ORGANIC LETTERS

2010
Vol. 12, No. 14
3185−3187

Pd(OAc)$_2$-Catalyzed Regioselective Arylation of Indoles with Arylsiloxane in Acidic Medium

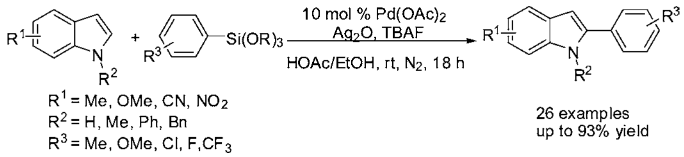
Zunjun Liang, Bangben Yao, and Yuhong Zhang*

Department of Chemistry, Zhejiang University, Hangzhou 310027, P. R. China

yhzhang@zju.edu.cn

Received May 18, 2010

ABSTRACT



Mild conditions have been developed to achieve a Pd(OAc)$_2$-catalyzed cross-coupling between indoles and arylsiloxanes in the presence of TBAF and Ag$_2$O in acidic medium. Electron-deficient arylsiloxanes presented high efficiency in this system to give the arylated indoles in excellent yields.

Transition-metal-catalyzed C−H bond activation has become an extremely powerful tool for the construction of C−C bonds in modern organic synthesis.[1] In particular, the direct arylation of indoles received considerable attention over the past decades because arylated indoles are important building blocks of natural products, materials, and pharmaceuticals.[2] Apart from aryl halides,[3] a variety of coupling species, including hypervalent iodine arylating agents[4] and organoboranes,[5] have been exploited in the direct C−H bond activation reactions of indoles. Compared with these coupling partners, organosilanes possess advantages such as good stability to reaction conditions and environmental benignity. The pioneering work of Hiyama has demonstrated that organosilanes are distinguished reagents for effecting a cross-coupling reaction (the Hiyama reaction).[6] Subsequent investigations led to the utility of various organosilanes as versatile cross-coupling partners with a variety of electrophiles.[7] However, the application of organosilanes in the reactions of direct C−H bond functionalizations is very limited,[8] and the corresponding direct coupling with indoles is still unexplored. Herein, we report a new palladium-catalysis system for the arylation of indoles by arylsiloxanes in acidic medium under very mild conditions (at room temperature). Electron-deficient arylsiloxanes presented high efficiency in this system to give the arylated indoles in excellent yields.

---

[1] (a) Lersch, M.; Tilset, M. *Chem. Rev.* **2005**, *105*, 2471. (b) Stuart, D. R.; Fagnou, K. *Science* **2007**, *316*, 1172. (c) Lewis, J. C.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res.* **2008**, *41*, 1013. (d) Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 11904. (e) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 12404. (f) Roy, A. H.; Lenges, C. P.; Brookhart, M. *J. Am. Chem. Soc.* **2007**, *129*, 2082. (g) Li, B.-J.; Tian, S.-L.; Fang, Z.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 1115. (h) Nakao, Y.; Kanyiva, K. S.; Hiyama, T. *J. Am. Chem. Soc.* **2008**, *130*, 2448. (i) Zhao, L.; Li, C.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 7075. (j) Ackermann, L.; Novák, P.; Vicente, R.; Hofmann, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 6045. (k) Wasa, M.; Engle, K. M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 3680.

[2] (a) Torssell, K. G. B. *Natural Product Chemistry*; Wiley: Chichester, 1983. (b) Thomson, R. H. *The Chemistry of Natural Products*; Blackie and Son: Glasgow, 1985. (c) Yamamura, K.; Ono, S.; Ogoshi, H.; Masuda, H.; Kuroda, Y. *Synlett* **1989**, 18. (d) Roncali, J. *Chem. Rev.* **1992**, *92*, 711. (e) Garg, N. K.; Sarpong, R.; Stolz, B. M. *J. Am. Chem. Soc.* **2002**, *124*, 13179. (f) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873.

[3] (a) Lane, B. S.; Sames, D. *Org. Lett.* **2004**, *6*, 2897. (b) Bellina, F.; Cauteruccio, S.; Rossi, R. *Eur. J. Org. Chem.* **2006**, *6*, 137–9. (c) Toure, B. B.; Lane, B. S.; Sames, D. *Org. Lett.* **2006**, *8*, 1979. (d) Wang, X.; Gribkov, D. V.; Sames, D. *J. Org. Chem.* **2007**, *72*, 1476. (e) Zhang, Z.; Hu, Z.; Yu, Z.; Lei, P.; Chi, H.; Wang, Y.; He, R. *Tetrahedron Lett.* **2007**, *48*, 2415. (f) Bellina, F.; Calandri, C.; Cauteruccio, S.; Rossi, R. *Tetrahedron* **2007**, *63*, 1970.

[4] Deprez, N. R.; Kalyani, D.; Krause, A.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 4972.

[5] (a) Yang, S.-D.; Sun, C.-L.; Fang, Z.; Li, B.-J.; Li, Y.-Z.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 1473. (b) Zhao, J.; Zhang, Y.; Cheng, K. *J. Org. Chem.* **2008**, *73*, 7428.

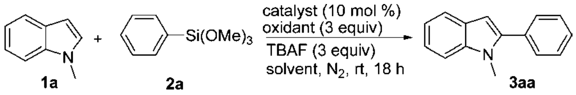
[6] (a) Hatanaka, Y.; Fukushima, S.; Hiyama, T. *Chem. Lett.* **1989**, 1711. (b) Gouda, K.-I.; Hagiwara, E.; Hatanaka, Y.; Hiyama, T. *J. Org. Chem.* **1996**, *61*, 7232. (c) Hiyama, T. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998; p 421. (d) Hiyama, T.; Shirakawa, E. *Top. Curr. Chem.* **2002**, *219*, 61. (e) Denmark, S. E.; Sweis, R. F. *Acc. Chem. Res.* **2002**, *35*, 835.

[7] (a) Nakao, Y.; Chen, J.; Tanaka, M.; Hiyama, T. *J. Am. Chem. Soc.* **2007**, *129*, 11694. (b) Lee, J.-Y.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 5616. (c) Zhang, L.; Wu, J. *J. Am. Chem. Soc.* **2008**, *130*, 12250. (d) Denmark, S. E.; Smith, R. C.; Chang, W.-T.; Muhuhi, J. M. *J. Am. Chem. Soc.* **2009**, *131*, 3104.

10.1021/ol101147b

Initially, we chose *N*-methylindole **1a** and trimethoxyphenyl-silane **2a** as the model substrates for surveying the reaction parameters (Table 1). It was found that the nature of oxidants, additives, and solvent play a critical role on the reaction efficiency. On the basis of the observation that basic conditions are preferred for reactions involving organosilanes, we performed the reaction under basic or neutral conditions. Unfortunately, the desired cross-coupling was not observed (Table 1, entries 1 and 2). It is important to note that the addition of AcOH led to the formation of cross-coupling product **3aa** and the best result was obtained when the amount of AcOH was 10 mmol (Table 1, entry 3). A trace of C3 arylated product was observed, showing the same high regioselectivity as observed for organoboranes.[5] Other palladium species, such as $PdCl_2$, $Pd(TFA)_2$, $Pd(CH_3CN)_2Cl_2$, $Pd(PPh_3)_4$, and $Pd(dba)_2$, were substantially less effective (Table 1, entries 4−8). Among the oxidants tested, the best result was obtained by the use of Ag_2O (Table 1, entry 3). A comparable reaction efficiency was presented by Ag_2CO_3 (Table 1, entry 9), while AgOAc and AgF showed poor reactivity (Table 1, entries 10 and 11). No reaction took place without catalysts or oxidants in this acidic system (Table 1, entries 12 and 13). The different solvents were also screened, and ethanol is the most suitable for this transformation. Slow addition of trimethoxyphenylsilane **2a** was found to further improve the reaction to give **3aa** in 85% GC yield (Table 1, entry 14. For details, see the Supporting Information). Increasing reaction temperature led to the low conversion (Table 1, entry 15). Thus, the reaction efficiently proceeded when 10 mol % of $Pd(OAc)_2$ was used in combination with Ag_2O (3 equiv) and TBAF (3 equiv) in ethanol at room temperature.

Table 1. Effects of Metals and Oxidants on the Arylation[a]

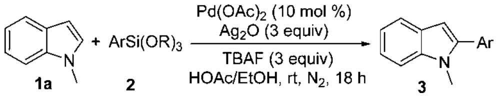


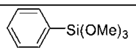
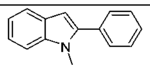
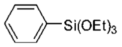
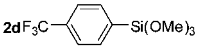
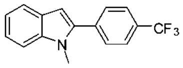
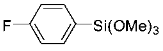
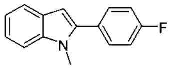
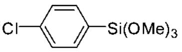
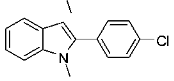
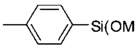
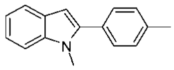
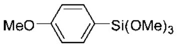
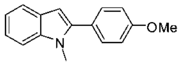
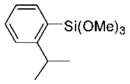
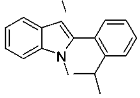
entry	catalyst	oxidant	yield (%)[b]
1	$Pd(OAc)_2$	Ag_2O	0[c]
2	$Pd(OAc)_2$	Ag_2O	0[d]
3	$Pd(OAc)_2$	Ag_2O	64
4	$PdCl_2$	Ag_2O	13
5	$Pd(TFA)_2$	Ag_2O	44
6	$Pd(CH_3CN)_2Cl_2$	Ag_2O	47
7	$Pd(PPh_3)_4$	Ag_2O	9
8	Pd $(dba)_2$	Ag_2O	11
9	$Pd(OAc)_2$	Ag_2CO_3	57
10	$Pd(OAc)_2$	AgOAc	48
11	$Pd(OAc)_2$	AgF	32
12		Ag_2O	0
13	$Pd(OAc)_2$		tr
14	$Pd(OAc)_2$	Ag_2O	85[e]
15	$Pd(OAc)_2$	Ag_2O	53[f]

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (1.5 mmol), catalyst (0.05 mmol), Ag_2O (1.5 mmol), TBAF (1.5 mL, 1 M in THF), AcOH (10 mmol), EtOH (4 mL), rt, 18 h, N_2. [b] GC yields based on *N*-methyl indole. [c] NaOH (2 mmol) instead of AcOH. [d] In the absence of AcOH. [e] **2a** (0.5 mmol × 3), TBAF (0.5 mL × 3, 1 M in THF). [f] 60 °C.

With the identification of the optimal reaction conditions, the scope of the reaction was investigated as shown in Table 2. It can be seen that a range of arylsiloxanes participate in the regioselective coupling reaction efficiently. Triethoxyphenylsilane **2b** and dimethoxydiphenylsilane **2c** showed the similar efficiency as with trimethoxyphenylsilane **2a** to give the arylated indole **3aa** in good yields (Table 2, entries 1−3). Notably, the reaction tolerated the electron-deficient arylsiloxanes, as trimethoxy (4-(trifluoromethyl) phenyl)silane **2d** coupled efficiently with indole **1a** to give **3ad** in 90% yield (Table 2, entry 4). Excellent yields were also obtained for other electron-deficient arylsilanes such as (4-fluorophenyl) trimethoxysilane **2e** and (4-chlorophenyl)trimethoxysilane **2f** (Table 2, entries 5 and 6). In contrast, arylsilanes with an electron-donating group in the aromatic ring presented relatively lower reactivity (Table 2, entries 7 and 8). This results are different from the reaction of indoles with organoboranes,[5] in which the electron-rich aryl boronic acids are more active. It should be noted that the tolerance of the reaction for C−Cl bond in indole made it attractive for the further assembly through the cross-coupling reactions. Arylsilanes with an ortho-substitutent delivered the corresponding arylated indole in lower yield (Table 2, entry 9), illustrating that the steric hindrance played the role to the reaction.

Table 2. Arylation of *N*-MethylIndole with Various Organosilanes[a]



entry	organosilanes **2**	product	yield (%) [b]
1	**2a**  Si(OMe)3		82, (**3aa**)
2	**2b**  Si(OEt)3		81, (**3aa**)
3	**2c** $Ph_2Si(OMe)_2$		78, (**3aa**)
4	**2d**  F3C, Si(OMe)3	 CF3	90, (**3ad**)
5	**2e**  F, Si(OMe)3	 F	91, (**3ae**)
6	**2f**  Cl, Si(OMe)3	 Cl	93, (**3af**)
7	**2g**  Si(OMe)3		81, (**3ag**)
8	**2h**  MeO, Si(OMe)3	 OMe	55, (**3ah**)
9	**2i**  Si(OMe)3		57, (**3ai**)

[a] Reaction conditions: indoles **1a** (0.5 mmol), **2** (0.5 mmol × 3), $Pd(OAc)_2$ (0.05 mmol), Ag_2O (1.5 mmol), TBAF (0.5 mL × 3), AcOH (10 mmol), EtOH (4 mL), rt, 18 h, N_2. [b] Isolated yields.

This arylation reaction also demonstrated a remarkable tolerance toward functional groups at the indoles as shown in Figure 1, and the substituent groups on the indoles influenced

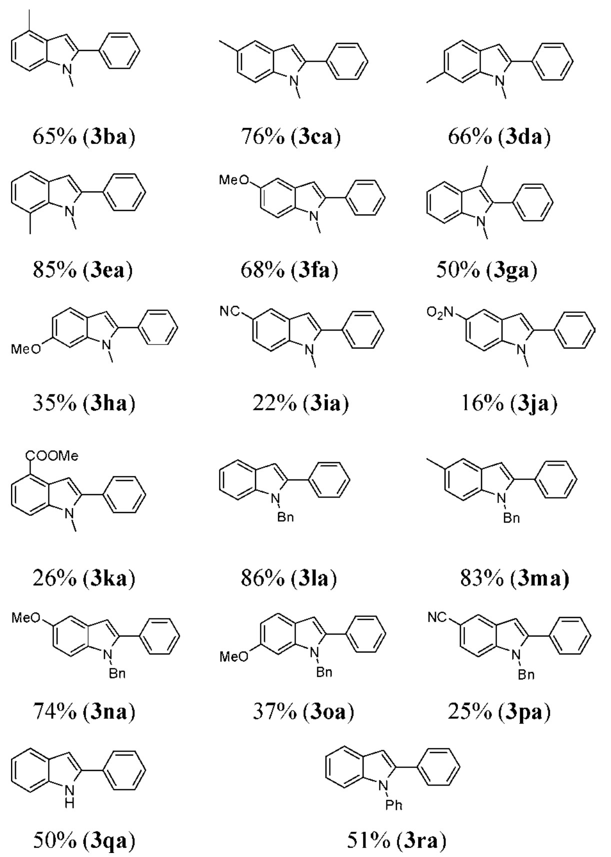
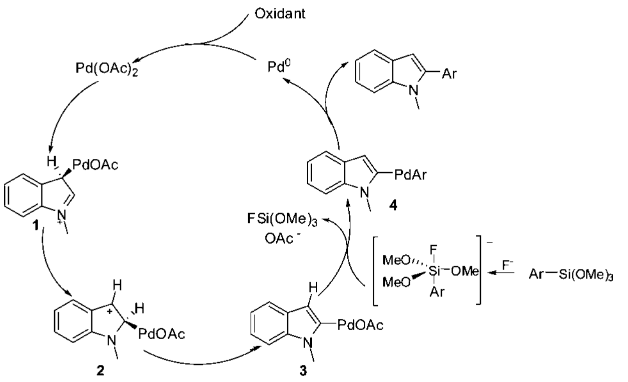


Figure 1. Arylation of various substituted indoles. Reaction conditions: indoles **1** (0.5 mmol), **2a** (0.5 mmol × 3), $Pd(OAc)_2$ (0.05 mmol), Ag_2O (1.5 mmol), TBAF (0.5 mL × 3), AcOH (10 mmol), EtOH (4 mL), rt, 18 h, N_2. Isolated yields.

the reactivity of this direct arylation reaction. The electron-rich indoles showed the better reactivity and furnished the products in moderate to good yields (**3ba**−**3fa**, **3ma**, and **3na**). The sterically demanding 3-methyl-*N*-methylindole **1g** delivered relatively lower yield (**3ga**). The reaction of 6-methoxy-*N*-methylindoles and 6-methoxy-*N*-benzylindole showed relatively lower reactivity with the analogous tendency as in the direct arylation of indoles with organoboranes[5b] and afforded low yields (**3ha** and **3oa**). The electron-deficient indoles participated in the reaction to give the corresponding cross-coupling products, but they are less active and displayed low yields (**3ia**−**3ka** and **3pa**). Notably, the free (N−H) indoles could also tolerate the reaction to give a 50% yield (**3qa**). *N*-Benzylindoles were good substrates for this arylation reaction as shown for the synthesis of **3la**−**3na** and afforded higher yields than *N*-phenylindole (**3ra**).

Related studies on the direct palladium-catalyzed arylation of indoles[9] established that the first electrophilic substitution of the indole ring at the C3-position followed by a C3→C2 migration[10] was the most possible pathway for the selective C2-arylation (Scheme 1, intermediate **1** to **2**). In our experiment, the electron-rich indoles are more reactive than the electron-deficient indoles, which is consistent with the electrophilic substitution mechanism. In addition, it is well-known that the fluoride plays a role in the activation of tetracoordinated silanes via the in situ formation of pentacoordinate silicate anion.[11] On the basis of these previous studies and our experimental results, a plausible mechanism for the arylation of indoles was proposed as shown in Scheme 1. First, the electrophilic palladation occurs at preferential C3-position of indole, which undergoes a 1,2-migration to form intermediate **2**. The subsequent deprotonation leads to the production of intermediate **3**, which reacts with the in situ generated pentavalent silicate to afford the (aryl)(indole)palladium(II) species **4**. The subsequent reductive elimination liberates the arylated indoles with the regenerate of the Pd(0), which is oxidated in the presence of the oxidant to complete the catalytic cycle.

Scheme 1. Plausible Catalytic Cycle



In summary, we have developed a new catalytic system for the arylation of indoles with arylsiloxanes through the C−H functionalization reaction under mild conditions. This transformation represents rare examples of organosilanes applied to C−H bond activations in acidic medium, which allows efficient synthesis of a variety of C2-arylated indoles. Further development of other C−H functionalizations by the use of organosilanes is in progress in our laboratories.

Acknowledgment. Funding from Natural Science Foundation of China (No. 20872126) and Zhejiang Provincial Natural Science Foundation of China (R407106) is acknowledged.

Supporting Information Available: General experimental procedures and spectroscopic data (^{1}H NMR, ^{13}C NMR, HRMS, and MS) for the corresponding products. This material is available free of charge via the Internet at http://pubs.acs.org.

OL101147B

---

(8) (a) Yang, S.-D.; Li, B.-J.; Wan, X.-B.; Shi, Z.-J. *J. Am. Chem. Soc.* **2007**, *129*, 6066. (b) Zhou, H.; Xu, Y.-H.; Chung, W.-J.; Loh, T.-P. *Angew. Chem., Int. Ed.* **2009**, *48*, 5355. (c) Hachiya, H.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 2202.

(9) (a) Jia, C.; Lu, W.; Kitamura, T.; Fujiwara, Y. *Org. Lett.* **1999**, *1*, 2097. (b) Wang, X.; Lane, B. S.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 4996. (c) Bressy, C.; Alberico, D.; Lautens, M. *J. Am. Chem. Soc.* **2005**, *127*, 13148. (d) Lebrasseur, N.; Larrosa, I. *J. Am. Chem. Soc.* **2008**, *130*, 2926.

(10) (a) Lane, B. S.; Brown, M. A.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 8050. (b) Saulnier, M. G.; Gribble, G. W. *J. Org. Chem.* **1982**, *47*, 757. (c) Grimster, N. P.; Gauntlett, C.; Godfrey, C. R. A.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 3125.

(11) (a) Hatanaka, Y.; Goda, K.; Hiyama, T. *J. Organomet. Chem.* **1994**, *465*, 97. (b) Fujita, M.; Hiyama, T. *J. Am. Chem. Soc.* **1985**, *107*, 8294. (c) Mowery, M. E.; DeShong, P. *J. Org. Chem.* **1999**, *64*, 1684. (d) Riggleman, S.; DeShong, P. *J. Org. Chem.* **2003**, *68*, 8106.