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Iridium-Catalyzed Silylation of Aryl C−H Bonds

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Supporting Information

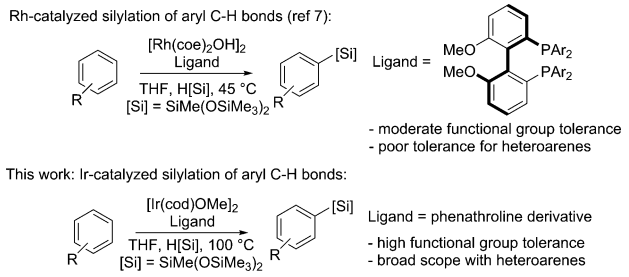
ABSTRACT: A method for the iridium-catalyzed silylation of aryl C−H bonds is described. The reaction of $HSiMe(OSiMe_3)_2$ with arenes and heteroarenes catalyzed by the combination of $[Ir(cod)(OMe)]_2$ and 2,4,7-trimethylphenanthroline occurs with the aromatic compound as the limiting reagent and with high levels of sterically derived regioselectivity. This new catalytic system occurs with a much higher tolerance for functional groups than the previously reported rhodium-catalyzed silylation of aryl C−H bonds and occurs with a wide range of heteroarenes. The silylarene products are suitable for further transformations, such as oxidation, halogenation, and cross-coupling. Late-stage functionalization of complex pharmaceutical compounds was demonstrated.

The functionalization of aryl and alkyl C−H bonds with main group reagents, such as boranes and silanes, occurs with unique regioselectivity dictated by the catalysts and provides intermediates that can be derivatized to a wide range of products. Prompted by initial observations of the borylation of arenes and alkanes by isolated metal−boryl complexes,[1] the catalytic borylation of C−H bonds with Rh- and Ir-complexes has been reported, including practical borylations of aryl C−H bonds.[1c,2] The mechanism of these reactions has been revealed in detail,[3] and applications of C−H borylation in the synthesis of several complex molecules have been reported.[4]

Silanes are produced on a larger scale than boranes and can serve as precursors to important commercial materials. Moreover, silanes can contain a broader combination of substituents than boranes and, with the proper choice of substituents, can generate valuable synthetic intermediates. However, the silylation of aryl C−H bonds is less developed than the borylation of aryl C−H bonds. Metal−silyl complexes are less reactive than metal−boryl complexes toward C−H bond functionalization, and most methods for the catalytic, intermolecular silylation of aryl C−H bonds require high temperatures, a large excess of the arene,[5] or the presence of directing groups.[6] Furthermore, trialkylsilanes have been the most commonly used silane reagent,[5c,6b,d−f] and the aryltrialkylsilane products formed from reactions of these compounds have limited synthetic utility because they undergo a narrower range of reactions than do arylboron compounds.

Recently, our group reported a Rh system that catalyzes undirected, intermolecular silylation of aryl C−H bonds (Scheme 1).[7] These reactions occurred with the inexpensive $HSiMe(OSiMe_3)_2$ as the Si source and with arene as the limiting reagent under mild conditions (45 °C). In addition, the arylsilane products are amenable to cross-coupling, oxidation, halogenation, and amination reactions because the silane reagent is activated by the two O-atoms connected to the Si.

Scheme 1. Silylation of Aryl C−H Bonds



However, two main drawbacks were evident from our studies on the Rh-catalyzed silylation of aryl C−H bonds. First, the reaction does not tolerate many of the common functional groups in medicinally important molecules, such as heavy halides, carbonyl groups, and cyano groups; also, the reactions did not occur at the C−H bonds of heteroarenes containing basic nitrogen atoms. Reactions of aryl bromides and aryl iodides led predominantly to protodehalogention of the carbon−halogen bond, and reactions of arenes containing ketone and ester functionalities led to hydrosilylation of the carbonyl groups (Tertiary amides were tolerated, however.). Coordinating groups, such as nitriles or pyridines, poisoned the catalyst. Second, the chiral biaryl ligands in the Rh catalyst for arene silylation are much more expensive than the bipyridine and phenanthroline ligands in the Ir catalysts for arene borylation, and the cost of the ligands can affect the utility of the reaction on a large scale.

We report the discovery of an iridium precursor and appropriately substituted phenanthroline ligand that catalyzes the silylation of arenes and heteroarenes with high functional group compatibility and high tolerance for basic heterocycles. This reactivity enables the silylation reaction to form building blocks for medicinal chemistry and to be used for the late-stage functionalization of compounds with biological activity.

To improve the functional group compatibility of the C−H silylation of arenes, we investigated Ir catalysts that might translate the high functional group compatibility of the Ir-catalyzed borylation reactions to the silylation of arenes and heteroarenes. To do so, we conducted silylations catalyzed by the combination of an Ir(I) precursor and various bidentate N-based ligands commonly used for the borylation of aryl C−H bonds.[1c,4c] This combination of catalyst components has been reported to induce the silylation of aryl C−H bonds with several

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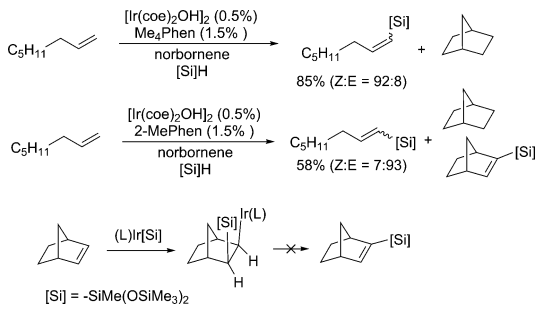
Scheme 2. Dehydrogenative Silylation of Alkenes with Me_4Phen and 2-MePhen as the Ligand[9]



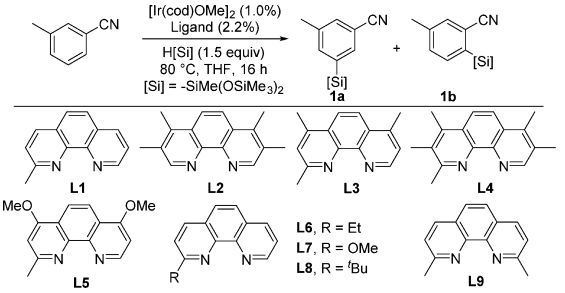
tetrafluorodisilanes, but the reactions were conducted with either neat arene or 10 equiv of arene.[5a,b]

To test the activity of Ir catalysts for the silylation of arenes, we conducted the reactions of 1 equiv of *m*-xylene with 1.5 equiv of $HSiMe(OSiMe_3)_2$ at 80 °C in THF with a catalyst generated from $[Ir(cod)OMe]_2$ and 3,4,7,8-tetramethyl-1,10-phenanthroline (Me_4Phen). Although this ligand leads to the most active current catalyst for the borylation of aryl and alkyl C−H bonds,[4c,8] the corresponding silylxylene was obtained in only 10% yield, as determined by GC. This result implied that a different ligand was necessary for the silylation of arenes with broad scope.

Several considerations pointed to a catalyst for the silylation of arenes in a synthetically valuable fashion. First, during our studies on the dehydrogenative silylation of alkenes,[9] we conducted reactions with a series of 2-substituted phenanthroline ligands and found that reactions catalyzed by complexes of 2-methyl-1,10-phenanthroline (2-MePhen, **L1**) generated a significant amount of product from dehydrogenative silylation of norbornene (Scheme 2). The dehydrogenative silylation of terminal alkenes catalyzed by complexes of Me_4Phen (**L2**) generated only the desired alkene silylation product and the hydrogenation byproduct norbornane. According to ^{2}H-labeling experiments, the silylation of terminal alkenes occurs by *syn*-insertion and *syn*-β-H elimination.[9] However, this mechanism would not lead to the dehydrogenative silylation of norbornene because the fused-ring structure would inhibit the β-H elimination. Thus, the silylation of norbornene likely occurred by direct C−H activation. This logic led us to consider that 2-substituted phenanthrolines could generate a more active silyl complex for the activation of C(sp^2)−H bonds than would Me_4Phen.

Second, the functionalization of arenes with boron reagents occurs faster with electron-poor arenes than it does with electron-rich arenes.[2c] Thus, we studied the silylation of 3-tolunitrile as a model substrate. This substrate is a suitable test of the method for several reasons. First, the nitrile group in this substrate, which can coordinate to the metal center, completely suppressed the Rh catalyst for the C−H silylation.[7] Second, because the nitrile group contains unsaturation, this substrate would test the chemoselectivity of the catalyst toward C−H silylation vs hydrosilylation. Third, this substrate would test whether the regioselectivity is controlled by steric, electronic, or directing effects because the nitrile is small and strongly electron withdrawing and can serve as an *ortho*-directing group.[10] Finally, most functionalized arenes and basic heteroarenes are more electron deficient than benzene; thus, an arene containing an electron-withdrawing group could be a more appropriate model for an arene in a medicinally active compound than would *m*-xylene.

Table 1. Evaluation of Reaction Conditions



entry	ligand	conversion (%)[a]	yield (%)[a,b]	1a:1b[a]
1	**L1**	29	26	19:1
2	**L2**	6	0	–
3	**L3**	38	36	26:1
4	**L4**	39	35	26:1
5	**L5**	34	30	24:1
6	**L6**	9	7	20:1
7	**L7**	22	19	6:1
8	**L8**	31	0	–
9	**L9**	45	38	11:1
10[c]	**L3**	53	49	26:1
11[c,d]	**L3**	93	90	25:1

[a]Determined by GC. [b]Combined yield of **1a** and **1b**. [c]Reaction run with 1 equiv of cyclohexene. [d]Reaction run at 100 °C.

We evaluated the reaction of 3-tolunitrile with catalysts ligated by a series of phenanthroline ligands containing 2-substituents (Table 1). Reaction with 2-MePhen (**L1**) as the ligand at 80 °C in THF for 16 h afforded the products (**1a** and **1b**) from C−H silylation in 26% yield. Surprisingly, the silylation of 3-tolunitrile with Me_4Phen (**L2**) as the ligand did not give any desired product, even though reaction of *m*-xylene under similar conditions with **L2** formed the corresponding silylxylene in 10% yield. Varying the electronic property on the position *para* to the nitrogen atoms led to a small increase in yields (**L3**−**L5**), the highest yield obtained with 2,4,7-trimethyl-1,10-phenanthroline (**L3**) as the ligand. Varying the substituent at the 2-position led to lower yields (**L6**−**L8**) of the arylsilane product. Except for the reaction with **L8** as the ligand, the yields were similar to the conversions.[11] The silylation reaction catalyzed by Ir-**L3** run with a hydrogen acceptor occurred in slightly higher yields than reactions without an acceptor (entry 10). Finally, the reaction conducted at 100 °C occurred to high conversion and afforded **1a** and **1b** in 90% yield (entry 11). Reactions conducted with other hydrosilanes containing at least one alkoxy group connected to silicon did not generate significant amounts of desired products (see the Supporting Information (SI)).

After establishing these conditions for the Ir-catalyzed silylation of arenes, we evaluated the functional-group compatibility of this process. The tolerance of the reaction for auxiliary functional groups is striking. The arene silylation is compatible with ester, ketone, bromide, iodide, nitrile, and sulfone functionalities (Scheme 3). Hydrosilylation of ketones and esters was not observed, and the product of protodehalogenation of an aryl iodide was observed in only 3% yield (**7**). In addition, the reaction proceeded with high levels of sterically derived regioselectivity. Various 1,3-disubstituted arenes underwent silylation exclusively at the mutually *meta* positions, except for 3-CF_3-anisole and 3-tolunitrile, which each afforded 4% of the product in which the silyl group was installed *ortho* to the relatively small OMe (**6**) and CN (**1**) groups. These results are

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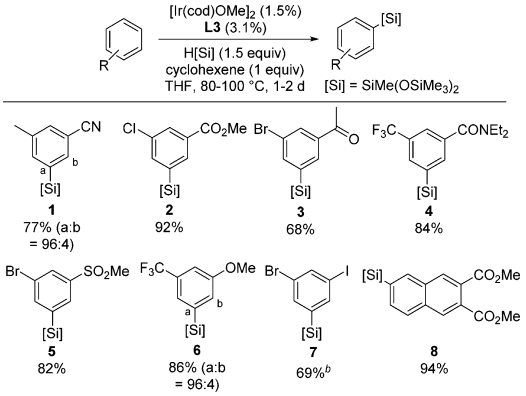
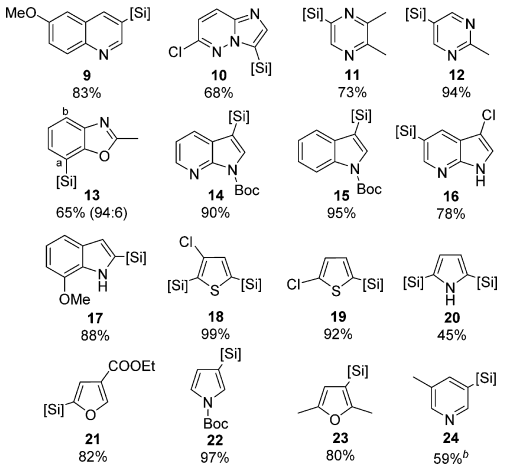
Scheme 3. C−H Silylation of Arenes[a]



[a]Yields of isolated products. [b]3% of inseparable protodeiodination product was also obtained.

Scheme 4. C−H Silylation of Heteroarenes[a]

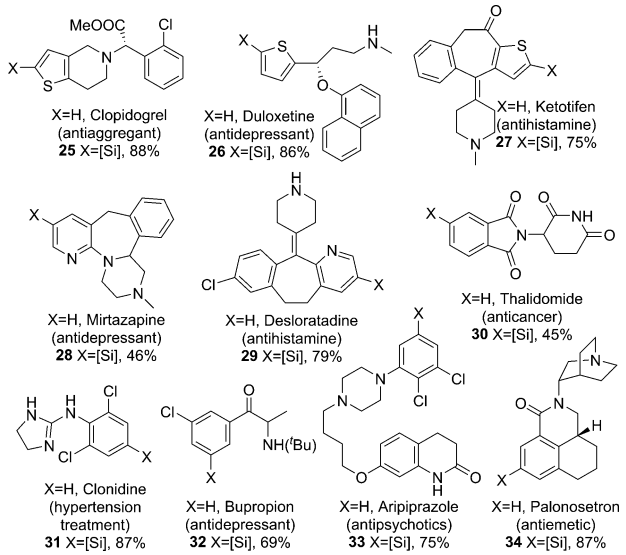


[a]Reactions conducted under conditions similar to the conditions in Scheme 3. For detailed procedures, see the SI. Yields of isolated products reported. [b]Reaction conducted at 120 °C for 2 d.

comparable to the results from borylation of 3-CF_3-anisole and 3-tolunitrile, in which 3% and 6% of the products containing the boryl group *ortho* to the OMe and CN group formed, respectively.[12]

The compatibility with heteroarenes, especially those containing basic nitrogen atoms, was also striking. Silylation of potentially coordinating pyrazines, pyrimidines, and azaindoles afforded the corresponding silylarenes in good yields (Scheme 4). Reaction of five-membered heteroarenes required lower temperatures than reactions of pyrimidines and pyrazines and proceeded with high levels of regioselectivity for functionalization of the C−H bonds α to the heteroatoms. Silylation of heteroarenes in which the α-positions are substituted (**23**) or sterically hindered because of a large substituent on the nitrogen (**22**) occurred at the β-positions. Silylation of the free NH group of 7-methoxyindole (**17**) and of pyrrole (**20**) did not occur under the reaction conditions. However, silylation of unprotected azaindoles first occurred at the N−H bond (**16**).[13,4c,14] Subsequent silylation at the sterically accessible C−H bond β to the pyridine nitrogen and hydrolysis of the N−Si bond furnished a single product from C−H silylation. Like the borylation of heteroarenes containing basic N-atoms,[2e,4c] the silylation occurred at the C−H bond β to the basic nitrogen over

Scheme 5. C−H Silylation of Pharmaceutical Compounds[a]



[a]Reactions conducted under conditions similar to the conditions in Scheme 3. For detailed procedures, see the SI. Yields of isolated products reported.

the C−H bond α to the basic nitrogen. Silylation of an unhindered pyridine, 3-picoline (**24**), required high temperature (120 °C), but formed the product in an acceptable 59% yield. The slow rate likely results from strong binding of the substrate to the metal center through the basic N-atom.

The conditions for the silylation of simple arenes were suitable for the functionalization of the active pharmaceutical ingredients (APIs) in some of the most prescribed drugs (Scheme 5),[15,16] indicating that the scope of the reaction is appropriate for applications in medicinal chemistry. Moreover, these reactions reveal the relative reactivity of different types of aryl and heteroaryl C−H bonds. For example, the silylation of clopidogrel, duloxetine, and ketotifen all occurred selectively at the 2-position of the thiophene moiety over the benzene or naphthalene ring (**25**−**27**). Silylation of the pyridine ring in mirtazapine also occurred over silylation of the benzene ring, although 14% of readily separable disilylation products were also obtained (**28**). In addition, the secondary alkyl amine moieties in duloxetine (**26**) and desloratadine (**29**) were protected *in situ* by silylation of the N−H bond and did not interfere with subsequent silylation of C−H bonds.[17] In contrast to this reactivity, the C−H borylation does not occur in the presence of secondary alkylamines. Furthermore, the imidazoline moiety in clonidine (**31**), the secondary amide in aripiprazole (**33**), and the imides in thalidomide (**30**) were all tolerated, and single isomers of the silylation products were obtained from these substrates because of the relative accessibility of the various C−H bonds.

Because of the presence of the Si−O bonds in the silyl substituent, the silylarene products are suitable for transformations that form C−heteroatom and C−C bonds, such as oxidations,[18] halogenations, and cross-couplings.[19] As shown in Scheme 6, reactions of both simple arenes and products from the silylation of APIs occurred to form the corresponding phenols, aryl halides, and biaryls in good isolated yields. The suitability of the methods for functionalization of aryl−Si bonds in several polycylic arylsilanes containing basic heterocycles and potentially reactive functionality (**41**, **44**, **45**) illustrates the suitability of

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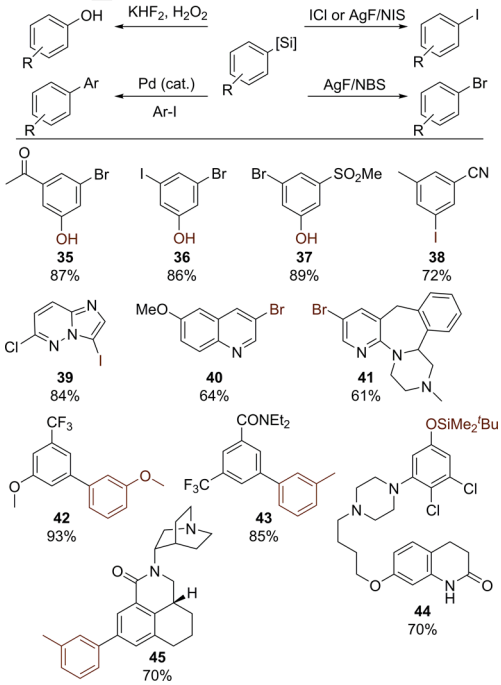
Scheme 6. Functionalization of Silylarene Products[a]



[a]For detailed procedures, see the SI. Yields of isolated products reported.

silylation and subsequent derivatization for the late-stage functionalization of complex molecules.

In summary, we have developed a method for the intermolecular C−H silylation of arenes that occurs with the arene as the limiting reagent and exhibits high levels of sterically derived regioselectivity. Compared to the Rh-catalyzed silylation of an aryl C−H bond, this Ir-catalyzed C−H silylation is compatible with a much broader scope of functional groups and occurs with a broader range of heteroarenes, making it particularly suitable for late-stage functionalization of complex pharmaceutical molecules. However, the reaction requires higher temperatures than the Rh-catalyzed silylation or the C−H borylation, and the regioselectivity of reactions with unsymmetrical 1,2-disubstituted arenes is lower (see the SI). Moreover, the range of reactions of the arylsilanes is narrower than that of aryl boronic esters. Thus, efforts to identify ligands that increase the rate and the regioselectivity of the process, along with methods for further functionalization of the silylarene products, are goals of future studies in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures and characterization of products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Waltz, K. M.; Hartwig, J. F. *Science* **1997**, *277*, 211. (b) Chen, H. Y.; Schlecht, S.; Semple, T. C.; Hartwig, J. F. *Science* **2000**, *287*, 1995. (c) Ishiyama, T.; Takagi, J.; Ishida, K.; Miyaura, N.; Anastasi, N.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 390.

(2) (a) Cho, J.-Y.; Tse, M. K.; Holmes, D.; Maleczka, R. E.; Smith, M. R. *Science* **2002**, *295*, 305. (b) Tajuddin, H.; Harrisson, P.; Bitterlich, B.; Collings, J. C.; Sim, N.; Batsanov, A. S.; Cheung, M. S.; Kawamorita, S.; Maxwell, A. C.; Shukla, L.; Morris, J.; Lin, Z.; Marder, T. B.; Steel, P. G. *Chem. Sci.* **2012**, *3*, 3505. (c) Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2010**, *110*, 890. (d) Kawamorita, S.; Ohmiya, H.; Hara, K.; Fukuoka, A.; Sawamura, M. *J. Am. Chem. Soc.* **2009**, *131*, 5058. (e) Preshlock, S. M.; Plattner, D. L.; Maligres, P. E.; Krska, S. W.; Maleczka, R. E.; Smith, M. R. *Angew. Chem., Int. Ed.* **2013**, *52*, 12915.

(3) Boller, T. M.; Murphy, J. M.; Hapke, M.; Ishiyama, T.; Miyaura, N.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 14263.

(4) (a) Fischer, D. F.; Sarpong, R. *J. Am. Chem. Soc.* **2010**, *132*, 5926. (b) Liao, X.; Stanley, L. M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2011**, *133*, 2088. (c) Larsen, M. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2014**, *136*, 4287.

(5) (a) Ishiyama, T.; Sato, K.; Nishio, Y.; Miyaura, N. *Angew. Chem., Int. Ed.* **2003**, *42*, 5346. (b) Saiki, T.; Nishio, Y.; Ishiyama, T.; Miyaura, N. *Organometallics* **2006**, *25*, 6068. (c) Tsukada, N.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 5022. (d) Murata, M.; Fukuyama, N.; Wada, J.-i.; Watanabe, S.; Masuda, Y. *Chem. Lett.* **2007**, *36*, 910. (e) Ezbiansky, K.; Djurovich, P. I.; LaForest, M.; Sinning, D. J.; Zayes, R.; Berry, D. H. *Organometallics* **1998**, *17*, 1455.

(6) (a) Kakiuchi, F.; Igi, K.; Matsumoto, M.; Chatani, N.; Murai, S. *Chem. Lett.* **2001**, *30*, 422. (b) Ihara, H.; Suginome, M. *J. Am. Chem. Soc.* **2009**, *131*, 7502. (c) Oyamada, J.; Nishiura, M.; Hou, Z. *Angew. Chem., Int. Ed.* **2011**, *50* (45), 10720. (d) Choi, G.; Tsurugi, H.; Mashima, K. *J. Am. Chem. Soc.* **2013**, *135*, 13149. (e) Tobisu, M.; Ano, Y.; Chatani, N. *Chem.—Asian J.* **2008**, *3*, 1585. (f) Kanyiva, K. S.; Kuninobu, Y.; Kanai, M. *Org. Lett.* **2014**, *16*, 1968.

(7) Cheng, C.; Hartwig, J. F. *Science* **2014**, *343*, 853.

(8) (a) Liskey, C. W.; Hartwig, J. F. *J. Am. Chem. Soc.* **2012**, *134*, 12422. (b) Liskey, C. W.; Hartwig, J. F. *J. Am. Chem. Soc.* **2013**, *135*, 3375.

(9) Cheng, C.; Simmons, E. M.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2013**, *52*, 8984.

(10) (a) Li, W.; Xu, Z.; Sun, P.; Jiang, X.; Fang, M. *Org. Lett.* **2011**, *13*, 1286. (b) Li, W.; Sun, P. *J. Org. Chem.* **2012**, *77*, 8362. (c) Du, B.; Jiang, X.; Sun, P. *J. Org. Chem.* **2013**, *78*, 2786.

(11) Reaction conducted with **L8** as the ligand led to mainly hydrosilylation of the nitrile group.

(12) The borylation reactions were conducted following the literature procedures (ref 1c).

(13) The difference among the reactivity of the N−H bonds in azaindoles, pyrroles, and indoles under the silylation conditions is similar to their reactivity under the borylation conditions (refs 4c and 14). For possible causes, see ref 4c.

(14) Takagi, J.; Sato, K.; Hartwig, J. F.; Ishiyama, T.; Miyaura, N. *Tetrahedron Lett.* **2002**, *43*, 5649.

(15) McGrath, N. A.; Brichacek, M.; Njardarson, J. T. *J. Chem. Educ.* **2010**, *87*, 1348.

(16) Top 100 Most Prescribed, Top Selling Drugs. http://www.medscape.com/viewarticle/825053 (accessed Oct 2014).

(17) The secondary amine moiety in bupropion was not silylated during the reaction, presumably because of the steric hindrance of the *tert*-butyl group (**31**).

(18) Tamao, K.; Ishida, N.; Tanaka, T.; Kumada, M. *Organometallics* **1983**, *2*, 1694.

(19) (a) Hatanaka, Y.; Hiyama, T. *J. Org. Chem.* **1988**, *53*, 918. (b) Denmark, S. E.; Regens, C. S. *Acc. Chem. Res.* **2008**, *41*, 1486.

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J. Am. Chem. Soc. 2015, 137, 592−595