Synthetic Methods

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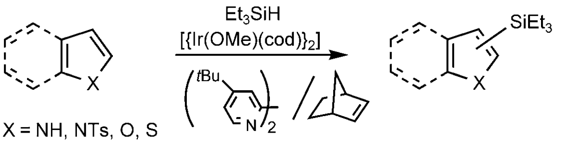
Efficient Iridium-Catalyzed C–H Functionalization/Silylation of Heteroarenes**

*Biao Lu and John R. Falck**

As a consequence of their unique chemical, physical, and biological properties, silyl-substituted arenes have attracted wide interest from the synthetic,[1] material science,[2] and pharmaceutical sectors.[3] Traditionally, silyl substituents have been introduced by the addition of aryl lithium or magnesium reagents to silicon electrophiles, and this method often necessitates the use of protecting groups.[4] Consequently, transition-metal-catalyzed cross couplings of aryl halides with disilanes or hydrosilanes have grown in popularity, especially if base- or nucleophile-sensitive functional groups are present.[5] More recently, direct C–H functionalization[6] has emerged as a conceptually and economically attractive alternative for the direct silylation of arenes. However, challenges remain and the general utility of this strategy is restricted in many instances by 1) poor regioselectivity, 2) stringent structural requirements, 3) noncommercial/expensive reagents, 4) harsh reaction conditions (typically 120–200 °C), and 5) impractical ratios of arene to the silicon reagent (10:1–60:1).[7–9] Herein, we report an efficient, regioselective protocol for the bipyridine-ligated, iridium-catalyzed[9] C–H functionalization/silyation of a wide variety of heteroarenes under comparatively mild conditions. Importantly, the reaction does not require protection of the N–H groups and uses only a small excess (3 equiv) of the inexpensive triethylsilane [Eq. (1)].



(1)

Indole **1** was selected as the model heteroarene for initial studies because of its prominence in many natural products and pharmaceuticals.[10] Whereas several laboratories have cogently demonstrated arylation[11] and borylation[12] of indoles by transition-metal-catalyzed C–H functionalization, corresponding silylations are much less efficient (Figure 1). In an instructive example, Ishiyama et al. reported[13] that unprotected **1** only gave complex product mixtures when using the [{Ir(OMe)(cod)}$_2$]/4,4-di-*tert*-butyl-2,2-bipyridine (dtbpy) (cod = cycloocta-1,5-diene) catalytic system in octane; silylated adducts could only be obtained by using N-substituted indoles at elevated temperatures (120 °C) with a large excess of substrate. It was, thus, not surprising that **1** was unreactive to triethylsilane under comparable reaction conditions and could be recovered unchanged despite prolonged heating (Table 1, entry 1). However, switching to THF as the solvent and lowering the temperature to 80 °C rewarded us with 2-(triethylsilyl)-1*H*-indole (**2**),[14] albeit in 4 % yield (Table 1, entry 2). This yield was then boosted to 15 % upon addition of cyclopentene as a co-reactant (Table 1, entry 3). Optimization ultimately led using the more hindered olefin, 2-norbornene,[15] which dramatically improved the yield of **2** (Table 1, entry 4).[16,17] Notably, 3-(triethylsilyl)-1*H*-indole was not detected in the crude reaction mixture by ^{1}H/^{13}C NMR analyses. Other solvents, including octane (Table 1, entry 5), DME (DME = 1,2-dimethoxyethane; Table 1, entry 6), and dioxane (Table 1, entry 7) were less satisfactory.

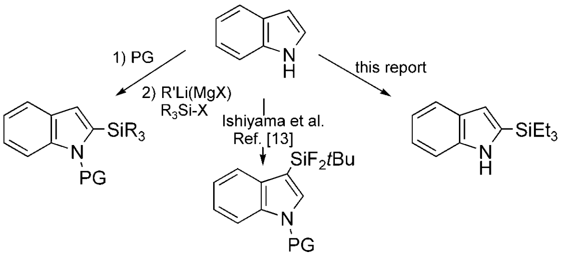
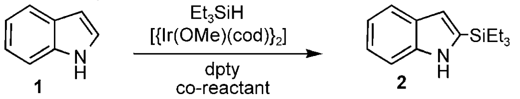


Figure 1. Comparison of silyl indole syntheses. PG = protecting group.

Table 1: Reaction parameters for C–H functionalization of indole **1** to **2**.[a]



Entry	Et$_3$SiH [equiv]	Co-reactant (equiv)	Solvent	Yield [%]
1	5	none	octane	0[b]
2	5	none	THF	4
3	5	cyclopentene (5)	THF	15
4	5	2-norbornene (5)	THF	85
5	5	2-norbornene (5)	octane	22
6	5	2-norbornene (5)	DME	49
7	5	2-norbornene (5)	dioxane	59
8	3	2-norbornene (3)	THF	87
9	1.5	2-norbornene (1.5)	THF	15
10	3	2-norbornene (0.5)	THF	7
11	1.5	2-norbornene (3)	THF	43

[a] Reaction conditions: [{Ir(OMe)(cod)}$_2$] (5 mol%) and 4,4-di-*tert*-butyl-2,2-bipyridine (10 mol%) at 80 °C for 24 h. [b] At 120 °C for 24 h.

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[*] Dr. B. Lu, Prof. J. R. Falck
Departments of Biochemistry and Pharmacology, University of Texas Southwestern Medical Center
5323 Harry Hines Blvd., Dallas, TX 75390-9038 (USA)
Fax: (+1) 214-648-6455
E-mail: j.falck@utsouthwestern.edu

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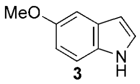
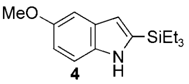
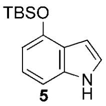
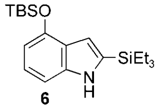
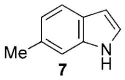
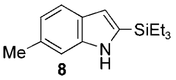
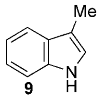
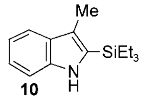
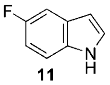
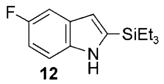
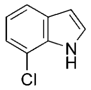
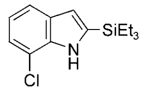
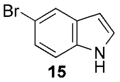
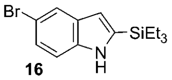
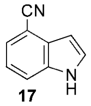
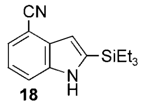
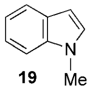
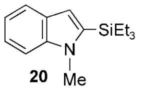
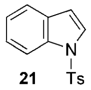
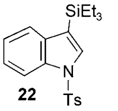
Reducing the number of equivalents of both Et_3SiH and 2-norbornene from 5 equivalents to 3 equivalents had no effect on the yield or the reaction rate (Table 1, entry 8), but additional reductions in the amount of either reagent were detrimental to the yield (Table 1, entries 9–11).

Having established suitable reaction conditions, we explored the scope and generality of the methodology starting with substituted indoles (Table 2). Generally, silylations of indoles bearing electron-donating substituents proceeded well; for example, substrates with groups such as 5-methoxy (**3**→**4**, Table 2, entry 1), 4-*tert*-butyldimethylsilyloxy (**5**→**6**, Table 2, entry 2), and 6-methyl (**7**→**8**, Table 2, entry 3). In contrast, 3-methylindole (**9**→**10**, Table 2, entry 4) reacted sluggishly, which we attribute to steric congestion, but the strict C2 regioselectivity was consistent with that found with other substrates of the series. Electron-withdrawing substituents, including 5-fluoro (**11**→**12**, Table 2, entry 5) and 7-chloro groups (**13**→**14**, Table 2, entry 6) were tolerated. More modest yields of silylated adducts were obtained with 5-bromo (**15**→**16**, Table 2, entry 7) and 4-cyano groups (**17**→**18**, Table 2, entry 8), which were accompanied by lesser amounts of unidentified byproducts; approximately 20 % of the starting material was recovered.

Table 2: C–H functionalization/triethylsilylation of substituted indoles.[a]

Entry	Indole	Adduct	Yield [%]
1	 **3**	 **4**	90
2	 **5**	 **6**	82
3	 **7**	 **8**	86
4	 **9**	 **10**	55[b]
5	 **11**	 **12**	76
6	 **13**	 **14**	64
7	 **15**	 **16**	52[b]
8	 **17**	 **18**	41[b]
9	 **19**	 **20**	49
10	 **21**	 **22**	70

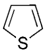
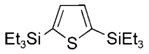
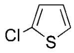
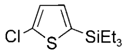
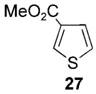
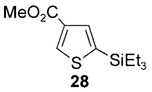
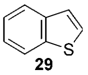
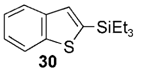
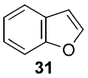
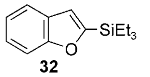
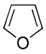
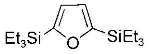
[a] Reaction conditions: [{Ir(OMe)(cod)}$_2$] (5 mol %), dtbpy (10 mol%), Et_3SiH (3 equiv), and norbornene (3 equiv) in THF at 80°C for 24 h. [b] Same as [a], except 10 mol% [{Ir(OMe)(cod)}$_2$]and 20 mol% dtbpy for 36–48 h. TBS = *tert*-butyldimethylsilyl; Ts = *p*-toluenesulfonyl.

Whereas the mechanistic details have yet to be elucidated, the observed regioselectivity is most consistent with a chelation-assisted reaction, that is, coordination between the iridium catalyst and indole nitrogen atom with subsequent insertion into the adjacent C–H bond.[12a] As anticipated, *N*-methylindole (**19**→**20**, Table 2, entry 9) behaved similarly, although the increased steric hindrance around the nitrogen center somewhat suppressed the yield (see Table 2, entry 4). Notably, tosylation of the ring nitrogen atom redirected the regioselectivity toward silylation at C3 (**21**→**22**, Table 2, entry 10), suggesting a change in the mechanism or a metal migration from C2 to C3 as proposed for palladium-mediated indole C–H functionalizations.[6b]

Gratifyingly, *S*- and *O*-heteroarenes were also suitable substrates (Table 3). Thiophene (**23**) was smoothly functionalized to the 2,5-disilyl derivative (**24**) in excellent yield (Table 3, entry 1) when 4 equivalents each of the triethylsilane and norbornene were used.[18] Not surprisingly, a 2-substituted thiophene underwent monosilylation at C5 in very good yield (**25**→**26**, Table 3, entry 2), whereas a 3-substituted thiophene gave rise to a 2:1 mixture of 5-triethylsilyl and 2,5-bis(silylated) adducts (**27**→**28**, Table 3, entry 3). Benzofuran (**31**) and furan (**33**) gave analogous results (Table 3, entries 5 and 6, respectively).

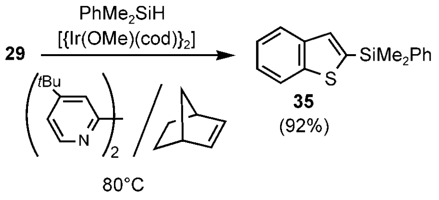
In summary, this report describes an efficient iridium-catalyzed C–H functionalization/silylation of *N*-, *S*-, *O*-heteroarenes including N-unsubstituted indoles under mild conditions and a modest excess (3 equiv) of Et_3SiH. The silylation is strongly promoted by 2-norbornene and features a high level of regioselectivity. Initial results indicate the general procedure described herein is also applicable to other

Table 3: C–H functionalization/triethylsilylation of *S*- and *O*-heteroarenes.[a]

Entry	Heteroarene	Adduct	Yield [%]
1	 **23**	 **24**	98[b]
2	 **25**	 **26**	91
3	 **27**	 **28**	67[c]
4	 **29**	 **30**	99
5	 **31**	 **32**	83
6	 **33**	 **34**	93

[a] Reaction conditions described in Table 2, footnote [a]. [b] Used triethylsilane (4 equiv) and norbornene (4 equiv). [c] 2,5-bis-triethylsilyl adduct obtained in 33 % yield.

triorganosilyl groups including those suitable for additional transformations; for example, **29**→**35** [Eq. (2)].[19]



(2)

Experimental Section

General procedure: A flamed-dried Schlenk tube was charged with heteroarene (0.2 mmol), [{Ir(OMe)(cod)}$_2$] (6.6 mg, 0.01 mmol) and dtbpy (5.4 mg, 0.02 mmol), and then evacuated and flushed with argon three times. Under a positive flow of argon, 2-norbornene (56 mg, 0.6 mmol) and dry THF (1 mL) were added. After stirring for 5 min, triethylsilane (98 μL, 0.6 mmol) was added dropwise and the reaction mixture was heated at 80 °C for 24 h or indicated time. The solvent was concentrated under reduced pressure and the residue was then purified by flash chromatography on silica gel to give 2-(triethylsilyl)heteroarene.

For 1-tosyl-indole, the 3-silylation product was obtained by using the above general procedure.

For furan (0.2 mmol) and thiophene (0.2 mmol), 2-norbornene (75 mg, 0.8 mmol) and triethylsilane (130 μL, 0.8 mmol) were employed.

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[1] Recent examples: a) S. E. Denmark, R. F. Sweis in *Metal-Catalyzed Cross-Coupling Reactions*, *Vol. 1*, 2nd ed. (Eds.: A. De Meijere, F. Diederich), Wiley-VCH, Weinheim, **2004**, pp. 163–216; b) Y. Nakao, A. K. Sahoo, H. Imanaka, A. Yada, T. Hiyama, *Pure Appl. Chem.* **2006**, *78*, 435; c) K. Suzawa, M. Ueno, A. E. H. Wheatley, Y. Kondo, *Chem. Commun.* **2006**, 4850; d) P. Pierrat, P. Gros, Y. Fort, *Org. Lett.* **2005**, *7*, 697; e) E. Abele, E. Lukevics, *Heterocycles* **2002**, *57*, 361.

[2] a) D. Bai, S. Han, Z.-H. Lu, S. Wang, *Can. J. Chem.* **2008**, *86*, 230; b) T. Kumagai, S. Itsuno, *Macromolecules* **2002**, *35*, 5323.

[3] A. K. Franz, *Curr. Opin. Drug Discovery Dev.* **2007**, *10*, 654.

[4] a) T.-H. Nguyen, A.-S. Castanet, J. Mortier, *Org. Lett.* **2006**, *8*, 765; b) C. G. Hartung, A. Fecher, B. Chapell, V. Snieckus, *Org. Lett.* **2003**, *5*, 1899.

[5] a) S. Denmark, J. M. Kallemeyn, *Org. Lett.* **2003**, *5*, 3483; b) E. McNeill, T. E. Barder, S. L. Buchwald, *Org. Lett.* **2007**, *9*, 3785; c) A. Hamze, O. Provot, M. Alami, J.-D. Brion, *Org. Lett.* **2006**, *8*, 931.

[6] a) R. G. Bergman, *Nature* **2007**, *446*, 39; b) I. V. Seregin, V. Gevorgyan, *Chem. Soc. Rev.* **2007**, *36*, 1173; c) K. Godula, D. Sames, *Science* **2006**, *312*, 67; d) A. R. Dick, M. S. Sanford, *Tetrahedron* **2006**, *62*, 2439; e) F. Kakiuchi in *Handbook of C−H Transformations*, *Vol. 1* (Ed.: G. Dyker), Wiley-VCH, Weinheim, **2005**, pp. 131–137, 265–266.

[7] Ru catalysis: a) F. Kakiuchi, K. Tsuchiya, M. Matsumoto, E. Mizushima, N. Chatani, *J. Am. Chem. Soc.* **2004**, *126*, 12792; b) F. Kakiuchi, M. Matsumoto, K. Tsuchiya, K. Igi, T. Hayamizu, N. Chatani, S. Murai, *J. Organomet. Chem.* **2003**, *686*, 134; c) F. Kakiuchi, K. Igi, M. Matsumoto, T. Hayamizu, N. Chatani, S. Murai, *Chem. Lett.* **2002**, 396.

[8] Pt catalysis: a) M. Murata, N. Fukuyama, J.-I. Wada, S. Watanabe, Y. Masyda, *Chem. Lett.* **2007**, *36*, 910; b) N. Tsukada, J. F. Hartwig, *J. Am. Chem. Soc.* **2005**, *127*, 5022; c) Y. Uchimaru, A. M. M. El Sayed, M. Tanaka, *Organometallics* **1993**, *12*, 2065.

[9] Ir catalysis: a) T. Saiki, Y. Nishio, T. Ishiyama, N. Miyaura, *Organometallics* **2006**, *25*, 6068; b) T. Ishiyama, K. Sato, Y. Nishio, N. Miyaura, *Angew. Chem.* **2003**, *115*, 5504; *Angew. Chem. Int. Ed.* **2003**, *42*, 5346.

[10] H.-J. Borschberg, *Curr. Org. Chem.* **2005**, *9*, 1465.

[11] a) D. R. Stuart, K. Fagnou, *Science* **2007**, *316*, 1172; b) N. R. Deprez, D. Kalyani, A. Krause, M. S. Sanford, *J. Am. Chem. Soc.* **2006**, *128*, 4972; c) N. P. Grimster, C. Gauntlett, C. R. A. Godfrey, M. J. Gaunt, *Angew. Chem.* **2005**, *117*, 3185; *Angew. Chem. Int. Ed.* **2005**, *44*, 3125; d) E. M. Ferreira, B. M. Stoltz, *J. Am. Chem. Soc.* **2003**, *125*, 9578.

[12] a) S. Paul, G. A. Chotana, D. Holmes, R. Reichle, P. E. Maleczka, M. R. Smith, *J. Am. Chem. Soc.* **2006**, *128*, 15552; b) T. M. Boller, J. M. Murphy, M. Hapke, T. Ishiyama, N. Miyaura, J. F. Hartwig, *J. Am. Chem. Soc.* **2005**, *127*, 14263; c) T. Ishiyama, Y. Nobuta, J. F. Hartwig, N. Miyaura, *Chem. Commun.* **2003**, 2924; d) T. Ishiyama, N. Miyaura, *Pure Appl. Chem.* **2006**, *78*, 1369.

[13] T. Ishiyama, K. Sata, Y. Nishio, T. Saiki, N. Miyaura, *Chem. Commun.* **2005**, 5065.

[14] Alternative synthesis of 2-triethylsilylindole: K. Kamikawa, S. Kinoshita, M. Furusyo, S. Takemoto, H. Matsuzaka, M. Uemura, *J. Org. Chem.* **2007**, *72*, 3394.

[15] Other unsaturated molecules, e.g., tetramethylethylene, 1-hexene, 1-heptyne, and diisopropyl azodicarboxylate, had no effect on the yield of **2**.

[16] For prior use of 2-norbornene in catalytic C−H activations, see references [7a and c]. The exact role of 2-norbornene as a promoter of the iridium-catalyzed reactions reported herein is unclear. The identification of norbornane, by GC-MS methods, in the reaction mixture suggests it functions as a sink for the hydrogen generated during the reaction. Additionally, it may play a more intimate role as a participant in the catalytic cycle. We speculate the bicyclic skeleton of norbornene affords greater steric shielding or stability towards unproductive β-hydride eliminations than comparable iridium complexes with cyclic or acyclic olefins. Unfortunately, attempts to detect Ir–norbornene intermediates by NMR methods were disappointing.

[17] Equivalent reactions of **1** in THF at 80 °C for 24 h by using Et_3SiH (3 equiv), 2-norbornene (3 equiv), and $Ru_3(CO)_{12}$, [{CpRhCl$_2$}$_2$] or [{RhCl(cod)}$_2$] instead of [{Ir(OMe)(cod)}$_2$]/4,4-di-*tert*-butyl-2,2-bipyridine, produced little, if any, **2**.

[18] 1.5 equivalents of Et_3SiH/1.5 equivalents of 2-norbornene provided **24** (8%) and 2-triethylsilylthiophene (23%). Both the yield and ratio of **24** to 2-triethylsilylthiophene increased progressively as the number of equivalents of Et_3SiH increased from 1.5 to 4.0.

[19] Tamao–Kumada–Fleming oxidation review: R. J. Mullins, S. L. Jolley, A. R. Knapp in *Name Reactions for Functional Group Transformations* (Eds.: J. J. Li, E. J. Corey), Wiley, Hoboken, **2007**, pp. 237–247.