Tetrahedron 65 (2009) 3120–3129

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Preparation of 2,3-disubstituted indoles by sequential Larock heteroannulation and silicon-based cross-coupling reactions

Scott E. Denmark *, John D. Baird

Roger Adams Laboratory, Department of Chemistry, University of Illinois, Urbana, IL 61801, United States

ARTICLE INFO

Article history:
Received 26 August 2008
Received in revised form 11 October 2008
Accepted 16 October 2008
Available online 22 October 2008

Keywords:
Cross-coupling
Indoles
Silanols
Palladium catalysis
Alkynes

ABSTRACT

A simple and convergent synthesis of 2,3-disubstituted indoles has been developed using a sequential Larock indole synthesis and silicon-based, cross-coupling reaction. Substituted 2-iodoanilines reacted with an alkynyldimethylsilyl *tert*-butyl ether to afford indole-2-silanols under the Larock heteroannulation conditions after hydrolysis. The corresponding sodium 2-indolylsilanolate salts successfully engaged in cross-coupling with aryl bromides and chlorides to afford multi-substituted indoles. The development of an alkynyldimethylsilyl *tert*-butyl ether as a masked silanol equivalent enabled a smooth heteroannulation process and the identification of a suitable catalyst/ligand combination provided for a facile cross-coupling reaction.

© 2008 Elsevier Ltd. All rights reserved.

1. Introduction

Substituted indoles are among the most common and important heterocycles in nature.[1] Additionally, the indole motif is represented within a range of pharmaceutical agents and materials (Chart 1). In nature, substituted indoles serve various purposes that range from cell signaling agents and biological function (seratonin **1**), to the structural building blocks of proteins (tryptophan **2**). Many indole-containing natural products, including such well-known indole plant alkaloids such as strychnine **3** and yohimbine **4** have been identified for their biological uses. Of the many types of substituted indoles, one particular sub-class of interest is those indoles bearing substitution at the C(2) and C(3) positions, and several promising therapeutic agents belong to this class. Gonadotropin releasing hormone antagonist **5** was identified for the treatment of developmental disorders.[2] Compound **6** is a glycine receptor antagonist that was identified for the treatment of stroke,[3] and fluvastatin **7** is a drug for the treatment of primary hypercholesterolemia.[4]

Given the importance of substituted indoles, it is not surprising that many methods exist for their formation.[5] Some classic methods[6] include the Fischer,[7] Leimgruber-Batcho,[8] Castro,[9] Nenitzescu,[10] indole syntheses. Among these, the venerable Fischer indole synthesis, discovered in 1883, is certainly the most well-

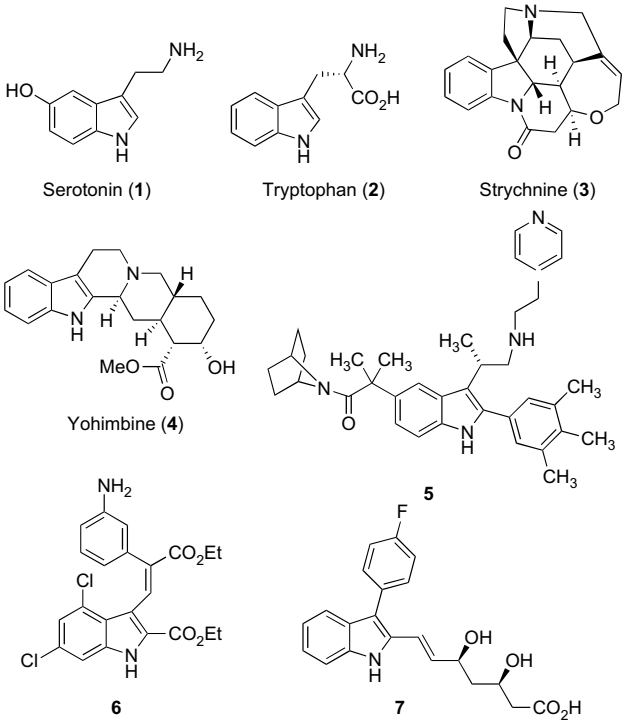


Chart 1.

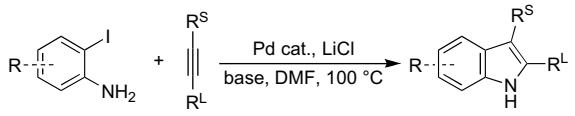
* Corresponding author. Tel.: +1 217 333 0066; fax: +1 217 333 3984.
E-mail address: sdenmark@illinois.edu (S.E. Denmark).

0040-4020/$ – see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2008.10.043

known and most commonly employed. However two major drawbacks usually identified with the Fischer process are: (1) unsymmetrical ketones give a mixture of isomeric products, depending upon the structure of the hydrazine and (2) harsh reaction conditions are required, typically refluxing in concentrated acid.[11] Because of the milder reaction conditions and defined placement of substituents, newer methods have recently achieved prominence such as the reductive cyclization reactions reported by Söderberg,[12] Cadogan[13] and Sundberg.[14]

In addition, more modern approaches to the synthesis of disubstituted indoles have emerged that take advantage of the current advances in transition metal chemistry.[15] Some newer methods to construct 2,3-disubstituted indoles include the radical cyclization of 2-alkenylisocyanides,[16] reductive cyclization of acylamido carbonyl compounds,[17] cyclization of *N*-(2-halophenyl)allenamides,[18] palladium-catalyzed cyclization of 2-alkynyltrifluoroanilines in the presence of an alkenyl- or aryl halide,[19] and palladium-catalyzed cyclization of 2-iodoanilines with disubstituted alkynes. Among these, the Larock indole synthesis has emerged as a versatile and powerful method for the formation of substituted indoles.[20]

In 1991, Larock and co-workers reported the synthesis of 2,3-disubstituted indoles by the Pd-catalyzed annulation of 2-iodoanilines and disubstituted alkynes (Scheme 1).[21] In contrast to other indole syntheses such as those from Fukuyama, Cacchi, or Furstner, the Larock procedure does not require a substituent or a protecting group on the aniline nitrogen. The reaction typically tolerates a range of functional groups on either partner and the heteroannulation is highly site selective. In general, the Larock heteroannulation favors the product in which the bulkier alkyne substituent resides at the C(2) position of the indole.[22] One example has appeared where reversed regioselectivity was observed, but the origin of this process remains unknown.[23] Thus, a limitation to the Larock process arises with alkynes that bear terminal substituents with similar steric demands. A recent illustration of this limitation to the Larock indole synthesis was reported where poor selectivities were observed when alkynes bearing cycloalkyl and aryl groups were employed.[24] Nevertheless, the reaction has been widely used in industrial (on a multi-kilogram scale) and academic settings,[25] and the transformation has achieved named reaction status.[26]



Scheme 1.

Larock modified the annulation process to access 3-substituted indoles by employing silyl-substituted alkynes. In this case, the bulky silyl group dominates the regioselectivity of the annulation and thus serves as a phantom directing group in the heteroannulation step. Silylated alkynes provide 2-silyl-3-substituted indoles with excellent regioselectivity. Subsequent desilylation affords 3-substituted indoles in good yield.

Although Larock and co-workers demonstrated the usefulness of silylated alkynes in this reaction, subsequent transformations of the resulting 2-silyl indoles have been limited to desilylation, bromination, or simple Heck-type cross-coupling with alkenes.[22] The ability to exploit the silyl group both for site selectivity in the annulation as well as a functional handle for further synthetic elaboration would add significant value to this reaction.

We have recently reported the palladium-catalyzed, cross-coupling of sodium 2-indolyldimethylsilanolates with aryl halides[27] as a promising alternative to the classical Stille,[28] Negishi,[29] and Suzuki[30] cross-coupling reactions. Silicon-based cross-coupling[31] methods offer several advantages over more conventional methods in view of the low toxicity, ease of preparation and handling, and stability of the silicon reagents.[32]

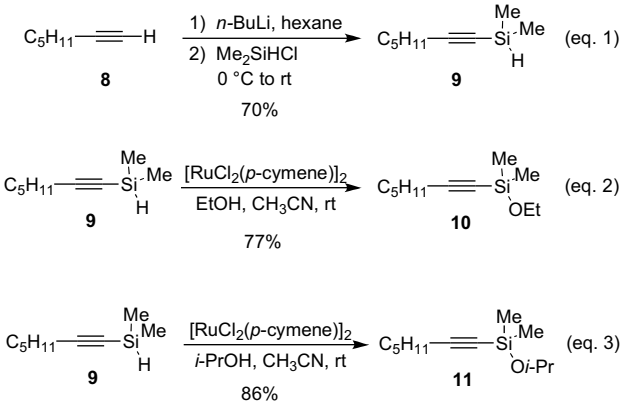
Replacement of the simple trimethylsilyl group employed by Larock with a masked silanol equivalent, such as a silyl ether, would serve two purposes by: (1) directing the heteroannulation and, after unmasking the silanol, (2) allowing for a silicon-based cross-coupling reaction. Furthermore, this strategy could take advantage of the commercial availability of numerous substituted anilines and terminal alkynes, as well as the ease of installation and manipulation of silicon-containing compounds.

The successful development of a sequential Larock heteroannulation and cross-coupling reaction involved several new challenges. First, the development of an alkynyl silyl ether that is stable under the heteroannulation conditions, but easily cleaved without protodesilylation posed a difficult challenge. This challenge is particularly important in light of studies that demonstrated that silyl ethers can be cleaved under basic conditions[33] and premature release of the silanol could lead to undesired side products. Furthermore, the cross-coupling of (2-indolyl)silanols bearing a substituent at the C(3) position has not been studied. The successful cross-coupling of a 3-substituted-(2-indolyl)silanol may prove challenging with some substrates because of the increased steric congestion near the silicon moiety. Moreover, the steric bulk of a protecting group on the nitrogen atom may also present a challenge in the cross-coupling step. Herein we describe in full our studies on the development of a sequential Larock heteroannulation/silicon-directed cross-coupling process for the synthesis of polysubstituted indoles.

2. Results

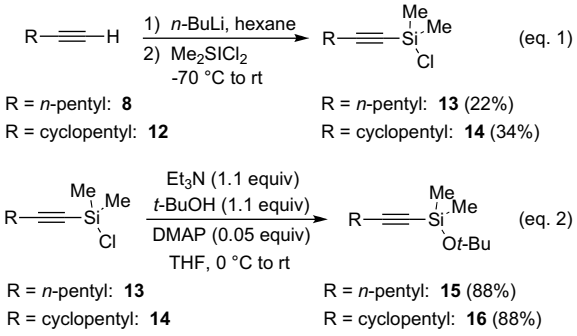
2.1. Synthesis of alkynyl silyl ethers

To identify a suitable alkynylsilane for the heteroannulation/cross-coupling process, we first selected (1-heptynyl)dimethylsilyl ethers because 1-heptyne is an easily handled, inexpensive alkyne and different silyl ethers can be readily installed. The silyl group must withstand the conditions of the heteroannulation and then undergo hydrolysis to the silanol without protodesilylation under mild conditions.[33] Thus, 1-heptyne was lithiated and the lithioalkyne trapped with dimethyl chlorosilane to afford silyl hydride **9** in 70% yield (Scheme 2, Eq. 1). Alcoholysis[34] of **9** in the presence of 2 mol % of $[RuCl_2(p\text{-cymene})]_2$ in acetonitrile/alcohol provided the ethoxysilyl ether **10** in 77% and the isopropoxysilyl ether **11** in 86% yield (Scheme 2, Eqs. 2 and 3). Unfortunately this route failed to access the *tert*-butoxysilyl ether, most likely because of the steric bulk of the alcohol.



Scheme 2.

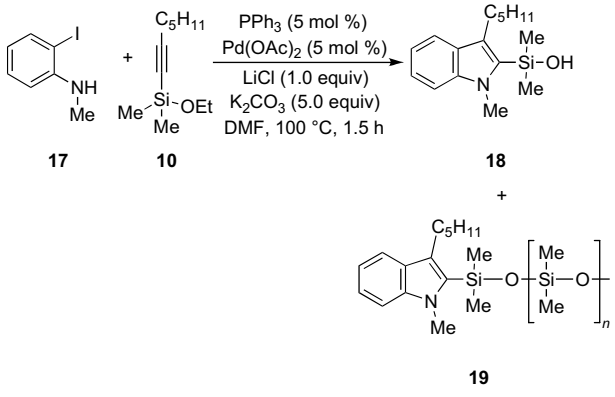
Instead, (1-heptynyl)-*tert*-butoxysilyl ether **15** was prepared in two steps from 1-heptyne via the intermediate chlorosilane **13** (Scheme 3). The synthesis of chlorosilane **13** proceeded in an unoptimized 22% yield by metalation of 1-heptyne with *n*-BuLi and trapping with dimethyldichlorosilane (Scheme 3, Eq. 1). To examine the effect of the 3-substituent, chlorosilane **14** bearing a cyclopentyl group was prepared 34% yield (also unoptimized) by metalation of cyclopentylacetylene with *n*-BuLi followed by trapping the lithioalkyne with dimethyldichlorosilane (Scheme 3, Eq. 1). Combining chlorosilane **13** with anhydrous *t*-BuOH in the presence of triethylamine and DMAP (0.05 equiv) produced the desired silyl ether **15** in 88% yield whereas chlorosilane **14** provided *tert*-butoxysilyl ether **16** in 88% yield (Scheme 3, Eq. 2).



Scheme 3.

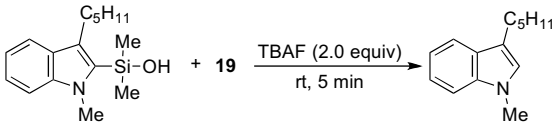
2.2. Optimization of the heteroannulation conditions

To investigate the feasibility of the Larock heteroannulation with these silyl ethers, 2-iodo-*N*-methylaniline[22] was chosen because the nitrogen substituent will survive the heteroannulation conditions and the resulting *N*-methyl(2-indolyl)silanol would be a suitable starting point for implementing the cross-coupling reactions. To evaluate the direct applicability of Larock's conditions, a mixture of aniline **17**, silyl ether **10** (1.2 equiv), K_2CO_3 (5.0 equiv), LiCl (1.0 equiv), $Pd(OAc)_2$ (0.05 equiv), and Ph_3P (0.05 equiv) was heated in DMF at 100 °C for 1.5 h.[22] The only products isolated (in low yield) were **18** and polysiloxane silanol derivatives **19** as an inseparable mixture in an approximate 76:24 ratio by ^1H NMR analysis (Scheme 4).



Scheme 4.

Treatment of this mixture with tetrabutylammonium fluoride (TBAF) afforded indole **20** as judged by TLC and ^1H NMR analyses (Scheme 5). Interestingly, none of the undesired constitutional isomer, *N*-methyl-3-(*n*-pentyl)indole was observed. Although the production of desired silanol **18** was encouraging, the formation of undesired siloxane side products prompted the evaluation of other bases for the heteroannulation process.

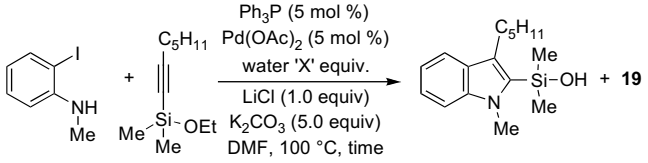


Scheme 5.

All of the other bases examined (including Na_2CO_3, Cs_2CO_3, NaOAc, Na_2HPO_4, NaO*t*-Bu, KO*t*-Bu, CsOH, and KOTMS) proved inferior to K_2CO_3 under the conditions in Scheme 4 and led to either decomposition of **10** or complex reaction mixtures. In the course of these studies, it became apparent that the irreproducibility of the reactions could be related to varying moisture levels in the DMF.

To probe the effect of water on this reaction, a series of experiments were conducted that varied the water content in the reaction from 1.0 to 5.0 equiv relative to aniline (Table 1). DMF from a Solvent Delivery System (SDS) was used in these experiments (KF approximately 40 μg H_2O/mL of DMF). The presence of water affected both the conversion of iodoaniline **17** as well as the ratio between **18** and **19**. The addition of 3.0 equiv of water proved optimal, providing a 69% conversion of aniline, but an approximate 61:39 ratio in favor of silanol **18** (entry 4). A loading of less than 3.0 equiv of water gave either poor conversion or a greater proportion of **19** (entries 1–3) as did increasing the water loading above 3.0 equiv (entries 5 and 6).

Table 1
The effect of water on heteroannulation of **17** with **10**



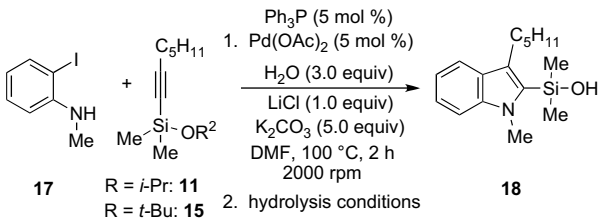
Entry	Water loading, equiv	Conversion, %[a] (**18**/**19**)			
		1 h		3 h	
1	0	0	—	0	—
2	1.0	0	—	Trace	—
3	2.0	87	38:62	86	17:87
4	3.0	36	66:44	69	61:39
5	4.0	27	54:46	Decomp.	—
6	5.0	0	—	0	—

[a] % Conversion measured by ^1H NMR analysis of crude reaction mixtures. GC analysis.

Because the formation of **19** most likely resulted from the cleavage of the ethoxysilyl ether we chose to test a more robust silyl ether would be stable under the heteroannulation conditions. Thus, the isopropyl silyl ether **11** was tested under the optimized reaction conditions for the Larock annulation with **17** using K_2CO_3, LiCl, $Pd(OAc)_2$, PPh_3, and 3.0 equiv of water under vigorous mechanical stirring (2000 rpm) (Table 2). In contrast to reactions using the ethoxysilyl ether **10**, which gave silanol after silica gel filtration, the reaction provided the isopropoxysilyl ether after filtration. An experiment conducted at 80 °C established that smooth conversion could still be obtained within 2 h at lower temperatures. Moreover, using *tert*-butoxysilyl ether **15** in conjunction with **17** provided the *tert*-butoxysilyl ether after filtration.

With a procedure for the clean formation of the silyl ethers, attention focused on identifying conditions to hydrolyze the silyl ether. A streamlined process was envisioned wherein the crude 2-indolylsilyl ether would be hydrolyzed directly to the silanol for final purification. Thus, a series of acidic and basic conditions were surveyed in conjunction with isopropoxysilyl ether in DMF and the reactions were monitored for completion by TLC analysis (Table 2).

Table 2
Survey of conditions for the hydrolysis of 2-indolylsilyl ethers

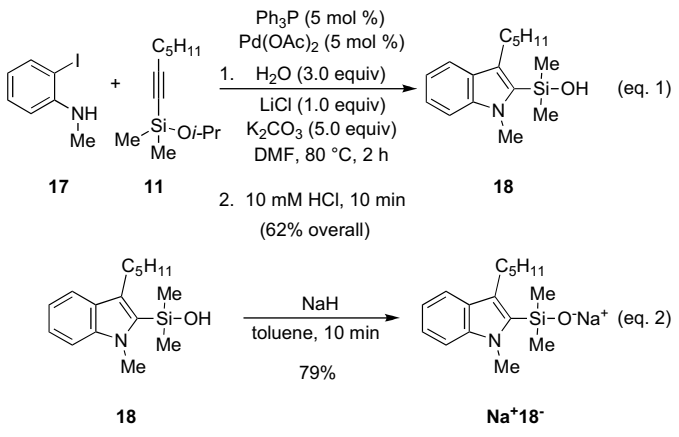


17 R = *i*-Pr: **11** R = *t*-Bu: **15** 18

Entry	R	Conditions	Time, h	Result[a]
1	*i*-Pr	10 M acetic acid	0.5	Decomposition
2	*i*-Pr	2 M acetic acid	0.5	Decomposition
3	*i*-Pr	0.2 M acetate buffer pH 5	6	No reaction
4	*i*-Pr	0.2 M acetate buffer pH 3	24	10% Hydrolysis
5	*i*-Pr	0.8 M HCl	6	Decomposition
6	*i*-Pr	0.08 M HCl	6	60% Silanol, 40% decomposition
7	*i*-Pr	0.009 M HCl	0.2	Complete hydrolysis
8	*i*-Pr	0.2 M NaOH	6	No reaction
9	*t*-Bu	0.001 M HCl	0.3	Complete hydrolysis

[a] Reactions monitored by TLC analysis.

These experiments revealed a delicate balance between hydrolysis of **21** to silanol **18** and desilylation to *N*-Me-3-pentylindole (**20**). Strongly acidic conditions gave decomposition products exclusively (entries 1, 2, and 5) whereas weak acids gave poor conversion (entries 3 and 4). However, very dilute HCl provided the silanol cleanly and quickly (entries 5–7). Basic conditions failed to provide any cleavage to silanol (entry 8). We were delighted to find that the *tert*-butoxysilyl ether could also be converted to the desired silanol with dilute HCl in acetonitrile (entry 9). Thus, both the isopropoxy- and the *tert*-butoxysilyl ethers could be used for the heteroannulation/hydrolysis sequence. In the studies described below, the choice was dictated by the conditions of the heteroannulation; the less reactive anilines that needed more vigorous conditions mandated the use of the more robust the *tert*-butoxysilyl ether. Conducting the Larock heteroannulation with **11** at 80 °C under the conditions described above followed by silica gel plug filtration and treatment with 0.01 M HCl afforded silanol **18** in 62% yield following silica gel column chromatography (Scheme 6, Eq. 1).



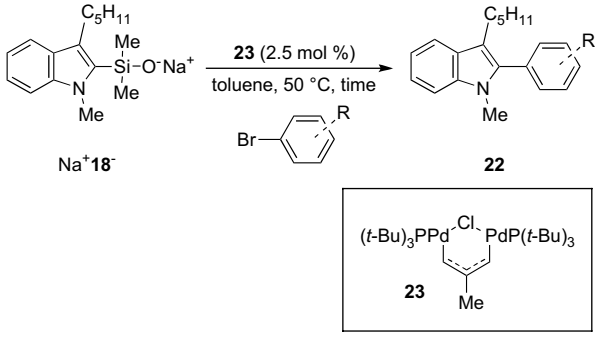
Scheme 6.

In our previous studies of cross-coupling of 2-indolyl-, 2-pyrrolyl-, 2-thienyl, and 2-furylsilanols, we found that the preformed silanolate salts were the superior coupling partners.[27c] Thus, Na^+ **18**$^-$ was prepared by the dropwise addition of a toluene solution of **18** in to a stirred suspension of NaH in toluene (preformation protocol).[27b] The removal of solvent under reduced pressure afforded Na^+**18**$^-$ as a semi-solid in 79% yield (Scheme 6, Eq. 2).

2.3. Cross-coupling of Na^+**18**$^-$ with substituted aryl bromides

The next challenge for this process was to evaluate the effect of the alkyl substituent at C(3) in the key cross-coupling reaction. The cross-coupling of Na^+**18**$^-$ with a range of substituted aryl bromides was surveyed using palladacycle catalyst **23**[35] (Table 3). Gratifyingly, the presence of the 3-pentylsubstituent did not appear to hinder the cross-coupling reaction in comparison to the simple *N*-methyl-2-indolylsilanol.[27c] In general, smooth cross-coupling was observed for electron-deficient as well as electron-neutral aryl bromides (entries 1 and 2). Sterically encumbered 1-bromonaphthalene and electron-rich 4-bromoanisole also coupled successfully (entries 3 and 5). However, 2-bromotoluene proved sluggish and provided the desired product in slightly attenuated yield (entry 4).

Table 3
Cross-coupling of Na^+**18**$^-$ with aryl bromides



Na⁺18⁻ 22 23

Entry	R	Time, h	Product	Yield,[a] %
1	4-CO_2Et	1	**22a**	73
2	H	6	**22b**	86
3	[b]	3	**22c**	81
4	2-Me	12	**22d**	65
5	4-OMe	2	**22e**	75

[a] Yield of isolated, analytically pure product.
[b] 1-Bromonaphthalene.

2.4. Expansion of substrate scope

The first step in the generalization of the sequential process involved the identification of a substituent on the nitrogen atom that is compatible with both steps, but is more easily cleaved than a methyl group.[36] Second, the ability to use 4-substituted anilines in the reaction would enable the preparation of 2,3,5-trisubstituted indoles in a highly convergent manner. Third, an expanded scope of the substituent at C(3) would further demonstrate the generality of this method and provide another point of diversification in the preparation of multi-substituted indoles. With these considerations in mind, studies were conducted on a series of *N*-benzyl-4-substituted-2-iodoanilines.

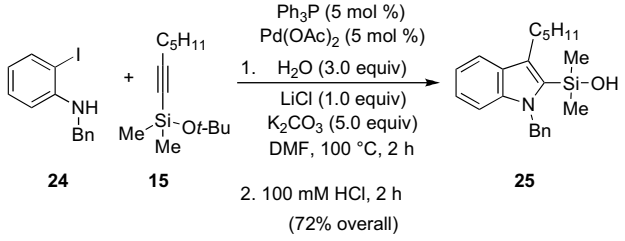
N-Benzyl indole derivatives are generally more easily deprotected than analogous *N*-Me derivatives,[37] and the electron-rich nature of the benzyl group should enable smooth cross-coupling with aryl bromides and chlorides. Toward this end, a series of *N*-

benzyl-4-substituted-2-iodoanilines bearing -H,[38] -Cl,[39] and -OMe[40] substituents at the 4-position were prepared by following literature procedures.

2.4.1. Larock heteroannulation with 4-substituted-N-benzyl-2-iodoanilines

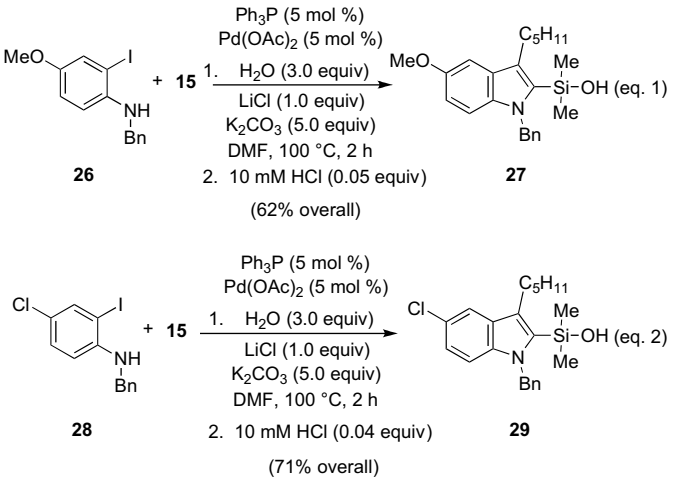
Orienting studies with *N*-benzyl-2-iodoaniline established that this substrate would react under conditions described above for the *N*-methyl variant. However, attempts to use either electron-deficient *N*-benzyl-4-chloro-2-iodoaniline (**28**) or electron-rich *N*-benzyl-4-methoxy-2-iodoaniline (**26**) under these conditions gave complex mixtures of decomposition products. It was speculated that the resulting *N*-benzyl-5-substituted-3-pentyl-(2-indolyl)isopropoxysilyl ethers were decomposing under the reaction conditions. To overcome this problem, recourse was made to the more robust *tert*-butoxydimethylsilyl ether.

Thus, a solution of *N*-benzyl-2-iodoaniline (**24**), K_2CO_3, LiCl, $Pd(OAc)_2$, Ph_3P, and 3.0 equiv of water was stirred for 1 h at 100 °C (Scheme 7). Following treatment with 100 mM HCl (0.04 equiv), silanol **25** was isolated in 72% yield.



Scheme 7.

The effectiveness of **15** in the heteroannulation reaction was evaluated with the *N*-benzyl-4-substituted-2-iodoanilines mentioned above under the optimized conditions at 100 °C in DMF. Although small-scale reactions using magnetic stirring proceeded to completion cleanly, problems were encountered when these reactions were executed on greater than 1.5 mmol scale. Upon reaction scale-up, either incomplete conversion or the formation of decomposition products was observed. These problems were solved through the use of a mechanical stirrer that provided strong, uniform agitation throughout the reaction. Filtration of the crude reaction mixtures through silica gel or Florisil, and treatment with HCl afforded the desired silanols (Scheme 8).

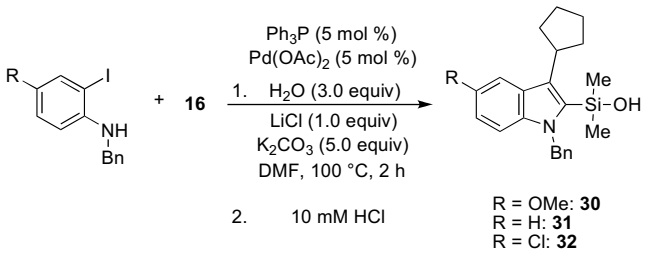


Scheme 8.

Gratifyingly, *N*-benzyl-4-methoxy-2-iodoaniline engaged in successful annulation to provide silanol **27** in 62% yield following hydrolysis (Scheme 8, Eq. 1). In addition, *N*-benzyl-4-chloro-2-iodoaniline reacted cleanly with silyl ether **15** and provided silanol **29** in 71% yield (Scheme 8, Eq. 2).

The next step in the expansion of substrate scope was to examine the ability to introduce a different alkyl substituent on the alkyne in the heteroannulation process. The sequential Larock heteroannulation and silicon-based cross-coupling reaction could provide a way to selectively access disubstituted indoles bearing sterically similar groups at C(2) and C(3). For this purpose a bulky cyclopentyl substituent was introduced on the alkyne. A series of experiments were conducted that combined silyl ether **16** with a benzylaniline under the optimized heteroannulation conditions (Table 4). Whereas electron-rich *N*-benzyl-4-methoxy-2-iodoaniline provided the silanol in moderate 59% overall yield (entry 1), the annulation proceeded smoothly for anilines bearing a chloride or hydrogen atom (entries 2 and 3). Efforts were next focused on the crucial cross-coupling reaction.

Table 4
Larock heteroannulation of *N*-benzyl-4-substituted-2-iodoanilines with **16**



Entry	R	Product	Yield,[a] %
1	OMe	**30**	59
2	H	**31**	71
3	Cl	**32**	71

[a] Yield of isolated, chromatographed product.

2.4.2. Cross-coupling of substituted sodium N-benzyl-(2-indolyl)-dimethylsilanolates with aryl bromides and chlorides

To establish the scope of the cross-coupling reaction, several representative acceptors were selected including electron-rich, heterocyclic, and electron-deficient aryl chlorides and bromides. Preliminary experiments using preformed sodium *N*-benzyl-3-pentyl-(2-indolyl)dimethylsilanolate (Na^+**25**$^-$) established that smooth cross-coupling could be achieved with electron-deficient aryl chlorides such as 4-chlorobenzotrifluoride and 4-chlorobenzophenone. In the presence of 2.5 mol % of allylpalladium chloride (APC) dimer and 5 mol % of *S*-Phos.[41] These reactions completely consumed the aryl halide in 1 h at 70 °C in toluene. However, 2-chloroanisole provided only partial conversion to product under these conditions. To address the poor reactivity of Na^+**25**$^-$ with less reactive chlorides, a survey was conducted with several biphenyl phosphine ligands (Chart 2). The cross-coupling of Na^+**25**$^-$ with 2-chloroanisole was evaluated in the presence of 2.5 mol % of APC and 5 mol % of ligand (Table 5).

The nature of the ligand had a significant impact on the efficiency of this cross-coupling reaction. Partial conversion of 2-chloroanisole was observed using **33** or X-Phos derivative **34** (entries 1 and 2). Whereas *S*-Phos afforded 44% conversion, *S*-Phos derivative **36** provided none of the desired product (entries 3 and 4). However, RuPhos **37** proved optimal and provided complete conversion of chloride in 12 h (entry 5).

With the discovery that RuPhos enables smooth cross-coupling with electron-rich aryl chlorides, focus shifted to studying the cross-

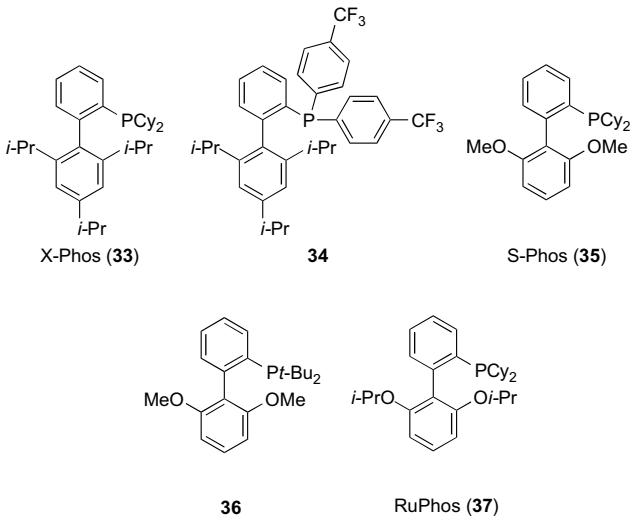
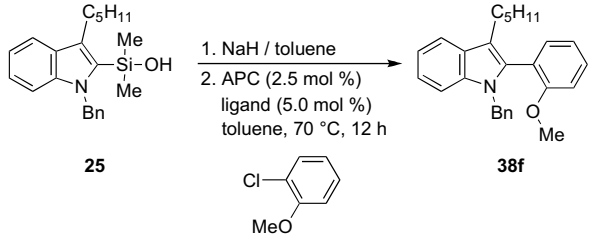


Chart 2.

coupling of sodium *N*-benzyl-5-substituted-3-pentyl-(2-indolyl)-dimethylsilanolates. The 3-pentyl-2-indolylsilanols prepared during the course of this study were converted to their sodium salts with NaH following the aforementioned general protocol.[27c] To evaluate the reactivity of these silanolates, a variety of aryl chlorides and bromides were chosen as cross-coupling partners (Table 6).

Table 5
Ligand optimization survey for the cross-coupling of preformed Na^+**25**$^-$ with 2-chloroanisole



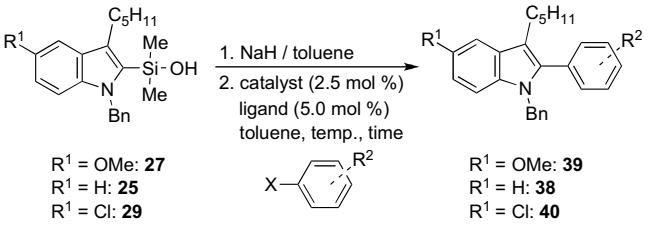
Entry	Ligand	Conversion,[a] %
1	**33**	17
2	**34**	54
3	**35**	44
4	**36**	—
5	**37**	100

[a] % Conversion determined by ^{1}H NMR analysis of crude reaction mixtures.

Overall, smooth cross-coupling was achieved for a range of substrates. The 5-methoxy derivative Na^+**27**$^-$ coupled readily with electron-deficient, heteroaryl, as well as electron-rich aryl chlorides (entries 1–3). However, reaction with 2-chloroanisole gave the products in slightly lower yield and required longer reaction time (entry 3). The parent Na^+**25**$^-$ afforded products in uniformly high yields (entries 4–6) although 4-chlorobenzonitrile reached completion in 1 h in the presence of *S*-Phos (entry 4). Because 2-indolylsilanol **29** bears a chloro substituent, Na^+**29**$^-$ was coupled with aryl bromides using palladacycle catalyst **23**. Whereas cross-coupling with electron-deficient substrates reached completion in 12 h (entries 7 and 8), electron-rich 4-chloroanisole required 24 h to reach completion (entry 9).

Although the facile cross-coupling observed with sodium *N*-benzyl-5-substituted-3-pentyl-(2-indolyl)dimethylsilanolates was encouraging, it by no means implied that the cross-coupling of the more sterically demanding cyclopentyl variant would be assured.

Table 6
Cross-coupling sodium *N*-benzyl-5-substituted-3-pentyl-(2-indolyl)dimethylsilanols with aryl chlorides and aryl bromides



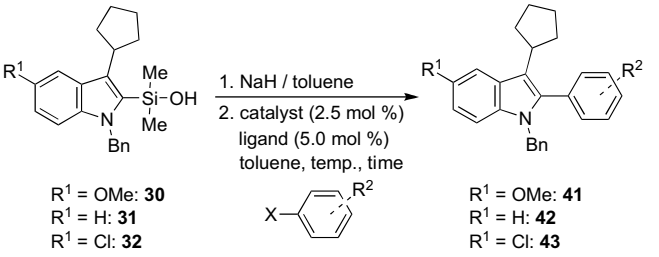
Entry	R^1	X	R^2	Cat.	Ligand	Temp, °C	Time, h	Product	Yield,[a] %
1	OMe	Cl	4-CN	APC	**35**	70	1	**39g**	87
2	OMe	Cl	[b]	APC	**37**	70	1	**39h**	81
3	OMe	Cl	2-OMe	APC	**37**	70	24	**39f**	71
4	H	Cl	4-CN	APC	**35**	70	1	**38g**	82
5	H	Cl	[b]	APC	**37**	70	12	**38h**	87
6	H	Cl	2-OMe	APC	**37**	70	12	**38f**	82
7	Cl	Br	4-CF_3	**23**	—	50	12	**40i**	88
8	Cl	Br	[b]	**23**	—	50	12	**40h**	88
9	Cl	Br	4-OMe	**23**	—	50	24	**40e**	72

[a] Yield of isolated, analytically pure product.
[b] 3-Bromopyridine.

To test the reactivity of the corresponding sodium *N*-benzyl-5-substituted-3-cyclopentyl-(2-indolyl)dimethylsilanolates, a series of aryl chlorides and bromides were surveyed (Table 7).

Cross-coupling 5-methoxy derivative Na^+**30**$^-$ provided good yields with electron-deficient, heteroaryl, and electron-rich aryl chlorides (entries 1–3). The parent Na^+**31**$^-$ underwent smooth cross-coupling with an electron-deficient chloride (entry 1), but reacted more slowly with heteroaryl or electron-rich chlorides to give products in moderate yields. The cross-coupling of 5-chloro derivative Na^+**32**$^-$ proved more challenging and provided the desired products in modest yields (entries 7 and 8). Unfortunately attempts to engage Na^+**32**$^-$ with 3-bromopyridine under these conditions gave only trace amounts of the desired product.

Table 7
Cross-coupling sodium *N*-benzyl-5-substituted-3-cyclopentyl-(2-indolyl)-dimethylsilanols with aryl chlorides and aryl bromides



Entry	R^1	X	R^2	Cat.	Ligand	Temp, °C	Time, h	Product	Yield,[a] %
1	OMe	Cl	4-CN	APC	**35**	70	1	**41g**	88
2	OMe	Cl	[b]	APC	**37**	90	12	**41h**	86
3	OMe	Cl	4-OMe	APC	**37**	90	12	**41e**	74
4	H	Cl	4-CN	APC	**35**	70	1	**42g**	89
5	H	Cl	[b]	APC	**37**	90	12	**42h**	69
6	H	Cl	4-OMe	APC	**37**	90	12	**42e**	65
7	Cl	Br	4-CF_3	**23**	—	50	12	**43i**	64
8	Cl	Br	4-OMe	**23**	—	50	12	**43e**	62

[a] Yield of isolated, analytically pure product.
[b] 3-Bromopyridine.

3. Discussion

A successful sequential reaction protocol was developed by optimization of a number of variables such as the silicon group on

the alkyne component in the Larock process, and identification of an appropriate ligand for the cross-coupling reaction.

3.1. Optimization of the Larock heteroannulation process

The heteroannulation reaction proceeded under the general conditions described by Larock and Yum.[21] Surprisingly, the reaction displayed a marked dependence on the base used such that K_2CO_3 proved optimal. Successful construction of the indole ring required only minor optimization of the reaction conditions including the addition of water and the use of a *tert*-butoxysilyl ether. Additionally, the stirring rate was found to impact the reaction efficiency when the reaction was executed on greater than 1.5 mmol scale. In addition, optimization studies identified that irreproducibility in the annulation reaction could be traced to the variability of moisture in the DMF. A survey of water loading demonstrated that ca. 3.0 equiv of water was optimal. Using less or more than 3.0 equiv of water provided either poor conversion or increased amounts of decomposition products. Although its exact role remains unknown, the water may help solubilize the salts in this heterogeneous reaction, or may serve to alter the dielectric constant of the solution. There is some precedent for the use of water in the Larock heteroannulation, although its role remains unclear.[25a]

The size of the silyl ether group on the alkyne component had a profound effect on the ability to expand the scope of the heteroannulation reaction. The ethoxysilyl ether **10** was the least stable to the heteroannulation conditions. Potentially, a base-promoted attack at the silicon center of alkyne **10**, or the indole-substituted silyl ether might induce a fragmentation that could give rise to the polysiloxane-containing indole **19**. Fortunately, switching to the bulkier isopropoxysilyl ether **11** enabled the facile preparation of **21**, and likely better shielded the silicon atom from attack. Further supporting the increased stability of **21** was the observation that the heteroannulation product **21** survived filtration through a plug of silica gel whereas the indole derived from alkyne **10** provided silanol upon exposure to mildly acidic silica gel.[42]

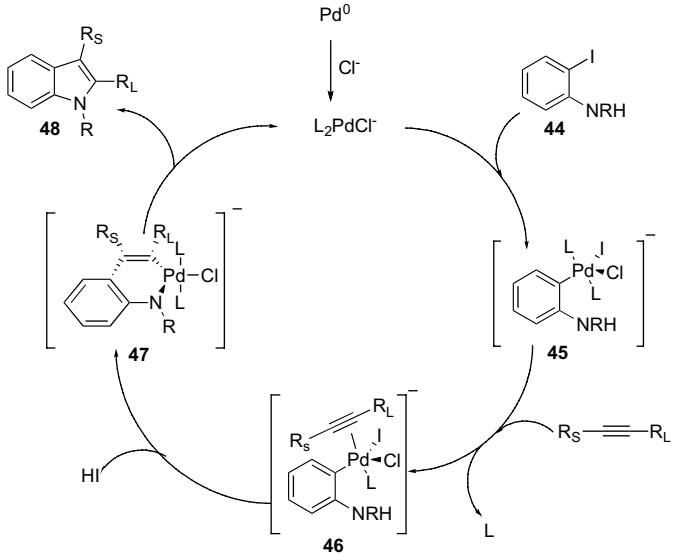
However, an unfortunate corollary of using the more stable isopropoxysilyl ether was the need to develop conditions for its removal following the heteroannulation. Whereas conditions had been developed in these laboratories for the facile hydrolysis of ethoxysilyl ethers,[33] the hydrolysis of an isopropoxysilyl ether on a sensitive indole substrate was more challenging. Gratifyingly, dilute (0.01 M) HCl afforded the desired silanol cleanly. Crucial to the success of this operation was the delicate balance of providing sufficient acid to effect cleavage, but not so much as to induce protiodesilylation. Generally, 4 mol % of HCl relative to the 2-indolylsilyl ether delivered from a stock concentration of between 10 and 50 mM gave satisfactory results. Notably, the hydrolysis of silyl ethers under acidic conditions has been reported to generate undesired disiloxanes.[33] However, none of the corresponding disiloxanes were observed during this process, perhaps because the bulk of the indole prevented dimerization.

The bulkier *tert*-butoxysilyl ether **15** was needed to enable the smooth heteroannulation with less reactive *N*-benzyl-4-substituted-2-iodoanilines. Particularly challenging were those anilines bearing electron-deficient groups at the 4-position. When an isopropoxysilyl ether was used in these cases, complex mixtures of decomposition products were observed. Potentially, the electron-withdrawing substituent inductively rendered the silicon atom more susceptible to attack by base and subsequent desilylation. Fortunately, the bulky *tert*-butoxysilyl ether **15** enabled smooth heteroannulation with *N*-benzyl-4-chloro-2-iodoaniline. The heteroannulation of *N*-benzyl-4-trifluoromethyl-2-iodoaniline remains an unsolved challenge and suggests that anilines bearing strongly electron-withdrawing groups may represent a limitation of this reaction.

Another surprising finding in this study was that the 4-substituent on the 2-iodoaniline had no noticeable effect on the rate of the heteroannulation reaction. *N*-Benzyl-4-methoxy-2-iodoaniline, *N*-benzyl-2-iodoaniline, and *N*-benzyl-4-chloro-2-iodoaniline all reacted completely within 2 h.

3.2. Site selectivity of the reaction

The proposed mechanism of this reaction involves several key steps (Scheme 9). Larock has suggested that the reaction begins with coordination of chloride to Pd^0 to form an anionic palladium species that undergoes oxidative addition to the aryl iodide.[20] Next, coordination of the alkyne to the Pd atom occurs (**46**) followed by *syn* migratory insertion. Displacement of the iodide by nitrogen affords palladacycle **47** that reductively eliminates to give the indole product and regenerate the palladium catalyst. It is worth noting that this mechanistic proposal is not supported by any experiments and remains speculative.



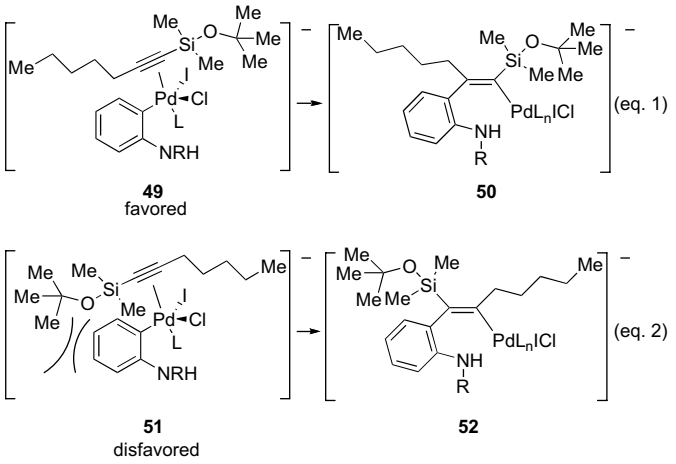
Scheme 9.

Larock and co-workers have observed exquisite selectivity for alkynyltrimethylsilanes in these reactions. The high selectivity is rationalized on the basis of steric interations.[22] The migratory insertion is speculated to occur such that the bulkier *tert*-butoxysilyl ether substituent on the alkyne is pointing away from the aniline in the coordination step to form **49** (Scheme 10, Eq. 1). According to Larock's proposal, the migratory insertion should occur such that steric strain near the shorter C–C bond is minimized (Scheme 10, Eq. 2).[20]

A similar hypothesis has been forwarded by Cacchi and co-workers during their studies on the hydroarylation of silylalkynes.[43] Cacchi proposed that the carbopalladation of the alkynylsilanes is directed by the steric bulk of the silane to minimize interaction between the silane and the arene.

3.3. The effect of the nitrogen substituent

The nitrogen substituent demonstrated no apparent effect on the heteroannulation reaction. Both *N*-methyl-2-iodoaniline as well as *N*-benzyl-2-iodoaniline afforded similar yields of silanols within similar endpoints of reaction. A firm conclusion on the effect of the nitrogen substituent on the cross-coupling reaction is difficult to draw because *N*-methyl indole variant **18** was cross-coupled with aryl bromides while the analogous *N*-benzyl silanol **25** was



Scheme 10.

cross-coupled with aryl chlorides. A more concrete comparison will have to await a full exploration of the scope of this reaction. Potentially, the less sterically hindered *N*-Me could be expected to be more reactive a priori.

3.4. Optimization of the cross-coupling process

The cross-coupling of Na^{+}**18**$^{-}$ with aryl bromides proceeded smoothly using palladacycle catalyst **23** under previously described conditions.[27c] The cross-coupling reaction did not reveal a strong dependence on electronic effects as the electron-deficient ethyl 4-bromobenzoate required 1 h to reach completion and afforded a 73% yield of **22a** while electron-rich 4-bromoanisole required 2 h for complete conversion to provide a 75% yield of **22e**. More revealing was the apparent effect of increasing steric bulk on the bromide as 2-bromotoluene required 12 h to reach completion and gave the product in slightly lower yield. Hindered 1-bromonaphthalene required slightly longer time than 4-bromoanisole but less than 2-bromotoluene. The presence of the *n*-pentyl group at C(3) may slow the rate of coupling through steric congestion.

To effect the successful cross-coupling with aryl chlorides, a careful selection of the ligand on the palladium catalyst was required. Cross-coupling of *N*-benzyl-3-*n*-pentyl-(2-indolyl)silanolate Na^{+}**25**$^{-}$ proceeded smoothly with electron-deficient aryl chlorides using the *S*-Phos ligand described by following the previously published conditions.[27c] However, cross-coupling of electron-rich or sterically encumbered aryl chlorides required the diisopropyl derivative of *S*-Phos, RuPhos **37**. Moreover, cross-coupling the more sterically encumbered 3-cyclopentyl-2-indolyl silanolate derivatives with electron-rich aryl chlorides required the RuPhos ligand in conjunction with higher temperatures (90 °C) to reach completion.

The RuPhos ligand was developed for the cross-coupling of sterically hindered arylzinc reagents with hindered aryl chlorides,[44] and subsequent studies have established its use in C–N coupling reactions.[45] While the exact origin of the success of the RuPhos catalyst remains unknown, Buchwald and co-workers have attributed the high reactivities of biphenyl-based ligands to the formation of a monoligated LPd(0) that is stabilized by a very weak interaction with the *ipso* carbon of the arene ring as demonstrated by X-ray crystallographic and computational studies.[41] It has been suggested that the steric bulk of these ligands facilitates ligand dissociation, while the weak Pd-*ipso* carbon is able to stabilize the Pd catalyst.[41] Potentially, the increased bulk provided by the RuPhos catalyst is better able to facilitate ligand dissociation, and provide an open coordination site on the palladium catalyst. At this juncture, it remains difficult to speculate why the RuPhos catalyst is much better for the cross-coupling of bulky indolyl silanolates with hindered or electron-rich aryl chlorides in this reaction, but one possibility may be that the reaction requires an open coordination site on palladium before either displacement or transmetalation and this ligand is influencing this process.

4. Conclusion and outlook

This study demonstrated the versatility and synthetic power of silicon reagents. Herein, the silicon atom assumed a dual role; first as a directing group in the Larock heteroannulation, and later as an activating group for a silicon-based cross-coupling reaction. This sequential Larock/cross-coupling strategy required only slight modification of Larock's original conditions, including the addition of water and rapid stirring. Crucial to the success of the reaction was the development and strategic use of a *tert*-butoxysilyl ether. This sequence is complementary to the Cacchi reaction in that this reaction places the alkyl group on the alkyne at the C(3) position of the indole and employs a cross-coupling reaction to install a group at the C(2) position.

Future studies involve expanding the scope of the substituent at the C(3) position by evaluating other alkynyl silyl ethers in the heteroannulation process and applying the sequence to 2-amino-3-iodopyridines to provide access to 7-aza-indoles, a class of biologically important compounds.[46] Application of this reaction to the synthesis of indole therapeutic agents will be reported in due course.

5. Experimental section

5.1. General experimental methods

See Supplementary data.

5.2. General procedure I. Preparation of dimethyl(1-methyl-3-pentyl-1*H*-indol-2-yl)silanol (18) from 15

To a flame-dried, 500-mL, 3-necked (thermal-couple, mechanical stirrer, septum) round-bottomed flask equipped with a mechanical stirrer were added 2.073 g (15.0 mmol, 5.0 equiv) of potassium carbonate, 127 mg (3.0 mmol, 1.0 equiv) of lithium chloride, 34 mg (0.15 mmol, 0.05 equiv) of palladium acetate, and 39 mg (0.15 mmol, 0.05 equiv) of triphenylphosphine under an atmosphere of argon. To this mixture was added 10.0 mL of DMF (KF=530 μg/mL). To an oven-dried 8-mL DRAM vial were added 699 mg (3.0 mmol, 1.0 equiv) of *N*-methyl-2-iodoaniline and 679 mg (3.0 mmol, 1.0 equiv) of *tert*-butoxy(hept-1-ynyl)dimethylsilane under an atmosphere of argon. To this vial was added 2.5 mL of DMF and the resulting solution was transferred to the 500-mL, round-bottomed flask above. The vial was washed with 2.5 mL of DMF and this rinse was added to the round-bottomed flask above. To the stirred solution was added 154 μL (8.5 mmol, 2.9 equiv) of water. The flask was submerged in a 105 °C oil bath (internal temperature 95–100 °C) and stirred (2000 rpm) for 2 h. After cooling, the crude reaction mixture was eluted through 5.0 g of SiO_2 on a glass frit filter with 150 mL of ethyl acetate into a 500-mL, round-bottomed flask. The resulting red solution was concentrated under reduced pressure to provide a dark-red oil that was diluted with 100 mL of CH_3CN. To this round-bottomed flask were added a magnetic stir bar and 1.2 mL (0.12 mmol, 0.04 equiv) of 100 mM HCl dropwise. After stirring at rt for 20 min, 90 mL of benzene was added and the solution was extracted with 90 mL of satd NH_4Cl and washed twice with 90 mL of H_2O, and the organic layer was dried over $MgSO_4$, filtered through #4 Whatman filter

paper (15 cm diameter), and concentrated under reduced pressure to a volume of approx. 20 mL whereupon it was immediately transferred to a glass frit filter containing 2.5 g of SiO_2. The solution was eluted with 200 mL of EtOAc and concentrated under reduced pressure. The resulting dark-red oil was purified by silica gel column chromatography (30×80 mm) with hexane/EtOAc, 4:1 (15×40-mL fractions). The combined fractions were further purified by silica gel column chromatography (30× 80 mm) by first eluting with 200 mL of hexane followed by a gradient to hexane/EtOAc, 9:1 (30× 8 mL fractions) to afford 477 mg (58%) of **18** as a light red oil. Attempts to obtain analytically pure material were unsuccessful, and the silanol was found to contain a small amount (ca. 10%) of polysiloxane contaminants. This material was found to provide satisfactory results in subsequent cross-coupling experiments. Data for **18**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (d, J=7.9, 1H, HC(4)), 7.30 (d, J=8.2, 1H, HC(7)), 7.24 (t, J=7.6, 1H, HC(6)), 7.08 (t, J=7.4, 1H, CH(5)), 3.90 (s, 3H, HC(10)), 2.86 (m, 2H, CH(1′)), 1.93 (s, 1H, HO(2″)), 1.61 (m, 2H, CH(2′)), 1.38 (m, 4H, CH(3′), CH(4′)), 0.91 (t, J=6.6, 3H, HC(5′)), 0.55 (s, 6H, HC(1″)); ^{13}C NMR (125.6 MHz, $CDCl_3$) δ 139.8 (C(8)), 133.9 (C(9)), 128.1 (C(2)), 126.8 (C(3)), 122.6 (C(6)), 119.3 (C(4)), 118.5 (C(5)), 109.1 (C(7)), 32.9 (C(10)), 32.8 (C(2′)), 32.3 (C(3′)), 25.7 (C(1′)), 22.7 (C(4′)), 14.1 (C(5′)), 2.8 (C(1″)); IR (film) cm^{-1} 3335 (br), 3053 (w), 2956 (s), 2927 (s), 2857 (m), 1653 (w), 1615 (w), 1573 (w), 1503 (m), 1484 (m), 1467 (m), 1423 (m), 1377 (m), 1354 (m), 1316 (m), 1259 (s), 1168 (m), 1141 (w), 1131 (w), 1044 (s), 1013 (m), 832 (s), 803 (s), 738 (s); MS (EI, 70 eV) m/z 275 (4), 218 (14), 207 (18), 201 (23), 158 (3), 144 (100), 115 (4), 77 (4); TLC R_f 0.31 (hexane/EtOAc, 4:1) [silica gel, $KMnO_4$]; HRMS m/z calcd for $C_{16}H_{25}NOSi$ (M^+): 275.1705; found: 275.1703.

5.2.1. Preparation of sodium dimethyl(1-methyl-3-pentyl-1H-indol-2-yl)silanolate (Na^+**18**$^-$)

To a flame-dried, 50-mL, round-bottomed flask equipped with a magnetic stir bar was added 42.0 mg (1.7 mmol, 1.0 equiv) of NaH and 2.0 mL of hexane inside a dry box. To this flask was added dropwise a solution containing 479 mg (1.7 mmol, 1.0 equiv) of **18** in 3.0-mL of hexane in a 25 mL conical flask. The conical flask was washed with 1.0-mL of hexane and this rinse was added to the mixture above. After stirring for 20 min, the resulting solution was concentrated under high vacuum (0.05 mmHg) to afford 411 mg (79%) of Na^+**18**$^-$ as a light yellow semi-solid. Data for Na^+**18**$^-$: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (d, J=7.8, 1H, HC(4)), 7.14 (d, J=8.3, 1H, HC(7)), 7.03 (t, J=7.1, 1H, HC(6)), 6.91 (t, J=7.1, 1H, CH(5)), 4.00 (s, 3H, HC(10)), 2.84 (t, J=8.3, 2H, CH(1′)), 1.61 (m, 2H, CH(2′)), 1.42 (m, 4H, CH(3′), CH(4′)), 0.94 (t, J=7.1, 3H, HC(5′)), 0.34 (s, 6H, HC(1″)).

5.3. General procedure II: cross-coupling isolated Na^+18^- aryl bromides (Table 3)

To an oven-dried, 5-mL, conical flask equipped with a stir bar were added sodium *N*-methyl-(3-pentyl)-2-indolyldimethylsilanolate (Na^+**18**$^-$) (357 mg, 1.2 mmol) and toluene (2.0 mL) under dry argon atmosphere inside a dry box. To this solution were added **23** (17.7 mg, 0.025 mmol) and 1.0 mmol of aryl bromide. After being stirred at the temperature for the time specified, the crude reaction mixture was filtered through a plug of silica gel (3 g) and eluted with EtOAc (200 mL) to give a red solution that was concentrated under reduced pressure. The resulting red 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 C18 reverse phase column chromatography (20×100 mm) and eluted 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, or further purification by recrystallization provided the products.

5.3.1. Preparation 1-methyl-2-(4-methoxyphenyl)-3-pentyl-1H-indole (**22a**) (Table 3, entry 1)

Following general procedure II was prepared a solution of Na^+**18**$^-$ (357 mg, 1.2 mmol) and toluene (2.0-mL) in a 5-mL round-bottomed flask under dry argon atmosphere inside a dry box. To this conical flask were added **23** (17.7 mg, 0.025 mmol) and ethyl 4-bromobenzoate (163 μL, 1.0 mmol). After being stirred in a 50 °C oil bath for 1 h, the crude reaction mixture was filtered through a plug of silica gel (3 g) and eluted with EtOAc (200 mL) to give a red solution that was concentrated under reduced pressure. The resulting red oil was purified by silica gel column chromatography (20×100 mm) and eluted with hexane/EtOAc, 4:1 (10×10-mL fractions) gradient to hexane/EtOAc 1:1 (20×10-mL fractions). The combined fractions were purified by C18 reverse phase column chromatography (20×100 mm) and eluted with MeOH/H_2O, 9:1 (30×10-mL fractions) to afford 257 mg (73%) of **22a** as a light yellow semi-solid. Data for **22a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.22 (d, J=8.6, 2H, HC(3′)), 7.70 (d, J=7.9, 1H, HC(4)), 7.51 (d, J=8.4, 2H, HC(2′)), 7.38 (d, J=8.4, 1H, HC(7)), 7.32 (t, J=8.1, 1H, HC(6)), 7.20 (t, J=8.0, 1H, HC(5)), 4.47 (q, J=7.3, 2H, HC(6′)), 3.63 (s, 3H, HC(10)), 2.75 (t, J=7.9, 2H, HC(1″)), 1.67 (m, 2H, HC(2″)), 1.48 (t, J=7.3, 3H, HC(7′)), 1.30 (m, 4H, HC(3″), HC(4″)), 0.88 (t, J=7.0, 3H, HC(5″)); ^{13}C NMR (125.6 MHz, $CDCl_3$) δ 166.4 (C(5′)), 137.5 (C(4′)), 136.9 (C(8)), 136.4 (C(9)), 130.4 (C(2′)), 129.6 (C(1′)), 129.5 (C(3′)), 127.6 (C(2)), 122.0 (C(5)), 119.3 (C(6)), 119.2 (C(4)), 114.9 (C(3)), 109.4 (C(7)), 61.0 (C(6′)), 31.8 (C(3″)), 31.8 (C(2″)), 30.9 (C(10)), 24.5 (C(1″)), 22.4 (C(4″)), 14.3 (C(7′)), 14.1 (C(5″)); IR (Nujol) cm^{-1} 3054 (w), 2956 (s), 2930 (s), 2871 (m), 2857 (m), 1716 (s), 1611 (s), 1468 (s), 1366 (s), 1273 (s), 1177 (s), 1107 (s), 1019 (s), 870 (m), 770 (m); MS (EI, 70 eV) 349 (M^+, 50), 292 (100), 264 (5), 219 (35), 124 (5); TLC R_f 0.32 (hexane/EtOAc, 9:1) [silica gel, UV]. Anal. Calcd for $C_{23}H_{27}NO_2$ (349.47): C, 79.05; H, 7.79; N, 4.01. Found: C, 78.65; H, 7.78; N, 4.17.

5.4. General procedure IV: cross-coupling pre-formed sodium *N*-benzyl-3,5-disubstituted-(2-indolyl)dimethylsilanolates with aryl chlorides and aryl bromides (Tables 6 and 7)

To a flame-dried, 5-mL, round-bottomed, flask equipped with a stir bar were added NaH (29 mg, 1.2 mmol, 1.2 equiv) and toluene (0.4 mL) under dry argon atmosphere inside a dry box. In a separate flame-dried, 5-mL, conical flask was added *N*-benzyl-3,5-disubstituted-(2-indolyl)dimethylsilanol (1.2 mmol, 1.2 equiv), which was dissolved in toluene (1.2 mL) and this silanol solution was added dropwise to the above suspension by glass pipette. The conical-bottomed flask containing the silanol was washed with toluene (0.4 mL) and that rinse was added to the reaction mixture. The resulting mixture was stirred for 10 min before aryl chloride or bromide (1.0 mmol, 1.0 equiv), Pd catalyst (0.025 mmol, 0.025 equiv), and ligand were added. The flask was sealed with a rubber septum and removed from the dry box. After being stirred at the temperature for the time specified, the crude reaction mixture was filtered through a plug of silica gel (3 g) and eluted with EtOAc (200-mL) to give a red solution that was concentrated under reduced pressure. The resulting red 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 C18 reverse phase column chromatography (20×100 mm) and eluted 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, or further purification by recrystallization provided the products.

5.4.1. Preparation of 4-(1-benzyl-5-methoxy-3-pentyl-1H-indol-2-yl)benzonitrile (**39g**) (Table 6, entry 1)

Following general procedure IV, a solution of Na^+**27**$^-$ was prepared by combining NaH (29 mg, 1.2 mmol, 1.2 equiv) and **27**

(458 mg, 1.2 mmol, 1.2 equiv) in toluene (2.0 mL) in a 5-mL round-bottomed flask under an atmosphere of argon. To this mixture 4-chlorobenzonitrile (138 mg, 1.0 mmol, 1.0 equiv), *S*-Phos (20.5 mg, 0.05 mmol, 0.05 equiv), and APC (9 mg, 0.025 mmol, 0.025 equiv) were added. After being stirred at 70 °C for 1 h, the black, crude reaction mixture was filtered through a plug of silica gel (3 g) and eluted with EtOAc (200 mL) to give a light yellow solution that was concentrated under reduced pressure. The resulting yellow semi-solid 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 concentration and recrystallization in boiling MeOH (2 mL) to afford 357 mg (87%) of **39g** as a white solid (needles). Data for **39g**: mp 73–74 °C (MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, J=8.0, 2H, HC(C2″)), 7.39 (d, J=8.0, 2H, HC(C3″)), 7.22 (m, 3H, HC(C4′), HC(C4)), 7.10 (m, 2H, HC(C5′), HC(C7)), 6.87 (m, 3H, HC(C3′), HC(C6)), 5.15 (s, 2H, HC(C1′)), 3.89 (s, 3H, HC(C10)), 2.67 (t, J=7.8, 2H, HC(C1‴)), 1.62 (t, 2H, HC(C2‴)), 1.26 (m, 4H, HC(C3″), HC(C4″)), 0.84 (t, J=7.0, 3H, HC(C5‴)); ^{13}C NMR (125.6 MHz, $CDCl_3$) δ 154.1 (C(5)), 138.0 (C(2′)), 137.1 (C(1″)), 136.2 (C(8)), 132.3 (C(9)), 132.0 (C(2″)), 130.9 (C(3″)), 128.6 (C(3′)), 128.2 (C(2)), 127.2 (C(7)), 125.8 (C(4′)), 118.6 (C(5″)), 115.7 (C(3)), 112.6 (C(5′)), 111.4 (C(4″)), 111.1 (C(6)), 101.4 (C(4)), 55.9 (C(10)), 47.7 (C(1′)), 31.7 (C(3‴)), 30.5 (C(2‴)), 24.5 (C(1‴)), 22.3 (C(4‴)), 14.0 (C(5‴)); IR (Nujol) δ 2936 (s), 2860 (s), 1456 (s), 1377 (m), 1224 (w), 1170 (w), 799 (w), 738 (w), 728 (w); MS (EI, 70 eV) m/z 408 (M^+, 46), 351 (74), 91 (100), 219 (9), 83 (80); TLC: R_f 0.19 (hexane/EtOAc, 9:1) [silica gel, UV]. Anal. Calcd for $C_{28}H_{28}N_2O$ (408.53): C, 82.32; H, 6.91; N, 6.86. Found: C, 82.18; H, 6.98; N, 6.95.

Acknowledgements

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

Supplementary data

Complete experimental details for all preparative procedures along with full characterization of all starting materials and products as well as optimization experiments (66 pages) are provided. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.10.043.

References and notes

1. Kawasaki, T.; Higuchi, K. *Nat. Prod. Rep.* **2005**, *22*, 761–793.
2. Walsh, T. F.; Toupence, R. B.; Ujjainwalla, F.; Young, J. R.; Goulet, M. T. *Tetrahedron* **2001**, *57*, 5233–5241.
3. Watson, T. J. N.; Horgan, S. W.; Shah, R. S.; Farr, R. A.; Schnettler, R. A.; Nevill, C. R.; Weiberth, F. J.; Huber, E. W.; Baron, B. M.; Webster, M. E.; Mishra, R. J.; Harrison, B. L.; Nyce, P. L.; Rand, C. L.; Gorlaski, C. T. *Org. Process Res. Dev.* **2000**, *4*, 477–487.
4. Jacotot, B.; Banga, J. D.; Pfister, P.; Mehra, M. *Br. J. Clin. Pharmacol.* **1994**, *38*, 257–263.
5. (a) Brown, R. K. In *Indoles Part One*; Houlihan, W. J., Ed.; Wiley: New York, NY, 1972; pp 227–559; (b) Sundberg, R. *Indoles*; Academic: San Diego, 1996; pp 7–53; (c) Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875–2911.
6. Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045–1075.
7. Robinson, B. *The Fischer Indole Synthesis*; Wiley-Interscience: New York, NY, 1982.
8. Clark, R. D.; Repke, D. H. *Heterocycles* **1984**, *63*, 214–221.
9. Castro, C. E.; Stephens, R. D. *J. Org. Chem.* **1963**, *28*, 2163.
10. Nenitzescu, C. D. *Bull. Soc. Chim. Romania* **1929**, *11*, 37–43.
11. Kurti, L.; Czako, B. *Strategic Applications of Named Reactions in Organic Synthesis*; Elsevier: London, 2005; pp 172–173.
12. Söderberg, B. C.; Chisnell, A. C.; O'Neil, S. N.; Shriver, J. A. *J. Org. Chem.* **1999**, *64*, 9731–9734.
13. (a) Cadogan, J. I. G.; Cameron-Wood, M. *Proc. Chem. Soc. (London)* **1962**, 361; (b) Cadogan, J. I. G. *Synthesis* **1969**, 11–17.
14. (a) Sundberg, R. J. *J. Org. Chem.* **1965**, *30*, 3604–3610; (b) Sundberg, R. J.; Tamazaki, T. *J. Org. Chem.* **1967**, *32*, 290–294.
15. Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873–2920.
16. Fukuyama, T.; Chen, X.; Peng, G. *J. Am. Chem. Soc.* **1994**, *116*, 3127–3128.
17. Fürstner, A.; Hupperts, A. *J. Am. Chem. Soc.* **1995**, *117*, 4468–4475.
18. Fuwa, H.; Sasaki, M. *Org. Biomol. Chem.* **2007**, *5*, 2214–2218.
19. (a) Arcadi, A.; Cacchi, S.; Marinelli, F. *Tetrahedron Lett.* **1992**, *33*, 3915–3918; (b) Lu, B. Z.; Zhao, W.; Wei, H.; Dufour, M.; Farina, V.; Senanayake, C. H. *Org. Lett.* **2006**, *8*, 3271–3274.
20. (a) Reviews: Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285–2309; (b) Larock, R. C. *Top. Organomet. Chem.* **2005**, *14*, 147–182.
21. Larock, R. C.; Yum, E. K. *J. Am. Chem. Soc.* **1991**, *113*, 6689–6690.
22. Larock, R. C.; Yum, E. K.; Refvik, M. D. *J. Org. Chem.* **1998**, *63*, 7652–7662.
23. Nishikawa, T.; Wada, K.; Isobe, M. *Biosci. Biotechnol. Biochem.* **2002**, *66*, 2273–2278.
24. Roschanger, F.; Liu, J.; Estanove, E.; Dufour, M.; Rodriguez, S.; Farina, V.; Hickey, E.; Hossain, A.; Jones, P. J.; Lee, H.; Lu, B. Z.; Varsolona, R.; Schroder, J.; Beaulieu, P.; Gillard, J.; Senanayake, C. H. *Tetrahedron Lett.* **2008**, *49*, 363–366.
25. (a) Brodfuehrer, P. R.; Chen, B. C.; Sattelberg, T. R.; Smith, P. R.; Reddy, J. P.; Stark, D. R.; Quinlan, S. L.; Reid, J. G.; Thottathil, J. K.; Wang, S. J. *J. Org. Chem.* **1997**, *62*, 9192–9202; (b) Chen, C.; Lieberman, D. R.; Larsen, R. D.; Reamer, R. A.; Verhoeven, T. R.; Reider, P. J. *Tetrahedron Lett.* **1994**, *35*, 6981–6984.
26. Kurti, L.; Czako, B. *Strategic Applications of Named Reactions in Organic Synthesis*; Elsevier: London, 2005; pp 260–261.
27. (a) Denmark, S. E.; Baird, J. D. *Org. Lett.* **2004**, *6*, 3649–3652; (b) Denmark, S. E.; Baird, J. D. *Org. Lett.* **2006**, *8*, 793–795; (c) Denmark, S. E.; Baird, J. D.; Regens, C. S. *J. Org. Chem.* **2008**, *73*, 1440–1455.
28. (a) Kosugi, M.; Shimizu, Y.; Migita, T. *J. Organomet. Chem.* **1977**, *129*, C36–C38; (b) Farina, V.; Krishnamurthy, V.; Scott, W. *Org. React.* **1997**, *50*, 1–652; (c) Mitchell, T. N. In *Metal-catalyzed Cross-coupling Reactions*, 2nd ed.; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, 2004; Chapter 3.
29. (a) Negishi, E.-i.; King, A. O.; Okukado, N. *J. Organomet. Chem.* **1977**, *42*, 1821–1823; (b) Knochel, P.; Millot, N.; Rodriguez, A. L.; Tucker, C. E. *Org. React.* **2001**, *58*, 417–731; (c) Knochel, P. *Science of Synthesis*; Thieme Verlag: Stuttgart, 2004; Vol. 3, 5–90; (d) Knochel, P.; Calaza, M. I.; Hupe, E. In *Metal-catalyzed Cross-coupling Reactions*, 2nd ed.; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, 2004; Chapter 11.
30. (a) Miyaura, N.; Yamada, K.; Suginome, A.; Suzuki, A. *J. Am. Chem. Soc.* **1985**, *107*, 972–980; (b) Suzuki, A. *Pure Appl. Chem.* **1994**, *66*, 213–222; (c) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483; (d) Hall, D. G. *Boronic Acids*; Wiley-VCH: Weinheim, 2005; pp 3–14; (e) Miyaura, N. In *Metal-catalyzed Cross-Coupling Reactions*, 2nd ed.; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, 2004; Chapter 2.
31. 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.; Shirakawa, E. *Top. Curr. Chem.* **2002**, *219*, 62–85; (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. *Aldrichimica Acta* **2003**, *36*, 75–85; (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.
32. Denmark, S. E.; Baird, J. D. *Chem.—Eur. J.* **2006**, *12*, 4954–4963.
33. Denmark, S. E.; Kallemeyn, J. M. *Org. Lett.* **2003**, *5*, 3483–3486.
34. Lee, M.; Ko, S.; Chang, S. *J. Am. Chem. Soc.* **2000**, *122*, 12011–12012.
35. Werner, H.; Kuhn, A. *J. Organomet. Chem.* **1979**, *179*, 439–445.
36. Kasiotis, K. M.; Haroutounian, S. A. *Bioorg. Chem.* **2006**, *34*, 1–14.
37. Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; Wiley-Interscience: New York, NY, 1999; pp 615–631.
38. Cropper, E. L.; White, A. J. P.; Ford, A.; Hii, K. K. *J. Org. Chem.* **2006**, *71*, 1732–1735.
39. McLaughlin, M.; Palucki, M.; Davies, I. W. *Org. Lett.* **2006**, *8*, 3307–3310.
40. Lizos, D. E.; Murphy, J. A. *Org. Biomol. Chem.* **2003**, *1*, 117–122.
41. Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685–4696.
42. The pH of the silica gel used in these laboratories was found to be slightly acidic (pH 6.6–7.0).
43. Arcadi, A.; Cacchi, S.; Marinelli, F. *Tetrahedron Lett.* **1986**, *27*, 6397–6400.
44. Milne, J. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 13028–13032.
45. (a) Zheng, N.; Anderson, K. W.; Huang, X.; Nguyen, H. N.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2007**, *46*, 7509–7512; (b) Charles, M. D.; Schultz, P.; Buchwald, S. L. *Org. Lett.* **2005**, *7*, 3965–3968.
46. Merour, J.; Benoit, J. *Curr. Org. Chem.* **2001**, *5*, 471–506.