JOC*Article*

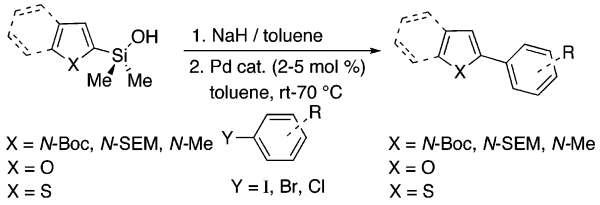
Palladium-Catalyzed Cross-Coupling of Five-Membered Heterocyclic Silanolates

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

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

denmark@scs.uiuc.edu

Received November 2, 2007

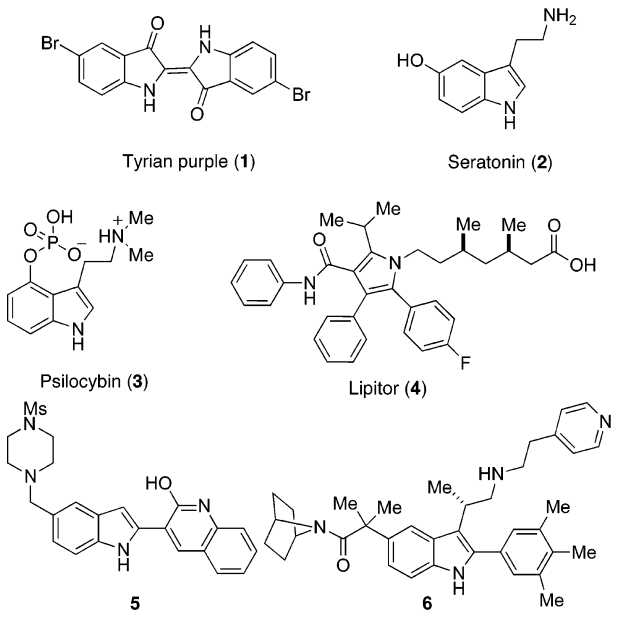


The preparation of π-rich 2-aryl heterocycles by palladium-catalyzed cross-coupling of sodium heteroarylsilanolates with aryl iodides, bromides, and chlorides is described. The cross-coupling process was developed through extensive optimization of the following key variables: (1) identification of stable, 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 NaO*t*-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 have 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 inhibitor[4]

CHART 1



(1) Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875−2911.
(2) Somei, M.; Yamada, F. *Nat. Prod. Rep.* **2004**, *21*, 278−311.
(3) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873−2920.

10.1021/jo7023784 CCC: $40.75
Published on Web 01/19/2008

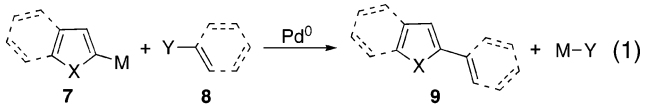
containing a hydroxy quinoline at C(2), and gonadotropin-releasing hormone antagonist[5] **6** features a 3,4,5-trimethylphenyl group.

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 hydrazones[8] or [2,3]-sigmatropic rearrangements of 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-arylindoles include the following: nucleophilic (Madelung−Houlihan[11] and Nenitzescu[12] synthesis), electrophilic (Bischler−Möhlau[13]), reductive (Reissert[14] 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 *o*-aminophenethyl alcohols,[18] Hegedus−Mori−Heck indole synthesis,[19] 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 (eq 1).



7 **8** **9**

X = N, O, S Y = I, Br, Cl

M = Sn, B, Zn, Si

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

(4) Fraley, M. E.; Hoffman, W. F.; Arrington, K. L.; Hungate, R. W.; Hartman, G. D.; McFall, R. C.; Coll, K. E.; Rickert, K.; Thomas, K. A.; McGaughey, G. B. *Curr. Med. Chem.* **2004**, *11*, 709−719.

(5) Schally, A. V.; Comaru-Schally, A. M. *Adv. Drug Delivery Rev.* **1997**, *28*, 157−169.

(6) Von Baeyer, A. *Ann. Chem.* **1866**, *140*, 295.

(7) (a) Sundberg, R. J. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Ress, C. W., Scriven, E. F. V., Bird, C. W., Eds.; Pergamon Press: Oxford, 1996; Vol. 2, p 119. (b) Gribble, G. W. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Ress, C. W., Scriven, E. F. V., Bird, C. W., Eds.; Pergamon Press: Oxford, 1996; Vol. 2, p 207. (c) Katritzky, A. R.; Pozharskii, A. F. In *Handbook of Heterocyclic Chemistry*; Pergamon: Oxford, 2000; Chapter 4. (d) Gilchrist, T. L. *Heterocyclic Chemistry*; Longman: Essex 1997.

(8) (a) Robinson, B. *The Fisher Indole Synthesis*; Wiley-Interscience: New York 1982. (b) Hughes, D. L. *Org. Prep. Proced. Int.* **1993**, *25*, 609−632.

(9) (a) Gassman, P. G.; van Bergen, T. J.; Gilbert, D. P.; Cue, B. W., Jr. *J. Am. Chem. Soc.* **1974**, *96*, 5495−5508. (b) Gassman, P. G.; van Bergen, T. J. *J. Am. Chem. Soc.* **1974**, *96*, 5508−5512. (c) Gassman, P. G.; Gruetzmacher, G.; van Bergen, T. J. *J. Am. Chem. Soc.* **1974**, *96*, 5512−5517.

(10) Bessard, Y. *Org. Proc. Res. Dev.* **1998**, *2*, 214−220.

(11) (a) Madelung, W. *Chem. Ber.* **1912**, *45*, 1128−1134. (b) Houlihan, W. J.; Parrino, V. A.; Uike Y. *J. Org. Chem.* **1981**, *46*, 4511−4515.

(12) Nenitzescu, C. D. *Bull. Soc. Chim. Rom.* **1929**, *11*, 37.

(13) (a) Bischler, A. *Chem. Ber.* **1892**, *25*, 2860−2879. (b) Möhlau, R. *Chem. Ber.* **1882**, *15*, 2480−2490.

(14) Reissert, A. *Chem. Ber.* **1897**, *30*, 1030.

(15) (a) Boger, D. L.; Boyce, C. W.; Garbaccio, R. M.; Goldberg, J. A. *Chem. Rev.* **1997**, *37*, 787−828. (b) Murphy, J. A.; Scott, K. A.; Sinclair, R. S.; Lewis, N. *Tetrahedron Lett.* **1997**, *38*, 7295−7298.

(16) Anastas, P. T.; Kirchhoff, M. M. *Acc. Chem. Res.* **2002**, *35*, 686−694.

(17) (a) Li, J. J.; Gribble, G. W. In *Palladium in Heterocyclic Chemistry*; Pergamon Press: Oxford, 2000; Chapter 3. (b) Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045−1075. (c) Söderberg, B. C.; Shriver, J. A. *J. Org. Chem.* **1997**, *62*, 5838−5845. (d) Wagaw, S.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 6621−6622. (e) Wagaw, S.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 10251−10263. (f) Brown, J. A. *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, L. S.; Allen, G. F.; Bozell, J. J.; Waterman, E. L. *J. Am. Chem. Soc.* **1978**, *100*, 5800−5807. (b) Mori, M.; Chiba, K.; Ban, Y. *Tetrahedron Lett.* **1977**, *12*, 1037−1040. (c) Terpko, M. O.; Heck, R. F. *J. Am. Chem. Soc.* **1979**, *101*, 5281−5283. (d) Mori, M.; Ban, Y. *Tetrahedron Lett.* **1979**, *19*, 1133−1136. (e) Kasahara, A.; Izumi, T.; Murakami, S.; Yanai, H.; Takatori, M. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 927−928. (f) Larock, R. C.; Babu, S. *Tetrahedron Lett.* **1987**, *28*, 5291−5294. (g) Matsuura, T.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6500−6503. (h) Overman, L. E.; Paone, D. V.; Stearns, B. A. *J. Am. Chem. Soc.* **1999**, *121*, 7702−7703.

(20) (a) Larock, R. C.; Yum, E. K. *J. Am. Chem. Soc.* **1991**, *113*, 6689−6690. (b) Larock, R. C.; Yum, E. K.; Refvik, M. D. *J. Org. Chem.* **1998**, *63*, 7652−7662. (c) Iritani, K.; Matsubara, S.; Utimoto, K. *Tetrahedron Lett.* **1988**, *29*, 1799−1802. (d) Rudisill, D.; Stille, J. K. *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, M. S.; de Leon, L. L.; McGuire, M. A.; Botha, G. *Tetrahedron Lett.* **1998**, *39*, 9347−9350.

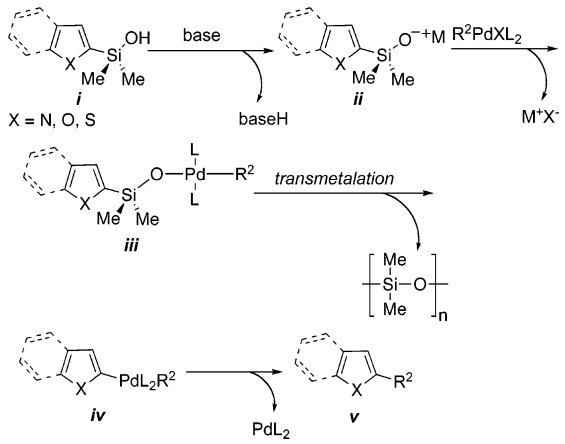
(21) (a) Hartung, C. G.; Fecher, A.; Chapell, B.; Snieckus, V. *Org. Lett.* **2003**, *5*, 1899−1902. (b) Ezquerra, J.; Pedregal, C.; Lamas, C.; Barluenga, J.; Perez, M.; Garcia-Martin, M. A.; Gonzáles, J. M. *J. Org. Chem.* **1996**, *61*, 5804−5812.

(22) (a) Campeau, L-C.; Fagnou, K.; *Chem. Commun.* **2006**, 1253−1264. (b) Stuart, D. R.; Fagnou, K. *Science* **2007**, *316*, 1172−1175. (c) Nakao, Y.; Kanyiva, K. S.; Oda, S.; Hiyama, T. *J. Am. Chem. Soc.* **2006**, *128*, 8146−8147. (d) Wang, X.; Lane, B. S.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 4996−4997. (e) Toure, B. B.; Lane, B. S.; Sames, D. *Org. Lett.* **2006**, *8*, 1979−1982. (f) Lane, B. S.; Brown, M. A.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 8050−8057. (g) Deprez, N. R.; Kalyani, D.; Krause, A.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 4972−4973. (h) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174−238. (i) Mee, S. P. H.; Lee, V.; Baldwin, J. E. *Angew. Chem., Int. Ed.* **2004**, *43*, 1132−1136.

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 protiodeborylation under conventional Suzuki cross-coupling conditions.[26] Protiodeborylation 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 nontoxic reaction byproducts.[30] Recent reports from these laboratories have shown that 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^2-$PdXL_n$ species, displacing X and generating a palladium−silanolate complex ***iii***. Following transmetalation and reductive elimination, a carbon−carbon bond is formed and the Pd(0) catalyst is regenerated.

SCHEME 1



The Brønsted base promoted cross-coupling of several classes of silanols (alkenylsilanols,[32] arylsilanols,[33] and heteroarylsilanols[34]) has been successfully developed with a number of bases including potassium trimethylsilanolate ($KOSiMe_3$), Cs_2CO_3, and NaO*t*-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, is a superior alternative.[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]

(23) (a) Campeau, L.-C.; Fagnou, K. *Chem. Soc. Rev.* **2007**, *36*, 1058−1068. (b) Tyrrell, E.; Brookes, P. *Synthesis* **2003**, 469−483. (c) Banwell, M. G.; Goodwin, T. E.; Ng, S.; Smith, J. A.; Wong, D. J. *Eur. J. Org. Chem.* **2006**, 3043−3060.

(24) Labadie, S. S.; 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.

(26) Payack, J. F.; Vazquez, E.; Matty, L.; Kress, M. H.; McNamara, J. *J. Org. Chem.* **2005**, *70*, 175−178.

(27) (a) Ishikura, M.; Agata, I.; Katagiri, N. *J. Heterocycl. 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, G. C. *Angew. Chem., Int. Ed.* **2006**, *45*, 1282−1284. (b) Billingsley, K. L.; Anderson, K. W.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 3484−3488. (c) Billingsley, K.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 3358−3366.

(29) Cragg, S. T. In *Patty's Toxicology*; Binham, E., Cohrssen, B., Powell, C. H., Eds.; Wiley; Hoboken, 2001; Vol. 7, pp 657−664.

(30) For reviews on silicon-based cross-coupling, see: (a) Hiyama, T. In *Metal Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998; Chapter 10. (b) Hiyama, T. *J. Organomet. Chem.* **2002**, *653*, 58−61. (c) Denmark, S. E.; Sweis, R. F. *Chem. Pharm. Bull.* **2002**, *50*, 1531−1541. (d) Denmark, S. E.; Sweis, R. F. *Acc. Chem. Res.* **2002**, *35*, 835−846. (e) Denmark, S. E.; Ober, M. H. *Aldrichim. Acta* **2003**, *36*, 57−85. (f) Denmark, S. E.; Sweis, R. F. In *Metal Catalyzed Cross-Coupling Reactions*, 2nd ed.; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, 2004; Chapter 4. (g) Denmark, S. E.; Baird, J. D. *Chem. Eur. J.* **2006**, *12*, 4954−4963.

(31) (a) Denmark, S. E.; Wehrli, D.; Sweis, R. F. *J. Am. Chem. Soc.* **2004**, *126*, 4865−4875. (b) Denmark, S. E.; Sweis, R. F. *J. Am. Chem. Soc.* **2004**, *126*, 4876−4882.

(32) Denmark, S. E.; Sweis, R. F. *J. Am. Chem. Soc.* **2001**, *123*, 6439−6440.

(33) Denmark, S. E.; Ober, M. H. *Org. Lett.* **2003**, *5*, 1357−1360.

(34) (a) Denmark, S. E.; Baird, J. D. *Org. Lett.* **2004**, *6*, 3649−3652. (b) Denmark, S. E.; Kallemeyn, J. M. *J. Org. Chem.* **2005**, *70*, 2839−2842.

(35) Denmark, S. E.; Baird, J. D. *Org. Lett.* **2006**, *8*, 793−795.

(36) Portions of this work have been previously communicated; see refs 34a and 35.

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 protiodesilylation, 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.).

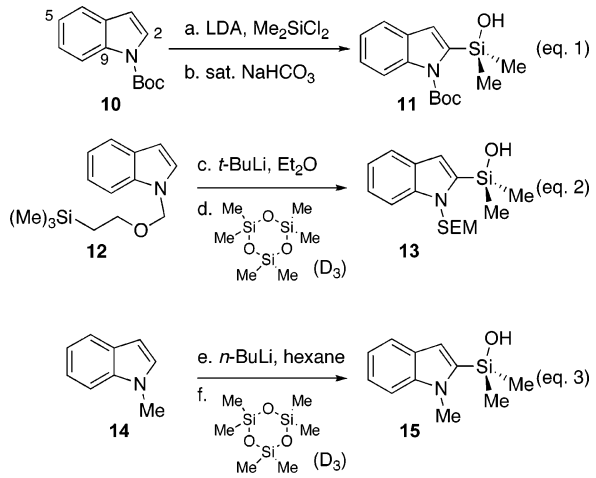
Finally, the electron-rich *N*-methyl derivative **15** was chosen for reactivity comparison studies to **11**, as well as 2-indolylstannanes.[24] In addition, **15** would obviously provide access to 2-substituted *N*-methylindole containing natural products and pharmaceutical agents.[7c]

The *N*-Boc-, *N*-SEM-, and *N*-methyl-protected dimethyl(2-indolyl)silanols 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 co-workers.[42] The procedure utilized noncryogenic 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 (D_3)[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.

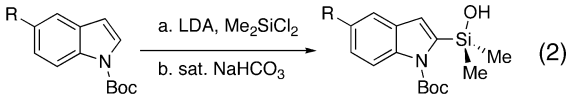
The *N*-methyldimethyl(2-indolyl)silanol (**15**) was easily prepared in a similar manner as the *N*-SEM derivative. In this case, metalation was achieved with *n*-butyllithium at 50 °C for 5 h, and the resulting lithio species was trapped with D_3 at 0 °C to afford **15** in 57% yield (Scheme 2, eq 3).

SCHEME 2[a]



[a] Conditions: (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*-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*-BuLi (1.05 equiv), Et_2O, reflux, 5 h; (f) D_3 (0.33 equiv) 0 °C to rt, Et_2O, 12 h, 57%.

1.2. Preparation of 5-Substituted Dimethyl(2-indolyl)-silanols. 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 (eq 2).[42]



R = OMe: **16**
R = CN: **17**
R = Me: **18**
R = Br: **19**

R = OMe: **20** (73%)
R = CN: **21** (74%)
R = Me: **22** (88%)
R = Br: **23** (76%)

Conditions: (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.

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) involving 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 Equlilibrative 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

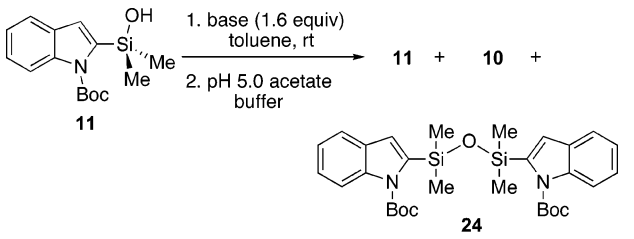
(37) Weedon, A. C.; Zhang, B. *Synthesis* **1992**, 95−100.
(38) Edwards, M. P.; Doherty, A. M.; Ley, S. V.; Organ, H. M. *Tetrahedron* **1986**, *42*, 3723−3729.
(39) Jiang, X.; Tiwari, A.; Thompson, M.; Chen, Z.; Cleary, T. P.; Lee, T. B. K. *Org. Proc. Res. Dev.* **2001**, *5*, 604−608.
(40) Zeng, Z.; Zimmerman, S. C. *Tetrahedron. Lett.* **1988**, *29*, 5123−5124.
(41) Whitten, J. P.; Matthews, D. P.; McCarthy, J. R. *J. Org. Chem.* **1986**, *51*, 1891−1894.
(42) Vazquez, E.; Davies, I. W.; Payack, J. F. *J. Org. Chem.* **2002**, *67*, 7551−7552.
(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-(trimethylsilylethoxy)methyl chloride (SEM-Cl)). In the current study, 1.1 equiv of SEM-Cl could be used without any reduction in yield.
(45) Butler, C. R.; Denmark, S. E. *Encyclopedia of Reagents for Organic Synthesis*; Wiley: New York, 2007; DOI 10.1002/047084289x.rm00784.

simple deprotonation to form an alkali metal silanolate.[35] The sodium *N*-Boc-dimethyl(2-indolyl)silanolate (Na^+**11**$^-$) and sodium *N*-methyldimethyl(2-indolyl)silanolate (Na^+**15**$^-$) could be prepared by equilibrative deprotonation with sodium *tert*-butoxide (NaO*t*-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 protiodesilylated product was observed, especially in the cross-coupling of **11** with aryl iodides.

To better understand the origin of the protiodesilylation, the following control experiment was conducted to determine whether protiodesilylation was occurring over time or immediately upon treatment with NaO*t*-Bu. A solution of **11** was added to a suspension of NaO*t*-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 protiodesilylation 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 protiodesilylation (57%) was observed after 1 h, and complete protiodesilylation was seen at 6 h (Table 1, entries 3 and 4).

Interestingly, when a stronger base was used, lithium hexamethyldisilazide (LiHMDS), protiodesilylation 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 and 6). These experiments suggested that, to achieve efficient formation of the silanolate, the deprotonation needed to be rapid, quantitative, and irreversible.

TABLE 1. Effect of Base on the Equlilibrative Deprotonation Protocol



			product yield,[a] %		
entry	base	time, h	**11**	**10**	**24**
1	NaO*t*-Bu	0.25	79	21	
2	NaO*t*-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

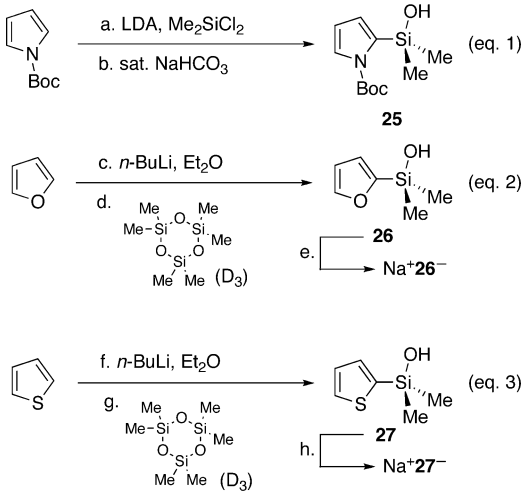
[a] The product ratio was determined by HPLC analysis by area %.

1.3.2. Preformation of Alkali Metal Silanolates. To independently generate the dimethyl (2-indolyl)silanolate Na^+**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, protiodesilylation was completely suppressed to provide Na^+**11**$^-$ cleanly by the preformation protocol. Unfortunately, generation the potassium silanolate K^+**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 Na^+**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, Na^+**11**$^-$ was a productive reagent for the cross-coupling reaction. Sodium *N*-SEM-dimethyl(2-indolyl)-silanolate (Na^+**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 noncryogenic lithiation procedure as described above for *N*-Boc-indole, Scheme 2. The preparation of the dimethyl(2-furyl)silanol **26** and dimethyl(2-thienyl)silanol **27** silanols (Scheme 3, eqs 2 and 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**−**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.

SCHEME 3[a]



[a] Conditions: (a) LDA (1.25 equiv), Me_2SiCl_2 (1.50 equiv), THF, 0 °C, 18 h; (b) sat. (aq) $NaHCO_3$, rt, 50%; (c) *n*-BuLi (1.05 equiv), Et_2O, −71 °C to rt, 4 h; (d) D_3 (0.33 equiv), −71 °C to rt, Et_2O, 16 h, 22%; (e) NaH (1.0 equiv), toluene, 99%; (f) *n*-BuLi (1.05 equiv), Et_2O, −70 °C to rt, 2 h; (g) D_3 (0.33 equiv), −71 °C to rt, Et_2O, 16 h, 72%. (h) NaH (1.0 equiv), toluene, 99%.

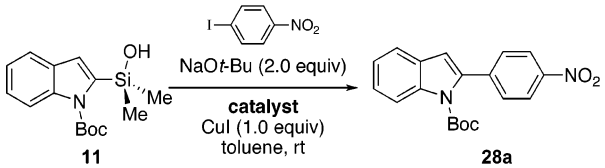
(46) Control experiments have established that protiodesilylation does not occur upon quenching with the acetate buffer.

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 ([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 protiodesilylation. 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 [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 24 h. 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 (LiO*t*-Bu) did not effect any cross-coupling of **11**. The counterion of the *tert*-butoxide bases had a pronounced effect on the cross-coupling reaction. Improved conversion (46%) was observed using NaO*t*-Bu, in the cross-coupling of **11** with 4-iodonitrobenzene; however, potassium *tert*-butoxide (KO*t*-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 ($PdCl_2$, $PdCl_2(PPh_3)_2$, and $Pd(OAc)_2$) provided only trace amounts of product (Table 2, entries 1−3), others such as $PdBr_2$ and $(CH_3CN)_2PdCl_2$ 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 $Pd_2(dba)_3{\cdot}CHCl_3$ was superior to the palladium(II) sources surveyed. With 5 mol % of $Pd_2(dba)_3{\cdot}CHCl_3$ the cross-coupling reaction of **11** gave complete (99%) conversion to the product (Table 2, entry 7). Interestingly reaction times were much shorter using $Pd_2(dba)_3{\cdot}CHCl_3$, in comparison to $Pd_2(dba)_3$; however, the simple addition of 0.05 equiv of $CHCl_3$ to the reaction mixture containing $Pd_2(dba)_3$ 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).

TABLE 2. Catalyst Optimization for the Cross-Coupling of 11



11 28a

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

[a] Conditions: 1.2 equiv of **11**, 2.0 equiv of NaO*t*-Bu, 1.0 equiv of CuI, 0.1 equiv of Pd, 0.6 M in **11** in toluene at room temperature. [b] Determined by HPLC analysis using biphenyl as an internal standard. [c] When the concentration was increased to 1.2 M in **11**, the reaction was complete in 6 h.

The remaining experiments evaluated the impact of varying the loading of CuI. A control experiment using 1.2 equiv of **11**, 1.0 equiv of 4-iodonitrobenzene, 2.0 equiv of NaO*t*-Bu, and 5 mol % of $Pd_2(dba)_3{\cdot}CHCl_3$ in the absence of CuI afforded 48% of **28a** after 6 h. The beneficial effect of increasing the amount of CuI was revealed as 1.0 equiv nearly doubled the yield of **28a** to 92% after 6 h. 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 performed in which the amount of CuI was varied (0.0−2.0 equiv), with 1.0 equiv of **11** and 2.0 equiv of NaO*t*-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

(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.-i.; Sonoda, M.; Hosomi, A. *J. Am. Chem. Soc.* **1998**, *120*, 11196−11197. (c) Taguchi, H.; Ghoroku, K.; Tadaki, M.; Tsubouchi, A.; Takeda, T. *Org. Lett.* **2001**, *3*, 3811−3814. (d) Taguchi, H.; Miyashita, H.; Tsubouchi, A.; Takeda, T. *Chem. Commun.* **2002**, 2218−2219. (e) Hanamoto, T.; Kobayashi, T.; Kondo, M. *Synlett* **2001**, 281−283. (f) Taguchi, H.; Ghoroku, K.; Tadaki, M.; Tsubouchi, A.; Takeda, T. *J. Org. Chem.* **2002**, *67*, 8450−8456. (g) Denmark, S. E.; Kobayashi, T. *J. Org. Chem.* **2003**, *68*, 5153−5159. (h) Denmark, S. E.; Tymonko, S. A. *J. Org. Chem.* **2003**, *68*, 9151−9154. Use of copper cocatalyst with stannanes: (i) Wang, Y.; Burton, D. J. *Org. Lett.* **2006**, *8*, 1109−1111. (j) Casado, A. L.; Espinet, P. *Organometallics* **2003**, *22*, 1305−1309. (k) Han, X.; Stolz, B. M.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 7600−7605. (l) Farina, V. *Pure Appl. Chem.* **1996**, *68*, 73−78. (m) Farina, V.; Kapadia, S.; Krishnan, B.; Wang, C.; Liebeskind, L. S. *J. Org. Chem.* **1994**, *59*, 5905−5911. Use of copper cocatalyst with boranes: (n) Savarin, C.; Liebeskind, L. S. *Org. Lett.* **2001**, *3*, 2149−2152. (o) Boland, G. M.; Donnelly, D. M. X; Finet, J.-P.; Rea, M. D. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2591−2597.

(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.

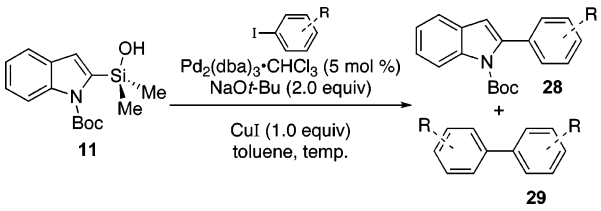
(50) Data for these experiments is provided in the Supporting Information. The assignment of the disiloxane component is tentative.

the remainder of mass was attributed to minor amounts of protiodesilylation (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-arylindole 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 and 8). Similarly, electronically neutral substrates (1-iodonaphthalene and iodobenzene) provided good yields (75 and 70% yield, respectively) albeit with a slightly greater amount of halide homocoupling byproduct (Table 3, entries 5 and 9).

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

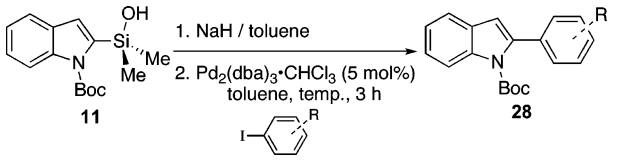


entry[a]	R	*T*, °C	time, h	product	yield,[b] % 28[b]	yield,[b] % 29[c]
1	4-NO_2	rt	6	**28a**	84	6
2	4-CF_3	rt	22	**28b**	82	3
3	4-CO_2t-Bu	rt	24	**28c**	84	trace
4	3-NO_2	40	12	**28d**	72	14
5	H	40	12	**28e**	70	12
6	2-Me	50	24	**28f**	73	14
7	4-OMe	50	24	**28g**	72	14
8	2-OMe	50	24	**28h**	75	15
9	*d*	60	24	**28i**	75	13

[a] Conditions: 1.2 equiv of **11**, 2.0 equiv of NaO*t*-Bu, 1.0 equiv of CuI, 0.1 equiv of Pd, 0.6 M in **11** in toluene. [b] Yield of isolated, analytically pure product. [c] Determined by ^{1}H NMR analysis of crude reaction mixtures. [d] 1-Iodonaphthalene.

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 Na^+**11**$^-$ is prepared by the preformation protocol. Thus, silanol **11** was deprotonated with NaH (1.0 equiv) in toluene, and when the effervescence had ceased (10 min), it was added to a mixture of $Pd_2(dba)_3$•$CHCl_3$ 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 Na^+**11**$^-$ enabled successful cross-coupling of substrates (ethyl 4-iodobenzoate and 4-iodobenzonitrile) that were problematic in the copper mediated cross-coupling reaction[51] in excellent yield (82 and 81%, respectively, Table 4, entries 2 and 3).

TABLE 4. Cross-Coupling of in Situ Generated Na^+11**$^-$ with Aryl Iodides**



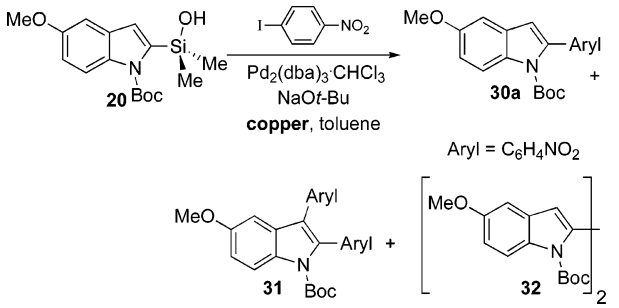
entry[a]	R	*T*, °C	product	yield,[b] %
1	4-OMe	80	**28g**	68
2	4-CO_2Et	rt	**28j**	82
3	4-CN	rt	**28k**	81

[a] Conditions: reaction concentration 0.6 M; **11** (1.2 equiv), NaH (1.2 equiv) in toluene, $Pd_2(dba)_3$•$CHCl_3$ (0.05 equiv). [b] Yield of chromatographed, recrystallized products.

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., $Pd_2(dba)_3$•$CHCl_3$ as the catalyst and NaO*t*-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

TABLE 5. Effect of Copper on the Cross-Coupling of 20



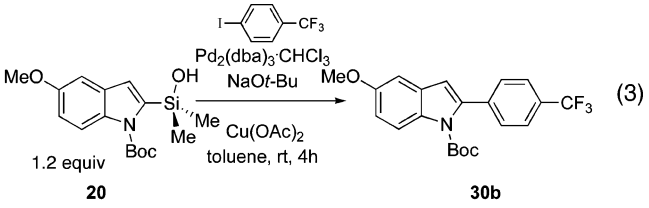
entry[a]	copper source	copper, equiv	time, h	yield,[b] % 30a	yield,[b] % 31a	yield,[b] % 32
1			3	15	5	
2	$Cu(OAc)_2$	1.0	0.5	59	2	2
3	$Cu(OAc)_2$	1.0	3			22
4	$Cu(OAc)_2$	0.25	3	87	3	
5[c]	$Cu(OAc)_2$	0.25	3	72	3	

[a] Conditions: 1.2 equiv of **20**, 2.0 equiv of NaO*t*-Bu, 0.1 equiv of Pd, 0.6 M in **20** in toluene at room temperature. [b] Yields based on ^{1}H NMR integration using hexamethylbenzene as an internal standard. [c] The reaction was run on a 1 mmol scale, yield of isolated analytically pure material.

(51) When ethyl 4-iodobenzoate was the substrate in the copper-mediated reaction a significant amount of transesterification was observed. This suggests that Na^+**11**$^-$ may be less nucleophilic than NaO*t*-Bu.

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 $Pd_2(dba)_3$•$CHCl_3$ 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 $Cu(OAc)_2$ and not the palladium catalyst. Fortunately, the formation of **32** could be suppressed by decreasing the amount of $Cu(OAc)_2$ 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).

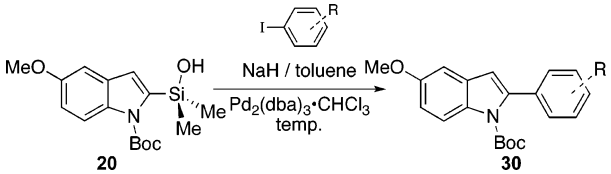
To determine if the formation of the 2,3-disubstituted indole byproduct was unique to the cross-coupling with 4-iodonitrobenzene, a different electron-deficient aryl iodide, 4-iodobenzotriflouride, was tested. After 4 h, an 82% yield of the desired 2-arylated indole **30b** was isolated, with no detectable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



Conditions: $Pd_2(dba)_2$•$CHCl_3$ (5 mol%); NaO*t*-Bu (2.0 equiv), $Cu(OAc)_2$ (0.25 equiv) toluene (0.3 M), rt, 4 h, 82%.

From our experience with preformation and coupling of the parent silanolate Na^+**11**$^-$, we choose to evaluate the copper-free cross-coupling with preformation of Na^+**20**$^-$, with a series of electron-deficient and electron-rich aryl iodides (Table 6). Silanolate Na^+**20**$^-$ was prepared with 1.0 equiv of NaH; however, ~20% protiodesilylation 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 **30g** (Table 6, entry 5).[53]

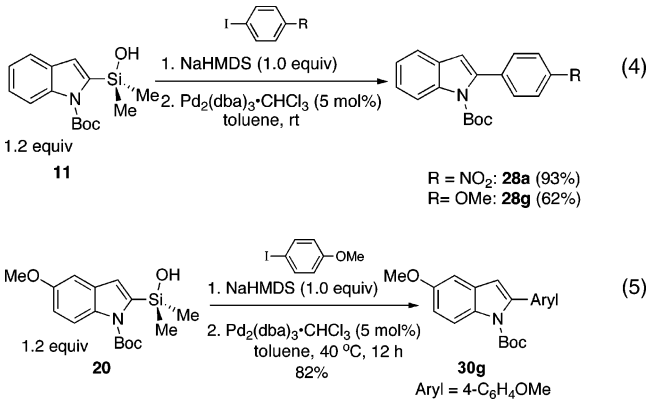
TABLE 6. In Situ Formation of Na^+20**$^-$ and Cross-Coupling with Aryl Iodides**



entry[b]	R^1	*T*, °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

[a] Yield of isolated analytically pure material. [b] Reaction concentration 0.6 M in **20**; **20** (1.2 equiv) and NaH (1.2 equiv) in toluene, $Pd_2(dba)_3$•$CHCl_3$ (0.05 equiv).

Clearly, protiodesilylation 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 protiodesilylation for the preformation of Na^+**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 Na^+**11**$^-$. The cross-coupled product was isolated in 93% yield after 12 h at room temperature (eq 4). Similarly, the cross-coupling of 4-iodoanisole with **11** afforded a 62% yield of **28g** 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 (eq 5).

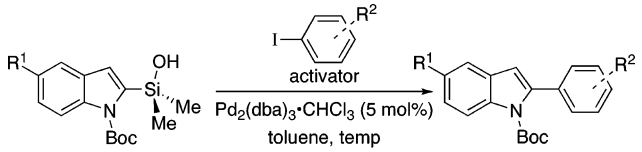


2.2.2. Scope in Aryl Iodide for Cross-Coupling with *N*-Boc-C(5)-substituted Dimethyl(2-indolyl)silanols. To test the generality in both components, a series of 2-indolylsilanols and aryl iodides were surveyed. 2-Indolylsilanols bearing methyl, bromo, and cyano substituents at the 5-position were evaluated together with a variety of electron-rich and electron-deficient aromatic iodides (Table 7). The sodium silanolates of *N*-Boc-dimethyl[(5-cyano)-2-indolyl]silanol (**21**) and *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 $Pd_2(dba)_3$•$CHCl_3$ in toluene, Na^+**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

(52) A significant rate enhancement was observed when copper(II) salts were used in the cross-coupling reaction of 3,5-disubstituted 4-silylisoxazoles with aromatic iodides; see: Denmark, S. E.; Kallemeyn, J. M. *J. Org. Chem.* **2005**, *70*, 2839−2842.

(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 Na^+**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 **30g**.

TABLE 7. Cross-Coupling of C(5)-Substituted 2-Dimethylindolylsilanols with Aromatic Iodides



R1 = CN: **21**
R1 = Me: **22**
R1 = Br: **23**

entry[a]	R1	activator	R2	time, h	T, °C	product	yield,[b] %
1	CN	NaHMDS	4-OMe	24	rt	**33g**	70
2	Me	NaHMDS	4-CO_2Et	3	rt	**34j**	82
3	Me	NaHMDS	3-CH_2OTBS	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_2Et	4	rt	**35j**	85
7[c]	Br		3-CH_2OTBS	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, $Pd_2(dba)_3$•$CHCl_3$ (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.

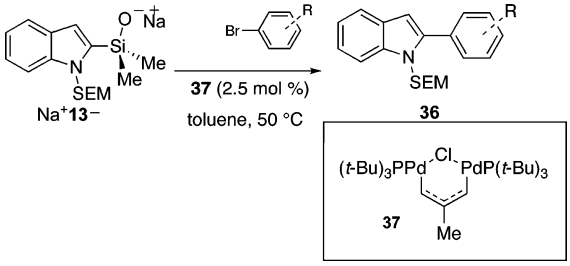
good yields (65−76%) of the corresponding products (Table 7, entries 3−5). Finally, the sodium silanolate of *N*-Boc-dimethyl-[(5-bromo)-2-indolyl]silanol (**23**) was isolated and used in the cross-coupling reactions.[54] Combining the salt Na^+**23**$^-$ in toluene with $Pd_2(dba)_3$•$CHCl_3$ (5 mol %) 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 C_6H_5−Br, 81 kcal/mol) or C−Cl bonds (BDE for C_6H_5−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 Na^+**11**$^-$. Unfortunately, a survey of phosphine ligands together with $[allylPdCl]_2$ (including di(*tert*-butyl)-biphenylphosphine, bisdiphenylphosphinobutane, and tri(*tert*-butyl)phosphine) failed to effect the cross-coupling of Na^+**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 *N*-Boc. 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 that 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.

TABLE 8. Cross-Coupling of Na^+13$^-$ with Substituted Aryl Bromides



entry[a]	R	product	yield,[b] %
1	4-CO_2*t*-Bu	**36c**	93
2	2-Me	**36f**	89
3	3-CH_2OTBS	**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.

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

(54) This silanol is a wax, and thus, preparation of the sodium silanolate allowed for more facile manipulation.

(55) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176−4211.

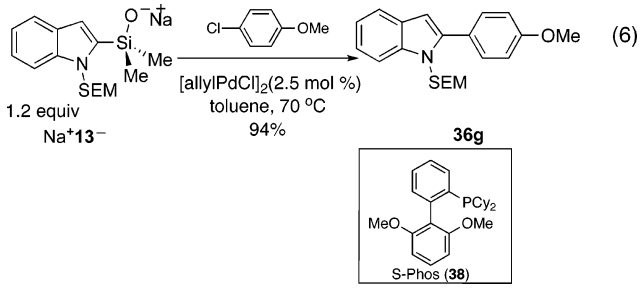
(56) (a) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722−9723. (b) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **1999**, *38*, 2411−2413. (c) Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550−9561. (d) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020−4028. (e) Navarro, O.; Kelly, R. A., III; Nolan, S. P. *J. Am. Chem. Soc.* **2003**, *125*, 16194−16195. For a recent review on the development of ligands for the cross-coupling of aryl chlorides, see: (f) Bedford, R. B.; Cazin, C. S. J.; Holder, D. *Coord. Chem. Rev.* **2004**, *248*, 2283−2321.

(57) Fu and co-workers 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, G. C. *Angew. Chem., Int. Ed.* **2006**, *45*, 1282−1284.

of the desired cross-coupled product (Table 8, entries 2 and 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]

In 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 ^{1}H 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 (eq 6).



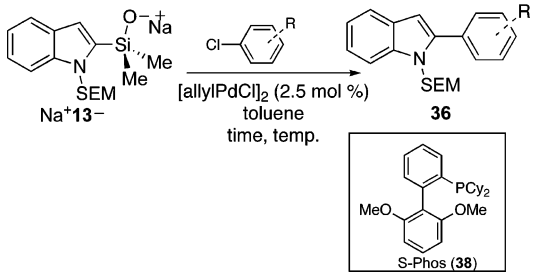
(6)

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*-Methyldimethyl(2-indolyl)silanols. To complete the study on the effect of the nitrogen substituent on reactivity, the *N*-Me derivative **15** was examined.

(58) Werner, H.; Kühn, A. *J. Organomet. Chem.* **1979**, *179*, 439−445.
(59) Denmark, S. E.; Tymonko, S. A.; Ober, M. H. Submitted.
(60) Denmark, S. E.; Kallemeyn, J. M. *J. Am. Chem. Soc.* **2006**, *128*, 15958−15959.
(61) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685−4696.

TABLE 9. Cross-Coupling of Na^+13**$^-$ with Substituted Aryl Chlorides**



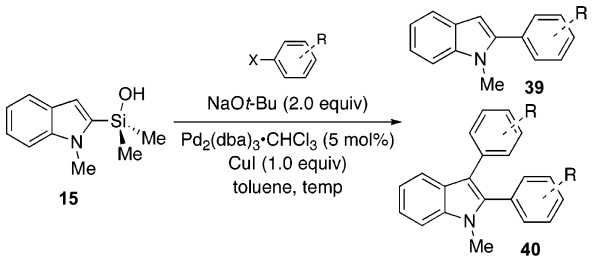
entry[a]	R	*T*, °C	time, h	product	yield,[b] %
1	4-CN	70	1	**36k**	92
2	4-COPh	70	1	**36n**	93
3	4-CF_3	70	1	**36b**	92
4	4-OMe	70	3	**36g**	94
5	2,6-Me_2	70	3	**36o**	88
6	2-OMe	70	3	**36h**	94
7	3-pyridyl	70	2	**36p**	84
8	2-pyridyl	90	3	**36q**	73
9	*c*	70	3	**36r**	86

[a] Conditions: Na^+**13**$^-$ (1.2 equiv), **37** (0.025 equiv) 0.6 M in Na^+**13**$^-$ in toluene. [b] Yield of isolated, analytically pure product. [c] 8-(1,3,7-Me_3)xanthine.

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 NaO*t*-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 and 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-disubsituted 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.

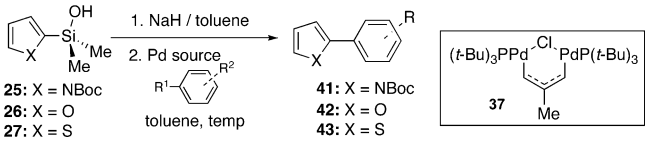
TABLE 10. Cross-Coupling of 15 with Substituted Aryl Halides



						yield, %	
entry[a]	X	R	*T*, °C	time, h	product	**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 NaO*t*-Bu, 1.0 equiv of CuI, 0.1 equiv of Pd, 0.6 M in **15** in toluene. [b] Yield of analytically pure products. [c] Determined by ^{1}H NMR analysis of crude reaction mixtures. [d] Addition of 0.2 equiv of dppb was required.

TABLE 11. Cross-Coupling Heteroaryl Silanolates with Substituted Aryl Iodides and Bromides



25: X = NBoc
26: X = O
27: X = S

41: X = NBoc
42: X = O
43: X = S

entry	X	R^1	R^2	catalyst	*T*, °C	time, h	product	yield,[a] %
1	*N*-Boc	I	4-CO_2Et	$Pd_2(dba)_3$·$CHCl_3$	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	**41g**	72
4	O	I	4-CO_2Et	$Pd_2(dba)_3$·$CHCl_3$	rt	1	**42j**	82
5[c]	O	I	4-CO_2Et	$Pd_2(dba)_3$·$CHCl_3$	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_2Et	**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_2Et	$Pd_2(dba)_3$·$CHCl_3$	rt	3	**43j**	78
15[f]	S	I	4-CO_2Et	$Pd_2(dba)_3$·$CHCl_3$	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_2Et	**37**	50	3	**43j**	67
20	S	Br	4-CN	**37**	50	3	**43k**	78
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

[a] Yield of chromatographed products purified by recrystallization or sublimation. [b] Required the use of 0.2 equiv of (2-furyl)$_3$As for complete conversion. [c] 1.2 equiv of Na^+**26**$^-$ was used. [d] Reaction stalled at 78% conversion. [e] 1-Bromonaphthalene. [f] 1.2 equiv of Na^+**27**$^-$ was used.

A control experiment in which the nitro-substituted product **39a** was resubjected 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 and 7).

2.4. Cross-Coupling of 2-Furyl-, 2-Thienyl-, and *N*-Boc-Dimethyl(2-pyrroyl)silanolates. The application of the 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-indolylsilanolates. 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 $Pd_2(dba)_3$·$CHCl_3$ 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)$_3$As 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).

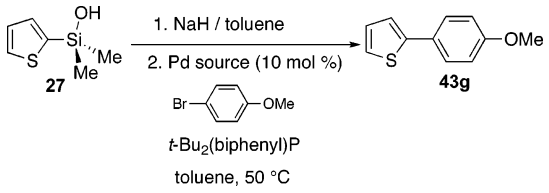
At this point, it was of interest to extend these heterocyclic silanolates for the cross-coupling of aryl bromides. Thus, a short survey of palladium sources in conjunction with 1,1-di(*tert*-butyl)phosphinobiphenyl at 50 °C, which has been successful for the cross-coupling of other silanols with aryl bromides,[63] was undertaken. Neither $PdCl_2$ nor $PdBr_2$ 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 was less dependent on the nature of the substituent. Whereas those reactions of bromides bearing either electron-withdrawing groups or *o*-methyl groups reached completion in 3 h, electron-rich and naphthyl bromides required a slightly longer reaction

(62) Alternatively, a control experiment that subjected *N*-methylindole to the reaction conditions failed to provide any arylated products.

(63) Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550−9561.

TABLE 12. Catalyst and Ligand Optimization for the Cross-Coupling of 27 with 4-Bromoanisole[a]



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[c]
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 ^{1}H NMR analysis. [d] $(2\text{-}MeC_3H_4)(Cl)Pd_2(P(t\text{-}Bu)_3)_2$.

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.

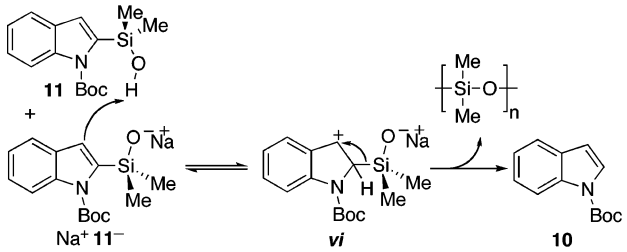
Discussion

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 NaO*t*-Bu as the base, approximately 20% protiodesilylation 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 (Na^+**20**$^-$). In contrast, when NaHMDS was employed as the base, Na^+**20**$^-$ was formed cleanly. These observations suggest that once the sodium silanolate was formed, it was stable in solution. Thus, the protiodesilylation process occurred upon initial mixing of the silanol and the base because the amount of protiodesilylated product did not increase with time (e.g., for *N*-Boc-2-indolylsilanol and NaO*t*-Bu 21% of **10** at 15 min and 18% of **10** at 1 h). To reconcile this behavior, we propose that protiodesilylation 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 protiodesilylated product **10** and polysiloxanes.

During the optimization studies for the formation of Na^+**11**$^-$, the effect of the counter cation was investigated. When silanol

SCHEME 4



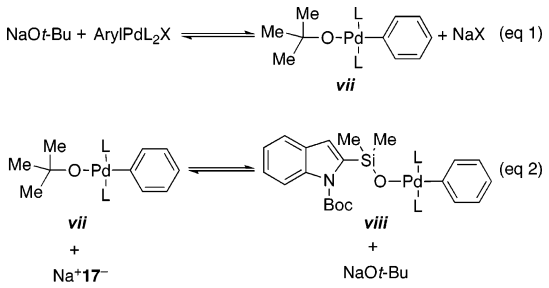
11 was mixed with LiHMDS, Li^+**11**$^-$ was prepared cleanly. Quenching Li^+**11**$^-$ with acetate buffer revealed protiodesilylated product **10** was not formed at early time points (1 h) and did not appear over a 6 h time course. This observation shows that the lithium silanolate was also stable in solution and that LiHMDS effected a clean kinetic deprotonation devoid of side processes. Preparing K^+**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 $KOSiMe_3$ a significant amount of desilylation was observed. In this case, the conjugate acid, $HOSiMe_3$, 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 silanolates of **11** and the 5-substituted silanolates Na^+**20**$^-$, Na^+**21**$^-$, and Na^+**22**$^-$ were easily prepared by the preformation protocol using a stoichiometric amount of NaH or NaHMDS, respectively. In addition, it was found that Na^+**11**$^-$, Na^+**13**$^-$, and 5-bromo substituted Na^+**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.

(64) Lickiss, P. D. *Adv. Inorg. Chem.* **1995**, *42*, 147−262.

The use of an excess of the activator can be problematic in the cross-coupling reaction for several reasons. Surplus activator (i.e., KO*t*-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).

SCHEME 5



An excess of the activator can also limit functional group compatibility. For example, when NaO*t*-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)silanolates provided valuable insight into the use of metal silanolates 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 counterion. Whereas the lithium silanolate from LiO*t*-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 NaO*t*-Bu was used, the more nucleophilic and stable sodium silanolate gave modest yields (46%). The use of KO*t*-Bu proved less successful and can be understood by the observed instability of the potassium silanolate. While the effect of the counterion 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 Na^+**11**$^-$. The superiority of NaHMDS compared to NaO*t*-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 $Pd_2dba_3{\cdot}CHCl_3$. The role of the chloroform in the reaction still remains unclear. Solubility studies have concluded that $Pd_2dba_3{\cdot}CHCl_3$ is less soluble in toluene at room temperature than Pd_2dba_3 (1.5×10^{-3} M vs 3.0×10^{-3}, respectively). 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 was 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 $Cu(OAc)_2$, 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 stannanes[47] 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 protiodesilylation, 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 protiodesilylated *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 NaO*t*-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-

(65) Bagdanoff, J. T.; Stoltz, B. M. *Angew. Chem.* **2004**, *116*, 357−361.

(66) Dichlorocarbene formation occurs under similar conditions; see: Han, J. L.; Ong, C. W. *Tetrahedron* **2005**, *61*, 1501−1507.

(67) Farina, V. *Adv. Synth. Catal.* **2004**, *346*, 1553−1582 and the references within.

(68) Lam, P. Y. S.; Deudon, S.; Averill, K. M.; Li, R.; He, M. Y.; DeShong, P.; Clark, C. G. *J. Am. Chem. Soc.* **2000**, *122*, 7600−7601.

rich indoles such as *N*-SEM and *N*-methyldimethyl(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 differentiate 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 the following: formation of a stable sodium silanolate in the absence of a conjugate acid, copper salts that are 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 preformed 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 NaO*t*-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

(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. (b) Forgione, P.; Brochu, M.-C.; St-Onge, M.; Thesen, K. H.; Bailey, M. D.; Bilodeau, F. *J. Am. Chem. Soc.* **2006**, *128*, 11350−11351.

ice/2-propanol bath for 15 min, and 12.96 mL (1.55 M in hexane, 20.1 mmol, 1.25 equiv) of an *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 satd aq $NaHCO_3$ (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 Na_2SO_4 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 semisolid. Data for **11**: bp 125 °C (7 × 10^{-5} mmHg, ABT); ^{1}H NMR (500 MHz, $CDCl_3$) 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 $C_{15}H_{21}NO_3Si$: 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 (Na^+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 dropwise 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 pipet, 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 Na^+**11**$^-$ as a white powder that was stored in a drybox. Data for Na^+**11**$^-$: ^{1}H 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 $C_{15}H_{20}NNaO_3Si$ (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 NaO*t*-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 $Pd_2(dba)_3$·$CHCl_3$ were added. The flask was sealed with a rubber septum and evacuated (0.1 mmHg) 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 mmHg) 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 °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 filtered through #4 Whatman filter paper. The solvent was removed under reduced pressure by 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 (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**: mp 129−132 °C (hexane); ^{1}H 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 $C_{19}H_{18}N_2O_4$: 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*-Boc-dimethyl-(2-indolyl)silanol (**11**) (349 mg, 1.2 mol, 1.2 equiv) in toluene (0.9 mL) was added dropwise using a Pasture pipet to the NaH suspension. Once effervescence ceased, ethyl 4-iodobenzoate (168 μL, 1.0 mmol, 1.0) was added along with $Pd_2(dba)_3$·$CHCl_3$ (52 mg, 0.05 mmol, 0.05 equiv). The flask was sealed with a rubber septum and removed from the drybox. After being stirred at rt for 3 h, the reaction mixture was transferred to a 125 mL separatory funnel and diluted with H_2O (25 mL) and EtOAc (20 mL). The organic layer was separated, and the aqueous layer was washed with EtOAc (5 × 25 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 °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 × 100 mm) and was eluted with toluene (20 × 10 mL fractions). Recrystallization of the material from the pure fractions from boiling (hexane/toluene, 20/1) afforded **28j** (298 mg, 82%) as white needles. The physical and spectroscopic data matched those from the literature.[24] Data for **28j**: mp 104−105 °C (hexane/toluene (20/1)); ^{1}H NMR (500 MHz, $CHCl_3$) 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); ^{13}C NMR (125 MHz, $CHCl_3$) 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 pipet to the NaH suspension. Once effervescence ceased, 2-bromotoluene (120 μL, 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 being stirred at 50 °C for 3 h, the reaction mixture was transferred to a 125 mL separatory funnel and diluted with H_2O (25 mL) and EtOAc (20 mL). The organic layer was separated, and the aqueous layer was washed with EtOAc (5 × 25 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated using rotary evaporation (23 °C, 20 mmHg). The crude product was purified by column chromatography (SiO_2 (20 × 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 mmHg, ABT); ^{1}H NMR (500 MHz, $CHCl_3$) 7.70 (d, J = 7.8, 1 H), 7.51 (d, J = 1.7, 1 H), 7.23 (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); ^{13}C NMR (125 MHz, $CHCl_3$) 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]-1*H*-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) via syringe dropwise. The solution was warmed to rt and stirred for 1 h, whereupon it was cooled to −70 °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 °C and H_2O (35 mL) was added. The aqueous layer was separated and extracted with EtOAc (3 × 30 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 °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 × 100 mm) by first eluting with hexane/EtOAc, 9/1 (300 mL) followed by hexane/EtOAc, 4/1 (30 × 50 mL fractions) to afford 2.76 g (62%) of **13** as a yellow oil. Data for **13**: ^{1}H 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 $C_{16}H_{27}NO_2Si_2$: 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 (Na^+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). 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 Na^+**13**$^-$: ^{1}H 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 (Na^+13**$^-$) with 4-Chloroanisole (36g) (Table 9, Entry 4).** To an oven-dried, 5-mL, conical-flask equipped with a magnetic stir bar were added Na^+**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 were added toluene (1.0 mL) and 4-chloroanisole (123 μL, 1.0 mmol, 1.0 equiv). After being stirred in a 70 °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 × 100 mm) and eluted with hexane/EtOAc, 9/1 (30 × 10 mL fractions). The combined fractions were further purified by C-18 reversed-phase column chromatography (30 g, 20 × 100 mm) and elution with (MeOH/H_2O, 9/1) (30 × 10 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**: ^{1}H 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 $C_{21}H_{27}NO_2Si$: C, 71.34; H, 7.70; N, 3.96. Found: C, 71.00; H, 7.68; N, 4.15.

Acknowledgment. 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.

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

JO7023784

(71) Reuter, K. H.; Scott, W. J. *J. Org. Chem*. **1993**, *58*, 4722−4726.