effect on protidesilylation, the exact role of copper in the rate enhancement remains unknown. If the copper salt facilitates the formation of an intermediate organocopper species, increasing copper loading should provide more of the protidesilylated N-Boc indole upon quench with aqueous buffer. This was not found; however, the copper salt in these reactions could serve an alternate function by forming a copper (I) silanolate.

Copper(II) acetate may also be playing a double role as well. The salt may behave as a Lewis acid and aid in the displacement of the Pd-I bond, thus facilitating attack of the silanolate on the aryl palladium halide. Alternately, the Cu(II) salt may undergo transmetalation from silicon to copper,⁶⁸ this hypothesis is supported by the observed homocoupling of 2-indolylsilanol **20** in the absence of palladium (Table 7, entry 3). However, further experiments to elucidate the exact role of copper salts were not explored, because it was found that copper additives were not needed in the cross-coupling reactions with preformed 2-indolylsilanolates. Employing a preformed *N*-Boc-dimethyl(2-indolyl)silanolate afforded the desired product cleanly, and in significantly shorter reaction times than using the silanol and NaOt-Bu with CuI.

2.4. Protecting Group on the Indole Nitrogen—The nitrogen substituent was shown to have a dramatic effect on the reactivity of the dimethyl(2-indolyl)silanolates. In general, more electron rich indoles such as: N-SEM and N-methyl-dimethyl(2-indolyl)silanolates were more reactive than the N-Boc derivative. The more electron-rich and nucleophilic N-SEM and N-methyl derivatives underwent smooth cross-coupling with less reactive aryl halides, whereas the N-Boc derivatives were the least reactive silanolates and were limited to cross-coupling with aryl iodides. This reactivity trend reflects the electron density at the C(2) position of the 2-indolylsilanols as indicated by the ^{13}C -NMR chemical shifts for the C(2) carbon (N-Boc, δ 131.1, N-SEM δ 128.4 and N-methyl δ 128.0).

The rate of cross-coupling of sodium *N*-Boc-dimethyl(2-indolyl)silanolates with aryl iodides was strongly dependent on the electrophile. Higher conversion was observed in reactions with aryl iodides bearing electron-withdrawing groups than reactions with aryl iodides bearing electron-donating groups. The strong influence of the substituent on the cross-coupling rate is suggestive of a turnover-limiting step that involves attack on the palladium center.⁶⁹ In this case, an electron-donating group provides a less electrophilic palladium, whereas electron-withdrawing groups would provide a more electrophilic palladium center. These observations suggest either a turnover limiting displacement step, or a turnover limiting transmetalation. However, to differentiating between these two limiting scenarios a complete elucidation of the mechanism must be done.

Sodium *N*-SEM-dimethyl(2-indolyl)silanolate represents a more electron rich indole and this silanolate was able to undergo cross-coupling with aryl bromides and aryl chlorides. In contrast to the N-Boc derivative, Na^+13^- reacted smoothly with electron-poor, electron-rich, and sterically encumbered substrates equally well to afford the desired cross-coupling products in excellent yields with little dependence on the steric or electronic nature of the aryl halide. Even heteroaryl chlorides were viable partners in coupling with this silanolate.

Sodium *N*-methyl(2-indolyl)silanolate also displayed enhanced reactivity compared to the *N*-Boc derivative. In this case both electron-rich and electron-poor aryl iodides were consumed within 3–6 h at rt. However, this more electron rich silanolate underwent a competing reaction with electron-poor aryl iodides to give 2,3-disubstituted indoles.⁷⁰ Control experiments suggest that the silicon is directing a Heck-type carbopalladation or an electrophilic aromatic substitution reaction involving an aryl Pd(II) iodide to install the aryl ring at the C(3) position of the indole. Employing the less reactive aryl bromides solved this problem and favored the cross-coupling reaction.

3. Extension to Pyrrole, Furan, and Thiophene Silanols

Applying the optimized conditions developed for the cross-coupling of dimethyl(2-indolyl)silanols toward other heterocycles highlights the generality of the method for the cross-coupling of silanolates. Generally, the cross-coupling of preformed or isolated sodium salts of *N*-Boc-2-pyrrolyl-, 2-furyl-, and dimethyl(2-thienyl)silanols proceeded smoothly with only minor deviations from the general protocols developed for 2-indolylsilanols. Aryl iodides bearing electron-donating groups required higher temperatures than those with electron-withdrawing groups or those bearing ortho substituents.

Although the cross-coupling of sodium *N*-Boc-dimethyl(2-pyrrolyl)silanolate failed for aryl bromides, this was not surprising since the cross-coupling reaction of the corresponding indole gave only trace amounts of the desired product. Within our current understanding of the general mechanism for silanolate cross-coupling,³¹ the marked reactivity difference between aryl iodides and aryl bromides with either Na^+11^- or Na^+25^- is interesting because these would be expected to proceed through the same aryl-Pd-silanolate complex following halide displacement. However we speculate that the N-Boc function may present increased steric

hindrance that slows the displacement step when a bulky phosphine ligand is used. Alternatively, the electron-withdrawing Boc group could slow the transmetalation step if the migrating group functions as a nucleophile that must displace a ligand on palladium (potentially a bulky phosphine ligand required for oxidative addition of aryl bromides that is not present in the reaction with aryl iodides) as the heteroaryl-Pd(II)-arene intermediate is formed. Identifying the origin of poor reactivity of these sodium silanolates with aryl bromides will likely require detailed kinetic analysis. In contrast, the cross-coupling of aryl bromides with sodium 2-thienyl- and (2-furyl)silanolates proceeded smoothly in the presence of palladacycle catalyst **37**.

Conclusion

A set of general reaction conditions has been developed for the cross-coupling of dimethyl(2-indolyl)silanols with aryl halides. The key experimental variables that led to successful cross-coupling include: formation of a stable sodium silanolate in the absence of a conjugate acid, copper salts can be used to increase cross-coupling efficiency when Brønsted base activators are used in conjunction with a silanol, and judicious choice of palladium catalyst and ligand for the appropriate halide (iodide, bromide, or chloride). It was found that the nitrogen substituent has a profound effect on the reactivity of the indole where an electron-withdrawing group on nitrogen strongly decreases reactivity. The use of pre-formed or in-situ prepared sodium silanolates with NaH offers a rate enhancement and increased substrate scope over the use of silanols with Brønsted bases like NaOt-Bu. The conditions developed for the cross-coupling of indole donors were readily applied to 2-pyrrolyl-, 2-furyl-, and dimethyl(2-thienyl)silanolates. Future studies will extend this method to the cross-coupling of other nitrogen heterocycles such as the problematic 2-pyridyl subunit.²² Furthermore, the expansion of the reaction scope with respect to other electrophiles such as aryl- and alkenyl triflates and tosylates will be reported in due course.

Experimental Section

Preparation of *N*-Boc-Dimethyl(2-indolyl)silanol (**11**)

To a flame-dried, three-necked, 300-mL, round-bottomed flask, fitted with an argon inlet adaptor, thermocouple, magnetic stir bar and septum was added *N*-Boc-indole (0.48 g, 16.0 mmol) followed by dry THF (7.5 mL). The solution was cooled to 0 °C, using an ice bath and dimethyldichlorosilane (3.12 g, 24.2 mmol, 1.5 equiv) was added. To this mixture was added *via* cannula a solution of LDA (prepared as described below) over 20 min.

The lithium diisopropylamide (LDA) solution was prepared by placing a solution of 2.82 mL (20.1 mmol, 1.25 equiv) of dry diisopropylamine in dry THF (3.0 mL) in a flame-dried, 50-mL, two-necked, round-bottomed flask fitted with an argon inlet adapter, magnetic stir bar and septum. The solution was cooled in a dry ice/2-propanol bath for 15 min and (12.96 mL, 1.55 M in hexane, 20.1 mmol, 1.25 equiv) of a *n*-BuLi solution was slowly added. The resulting mixture was stirred for 5 min before being allowed to warm to 0°C (ice bath) slowly. The solution was stirred for 20 min at 0°C before being added to the solution prepared above. The reaction mixture was stirred at 0°C for 18 h whereupon sat. aq. NaHCO₃ (15.0 mL) solution was added and the contents were transferred to a 250-mL separatory funnel. The aqueous layer was separated and extracted with EtOAc (4 × 35 mL). The combined organic layers were dried over Na₂SO₄ and filtered through #4 Whatman filter paper. The solvent was removed under reduced pressure using rotary evaporation (23°C, 20 mmHg) to give a yellow oil which was immediately purified by silica gel chromatography (350 g, 60 × 100 mm) by first eluting with hexane (300 mL) followed by hexane/EtOAc, 9/1 (30 × 50 mL fractions) to afford 3.34 g (71%) of **11** as a clear, colorless semi-solid. Data for **11**: bp. 125°C (7×10⁻⁵ mmHg, ABT); ¹H NMR: (500 MHz, CDCl₃) 7.96 (dd, *J* = 8.53, 0.733, 1 H), 7.56 (d, *J* = 7.81, 1 H), 7.30 (dt, *J* = 8.53,

1.22, 1 H), 7.21 (dt, $J = 7.81, 0.733$, 1 H), 6.89 (s, 1 H), 2.80 (s, 1 H), 1.73 (s, 9H), 0.45 (s, 6H); ^{13}C NMR: (125.6 MHz, CDCl_3) 152.4, 140.8, 137.2, 131.1, 124.9, 122.7, 121.2, 119.5, 115.5, 84.8, 28.1, 0.13 IR: 3405, 2977, 2248, 1903, 1720, 1517, 1471, 1444, 1376, 1336, 1251, 1213; MS: (EI, 70 eV) 291, 235, 220, 218, 192, 191, 176, 173, 130, 75, 57; R_f 0.36 (hexane/EtOAc, 4/1) [silica gel, UV]. Anal. Calcd. for $\text{C}_{15}\text{H}_{21}\text{NO}_3\text{Si}$: C, 61.82; H, 7.26; N, 4.81. Found: C, 61.54; H, 7.26; N, 4.80.

Preparation of Sodium *N*-Boc-Dimethyl(2-indolyl)Silanolate ($\text{Na}^+\mathbf{11}^-$)

To a flame-dried, 25-mL, conical flask with stir bar was added (93 mg, 3.86 mmol, 1.0 equiv) of NaH and toluene (2.0 mL) inside a drybox. In a separate flame-dried, 5-mL, conical flask was prepared a solution of **11** (1.20 g, 4.1 mmol, 1.06 equiv) in toluene (2 mL). The silanol solution was added drop-wise to the stirred suspension of NaH at room temperature. After effervescence had ceased, the resulting suspension was stirred for an additional 30 min. The supernatant was removed carefully by Pasteur pipette the precipitate was washed with toluene (1.0 mL), and the supernatant was removed once again. Residual solvent was removed under high vacuum (0.1 mmHg) to afford 1.04 g (86%) of $\text{Na}^+\mathbf{11}^-$ as a white powder that was stored in a drybox. Data for $\text{Na}^+\mathbf{11}^-$: ^1H NMR: (500 MHz, C_6D_6) 7.98 (d, $J = 8.3$, 1 H), 7.47 (d, $J = 7.6$, 1 H), 7.26 (t, $J = 7.7$, 1 H), 7.17 (t, $J = 7.6$, 1 H), 6.86 (s, 1 H), 1.31 (s, 9H), 0.49 (s, 6H); HRMS: calcd. for $\text{C}_{15}\text{H}_{20}\text{NNaO}_3\text{Si}$ (M^{+1}), 314.1188; found: 314.1183.

Representative Procedure for Equilibrative Deprotonation of *N*-Boc-Dimethyl(2-indolyl)silanol (**11**) in the Cross-Coupling Reaction with Aryl Iodides

Preparation of *N*-Boc-2(4'-nitrophenyl)indole (28a**) (Table 3, entry 1)**—To a flame-dried, 5-mL, round-bottomed flask, equipped with a magnetic stir bar was added (192 mg, 2.0 mmol, 2.0 equiv) of NaOt-Bu and CuI (190 mg, 1.0 mmol, 1.0 equiv) inside a dry box. The flask was removed from the drybox and 4-iodonitrobenzene (249 mg, 1.0 mmol), and (52 mg, 0.05 mmol, 0.05 equiv) of $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$. The flask was sealed with a rubber septum and evacuated (0.1 mm Hg) for a period of 5 min. The flask was then back-filled with dry argon and this cycle was repeated twice. Finally the solids were dissolved in toluene (600 μL) and the mixture was stirred for 10 min before addition of the silanol solution prepared below. In a separate flame-dried, 5-mL, conical flask was added of **11** (349 mg, 1.2 mmol, 1.2 equiv), which was placed under high vacuum (0.1 mm Hg) for 5 min before being back-filled with argon. The silanol was dissolved in toluene (300 μL) and this solution was added to the above mixture by syringe. The round-bottomed flask containing silanol was washed with toluene (100 μL) and that rinse was added to the reaction mixture. After being stirred at 50 $^\circ\text{C}$ for 24 h, the dark-red, crude reaction mixture was transferred to a 125-mL separatory funnel containing deionized H_2O (60 mL), and EtOAc (20 mL). The organic layer was separated, and the aqueous layer was washed with EtOAc (5×20 mL). The combined organic layers were dried over MgSO_4 and were filtered through #4 Whatman filter paper. The solvent was removed under reduced pressure by rotary evaporation (23 $^\circ\text{C}$, 20 mmHg) to give a dark-red residue. A solution of the residue in toluene (0.5 mL) was loaded onto a silica gel column (22 g, 20×100 mm), which was eluted with toluene (20×10 mL fractions). Recrystallization of the material from the pure fractions (hexane, 50 mL) afforded 234 mg (84%) of **28a** as yellow needles. Data for **28a**: m.p.: 129–132 $^\circ\text{C}$ (hexane); ^1H NMR: (500 MHz, CDCl_3) 8.28 (d, $J = 8.3$, 2 H), 8.19 (d, $J = 8.3$, 1 H), 7.50 (m, 3 H), 7.38 (dd, $J = 7.8, 7.1$, 1 H), 7.29 (dd, $J = 7.5, 7.3$, 1 H), 6.69 (s, 1 H), 1.4 (s, 9H); ^{13}C NMR: (125.6 MHz, CDCl_3) 149.8, 146.9, 141.4, 137.9, 137.8, 129.3, 128.9, 125.4, 123.4, 123.1, 121.0, 115.5, 112.1, 84.4, 27.7 IR: 2980, 1736, 1601, 1558, 1517, 1451, 1394, 1325, 1225, 1213, 1160, 1133, 1107, 1026, 911, 858; MS: (EI, 70 eV) 338, 324, 323, 268, 267, 223, 208, 180, 178, 57; R_f 0.32 (hexane/EtOAc, 9/1) [silica gel, UV]. Anal. Calcd. for $\text{C}_{19}\text{H}_{18}\text{N}_2\text{O}_4$: C, 67.44; H, 5.36; N, 8.28. Found: C, 67.39; H, 5.27; N, 8.23

Representative Procedure for the Cross-coupling of Preformed Sodium *N*-Boc-Dimethyl(2-indoyl)silanolates (Na⁺11⁻) with Aryl Iodides

Preparation of *N*-Boc-2[4'-(ethoxycarbonyl)phenyl]indole (**28j**) (Table 4, entry 2)

—To a flame-dried, 5-mL, round-bottomed flask equipped with a magnetic stir bar was added washed 98% NaH (29 mg, 1.2 mmol, 1.2 equiv) inside a drybox, followed by toluene (0.1 mL). Then a solution of *N*-Bocdimethyl(2-indolyl)silanol (**11**) (349 mg, 1.2 mol, 1.2 equiv) in toluene (0.9 mL) was added dropwise using a Pasteur pipette to the NaH suspension. Once effervescence ceased ethyl 4-iodobenzoate (168 μ L, 1.0 mmol, 1.0) was added along with Pd₂(dba)₃•CHCl₃ (52 mg, 0.05 mmol, 0.05 equiv). The flask was sealed with a rubber septum and removed from the drybox. After stirring at rt for 3 h, the reaction mixture was transferred to a 125 mL separatory funnel and diluted with H₂O (25 mL) and EtOAc (20 mL). The organic layer was separated, and the aqueous layer was washed with EtOAc (5 $\times$ 25 mL). The combined organic layers were dried over MgSO₄ and were filtered through #4 Whatman filter paper. The solvent was removed under reduced pressure using rotary evaporation (23°C, 20 mmHg) to give a dark-red residue. A solution of the residue in toluene (0.5 mL) was loaded onto a silica gel column (175 g, 20 $\times$ 100 mm) and was eluted with toluene (20 $\times$ 10 mL fractions). Recrystallization of the material from the pure fractions from boiling (hexane/toluene, 20/1), afforded **28j** (298 mg, 82%) as a white needles. The physical and spectroscopic data matched those from the literature.²⁴ Data for **28j**: m.p. 104–105°C (hexane/toluene (20/1)); ¹H NMR: (500 MHz, CHCl₃) 8.21 (d, *J* = 8.3, 1 H), 8.09 (d, *J* = 8.5, 2 H), 7.57 (d, *J* = 7.3, 1 H), 7.50 (d, *J* = 8.5, 2 H), 7.35 (t, *J* = 8.4, 1 H), 7.26 (t, *J* = 8.1, 1 H), 6.63 (s, 1 H), 4.41 (q, *J* = 7.1, 2 H), 1.42 (t, *J* = 7.2, 3 H), 1.34 (s, 9H); ¹³C NMR: (125 MHz, CHCl₃) 65.5, 150.0, 139.5, 138.9, 137.6, 130.9, 129.1, 128.9, 128.35, 124.7, 123.1, 120.7, 115.3, 110.9, 83.9, 81.1, 28.2, 27.6; *R*_f = 0.12 (hexane/EtOAc, 9/1) [silica gel, UV].

Representative Procedure for the Cross-coupling of Preformed Sodium Dimethyl(2-furyl)silanolate (Na⁺26⁻) with Aryl Bromides

Preparation of 2-(2-Methylphenyl)furan (42f) (Table 11, entry 11)—To a flame-dried, 5-mL, round-bottomed flask equipped with a magnetic stir bar was added washed 98% NaH (29 mg, 1.2 mmol, 1.2 equiv) inside a drybox, followed by toluene (0.2 mL). Then a solution of dimethyl(2-furyl)silanol (**26**) (170 mg, 1.2 mol, 1.2 equiv) in toluene (0.8 mL) was added dropwise using a Pasteur pipette to the NaH suspension. Once effervescence ceased 2-bromotoluene (120 μ L, 1.0 mmol) was added along with **37** (18 mg, 0.025 mmol, 0.025 equiv). The flask was sealed with a rubber septum and removed from the drybox. After stirring at 50°C for 3 h, the reaction mixture was transferred to a 125 mL separatory funnel and diluted with H₂O (25 mL) and EtOAc (20 mL). The organic layer was separated, and the aqueous layer was washed with EtOAc (5 $\times$ 25 mL). The combined organic layers were dried over MgSO₄, filtered and concentrated using rotary evaporation (23°C, 20 mmHg). The crude product was purified by column chromatography (SiO₂ (20 $\times$ 100 mm), hexane/EtOAc 9/1) and distillation afforded 113 mg (71%) of **42f** as a clear, colorless oil. The physical and spectroscopic data matched those from the literature.⁷¹ Data for **42f**: bp. 105°C (0.5 mm Hg, ABT); ¹H NMR: (500 MHz, CHCl₃) 7.70 (d, *J* = 7.8, 1 H), 7.51 (d, *J* = 1.7, 1 H), 3 (m, 3 H), 6.55 (d, *J* = 3.2, 1 H), 6.51 (dd, *J* = 3.3, 1.8, 1 H), 2.50 (s, 3 H); ¹³C NMR: (125 MHz, CHCl₃) 153.6, 141.7, 134.55, 131.1, 130.2, 127.4, 127.0, 126.0, 111.3, 108.5, 21.8; *R*_f = 0.55 (hexane/EtOAc, 9/1) [silica gel, UV]; GC: *t*_R **42c**, 6.30 min (100.0%) (HP-5, 15 psi).

Preparation of 2-(Hydroxydimethylsilyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]-1H-indole (13**)**—To a flame-dried, three-necked, 300-mL, round-bottomed, flask fitted with an argon inlet adaptor, thermocouple, magnetic stir bar and septum was placed *N*-SEM indole (3.425 g, 13.8 mmol) followed by hexane (24 mL) and diethyl ether (16.0 mL). The solution was cooled to 0 °C (internal) in an ice bath. To this mixture was added *tert*-butyllithium (9.0 mL, 1.62 M, 14.5 mmol, 1.05 equiv) of via syringe dropwise. The solution was warmed to rt

and stirred for 1 h whereupon it was cooled to $-70\text{ }^{\circ}\text{C}$ in a dry ice/2-propanol bath and hexamethylcyclotrisiloxane (1.01 g, 4.55 mmol, 0.33 equiv) was added. The reaction mixture was warmed to rt and stirred for 18 h whereupon it was cooled to $0\text{ }^{\circ}\text{C}$ and H_2O (35 mL) was added. The aqueous layer was separated and extracted with EtOAc ($3 \times 30\text{ mL}$). The combined organic layers were dried over MgSO_4 and filtered through #4 Whatman filter paper. The solvent was removed under reduced pressure using rotary evaporation ($23\text{ }^{\circ}\text{C}$, 20 mmHg) to a volume of approximately 50 mL that was immediately eluted through a silica gel plug (10 g) with EtOAc (50 mL). The solvent was removed under reduced pressure to give a red oil that was purified by silica gel chromatography ($60 \times 100\text{ mm}$) by first eluting with hexane/EtOAc, 9/1 (300 mL) followed by hexane/EtOAc, 4/1 ($30 \times 50\text{ mL}$ fractions) to afford 2.76 g (62%) of **13** as a yellow oil. Data for **13**: ^1H NMR: (500 MHz, CDCl_3) 7.66 (d, $J = 7.7$, 1 H), 7.46 (d, $J = 8.2$, 1 H), 7.29 (t, $J = 7.7$, 1 H), 7.16 (t, $J = 7.7$, 1 H), 6.86 (s, 1 H), 5.66 (s, 2 H), 3.83 (s, 1 H), 3.52 (t, $J = 8.5$, 2 H), 0.93 (t, $J = 8.4$, 2 H), 0.53 (s, 6H), -0.03 (s, 9H); ^{13}C NMR: (125.6 MHz, CDCl_3) 140.2, 139.9, 128.4, 123.0, 121.1, 120.0, 114.2, 109.0, 74.2, 65.9, 17.8, 0.82, -1.2 ; IR: 3390, 3061, 3028, 2954, 2896, 1917, 1771, 1653, 1608, 1575, 1497, 1468, 1444, 1404, 1345, 1316, 1300, 1251, 1219, 1167, 1128, 1070, 973, 896, 835. MS: (EI, 70 eV) 321, 291, 276, 248, 204, 189, 174, 130, 117, 103, 73; $R_f = 0.13$ (hexane/EtOAc, 9/1) [silica gel, UV]. Anal. Calcd. $\text{C}_{16}\text{H}_{27}\text{NO}_2\text{Si}_2$: C, 59.76; H, 8.46; N, 4.36. Found: C, 59.59; H, 8.50; N, 4.46.

Preparation of Sodium *N*-SEM-Dimethyl(2-indolyl)silanolate ($\text{Na}^+\text{13}^-$)—To a flame-dried, two-necked, 100-mL, round-bottomed flask fitted with an argon inlet adaptor, magnetic stir bar and septum was placed NaH (225 mg, 9.40 mmol, 1.0 equiv) followed by toluene (5.0 mL) toluene. The stirred suspension was cooled in an ice bath. To this suspension was added via cannula a solution of **13** over 10 min. The indole solution was prepared by placing a solution of **13** (3.01 g, 9.4 mmol) in toluene (10 mL) in a flame-dried, 50-mL, two-necked, conical flask fitted with an argon inlet adapter, magnetic stir bar and septum. Upon addition to the mixture above, the conical flask was washed with toluene (5 mL) and this rinse was added to the mixture above. The solution was warmed to rt and stirred for 30 min whereupon the solvent was removed under reduced pressure (0.05 mmHg) for a period of 12 h. The resulting off-white powder, 3.18 g (99%) was stored inside a drybox. Data for $\text{Na}^+\text{13}^-$: ^1H NMR: (500 MHz, C_6D_6) 7.69 (d, $J = 7.6$, 1 H), 7.17 (m, 2 H), 6.89 (s, 2 H), 5.42 (s, 2 H), 3.44 (t, $J = 8.8$, 2 H), 0.88 (t, $J = 8.1$, 2 H), 0.58 (s, 6H), -0.25 (s, 9H); ^{13}C NMR: (125.6 MHz, CDCl_3) 147.3, 140.6, 129.8, 122.4, 121.2, 120.3, 113.0, 109.1, 74.5, 67.7, 19.0, 5.4, -2.0 .

Representative Procedure for the Cross-coupling of *N*-SEM-Dimethyl(2-indolyl)silanolate with Aryl Chlorides

Cross-Coupling of Isolated *N*-SEM-Dimethyl(2-indolyl)silanolate ($\text{Na}^+\text{13}^-$) with 4-Chloroanisole (36g) (Table 9, entry 4)—To an oven-dried, 5-mL, conical-flask, equipped with a magnetic stir bar was added $\text{Na}^+\text{13}^-$ (412 mg, 1.2 mmol, 1.2 equiv), S-Phos (20.5 mg, 0.05 mmol, 0.05 equiv), and allylpalladium chloride dimer (9.1 mg, 0.025 mmol, 0.025 equiv) under dry argon atmosphere inside a drybox and sealed with a rubber septum. To this conical flask was added toluene (1.0 mL) and 4-chloroanisole (123 μL , 1.0 mmol, 1.0 equiv). After being stirred in a $70\text{ }^{\circ}\text{C}$ oil bath for 3 h, the crude reaction mixture was filtered through a plug of silica gel (5 g) and eluted with EtOAc (200 mL) to give a bright yellow solution that was concentrated under reduced pressure using rotary evaporation (room temperature, 20 mmHg). The resulting yellow oil was purified by silica gel column chromatography ($20 \times 100\text{ mm}$) and eluting with hexane/EtOAc, 9/1 ($30 \times 10\text{ mL}$ fractions). The combined fractions were further purified by C-18 reverse phase column chromatography (30 g, $20 \times 100\text{ mm}$) and eluting with (MeOH/ H_2O , 9/1) ($30 \times 10\text{ mL}$ fractions). The resulting clear, faint-yellow oil was placed under reduced pressure (0.05 mmHg) for a period of 12 h to

afford 333 mg (94%) as a clear, light-yellow oil. Data for **36g**: ^1H NMR: (500 MHz, CDCl_3) 7.61 (d, $J = 7.7$, 1 H), 7.57 (d, $J = 8.8$, 2 H), 7.50 (d, $J = 8.2$, 1 H), 7.24 (t, $J = 7.6$, 1 H), 7.16 (t, $J = 7.5$, 1 H), 7.00 (d, $J = 8.8$, 2 H), 6.54 (s, 1 H), 5.44 (s, 2 H), 3.87 (s, 3 H), 3.51 (t, $J = 8.8$, 2 H), 0.89 (t, $J = 8.3$, 2 H), -0.05 (s, 9 H); ^{13}C NMR: (125 MHz, CDCl_3) 159.6, 141.6, 138.1, 130.8, 128.3, 124.9, 121.9, 120.5, 120.3, 114.0, 110.1, 102.4, 72.8, 65.8, 55.3, 17.9, -1.5 ; IR: (neat) 3056, 3000, 2951, 2894, 2835, 2535, 2028, 1888, 1612, 1575, 1549, 1500, 1460, 1418, 1386, 1343, 1310, 1287, 1250, 1179, 1163, 1148, 1122, 1074, 1037, 920, 860, 836; $R_f = 0.32$ (hexane/EtOAc, 9/1) [silica gel, UV]. Anal. Calcd. for $\text{C}_{21}\text{H}_{27}\text{NO}_2\text{Si}$: C, 71.34; H, 7.70; N, 3.96. Found: C, 71.00; H, 7.68; N, 4.15.

Acknowledgements

We are grateful to the National Institutes of Health for generous financial support (R01 GM63167). J.D.B. thanks Pfizer, Inc for a graduate fellowship, and C.S.R. thanks Lilly Research Laboratories for a graduate fellowship.

References

1. Humphrey GR, Kuethe JT. Chem. Rev 2006;106:2875–2911. [PubMed: 16836303]
2. Somei M, Yamada F. Nat. Prod. Rep 2004;21:278–311. [PubMed: 15042150]
3. Cacchi S, Fabrizi G. Chem Rev 2005;105:2873–2920. [PubMed: 16011327]
4. Fraley ME, Hoffman WF, Arrington KL, Hungate RW, Hartman GD, McFall RC, Coll KE, Rickert K, Thomas KA, McGaughey GB. Curr. Med. Chem 2004;11:709–719. [PubMed: 15032725]
5. Schally AV, Comaru-Schally AM. Adv. Drug Delivery Rev 1997;28:157–169.
6. Von Baeyer A. Ann. Chem 1866;140:295.
7. Sundberg, RJ. Comprehensive Heterocyclic Chemistry II. Katritzky, AR.; Ress, CW.; Scriven, EFV.; Bird, CW., editors. Vol. vol 2. Oxford: Pergamon Press; 1996. p. 119 Gribble, GW. Comprehensive Heterocyclic Chemistry II. Katritzky, AR.; Ress, CW.; Scriven, EFV.; Bird, CW., editors. Vol. Vol. 2. Oxford: Pergamon Press; 1996. p. 207 Katritzky, AR.; Pozharskii, AF. Handbook of Heterocyclic Chemistry. Oxford: Pergamon; 2000. Chapter 4 Gilchrist, TL. Heterocyclic Chemistry. Essex: Longman; 1997.
8. Robinson, B. The Fisher Indole Synthesis. New York: Wiley-Interscience; 1982. (b) Hughes DL. Org. Prep. Proced. Int 1993;25:609–632.
9. (a) Gassman PG, van Bergen TJ, Gilbert DP, Cue BW Jr. J. Am. Chem. Soc 1974;96:5495–5508. (b) Gassman PG, van Bergen TJ. J. Am. Chem. Soc 1974;96:5508–5512. (c) Gassman PG, Gruetzmacher G, van Bergen TJ. J. Am. Chem. Soc 1974;96:6508–6510.
10. Bessard Y. Org. Proc. Res. Dev 1998;2:214–220.
11. (a) Madelung W. Chem. Ber 1912;45:1128. (b) Houlihan WJ, Parrino VA, Uike Y. J. Org. Chem 1981;46:4511–4515.
12. Nenitzescu CD. Bull. Soc. Chim. Rom 1929;11:37.
13. (a) Bischler A. Chem. Ber 1892;25:2860. (b) Möhlau R. Chem. Ber 1882;15:2480.
14. Reissert A. Chem. Ber 1897;30:1030.
15. (a) Boger DL, Boyce CW, Garbaccio RM, Goldberg JA. Chem. Rev 1997;37:787–828. [PubMed: 11848889] (b) Murphy JA, Scott KA, Sinclair RS, Link JS. Tetrahedron Lett 1997;38:7295–7298.
16. Anastas PT, Kirchhoff MM. Acc. Chem. Res 2002;35:686–694. [PubMed: 12234198]
17. Li, JJ.; Gribble, GW. Palladium in Heterocyclic Chemistry. Oxford: Pergamon Press; 2000. (b) Gribble GW. J. Chem. Soc., Perkin Trans. 1 2000:1045–1075. (c) Söderberg BC, Shriver JA. J. Org. Chem 1997;62:5838–5845. (d) Wagaw S, Yang BH, Buchwald SL. J. Am. Chem. Soc 1998;120:6621–6622. (e) Wagaw S, Yang BH, Buchwald SL. J. Am. Chem. Soc 1999;121:10251–10263. (f) Brown JA. Tetrahedron Lett 2000;41:1623–1626. (g) Watanabe M, Yamamoto T, Nishiyama M. Angew. Chem., Int. Ed 2000;39:2501–2504.
18. Aoyagi Y, Mizusaki T, Ohta A. Tetrahedron Lett 1996;37:9203–9206.
19. (a) Hegedus LS, Allen GF, Waterman EL. J. Am. Chem. Soc 1978;100:5800–5807. (b) Mori M, Chiba K, Ban Y. Tetrahedron Lett 1977;12:1037–1040. (c) Terpkio MO, Heck RF. J. Am. Chem. Soc

- 1979;101:5281–5283. (d) Mori M, Ban Y. *Tetrahedron Lett* 1979;13:1133–1136. (e) Kasahara A, Izumi T, Murakami S, Yanai H, Takatori M. *Bull. Chem. Soc. Jpn* 1986;59:927–928. (f) Larock RC, Babu S. *Tetrahedron Lett* 1987;28:5291–5294. (g) Matsuura T, Overman LE, Poon DJ. *J. Am. Chem. Soc* 1998;120:6500–6503. (h) Overman LE, Paone DV, Stearns BA. *J. Am. Chem. Soc* 1999;121:7702–7703.
20. (a) Larock RC, Yum EK. *J. Am. Chem. Soc* 1991;113:6689–6690. (b) Larock RC, Yum EK, Refvik MD. *J. Org. Chem* 1998;63:7652–7662. (c) Iritani K, Matsubara S, Utimoto K. *Tetrahedron Lett* 1988;29:1799–1802. (d) Rudisill D, Stille JK. *J. Org. Chem* 1989;54:5856–5866. (e) Cacchi S, Carnicelli V, Marinelli F. *J. Organomet. Chem* 1994;475:289–296. (f) Kondo Y, Shiga F, Murata N, Sakamoto T, Yamanaka H. *Tetrahedron* 1994;50:11803–11812. (g) Yu MS, Leon LL, McGuire MA, Botha G. *Tetrahedron Lett* 1998;39:9347–9350.
21. (a) Hartung CG, Fecher A, Chapell B, Snieckus V. *Org. Lett* 2003;5:1899–1902. [PubMed: 12762681] (b) Ezquerro J, Pedregal C, Lamas C, Barluenga J, Perez M, GarciaMartin MA, Gonzales JM. *J. Org. Chem* 1996;61:5804–5812.
22. (a) Campeau L-C, Fagnou K. *Chem. Commun* 2006:1253–1264. (b) Stuart DR, Fagnou K. *Science* 2007;316:1172–1175. [PubMed: 17525334] (c) Nakao Y, Kanyiva KS, Oda S, Hiyama T. 2006;128:8146–8147. (d) Wang X, Lane BS, Sames D. *Am. Chem. Soc* 2005;127:4996–4997. (e) Toure BB, Lane BS, Sames D. *Org. Lett* 2006;8:1979–1982. [PubMed: 16671761] (f) Lane BS, Brown MA, Sames D. *Am. Chem. Soc* 2005;127:8050–8057. (g) Deprez NR, Kalyani D, Krause A, Sanford MS. 2006;128:4972–4973. (h) Alberico D, Scott ME, Lautens M. *Chem. Rev* 2007;107:174–238. [PubMed: 17212475] (i) Mee SPH, Lee V, Baldwin JE. *Angew. Chem. Int. Ed* 2004;43:1132–1136.
23. (a) Campeau L-C, Fagnou K. *Chem. Soc. Rev* 2007;36:1058–1068. [PubMed: 17576474] (b) Tyrrell E, Brookes P. *Synthesis* 2003:469–483. (c) Banwell MG, Goodwin TE, Ng S, Smith JA, Wong DJ. *Eur. J. Org. Chem* 2007:3034–3060.
24. Labadie SS, Teng E. *J. Org. Chem* 1994;59:4250–4254.
25. Amat M, Hadida S, Pshenichnyi G, Bosch J. *J. Org. Chem* 1997;62:3158–3175. [PubMed: 11671699]
26. Payack JF, Vazquez E, Matty L, Kress MH, McNamara J. *J. Org. Chem* 2005;70:175–178. [PubMed: 15624920]
27. (a) Ishikura M, Agata I, Katagiri N. *J. Heterocyclic Chem* 1999;36:873–879. (b) Ishikura M, Takahashi N, Takahashi H, Yanada K. *Heterocycles* 2005;66:45–50.
28. (a) Kudo N, Perseghini M, Fu GC. *Angew. Chem. Int. Ed* 2006;45:1282–1284. (b) Billingsley KL, Anderson KW, Buchwald SL. *Angew. Chem. Int. Ed* 2006;45:3484–3488. (c) Billingsley K, Buchwald SL. *J. Am. Chem. Soc* 2007;129:3358–3366. [PubMed: 17326639]
29. Cragg, ST. *Patty's Toxicology*. Binham, E.; Cochrissen, B.; Powell, CH., editors. Hoboken: Wiley; 2001.
30. For reviews on silicon-based cross-coupling, see: (a) Hiyama T, Diederich F, Stang PJ. *Metal Catalyzed Cross-Coupling Reactions*. 1998 Weinheim Wiley-VCH Chapter 10. (b) Hiyama T. *J. Organomet. Chem* 2002;653:58–61. (c) Denmark SE, Sweis RF. *Chem. Pharm. Bull* 2002;50:1531–1541. (d) Denmark SE, Sweis RF. *Acc. Chem. Res* 2002;35:835–846. (e) Denmark SE, Ober MH. *Aldrichimica Acta* 2003;36:57–85. (f) Denmark SE, Sweis RF, de Meijere A, Diederich F. *Metal Catalyzed Cross-Coupling Reactions* (2nd ed.). 2004 2nd ed. Weinheim Wiley-VCH Chapter 4. (g) Denmark SE, Baird JD. *Chem. Eur. J* 2006;12:4954–4963. 4963
31. (a) Denmark SE, Wehrli D, Sweis RF. *J. Am. Chem. Soc* 2004;126:4865–4875. [PubMed: 15080691] (b) Denmark SE, Sweis RF. *J. Am. Chem. Soc* 2004;126:4876–4882. [PubMed: 15080692]
32. Denmark SE, Sweis RF. *J. Am. Chem. Soc* 2001;123:6439–6440. [PubMed: 11427080]
33. Denmark SE, Ober MH. *Org. Lett* 2003;5:1357–1360. [PubMed: 12688758]
34. (a) Denmark SE, Baird JD. *Org. Lett* 2004;6:3649–3652. [PubMed: 15387570] (b) Denmark SE, Kallemeyn JM. *J. Org. Chem* 2005;70:2839–2842. [PubMed: 15787583]
35. Denmark SE, Baird JD. *Org. Lett* 2006;8:793–795. [PubMed: 16468769]
36. Portions of this work have been previously communicated, refs 34a, 35
37. Weedon AC, Zhang B. *Synthesis* 1992:95–100.
38. Edwards MP, Doherty AM, Ley SV, Organ HM. *Tetrahedron* 1986;42:3723–3729.

39. Jiang X, Tiwari A, Thompson M, Chen Z, Cleary TP, Lee TB. *Org. Proc. Res. Dev* 2001;5:604–608.
40. Zeng Z, Zimmerman SC. *Tetrahedron. Lett* 1988;29:5123–5124.
41. Sugita K, Shigeno K, Neville CF, Thomas EJ. *Tetrahedron Lett* 1991;32:2269–2270.
42. Vazquez E, Davies IW, Payack JF. *J. Org. Chem* 2002;67:7551–7552. [PubMed: 12375996]
43. Silanol **11** can be prepared reproducibly on >10 g scale.
44. Ley and co-workers (ref. 38) report the use of 1.5 equiv of (2-(trimethylsilyl-ethoxy)methyl chloride (SEM-Cl)). In the current study 1.1 equiv SEM-Cl could be used without any reduction in yield.
45. Butler CR, Denmark SE. *Encyclopedia of Reagents for Organic Synthesis*. 2007 in press
46. Control experiments have established that protidesilylation does not occur upon quenching with the acetate buffer.
47. Hosomi and co-workers have shown that copper additives may be able to suppress desilylation for some heterocyclic silanes (a) Ito H, Hosomi A. *J. Synth. Org. Chem* 2000;58:274. Use of copper cocatalyst with silanes: (b) Ito H, Ishizuka T, Tateiwa J, Sonoda M, Hosomi A. *J. Am. Chem. Soc* 1998;120:11196–11197. 11197 (c) Taguchi H, Ghoroku K, Tadaki M, Tsubouchi A, Takeda T. *Org. Lett* 2001;3:3811–3814. 3814 [PubMed: 11700145] (d) Taguchi H, Miyashita H, Tsubouchi A, Takeda T. *Chem. Commun* 2002:2218–2219. 2219 (e) Hanamoto T, Kobayashi T, Kondo M. *Synlett* 2001:281–283. 283 (f) Taguchi H, Ghoroku K, Tadaki M, Tsubouchi A, Takeda T. *J. Org. Chem* 2002;67:8450–8456. 8456 [PubMed: 12444624] (g) Denmark SE, Kobayashi T. *J. Org. Chem* 2003;68:5153–5159. 5159 [PubMed: 12816470] (h) Denmark SE, Tymonko SA. *J. Org. Chem* 2003;68:9151–9154. 9154 [PubMed: 14604401] Use of copper cocatalyst with stannanes: (i) Wang Y, Burton DJ. *Org. Lett* 2006;8:1109–1111. 1111 [PubMed: 16524280] (j) Casado AL, Espinet P. *Organometallics* 2003;22:1305–1309. 1309 (k) Han X, Stolz BM, Corey EJ. *J. Am. Chem. Soc* 1999;121:7600–7605. 7605 (l) Farina V. *Pure Appl. Chem* 1996;68:73–78. 78 (m) Farina V, Kapadia S, Krishnan B, Wang C, Liebeskind LS. *J. Org. Chem* 1994;59:5905–5911. 5911 Use of copper cocatalyst with boranes: (n) Savarin C, Liebeskind LS. *Org. Lett* 2001;3:2149–2152. 2152 [PubMed: 11440566] (o) Boland GM, Donnelly DMX, Finet JP, Rea MD. *J. Chem. Soc., Perkin Trans. 1* 1996:2591–2597. 2597
48. See the Supporting Information for the results from the copper survey.
49. Treatment *N*-Boc(2-indolyl)dimethylsilanol with mesitylcopper gave mostly desilylation. We speculate that the deprotonation did not proceed cleanly resulting in *N*-Boc indole formation.
50. Data for these experiments is provided in the Supporting Information. The assignment of the disiloxane component is tentative.
51. When ethyl 4-iodobenzoate was the substrate in the copper mediated reaction a significant amount of transesterification was observed. This suggests that $\text{Na}^+\text{11}^-$ may be less nucleophilic than $\text{NaO}t\text{-Bu}$.
52. A significant rate enhancement was observed when copper(II) salts were used in the cross-coupling reaction of 3,5-disubstituted 4-silyloxazoles with aromatic iodides, see: Denmark SE, Kallemeyn JM. *J. Org. Chem* 2005;70:2839–2842. 2842 [PubMed: 15787583]
53. To improve the yield in the cross-coupling of electron-rich substrates re-optimization of the cross-coupling conditions was carried out. When the cross-coupling reaction of 1.2 equiv of $\text{Na}^+\text{20}^-$ with 4-iodoanisole was performed at room temperature, a significant amount of unreacted aryl iodide was observed after 24 h. Increasing the temperature to 40 or 50 °C did not influence the rate; in fact, the reaction stalled after 12 h. Finally, ligands such as: tris(2-furylphosphine) and triphenylarsine also did not improve the yield of **30c**.
54. This silanol is a wax and thus, preparation of the sodium silanolate allowed for more facile manipulation.
55. Littke AF, Fu GC. *Angew. Chem. Int. Ed* 2002;41:4176–4211.
56. (a) Old DW, Wolfe JP, Buchwald SL. *J. Am. Chem. Soc* 1998;120:9722–9723. 9723 (b) Littke AF, Fu GC. *Angew. Chem. Int. Ed* 1999;38:2411–2413. 2413 (c) Wolfe JP, Singer RA, Yang BH, Buchwald SL. *J. Am. Chem. Soc* 1999;121:9550–9561. 9561 (d) Littke AF, Dai C, Fu GC. *J. Am. Chem. Soc* 2000;122:4020–4028. 4028 (e) Navarro O, Kelly RA III, Nolan SP. *J. Am. Chem. Soc* 2003;125:3804–3805. 3805 For a recent review on the development of ligands for the cross-coupling of aryl chlorides see (f) Bedford RB, Cazin CSJ, Holder D. *Coord. Chem. Rev* 2004;248:2283–2321. 2321

57. Fu and coworkers have recently reported a general procedure for the cross-coupling of nitrogen heterocycles that demonstrated excellent scope for a variety of aza-heterocycles. However, the cross-coupling of *N*-Boc(2-indolyl)boronic acid with a heteroaryl bromide provided the indole product in low yield: see Kudo N, Perseghini M, Fu GC. *Angew. Chem. Int. Ed* 2006;45:1282–1284.1284
58. Werner H, Kuhn A. J. *Organomet. Chem* 1979;179:439–445.
59. Denmark SE, Tymonko SA, Ober MH. submitted
60. Denmark SE, Kallemeyn JM. *J. Am. Chem. Soc* 2006;128:15958–15959. [PubMed: 17165708]
61. Barder TE, Walker SD, Martinelli JR, Buchwald SL. *J. Am. Chem. Soc* 2005;127:4685–4696. [PubMed: 15796535]
62. Alternatively, a control experiment that subjected *N*-methylindole to the reaction conditions failed to provide any arylated products.
63. Wolfe JP, Singer RA, Yang BH, Buchwald SL. *J. Am. Chem. Soc* 1999;121:9550–9561.
64. Lickiss PD. *Advances in Inorganic Chemistry* 1995;42:147–262.
65. Bagdanoff JT, Stoltz BM. *Angew. Chem* 2004;116:357–361.
66. Dichlorocarbene formation occurs under similar conditions, see Han JL, Ong CW. *Tetrahedron* 2005;61:1501–1507.1507
67. Farina V. *Adv. Synth. Catal* 2004;346:1553–1582.and the references within.
68. Lam PYS, Deudon S, Averill KM, Li R, He MY, DeShong P, Clark CG. *J. Am. Chem. Soc* 2000;122:7600–7601.
69. Turnover-limiting oxidative addition is unlikely because the oxidative addition of aryl iodides is generally considered to be fast and irreversible under the reaction conditions.
70. For references of diarylation of 5-membered heterocycles see. (a)Nakano M, Satoh T, Miura M. *J. Org. Chem* 2006;71:8309–8311.8311 [PubMed: 17025334](b)Forgione P, Brochu M-C, St-Onge M, Thesen KH, Bailey MD, Bilodeau F. *J. Am. Chem. Soc* 2006;128:11350–11351.11351 [PubMed: 16939247]
71. Reuter KH, Scott WJ. *J. Org. Chem* 1993;58:4722–4726.

Scheme 1.

^aConditions: (a) LDA (1.25 equiv), Me_2SiCl_2 (1.50 equiv), THF, 0 °C, 18 h; (b) sat. aq. NaHCO_3 , rt, 71%; (c) $t\text{-BuLi}$ (1.05 equiv), Et_2O , 0 °C to rt, 1 h; (d) D_3 (0.33 equiv), -70 °C to rt, Et_2O , 12 h, 62%; (e) $n\text{-BuLi}$ (1.05 equiv), Et_2O , reflux, 5 h; (f) D_3 (0.33 equiv) 0 °C to rt, Et_2O , 12 h, 57%.

Scheme 2a.

^aConditions: (a) LDA (1.25 equiv), Me₂SiCl₂ (1.50 equiv), THF, 0 °C, 18 h; (b) sat. aq. NaHCO₃, rt, 50%; (c) *n*-BuLi (1.05 equiv), Et₂O, -71 °C to rt, 4 h; (d) D₃ (0.33 equiv), -71 °C to rt, Et₂O, 16 h, 22%; (e) NaH (1.0 equiv.), toluene, 99%; (f) *n*-BuLi (1.05 equiv), Et₂O, -70 °C to rt, 2 h; (g) D₃ (0.33 equiv), -71 °C to rt, Et₂O, 16 h, 72%. (h) NaH (1.0 equiv.), toluene, 99%.

Scheme 3a.

Scheme 4.

J Org Chem. Author manuscript; available in PMC 2009 September 15.

Tyrian purple (1)

Serotonin (2)

Psilocybin (3)

Lipitor (4)

5

6

Chart 1.

Table 1

Effect of Base on the Equilibrative Deprotonation Protocol.

product yield % ^a			
entry	base	time, h	11	10	24			
1	NaO <i>t</i> -Bu	0.25	79	21	-			
2	NaO <i>t</i> -Bu	1	82	18	-			
3	KOSiMe ₃	1	43	57	-			
4	KOSiMe ₃	6	5	95	-			
5	LiHMDS	1	97	-	3			
6	LiHMDS	6	96	-	4			

^aThe product ratio was determined by HPLC analysis by area %.

Table 2Catalyst Optimization for the Cross-Coupling of **11**.

entry ^a	Pd source	Product, % ^b	
		12 h	24 h
1	PdCl_2	-	3
2	$\text{PdCl}_2(\text{PPh}_3)_2$	-	15
3	$\text{Pd}(\text{OAc})_2$	-	17
4	$[\text{allylPdCl}]_2$	22	46
5	PdBr_2	55	94
6	$(\text{CH}_3\text{CN})_2\text{PdCl}_2$	57	98
7	$\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$	87	>99
8 ^c	$\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$	>99	-

^a Conditions: 1.2 equiv of **11**, 2.0 equiv of $\text{NaO}-t\text{Bu}$, 1.0 equiv of Cul , 0.1 equiv of Pd , 0.6 M in **11** in toluene at room temp.^b Determined by HPLC analysis using biphenyl as an internal standard.^c Reaction concentration was increased to 1.2 M in **11** was complete in 6 h.

Table 3
Cross-Coupling of *N*-Boc-dimethyl-1-2-indolylsilanol **11** with Substituted Aryl Iodides.

entry ^a	R	temp, °C	time, h	product	28 ^b	29 ^c	yield, % ^b
1	4-NO ₂	rt	6	28a	84	6	6
2	4-CF ₃	rt	22	28b	82	3	3
3	4-CO ₂ <i>t</i> -Bu	rt	24	28c	84	trace	trace
4	3-NO ₂	40	12	28d	72	14	14
5	H	40	12	28e	70	12	12
6	2-Me	50	24	28f	73	14	14
7	4-OMe	50	24	28g	72	14	14
8	2-OMe	50	24	28h	75	15	15
9	<i>d</i>	60	24	28i	75	13	13

^a Conditions: 1.2 equiv of **11**, 2.0 equiv of NaOt-Bu , 1.0 equiv CuI , 0.1 equiv Pd , 0.6 M in **11** in toluene.

^b Yield of isolated, analytically pure product.

^c Determined by ¹H NMR analysis of crude reaction mixtures.

^d 1-Iodonaphthalene.

Table 4Cross-Coupling of In-Situ Generated $\text{Na}^+\mathbf{11}^-$ with Aryl Iodides.

entry ^a	R	temp, °C	product	Yield, ^b %
1	4-OMe	80	28g	68
2	4-CO ₂ Et	rt	28j	82
3	4-CN	rt	28k	81

^a Conditions: The reaction concentration was 0.6 M, **11** (1.2 equiv), NaH (1.2 equiv) in toluene, Pd₂(dba)₃·CHCl₃ (0.05 equiv).^b Yield of chromatographed, recrystallized products.

Table 5

Effect of Copper on the Cross-Coupling of **20**.

entry ^a	copper source	copper, equiv	time, h	yield, % ^b		
				30a	31a	32
1	-	-	3	15	5	-
2	Cu(OAc) ₂	1.0	0.5	59	2	2
3	Cu(OAc) ₂	1.0	3	-	-	22
4	Cu(OAc) ₂	0.25	3	87	3	-
5 ^c	Cu(OAc) ₂	0.25	3	72	3	-

^a Conditions: 1.2 equiv of **20**, 2.0 equiv of NaOr-Bu, 0.1 equiv of Pd, 0.6 M in **20** in toluene at room temp.

^b Yields based on ¹H-NMR integration using hexamethylbenzene as an internal standard.

^c The reaction was run on 1 mmol scale, yield of isolated analytically pure material.

Table 6

In Situ Formation of Na⁺**20**⁻ and Cross-Coupling with Aryl Iodides.

entry ^b	R ¹	temp, °C	time, h	product	yield, % ^a
1	4-NO ₂	rt	3	30a	80
2	4-CF ₃	rt	3	30b	87
3	4-CN	rt	3	30k	77
4	4-CH ₃	40	24	30l	68
5	4-OMe	50	24	30g	52

^aYield of isolated analytically pure material.

^bThe reaction concentration was 0.6 M in **20**, **20** (1.2 equiv) and NaH (1.2 equiv) in toluene, Pd₂(dba)₃·CHCl₃ (0.05 equiv).

Cross-Coupling of C(5) Substituted 2-Dimethylindolylsilanols with Aromatic Iodides.

Table 7

entry ^a	R ¹	activator	R ²	time, h	temp, °C	product	yield, % ^b
1	CN	NaHMDS	4-OMe	24	rt	33g	70
2	Me	NaHMDS	4-CO ₂ Et	3	rt	34j	82
3	Me	NaHMDS	3-CH ₂ OTBS	24	50	34m	76
4	Me	NaHMDS	2-Me	3	50	34f	65
5	Me	NaHMDS	4-OMe	24	50	34g	71
6	Br	-	4-CO ₂ Et	4	rt	35j	85
7 ^c	Br	-	3-CH ₂ OTBS	12	80	35m	63
8	Br	-	2-Me	24	50	35f	54
9	Br	-	4-OMe	24	80	35g	56

^a Conditions: silanol or silanolate (1.2 equiv), HMDS (1.2 equiv) 0.6 M in silanol or silanolate in toluene, Pd₂(dba)₃·CHCl₃ (0.05 equiv).

^b Yield of isolated, analytically pure product. Silanolates of **21** and **22** were generated using the preformation protocol. Na⁺**23**⁻ was used as the isolated salt.

^c 2.0 equiv of Na⁺**23**⁻ was used.

Table 8Cross-Coupling of Na⁺**13**[−] with Substituted Aryl Bromides.

entry ^a	R	product	yield, % ^b
1	4-CO ₂ <i>t</i> -Bu	36c	93
2	2-Me	36f	89
3	3-CH ₂ OTBS	36m	83
4	4-OMe	36g	93

^a Conditions: Na⁺**13**[−] (1.2 equiv), **37** (0.025 equiv) 0.6 M in Na⁺**13**[−] in toluene, 50 °C.^b Yield of isolated, analytically pure product.

Table 9

Cross-Coupling of $\text{Na}^+\mathbf{13}^-$ with Substituted Aryl Chlorides.

entry ^a	R	temp, °C	time, h	product	yield, % ^b
1	4-CN	70	1	36k	92
2	4-COPh	70	1	36n	93
3	4-CF ₃	70	1	36b	92
4	4-OMe	70	3	36g	94
5	2,6-Me ₂	70	3	36o	88
6	2-OMe	70	3	36h	94
7	3-pyridyl	70	2	36p	84
8	2-pyridyl	90	3	36q	73
9	<i>b</i>	70	3	36r	86

^a Conditions: $\text{Na}^+\mathbf{13}^-$ (1.2 equiv), **37** (0.025 equiv) 0.6 M in $\text{Na}^+\mathbf{13}^-$ in toluene.

^bYield of isolated, analytically pure product. ^b 8-(1,3,7-Me₃)xanthine

Table 10

Cross-Coupling of **15** with Substituted Aryl Halides.

entry ^a	X	R	temp, °C	time, h	product	yield, %	
						39 ^b	40 ^c
1	I	4-NO ₂	rt	3	39a	62	16
2	I	4-CN	rt	3	39k	62	32
3	I	H	rt	3	39e	82	-
4	I	2-thienyl	rt	6	39s	73	-
5	I	4-OMe	rt	3	39g	80	-
6	Br	4-NO ₂	55	20	39a	84 ^d	5
7	Br	4-CN	55	20	39k	80 ^d	5

^a Conditions: 1.2 equiv of **15**, 2.0 equiv of NaOt-Bu, 1.0 equiv CuI, 0.1 equiv Pd, 0.6 M in **15** in toluene.

^b Yield of analytically pure products.

^c Determined by ¹H NMR analysis of crude reaction mixtures.

^d Addition of 0.2 equiv of dppb was required.

Table 11
Cross-Coupling Heteroaryl Silanols with Substituted Aryl Iodides and Bromides

entry	X	R ¹	R ²	catalyst	temp, °C	time, h	product	yield, %
1	N-Boc	I	4-CO ₂ Et	Pd ₂ (dba) ₃ •CHCl ₃	rt	3	41j	76
2	N-Boc	I	2-Me	Pd ₂ (dba) ₃ •CHCl ₃	rt	3	41f	80
3	N-Boc	I	4-OMe	Pd ₂ (dba) ₃ •CHCl ₃	50	36	42g	72
4	O	I	4-CO ₂ Et	Pd ₂ (dba) ₃ •CHCl ₃	rt	1	42j	82
5 ^c	O	I	4-CO ₂ Et	Pd ₂ (dba) ₃ •CHCl ₃	rt	1	42j	79
6	O	I	2-Me	Pd ₂ (dba) ₃ •CHCl ₃	rt	3	42f	61
7 ^b	O	I	4-OMe	Pd ₂ (dba) ₃ •CHCl ₃	50	24	42g	71
8 ^d	O	Br	4-OMe	37	50	6	42g	66
9	O	Br	4-CO ₂ Et	37	50	3	42j	60
10	O	Br	4-CN	37	50	3	42k	73
11	O	Br	2-Me	37	50	3	42f	71
12	O	Br	4-CF ₃	37	50	3	42b	71
13	O	Br	^e	37	50	6	42i	69
14	S	I	4-CO ₂ Et	Pd ₂ (dba) ₃ •CHCl ₃	rt	3	43j	78
15 ^f	S	I	4-CO ₂ Et	Pd ₂ (dba) ₃ •CHCl ₃	rt	3	43j	87
16	S	I	2-Me	Pd ₂ (dba) ₃ •CHCl ₃	rt	3	43f	79
17	S	I	4-OMe	Pd ₂ (dba) ₃ •CHCl ₃	80	24	43g	72
18	S	Br	4-OMe	37	50	3	43g	71
19	S	Br	4-CO ₂ Et	37	50	3	43j	67
20	S	Br	4-CN	37	50	3	43k	78

entry	X	R ¹	R ²	catalyst	temp, °C	time, h	product	yield, ^a %
21	S	Br	2-Me	37	50	3	43f	77
22	S	Br	4-CF ₃	37	50	3	43b	86
23	S	Br	^e	37	50	7	43i	74

^aYield of chromatographed products purified by recrystallization or sublimation.

^bRequired the use of 0.2 equiv of 2-furyl)3As for complete conversion.

^c1.2 equiv of Na⁺26⁻ was used

^dReaction stalled at 78% conversion.

^e1-Bromonaphthalene.

^f1.2 equiv of Na⁺27⁻ was used

Table 12Catalyst and Ligand Optimization for the Cross-Coupling of **27** with 4-Bromoanisole.

entry	Pd source	ligand, 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 ^b
5	37 ^d	0	3	100

^a **27** (1.2 equiv) and NaH (1.2 equiv) in toluene, 0.6 M in **27** in toluene, Pd (0.1 equiv), 50 °C.^b Area % by GC analysis.^c Accompanied with 11% of the product of aryl bromide homocoupling, as determined by ¹H NMR analysis.^d (2-MeC₃H₄)(Cl)Pd₂(P(*t*-Bu)₃)₂